Novel 1,1-sulfonyl-sulfonamido alkenes for crosslinking and conjugation applications

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Novel 1,1-sulfonyl-sulfonamido alkenes for crosslinking and conjugation applications

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DECLARATION

The work described in this thesis was carried out in the Department of Chemistry at Durham University (UK) between May 2017 and March 2021, under the supervision of Prof. Andrew Whiting. The material contained has not been previously submitted for a degree at this or any other university. The research reported within this thesis has been conducted by the author unless indicated otherwise.

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Abstract

The current project consists of the study of new types of cross-linker molecules for VOC-free waterborne coatings. In fact, in the last decades, demand for environmentally-friendly coatings has driven the formulation market towards water borne technologies. However, the requirement for higher performance in waterborne coatings has led to an increased level of research in this field.

Herein, it is proposed a new crosslinking mechanism for water-borne coatings based on a latent reactive group, which is unveiled through during water evaporation. Particularly attractive molecules in this scenario are sulfone moieties since they have been widely studied in a broad range of pharmaceuticals and natural products due to their chemical and physical properties. Indeed, they are particularly good at acting as activating, electron-withdrawing, substituents, and they have an interesting ability to form α-carbanions with respect to the sulfone group which enables alkylation, acylation and aldol-like processes.

Within the frame of the use of sulfone compounds in organic synthesis, a literature review is presented as a first chapter. After a first brief introduction on general aspects of sulfones, the first section focuses on the most common methods for the synthesis of sulfones, followed by sulfones' reactions which revolves around its ability to activate adjacent groups towards deprotonation, and hence, forming stabilised carbanions. Finally, focus is drawn to α,β-unsaturated sulfones and α,β-unsaturated gem-disulfones as good Michael acceptors and their ability to react with suitable nucleophilic heteroatoms, such as alcohols, thiols and amines.

Within the study of novel cross-linkers in the second chapter, an introduction to water-borne coatings and emulsion polymerisation is outlined. Further details on previous studies conducted in this group are also reported. Therefore, in this study efforts were focused on gaining and optimising the synthetic pathway which led to the target cross-linkers. In particular, a first section describes the optimisation of sulfonyl sulfonamide systems' synthesis, constructed by dimerisation of mesyl chloride to give a *bis*-sulfone halide which can be trapped by an amine. This amine encloses a desirable spacer and functional group. This method permitted the synthesis of various sulfonyl sulfonamide analogues in which the functional group was a polymerisable group such acrylate and styrene. Focus was then brought to the exploitation of the introduction of the unsaturated crosslinking moiety into the previously synthesised sulfonyl sulfonamide monomers. Therefore, novel vinyl sulfonyl sulfonamide monomers were obtained through Knoevenagel-type reaction and their ability to react with suitable nucleophilic heteroatoms, such as alcohols, thiols and amines were tested. High reactivity was found in the case of thiol-Michael additions, whereas lower reactivity was found in the case of alcohols and amines, with this latter going through retro-aldol-type reactions. Moreover, vinyl sulfonyl sulfonamides seemed to have the tendency to react with a second molecule of vinyl sulfonyl sulfonamide, opening to the possibility of cross-linking without the presence of an external nucleophile.

In a second section, previously synthesised vinyl sulfonyl sulfonamide monomers were firstly employed in free-radical co-polymerisation with methyl methacrylate and styrene and, secondly, integrated into emulsion polymerisation, following a general formulation for coating technology, as used at our collaborators, i.e. AkzoNobel.

Finally, vinyl sulfonyl sulfonamides were employed in the field of bioconjugations involving preliminary proof-of-concept studies on this subject, which was able to demonstrate efficient and quantitative conjugation of a fluorophore compound to amino acid analogues, and a cyclic peptide, cRGD.

The following graphical abstract summarises the project contained in this thesis.

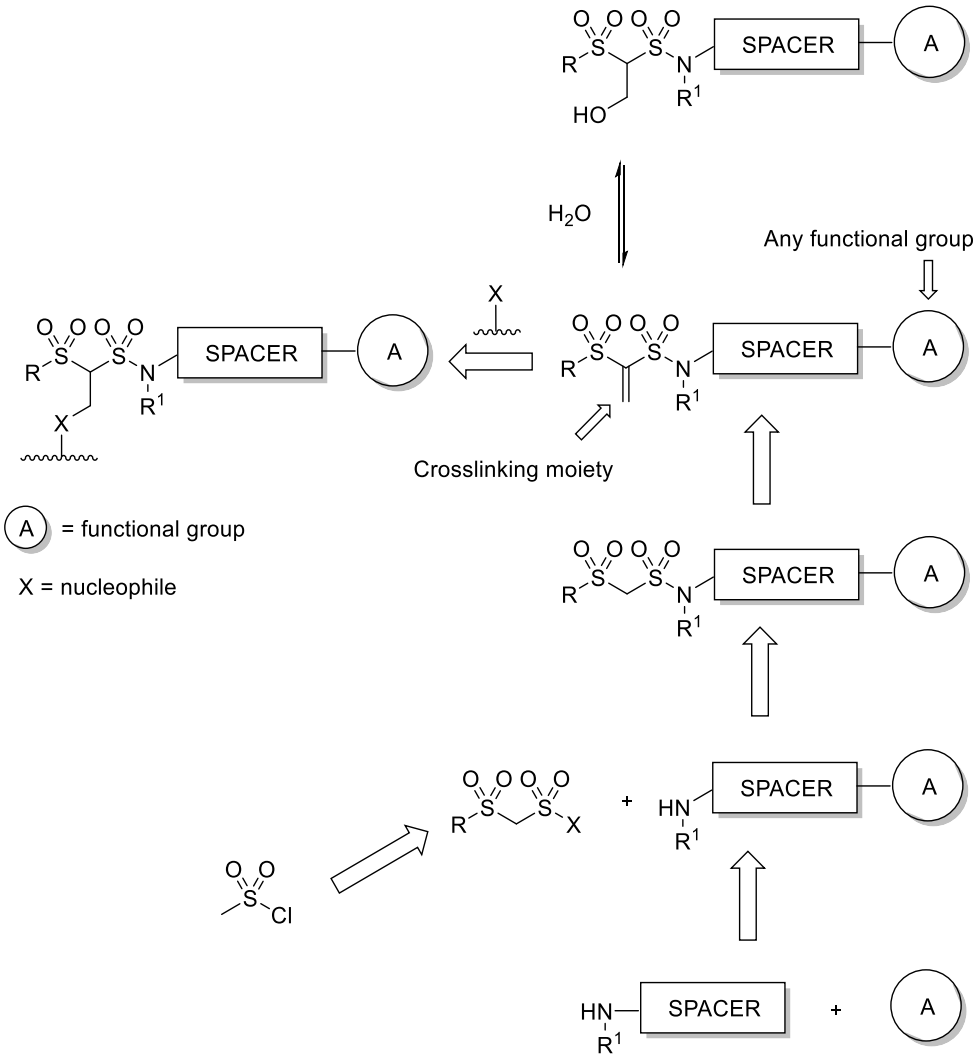

Figure I. General scheme outlining the main chemical ideas to be developed in this work.

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Abbreviations

Å	Angström (s)
AAEM	Acetoacetoxyethyl methacrylate
Ac	Acetyl
acac	Acetylacetonate
ADH	Adipic acid dihydrazide
AEMA	Amino ethyl methacrylate hydrochloride
AIBN	Azo*bis*isobutyronitrile
App.	Apparent splitting (NMR spectroscopy)
APS	Ammonium persulfate
aq.	Aqueous
Ar	Aryl
ASAP	Atmospheric solids analysis probe
BA	Butyl acrylate
Boc	Tert-butyloxycarbonyl group
BPO	Benzoyl peroxide
BQ	1,4-Benzoquinone
^{t}Bu	Tert-butyl
t-BuONO	Tert-butyl nitrite
°C	Degrees Celsius
ca.	Approximately
CAN	Ceric ammonium nitrate
cat	Catalytic
Cbz	Benzyloxycarbonyl
COSY	Correlation spectroscopy
CPME	Cyclopentyl methyl ether
δ	Chemical shift (NMR)
d	Doublet
DAAM	Diacetone acrylamide
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DIPEA	*N,N*-Diisopropylethylamine
DIW	Deionised water

DMAP	4-(*N,N*-Dimethylamino)pyridine
DMF	*N,N*-Dimethyl formamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMSO	Dimethyl sulfoxide
DSC	Differential scanning calorimetry
DOSY	Diffusion ordered spectroscopy
E	Electrophile
e.e.	Enantiomeric excess
EDDA	Ethylenediaminediacetic acid
e.g.	Exempli gratia (for example)
eq.	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
et al.	*Et altri*
EWG	Electron withdrawing group
FT-IR	Fourier transform infrared spectroscopy
g	Gram (s)
h	Hour (s)
HEMA	Hydroxyethyl methacrylate
HESS	4-Hydroxyethylsulfonylstyrene
HMBC	Heteronuclear multiple bond correlation
HPLC	High performance liquid chromatography
HPMA	Hydroxypropyl methacrylate
HSQC	Heteronuclear single quantum coherence
HRMS	High resolution mass spectroscopy
Hz	Hertz
i.e.	Id est (in other words)
IR	Infra-red spectroscopy
J	Coupling constant (NMR spectroscopy)
KHMDS	Potassium *bis*(trimethylsilyl)amide
LDA	Lithium di-isopropylamide
LRMS	Low resonance mass spectrometry
LTQ-FT	Linear triple quadrupol fourier transform
m	Multiplet (NMR); milli; medium (IR)
M^+	Molecular ion peak (Mass spectrometry)

MAA	Methacrylic acid
MACHO	Metal complexes containing MACHO ligands of the type $HN(CH_2CH_2PR_2)_2$, where are R = phenyl or isopropyl
Me	Methyl
MEHQ	4-Methoxyphenol, 4-methoxyhydroquinone
MEK	Methyl ethyl ketone
MFFT	Minimum film formation temperature
min	Minute (s)
MMA	Methyl methacrylate
mol	Mole (s)
M	Metal
MS	Molecular Sieves; Mass spectrometry
m/z	mass to charge ratio (Mass spectrometry)
NaPS	Sodium persulfate
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
PDC	Pyridinium dichromate
PEG	Poly(ethylene glycol)
PIDA	(Diacetoxyiodo)benzene
Ph	Phenyl
PMMA	Poly methyl methacrylate
ppm	Part (s) per million
^{i}Pr	Isopropyl
PSD	Particle size distribution
q	Quartet
R_f	Retention factor (TLC)
r.t.	Room temperature
s	Singlet; strong (IR)
sat.	Saturated
SEC	Size exclusion chromatography
SSNMR	Solid state nuclear magnetic resonance
t	Triplet
T	Temperature
TBAB	Tetrabutylammonium bromide
TBAI	Tetrabutylammonium iodide

TBHP	tert-Butyl hydroperoxide
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TfOH	Triflic acid
Tg	Glass transition temperature
TGA	Thermogrametric analysis
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
TMSCl	Chlorotrimethylsilane
TQD	Triple Quadrupol Detector
UV	Ultraviolet
VOC	Volatile organic compound
w	Weak (Infrared spectroscopy)
wt	Weight

1 Introduction

1.1 Introduction to sulfone chemistry

Over the last fifteen years, the study and use of sulfones has increased dramatically due to their versatile application in organic synthesis and in various other fields such as agrochemicals, polymers and pharmaceuticals. A number of publications have been devoted to the study of sulfone chemistry with an impressive growth in the last decades. In fact, it has been recognised, depending on the surrounding environment, that either electrophilic or nucleophilic behaviour is possible. Despite the number of studies on sulfides, sulfoxides, sulfones and various derivatives, much of the chemistry in this area remains unpredictable.[1]

In this review, the emphasis will be on the synthetic uses and preparative routes to the sulfone group.

1.2 General and theoretical aspects

As mentioned above, sulfur compounds can be reducing or oxidising agents, anions or cations, nucleophiles or electrophiles (most reactions use a sulfur as nucleophile and sulfur based leaving group), and therefore, it has been defined as a 'chemical chameleon' by Trost.[2] Sulfur is a p-block element of group VI (six electrons in its outer shell) and therefore, its electronic structure may be written as $1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p_x^2\ 3p_y^1\ 3p_z^1$. However, sulfur is allowed to have oxidation states 0, 2, 4 or 6 and coordination numbers from 0 to 7. In fact, sulfur can form stable compounds such as SF_4 and SF_6 which were initially proposed to involve expansion of the valence shell through participation of the 3d orbitals.[3]. However, although numerous textbook introductions explain bonding in sulfur groups using octet violation of the Lewis-Langmuir octet principle, the participation of 3d orbitals is still a matter of debate.

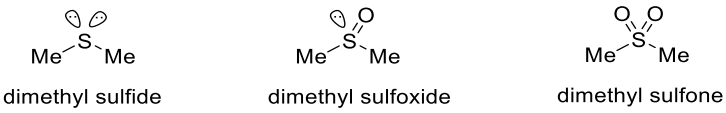


Figure 1. Compounds of sulfur.

Dimethyl sulfide σ molecular orbital bonds may be explained by the overlapping of singly occupied 3 x sp^3 hybridised orbitals on sulfur with singly occupied 2 x sp^3 hybridised orbitals on carbon, while two pairs of electrons in the valence shell remain in the $3sp^3$ orbitals, through which repulsion leads to a tetrahedral shape (Figure 1).[4] Due to their high energy non-bonding lone pairs, sulfides (II), as well as thiols and thiolates, are considered to be good, soft nucleophiles. Although thiols are more acidic than alcohols, they are better nucleophiles than oxygen compounds towards saturated carbon atoms undergoing facile S_N2 reactions.[5]

In a sulfoxide, a third bond with oxygen is formed, in which the contribution of a *3d* orbital on sulfur is hypothesised. One of the two electrons in the unshared pair of electrons in the previous example is promoted to a $3d_{xy}$ orbital. Therefore, the overlap of the singly occupied $3sp^3$ orbital of sulfur with $2sp^2$ of oxygen forms a σ-bond, while the sidewise overlap of $3d_{xy}$ orbital of sulfur with $2p_y$ of oxygen forms a π-bond. Sulfoxides can also present chirality, which makes these types of compounds relevant in bioactive drugs.

In the case of a sulfone, a further oxygen bond is formed, which can be pictured as explained above, represented as a tetrahedral structure. Sulfur atoms in this high oxidation state S(VI) are considered good, soft electrophiles. However, at higher oxidation states, sulfur becomes a harder electrophile can also be a good, soft nucleophile. In fact, sulfones are not subject to nucleophilic attack, and that is why they have been widely used over the years in organic synthesis.

Unfortunately, it is still unclear as to the nature of the sulfur oxygen bonds in sulfoxides and sulfones, and these are often represented involving various combinations of coordinate and double bonds. In fact, bond lengths, dipole moments, bond energies, infrared spectra, and molecular refraction all provide little support for significant d-orbital

participation, suggesting that the sulfur-oxygen bond may be satisfactorily interpreted as a coordinate bond[6]. However, there are many hypervalent molecules formed by sulfur (SF_6 as mentioned before) and its neighbours in the second row of the period table which appear to require a bonding role for *d*-orbitals.

Before WWII, the high carbon acidity of *bis*(sulfonyl)methane was noted, and it was presumed to be a result of the expansion of the valence shell of the central sulfur atom beyond the octet (Figure 2).[7]

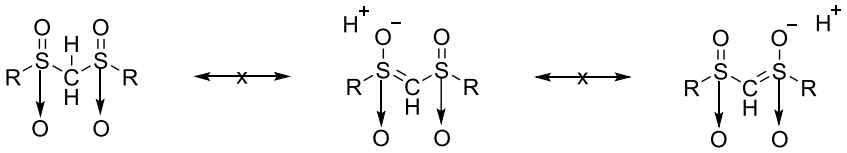


Figure 2. First, outdated, explanation of the high α-carbon acidity of sulfones.

As shown later in this review, the majority of sulfone chemistry revolves around its ability to activate adjacent groups towards deprotonation, forming stabilised carbanions and even polyanions. It can be briefly mentioned that sulfonyl carbanions are sterically stable and exist in either pyramidal (sp^3) structure in which the lone pair on carbon is approximately gauche to the two sulfone oxygens (Figure 3-A) and a planar one having a sp^2 carbanionic centre[4, 8] (Figure 3-B). In both cases, the fairly high energy barrier for both rotation and pyramidal inversion of the C-S bond in α-sulfur stabilised carbanions encourage a retention of configuration during reactions.

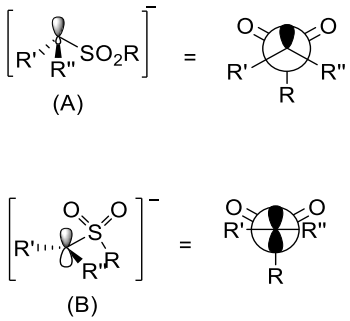


Figure 3. Two possible representations of sulfonyl carbanions structure: (A) pyramidal sp^3 and (B) planar sp^2.

Despite the lower electronegativity of the sulfur atom (2.5) compared to oxygen (3.5), the α-thiocarbanion is known to be more stabilised than the corresponding α-oxycarbanion.

In fact, considering the same substituent, the p*Ka* values of the α-methylene protons of a sulfide is ~45, sulfoxide ~35 and for sulfone ~29 in DMSO, and therefore, sulfones are considered as excellent anion stabilisers. Additional stabilising processes such as p–d, spx–d delocalisation and hyperconjugation have been proposed to explain the generally strong withdrawing effect of the sulfonyl groups.[9] In fact, unlike carbonyl groups, sulfones do not give resonance stabilisation to give the corresponding enolate-like system.

When dealing with deprotonation, it is important to understand equilibrium acidities, and therefore, p*Ka*'s, and a number of values studied by Bordwell *et al.* in DMSO are reported in Table 1.[10]

Table 1. p*K*a of a selection of sulfones from Bordwell's research.[8c, 10-11]

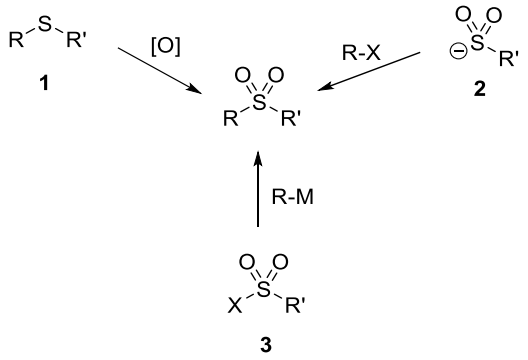
Substrate	p*Ka*	Substrate	p*Ka*
$MeSO_2Me$	31.1	$PhSO_2CH_2SMe$	23.4
$PhSO_2Me$	29.0	$PhSO_2CH_2SO_2Ph$	12.2
$PhSO_2Et$	31.0	$PhSO_2CH_2CN$	12.0
$MeSO_2CF_3$	18.8	$PhSO_2CH_2COPh$	11.4
$PhSO_2CH_2OMe$	30.7	$PhSO_2CH_2NO_2$	7.1

From an overview of the values (Table 1), it can be seen that sulfone groups are not strongly acidifying and, in comparison with a carbonyl and a nitro groups, the order would be: $PhSO_2Me$<$PhCOMe$<<$MeNO_2$ with relative p*Ka*'s of 29, 24.7 and 17.2 respectively in DMSO. Interestingly, in the case of a *bis*-sulfones, the acidity increases, revealing similar effects when CN or SO_2Ph moieties are added. However, when a carbon is added, the p*Ka* increases as well as when a heteroatom is added, due to the higher electronegativity. As expected, fluorine substitution gives a rise in acidity at the α-carbon.

For these reasons, the conditions required for sulfonyl carbanion formation and its subsequent reaction should be chosen carefully. It is crucial to consider the solvent and the type of metal counterion, and based on these considerations a considerable number of sulfone compounds have been employed through their carbanions to undergo wide ranges of reactions, as is reported in this work.

1.3 Sulfones

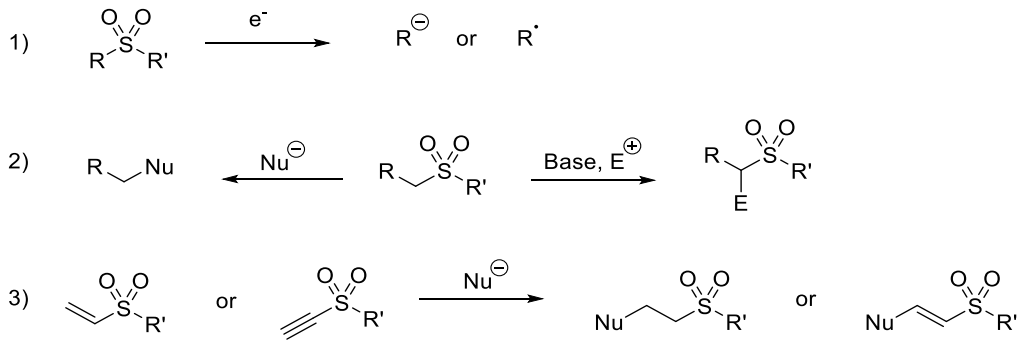
The most common methods for the synthesis of sulfones are the oxidation of the corresponding sulphides **1**, followed by alkylation of sulfinate salts **2** and reactions of sulfonic acid derivatives **3**, such as sulfonate esters or sulfonyl chloride.



Scheme 1. Main sulfones synthesis.

The oxidation of a sulfide **1** (Scheme 1) is the most common method of accessing sulfones, however, the use of sulfides is preferentially avoided due their often pungent smell. Two other methods consist of the alkylation of nucleophilic sulfinate anions **2** (Scheme 1) and the coupling of sulfonyl halides or anhydrides with carbon nucleophiles **3** (Scheme 1).

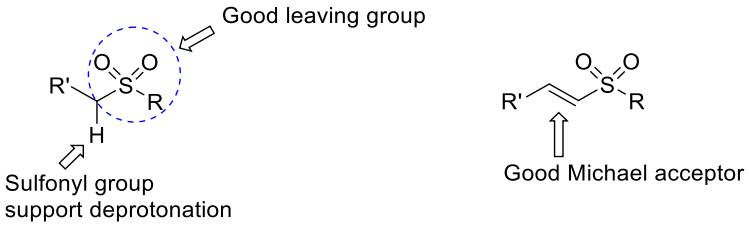
Sulfones are used as versatile synthetic intermediates in organic chemistry.



Scheme 2. General reactions of sulfones.

In fact, C-S bonds are susceptible to reduction by alkali metals and can be cleaved to generate both carbanions and carbon-centred radicals (Scheme 2-1). Sulfone moieties are also good leaving groups[12] which can be easily removed by producing a sulfinate anion

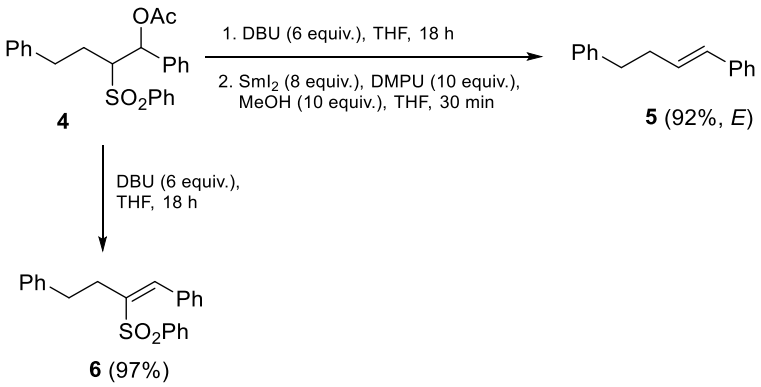
since they are frequently undesired in target molecules[13] or can activate adjacent protons for deprotonation (Scheme 2-2). Sulfone groups are also particularly good activating, electron-withdrawing substituents in Michael acceptors[4, 8c, 14] (Scheme 3).



Scheme 3. Chemistry of the sulfone moieties.

Of great synthetic importance is the ability of sulfones to form α-carbanions which can then be used in α-alkylation, acylation and aldol-like processes.[1, 15] In most cases, sulfones are structured to undergo deprotonation only at one site, through the use of blocking groups such as tosyl and phenyl on one end of the sulfone, leaving a deprotonatable C-H on the other.

The ability of sulfones to form carbanions enables the formation of C=C bonds (Scheme 4) such as in the Julia-Lythgoe olefination.[16]

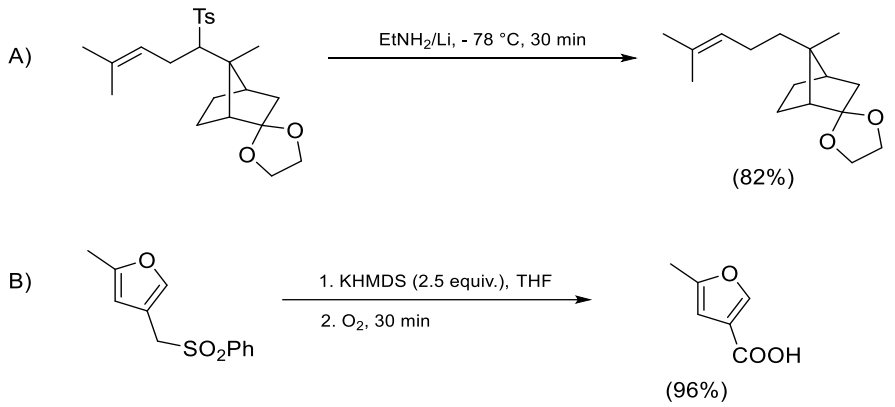


Scheme 4. Julia olefination.[16a]

The elimination can be mediated by a base forming the corresponding alkenes *via* loss of sulfinic acid. Similarly, metal mediated eliminations, usually named Julia reactions, are multistep syntheses which enable the preferential preparation of (*E*)-alkenes **5**. Further investigations were conducted by B. Lythgoe and P. J. Kocienski[17] enabling the synthesis of

Z-alkenes. The synthesis of vinyl sulfones enables the preparation of Michael acceptors, to which nucleophilic additions can be carried out.

Sulfone moieties are often used because they can easily be interconverted to a range of other functional groups, including heteratoms, carbonyl compounds (Scheme 5-B)[18] or reduced to the corresponding C-H derivative.[2, 12] Reductive desulfonylation can be mediated by active metals and salts, tin hydrides, and transition-metals (Scheme 5-A).[19]



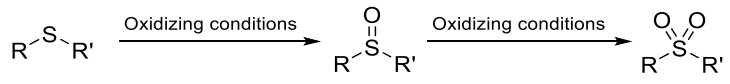
Scheme 5. Example of reductive desulfonylation (A) and oxidative sulfonylation (B).

1.3.1 Synthesis of sulfones

As noted above, the most common methods for the synthesis of sulfones are the oxidation of sulfides, alkylation of sulfinate salts and reactions of sulfonic acid derivatives. Other miscellaneous synthetic approaches are also listed below. For a more in-depth review refer to "Recent advance in the synthesis of sulfones".[20]

1.3.1.1 Oxidation of sulfides

The most widely used method to synthesize sulfones is by oxidation of sulfides (Scheme 6).



Oxidizing conditions:

$KMnO_4/MnO_2$, neat, rt	83-93%
urea-H_2O_2, neat, 85 C	87%
30% aq H_2O_2, 75 C	68%
NaOCl, cyanuric acid (10 mol%), toluene, rt	96%

Scheme 6. Oxidation of sulfides *via* the sulfoxide.

To achieve complete conversion to the target sulfone an excess of oxidizing agents in combination with high temperatures or long reaction times are often needed. Generally, the first oxidising step in order to form the sulfoxide is much more rapid than the second oxidation step to form the sulfone. The most frequently used oxidants are peracids or hydrogen peroxide and acetic acid,[21] even though a wide selection of other reagents are also available.[22]

1.3.1.2 Alkylation and arylation of sulfonated salts

Another way to form sulfones is the reaction of groups such as alkenes, alcohols, epoxides, alkyl halides and carbonyl compounds with sulfinic acids or their derived metal salts. In fact, sulfinates are strong nucleophiles and they can react with different electrophiles even though in the presence of hard alkylating agents the sulfinate ester can form as a by-product.[20, 23] Both electron rich and electron poor polarised double bonds react readily with sulfonic acids, yet the isolation of sulfinic acids is complicated by their tendency to autooxidise and they are usually stored in the form of metal salts.[8c]

The synthesis of 5- and 6-membered heterocyclic sulfones are of particular interest as useful intermediates and active compounds[24] in medicinal chemistry (Figure 4).

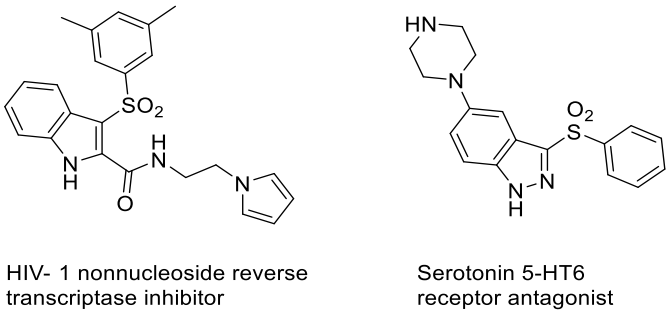
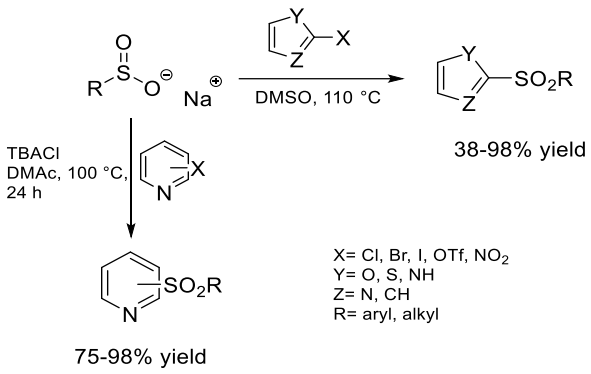


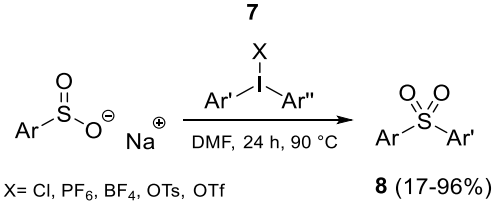
Figure 4. Examples of medicinally active five membered heteroaryl sulfones.

The synthesis of these with sodium sulfinates permits the avoidance of transition metals, where Pd or Cu catalysed cross-coupling reaction between sulfinate salts and aryl halides, aryl boronic acids, or special arenes are used (Scheme 7).[25]



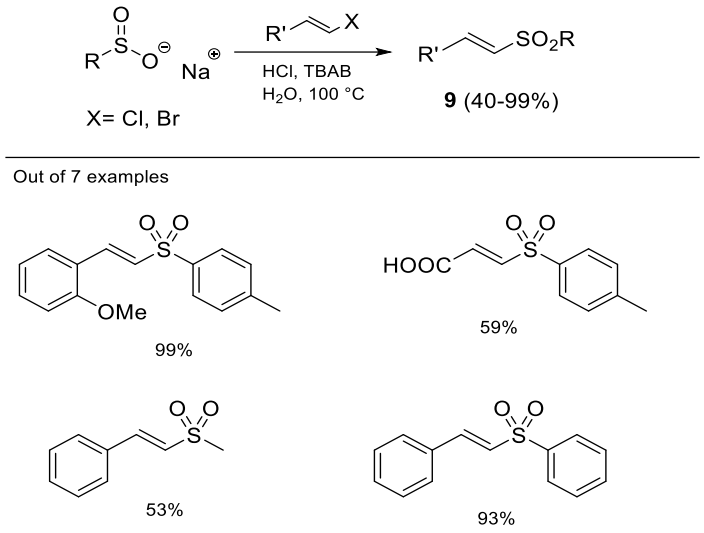
Scheme 7. Sulfonylation of five and six-member ring.

Unsymmetrical diaryliodonium salts **7** can be used to react with sodium sulfinates resulting in the transfer of one aryl moiety, although this is limited to the migration of activated arenes[26] (Scheme 8).



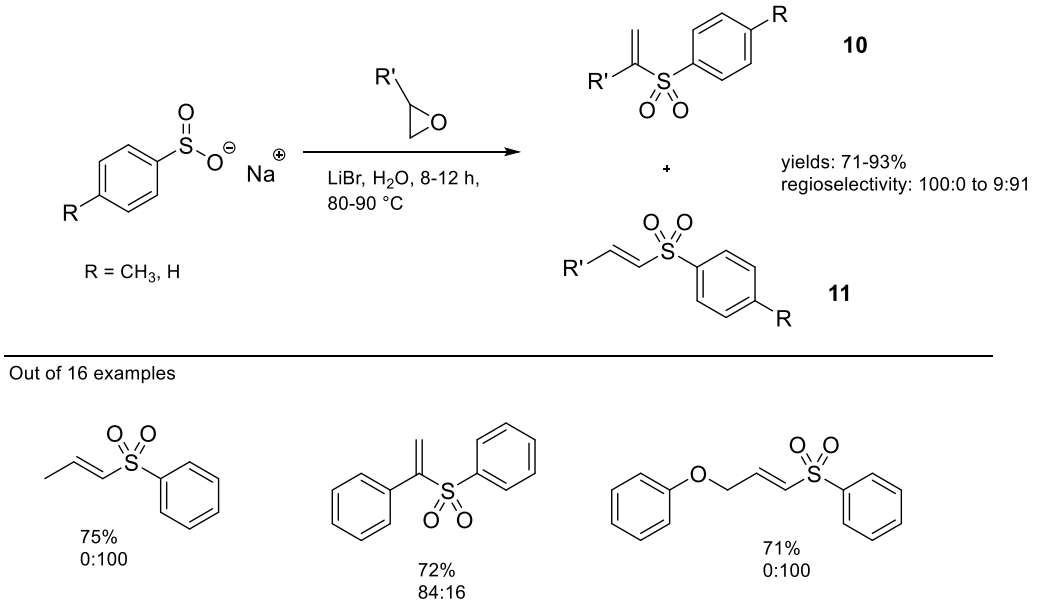
Scheme 8. Arylation of sodium sulfinates.

Other research has also studied a transition metal-free method for the synthesis of aryl sulfones and some other extensions employing vinyl halides **9** (Scheme 9).[27]



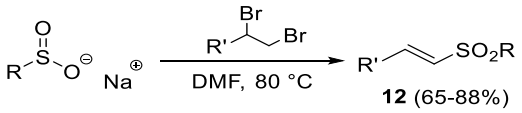
Scheme 9. Transition metal-free coupling for the synthesis of vinyl sulfone.

An eco-friendly process for the synthesis of vinyl sulfones via reaction of sulfinates with terminal epoxides in water, catalysed by lithium bromide, has been developed. Unfortunately, a mixture of regioisomers **10** and **11** was obtained in most cases (Scheme 10).[28] The first step involves the opening of the epoxide by the sulfinate, forming the β-hydroxy sulfone which then dehydrates.



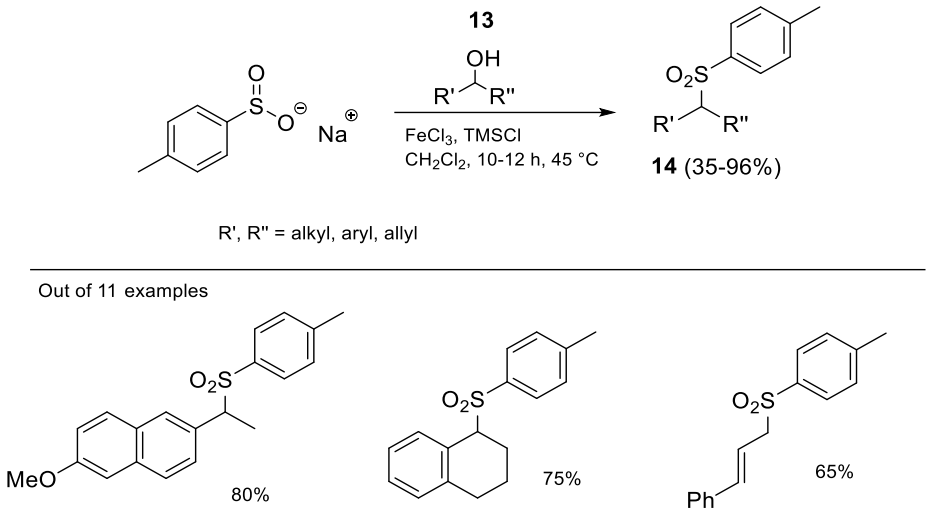
Scheme 10. Transition metal-free coupling for the synthesis of vinyl sulfone.

Another way to access vinyl sulfones (mainly as the *E* stereoisomer, **12**) is the reaction between sodium sulfinates with 1,2-dibromides (Scheme 11), via nucleophilic displacement of one bromide followed by activation of the second towards elimination.



Scheme 11. Catalyst free synthesis of vinyl sulfones.

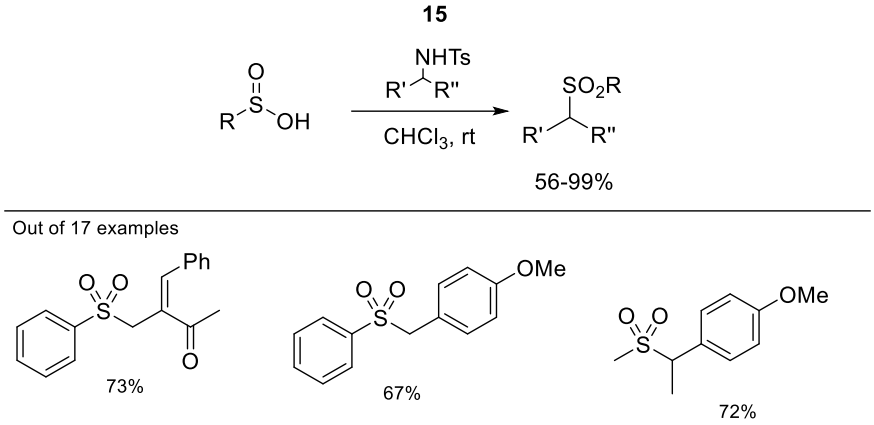
Sulfinates can also react with alcohols **13** which are catalyzed by iron(III) chloride with TMSCl as an additive [29] for the synthesis of aryl alkyl sulfone (Scheme 12). Hydroxy are inefficient leaving groups and their direct sulfonylation by sulfinate salts through nucleophilic substitution is generally difficult, which usually requires preactivation. Although several methods have been reported to improve the synthesis of benzylic and allylic sulfones, they require expensive reagents and catalysts and/or harsh reaction conditions. For example, the direct sulfonation of benzyl carbamates and allylic alcohols using palladium catalysts requires expensive phosphine ligands to promote the reaction which is undesirable due to their toxicity and sensitivity to air as well as moisture.[30] [31]



Scheme 12. Sulfonylation of activated alcohols towards nucleophilic substitutions.

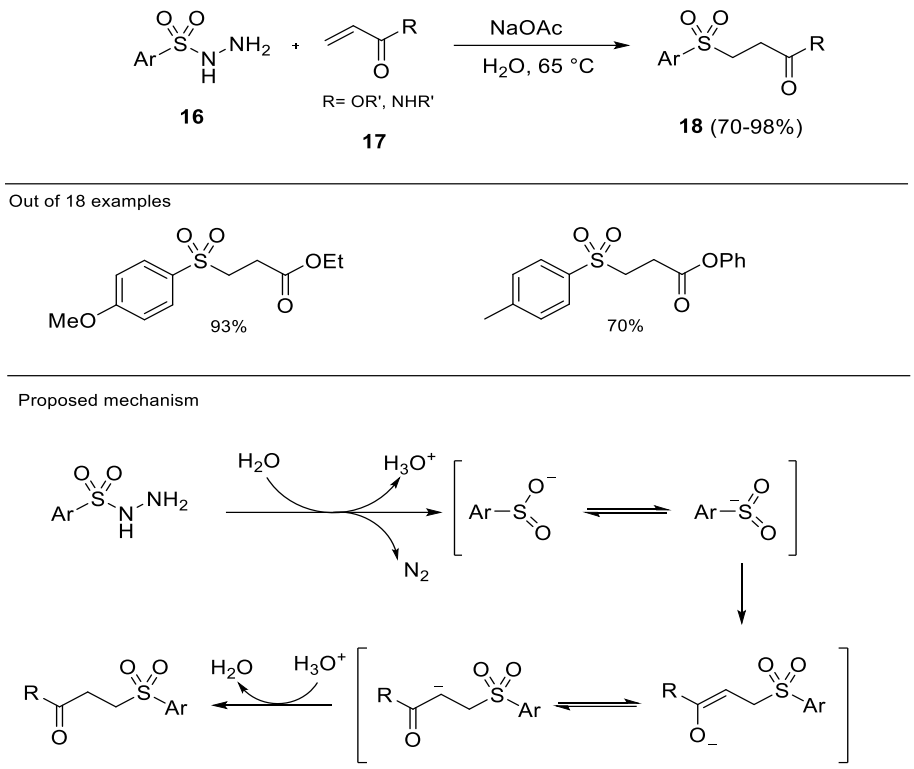
Although *sp*^{3} C–N bond cleavage can be obtained by metals and strong bases under various reaction conditions, amines and amine derivatives have rarely been applied to the alkylation of protic nucleophiles.[32] To facilitate the amino group to act as a good leaving group towards a range of nucleophiles when this is electron-withdrawing groups are used.[33] Liu and co-workers described the unprecedented sulfinic acids alkylation with allylic and benzylic sulfonamide **15** via *sp*^{3} C–N bond cleavage in catalyst free conditions[34]

(Scheme 13). The alkylation reaction of sulfinate anions is not always straightforward since sulfinic acid and their salts are not powerful nucleophiles.[35]



Scheme 13. Sulfinic acid catalyst-free alkylation.

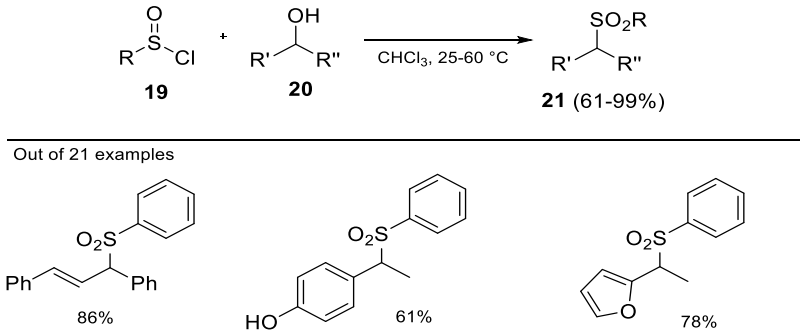
Sulfonyl hydrazides **16** can be treated with base or water under high temperature conditions in order to generate the sulfinyl anion accompanied by the release of N_2. As an example, sulfonyl hydrazide **16** can form the corresponding ethyl sulfone **18** reacting via reaction with acceptor **17** in water[36] (Scheme 14). In Yang *et al.*[36a] proposed mechanism sulfonylhydrazide is transformed in the presence of water, with the generation of hydronium ions and the release of N2, into an sulfinyl anion which can resonate with the sulfur-centered anion. Therefore, the sulfur-centered anion is selectively added to the activated alkene leading to the oxygen-centered anion, which can resonate with the carbon-centered anion. Finally, the intermediate affords β-sulfone ester by a subsequent proton transfer (PT) from hydronium ions.



Scheme 14. Synthesis of mono-substituted ethyl sulfone from sulfonyl hydrazide.

An interesting sulfinate precursor is the 1,2-*bis*(phenylsulfonyl)ethane which can form a palladium-sulfinate complex. In the presence of an activated alkyne, the corresponding vinyl sulfone is formed.[36b]

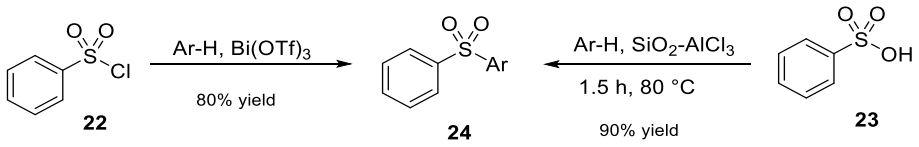
Finally, a sulfinyl chloride **19** can go through the formation of a sulfonic acid or sulfinate ester and react with benzyl and allylic alcohols **20** in catalyst free conditions, forming the corresponding sulfones[37] **21** in good yields (Scheme 15). The proposed mechanism to obtain sulfone **21** proceed through condensation reaction of the alcohol with the sulfinyl chloride to form the sulfinate ester and HCl. Therefore, the sulfinate ester rearrange under acidic conditions to give the final sulfone *via* formation of sulfinic acid which acts as a nucleophile which couples to the carbocation generated from alcohol **20**.



Scheme 15. Sulfonylation of benzylic and allylic alcohols.

1.3.1.3 Friedel-Crafts-type sulfonylation and addition reactions to alkenes/alkynes

Sulfonyl halides **22** are widely used for sulfonylation in Friedel-Crafts-type reactions using a strong Lewis or Brønsted acid catalyst. Unfortunately, Friedel-Crafts reactions need stoichiometric amounts of catalyst (typically aluminium trichloride, iron(III) chloride or phosphoric acid); harsh conditions which result in low regioselectivity and generate hazardous by-products.[38] The synthesis of aryl sulfones **24** can also involve sulfonic acid **23** in the presence of a (hetero)arene using a suitable Lewis or Brønsted acid catalyst (Scheme 16).[39]

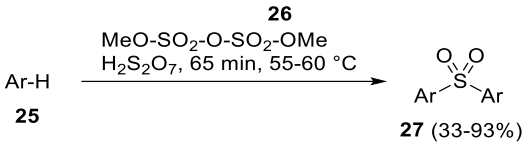


Scheme 16. Sulfonylation of heteroarenes in the presence of a Lewis or Brønsted acid catalyst.

For these reasons, studies have been focusing on more sustainable synthesis, such as lowering catalyst loadings, solvent free reactions or direct sulfonylation with sulfonic acids.[40]

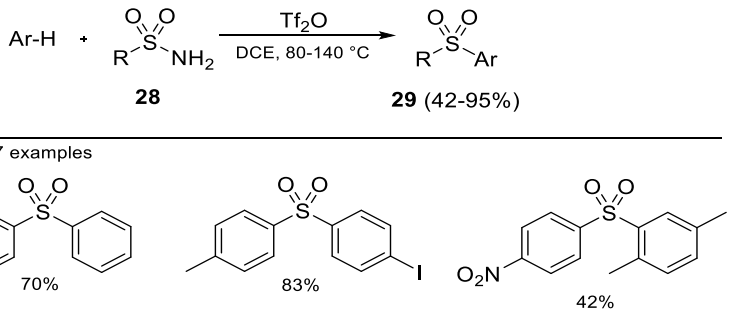
An efficient sulfonylation at room temperature occurred when a sulfonic acid is activated by phosphorous pentoxide or triflic anhydride.[40j, 41] When sulfonation of arenes is performed with sulfuric acid, sulfones can be generated as by-product. Symmetrical diaryl sulfones **27** can also be generated as major products when water is eliminated during the

reaction.[20] The same product can be achieved by reacting arene **25** with dimethyl pyrosulfate in the presence of sulfuric acid **26**[42] (Scheme 17).



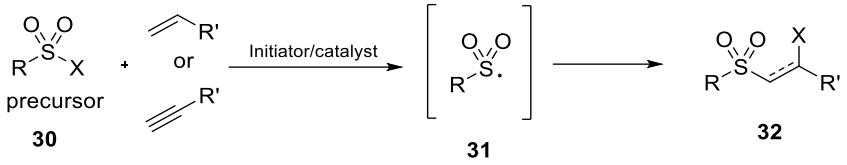
Scheme 17. Synthesis of symmetrical di-aryl sulfones.

Symmetrical and unsymmetrical di-aryl sulfones **27** and **29** can be also synthesised starting from the arenes, acid conditions (TfOH, TFAA) in the presence of a persulfate salt.[43] Sulfonamides **28** can also be a good sulfonylating agents for arenes when activated by triflic anhydride (Tf_2O)[44] (Scheme 18). In fact, in the presence of triflic anhydride, sulfonamide **28** can form the sulfiminium salt (Vilsmeier-Haack like process) which, after Friedel-Crafts sulfonylation with the arene and hydrolysis, compound **29** is generated.



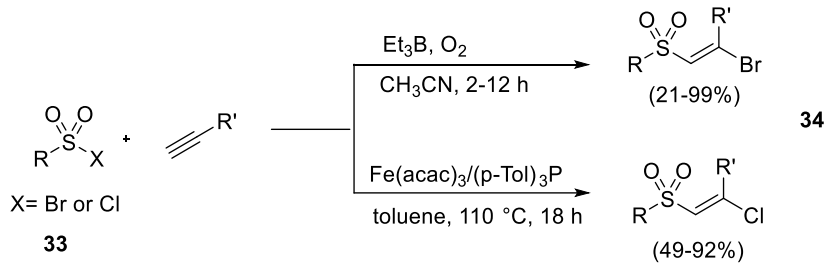
Scheme 18. Sulfonylation of arenes with sulfonamides.

Another important method for the synthesis of sulfones is by the atom-transfer radical addition (ATRA) process (Scheme 19). Sulfonyl radicals **31** are formed in the presence of radical initiators [copper(I) chloride] from sulfonyl halides, sulfonyl selenides, sulfonyl hydrazides, or sulfonyl azides **30**, or by the oxidation of sulfinates.[45] In the last decades, improvements have been made and ruthenium complexes can be considered the most useful catalysts for this reaction[46] due to their high efficiency (loadings as low as 0.1 mol% and high turnover frequencies) and is an important method in order to obtain vinyl sulfones.



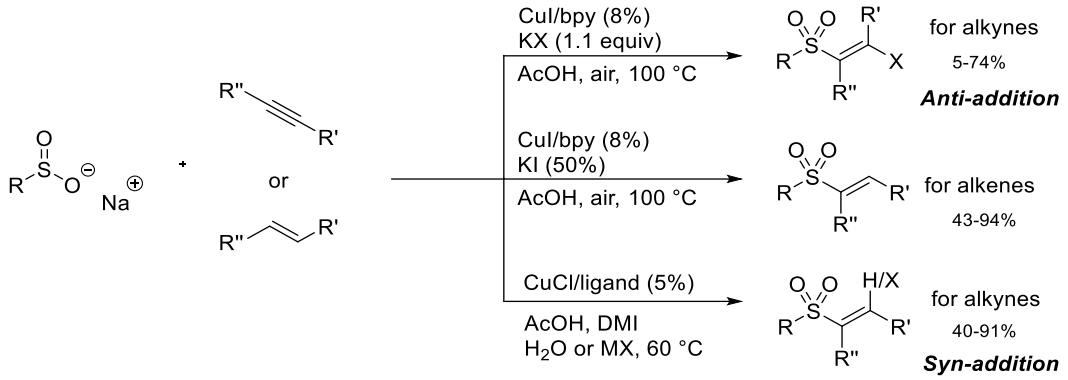
Scheme 19. Sulfonylation of alkenes and alkynes via sulfonyl radicals.

Among the many other, related reactions reported in the literature, it is worth noting the iron catalysed regio- and stereo-selective addition of sulfonyl chlorides **33** to terminal alkynes[47] to synthesise vinyl sulfones (mostly in the *E*-form) **34**, which can also be made by using reaction of triethylborane (Et_3B) with molecular oxygen to generate the ethyl radical species and subsequently the sulfonyl radical.(Scheme 20).[48] These sulfonyl radicals can be regioselectively trapped by terminal alkynes to give compound **34**.



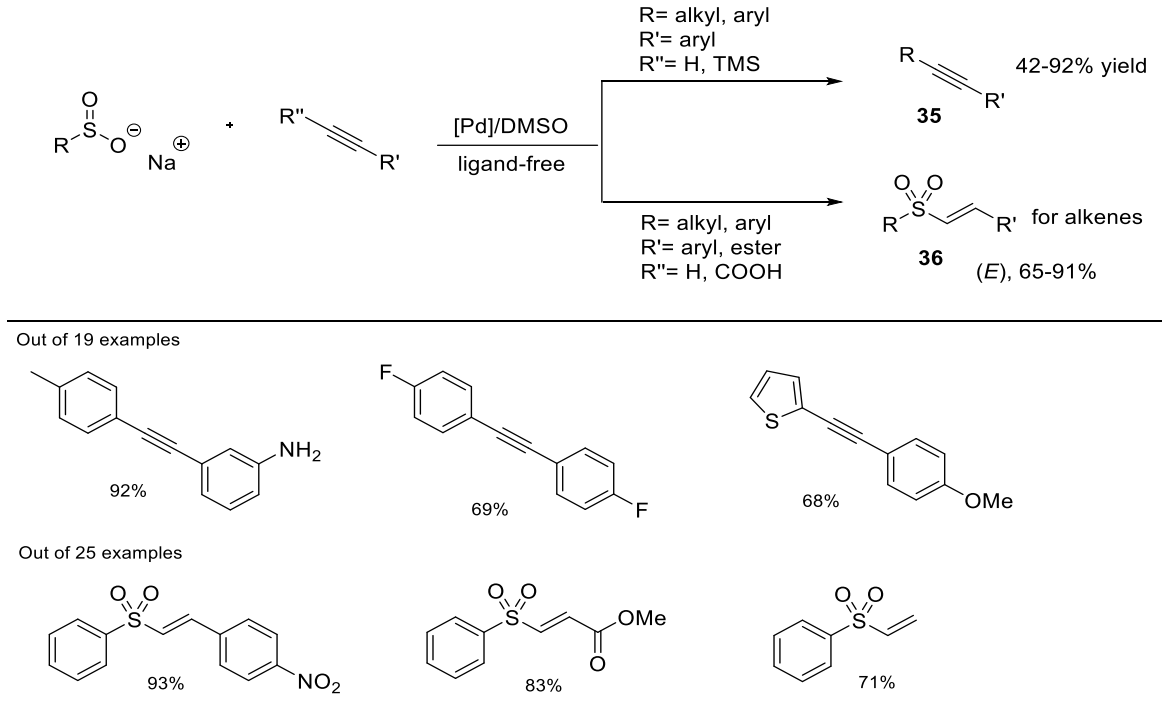
Scheme 20. Sulfonylation of terminal alkynes.

Another suitable way to stereoselectively access (*E*)-vinyl sulfones has been reported by Taniguchi[50] via an addition-elimination process of sodium sulfinates with alkenes or alkynes (Scheme 21). This approach explored a one-step copper-catalyzed reaction in air, where oxygen is necessary for promotions of these procedure. It was shown that (*E*)-alkenyl sulfones could be achieved even when starting from (*E*)- or (*Z*)-alkenes, without formations of other stereoisomers. Focusing on the sulfonylation of alkynes it was found that both syn- and anti-selective additions were possible using copper catalysts, to afford (*E*)-alkenyl sulfones and (*E*)-β-haloalkenyl sulfones. In particular, (*E*)-alkenyl sulfones could be synthesized using a CuCl catalyst, meanwhile, the use of a CuI catalyst in the presence of potassium halide afforded (*E*)-β-haloalkenyl sulfones from terminal or internal alkynes.



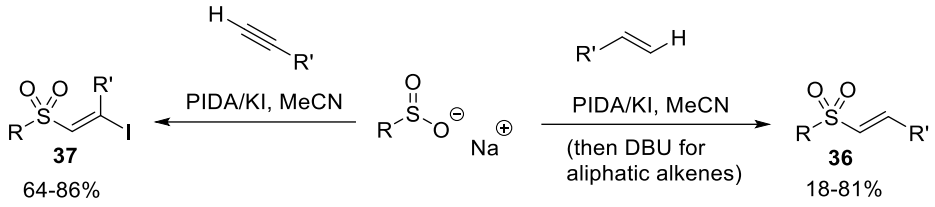
Scheme 21. (*E*)-Vinyl sulfones achieved by Cu catalysed reaction.

(*E*)-Vinyl sulfones **36** and unsymmetrical internal alkynes **35** can also be accessed *via* palladium-catalysed cross-coupling of sulfinate salts to alkynes (Scheme 22).[51] These reactions proceeds under ligand-free and mild conditions, providing good yields of coupling products and tolerating a variety of functional groups. The best conditions for the formation of compounds **35** and **36** were found to be 5 mol% $PdCl_2$ in DMSO at 80 °C for 8 h, in which the selective formation of C-C and C-S bonds seems to be dictated by the electronic effects on the aromatic ring of the phenylacetylene. Moreover, coupling reaction with alkynes acid resulted in decarboxylation and formation of a C-S bond giving the vinyl sulfone.



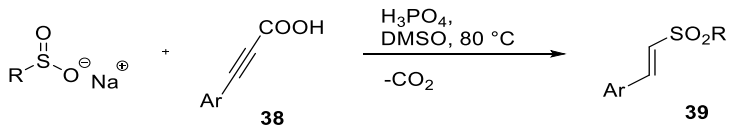
Scheme 22. (*E*)-Vinyl sulfones synthesis palladium-catalysed.

An alternative to the previously cited methods for the synthesis of vinyl sulfones **36** and β-iodovinyl sulfones **37** is presented in Scheme 23 using hypervalent iodine reagents, and again, employing single electron transfer processes.[52] This method employs (diacetoxyiodo)benzene (DIB)/KI to promote the reaction of sodium arenesulfinates with alkenes to yield vinyl sulfones, and with alkynes to form β-iodovinyl sulfones. Furthermore, it was noticed that in the case of aliphatic alkenes, a two-step reaction involving β-iodosulfonylation followed by base-induced dehydroiodination was required achieve compound **36**.



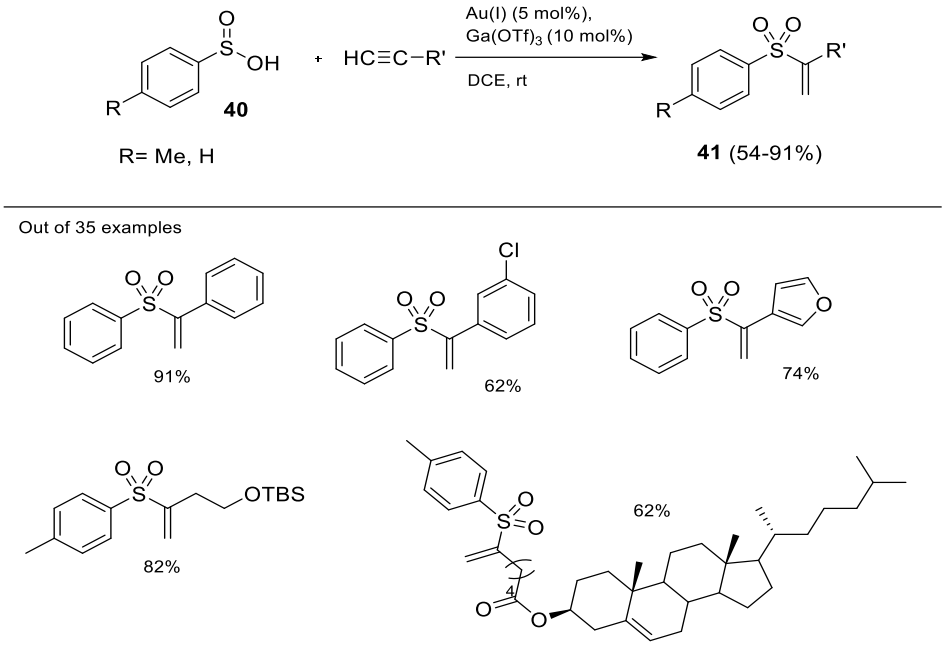
Scheme 23. $PhI(OAc)_2$/KI-mediated reaction to synthesize vinyl sulfones and β-iodovinyl sulfones.

The decarboxylative couplings of sodium sulfinates for vinyl sulfone synthesis should also be mentioned. This goes through a sulfonyl radical formation, followed by addition to the alkene and can be performed under various reagents: PIDA,[53] copper(I) chloride,[50c] iodine and TBHP,[54] or iodine.[55] Surprisingly, (*E*)-vinyl sulfones **36** and **39** are also obtained *via* palladium-catalysed[51] (Scheme 22) or phosphoric acid mediated decarboxylative coupling reactions of sodium sulfinates with aryl propiolic acids **38**[56] (Scheme 24).



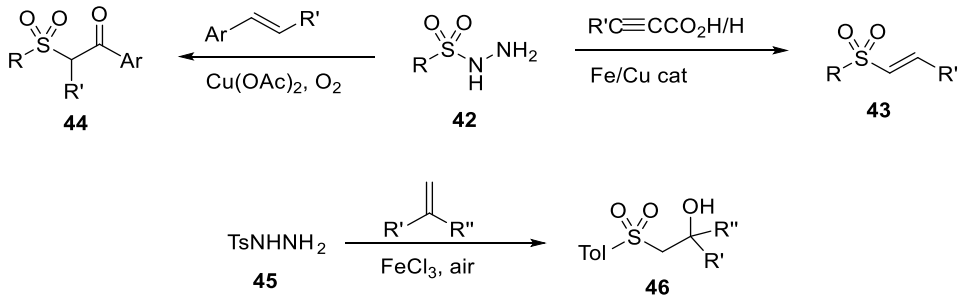
Scheme 24. Sodium sulfinate in the presence of a phosphoric acid mediated vinyl sulfone synthesis.

An example of the synthesis of α-substituted vinyl sulfones **41** is the gold-catalysed [in the presence of gallium(III) triflate] reaction by Shi and co-workers, reported to be a Markovnikov-type addition of sulfinic acid **40** to alkynes[57] (Scheme 25).



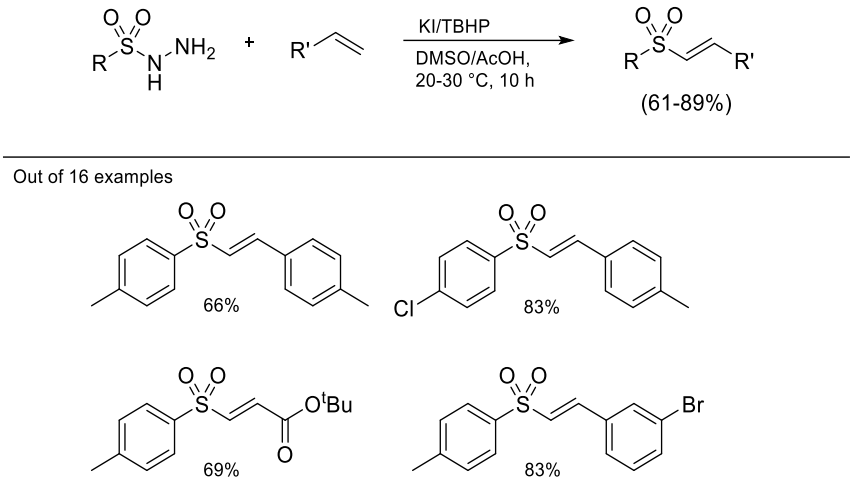
Scheme 25. α-Substituted vinyl sulfone synthesis in the presence of a gold catalyst.

Also, in the case of ATRA, sulfonyl hydrazides **42** are considered valid options for the sulfonylation of double and triple bonds. For example, copper(II) and iron(II) catalysed reaction yield (*E*)-vinyl sulfones **43**,[58] iron-catalysis gives β-hydroxy sulfones **46**[59] and with copper(II) catalysis affords the corresponding β-keto sulfones **44**[60] (Scheme 26).



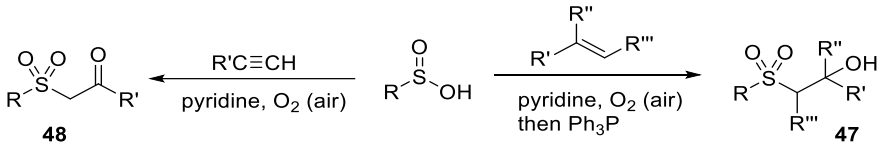
Scheme 26. Reactions of sulfonyl hydrazides in the presence of iron and/or copper catalysts.

Finally, it is worth mentioning that the generation of sulfonyl radicals from sulfonyl hydrazides with catalytic amounts of potassium iodide and TBHP[61] (Scheme 27) can also be used to access vinyl sulfones.



Scheme 27. Generation of vinyl sulfones *via* addition of KI/TBHP.

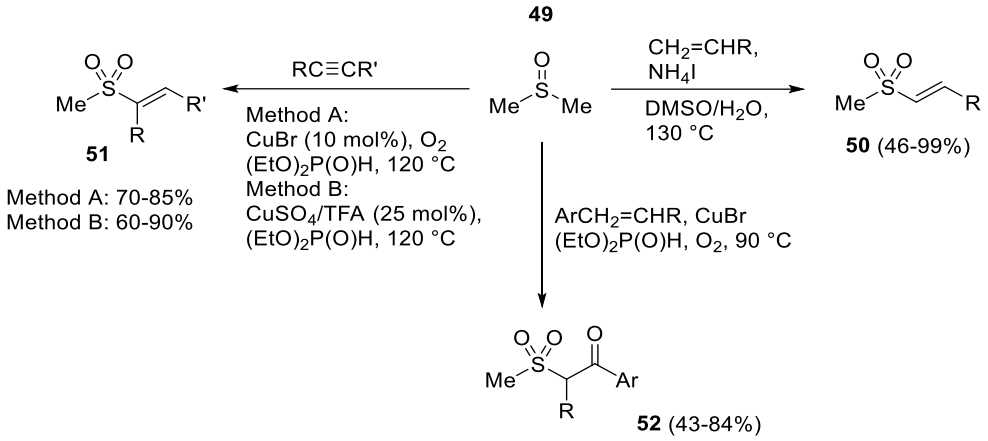
Lei and co-workers[62] developed an attractive method to construct secondary and tertiary β-hydroxy sulfones **47** *via* intermolecular oxysulfonylation of sulfinic acids to give β-hydroperoxy sulfones which are then reduced by the addition of triphenylphosphine. This might involve a radical process, but the reaction rate is considerably enhanced by the addition of pyridine (Scheme 28). Interestingly, when terminal alkynes are added to sulfinic acids under the same conditions, β-keto sulfones **48** are obtained.[63] In the proposed mechanism of both reactions, the addition of pyridine generates the sulfinyl anion, which undergo autoxidation with dioxygen via single electron transfer (SET) process affording an oxygencentered sulfone radical resonating with the sulfonyl radical. This reaction exhibits a wide-range of functional-group tolerance. The role of pyridine is not only the one of being a base, but also plays a crucial role in reducing the activity of sulfinic acids.



Scheme 28. Synthesis of β-hydroxy sulfones and β-keto sulfones from sulfinic acid.

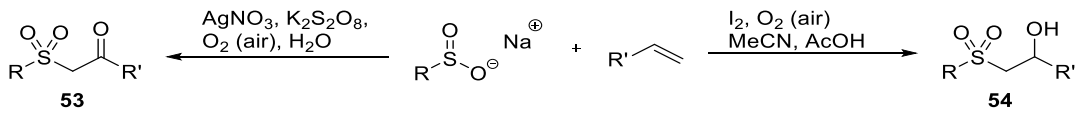
Three other, different procedures, for the synthesis of (*E*)-vinyl methyl sulfones and β-keto sulfones from DMSO are reported in Scheme 29. In particular, two procedures for the synthesis of (*E*)-vinyl methyl sulfones **51** are shown, and are both copper catalysed.[64] However, using the same conditions, the reaction with alkenes leads to β-keto sulfones **52**

instead of (*E*)-vinyl methyl sulfones **51**[64b] (Scheme 29). Li and co-workers also reported a novel and efficient method for the synthesis of (*E*)-vinyl methyl sulfones **50**, achieved by addition of ammonium iodide to DMSO **49** and alkenes.[65] Such route have provided an inexpensive and efficient method for the synthesis of (*E*)-vinyl methyl sulfones in metal free conditions.



Scheme 29. DMSO as a starting material to achieve vinyl sulfones and β-keto sulfones.

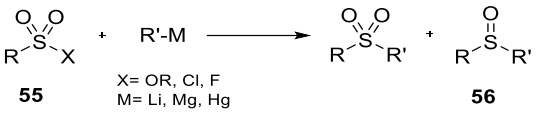
Finally, addition of alkenes to sulfinate anions can lead to β-hydroxy **54** or β-keto **53** sulfones depending on the conditions. Catalytic amounts of iodine can radically initiate and reduce the initially formed β-hydroperoxo sulfone in the presence of oxygen which acts a terminal oxidant[66] (Scheme 30). Alternatively, if the same starting materials are treated with silver(I) nitrate and potassium persulfate, β-keto sulfones **53** are produced.[67]



Scheme 30. Synthesis of β-keto and β-hydroxy sulfones from sodium sulfinates.

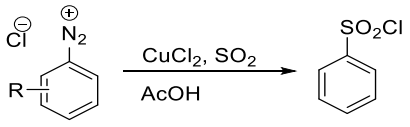
1.3.1.4 Organometallic reactions

Many more synthetic approaches for the synthesis of sulfones can be found in the literature, including the use of organometallic reagents which can react with several types of sulfonic acid derivatives **55**. However, these reactions tend to be low yielding due to the concomitant formation of the corresponding sulfoxides **56** (Scheme 31).



Scheme 31. Sulfone preparation with organometallic reagents.

During the last decades, more efficient reactions have emerged. An alternative new approach is the transition metal catalysed coupling reaction for the regiospecific synthesis of sulfones. These types of reactions start from sulfonyl halides (electrophilic coupling) or sulfinates (nucleophilic coupling) and involve milder reaction conditions compared to the reactions listed above.[68] Unfortunately, most of the starting materials in these reactions, which already contain a sulfur moiety, are often not commercially available.[20] For this reason, an attractive research area concerns new processes which allows sulfone synthesis from simpler and readily available sources. Therefore, one-pot, multi-component syntheses incorporating a simple sulfonyl moiety and two sulfur-free compounds have become of interest.[69] The simplest compound, in order to incorporate a sulfonyl moiety, is obviously sulfur dioxide which is, however, a toxic corrosive gas, and therefore, restricted for safety reasons. Nevertheless, synthetic methods involving the use of sulfur dioxide have been reported[70] (**Scheme 32**).



Scheme 32. Sulfur dioxide as a source for the synthesis of sulfones.

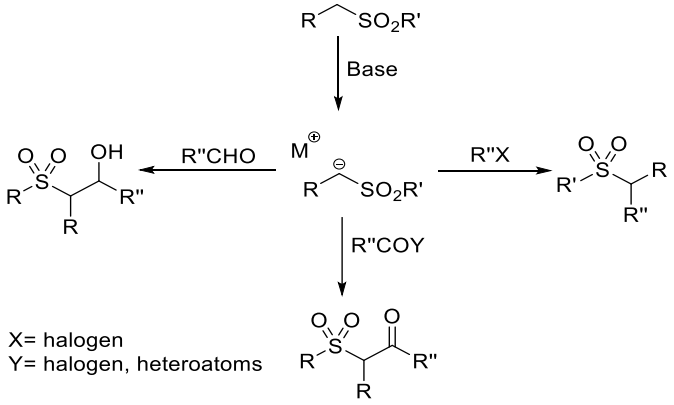
1.3.2 Reaction of Sulfones

The majority of sulfone chemistry revolves around its ability as a functional group to activate adjacent groups towards deprotonation, forming stabilized carbanions and even polyanions. Furthermore, sulfones are not subject to nucleophilic attack which is why they have been widely used over the years in organic synthesis.

1.3.2.1 Reactions and uses of simple sulfones in organic synthesis

This section is focused on the reactions of sulfones lacking any additional carbanion-stabilising group, such as carbonyls or heteroatoms, which will be reviewed briefly in the following section.

Some of the most important reactions of sulfones are shown in Scheme 33, where after deprotonation and formation of the α-carbanions, the sulfones can easily form carbon-carbon bond through alkylation, acylation or aldol-like processes.

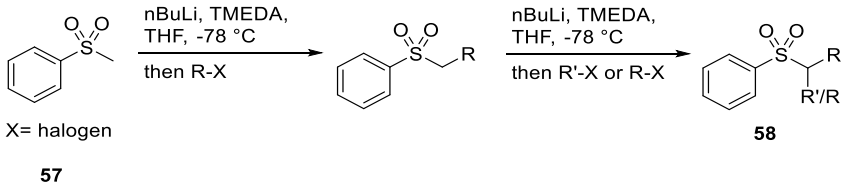


Scheme 33. General scheme of alkylation, acylation and aldol reactions on non-activated sulfones.

In order to keep this review relevant to the project a restricted number of examples are discussed in the following chapters.

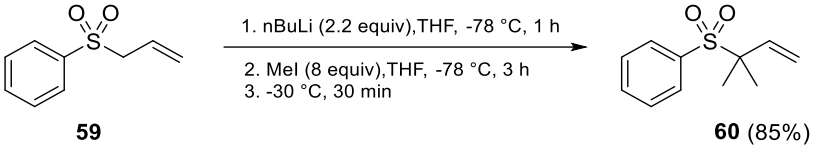
Of common use are sulfones incorporating a blocking group like tolyl, phenyl or a *tert*-butyl to direct deprotonation only on one site.

Known since 1939,[71] the most common procedure in order to α-alkylate sulfones is by deprotonation with *n*BuLi and subsequently alkylation using an alkyl halide. Rehova *et al.*[72] showed the synthesis of unsymmetrically or symmetrically branched sulfones **58** by sequential alkylation of methyl phenyl sulfone **57** with an alkyl halide by deprotonation with BuLi in the presence of TMEDA in good to excellent yields in a one-pot procedure (Scheme 34).



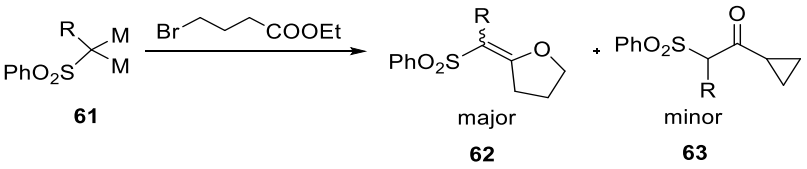
Scheme 34. Alkylation of sulfones.

In addition, alkylating the α-sulfone carbanion using a β-unsaturated sulfone **59**[73] is also known (Scheme 35).



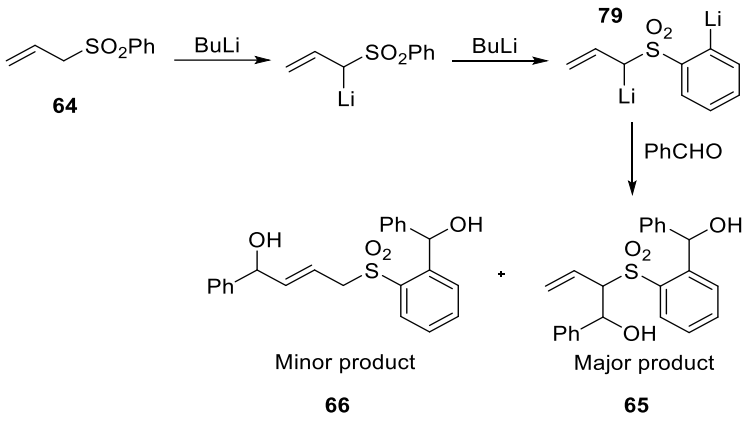
Scheme 35. Alkylation of prenyl sulfones.

The advantage of using dianion sulfones in acylation reactions is lower consumption of the sulphonyl carbanion compared to the monoanion.[76] Acylation of a di-lithio sulfone leads directly to the anion of the β-ketosulfone product. An *in situ* acylation-alkylation sequence was found to be possible by reacting α,α-dilithiosulfones **61** with a bromoester such as ethyl 4-bromobutyrate[77] (Scheme 36).



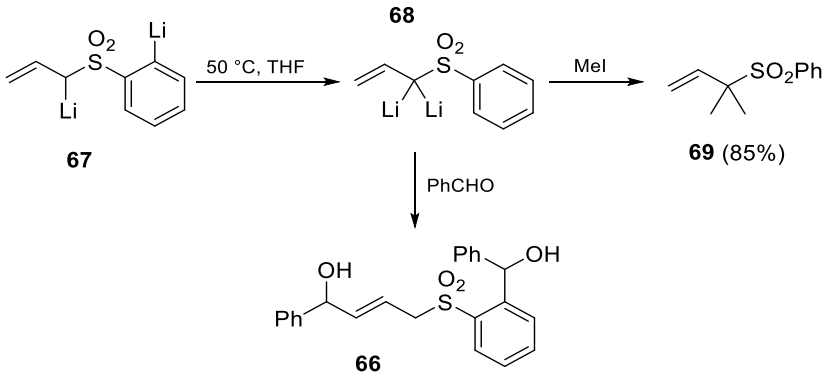
Scheme 36. β-acylation of the α,α-metalsulfone.

The mechanism proposed involves firstly, the formation of the β-keto sulfonyl anion which then undergoes *O*-alkylation **62**. The equilibrium between the β-keto sulfonyl anion and the enolate anion forms the minor by-product **63**. Further studies have been carried out by Savoia *et al.* leading to hydroxy ketone products.[78] Interestingly, it has also been shown that in the case of allyl phenyl sulfone **64**, another kinetically controlled deprotonation occurs in the *ortho*-position resulting in **65** and **66**, as shown in Scheme 37.



Scheme 37. Di-deprotonation of vinyl phenyl sulfones.

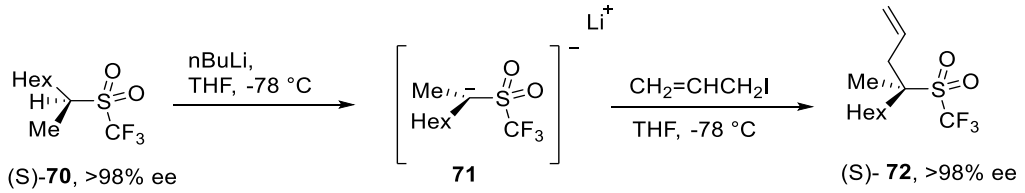
Even though the geminal sulfone aldol-adduct is the major product **65**, in Scheme 37, when the intermediate **67** is heated, it undergoes complete isomerisation leading to the α,α-di-lithiosulfone **68** giving either the 1,3-adduct species **66** in the case of an aldehyde, or an α,α-disubstituted product in the case of an alkylation/cycloalkylation **69** (Scheme 38). However, the α,α-alkylation of the sulfone is obtained even without heating, where a transmetallation at the α-position is proposed after initial reaction. Although, when titanation occurs, either a γ-adduct or the dienyl sulfone forms.[79]



Scheme 38. Isomerization of the α,α-dilithiosulfone.

G. Raabe *et al.*[80] were able to obtain enantiomerically pure dialkyl-substituted lithium α-trifluoromethylsulfonyl carbanion salts **71** by deprotonation with BuLi. The alkylation of the chiral lithium α-trifluoromethylsulfonyl carbanion salts proceeded with high enantioselectivities to yield tertiary triflones **72**, where the attack of the electrophile at the carbanion of the salt always occurred anti to the trifluoromethyl group. In fact, as explained in section 1.2 (page 1) due to the remarkable stability and the high energy

barrier of both rotation around the C-S bond or pyramidal inversion, α-sulfonyl carbanions usually retain their original configuration in reactions with electrophiles. The overall two-step transformation of the dialkyl-substituted chiral triflone by means of the corresponding chiral carbanion and its reaction with an electrophile under formation of the tertiary triflone proceeds under retention of configuration (Scheme 39).



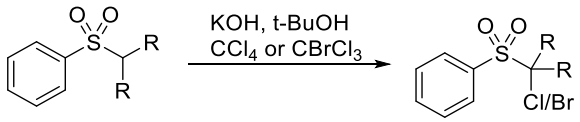
(S)-**70**, >98% ee

71

(S)- **72**, >98% ee

Scheme 39. Formation of the tertiary triflone.

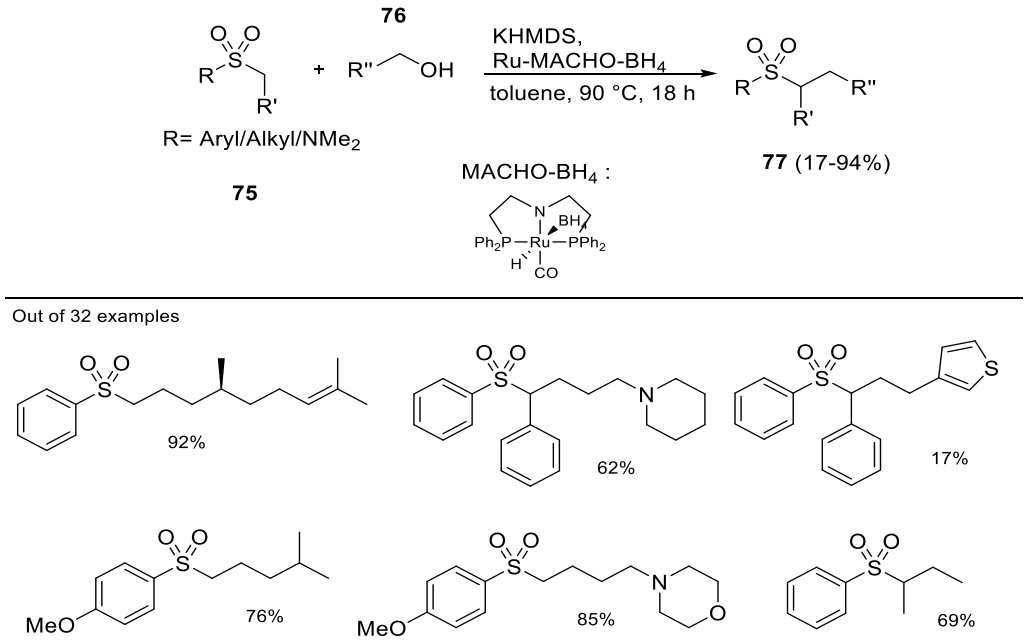
Halogenation at the α-position can also be easily achieved, for example, as reported in the studies of Meyers and co-workers[81] that showed how most alkyl phenyl sulfones **73** are α-chlorinated with CCl_4 and α-brominated with $CBrCl_3$ in KOH–tBuOH *via* radical–anion radical pair (RARP) reactions (Scheme 40).



73 **74**

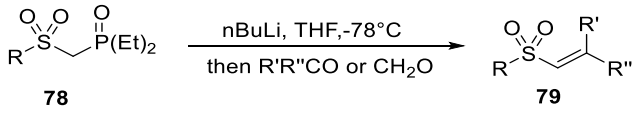
Scheme 40. Halogenation of sulfones.

A recent study developed a Ru(II) catalysed sulfone **75** and alcohol **76** coupling reaction that does not rely on utilising halogen substrates (Scheme 41). A broad range of linear sulfones **77** were synthesised which can be further utilized in the Julia olefination.



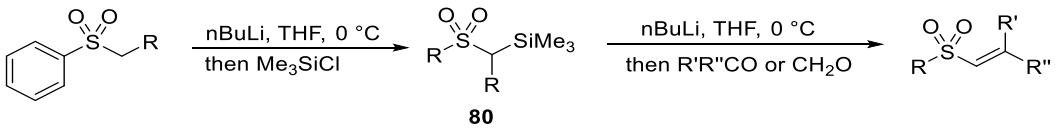
Scheme 41. Sulfones and alcohol coupling.

When carbonyl groups such as aldehydes and ketones are utilised as substrate in reactions with sulfones, they are usually converted into vinylic sulfones. Several routes are available for the preparation of unsaturated sulfones **91**. Several methods make use of Knoevenagel-type condensations of aldehydes with alkyl sulfonyl acetic acids followed by decarboxylation,[82] whereas other routes utilise the carbanion of diethyl sulfonyl methyl phosphonate **78** in a Wittig-type reaction[83] (Scheme 42).



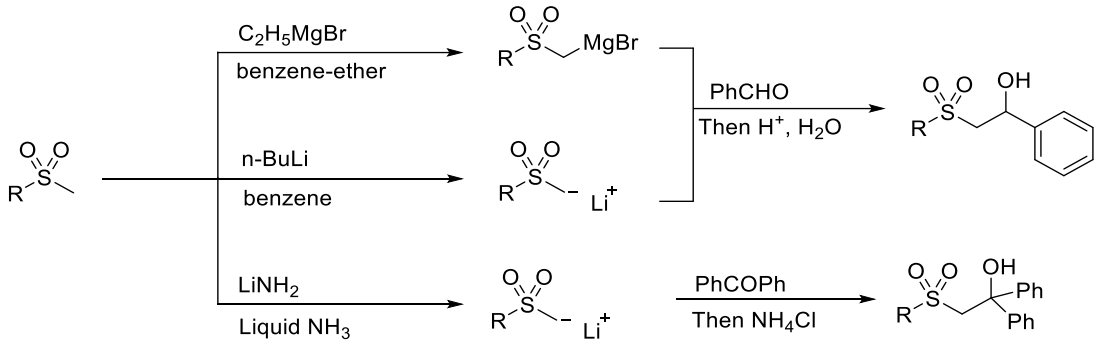
Scheme 42. Wittig type reaction to form α,β-unsaturated sulfones.

A revisited method is the use of α-silyl sulfones **80**[84] as shown in Scheme 43 involving vinyl sulfone synthesis using the Peterson reaction.[85]



Scheme 43. Condensation of α-silyl sulfones with carbonyl compounds.

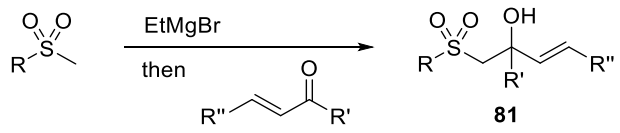
However, depending on the synthetic conditions, additions of carbonyl groups to sulfones can lead to β-hydroxy sulfones. The first preparations of these types of systems were reactions involving Grignard[86] or lithium[87] reagents adding to carbonyl compounds to form the corresponding β-hydroxy sulfones (Scheme 44). However, the use of Grignard reagents was reported to be complicated by di-metalation of the di-alkyl sulfone.[88] Grignard derivatives of sulfones are also characteristically insoluble in most common solvents used for Grignard reactions, and therefore, metalation with n-butyllithium is preferred.[86b]



Scheme 44. Procedures with either the Grignard or lithium reagents to synthesize β-hydroxy sulfones.

Hydroxy sulfones **81** have also been obtained from the reaction of magnesium sulfones with α,β-unsaturated ketones or aldehydes[89] (Scheme 45).

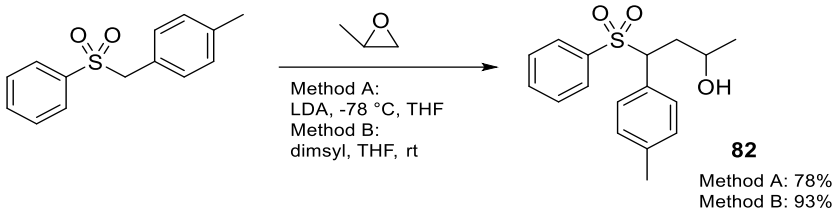
The unwillingness of sulfonyl carbanions to undergo conjugate addition with α,β-unsaturated carbonyl compounds has been well established.



Scheme 45. Sulfones 1,2-addition to α,β-unsaturated carbonyl

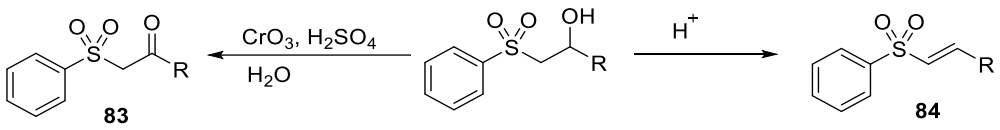
A few ways for the synthesis of β-hydroxy sulfones from simple sulfones have been reported. Some of these go through regioselective ring opening of epoxides with various catalytic systems. Other examples of β-hydroxy sulfones involving epoxides have been studied by Kurth and co-workers[90] involving polymer-bound α-sulfonyl monocarbanions generated by LDA or dimsyl anion which undergo alkylation with epoxides to generate

hydroxy sulfones **82** (Scheme 46). Polyethylene glycol 4000 had also been used as a phase transfer agent and solvent in the case of the preparation of β-hydroxy sulfones from different oxirane and sulfonate salts under neutral condition.[91]



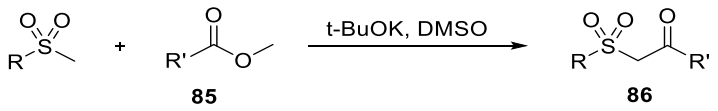
Scheme 46. Synthesis of hydroxy sulfones *via* epoxides.

It is also worth mentioning the transformation of β-hydroxy sulfones into either β-keto sulfones **83** *via* the Jones oxidation,[87, 92] PDC,[93] or the Dess-martin reagent.[94] Similarly, vinyl sulfones **84** can be accessed through dehydration (Scheme 47). β-Hydroxy sulfone products are rather unstable due to their potential for dehydration and subsequent polymerization. Another problem with such products is the facile reversion of the ketone and sulfone starting materials, for example, when treated with potassium hydroxide they exhibit a retro-aldol reaction. This has been studied by Kocienski *et al.*,[95] noted to be involved in the Julia elimination when attempting derivatisation of β-hydroxy sulfones obtained from ketones.



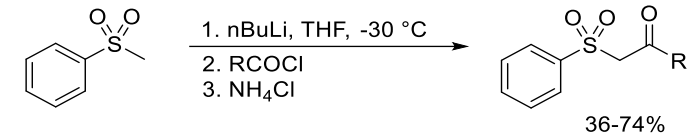
Scheme 47. Possible transformations of β-hydroxy sulfones.

Meanwhile, the addition of aldehydes or ketones (including cyclic ones) leads to the formation of β-hydroxy sulfones or vinyl sulfones, whereas the addition of esters **85** leads to β-keto sulfones **86**. A specific example comes from the work of Zhang *et al.*[96] where they utilised potassium *tert*-butoxide suspended in dimethyl sulfone (Scheme 48).



Scheme 48. Synthesis of β-keto sulfones.

β-Keto sulfones can also be synthesised through the addition of acyl groups which requires the use of less harsh conditions. Two equivalents of BuLi are needed in order to avoid undesirable self-quenching to form the dianion of methyl phenyl sulfone. The acyl chloride is then added to form the enolate which is then quenched with saturated ammonium chloride to give the β-keto sulfones[89] (Scheme 49).



R= cyclopropyl, *i*Pr, Et, Me, Cy, Ph

Scheme 49. Synthesis of β-keto sulfones form acyl chloride.

1.3.2.2 Reaction and uses of β-sulfonylmethylene compounds

α-Sulfonyl carbanions having additional functionality directly attached to the anionic centre undergo many reactions analogous to those described earlier. However, the addition of a second functional group such as a carbonyl, cyano, nitro or sulfone is able to increase stability of the carbanion which may significantly modify the reactivity. For example, whereas simple sulfonyl carbanions will undergo 1,2-addition to α,β-unsaturated carbonyl compounds, sulfones having additional stabilisation are softer and less basic, and will therefore often undergo 1,4-additions.

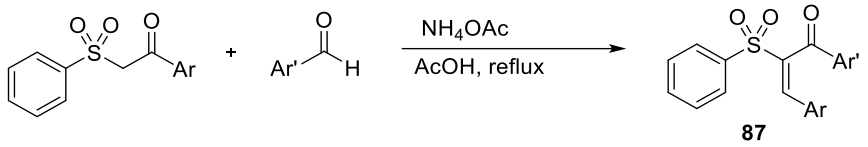
1.3.2.3 β-Ketosulfones

β-Keto sulfones are compounds that present a moderate to strong acidity of the α-carbon protons, due to the presence of two electron-withdrawing functionalities, i.e. both the carbonyl and sulfonyl groups. The p*Ka* of a the β-keto sulfone[97] is calculated to be between 9-10, falling in between β-diketones (p*Ka* ca. 8) and β–disulfones (*pKa* ca. 14).

As stated above, carbonyl compounds can undergo enolisation enabling other types of synthesis, whereas sulfones are not able to undergo enolisation which rather enables the deprotonation of the neighbouring methylene group and stabilisation of the highly reactive anion.[98] This highly reactive species can react with numerous electrophiles

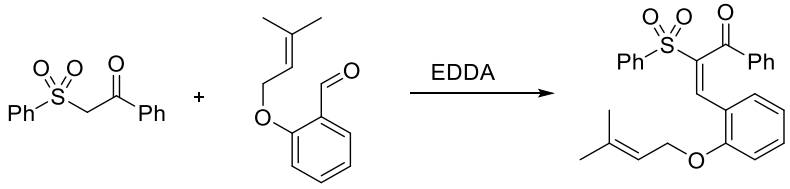
making them important substrates in organic synthesis. β-Keto sulfones are often employed in similar reactions to β-dicarbonyl compound reactions, such as Knoevenagel condensations; an important route to obtain vinyl sulfonyl ketones, and potentially useful substrates for Diels-Alder[99] and Michael additions.

An interesting example of this condensation for the synthesis of unsaturated β-keto sulfones **87** using microwave irradiation and KF-alumina as a base has been studied by Didier *et al.*[100] (Scheme 50).



Scheme 50. Knoevenagel condensation of β-keto sulfones using microwaves.

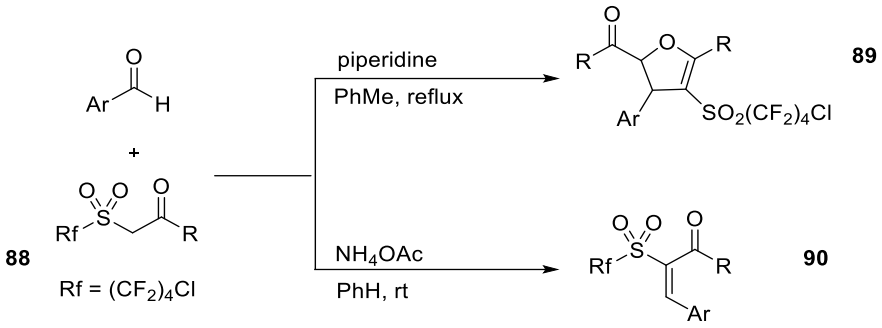
In other occasions, Knoevenagel condensation was achieved by the treatment of a β-keto sulfones and an aldehyde with ethylenediaminediacetic acid (EDDA), followed by intramolecular Diels–Alder reaction (Scheme 51).[99]



Scheme 51. Knoevenagel condensation of β-keto sulfones.

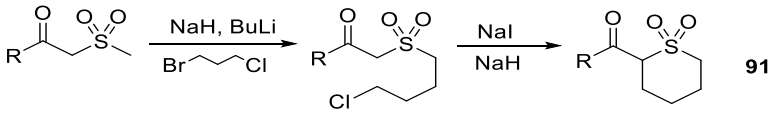
However, it is worth mentioning that the unexpected formation of tetrasubstituted *trans*-2,3-dihydrofurans under Biginelli or Knoevenagel condensation reaction conditions was found when β-keto polyfluoro alkane sulfones **88** were reacted with aromatic aldehydes.[101] In fact, due to the high reactivity of this type of molecule, after Knoevenagel condensation to give the unsaturated β-keto sulfone, which is a good electrophilic Michael acceptor, the product is then attacked by the anion of another molecule of β-keto sulfone. Finally, intramolecular nucleophilic displacement occurs to give the cycloadduct **89**. Later on, it was shown that it was possible to achieve unsaturated β-keto sulfone formation from

β-keto polyfluoro alkane sulfones **90** using ammonium acetate as a catalyst[102] (Scheme 52).



Scheme 52. Knoevenagel condensation of β-keto sulfones bearing fluoroalkyl group at sulfonyl moiety.

Through the Ramberg-Bäcklund rearrangement, this method of double deprotonation can be used to access cyclic derivatives **91** (Scheme 53).[103]



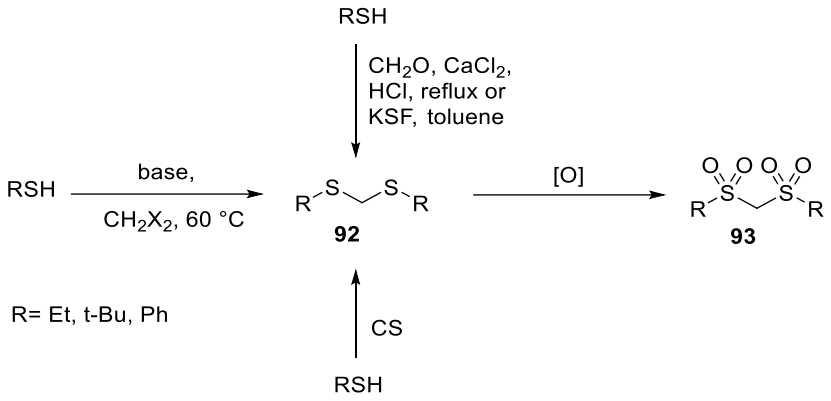
Scheme 53. Ramberg-Bäcklund rearrangement.

1.3.2.4 β-Sulfonylsulfones

Although there has been a lot of studies on sulfones, geminal *bisbis*-sulfones have received less attention despite their interesting synthetic possibilities. Being good electron withdrawing groups, sulfonyl sulfones are attractive intermediates due to their ability to promote deprotonation of the geminal carbon and react with numerous electrophiles. The advantage of using sulfonyl sulfones, compared for example, to malonates, is their ability to be easily removed once their synthetic scope has been accomplished. Another peculiarity is the capacity of geminal unsaturated sulfonyl sulfones, is to act as extremely potent Michael acceptors as well as their ability in participating in Diels-Alder reactions as good dienophiles.

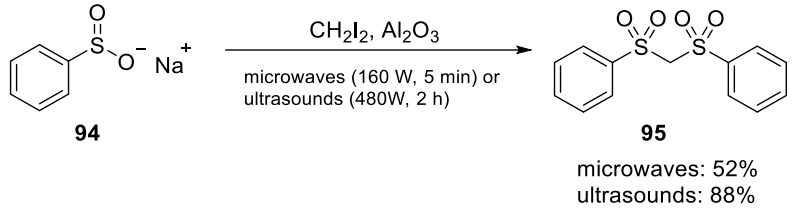
Synthesis of β-sulfonyl sulfones

The most common method to prepare gem-*bis*-sulfones **93** is from the oxidation[104] of the corresponding sulfide **92** (Scheme 54). A variety of oxidising agents have been used, such as hydrogen peroxide[105] (without or in the presence of a catalyst[106]), potassium permanganate,[107] organic peroxides, peracids[108] and dioxiranes.[109] The corresponding *bis*-sulfide can be accessed through alkylation of a thiol with dihalomethane after deprotonation with a base such as NaOH, or K_2CO_3.[110] Treatment of thiols with carbon monosulfide also leads to the formation of *bis*-sulfides.[111] The synthesis of *bis*(phenylthio)methane can also be achieved by refluxing a mixture of thiophenol, formalin, anhydrous calcium chloride and catalytic amounts of concentrated hydrochloric acid.[112]



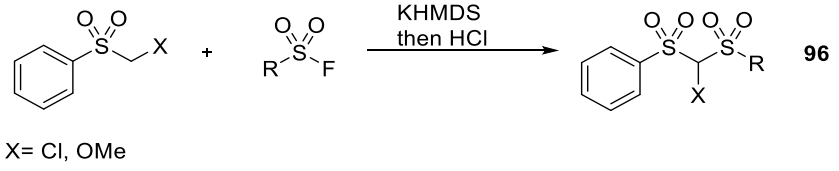
Scheme 54. Representative oxidation of gem-*bis*-sulfides to give gem-*bis*-sulfones.

Villemin and co-workers[113] have shown the possibility to obtain *bis*-sulfones **95** from organic halides absorbed without solvent onto sodium phenyl sulfinate **94** on alumina under microwave or ultrasound activation conditions (Scheme 55).



Scheme 55. *Bis*-phenyl sulfones from sodium phenyl sulfinate.

A strategy to synthesise α-halogen substituted disulfonylmethane derivatives **96** was development by Prakash and co-workers[116] involving the addition of phenyl sulfonyl methane, fluoro-functionalized to α-methoxy or α-chloro sulfone, treated with KHMDS and subsequently hydrogen chloride (Scheme 56).

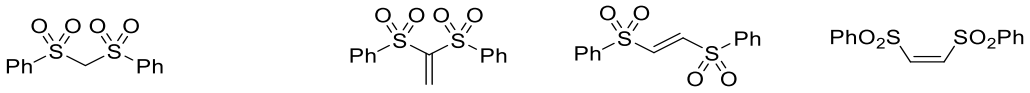


Scheme 56. Synthesis of α-methoxy or α-chloro *bis*-sulfonyl methane.

Reactions of sulfonyl sulfones

Although *bis*-sulfones are versatile moieties that are extremely useful in total synthesis, it is still a field that needs to be more widely explored. In fact, most reactions involve the use

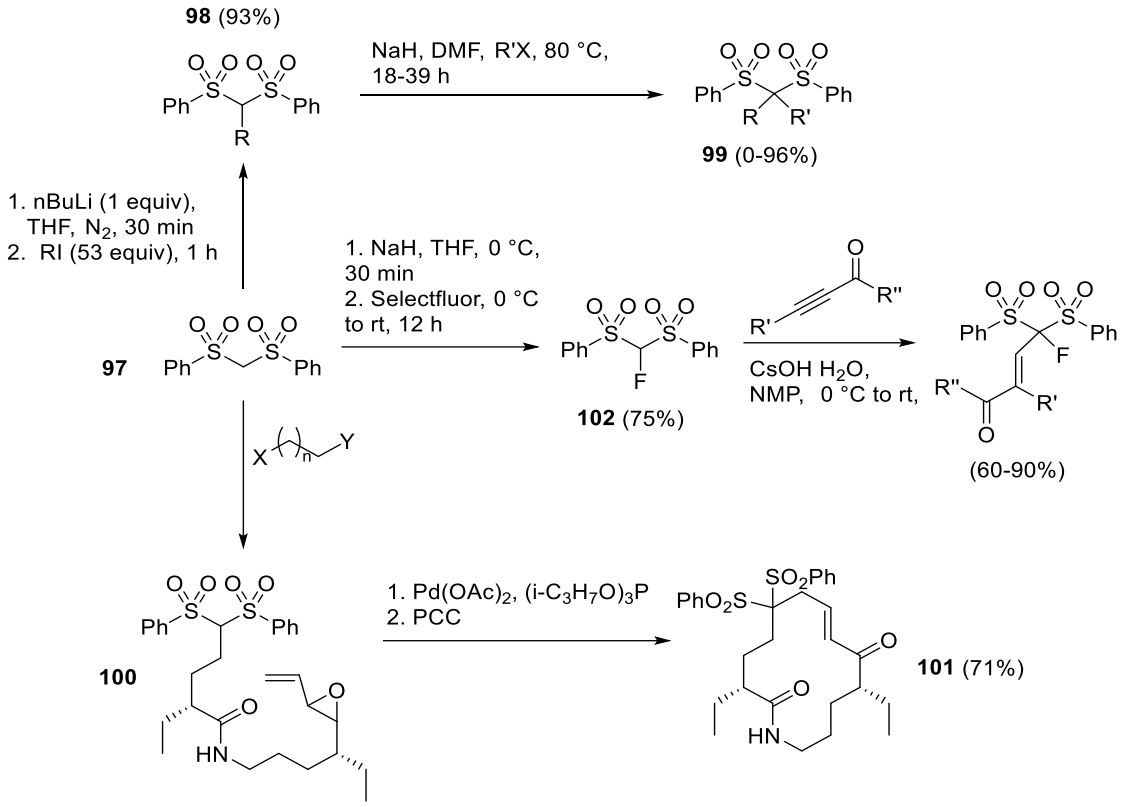
of phenyl sulfonyl groups, which are atom-heavy synthons, and improvements in this area would enhance the utility of this building block in organic synthesis. Gem-*bis*-sulfones are flexible functions as they can act as both nucleophiles and electrophiles (when unsaturated) (Scheme 57), acting as donors and acceptors in a variety of cycloaddition reactions but they can also be used to access radicals. *Bis*-sulfone reactions rely upon the great reactivity of the geminal carbon, which has the ability to form up to four new bonds, facilitating the construction of complex molecules or to simply introduce a carbon group as extensively explained in a review by Trost.[12] The general strategy in the use of *bis*-sulfones as an auxiliary group usually involves functionalisation of one, or both, C-H bonds, followed by elimination of the two sulfones.



Scheme 57. Nucleophilic and electrophilic *bis*-sulfones.

In this section, only a brief overview of the reactions of nucleophilic *bis*-sulfones will be shown, as the rest of the review will concentrate on reaction of unsaturated *bis*-sulfones in Section 1.4.2, for the purpose of this project.

Due to the great reactivity of the geminal carbon, *bis*-sulfones can be easily monoalkylated **98**.[117] However, the formation of a dialkylated compounds **99** can be more problematic depending on the bulkiness of the second R' which has been introduced. This is due to the sterically hindered $PhSO_2$ groups, commonly used in *bis*-sulfones. In fact, it has been shown that the use of 1,3-benzodithiole tetraoxide for di-alkylation can be achieved in good yields.[118] *Bis*-sulfones can introduce not only methyl, but also methylene groups (including dianions, radical anions and diradicals), often difficult to install directly. *Bis*-sulfones are also widely used to introduce fluoromethyl anion **102**.[119] The corresponding α-fluoro *bis*-sulfone is synthesised by electrophilic fluorination in order to then provide the fluoromethyl anion.



Scheme 58. Exemplification of the most important reactions when using *bis*-sulfones moieties.

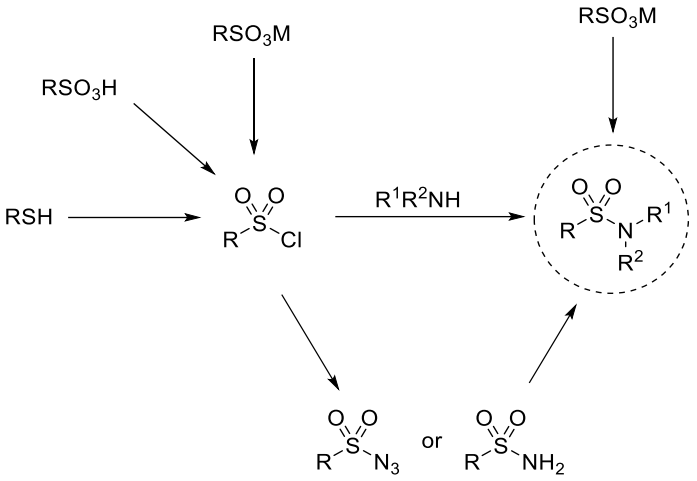
Bis-sulfones have been used as an auxiliary in total synthesis to also facilitate cyclisation reactions to access **101** or to couple fragments of comparable complexity[108d, 120] (Scheme 58).

1.3.2.5 β-Sulfonylsulfonamides

Sulfonamides constitute an important class of drugs, with several types of sulfonamide-containing pharmacological agents possessing antibacterial,[121] anti-carbonic anhydrase,[122] diuretic[123] and hypoglycemic[124] activities, among others.[125] Due to these reasons, sulfonamides are generally used not only as an auxiliary or protecting group moiety in total synthesis but also as an integral part of the final compound.[126]

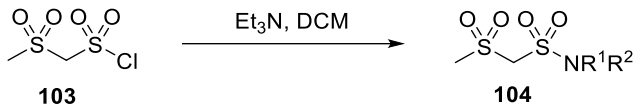
The easiest and most common way to access sulfonamides is to react the corresponding sulfonyl chloride with an amine in the presence of a base[127] (Scheme 59). The required sulfonyl chloride can be synthesised using a number of different strategies, starting for example from a thiol,[128] sulfonate salt[129] or sulfonic acid.[130] The limitations of all these

approaches is that the chemical space accessible is defined by the availability of the corresponding sulfonyl chlorides.



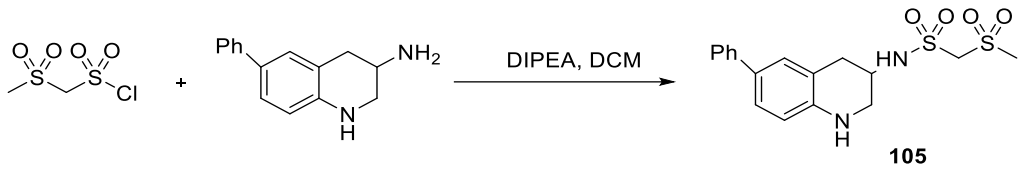
Scheme 59. Synthesis of sulfonamides from sulfonyl chloride.

Although there has been lots of studies on sulfonamides, and their medicinal properties have been well recognised, very limited work has been done on sulfonyl methylene sulfonamides. Up until now, only two methods have been applied for their synthesis. Similarly, to sulfonamides, sulfonyl methylene sulfonamides **104** can be obtained from the corresponding sulfonylmethylene sulfonyl chloride **103** through the reactions with a nucleophilic amine in the presence of a base, i.e. Et_3N (Scheme 60). However, substrates like (methylsulfonyl)methylene sulfonyl chloride **103** are expensive and their synthesis from sulfides preferably avoidable due to their strong charctoristic pugnet odor.



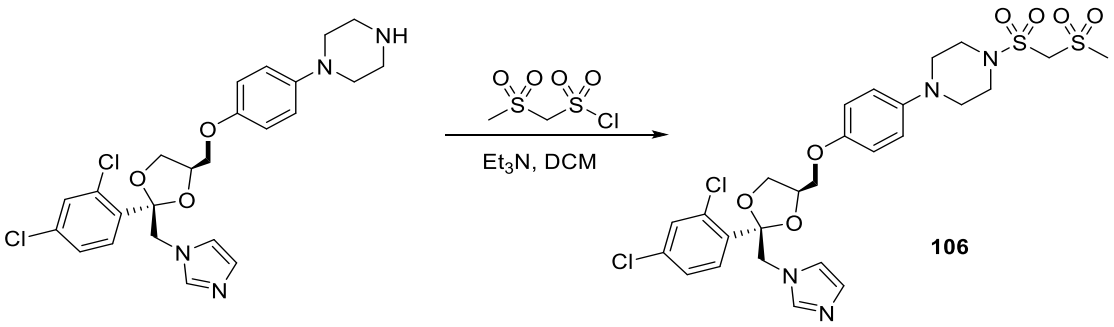
Scheme 60. Synthesis of sulfonyl methylene sulfonamides from sulfonyl methylene sulfonyl chloride.

This approach has been taken by Bendale *et al.*[131] in a study to develop tetrahydroquinolines based antimalarials **105** as shown in Scheme 61.



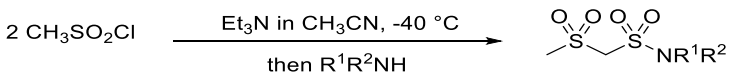
Scheme 61. Synthesis of sulfonyl methylen sulfonamides.

Another example is the synthesis of (±)-ketoconazole **106** by Blass and co-workers[132] (Scheme 62).



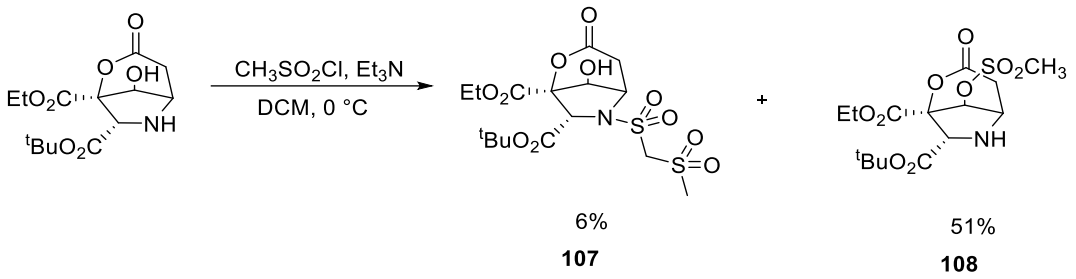
Scheme 62. Synthesis of sulfonyl methylene sulfonamides from sulfonyl methylen sulfonyl chloride.

A more affordable way of synthesising sulfonyl methylene sulfonamides is from mesyl chloride, first developed by Opitz[133] in 1966, and investigated in more depth in 1990.[134] A base like Et_3N is used to deprotonate mesyl chloride forming α-sulfonylsulfene which can be trapped by the addition of a second amine, to form a stable sulfonyl methylene sulfonamide adduct (Scheme 63).



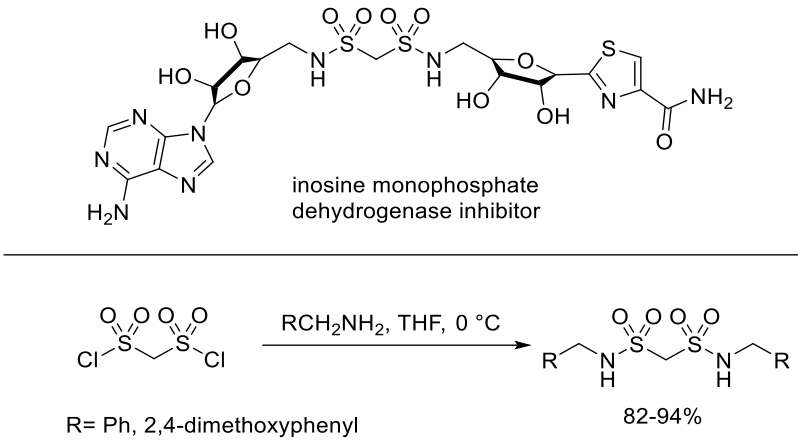
Scheme 63. Sulfonyl methylen sulfonamides from mesyl chloride.

In 1984, in the investigation of *O- versus N*-methanesulfonylation, Stoodley and Whiting[135] unexpectedly obtained the sulfonyl methylene sulfonamide (which mechanism is discussed in section 2.3.1.6, page 89) of oxazabicyclo-octane **107** in similar conditions (Scheme 64), replicated on an oxazabicyclo-octane analogue in 1989.[136]



Scheme 64. Sulfonyl methylene sulfonamides of oxazabicyclo-octane.

More recently, methylene *bis*(sulfonamides) have been used in medicinal chemistry to link NAD (nicotinamide adenine dinucleotide) analogues through reactions with two protected nucleosides,[137] also used similarly in the synthesis of inhibitors of human inosine monophosphate dehydrogenase (Scheme 65).[138]



Scheme 65. Methylene *bis*(sulfonamide) linked NAD analogue as IMP inhibitor and the synthesis of *bis*-sulfonamide.

1.4 α,β-Unsaturated sulfones

α,β-Unsaturated sulfones are extremely good Michael acceptors which react with suitable nucleophilic heteroatoms, such as alcohols, thiols and amines. Michael additions of vinyl sulfones are of particular value in organic synthesis due to the fact that competing addition to the sulfone functional group is not possible, unlike for equivalent carbonyl species. They can also serve as efficient partners in cycloaddition reactions[139] (Diels-Alder) or give reactions with organometallics.[140] Due to the mild conditions required to react with a amine, alcohol or thiol groups naturally present in biomolecules, they have been used in bioconjugation and immobilization of biomolecules.

However, in the case of the presence of a second electron withdrawing group, as in sulfonyl vinylidene sulfones systems, Michael addition will be even more facile. While the potential of sulfonyl vinylidene sulfones has only been recently recognised, only a modest number of studies are present in the literature, with no documentation on sulfonyl vinylidene sulfonamides (Figure 5).

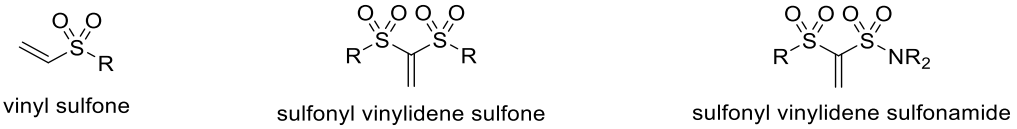


Figure 5. General structures of vinyl sulfone, sulfonyl vinylidene sulfone and sulfonyl vinylidene sulfonamide.

This chapter will focus on the synthesis of α,β-unsaturated sulfones and α,β-unsaturated *bis*-sulfones and the Michael additions to these with enolates and heteroatoms, and in particular amines, thiols and alcohols.

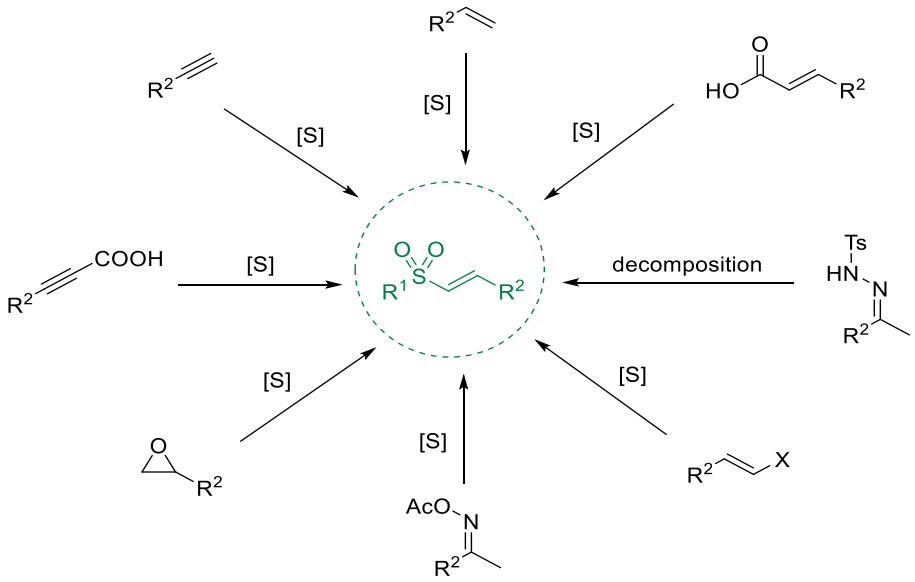
1.4.1 Simple α,β-unsaturated sulfones

1.4.1.1 Synthesis of α,β-unsaturated sulfones

Vinyl sulfones has been recognised in recent years for their interesting reactivity. Studies on the synthesis of this important building block is considerable, thanks especially to the

pioneering work of Julia.[141] The Fuchs's group has also contributed to demonstrate the importance of vinyl sulfones as intermediates in organic synthesis.[142]

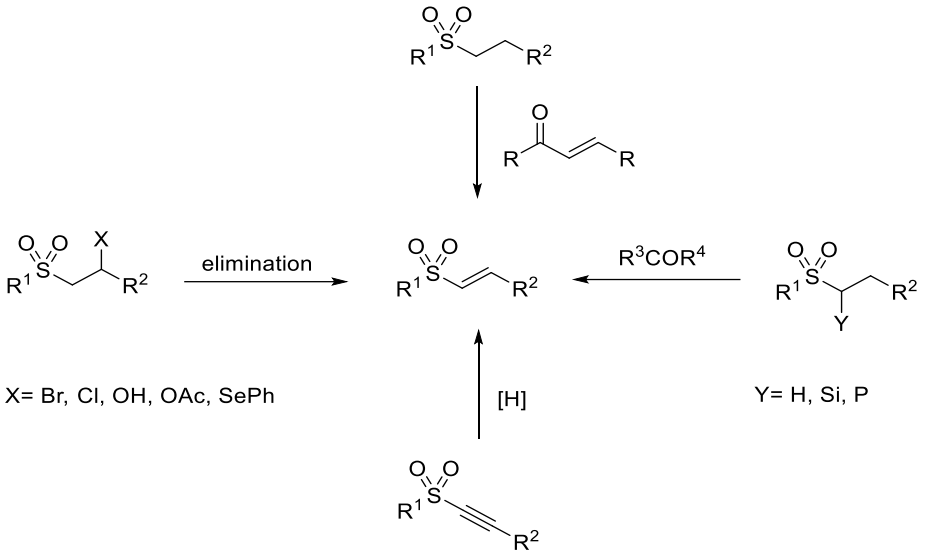
An important strategy for the construction of vinyl sulfones is the direct cross-coupling of a sulfonyl derivatives with an alkene, alkyne or epoxide (Scheme 66). As described in Section 1.3.1, a vast number of sulfone sources are available such as sulfonyl hydrazide, sulfinic acid, thiols, DMSO and sulfinate salts, of which this latter have been mostly used due to their stability.



[S] = sulfones source: RSO_2Na, RSO_2NHNH_2, RSO_2H, RSH, etc.

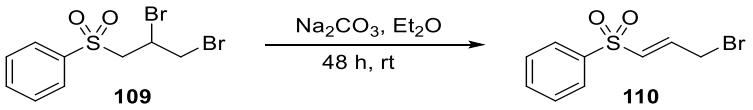
Scheme 66. General methods for the synthesis of vinyl sulfones.[143]

However, more classic synthetic routes from previously synthesised sulfones such as Knoevenagel condensations, Horner-Wadsworth-Emmons reactions of sulfonyl phosphonates[144] and carbonyl compounds, β-elimination of β-heterosulfones[145] or β-seleno-sulfones[146] and reduction of the corresponding alkenyl sulfones[147] have been also widely used (Scheme 67).



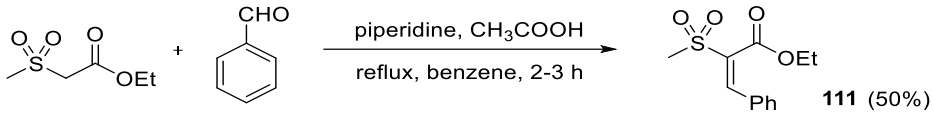
Scheme 67. General methods for the synthesis of vinyl sulfones starting from sulfones.

Worthy of mention is the elimination of β-heterosulfones, generally obtain by combination of a sulfonyl carbanion and a carbonyl compound, or simple alkene, as explained in Section 1.3. An example is the use of sodium carbonate to eliminate the bromo **109** in a work for the synthesis of quinoline-based phenyl sulfone derivatives as anti-trypanosomal agent[148] (Scheme 68).



Scheme 68. Example of synthesis of vinyl sulfones from β-bromo substituted sulfones.

However, most of the syntheses of vinyl sulfones are variants of the addition of a sulfonyl carbanion to a carbonyl compound, followed by dehydration of the hydroxyl intermediate in the case of a simple carbonyl group (aldol type reaction). Some modifications of this use a phosphorous derivative in a Wittig-like reaction or silicon in a Peterson-like reaction. The classic Knoevenagel strategy, condensation reaction of an aldehyde with the sulfone, is the easiest way to obtain vinyl sulfones. An example is the work done by Happer and Steenson[149] for the synthesis of styryl sulfones **111** from aromatic aldehydes with a sulfonylacetic ester (Scheme 69).

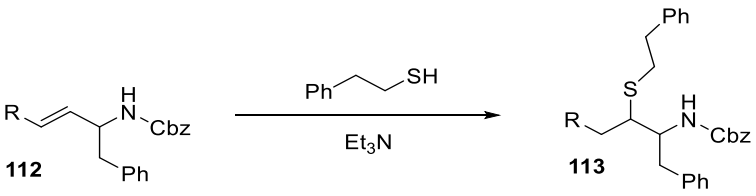


Scheme 69. Knoevenagel type condensation reaction for the synthesis of vinyl sulfones.

1.4.1.2 Reactions of α,β-unsaturated sulfones

Vinyl sulfones can give a variety of different reactions, such as electrophilic additions, nucleophilic additions (additions to heteroatoms and Michael additions) and cycloadditions (Diels-Alder reaction).

Although unsaturated sulfones are not particularly important for their electrophilic additions, it is still possible to access these types of reactions through halogenations. On the other hand, nucleophilic additions have been a point of strength in the use of vinyl sulfones in organic synthesis. Alcohols add to α,β-unsaturated sulfones in the presence of a base to give the corresponding adducts in good yield. Mercaptans and thiophenols, as well as amines, also add to vinyl sulfones in a similar way to give the corresponding alkylthio or alkylamino sulfones. Reddick reported the relative rates of Michael additions of 2′-(phenethyl)thiol to representative vinyl sulfonyl Michael acceptors **112**[150] (Scheme 70). The data in Table-Scheme 70 shows that the pseudo-first-order rates of Michael addition of thiols to this class of compounds vary by up to 3 orders of magnitude as a function of the nature of the sulfonyl unit. Brifely it can be notice that the vinyl sulfonamide analogue (R= SO_2NHBn) was the least reactive substrate, with a reactivity comparable to the one of α,β-unsaturated esters. On the other hand, phenyl vinyl sulfonate ester (R= SO_2OPh) underwent conjugate addition at a rate *ca.* 3000-fold higher than the vinyl sulfonamide SO_2NHBn. However, it is unclear why the vinyl sulfone (R= SO_2Ph) is much more reactive than the vinyl sulfonamides, in which the inductive effect of the nitrogen would have suggested a greater reactivity.

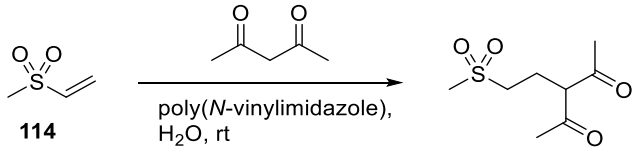


R	Relative k^a	R	Relative k^a
SO_2OPh	3000	SO_2NHOBn	50
COMe	2700	CO_2Me	17
SO_2Ph	120	$SO_2N(Me)Bn$	3
SO_2OEt	90	SO_2NHBn	1
$SO_2N(Me)OBn$	150		

[a]Relative pseudo-first order rate constant.

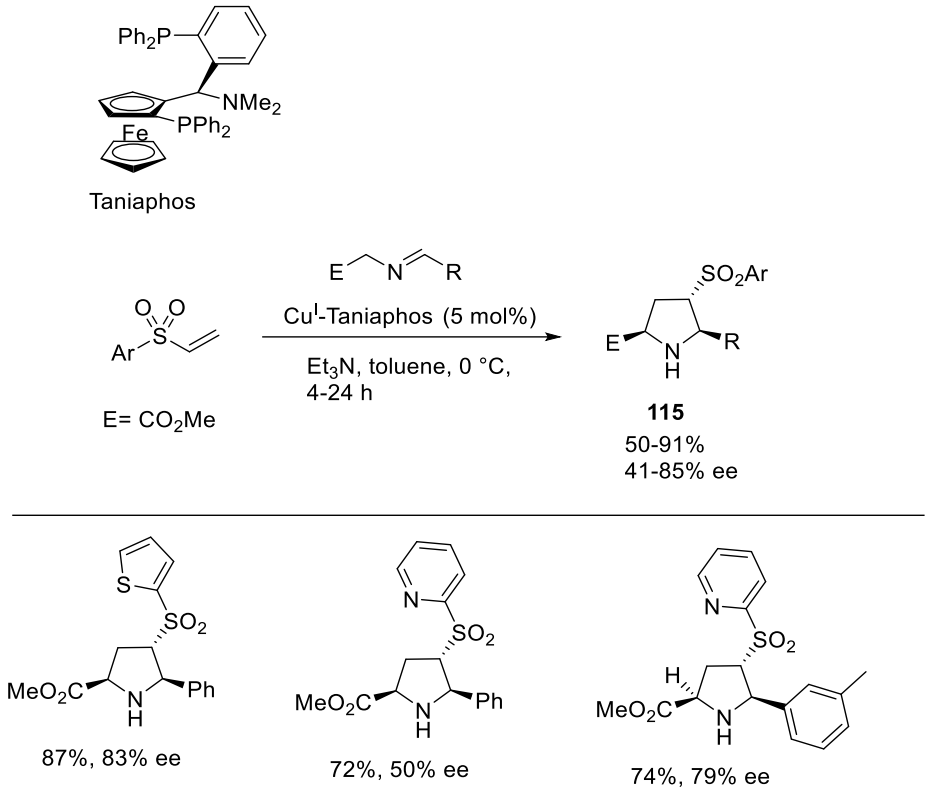
Scheme 70. Nucleophilic addition of thiols to vinyl sulfones and relative pseudo-first order constant rate.[150]

Michael additions to vinyl sulfones are a useful way to form C-C bonds and introduce a variety of organic units. Tarasenko *et al.*[151] studied the possibility to apply poly(*N*-vinylimidazole) as the basic catalyst for the Michael addition of the CH-acids to electron deficient alkenes as vinyl sulfones **114** (Scheme 71).



Scheme 71. Michael addition of vinyl sulfones.

α,β-Unsaturated sulfones have been also widely used as dienophiles in [2+4]-cycloaddition reactions. An interesting example of this kind is the metal-catalysed asymmetric 1,3-dipolar cycloaddition of vinyl sulfones to azomethine ylides[152] (Scheme 72).

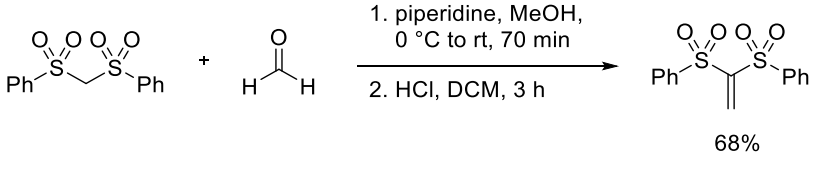


Scheme 72. Cycloadditions of vinyl sulfones.

1.4.2 α,β-Unsaturated gem-disulfones

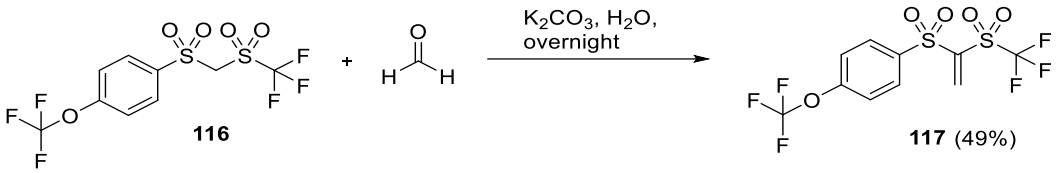
1.4.2.1 Synthesis of α,β-unsaturated sulfonyl sulfones

Stetter and Riberi[153] were the first to synthesise α,β-unsaturated *bis*-sulfones through condensation of di-phenylsulfonyl methane with formaldehyde at high temperature (*ca.* 140 °C) and studied their reactivity in early 1972. However, in 1973, this modification of Knoevenagel-type reaction was revisited by L. A. Carpino[154] and later in 2009 by Sulzer Mossé[155] (Scheme 73). In this condensation reaction first piperidine reacts with formaldehyde, and then slowly the gem-di-(sulfone) adds. The piperidine adduct would then form the sulfonyl vinylidene sulfone upon addition of HCl. Slight variations upon this procedure were then adopted by Dieskau.[110c]



Scheme 73. Condensation reaction for the synthesis of a disulfonyl vinylidene systems.

A similar ways to obtain sulfonyl vinylidene sulfone scan be found in a work of Wickiser and co-workers[156] for the synthesis of 1-(arylsulfonyl)-1-[(trifluoromethyl)sulfonyl]methane derivatives **117**. This method involves reacting the trifluoride substituted sulfonyl sulfone **116** with formaldehyde to obtain the corresponding vinyl compound (Scheme 74).

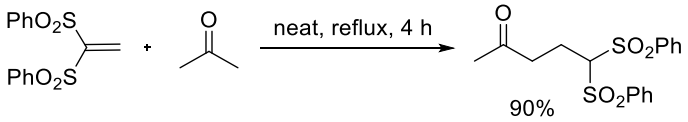


Scheme 74. Condensation reaction with potassium carbonate

Condensation reactions are the only method reported in the literature in order to obtain ethylene *bis*-sulfones.[157]

1.4.2.2 Nucleophilic additions of α,β-unsaturated sulfonyl sulfones

Nucleophilic additions to sulfonyl vinylidene sulfones remain essentially limited to the example listed in Section 1.4.1.2. However, in the case of sulfonyl vinylidene sulfones, these can made even more useful by the incorporation of an additional carbanion-stabilising group. The use of these highly reactive sulfonyl vinylidene sulfones needs milder conditions to produce the nucleophilic additions, which could be potentially useful for a range of reactions, including Michael addition reactions that can be easily accessed and in some cases conducted under neutral conditions[158] (Scheme 75).



Scheme 75. Michael-type addition reactions of a *bis*-sulfonyl vinylidene system.

A study by Rodrigo and co-workers[159] evaluated the reactivity of *bis*-sulfonyl vinylidene compounds in Michael reactions, radical additions and cycloadditions with a wide variety of substrates. α,β-Unsaturated *bis*-sulfone vinylidene compounds have proven to be at least two orders of magnitude more reactive than the corresponding vinyl sulfone, and

hence, such systems have considerable potential for a number of uses, including crosslinking addition reactions.

1.5 Summary

Sulfones are extremely versatile compounds which have generated growing interest due to their wide fields of application. Depending on the surrounding environment, either electrophilic or nucleophilic behaviour is possible, and have been defined by B.M. Trost as "chemical chameleons".[12, 14a] Due to the recent growing interest in these compounds, major improvements in the synthetic preparation of sulfones and related applications have been made. Despite the number of studies on sulfides, sulfoxides, sulfones and various derivatives, much of the chemistry in this area remains unpredictable.[1]

In summary, the most common methods for the synthesis of sulfones are the oxidation of sulfides, alkylation of sulfinate salts and reactions of sulfonic acid derivatives. The oxidation of a sulfide is the most common method of accessing sulfones, however, the use of sulfides is most likely avoidable due their pungent smell. The other two methods consist in the alkylation of nucleophilic sulfinate anions and the coupling of sulfonyl halides or anhydrides with nucleophilic carbons.

Sulfones are used as versatile synthetic intermediates in organic chemistry. They serve mostly as synthetic tools because of their key aspect and properties, being reactions, wide ranging applications and complimentary functionalities. In fact, C-S bonds are susceptible to reduction and can be cleaved to generate both carbanions and carbon-centred radicals. Sulfone moieties are also good leaving groups which can be easily removed by producing a sulfinate anion since they are frequently undesired in target molecules[13] or can activate adjacent protons for deprotonation. Sulfone groups are also particularly good activating, electron-withdrawing substituents in Michael acceptors.[4, 8c, 14] A key aspect of sulfones in their ability form α-carbanions which enables α-alkylation, acylation and aldol-like processes.[1, 15] In most cases, sulfones are structured in order to undergo deprotonation only on one site, through using blocking groups such as tosyl and phenyl are often used on side, leaving a deprotonatable C-H on the other.

Elimination reactions on the α-position in respect to the sulfone moiety enable the formation of C=C bonds such as in the Julia olefination. Development of the methodology for the preparation of vinyl sulfones is of significant interest to organic chemists. Recently, numerous useful methods have been developed, mainly including direct sulfonylation of olefins and alkynes, decarboxylative sulfonylation of α,β-unsaturated carboxylic acids and decomposition of tosylhydrazones. α,β-Unsaturated sulfones are extremely good Michael acceptors and they can easily react with suitable nucleophilic heteroatoms, such as alcohols, thiols and amines. Michael additions of vinyl sulfones are of particular value in organic synthesis due to the fact that competing addition to the sulfone functional group is not possible, unlike for carbonyl group. Due to the mild conditions required to react with a amine, alcohol or thiol groups naturally present in biomolecules, they have been used in bioconjugation and immobilization of biomolecules. In the case of the presence of a second electron withdrawing group, as in sulfonyl vinylidene sulfones systems, Michael addition are even more facile. The potential of sulfonyl vinylidene sulfones has been only recently recognised and only a modest number of studies are present in the literature, with no documentation on sulfonyl vinylidene sulfonamides. Sulfonyl vinylidene sulfonamides systems synthesis and applications remain unexplored and new innovative possibilities still lie ahead.

2 Results and Discussion

2.1 A challenge for coating technology

The requirements for eco-certifications, which verifies that a certain more sustainable practice has been followed in the production of a given good or service, is restricting allowed output levels of volatile organic compound emissions, a major problem for the coatings industry. Although for most decorative paints, the level of VOC emitted is very low, challenges remain with gloss paints, where the option of a water borne formulation is often seen as a compromise. Novel solutions to reduce VOC emissions while increasing gloss paints performance would allow them to compete more favourably with established solvent-borne offerings.[160]

2.1.1 Introduction to economics and environments

Coating is the covering of a surface which provides protection, decoration and many other functions for commodities. The word "paint" is used as an encapsulating term even though it is just one part of a larger class of coatings materials. In order to achieve chemical and mechanical protection, all paints must have approximately the same properties when wetting substrates, transforming, therefore, into a smooth film and then solidifying or drying over time. Hence, in order to be performance coatings, attention should be applied to not only the coating application but also and specially to the film formation. Key parameters governing such film formation are surface tension and viscosity.[160e, f, 161]

Surface protection is the most important function of most coatings, and is vital for many markets and applications sectors, for example, in the automotive industry where vehicle body coatings need to be resistant to the aggressive external environment. In fact, the combination of light, rain, heat, salinity, moisture etc, modern coatings require great wear resistance, and physical and chemical stability properties. Even though surface protection

is one of the most important features in coatings technologies, it is also true that it can be used for other functions. For example, specially developed coatings can be used where there is a need for high grip properties, such as on floors and steps, or even contrary-wise, to reduce the adhesiveness and increase smoothness of surfaces. Moreover, coatings with antibacterial properties are widely used on ships as antifouling materials to prevent the growth of algae and barnacles, and increasingly in food preparation technology sectors. The deposition of living and non-living matter on a ships' hull increases drag, leading to a greater expense in energy, and therefore, costs and emissions. Biofouling also has a great impact on medical devices which includes causing infections that can even lead to death. The electrical sector can also benefit from coatings technologies, including the provision of either effective insulation properties, or the opposite application, of improving the electrical conductivity of a substrate. This vast number of applications of coatings technologies explains the need for wide-ranging types of coatings that provide the necessary complexity of physical and chemical properties that each formulation needs to have based on the application area. In addition, it is important to note that the final coating result and its performance, is not only defined by the paint manufacture but also from the way the particular coating system is applied, i.e. by the coatings users or processors. Indeed, this is why identical product composition does not always achieve the same defined standard at the point of use.[162]

The 20th century was characterised by an increasing number of manufacturing and processing plants being employed for materials production. Consequently, there has been a major increase in volatile organic compound (VOC) emissions into the atmosphere and as a result, new legislation needed to be considered, which was later imposed by the European Commission (EC) and the United States Environmental Protection Agency (EPA). The paint and coating industries have recently been guided by new and increasingly stringent legal requirements in order to be more environmentally and health aware. With the formation of the European Union and the introduction of free trade, new common laws needed to be established and as a consequence, the 1999/13/EC directive[163] was introduced. This directive, with the recently amended to become the Paints Directive

2004/42[164], which sets limits on emissions of volatile organic compounds (VOCs - are broadly defined as: organic compounds having an initial boiling point less than or equal to 250°C measured at a standard pressure of 101.3 kPa) to prevent or reduce the effects on the environment and to human health. This legislation has had a great impact upon the product formulation of coatings, and upon their application and processing. Consequently, research has focused upon replacing organic solvents, either as a whole, or in part, by replacement with water, as well as through moving to totally solvent-free systems such as powder coatings. Attention has also been given to the production process, which is responsible in large part for air pollution from VOC emissions. The way to approach the issues around VOCs in coating, therefore involves the control of an intricate combination of chemical, physical, environmental, health and safety, economic variables.

2.1.2 Coating's composition

The main components in coatings formulation are *resins* (film-forming agents also called binders), *pigments*, *additives*, *solvents* (if not solvent-free) and *extenders*. These terms are defined in the EN ISO 4618 (2014) and in the German standard DIN 55945 (2007-03). Even though older standards make a distinction in *binders* and *film-forming agent*, the distinction never really took place and both terms are equally utilized. In fact, binder is defined by EN ISO 4618 as "the non-volatile part of a medium, where medium is defined as all constituents of the liquid phase of a coating material".

A *film-forming agent* is one of the main constituents of a coating formulation. They are polymers (resins) with a molecular mass between 500 and ca. 30000 Da (which in latex systems this can be high as 1 to 5 million Da) that forms a continuous solid film by producing crosslinked macromolecules on the substrate surface binding all other present ingredients to each other. Therefore, they confer the fundamental properties of the formulation and determine the application method, drying and hardening behaviour, adhesion to the substrate, mechanical properties and chemical resistance of the final coating.

The *solvent* is the medium (usually organic) in which the binder, pigments and additives are dispersed. They are important as they modify the paint viscosity, a key point for the application method. The solvent evaporation rate also plays an important role since a solid film is formed during its evaporation and attention should be also directed to the solubility properties with respect to the coatings components and its toxicity profile.

Pigments are organic or inorganic compounds which give the coating colour, as well as hiding the substrate surface. However, pigments can also change the properties of the final coating by increasing the hardness and decreasing the ductility of the finished coating. In general, they can help to prevent the degradation of the substrate and of the painting itself by the absorption of UV radiation and protection against corrosion.

Extenders are inorganic substances added to the paint in order to increase the paint viscosity and to influence the mechanical properties of both the formulation and final coating. Even though extenders have a refractive index of less than 1.7 (which is why they cannot be consider as hiding powders that is the ability to obscure a background of contrasting colour), they must be included in formulation calculations together with pigments when determining the total pigment concentration. If there are no pigments or extenders the material would be a clear coating system.

Plasticisers and *additives* optimise the film properties. Plasticisers are inert compounds (organic liquids of high viscosity and low volatility) that are important for reducing the film forming temperature, and for improving both flexibility and adhesion properties of the coating. Additives are multifunctional substances that can vary several of the properties of the paint and final coating, e.g. by affecting flow behaviour, and wetting, optical and mechanical properties, while consequently improving manufacturing and processing. Although plasticisers and additives are usually added in minute quantities, they can increase the film resistance, delaying the ageing process.

2.1.2.1 Film Forming Agents

As described previously, binders are high molecular mass molecules that constitute the core of a coating formulation. The essential criteria for the coating formulation is to meet good adhesion and cohesion properties while maintaining elasticity, and therefore, without being brittle. The coating material also needs to be able to wet the substrate in the liquid form (solution, dispersion or molten powder) and create a smooth homogenous solid film. Binders can be classified by different aspects,[165] i.e. chemical structure and functional group, film forming method and manufacturing process.

Polymeric materials can achieve the complexity of properties that a coating material needs by mechanically linking the molecular chains. A solid state can be achieved by either *physical drying* (evaporation of the solvent) or by *chemical hardening* (crosslinking of the polymer chains which causes the enlargement of the molecule). Film forming agents, and the coating that they form, that solidify by solvent evaporation are called *thermoplastic* (e.g. cellulose nitrate, cellulose acetobutyrate, acrylates and PVC etc.) and can be reliquefied by heating or dissolved again by the use of a solvent. Examples of physical hardening binders are cellulose resin, acrylic resins, chlorinated rubber resins and vinyl resins. Such polymers are commonly processed by extrusion or injections and they may be heated reshaped and cooled any number of times. *Thermosetting polymers (duromers),* on the other hand, form irreversible chemical bonds during the curing process (additional chemical bonds formed between adjacent polymer chains) giving rise to an insoluble coating which cannot be reliquefied by its solvent and does not melt upon heating, rather it decomposes without reforming the original structure upon cooling. Chemical hardening permits the use of lower molecular weight polymers and, consequently, enables reducing the amount of solvent employed, which in turn enables a reduction of emissions. Examples of thermosetting polymers are natural oils (e.g. linseed oil), and alkyd (a polyester resin modified by the addition of fatty acids and other components), amino, epoxy, phenolic, polyurethane and silicon resin. These types of polymers can be processed only by mechanical methods or by a moulding process before crosslinking occurs.

Film forming agents can have three different structures: linear; branched; or dendritic. The different structures, shapes and sizes all have an impact upon the properties of the final film, e.g. branched polymers allow higher numbers of linkage groups to be effective during chemical drying resulting in harder, more crosslinked coatings.

The most used classification of binders is as either natural, modified or synthetic. Natural film forming agents were the first resins used for surface protection. They are also known as natural or fatty oils (polyunsaturated fatty acid esters of glycerine) and they were firstly largely used as inexpensive raw materials. In fact, unsaturated fatty acids can go from liquid to solid by reacting with oxygen present in the atmosphere and are mostly extracted from plants and marine animals. However, natural materials were largely supplanted by synthetic resins in the early twentieth century due to being able to access a more tailored product, i.e. with better reproducibility and a greater availability. In fact, synthetic binders can be formulated with different desired properties.

Polymerisation mechanisms can be divided in two main categories: *chain growth* and *step growth* polymerisation. *Step growth polymerisation* involves a step-wise growth by successive reactions that occur between any molecular species carrying two mutually reactive functional groups. It usually requires a catalyst; however, no initiator is needed. In the *chain growth mechanism,* the chain grows with the addition of one monomer at a time, thus the active site is always located at the end of the chain. It is generally used for the polymerisation of vinyl monomers like ethylene, propylene, styrene, vinyl chloride, methyl methacrylate, acrylic acid and acrylonitrile. The mechanism involves three main steps, i.e. *initiation* (reaction between the catalyst/initiator and a monomer unit), *propagation* (reaction between the previous activated monomer and further monomer unit) and *termination* (deactivation of the growing chain). An additional mechanism can often occur in the presence of a transfer agent (the initiator, monomer, solvent, polymer or an added chain transfer agent) in which the growing chain terminates and another active site, capable of propagation, is formed on the transfer agent. Polymerisations which follow the chain-growth mechanism are the *free radical polymerisation (FRP)*, *controlled*

radical polymerisation (ATRP, RAFT, NMP), *living ionic polymerisation* (anionic polymerisation and cationic polymerisation), *ring opening polymerisation* (ROP) and *coordination polymerisation.*[166]

The most used polymerisation reaction in order to synthesise binders involves polycondensation (*step growth reaction*) and polyaddition (*chain growth reaction*). Condensation reactions also involve the formation of by-products, such as water or methanol, whereas polyadditions involve the reaction of unsaturated monomers producing, therefore, no cleavage products. Low molecular weight polymers (resins) are made through both polycondensation and polyaddition reactions.[166]

2.1.2.2 Plasticisers and Additives

Plasticisers and additives are auxiliary products that are added to the coating formulation in order to improve particular technical properties. Generally, a small amount is sufficient in order to produce evident changes in the coating properties.

Several different additives are often added to coatings formulations based on the types of application and properties needed. For example, levelling agents are used to encourage the formation of a smooth and uniform surface during film formation. Wetting agents, probably the most commonly used additive, are surfactants which help to disperse and prevent flocculation and sedimentation of the pigment. Film-formation promoters reduce the film-forming temperature in order to achieve a uniform, pore-free surface. Other, yet nonetheless significant, types of additives are anti-foaming agents, anti-floating and anti-flooding agents, anti-skinning agents, matting agents, thickening agents, catalysts, corrosion inhibitors, and preservatives (biocides and fungicides). The use of anti-foaming agents is fundamental to avoid the trapping of air and, therefore, preventing the formation of not only an unappealing film but also avoiding any consequential change of properties. Some examples of anti-foaming agents are hydrophobic silica, silicon oils and mineral oils. It is also worth mentioning that thickening agents, like silicates, titanium chelates,

cellulose ethers and synthetic organic compounds, are also used in order to control the rheological properties of the coating formulation.[162]

Due to the restricted chain mobility of polymers, it is hard to obtain simultaneously high levels of hardness and good elasticity. However, plasticisers must not be used in excess in order to avoid, in some cases, the formation of a sticky surface. Plasticisers sterically hinder, by nonpolar/polar interactions, the intermolecular interactions (van der Waals forces) that are established along the polymer chain and which limit the mobility of it.[165] As a consequence, the T_g (glass transition temperature) and the MFFT (minimum film formation temperature) of the polymer drops (T_g is the temperature at which an amorphous material goes from a hard, glassy state to a rubbery state and is a characteristic parameter of the material in coating technology).

2.1.2.3 Solvents

Solvents are organic or inorganic liquids used to disperse or dissolve the different raw materials of the coating formulation in order to obtain the desired rheological properties for its application. After the coating has been applied, the solvent evaporates leaving the solid film. Solvents play an important role in the formulation, since they can interact with the film forming agent varying the coiling of the polymer chains and hence, modifying the mechanical strength of the resulting coating. Therefore, it is important, especially for physically drying coatings, to select and combine the right solvent with a particular resin in order to obtain the desired rheological properties (flowability and stability) to enable processing, as well for obtaining the correct evaporation properties.[167] The number of solvents that can be used are many and varied, but can be divided generally into either aromatic or aliphatic compounds, esters (ethyl acetate), alcohols (propanol and butanol), glycol ethers and ketones. In some other cases, solvents can also be used as a reacting chemical during the film formation, with the effect of remaining, therefore, in the coating after formation, and of course, in the process, potentially reducing organic emissions as a result. Paints are often classified based on their system type, i.e.: *solvent-borne*; *solvent-free;* or for high-solid paints: *water-borne* paints; and *coating powders*.

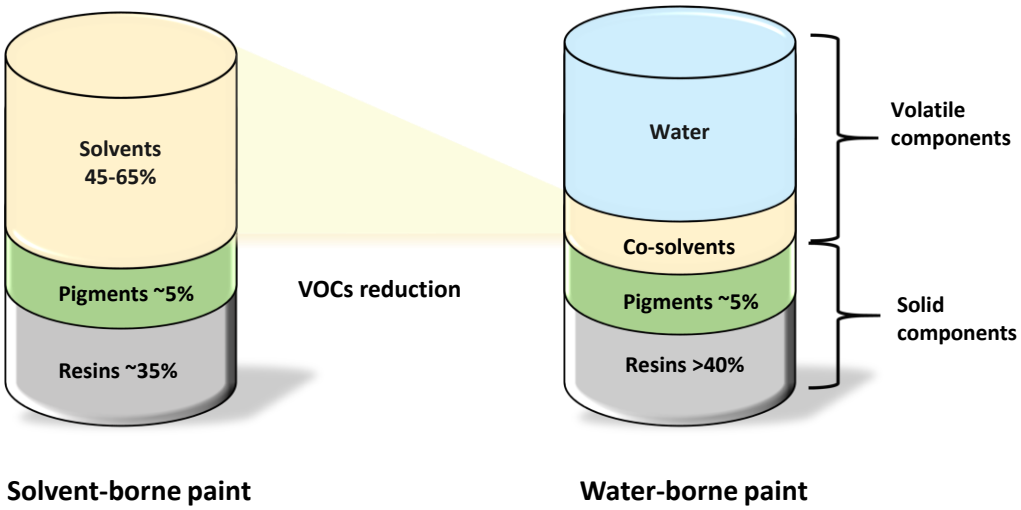


Figure 6. Example of the main components in for the two main types of coating formulation, i.e. solvent- and water-borne.

As mentioned before, due to environmental pollution impact and health problems, it is recognised that solvents are hazardous materials, and hence, restrictions in their use have been introduced by governments in recent years. Therefore, the coating industries have started to introduce more eco-friendly solvents, including water-based systems. Hence, water-borne polymers, such as latex suspensions, prepared *via* emulsion polymerisation have become of particular interest. However, water-borne polymers possess some considerable drawbacks, such as poor mechanical strength, low hardness, water sensitivity, and sensitivity to heat-softening. As a result, their performance is usually inferior to solvent-borne coatings because of the hydrophilic groups and surfactants which are introduced to disperse the resins in the aqueous media which have the downstream negative effects on the final coating. Differences in the film formation mechanisms between water-borne and solvent-borne coatings also has a major impact on the final product. One possible approach to improve the balance in the properties between water-borne and solvent-based coatings is to form thermosetting films *via* crosslinking under appropriate cure conditions. However, despite all the R&D in recent years, this proved challenging to achieve because of the complexity of the mixture of physical and chemical properties required in order to make such a system perform well, particularly avoiding premature crosslinking. As a result, organic solvents have not been replaced to date and such system remain the choice for a wide range of coatings industries and applications,

and therefore, it is a major and unmet chemical and technical challenge to the coatings industry to solve.

2.1.3 Emulsion polymerisation

Emulsion polymerisation is a polymerisation technique which employs radical chain polymerisation mechanism, i.e. the emulsification of one or more monomers such as vinyl acetate, ethylene, styrene, acrylonitrile, acrylates and methacrylate in a continuous aqueous phase stabilised by surfactants.

As shown in Figure 7, the monomers in the aqueous phase are mostly dispersed as micelle, although a small amount will dissolve in the continuous phase due to their low solubility properties. A water-soluble initiator, initially reacts with the low level of monomer dissolved in the continuous phase, creating a low weight polymer chain. The growing polymer chain becomes insoluble in water and migrates to a surfactant micelle, which present a higher surface compared to the monomer droplets. The monomer droplets, acting as a reservoir, release monomer into the water, replacing the monomers that have reacted. These monomers either undergo through the process just described above, or diffuse into the micelle containing radicals, where the chain growth takes place. The final product is, therefore, a dispersion of polymer particles in water, called *latex*.

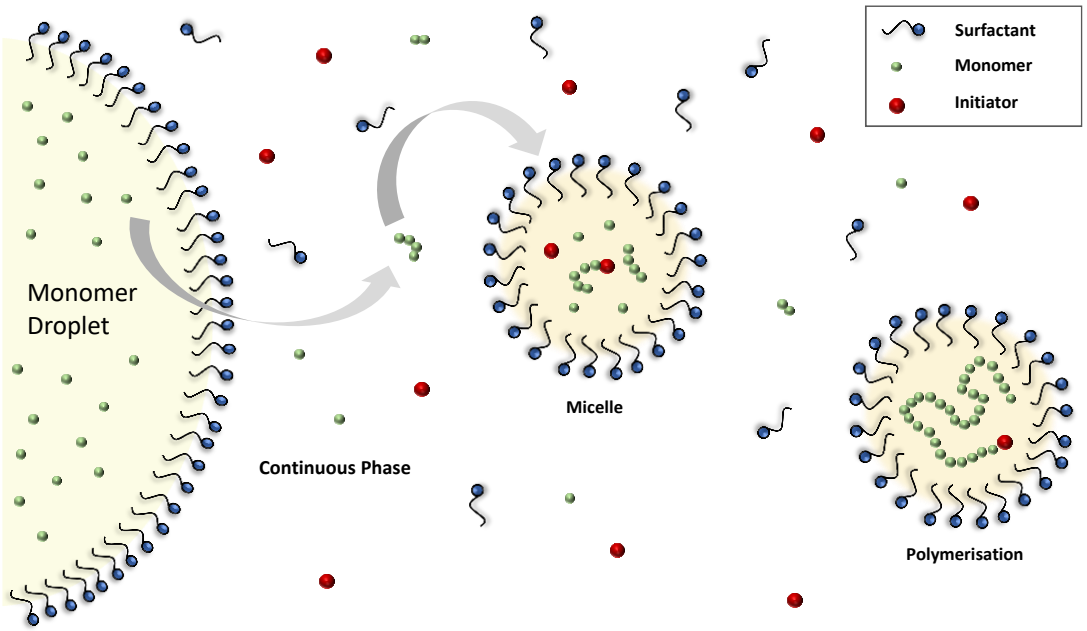


Figure 7. The emulsion polymerisation process.

It is important to distinguish the different and currently used terms in relation to phases, as employed in polymer science. A *dispersion* is a colloidal distribution of solid particles in a liquid phase. If the solid dispersion is not colloidal (d >1 μm), then this is called a *suspension*. An *emulsion* is the dispersion, in the form of droplets, of two immiscible liquids. Finally, the term *latex* can be defined as a colloidal dispersion of a polymer in a liquid only when it has been prepared by emulsion polymerisation.

The emulsion polymerisation process can be operated in either a *batch mode*, *semi-continuous* or *continuous* manner, which have considerable effects on the resulting molecular structure and particle morphology. The most widely used process in industry in order to produce a copolymer product with the desired properties is the *semi-continuous* (or *semi-batch*) emulsion co-polymerisation process. In the semi-batch process, an initial amount of starting materials is charged into the reactor and the rest of the formulation is continuously fed into the reactor then over a period of time. The initial charge contains a preformed seed latex, a fraction of the total amount of water to be used, surfactant and initiator (usually water-soluble). The semi-batch process is used principally to avoid the lack of reproducibility of the nucleation stage when the seed is produced *in situ.* This

enables the creation of *core-shell particles*, which have a layer structure, especially important in the coatings industry.

2.1.3.1 Film formation

Despite the different application methods (spaying, brushing, etc.), the desired outcome from a coating application will always be a continuous smooth film with good adhesion to the substrate surface. As previously mentioned, the final formulation could either be a liquid (if a solvent is used), or a solid (in the case of a solvent free formulation). In the latter formulation, a powder coating is employed that needs to be melted when applied, and therefore, this is only suitable for a certain type of applications where this technically and practically feasible. In order to achieve a uniform and smooth solid film, the two fundamental parameters that need to be considered are: viscosity; and surface tension.

After the substrate has been wetted by the liquid film, the liquid film starts solidifying, going through physical and/or chemical changes that result in hardening. This process involves several steps in which the film undergoes several viscosity and rheological changes. In fact, with inevitable evaporation of the solvent, the concentration of the binders increases and, consequently, the physical and chemical interactions between molecules increases (e.g. entanglement) resulting in ever increasing viscosity as the process proceeds. In the case of chemical drying, during the evaporation process, chemical curing reactions take place and the crosslinking of the resin leads to an increase in molecular weight, and hence, of the viscosity, forming an increasingly interconnected network of intermolecular bonds which drives the coating to solidify. In contrast, in the process involving only physical drying, no molecular enlargement or increase intermolecular bonds is involved. It follows, therefore, that in the case of chemical drying, it is usually started by either heating or catalysis, and the mean molecular weight of the resin will be much lower than for physical drying. The result is a highly crosslinked insoluble network which cannot be reliquefied upon heating. Because of these advantages, chemical hardening is a preferable drying/hardening process despite the complex formulation needed to achieve it successfully. However, physical drying methods are still

in use due to their simpler and economical formulation and because usually, no heating is required. In the case of physical drying, two different film forming processes take place depending on whether there a polymeric solution or polymeric dispersion is employed. When the film undergoes physical drying, and there is a polymeric solution, it is fundamentally important to choose the right solvent. In fact, the film forming agents chosen need to be well solvated in order to be able to 'stretch' during film forming, so that the polymers can properly entangled during the curing process. On the contrary, in the case of poor solvation, the polymer will dry in a coiled form, without being able to entangle with the other polymer chains, leading to a physically weaker film. Hence, the alternative is to use polymer particles that are dispersed (*latex*), and as the film starts to form during solvent evaporation, attraction forces (*van der Waals*) prevail over the repulsion forces (*steric and electrostatic repulsions*) between particles. When the particles finally touch, complete fusion takes place with the loss of their spherical particles' nature and the opportunity for an even coating to be created (Figure 8). This phenomenon is driven by the reduction of the total surface area, resulting in a thermodynamically more stable system.

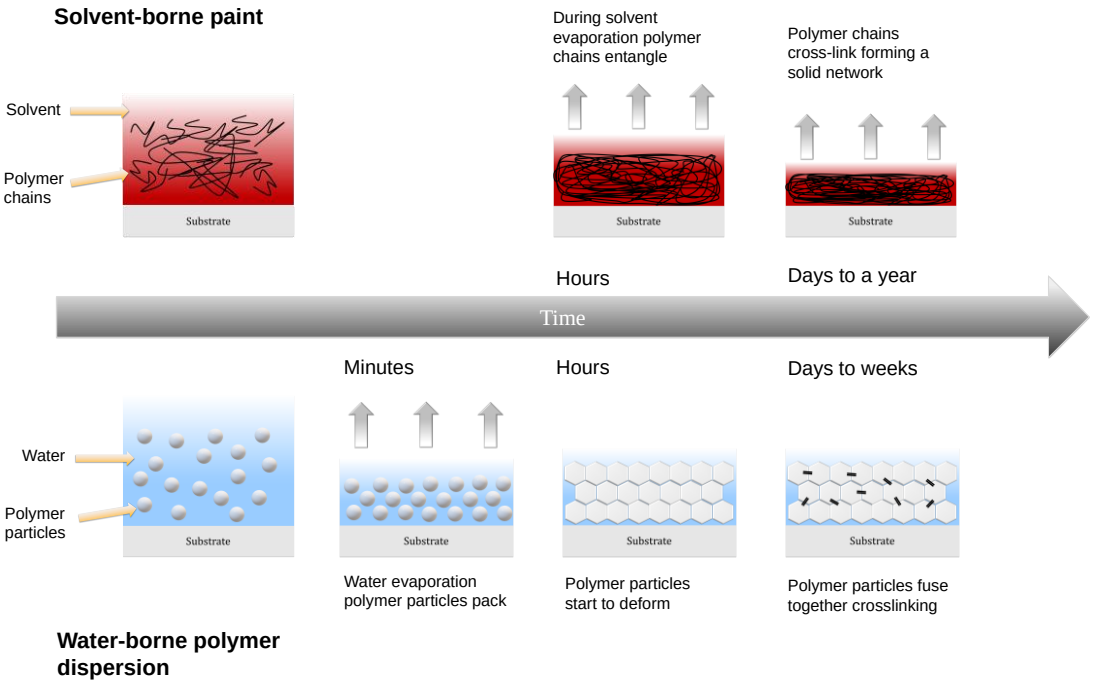


Figure 8. Film formation of a water-borne versus a solvent-borne coating.[160f]

When talking about film formation of water-borne versus solvent-borne some main differences can be highlighted (Figure 8). The film formation process in the case of a water-borne dispersion, the water is able to rapidly (10-15min) evaporate and the particles starting to pack increasing the viscosity dramatically. This will limit the *open time* of the paint defined as the period of time in which the painter can make correction to the wet paint without leaving brush marks. In a further stage the remaining water evaporates, and the particles deform and, after days, these will merge to a uniform entity in which the polymer chains will entangle and crosslink. The short open time of water-borne paints is one of the reasons of the limit success in high gloss decorative coatings.

In the case of a solvent-borne coating, upon solvent evaporation the polymer chains start to interact and the molecular weight increases, although remaining lower when compared to the water-borne. The entanglement of the stretched polymer chains traps the solvent slowing its evaporation, with an *open time* of several hours. The viscosity will increase dramatically only when all the solvent will have evaporate, giving an uniform film which will remain tacky for a long period of time.[160f]

The flow properties during this application process are fundamental to give a homogeneous film. For successful coating application, the minimum film-forming temperature (*MFFT*), which is the temperature at which the binder forms a clear and homogeneous film, needs to be reached or exceeded. The minimum film forming temperature is closely related to the T_g of the polymer. Therefore, below the T_g, the polymer still behaves as hard spheres, retaining their shape, and also, after solvent evaporation, leads to a mechanically unstable film. On the contrary, if the *MFFT* is reached, the polymer spheres become softer, flowing into each other and coalescing. The minimum film-forming temperature can be lowered in three main ways: 1) by adding organic solvents to the water dispersion (*coalescing agent*); 2) by lowering the molecular weight of the polymers or; 3) in the case of co-polymers, by increasing the amount of monomers that will contribute to a lower final T_g.[162, 168]

When talking about *chemical curing* (*crosslinking*), film formation occurs as a result of intermolecular bonding between the polymer chains. When the solvent is present, this process can occur simultaneously with the physical drying, as described above. Curing may be initiated then by different methods: 1) heat carrier (air); 2) radiation (IR, UV, electron beam etc.); 3) electrical methods; and 4) by use of catalysts. After the activation, depending on the reactive groups, the shorter polymer chains start to crosslink *via* poly-addition or poly-condensation to each other, increasing the molecular weight and forming a *duromeric* material. However, crosslinking does not necessarily need to be excessive, i.e. in order to avoid the potentially inverse effect, of forming a brittle material. The curing temperature and curing time also both play an important role in the mechanical properties (especially in poly-condensation) of the final coating.

2.1.3.2 Existing cross-linking methods

As explained above, cross-linking is an important method for enhancing both the adhesion and mechanical strength, water and chemical resistance, and durability of films formed from waterborne polymers, in order to achieve the same performance as solvent-based coatings. The crosslinking process consists of mutual bonding (ionic or covalent) between two or more polymer chains to each other. The types of crosslinking methods available for water-borne paints can be mainly divided in two types: firstly, a polymer that is to be crosslinked by a low molecular mass crosslinking agent, added prior to deposition of the coating to the substrate (a two-pack system); and secondly, two different polymers containing complementary reactive groups (a one pack-system). Crosslinking systems are usually designed to undergo curing at elevated temperatures (stoving), irradiation (if polymerisable), oxidative drying or through moisture curing.

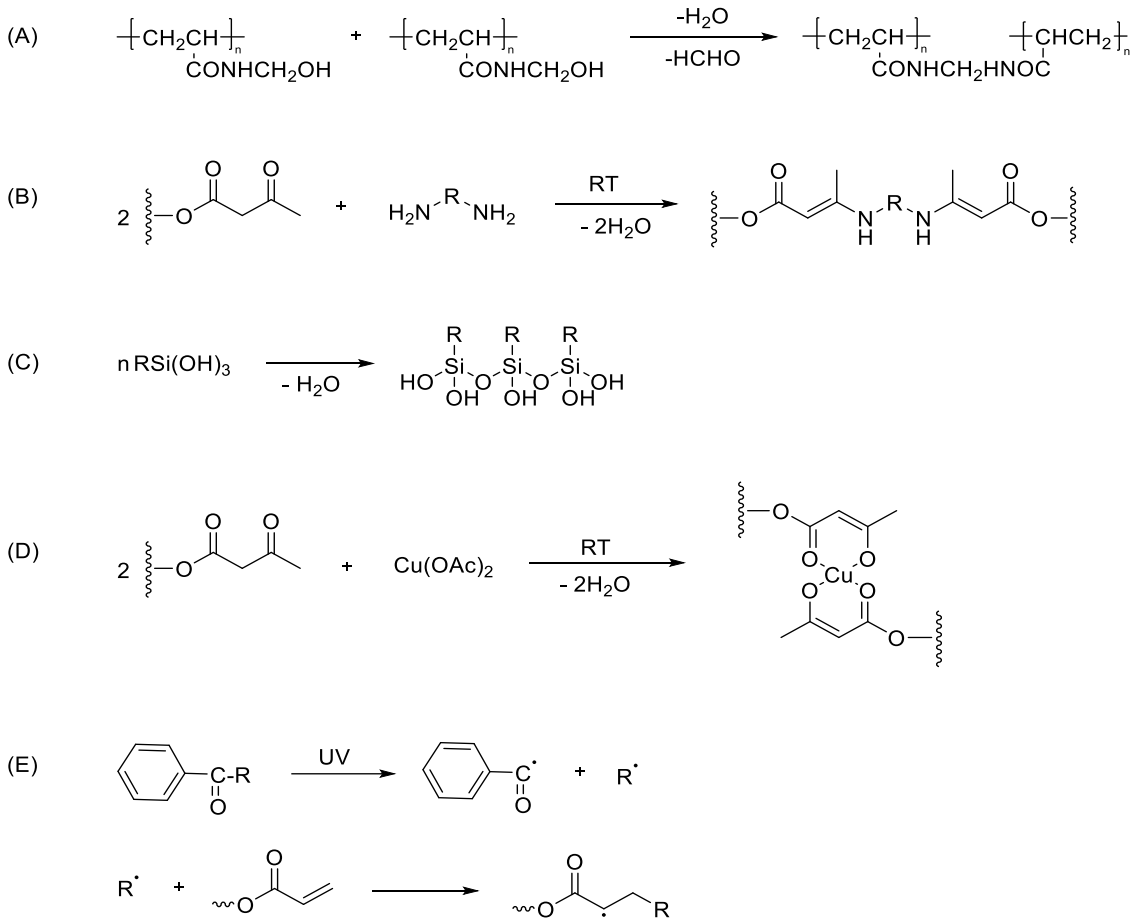
The two-pack systems have the advantage of having a longer shelf life when compared to one-pack systems due to the fact that the crosslinking moiety is added prior to the application of the coating and, therefore, no premature crosslinking can occur. However, upon coalescence of the particles during film formation, the crosslinking agent accumulates between the particles, generating a densely crosslinked film at the interface,

limiting the polymer chains' mobility, and therefore, resulting in an inhomogeneous film. The curing reaction begins as soon as the base paint and hardener are mixed, thus these systems also have also a short pot life once the crosslinking moiety is added.

In the adoption of a one pack-system, the functional groups are incorporated in the polymer chains, in this may lead to premature crosslinking, thus in a lower quality coating. However, most one-pack systems trigger crosslinking upon evaporation of water during drying or by decrease of the pH in the film. Hence, there has been increased interest in one-pack mechanisms over the conventional two-pack (not available for decorative coatings systems), especially in acrylic emulsions, since they potentially offer solutions for high-performances in water-based coating materials. Self-crosslinking of acrylic emulsion can be divided in mainly five groups: self-condensation of a methylolacrylamide group; keto-dihydrazide/diamine; self-condensation of organofunctional silane; self-condensation of metal chelates; UV curing (Scheme 76).

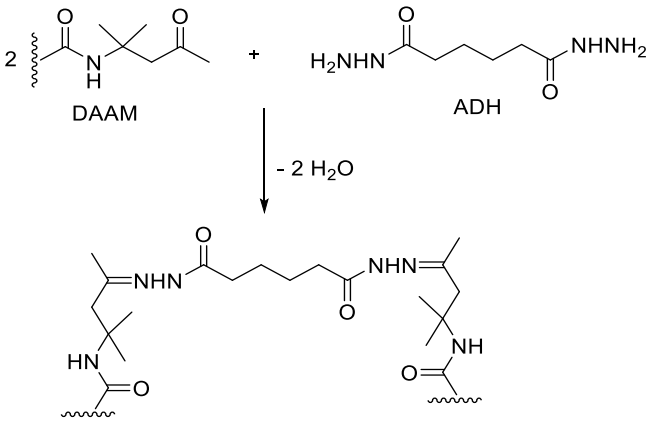
N-methylolacrylamide (NMA) is a bifunctional monomer group presenting a vinyl group, used for the co-polymerisation of this with other monomers, and a hemiaminal group which remains free for further self-condensation reaction between two adjacent polymer chain. The condensation reaction releases water and formaldehyde, the latter being a carcinogenic compound, making this crosslinking method unacceptable for most applications. Although there have been attempts at by-passing this issue by incorporation of formaldehyde scavengers, coatings manufacturers have been focusing on alternative techniques.

The most used crosslinking system in waterborne acrylics is *keto-dihydrazide/diamine*. This crosslinking strategy is based on the reaction of a carbonyl group (attached to the polymer chain) with an amino group of a di-hydrazide (crosslinker) (Scheme 76-B).



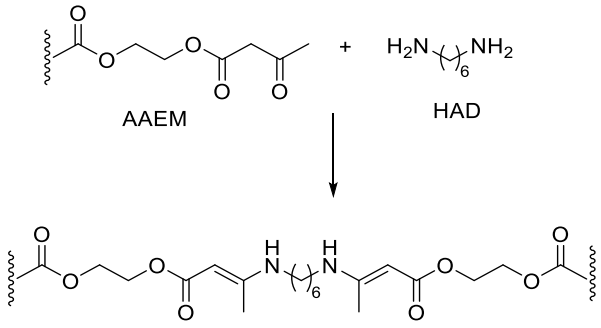
Scheme 76. Self-crosslinking of acrylic emulsion: (A) self-condensation of methyloacrylamide; (B) Keto-dihydrazide; (C) organosilane; (D) Metal complex [chelates, salts]; (E) UV curable.

This type of mechanism is stimulated by water evaporation which occurs at room temperature. Numerous types of carbonyl functional monomers have been synthesised, however, diacetone acrylamide (DAAM) is the one that has attracted most interest due to its good reactivity ratio with various co-monomers. For example, this system reacts readily with different dihydrazides, however, reaction with adipic acid dihydrazide (ADH) is the most commonly used although this can present poor solubility in water and vulnerability to alkaline and acid (Scheme 77). This type of keto-hydrazide technology has the advantage of long storage stability since the reaction was found to be acid catalysed, where the spontaneous change in pH is driven by ammonia evaporation during drying. However, the use of ADH is currently subject to derogation by the Commission Decision 2014/312/EU, and its future ban from the use in EcoLabels products will require alternative crosslinkers.[169]



Scheme 77. Crosslinking reaction between DAAM and ADH.

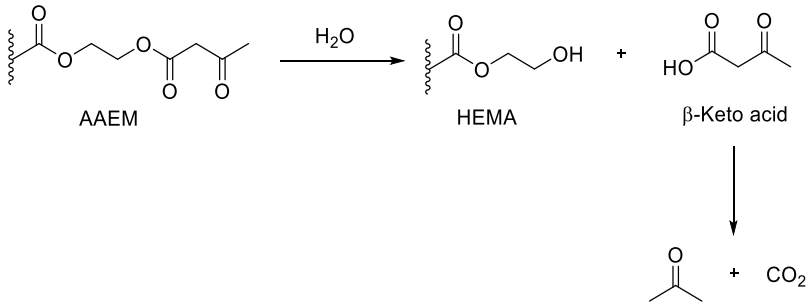
Following these types of mechanisms, acetoacetoxy functional monomers have been also studied for the crosslinking in water-based coatings. This reaction is based on keto-enol tautomerism, where the enolic functional group reacts with an amine at room temperature giving an enamine. Among the different acetoacetyl functional monomers, acetoacetoxyethyl methacrylate (AAEM) is most commonly used in combination with 1,6-hexanediamine (HAD) as a crosslinker. This system gives excellent adhesion properties due to its polar nature.



Scheme 78. Crosslinking reaction between AAEM and HAD.

Although this system can give excellent resistance properties for the final film, acetoacetyl functional monomers have limited use due to the acetoacetyl functional groups being prone to hydrolysis during processing (due to high temperatures) or storage (due to pH of ca. 3), leading to the formation of hydroxy ethyl methyl acrylate (HEMA) and β-keto acid in the case of AAEM as shown in Scheme 79. While β-keto-acids decompose into acetone and carbon dioxide, HEMA remains inert to crosslinking, thus reducing the final performances. This can be prevented during storage by the addition of ammonia, which

can act as a protecting group to the AAEM forming the relative enamine, resistant to hydrolysis. The ammonia evaporates during film formation, unveiling the reactive AAEM group. While hydrolysis during storage can be prevented, so far no solution seems to be available for the high temperatures used during polymerisation, which partially hydrolysed the crosslinker.



Scheme 79. Hydrolysis reaction of AAEM.

Organofunctional silane monomers as crosslinking systems for waterborne coatings have been also explored. Such silanes present a polymerisable group and a hydrolysable moiety (i.e. alkoxy group) which liberates alcohols upon hydrolysis that provides the linkage via self-condensation. Also, in this case, hydrolysis is triggered by the lowering of the pH during film formation. Organofunctional silane monomers react to form an interpenetrating polymer network (IPN) of two polymers, which gives improved barrier properties.

Crosslinking can also be achieved by the reaction of a carboxyl group attached to the polymer backbone with a *metal ion* (*chelation*) (Scheme 76-D). Although metal ion crosslinked emulsions give superior properties compared to conventional emulsions, this has also limited development due to the formation of an opalescent film.

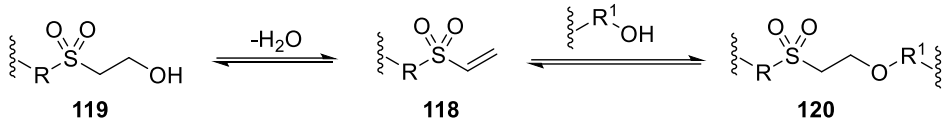
UV-curing also has widespread applications in various sectors of the coatings industry since it overcomes the use of high temperatures for crosslinking. Hence, after deposition on the substrate, the coating is exposed to UV light (wavelength 240-450 nm) which dissociates the photoinitiator into the free radicals (Scheme 76-E). These free radicals attack the unsaturation in multifunctional acrylates which results in crosslinking between

two mutual polymer chain. However, these technologies become less practical for the coating of large substrates.

Despite many great advances in crosslinking technologies over recent years, the achievement of high-performance coating involving a genuinely environmentally friendly coatings system, remains elusive and new technologies and chemistries are required.

2.1.4 Alternative ideas to the existing crosslinkers

A new concept in the field of crosslinking technologies was introduced in 2005 by Berrisford and co-workers[170] consisting in the use of a dynamic equilibrium when water is present, to provide both protection and to unveil the latent functional group at appropriate times in waterborne coatings.



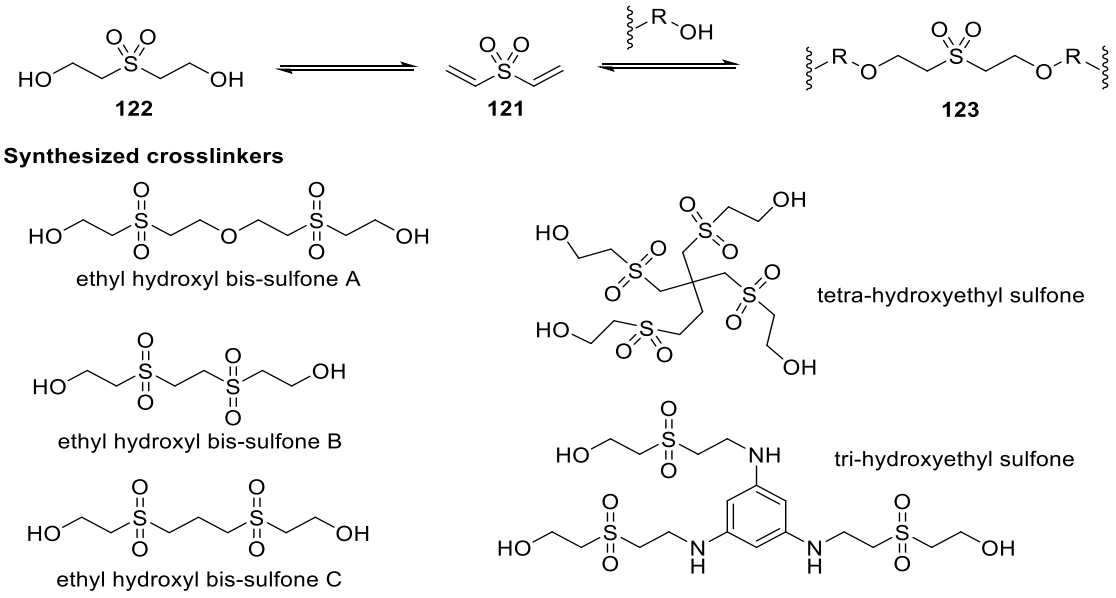
Scheme 80. 2-Hydroxyethylsulfones in equilibrium with vinyl sulfones and its crosslinking reaction.

In fact, the new functional monomer, a hydroxyethyl sulfone, which is copolymerised into the backbone polymer chain, is unreactive towards heteroatomic and carbon nucleophiles (Scheme 80). During film formation, however, loss of water from the hydroxyethyl sulfone **119** occurs, since it is in equilibrium with the vinyl sulfone **118** (a good Michael acceptor as explained in section 1.4), which can then react with a second functional monomer containing nucleophilic moieties leading to crosslinking (**120**). Unfortunately, to-date, only 4-hydroxyethylsulfonylstyrene (HESS) was synthesised and successfully tested in emulsion polymerisation systems. Preliminary studies on this molecule have shown crosslinking dependence upon pH, good storage life and enhanced mechanical properties in the resulting film, providing proof-of-concept of the potential of this new approach. However, time of reaction between HESS and the nucleophile was found to be slow for the needed application, hence, further studies were needed.

2.1.4.1 Previous work

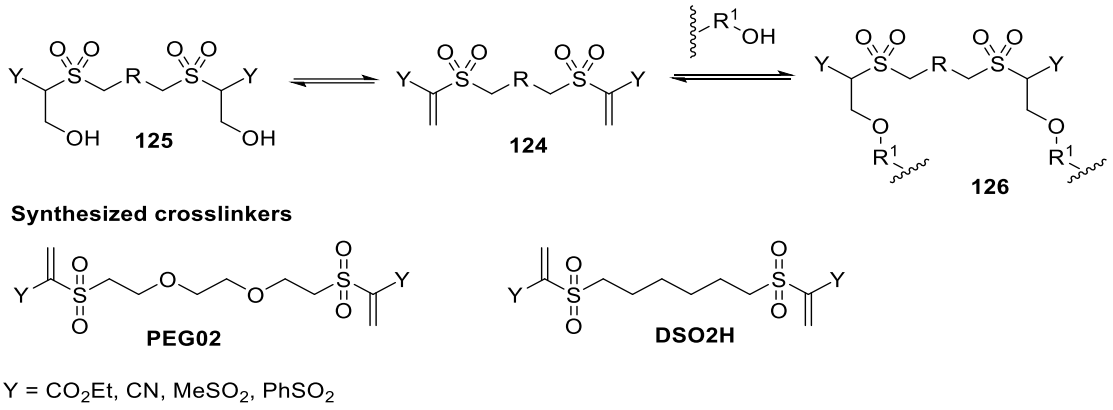
Encouraged by the preliminary results of HESS, further studies were conducted in this group by Dr C. W. Leu,[171] which is to-date unpublished work and involved examining the synthesis of three new generations of hydroxyl sulfones to see if improved reactivity and coating compatibility could be developed.

In the *first generation,* it was decided to move towards di-vinyl sulfone systems due to the difficulties in synthesising vinyl sulfones containing co-polymerisable groups on one end (Scheme 81). The idea involved having a bi-functional crosslinker that could be added at the end of the emulsion polymerisation process, which would be stable as the di-hydroxyl system **122** until film formation. However, these types of molecules were not reactive enough and only low levels of crosslinking were achieved with no increase in performance of the final film.



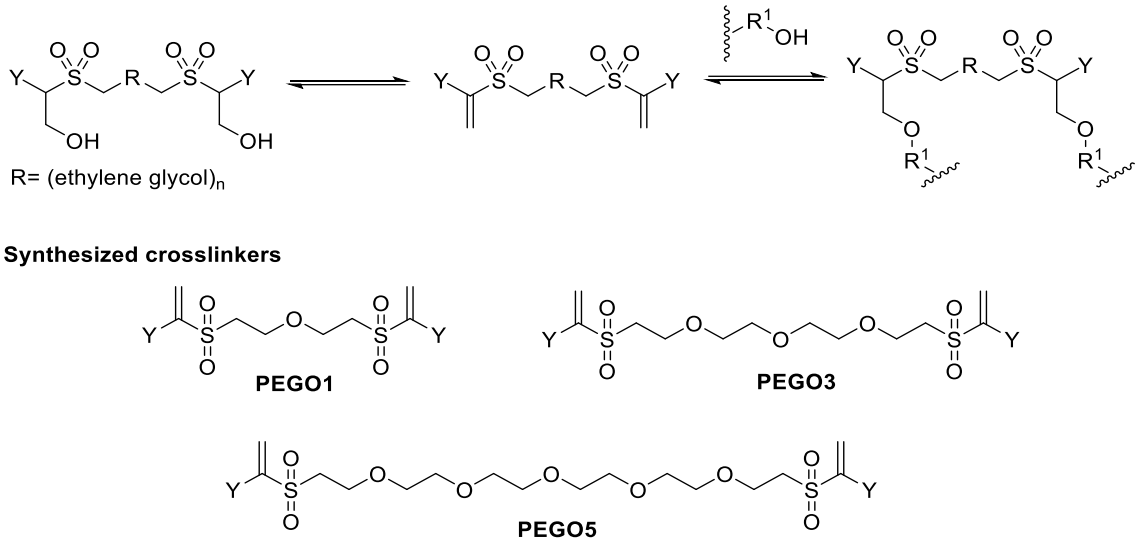
Scheme 81. First generation vinyl sulfones.

In order to try and overcome the reactivity problems found in the first-generation systems, a second generation of crosslinkers were designed, with the inclusion of electron withdrawing groups such as carbonyl, cyano or even second a sulfonyl (Scheme 82). However, the introduction of these doubly activated disulfonyl, carboxy-sulfonyl and cyano-sulfonyl systems led to a final intractable product, which was not suitable for layering of a homogeneous film.



Scheme 82. Second generation crosslinkers.

In the *third generation* of this study focusing on new crosslinking solutions, the doubly activated cross-linkers discussed above were re-designed to be more fluid and malleable through the introduction of one or more ethylene glycol spacing groups. It is worth mentioning that generally, crosslinkers should remain as small (low molecular weight) molecules in order to give the final product high performance mechanical properties. However, also in this case, the problems encountered with these types of crosslinking formulations were several. In fact, doubly activated carboxy-sulfonyl systems were able to undergo intramolecular condensation reactions due to the high reactivity of carbonyl systems and their ability to undergo keto-enol tautomerism. Moreover, it was not always possible to synthesise the vinyl Michael acceptor required in these doubly activated compounds and therefore, test their subsequent reactivity. However, it was seen that prior to attempts to form the vinyl derivatives, that types of compounds were also too water soluble, partitioning themselves in the aqueous phase. Such solubility issues led to the problematic accumulation of the crosslinkers between the polymer particles while coalescing during film formation, causing premature crosslinking reactions, i.e. the crosslinking at the interface which results in streaky films. All of these issues meant that the third-generation systems were still not the desired crosslinking solution.



Scheme 83. Third generation crosslinkers.

2.2 This work - the 4th generation crosslinking solution

In light of the results obtained by Dr Leu in the Whiting group prior to this project, it was clear that while the various generations of vinyl sulfone-based crosslinkers had some capabilities, there was a need for a major change in direction and the development of new chemistries that would keep molecular weights low, reduce side reactions from functional groups such as carbonyl functions, and provide the ability to tune solubility effects and hence, phase partitioning. In particular, the crosslinker should work better when co-polymerised in the backbone polymer chain in order to avoid accumulation of the crosslinkers in certain areas leading to heterogeneous films. Hence, the crosslinker would be best if asymmetric, i.e. more readily attached to the polymer while leaving the crosslinking group free to react. This new design present several synthetic challenges, since in order to achieve an environmentally clean synthesis, it was felt that it was necessary to avoid the use of reagents such as sulfides and epoxides. Moreover, in order to reach the level of reactivity required for crosslinking to take place, it would be necessary to maintain a doubly activated system. However, that also meant avoiding the sulfonyl-carbonyl groups of previous generation due to the issues described above, and therefore the idea of employing a di-sulfonyl system was considered as a potential solution, but this raised the question as to how to access unsymmetric systems that could be suitably incorporated into a polymer backbone. Through these considerations, the general design outlined in Figure 9, involving a spacer between a polymerisable group and the di-sulfonyl-activated vinyl crosslinking moiety was envisaged, since this should be able to be sufficiently flexible to vary the physical and chemical properties to meet those required for the final formulation.

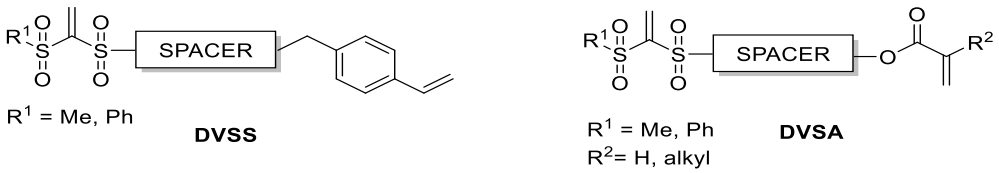


Figure 9. Ideal structures of fourth-generation crosslinker; di-vinylsulfonestyrene (DVSS) and di-vinylsulfoneacrylate (DVSA).

Therefore, for the formulation of the current research project, the development programme would consist of the study of new types of cross-linker molecules for VOC-free waterborne coatings using the design ideas outlined in Figure 9 above.

2.2.1 Specific aims and objectives

Using the objectives set for the design of the novel fourth generation cross-linker systems, an asymmetric structural design was required, i.e. through the use of a sulfonyl as a second EWG together with the introduction of a polymerisable functional group. This design plan led to the types of structures shown in Figure 10. In particular, the introduction of sulfonyl sulfonamides as the new doubly activated system allowed not only the ability to moderate reactivity compared to sulfonyl-cyano or sulfonyl-carbonyl, or even di-sulfonyl system, but most importantly, it also provided a new and facile entry into asymmetrical structures thanks to the amino group, and sulfonamides bonds are chemically stable which would be important for any subsequent coatings applications. The question, however, would be how to access such systems readily.

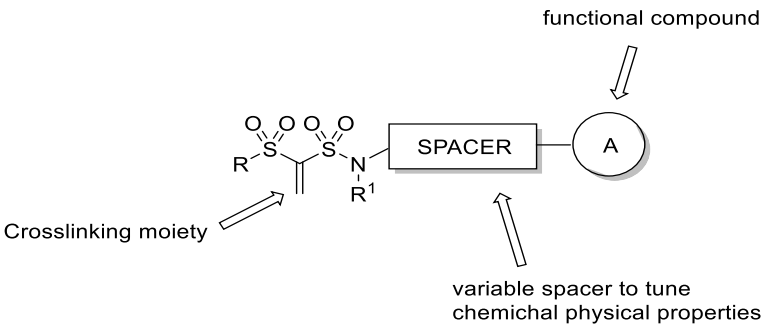
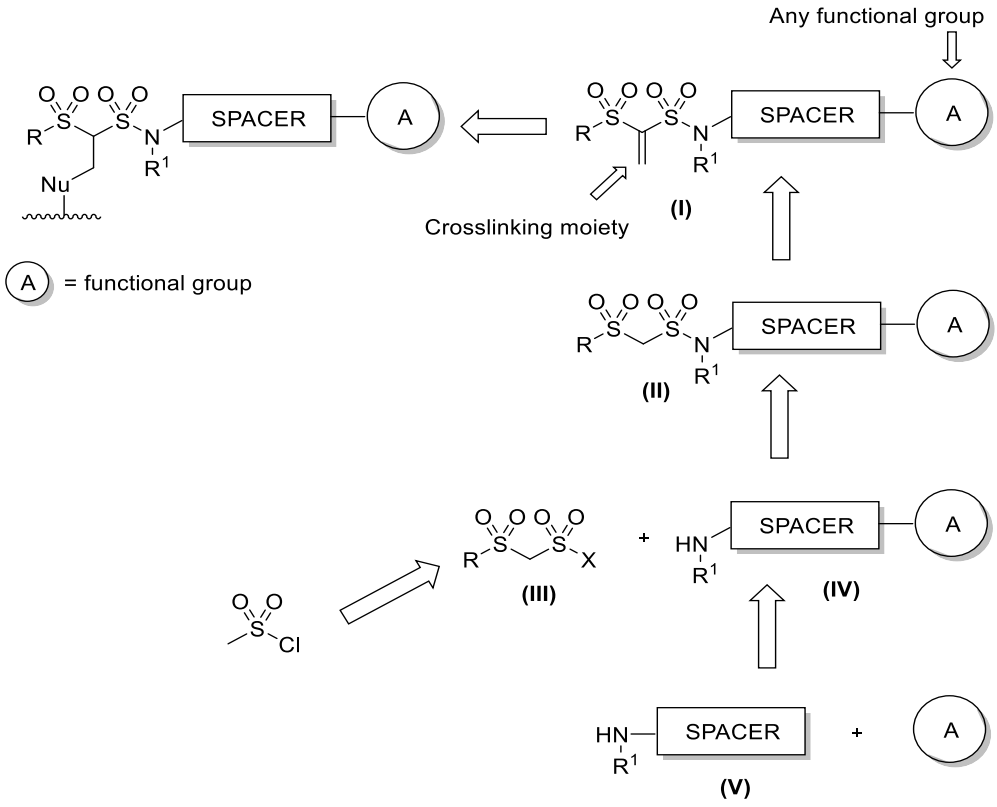


Figure 10. Key targets vinyl sulfonyl sulfonamides

The key point about this new strategy is that it would permit the attachment of most kinds of desired functional groups to the good Michael acceptor (vinyl sulfonyl sulfonamide function) through the synthetic flexibility of the formation of a sulfone-amino group. For the purpose of this project, our studies focused on the synthesis of particular polymerisable structures, suitable in use in emulsion polymerisation. However, it was also obvious that this type of functionality could be used in wider range of applications, and in fact, in different fields of chemical and even biochemical research (*vide infra*). Indeed, is

not surprising that there were numerous studies on the use of α-vinyl sulfones for bioconjugation[172], which will be discussed later.

Before considering the specific structures to synthesise, a general synthetic strategy to access the systems shown in Figure 10 is shown in Scheme 84. In our approach, the introduction of the unsaturated crosslinking moiety **(I)**, i.e. the vinyl sulfonyl sulfonamide group, would be ideally left until the last step, due to its potentially high reactivity. The main focus therefore would be on the formation of the sulfonyl sulfonamide system **(II),** constructed by reacting a *bis*-sulfone halide **(III)** and an amine **(IV)** enclosing a desirable spacer and functional group.



Scheme 84. Exemplified development process for the target molecule.

As explained in section 1.4.2, synthetic routes to access sulfonyl sulfonamides are very restricted and their chemistry largely unexplored. Therefore, the first synthetic problem to address was the synthesis of the sulfonyl sulfonamide system **(II)**, while avoiding any sulfide or thiol-based chemistry. The methods available at the time this project was started were relatively narrow, but direct access to **(III)** was thought possible through the use of

alkyl sulfonyl chlorides.[133, 134b, 173] These types of reagents are commercially available in some cases, especially methylsulfonyl chloride (mesyl chloride) which can be used to access methylsulfonyl-methylenesulfonyl chloride *in situ*, as explained in section 1.4.2.1, i.e. using the chemistry developed by Opitz *et al*.[133, 134b]. Such reactions involve the formation of a sulfene, which can 'dimerise' to a methylsulfonyl-methylenesulfene betaine derivative, through direct base-mediated elimination from the corresponding alkyl sulfonyl chloride. This intermediate can then be trapped by subsequent reaction with the appropriate amine **(IV)**.[133, 134b, 173-174]

The envisaged crosslinking process for the sulfonyl vinyl sulfonamide system is shown in Scheme 85. This involves the incorporation of the crosslinker into polymer chains used to make the coating formulation, hence, the first stage of the process would be the storage phase, where the latex coating would have been prepared but would be unreactive due to the presence of a large amount aqueous medium (*stage 1*). After application of the coating, the loss of water would drive the equilibrium towards the vinyl functionality (*stage 2*) since the beta-hydroxyl group relative to both the sulfonyl and sulfonamide groups would generate the vinyl-sulfone sulfonamide under either basic or acidic conditions. Film formation can then occur through crosslinking taking place via conjugate addition (*stage 3*) of complementary hydroxyl groups derived from the other polymer chains, made from either HEMA or HMPA-based monomers (Scheme 85).

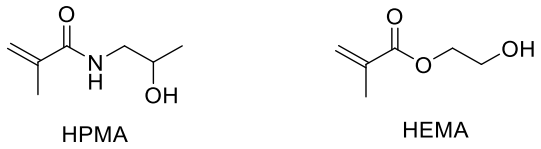
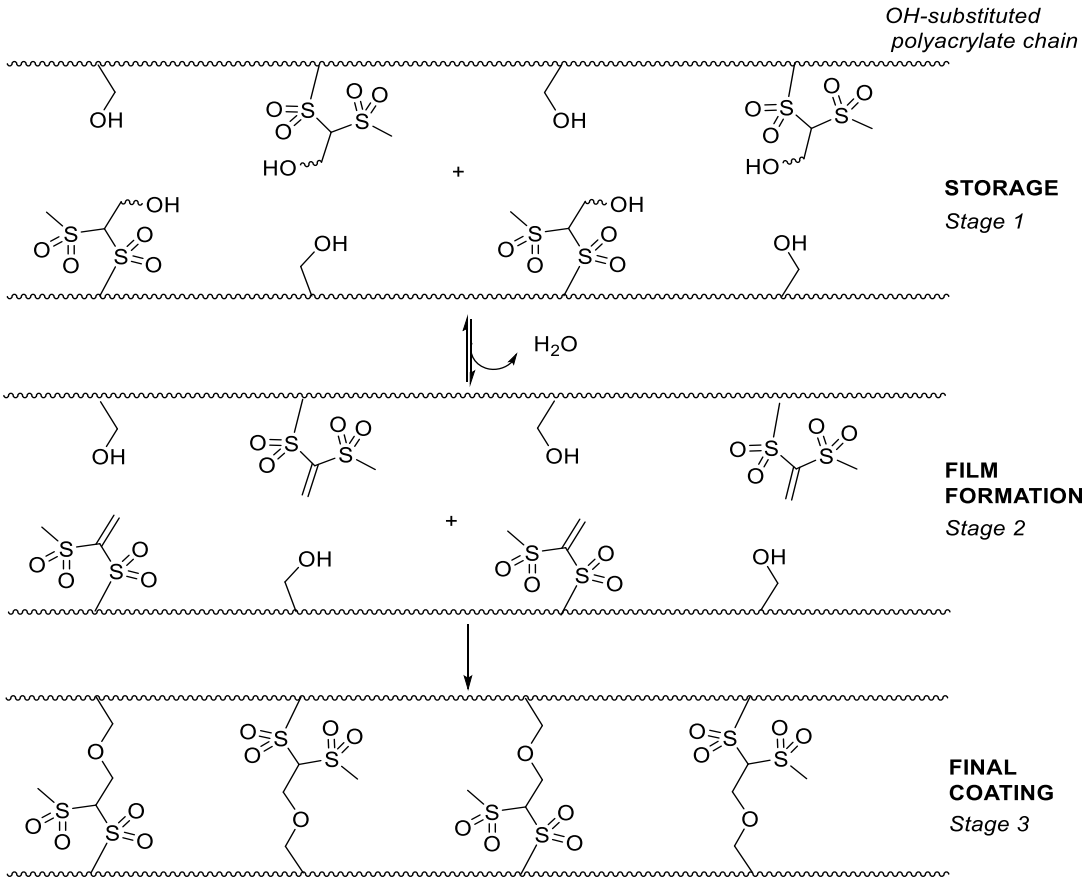


Figure 11. Examples of hydroxy functional monomers: *N*-(2-hydroxypropyl)methacrylamide (HPMA) and hydroxyethylmethacrylate (HEMA).



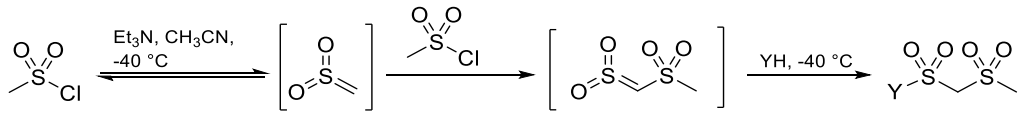
Scheme 85. Envisaged, or ideal crosslinking mechanism.

2.3 Methodology and development

2.3.1 Methylsulfonyl-methylenesulfonamide synthesis

2.3.1.1 Preliminary assessment of the Opitz' reaction

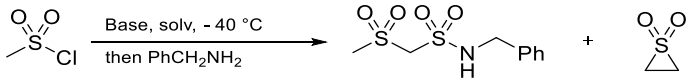
The first step of the proposed synthetic route was the synthesis of methylsulfonyl-methylenesulfonamide analogues. The main intention was to avoid the use of sulfides, which are known for their persistent and unpleasant smell, and therefore, the work reported by Opitz *et al.*[133-134, 173-174] in 1966 on the synthesis of methylsulfonyl-methylenesulfonyl derivatives, as explain in section 1.4.2, appeared to be an attractive alternative. Such reactions, also later reported by Goralski,[175] involve the formation of a sulfene dimer from an alkyl sulfonyl chloride via elimination of HCl in the presence of base, which can then react with an appropriate amine, as outlined in Scheme 86 (reaction mechanism will be discussed in section 2.3.1.6, page 89).



Scheme 86. Opitz *et al.* synthesis of sulfonylmethylsulfonyl derivatives.

For preliminary tests on this reaction, the use of mesyl chloride and benzylamine was employed as an example amine for trapping the sulfonyl sulfene intermediate formed *in situ* (see Table 2).

Table 2. Preliminary tests of Opitz method using benzylamine.



Entry	Base (equiv.)	Benzylamine (equiv.)	Temperature (°C)	Solvent	Ratio[a] 127a:128	Yield 127a (%)
1	Et_3N (1.5)	0.5	-40	MeCN	1:1	2[a]
2	Et_3N (1.5)	0.5	0	MeCN	0:1	-
3	Et_3N (1.5)	0.5	rt	MeCN	0:1	-
4	Et_3N (1.5)	0.5	-40	MeCN (dry)	5:1	27[a]
5	Et_3N (1.5)	0.5	-40	DCM (dry)	10:1	62[b]

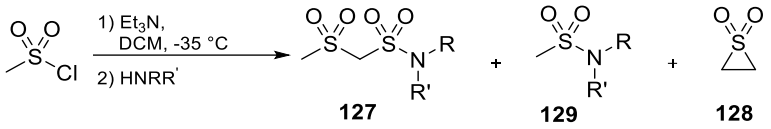
[a] Estimated by ^{1}H-NMR of the crude reaction product and after aqueous work up; [b] Isolated yield. Compounds **127a** and **128** where the only isolated products, probably due to removal of water soluble by-products during work-up.

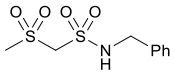
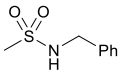
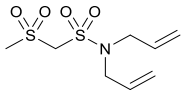
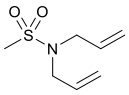
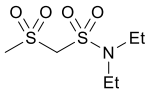
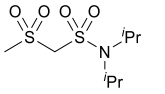
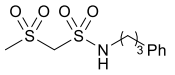
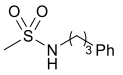
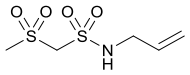
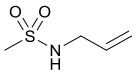
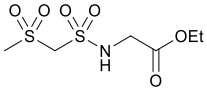
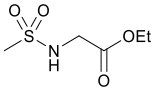
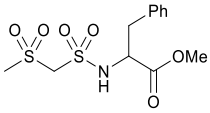
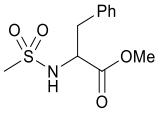
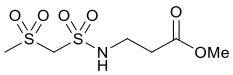
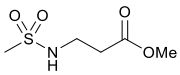
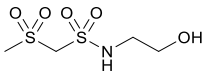
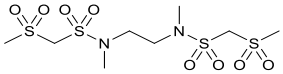
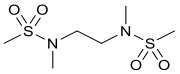
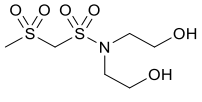
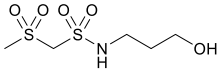
Opitz' original method[133, 134b] reported the use of acetonitrile in the presence of triethylamine, as the best conditions for these reactions. Our preliminary attempts at using these conditions did not give the desired results, as shown in Table 2 (Entry 1). However, it was observed that this result could be the consequence of a lack of information from the original procedures as reported.[133, 134b] In fact, it was found that the addition of mesyl chloride to base for the formation the sulfene, hence of the betaine intermediate, was highly exothermic, hence, its addition-rate needed to be both slowed and controlled. As well as examining addition of reagent rates, increasing of the temperature from -40 °C to 0 °C was also examined, but did not give improved results (see Table 2, Entry 2). Hence, more tests were conducted to both increase reaction temperature and examine the dryness of reagents and solvents. However, higher reaction temperature actually made it more difficult to control the exothermic reaction and, therefore, the addition-rate of sulfonyl chloride needed to be further reduced (Table 2, Entry 3). Interestingly, the increased temperature also revealed the unexpected formation of what was later understood to be the episulfone **128** as a by-product from the reaction. It was also observed that when the temperature was not carefully controlled between -35/-40°C, increasing amounts of the episulfone **128** were formed (see Entry 1 *vs* Entry 2 *vs* Entry 3, Table 2). Maintaining the temperature at -40 °C accompanied by careful addition of the mesyl chloride, allowed the formation of the methylsulfonylmethylenesulfonamide **127b** more efficiently, even though the yield was still not satisfactory (Table 2, Entry 4). Finally, changing the solvent from dry acetonitrile to DCM, being less polar, seemed to make the reaction work up and product isolated easier, with reduced tendency to form emulsions during work-up, with the net result shown in Table 2 (Entry 5) and providing a 62% yield after crystallisation of the *N*-benzyl methylenesulfonylsulfonamide **127a**. It was also found through testing different crystallisation solvents for the product **127a**, that this methylsulfonyl-sulfonamide was best isolated by direct crystallisation from ethanol; a solvent which subsequently proved to be a good solvent for the majority of the methylsulfonylmethylenesulfonamides made during this project.

Having carried out preliminary studies on the mesyl chloride-based sulfonyl-sulfene generation and benzylamine trapping reaction, the final reaction conditions (Table 2, Entry 5) were then employed in order to examine their application with a number of amines, as reported in Table 3. Hence, reaction of mesyl chloride with triethylamine in DCM afforded the desired sulfonyl sulfonamides **127** in yields varying from 10 to 90%. However, these initial conditions (Table 2, Entry 5 also reported in Table 3, Entry 1) formed, together with *N*-benzyl methylsulfonyl-methylenesulfonamide **127a**, a second compound later identified as the episulfone **128**, present in 10% conversion according to ^{1}H NMR.

When trapping the sulfonyl sulfene intermediate with other amines surprising results were obtained (see Entries 2-13, Table 3). Isolated together with the methylmethylene sulfonamide products **127** and episulfone **128** formation, was the simple methylsulfonamide product **36**. For example, in Entry 2 (Table 3), when using diallylamine, the methylsulfonyl methylenesulfonamide product **127b** was produced in good isolated yield (50%), together with low yields of both the diallylsulfonamide **129b** and episulfone **128**, (18 and 15% yields, respectively). Although in most cases the other amines used were similar, the formation of methylsulfonyl methylenesulfonamide was highly variable. In some cases (Entries 10-13) no methylsulfonyl methylenesulfonamide could be isolated, and small amounts of both sulfonamide **129** and episulfone **128** were the only other observable products. An exception can be observed in the case of *N,N'*-dimethyl-ethylenediamine (Entry 11, Table 3), which gave complete conversion of the mesyl chloride to episulfone **128**.

Table 3. Synthesis of sulfonyl methylene sulfonamide systems.



Entry	HNRR'	Sulfonyl methylene sulfonamide 127 (%)[b]	Sulfonamide 129 (%)[c]	Episulfone 128 (%)[c]
1	Benzylamine	 **a** (62)	 **a** (0)	10
2	Diallylamine	 **b** (50)	 **b** (18)	15
3	Diethylamine	 **c** (53)	 **c** (3)	5
4	Di-*iso*-propylamine	 **d** (50)	 **d** (0)	6
5	3-Phenylpropylamine	 **e** (47)	 **e** (4)	6
6	Allylamine	 **f** (42)	 **f** (0)	12
7	Ethyl glycinate HCl[a]	 **g** (10)	 **g** (0)	12
8	L-Phenylalanine methyl ester HCl[a]	 **h** (55)	 **h** (0)	0
9	Methyl 3-aminobutyrate HCl[a]	 **i** (90)	 **i** (0)	15
10	Ethanolamine	 **l** (0)	Complex NMR; none of the desired product	
11	*N,N'*-Dimethyl-ethylenediamine	 **m** (0)	 **m** (0)	100
12	Diethanolamine	 **n** (0)	Complex NMR; none of the desired product	
13	3-Amino-1-propanol	 **o** (0)	Complex NMR; none of the desired product	

[a]Additional 0.5 equiv. of Et_3N was added in order to neutralise the amine HCl salt; [bis]olated compound yield; [c]Yield calculated by ^{1}H-NMR based on the crude product after work up.

Therefore, due to the highly variable results and the propensity to form episulfone **128** (Table 3), it was necessary to examine this reaction in greater detail for a better understanding of the reaction mechanism. In addition, it was also preferable, perhaps necessary, to develop a chemical process for the synthesis of these methylsulfonyl methylenesulfonamide systems that avoided chlorinated solvents such as dichloromethane, in order to access a more sustainable and green chemical process that would be suitable for scale up in the longer term. To that end, a further range of solvents, bases and temperatures were examined.

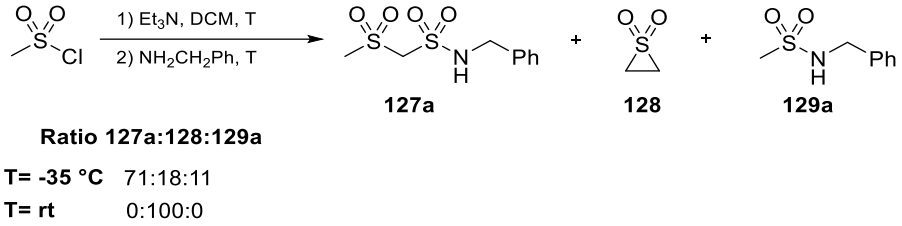
2.3.1.2 Optimizing reaction conditions

Having demonstrated in Table 3 that the base-induced 'dimerisation' of mesyl chloride is a practical and attractive strategy to access methylsulfonyl methylenesulfonamides **127** with, however, the inability to obtain reliably high yields in the case of all amines, forced a re-examination the entire reaction and the mechanism involved. To do this, different conditions were tested in order to establish the most suitable ones and to try and understand the surprisingly complex nature of the amine trapping reaction of the sulfonyl sulfene intermediate.

2.3.1.3 β-Elimination (formation of episulfones)

The results summarised in Table 3 clearly show that episulfone **128** and sulfonamides **129** were the only other isolated by-products seemingly forming from these reactions, in addition to the expected methylsulfonyl methylenesulfonamides **127**. Although the reason why the sulfonamides **129** might be formed seem to be easily explained, the formation of episulfone **128** did not seem so straightforward. In fact, the formation of the latter alone suggested a more complicated reaction mechanism and possible equilibria between different species that needed to be understood and controlled in order to achieve an efficient and general synthesis of the desired products **128**. This was exemplified by two reactions outlined in Scheme 87, whereby mesyl chloride was reacted with triethylamine, followed by benzylamine at -35 °C and RT. When the crude NMR alone examined, clear

formation of the episulfone **128** was observed as the only product formed at RT, compared with a 71:18:11 ratio of products **127a**:**128**:**129a**, at -35 °C in DCM (Scheme 87); a result that demonstrated the major impact that temperature alone can play upon the species in solution, and their trapping by the amine nucleophile.



Scheme 87. Synthesis of benzyl methylsulfonyl methylenesulfonamide **127a** at RT and at -35 °C.

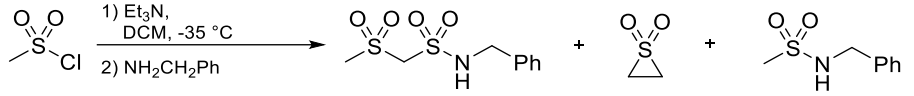
2.3.1.4 Examination of different solvents

To further optimise the synthesis of methylsulfonyl methylenesulfonamides **127**, make it more suitable for industrial purposes and finding alternatives to dichloromethane, other solvents were screened. Where possible, solvents used were dried as specified in Table 4, in order to avoid the potential formation of methanesulfonic acid and, all other variables were kept constant. Solvents were chosen in order to vary the polarity of the medium to understand the importance of this variable but still keeping in mind that green alternatives to DCM needed to be found if possible. Table 4 reports the different solvents employed, ordered with respect to their polarity.

From Table 4, it can be observed that an increasing yield of the wanted product **127a** (0% Entry 1 to 53% Entry 7, Table 4) was obtained when solvents with higher polarity were used. In fact, when using toluene (Entry 1, Table 4), no product was identified due to a very complex mixture of products observed in the ^{1}H NMR spectrum. It was interesting to note that when using MTBE (Entry 2, Table 4) or CPME (Entry 3, Table 4) no compound **127a** was formed, only the by-products **128** and **129** being obtained. Although it seemed that there was no correlation on how the two by-products' ratio dropped, their yields lowered to 0% when a polar aprotic solvent like MEK was used (Entry 7, Table 4). MEK is a widely used solvent in the field of coatings and, for this reason it was considered useful to examine here. In fact, surprisingly good yields were obtained using methyl ethyl ketone or acetone

(53% Entry 6 and 46% Entry 7, respectively, Table 4) compared to 62% in dry DCM, as obtained in Table 3.

Table 4. Methylene sulfonyl sulfonamide reaction scope and optimisation.



127a **128** **129a**

Entry	Base (equiv.)	Solvent[a] (concentration/M)	Temperature (°C)	Product 141a yield(s)[b] (%)	Ratio products 127a:128:129a[b]
1	Et_3N (1.5)	Toluene (1.3)	-35	Final mixture too complex	
2	Et_3N (1.5)	MTBE* (1.3)	-35	0	0:57:43
3	Et_3N (1.5)	CPME* (1.3)	-35	0	0:9:91
4	Et_3N (1.5)	EtOAc* (1.3)	-35	14	42:58:0
5	Et_3N (1.5)	2-MeTHF* (1.3)	-35	10	15:51:34
6	Et_3N (1.5)	Acetone* (1.3)	-35	46	79:4:17
7	Et_3N (1.5)	MEK* (1.3)	-35	53	100:0:0

[a]Reactions conducted under Ar using dry solvents unless otherwise specified (*). [b]Ratios were calculated by ^1H NMR (400 MHz) on the crude isolated product after workup.

Interestingly, when EtOAc (Entry 4, Table 4) or 2-MeTHF (Entry 5, Table 4) were used, high ratios of episulfone **128** where formed, lowering the overall yield of compound **127a**.

However, overall, these results seemed to be in contrast with results found when using acetonitrile *versus* DCM (Table 2), which suggested that the more polar solvent (MeCN) led to lower yields of compound **128**.

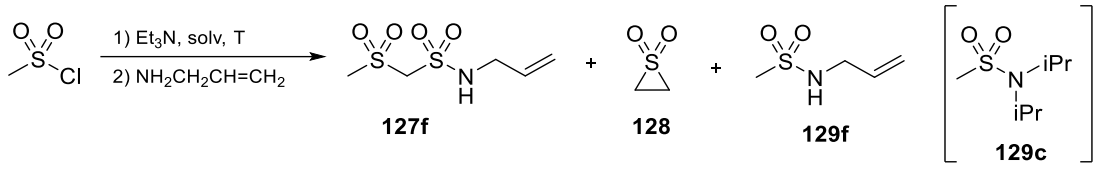
2.3.1.5 Examination of different temperatures and bases

In order to make the reaction more industrially appealing, it would be ideal to work at room temperature to reduce costs. Therefore, the reaction was tested at more suitable temperatures, i.e. -10 °C, 0 °C and room temperature. Moreover, for a deeper understanding of the variables that influences this reaction, also lower temperatures (-60 °C and -78 °C were tested. MEK was used in the test of different temperatures as it was found to be an optimal solvent in previous experiments. In these experiments allylamine was used instead of benzylamine (Table 5).

It was first noticed that, due to the exothermic feature of the reaction, it was challenging to keep the temperature constant, particularly when performed at room temperature. At

higher temperatures, the reaction mixture turned to a dark yellow suspension, which is probably due to the formation of compound **128**.

Table 5. Examination of different temperature and solvents.



Entry	Base (equiv.)	Solvent[a] (concentration/M)	Temperature (°C)	HNRR[1]	Product yield(s)[b] (%)	Ratio products 127f:128:129f[b]
1	Et_3N (1.5)	MEK (1.3)	-60	$NH_2CH_2CH=CH_2$	**127f** (0)	0:0:100
2	Et_3N (1.5)	MEK (1.3)	-10	$NH_2CH_2CH=CH_2$	Final mixture too complex	
3	Et_3N (1.5)	MEK (1.3)	0	$NH_2CH_2CH=CH_2$	**127f** (1)	20:79:1
4	Et_3N (1.5)	MEK (1.3)	rt	$NH_2CH_2CH=CH_2$	**127f** (5)	39:61:0
5	Et_3N (1.5)	Pet ether (1.3)*	rt	$NH_2CH_2CH=CH_2$	**127f** (0)	0:80:20
6	LDA (1.1)	THF (1.3)	-35	$NH_2CH_2CH=CH_2$	**129c** (86)	0:0:100 (**129c**)
7	LDA (1.1)	THF (1.3)	-78	$NH_2CH_2CH=CH_2$	**129c** (60)	0:0:100 (**129c**)

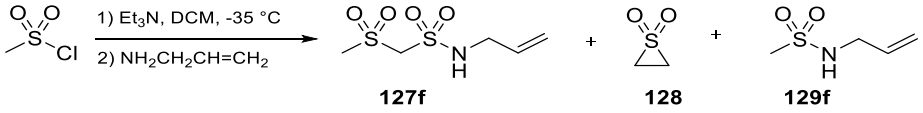
Reactions were conducted under argon and solvents were used dry unless otherwise specified. [a]Solvents were used dry unless specified (*). [b] When possible, ratios were calculated by ^{1}H NMR (400 MHz) after workup.

At lower temperatures (Table 5, Entry 1) only compound **129f** was obtained, with no formation of episulfone **128** or sulfonyl sulfonamide **127f** in MEK, i.e. at -60 °C. However, when the temperature was increase to -10 °C (Table 5, Entry 2) a complex ^{1}H NMR spectrum and TLC was obtained, indicating the formation of a number of products that were not easy to identify. When the reaction was conducted at either 0 °C or RT in MEK (Table 5, Entries 3 and 4) the episulfone **128** was the major product (79 and 61% respectively) with smaller amounts of **127f** (20 and 39% respectively). When the less polar petroleum ether was used under conditions otherwise similar to Entry 4 (Table 5), amount of **127f** reduced to 0% and the amount of episulfone **128** increased to be the predominant product (80%) and with the re-appearance of the simple sulfonamide **129f** (20%). Finally, two further experiments were carried out in THF using LDA as kinetic base at both -35 and -78 °C (Table 5, Entries 6 and 7, respectively), which both, interestingly produced solely the simple sulfonamide **129f**. Taken together with all the other results in Table 5, these reactions seemed to suggest that the kinetically preferred product in these types of reactions are the simple sulfonamides **129**, i.e. from generation of sulfene and immediate trapping by amine to derive the methylsulfonamide **129**. Under all other conditions, thermodynamic effects start to take effect, whereupon the fate of first sulfene

species is to dimerise and then under a range of reactions depending at least upon temperature and solvent, to derive methylsulfonyl-sulfene derived products, either by amine trapping (to access **127**) or an intramolecular cyclisation reaction to generate episulfone **128**. Clearly, a deeper understanding of the more complex equilibria leading to these products was required. Also, since the isolated yields of methylsulfonyl-methylenesulfonamide **127f** was still not optimised to a high enough level to be useful for generally efficiently accessing methylsulfonyl-methylenesulfonamides in general, further work was required.

With the results from Table 5 pointing at least to some clear trends with respect to kinetic control, and the effects of temperature and solvent to some extent, a more focussed examination of base effects were undertaken. The amount and type of base would be expected be also an important variable in these types of sulfene-mediated reactions, and hence, as investigated in Table 6, different bases especially were examined under the DCM conditions mainly.

Table 6. Examination of different bases.



Entry	Base (equiv.)	Solvent[a] (concentration/M)	Temperature (°C)	HNRR[1]	Product yield(s)[b] (%)	Products ratio 127f:128:129f[b]
1	Et_3N (0.5)	DCM (1.3)	-35	$NH_2CH_2CH=CH_2$	**127f** (14)	24:4:72
2	Et_3N (1)	DCM (1.3)	-35	$NH_2CH_2CH=CH_2$	**127f** (18)	37:7:56
3	Et_3N (1.5)	DCM (1.3)	-35	$NH_2CH_2CH=CH_2$	**127f** (53)	72:18:10
4	Et_3N (1), pyridine (0.5)	DCM (0.5)	-35	$NH_2CH_2CH=CH_2$	**127f** (36)	38:7:55
5	Et_3N (1.5), pyridine (0.5)	DCM (1.3)	-35	$NH_2CH_2CH=CH_2$	**127f** (54)	83:12:5
6	Pyridine (1.5)	DCM (1.3)	-35	$NH_2CH_2CH=CH_2$	**129f** (76)	0:0:100
7	Allylamine (1.5)	DCM (1.3)	-35	$NH_2CH_2CH=CH_2$	**129f** (92)	0:0:100
8	*i*Pr_2NEt (1.5)	DCM (1.3)	-35	$NH_2CH_2CH=CH_2$	**128** (41)	0:100:0
9	Et_3N (1.5)	DCM (0.5)	-35	$NH_2CH_2CH=CH_2$	**127f** (65)	91:8:1
10	Me_3N 13% wt.CH_3CN (1.5)	CH_3CN (0.04)	-35	$NH_2CH_2CH=CH_2$	**127f** (58)	100:0:0

[a]Reactions conducted under Ar using dry solvents unless otherwise specified (*). [b]Ratios were calculated by ^1H NMR (400 MHz) on the crude isolated product after workup. Standard amount of MsCl used is 1 equiv.

Looking closely at the results in Table 6, the lower quantities of Et_3N (0.5-1 equivalent, Entries 1 and 2, Table 6) in DCM led to the formation of **127f** in low yields, which reinforces once again the importance of lower temperature in this process. However, the main

products obtained under these conditions were the sulfonamides **129f** as shown in both cases. In fact, as the equivalents of base increased from 0.5 to 1.5 (Entries 1-3, Table 6) the amount of methylsulfonamide **129f** decreased, while the amount of methylsulfonyl-methylenesulfonamide **129f** and episulfone **128** increased., This led to us thinking further about the role of the base, especially in terms of either stability of the sulfene intermediate, or the sulfene dimer through the formation of zwitterionic species, which are then trapped by the amine nucleophile. We therefore decided to look more widely at different nucleophilicities and basicity of the amine, and their impact upon the reaction outcome. In fact, as observed in Table 6, there was a peculiar dependence on the type of base used. For example, in Entry 5 (Table 6), where sufficient pyridine was added that should be able to trap, or intercept, the methylsulfonyl-sulfene dimer intermediate after formation through use of Et_3N, there was indeed an increase in the efficiency of the amine trapping reaction, meaning an increased yield of **127f** over the previous 4 entries, and a concomitant reduction in **128** and **129f**. Moreover, the use of pyridine as a base (Entry 5) seems to have no impact in the formation of the *bis*-sulfone and, as the amount of triethylamine drops, the amount of sulfonyl sulfonamide drops as well (Entry 4 *versus* Entry 5). Using only pyridine showed (Entry 6, Table 6) that it was possible to obtain either 100% conversion to the methylsulfonamide, showing that pyridine acts as an excellent sulfonyl transfer agent, while preventing sulfene dimerisation, a result which was similar to using the trapping amine from the beginning, i.e. Entry 7 (Table 6) which also provided 100% of the diallyamine methyl sulfonamide. Perhaps the major breakthrough in our understanding came from a 100% conversion to episulfone **128** when *N,N*-di*iso*propylethylamine was employed as base (Entry 8, Table 6) which suggested to us that this more hindered amine was less likely to intercept the methylsulfonyl sulfene intermediate, but could be responsible for further deprotonation, and onwards reaction to give episulfone **128**. This was reinforced by the two further results in Table 6 involving Et_3N and Me_3N, Entries 9 and 10. While the more basic and hindered base *N,N*-di*iso*propylethylamine gave episulfone alone, moving to the intermediate hindered and basic amine Et_3N gave 91% methylsulfonyl sulfonamide **127f** (Entry 9, Table 6) while the less basic and more nucleophilic Me_3N gave this latter product as the sole species in 100% yield (Entry 10,

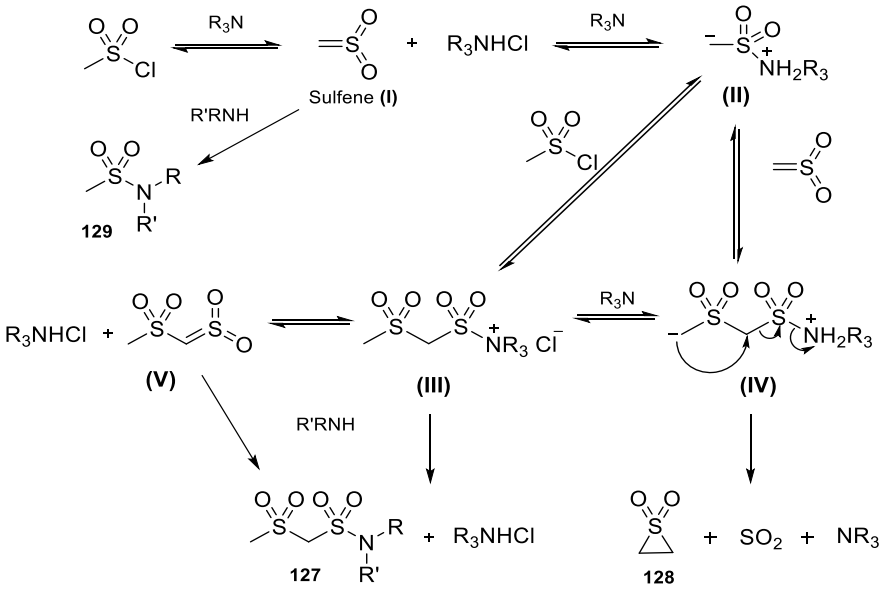
Table 6). This strongly suggested that the more nucleophilic bases lead to the formation of the methylsulfonyl-sulfene dimer species, presumably trapping/stabilising it through the formation of a zwitterion. It should also be noted that for this last reaction (Entry 10, Table 6) acetonitrile was used instead of dichloromethane and therefore different variables have been introduced at the same time. However, commercially available Me_3N is only available in limited types of solvents, of which the most common is ethanol. Solvents such ethanol could potentially act as trapping agents themselves, competing with the amine. Among the possible solvents in which Me_3N is available, acetonitrile seemed to be the best candidate. Unfortunately, the maximum solubility of Me_3N in acetonitrile is ca. 13 wt%, giving no control over the reaction concentration. However, comparing Entry 4 (Table 2) with Entry 10 (Table 6), an increase in yield of the methylsulfonyl sulfonamide **127f** was noted, from 27% to 58%, with no formation of either methylsulfonamide **129f** or episulfone **128**. This was probably partly achieved due to a lower concentration of the reaction, as observed to some extent in other reactions.

2.3.1.6 Reaction mechanism

With these experiments in hand, it was possible to generate a better, and more detailed, idea of the reaction mechanism and the variables that might influence it. Our mechanistic hypothesis, based partly upon that from Opitz,[133-134, 173-174] is shown in Scheme 88.

In the case of aliphatic sulfonyl chlorides, the α-CH proton is removed by the trialkylamine base and rapid chloride elimination follows, leading to sulfene **(I)** (if starting with mesyl chloride). The products obtained have been explained by Opitz[134b, 174] assuming that the sulfene **(I)**, stabilised as the corresponding betaine **(II)**, immediately adds to unreacted sulfonyl chloride by chloride substitution, to give the methylsulfonyl methylene ammonium chloride adduct **(III)**, in equilibrium with sulfonyl sulfene **(V).** The episulfone **128** is then either formed by 1,2-addition of the sulfene betaine adduct **(II)** to another molecule of sulfene **(I)** to form an α-sulfonylmethyl anion methylenesulfonyl trialkylammonium chloride species **(IV)**, and elimination of SO_2 through a Ramberg-Backlünd reaction giving the three-membered ring sulfone **128**, or by forming the same

intermediate **(IV)** *via* methylsulfonyl deprotonation of species **(III)** followed by the same cyclisation reaction. Compound **127** then, is formed by ammonium-sulfonyl substitution of betaine **(III)** or sulfonyl sulfone **(V)**, i.e. trapping by the addition of the secondary or primary amine to give the thermodynamically stable and neutral product methylsulfonyl methylenesulfonamide **127**.[134a, 174]



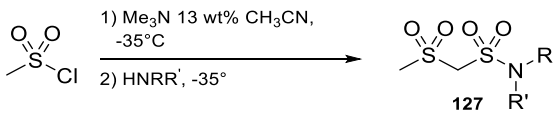
Scheme 88. Hypothesis of the reaction mechanism in the formation of methylsulfonyl methylenesulfonamides and other by-products.

Scheme 88 encapsulates the really quite complex equilibria operating in this finely balanced reaction process, and perhaps those most important parameters of solvent polarity, base and temperature are the most important. The latter, temperature, appears to be key especially, with low temperature (-35 °C), reactions occurring with highest chemoselectively mostly leading to adduct **127** meanwhile, the formation of episulfone **128** and sulfonamide **129** is observed more at temperatures, i.e. above -35 °C and especially associated with basicity *versus* nucleophilicity of the tertiary amine base in 'trapping' and stabilising key intermediates, such as **(II)** and then particularly **(III)**, with as trimethylamine being best at lower temperature, allowing time for **(III)** to build up and be trapped, by the incoming secondary or primary amine R'RNH.

2.3.1.7 Application to different amines

To confirm the reliability and general applicability of the most efficient methylsulfonyl methylenesulfonamide formation conditions (Table 6, Entry 10), a number of compounds from Table 3 were re-synthesised using the new conditions, named as Method B and reported in Table 7.

Table 7. Revisited procedure for the synthesis of sulfonyl sulfone amide (Method B).



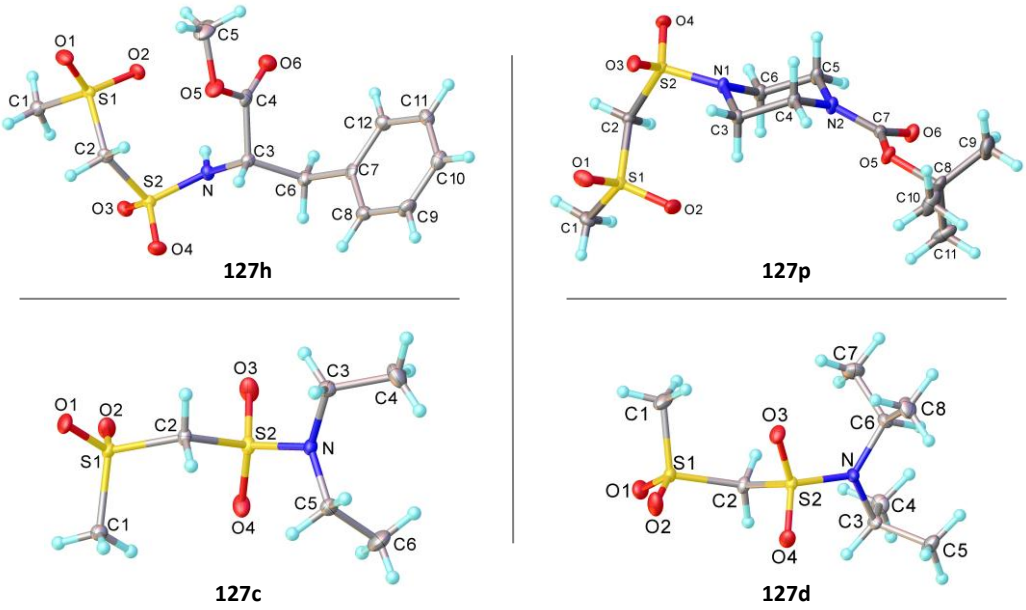
Entry	Amine	Product yield[a] (%)	Ratio products 127:128:129[c]	Product yield[a] (%) Method A
1	Ethyl glycinate HCl	**127g** (75)	100:0:0	10
2	*N,N'*-dimethyl ethylene diamine	**127m** (100)	100:0:0	No reaction
3	Amino ethoxy ethanol	Final mixture too complex with Method B and A		
4	*L*- Phenylalanine methyl ester HCl[a]	**127h** (85)	100:0:0	60
5	Diethyl amine	**127c** (90)	100:0:0	68
6	*N*-methyl allylamine	**127o** (89)	100:0:0	No comparison
7	*N*-Boc piperazine	**127p** (80)	100:0:0	No comparison

[a]Ratios were calculated by ^{1}H NMR (400 MHz) on the crude product after workup.

Examination of the results in Table 7 makes it clear that in most examined cases, the new Method B gave excellent product yields and most importantly, complete selectivity for the formation of the methylsulfonyl methylenesulfonamides **127**. The improvement over Method A (Table 3) saw yields in the range of 75 to 100%, compared to 10 to 68%, partly due to the fact that no further purification was generally needed when using Method B, with products being isolated directly through direct crystallisation from ethanol, with some products producing crystals suitable for single crystal structure analysis (see

Figure **12**), confirming the structures of **127h**, **127c**, **127d** and **127p**. In particular, a drastic difference was observed in the case of Entry 1 (Table 7), in which the yield of the final compound **127g** was noticeably higher (75% *versus* 10%), and also, in Entry 2 (Table 7), this compound **127m** could not be synthesised at all with the previous Method A approach. For further consolidation of the method, two extra amines were used (Entries 6 and 7, Table 7), involving *N*-methylallyamine and *N*-Boc-piperazine, respectively, which

efficiently give compounds **127o** and **127p** in good yields (80-89%). Interestingly, only when amino ethoxy ethanol was employed (Entry 3, Table 7) was a complex mixture of different compounds obtained, just as for Method A, and similarly not readily identified from the crude ^{1}H NMR spectrum. Importantly, however, in all cases examined (Table 7), no formation of either the sulfonamides **129** or episulfone **128** was observed.



Compound	Bond lengths S-N (Å)	Bond lengths C7-N (Å)	Bond angles SNC3 (°)
127h	1.606 (2)		124.51 (17)
127p	1.6145 (12)	1.3592 (18)	121.82 (10)
127c	1.6072 (10)	117.35 (8)	
127d	1.5995 (9)		116.80 (7)

Figure 12. X-ray structure of **127d**, **127h**, **127c** and **127p** (for crystallographic data see Appendix).

All crystal structures it can be noticed that a nitrogen-pyramidal N-methylsulfonyl amide is present showing nond angles in the range of 116-124° (

Figure **12**). Greater nitrogen pyramidalization is observed in the case of sulfonamide **127d**, with an N-S bond of 1.5995 Å. The S-N bond lengths result shorter (1.5995-1.6145 Å) when compared to sulfonamides average (ca. 1.66 Å) distance.[176] It is worth noting a delocalised nitrogen lone pair into the carbonyl pi-system which shortens the C-N bond length (1.359 Å).

With the optimised procedure, Method B, in hand, the possibility of synthesising novel bi-functional methylsulfonyl methylenesulfonamides of type **130** was investigated. The idea that such systems could be used to generate compounds of type **131** presenting a novel crosslinker with dual reaction centres rather than more traditional fashion, where the two reactive ends would connect the polymer chains was interesting. The dual vinyldisulfonyl systems would be capable of bridging across pre-formed polymer chains carrying nucleophilic functions and would therefore be used after polymerisation of the main coatings components to provide crosslinking under later stage drying.

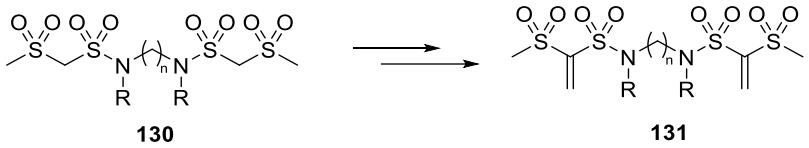
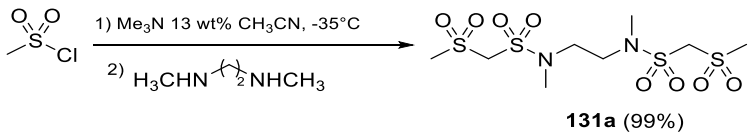


Figure 13. General structures for bifunctional electron deficient vinyl disulfonyl crosslinkers.

Readily available *N,N′*-dimethylethanediamine was employed as a trapping amine using Method B, for the synthesis of methylsulfonyl methylenesulfonamide **130a**, which was achieved by doubling the amount of base and mesyl chloride normally employed (Scheme 89). Compound **130a** was obtained in high selectivity and yield and in fact, the pure product simply precipitated directly as a highly insoluble compound in the polar solvent system; a common observation due to the presence of the *bis*-sulfonyl sulfone functionality.

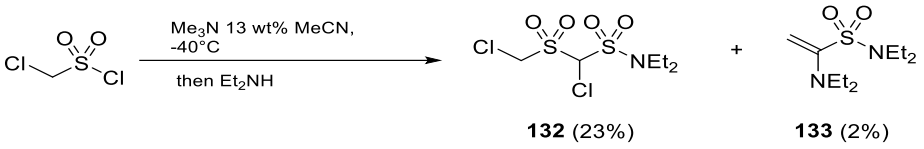


Scheme 89. Synthesis of compound **130a** employing Method B.

The realisation of the synthesis of these novel structures, typified by **130a**, opened up the opportunity to investigate other types of crosslinking systems, different to those initially proposed, in which the crosslinking function could also be attached to a group that could be incorporated into the polymer chain of a coating system by co-polymerisation. Section 2.3.2.5 discusses the further investigation on this topic and the synthesis of novel the systems **131** is presented.

2.3.1.8 Use of other sulfonyl chlorides

The successful optimisation of mesyl chloride as a reagent to form methylsulfonyl methylenesulfonamides through the formation of sulfene intermediates was based upon research by Opitz and co-workers.[133, 134b, 173-174] However, only limited literature reports was found on other types of sulfonyl chlorides being used.[177] Besides scientific curiosity, it was also useful to be able to obtain a sulfonyl sulfonamide analogues in which the α-carbon could provide easy access to further modifications. For example, if chloromethanesulfonyl chloride was used under the same conditions used to form methylsulfonyl-methylenesulfoinamide, it might be possible to isolate a chlorinated analogue, i.e. **132**. Hence, this reaction was investigated (Method B) as outlined in Scheme 90, quenching with diethylamine. Although the reaction resulted in a mass recovery of only 37%, three compounds were shown to have formed according to TLC, of which only two could be isolated by silica gel chromatography (Scheme 90).



Scheme 90. Use of chloromethanesulfonyl chloride in place of mesyl chloride in Method B.

The expected chloromethyl compound **132** was isolated as the major product in 23% yield along with 2% of a proposed compound **133**. Although the mechanism involved in the formation of **132** should not greatly differ from the one previously (Scheme 88) for mesyl chloride, the fact that the main product was indeed **132** did reinforce the mechanism proposed and opens up the feasibility of using this reaction for different sulfonyl chlorides.

2.3.1.9 Sulfonyl sulfonamide monomers

In order to access stable emulsion polymer systems capable of crosslinking, the crosslinker would ideally have a high solubility in organic compounds and a low solubility in water. The reason for this is to be found in the process of emulsion polymerisation, where all the monomers are first mixed and then pumped into the reactor over a period of time, at a certain flow rate, contemporary to other reagents. As explained in section 2.1.3, the

monomers continuously diffuse through water from the monomer droplet to the micelle, where polymerisation occur. This is a very delicate process in which all variables need to be highly controlled in order to obtain a stable final emulsion.

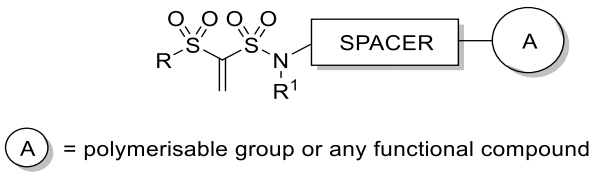


Figure 14. General structure of the proposed crosslinker.

The general structure of the proposed crosslinker shown in Figure 14 presents a polar vinyl *bis*-sulfonyl moiety on one end, and a polymerisable functional group (e.g. styrene or methyl methacrylate) on the other end. The physical and chemical properties of the proposed crosslinker (Figure 14) should be capable of tuning through varying the spacer between the methylsulfonyl-methylenesulfonamide function and the polymerisable group. Hence, the properties of the spacer would be used to control the properties of the crosslinker, and therefore used to alter the properties of the final coating, e.g. crosslinkers should be kept short in order to have "rigid" films. In addition, it was crucial that the final crosslinker (general structure Figure 14) could solubilise the rest of the monomers employed in the polymer formation formulation system, including monomers such as methyl methacrylate and butylacrylate, commonly used in emulsion polymerisation in the field of coating technology. Again, the molecular design in Figure 15 uses the tuneable capabilities of the spacer unit to deliver solubility property changes in the overall crosslinker design.

As shown in Figure 15, the initial aim was to target different spacers to understand how these types of compounds would behave in terms of physical and chemical properties, and therefore be of use under emulsion polymerisation conditions. Hence, a range of different monomers were suggested with the aim of probing these properties, including simple alkyl and short PEG spacers, as well as a piperazine spacer to understand the prospects of achieving the desired chemical-physical (especially solubility) properties of the crosslinkable monomer. For the polymerisable functional group A (Figure 15), styrene and

methyl methacrylate moieties were chosen to be inserted and tested as polymerisable groups.

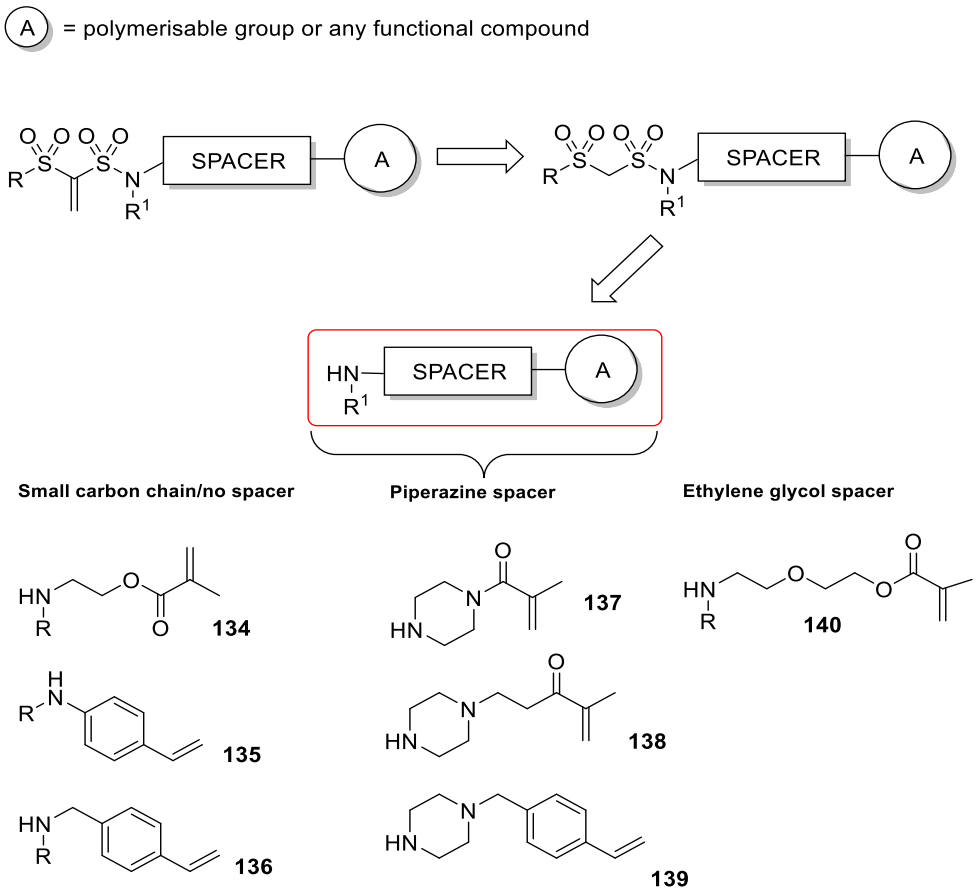
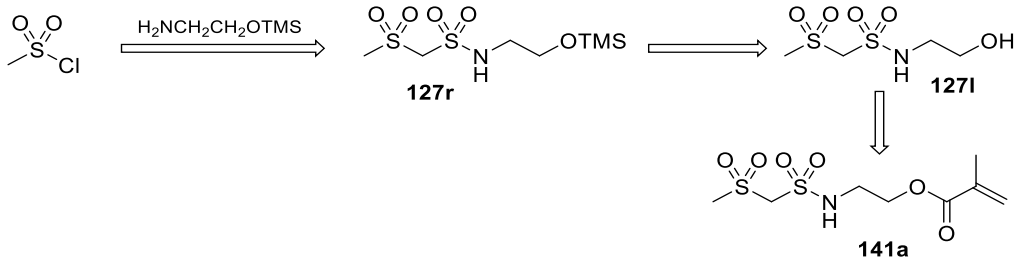


Figure 15. Illustration of target spacers with polymerisable groups.

2.3.1.10 Small carbon chain spacer

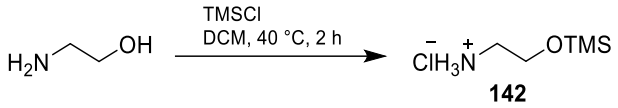
Methyl methacrylates 134

A first synthetic strategy to compound **141** is shown in Scheme 91. The plan was to use protected ethanolamine to access methylsulfonyl-methylenesulfonamide **127r**, followed by unmasking of the hydroxyl group. Compound **127l** would then be reacted with methacryloyl chloride to yield the final product **141a**.



Scheme 91. Synthetic strategy to **141a**.

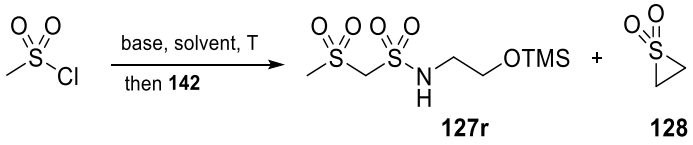
Therefore, to ensure chemoselective reaction on the nitrogen atom of ethanolamine, silylation of the starting ethanolamine was achieved in good yield following the methodologyof Dvořák *et al.*[178]



Scheme 92. Protection of the hydroxyl group of ethanolamine.

The protected ethanolamine analogue **142** was used for the synthesis of methylsulfonyl-methylenesulfonamide **127r** (Scheme 92), using both conditions outlined in Methods A and B (*vide supra*) in the presence of sufficient excess base to neutralise the ammonium salt of the amine.

Table 8. Synthesis of methylsulfonyl-methylenesulfonamide **127r.**



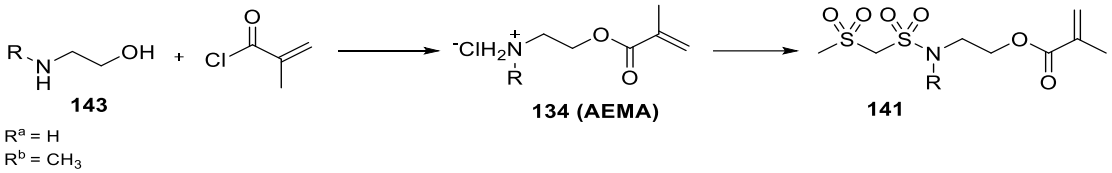
Entry	Base (equiv.)	Solvent (concentration/M)	Temperature (°C)	Amine (equiv.)	Product (%)
1	Me_3N (1.5)	CH_3CN (0.5)	-35	**142** (0.5) + Me_3N (0.5)[b]	**127r** (5)
2	Me_3N (1.5)	CH_3CN (0.5)	-40	**142** (0.5) + Me_3N (0.5)[a]	**127r** (3)
3	Me_3N (1.5)	CH_3CN (0.5)	-40	**142** (1) + Me_3N (1)[a]	**127r** (3)
4	Et_3N (1.5)	DCM (0.5)	-35	**142** (0.5)	**128** (82)
5	Et_3N (1.5)	DCM (0.5)	-35	**142** (0.5) + Et_3N (0.5)[a]	**128** (60)

[a]A solution of the amine (0.5 M) in DCM + triethylamine was prepared before the addition. [b]Base added to the reaction mixture before adding the amine.

From the results in Table 8, it was clear that the use of Method B, using acetonitrile and trimethylamine, even with increasing amounts used, gave poor yields of the desired product **127r**, ranging in the 3-5% range (Entries 1-3, Table 8). In all these cases, **127r** was the main obtained product although in poor yields, containing minor traces of by-

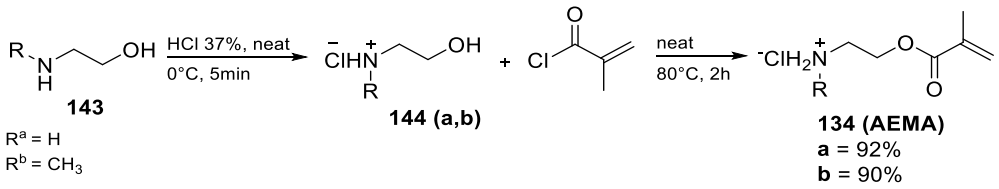
products among which episulfone was detected. Changing the reaction conditions to Method A and using different amounts of triethylamine gave the episulfone **128** in 60-82% (Entries 4 and 5, Table 8).

The lack of an efficient entry to **127r** (Table 8) meant that a new synthetic route to compound **127q** was required. It was envisaged that this could employ 2-aminoethyl methacrylate hydrochloride **134**, which could be prepared from methacryloyl chloride with 2-aminoethanol hydrochloride.[179] Hence, as outlined in Scheme 93, AEMA **134** (amino ethyl methacrylate hydrochloride) could be employed to synthesise the 2-aminoethyl methacrylate *bis*-sulfone **141**, as explained in paragraph 2.3.1.9, preferably carried out using Method B, since this led to higher yields due to a reduced formation of the episulfone by-product (Scheme 93).



Scheme 93. Synthetic strategy to access compound **141**.

Therefore, ethanolamine **143a** was first added to concentrated HCl in order to form the ammonium salt, and in this way, methacryloyl chloride could react selectively with the hydroxyl group to give compound **134a**, which occurred smoothly in 92% yield (Scheme 94).



Scheme 94. Synthesis of compounds **134a** and **b**.

Similarly, the use of the *N*-methyl ethanolamine with HCl, followed by methacryloyl chloride gave compound **134b**, in 90% yield (Scheme 94).

Styrene analogues 135 and 136

Compound **135** (R = H, 4-vinylaniline, Figure 16) is commercially available and, therefore, no synthesis was required. This could be directly employed in the synthesis of sulfonyl sulfonamide as the reactive group for polymerisation, as well as the amine function required for the synthesis of methylsulfonyl-methylenesulfonamide are present as outlined in Figure 15.

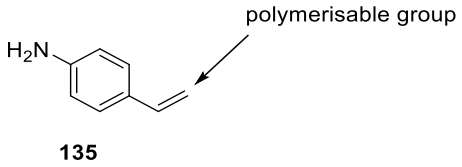
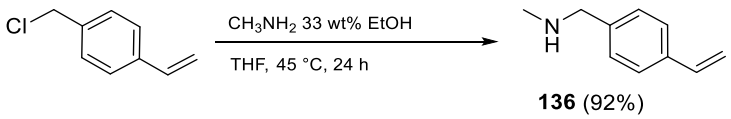


Figure 16. 4-Vinylaniline.

The synthesis of the *N*-methyl analogue, **136**, was achieved from 4-vinylbenzyl chloride (Scheme 95).[180] Hence, compound **136** was easily prepared in good yield by reacting of 4-vinylbenzyl chloride with methylamine (33 wt% in ethanol) to give the secondary amine in 92% yield.



Scheme 95. Synthesis of amine **136** from chloromethylstyrene.

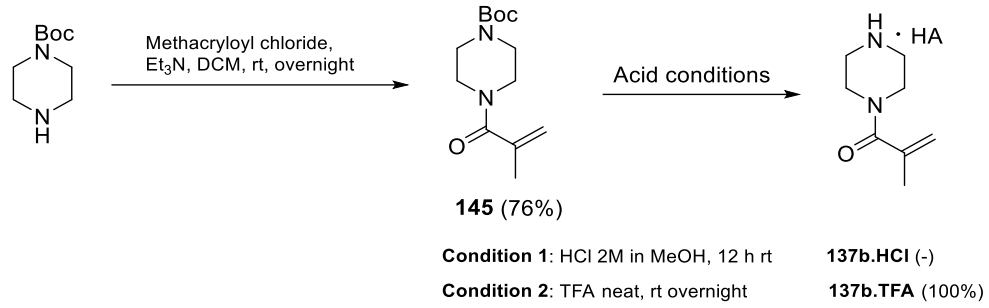
Both compounds **136** and **135** were used later in the formation of methylsulfonyl-methylenesulfonamides (see paragraph 2.3.1.9).

2.3.1.11 Piperazine spacer

Piperazine was also introduced as a spacer between the methylsulfonyl-methylenesulfonamide moiety and the polymerisable functional group (A), as outlined in Figure 15. Both methyl methacrylate and styrene polymerisable functions were used, partly to probe solubility effects on the resulting crosslinkers.

Methyl Methacrylate 137

The first synthesised monomer carrying a piperazine spacer was compound **137** (Scheme 96). In this synthesis, *N*-Boc-piperazine was reacted with methacryloyl chloride in the presence of triethylethylamine, following Kovalenko's procedure,[181] to give compound **145** in 76% yield (Scheme 96).



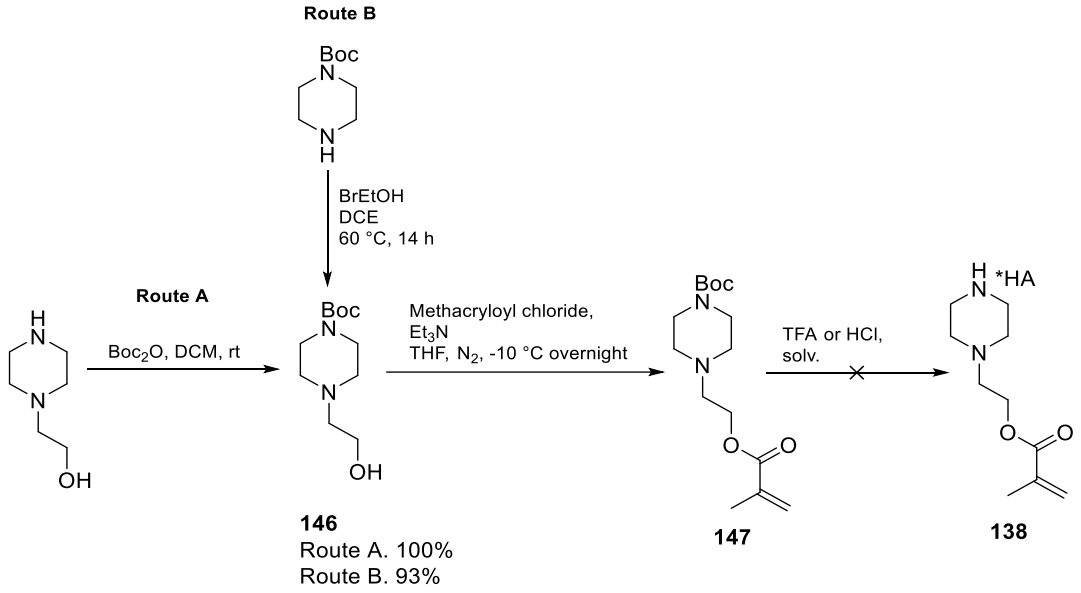
Scheme 96. Synthesis of compound **145** followed by *N*-Boc deprotection to access salt **137b**.

Although *N*-Boc deprotection of **145** was not observed with 2M HCl in MeOH, quantitative deprotection was accomplished when TFA was used (Scheme 96), providing the TFA salt, **137b** which was both stored and used in its salt form.

Methyl methacrylate 138

In order to balance the non-polarity given by the sulfonyl sulfone final target and give more flexibility to the final monomer, two carbons were introduced between the piperazine and the methyl methacrylate to obtain **138** (Scheme 97). The synthetic route to compound **138** started from either from *N*-Boc piperazine (route B) or from *N*-(2-hydroxyethyl) piperazine (route A), both giving **146** in good yields (93-100%). This latter compound was reacted with methacryloyl chloride under an inert atmosphere in the presence of triethylamine to give **147** when using the conditions as reported by P. G. Parzuchowski and co-workes.[182] As confirmed by the literature, this last compound proved unstable even when stored at fridge temperatures. For this reason, it was not possible to measure and calculate the yield before decomposition, as this would happen during solvent removal.

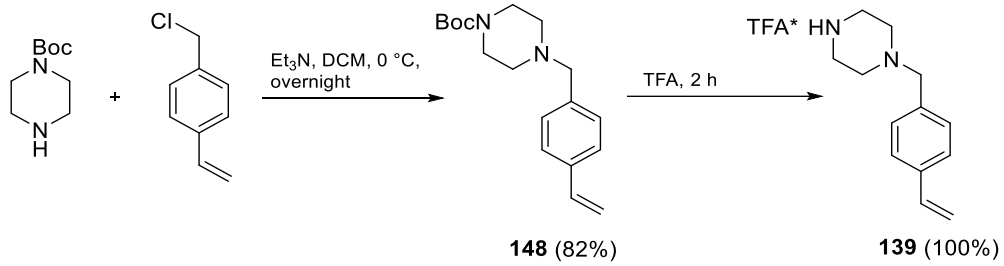
The synthesis of the target **138** was abandoned due to the instability of the precursor which would not in any way meet the requirements of shelf-life needed for the crosslinker.



Scheme 97. Proposed synthetic route to **138**.

Styrene 139

For the synthesis of compound **139**, *N*-Boc-piperazine was reacted with 4-vinylbenzyl chloride in order to give **148** in good yield (82%). Once again, deprotection of the amine was achieved by using TFA to give **139** in 100% yield (Scheme 98).



Scheme 98. Synthesis of styrene **139**.

2.3.1.12 Ethylene glycol spacer

PEG Methyl Methacrylate 140

The final spacer introduced into the general polymerisable crosslinker system (Figure 17) was an ethylene glycol system, which was inserted in order to tune the solubility of the vinyl sulfonyl sulfonamide monomer. The general structure of the target amine therefore required was **140**, as shown in Figure 17.

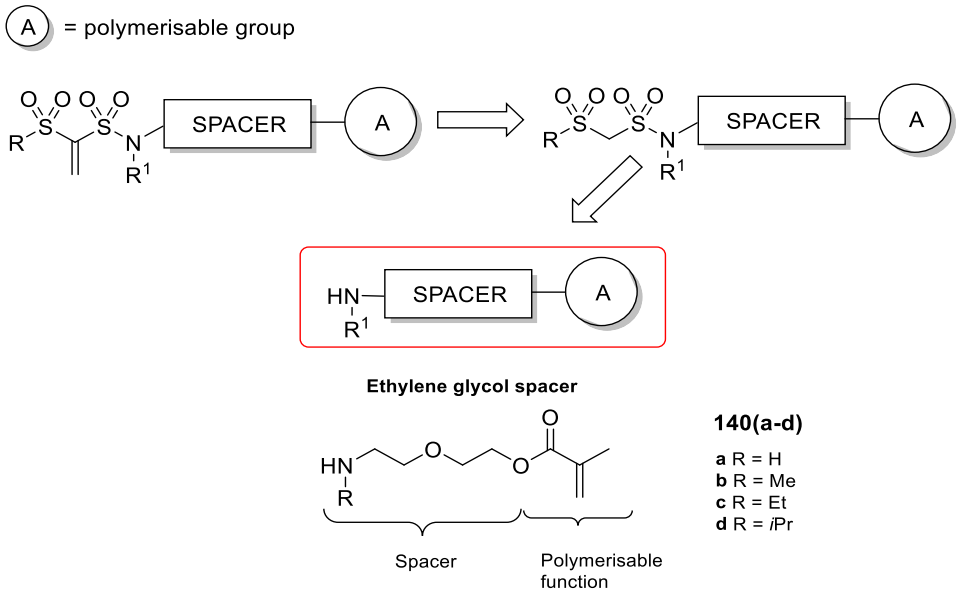
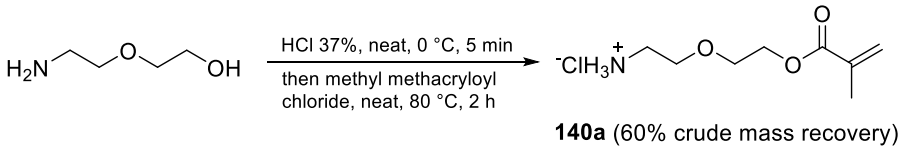


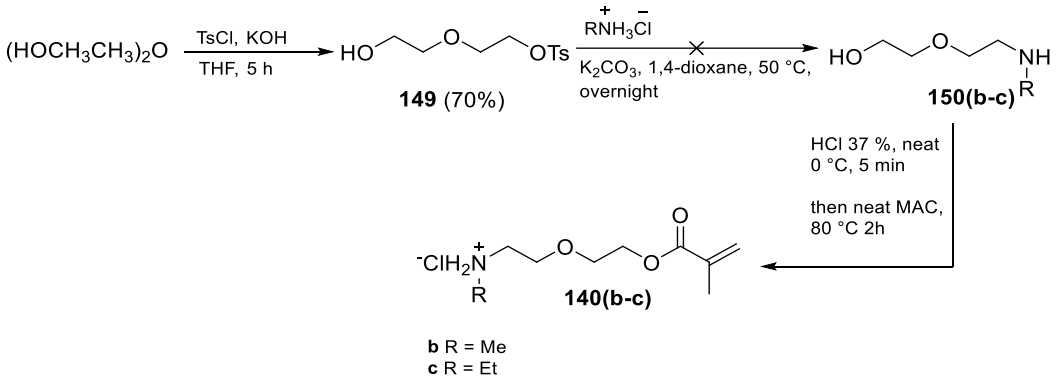
Figure 17. General structure of PEG methyl methacrylate amine **140**.

The synthesis of primary amine salt **140a** was straightforward. Diethyleneglycol amine was first added to concentrated HCl, followed by reaction with methacryloyl chloride to afford ester **140a** (Scheme 99) in 60% crude mass recovery. Although, compound **140a** was synthesised, there were challenges in the purification due to its polarity which meant that it was used crude for the synthesis of the corresponding methylsulfonyl methylenesulfonamide.



Scheme 99. Synthesis of compound **140a**.

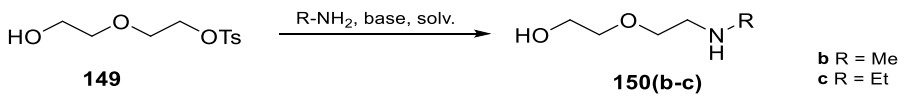
The synthesis of further secondary amine analogues of type **140** (Figure 17), proved more challenging (Scheme 100). A first approach applied tosylation of diethylene glycol giving the monotosylate **149** in 70% yield, with the aim of submitting it to attempted nucleophilic substitution with various primary amine to give compounds of form **150.** Subsequently, **150** would have been reacted with methacryloyl chloride, to give the final compounds **140** (Scheme 100).



Scheme 100. Proposed synthetic route to compound **140**.

Having efficiently prepared monotosylate **149**, nucleophilic substitution with different amines was examined under the conditions reported by Jiang and co-workers[183] (Table 9).

Table 9. Nucleophilic substitutions of tosylate **149**.

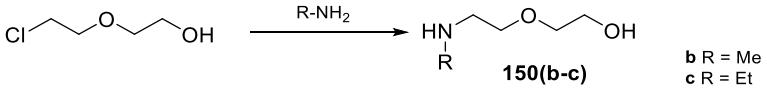


Entry	Base (eq)	Solvent	RNH_2 (equiv.)	T (°C)	Result
1	K_2CO_3 (5)	1,4-Dioxane	$CH_3N^+H_3$-Cl- (10)	50	×
2	K_2CO_3 (1.5)	1,4-Dioxane	$EtN^+H_3Cl^-$ (1.5)	70	×
3	K_2CO_3 (5)	THF	$CH_3N^+H_3Cl^-$ (10)	50	×
4	K_2CO_3 (5)	THF	CH_3NH_2 33 wt% MeOH (10)	50	✓(5% yield)

As shown in Table 9, potassium carbonate was used in the presence of either ethylamine or methylamine as their salts in either 1,4-dioxane or THF at different temperatures (Entries 1-3, Table 9) which unfortunately gave no reaction, and the substrate was fully recovered in all cases. However, moving to using a methanolic solution of methylamine (Entry 4, Table 9) did give reaction but unfortunately, none of the usual purification techniques (silica gel chromatography, acid-base extractions, Kügelrohr distillation etc.) were able to clean the final product from excess potassium carbonate in a suitably efficient

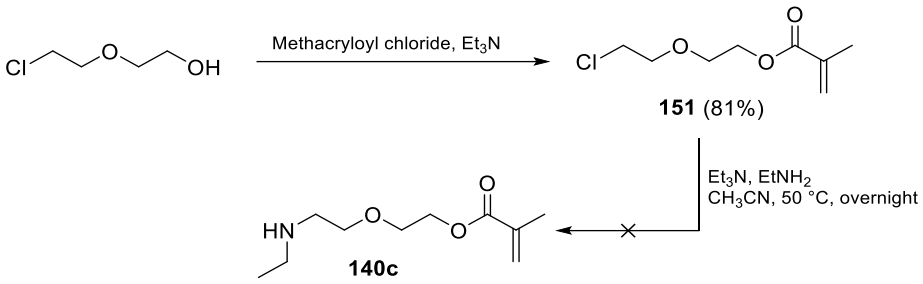
manner. Although it was possible to isolate a 5% yield of amine **150b** by Kügelrohr distillation, the difficulties of separation and purification suggested that the product forms a derivative such as a carbamate, and therefore, an alternative preparative procedure was required. Therefore, the synthetic strategy was modified in order to achieve access to amines **163** (Table 10) through using 2-(2-chloroethoxy)ethanol as a substrate and generating the iodide *in situ*.

Table 10. Attemped synthesis of **150** via S_N2 reaction.



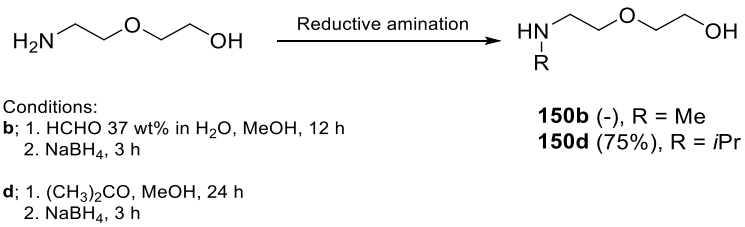
Entry	Nucleophile	Base	Solvent	Temp. (°C)	Result
1	$MeNH_2$ 40 wt% in H_2O (10 equiv.)	KI 10 mol%	CH_3CN	Reflux, overnight	No reaction
2	$MeNH_2$ 40 wt% in H_2O (10 equiv.)	KI 10 mol%	MeOH	Reflux, overnight	No reaction
3	$MeNH_2$ 40 wt% in H_2O (10 equiv.)	NaI 10 mol%	Acetone	rt (8 h)	No reaction
4	$EtN^+H_3Cl^-$ (3 equiv)	TBAI 10 mol%, Et_3N (3 equiv.)	CH_3CN	rt overnight	No reaction

Table 10 shows that despite the different conditions used to convert 2-(2-chloroethoxy)ethanol to amines **150**, no reaction took place (Entries 1-4, Table 10) in the presence of either methylamine or ethylamine as nucleophile. This was despite a range of reaction conditions being tested including reflux in different solvents (acetonitrile or methanol) and under Finkelstein conditions using different iodide sources to covert the chloride to the more reactive iodide. Therefore, at this point it was decided to first react 2-(2-chloroethoxy)ethanol with methacryloyl chloride, in the presence of triethylamine, which gave compound **151** (81%), followed by reaction with ethylamine (generated *in situ*) (Scheme 101). However, despite the functionalised hydroxyl group of **151**, the chloride again failed to react with ethylamine with only starting material being isolated (Scheme 101).



Scheme 101. Alternative synthetic route to compound **140a**.

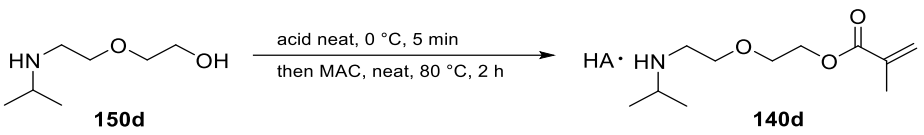
Due to the failure of the previous attempted syntheses of **150** and **140**, a reductive amination approach was adopted as outlined in Scheme 102. Starting with commercially available aminoethoxyethanol, alkylation was attempted to give compounds **150b-d**. The reductive amination was tested employing formaldehyde 37 wt% in H_2O (condition b, Scheme 106) to give **150b** but, unfortunately, yielding to a complicated mixture of compounds. In a second attempt using acetone (conditions d, Scheme 102) to give **150d**, this was obtained in good yield (75%).



Scheme 102. Reductive amination for the synthesis of doubly alkylated aminoethoxyethanol.

Having finally isolated **150d**, it was used for the synthesis of compound **150d** (Table 11) employing the method previously reported in Scheme 94. The use of 37% HCl for the salt formation of **150d** led to the synthesis of **150d** containing unidentified impurities (Entry 1, Table 11). Unfortunately, it was not possible to purify product **150d** using silica gel chromatography, although it was possible to recover 52% of the crude product but in unsatisfactory purity.

Table 11. Synthesis of ethylene glycol spacer **150d**.



150d **140d**

Entry	Acid	Solvent	Temp. (°C)	Time (h)	Yield[a] (%)
1	HCl conc. (1 equiv.)	Neat	80	2	ca. 100
2	TFA (1 equiv)	Neat	80	2	ca. 100
3	AcOCl + EtOH	CH_3CN	80	3	complex NMR

[a]The final products were not purified, yields are referred to the crude compound.

In a second attempt at synthesising **140d** (Entry 2, Table 11) TFA was used instead of HCl. This was done in order to limit the water that could be retained more easily by the hydrophilic **150d**, therefore, hydrolysing methacryloyl chloride to the corresponding acid. The use of TFA led to a cleaner product **140d**, which contained a minor quantity of the corresponding unacylated HCl salt **150d**, presumably formed during the reaction of methyl acryloyl chloride (MAC) and **150d**. Lastly, HCl was generated *in situ* (Entry 3, Table 11) from the reaction of AcOCl with EtOH in order to limit the presence of water. Although the reaction went to completion and **140d** was obtained (Entry 3, Table 11), higher amounts of impurities were produced in comparison to Entry 1, which in both cases, could not be easily removed. This highlighted the main problems with this synthetic route, that being that reaction **150d** was not easily monitored (baseline by TLC and either C18 silica was needed or NMR monitoring); the starting material **150d** was hygroscopic which was problematic for the next step reaction with methacryloyl chloride (readily hydrolysed); and purification of the product **140d** was not possible using silica gel chromatography. Therefore, **140d** was used in the next reaction without any purification.

2.3.1.13 Methylsulfonyl-methylenesulfonamide monomers

With the synthesis of different amine monomers tackled in the previous section, the use of these seven compounds for the synthesis of methylsulfonyl-methylenesulfonamide monomers (Figure 18) could then be investigated.

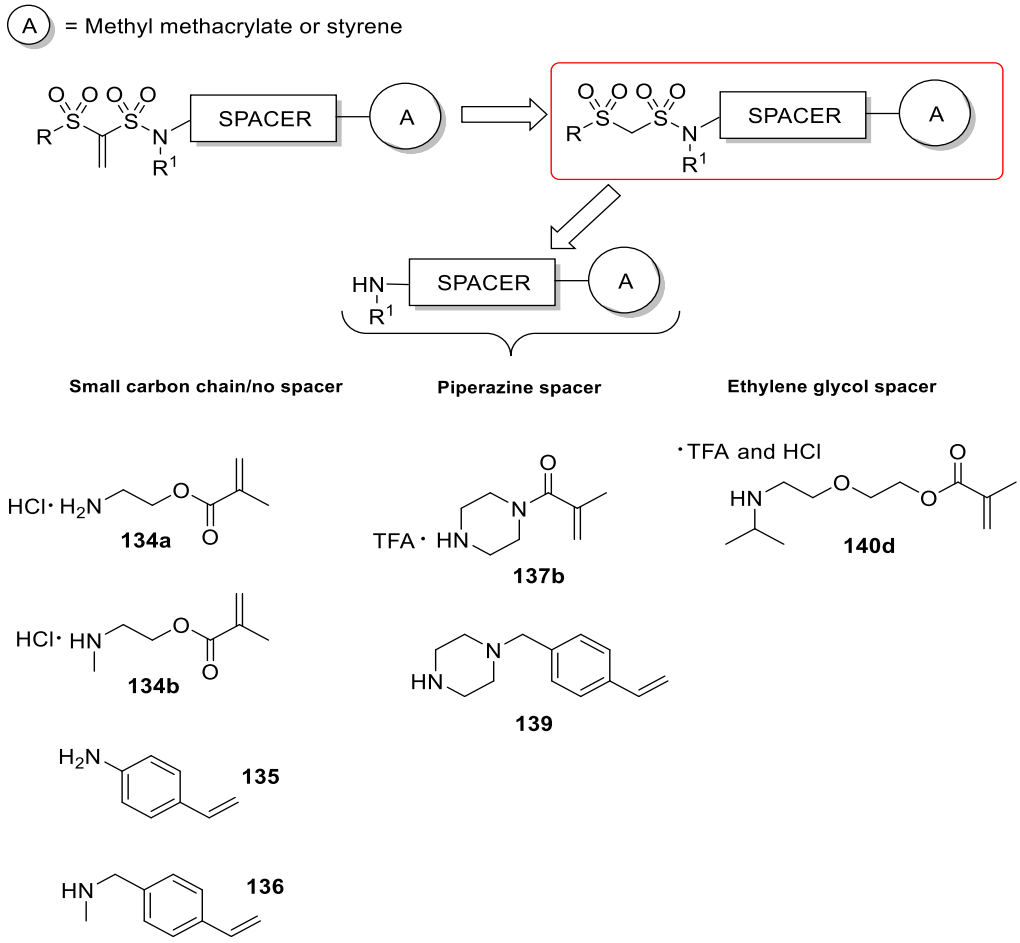
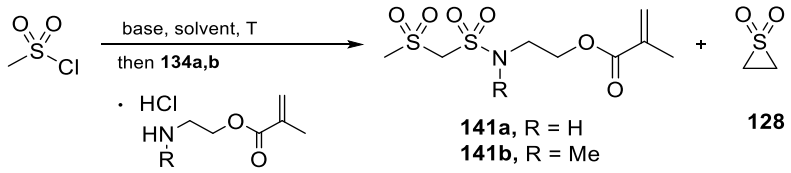


Figure 18. Amines to be used in the synthesis of methylsulfonyl-methylenesulfonamide monomers.

Initially, compounds **134a** and **b** were used as trapping agents for the formation of methylsulfonyl methylenesulfonamides **141a** and **b**. Both Methods A and B (triethylamine *vs*. trimethylamine) were examined, as shown in Table 12.

Table 12. Synthesis of methylsulfonyl-methylenesulfonamide **141(a,b)** using previously prepared **134a** or **134b**.

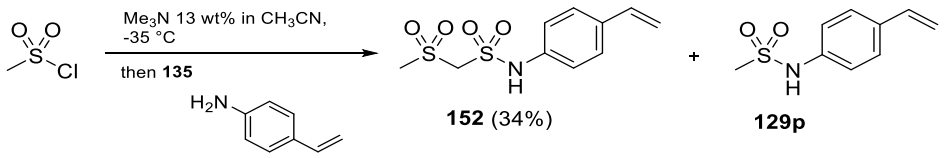


Entry	Base	Solvent	Temp. (°C)	Amine	Product (%)
1	Me_3N 13% in CH_3CN (1.5 equiv.)	CH_3CN (0.3M)	-40	**134a** (0.5 equiv.) + Me_3N (0.5 equiv.)[a]	**141a** (90)
2	Me_3N 13% in CH_3CN (1.5 equiv.)	CH_3CN (0.3M)	-40	**134b** (0.5 equiv.) + Me_3N (0.5 equiv.)[a]	**141b** (86)[b]
3	Et_3N (1.5 equiv.)	DCM (0.3M)	-40	**134a** (0.5 equiv.) + Et_3N (0.5 equiv.)[a]	**141a** (74)[c] **128** (26)[c]

[a] Base added to the reaction mixture before adding the amine; [b]Yield on 30 g scale; [c]Percentages calculated by ^{1}H-NMR.

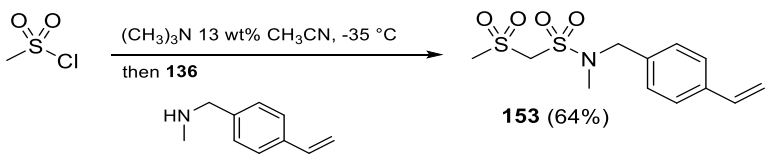
From Table 12, the use of trimethylamine in acetonitrile (Method B, Entries 1 and 2) validated the optimised methods, since compounds **141a** and **b** were isolated in good yields (90 and 86%, respectively) and no purification was required. These results contrasted with Method B (DCM/triethylamine, Entry 3, Table 12) applied to **134a** which although it gave 74%, 90% had been obtained using Me_3N (Entry 1, Table 12), and the episulfone **128** was also produced, meaning that purification was needed. Overall, Method B using Me_3N in CH_3CN remained the best option for the synthesis of the methylsulfonyl methylenesulfonamides.

Next, the synthesis of compound **152** was examined using commercially available 4-vinylaniline (Scheme 103) but unfortunately, this led to a 1:1 mixture of sulfonamide **129p** and methylsulfonyl-methylenesulfonamide **152** (Scheme 103), from which a 34% yield of the required **152** was obtained by crystallisation from EtOH.



Scheme 103. Synthesis of methylsulfonyl-methylenesulfonamide styrene crosslinker analogue.

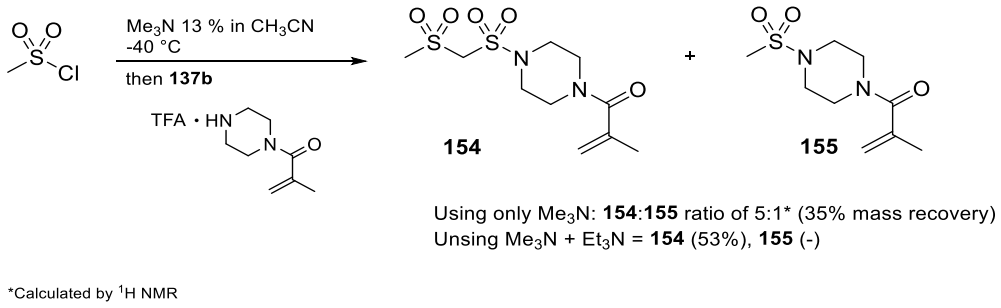
The poor reactivity of the aniline function of **135** meant that the corresponding benzylamine analogue **136** was used instead, for the formation of the methylsulfonyl methylenesulfonamide **153**, which occurred smoothly and with no contamination of the methylsulfonamide by-product. Hence, **153** was obtained in 64% yield using the optimised Method B procedure (Scheme 104).



Scheme 104. Synthesis of compound **153**.

Next, the synthesis of methylsulfonyl-methylenesulfonamide **154** was examined following the standard procedure (Method B). This was initially found to be problematic, due, once again, to the formation of sulfonamide **155**, however, it was found to be caused by the

decreasing concentration of the volatile Me_3N-acetonitrile solution, which over time and storage became unpredictable. Due to the difficulty of easily establishing the real concentration of the trimethylamine-acetonitrile a theoretical excess (at least 3 equivalents) was employed to make sure that there were at least 1.5 equivalents available. Despite this, initial trials resulted in 35% mass recovery of which ca. 83% was the desired methylsulfonyl methylene sulfonamide **154** and ca. 17% was sulfonamide **155** according to NMR calculations (see Scheme 105). This was easily solved, however, by the addition of triethylamine to the reaction mixture prior to addition of **137b**. This gave the chance to form the methylsulfonyl methylenesulfone adduct **154** without the formation of the episulfone **128** or sulfonamide **155** whilst maintaining the equilibria (discussed in Scheme 88) towards the sulfonyl sulfene intermediate, until trapped by **137b**. The final procedure gave 53% yield of **154** (X-ray structure shown in Figure 19) which isolated in a highly pure state directly and was used without further purification.



Scheme 105. Synthesis of compound **154**.

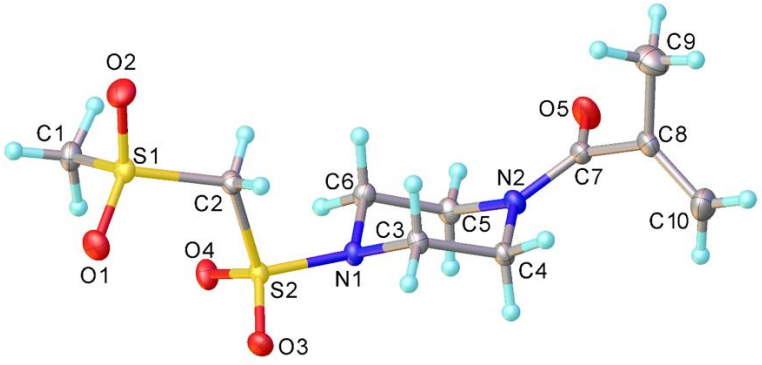


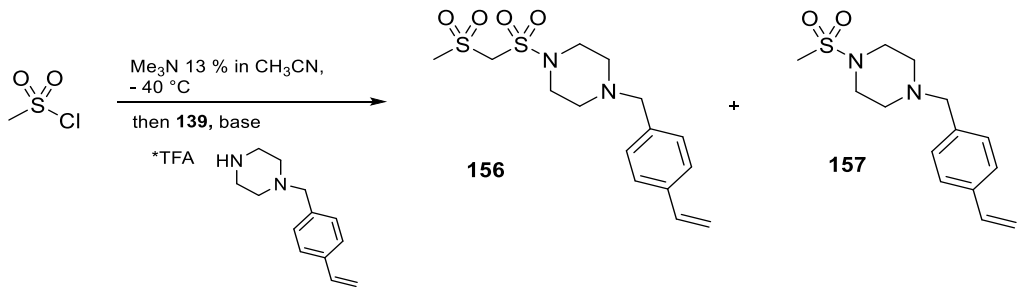
Figure 19. X-ray structure of compound **154** (crystallographic data can be found at page 286).

Interestingly, the crystal structure of sulfonamide-carboxamide **154** is worthy of comment with respect to the two types of amide and their different geometries. Figure 19 shows the

expected pyramidalized geometry about the sulfonamide nitrogen N1 with a bond angle C3N1S2 of 117°, with the nitrogen lone pair being pseudo-axial confirmed by the the S-N bond length found to of 1.629 Å, which is in line with the average (~1.66 Å) distance of sulfonamides reported using X-ray crystal data.[176] On the other hand, the carboxamide nitrogen N2 is characterised by a wider angle 126° (C7N2C4) denoting a more planar system and the nitrogen lone pair is delocalized into the carbonyl pi-system confirmed by the shorter C-N bond length (1.349 Å).

In parallel, the same problem relating to the concentration of the trimethyalamine-acetonitrile solution used was also encountered in the synthesis of the styrene analogue **156** as shown in Table 13.

Table 13. Synthesis of methylsulfonyl-methylenesulfonamide **156** using previously prepared **139**.



Entry	Base	Temp. (°C)	Solvent neutralisation amine	Base neutralisation amine	Product (%)
1	Me_3N 13% in CH_3CN (3 equiv.)	-40	CH_3CN	Me_3N 13% CH_3CN (0.5 equiv.)	**157** (85)
2	Me_3N 13% in CH_3CN (3 equiv.)	-40	CH_3CN	Me_3N 13% CH_3CN (1 equiv.)	**156** (39)[a] **157** (13)[a]
3	Me_3N 13% in CH_3CN (3 equiv.)	-40	THF	Et_3N (1 equiv.)	**156** (79)

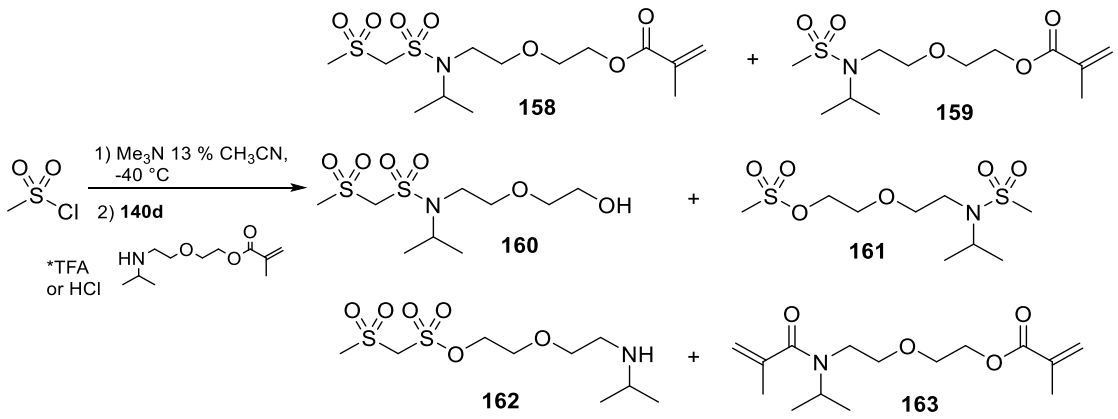
[a] Percentage calculated by ^{1}H-NMR.

A few attempts were needed to prepare **156** since either only the sulfonamide **157** (Entry 1, Table 13) or a mixture of the sulfonamide **157** and the desired methylsulfonyl-methylenesulfonamide **156** was obtained (Entry 2, Table 13). Compound **156** was finally achieved efficiently in an optimised procedure which gave 79% yield, with no presence of the sulfonamide **157**. This was achieved by using a total of 4 equivalents of triethylamine; 3 equivalents for the reaction with a further 1 equivalent used to release the free amine of the starting salt **139** (Entry 3, Table 13). This confirmed that an excess of base (whether a

genuine excess or not due to the vagueries of the trimethylamime concentration!) was needed to avoid simple sulfonamide formation.

Finally, the synthesis of compound **158** was explored which required amine **140d** (section 2.3.1.9-ethylene glycol space) as trapping agent for the mesyl chloride dimersation reaction. As mentioned in section 2.3.1.9, with respect to the synthesis of amine **140d.TFA** and **140d.HCl**, the final product was not purified, and several different unidentified and inseparable by-products were therefore present. Crude **140d.TFA** or crude **140d.HCl** were then used directly for the synthesis of methylsulfonyl-methylenesulfonamide **158** (Table 14). Hence, as expected, this reaction led to the formation of numerous different sulfonamides and sulfonyl sulfonamides, **158**-**162** (Table 14).

Table 14. Attempted formation of methylsulfonyl methylenensulfonamide **158** from amine **140d**.



Entry	Base	Amine	Base neutralisation amine	Product(s) (%)
1	Me_3N 13% in CH_3CN (1.5 equiv.)	**140d.TFA**	Me_3N 13% CH_3CN (0.5 equiv.)	No product
2	Me_3N 13% in CH_3CN (2 equiv.)	**140d.TFA**	Me_3N 13% CH_3CN (0.7 equiv.)	**160** (1%); **158** (5%); **163** (1%)
3	Me_3N 13% in CH_3CN (2 equiv.)	**140d.TFA**	Me_3N 13% CH_3CN (1 equiv.)	complex mixture
4	Me_3N 13% in CH_3CN (2 equiv.)	**140d.TFA**	Et_3N (0.5 equiv.)	complex mixture
5	Me_3N 13% in CH_3CN (3 equiv.)	**140d.TFA**	Et_3N (0.6 equiv.)	crude yield 28%; **158**:**159** (4:1)
6	Me_3N 13% in CH_3CN (1.5 equiv.)	**140d.HCl**	Me_3N 13% CH_3CN (1 equiv.)	**158** (34%); **159** (3%); **162** (10%)
7	Me_3N 13% in CH_3CN (3 equiv.)	**140d.HCl**	Me_3N 13% CH_3CN (2 equiv.)	**158** (28%); **160** (4%); **161** (1%)
8	Me_3N 13% in CH_3CN (3.5 equiv.)	**140d.HCl**	Me_3N 13% CH_3CN (1 equiv.)	complex mixture
9	Me_3N 13% in CH_3CN (3 equiv.)	**140d.HCl**	Et_3N (0.5 equiv.)	**158** (20%)
10	Me_3N 13% in CH_3CN (3 equiv.)	**140d.HCl**	Et_3N (0.6 equiv.)	**158** (22%)
11	Me_3N 13% in CH_3CN (3 equiv.)	**140d.HCl**	Et_3N (1 equiv.)	**158** (36%)

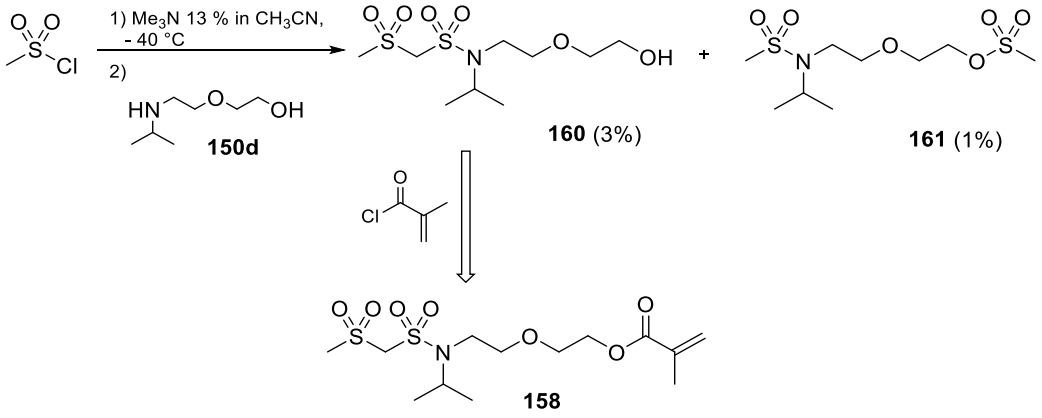
Compounds **158** to **163** were obtained in different percentages depending on whether the corresponding HCl or TFA salt were used and the addition rate of these. In particular, when only 0.5 equivalents of trimethylamine were used to free **140d.TFA** amine (Entry 1, Table

14) no compound could be seen in the NMR spectrum after a basic work up and only methyl methacryloyl chloride could be reisolated. With increasing amounts of trimethylamine being used in the formation of sulfonylsulfonamide, a complex mixture was obtained (Entry 3, Table 14) with a crude mass recovery of 43%. Separation of different sulfonylsulfonamide could be achieved for Entry 2 (Table 14). In fact, in the presence of initial 2 equivalents of trimethylamine for the formation of the sulfene adduct, and the secondary addition of 0.7 equivalents of trimethylamine prior addition of **140d.TFA**, led only to 43% mass recovery of the crude reaction mixture. Upon purification of the crude by silica gel chromatography, 5% of **158,** 1% **160** and 1% of **163** could be achieved. Moreover, when extra triethylaminewas used instead of trimethylamine to free the amine salt **140d.TFA**, the final mixture result was also too complex, and 6 compounds showed up on TLC with a 44% mass recovery of the crude mixture (Entry 4, Table 14). Increasing the amount of base (both trimethylamine and triethylamine) only 28% crude yield could be obtained, in which no purification was attempted but calculation from the ^{1}H NMR suggested the presence of **158**:**159** (4:1), indicating extra base was needed (Entry 5, Table 14). However, switching the trapping amine from a TFA salt (Entry 1-5) to a HCl salt (Entry 6-11), slight improvements could be obtained. In fact, although in Entry 6 to 11 the overall yield of compound **158** remained low (in the range of 20 to 36% yield) when compared to Entry 1-5, an improvement can be highlighted. Initially, isolation by silica gel chromatography of the different by-products was attempt in Entry 6 and 7 (Table 14) yielding 3% of **159** and 10% **162** in the case of Entry 6; and 4% of **160** and 1% **161** in the case of Entry 7. In later reactions, only the target compound **158** was isolated due to the numerous by-products obtained in each reaction. Replacing Me_3N with Et_3N in the quenching of the amine salt gave more reliable results, probably due to the unknown real concentration of the trimethylamine solution in acetonitrile, whereas, rising the amounts of base used, from 0.5 equivalent (Entry 9, Table 14) to 1 equivalent of Et_3N (Entry 11, Table 14) permitted to increase the yield of compound **158** from 20 to 36% (Entry 9 *versus* Entry 11). However, in all purifications **158** was obtained together with a second compound, thought to be **160,** due to almost overlapping spot in the TLC plate.

Therefore, due to difficulties in isolating **158**, a repeat reaction was carried out as outlined in Scheme 106, using the mixture of products and seeing if the residual alcohol **160** could be acylated with extra methacryloyl chloride in the presence of a base (Et_3N) and DMAP as acyl-transfer catalyst (under dry conditions). Unfortunately, according to both TLC and ^1H NMR, this approach failed.

Scheme 106. Reacting by-product **160** of crude mixture from reaction Table 14.

Therefore, it was decided to examine reordering of the sequence of reactions as shown in Scheme 107. Hence, the intention was to react amino alcohol **150d** with mesyl chloride first to obtain **160**, which could then react with methacryloyl chloride to obtain **158** (Scheme 107).

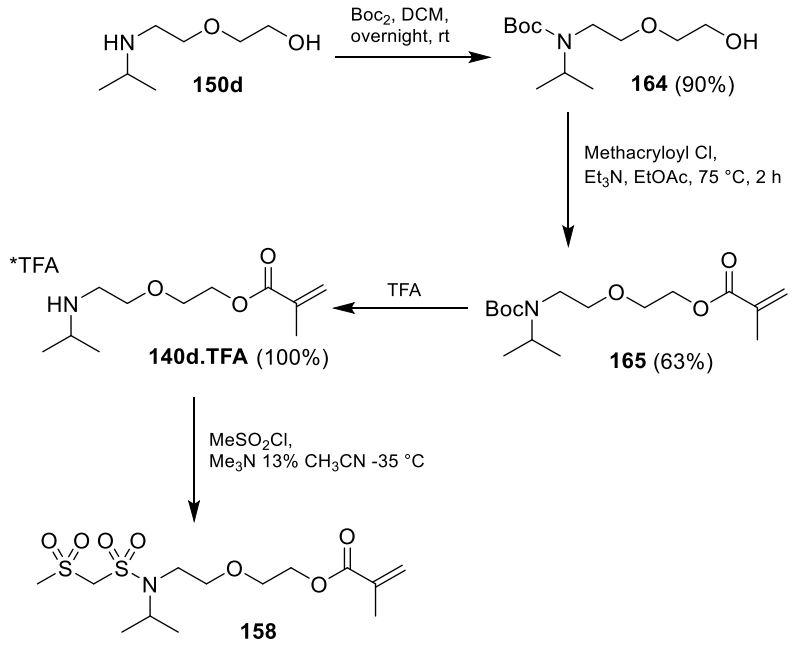


Scheme 107. Synthesis of compound **160** in the attempted synthesis of **158**.

However, the reaction of **150d** gave the desired target alcohol **160** but in very poor yield (3%) (Scheme 107) together with a number of by-products (detected by TLC), of which only sulfonamide **161** was separated in 1% yield. Therefore, in order to by-pass these issues, the hydroxyl group of **150d** had to be protected in order to realise the advantages

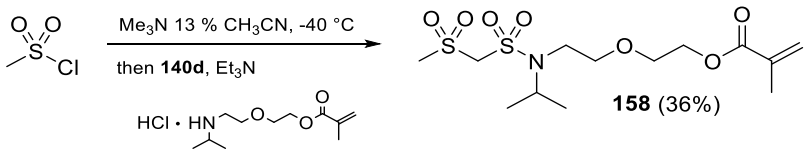
to this synthetic approach and unfortunately was not investigated further due to the lack of the time.

However, as an alternative, it was found that protecting the nitrogen moiety of compound **150d** as an *N*-Boc-group (to derive **164**) was satisfactory, the product from which could then reacted with methacryloyl chloride to give **165** (Scheme 108). Putting theory into practice, secondary amine **150d** was *N*-protected to give **164** in 90% yield, and *O*-acylation gave ester **165** in 63% yield (Scheme 108). This synthetic route was not investigated further due to a lack of time.



Scheme 108. New synthetic route to obtain **158** in better yields.

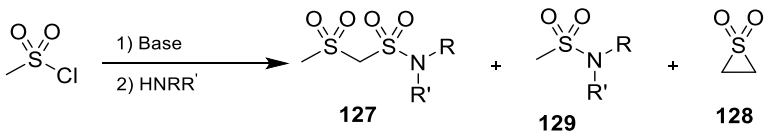
Therefore, the optimum conditions for the synthesis of **158** required the use of 3 equivalents of trimethylamine and 1 equivalent of triethylamine (with respect to the mesyl chloride) as shown in Scheme 109 from investigations reported in Table 14. Moreover, the corresponding amine HCl salt **140d.HCl** was found to be a better option compared to the TFA salt **140d.TFA**, since the latter gave a higher amount of by-products as shown in Table 14. However, although we were able to obtain compound **158** in modest isolated yield (36%) on a scale of 20 g, the reproducibility of this reaction (Scheme 109) remained an issue which would need to be addressed for further scale up and industrial application.



Scheme 109. Final conditions used for the synthesis of compound **158**.

2.3.1.14 Summary

The synthesis of sulfonyl sulfonamides avoiding the use of sulfides, which are known for their persistent and unpleasant smell, has been assed assessed mainly by Opitz *et al.,*[133-134, 173-174] in the late '60. Such reactions, also later reported by Goralski,[175] involving the formation of a sulfene dimer from an alkyl sulfonyl chloride via elimination of HCl in the presence of base, which can then react with an appropriate amine. However, in our hands, the Opitz' original[1] method using triethylamine in acetonitrile as solvent for these reactions led to the isolation of methylsulfonylmethylenesulfonamide **127** as well as by-products such as the corresponding sulfonamide, and even episulfone. Instead, better conditions for the synthesis of methylsulfonylmethylenesulfonamide **127** were found to be achieved when using a more nucleophilic such as trimethylamine in acetonitrile. On the other hand, higher amounts of episulfone **128** were obtained when less-nucleophilic, i.e. more basic bases such as DIPEA were used. This reaction can also lead to higher amounts of the simple sulfonamide **129** if the temperature is not kept low enough (ca. 35 °C) or insufficient base is used.



Scheme 110. General reaction for the synthesis of methylsulfonylmethylenesulfonamide **127**.

The final optimised procedure was also successfully employed for the synthesis of *bis*-sulfonyl sulfonamide (general structure **143**). Moreover, when chloromethanesulfonyl chloride was employed as a starting material instead of mesyl chloride in this same optimised procedure, compound **145** could be obtained, but this was also amongst another, unidentified products.

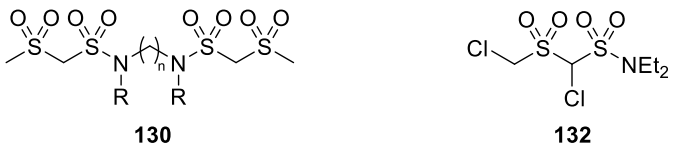
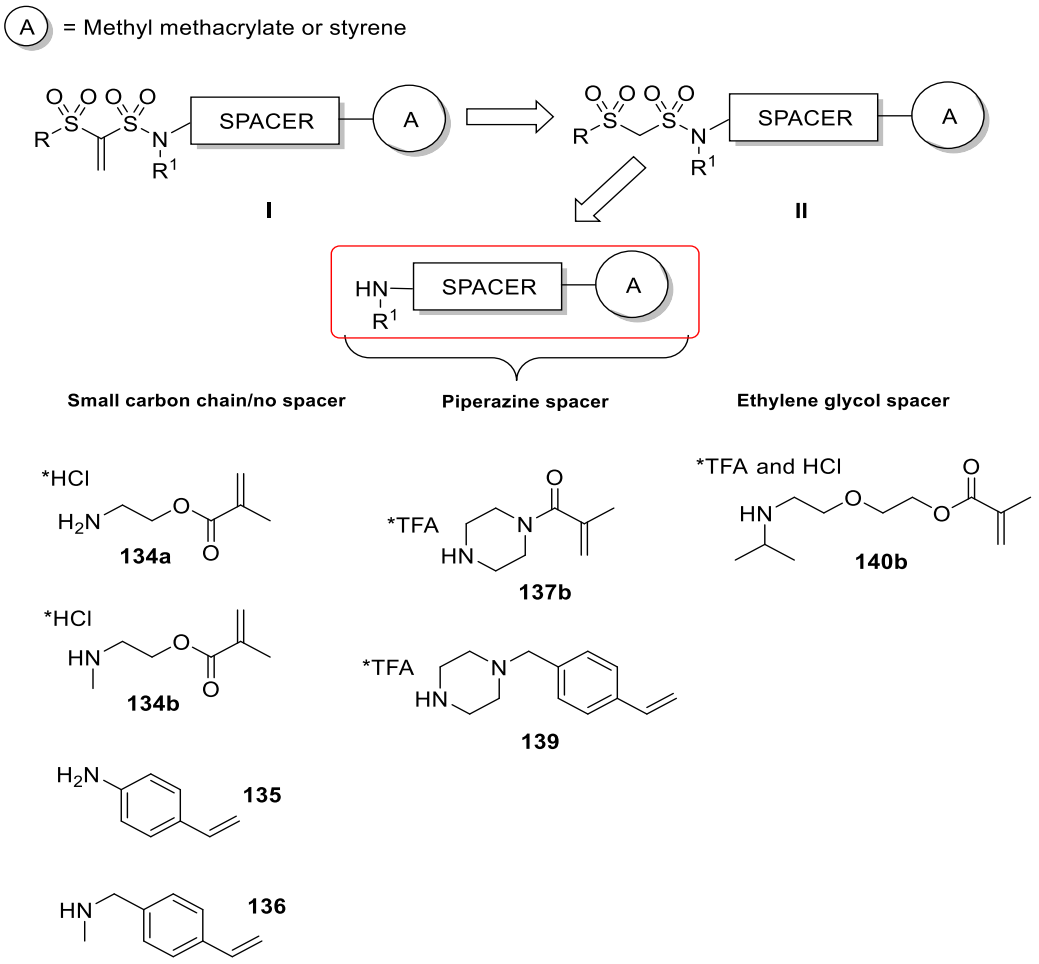


Figure 20. Other compounds obtained employing method used for the synthesis of compounds **127**; In the case of **130**, same procedure but different equivalents of reagents were used; In the case of **132**, same method was used but mesyl chloride was replaced by chloromethanesulfonyl chloride.

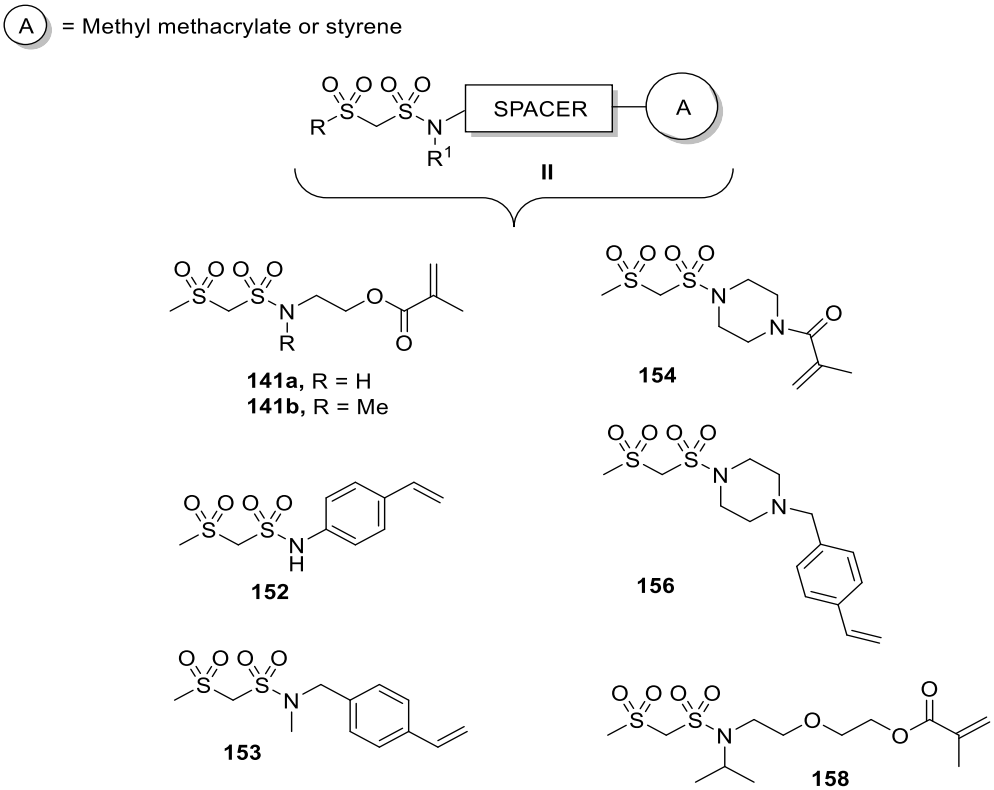
For the main aims of this project, several amines containing a polymerisable group (methyl methacrylate or styrene) with a tuneable spacer were synthesised, as shown in Scheme 111. In fact, the general structure of the proposed crosslinker (Scheme 111) presents a highly non-polar vinyl *bis*-sulfonyl moiety on one end, and a polymerisable functional group (e.g. styrene or methyl methacrylate) on the other end. The physical and chemical properties of the proposed crosslinker (Scheme 111) would be capable of tuning through varying the spacer between the methylsulfonyl-methylenesulfonamide function and the polymerisable group. Hence, the properties of the spacer would be used to control the properties of the crosslinker, and therefore used to alter the properties of the final coating, e.g. crosslinkers should be kept short in order to have "rigid" films. In addition, it was crucial that the final crosslinker **I** was also able to solubilise with the rest of the monomers used in a polymer formation formulation system, including monomers such as methyl methacrylate and butylacrylate, commonly used in emulsion polymerisation in the field of coating technology.



Scheme 111. Synthesised amine to be employed in formation of sulfonyl sulfonamide monomers.

Hence, a range of different monomers were designed with the aim of probing these properties, including simple alkyl and short PEG spacers, as well as a piperazine spacer to understand the prospects of achieving the desired chemical-physical (especially solubility) properties of the crosslinkable monomer.

Finally, the synthesised amines, listed in Scheme 111, were employed for the synthesis of sulfonyl sulfonamide monomers to give compounds of general structure **II** (Scheme 112). These compounds represent the substrates for the synthesis of the final general target, crosslinker **I** (Scheme 111), on which achievement will be addressed in the next section 2.3.4.2.



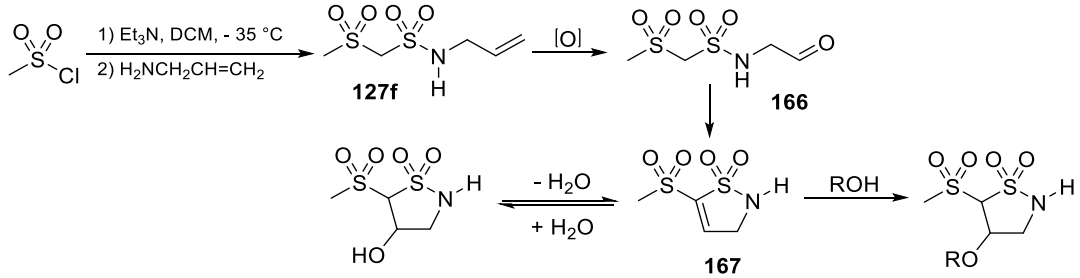
Scheme 112. Sulfonyl sulfonamide monomers of general structure II prepared in this study.

2.3.2 Vinyl-1-sulfonyl-1'sulfonamide synthesis

This section will cover the strategies used to achieve synthesis of vinyl-1-sulfonyl-1'sulfonamide. Preliminary reactions were undertaken on example substrates and optimised further reactions were then tested upon monomers synthesised in the previous section.

2.3.2.1 Intramolecular Knoevenagel-type reaction

As reported in the introduction, there is limited literature available on *bis*-sulfone (with the exception of *bis*(phenylsulfonyl)methane[157a, b, 184]) and no literature is available on sulfonyl methylenesulfonamides. Therefore, the existing procedures available for *bis*(phenylsulfonyl)methane[157a, b, 184] were taken as a starting point to synthesise vinyl sulfonyl sulfonamides. In particular, A. Quintard *et al.*[157a] reported a Knoevenagel-type addition which involved the use of *para*-formaldehyde and piperidine. In order to avoid the use of external aldehydes (especially toxic formaldehyde), a first strategy examined relied upon an intramolecular Knoevenagel type reaction, after an aldehyde functionality had been introduced into the structure, for example, **166**. This latter compound **166** could in turn be derived from the oxidation of allyl sulfonamide **127f**, as shown in Scheme 113. Hence, intramolecular condensation of **166** should provide the vinyl group as in **167** and the free N-H could then be functionalised with a polymerizable moiety in order to incorporate the crosslinker into a polymer backbone.



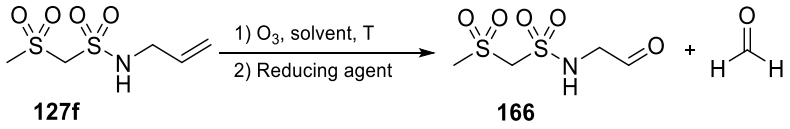
Scheme 113. Proposed synthetic route to obtain vinyl sulfonyl sulfonamide **167** through intramolecular condensation.

Starting material (Scheme 113) **127f** was previously synthesised following the standard Method A and hence, two different methods were employed to oxidase olefin **127f** to access aldehyde **166**, i.e. ozonolysis[185] and Wacker-Tsuji[186] reaction.

2.3.2.2 Ozonolysis

The mechanism of ozonolysis begins with a dipolar cycloaddition of ozone to the alkene, forming the 1,2,3-trioxolane or "primary" ozonide.[187] After the formation of the primary ozonide, there follows a rapid ring cleavage and recombination at low temperature to form the secondary ozonide intermediate, reduction of which forms the final ketones and/or aldehydes depending on the substitution on the double bond.[185, 187b] Numerous reducing reagents can be employed including dimethyl sulfide, a mild reagent that reduces the ozonides, though it can sometimes fail,[188] and is therefore usually used in excess. Or, as an alternative, the reaction can be conducted in $MeOH/CH_2Cl_2$ to generate hydroperoxyacetals which are more efficiently reduced.[189] Also, thiourea has been widely used as an effective reducing agent for hydroperoxyacetals,[190] as have metals such as Zn/CH_3COOH which is a good reducing agent, sufficiently powerful to reduce most peroxides.[188, 191] A relatively simple approach is also to conduct the reaction in the presence of water which acts as an *in situ* reducing agent by trapping the ozonide.[192]

Table 15. Ozonolysis reaction of allylsulfonamide **127f** to obtain **166**.



127f **166**

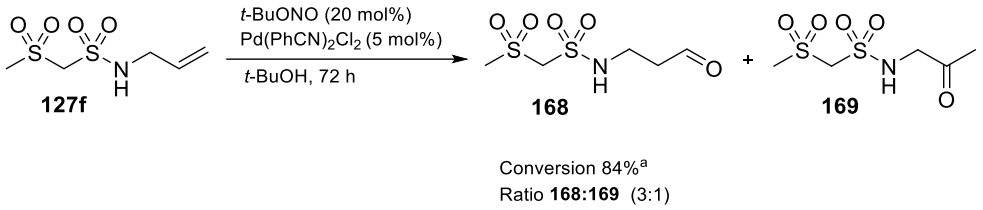
Entry	Reducing agent (time, temp.)	Solvent	Temperature (°C)	Product 166
1	$(CH_3)_2S$ 2 equiv. (3 h, rt)	CH_2Cl_2/MeOH	-78	
2	$(CH_3)_2S$ 2 equiv. (24 h, rt)	CH_2Cl_2/MeOH	-78	complex mixture
3	Zn/CH_3COOH 2 equiv. (18 h, rt)	CH_2Cl_2/MeOH	-78	crude ^1H NMR shows
4	$(CH_3)_2S$ 2 equiv. (15 h, rt)	THF	-78	formation of aldehyde
5	$(CH_3)_2S$ 1 equiv. (6 h, rt)	MeOH	-78	
6	$SC(NH_2)_2$ 2 equiv. (10 h, rt)	CH_2Cl_2/MeOH	-78	
7	H_2O (0 °C)	$(CH_3)_2CO/H_2O$	0	

Hence, the allyl system **127f** was exposed to ozonolysis, as shown in Table 15, and quenched with different reducing agents. When dimethyl sulfide was used as the reducing agent (Entries 1 and 2, Table 15), the crude ^1H NMR spectrum was surprisingly complex

but did include the expected singlet at 9.64 ppm indicating the formation of an aldehyde, but this was not readily separated. In order to avoid the formation of DMSO, the alternative and mild zinc reducing reagent was tested (Entry 3). The crude ^{1}H NMR from Entry 3 (Table 1) showed two singlets at 9.64 and 9.74 ppm and, after removal of zinc through filtration through Celite, only minor peaks in the lower field of the ^{1}H NMR spectrum were left, with no sign of either the starting material or aldehyde attributable to compound **166** being present. In order to improve the solubility of the starting material **127f**, the reaction was also performed in THF (Entry 4, Table 15), however, afforded none of compound **166**. Similarly, in Entry 6 (Table 15), thiourea scavenger was used for its easy elimination without the need of a particular purification which could perturb the products stability. Unfortunately, no formation of the aldehyde could be seen by ^{1}H NMR and another attempt was performed by following the work of Schiaffo and Dussault[192] in water, but again, no aldehyde was formed (Entry 7, Table 15). Therefore, in conclusion, there was evidence of the generation of an aldehyde which was unfortunately difficult to purify due to either the presence of DMSO generated from the reduction, and/or the probable instability to work-up/purification of the generated aldehyde and an alternative approach was examined using a Wacker-Tsuji oxidation.

2.3.2.3 Wacker-Tsuji oxidation

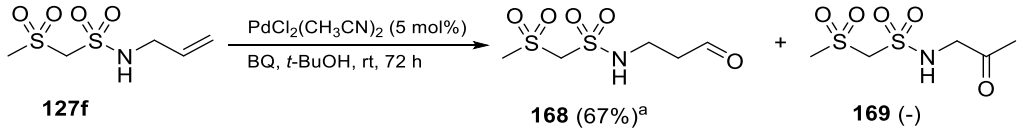
The Wacker-Tsuji reaction oxidises terminal alkenes which could therefore be employed to generate an aldehyde system such as **168** from **141f**. For this reaction (Scheme 114) a relatively new aldehyde-selective aerobic version of this reaction was examined according to the work of Ning *et al*.[186] using a redox co-catalyst and *t*-BuONO as oxidant in the presence of palladium(II) in *t*-BuOH at room temperature.



[a]Conversion refers to a scale of 100 mg; when the reaction is scaled-up to 2 g the conversion decreases to 36% (72 h). Conversion and selectivity were calculated by ^{1}H NMR and product **168** and **169** were not isolated.

Scheme 114. Aldehyde selective Wacker-Tsuji oxidation of **127f**.[186]

The reaction shown in Scheme 114 resulted in the conversion of **127f** to a mixture of aldehyde **168** and ketone **169** in a 3:1 ratio respectively. After the removal of palladium through a pad Celite layered with silica gel, a conversion of 84% was recorded. However, these compounds **168** and **169** could not be easily separated and when the reaction was scaled-up, and the conversion drastically dropped when the reaction was performed under O_2 (1 atm). Therefore, an alternative method was pursued in order to achieve compound **168** (Scheme 115). In particular, Feringa and co-workers[193] method employs a catalysts such as [$(PhCN)_2PdCl_2$] and *p*-benzoquinone as oxidant in *t*-BuOH under ambient conditions for the synthesis of protected β-amino aldehydes via alkene oxidation of the corresponding allylic compound. This was therefore explored.



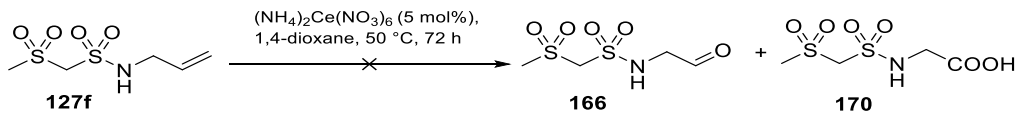
[a] Calculations based on the ^{1}H-NMR spectrum.

Scheme 115. Pd-catalyzed Wacker-Tsuji reaction of **127f**.

Applying Feringa and co-workers' conditions towards **127f** (Scheme 115), aldehyde **168** was produced with 67% conversion after 72 h of reaction with no sign of ketone **168**. However, attempts to scale up this reaction through the use of longer reaction times decreased the conversion, and alternative conditions were therefore required.

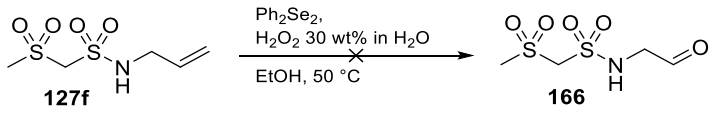
Wang *et al.* reported a novel cerium(IV) ammonium nitrate (CAN)-catalysed aerobic oxidative cleavage of the C=C bond of styrene which gave generally good yields of aldehyde and carboxylic acid products using low catalyst loading (5 mol% of CAN).[194] Therefore, this method was employed on substrate **127f** in order to generate the aldehyde species **166**

(Scheme 116) at 50 °C in order to avoid any decomposition of the starting material or potential formation of by-products. The reaction was followed for 72 h, but no formation of the aldehyde **170** or carboxylic acid was revealed, and a full mass recovery of the starting material **127f** was achieved.



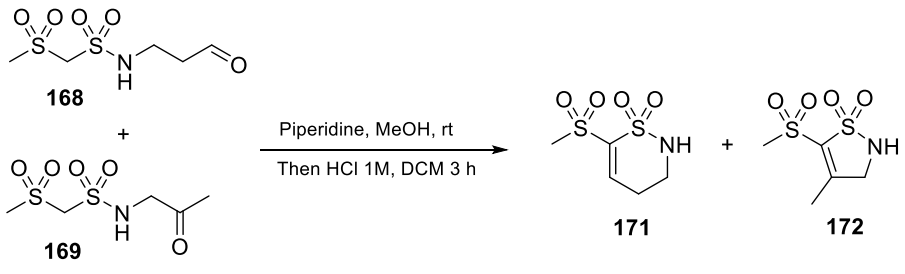
Scheme 116. Attempted aerobic oxidation by cerium (IV) ammonium nitrate of **127f**.

In parallel, an organoselenium-catalysed alkene oxidation reaction in ethanol with hydrogen peroxide was also used for substrate **127f**.[195] In this case, the reaction was heated at 50 °C again in order to avoid any decomposition of the starting material, however, no aldehyde was detected after 72 h and starting material decomposed (Scheme 117).



Scheme 117. Organoselenium-catalysed oxidative double bond cleavage of **127f**.

Since none of the reactions attempted above were useful except for the reaction reported in Scheme 114, which gave a mixture of aldehyde and ketone **168** and **169**, this mixture was ultimately used for the formation of vinyl sulfonyl sulfonamide through an intramolecular Mannich-type reaction, using piperidine, as shown in Scheme 118.

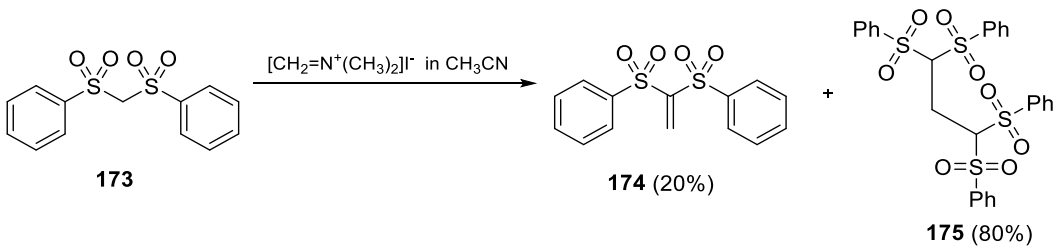


Scheme 118. Intramolecular Mannich type reaction.

^{1}H NMR showed the disappearance of the aldehyde peak at 9.81 ppm, although the presence of the sulfonyl α-carbon at 4.48 ppm suggested that no intramolecular addition took place. However, two doublets at ca. 7.00 ppm were present in trace amounts, which could indicate initial formation of a vinyl sulfonyl sulfonamide of **171** or **172**. Overall, the crude ^{1}H NMR spectrum showed an overly complex result, supported by multiple products according to TLC and no purification was carried out. This synthetic route was abandoned due to the overall poor results achieved.

2.3.2.4 Eschenmoser's salt Mannich-type reaction

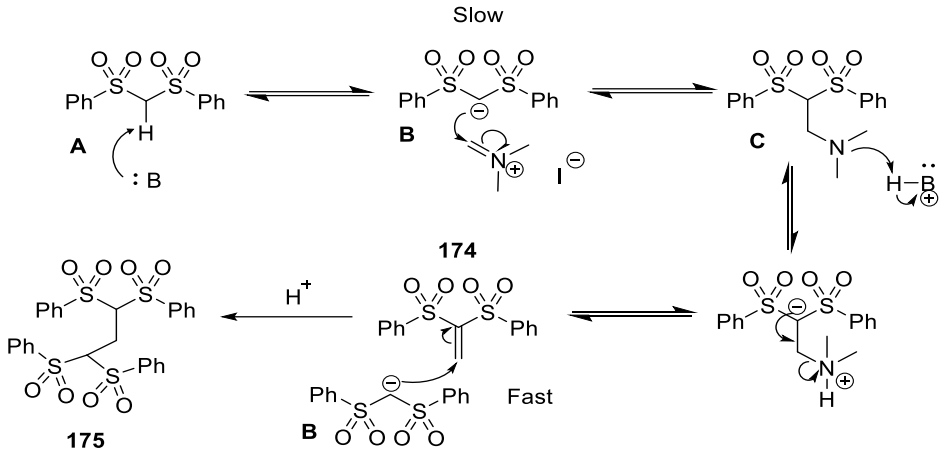
Due to the lack of a simple route to cyclic vinylsulfonyl derivatives described above, attention was focussed on terminally unsubstituted 1,1'-disulfonyl analogues of the various methansulfonyl methylenesulfonamide derivatives. An alternative to the previous synthetic route of using formaldehyde to condense on the methylene of the disulfonyl system would be the adoption of Eschenmoser's salt. To start with, therefore, the readily available *bis*(phenylsulfonyl)methane **173** was used to test the potential for applying this approach, as outlined in Scheme 119.



Scheme 119. Synthesis using Eschenmoser's salt vinyl-disulfonyl compound **174**.

Hence, reaction of **173** in MeCN with Eschenmoser's salt led to the formation of two products, as indicated by ^{1}H NMR and DOSY spectra. One product correlated to the expected vinyl sulfone **174** and the second had a much higher molecular weight (between 600/700 Da estimated by DOSY calculations),[196] which was later found to be **175**. The formation of this latter species has been reported to form under either basic or neutral conditions by De Lucchi *et. al.,*[197] Neplyuev and collaborators[198] and Sulzer-Mossé.[199] The formation of the product **175** can also be explained by 1,4-addition of the highly reactive

1,1-*bis*(benzenesulfonyl)ethylene, formed *in situ*, to the *bis*(phenylsulfonyl)methane still present during reaction. A. Alexakis *et al.*[155] suggested temperature as well as the sequence of reagent addition could influence the proportion of by-product **175**. The proposed mechanism is shown in Scheme 120.

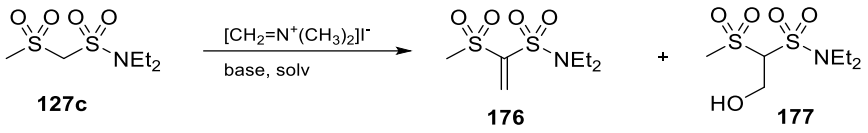


Scheme 120. Proposed mechanism to the formation of **175**.

In the proposed mechanism, Scheme 120, anion B forms readily in the presence of a base (B) and is trapped by the iminium salt, and after elimination, affords the desired product **174**. However, this is presumably a better electrophile and trapping agent than is the iminium salt, and it more rapidly reacts with anion A to give the methylene bridged 'dimer' **175**.

With this in mind, different reaction conditions for this Mannich-type reaction using Eschenmoser's salt were screened using TLC in order to minimise the formation of the methylene dimer-type species, i.e. such as **175** (see Table 16). To do this, and to move away from the model disulfonyl compound **173**, the reaction of the *N,N'*-diethylsulfonamide **127c** was used as a test substrate, which was reacted under various conditions in order to identify suitable reaction conditions to selectively form the condensation product **176**, as outlined in Table 16.

Table 16. TLC screening of Mannich-type reaction to obtain either **176** or **177**.



127c **176** **177**

Entry	Base (equiv.)	Eschenmoser's salt (equiv.)	Solvent	Temperature (°C)	Work-up	Products[a]
1	Et_3N (1)	1	CH_3CN dry	rt	H_2O	recovered SM
2	*t*-BuOK (1)	1	THF dry	-70	H_2O	recovered SM
3	*t*-BuOK (1)	1	CH_3CN dry	-10	H_2O	recovered SM
4	KOH	2	CH_3CN	rt	H_2O	**127c+ 176+ 177**
5	Et_3N (2)	3	CH_3CN	0	H_2O	**127c+ 176+ 177**
6	Et_3N (1)	3	CH_3CN	rt	HCl 1M (3equiv.)	**176+ 177**
7	Et_3N (2)	3	CH_3CN	rt	H_2O	**127c+ 176+ 177**
8	Et_3N (1)	3	CH_3CN	rt	H_2O	**141c+ 176+ 177**
9	Et_3N (0.5)	3	CH_3CN	rt	H_2O	**141c+ 176+ 177**
10	Et_3N (1)	6	CH_3CN	rt	H_2O	**176**
11	Et_3N (1)	1.5	CH_3CN	rt	HCl 1M	**127c+ 176+ 177**
12	Et_3N (1)	3	Toluene	rt	H_2O	**127c+ 176+ 177**
13	Et_3N (1)	5	CH_3CN	rt	HCl 1M (3eq)	**176+ 177**

[a]Isolation of compounds **176** and **177** were achieved with reaction encountered in later sections. All reactions in this table were followed by TLC only, and therefore no ratio between the different species is reported.

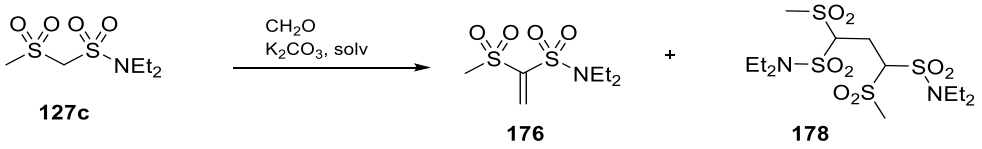
Entries 1-3 tested conditions with 1 equivalent of iminium salt and different types of bases (Et_3N and t-BuOK), solvents (dry THF and CH_3CN) and temperatures (room temperature to -70°C). However, it seemed that extra iminium salt was needed partially because this hydrolizes, seemingly inactivating the reagent and giving no reaction. By increasing the amount of iminium salt to 2 equivalents (Entry 4, Table 16), it was noticed that the reaction was leading to a mixture of three species, **176**, **177** and **127c**. Although the synthesis of the hydrated form did not represent an issue, the crude product still had unreacted starting material present, indicating that more iminium salt was needed in order to push the reaction to completion.

After this encouraging result, the aim became accessing **177** rather than **176** due to this being potentially easier and possible longer-term stability. Therefore, the next entries (Entries 5-13, Table 16) were focused on the optimization of the hydroxyl compound **177**. In Entries 5-13 (Table 16), increasing amounts of iminium salt (from 3 to 6 equivalents), different amounts (0.5 to 2 equivalents) of base (Et_3N) and different acid or neutral work up conditions were used. The conditions in which 100% conversion was achieved are reported in Entries 6, 10 and 13. In particular a mixture of the vinyl **176** and the hydroxyl

189 were found when using 3 and 5 equivalents of Eschenmoser's salt followed by HCl 1M washing (Entry 6 and 13) meanwhile, when 6 equivalents of Eschenmoser's salt were used (Entry 10, Table 16) only vinyl sulfone was achieved. These preliminary reactions were enough to get an idea of the conditions to use to obtain the vinyl *bis*-sulfone, although it was not possible to solely achieve the hydrated compound **189**.

Literature[200] also suggested that a base such as K_2CO_3 in the presence of formaldehyde can give Knoevenagel condensation in compounds like β-diketones. In the experimentation of these conditions, it was surprisingly found that most trials (Entry 2-5, 7; Table 17) compound **190** was the only product. Vinyl *bis*-sulfone **188** was formed only in Entry 1 (Table 17), when a slight excess of formaldehyde was used. However, when 5 equivalents of formaldehyde were added (Entry 6 and 8, Table 17), the ^{1}H-NMR spectra of the crude was either too complicated to identify the formed products or only **190** could be identified.

Table 17. TLC screening of Knoevenagel condensation in the presence of potassium carbonate.



Entry	Solvent	K_2CO_3 (equiv.)	CH_2O 37% H_2O (equiv.)	Results[a]
1	DCM	1	1.5	**176+178**
2	Toluene	1	1.1	**178**
3	Toluene	5	1.1	**178**
4	CH_3CN	1	1.1	**178**
5	CH_3CN	5	1.1	**178**
6	DCM	1	5	Reaction crude too complicated
7	Toluene	1	5	**178**
8	CH_3CN	1	5	Reaction crude too complicated

[a]Isolation of compounds **127c** and **176** were achieved with reaction encountered in later sections. Compound **178** was obtained pure enough from in Entry 2 and therefore, characterisation could be completed. Reactions in this table were followed by TLC only, and therefore no ratio between the different species is reported. For Entry 6 and 8, ^{1}H NMR was utilized as an aid to the complex mixture.

Reactions using potassium carbonate were not investigated further since most of conditions resulted in compound **178**, which was confirmed by crystal structure (Figure 21).

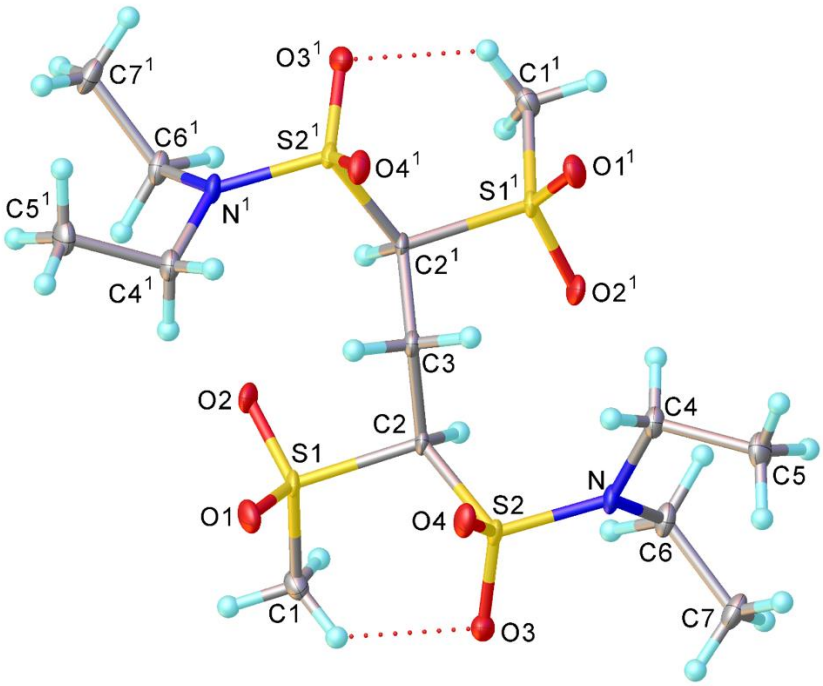
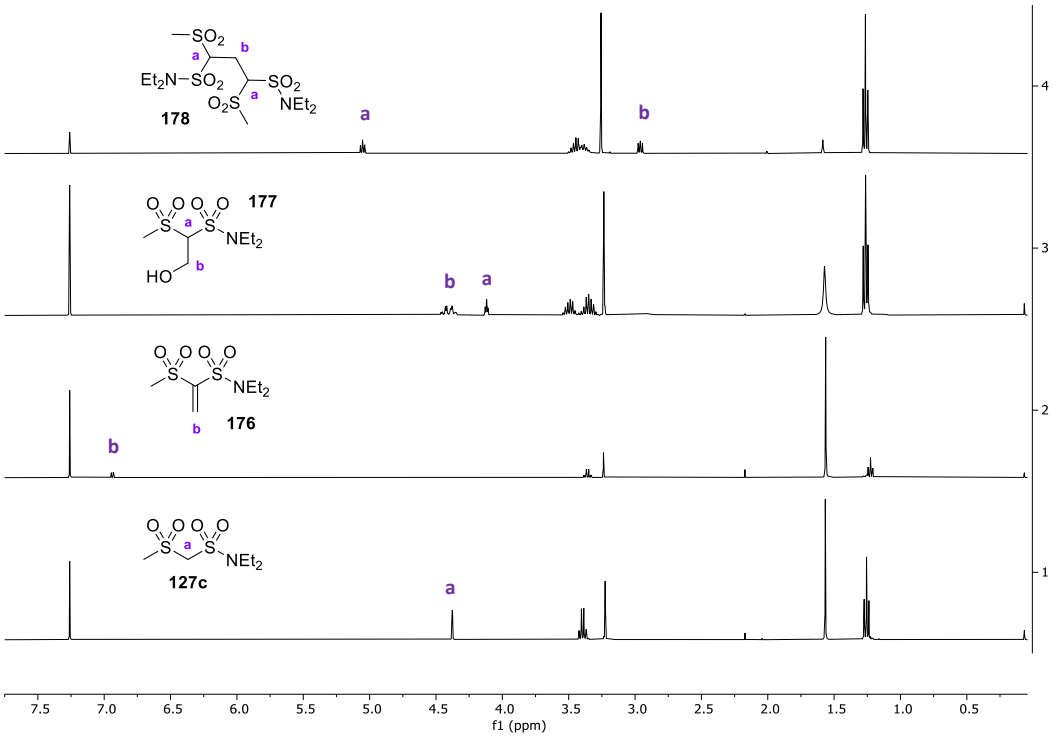


Figure 21. Single crystal X-ray structure of compound **178** (see page 290 for crystallographic data).

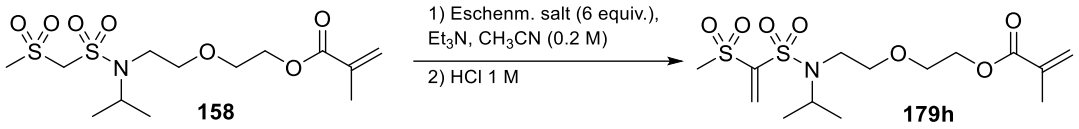
^{1}H-NMR of the isolated compounds **127c**, **176**, **177** and **178** are reported in Figure 22.



Isolation of compounds were achieved at different stages of this work: **127c** was synthesized in section 2.3.1.1; **176** was synthesized and isolated in section 2.3.2.6; **177** was achieved and isolated in section 2.3.2.8; compound **178** was obtained as the only product in Table 17.

Figure 22. ^{1}H-NMR in $CDCl_3$ comparing the different isolated products **127c**, **176**, **177** and **178**.

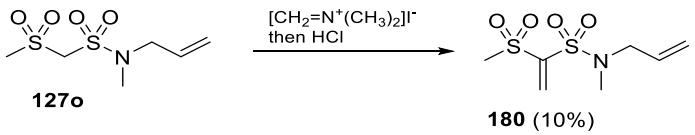
Due to the encouraging result from the Eschenmoser's salt (Table 16, Entry 10), this were applied to previously sthesised **158**. Although, ^{1}H-NMR spectrum shows the formation of **179h** as demonstrated by a peak at 6.96 ppm, the reaction product was not clean with a crude yield of only 24%.



Scheme 121. Synthesis of **179h** using Eschenmoser's salt.

Unfortunately, this procedure was not efficient enough, nor suitable for potential scale up application especially due to the high amount of iminium salt needed (6 equivalents) and the low yield achieved.

Difficulties in synthesising the PEG-analogue **179h**, led us to try the reaction on a simpler substrate such as **127o** that could still be copolymerise and therefore, incorporated into an emulsion polymerisation system. *N*-Methyl-*N*-allylamine is commercially available and the synthesis of methylsulfonyl-methylenesulfonamide **127o** was straightforward, obtained with a yield of 89% without the need for purification as reported in section 2.3.1.7. It was also therefore used as a test substrate for the Eschenmoser's salt-based vinyl sulfone formation, i.e. Scheme 122. However, this generated non-identified by-products, hypothetically correlated to the hydroxyl and the self-condensation products and purification yielded to only 10% of **180**. Interestingly, this product **180** was not soluble in either methyl methacrylate or styrene.



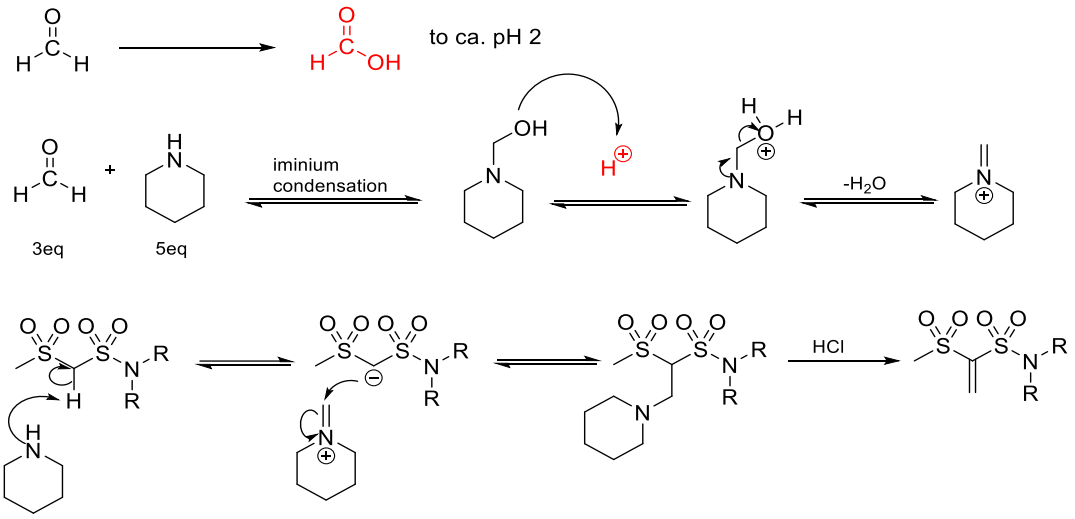
Scheme 122. Synthesis of *N*-methyl-*N*-allyl vinyl disulfone.

It is useful to keep in mind that large quantities of crosslinker would be needed to be tested in a latex formulation and therefore, that all monomers would need to be miscible with the

other reagents used. This procedure was therefore abandoned due to the inconvenience and low yields in using the iminium salt.

2.3.2.5 Knoevenagel type condensation

Knoevenagel condensation reactions compounds that contain two electron-withdrawing groups is a very important organic reaction which has been frequently used for the production of fine chemicals and heterocyclic compounds of biological significance. A base catalysed Knoevenagel condensation, employed by A. Quintard *et. al*[157a] on *bis*(phenylsulfonyl)methane, was therefore used on the sulfonyl sulfonamides generated in this study. In this procedure, which initially worked well giving good results, suddenly started to show no reaction taking place and only starting materials could be recovered. It was later found, that over time, stored formaldehyde generates small amounts of formic acid, changing the solution pH and therefore, reaction efficiency depended upon reagent quality. It became clear that the formic acid contained in old bottles of formaldehyde was acting as a key acid catalyst for this condensation, i.e. as shown in Scheme 123.

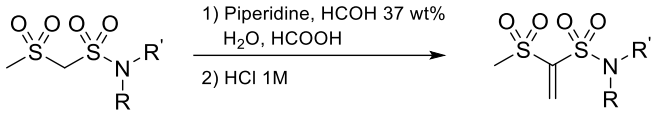


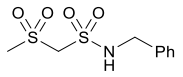
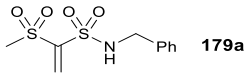
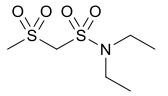
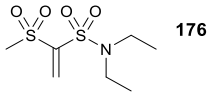
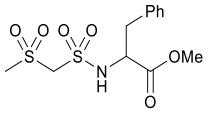
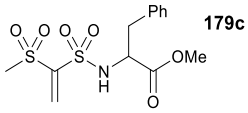
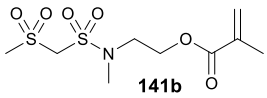
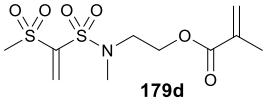
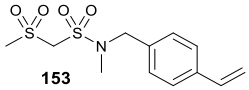
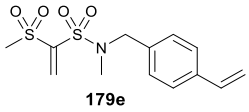
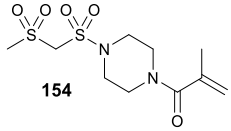
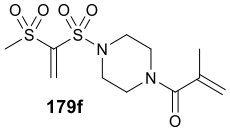
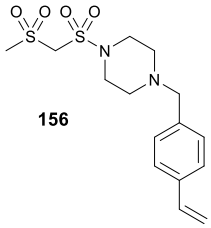
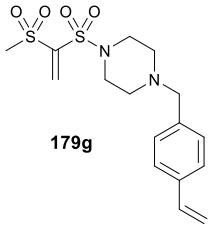
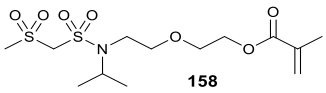
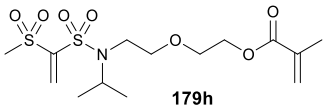
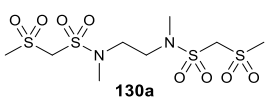
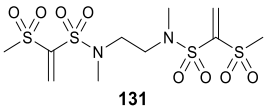
Scheme 123. Proposed mechanism of the acid catalysed Knoevenagel-type condensation.

This reactivity issue, once identified, was readily overcome by bringing aqueous formaldehyde solutions to *ca.* pH 2 by the addition of formic acid and a number of optimised reactions could then be carried out under standardised conditions, as shown in Table 18.

As shown in Table 18, the overall yields of most employed substrates were remarkably high and consistent, certainly for Entries 1-5 (Table 18). Although the acid catalysed reaction gave complete conversion of the substrate it was found that different substrates needed different workup, and therefore, different solvents (MeOH or EtOAc). In fact, following the original procedure[157a], the reaction was carried out in MeOH in which the intermediate piperidine adduct with the sulfonyl sulfonamide was precipitated upon addition of cold water (Entries 1-2, Table 18) and these two products could be isolated for the next step via filtration. However, when more polar substrates were used, such as **127h**, **141b**, **153** and **158**, the formation of the corresponding piperidine adduct did not result to be insoluble in MeOH/H_2O. Therefore, upon addition of cold water no precipitation and isolation of the enamine intermediate could be achieved upon filtration, hence, the excess reagents formaldehyde and piperidine must be removed in different ways.

Table 18. Knoevenagel reaction on previously synthetized methylsulfonyl-methylenesulfonamide.

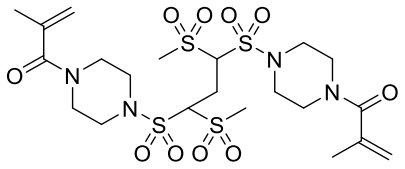


Entry	Starting material	Product	Solvent	Reaction time (days)[a]	Yield (%)
1	 **127a**	 **179a**	MeOH	2	92
2	 **127c**	 **176**	MeOH	2	84
3	 **127h**	 **179c**	EtOAc	5	96
4	 **141b**	 **179d**	EtOAc	3	90
5	 **153**	 **179e**	EtOAc	3	45[b]
6	 **154**	 **179f**	EtOAc	30 min	23[b]
7	 **156**	 **179g**	EtOAc	1h	10[b]
8	 **158**	 **179h**	EtOAc	3	90
9	 **130a**	 **131**	EtOAc or MeOH	-	0

[a]Refers to the time to achieve full conversion of the starting material into the intermediate piperidine adduct; [b]Yield after column chromatography.

In general, for these types of reactions shown in Table 18, a reliable procedure turned out to be: first a wash with water to remove any formaldehyde left in the reaction mixture

after step 1; and then, second wash with 1M HCl until the final aqueous phase became acidic, i.e. showing complete hydrolysis of the piperidine adduct intermediate. This procedure gave, for most substrates (Entries 3-5, 8, Table 18), 100% conversion and achievement of compounds **179a-e** in excellent yields in the range of 80-96%. Surprisingly, for sulfonyl sulfone piperazine **154** (Entries 6, Table 18), this procedure led to 45% yield of the methylene bridged dimer compound **181** (Figure 23) instead of the vinyl sulfones **179f**.



181

Figure 23. Product generated from selfcondensation (Entry 6, Table 18).

The unexpected isolation of the methylene bridged dimer compounds **181** (Figure 23) is proposed to be due to the excess of piperidine still present during the second, hydrolysis step, as acid was added. Therefore, different ways to remove this excess piperidine after step 1 was examined. In particular, when a $CuSO_4$ solution was used to remove excess of piperidine in the reaction mixture, this unfortunately led also to a great loss of the substrate even when used at very low concentrations (1 equivalent 1% $CuSO_4$). Moreover, quenching or removal of the remaining piperidine was attempted with the use of acetyl chloride, stripping with toluene or scavenging with tosic acid or other carboxylic acids. While these strategies all led to poor results and significant mass losses, some others gave better results. For example, using a scavenger such as thiourea it was possible to remove most of the piperidine present, although this resulted in a very inconvenient procedure for larger scales. Therefore, other methods were employed for the removal of excess piperidine such as filtration through a silica gel plug, which was initially avoided due to the hypothetical instability of the product on silica. Another method that proved successful was the removal of excess of piperidine by using an initial 4 equivalents of HCl 1M for extraction, followed by addition of 2 equivalents HCl (1M) which was left to react for 4 h. This method allowed us to avoid any self-condensation reaction of **154**, and hence,

formation of compound **181**, X-ray structure shown in Figure 24. Compound **179g** (Entry 7, Table 18) was also achieved employing the same procedure, although with an unsatisfactory 10% yield.

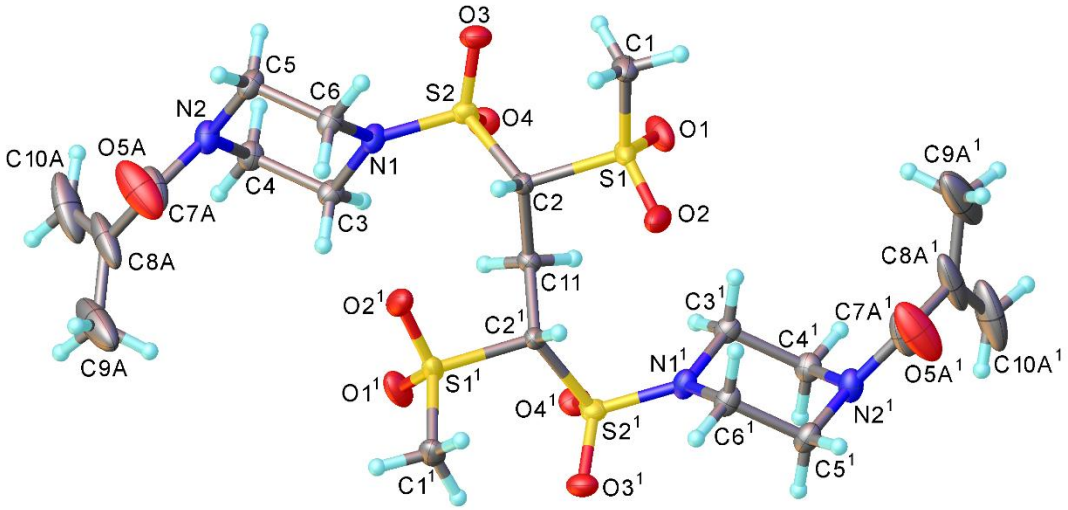
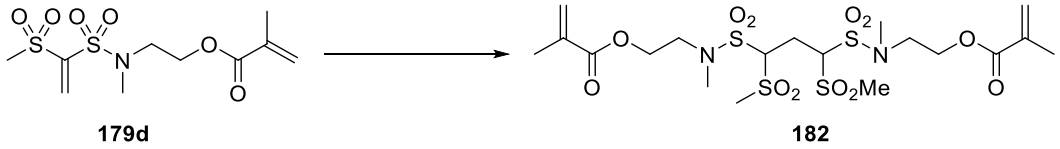


Figure 24. Single crystal X-ray structure of compound **181**.

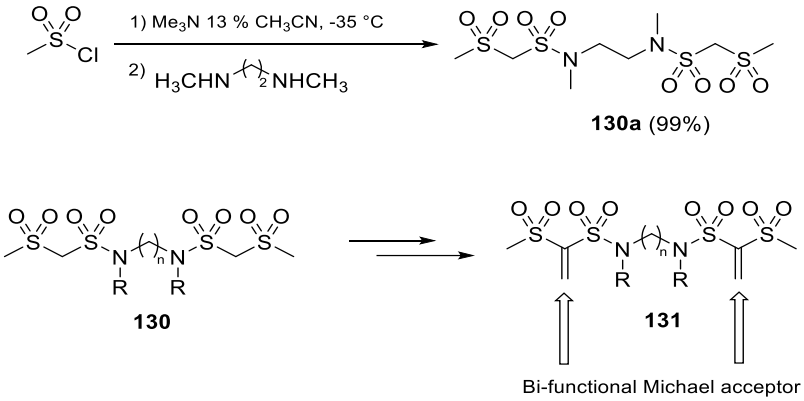
The reason why substrates **154** (see Table 18) give rise to a more facile self-condensation methylene-bridging reaction is still not completely clear. However, it is possible say that there is a strong correlation between the time of reaction, the polarity of the substrate and the formation of by-products, like **181** (Figure 23). In fact, the higher the polarity of the compound, the faster the reaction (Entries 6 and 7, Table 18), the easier is the formation of self-condensation by-products.

It was also found that, when stored in solution these structures can eventually self-condense. For example, it was found that compound **179d** (Scheme 124) converted to **182** over 6 months in DCM, achieving 100% conversion.



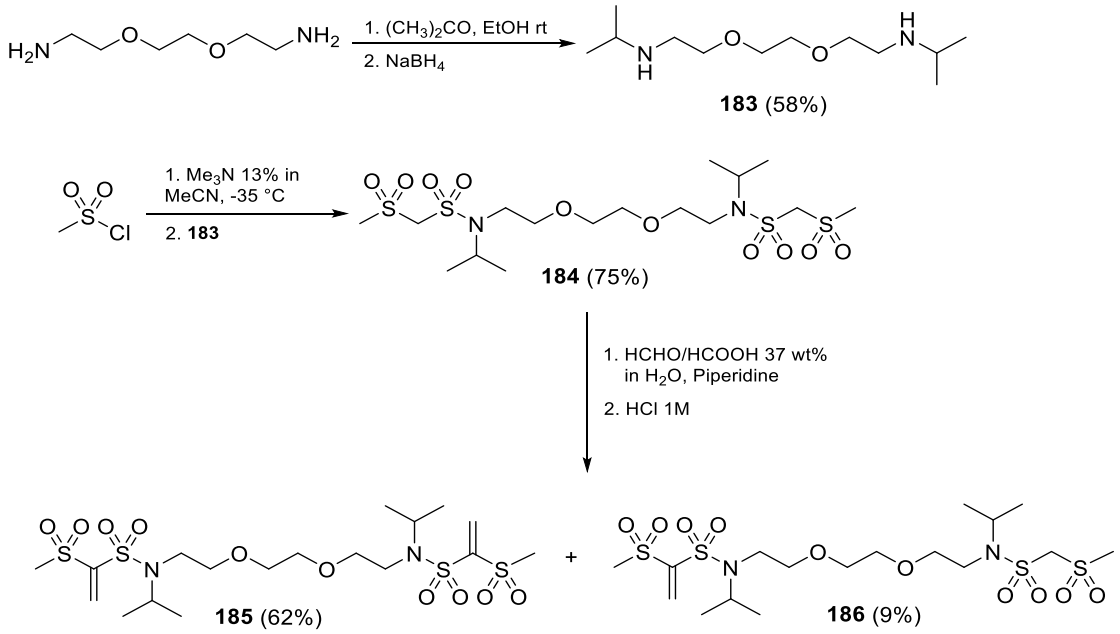
Scheme 124. Self-reaction of compound **179d** to **182** when left in solution.

In the last entry in Table 18 (Entry 9), the double disulfonyl system is the only one in that table that does not contain a co-polymerisable function group. This is because it was intended to synthesise a crosslinker compound which, rather than presenting a co-polymerisable functional group, had a bi-functional Michael acceptor (**131**, Scheme 125) as explained in section 2.3.1.8. With this in mind substrate **130a** was easily synthesised in excellent yields (99%) using the standard procedure Method B using ready available *N,N*′-dimethylethylenediamine as shown in Scheme 125.



Scheme 125. Synthesis of compound **130a** and synthesis to a bi-functional acceptor.

Unfortunately, compound **130a** was not soluble in most solvents, including EtOAc, MeOH, THF, CH_3CN and EtOH, and therefore, no reaction was achieved when trying to access the corresponding divinyl analogue **131** (Table 18, Entry 9). In fact, although sulfones are known for their high polarity and solubility in high polarity solvents, from general observation in this work, sulfonyl sulfonamides have generally poor solubility in many solvents. Like polysulfones, compound **130** appeared to be soluble only in *N*-methyl pyrrolidone or dimethylacetamide, which are challenging solvents to use due to their high boiling point and not useful for polymerisation applications. Therefore, it was decided to counterbalance this low solubility of the sulfonyl sulfonamide system by inserting a spacer with increased polar properties between the two reactive end groups, i.e. re-designing to compound such as **185**, through a spacer unit of type **183** shown in Scheme 126.



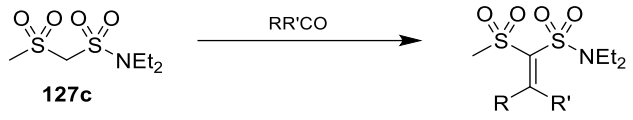
Scheme 126. Synthetic route to compound **185**.

Therefore, the synthesis of **185** was initiated through a two-step reductive amination of 1,2-*bis*(2-aminoethoxy)ethane with acetone to give the *N,N'*-di-*iso*-propyl derivative in 58% yield (Scheme 126). Synthesis of *bis*-sulfonyl sulfonamide **184** was also easily achieved in 75% yield with the use of Method B examined in section 2.3.1.7 (page 91), although doubling the equivalents normally used of mesyl chloride and base to provide the double-sulfonyl sulfonamide **184**. Finally, since **184** appeared to be at least soluble enough in EtOAc, it could be used for the synthesis of compound **185**. Hence, **184** was treated with excess of piperidine and formaldehyde, then quenched with 8 equivalents of HCl (1M) and extracted, followed by an extra 3 equivalents of HCl (1M) to complete elimination of piperidine over a period of 5 hours. The final compound, **185**, was isolated in 62% yield after silica gel chromatography, as well as the minor secondary compound **186** (9%), i.e. the mono-vinyl analogue.

2.3.2.6 Vinyl sulfonyl sulfonamides synthesis employing different ketones/aldehydes

Encouraged by the successful results obtained employing formaldehyde in Knoevenagel-type reaction, it was necessary to explore the feasibility of this method with other ketones and aldehydes, to check the possible scope of the reaction. Compound **127c** was chosen as a test substrate due to its facile synthesis and absence of functional groups that could interfere with the reaction. A first set of test experiments are summarised in Table 19.

Table 19. Alternative methods to ethylenesulfonyl-sulfonamide **187**.



Entry	RR'CO (equiv.)	Base (equiv.)	Solvent	Result
1	$(CH_3)_2CO$ (3)/HCOOH	Piperidine (5)	EtOAc	No reaction after 3 days
2	$(CH_3)_2CO$ (5)/HCOOH/H_2O	Piperidine (5)	MeOH	No reaction after 4 weeks
3	CH_3CHO (3)/HCOOH	Piperidine (5)	EtOAc	No reaction after 1 week
4	PhCHO (3)/HCOOH	Piperidine (5)	EtOAc	No reaction after 3 days
5	PhCHO (3)/HCOOH	Piperidine (5)	MeOH	No reaction after 3 days
6	PhCHO (1)	DBU 20mol%	DCE, 1 day rt, 4 h 80 °C	No reaction
7	PhCHO (1)	tBuOK (2)	DMA, 1 day rt 4 h 80 °C, 15 h 120 °C	Reaction with DMA, degradation of starting material
8	PhCHO (1)	$Et_3N/ZnCl_2$ /TMSCl	CH_3CN, 1 day rt, 4 h 80 °C	No reaction

To start with, the method explained in the previous section 2.3.2.5 (page 131) was applied, using acetone, acetaldehyde or benzaldehyde instead of formaldehyde (Entry 1-5, Table 19). Formic acid was added to catalyse the reaction and, for Entry 2 (Table 19), water was added to see if this could aid the reaction. As seen above for formaldehyde, reaction times could be fairly long, and therefore, longer times were expected for these less reactive systems. However, even after 4 weeks no reaction took place and all starting material was recovered. Hence, a range of further, more forcing conditions were examined (Table 19), but without any sign of reactivity, and partly through lack of time, no further work was carried out in order to try and solve the major reactivity issues around other carbonyl systems.

2.3.2.7 Solubility tests

In order for the crosslinker to be integrated into a latex polymer formulation without modifying the delicate balance of the emulsion polymerisation process, the monomers need to meet specific solubility requirements. As described in previous unpublish work in the Whiting group (section 2.1.4.1), a high solubility in water of the crosslinkers can be self-defeating. In fact, to take part in the polymerisation process which happens in the monomer droplets, the crosslinker needs an aqueous solubility maximum of 5%. On the other hand, a high affinity is required for the monomer droplets where polymerisation takes place (composed of main monomers, such as methyl methacrylate). Therefore, it is necessary for the crosslinker to have a high solubility in the monomers mixture of at least 15-25%. Bi-functional vinyl sulfonyl sulfonamide **185** was synthesised with the idea of being added at the end of polymerisation as a 2-pack crosslinker system, and for this reason, a high solubility in water was required. With this in mind, the synthesised crosslinkers, shown in Figure 25, were solubility tested in both methyl methacrylate and water.

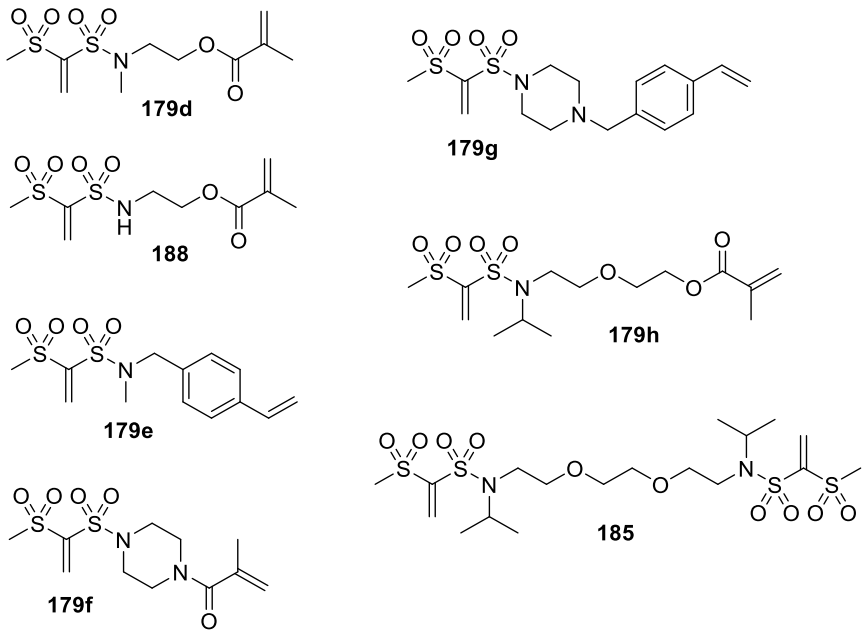


Figure 25. Synthesised crosslinkers to be tested for suitable solubility properties.

All of the monomers shown in Figure 25 presented poor solubility in water, mainly due to the presence of sulfonyl sulfonamide functions. However, due to the presence of an

equilibrium between the vinyl and the hydrated derivative, the hydroxyalkyl group, this could lead to an increase of solubility through the hydration process. This could be particularly important at higher pH. For this reason, as an example crosslinker, **179d**, was tested in water when this was brought to *ca*. pH 8.5 (Figure 26).

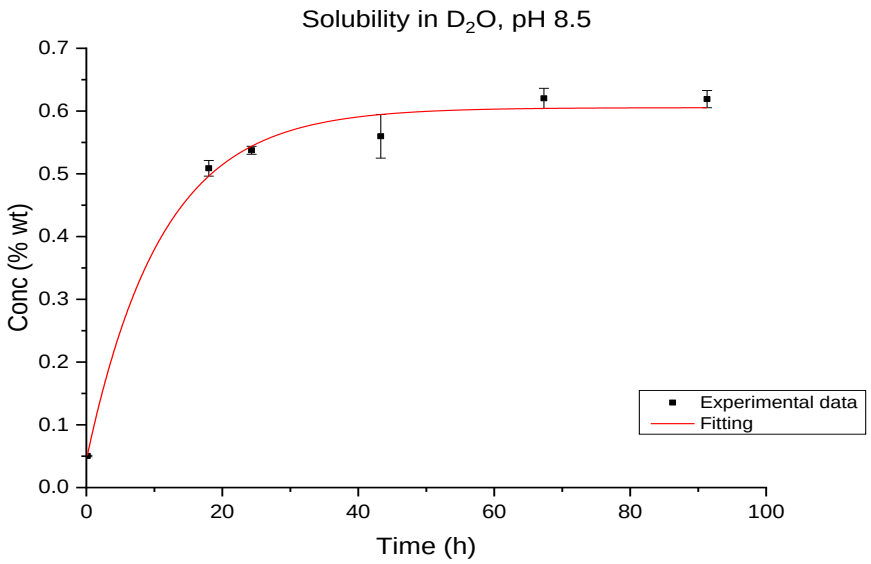


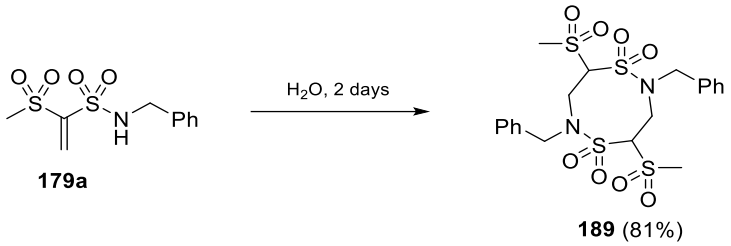
Figure 26. Solubility of **179d** in D_2O followed by ^{1}H-NMR using dimethyl sulfone as an internal standard.

As envisaged, the crosslinker **179d** did hydrate over a period of approximately 30 hours, increasing the solubility of the monomer in water, as shown Figure 26. The crosslinker **179d** showed an initial concentration at time zero in water of 0.05%, and after about 35 h, this reached a maximum concentration of 0.6%, probably due to the fact the crosslinker became fully hydrated increasing its solubility.

Solubility measurements of this type were not always so promising in non-aqueous systems, which revealed poor solubility for crosslinkers **179d** and **179e** in MMA (about 0.4%). On the other hand, crosslinkers **179f**, **179g** and **179h** showed different degrees of solubility in methyl methacrylate, with the latter being completely miscible.

It should be noted that although compound **188** was included as one of the possible linking monomers, it had to be later removed from consideration as a crosslinking monomer, upon finding that the sulfonamide function needed to be non-hydrogen substituted when

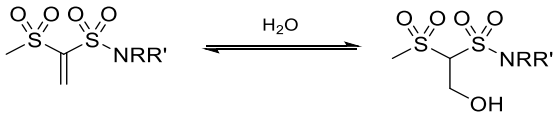
combined with the vinyl Michael acceptor, and hence, no solubility tests were performed. This was due to self-Michael addition, involving the surprisingly nucleophilic NH showing an ability to react with another molecule of vinyl sulfone. Presence of such self-dimerising structures were found with compound **179a** in water which, over a period of time of 2 days, gave **189** cleanly in 81% yield (Scheme 127).



Scheme 127. Formation of compound **189** form self-reaction of **179a**.

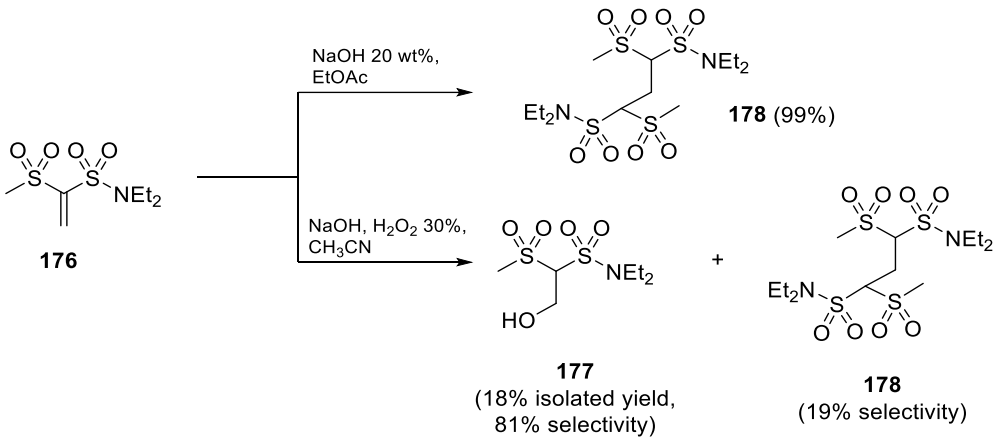
2.3.2.8 Synthesis of hydroxyethyl sulfonyl sulfonamides

The small set of experiments highlighted in this section, were aimed at obtaining hydroxyl ethyl sulfonyl sulfonamide derivatives, if possible, in a stable form, from the corresponding vinyl sulfonyl sulfonamide through hydration when water was present (Scheme 128).



Scheme 128. Vinyl sulfonyl sulfonamide equilibrium in the presence of water.

As a test experiment, compound **176** was used since all possible by-products had been previously isolated. Therefore, in order to obtained only the hydrated form, **177**, the corresponding vinyl sulfonyl sulfonamide **176** was placed in a highly basic environment in which NaOH 20 wt% (5 equivalents) were added in ethyl acetate. The reaction yielded to 99% of self-condensation product **178** after 12 h.



Scheme 129. Attemps in synthesis of compound **177**.

However, it was possible to achieve compound **177** by reacting vinyl sulfonyl sulfonamide **176** with sodium hydroxide in the presence of hydrogen peroxide. This led to a full conversion of the starting material to 81% selectivity of **177** and 19% selectivity of **178** (calculated by ^{1}H NMR), after a 74% mass recovery. However, purification through silica chromatography yielded only 18% of compound **177**. These experiments show the potential reactivity of **176** both towards facile hydration and especially towards retro-aldol-like condensation, even under neutral conditions, but even more accelerated under basic conditions. The difficulty of silica purification also suggested possible silica surface reaction; a process dissimilar to the crosslinking process anticipated to drive polymer crosslinking.

2.3.2.9 Summary

In this section, strategies to achieve synthesis of vinyl-1-sulfonyl-1'sulfonamide have been covered. Initially, in order to avoid the use of external aldehydes (especially toxic formaldehyde), a first strategy examined relied upon an intramolecular Knoevenagel-type reaction, after an aldehyde functionality had been introduced into the structure as exemplified in Scheme 113, page 120.

Ozonolysis reactions were undertaken on substrate **127f** and, although an aldehyde peak could be seen in the crude NMR, the reaction mixture resulted complicated and **166** was never isolated. Further Pd-catalysed oxidation reactions such as Wacker-Tsuji were undertaken in which however, wanted compounds were never isolated and intramolecular Knoevenagel type reaction to give structure such as **167** were never achieved.

As a consequence, this strategy was abandoned for the use of iminium salts to achieve vinyl sulfonyl sulfonamides. This reaction reproducibility was hard to control and inconvenient for larger scale reactions. Moreover, compounds such as **178** (Figure 27)surprisingly achieved when formaldehyde was used in combination with base for the synthesis of vinyl sulfonyl sulfonamide.

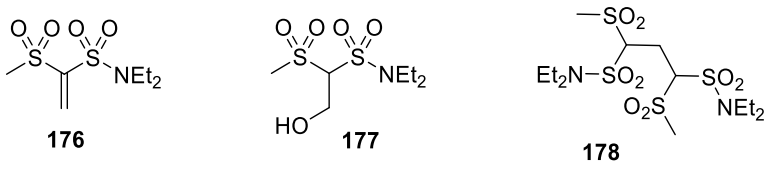


Figure 27. By-products forming from the use of iminium salts or condensation with formaldehyde and base.

The synthesis of vinyl sulfonyl sulfonamides was finally achieved through a base catalysed Knoevenagel condensation in the presence of formic acid. Using this general procedure potential crosslinkers listed in Figure 28 were synthesised. Nevertheless, in order to be used as crosslinkers in emulsion polymerisation, it was necessary for the crosslinker to have reasonable solubility in the monomers mixture (mostly methyl methacrylate and butyl acrylate) of at least 15-25%. Amongst the crosslinkers reported in Figure 28, only

crosslinkers **179f**, **179g** and **179h** showed different degrees of solubility in methyl methacrylate, with the latter being completely miscible. All other compounds exhibit poor solubility, and therefore, these could not be employed for final tests in emulsion polymerisation. Finally, it should be noted that although compound **188** was included as one of the possible linking monomers, it had to be later removed from consideration a crosslinking monomer, upon finding that the sulfonamide function needed to be non-hydrogen substituted when combined with the vinyl Michael acceptor, and hence, no solubility tests were done. This was due to self-Michael addition, involving the surprisingly nucleophilic NH, showing an ability to react with another molecule of vinyl sulfone.

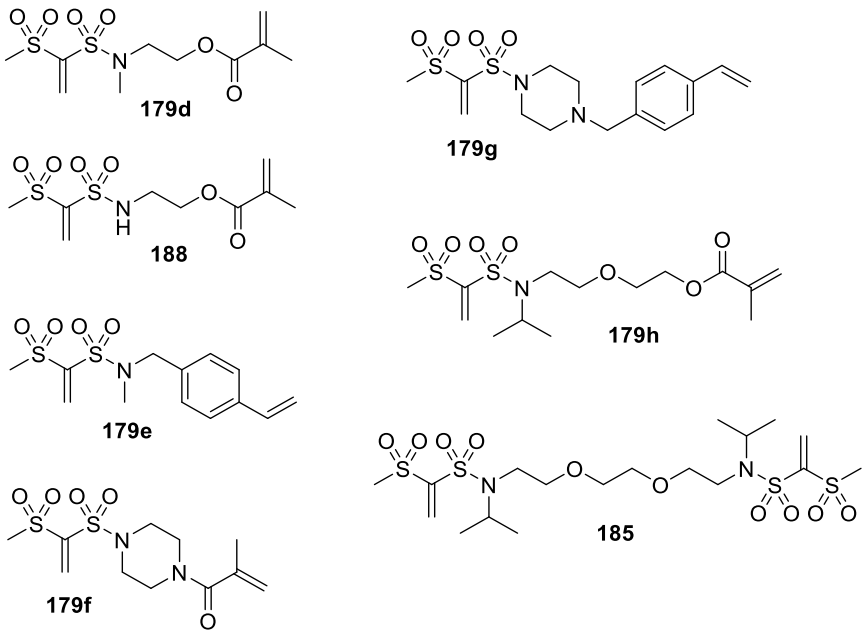


Figure 28. Synthesised crosslinkers.

Unlike the other synthesised crosslinkers, **185**, is not meant to be co-polymerised in an emulsion polymerisation process but added at the end of the latex formation in order to crosslink thanks to the presence of two Michael acceptors sites.

2.3.3 Vinyl-sulfonyl-sulfonamide conjugate additions

2.3.3.1 Additions of different nucleophiles

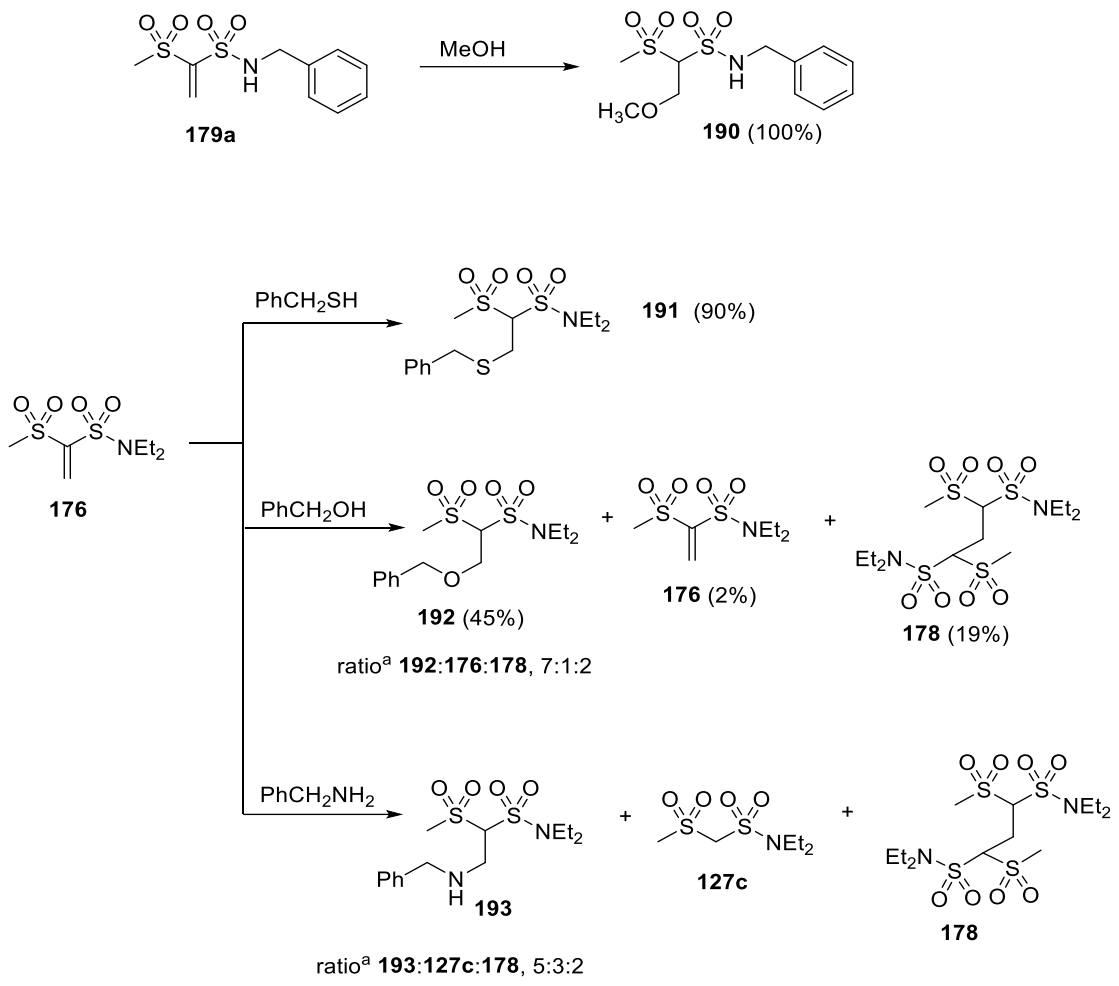
Bis-vinyl sulfones and vinyl sulfones are widely used electron-deficient π-systems in Michael additions as explained in section 1.4. To define the scope of potential reaction partners of ethylene sulfonyl sulfonamides, reactivity towards thiols, amines and alcohols were tested (Scheme 130). Substrate **176** was once again employed due to its facile synthesis and absence of particular functional group that could interfere with the reaction. Moreover, most by-products that could generate from this substrate have been isolated, facilitating their identification.

Although, it was important to understand the reactivity towards different nucleophiles, hydroxyl groups were of particular interest due to their wide presence as side chains on polymer coatings. As a first simple test, substrate **179a** (Scheme 130) was dissolved in methanol, after which methanol could be easily removed to yield compound **190** (100%).

Typically, thiol–Michael reactions proceed through either a base-catalysed or a nucleophile-initiated pathway, both well-documented.[201] Over the years, thiol-Michael addition reactions have been tailored to progress under mild, solventless reaction conditions using mild catalysts to yield a highly efficient, modular click reaction. In this case, reaction of vinyl *bis*-sulfone like **176** with benzyl mercaptan under neutral conditions gave stoichiometric addition in dry THF denoting a high reactivity towards thiols. *bis*

Meanwhile, when the same conditions were applied to benzyl amine and benzyl alcohol, full conversion of the starting material could not be always achieved, and by-products were obtained. Due to the presence of a new chiral centre and the presence of diastereoisomers, isolation by column chromatography was needed. Unfortunately, the vinyl sulfonyl sulfonamide **176** and amine adducts **193** seemed to be unstable on silica and purification was not possible. To avoid any influence from the solvent (in this case THF) reactions for amines and alcohols nucleophiles were successively conducted using these as solvents. Unfortunately, as the nucleophiles were used as solvents, it was not

possible to follow the reaction by NMR. Moreover, final products such as **193** was not stable on silica, hence, TLC was not an appropriate monitoring tool. Therefore, the reactions were given two weeks to react at room temperature, and afterwards, the excess of nucleophile was removed by Kügelrohr distillation. The reactions examined, and results obtained are summarised in Scheme 130.



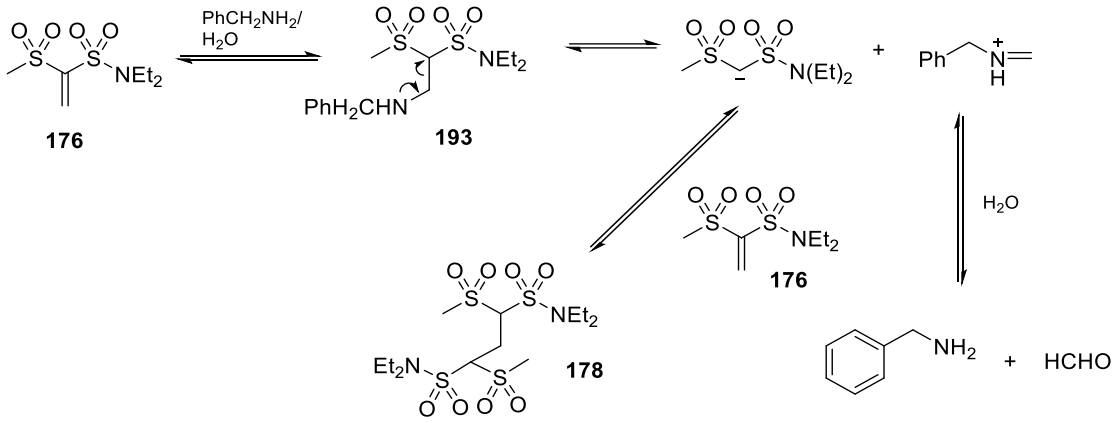
[a]Ration calculated on the crude ^{1}H NMR.

Scheme 130. Michael addition of different nucleophiles to compound **176** and **179a**, employed as a model.

In the case of reaction of **176** with benzyl alcohol, the ^{1}H NMR showed reaction with the nucleophile, but this seemed to not reach completion even after two weeks, as the ^{1}H NMR showed remaining vinyl sulfonyl sulfonamide **176** (double bond at 6.93 ppm, 2% isolated yield), showing that it was likely equilibrium process, and equilibrium had been reached. Beside this, 19% of compound **178**, arising from the self-condensation of two molecules of the same vinyl sulfonyl sulfonamide **176**, was also formed. Minor quantities of

hydroxylalkyl sulfonyl sulfonamide that were present in the starting material and were found in the same ratio at the end of the reaction. The three different products were isolated by silica gel chromatography and compound **192** was isolated in 45% yield (noting a certain instability on silica).

Accordingly, the reaction of **176** with benzylamine gave mainly three compounds: amine adduct **193**; sulfonyl sulfonamide **127c**; and compound **178**. As mentioned previously, adduct **193** was unstable on silica, as well as on neutralised silica and no separation of the different compounds was achieved, even with neutral alumina. For this reason, the different compounds could not be separated and **193** not isolated in a pure form. However, it was clear that from the disappearance of the methylene peak at 6.99 ppm and the appearance of a triplet at 4.14 ppm, typical of the proton on the α-C in respect to the sulfones when this has reacted with a nucleophile, that reaction as occurred with the amine nucleophile. In fact, when a more electron-withdrawing group reacts with the methylene moiety, like in the case of self-condensation, this triplet is shift to ca. >5 ppm (in this case 5.04 ppm). Unequivocal presence of the α-CH_2 of the sulfonyl sulfonamide **127c** was manifested by the singlet at 4.38 ppm. It is hard to know if sulfonyl sulfonamide **127c** was present before distillation or it was induced by this, however, it is possible to say that compound **127c** was also seen when benzylamine was used stoichiometrically in THF and no distillation was used. It is reasonable to think that the formation of the methylsulfonyl-methylenesulfonamide **127c** originates from a retro-aldol type reaction shown in Scheme 131. In support of this mechanism there is the presence of a small singlet at 8.40 ppm in the ^{1}H-NMR and a peak at 162 ppm in the ^{13}C-NMR showing the presence of an amide. It is also important to notice that in this case hydroxyl sulfonyl sulfonamide, which was present in traces in the starting material, was all reacted at the end to the reaction.

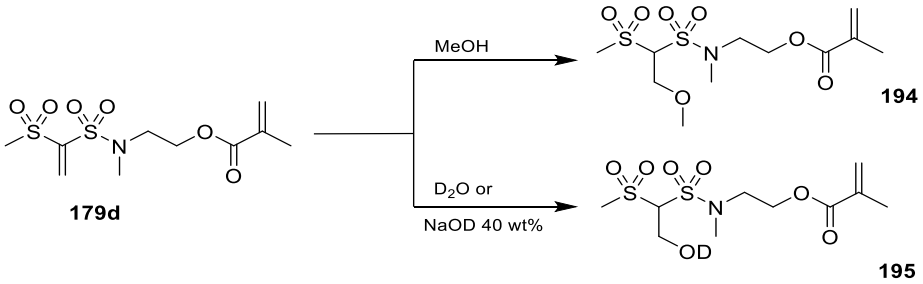


Scheme 131. Proposed mechanism in the formation of **178**.

On the other hand, reaction of **176** with benzyl alcohol never showed any presence of the sulfonyl sulfonamide **127c**, indicating that in this case, a concerted mechanism might be occurring. Also, in this case, a very minor singlet at 10 ppm in the ^{1}H-NMR was present. Moreover, it is interesting to note that no by-products were obtain from additions of benzyl thiol (Scheme 130), which reaction gave the only compound **191**, suggesting a different mechanism is taking place.

2.3.3.2 Kinetic studies

Preliminary kinetic tests of vinyl sulfonyl sulfonamide systems in crosslinking model reactions were conducted in neutral or basic conditions in order to appreciate the different reaction time. As shown from the solubility tests in section 2.3.2.7, none of the sulfonyl sulfonamides previously synthesised were found to be sufficiently soluble in water and, therefore, DMSO was used as a solvent. Different equivalents of MeOH or D_2O or NaOD (40 wt%) were added to **179d** in DMSO and the reaction followed over time by ^{1}H NMR (Scheme 132).



Scheme 132. Kinetic tests of crosslinking reactions utilizing model compound **179d**.

Figure 29 shows, under neutral conditions, the addition of 1.2, 2.4, 4.8 and 7.2 equivalents of methanol in DMSO-d6. This resulted in an increasing exponential decay in the concentration of the starting material **179d**, which reaches steady state after about 10 hours in the case of a large excess of reagent, suggesting the achievement of an equilibrium.

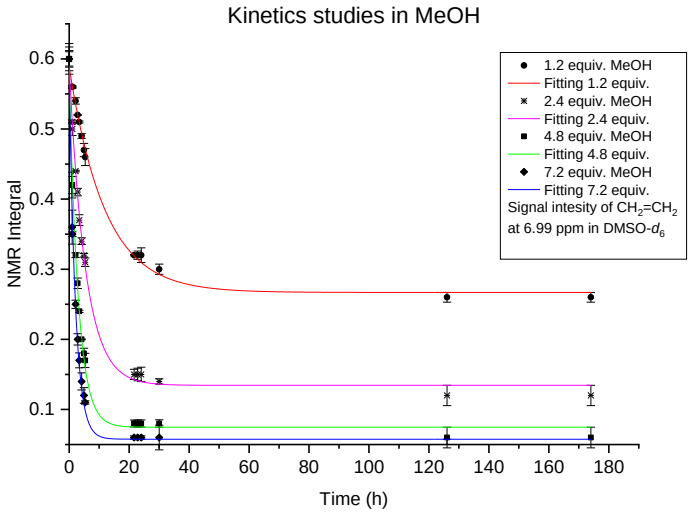


Figure 29. Kinetic study of the model reaction of **179d** with MeOH in DMSO-d_6.

The same trend was highlighted in the case of deuterated water, as reported in Figure 29.

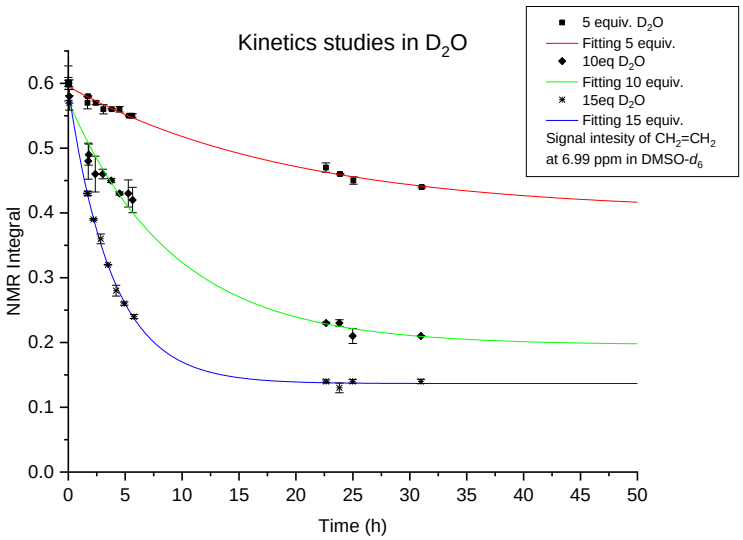


Figure 30. Kinetics studies adding increasing equivalents of deuterated water (5, 10 and 15 equivalents) to **179d**.

However, under basic conditions, the reactions were almost instantaneous, and over time, this reached complete reaction (hydration) rather than establishing a more intermediate equilibrium (Figure 31).

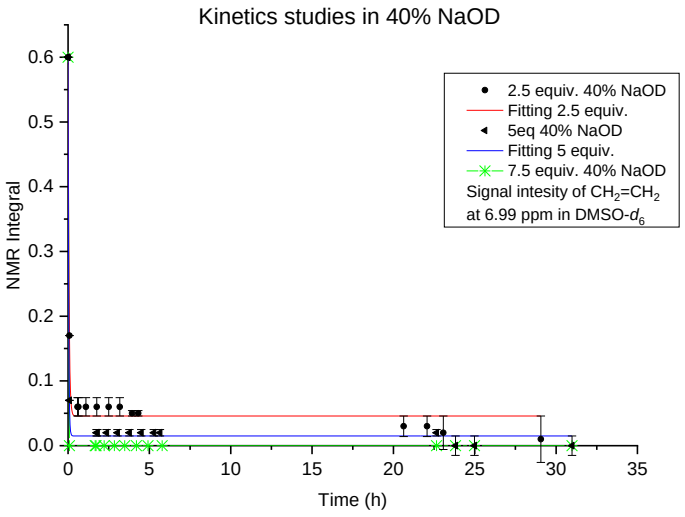


Figure 31. Kinetic study of the model reaction of **179d** with NaOD 40 wt% D_2O in DMSO-d_6.

Unfortunately, this type of model reaction did not permit a realistic calculation of the pH of the system but was nonetheless indicative of the behaviour of these systems under basic conditions. It is interesting to note that for an excess of reagent, the concurrency of high

basicity and excess of D_2O, ended in an almost instantaneous completion of the reaction (green line, Figure 32).

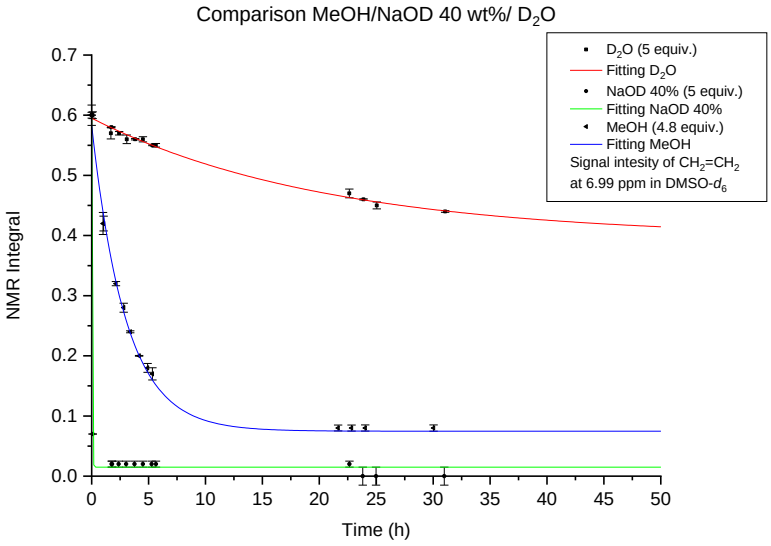


Figure 32. Comparison of the kinetics of the three different reactions when same equivalents of reactant was added.

2.3.3.3 Summary

The use of *bis*-vinyl sulfones and vinyl sulfones as electron-deficient π-systems in Michael additions has been widely documented. However, due to the lack of studies in the case of vinyl sulfonyl sulfonamides, their reactivity towards thiols, amines and alcohols needed to be tested.

Results showed high reactivity of vinyl sulfonyl sulfonamides in thiol-Michael additions. Unlike for vinyl sulfones, this reaction proceeded efficiently without the use of a basic catalyst. On the other hand, reaction with alcohol required its use in great excess in order to achieve reaction, which however, never got to completion. Also Michael additions of vinyl sulfonyl sulfonamide towards amines needed large excess of the nucleophile, but the Michael addition adduct could never be isolated due to its instability on silica gel. In fact, although formation of the adduct was suggested by mass spectrometry, no isolation of the compound could be obtained. Moreover, sulfonyl sulfonamide system was present in the crude NMR, suggesting retro-aldol reaction taking place. Finally, in both Michael addition of vinyl sulfonyl sulfonamide with amine or alcohol, reaction between two molecules of vinyl sulfonyl sulfonamides took place. Although we have proposed a reaction mechanism, this is still not fully clear, and more studies need to be done in order to fully confirm this hypothesis.

Preliminary studies on the time of reaction of vinyl sulfonyl sulfonamide in the presence of methanol or water were also conducted. In particular, it has been confirmed that, in neutral conditions, an excess of alcohols is needed and that, equilibrium seems to be reached after ca. 20 hours of reaction time. The disappearance of the π-system of vinyl sulfonyl sulfonamide was followed through ^{1}H NMR and therefore, the possible hydration of this in the presence of deuterated water in neutral and basic conditions. As expected, results showed an instantaneous reaction with complete disappearance of the vinylidene group when basic conditions were used meanwhile, in neutral conditions, reactions reached steady state after about 10 hours in the case of a large excess of reagent, suggesting the achievement of an equilibrium.

2.3.4 Emulsion polymerisation

Crosslinking monomers were specifically designed with the major project objectives set around the idea of using the 4th generation vinyl sulfonyl sulfonamides Figure 33. The proposed compounds present an asymmetric structure, while continuing to use of a sulfonyl moiety as second EWG and introduction of a polymerisable functional group attached. These monomers were required in order to meet certain solubility criteria in order to be co-polymerised in emulsion polymerisation reactions. In particular, they needed to be miscible with standard monomers such as methyl methacrylate, styrene, butyl acrylate etc., usually employed in emulsion polymerisation preparations, meanwhile trying to maintain a low solubility in water.

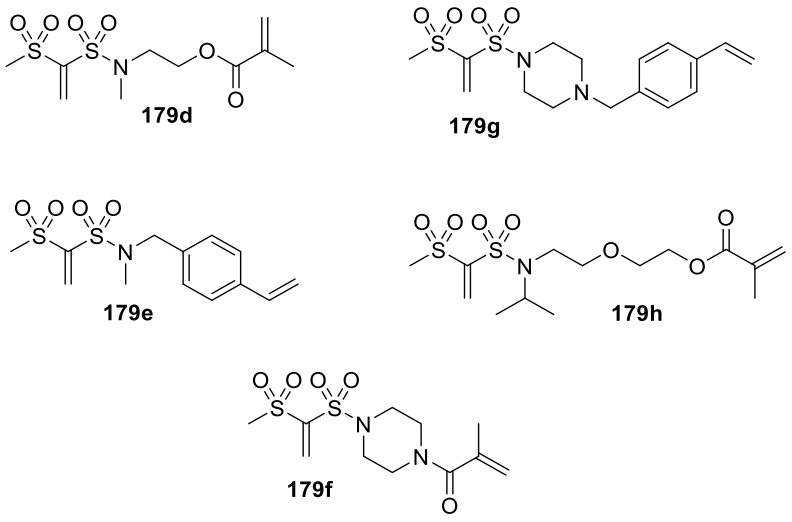


Figure 33. Proposed monomers to be synthesised.

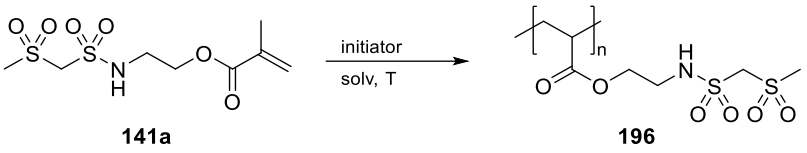
From the work discussed earlier, on the synthesis of sulfonyl sulfonamides, a general observation is that such compounds were often found to have very low solubility in most organic solvents, including monomers (MMA, BA, styrene etc) and water. In fact, as explained in section 2.3.2.7, compounds **179d** and **179e** showed no solubility in standard monomers (MMA and BA), and even compounds **179f** and **179g** showed only partial solubility, with compound **179h** being the exception in exhibiting full miscibility with methyl methacrylate and butyl acrylate. For this reason, compounds **179d** and **179e** could not be employed in emulsion polymerisation tests but, due to their facile and high yielding synthetic route, these two compounds were still employed in free radical polymerisation

reactions. In fact, due to the complexity and the number of variables in emulsion polymerisation, it was decided to proceed firstly with preliminary co-polymerisation with only methyl methacrylate or butyl acrylate and **179d-e** in order to study the reactivity of these types of such systems under free radical polymerisation conditions.

2.3.4.1 Free radical polymerisation

Given the novelty of the new compounds being made as polymer monomers, i.e. **179d** and **179e**, it was necessary to verify how such compounds behaved under polymerisation conditions. However, the presence of the vinyl sulfonyl sulfonamide moiety could constitute a second potential reactive site for polymerisation and therefore, in order to avoid such side reactions, compound **141a** was initially employed for homopolymerisation (Table 20) in order to examine the simple polymerisation in the absence of any potentially competing functional group.

Table 20. Attempt in homopolymerizing compound **141b** by free radical polymerization.



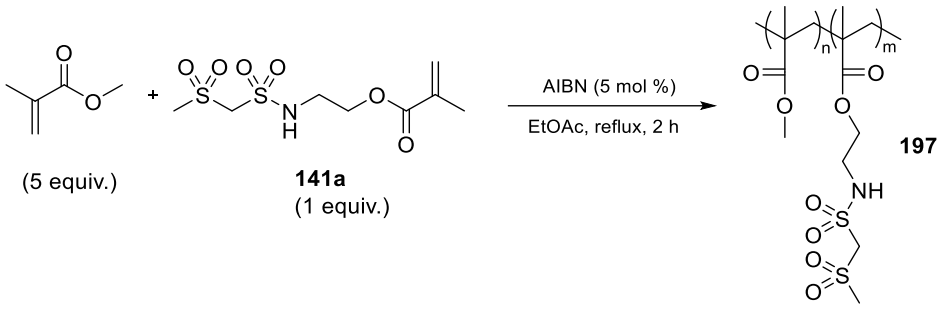
141a **196**

Entry	Initiator	Solvent	T (°C)	Time (h)	Results
1	AIBN (5 mol%)	Toluene	70	24	×
2	AIBN (1.5 mol%)	MEK	50	24	×
3*	AIBN (1.5 mol%)	MEK	50	24	×
4*	AIBN (4 mol%)	MEK	60	48	×
5*	BPO (4 mol%)	EtOAc	reflux	48	×

* Starting material columned in order to eliminate the inhibitor (MEHQ). All polymerisations were perfomed under Ar.

Surprisingly, **141a** did not seem to be reactive enough towards self-polymerisation in the presence of radical initiators under various conditions (see Table 20). Initial polymerisation was performed in toluene with 5 mol% AIBN (Entry 1, Table 18), however, no polymer was formed and starting material could be detected by ^{1}H-NMR spectroscopy. Thermogravimetric analysis (TGA) was conducted on both **141a** and **179d** monomers in order to exclude instability and degradation related to higher temperatures used in polymerisation. TGA revealed that both monomers were stable, up to 200 °C in the case of **141a** and up to ca. 150 °C in the case of **179d**, therefore, both were clearly stable under

the polymerisation temperature conditions. Consequently, other conditions were tried such as the use of MEK as a solvent, in which compound **141a** showed better solubility (Entry 2, Table 18). However, there was no change, hence, the radical inhibitor MEHQ present in the monomer was removed prior to the polymerisation reaction (Entry 3, Table 18) but only a full recovery of starting material resulted. Therefore, higher amounts of initiator (4 mol% AIBN), slightly higher temperatures and longer times of reaction were tried, but again, with no success. Finally, in Entry 5 (Table 18), BPO (4 mol%) was used but only starting material could be once again recovered. Hence, in order to try and help with the seeming low reactivity of these types of monomers, free radical polymerisation was performed in the presence of either MMA or styrene, as outlined in Scheme 133, i.e. to access a heteropolymer product. Free radical co-polymerisation of methyl methacrylate together with **141a** gave co-polymer **197** as demonstrated from the ^{1}H NMR (Figure 34).



Scheme 133. Co-polymerisation of **141a** and MMA.

As shown in Figure 34, the peaks at 6.11 and 5.70 ppm relative to the acrylate monomer **141a** (top spectrum) were not present in the ^{1}H-NMR spectrum of **197** (bottom spectrum), meanwhile, broadening of the rest of the peaks such as the one at 5.18 ppm (bottom spectrum), suggests polymerisation has occur. Moreover, typical peaks of PMMA at 0.87 ppm and 1.90 ppm (reported in the literature)[202] were present, confirming efficient co-polymerisation.

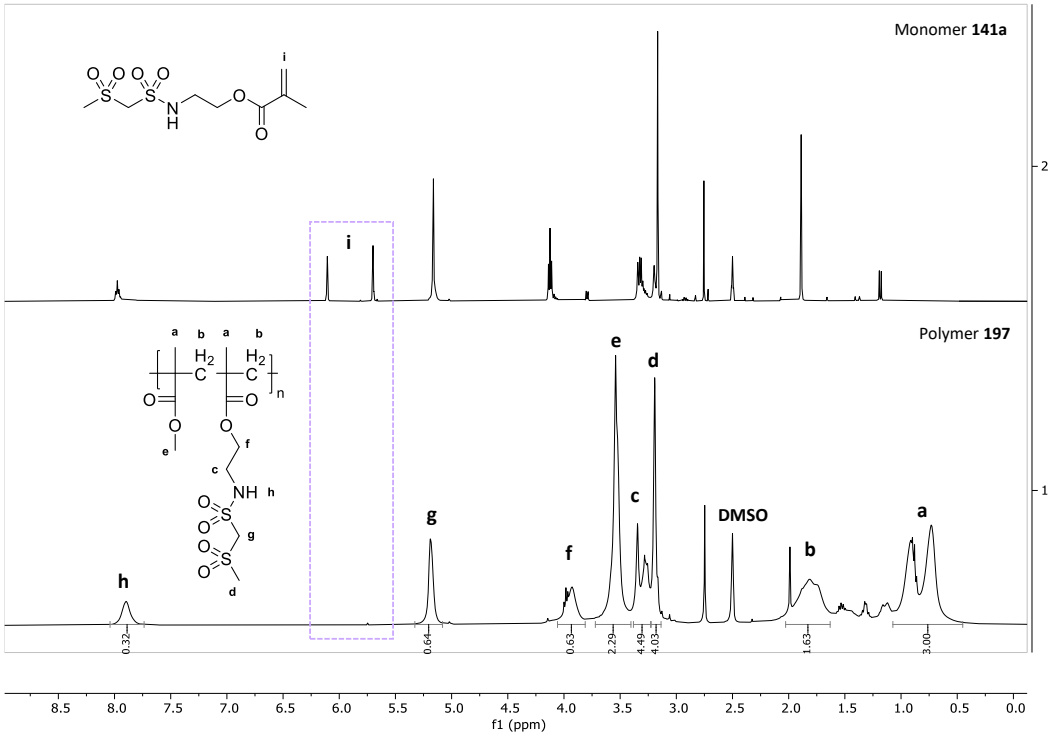


Figure 34. ^{1}H NMR spectrum (DMSO-d_6, 400 MHz) of **141a** on top and **197** at the bottom.

The proton NMR spectrum of co-polymer **197** (Figure 34) showed the ratio between MMA/**141a** (i.e. peak A 3H *versus* peak G 2H) to be 3:1 which (although it does not reflect exactly the equivalents used for the polymerisation, MMA/**141a,** 5:1) still indicated that the polymer was not the homopolymer of **141a**, rather a co-copolymer **197**.

The mass distribution shown in Figure 35 of **197** also indicated the presence of a polymer, confirming the deductions made from the ^{1}H NMR. However, two small peaks at low MW were present, which could have indicated that smaller oligomers had formed. Unfortunately, the molecular weight could not be precisely calculated, only roughly estimated, since the parameter dn/dc used was the one relative to PMMA.

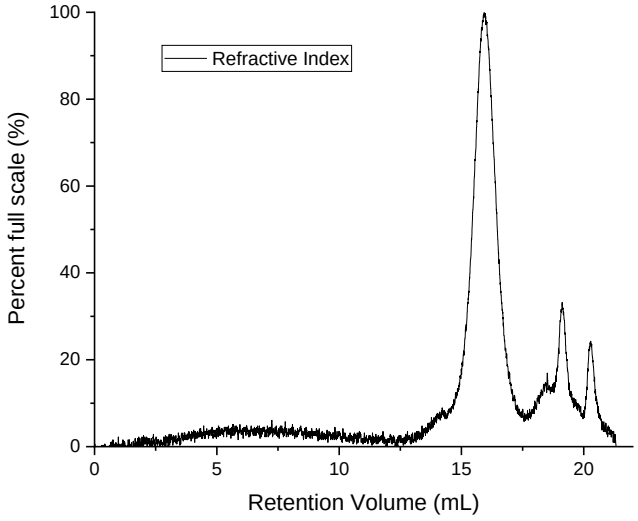
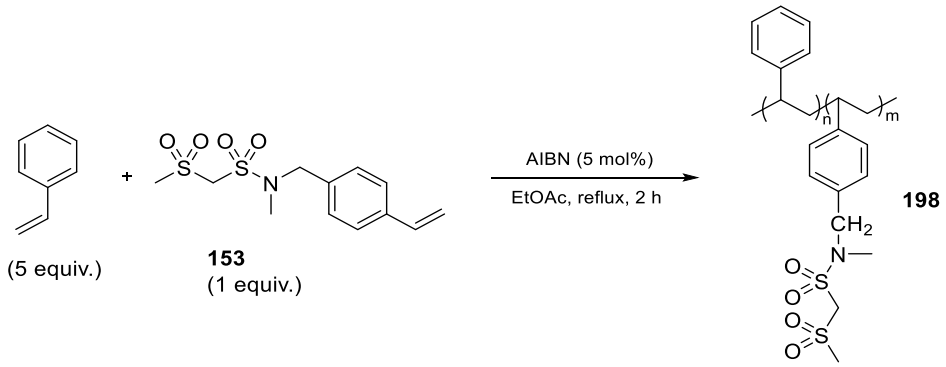


Figure 35. GPC in THF of compound **197**; Molecular weight analysis was carried out by size exclusion chromatography (SEC) using a Viscotek TDA 302 with detectors for refractive index, light scattering and viscosity. 2 300 mm PLgel 5 µm mixed C-columns were used with a linear molecular weight range of 200 – 2 000 000 g mol^{-1}. THF was used as the eluent at a flow rate of 1.0 $mLmin^{-1}$ at a temperature of 35 ˚C. Triple detection SEC was utilised for molecular weight determination with light scattering, using PMMA dn/dc value of 0.085 mLg^{-1}. This gave values for the number-average molecular weight (M_n) and weight-average molecular weight (M_w). Samples were prepared for SEC analysis by dissolving 1 mg of **197** in 1 mL THF for a concentration of 1 mg mL^{-1}.

Likewise, co-polymer **198** was synthesised from the reaction of **153** with styrene (Scheme 134).



Scheme 134. Co-polymerisation of **153**-styrene.

Similar observations to **197** could also be made in the case of compound **198**, where ^{1}H NMR showed that the monomer **153** had all been consumed as peaks at 5.27 and 5.84 ppm are not anymore present in the spectrum (bottom). ^{1}H NMR in Figure 36 clearly showed broad peaks for polystyrene at 6.91 and 1.51 ppm (top *versus* bottom spectrum), as well as other broad peaks all attributable to the polymerisation of compound **153**.

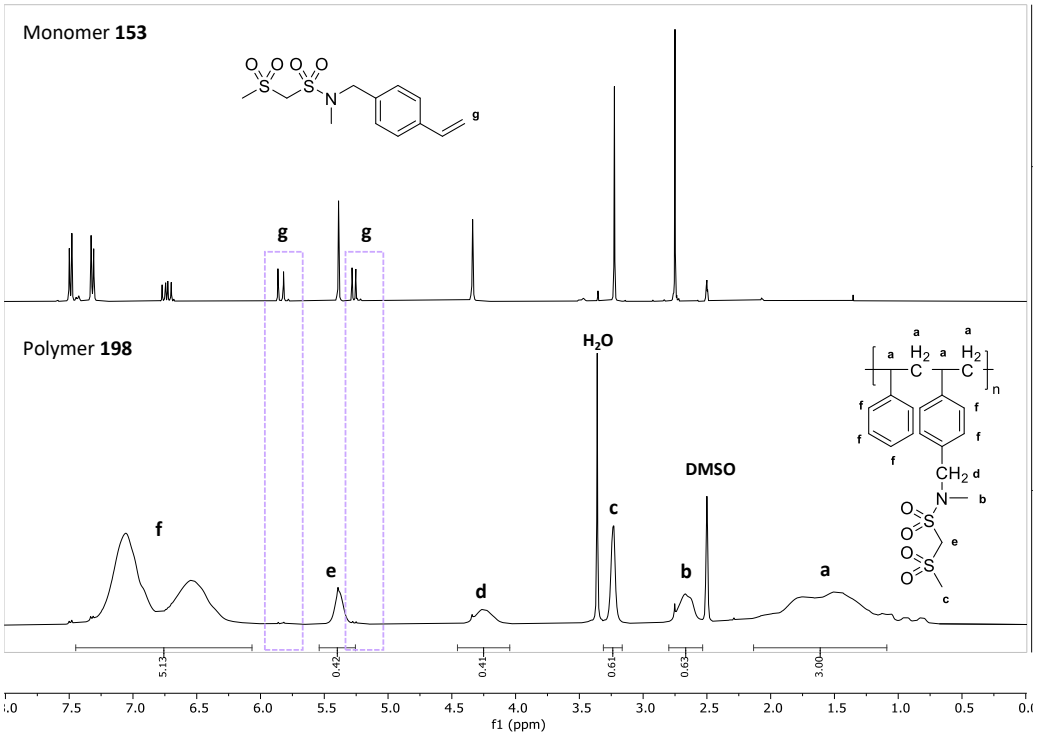


Figure 36. ^{1}H NMR spectrum (DMSO-d_6, 400 MHz) of **153** at the top and **198** at the bottom.

For the styrene analogue **198**, the ratio between the ^{1}H NMR peaks reflected the ratio of monomer **153**:styrene of 1:5. In fact, comparing peaks A (3H) with peak E (2H) or D (2H) or C (3H) of the bottom spectrum, the ratio was consistently about 1:5, confirming that the co-polymerisation had occurred efficiently. In the same way, GPC analysis (showed in Figure 37) gave a wide MW distribution of about 11000 Da, and again in this case, the molecular weight could not be precisely calculated but only roughly estimated since the parameter dn/dc used was the one related to polystyrene.

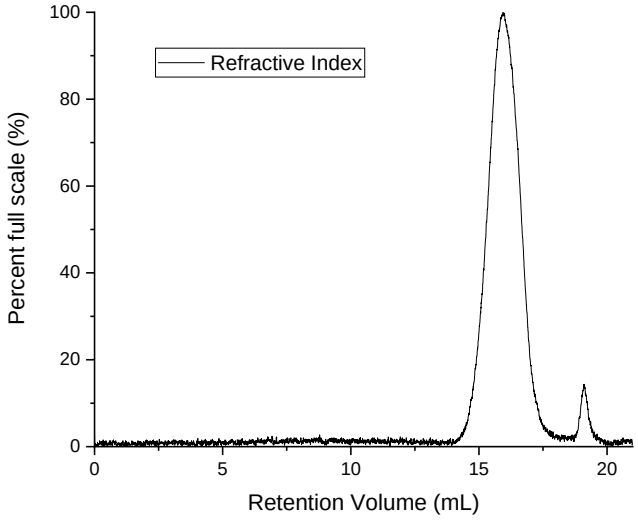
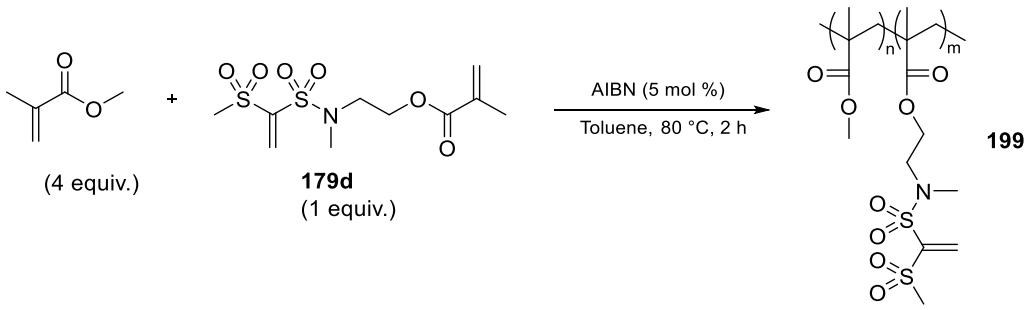


Figure 37. GPC in THF of compound **198**; Molecular weight analysis was carried out by size exclusion chromatography (SEC) using a Viscotek TDA 302 with detectors for refractive index, light scattering and viscosity. 2 300 mm PLgel 5 µm mixed C-columns were used with a linear molecular weight range of 200 – 2 000 000 $gmol^{-1}$. THF was used as the eluent at a flow rate of 1.0 $mLmin^{-1}$ at a temperature of 35 ˚C. Triple detection SEC was utilised for molecular weight determination with light scattering, using PST dn/dc value of 0.189 mLg^{-1}. This gave values for the number-average molecular weight (M_n) and weight-average molecular weight (M_w). Samples were prepared for SEC analysis by dissolving 1 mg of **198** in 1 mL THF for a concentration of 1 mg mL^{-1}.

After these encouraging co-polymerisation results, the same types of polymerisations were then examined by using the vinyl sulfonyl sulfonamide crosslinkers **179d**, as shown in Scheme 135.



Scheme 135. Co-polymerisation of **179d** and MMA.

Unfortunately, monomers **179d** was not particularly soluble in ethyl acetate and, therefore, a solvent switch to toluene was required. In this case a white solid was synthesised, although the product obtained was not soluble in any common solvents used for liquid state ^1H NMR, hence, only solid-state NMR (showed in Figure 38) could be employed to determine if polymerisation was successful.

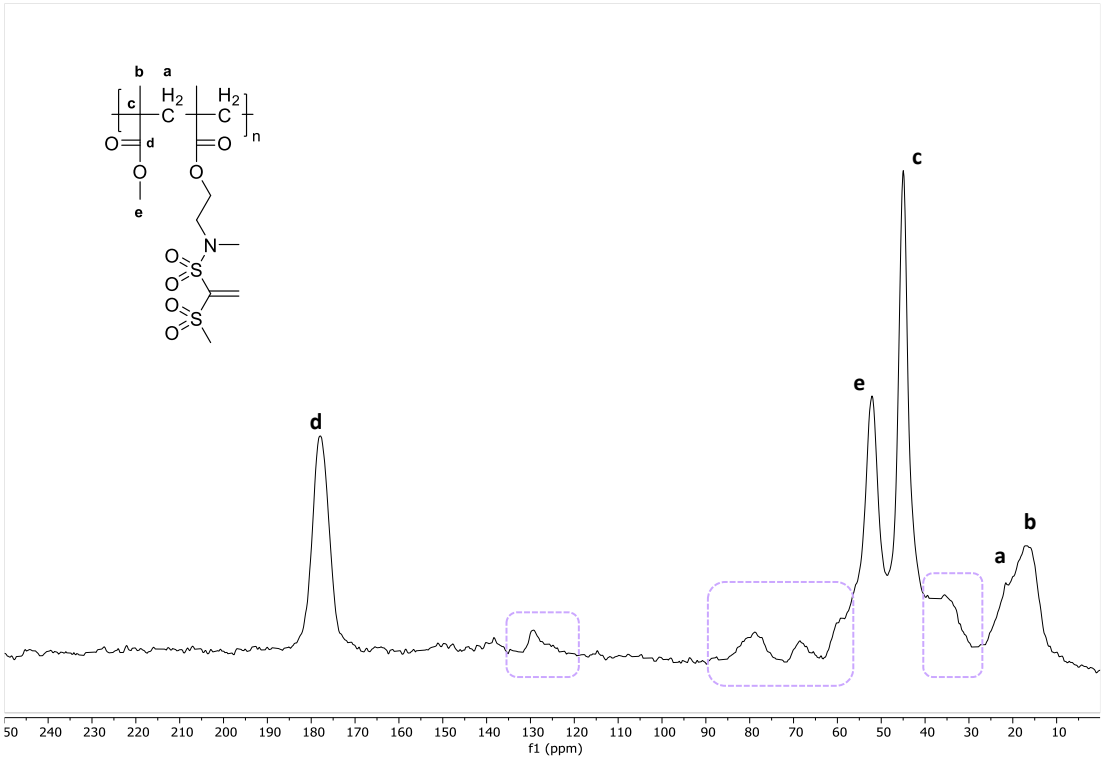
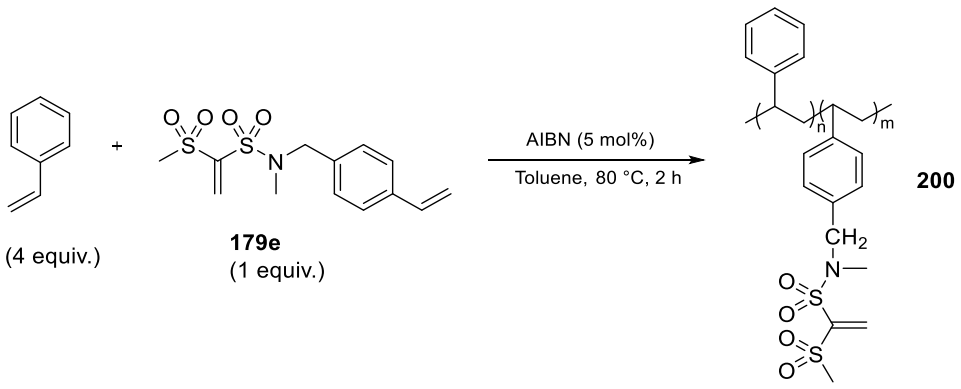


Figure 38. SSNMR of co-polymer **179d**-MMA (**199**).

As shown in Figure 38, the spectrum was dominated by signals from the PMMA, i.e. the broad resonance at 17.4 ppm plus those at 45.1, 52.3 and 177.8 ppm are all from PMMA. However, there are also some other signals present that suggest the presence of a copolymer. The presence of the second component is minor, according to the ratio MMA:monomer (4:1).

Co-polymerisation of vinyl sulfonyl sulfonamide **179e** with styrene was equally tried as shown in Scheme 136.



Scheme 136. Co-polymerisation of **179e**-styrene.

Also in this case **179e** was not particularly soluble in ethyl acetate and the toluene was used. The white solid synthesised from the co-polymerisation was not soluble in any common solvent as experience for polymer **199**, suggesting the formation of a crosslinked polymer. Similarly, solid-state NMR was employed for the analysis of **200** as shown in Figure 39.

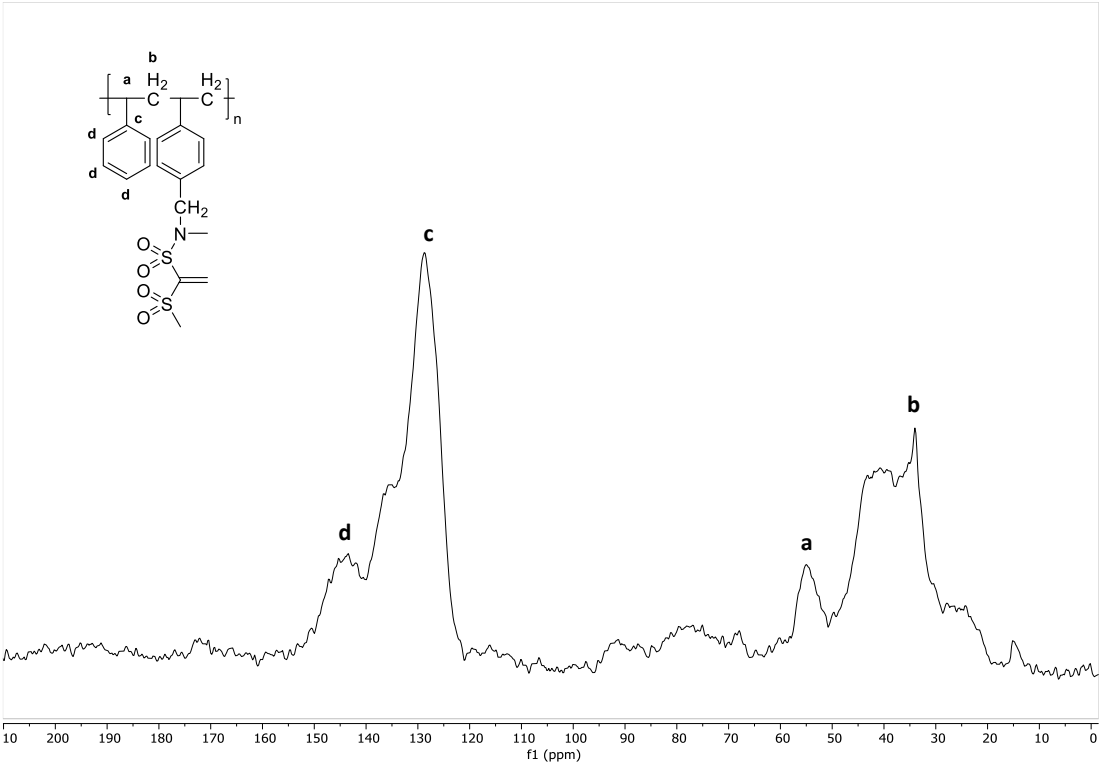


Figure 39. SSNMR of co-polymer **200**-styrene.

The appearance of the spectrum is typical of that from a polymer, particularly a polystyrene-based one as shown by broad peaks at 45, 50, 132 and 150 ppm with no long-range order and additional peaks not related to the standard polystyrene. Sometimes, polystyrene-based materials swell in a solvent (i.e. THF) and, if they do, it can result in significantly increased resolution in the ^{1}H and ^{13}C spectra. Unfortunately, attempts in swelling the polystyrene-based polymer **200** and polymethylmethacrylate-based polymer **199** failed as no HSQC or carbon spectrum could be observed, meaning that the bulk of the sample is still behaving as a solid. These results are a further suggestion that **199** and **200** are crosslinked co-polymers. This raise concerns as to whether the reactive functionality

of the new monomers would remain intact during polymerisation and be able to work as latent crosslinkers in coating formulations.

2.3.4.2 Preliminary emulsion polymerisation

The synthesis of latexes by copolymerisation with vinyl sulfonyl sulfonamide monomers provides latent functional groups which remain dormant until loss of water occurs during film formation. The loss of water triggers the formation of the highly reactive vinyl sulfonyl sulfone group that provides the possibility of crosslinking during drying of films. As investigated in section 2.3.3.1, the vinyl group can react with either a nucleophile (thiol or alcohol) or with a second unit of hydroxyl sulfonyl sulfonamide, although self-reaction would require increasing amounts of crosslinker to achieve a sufficient degree of crosslinking.

In a decorative coating technology, the most appealing nucleophiles are hydroxyl functionalities for which compounds such as hydroxypropyl methacrylate (HPMA) and hydroxyethyl methacrylate (HEMA) have been widely used for decades. In this section, an initial non-automated evaluation of the behaviour of vinyl sulfonyl sulfonamide monomers in emulsion polymerisation was investigated. Unfortunately, at this stage only monomer **179d** was available in enough quantities to be tested. As explained above, **179d** was found to be insoluble in monomers such as methyl methacrylate (MMA) and butyl acrylate (BA) used in emulsion polymerisation, hence, it was not considered suitable for automated emulsion polymerisation. However, for initial assessment and proof of concept, several emulsion polymerisations were carried out on **179d** monomer, using a procedure provided and developed by Peter A. Lovell and co-workers at University of Manchester.

As explained in section 2.1.3, emulsion polymerisation in a semi-batch procedure can be in summary described in two steps. A first step, in which some fraction of the reactants is charged into the reactor to form the seed-latex (initial charge). This avoids the lack of reproducibility of the nucleation stage when the seed is produced *in situ*. In a second step, the rest of the formulation reagents, and therefore the functional monomers, are fed into

the reaction mixture at a constant flow rate. Note that in many cases time-dependent feed rates are used. The end result and polymer quality vary greatly depending upon the composition and the amount of initial charge, as well as the composition and flow rates of the feeds and temperature of the reaction mixture. This is a complicated and delicate process where slight changes to one of the numerous variables can impact the polymer properties including copolymer composition, molecular weight distribution, polymer architecture, particle morphology and particle size distribution.

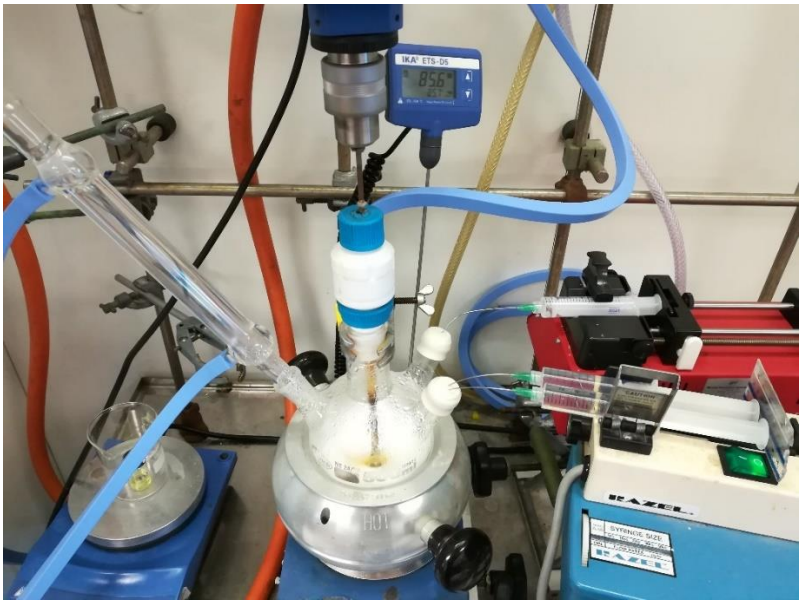


Figure 40. Representation of growth stage in emulsion polymerisation.

Seed-latex and consequently a growth of the seed-latexes (shell copolymer) were processed as follows.

2.3.4.3 Seed-latex

A stock of crosslinker-free seed latex was prepared with a monomer mixture of 50 mol% MMA and 50 mol% BA, so that the copolymer Fox Tg of approximately -5 °C would be close to the second feed polymer phase Fox Tg. Detailed procedures and reagents content can be found in the experimental section. Final latex solids content was expected to be 4.83 wt%, meanwhile standard particle size in the case of a seed latex should result in ca. 100 nm.

Different seed-latexes were synthesised (Table 21) maintaining the same quantities of reagents (monomers, water and surfactant) but varying the time of polymerisation, temperature, amount of initiator and inhibitor removal. These adjustments were necessary in order to understand the low conversion in the polymer. In fact, for emulsion polymerisation total conversion is usually reached, hence a level of conversion of 89.6% (Entry 1) was considered insufficient as any unreacted monomer can take part in polymerisation during the growth stage, modifying the final result.

Table 21. Characterisations of the core-latex.

Entry	Inhibitor removal	Initiator (%)	Temperature (°C)	Time (min)	Solid content (%)*	Conversion (%)*	DLS	
							Z-AVE d.nm	PdI
1	No	2.4	70	90	4.32	89.6	111	0.013
2	No	2.4	70	90	3.58	74.2	115	0.03
3	Yes	2.4	85	150	4.08	84.6	106	0.03
4	Yes	3.0	85	150	3.90	80.5	116	0.03
5	No	3.5	85	150	4.49	92.2	114	0.02

*Average of three repetitions.

Moreover, due to numerous variables that dominate the process, reproducibility seemed to be another issue (Entry 1 *vs* Entry 2) as the conversions lowered under the same conditions. Removal of the inhibitors normally contained in the commercially available monomers was a first approach to the problem, which unfortunately did not give any improvement. In later attempts in obtaining full conversion by increasing the temperature and time of polymerisation (Entry 3) and successively, the amount of initiator used from 2.4% to 3% (Entry 4), conversions were still only between 80-85%. In a last reaction, inhibitors were not removed, and the initiator quantity raised to 3.5% from the initial 2.4% (Entry 5) to give a conversion of 92%.

Overall, DLS measurements reported the expected particle size, around 110 nm, with a narrow polydispersity index (PDI reported in Table 21).

2.3.4.4 Growth of seed-latex

Although the seed-latex did not reach full conversion, these were employed to synthesize the shell latex, in which a "shell" of copolymerised functional and non-functional monomer

is grown over the seed particles. Therefore, the seed-latex previously formed was charged into the reaction flask and the monomer mixture (MMA, BA, HEMA, MAA and crosslinker) fed into the vessel over a period of 4 h, simultaneously with surfactants and initiator. The final latex was brought to pH ~8.5, with an expected particle size in the region of ~250 nm and a solids content of ~ 45%. The amount of reagents used for the different preparation of the four latexes are reported in Table 22.

Table 22. Standard procedure for growth of seed latex.

Reagents		Entry			
		1	**2**	**3**	**4**
Seed-latex* (g)		50.0[a]	50.0[a]	194[a]	97.0[b]
Monomers (g)	MMA	17.4	16.3	45.3	22.6
	BA	26.9	26.2	103	52.4
	HEMA	2.35	2.35	20.2	10.5
	MAA	1.00	1.00	-	-
	179d	-	1.88	-	4.54[c]
Surfactants (g)	Dowfax2A1	0.30	0.30	1.13	0.56
	RhodapexAB/20	0.30	0.30	1.13	0.56
Initiator (g)		0.12 (NaPS)	0.12 (NaPS)	0.45 (APS)	0.29 (NaPS)
DIW (g)		11.0	11.0	38.0	19.0
Total mass (g)		109	109	401	210
Expected solid content (%)		45.9	45.9	44.2	44.7

* for polymer % see Table 21; a =Entry 1 of Table 21 was used as latex; b = Entry 2 of Table 21 was used as latex; c=1 g of crosslinker was dissolved in 1 mL of DCM; APS =ammonium persulfate. Inhibitors were not removed.

Considering Entries 1-3 the same seed latex was employed and therefore, the expected solid content was calculated accordingly. Moreover, although the reactions were conducted on different scale, the same ratio between the reagents were maintained except in the cases in which the crosslinker was introduced and, therefore, a lower percentage of BA and MMA was calculated. In these preliminary emulsion polymerisations, the intent was to understand if any evident formation of crosslinking could take place during latex synthesis and, moreover, to start to test the properties of the final product. Therefore, two different latexes were synthesised, one containing 1.5 mol% of crosslinker **179d** (Entry 2) and a second one containing 2 mol% of crosslinker (Entry 4). For each of these formulations a crosslinker-free latex was prepared (Entry 1 and 3), due the fact that one would contain MAA as well. For Entry 4 the crosslinker was fed in the reactor vessel with

the aid of DCM, due to the insolubility of the vinyl sulfonyl sulfonamide **179d** in other monomers. Therefore, compound **179d** was solubilised in DCM (**179d** 75 wt% in DCM) which was added to the MMA/BA mixture, resulting in a homogenous solution. Unfortunately, the final emulsion polymerization contained evident amounts of grit and low solid content. In the following Table 23 characterisations of the synthesised latex are shown.

Table 23. Characterisation of latex.

Entry	DLS*		Solid content (%)*	Gel content (%)*	Conversion (%)
	Z-AVE d.nm	PdI			
1	281.2	/	37.5	49	81.7
2	293.3	/	36.7	89	80.0
3	283.0	0.153	42.2	Not done	95.5
4	319.5	0.128	36.4	89.6	80.5

*Average or three measurements

As experienced in the case of the seed latexes, the solid content was always low compared to the standard emulsion polymerizations, resulting in a conversion of ca. 80% except in the case of Entry 3 (Table 23), in which a conversion of 95.5% was reached. Particle sizes resulted in being slightly higher than what was anticipated but still within range (280-319nm). The gel content is the most significant measurement since it is an indication of crosslinked polymers. This method consists in a 7 h continuous extraction under reflux of a dry film of latex with THF. After the extraction, the sample is dried, and the gel content calculated as the ratio between the dry polymer remaining after the extraction and the initial amount of dry polymer. If the density of cross-linking is low, the latex dissolves, meanwhile highly cross-linked latexes will swell and form a gel. As shown in Table 23, Entry 2 and 4 show a high degree of gel content especially when compared to the crosslinker-free latex (Entry 1). This is an indication of crosslinking.

Although this latter result suggests a high degree of crosslinked polymer, more characterisations of the latex are need in order to confirm the hypothesis and establish the benefit of the final coating formulation. Moreover, a more reliable automated synthesis in which an elaborated coating formulation is formed is needed. In the automated process,

compound **179h**, which was miscible in high proportions in either MMA or BA, was synthesized in high quantities and used as the crosslinker for the emulsion polymerisation.

2.3.4.5 Application of the crosslinker in water-borne coatings

In order to prove the potential benefit in employing vinyl sulfonyl sulfonamides in coatings, compound **179h** has been incorporated as a crosslinker in a standard emulsion polymerisation formulation, which has been compared with two existing commercial crosslinking systems, diacetone acrylamide (DAAM) (requires post-addition of adipic acid dihydrazide, ADH) and acetoacetoxyethyl methacrylate (AAEM). 2-hydroxyethyl methacrylate (HEMA) has been used to provide the complementary hydroxyl group functionality to compound **179h**. Two different series of batches were prepared, one containing a lower percentage (**batches L**) of crosslinker and another one containing a higher percentage (**batches H**) of crosslinker as explained later.

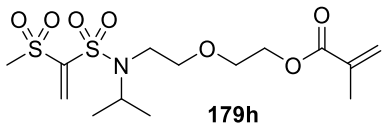


Figure 41. Crosslinker used in the automated emulsion polymerisation.

Latexes were made in two stages. A large volume seed stage was prepared by the method below and aliquots were taken from this to form the initial charge in each robotically controlled reactor. The experiment was conducted by D. Anand and data were provided by Dr. M. Irwin and S. Ketleriute at AkzoNobel site. The detailed process can be found in the experimental section.

The seed stage was prepared in a flanged glass reactor, fitted with an immersion thermocouple, overhead propeller stirrer, reflux condenser and nitrogen inlet. A particle size of 43 nm was recorded for the seed latex. The growth stage of latex synthesis was completed using a computer-controlled Chemspeed A100 Autoplant, fitted with 20 90 mL stainless steel reactors. Each reactor comprised a mechanical anchor-type stirrer, an immersion thermocouple and three syringe pumps connected to separate supply tanks (Figure 42).

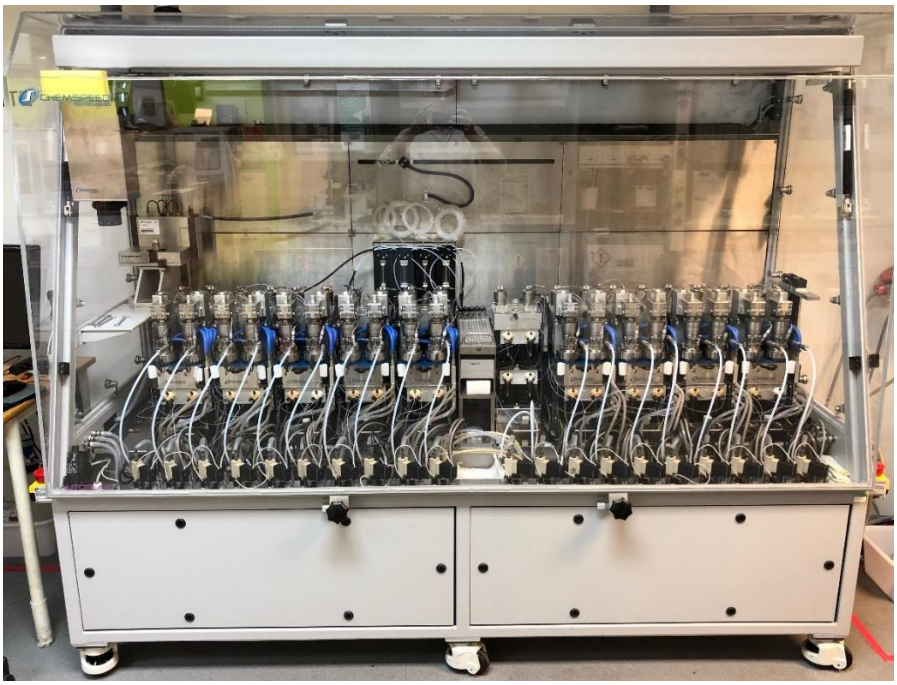


Figure 42. Computer-controlled Chemspeed A100 Autoplant.

A representation of the synthesised latexes is shown in Figure 43, where low percentage (batches L) and high percentage (batches H) of different crosslinkers have been used as explained below. These have been compared with three references called “controls”. The controls, batches L and batches H latexes have been synthesized with the automated feed stage method.

The three reference batches consist of the following controls: control 1 (**C1**) containing no crosslinker or functional monomers, control 2 (**C2**) containing HEMA in low percentage and control 3 (**C3**) containing HEMA in high percentage as represented in Figure 43. A lower and a higher percentage of HEMA is needed accordingly to the low and high percentage of crosslinker used in batches L and H.

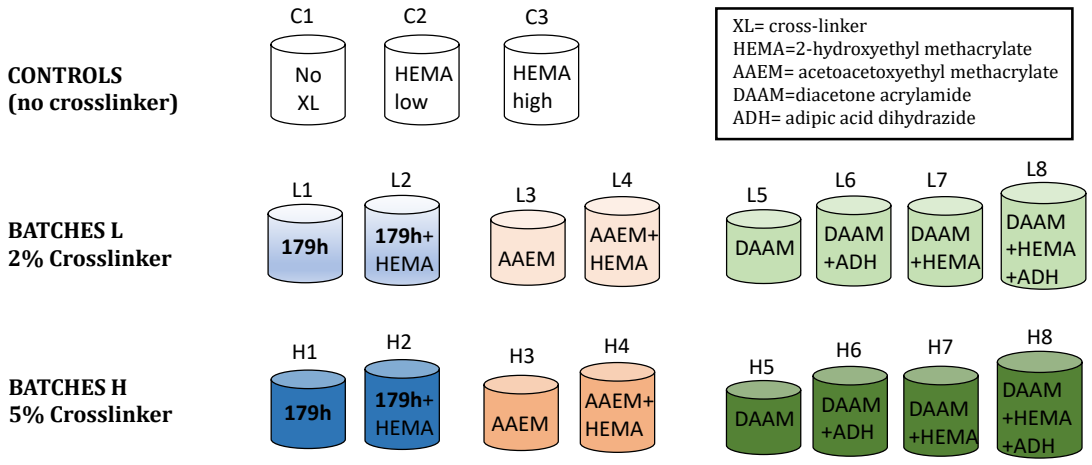


Figure 43. Graphic representation of the main differences between the prepared latexes formulations.

A first series, batches L were simultaneously synthesized by adding to the same formulation a low percentage of the different crosslinkers and therefore: batch **L1** (compound **179h**), batch **L3** (AAEM) and batch **L5** (DAAM).

In a second set of batches L, a low percentage of crosslinker and the complementary functional group were added to the formulation to permit crosslinking. As follows: batch **L2** (**179h**+HEMA), batch **L4** (AAEM+HEMA), batch **L6** (DAAM+ADH), batch **L7** (DAAM+HEMA) and batch **L8** (DAAM+HEMA+ADH).

Batches H were prepared following the method adopted for batches L, but using a higher percentage of cross-linkers. For this reason, the formulation of batches H was adjusted in order to approximately obtain the same Fox Tg as batches L and avoid the addition of extra coalescing agent. A first series of batches H were simultaneously prepared by adding to the standard formulation a high percentage of crosslinker and therefore: batch **H1** (compound **179h**), batch **H3** (AAEM) and batch **H5** (DAAM). In a second set of batches H a high percentage of the crosslinker and of the complementary functional group were added to the formulation to permit crosslinking, and therefore: batch **H2** (**191h**+HEMA), batch **H4** (AAEM+HEMA), batch **H6** (DAAM+ADH), batch **H7** (DAAM+HEMA) and batch **H8** (DAAM+HEMA+ADH).

All formulations were synthesized simultaneously by the computer-controlled robot, all employing the same premade seed-latex.

The final formulations were characterized by MFFT, DSC, hardness, particles size, solid content and solvent resistance (H_2O and EtOH).

2.3.4.6 Particle size and solid content

As introduced in section 2.3.4.2, particle size is of great importance since it influences chemical and physical properties such as viscosity, suspension and emulsion stability, film uniformity and hardness, gloss and opacity of the final polymer coating. In practice, dispersed systems are rarely monodispersed, but they rather contain a range of particle sizes, described by a PSD (particle size distribution). However, for a simpler representation, the system can be characterized through the use of an average diameter as reported in Figure 44.

Solid content is also another important parameter in order to evaluate the polymerisation conversion. This consists in measuring the difference in weight of latex once dried at 120 °C for 1 h.

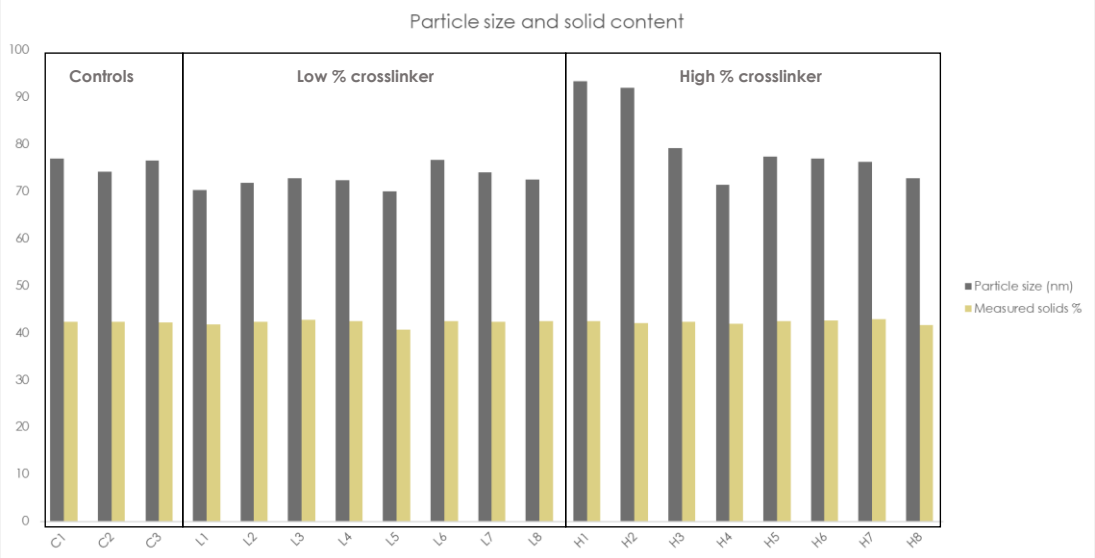


Figure 44. Particles size distribution and solid content of controls, batches L and batches H.

Although some extra grit was found in the **179h** containing reactors, the solid content is consistent in all emulsion polymerisations (between 40.6-42.8%) with a conversion that varies between 93% (batch L5) and 99.7% (batch H7).

A higher value in particle size can be noticed when crosslinker **179h** is contained in high quantities: 93 nm, PDI 0.068 for batch H1 and 92 nm, PDI 0.051 for batch H2 (Figure 44).

2.3.4.7 Minimum film-forming temperature and glass transition temperature

A very important characteristic of a latex is the temperature at which it forms a clear and homogeneous film. This temperature is called the minimum film-forming temperature (MFFT), and is determined experimentally by drawing, on a special panel that provides a temperature gradient along its length, a latex film of a consistent thickness. The latex film that dries over this temperature gradient, present a transition from a cracked to a clear film, and such transition is the MFFT.

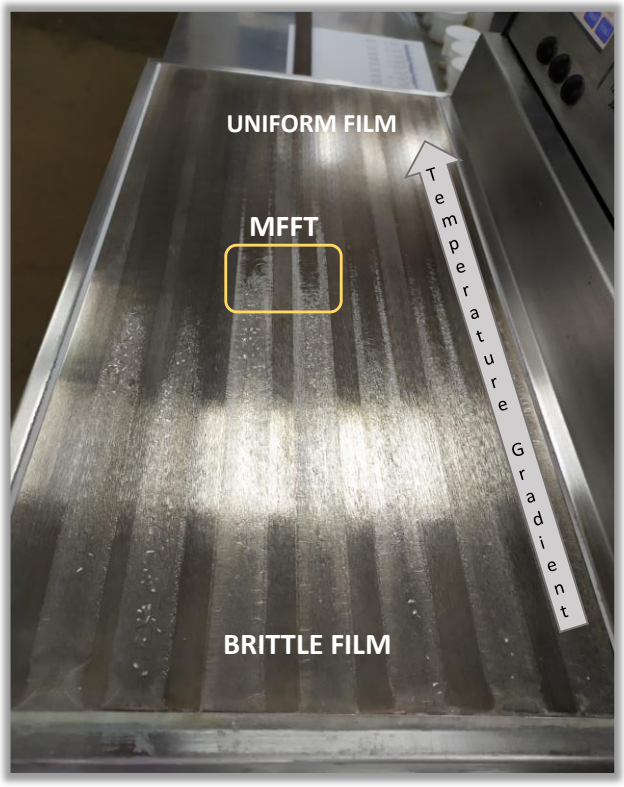


Figure 45. Determination of the minimum film-forming temperatures.

If a paint film dries below the MFFT of its polymer, the film will be relatively brittle since the particles did not uniformly coalesce upon drying, not making it possible for the polymer chains to entangle and crosslink. The MFFT of an emulsion polymer is usually a few degrees Celsius lower than its glass transition temperature (T_g) due to the presence of water which can act as a plasticiser. The MFFT of paints can also be further lowered by

addition of coalescing agent such as texanol which, however, contributes to the amount of VOC emitted. Indicative temperatures for MFFT are between 5 and 40°C, which varies depending on the temperature of the application site, which needs to be higher than the MFFT. Therefore, generally the lower the MFFT the better. The minimum film-forming temperature is related to the T_g, and this latter is dictated by the type of monomer blend that forms the polymer as well as the degree of crosslinking (explained in section 2.1.3).

Figure 46 shows MFFT analysis jointly with the measured (DSC) and calculated (Flory-Fox equation) glass transition temperature (Fox T_g).

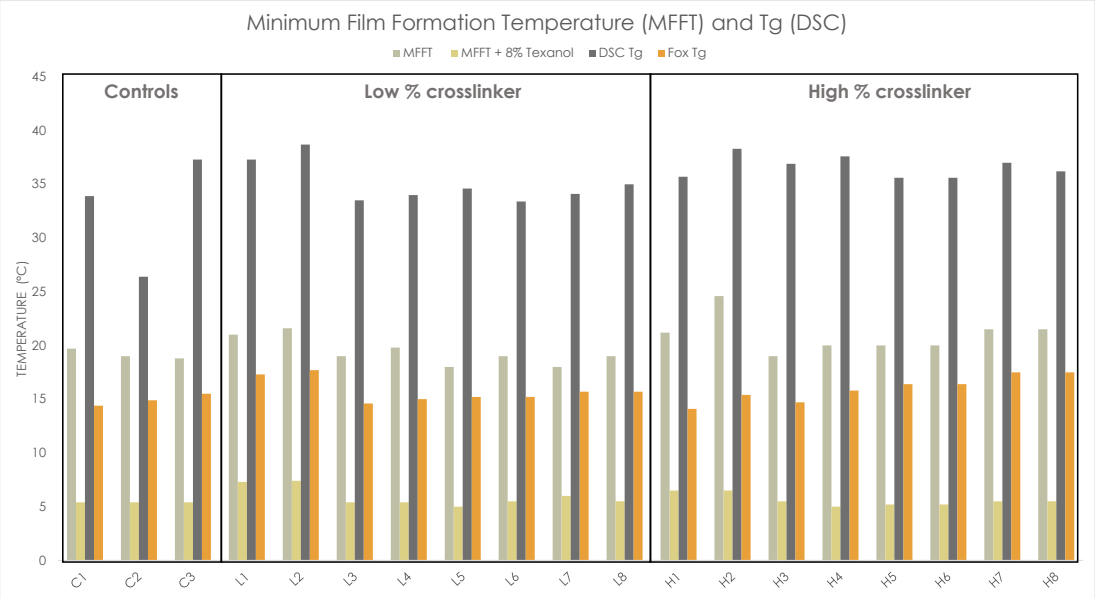


Figure 46. MFFT (with and without texanol), Tg (DSC) and calculated Tg (Fox Tg).

Overall, it can be noticed that the T_g of batch L2 (2% **179h**+ HEMA) is on average 3-4 °C higher than the other formulations (batches L). Although a minor difference, this can be seen also in the case of higher quantities of crosslinker, where a peak in the measured T_g is reached by batch H2 (5% **179h**+HEMA). The same tendency is reported for the MFFT with a difference of ~15 °C compared with its measured T_g. These values drop to 5-7 ±1 °C upon addition of the coalescing agent texanol. In formulations containing **179h**+HEMA (batches L2 and H2) the highest T_g and MFFT was registered, not only when compared to their relative systems without HEMA (batches L1 and H1) but also when compared to other commercially used crosslinking technologies (batches L4, L8, H4 and H8). This can

suggest a higher degree of crosslinking as well as a higher Tg of the crosslinking monomer **179h**, which influences the one of the final polymers.

2.3.4.8 Pendulum Hardness

The goal of crosslinked coatings is the production of coatings with enhanced properties such as higher hardness, an important factor affecting the abrasion and scratch resistance which is highly influenced by the T_g of the resin. The measurement consists of a pendulum which is free to swing on two balls resting on a coated test panel. The amplitude of the pendulum's oscillation will decrease more quickly when supported on a softer surface and therefore the hardness of any given coating is measured by the number of oscillations made by the pendulum within the specified limits of amplitude (determined by photosensors). The number of swings made by the pendulum are electronically recorded. Surface smoothness, film thickness, temperature and relative humidity must all be carefully controlled for a reliable measurement.

Comparison of the different formulations over a period of time of maximum 62 days is shown in Figure 47, as an increasing degree of crosslinking could be expected over time.

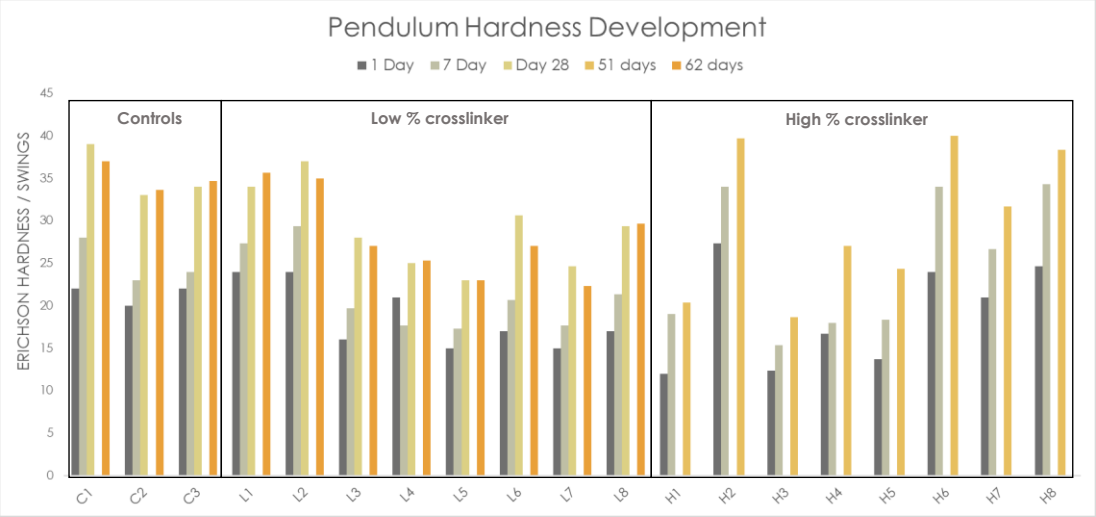


Figure 47. Pendulum hardness results.

Although relatively to all batches L, a slightly higher hardness is registered for the low percentage HEMA+**179h** (batch L2), this can still be considered on average. The hardness

result for the high percentage of HEMA+**179h** still cannot be considered particularly high, however, this is at the same level of the commercially available crosslinking technology (DAAM+HEMA+ADH), used in batch H6 and H8. This indicates that high quantities of crosslinkers (≥5%) are needed to start to appreciate any significant difference in the hardness of the final coating.

2.3.4.9 Solvent resistance

Solvent resistance test is a good method to determine the quality of crosslinking. In fact, as the degree of crosslinking increases the ability of a coating, generated upon drying of the latex, to resist solvents such as MEK, THF, H_2O or EtOH is generally improved.

The test consists of the deposition of a uniform wet film (thickness 100 μm) on a glass panel, which is left to dry for a minimum of 14 hours. A drop of 1:1 H_2O/EtOH solution, and one of only H_2O were placed on the film formed surface. The spots were covered with a watch glass for one hour, to limit their evaporation. The panels were observed during this period of time for any bubbling, swelling or whiteness. After this time, the watch glass was removed, and the solvents wiped off, being careful to not further damage the surface. Any discoloration, swelling, or other attack was examined after the drying of the film. The process was repeated after one week and after one month of film formation. As an example, results for this test on emulsion containing high percentages of crosslinkers (batches H) are shown in Figure 48. It is clear the high resistance that the **179h** containing formulations (batch H1 and H2) have during solvent contact (no swelling) and upon drying. It is evident the significant difference not only with non-crosslinked systems such as AAEM (batch H3) but also when compared to the relative crosslinked system such as HEMA+AAEM (batch H4). Results of **179h** containing latexes are comparable to batch H8 (DAAM+HEMA+ADH), which crosslinking system is of common use in coating technology.

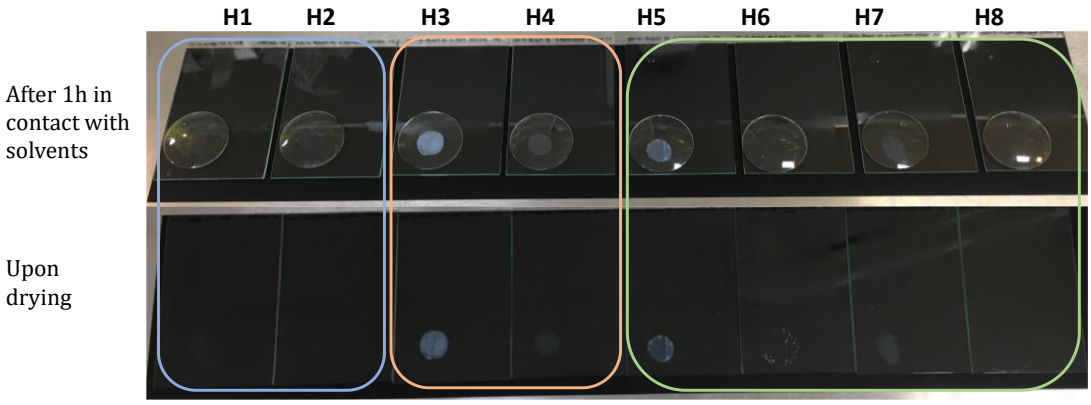


Figure 48. Solvent resistance test of batches with high percentage of crosslinker after 1 day.

Figure 49 lists the results of a hour solvent spot test with a H_2O/EtOH (1:1) solution, over a period of 62 days, in which the degree of crosslinking increases. For practical reason, the rating was assigned according to the criteria listed in Table 24.

Table 24. Rating criteria to evaluate solvent resistance of the of the coating's film.

Rating	Water/ethanol spot
1	Complete film solvation / permanent macro damage
2	Rapid film whitening, some recovery after solvent removal
3	Film whitening, recovers after solvent removal, barely visible haze remains
4	At least 5 minutes delay before film whitening, recovers after solvent removal
5	No whitening and film undamaged

Nevertheless, the evaluation of the solvent resistance remains a subjective evaluation test and therefore, numbers assigned in **Figure 49** are only to be considered indicative.

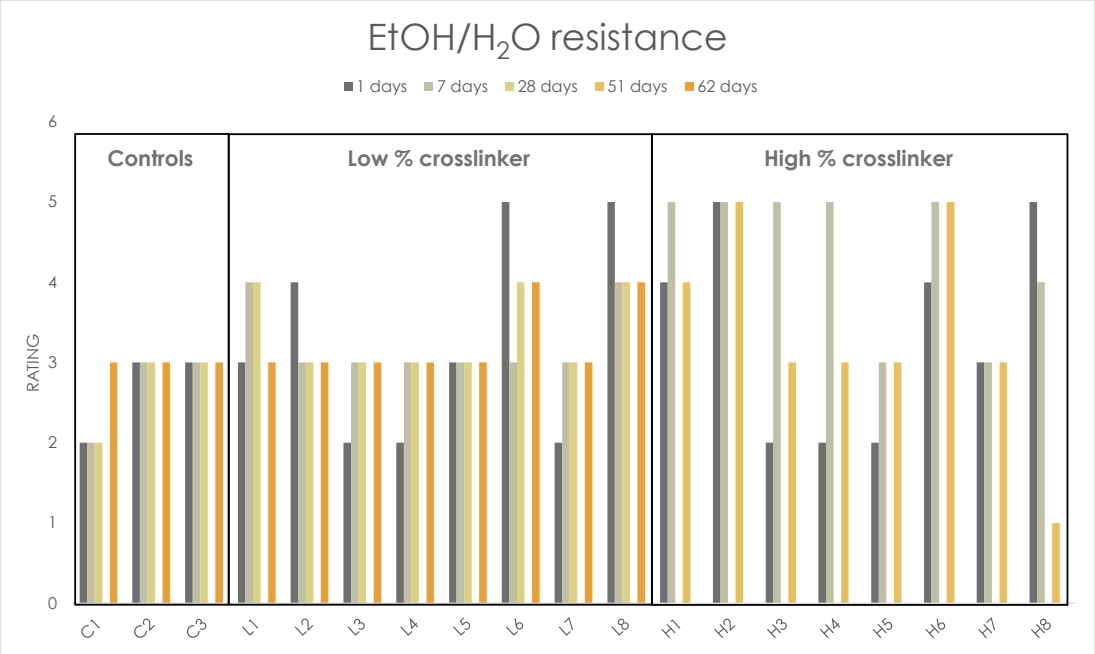


Figure 49. Solvent resistance to a solution of EtOH/H_2O (1:1).

Although the rate given is indicative, for latexes containing low quantities of crosslinker (batches L) the differences in performances are not significant, with **179h** containing emulsion showing good resistance to water/ethanol. On the contrary, full resistance is achieved and maintained over a period of time when 5% **179h**+HEMA is used. Other crosslinking systems (batch H6 and H8) also showed high resistance to the EtOH/H_2O solution, resistance which unexpectedly decays over time in the case of batch H8. A further consideration should be made on the average high resistance to solvents of batch H1 which contains **179h** but no HEMA. It can be deduced that a low degree of crosslinking is occurring also in the absence of the HEMA (hydroxyl functionality). This is in line with what was found in section 2.3.3, in which two molecules of vinyl sulfonyl sulfonamide can self-react giving rise to crosslinking.

In an experiment to establish if the crosslinking starts to occur within the latex formulation (as the **179h** crosslinker is introduced in the formulation in its active form), a drop of latex from batches L1, L2, H1 and H2 was added into four different vials containing THF. This solvent should swell/dissolve the polymer particles if these are not crosslinked.

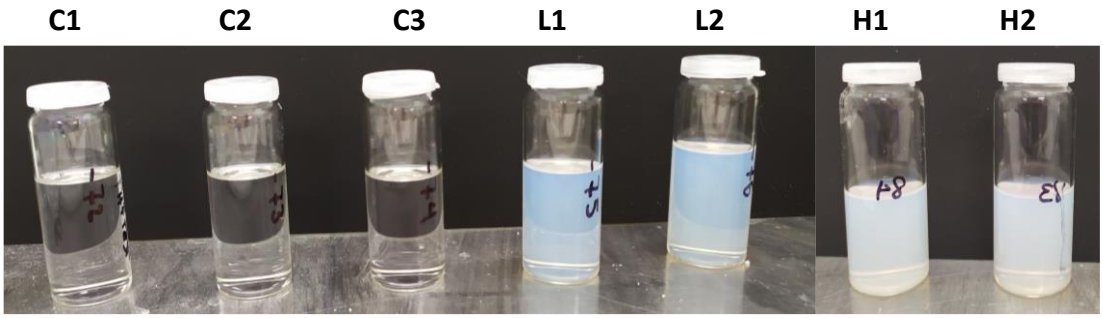


Figure 50. Solubility of the **179h** latexes systems in THF.

As shown in Figure 50, the control vials C1, C2 and C3 resulted in a completely clear solution, denoting full solubility to no presence of crosslinking (as no crosslinker is present). However, in the vials containing crosslinker **179h** a suspension is present, indicating no dissolution or more probably some dissolution of the polymer latex. Although it is hard to know the degree of dissolution of the latexes, it is possible to notice that L1 and L2 are more translucent than H1 and H2, hence likely that more of the latex particles have dissolved in L1/L2 than H1/H2. The insolubility of the latex particles is an indication of some pre-crosslinked material present in L1/L2, and H1/H2 Moreover, there is no appreciable difference when comparing L1 with L2, and H1 with H2. This suggests that pre-crosslinking is likely to be occurring between two molecules of **179h** rather than between **179h** and HEMA.

2.3.4.10 Summary

Research in this section focussed on the use of previously synthesised crosslinkers as monomers in free radical polymerisation and emulsion polymerisation process. Initial studies were directed towards the homopolymerisation of one of the easily accessible sulfonyl sulfonamide monomers, in which, surprisingly, polymerisation could never be obtained. On the other hand, copolymerisation of sulfonyl sulfonamide monomers (both containing styrene or methyl methacrylate moieties) could be easily achieved when reacted with methyl methacrylate or styrene. However, when vinyl sulfonyl sulfonamide monomers were copolymerised with either methyl methacrylate or styrene, crosslinked polymers were obtained. This suggests that the vinylidene moiety might not remain intact during polymerisation, hence, not being able to work as a latent crosslinker.

Preliminary work on emulsion polymerisation conducted in our labs outlined difficulties in reproducibility of the experiments, with issues in obtaining full conversion. However, this preliminary work has highlighted high gel content in the latexes containing vinyl sulfonyl sulfonamide, suggesting crosslinking taking place.

Conducting emulsion polymerisation using a computer-controlled reactor at AkzoNobel site permitted high reproducibility and the possibility of comparing formulations containing vinyl sulfonyl sulfonamides with other commercial crosslinkers such as AAEM and DAAM. The final formulations were characterized by MFFT, DSC, hardness, particles size, solid content and solvent resistance (H_2O and EtOH). Amongst these tests, in which formulations enclosing 5% of vinyl sulfonyl sulfonamide crosslinker performances were similar to the commercial crosslinkers AAEM and DAAM, excellent results were given in the resistance of the film coatings towards H_2O and EtOH. Although further investigations are needed, it can be concluded that the use of vinyl sulfonyl sulfonamides as crosslinkers in emulsion polymerisation has generated coatings films of comparable performances to the commercial AAEM and DAAM, hence, of promising employability in this sector. Nevertheless, further studies are needed to be undertaken to address concerns about premature crosslinking during polymerisation.

2.4 Other crosslinker applications: Bioconjugation

Bioconjugation is the formation of a covalent bond between two molecules, in which, at least one of the two molecules is a biologically active species. In medicinal chemistry, bioconjugation to proteins and peptides is extremely attractive due to the need for developing better and increasingly selective diagnostic tools, i.e. for use as targeted imaging agents. In fact, a protein could in theory be conjugated with any number of other useful entities, including drugs, enzymes, inorganic or organic materials, dyes and fluorescent reporter molecules, and polymers etc., thus creating new complexes that have within them, the combined properties of the system conjugated together. For example, a fluorescent molecule could be bioconjugated to an antibody in order to be detectable when binding to another specific biomolecule, such as cell surface receptor. Proteins are made of chains of natural amino acids whose side-chains present different functional groups, which can be usefully targeted as attachment points in bioconjugation reactions.[203] However, despite the progress made over many years, chemoselective bioconjugation reactions that can be performed under physiological conditions, in the presence of many different amino acid residues makes the bioconjugation of peptides and proteins challenging and new methodologies for such bioconjugation as still required.

Perhaps the most commonly targeted functional groups used for bioconjugation in peptides and proteins are amines and thiols, i.e. due to their good nucleophile properties. This means that amino acid residues derived from lysine and cysteine are two important amino acids in bioconjugation due to their amino and thiol functions.[204] Strategies targeting alcohol groups, however, have also been reported but with several disadvantages such as low nucleophilicity and bioconjugation often thwarted by the presence of water[205], and therefore, they have been rarely used. On the contrary, carboxylic acids have been successfully employed as a reactive site for covalent bonding in bioconjugation through ester formation, though again, there are disadvantages as well such as facile hydrolysis by esterase enzymes.

Lysine is highly popular in bioconjugation since encloses a very good nucleophilic primary amine side chain[206] and due to its presence in most proteins.[207] This primary amine is usually very reactive towards electrophiles without the need of any activation.[208] However, the large number of lysines contained in many biomolecules makes the amine a disadvantageous target when selectivity is required.[204a] Organic chemistry offers a wide-range of reactions that can be employed for the formation of covalent bonds with primary amines. In fact, numerous electrophilic reagents are available for bioconjugation to amines, such as *N*-hydroxysuccinimide (NHS) esters, sulfonyl chlorides, vinyl sulfones, iso-thiocyanates, and squaric acids.[204b] Although *N*-hydroxysuccinimides are perhaps the most common reagents used to target primary amines, vinyl sulfones have also been widely used.[203, 209] The main advantage of vinyl sulfones is that they are stable in aqueous solutions and they do not form by-products upon reaction.[172b] However, these types of amine addition reactions can be slow, therefore, often incomplete and happen only at higher pH (pH>9.3) whereas vinyl sulfones have been found to be more reactive towards thiols, and therefore, they are more commonly used when targeting cysteine.

The thiol contained in cysteine is a stronger nucleophile at pH below 9 compared to the primary amine in lysine.[203] However, cysteines have a relatively low natural abundance in proteins, and they are usually found in di-sulfide bridges with other cysteines. In fact, thiols are versatile groups that can easily form di-sulfides[210] but can also be alkylated with suitable electrophiles, such as α-halocarbonyls (*e.g.* iodoacetamide) and Michael acceptors (*e.g*. maleimides or vinyl sulfones).[207b] Maleimides are one of the most commonly use reagent when thiols are targeted. The major disadvantage is that reducing agents are usually used and then removed prior to reaction in order to ensure the presence of the free thiols. Vinyl sulfones are also a commonly used chemical functional group for the covalent bioconjugation *via* free thiol. The use of these groups has the advantages of being reactive under mild conditions[209] and remaining stable in aqueous solution for extended periods of time at neutral pH.[172a] However, at higher pH, vinyl-sulfones become reactive also towards amines and hydroxyls.[203] Therefore, disadvantages in most thiol-targeted bioconjugation protocols are the issues around cross-reactivity with other nucleophilic

functional groups in particular amine, becoming competitve with the bioconjugtion process.[207b]

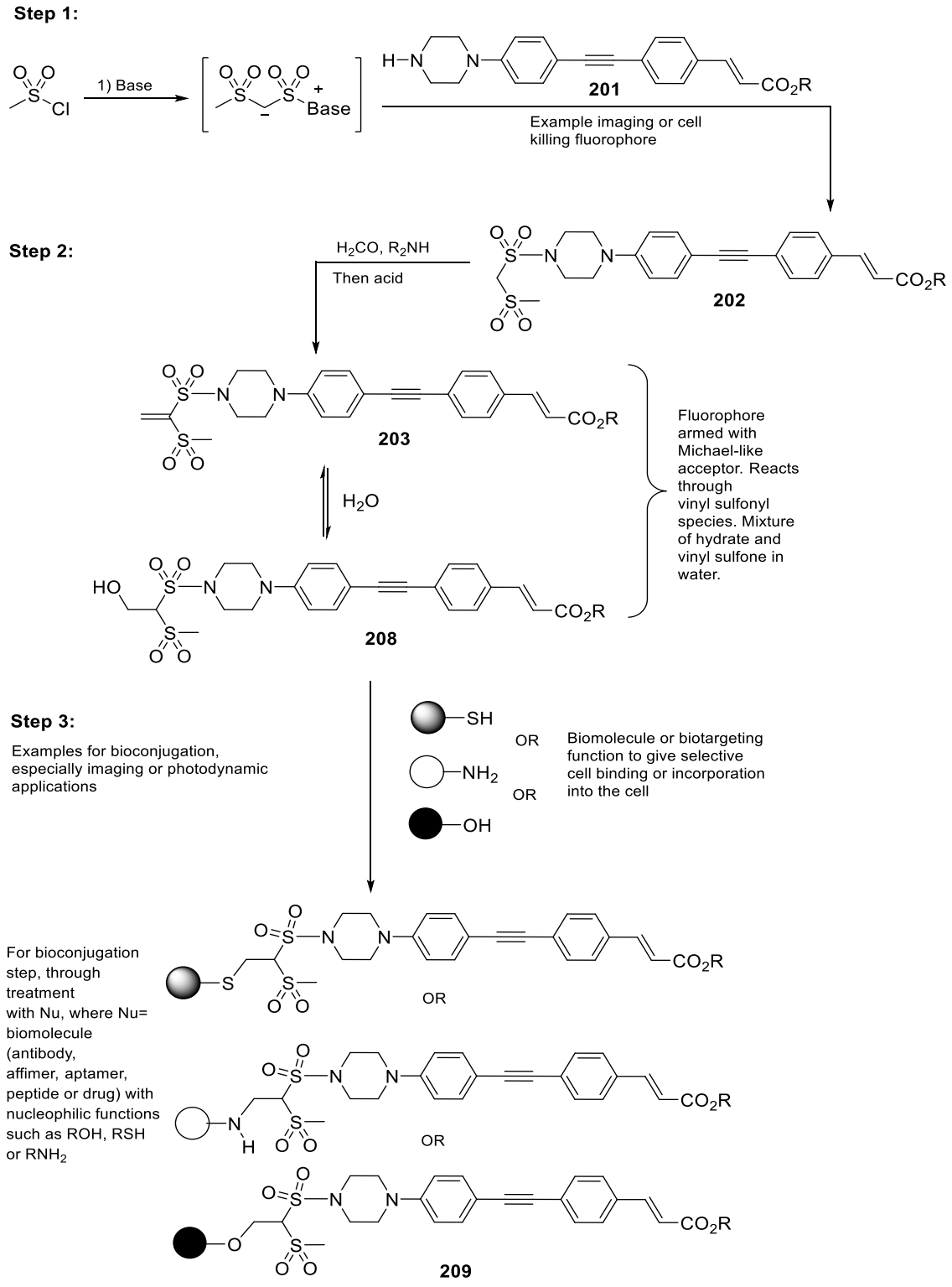
Tyrosine residues possess a phenolic hydroxyl group. This group is challenging to target due to the fact that the amino acid is usually found buried within the protein structures because of its nonpolar character.[204a] The bioconjugation reactions used mostly in this case are Mannich types reactions,[211] palladium-catalyzed alkylation,[212] cerium(IV)ammonium nitrate-catalyzed oxidative coupling[204a] and reaction with diazonium salts for diazo arylation in the ortho-position.[213] Vinyl sulfones have not been reported in the literature for the bioconjugation of tyrosine hydroxyl groups.

Bioconjugation to carboxylic side-chains of glutamic and aspartic acids is also quite common since they are highly expressed on the surface of proteins. However, vinyl sulfones have not been highlighted in any reaction between this functional group.[214]

Herein we report preliminary investigations into the bioconjugation of ethylene sulfonyl sulfonamides, attached to biocompatible imaging fluorophores to different amino acids and peptides as a proof of principle.

2.4.1 Results and discussion

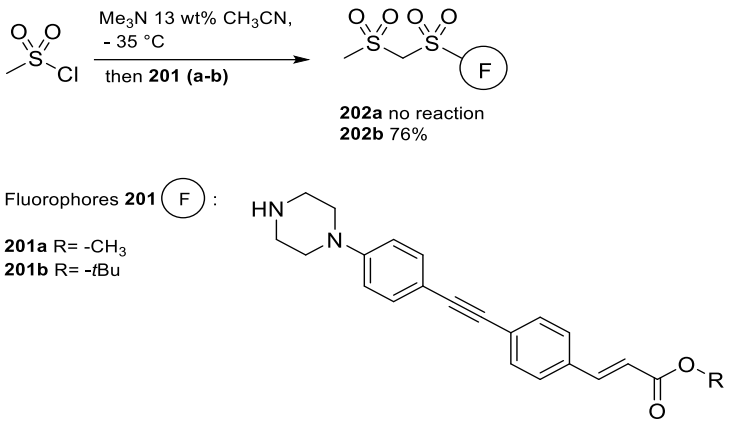
The way in which the bioconjugation application would be applied is outlined in Scheme 137. A fluorophore such as **201** could be used to trap the same type of betaine species, to access sulfonyl methylene sulfonamides, such as **202**. The subsequent formation of a vinyl sulfone system such as **203** would be conducted with formaldehyde (or other aldehydes or ketones), and again, can exist as either dehydrated vinyl sulfone form **203**, or in water, hydrate as in **208**. Typically, the direct product isolated from the formaldehyde reaction is the vinyl sulfone species, and this is reacted under a range of conditions with different biologically active molecules to provide the conjugates of type **209**.



Scheme 137. Fluorophore-bioconjugate general concept.

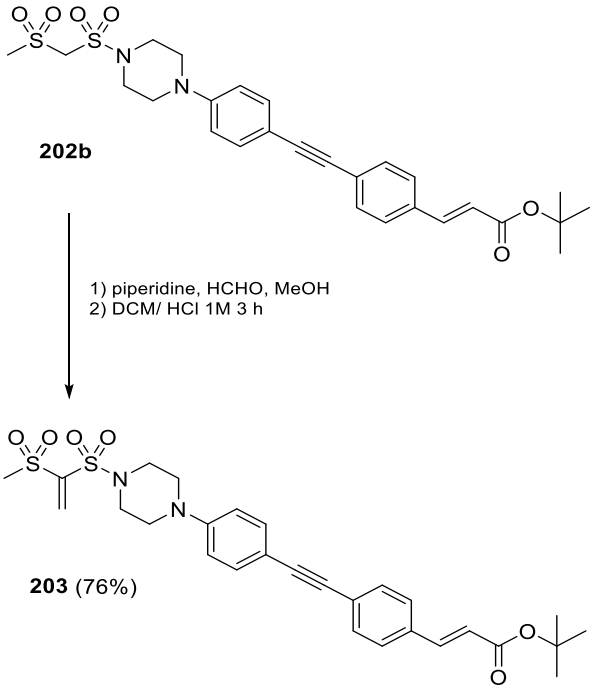
Bioimaging fluorophores **201 (a-b)**[215] were provided by LightOx Ltd. in order to test the efficiency of the conjugating concept with more complex nucleophiles (amino acids, peptides, proteins etc.) and challenging systems.

A representative *bis*-sulfonyl-fluorophore was synthesised and tested as shown in Scheme 138. A first attempt was carried out with **201a**, however, this was not soluble in dichloromethane or acetonitrile and therefore, no reaction was achieved. On the contrary, **201b** was completely soluble in acetonitrile and reaction was achieved in good yield (76%) with no need of further purification to give **202b**. Final procedure follows method B developed in section 2.3.1.



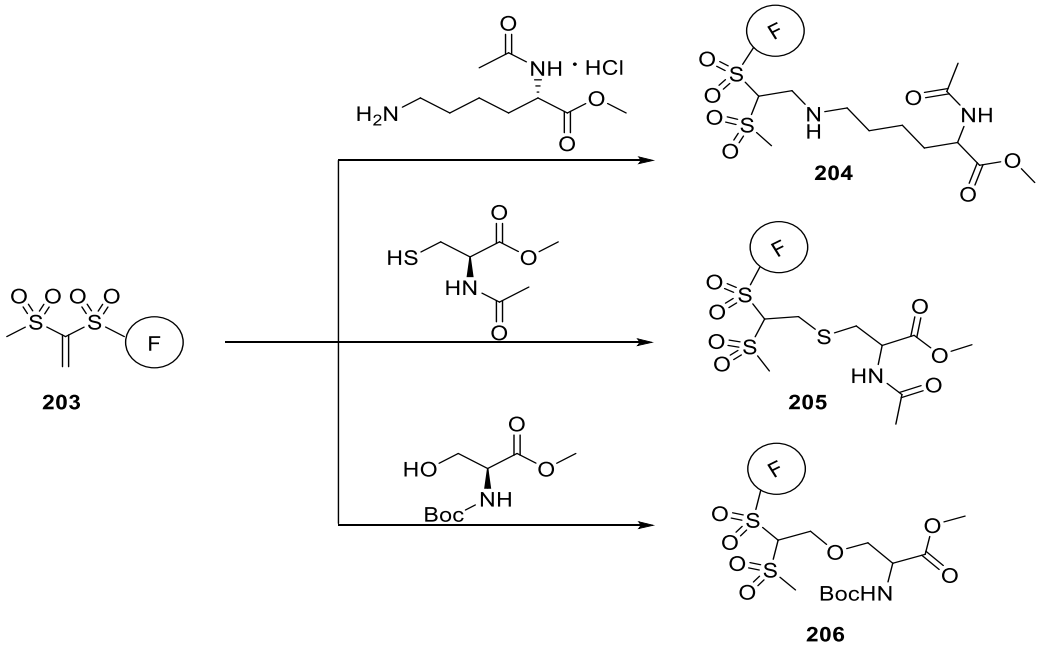
Scheme 138. Synthesis of sulfonyl sulfonamide fluorophore **202b**.

Compound **202b** was then employed to achieve the corresponding vinyl sulfone. When this was carried out in EtOAc, the reaction was faster (three days) but only 57% mass recovery was achieved, and the final compound needed purification. On the other hand, reaction in MeOH was slower (seven days) but the final product **203** was produced cleanly in 76% yield (Scheme 139).



Scheme 139. Synthesis of ethylene sulfonyl sulfonamide fluorophore **203**.

Consequently, three different amino acids, N_{α}-acetyl-*L*-lysine methyl ester hydrochloride, *N*-acetyl-L-cysteine methyl ester and Boc-*L*-serine methyl ester, were used for preliminary tests of bioconjugation of **203** to thiols, primary amines, and alcohols. To assess solely these moieties, other functional groups within the amino acid were protected.



Scheme 140. Bioconjugation of compound **203** to protected amino acids.

All reactions were run at room temperature in dry THF in order to have no competition with water. Although it is clear that this would be inevitable in a physiological system, to have a better picture of behaviour of these bio-conjugating compounds, variables were introduced gradually.

N_{α}-acetyl-*L*-lysine methyl ester hydrochloride was reacted with ethylene sulfonyl sulfonamide **203** in dry THF with the aid of Et_3N (1 equivalent) to free the amine. The reaction was monitored through ^1H NMR since, as noted in section 2.3.3.1, amine adducts with vinyl sulfonyl sulfonamides are not stable on silica. Disappearance of the methylene signal at 6.98 ppm after 24 hours indicate that reaction had occurred. Column chromatography did not allow recovery of the product **204** but only gave starting material **203** suggesting once again removal of the amino acid in acid conditions (silica). However, DOSY of the crude clearly shows the presence of mainly three compounds, one related to the base triethyl amine still present in the crude, and it can be noted that peaks belonging to the used amino acid are part of this high molecular weight compound (Figure 51). The third compound is of similar molecular weight to the second compound, and of similar structure as it can be seen from the presence of same peaks between 6-8 ppm and 3-3.6 ppm. Moreover, through mass spectrometry analysis it was highlighted a peak at 759.5 m/z corresponding to the $[M+H]^+$ ion peak, suggesting once more the formation of **204**.

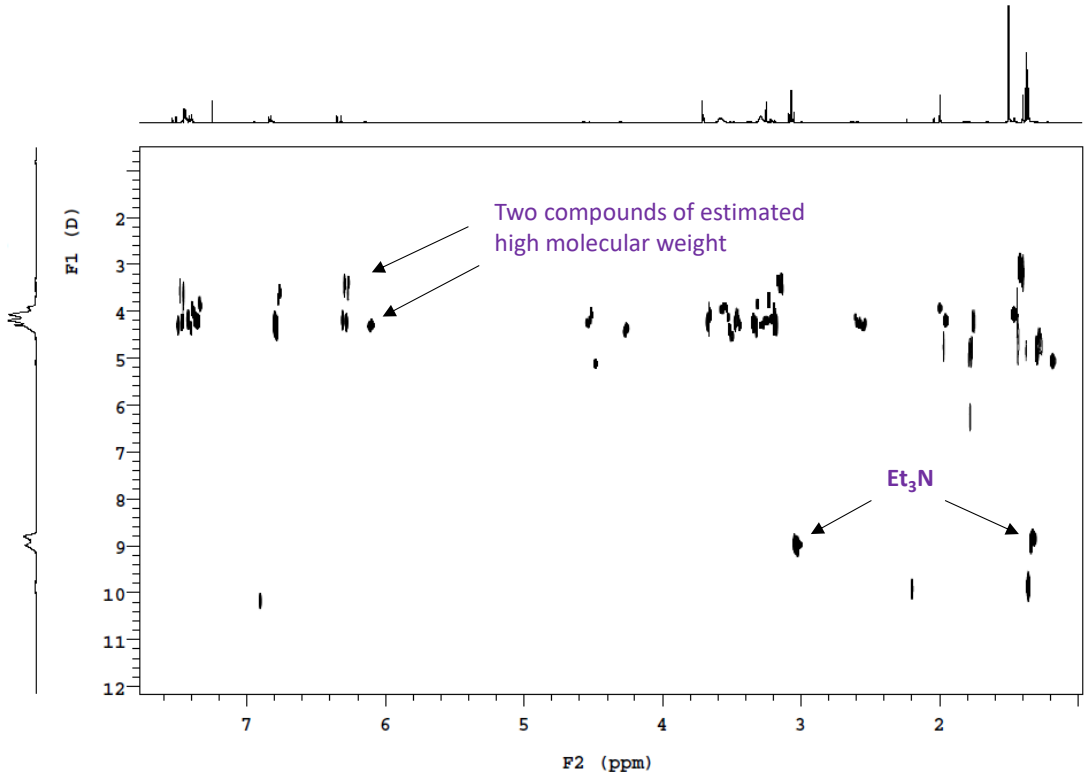


Figure 51. DOSY of reaction crude **204**.

The high reactivity of vinyl sulfones towards thiols has been documented in the literature.[216] With the presence of a second electron withdrawing group such as in vinyl sulfonyl sulfone amides the expectancy is in an increment of reactivity towards these thiol-Michael additions. In fact, compound **205** was efficiently obtained after reaction of *N*-acetyl-*L*-cysteine methyl ester with compound **203** (Scheme 140). The final product resulted in being stable over silica in which however, the two formed diastereoisomers could not be separated by column chromatography.

In a study conducted by U.P Dahal *et al.,*[217] intrinsic reactivities were determined for a series of electrophiles (acrylamides, nitriles, cyanamides, sulfones, and sulfonamides) using *N*-α-acetyl-*L*-lysine as a model amine-based nucleophile (carried out at pH 10.2). Results were compared with reactivities towards glutathione as a thiol-based nucleophile. It was found that the α,β-unsubstituted vinyl sulfones had highest reactivities towards *N*-α-acetyl-*L*-lysine (even when compared to acrylamides). This reactivity rate would decrease in the case of alkyl substitution on the vinyl moiety, replacement of the *N*-aryl group by cyclohexyl group and generally by ring strain, electronic and substitution effects.

Finally, vinyl sulfonamides reacted more slowly than vinyl sulfones. Interestingly, it was found that all α,β-unsaturated sulfones and sulfonamides reacted faster with *N*-α-acetyl-*L*-lysine than with glutathione and therefore a partial selectivity towards amines.

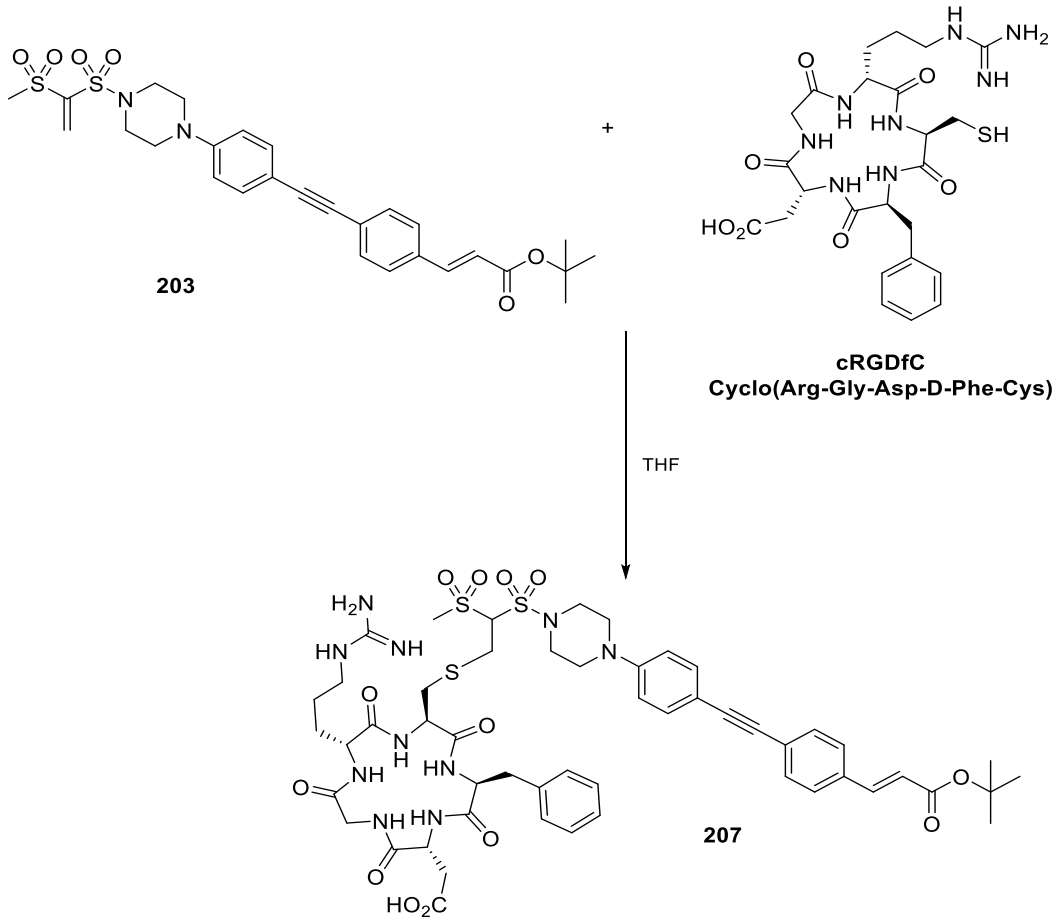
Although in our assessment no kinetic studies were conducted, it can be stated that more stable conjugates are achieved when vinyl sulfonyl sulfonamides are reacted with thiols rather than amines. This behaviour could be highlighted in previous experiments reported in section 2.3.3.1, where a partial retro-Mannich-like reaction brought to the synthesis of the methylene sulfonyl sulfonamide among other. However, reactions of vinyl sulfones towards lysine at higher pH (>9.3) have been shown to occur, conditions not always compatible with the biological function of proteins.[172b]

Finally, no reaction was gained between Boc-L-serine methyl ester and vinyl sulfonyl sulfonamide **203** after one month, and the starting material was fully recovered (Scheme 145). This is in contrast with preliminary assessments in section 2.3.3.1, in which reactivity towards hydroxyl group was found to occur and being stable. Further studies should be undertaken.

2.4.1.1 Bioconjugation to cRGD

The cRGD is a cyclic tripeptide, mainly composed of arginine, glycine, and aspartate, that can be found in many extracellular matrix proteins (ECM) such as fibronectin, vitronectin, laminin etc. and is responsible for the binding of these ECM proteins to their receptors on the cell surfaces. Such RGD cell binding motif has high relevance in the fields of oncology, tissue engineering and regenerative medicine and therefore of great interest in bioconjugation.

Considering the high reactivity towards thiols-containing compounds, cyclic peptide-based (cRGDfC) was reacted with compound **203** previously synthesized and its efficient fluorophore-functionalization demonstrated (Scheme 141).



Scheme 141. Bioconjugation to cRGDfC.

As ducted in the case of the amino acids bioconjugation, compound **203** (1 equivalent) was reacted with cRGDfC peptide (1 equivalent) in THF at room temperature although reactivity assessments at a more physiologically relevant pH of 7.4 will be needed in future experiments. Unfortunately, due to the small quantities used, the reaction could not be followed by TLC or NMR. Therefore, the solvent of the reaction mixture was removed after 5 hours and the final compound studied by MS and HPLC.

Mass spectrometry analysis confirmed the formation of the bio-conjugate **207** with a peak at 1135.4 m/z, confirmed by accurate mass. In both mass spectrometry and HPLC the presence of cRGDfC peptide could be detected, probably due to a mistaken excess of this compared to the fluorophore. In fact, HPLC chromatogram of the crude (Figure 52-top) shows almost no sign of compound **203** (18.66 min), which therefore has quantitively reacted with the peptide (0.97 min).

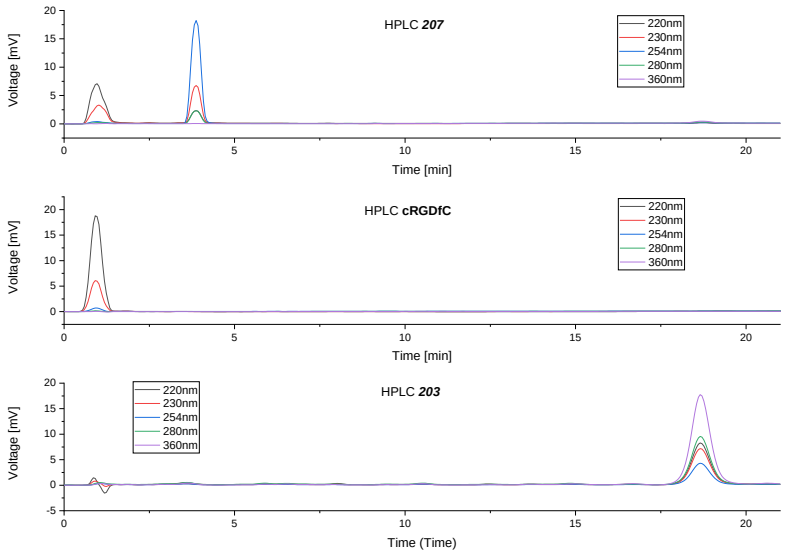


Figure 52. HPLC chromatograms; TFA (0.1%) in H_2O and CH_3CN were used as mobile phase under isocratic flow (20 min); using 60% H_2O (0.1% TFA) and 40% CH_3CN, 1 mL/min flow, 25 °C; 220 nm, 230 nm, 254 nm, 280nm and 360 nm.

The final bio-conjugate **207** can be seen at 3.87 min (Figure 52-top), highlighting that no other by-product was formed, and selective bio-conjugation (presumably on the thiol) can be achieved.

2.4.2 Summary

In medicinal chemistry, bioconjugation to proteins and peptides is extremely attractive due to the need for developing better and increasingly selective diagnostic tools, i.e. for use as targeted imaging agents. In section 2.3.1 formation of sulfonyl sulfonamides through the dimerisation of mesyl chloride have been studied. These sulfonyl sulfonamides can condense with aldehydes and ketones, for example formaldehyde, to give vinyl sulfonyl sulfonamide species which exist in equilibrium with its hydroxymethyl adducts when water is present. The formation of vinyl sulfonyl sulfonamide species represent the reactive Michael acceptor for bioconjugation chemistry if the incoming nucleophile is a biologically relevant compound such as amino acid, peptide, protein, antibody, fluorophore for imaging, small molecule drug etc. In this regard, preliminary studies have been undertaken in section.

A fluorophore for imaging applications was provided by LightOx Ltd. and used as a trapping amine for the synthesis of sulfonyl sulfonamide in good yields. From this, vinyl sulfonyl sulfonamide species was formed and used for preliminary tests as a Michael acceptor for bioconjugation. Therefore, a vinyl sulfonyl sulfonamide-fluorophore was used for tests of bioconjugation with three different amino acids: N_{α}-acetyl-*L*-lysine methyl ester hydrochloride, *N*-acetyl-*L*-cysteine methyl ester and Boc-*L*-serine methyl ester has representations of thiols, primary amines, and alcohols. To assess and compare the reactivity these moieties towards bioconjugation, other functional groups within the amino acid were protected. The results from this first trial reactions indicated an efficient and quantitative bioconjugation with thiols. On the other hand, the bioconjugate with the amine species, N_{α}-acetyl-*L*-lysine methyl ester hydrochloride, was never isolated, but its formation *in situ* was supported by mass spectrometry and DOSY. Instead, no reaction could be achieved between the Boc-L-serine methyl ester and the vinyl sulfonyl sulfonamide-fluorophore specie.

Finally, considering the high reactivity towards thiols-containing compounds, cyclic peptide-based (cRGDfC) was reacted with a vinyl sulfonyl sulfonamide-fluorophore and

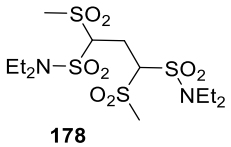
its efficient fluorophore-functionalisation was demonstrated by mass spectrometry, with full conversion of the vinyl sulfonyl sulfonamide to the bioconjugate, as also shown by HPLC.

In conclusion, this preliminary study proves that vinyl sulfonyl sulfonamide systems represent a valid bioconjugation moiety for reaction with thiols, when this is present in i.e. amino acid, peptide, protein, antibody etc. Further assessment needs to be undertaken in biological environments to confirm vinyl sulfonyl sulfonamide selectivity towards thiols.

2.5 Concluding remarks and future work

The synthesis of sulfonyl sulfonamides, assessed mainly by Opitz *et al.*[133-134, 173-174], has been investigated and optimised. This reaction involves the formation of a sulfene dimer from an alkyl sulfonyl chloride via elimination of HCl in the presence of base, which can then react with an appropriate amine. However, this reaction was found to be a delicate equilibrium between different species, highly dominated by temperature and nucleophilicity of base used. In fact, when temperatures were not kept to a minimum of -35 °C or insufficient base was used, the main product resulted in being the simple sulfonamide. On the other hand, episulfone was obtained when less nucleophilic bases such as DIPEA were used. The best conditions for the synthesis of methylsulfonylmethylenesulfonamide were found to be achieved when using good nucleophiles such as trimethylamine as base in acetonitrile at low temperature (-35 °C). Several amines containing a polymerisable group (methyl methacrylate or styrene) and a tuneable spacer were synthesised and employed as the trapping amine in the previously optimised procedure to give sulfonyl sulfonamide. The tuneable spacer was used to successfully control the properties of the final crosslinker, and especially its solubility in solvents and monomers such as methyl methacrylate and butylacrylate, commonly used in emulsion polymerisation in the field of coating technology. Several sulfonyl sulfonamide monomers were, therefore, synthesised in order to be able to test different structures in the emulsion polymerisation.

Initial attempts at the synthesis of vinyl-1-sulfonyl-1'sulfonamides via intramolecular condensation of an aldehyde present in the structure resulted was challenging. In fact, the formation of an aldehyde from a sulfonylsulfone(allyl)amine through ozonolysis or palladium catalysed oxidation led only to complicated reaction mixtures. The use of iminium salts to achieve vinyl sulfonyl sulfonamides was also unsuccessful. The reaction reproducibility was hard to control and inconvenient for larger scale reactions. Moreover, it was found that compounds such as **178** (Figure 53) were easily formed when these conditions were used.



178

Figure 53. By-product forming from the use of iminium salts or condensation with formaldehyde and base.

Synthesis of vinyl sulfonyl sulfonamides was finally obtained through a base catalysed Knoevenagel condensation in the presence of formic acid. Using this general procedure on sulfonyl sulfonamide monomers as substrates, potential crosslinkers were synthesised. Nevertheless, in order to be used as crosslinkers in emulsion polymerisation it was necessary for the crosslinker to have a solubility in the monomer's mixture (mostly methyl methacrylate and butyl acrylate). Amongst the synthesised crosslinkers, only **179f**, **179g** and **179h** (Figure 54) showed different degrees of solubility in methyl methacrylate, with the latter being completely miscible.

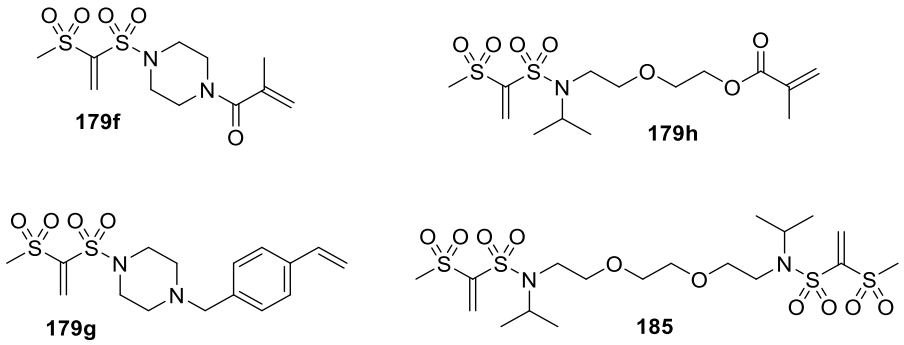


Figure 54. Synthesised crosslinkers.

It was also found that the sulfonamide function needed to be non-hydrogen substituted when combined with the vinyl Michael acceptor, and hence, all vinyl sulfonyl sulfonamides containing a secondary amine were discarded. This was due to self-Michael addition, involving the surprisingly nucleophilic NH showing an ability to react with another molecule of vinyl sulfone. Moreover, *bis*-vinyl sulfonyl sulfonamide systems such as compound **185** (Figure 54) were synthesised with the intent of forming a crosslinker that would provide two cross-linking sites thanks to the presence of two Michael acceptors moieties.

The use of vinyl sulfonyl sulfonamides in Michael addition reactions with thiols, amines and alcohols have revealed high reactivity towards thiols, which reaction proceeded efficiently and quantitively under neutral conditions. On the other hand, alcohols and amines were much less reactive, and a large excess of nucleophile was needed. Moreover, in the case of Michael addition using an amine as nucleophile, sulfonyl sulfonamide systems was formed, suggesting retro-aldol reactions were taking place. Finally, in both the Michael addition of vinyl sulfonyl sulfonamide with amine or alcohol, reaction between two molecules of vinyl sulfonyl sulfonamides took place, giving rise to compounds such as **178** (Figure 53). Although we have proposed a reaction mechanism, this is still not fully clear, and more studies need to be done.

Co-polymerisation of sulfonyl sulfonamides was achieved successfully with both styrene and methyl methacrylate. However, when the same conditions were used in the case of vinyl sulfonyl sulfonamides, the analysis on the final compound suggested the presence of a highly crosslinked polymer. Finally, the most promising crosslinker **179h** (Figure 54) was tested in an emulsion polymerisation process and compared with two existing commercial crosslinking systems, diacetone acrylamide (DAAM) and acetoacetoxyethyl methacrylate (AAEM). Preliminary tests on the final coatings properties deriving from the use of **179h** resulted of comparable performances to the one containing the commercial crosslinker DAAM. In particular, when high percentages of crosslinker were used, high resistance to solvents such as water and ethanol was reached in shorter times compared to DAAM.

Vinyl sulfonyl sulfonamide were found to be good candidates also for the bioconjugation of peptides to target imaging agents such as fluorophores. Once again, vinyl sulfonyl sulfonamides resulted in being excellent thiol-Michael acceptors and full conversion to the fluorophore-peptide cRGD conjugate could be obtained.

In the course of this project, several challenges have been encountered, mainly regarding the chemoselectivity in Knoevenagel type reaction in order to synthesised vinyl sulfonyl sulfonamide. In fact, depending on the substrate structure, reaction of one molecule sulfonyl sulfonamide to another molecule of sulfonyl sulfonamide to obtain structures

such as **178** (Figure 53) were in some cases obtained. Moreover, the time of reaction varied greatly depending on the sulfonyl sulfonamide substrate used, making the synthesis of some of these too long. The reason for such a difference in reaction time is still unclear and further studies are needed on this subject. Moreover, we were not able achieve vinylidene sulfonyl sulfonamide using other types of carbonyl functional groups, binding us to the use of formaldehyde.

The high reactivity of vinyl sulfonyl sulfonamide makes these systems unstable, with the tendency of self-reacting. Therefore, it would be preferable to synthesise the corresponding hydroxyethylenesulfonyl sulfonamide, which would provide higher stability during storage and during copolymerisation processes.

Scale up of compound **179h** for further tests as a crosslinker in coating technology would require optimisation of the currently inefficient total synthesis.

Finally, exploitation of vinyl sulfonyl sulfonamide systems in other fields such as bioconjugation has been only marginally addressed and further investigations would be needed.

3 Experimental section

3.1 General considerations

All the reactions that constitute this project were performed under air unless otherwise specified. The reagents were purchased directly from standard chemical suppliers and used as received from the supplier without further purification unless otherwise specified. All solvents were used as received from the supplier, except DCM and acetonitrile which were stored over dehydrating reagents and were deoxygenated before use where specified. Molecular sieves, 3 Å 1-2 mm or 4 Å 1-2 mm beads were supplied from Alfa Aesar, dried and stored at 220 °C before use.

The purification of the reaction products was performed using medium pressure column chromatography, which was carried out using different supports; silica gel as supplied from Sigma-Aldrich (230-400 mesh, 40-63 μm, 60 Å); Merck® aluminium TLC plate, silica gel coated with fluorescent indicator F254s (specific surface area 480 - 540 m^2/g) were used. TLC plates were visualised under a UV lamp operating at short (254 nm) and long (365 nm) wavelength ranges. The visualisation was aided by dipping the plates into an alkaline potassium permanganate solution. Solvent removal was carried out using Büchi R-114 and R-100 rotary evaporator. Low pressure for general purposes (i.e. Büchner filtration) was conducted using various mechanical vacuum pumps. Most purified products were placed under a high vacuum environment generated by various high vacuum generators. Low-pressure distillation was carried out using a Büchi B-585 glass oven (Kügelrohr).

Deuterated chloroform ($CDCl_3$) and DMSO were used as solvents for routine NMR measurements unless otherwise stated. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Neo-400 spectrometer with operating frequencies of 400.20 MHz for ^1H and 100.63 MHz for ^{13}C, operating at ambient probe temperature. High field NMR for the exact

analysis and assignment of the signals in more complex compounds, COSY, HSQC, HMBC and DOSY spectra were recorded by a Varian VNMRS-700 spectrometer. Where HSQC and HMBC were recorded, assignments of ^{13}C is present. Coupling constants (*J*) are given in Hz, and the multiplicity of the NMR signals is described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), br (broad) and app. (apparent splitting). ^{1}H NMR and ^{13}C NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane, references to the chemical shifts of residual solvent resonances.

Solid-state carbon-13 NMR spectra were obtained at 100.63 MHz using a Bruker Avance IIIHD spectrometer and a 4 mm (rotor outside diameter) magic-angle spinning probe. They were recorded using cross polarisation with TOSS spinning sideband suppression with a 1 s recycle delay, 4 ms contact time, at a spin-rate of 10 kHz and at 20 °C. Spectral referencing was with respect to external, neat tetramethylsilane, carried out by setting the high-frequency signal from adamantane to 38.5 ppm.

Mass spectra were obtained using a TQD mass spectrometer and an Acquity UPLC (Waters Ltd, UK) for low-resolution ESI+ or ESI-, and low-resolution ASAP, atmospheric pressure solids analysis probe ionisation unless stated elsewhere. This instrument is setup for flow injection analysis (FIA) or ultra-performance liquid chromatography (UPLC); column dimensions Acquity UPLC BEH C18 1.7µm (2.1mm x 50mm). Accurate mass measurements were obtained using a QtoF Premier mass spectrometer with an Acquity UPLC (Waters Ltd, UK).

IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer.

Single crystal X-ray crystallography data was collected by Bruker D8 Venture diffractometer. High intensity Mo/Cu Dual IµS2 sources, focusing mirrors, CMOS area detector, 3 circle goniometer. Ancillary equipment: Cryostream 700+ (Oxford Cryosystems) open flow nitrogen cryostat (temp. range: 80 – 500 K). The crystal was kept at 120 K during data collection. The structures were solved by direct methods using SHELXS software,[218] and refined by full-matrix least squares using SHELXL[219] and OLEX2

software.[219] All crystallographic data was acquired by Dr Andrei S. Batsanov at Durham University.

Elemental analysis were carried out on an Exeter CE-440 Elemental Analyser.

Melting points were measured by SANYO Gallenkamp Melting Point Apparatus with SAMCO capillary tubes.

Molecular weight analysis was carried out by size exclusion chromatography (SEC) using a Viscotek TDA 302 with detectors for refractive index, light scattering and viscosity. 2 300 mm PLgel 5 μm mixed C-columns were used with a linear molecular weight range of 200 – 2 000 000 $gmol^{-1}$. Chloroform was used as the eluent at a flow rate of 1.0 $mLmin^{-1}$ at a temperature of 30 ^{o}C. Triple detection SEC was utilised for molecular weight determination with light scattering, using values of 0.16. This gave values for the number-average molecular weight (M_n) and weight-average molecular weight (M_w). Samples were prepared for SEC analysis by dissolving 1 mg of compound in 1 mL of chloroform for a concentration of 1 mg mL^{-1} unless otherwise specified. All crystallographic data was acquired by Dr. Antonella Pagliarulo at Durham University.

Thermogravimetric analysis (TGA) of the mass of a substance was monitored as a function of temperature on a TGA-8000 (Perkin Elmer, Shelton, CT). Samples were analysed from a beginning temperature scan of 25 °C to an approximately temperature of 450 °C at a rate of 10 °C/min under a nitrogen purge.

The particle sizes distributions of the latex were measured by Zetasizer μV (Malvern Instruments Ltd.) dynamic light scattering (DLS) at 25 °C when performed at Durham University. When dynamic light scattering was performed at AkzoNobel site a Zetasizer Nano ZS was used at a temperature of 25 °C. The samples were prepared by dilution of the latex, 1% w/w with DI water.

Differential scanning calorimetry (DSC) for the recording of glass transition temperature (Tg) was performed using a DSC Q2000 V24.11 (Mettler Toledo) with 3 cycle (-50 to 180 °C) at AkzoNobel site.

HPLC analysis was performed on Agilent 1100 series instrument, fitted with a Perkin Elmer series 200 degasser. Symmetry C18 column (5μm 100 Å, LC Column 150 x 3.90 mm) was used for the HPLC analysis. Trifluoroacetic acid (0.1%) in water and acetonitrile were used as mobile phase under isocratic flow (20 min); using 60% H_2O (0.1% TFA) and 40% CH_3CN, 1 mL/min flow, 25 °C; 220 nm, 230 nm, 254 nm, 280 nm and 360 nm.

The MFFT of the latex were measured Rhopoint instrument (operating range, -10 ˚C to 40 ˚C). The desired temperature range has been set and waited until the instrument is ready for coating. Emulsions of latex were applied using 75 μm cube applicator. Film formation typically takes place in 10-15 mins and MFFT of the free latices were measured in duplicate. 8 wt% of coalescing agents (texanol) was added to the latexes and the resultant dispersion was applied using the same film applicator. When films were formed, the temperature cursor was moved on the track of the film and noted down the temperature where the film coalesced. The average values from different measurements were reported.

The hardness of the coating was measured with a Qualtech Products Industry Pendulum Hardness.

3.2 General methods

3.2.1.1 Computer controlled latex synthesis

Latex synthesis was completed using a computer-controlled Chemspeed A100 Autoplant, fitted with 20 x 90 mL stainless steel reactors. Each reactor comprised a mechanical anchor-type stirrer, an immersion thermocouple and three syringe pumps connected to separate supply tanks. Initial reactor charge was achieved by means of an automated overhead arm equipped with four syringe pumps. Reactors were purged with nitrogen before reactions commenced. Monomer and surfactant co-mixtures and initiator solutions were fed separately and chilled to 10 °C prior to transfer via computer-controlled syringe pump.

3.2.1.2 Solvent resistance of the latex

On a glass panel a uniform wet film (thickness 300 μm) was deposited and left to dry for a minimum of 14 h. A drop of a solution of 1:1 H_2O/EtOH, and one of only H_2O were adjusted on the film formed surface. The spots were covered with a watch glass for 1 h, to limit their evaporation. The panels were observed during this period of time for any bubbling, swelling or whiteness. After this time, the watch glass was removed, and the solvents wiped off, being careful to not further damage the surface. Any discoloration, swelling, or other attack was examined after the drying of the film. The process was repeated after one week and after one month of film formation.

3.2.1.3 Solubility

The solubility of the various crosslinkers was determined with two different methods. In the case of solubility tests in water, a small sample of the crosslinker, approximately 30-40 mg, was placed in an NMR tube and a precise volume of D_2O (0.6 mL) was added. Dimethyl sulfone was used as an internal standard. ^1H NMR spectra of the sample were recorded overtime, until no more changes could be detected. Meanwhile, the sample was

continually shaken. The solubility of the crosslinkers in the monomers was determined by dissolving the sample in the medium and observing if any obvious suspension was visible.

3.2.1.4 Solid content procedure

In a pre-weighted dish 1.00 g of latex was weight and put in an oven at 120 °C for 1 h. The remaining solids were then weighted.

3.2.1.5 Method for the determination of gel content in latex samples

The method consisted of a continuous extraction using Soxhlet extraction of the sample with tetrahydrofuran (THF) under reflux for 7 h. The refluxing solvent repeatedly washed the sample, continuously extracting the soluble polymer into the flask with the solvent and the insoluble gel was left inside the thimble. The thimble was then dried, reweighted and the gel content was calculated. The latex sample was shaken until homogenous. The thimble containing three filter papers was accurately weighed and around 1.00 g of the sample was added onto the filter paper and the weight recorded. The extraction was carried out on a wet sample as well as on the dried film (to dry the sample, it was left inside the thimble in the fume cupboard overnight). Extraction solvent (THF) was poured into a distillation flask (approx. 150 ml), a few anti-bumping granules were added and the Soxhlet extractor was placed onto the flask, with the thimble with sample inside the Soxhlet extractor, and condenser added. The extraction system was heated to reflux for 7 h after which the thimble containing the non-soluble polymer (gel) was carefully removed and left in the fume cupboard overnight to allow for any residual THF to evaporate. Final drying was carried out in an oven at 110 °C for 2 h. After removal of the thimble from the oven and cooling to room temperature, the thimble was reweighed.

The gel content was calculated using the following equation:

$$\text{Gel Content } (\%) = \frac{\left(\mathrm{W}_{thimble+gel} - \mathrm{W}_{thimble}\right) \cdot 100}{\mathrm{W}_{sample}}$$

Equation 1. Calculation of gel content.

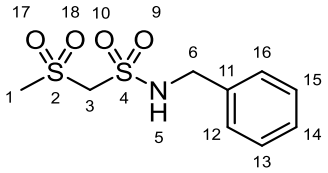
The gel content of each sample was determined twice, and the results reported as an average.

3.3 Synthesis of methylsulfonyl-methylenesulfonmides and by-products

3.3.1 General Method A for the preparation of methylsulfonylmethylenesulfonamide analogues

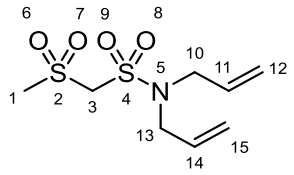
A solution of Et_3N (2.7 mL, 19.5 mmol) in DCM dry (10.0 mL) was cooled to -35 °C and mesyl chloride (1.0 mL, 13.0 mmol) added using a syringe pump (rate 2.50 mL/h). Afterwards, the amine (6.5 mmol) was added dropwise to the pale-yellow suspension and the resulting suspension was left to warm to room temperature. The suspension was diluted with DCM (100 mL) and washed with 5% aqueous HCl (3 × 10 mL), $NaHCO_3$ (3 × 10 mL) and brine (3 × 10 mL). The organic phase was separated, dried ($MgSO_4$) and concentrated under reduced pressure.

3.3.1.1 *N*-Benzyl-1-methylsulfonylmethanesulfonamide prepared using Method A, 127a



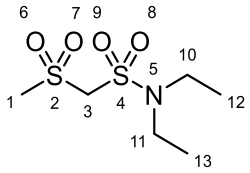
Obtained as a pale yellow solid which was recrystallised from EtOH to give an off-white solid (1.06 g, 62%): m.p. 146 - 147 °C; IR (neat) ν_{max} (*inter alia*) 3273 (m, NH), 2982 (m, CH), 1305 (s, S=O), 1150 (s, S=O), 855 (m, NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.33 (m, 5H, Ph), 5.50 (br. t, 1H, H5), 4.36 (d, *J* = 6.4 Hz, 2H, H6), 4.20 (s, 2H, H3), 3.20 (s, 3H, H1) (addition of D_2O caused the peak at δ 5.50 ppm to disappear and that at δ 4.36 ppm to simplify to a s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.9, 128.9, 128.4, 128.2, 68.3, 47.8, 41.9; LRMS (ASAP) m/z $[M+H]^+$ 264.036 (3.31%), [2M+H] 527.060 (100%); HRMS (ASAP) m/z calculated $C_9H_{14}NO_4S_2$ $[M+H]^+$ 264.0364, found 264.0356; Anal. Calcd. (%) C, 41.04; H, 4.98; N, 5.32; Found (%) C, 40.83; H, 4.91; N, 5.27. Preparation reported in the literature, but no data supplied.[220]

3.3.1.2 *N,N-Bis*(1-prop-2-enyl)-1-methanesulfonylmethanesulfonamide prepared using Method A, 127b



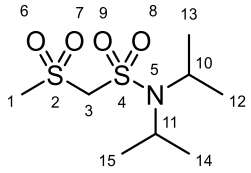
Obtained as a pale yellow solid which was recrystallised from EtOH to give an off-white solid (0.84 g, 50%): m.p. 113 - 114 °C; IR (neat) ν_{max} (*inter alia*) 2980 (w, CH), 2923 (w, CH), 1310 (s, S=O), 1154 (s, S=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 17.4, 10.0, 6.3 Hz, 2H, H11/14), 5.31 (ddd, *J* = 17.3, 10.1, 1.3 Hz, 4H, H12/15), 4.45 (s, 2H, H3), 3.96 (d, *J* = 6.2 Hz, 4H, H10/13), 3.22 (s, 3H, H1); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.0, 119.9, 70.6, 50.2, 42.3; LRMS (ASAP) m/z $[M+H]^+$ 254.046 (100%); Anal. Calcd. (%) C, 37.93; H, 5.97; N, 5.33; Found (%) C, 37.81; H, 5.91; N, 5.48.

3.3.1.3 *N,N*-Diethyl-1-methanesulfonylmethanesulfonamide prepared using Method A, 127c



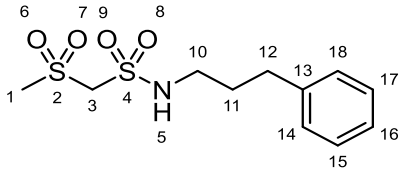
Obtained as a pale-yellow solid which was crystallised from EtOH to give an off-white solid (1.16 g, 78%): m.p. 138 - 140 °C; IR (neat) ν_{max} (*inter alia*): 2978 (w, CH), 2921 (w, CH), 1304 (s, S=O), 1148 (m, S=O), 1109 (m, C-N) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (s, 2H, H3), 3.39 (q, *J* = 7.2 Hz, 4H, H10/11), 3.22 (s, 3H, H1), 1.25 (t, *J* = 7.2 Hz, 6H, H12/13); ^{13}C NMR (101 MHz, $CDCl_3$) δ 69.6, 42.7, 42.0, 14.3; LRMS (ASAP) m/z $[M+H]^+$ 230.043 (100%); Anal. Calcd. (%) C, 31.43; H, 6.59; N, 6.11; Found (%) C, 31.13; H, 6.56; N, 5.97.

3.3.1.4 *N,N*-Diisopropyl-1-methanesulfonylmethanesulfonamide prepared using Method A, 127d



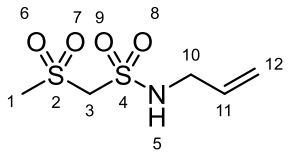
Obtained as a pale yellow solid which was crystallised from EtOH to give an off-white solid (0.85 g, 50%): m.p. 170 - 172 °C; IR (neat) ν_{max} (*inter alia*): 2988 (w, CH), 2973 (w, CH), 2929 (w, CH), 1303 (s, S=O), 1160 (m, S=O), 1103 (s, C-N) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (s, 2H, H3), 3.93-3.80 (h, *J* = 6.8 Hz, 2H, H11/10), 3.24 (s, 3H, H1), 1.35 (d, *J* = 6.8 Hz, 12H, H12/13/14/15); ^{13}C NMR (101 MHz, $CDCl_3$) δ 73.1, 49.7, 42.3, 22.1. LRMS (ASAP) m/z $[M+H]^+$ 258.080 (100%); Anal. Calcd. (%) C, 37.34; H, 7.44; N, 5.44; Found (%) C, 37.21; H, 7.43; N, 5.36.

3.3.1.5 *N*-(3-Phenylpropyl)-1-methanesulfonylmethanesulfonamide prepared using Method A, 127e



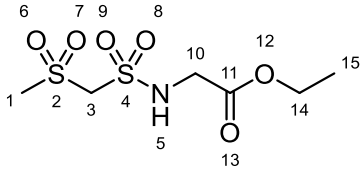
Obtained as a pale yellow solid which was crystallised from EtOH to give an off-white solid (0.9 g, 47%): m.p. 120 - 122 °C; IR (neat) ν_{max} (*inter alia*): 3271 (m, NH), 3024 (w, CH aryl), 2978 (w, CH), 2924 (w, CH), 1305 (s, S=O), 1158 (s, S=O), 766 (m, NH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 2H, H14/18), 7.24-7.15 (m, 3H, H15/16/17), 5.10 (br. t, *J* = 6.0 Hz, 1H, H5), 4.39 (s, 2H, H3), 3.24 (s, 3H, H1), 3.18 (q, *J* = 7.0 Hz, 2H, H10), 2.71 (t, *J* = 7.3 Hz, 2H, H12), 1.95 (p, *J* = 7.0 Hz, 2H, H11) (addition of D_2O caused the peak at δ 5.10 ppm to disappear and that at δ 3.16 ppm to simplify to a t, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4, 128.6, 128.3, 126.2, 67.5, 43.4, 41.9, 32.5, 31.3; LRMS (ASAP) m/z $[M+H]^+$ 292.058 (100%). Anal. Calcd. (%) C, 45.34; H, 5.88; N, 4.81; Found (%) C, 45.12; H, 5.84; N, 4.75.

3.3.1.6 *N*-(Prop-2-enyl)-1-methanesulfonylmethanesulfonamide prepared using Method A, 127f



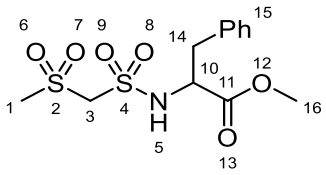
Obtained as a pale yellow solid which was crystallised from EtOH to give an off-white solid (0.59 g, 53%): m.p. 89 - 91 °C; IR (neat) ν_{max} (*inter alia*) 3275 (m, NH), 2984 (w, CH), 2923 (w, CH), 1303 (s, S=O), 1153 (m, S=O), 767 (m, NH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddt, *J* = 17.2, 10.2, 6.1 Hz, 1H, H11), 5.37 (dd, *J* = 17.2, 1.2 Hz, 1H, H12), 5.29 (dd, *J* = 10.2, 1.2 Hz, 1H, H12), 5.24 (br t, 1H, H5), 4.45 (s, 2H, H3), 3.83 (app. tt, *J* = 6.2, 1.5 Hz, 2H, H10), 3.23 (s, 3H, H1) (addition of D_2O caused the peak at δ 5.24 ppm to disappear and that at δ 3.83 ppm to simplify to a d, J = 6.2, Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.1, 119.0, 68.5, 46.2, 41.8; LRMS (ASAP) m/z $[M+H]^+$ 214.019 (100%); Anal. Calcd. (%) C, 28.16; H, 5.2; N, 6.57; Found (%) C, 28.05; H, 5.15; N, 6.49.

3.3.1.7 *N*-Ethyl 2-(methanesulfonylmethanesulfonamido)acetate prepared using Method A, 127g



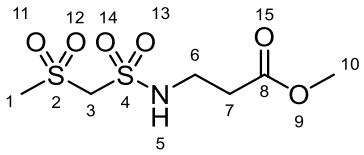
Obtained as a pale yellow solid which was crystallised from THF to give an off-white solid (0.17 g, 10%): m.p. 60 – 65 °C; IR (neat) ν_{max} (*inter alia*): 3302 (w, NH), 2998 (w, CH), 2936 (w, CH), 1738 (s, C=O), 1305 (s, S=O), 1217 (s, C-O), 1155 (s, NH), 1101 (s, C-O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (br t, *J* = 5.8 Hz, 1H, H5), 4.79 (s, 2H, H3), 4.25 (q, *J* = 7.2 Hz, 2H, H14), 4.05 (d, *J* = 6.1 Hz, 2H, H10), 3.24 (s, 3H, H1), 1.30 (t, *J* = 7.2 Hz, 3H, H15) (addition of D_2O caused the peak at δ 5.72 ppm to disappear and that at δ 4.05 ppm to simplify to a s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 70.5, 62.2, 45.0, 42.3, 14.1; LRMS (ASAP) m/z $[M+H]^+$ 260.020 (100%); Anal. Calcd. (%) C, 27.79; H, 5.05; N, 5.4; Found (%) C, 27.42; H, 4.97; N, 5.29.

3.3.1.8 *(S)-N*-Methyl-2-(methanesulfonylmethanesulfonamide)-3-phenylpropanoate prepared using Method A, 127h



Obtained as a pale yellow solid which was crystallised from EtOH to give an off-white solid (1.3 g, 60%): m.p. 122 - 123 °C; IR (neat) ν_{max} (*inter alia*): 3328 (w, NH), 3045 (w, C=C), 2985 (w, CH), 2930 (w, CH), 1742 (m, C=O), 1316 (m, S=O), 1137 (s, S=O), 751 (m, NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 3H, Ph), 7.20 (d, *J* = 3.2 Hz, 2H, Ph), 5.54 (d, *J* = 9.1 Hz, 1H, H5), 4.57 (ddd, J = 9.1, 7.5, 5.3 Hz, 1H, H10), 4.46 (d, *J* = 15.0 Hz, 1H, H3'), 4.09 (d, *J* = 15.0Hz, 1H, H3), 3.80 (s, 3H, H16), 3.21 (dd, *J* = 14.0, 5.3 Hz, 1H, H14'), 3.15 (s, 3H, H1), 3.08 (dd, *J* = 14.0, 7.5 Hz, 1H, H14) (addition of D_2O caused the peak at δ 5.54 ppm to disappear and that at δ 4.57 ppm to simplify to a dd, *J* = 7.5, 5.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 135.0, 129.4, 129.0, 127.7, 70.5, 57.9, 52.9, 42.2, 39.0; LRMS (ASAP) m/z $[M+H]^+$ 336.053 (100%); Anal. Calcd (%) C, 42.97; H, 5.11; N, 4.18. Found (%) C, 43.00; H, 5.19; N, 4.10.

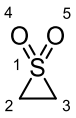
3.3.1.9 *N*-Methyl-3-(methanesulfonylmethanesulfonamido)propanoate prepared using Method A, 127i



Obtained as a pale yellow solid which was crystallised from EtOH to give an off-white solid (1.48 g, 90%): m.p. 48 - 49 °C; IR (neat) ν_{max} (*inter alia*): 3285 (m, NH), 2979 (w, CH), 2920 (w, NH), 1731 (s, C=O), 1308 (s, S=O), 1159 (s, S=O), 611 (m, NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.67 (br. s,1H, H5), 4.48 (s, 2H, H3), 3.73 (s, 3H, H10), 3.48 (q, *J* = 6.1 Hz, 2H, H6), 3.22 (s, 3H, H1), 2.66 (t, *J* = 6.1 Hz, 2H, H7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 68.7, 52.4, 42.2, 39.6; LRMS (ASAP) m/z $[M+H]^+$ 260.0 (100%), $[2M+H]^+$ 519.1 (34%); Anal. Calcd (%) C, 27.79; H, 5.05; N, 5.4; Found (%) C, 27.53; H, 4.99; N, 5.30.

3.3.2 Synthesis of episulfone, **128**

A solution of *N,N'*-di*iso*propylethylamine (2.70 mL, 19.5 mmol) in DCM dry (10.0 mL) was cooled to -40 °C and mesyl chloride (1.00 mL, 13.0 mmol) was added using a syringe pump (rate 2.50 mL/h). Afterwards, the amine (6.5 mmol) was added dropwise to the pale-yellow suspension. After addition, the suspension was left to warm to room temperature. The suspension was diluted with DCM (100 mL) and washed with 5% aqueous HCl (3 × 10 mL), $NaHCO_3$ (3 × 10.0 mL) and brine (3 × 10.0 mL). The organic phase was separated, dried ($MgSO_4$) and concentrated under reduced pressure. Procedure reported in the literature.[134a, 173]

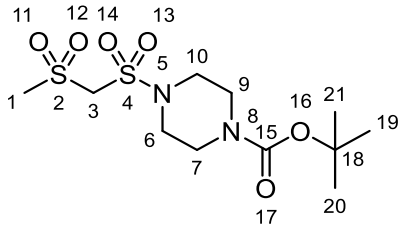


Obtained as a dark orange/yellow oil (38 mg, 41%): IR (neat) ν_{max} (*inter alia):* 1304 (s, S=O), 1164 (s), 793 (m), 443 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.14 (s, 4H, H3/2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 31.4; All spectroscopic and analytical properties were identical to those reported in the literature.[221]

3.3.3 General Method B for the preparation of methylsulfonyl-methylenesulfonamide analogues

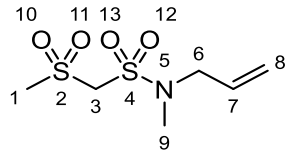
A 13 wt% solution of Me_3N in CH_3CN was cooled to -40 °C and mesyl chloride was added dropwise using a syringe pump. Afterwards, Et_3N or Me_3N as a 13 wt% CH_3CN was added to the solution before adding compound the amine salt and left to react for 15 min at -40 °C to then warm up to room temperature. When the amine was not in the form of a salt, no extra base was added, and the amine was added and left to react for 15 min at -40 °C to then warm up to room temperature. The suspension was then concentrated under reduced pressure and diluted in DCM or EtOAc for the workup; the organic phase was washed with HCl 5% (3x), $NaHCO_3$ (3×), brine (3x) and dried over $MgSO_4$. The organic phase was concentrated under reduced pressure to give the final product.

3.3.3.1 tert-Butyl 4-methanesulfonylmethanesulfonylpiperazine-1-carboxylate prepared using Method B, 127p



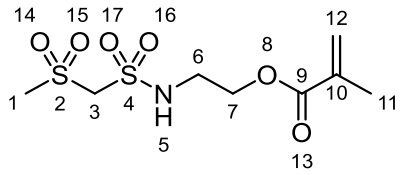
Reagents used in Method B: mesyl chloride (13.0 mmol, 1.0 mL), Me_3N 13 wt% CH_3CN (40.0 mmol, 25.0 mL), amine (6.5 mmol, 1.20 g). Obtained as a white solid without any further purification (1.76 g, 80%): m.p. 163 - 164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (s, 2H, H3), 3.53 (br t, *J* = 5.0 Hz, 4H, H6/10), 3.38 (br t, *J* = 5.1 Hz, 4H, H7/9), 3.21 (s, 3H, H1), 1.46 (s, 10H, H19/20/21); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 80.8, 68.5, 46.1, 43.9, 42.4, 28.5. LRMS (ESI) m/z $[M-H]^-$ 341.7 (100%); HRMS (ESI) m/z calculated $C_{11}H_{21}N_2O_6S_2$ $[M-H]^-$ 341.0822, found 341.0841.

3.3.3.2 1-Methanesulfonyl-*N*-methyl-*N*-(prop-2-en-1-yl)methanesulfonamide prepared using Method B, 127o



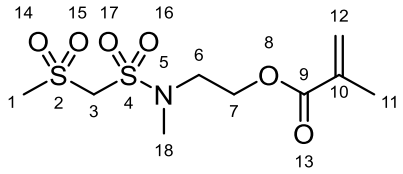
Reagents used in Method B: mesyl chloride (0.100 mol, 7.70 mL), Me_3N 13 wt% CH_3CN (0.300 mol, 174 mL), amine (0.05 mol, 4.80 mL). Obtained as a white solid without any further purification (10.1 g, 89%): m.p. 114 - 115 °C; IR (neat) υ_{max} (*inter alia*) 2978 (w, CH), 2920 (w, CH), 1308 (s, S=O), 1155 (s, S=O), 919 (m, C=C), 764 (m, C-H), 465 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.1, 10.1, 6.2 Hz, 1H, H7), 5.32 (ddd, *J* = 17.1, 10.1, 1.5 Hz, 2H, H8), 4.43 (s, 2H, H3), 3.90 (d, *J* = 6.2 Hz, 2H, H6), 3.22 (s, 3H, H1), 2.95 (s, 3H, H9); ^{13}C NMR (176 MHz, $CDCl_3$) δ 132.1, 119.9, 68.7, 53.4, 42.4, 34.8. LRMS (ESI) m/z $[M+H]^+$ 228.1 (100%); HRMS (ESI) m/z calculated $C_6H_{14}NO_4S_2$ $[M+H]^+$ 228.0362, found 228.0364.

3.3.3.3 2-(Methanesulfonylmethanesulfonamido)ethyl 2-methylprop-2-enoate prepared using Method B, 141a



Reagents used in Method B: mesyl chloride (6.50 mmol, 0.50 mL), Me_3N 13 wt% CH_3CN (9.75 mmol, 6.90 mL), Me_3N 13 wt% CH_3CN (3.30 mmol, 4.60 mL), amine **134a** (0.05 mol, 4.80 g). Obtained as a white solid (0.87 g, 90%): m.p. 62 – 66 °C; IR (neat) υ_{max} (*inter alia*) 3286 (w, NH), 2990 (w, CH), 2930 (w, CH), 1693 (m, C=O), 1310 (s, S=O), 1133 (s, S=O), 950, 775 (m, NH), 465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.14 (s, 1H, H12'), 5.62 (app. t, *J* = 1.5 Hz, 1H, H12), 4.57 (s, 2H, H3), 4.28 (t, *J* = 5.4 Hz, 2H, H7), 3.47 (t, *J* = 5.4 Hz, 2H, H6), 3.21 (s, 3H, H1), 1.94 (s, 3H, H11), (addition of D_2O caused the peak at δ 5.64 ppm to disappear and that at δ 3.50 ppm to simplify to a t, 2H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 167.2, 135.8, 126.7, 68.6, 63.2, 43.1, 42.1, 18.3; LRMS (ESI) m/z $[M+H]^+$ 286.0 (100%); HRMS (ESI) m/z calculated $C_8H_{15}NO_6S_2$ $[M+H]^+$ 286.0422, found 286.0419.

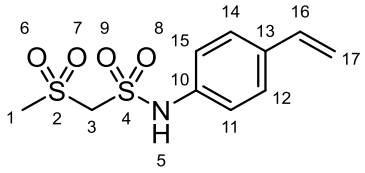
3.3.3.4 (*N*-Methylmethanesulfonylmethanesulfonamido)ethyl 2-methylprop-2-enoate prepared using Method B, 141b



Reagents used in Method B: mesyl chloride (0.200 mol, 15.5 mL), Me_3N 13 wt% CH_3CN (0.300 mol, 208 mL), Me_3N 13 wt% CH_3CN (0.100 mol, 69.0 mL), amine **134b** (0.100 mol, 18.0 g). Obtained as a white solid (26.9 g, 86%): m.p. 65 – 67 °C; IR (neat) υ_{max} (*inter alia*): 3286 (m, NCH_3), 2990 (w, CH), 2930 (w, NCH_3), 1693 (m, C=O), 1310 (s, S=O), 1133 (s, S=O), 465 (m, NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.12 (s, 1H, H12), 5.59 (app. t, *J* = 1.6 Hz, 1H, H12), 4.52 (s, 2H, H3), 4.29 (t, *J* = 5.4 Hz, 2H, H7), 3.57 (t, *J* = 5.4 Hz, 2H, H6), 3.18 (s, 3H, H1), 3.01 (s, 3H, H18), 1.92 (t, *J* = 1.2 Hz, 3H, H11); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 135.9, 126.5, 68.2, 61.8, 49.8, 42.3, 35.8, 18.4; LRMS (ASAP) m/z $[M+H]^+$ 300.1

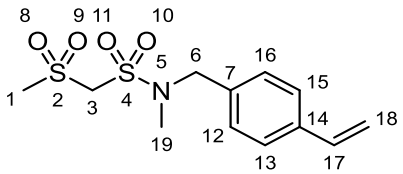
(100%); HRMS (ESI) m/z calculated $C_9H_{17}NO_6S_2$ $[M+H]^+$ 300.0582, found 300.0576; Anal. Calcd (%) C, 36.11; H, 5.72; N, 4.68. Found (%) C, 35.84; H, 5.69; N, 4.49.

3.3.3.5 *N*-(4-Ethenylphenyl)-1-methanesulfonylmethanesulfonamide prepared using Method B, 152



Reagents used in Method B: mesyl chloride (40.0 mmol, 3.10 mL), Me_3N 13 wt% CH_3CN (60.0 mmol, 42.0 mL), amine **135** (20.0 mmol, 2.34 g). Obtained 3.65 of crude, recrystallised from EtOH to obtain a white solid (1.87 g, 34%): m.p 167 - 168 °C; IR (neat) υ_{max} (*inter alia*): 3247 (m, NH), 2971 (w, CH), 2910 (w, NH), 1309 (s, S=O), 1154 (s, S=O), 454 (m, NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.5 Hz, 2H, H11/15), 7.32 (d, *J* = 8.5 Hz, 2H, H12/14), 7.11 (br s, 1H, H5), 6.70 (dd, *J* = 17.6, 10.9 Hz, 1H, H16), 5.75 (dd, *J* = 17.6, 0.7 Hz, 1H, H17), 5.30 (dd, *J* = 10.9, 0.7 Hz, 1H, H17), 4.34 (s, 2H, H3), 3.29 (s, 3H, H1) (addition of D_2O caused the peak at δ 7.11 ppm to disappear); ^{13}C NMR (151 MHz, DMSO-d6) δ 136.5, 135.9, 133.5, 127.0, 120.6, 113.6, 67.8, 42.0; LRMS (ASAP) m/z $[M+H]^+$ 276.037 (100%); HRMS (ASAP) m/z calculated $C_{10}H_{14}NO_4S_2$ $[M+H]^+$ 276.0366, found 276.0364; Anal. Calcd. (%) C, 43.62; H, 4.76; N, 5.09. Found (%) C, 43.59; H, 4.58; N, 4.93.

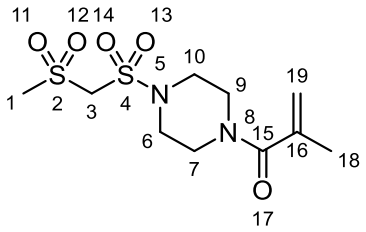
3.3.3.6 *N*-[(4-Ethenylphenyl)methyl]-1-methanesulfonyl-*N*-methylmethanesulfonamide prepared using Method B, 153



Reagents used in Method B: mesyl chloride (75.2 mmol, 5.80 mL), M_3N 13% CH_3CN (113 mmol, 78.0 mL), amine **136** (37.6 mmol, 5.00 g). Obtained as a white solid (11.4 g, 64%): m.p. 136 – 142 °C; IR (neat) υ_{max} (*inter alia*) 3246 (m, $C=CH_2$), 2971 (w, CH), 2911 (w, NCH_3), 1303 (m, S=O), 1154 (m, S=O), 917, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.2 Hz, 2H, H12/16), 7.31 (d, *J* = 8.2 Hz, 2H, H13/15), 6.71 (dd, *J* = 17.6, 10.9 Hz, 1H,

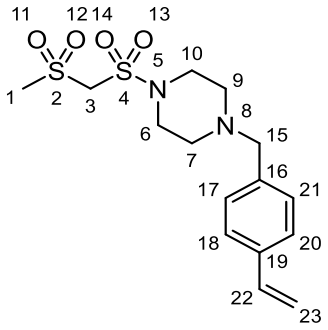
H17), 5.77 (dd, *J* = 17.6, 0.9 Hz, 1H, H18), 5.28 (dd, *J* = 10.9, 0.9 Hz, 1H, H18), 4.46 (s, 2H, H3), 4.44 (s, 2H, H6), 3.25 (s, 3H, H1), 2.88 (s, 3H, H19); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8, 136.3, 134.5, 128.6, 126.8, 114.6, 68.4, 54.4, 42.3, 34.7; LRMS (ASAP): m/z [M+H]+ 304.068 (49%); HRMS (ASAP): m/z calculated $C_{12}H_{17}NO_4S_2$ $[M+H]^+$ 303.0599, found 303.0603.

3.3.3.7 1-(4-Methanesulfonylmethanesulfonylpiperazin-1-yl)-2-methylprop-2-en-1-one prepared using Method B, 154



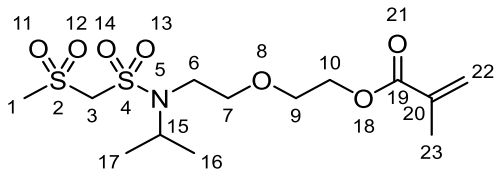
Reagents used in Method B: mesyl chloride (26.5 mmol, 2.10 mL), Me_3N 13 wt% CH_3CN (79.4 mmol, 49.0 mL), amine **137b** (13.2 mmol, 3.55 g), Et_3N (13.2 mmol, 1.84 mL). Obtained as a white solid (2.17 g, 53%): m.p. (°C) 148 - 150; IR (neat) υ_{max} (*inter alia*) 2971 (w, CH), 2911 (w, NCH_3), 1303 (m, S=O), 1154 (m, S=O), 917, 776, 454 (m, NH) cm^{-1}; ^{1}H NMR (599 MHz, $CDCl_3$) δ 5.24 (app. t, *J* = 1.1 Hz, 1H, H19), 5.05 (app. t, *J* = 1.1 Hz, 1H, H19), 4.45 (s, 2H, H3), 3.69 (br, 4H, H6/10), 3.43 (t, *J* = 5.1 Hz, 4H, H7/9), 3.21 (s, 3H, H1), 1.95 (t, *J* = 1.4 Hz, 3H, H18); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.5 (C15), 139.8 (C16), 116.5 (C19), 68.7 (C3), 46.4 (C7/9), 42.4 (C1), 41.5 (C6/10), 20.6 (C18). LRMS (ASAP): m/z $[M+H]^+$ 311.067 (100%); HRMS (ASAP): m/z calculated $C_{10}H_{19}N_2O_5S_2$ $[M+H]^+$ 311.0746, found 311.0735.

3.3.3.8 1-[(4-Ethenylphenyl)methyl]-4-methanesulfonyl-methanesulfonylpiperazine prepared using Method B, 156



Reagents used in Method B: mesyl chloride (49.5 mmol, 3.81 mL), Me_3N 13 wt% CH_3CN (148 mmol, 91.0 mL), amine **139** (24.7 mmol, 5.00 g), Et_3N (49.5 mmol, 6.88 mL). Obtained as a white powder (6.89 g, 79%). The compound was used with no further purification: m.p. 173 – 175 °C; IR (neat) υ_{max} (*inter alia*) 3023 (w), 2921 (w, CH), 2911 (w, NCH_3), 1307 (s, S=O), 1158 (s, S=O), 954 (s), 755 (s), cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.0 Hz, 2H, H17/21), 7.26 (d, *J* = 8.0 Hz, 2H, H18/20), 6.71 (dd, *J* = 17.6, 10.9 Hz, 1H, H22), 5.74 (d, *J* = 17.6 Hz, 1H, H23), 5.24 (d, *J* = 10.9 Hz, 1H, H23), 4.39 (s, 2H, H3), 3.53 (s, 2H, H15), 3.43 (t, *J* = 5.0 Hz, 4H, H6/10), 3.21 (s, 3H, H1), 2.53 (t, *J* = 5.0 Hz, 4H, H7/9); ^{13}C NMR (176 MHz, $CDCl_3$) δ 137.2 (C19), 137.0 (C16), 136.6 (C22), 129.3 (C18/20), 126.4 (C17/21), 113.9 (C23), 68.5 (C3), 62.4 (C15), 52.6 (C7/9), 46.3 (C6/10), 42.4 (C1); LRMS (ASAP): m/z $[M+H]^+$ 359.1 (100%); HRMS (ASAP): m/z calculated $C_{15}H_{23}N_2O_4S_2$ $[M+H]^+$ 359.1099, found 359.1096.

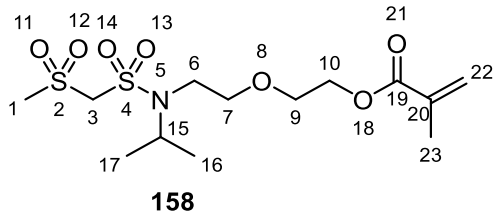
3.3.3.9 2-{2-[*N*-(Propan-2-yl)methanesulfonyl-methanesulfonamido]ethoxy}ethyl 2-methylprop-2-enoate prepared using Method B, 158



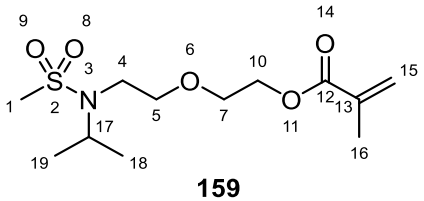
Reagents used in Method B: mesyl chloride (204 mmol, 15.7 mL), Me_3N 13 wt% CH_3CN (612 mmol, 427 mL), amine **140d** (102 mmol, 25.7 g), Et_3N (204 mmol, 28.0 mL). The crude product was purified by silica gel chromatography (Hex:EtOAc, 8:2) to obtained **158** as clear gel (13.7 g, 36%): IR (neat) υ_{max} (*inter alia*): 2928 (w, C-H), 1715 (w, C=O), 1314

(s, S=O), 1161 (s, S=O), 766 (m, C-H) cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.13 (s, 1H, H22), 5.59 (app. t, *J* = 1.6 Hz, 1H, H22), 4.62 (s, 2H, H3), 4.32 (t, *J* = 4.8 Hz, 2H, H10), 4.16 (hept, *J* = 6.8 Hz, 1H, H15), 3.73 (t, *J* = 4.8 Hz, 2H, H9), 3.65 (t, *J* = 5.5 Hz, 2H, H6), 3.50 (t, *J* = 5.5 Hz, 2H, H7), 3.21 (s, 3H, H1), 1.95 (s, 3H, H23), 1.27 (d, *J* = 6.8 Hz, 6H, H16/17); ^{13}C NMR (176 MHz, $CDCl_3$) δ 167.4 (C20), 136.3 (C19), 126.0 (C22), 71.3 (C10), 70.7 (C3), 69.3 (C7), 63.7 (C6), 51.6 (C15), 43.4 (C9), 42.4 (C1), 21.8 (C17/16), 18.5 (C23); LRMS (ESI) m/z $[M-H]^-$ 370.2 (100%); HRMS (ESI) m/z calculated $C_{13}H_{26}NO_7S_2$ $[M+H]^+$ 372.1151, found 372.1149.

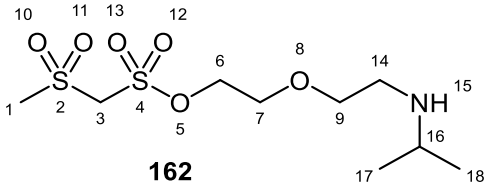
3.3.3.10 Method B for the synthesis of compounds 158, 159, and 162



158



159

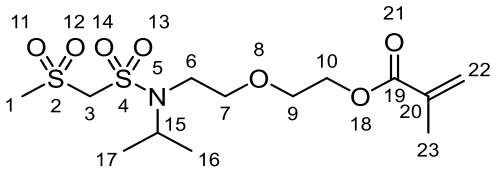


162

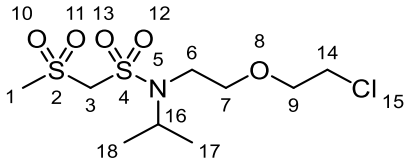
Reagents used in Method B: mesyl chloride (3.98 mmol, 0.310 mL), Me_3N 13 wt% CH_3CN (5.98 mmol, 4.17 mL), amine **140d** (1.99 mmol, 0.500 g), Me_3N 13 wt% CH_3CN (3.98 mmol, 2.80 mL). The crude was purified by silica gel chromatography (Hex:EtOAc, 8:2) to obtain three compounds: 2-{2-[*N*-(Propan-2-yl)methanesulfonyl-methanesulfonamido]ethoxy}ethyl2-methylprop-2-enoate, **158** as clear oil (0.23 g, 34%): all spectroscopic and analytical properties were identical to those reported in experiment 3.3.3.9 above; and 2-{2-[*N*-(propan-2-yl)methanesulfonamido]ethoxy}ethyl-2-methylprop-2-enoate, **159** obtained as a clear liquid (20 mg, 3%): ^{1}H NMR (599 MHz, $CDCl_3$) δ 6.11 (s, 1H, H15), 5.58 (t, *J* = 1.6 Hz, 1H, H15), 4.29 (t, *J* = 4.7 Hz, 2H, H4), 4.05 (hept, *J* = 6.8 Hz, 1H, H17), 3.71 (t, *J* = 4.7 Hz, 2H, H5), 3.64 (t, *J* = 6.3 Hz, 2H, H10), 3.31 (t, *J* = 6.3 Hz, 2H, H7), 2.87 (s, 3H, H1), 1.94 (s, 3H, H16), 1.21 (d, *J* = 6.7 Hz, 6H, H19/18); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.4 (C12), 136.3 (C13), 125.9 (C15), 71.2 (C10), 69.2 (C5), 63.9

(C4), 49.9 (C17), 42.4 (C7), 39.9 (C1), 21.6 (C19/18), 18.4 (C16); LRMS (ESI) m/z [M-$MeSO_2$+H]$^-$ 216.333 (86%); and 2-{2-[(propan-2-yl)amino]ethoxy}ethyl-methanesulfonylmethanesulfonate, **162** obtained as a clear liquid (7 mg, 10%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (s, 2H), 4.26 – 4.21 (m, 2H), 4.18 (q, *J* = 7.0 Hz, 1H), 3.72 – 3.66 (m, 2H), 3.64 (t, *J* = 5.6 Hz, 2H), 3.52 (t, *J* = 5.4 Hz, 2H), 3.22 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 71.2 (C-OR), 70.9 (C-OR), 69.3, 51.7, 43.2, 42.3, 21.8 (C-NR), 21.1 (C-SO_2); LRMS (ESI) m/z [M+K]$^+$ 342.278 (7%).

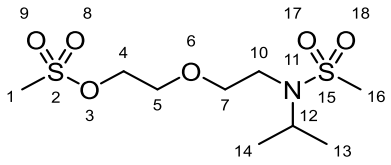
3.3.3.11 Method B for the synthesis of compounds 158, 160, and 161



158



160

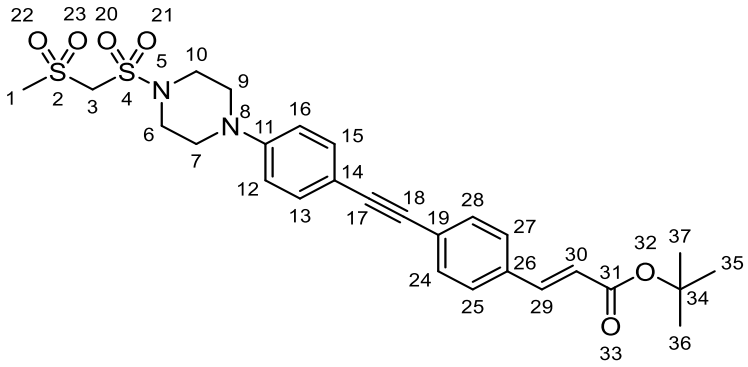


161

Reagents used in Method B: mesyl chloride (5.63 mmol, 0.44 mL), Me_3N 13 wt% CH_3CN (16.9 mmol, 9.77 mL), amine **140d** (2.82 mmol, 0.708 g), Me_3N 13 wt% CH_3CN (11.2 mmol, 6.51 mL). The crude product was purified by silica gel chromatography (Hex:EtOAc, 8:2) to obtain three compounds: **158** as clear gel (0.293 g, 28%): all spectroscopic and analytical properties were identical to those reported in experiment 3.3.3.9 above; N-[2-(2-Hydroxyethoxy)ethyl]-1-methanesulfonyl-N-(propan-2-yl)methanesulfonamide, **160** obtained a clear liquid (36 mg, 4%): ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.68 (s, 2H, H3), 4.16 (h, *J* = 6.8 Hz, 1H, H16), 3.74 (t, *J* = 5.6 Hz, 2H, H6), 3.68 – 3.63 (m, 4H, H9/14), 3.52 (t, *J* = 5.6 Hz, 2H, H7), 3.20 (s, 3H, H1), 1.27 (d, *J* = 6.8 Hz, 6H, H17/18). ^{13}C NMR (176 MHz, $CDCl_3$) δ 71.3 (C6), 71.1 (C9), 70.8 (C3), 51.6 (C16), 43.2 (C7), 42.9 (C14), 42.4 (C1), 21.8 (C17/18). LRMS (ESI) m/z [M+Na]$^+$ 344.178 (100%), 346.876 (18%); and 2-{2-[*N*-(propan-2-yl)methanesulfonamido]ethoxy}ethyl-methanesulfonate, **161** a clear liquid (8 mg, 1%): ^{1}H

NMR (700 MHz, $CDCl_3$) δ 4.37 – 4.33 (m, 2H, H4), 4.06 (hept, *J* = 6.7 Hz, 1H, H12), 3.77 – 3.73 (m, 2H, H5), 3.66 (t, *J* = 6.5 Hz, 2H, H10), 3.31 (t, *J* = 6.5 Hz, 2H, H7), 3.05 (s, 3H, H1), 2.88 (s, 3H, 16), 1.23 (d, *J* = 6.7 Hz, 6H, H13/14); ^{13}C NMR (176 MHz, $CDCl_3$) δ 71.4 (C10), 68.9 (C5), 68.8 (C4), 49.9 (C12), 42.1 (C7), 39.7 (C16), 37.8 (C1), 21.6 (C13/14); LRMS (ESI) m/z $[M+Na]^+$ 326.205 (69%).

3.3.3.12 tert-Butyl-3-(4-{2-[4-(4-methanesulfonylmethanesulfonylpiperazin-1-yl)phenyl]ethynyl}phenyl)prop-2-enoate prepared using Method B, 202

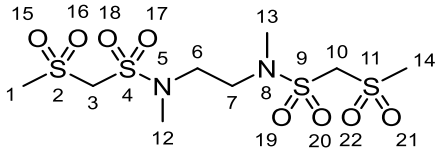


Reagents used in Method B: mesyl chloride (2.00 mmol, 0.160 mL), Me_3N 13 wt% CH_3CN (3.00 mmol, 2.14 mL), amine **201** (1.00 mmol, 0.400 g). Obtained as a yellow solid (0.428 g, 76%): m.p. 229-234 °C; IR (neat) υ_{max} (*inter alia*) 2977 (w, C-H), 2214 (w, C≡C), 1702 (m, C=O), 1314 (s, S=O), 1164 (s, S=O), 951 (s, C=C), 825 (s, C=C), 767 (C-H) cm^{-1}; ^1H NMR (599 MHz, DMSO-d6) δ 7.72 (d, *J* = 8.3 Hz, 2H, H25/27), 7.55 (d, *J* = 16.0 Hz, 1H, H30), 7.51 (d, *J* = 8.3 Hz, 2H, H24/28f), 7.43 (d, *J* = 8.8 Hz, 2H, H13/15), 7.01 (d, *J* = 8.8 Hz, 2H, H12/16), 6.55 (d, *J* = 16.0 Hz, 1H, H29), 5.33 (s, 2H, H3), 3.42 – 3.35 (br d, 8H, H6/7/9/10), 3.19 (s, 3H, H1), 1.49 (s, 9H, H35/36/37); ^{13}C NMR (150 MHz, DMSO-d6) δ 165.9 (C31), 150.7 (C14), 143.1 (C30), 134.2 (C19), 133.0 (C13/15), 131.9 (C24/28), 128.9 (C25/27), 125.1 (C26), 121.0 (C29), 115.7 (C12/16), 112.0 (C11), 92.8 (C17), 88.2 (C18), 80.5 (C34), 67.3 (C3), 47.6 (C7/9), 45.4 (C6/10), 42.6 (C1), 28.3 (C35/36/37); LRMS (ASAP) m/z $[M+H]^+$ 545.2 (37%), 389.2 (100%); HRMS (ASAP) m/z calculated $C_{27}H_{32}N_2O_6S_2$ $[M+H]^+$ 554.1701, found 554.1702. UV-Vis ($CHCl_3$): λ_{max} 351, λ_{em} 357.

3.3.4 Synthesis of *bis*-sulfonyl sulfonamides

3.3.4.1 1-Methanesulfonyl-*N*-methyl-*N*-[2-(*N*-methylmethanesulfonylmethanesulfonamido)ethyl]methanesulfonamide, 130a

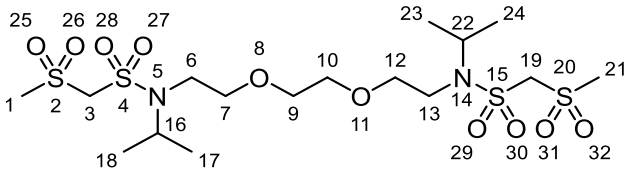
A 13 wt% solution of Me_3N in CH_3CN (39.0 mmol, 24.0 mL) was cooled to -40 °C and mesyl chloride (13.0 mmol, 1.00 mL) was added dropwise using a syringe pump. Afterwards, the *bis*-amine (3.30 mmol, 0.350 mL) was added and left to react for 15 min at -40 °C to then warm up to room temperature. The suspension was then filtered on a Büchner funnel and the filtrate washed with water. The filtrate was dried under reduced pressure to give the final product.



Obtained as a white solid (1.29 g, 99%): m.p. 192-193 °C; IR (neat) υ_{max} (*inter alia*): 2991 (w, C-H), 2917 (w, C-H), 1463 (w, C-H), 1291 (s, S=O), 1158 (s, S=O), 996 (m, C-N), 786(m, C-H) cm^{-1}; ^1H NMR (599 MHz, DMSO-d6) δ 5.28 (s, 4H, H3/10), 3.35 (s, 4H, H6/7), 3.18 (s, 6H, H1/14), 2.88 (s, 6H, H12/13); ^{13}C NMR (151 MHz, DMSO-d6) δ 66.8 (C3/10), 47.9 (C6/7), 42.1 (C1/14), 34.9 (C12/13); LRMS (ESI) m/z $[M+Na]^+$ 423.9 (100%); HRMS (ESI) m/z calculated $C_8H_{21}N_2O_8S_4$ $[M+H]^+$ 401.0188, found 401.0181.

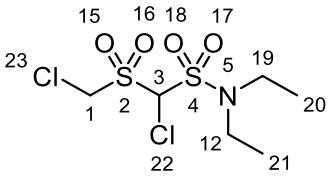
3.3.4.2 1-Methanesulfonyl-*N*-(propan-2-yl)-*N*-[2-(2-{2-[*N*-(propan-2-yl)methanesulfonylmethanesulfonamido]ethoxy}ethoxy)ethyl]methanesulfonamide, 184

A 13 wt% solution of Me_3N in CH_3CN (25.9 mmol, 16.0 mL) was cooled to -40 °C and mesyl chloride (8.62 mmol, 0.660 mL) was added dropwise using a syringe pump. Afterwards, the *bis*-amine **183** (2.16 mmol, 0.50 g) was added and left to react for 15 min at -40 °C to then warm up to room temperature. The suspension was then concentrated under reduced pressure and diluted in DCM or EtOAc for the workup; the organic phase was washed with HCl 5% (3x), $NaHCO_3$ (3×), brine (3x) and dried over $MgSO_4$. The organic phase was concentrated under reduced pressure to give the final product.

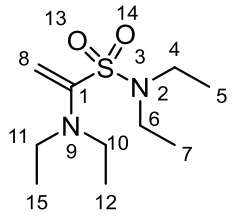


Obtained as a yellow thick liquid (0.88 g, 75%): IR (neat) υ_{max} (*inter alia)* 2986 (w, C-H), 1310 (s, S=O), 1122(s, S=O), 964 (m, C-N), 767(m, C-H) cm^{-1}; ^{1}H NMR (599 MHz, $CDCl_3$) δ 4.82 (s, 4H, H3/19), 4.19 (hept, *J* = 6.7 Hz, 2H, H16/22), 3.65 (s, 4H, H9/10), 3.62 (t, *J* = 5.4 Hz, 4H, H7/9), 3.53 (t, *J* = 5.4 Hz, 4H, H6/13), 3.21 (s, 6H, H1/21), 1.26 (d, *J* = 6.8 Hz, 12H, H18/17/23/24); ^{13}C NMR (151 MHz, $CDCl_3$) δ 71.2 (C7/9), 71.1 (C3/19), 70.1 (C9/10), 51.6 (C16/22), 42.7 (C6/13), 42.3 (C1/21), 21.9 (C17/18/23/24); LRMS (ESI) m/z $[M+H]^+$ 545.367 (100%); HRMS (ESI) m/z calculated $C_{16}H_{37}N_2O_{10}S_4$ $[M+H]^+$ 545.1331, found 545.1344.

3.3.5 Use of chloromethanesulfonyl chloride for the formation of sulfonyl sulfonamides, providing **132** and **133**



132



133

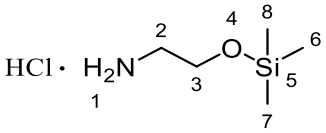
A 13 wt% solution of Me_3N in CH_3CN (24.0 mmol, 15.0 mL) was cooled to -40 °C and chloromethanesulfonyl chloride (8.00 mmol, 0.720 mL) was added dropwise using a syringe pump. Afterwards, diethylamine (4.00 mmol, 0.410 mL) was added and left to react for 15 min at -40 °C to then warm up to room temperature. The suspension was then concentrated under reduced pressure and diluted in DCM or EtOAc for the workup; the organic phase was washed with HCl 5% (3x), $NaHCO_3$ (3x), brine (3x) and dried over $MgSO_4$. The organic phase was concentrated under reduced pressure and the crude mixture purified by silica gel chromatography (Et_2O:Hex, 8:2) to yield two compounds: 1-chloro-1-chloromethanesulfonyl-*N*,*N*-diethylmethanesulfonamide **132** obtained as a clear oil (0.27 g, 23%): IR (neat) υ_{max} (*inter alia*): 2941 (w, C-H), 1702 (w, C=O), 1464 (w, C-H, methylene), 1352 (s, S=O), 1152 (s, S=O), 1020 (s, C-N), 732 (m, C-H) cm^{-1}; ^{1}H NMR (599

MHz, $CDCl_3$) δ 5.83 (s, 1H, H3), 5.06 (d, *J* = 12.5 Hz, 1H, H1), 4.86 (d, *J* = 12.5 Hz, 1H, H1), 3.45 (s, 4H, H12/19), 1.26 (t, *J* = 7.3 Hz, 6H, H21/20); ^{13}C NMR (151 MHz, $CDCl_3$) δ 77.5 (C3), 56.1 (C1), 43.7 (C12/19), 14.4 (C20/21); LRMS (ASAP) m/z $[M+H]^+$ 297.968 (100%), 299.969 (80%); HRMS (ASAP) m/z calculated $C_6H_{14}Cl_2NO_4S_2$ $[M+H]^+$ 297.9741, found 297.9744; and proposed structure **133** was obtained as a clear oil (35 mg): ^1H NMR (599 MHz, $CDCl_3$) δ 6.39 (d, *J* = 2.5 Hz, 1H), 5.91 (d, *J* = 2.5 Hz, 1H), 3.57-3.50 (m, 2H), 3.3-3.30 (m, 6H), 1.22 (t, *J* = 7.1 Hz, 12H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.9, 122.7, 47.4, 42.9, 14.4, 13.6.

3.4 Spacer synthesis

3.4.1 Procedure for the preparation of 2-((trimethylsilyl)oxy)ethan-1-amine hydrochloride, **142**

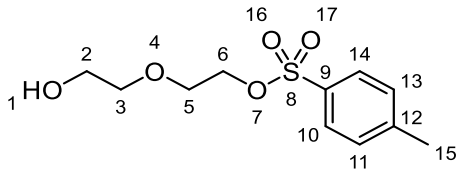
The literature procedure was adopted.[178] TMSCl (98.0 mmol, 10.6 g) was added to a solution of the corresponding amino alcohol (98.0 mmol, 6.00 mL) in dry dichloromethane (65.0 mL). The mixture was stirred 2 h at 40 °C, and then concentrated *in vacuo* to give the desired products in the form of hydrochlorides salt, which were directly used without further purification.



Obtained as a pale yellow solid (16.6 g, 100%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (br s, 3H, H1), 3.84 (t, *J* = 5.4 Hz, 2H, H3), 3.11 (t, *J* = 5.4 Hz, 2H, H2), 0.16 (s, 9H, H6/7/8). All other spectroscopic and analytical properties were identical to those quoted in the literature[178].

3.4.2 Synthesis of 2-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}ethanol, **149**

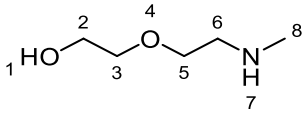
A solution of diethylene glycol (142 mmol, 13.4 mL) in THF (50.0 mL) was cooled in an ice bath before adding potassium hydroxide (56.6 mmol, 3.17 g). Then, *p*-toluenesulfonyl chloride (46.7 mmol, 8.87 g) was slowly added, and the reaction allowed to stir for 5 h. The reaction solution was poured into water and extracted with ethyl acetate (2 x 30 mL). The combined extracts were washed with saturated brine, dried over sodium sulfate, and concentrated under reduce pressure. The crude mixture was purified by silica gel (DCM:MeOH, 9:1) chromatography.



Obtained as a solid (25.6 g, 70% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (t, *J* = 8.3 Hz, 2H, H10/14), 7.34 (t, *J* = 8.3 Hz, 2H, H11/13), 4.19 (t, *J* = 4.5 Hz, 2H, H6), 3.67 (p, *J* = 4.8 Hz, 4H, H3/5), 3.52 (t, *J* = 4.8 Hz, 2H, H2), 2.44 (s, 3H, H15). All other spectroscopic and analytical properties were identical to those quoted in the literature.[222]

3.4.3 Synthesis of 2-[2-(methylamino)ethoxy]ethanol, **150b**

Compound **162** (7.69 mmol, 2.00 g) was dissolved in THF (30 mL), followed by addition of methylamine hydrochloride (115 mmol, 15.4 mL). Potassium carbonate (30.8 mmol, 4.25 g) was then added and left to stir at 50 °C overnight. Solvent was removed under reduced pressure and the crude was purified by Kügelrohr distillation (40 °C, 1 h) to obtain compound **150b** as a clear liquid (50 mg, 6%).

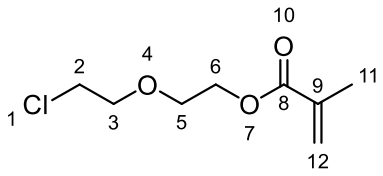


^{1}H NMR (599 MHz, $CDCl_3$) δ 3.68 (t, *J* = 3.5 Hz, 2H, H3), 3.59 (t, *J* = 4.5 Hz, 2H, H5), 3.56 (t, *J* = 3.5 Hz, 2H, H2), 2.92 (br s, H1), 2.75 (t, *J* = 4.5 Hz, 2H, H6), 2.42 (s, 3H, H8); ^{13}C NMR (151

MHz, $CDCl_3$) δ 72.7 (C2), 69.9 (C5), 61.8 (C3), 51.4 (C6), 36.2 (C8); LRMS (ESI) m/z $[M+H]^+$ 120.618 (100%). HRMS (ESI) m/z calculated $C_5H_{14}NO_2$ $[M+H]^+$ 120.1025, found 120.1028. All other spectroscopic and analytical properties were identical to those quoted in the literature.[223]

3.4.4 Synthesis of 2-(2-chloroethoxy)ethyl 2-methylprop-2-enoate, **151**

A literature procedure was adopted.[224] Methacryloyl chloride (9.68 mmol, 0.940 mL) was added dropwise over a solution of 2-(2-chloroethoxy)ethanol (8.06 mmol, 0.850 mL) in 10 mL of anhydrous dichloromethane in the presence of triethylamine (9.68 mmol, 1.35 mL) at 0 °C. Afterwards, the reaction was allowed to reach room temperature and maintained overnight under inert atmosphere. After, the solution was filtered to remove triethylamine hydrochloride, washed with water and dried over anhydrous sodium sulfate.



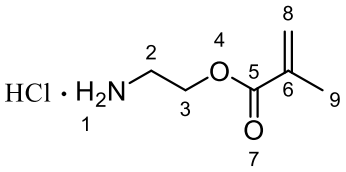
The resulting compound was obtained as a yellow liquid (1.27 g, 81%) and was used in the next step without purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (s, 1H, H12), 5.58 (s, , 1H, H12), 4.31 (t, *J* = 4.8 Hz, 2H, H6), 3.77 (m, two overlapping peaks, 4H, H2/3), 3.63 (t, *J* = 6.0 Hz, 2H, H5), 1.95 (t, *J* = 1.6 Hz, 3H, H11). All other spectroscopic and analytical properties were identical to those quoted in the literature.[224]

3.4.5 Procedure for the preparation of amino methyl methacrylate hydrochloride

3.4.5.1 Synthesis of 2-azaniumylethyl 2-methylprop-2-enoate chloride, 134a

The literature procedure was adopted.[225] Aminoethanol hydrochloride (0.244 mol, 17.4 mL) was prepared via the neutralization of the relative aminoethanol with the calculated amount of hydrochloride 37% (20.3 mL) and complete drying under vacuum at 70 °C. The mixture of 2-aminoethanol hydrochloride and methacryloyl chloride (an excess of 10%,

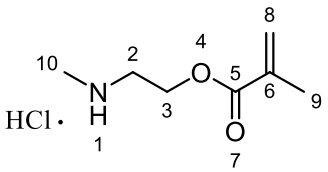
0.120 mol, 11.5 mL) was heated up to 80 °C and maintained for 2 h. The reaction mixture was cooled and dissolved in tetrahydrofuran. The solution of the crude was poured into diethyl ether to remove the unreacted methacryloyl chloride. The final product **134a** was isolated as a white powder after filtration (16.2 g, 92%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (br s, 3H, H1), 6.28 (s, 1H, H8), 5.62 (br. s, 1H, H8), 4.49 (br. s, 2H, H3), 3.37 (s, 2H), 1.95 (s, 3H, H9). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 135.5, 127.3, 60.8, 39.4, 18.5. All other spectroscopic and analytical properties were identical to those quoted in the literature.[226]

3.4.5.2 Methyl({2-[(2-methylprop-2-enoyl)oxy]ethyl})azanium chloride, 134b

A procedure similar to that in the literature was adopted.[225] Aminoethanol hydrochloride (0.491 mol, 39.2 mL) was prepared via the neutralisation of the relative aminoethanol with the calculated amount of hydrochloride 37% (40.6 mL) and complete drying under vacuum at 70 °C. The mixture of 2-aminoethanol hydrochloride and methacryloyl chloride (an excess of 10%, 0.440 mol, 42.7 mL) was heated up to 80 °C and maintained for 2 h. The reaction mixture was cooled and dissolved in tetrahydrofuran. The solution of the crude was poured into diethyl ether (15 mL) to remove the unreacted methacryloyl chloride. The final product **134b** was isolated as a white powder after filtration (50.1 g, 90%).

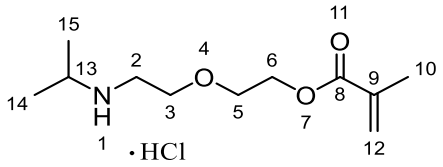


m.p. 101 – 110 °C; IR (neat) ν_{max} (*inter alia*) 2930 (w, CH), 2726 (w, CH), 2489, 2446, 1712 (m, C=O), 1156 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (br. s, 2H, H1), 6.31 (s, 1H, H8), 5.66 (br . t, 1H, H8), 4.55 (br. t, 2H, H3), 3.31 (br. t, 3H, H2), 2.77 (s, 3H, H10) 1.96 (s, 3H, H9);

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 135.3, 127.3, 59.6, 47.8, 33.4, 18.3; LRMS (ASAP) m/z $[M+H]^+$ 180.1 (50%). All other spectroscopic and analytical properties were identical to those quoted in the literature.[227]

3.4.5.3 (2-{2-[(2-Methylprop-2-enoyl)oxy]ethoxy}ethyl)(propan-2-yl)azanium chloride, 140d.HCl

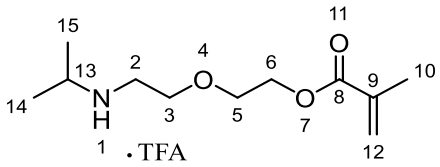
A procedure similar to that in the literature was adopted.[225] 2-Isopropylamino ethoxyethanol **150d** (6.12 mmol, 0.90 mg) was prepared via the neutralization of the relative aminoethanol with the calculated amount of hydrochloride 37% (0.510 mL) and complete drying under vacuum at 70 °C. The mixture of 2-isopropyl amino ethoxyethanol and methacryloyl chloride (an excess of 10%, 6.73 mmol, 0.660 mL) was heated up to 80 °C and maintained for 2 h. The reaction mixture was left to cool to room temperature and the solvent was removed under reduced pressure. Compound **140d.HCl**, was obtained as a crude yellow oil (1.61 g) which was used in further reactions without further purification:



^{1}H NMR (700 MHz, $CDCl_3$) δ 9.34 (br s, 2H, H1), 6.13 (br. s, 1H, H12), 5.60 (app. t, *J* = 1.7 Hz, 1H, H12), 4.34 (t, *J* = 4.7 Hz, 2H, H6), 3.96 (t, *J* = 5.4 Hz, 2H, H3), 3.77 (t, *J* = 4.7 Hz, 2H, H5), 3.48 (hept, *J* = 6.4 Hz, 1H, H13), 3.17 (t, *J* = 5.4 Hz, 2H, H2), 1.94 (t, *J* = 1.7 Hz, 3H, H10), 1.46 (d, *J* = 6.4 Hz, 6H, H14/15); ^{13}C NMR (176 MHz, $CDCl_3$) δ 167.7 (C8), 136.2 (C9), 126.3 (C12), 69.7 (C5), 66.5 (C3), 63.7 (C6), 50.8 (C13), 43.9 (C2), 19.3 (C14/15), 18.5 (C10); LRMS (ESI): m/z $[M+H]^+$ 216.333 (100%), 217.283 (21%). HRMS (ESI) m/z calculated $C_{11}H_{22}NO_3$ $[M+H]^+$ 216.1600, found 216.1606.

3.4.5.4 Procedure for the preparation (2-{2-[(2-Methylprop-2-enoyl)oxy]ethoxy}ethyl)(propan-2-yl)azanium trifuoloracetate, 140d.TFA

A procedure similar to that in the literature was adopted.[225] 2-Isopropylamino ethoxyethanol **150d** (25.2 mmol, 3.70 mg) was prepared via the neutralization of the relative aminoethanol with the calculated amount of TFA (29.9 mmol, 2.10 mL) and complete drying under vacuum at 50 °C. The mixture of 2-isopropylaminoethoxyethanol and methacryloyl chloride (an excess of 10%, 29.9 mmol, 2.70 mL) was heated up to 80 °C and maintained for 2 h. The reaction mixture was left to cool to room temperature and the solvent was removed under reduced pressure. Compound **140d.TFA**, was obtained as a crude yellow oil (8.3 g) which was used in further reactions without further purification.

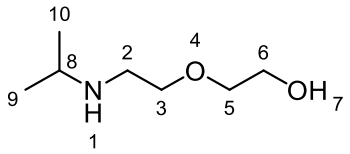


For pure product and characterisation refer to those reported in experiment 3.4.8.2.

3.4.6 Reductive amination

3.4.6.1 Synthesis of 2-[2-(isopropylamino)ethoxy]ethanol, 150d

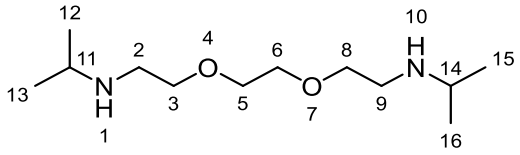
2-Aminoethoxyethanol (0.300 g, 2.85 mmol) was dissolved in ethanol (5.00 mL), followed by addition of acetone (0.419 g, 5.70 mmol), at room temperature and left to react for 12 h. Sodium borohydride (0.216 g, 5.70 mmol) was added to the reaction solution and stirred at rt for 2 h. The solvent was removed under reduced pressure, water and ethyl acetate were added to the concentrate and the layers were separated. The aqueous phase was extracted with ethyl acetate (5.00 mL x 3), and the combined organic phases were washed with water (5.00 mL) and saturated brine (5.00 mL x 2) after washing, the organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the product.



Obtained as a clear liquid (4.45 g, 80%): IR (neat) υ_{max} (*inter alia*): 2965 (w, O-H), 2868, 1123 (C-O-C), 1064 (s, C-O) cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 3.72 (t, *J* = 4.5 Hz, 2H, H5), 3.63 (t, *J* = 5.1 Hz, 2H, H3), 3.60 (t, *J* = 4.5 Hz, 2H, H6), 2.84 – 2.81 (m, overlapping with other signals, 1H, H8), 2.80 (t, *J* = 5.1 Hz, 2H, H6), 2.34 (br s, H7), 1.07 (d, *J* = 6.2 Hz, 6H, H9/10); ^{13}C NMR (176 MHz, Chloroform-d) δ 72.6 (C6), 70.9 (C3), 62.1 (C5), 48.9 (C8), 47.1 (C2), 22.9 (C9/10); LRMS (ESI) m/z $[M+H]^+$ 148.2 (100%); HRMS (ESI) m/z calculated $C_7H_{18}NO_2$ $[M+H]^+$ 148.1338, found 148.1331. All spectroscopic and analytical properties were identical to those quoted in the literature.[228]

3.4.6.2 Synthesis of 2,13-dimethyl-6,9-dioxa-3,12-diazatetradecane, 183

1,2-*Bis*(2-aminoethoxy)ethane (5.05 g, 34.0 mmol) was dissolved in ethanol (30.0 mL), followed by addition of acetone (5.92 g, 102 mmol), at room temperature and left to react for 12 h. Sodium borohydride (3.86 g, 102 mmol) was added to the reaction solution and stirred at rt for 2 h. The solvent was removed under reduced pressure, water and ethyl acetate were added to the concentrate and the layers were separated. The aqueous phase was extracted with ethyl acetate (5.00 mL x 3), and the combined organic phases were washed with water (10.0 mL) and saturated brine (10.0 mL x 3) after washing, the organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give.



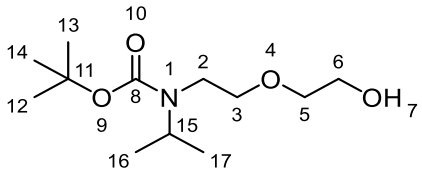
Obtained as a clear liquid (4.55 g, 58%): IR (neat) υ_{max} (*inter alia*): 2967 (m, C-H), 2862 (m, C-H), 1472 (w, C-H), 1120 (s, C-N), 740 (w-H) cm^{-1}; ^{1}H NMR (599 MHz, $CDCl_3$) δ 3.61 (s, 4H, H5/6), 3.58 (t, *J* = 5.4 Hz, 4H, H3/8), 2.80-275 (m, overlapping with other signals, 2H,

H11/14), 2.77 (dd, *J* = 5.4 Hz, 4H, H2/9), 1.05 (d, *J* = 6.3 Hz, 12H, H12/13/15/16); ^{13}C NMR (151 MHz, $CDCl_3$) δ 71.0 (C3/8), 70.4 (C5/6), 48.7 (C11/14), 47.1 (C2/9), 23.1 (C12/13/15/16); LRMS (ESI) m/z $[M+H]^+$ 233.280 (100%); HRMS (ESI) m/z calculated $C_{12}H_{29}N_2O_2$ $[M+H]^+$ 233.2229, found 233.2240. Compound present in the literature without spectroscopic properties.[229]

3.4.7 Procedure for the *N*-Boc protection

3.4.7.1 Synthesis of tert-butyl *N*-[2-(2-hydroxyethoxy)ethyl]-N-isopropylcarbamate, 164

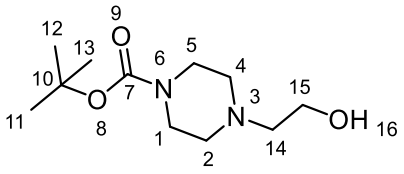
Compound **150d** (13.6 mmol, 2.00 g) was dissolved in 20.0 mL of DCM. Di-*tert*-butyl dicarbonate (16.3 mmol, 3.56 g) was added and left to react overnight at room temperature. The solvent was removed under reduce pressure to give the crude product which was purified by silica gel chromatography (Hex:EtOAc, 9:1).



Obtained as a clear liquid (3.01 g, 90%): IR (neat) υ_{max} (*inter alia*): 3458 (w, O-H), 2965 (w, C-H), 1663 (m, C=O), 1367 (m, O-H), 1119 (s, C-N) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.70 (br s, 2H, H6), 3.55 (t, 4H, H3/5, overlapping with another peak), 3.26 (br s, 2H, H2), 1.44 (s, 9H, H12/13/14), 1.11 (d, *J* = 6.8 Hz, 6H, H16/17); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.5 (C8), 79.6 (C11), 72.3 (C5), 70.3 (C15), 61.9 (C6), 47.1 (C3), 42.8 (C2), 28.6 (C12/13/14), 20.9 (C16/17); LRMS (ESI) m/z $[M\text{-}Boc+H]^+$ 148.142 (100%); HRMS (ESI) m/z calculated $C_{12}H_{26}NO_4$ $[M+H]^+$ 248.1862, found 248.1889.

3.4.7.2 *tert*-Butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate, 146

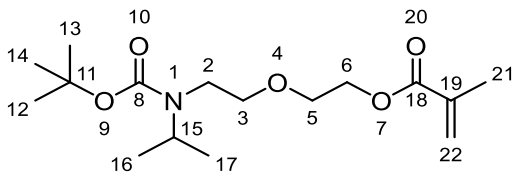
In a round bottom flask 2-(ethanol)piperazine (62.0 mmol, 7.54 mL) were dissolved in 20.0 mL of DCM. Di-tert butyl dicarbonate (74.4 mmol, 16.2 g) was added and left to react overnight at room temperature. Therefore, solvent was removed under reduce pressure to give the **146** which was used without any further purification.



Obtained as a yellow oil (14.3 g, 100%): IR (neat) υ_{max} (*inter alia*): 3438 (br, O-H), 2979 (w, C-H), 1689 (s, C=O), 1422 (m, O-H), 1170 (s, C-O), 1129 (s, C-N), 1005 (m, C=C), 770 (w, C-H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (dd, *J* = 9.9, 5.1 Hz, 2H), 3.41 (t, *J* = 5.2 Hz, 4H), 2.77 (s, 1H), 2.53 (t, *J* = 5.4 Hz, 2H), 2.43 (t, *J* = 5.1 Hz, 4H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.84, 79.86, 77.36, 59.47, 57.82, 52.81, 44.21, 28.54; LRMS (ESI) m/z $[M+H]^+$ 231.8 (100%); HRMS (ESI) m/z calculated $C_{11}H_{23}N_2O_3$ $[M+H]^+$ 231.1709, found 231.1718. All spectroscopic and analytical properties were identical to those quoted in the literature.[230]

3.4.7.3 Synthesis of compound 2-{2-[(tert-butoxycarbonyl)(isopropyl)amino]ethoxy}ethyl 2-methylprop-2-enoate, 165

Methacryloyl chloride (5.3 mmol, 0.520 mL) was added to a solution of compound **164** (4.82 mmol, 1.19 g) and Et_3N (4.82 mmol, 0.670 mL) in EtOAc (20.0 mL). The reaction mixture was heated up to 80 °C and maintained for 2 h. The reaction mixture was left to cool to room temperature and the solvent was removed under reduced pressure. The crude mixture was purified through silica gel chromatography (Hex:EtOAc, 7:3) to give a clear liquid (0.95 g, 63%).

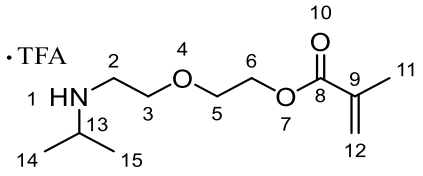


IR (neat) υ_{max} (*inter alia*): 2981 (w, C-H), 1688 (m, C=O), 1367 (m, O-H), 1125 (s, C-N), 773 (w, C-H) cm^{-1}; ^{1}H NMR (599 MHz, $CDCl_3$) δ 6.12 (s, 1H, H22), 5.56 (s, 1H, H22), 4.27 (t, *J* = 4.8 Hz, 2H, H6), 3.69 (t, *J* = 4.8 Hz, 2H, H5), 3.55 (br s, 2H, H2), 3.23 (br s, 2H, H3), 1.94 (s, 3H, H21), 1.45 (s, 9H, H12/13/14), 1.11 (d, *J* = 6.8 Hz, 6H, H16/17); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.5 (C18), 136.3 (C19), 125.8 (C22), 79.5 (C11), 70.6 (C2), 69.1 (C5), 64.0 (C6), 46.8 (C15), 41.7 (C3), 28.6 (C12/13/14), 20.8 (C16/17), 18.4 (C21); LRMS (ESI) m/z $[M+Na]^+$ 338.3 (100%). HRMS (ESI) m/z calculated $C_{16}H_{29}NO_5$ $[M+H]^+$ 316.2124, found 316.2133.

3.4.8 General procedure for *N*-Boc deprotection with TFA

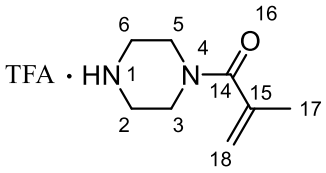
In a round bottom flask *N*-Boc protected amine was dissolve in MeOH and cooled in a bath of ice. Therefore, TFA was added dropwise and left to react 3 h. At reaction completed the solvent was removed by rotary evaporation to give the final compound.

3.4.8.1 Isopropyl(2-{2-[(2-methylprop-2-enoyl)oxy]ethoxy}ethyl)azanium trifluoro acetate prepared using general procedure for *N*-Boc deprotection with TFA, 140d.TFA



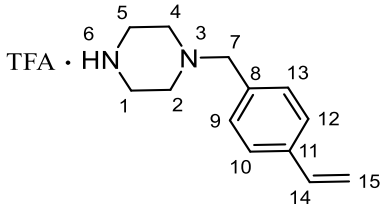
Reagent used in the procedure: *N*-Boc protected amine **165** (0.95 mmol, 30 mg), MeOH (1 mL), TFA (11.4 mmol, 1.25 g). Obtained as a clear liquid (0.325 g, 101%): ^{1}H NMR (599 MHz, $CDCl_3$) δ 8.35 (br s, 2H, H1), 6.13 (s, 1H, H12), 5.62 (s, 1H, H12), 4.34 (t, *J* = 2.8 Hz, 2H, H6), 3.80 (t, *J* = 4.3 Hz, 2H, H3), 3.74 (t, *J* = 2.8 Hz, 2H, H5), 3.49 – 3.39 (m, 1H, H13), 3.21 (br s, 2H, H2), 1.94 (s, 3H, H10), 1.40 (d, *J* = 6.1 Hz, 6H, H14/15); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.1 (C8), 161.5 (TFA), 161.2 (TFA), 136.1 (C9), 126.6 (C12), 116.7 (TFA), 114.8 (TFA), 70.1 (C5), 65.9 (C3), 63.6 (C6), 51.3 (C13), 45.1 (C2), 19.2 (C14/15), 18.4 (C10).); LRMS (ESI): m/z $[M+H]^+$ 216.291 (100%), 217.283 (21%). HRMS (ESI) m/z calculated $C_{11}H_{22}NO_3$ $[M+H]^+$ 216.1600, found 216.1606.

3.4.8.2 4-(2-Methylprop-2-enoyl)piperazin-1-ium trifluoroacetate prepared using general procedure for *N*-Boc deprotection with TFA, 137b



Reagent used in the procedure: *N*-Boc protected amine **145** (6.00 mmol, 1.50 g), MeOH (4 mL), TFA (71.4 mmol, 5.47 mL). Obtained as a clear liquid (1.63 g, ca. 100%): IR (neat) υ_{max} (*inter alia*): 3000 (broad w, N-H), 1786 (m, C=O), 1608 (m, C=C), 1367 (m, C-H), 1132 (s, C-N), 703 (w, C-H) cm^{-1}; ^{1}H NMR (599 MHz, DMSO-d6) δ 9.00 (br s, 2H, H1), 5.24 (s, 1H, H18), 5.08 (s, 1H, H18), 3.66 (t, *J* = 5.3 Hz, 4H, H3/5), 3.12 (br s, 4H, H2/6), 1.86 (s, 3H, H17); ^{13}C NMR (151 MHz, DMSO) δ 170.1 (C14), 158.6 (TFA), 139.2 (C15), 116.6 (TFA), 116.1 (C18), 114.6 (TFA), 42.7 (C2/6), 20.0 (C17); LRMS (ESI) m/z $[M+H]^+$ 155.6 (100%); HRMS (ESI) m/z calculated $C_8H_{15}N_2O$ $[M+H]^+$ 155.1184, found 155.1174.

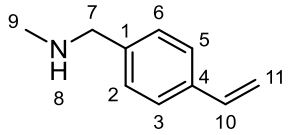
3.4.8.3 1-[(4-Ethenylphenyl)methyl]piperazine prepared using general procedure for *N*-Boc deprotection with TFA, 139



Reagent used in the procedure: *N*-Boc protected amine **148** (3.3 mmol, 1.00 g), MeOH (2.00 mL), TFA (40.0 mmol, 3.00 mL). Obtained as a clear liquid (1.08 g, 104%): Obtained as a yellow solid: m.p. 89-91 °C; IR (neat) υ_{max} (*inter alia*): 3000 (broad w, N-H), 1786 (m, C=O), 1631 (m, C=C), 1452 (w, C-H), 1135 (s, C-N), 701 (w, C-H) cm^{-1}; ^{1}H NMR (599 MHz, $CDCl_3$) δ 9.24 (br s, 3H, H6), 7.46 (d, *J* = 8.0 Hz, 2H, H9/13), 7.37 (d, *J* = 8.0 Hz, 2H, H10/12), 6.69 (dd, *J* = 17.6, 10.9 Hz, 1H, H14), 5.80 (d, *J* = 17.6 Hz, 1H, H15), 5.36 (d, *J* = 10.9 Hz, 1H, H15), 4.32 (s, 2H, H7), 3.82 – 3.47 (br d, 8H, H1/2/4/5); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.1 (TFA), 140.5 (C11), 135.5 (C14), 131.3 (10/12), 127.5 (C9/13), 125.44 (C8), 116.6 (C15), 114.31 (TFA), 61.6 (C7), 48.2 (C1/5), 41.2 (C2/4); LRMS (ESI) m/z $[M+H]^+$ 203.217 (100%); HRMS (ESI) m/z calculated $C_{13}H_{19}N_2$ $[M+H]^+$ 203.1548, found 203.1555.

3.4.9 Synthesis of *N*-methyl-4-vinylbenzylamine [(4-ethenylphenyl)methyl](methyl)amine, **136**

Vinylbenzyl chloride (0.150 mol, 16.0 mL) was added to a three neck round bottom flask to which, it was subsequently add methylamine 33 wt% in ethanol (2.10 mol, 130 mL). THF was added (500 mL) and the flask was filled with argon and the reaction was allowed to stir at 45 °C for 24 h. The reaction was concentrated under reduce pressure and diluted with DCM for the workup; the organic phase was washed with NaOH (1 M) x3 with DI water x1, with brine x1 and dried over magnesium sulfate. The solvent was removed under reduced pressure to give a yellow oil.[180]

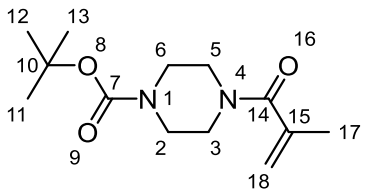


Compound **136**, [(4-ethenylphenyl)methyl](methyl)amine was obtained as a yellow oil (15.2 g, 92%): IR (neat) υ_{max} (*inter alia*): 2929 (w, C-H), 1263 (m, C-N), 738 (w, C-H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.8 Hz, 2H, H2/6), 7.28 (d, *J* = 8.2 Hz, 2H, H3/5), 6.71 (dd, *J* = 17.6, 10.9 Hz, 1H, H10), 5.74 (dd, *J* = 17.6, 1.0 Hz, 1H, H11), 5.22 (dd, *J* = 10.9, 1.0 Hz, 1H, H11), 3.74 (s, 2H, H7), 2.45 (s, 3H, H9); LRMS (ASAP) m/z $[M+H]^+$ 148.1 (30%); HRMS (ASAP) m/z calculated $C_{10}H_{14}N$ $[M+H]^+$ 148.1126, found 148.1124. All spectroscopic and analytical properties were identical to those quoted in the literature.[180]

3.4.10 Synthesis of *tert*-butyl 4-(2-methylprop-2-enoyl)piperazine-1-carboxylate, **145**

Compound **145** was prepared according to a published procedure.[181] In 50.0 mL round-bottom flask equipped with dropping funnel of Boc-piperazine (15.8 mmol, 2.00 g) and of triethylamine (11.7 mmol, 1.63 mL) were dissolved in 20.0 mL of DCM. Flask was cooled down to 0 °C and of methacryloyl chloride (9.77 mmol, 0.950 mL) was added dropwise. The resulting mixture was stirred overnight at room temperature. Thereafter, water was added and the product was extracted with DCM (3 x 15.0 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed by rotary

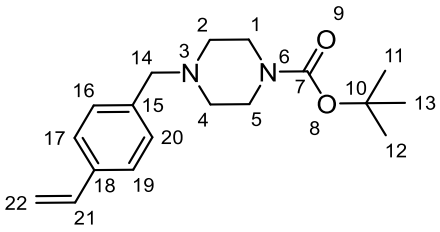
evaporation. The final crude was crystallised in hexane to give the purified product (2.06 g, 76%).



m.p. 96 - 98 °C; IR (neat) υ_{max} (*inter alia*) 2982 (w, C-H), 1681 (m, C=O), 1613 (m, C=C), 1165 (s, C-O), 996 (m, C=C), 760 (w, C-H) cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.21 (app. t, *J* = 1.3 Hz, 1H, H18), 5.03 (app. t, *J* = 1.3 Hz, 1H, H18), 3.55 (br s, 4H, H2/6), 3.42 (br s, 4H, H3/5), 1.95 (t, *J* = 1.3 Hz, 3H, H17), 1.47 (s, 9H, H11/12/13); ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.5 (C14), 154.7 (C7), 140.3 (C15), 115.9 (C18), 80.5 (C10), 43.9 (C3/5), 41.4 (C6/2), 28.5 (C11/12/13), 20.7 (C17); LRMS (ASAP) m/z $[M\text{-}Boc+H]^+$ 155.108 (100%); HRMS (ASAP) m/z calculated $C_8H_{15}N_2O$ $[M\text{-}Boc+H]^+$ 155.1184, found 155.1185. All spectroscopic and analytical properties were identical to those quoted in the literature.[182]

3.4.11 Synthesis of *tert*-butyl 4-[(4-ethenylphenyl)methyl]piperazine-1-carboxylate, **148**

Compound **148** was prepared according to a published procedure.[181] In 50.0 mL round-bottom flask equipped with dropper funnel of Boc-piperazine (71.5 mmol, 13.3 g) and of triethylamine (78.0 mmol, 10.9 mL) were dissolved in 50.0 mL of DCM. The flask was cooled down to 0 °C and of 4-vinyl benzyl chloride (65.0 mmol, 9.20 mL) was added dropwise. The resulting mixture was stirred overnight at room temperature. Thereafter, water was added and the product was extracted with DCM (3 x 20.0 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The final compound was used with no further purification for the next reaction step.



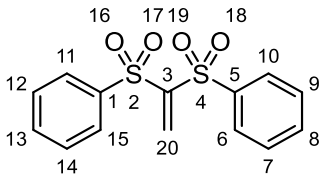
Obtained as a pale yellow solid (16.0 g, 82%): m.p. 81 – 83 °C; IR (neat) υ_{max} (*inter alia*): 2981 (w, C-H), 1678 (s, C=O), 1422 (s, C-H), 1164 (s, C-O), 1001 (s, C-N), 861 (s, C=C), 760 (m, C-H) cm^{-1}; ^{1}H NMR (599 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.0 Hz, 2H, H16/20), 7.28 (d, *J* = 8.0 Hz, 2H, H17/19), 6.70 (dd, *J* = 17.7, 10.8 Hz, 1H, H21), 5.73 (d, *J* = 17.7 Hz, 1H, H22), 5.23 (d, *J* = 10.8 Hz, 1H, H22), 3.52 (s, 2H, H14), 3.44 (br s, 4H, H1/5), 2.40 (br s, 4H, H2/4), 1.45 (s, 9H, H11/12/13); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.9 (C7), 136.9 (C15), 136.6 (C21), 129.6 (C17/19), 126.3 (C16/20), 113.8 (C22), 79.7 (C10), 62.8 (C14), 52.9 (C2/4), 43.2 (C1/5), 28.6 (C11/12/13); LRMS (ESI) m/z $[M+H]^+$ 303.9 (100%); HRMS (ESI) m/z calculated $C_{18}H_{23}N_2O_2$ $[M+H]^+$ 303.2073, found 303.2084. All spectroscopic and analytical properties were identical to those quoted in the literature.[231]

3.5 Vinyl sulfonyl sulfonamide synthesis

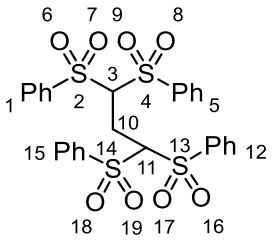
3.5.1 General procedure using Eschenmoser's salt reactions

To a solution of methylsulfonyl-methylenesulfonamide and triethylamine in dry MeCN, dimethylammonium iodide was added and stirred at room temperature and reaction monitored by TLC. Once the reaction was completed, water was added and left to stir of 15 min. Therefore, after removal of solvent under reduce pressure, DCM was added and washed with water, dried over $MgSO_4$ and the solvent was removed by rotary evaporation.

3.5.1.1 General procedure using Eschenmoser's salt was employed for the formation of vinyl sulfonyl sulfonamide to provide 174 and 175



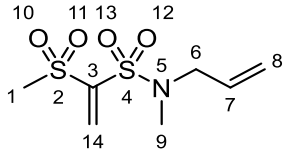
174



175

Reagents used in the procedure: **173** (0.169 mmol, 50.0 mg), Et_3N (0.338 mmol, 47 μL), CH_3CN (2.00 mL), dimethylammonium iodide (0.169 mmol, 31.0 mg). The reaction gave a crude mixture (43.0 mg) of two compounds characterised as a mixture (*ca.* 1:4): [1-(benzenesulfonyl)ethenesulfonyl]benzene, **174**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.99-7.94 (m, 4H, H12/15/1/10), 7.70-7.65 (m, 2H, H8/13), 7.59-7.54 (m, 4H, H/12/14), 7.22 (s, 2H, H20); All other spectroscopic and analytical properties were identical to those quoted in the literature;[157a] and [1,3,3-tris(benzenesulfonyl)propanesulfonyl]benzene, **175:** ^1H NMR (599 MHz, $CDCl_3$) δ 7.93 – 7.88 (m, 8H), 7.74 – 7.70 (m, 4H), 7.59 – 7.55 (m, 8H), 5.67 (t, *J* = 6.5 Hz, 2H, H3), 3.00 (t, *J* = 6.5 Hz, 2H, H10). Some analytical and spectroscopic properties were identical to those reported in the literature.[155]

3.5.1.2 1-Methanesulfonyl-*N*-methyl-*N*-(prop-2-en-1-yl)ethenesulfonamide using general procedure using Eschenmoser's salt reactions, 180



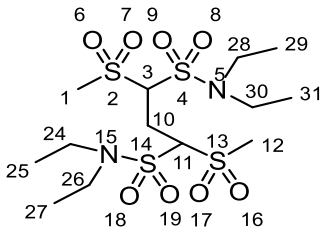
Reagents used in the procedure: **127o** (13.2 mmol, 3.00 g), Et_3N (26.4 mmol, 1.90 mL), CH_3CN (24.0 mL), dimethylammonium iodide (132 mmol, 12.0 g). The final mixture was filtered through a silica plug (Hex:EtOAc, 8:2) and obtained as a clear oil (0.29 g, 10%): ^1H NMR (599 MHz, $CDCl_3$) δ 7.01 (d, *J* = 1.24 Hz, 1H, H14), 6.93 (d, *J* = 1.24 Hz, 1H, H14) 5.73 (ddt, *J* = 17.1, 10.1, 6.1 Hz, 1H, H7), 5.32 – 5.23 (m, 2H, H8), 3.83 (d, *J* = 6.1 Hz, 2H, H6), 3.24 (s, 3H, H1), 2.85 (s, 3H, H9); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.6 (C3), 137.7 (C14), 132.5

(C7), 119.4 (C8), 53.5 (C6), 43.8 (C1), 34.4 (C9); LRMS (ESI) m/z $[M+H]^+$ 140.159 (100%); HRMS (ESI) m/z calculated $C_7H_{14}NO_4S_2$ $[M+H]^+$ 240.0364, found 240.0380.

3.5.2 Knoevenagel type reaction using potassium carbonate

3.5.2.1 Synthesis of 3-(diethylsulfamoyl)-1,3-dimethanesulfonylpropyl]-*N*-ethylethanesulfonamido, 178

To a solution of methylsulfonyl-methylenesulfonamide **127c** (0.440 mmol, 100 mg) and potassium carbonate (0.440 mmol, 60.0 mg) in toluene (4.00 mL), formaldehyde 37% (0.480 mmol, 36 µL) was added and stirred at room temperature and reaction monitored by TLC. Once the reaction was completed, water was added and the two phases separated and the organic layer dried over $MgSO_4$ and the solvent was removed under reduced pressure to give **178** (95 mg, 91%).



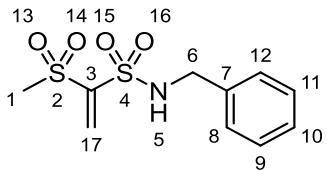
^{1}H NMR (700 MHz, $CDCl_3$) δ 5.06 (t, *J* = 6.0 Hz, 2H, H3/11), 3.45– 3.29 (m, 8H, H24/26/28/30), 3.26 (s, 6H, H1/12), 2.96 (t, *J* = 6.0 Hz, 2H, H10), 1.27 (t, *J* = 7.2 Hz, 12H, H25/27/29/31); ^{13}C NMR (176 MHz, $CDCl_3$) δ 75.7 (C3/11), 43.5 (C24/26/28/30), 41.2 (C1/12), 22.9 (C10), 14.8 (C25/27/29/31); LRMS (ESI) m/z $[M+H]^+$ 471.249 (100%); HRMS (ESI) m/z calculated $C_{13}H_{30}N_2O_8S_4$ $[M+H]^+$ 471.0963, found 471.0968. Crystal structure was obtained after recrystallisation from EtOH (page 290, Appendix).

3.5.3 General Method C for the synthesis of vinyl-1-sulfonyl-1'-sulfonamides

Modified procedure of the original present in the literature:[184] To a solution of formaldehyde 37 wt% in H_2O, was added formic acid (95%) until pH 2 was reached and this was used in the following reaction. HCHO/HCOOH 37 wt% in H_2O (acidified to pH 2)

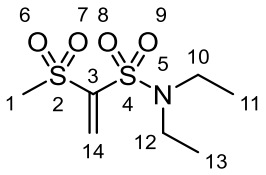
was added to MeOH at 0 °C, followed by piperidine. Sulfonyl sulfonamide was slowly added and the reaction was followed by TLC. Cold water was added to the reaction mixture and left stirring for 10 min. The precipitate was filtered and washed with of cold water to obtain a solid which was dissolved in DCM and 1M HCl aqueous solution. The reaction mixture was left to stir vigorously for 3 h. Additional aqueous 1M HCl was added to the mixture before separating the organic layer. The aqueous layer was extracted with DCM, the organic extracts were combined and dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the product.

3.5.3.1 *N*-Benzyl-1-methanesulfonylethene-1-sulfonamide prepared using general Method C, 179a



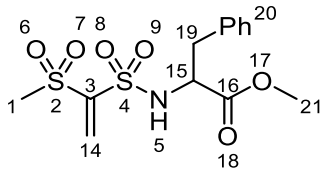
Starting materials: compound **127a** (1.20 mmol, 0.30 g), formaldehyde 37% in H_2O at pH4 (3.60 mmol, 0.29 mL), piperidine (6.00 mmol, 0.59 mL) and MeOH (3.2 mL), H_2O (2.00 mL), DCM (1.00 mL), 1M HCl (1.80 mL). Compound **179a**, was obtained as a white solid (0.31 g, 92%): m.p. 197 – 198 °C; IR (neat) ν_{max} (*inter alia*): 3256 (m, NH), 2035 (w, CH), 2929 (w, NH), 1302 (s, S=O), 1164 (s, S=O), 521 (m, NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 5H, Ph), 6.88 (d, *J* = 1.4 Hz, 1H, H17), 6.86 (d, *J* = 1.4 Hz, 1H, H17), , 5.30 (br t, 1H, H5), 4.19 (d, *J* = 6.3 Hz, 2H, H6), 3.25 (s, 3H, H1) (addition of D_2O caused the peak at δ 5.30 ppm to disappear and that at δ 4.19 ppm to simplify to a s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7 (C3), 136.8 (C17), 135.1 (Ph), 128.9 (Ph), 128.5 (Ph), 48.1 (C-SO_2R), 43.6 (C-N); LRMS (ASAP) m/z $[M+H]^+$ 276.0 (100%); Anal. Calcd (%) C, 43.62; H, 4.76; N, 5.09. Found (%) C, 43.45; H, 4.85; N, 5.17.

3.5.3.2 *N,N*-Diethyl-1-methanesulfonylethene-1-sulfonamide prepared using general Method C, 176



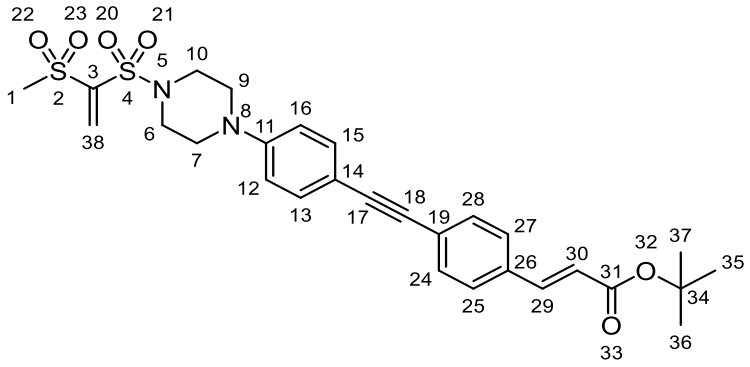
Starting materials: compound **127c** (1.20 mmol, 0.270 g), formaldehyde 37% in H_2O at pH 4 (3.60 mmol, 0.290 mL), piperidine (6.00 mmol, 0.590 mL) and MeOH (3.20 mL), H_2O (2.00 mL), DCM (1.00 mL), 1M HCl (1.80 mL). Compound **176** was obtained as a white solid (0.24 g, 84%): IR (neat) ν_{max} (*inter alia*): 2983 (w, CH), 1310 (s, S=O), 1134 (s, S=O), 520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 1.1 Hz, 1H, H14), 6.93 (d, *J* = 1.1 Hz, 1H, H14), 3.36 (q, *J* = 7.2 Hz, 4H, H10/12), 3.24 (s, 3H, H1), 1.23 (t, *J* = 7.2 Hz, 6H, H11/13); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7 (C14), 136.8 (C3), 43.8 (C1), 43.0 (C10/12), 14.5 (C11/13); LRMS (ASAP) m/z $[M+H]^+$ 242.046 (100%); Anal. Calcd (%) C, 34.84; H, 6.27; N, 5.8. Found (%) C, 35.01; H, 6.48; N, 5.83.

3.5.3.3 Methyl 2-(1-methanesulfonylethenesulfonamido)-3-phenylpropanoate prepared using general Method C, 179c



Starting materials: compound **127h** (0.896 mmol, 0.300 g), formaldehyde 37% in H_2O at pH 2 (2.69 mmol, 0.210 mL), piperidine (4.48 mmol, 0.440 mL) and MeOH (3.00 mL), H_2O (8.00 mL), DCM (3.00 mL), 1M HCl (5.00 mL). Compound **179c** was obtained as a white solid (0.30 g, 96%): m.p. 197 – 198 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 4H, Ph), 7.20 – 7.13 (m, 2H, Ph), 6.75 (s, 2H, H14), 5.54 (d, *J* = 8.6 Hz, 1H, H5), 4.37 (ddd, *J* = 8.6, 6.6, 5.9 Hz, 1H, H15), 3.72 (s, 3H, H21), 3.20 (s, 3H, H1), 3.12 (ddd, *J* = 13.8, 6.6, 5.7 Hz, 2H, H19); LRMS (ESI) m/z $[M-H]^-$ 346.002 (20%); HRMS (ESI) m/z calculated $C_{13}H_{18}NO_6S_2$ $[M+H]^+$ 348.0576, found 348.0552.

3.5.3.4 *tert*-Butyl 3-[4-(2-{4-[4-(1-methanesulfonylethenesulfonyl)piperazin-1-yl]phenyl}ethynyl)phenyl]prop-2-enoate prepared using general Method C, 203



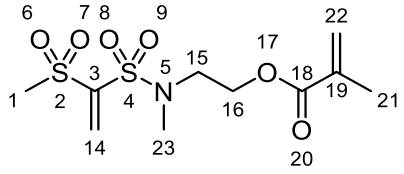
Starting materials: compound **202b** (0.37 mmol, 0.200 g), formaldehyde 37% in H_2O at pH 2 (1.11 mmol, 0.080 mL), piperidine (1.84 mmol, 0.180 mL) and MeOH (1.00 mL), H_2O (2.70 mL), DCM (3.00 mL), 1M HCl (1.50 mL). Compound **203** was obtained as a yellow solid (0.156 g, 76%): m.p. 188 – 189 °C; IR (neat) υ_{max} (*inter alia*) 2976 (w, C-H), 2207 (w, C≡C), 1697 (m, C=O), 1631 (m, C=C), 1595 (m, C=C), 1316 (s, S=O), 1133 (s, S=O), 953 (s, C=C) cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.56 (d, *J* = 15.9 Hz, 1H, H30), 7.48 (q, *J* = 8.5 Hz, 4H, H12/13/15/16), 7.43 (d, *J* = 9.0 Hz, 2H, H25/27), 7.04 (d, *J* = 1.4 Hz, 1H, H38), , 6.93 (d, *J* = 1.3 Hz, 1H, H38), 6.86 (d, *J* = 9.0 Hz, 2H, H24/28), 6.37 (d, *J* = 15.9 Hz, 1H, H29), 3.50 (t, *J* = 5.3 Hz, 4H, H6/10), 3.33 (t, *J* = 5.3 Hz, 4H, H7/9), 3.25 (s, 3H, H1), 1.53 (s, 9H, H35/36/37); ^{13}C NMR (176 MHz, $CDCl_3$) δ 166.2 (C31), 150.2 (C26), 149.7 (C3), 142.7 (C30), 137.8 (C38), 134.0 (C14), 132.9 (C25/27), 131.7 (C13/15), 127.9 (C12/16), 125.3 (C11), 120.6 (C29), 116.1 (C24/28), 114.4 (C19), 91.7 (18), 88.1 (C17), 80.6 (C34), 48.7 (C7/9), 45.8 (C6/10), 43.8 (C1), 28.2 (C35/36/37; LRMS (ASAP) m/z $[M+H]^+$ 557.177 (100%). HRMS (ESI) m/z calculated $C_{28}H_{32}N2O_6S_2$ $[M+H]^+$ 557.1780, found 557.1774. UV-Vis ($CHCl_3$): λ_{max} 350, λ_{em} 491.

3.5.4 General Method D for the synthesis of vinyl-1-sulfonyl-1'-sulfonamides and related by-products

Modified procedure of the original present in the literature:[184] To a solution of formaldehyde 37 wt% in H_2O, formic acid (95%) was added until pH 2 was reached and this was used in the following reaction. HCHO/HCOOH 37 wt.% in H_2O (acidified to pH 2)

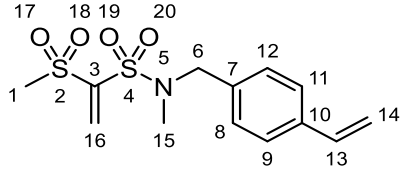
was added to EtOAc at 0 °C, followed by piperidine. Sulfonyl sulfonamide was slowly added and the reaction was followed by TLC. Terminated, the solution was quenched/extracted three times with cold brine and subsequently with 1 M HCl until the final aqueous phase resulted in an acid pH. The organic extracts were combined and dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the product.

3.5.4.1 2-(*N*-Methyl 1-methanesulfonylethenesulfonamido)ethyl 2-methylprop-2-enoate prepared using general Method D, 179d



Starting materials: compound **141b** (23.4 mmol, 7.00 g), formaldehyde 37% in H_2O at pH 2 (70.2 mmol, 5.22 mL), piperidine (117 mmol, 11.6 mL), EtOAc (39.0 mL). Compound **179d**, was obtained as a white sticky gel (6.54 g, 90%): IR (neat) ν_{max} (*inter alia*): 1716 (m, C=O), 1438, 1313 (s, S=O), 1133 (s, S=O), 951, 723 cm^{-1}; ^1H NMR (599 MHz, $CDCl_3$) δ 7.01 (dd, *J* = 1.3, 0.8 Hz, 1H, H14), 6.93 (dd, *J* = 1.0, 0.8 Hz, 1H, H14), 6.14 (dq, *J* = 1.8, 1.0 Hz, 1H, H22), 5.60 (dq, *J* = 2.3, 0.7 Hz, 1H, H22), 4.29 (t, *J* = 5.5 Hz, 2H, H16), 3.54 (t, *J* = 5.5 Hz, 2H, H15), 3.22 (d, *J* = 0.8 Hz, 3H, H1), 2.95 (s, 3H, H23), 1.95 (dd, *J* = 1.6, 0.8 Hz, 3H, H21).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.1 (C18), 149.0 (C3), 138.1 (C14), 135.9 (C19), 126.3 (C22), 62.1(C16), 49.8 (C15), 43.8 (C1), 35.6 (C23), 18.3 (C21); LRMS (ASAP) m/z $[M+H]^+$ 312.052 (100%).

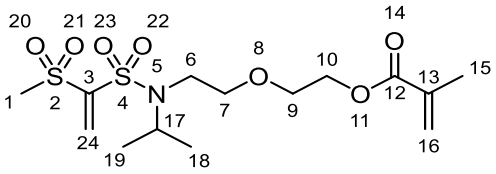
3.5.4.2 *N*-[(4-Ethenylphenyl)methyl]-1-methanesulfonyl-*N*-methylethene-1-sulfonamide prepared using general Method D, 179e



Starting materials: compound **153** (4.95 mmol, 1.50 g), formaldehyde 37% in H_2O at pH 2 (14.8 mmol, 1.10 mL), piperidine (24.8 mmol, 2.45 mL), EtOAc (8.00 mL). Compound 191e, was obtained as a sticky yellowish solid, purified by silica gel chromatography

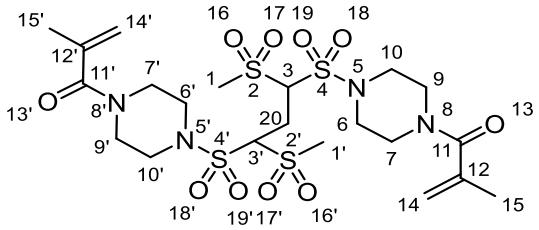
(Hex/EtOAc, 4:1) (0.71 g, 45%) which lead to the loss of most of the compound (crude 1.50 g, 96 % estimated by spectrum NMR): IR (neat) ν_{max} (*inter alia*): 1408, 1313 (m, S=O), 1164 (m, S=O), 990 (m, C=C), 924 (m, C=C), 780 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.2 Hz, 2H, C8/12), 7.31 (d, *J* = 8.2 Hz, 2H, C9/11), 7.06 (d, *J* = 1.3 Hz, 1H, H16), 6.97 (d, *J* = 1.3 Hz, 1H, H16), 6.71 (dd, *J* = 17.6, 10.9 Hz, 1H, H13), 5.76 (dd, *J* = 17.6, 0.9 Hz, 1H, H14), 5.27 (dd, *J* = 10.9, 0.9 Hz, 1H, H14), 4.37 (s, 2H, H6), 3.29 (s, 3H, H1), 2.77 (s, 3H, H15); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.5 (C3), 137.9 (C16), 137.6 (C10), 136.3 (C13), 135.0 (C7), 128.5 (C9/11), 126.7 (C8/12), 114.4 (C14), 54.4 (C6), 43.8 (C1), 34.4 (C15); LRMS (ASAP+) m/z $[M+H]^+$ 316.1 (14%).

3.5.4.3 2-{2-[*N*-(Propan-2-yl)1-methanesulfonylethenesulfonamido]ethoxy}ethyl 2-methylprop-2-enoate prepared using general Method D, 179h



Starting materials: compound **158** (5.39 mmol, 2.00 g), formaldehyde 37% in H_2O at pH 2 (16.2 mmol, 1.30 mL), piperidine (26.9 mmol, 2.95 mL), EtOAc (8.00 mL). Compound **179h**, was obtained as a clear liquid (1.89 g, 90%): IR (neat) υ_{max} (*inter alia*): 2977 (w, C-H), 1714 (m, C=O), 1314 (s, S=O), 1150 (s, S=O), 1111 (s, C-N), 793 (m, C-H) cm^{-1}; ^{1}H NMR (600 MHz, *CDCl₃*) δ 6.96 (d, *J* = 1.2 Hz, 1H, H24), 6.95 (d, *J* = 1.2 Hz, 1H, H24), 6.13 (dq, *J* = 2.0, 1.1 Hz, 1H, H16), 5.58 (dq, *J* = 2.0, 1.6 Hz, 1H, H16), 4.28 (t, *J* = 4.9 Hz, 2H, H10), 3.94 (hept, *J* = 6.6 Hz, 1H, H17), 3.70 (t, *J* = 4.9 Hz, 2H, H9), 3.64 (t, *J* = 6.3 Hz, 2H, H7), 3.46 (t, *J* = 6.3 Hz, 2H, H6), 3.23 (s, 3H, H1), 1.95 (dd, *J* = 1.6, 1.1 Hz, 3H, H15), 1.21 (d, *J* = 6.8 Hz, 6H, H18/19); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.3 (C12), 150.6 (C3), 137.2 (C24), 136.1 (C13), 125.8 (C16), 71.5 (C6), 69.0 (C7), 63.7 (C10), 50.5 (C17), 46.0 (, 43.9 (C1), 43.6 (C6), 21.3 (C18/19), 18.3 (C15); LRMS (ASAP) m/z $[M+H]^+$ 384.115 (100%); HRMS (ASAP): m/z calculated $C_{14}H_{26}NO_7S_2$ $[M+H]^+$ 384.1151, found 384.1143.

3.5.4.4 1-(4-{1,3-Dimethanesulfonyl-3-[4-(2-methylprop-2-enoyl)piperazin-1-ylsulfonyl]propanesulfonyl}piperazin-1-yl)-2-methylprop-2-en-1-one prepared using general Method D, 181



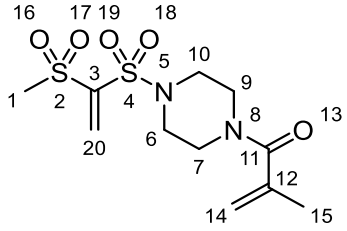
Starting materials: compound **154** (6.77 mmol, 2.10 g), formaldehyde 37% in H_2O at pH 2 (20.3 mmol, 1.62 mL), piperidine (33.9 mmol, 3.34 mL), EtOAc (23.0 mL). Compound **181** was obtained as a white solid (0.968 g, 45%): m.p. 214 – 215 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.25 (s, 2H, H14/14'), 5.05 (s, 2H, H14/14'), 4.99 (t, *J* = 6.3 Hz, 2H, H3/3'), 4.96 (t, *J* = 6.7 Hz, 1H), 3.64 (s, 8H, H1/10/6'/10'), 3.49 (s, 8H, H7/9/7'/9'), 3.29 (s, 4H, H1/1'), 3.22 (s, 2H, H1'/1), 3.05 (q, *J* = 6.7 Hz, 1H, H20), 2.93 (t, *J* = 6.3 Hz, 1H, H20), 1.95 (s, 6H, H15/15'); ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.5 (C11/11'), 139.8 (C12/12'), 116.6 (C14/14'), 76.0 (C3/3'), 75.8 (C3/3'), 47.0 (C7/9/7'/9'), 41.9 (C1/1'), 40.2 (C1/1'),23.19 (20), 21.3 (C20), 20.6 (C15/15'); LRMS (ESI) m/z $[M+H]^+$ 633.185 (100%). Compound **181** was crystallised from EtOH to obtain X-ray data (page 294, Appendix).

3.5.5 Synthesis of piperazine vinyl-1-sulfonyl-1'sulfonamide

3.5.5.1 1-[4-(1-Methanesulfonylethenesulfonyl)piperazin-1-yl]-2-methylprop-2-en-1-one, 179f

Modified procedure of the original present in the literature:[184] To a solution of formaldehyde 37 wt% in H_2O, formic acid (95%) was added until pH 2 was reached and this was used in the following reaction. HCHO/HCOOH 37 wt% in H_2O (2.91 mmol, 0.23 mL, acidified to pH 2) was added to EtOAc (10.0 mL) at 0 °C, followed by slow addition of piperidine (4.85 mmol, 0.48 mL). Sulfonyl sulfonamide **154** (0.97 mmol, 0.30 g) was added and the reaction was followed by TLC. Terminated, the solution was quenched/extracted with cold water (10.0 mL × 2) and subsequently with 1 M HCl (3.90 mL). The organic phase separated, solvent reduced to ca. 2.00 mL and left to stir with 1 M HCl (1.50 mL) for 3 h. The organic phase separated from the aqueous phase, dried ($MgSO_4$) and the solvent

evaporated under reduced pressure to give a crude product. Compound **179f**, was obtained as a clear liquid, purified by silica gel chromatography (Hex:EtOAc, 4:1) (70.9 mg, 45%).

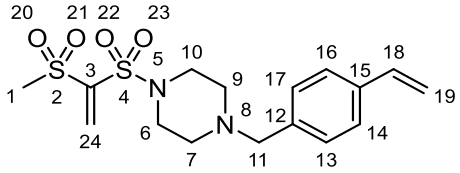


IR (neat) υ_{max} (*inter alia*): 2922 (w, C-H), 1620 (m, C=O), 1309 (s, S=O), 1172 (m, S=O), 949 (m, C=C), 791 (m, C-H) cm^{-1}; ^{1}H NMR (599 MHz, $CDCl_3$) δ 7.02 (d, *J* = 1.4 Hz, 1H, H20), 6.91 (d, *J* = 1.5 Hz, 1H, H20), 5.21 (dq, *J* = 2.6, 1.7 Hz, 1H, H14), 5.02 (dq, *J* = 2.6, 1.1 Hz, 1H, H14), 3.68 (br s, 4H,6/10), 3.34 (t, *J* = 5.5 Hz, 4H, H7/9), 3.23 (s, 3H, H1), 1.93 (dd, *J* = 1.7, 1.1 Hz, 3H, H15)); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4 (C11), 149.6 (C3), 139.8 (C12), 138.2 (C20), 116.5 (C14), 46.0 (C7/9), 43.9 (C1), 20.6 (C15); LRMS (ESI) m/z $[M+H]^+$ 323.238 (100%); HRMS (ESI): m/z calculated $C_{11}H_{19}N_2O_5S_2$ $[M+H]^+$ 323.0735, found 323.0741.

3.5.5.2 1-[(4-Ethenylphenyl)methyl]-4-(1-methanesulfonylethenesulfonyl)piperazine, 179g

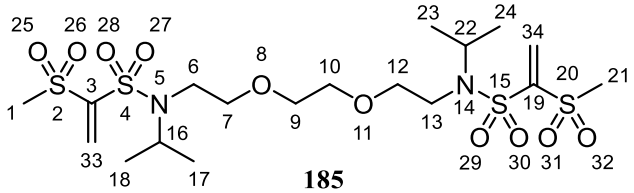
Modified procedure of the original present in the literature:[184] To a solution of formaldehyde 37 wt% in H_2O, formic acid (95%) was added until pH 2 was reached and this was used in the following reaction. HCHO/HCOOH 37 wt% in H_2O (1.68 mmol, 0.13 mL, acidified to pH 2) was added to EtOAc (5 mL) at 0 °C, followed by slow addition of piperidine (2.80 mmol, 0.280 mL). Sulfonyl sulfonamide **156** (0.560 mmol, 0.200 g) was added and the reaction was followed by TLC. Terminated, the solution was filtered through a plug of silica gel, the filtrate quenched/extracted with cold water (5 mL x2). The organic phase was separated, solvent reduced to ca. 2 mL and left to stir with 1 M HCl (1 mL) for 30min and the organic phase separated from the aqueous phase. To the aqueous phase the sat. NaHCO3 was added until pH 8/9 was reached and extracted with DCM (5 mL x 3). The organic phases were collected, dried ($MgSO_4$) and the solvent evaporated under reduced

pressure to give a crude product. Compound **179g**, was obtained as a clear liquid, purified by silica gel chromatography (Hex:EtOAc, 4:1) (20 mg, 10%).

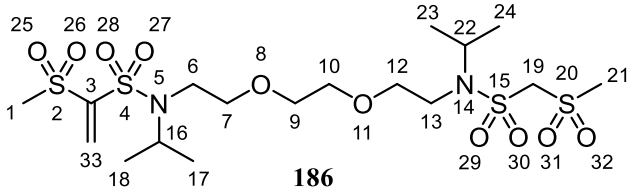


^{1}H NMR (599 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.5 Hz, 2H, H13/17), 7.29 – 7.24 (m, 2H, H14/16), 7.00 (t, *J* = 1.4 Hz, 1H, H24), 6.86 (d, *J* = 1.4 Hz, 1H, H24), 6.70 (dd, *J* = 17.5, 10.9 Hz, 1H, H19), 5.74 (dd, *J* = 17.5, 0.7 Hz, 1H, H19), 5.23 (dd, *J* = 10.9, 0.7 Hz, 1H, H18), 3.52 (s, 2H, H11), 3.35 (t, *J* = 5.0 Hz, 4H, H6/10), 3.23 (s, 3H, H1), 2.53 (t, *J* = 5.0 Hz, 4H, H7/9); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.9 (C3), 137.5 (C24), 137.30 (C12), 136.88 (C15), 136.6 (C18), 129.2 (C14/16), 126.3 (C13/17), 113.9 (C19), 62.4 (C11), 52.6 (C7/9), 46.2 (C6/10), 43.9 (C1); LRMS (ESI) m/z $[M+H]^+$ 371.275 (100%); HRMS (ESI): m/z calculated $C_{16}H_{23}N_2O_5S_2$ $[M+H]^+$ 371.1099, found 371.1100.

3.5.6 Procedure for *bis*-vinyl sulfonylsulfonamide **185** and **186**



185



186

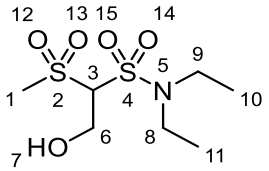
Modified procedure of the original reported in the literature:[184] To a solution of formaldehyde 37 wt% in H_2O, formic acid (95%) was added until pH 2 was reached and this was used in the following reaction. HCHO/HCOOH 37 wt% in H_2O (4.41 mmol, 0.360

mL, acidified to pH 2) was added to EtOAc (10.0 mL) at 0 °C, followed by slow addition of piperidine (7.35 mmol, 0.72 mL). Sulfonyl sulfonamide **184** (0.735 mmol, 0.40 g) was added and the reaction was followed by TLC. Terminated, the solution was quenched/extracted with cold water (10 mL × 2) and subsequently with 1 M HCl (6 mL). The organic phase separated, solvent reduced to ca. 2 mL and left to stir with 1 M HCl (3 mL) for 4 h. The organic phase was separated from the aqueous phase, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. The crude mixture was purified by silica gel chromatography (Hex:EtOAc, 3:1) to yield two compounds: 1-methanesulfonyl-*N*-(propan-2-yl)-N-[2-(2-{2-[*N*-(propan-2-yl)1-methanesulfonylethenesulfonamido]ethoxy}ethoxy)ethyl]ethene-1-sulfonamide, **185** obtained as a clear liquid (0.233 g, 63%): ^{1}H NMR (599 MHz, $CDCl_3$) δ 6.95 (dd, *J* = 3.1, 1.4 Hz, 4H, H33/34), 3.97 (hept, *J* = 6.8 Hz, 2H, H16/22), 3.63 (t, *J* = 6.6 Hz, 4H, H6/13), 3.61 (s, 4H, H9/10), 3.46 (t, *J* = 6.6 Hz, 4H, H7/12), 3.23 (s, 6H, H1/21), 1.23 (d, *J* = 6.7 Hz, 12H, H17/18/23/24); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.8 (C3/19), 137.3 (C33/34), 71.6 (C6/13), 70.6 (C9/10), 50.8 (C16/22), 44.0 (C1/21), 43.2 (C7/12), 21.6 (C17/18/23/24); LRMS (ESI) m/z $[M+H]^+$ 569.384 (100%); HRMS (ESI): m/z calculated $C_{18}H_{37}N_2O_{10}S_4$ $[M+H]^+$ 569.1331, found 569.1338; and 1-methanesulfonyl-*N*-(propan-2-yl)-*N*-[2-(2-{2-[*N*-(propan-2-yl)methanesulfonylmethanesulfonamido]ethoxy}ethoxy)ethyl]ethene-1-sulfonamide, **186** obtained as a clear liquid (34 mg, 9%): ^{1}H NMR (599 MHz, $CDCl_3$) δ 6.95 (dd, *J* = 3.5, 1.8 Hz, 2H, H33), 4.79 (s, 2H, H19), 4.20 (h, *J* = 6.8 Hz, 1H, H22), 3.97 (hept, *J* = 6.8 Hz, 1H, H16), 3.66 – 3.60 (m, overlapping with another signal, 8H, H13/9/10/6), 3.53 (t, *J* = 5.3 Hz, 2H, H12), 3.48 (t, *J* = 6.8 Hz, 2H, H7), 3.23 (s, 3H, H1), 3.21 (s, 3H, H21), 1.27 (d, *J* = 6.8 Hz, 6H, H23/24), 1.22 (d, *J* = 6.8 Hz, 6H, H17/18); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.8 (C3), 137.4 (C33), 71.4 (C6), 71.3 (C13), 71.2 (C19), 70.5 (C19), 70.4 (C10), 51.7 (C22), 50.6 (C16), 44.1 (C1), 43.2 (C12), 43.0 (C7), 42.4 (C21), 21.9 (C23/24), 21.5 (C17/18); LRMS (ESI) m/z $[M+Na]^+$ 579.340 (100%); HRMS (ESI): m/z calculated $C_{17}H_{37}N_2O_{10}S_4$ $[M+H]^+$ 557.1331, found 557.1337.

3.6 Procedure of β-hydroxy ethane sulfonyl sulfonamide

3.6.1 Synthesis of *N,N*-diethyl-2-hydroxy-1-methanesulfonylethanesulfonamide, **177**

Modified procedure of the original present in the literature:[232] A solution of vinyl sulfone **176** (1.24 mmol, 0.37 g) and 30% H_2O_2 (9.92 mmol, 1.30 mL) in CH_3CN (50.0 mL) at rt were treated dropwise with a solution of NaOH (2.48 mmol, 120 mg) in H_2O (0.60 mL). Stirring was continued for 1 h before NH_4Cl (10 mL) was added. Extraction with EtOAc (3 × 25 mL), washing of the combined organic extracts with brine (20 mL) dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give a crude product. Compound **177**, was obtained as a clear liquid, purified by silica gel chromatography (Hex:EtOAc, 4:1) (58 mg, 18%).



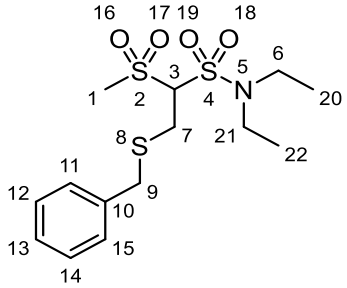
^{1}H NMR (700 MHz, $CDCl_3$) δ 4.43 (dd, *J* = 17.3, 13.2, 4.3 Hz, 1H, H6), 4.12 (t, *J* = 4.2 Hz, 1H, H3), 3.48 (dq, *J* = 14.4, 7.2 Hz, 2H, H8'/9'), , 3.33 (dq, *J* = 14.4, 7.1 Hz, 2H, H8/9), 3.23 (s, 3H, H1), 2.91 (br s, 1H, H7), 1.26 (t, *J* = 7.2 Hz, 6H, H10/11); ^{13}C NMR (176 MHz, $CDCl_3$) δ 81.9 (C3), 59.5 (C6), 43.1 (C8/9), 41.9 (C1), 14.7 (C10/11); LRMS (ESI) m/z $[M-H]^-$ 258.2 (100%); HRMS (ESI) m/z calculated $C_7H_{18}NO_5S_2$ $[M+H]^+$ 260.0626, found 260.0631.

3.7 Conjugate addition reactions of vinyl sulfonyl sulfonamide

3.7.1 General procedure for thiol trapping using vinyl-1-sulfonyl-1'sulfonamide

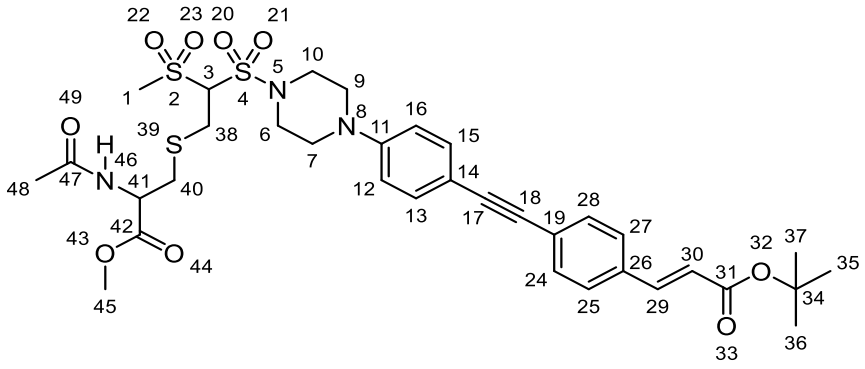
Vinyl sulfone was added to a solution of THF and benzyl thiol. The reaction was followed by TLC until completion. Once terminated, THF was removed under reduced pressure to give the final product.

3.7.1.1 2-(Benzylsulfanyl)-*N,N*-diethyl-1-methanesulfonylethanesulfonamide prepared using general procedure for thiol trapping, 191



Starting materials: **176** (0.50 mmol, 0.12 g), THF (5 mL), benzyl thiol (0.50 mmol, 0.062 g). Compound **191** was obtained as a crude (0.19 g) and purified by silica gel chromatography (EtOAc:Hex, 1:4) to give a clear liquid (0.16 g, 90%): ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.37 – 7.34 (m, 2H, H11/15), 7.32 (t, *J* = 7.4 Hz, 2H, H12/14), 7.26 (t, *J* = 7.4 Hz, 1H, H13), 4.10 (t, *J* = 5.6 Hz, 1H, H3), 3.82 (s, 2H, H9), 3.36 – 3.21 (m, 4H, H6/21), 3.19 – 3.14 (m, , 2H, H7), 3.13 (s, 3H, H1), 1.19 (t, *J* = 7.3 Hz, 6H, H20/22); ^{13}C NMR (176 MHz, $CDCl_3$) δ 137.6 (C10), 129.2 (C11/15), 128.8 (C12/14), 127.6 (C13), 81.4 (C3), 43.3 (C6/21), 41.5 (C1), 37.9 (C9), 27.4 (C7), 14.8 (C20/22); LRMS (ESI) m/z $[M-H]^-$ 364.2 (100%). HRMS (ESI) m/z calculated $C_{14}H_{24}NO_4S_3$ $[M+H]^+$ 366.0867, found 366.0863.

3.7.1.2 *tert*-Butyl 3-[4-(2-{4-[4-(2-{2-acetamido-3-methoxy-3-oxopropyl]sulfanyl}-1-methanesulfonylethanesulfonyl)piperazin-1-yl]phenyl}ethynyl)phenyl]prop-2-enoate using general procedure for thiol trapping, 205

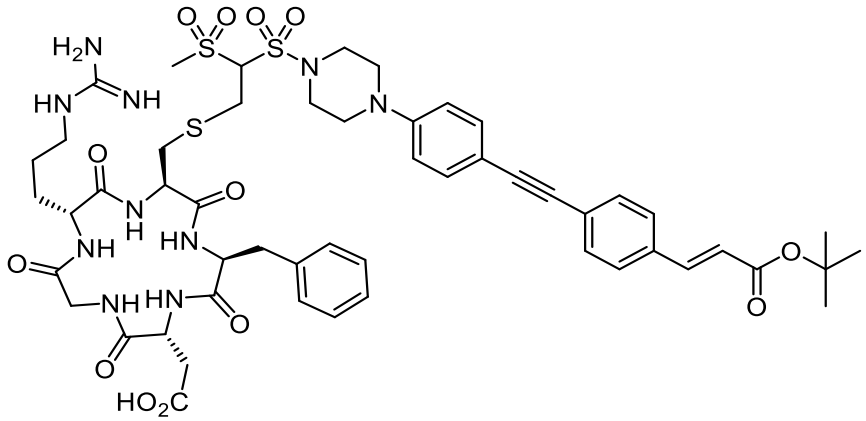


Starting materials: **203** (30 mg, 8.98 x 10^{-2} mmol), THF (1.00 mL), *N*-acetyl-*L*-cysteine methyl ester (9 mg, 8.98 x 10^{-2} mmol). Compound **205** was obtained as a yellow solid

which was purified by silica gel chromatography in DCM/MeOH, 9.8:0.2 (15 mg of a ca. 1:1 mixture of two diastereoisomers, 50%): IR (neat) max (*inter alia*): 1519 (s, C-H), 1314 (s, S=O), 1148 (s, C-O), 959 (C=C), 826 (C=C), 728 (C-H) cm^{-1}; ^{1}H NMR (599 MHz, $CDCl_3$) δ 7.56 (d, *J* = 15.9 Hz, 2H, H29), 7.51 – 7.46 (m, 8H, H24/25/27/28), 7.44 (t, *J* = 9.0 Hz, 4H, H12/16), 6.87 (d, *J* = 9.0 Hz, 4H, H13/15), 6.36 (d, *J* = 15.9 Hz, 2H, H30 overlapping with another peak), 6.36-6.30 (m, 2H, H46, overlapping with another peak), 4.95 (td, *J* = 7.7, 4.4 Hz, 1H, H41), 4.90-4.87 (m, 2H, H41/3, two overlapping peaks), 4.67 (t, *J* = 5.5 Hz, 1H, H3), 3.79 (s, 3H, H45), 3.78 (s, 3H, H45), 3.66-3.58 (br s, 8H, H6/10), 3.51 – 3.44 (m, 2H, H38, coupling with another overlapping peak at 3.29-324ppm), 3.42 (d, *J* = 3.6 Hz, 1H, H38, coupling with another overlapping peak at 3.33-3.30), 3.36 – 3.30 (br s, 8H, H7/9), 3.29 (s, 3H, H1, overlapping with other peaks), 3.25 (s, 3H, H1, overlapping with other peaks), 3.22 (dd, *J* = 4.4, 2.3 Hz, 1H, H40), 3.19 (dd, *J* = 4.4, 2.3 Hz, 1H, H40), 2.96 (dd, *J* = 14.4, 6.2 Hz, 1H, H40), 2.88 (dd, *J* = 14.4, 7.7 Hz, 1H, H40), 2.06 (s, 6H, H48), 1.53 (s, 18H, H35/36/37); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4 (C42), 171.3 (C42), 170.4 (C47), 170.3 (C47), 166.3 (C31), 150.5 (C14), 142.8 (C29), 134.2 (C26), 133.0 (C12/16), 131.9 (C25/26), 128.0 (24/28), 125.4 (C19), 120.8 (C12/16), 116.20 (C13/15), 114.5 (C17), 91.8 (C11), 88.3 (C19), 81.2 (C3), 80.8 (C3), 53.2 (C45), 53.1 (C45), 52.3 (C41), 51.8 (C41), 49.3 (C7/9), 49.2 (C7/9), 46.7 (C6/10), 46.5 (C6/10), 42.0 (C1), 41.9 (C1), 37.3 (C40), 36.5 (C40), 28.3 (C35/36/37, overlapping with a second carbon), 27.8 (C38), 23.4 (C48), 23.3 (C48); LRMS (ESI) m/z $[M-H]^-$ 732.3 (100%); HRMS (ESI) m/z calculated $C_{34}H_{43}N_3O_9S_3$ $[M-H]^-$ 732.2056, found 732.2083.

3.7.2 Bio-conjugation of vinyl sulfonyl sulfonamide **203** to cRGDfC, **207**

cRGDfC (1 mg) was dissolved in 1.00 mL water to give 1.73 mM stock solution. A 7.72 mM solution in THF of **203** was prepared by adding 2.15 mg of **203** in 500 µL of THF. The prepared solution of **203** (7.2 mM in THF, 13 µL) was added to 200 µL of THF and, secondly, of cRGDfC (1.73 mM in water, 57.9 µL). Solvent was removed under reduced pressure after 7 h to give the final product which was analysed by ESI-MS.

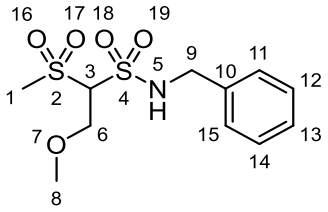


LRMS (ESI) m/z $[M+H]^+$ 1135.4042 (100%). HRMS (ESI) m/z calculated $C_{52}H_{67}N_{10}O_{13}S_3$ $[M+H]^+$ 1135.4051, found 1135.4042.

3.7.3 Nucleophilic addition of alcohol to vinyl sulfonyl sulfonamide

3.7.3.1 Synthesis of *N*-benzyl-1-methanesulfonyl-2-methoxyethanesulfonamide, 190

Compound **179a** (0.50 mmol, 0.14 g) was left stirring in an excess of MeOH (used as a solvent, 0.25 M) and followed by TLC. Once the reaction was completed, MeOH was removed under reduced pressure to give the final pure product. Compound **190** was obtained as a white solid (0.15 g, 100%):

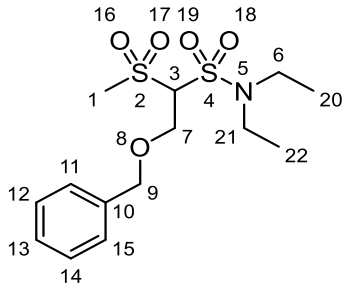


m.p. 189 – 192 °C; IR (neat) ν_{max} (*inter alia*): 2933 (w, CH), 2920 (w, NH), 1313 (s, SO_2), 1135 (s, SO_2), 737 (s, NH), 466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 5H, Ph), 5.55 (br t, *J* = 6.3 Hz, 1H, H5), 4.39 (dd, *J* = 14.2, 6.5 Hz, 1H, H9), 4.33 (dd, *J* = 14.2, 6.2 Hz, 1H, H9), 4.18 (dd, *J* = 11.2, 3.8 Hz, 2H, H6), 4.13 (dd, *J* = 11.2, 4.3 Hz, 1H, H6), 3.95 (t, *J* = 3.9 Hz, 1H, H3), 3.42 (s, 3H, H8), 3.20 (s, 3H, H1); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7, 136.8,

135.1, 129.2, 128.9, 128.5, 128.4, 48.1, 43.6; LRMS (ASAP) m/z $[M+H]^+$ 308.257 (100%); HRMS (ESI) m/z calculated $C_{11}H_{18}NO_5S_2$ $[M+H]^+$ 308.0626, found 308.0629.

3.7.3.2 Synthesis of 2-(benzyloxy)-*N,N*-diethyl-1-methanesulfonylethanesulfonamide, 192

Compound **176** (2.91 mmol, 0.70 g) was left stirring in an excess of benzyl alcohol (used as a solvent, 3 mL) and followed by TLC. The reaction was stop after 20 days although still incomplete. Benzyl alcohol was removed by Kugelrohr distillation (85 °C, 20 min), and the residue purified by silica gel chromatography (Et_2O:Hex, 3:7) to give **192** (0.46 g, 45%), **176** (14 mg, 2%, characterised elsewhere) and **178** (0.13 g, 19%, characterised elsewhere).

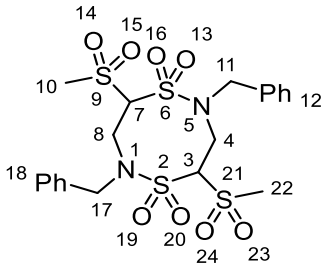


Compound **192** was obtained as a clear liquid: ^{1}H NMR (599 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 5H, Ph), 4.65 (d, *J* = 11.7 Hz, 1H, H9'), 4.60 (d, *J* = 11.7 Hz, 1H, H9), 4.28 (dq, *J* = 11.2, 3.9 Hz, 2H, H7), 4.12 (t, *J* = 3.9 Hz, 1H, H3), 3.49 – 3.38 (m, 2H, H21'/6'), 3.33 – 3.26 (m, 2H, H6/21), 3.25 (s, 3H, H1), 1.22 (t, *J* = 7.2 Hz, 6H, H20/22); ^{13}C NMR (151 MHz, $CDCl_3$) δ 136.8 (C10), 128.7 (Ph), 128.3 (Ph), 128.0 (Ph), 80.6 (C3), 74.2 (C9), 66.3 (C7), 43.3 (C1, two carbon overlapping, C6/21), 14.9 (C20/22); LRMS (ESI) m/z $[M+H]^+$ 350.336 (100%); HRMS (ESI) m/z calculated $C_{14}H_{24}NO_5S_2$ $[M+H]^+$ 350.1096, found 350.1096.

3.7.4 Self-reactions of vinyl-1-sulfonyl-1'sulfonamide

3.7.4.1 Synthesis of 2,6-dibenzyl-4,8-dimethanesulfonyl-1lambda6,5lambda6,2,6-dithiadiazocane-1,1,5,5-tetrone, 189

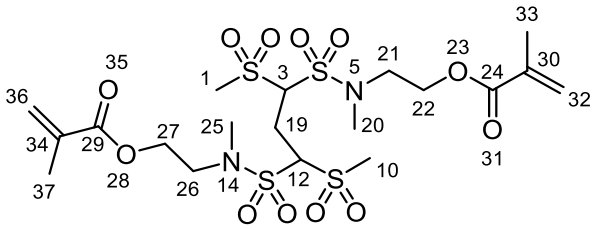
Compound **179a** (1.82 mmol, 0.50 g) was left stirring in an excess of water (used as a solvent, 5.00 mL) and CH_3CN (4.00 mL) and followed by TLC. After two days the white precipitate was filtered to give compound **189** as a white solid (0.40 g, 81%):



m.p. 197 – 199 °C; IR (neat) ν_{max} (*inter alia*): 2933 (w, CH), 1312 (s, S=O), 1134 (s, S=O), 735 (s, C-H) cm^{-1}; ^{1}H NMR (599 MHz, DMSO-d6) δ 7.50 – 7.32 (m, 10H, Ph 12/18), 5.98 (d, *J* = 11.3 Hz, 2H, H8'/4'), 5.03 (d, *J* = 15.8 Hz, 2H, H11/17), 4.46 – 4.38 (m, 4H, H7/3/17/11, two peaks overlapping), 3.73 (d, *J* = 15.8 Hz, 2H, H4/8), 3.37 (s, 6H, H10/22); ^{13}C NMR (151 MHz, DMSO-d6) δ 134.0 (Ph), 128.9 (Ph), 128.7 (Ph), 128.4 (Ph), 72.9 (C3/7), 47.9 (C11/17), 42.4 (C10/22), 40.1 (C4/8); LRMS (ASAP) m/z $[M/2+H]^+$ 276.0 (100%); Anal. Calcd (%) C, 43.62; H, 4.76; N, 5.09. Found (%) C, 43.56; H, 4.90; N, 5.04.

3.7.4.2 Obtainment of 2-{*N*-methyl1,3-dimethanesulfonyl-3-[methyl({2-[(2-methylprop-2-enoyl)oxy]ethyl})sulfamoyl]propanesulfonamido}ethyl 2-methylprop-2-enoate, 182

Compound **182** was found as the only product after 6 months of storage at low temperature (fridge temperature) in a DCM solution of **179d**.



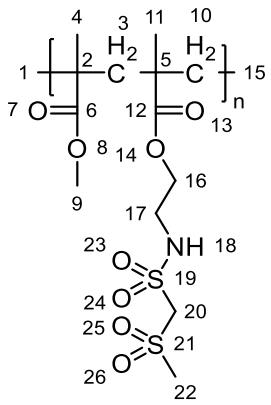
Obtained as a white solid: ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.16 (s, 2H, H32/36), 5.60 (t, *J* = 1.6 Hz, 2H, H32/36), 5.02 (t, *J* = 6.2 Hz, 2H, H3/12), 4.32 (t, *J* = 5.4 Hz, 4H, H22/27), 3.77 – 3.50 (br s), 3.26 (s, 6H, H1/10), 3.08 (s, 6H, H20/25), 2.97 (t, *J* = 6.3 Hz, 2H, H19), 1.95 (dd, *J* = 1.6, 0.9 Hz, 6H, H33/37); ^{13}C NMR (176 MHz, $CDCl_3$) δ 167.2 (C24/29), 135.9 (C30/34), 126.6 (C32/36), 75.0 (C3/12), 61.5 (C22/27), 50.0 (C21/26), 41.1 (C1/10), 36.0 (C20/25), 22.6 (C19), 18.4 (C33/37); LRMS (ESI) m/z $[M+H]^+$ 611.3 (100%).

3.8 Polymerisation and characterisation

3.8.1 General procedure for free radical polymerisation

3.8.1.1 Synthesis of P(MMA-*co*-141a), 197

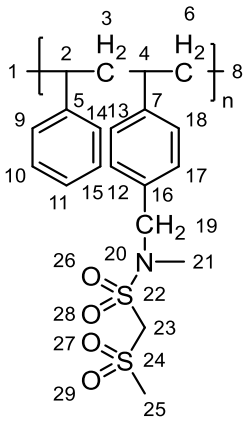
The cross-linker **141a** (1.99 mmol, 0.51 g) and the monomer MMA (9.98 mmol, 1.00 g) with the initiator AIBN (0.50 mmol, 81 mg) were dissolve in the EtOAc (15 mL). The solution was degassed through three freeze-pump-thaw cycles, the round bottom flask was sealed, and the mixture was refluxed for 2 h. After cooling, the reaction mixture was slowly poured into a large amount of diethyl ether and the resulting precipitate was filtrated to give the final product (1.18 g, 78%).



^{1}H NMR (400 MHz, DMSO-d6) δ 5.28 – 5.08, 4.04 – 3.85, 3.65 – 3.45, 3.22 – 3.17, 1.97 – 1.60, 1.03 – 0.59. IR (neat) ν_{max} (*inter alia*): 3025 (w, C-H), 2924 (w, C-H), 1316 (s, S=O), 1129 (s, C-O), 698 (s, C-H) cm^{-1}; Mn=13000; Mw=26000; Mw/Mn = 2.00.

3.8.1.2 Synthesis of P(ST-*co*-153), 198

The cross-linker **153** (1.92 mmol, 0.58 g) and the monomer styrene (9.60 mmol, 1.00 g) with the initiator AIBN (0.50 mmol, 81 mg) were dissolve in the EtOAc (15 mL). The solution was degassed through three freeze-pump-thaw cycles, the round bottom flask was sealed, and the mixture was refluxed for 2 h. After cooling, the reaction mixture was slowly poured into a large amount of diethyl ether and the resulting precipitate was filtrated to give the final product (0.78 g, 49 %).



^{1}H NMR (400 MHz, DMSO-d6) δ 7.33 – 6.78, 6.78 – 6.16, 5.48 – 5.25, 4.38 – 4.07, 3.28 – 3.12, 2.76 – 2.56, 1.99 – 1.08. IR (neat) ν_{max} (*inter alia*): 3328 (w, NH), 3045 (w, C=C), 2985 (w, CH), 2930 (w, CH), 1742 (m, C=O), 1316 (m, SO_2), 1137 (s, SO_2), 751 (m, NH); Mn=8000; Mw= 11000; Mw/Mn = 1.38.

3.8.2 Emulsion polymerisation

3.8.2.1 Non-automatic procedure

Seed stage method

A stock seed latex was prepared on a 531.4 mL scale. A monomer mixture of 50 mol% MMA and 50 mol% BA was used. A 50:50 (active) mixture of Rhodapex AB/20 and Dowfax 2A1 was used at 0.5 wt% (0.25 wt% each) with respect to monomer. The reaction vessel was placed in a water bath at 85 °C and purged with N_2 for 20 min. Deionised water (DIW) (500 g), Rhodapex AB/20 (0.06 g active) and Dowfax 2A1 (0.06 g active) were added and stirred under N_2 for a further 30 min. A mixture of MMA (10.97 g) and BA (14.06 g) were then added, followed by NaPS (0.6 g) in DIW (5.6 g). The reaction mixture was heated with stirring for 90 min before cooling to ambient temperature.

Shell latex method

Procedure reported is for the best resulted conversion of crosslinker containing latex in Table 22, Entry 4 (Section 2.3.4.4):

Seed latex (97.0 mL) was charged into reaction flask and taken to 85 °C with stirring, under nitrogen. The monomer mixture 50 mol% MMA and 50 mol% BA (1.125 g) was fed into vessel and the seed allowed to swell for 30 min. At time t = 0, NaPS (0.052 g) in DIW (3.0 g) was added and the monomers (79.55 g) and aqueous feeds started simultaneously, then added over 4 h. The aqueous feed consisted of surfactant (1.125 g active), NaPS (0.104 g) and DIW (15 g) and HEMA (10.45 g). On completing the feeds, NaPS (0.087 g) in DIW (1 g) was added and reaction allowed to proceed for a further 60 min before cooling the latex and collecting it after filtration through a 80 μm sieve. NaOH 2% was added to the solution to get a pH 8.5.

3.8.2.2 Computer controlled

Seed stage method

A 2L flanged glass reactor was fitted with an immersion thermocouple, overhead stirrer and propeller stirrer, reflux condenser and nitrogen inlet (ca. 20 L / hour flow). The flask was then partially submerged in a water bath which was connected to the thermocouple via a Julabo LC4 temperature controller. The flask was charged with 878.4 g demineralized water, 18.76 g Kemsurf OS38 and 0.320 g Dowfax 2A1. To this, 1.640 g acrylic acid, 27.07 g butyl acrylate, 23.94 g methyl methacrylate and 11.63 g styrene were added while stirring to create a dispersion. The flask was heated to 85 °C and 4.23 g of ammonium persulfate dissolved in 33.98 g demineralized water was added as a shot. Temperature was maintained while stirring for 30 min before the flask was rapidly cooled. A particle size of 43 nm was recorded.

Table 25. Seed stage formulation.

Step name	Material	Material type	Seed stage wt (g)
Reactor charge	Water demineralised	Solvent	878.4
Reactor charge	Kemsurf OS38	Surfactant	18.76
Reactor charge	Dowfax 2A1	Surfactant	0.32
Seed monomer	Acrylic Acid	Monomer	1.64
Seed monomer	Butyl acrylate	Monomer	27.07
Seed monomer	Methyl Methacrylate	Monomer	23.94
Seed monomer	Styrene	Monomer	11.63
Initiator	Ammonium persulphate	Initiator	4.230
Initiator	Water demineralised	Solvent	33.98
TOTAL			1000

Feed stage method (shell latex)

The second stage of latex synthesis was completed using a computer-controlled Chemspeed A100 Autoplant, fitted with 20 90 mL stainless steel reactors. Each reactor comprised a mechanical anchor-type stirrer, an immersion thermocouple and three syringe pumps connected to separate supply tanks. Initial reactor charge was achieved by means of an automated overhead arm equipped with four syringe pumps. Reactors were purged with nitrogen before reactions commenced. Monomer and surfactant co-mixtures and initiator solutions were fed separately and chilled to 10 °C prior to transfer via computer-controlled syringe pump.

Seed latex (27.12 g) was charged into the reactor and heated to 85 °C with stirring, under nitrogen. The monomer mixture feed 1 (28.01 g) and aqueous feed were fed into the vessel simultaneously over a period of 5 h. The aqueous feed consisted of surfactant Kemsurf OS38 (0.541 g) and Dowfax 2A1 (0.140 g active), APS (0.026 g) and DIW (1.079 g). The emulsion was left to react an extra 30 mins at the end of the feeding and then cooled to 70 °C. Afterwards, tert-butyl hydroperoxide (0.029 g) in DIW (0.428 g) and Bruggolite FF6 (0.035 g) in DIW (0.428 g), as well as antifoam 1, were added as shots to be then cooled to 60 °C. Once the reactor had reached the temperature, ammonia 28% (0.423 g) was added to adjust the pH and left to react for 20 mins. The reactor was further cooled down to 38

°C and antifoaming agent Tegofoamex 1488 (0.142 g) in DIW (0.347 g) were added. The emulsion was cooled to RT and decanted. ADH was manually added, if required.

Two series of batches were prepared simultaneously, one containing a lower percentage (batches L) of crosslinker and another one containing a higher percentage (batches H) of crosslinker as explained in more details in section 2.3.4.5. These have been compared with three references called “controls”. All quantities used are listed in Table 26, Table 27 and Table 28.

Table 26. Controls formulations.

Step name	Material	Material type	C1 wt (g)	C2 wt (g)	C3 wt (g)
Seed latex	Latex	/	27.12	27.12	27.12
Feed monomer 1	Acrylic Acid	Monomer	0.69	0.69	0.69
Feed monomer 1	Butyl acrylate	Monomer	11.63	11.48	11.27
Feed monomer 1	Methyl Methacrylate	Monomer	10.29	10.16	9.97
Feed monomer 1	Styrene	Monomer	4.99	4.93	4.83
Feed monomer 1	Acetoacetoxyethyl Methacrylate	Monomer	0.00	0.00	0.00
Feed monomer 1	Diacetone Acrylamide	Monomer	0.00	0.00	0.00
Feed monomer 1	2-Hydroxyethyl methacrylate	Monomer	0.00	0.34	0.84
Feed monomer 1	9b methacrylate	Functional monomer	0.00	0.00	0.00
Surfactant feed 1	Water demineralised	Solvent	8.55	8.55	8.55
Surfactant feed 1	Kemsurf OS38	Surfactant	0.53	0.53	0.53
Surfactant feed 1	Dowfax 2A1	Surfactant	0.14	0.14	0.14
Feed oxidant 1	Water demineralised	Solvent	1.06	1.06	1.06
Feed oxidant 1	Ammonium persulphate	Oxidant / reductant	0.03	0.03	0.03
Antifoam	Tegofoamex 1488	Antifoam	0.07	0.07	0.07
Rinse	Water	Solvent	0.83	0.83	0.83
Mop-up oxidant	Water demineralised	Solvent	0.42	0.42	0.42
Mop-up oxidant	tert-Butyl hydroperoxide	Oxidant / reductant	0.03	0.03	0.03
Mop-up reductant	Water demineralised	Solvent	0.42	0.42	0.42
Mop-up reductant	Bruggolite FF6	Oxidant / reductant	0.03	0.03	0.03
pH adjust / neutralisation	Ammonia (28%)	Base	0.42	0.42	0.42
Cross-linker	Water demineralised	Solvent	2.27	2.27	2.27
Cross-linker	Adipic dihydrazide	Cross-linking agent	0.00	0.00	0.00
Antifoam	Tegofoamex 1488	Antifoam	0.07	0.07	0.07
		TOTAL	69.58	69.58	69.58

Table 27. Batches L, low concentration of crosslinker formulations.

Step name	Material	Material type	L1 wt (g)	L2 wt (g)	L3 wt (g)	L4 wt (g)	L5 wt (g)	L6 wt (g)	L7 wt (g)	L8 wt (g)
Seed latex	Latex	/	27.12	27.12	27.12	27.12	27.12	27.02	27.12	27.02
Feed monomer 1	Acrylic Acid	Monomer	0.69	0.69	0.69	0.69	0.69	0.69	0.69	0.69
Feed monomer 1	Butyl acrylate	Monomer	11.20	11.06	11.39	11.25	11.44	11.40	11.30	11.26
Feed monomer 1	Methyl Methacrylate	Monomer	9.91	9.78	10.08	9.95	10.12	10.09	9.99	9.96
Feed monomer 1	Styrene	Monomer	4.81	4.74	4.89	4.83	4.91	4.89	4.85	4.83
Feed monomer 1	Acetoacetoxy ethyl Methacrylate	Monomer	0.00	0.00	0.55	0.55	0.00	0.00	0.00	0.00
Feed monomer 1	Diacetone Acrylamide	Monomer	0.00	0.00	0.00	0.00	0.44	0.43	0.44	0.43
Feed monomer 1	2-Hydroxyethyl methacrylate	Monomer	0.00	0.34	0.00	0.34	0.00	0.00	0.34	0.33
Feed monomer 1	**179h** methacrylate	Functional monomer	0.99	0.99	0.00	0.00	0.00	0.00	0.00	0.00
Surfactant feed 1	Water demineralised	Solvent	8.55	8.55	8.55	8.55	8.55	8.52	8.55	8.52
Surfactant feed 1	Kemsurf OS38	Surfactant	0.53	0.53	0.53	0.53	0.53	0.53	0.53	0.53
Surfactant feed 1	Dowfax 2A1	Surfactant	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14
Feed oxidant 1	Water demineralised	Solvent	1.06	1.06	1.06	1.06	1.06	1.06	1.06	1.06
Feed oxidant 1	Ammonium persulphate	Oxidant / reductant	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Antifoam	Tegofoamex 1488	Antifoam	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
Rinse	Water tap	Solvent	0.83	0.83	0.83	0.83	0.83	0.83	0.83	0.83
Mop-up oxidant	Water demineralised	Solvent	0.42	0.42	0.42	0.42	0.42	0.42	0.42	0.42
Mop-up oxidant	tert-Butyl hydroperoxide	Oxidant / reductant	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Mop-up reductant	Water demineralised	Solvent	0.42	0.42	0.42	0.42	0.42	0.42	0.42	0.42
Mop-up reductant	Bruggolite FF6	Oxidant / reductant	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
pH adjust / neutralisation	Ammonia (28%)	Base	0.42	0.42	0.42	0.42	0.42	0.42	0.42	0.42
Cross-linker	Water demineralised	Solvent	2.27	2.27	2.27	2.27	2.27	2.26	2.27	2.26
Cross-linker	Adipic dihydrazide	Cross-linking agent	0.00	0.00	0.00	0.00	0.00	0.24	0.00	0.24
Antifoam	Tegofoamex 1488	Antifoam	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
		TOTAL	69.58	69.58	69.58	69.58	69.58	69.58	69.58	69.58

Table 28. Batches H, high concentration of crosslinker formulations.

Step name	Material	Material type	H1 wt [g]	H2 wt [g]	H3 wt [g]	H4 wt [g]	H5 wt [g]	H6 wt [g]	H7 wt [g]	H8 wt [g]
Seed latex	Latex	/	27.12	27.12	27.12	27.12	27.12	26.89	27.12	26.89
Feed monomer 1	Acrylic Acid	Monomer	0.69	0.69	0.69	0.69	0.69	0.68	0.69	0.68
Feed monomer 1	Butyl acrylate	Monomer	11.91	11.51	11.03	10.67	11.16	11.06	10.80	10.70
Feed monomer 1	Methyl Methacrylate	Monomer	8.35	8.06	9.76	9.44	9.87	9.79	9.55	9.47
Feed monomer 1	Styrene	Monomer	4.17	4.03	4.73	4.58	4.79	4.75	4.63	4.59
Feed monomer 1	Acetoacetoxyethyl Methacrylate	Monomer	0.00	0.00	1.38	1.38	0.00	0.00	0.00	0.00
Feed monomer 1	Diacetone Acrylamide	Monomer	0.00	0.00	0.00	0.00	1.09	1.08	1.09	1.08
Feed monomer 1	2-Hydroxyethyl methacrylate	Monomer	0.00	0.84	0.00	0.84	0.00	0.00	0.84	0.83
Feed monomer 1	**179h** methacrylate	Functional monomer	2.47	2.47	0.00	0.00	0.00	0.00	0.00	0.00
Surfactant feed 1	Water demineralised	Solvent	8.55	8.55	8.55	8.55	8.55	8.47	8.55	8.47
Surfactant feed 1	Kemsurf OS38	Surfactant	0.53	0.53	0.53	0.53	0.53	0.53	0.53	0.53
Surfactant feed 1	Dowfax 2A1	Surfactant	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14
Feed oxidant 1	Water demineralised	Solvent	1.06	1.06	1.06	1.06	1.06	1.05	1.06	1.05
Feed oxidant 1	Ammonium persulphate	Oxidant / reductant	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Antifoam	Tegofoamex 1488	Antifoam	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
Rinse	Water tap	Solvent	0.83	0.83	0.83	0.83	0.83	0.83	0.83	0.83
Mop-up oxidant	Water demineralised	Solvent	0.42	0.42	0.42	0.42	0.42	0.42	0.42	0.42
Mop-up oxidant	tert-Butyl hydroperoxide	Oxidant / reductant	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Mop-up reductant	Water demineralised	Solvent	0.42	0.42	0.42	0.42	0.42	0.42	0.42	0.42
Mop-up reductant	Bruggolite FF6	Oxidant / reductant	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
pH adjust/ neutralisation	Ammonia (28%)	Base	0.42	0.42	0.42	0.42	0.42	0.41	0.42	0.41
Cross-linker	Water demineralised	Solvent	2.27	2.27	2.27	2.27	2.27	2.25	2.27	2.25
Cross-linker	Adipic dihydrazide	Cross-linking agent	0.00	0.00	0.00	0.00	0.00	0.59	0.00	0.59
Antifoam	Tegofoamex 1488	Antifoam	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
		TOTAL	69.58	69.58	69.58	69.58	69.58	69.58	69.58	69.58

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APPENDIX

Crystallographic data

A. *N,N-Diethyl-1-methanesulfonylmethanesulfonamide, 127c*

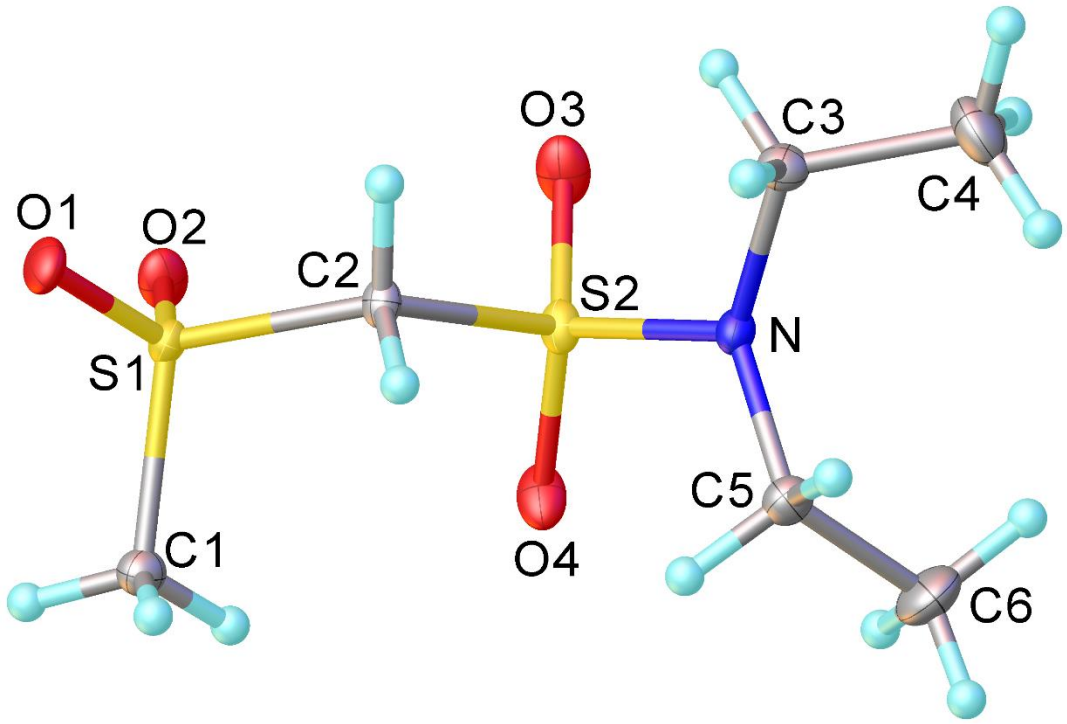

Table A1. Crystal data and structure refinement for 127c.

Identification code	20srv136
Empirical formula	C6H15NO4S2
Formula weight	229.31
Temperature/K	120
Crystal system	monoclinic
Space group	P21/c
a/Å	12.3699(8)
b/Å	8.6324(6)
c/Å	9.9851(7)
α/°	90
β/°	100.212(3)
γ/°	90
Volume/Å3	1049.34(12)
Z	4
ρcalcg/cm3	1.451
μ/mm-1	0.492
F(000)	488.0
Crystal size/mm3	0.468 × 0.226 × 0.096
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.786 to 65.152
Index ranges	-18 ≤ h ≤ 18, -13 ≤ k ≤ 13, -15 ≤ l ≤ 15
Reflections collected	25747
Independent reflections	3806 [Rint = 0.0683, Rsigma = 0.0453]
Data/restraints/parameters	3806/0/179
Goodness-of-fit on F2	1.048
Final R indexes [I>=2σ (I)]	R1 = 0.0325, wR2 = 0.0769
Final R indexes [all data]	R1 = 0.0485, wR2 = 0.0831
Largest diff. peak/hole / e Å-3	0.49/-0.46

Table A2. Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å2×103) for 127c. Ueq is defined as 1/3 of of the trace of the orthogonalised UIJ tensor.

Atom	x	y	z	U(eq)
S1	4317.6(2)	1529.1(3)	6198.5(3)	11.00(7)
S2	2298.1(2)	3544.4(3)	5634.1(3)	12.61(8)
O1	4911.4(7)	705.7(10)	7359.0(9)	17.64(19)
O2	3711.6(7)	632.2(10)	5102.6(9)	17.65(19)
O3	1506.8(8)	2334.6(11)	5329.1(10)	20.9(2)
O4	2779.7(8)	4224.9(11)	4564.5(9)	20.1(2)
N	1774.5(8)	4914.1(11)	6403.0(10)	12.44(19)
C1	5233.5(11)	2761.5(14)	5555.9(13)	15.6(2)
C2	3399.7(10)	2787.9(13)	6873.8(12)	11.7(2)
C3	1210.3(10)	4470.9(15)	7537.8(13)	15.9(2)
C4	154.0(12)	5359(2)	7483.4(18)	28.0(3)
C5	2303.5(11)	6458.0(14)	6489.7(14)	16.9(2)
C6	1729.7(15)	7545.3(18)	5394.8(18)	30.6(3)

Table A3. Anisotropic Displacement Parameters (Å2×103) for 127c. The Anisotropic displacement factor exponent takes the form: -2π2[h2a*2U11+2hka*b*U12+...].

Atom	U11	U22	U33	U23	U13	U12
S1	11.99(13)	9.05(12)	11.50(13)	0.04(9)	0.81(10)	1.63(9)
S2	12.48(13)	15.12(14)	9.23(13)	-1.26(10)	-0.83(9)	3.57(10)
O1	17.9(4)	17.3(4)	17.3(4)	6.0(3)	1.9(3)	6.9(3)
O2	16.7(4)	14.8(4)	20.6(4)	-7.6(3)	0.9(3)	0.1(3)
O3	15.8(4)	21.6(4)	22.8(5)	-9.3(4)	-3.6(4)	0.0(3)
O4	22.6(5)	26.9(5)	11.2(4)	4.3(4)	4.6(3)	9.6(4)
N	13.7(5)	11.7(4)	12.4(5)	1.1(3)	3.4(4)	3.0(3)
C1	16.5(6)	14.3(5)	16.7(6)	0.0(4)	4.9(5)	0.0(4)
C2	12.4(5)	12.6(5)	9.5(5)	-0.3(4)	-0.2(4)	2.5(4)
C3	17.2(6)	16.9(5)	14.7(5)	1.5(4)	5.2(4)	0.2(4)
C4	18.2(7)	36.3(9)	31.4(8)	-0.3(7)	9.9(6)	5.2(6)
C5	17.8(6)	13.7(5)	19.4(6)	0.6(5)	3.8(5)	-0.1(4)
C6	35.1(9)	20.2(7)	36.8(9)	13.3(6)	7.4(7)	3.8(6)

Table A4. Bond Lengths for 127c.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O1	1.4441(9)	S2	N	1.6072(10)
S1	O2	1.4380(9)	S2	C2	1.7938(11)
S1	C1	1.7563(13)	N	C3	1.4825(16)
S1	C2	1.7878(12)	N	C5	1.4805(16)
S2	O3	1.4268(10)	C3	C4	1.5077(19)
S2	O4	1.4375(10)	C5	C6	1.518(2)

Table A5. Bond Angles for 127c.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
O1	S1	C1	108.78(6)	O4	S2	N	108.03(5)
O1	S1	C2	105.26(5)	O4	S2	C2	107.29(6)
O2	S1	O1	117.90(6)	N	S2	C2	105.03(5)
O2	S1	C1	109.34(6)	C3	N	S2	117.35(8)
O2	S1	C2	109.51(5)	C5	N	S2	118.61(8)
C1	S1	C2	105.28(6)	C5	N	C3	116.79(10)
O3	S2	O4	119.97(6)	S1	C2	S2	114.62(6)
O3	S2	N	108.73(6)	N	C3	C4	111.33(11)
O3	S2	C2	106.82(6)	N	C5	C6	111.66(11)

Table A6. Torsion Angles for 127c.

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
S2	N	C3	C4	-137.49(11)	O4	S2	N	C5	-31.77(10)
S2	N	C5	C6	97.79(12)	O4	S2	C2	S1	-52.34(8)
O1	S1	C2	S2	-163.13(7)	N	S2	C2	S1	-167.13(6)
O2	S1	C2	S2	-35.45(9)	C1	S1	C2	S2	82.00(8)
O3	S2	N	C3	47.21(10)	C2	S2	N	C3	-66.83(10)
O3	S2	N	C5	-163.46(9)	C2	S2	N	C5	82.50(10)
O3	S2	C2	S1	77.50(8)	C3	N	C5	C6	-112.71(13)
O4	S2	N	C3	178.90(8)	C5	N	C3	C4	72.62(14)

Table A7. Hydrogen Atom Coordinates (Å×104) and Isotropic Displacement Parameters (Å2×103) for 127c.

Atom	x	y	z	U(eq)
H1A	5586(15)	3370(20)	6282(19)	28(5)
H1B	4820(14)	3341(19)	4825(17)	21(4)
H1C	5730(14)	2090(20)	5218(18)	24(4)
H2A	3801(13)	3617(18)	7319(16)	15(4)
H2B	3117(13)	2199(19)	7483(17)	20(4)
H3A	1705(13)	4675(18)	8371(17)	18(4)
H3B	1094(13)	3371(19)	7512(17)	19(4)
H4A	-295(16)	5110(20)	6670(20)	33(5)
H4B	287(16)	6470(20)	7560(20)	35(5)
H4C	-177(17)	5090(20)	8230(20)	44(6)
H5A	3083(14)	6323(18)	6452(16)	19(4)
H5B	2268(14)	6870(20)	7385(19)	27(4)
H6A	1791(14)	7150(20)	4470(20)	29(5)
H6B	2039(18)	8620(30)	5530(20)	48(6)
H6C	903(19)	7640(20)	5420(20)	48(6)

B. *N,N-Diisopropyl-1-methanesulfonylmethanesulfonamide, 127d*

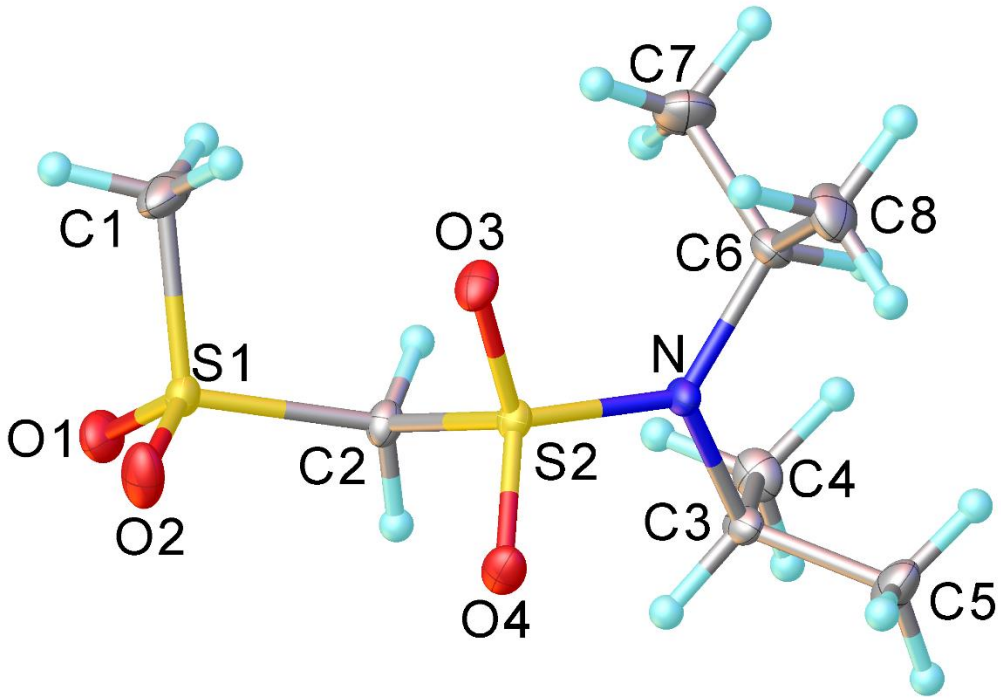

Table B1. Crystal data and structure refinement for 127d.

Identification code	20srv114
Empirical formula	C8H19NO4S2
Formula weight	257.36
Temperature/K	120
Crystal system	monoclinic
Space group	P21/n
a/Å	10.3028(7)
b/Å	8.9333(6)
c/Å	13.4871(10)
α/°	90
β/°	98.658(3)
γ/°	90
Volume/Å3	1227.18(15)
Z	4
ρcalcg/cm3	1.393
μ/mm-1	0.429
F(000)	552.0
Crystal size/mm3	0.227 × 0.165 × 0.13
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.386 to 66.44
Index ranges	-15 ≤ h ≤ 15, -13 ≤ k ≤ 13, -20 ≤ l ≤ 20
Reflections collected	31254
Independent reflections	4683 [Rint = 0.0416, Rsigma = 0.0315]
Data/restraints/parameters	4683/0/147
Goodness-of-fit on F2	1.028
Final R indexes [I>=2σ (I)]	R1 = 0.0300, wR2 = 0.0728
Final R indexes [all data]	R1 = 0.0463, wR2 = 0.0783
Largest diff. peak/hole / e Å-3	0.42/-0.40

Table B2. Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å2×103) for 127d. Ueq is defined as 1/3 of of the trace of the orthogonalised UIJ tensor.

Atom	x	y	z	U(eq)
S1	6628.4(2)	3327.3(3)	4.1(2)	13.44(7)
S2	6545.1(2)	1949.8(3)	2060.4(2)	11.28(6)
O1	6559.7(8)	4815.4(9)	-417.4(6)	20.43(17)
O2	7830.1(8)	2508.1(10)	39.6(6)	24.37(18)
O3	6007.4(8)	659.6(8)	1513.8(5)	17.34(16)
O4	7922.2(7)	1986.1(9)	2430.9(6)	17.88(16)
N	5729.5(8)	2262.5(10)	2958.7(6)	12.91(16)
C1	5328.2(13)	2275.2(14)	-636.4(9)	25.9(3)
C2	6228.0(10)	3543.8(11)	1244.1(7)	13.78(18)
C3	6148.4(10)	3568.8(11)	3618.9(8)	14.37(18)
C4	5104.0(11)	4794.8(13)	3500.0(9)	20.2(2)
C5	6502.4(12)	3068.4(14)	4699.1(8)	23.1(2)
C6	4481.0(10)	1486.7(12)	3078.4(8)	16.23(19)
C7	3415.2(12)	1658.7(16)	2172.2(10)	28.4(3)
C8	4718.7(13)	-136.4(14)	3402.0(10)	25.8(2)

Table B3. Anisotropic Displacement Parameters (Å2×103) for 127d. The Anisotropic displacement factor exponent takes the form: -2π2[h2a*2U11+2hka*b*U12+...].

Atom	U11	U22	U33	U23	U13	U12
S1	15.23(12)	14.82(12)	10.49(11)	0.66(8)	2.66(8)	-0.61(8)
S2	13.13(11)	11.06(11)	9.92(11)	-0.68(8)	2.60(8)	1.75(8)
O1	25.9(4)	17.9(4)	17.5(4)	5.0(3)	3.6(3)	-3.5(3)
O2	22.7(4)	33.1(5)	19.2(4)	4.5(3)	9.4(3)	9.7(4)
O3	26.2(4)	11.9(3)	14.3(3)	-2.9(3)	4.1(3)	-0.5(3)
O4	13.2(3)	24.6(4)	15.9(3)	-0.8(3)	2.6(3)	5.2(3)
N	13.9(4)	14.3(4)	11.3(4)	-3.1(3)	4.6(3)	-2.7(3)
C1	33.9(6)	24.4(6)	17.0(5)	-2.2(4)	-3.7(4)	-10.7(5)
C2	19.1(5)	11.6(4)	10.9(4)	-0.3(3)	3.3(3)	1.4(4)
C3	14.3(4)	15.2(4)	14.2(4)	-5.5(3)	4.0(3)	-1.9(3)
C4	21.8(5)	16.1(5)	24.0(5)	-3.2(4)	8.2(4)	1.7(4)
C5	23.2(5)	31.2(6)	14.2(5)	-5.6(4)	-0.2(4)	4.1(5)
C6	14.2(4)	18.3(5)	16.8(5)	-0.5(4)	4.4(4)	-4.4(4)
C7	15.8(5)	39.0(7)	28.5(6)	-1.4(5)	-2.6(4)	-3.0(5)
C8	33.7(7)	19.8(5)	25.7(6)	3.5(4)	10.3(5)	-7.0(5)

Table B4. Bond Lengths for 127d.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O1	1.4434(8)	S2	C2	1.7994(10)
S1	O2	1.4328(8)	N	C3	1.4918(13)
S1	C1	1.7538(12)	N	C6	1.4911(13)
S1	C2	1.7923(10)	C3	C4	1.5267(15)
S2	O3	1.4338(8)	C3	C5	1.5151(15)
S2	O4	1.4319(8)	C6	C7	1.5229(16)
S2	N	1.5995(9)	C6	C8	1.5234(16)

Table B5. Bond Angles for 127d.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	S1	C1	108.12(6)	N	S2	C2	104.93(5)
O1	S1	C2	105.29(5)	C3	N	S2	116.80(7)
O2	S1	O1	118.33(5)	C6	N	S2	124.12(7)
O2	S1	C1	109.56(6)	C6	N	C3	118.41(8)
O2	S1	C2	110.07(5)	S1	C2	S2	116.07(5)
C1	S1	C2	104.56(5)	N	C3	C4	111.25(8)
O3	S2	N	108.87(4)	N	C3	C5	110.44(9)
O3	S2	C2	107.52(5)	C5	C3	C4	112.12(9)
O4	S2	O3	118.91(5)	N	C6	C7	113.31(9)
O4	S2	N	109.74(5)	N	C6	C8	111.67(9)
O4	S2	C2	105.94(5)	C7	C6	C8	113.04(10)

Table B6. Torsion Angles for 127d.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
S2	N	C3	C4	112.96(9)	O4	S2	N	C6	-141.39(8)
S2	N	C3	C5	-121.86(8)	O4	S2	C2	S1	80.15(7)
S2	N	C6	C7	-56.94(12)	N	S2	C2	S1	-163.78(6)
S2	N	C6	C8	72.10(11)	C1	S1	C2	S2	78.17(7)
O1	S1	C2	S2	-168.00(6)	C2	S2	N	C3	-65.30(8)
O2	S1	C2	S2	-39.43(8)	C2	S2	N	C6	105.18(9)
O3	S2	N	C3	179.84(7)	C3	N	C6	C7	113.40(11)
O3	S2	N	C6	-9.68(10)	C3	N	C6	C8	-117.57(10)
O3	S2	C2	S1	-47.98(7)	C6	N	C3	C4	-58.08(12)
O4	S2	N	C3	48.13(9)	C6	N	C3	C5	67.10(11)

Table B7. Hydrogen Atom Coordinates (Å×104) and Isotropic Displacement Parameters (Å2×103) for 127d. Continued…

Atom	x	y	z	U(eq)
H1A	4496.49	2790.61	-601.92	41(3)
H1B	5312.88	1284.97	-325.64	41(3)
H1C	5448.61	2162.09	-1339.55	41(3)
H2A	5284.02	3796.09	1187.09	17
H2B	6729.53	4405.92	1564.96	17
H3	6958.53	3994.63	3402.38	17
H4A	4889.02	5067.86	2790.49	34(2)
H4B	5439.86	5675.7	3889.59	34(2)
H4C	4312.89	4427.68	3743.46	34(2)
H5A	5712.27	2707.83	4947.29	33(2)
H5B	6873.19	3914.16	5110.16	33(2)
H5C	7150.57	2259.39	4738.66	33(2)
H6	4142.19	1999.78	3646.77	19
H7A	3323.58	2717.91	1985.69	38(3)
H7B	2580.03	1285.54	2338.95	38(3)
H7C	3656.18	1083.22	1608.61	38(3)
H8A	5023.32	-703.13	2859.01	34(2)
H8B	3898.95	-574.2	3554.11	34(2)

Table B7. Hydrogen Atom Coordinates (Å×104) and Isotropic Displacement Parameters (Å2×103) for 127d. Continued…

Atom	x	y	z	U(eq)
H8C	5386.66	-176.16	4001.16	34(2)

C. *N-Methyl 2-(methanesulfonylmethanesulfonamide)-3-phenylpropanoate, 127h*

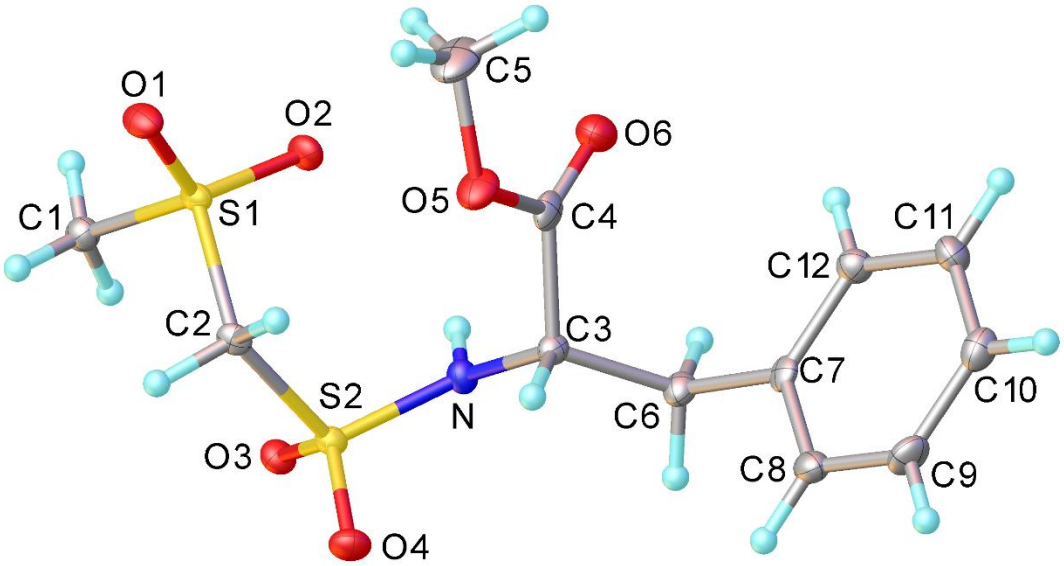

Table C1. Crystal data and structure refinement for 127h.

Identification code	20srv115
Empirical formula	C12H17NO6S2
Formula weight	335.38
Temperature/K	120
Crystal system	orthorhombic
Space group	P212121
a/Å	5.4640(4)
b/Å	8.0402(5)
c/Å	33.946(3)
α/°	90
β/°	90
γ/°	90
Volume/Å3	1491.29(18)
Z	4
ρcalcg/cm3	1.494
μ/mm-1	0.383
F(000)	704.0
Crystal size/mm3	0.263 × 0.073 × 0.049
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.8 to 60.194
Index ranges	-7 ≤ h ≤ 7, -9 ≤ k ≤ 11, -29 ≤ l ≤ 47
Reflections collected	14188
Independent reflections	4380 [Rint = 0.0371, Rsigma = 0.0512]
Data/restraints/parameters	4380/1/207
Goodness-of-fit on F2	1.011
Final R indexes [I>=2σ (I)]	R1 = 0.0336, wR2 = 0.0707
Final R indexes [all data]	R1 = 0.0447, wR2 = 0.0734
Largest diff. peak/hole / e Å-3	0.31/-0.41
Flack parameter	-0.07(3)

Table C2. Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å2×103) for 127h. Ueq is defined as 1/3 of of the trace of the orthogonalised UIJ tensor.

Atom	x	y	z	U(eq)
S1	2842.4(10)	3549.1(7)	7255.2(2)	12.20(12)
S2	1376.4(10)	6449.9(7)	6740.6(2)	11.81(12)
O1	2031(3)	1871.8(18)	7321.7(5)	19.4(4)
O2	5171(3)	3785(2)	7061.7(5)	16.4(4)
O3	2253(3)	7521.6(17)	7044.8(4)	15.5(4)
O4	-721(3)	6909.2(19)	6510.6(5)	18.5(4)
O5	3113(4)	2415.4(19)	6211.8(5)	22.3(4)
O6	6956(3)	3377(2)	6138.7(5)	23.5(4)
N	3651(4)	6208(2)	6446.6(5)	13.3(4)
C1	2785(5)	4648(3)	7701.7(7)	16.0(5)
C2	558(4)	4495(3)	6956.2(7)	13.0(4)
C3	3549(5)	5276(2)	6074.6(6)	12.7(4)
C4	4788(5)	3592(3)	6139.7(6)	15.8(5)
C5	4085(7)	800(3)	6317.9(9)	35.2(8)
C6	4854(4)	6308(3)	5759.7(6)	16.2(5)
C7	4795(4)	5561(3)	5350.1(7)	13.8(5)
C8	2878(5)	5909(3)	5099.3(7)	18.2(5)
C9	2825(5)	5265(3)	4719.5(6)	21.6(5)
C10	4709(5)	4267(3)	4586.4(7)	20.5(6)
C11	6641(5)	3899(3)	4834.2(7)	19.3(5)
C12	6679(5)	4538(3)	5215.3(7)	16.9(5)

Table C3. Anisotropic Displacement Parameters (Å2×103) for 127h. The Anisotropic displacement factor exponent takes the form: -2π2[h2a*2U11+2hka*b*U12+...].

Atom	U11	U22	U33	U23	U13	U12
S1	9.0(3)	11.2(2)	16.4(2)	0.9(2)	1.5(2)	-0.1(2)
S2	10.1(3)	11.1(2)	14.3(2)	-0.9(2)	-0.4(2)	0.1(2)
O1	18.4(9)	12.0(7)	27.7(9)	1.9(6)	4.8(8)	-0.5(7)
O2	9.3(8)	19.3(8)	20.5(8)	1.6(7)	2.2(6)	-0.3(7)
O3	16.2(9)	13.6(7)	16.7(7)	-2.9(6)	0.9(7)	0.1(8)
O4	14.9(9)	19.4(8)	21.3(8)	0.8(6)	-3.6(7)	3.9(7)
O5	32.6(12)	11.0(7)	23.3(8)	1.1(6)	1.5(8)	-3.1(9)
O6	24.0(10)	23.6(8)	22.9(8)	0.8(7)	2.2(7)	6.4(9)
N	11.8(9)	15.1(9)	12.9(9)	-1.3(7)	0.3(8)	-1.5(9)
C1	14.0(12)	17.0(10)	16.9(11)	1.3(9)	0.6(10)	0.0(11)
C2	8.0(10)	13.6(10)	17.4(11)	-1.3(8)	-1.1(9)	-1.5(9)
C3	14.9(12)	11.7(9)	11.6(10)	-0.8(8)	-0.9(9)	0.1(10)
C4	23.8(13)	15.7(10)	8.0(9)	-1.9(9)	0.7(9)	-2.2(12)
C5	62(2)	12.7(11)	31.3(15)	3.3(10)	4.5(15)	4.4(15)
C6	20.3(13)	12.4(10)	16.0(10)	1.5(8)	2.0(9)	-0.5(11)
C7	15.7(13)	11.7(10)	13.9(10)	3.9(8)	3.1(9)	-4.6(10)
C8	17.4(12)	17.0(10)	20.3(11)	4.9(8)	2.5(10)	2.7(11)
C9	21.0(14)	26.3(12)	17.4(11)	6.3(9)	-6.6(10)	0.8(12)
C10	26.0(15)	20.5(11)	15.0(11)	1.3(9)	-0.7(10)	-3.6(11)
C11	19.2(14)	20.5(11)	18.3(11)	-1.2(8)	4.1(10)	3.3(11)
C12	14.6(13)	18.0(10)	18.1(11)	0.9(8)	-0.7(9)	0.5(10)

Table C4. Bond Lengths for 127h.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O1	1.4374(16)	N	C3	1.469(3)
S1	O2	1.4443(17)	C3	C4	1.530(3)
S1	C1	1.755(2)	C3	C6	1.530(3)
S1	C2	1.780(2)	C6	C7	1.515(3)
S2	O3	1.4277(15)	C7	C8	1.378(3)
S2	O4	1.4352(18)	C7	C12	1.395(3)
S2	N	1.606(2)	C8	C9	1.389(3)
S2	C2	1.790(2)	C9	C10	1.381(4)
O5	C4	1.339(3)	C10	C11	1.382(4)
O5	C5	1.449(3)	C11	C12	1.392(3)
O6	C4	1.197(3)			

Table C5. Bond Angles for 127h.

Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
O1	S1	O2	117.78(10)	N	C3	C4	108.10(17)
O1	S1	C1	109.34(10)	N	C3	C6	107.83(17)
O1	S1	C2	105.91(11)	C6	C3	C4	112.01(19)
O2	S1	C1	110.03(12)	O5	C4	C3	110.4(2)
O2	S1	C2	107.61(10)	O6	C4	O5	125.1(2)
C1	S1	C2	105.36(12)	O6	C4	C3	124.5(2)
O3	S2	O4	120.40(10)	C7	C6	C3	114.61(18)
O3	S2	N	105.26(10)	C8	C7	C6	120.2(2)
O3	S2	C2	108.54(9)	C8	C7	C12	118.5(2)
O4	S2	N	108.13(10)	C12	C7	C6	121.3(2)
O4	S2	C2	104.40(11)	C7	C8	C9	120.9(2)
N	S2	C2	109.94(11)	C10	C9	C8	120.3(2)
C4	O5	C5	115.4(2)	C9	C10	C11	119.6(2)
C3	N	S2	124.51(17)	C10	C11	C12	119.9(2)
S1	C2	S2	115.66(13)	C11	C12	C7	120.8(2)

Table C6. Hydrogen Bonds for 127h.

D	**H**	**A**	**d(D-H)/Å**	**d(H-A)/Å**	**d(D-A)/Å**	**D-H-A/°**
N	H	O4[1]	0.827(19)	2.45(2)	3.134(3)	141(2)
C2	H2A	O2[2]	0.99	2.25	3.020(3)	133.4

[1]1+X,+Y,+Z; [2]-1+X,+Y,+Z

Table C7. Torsion Angles for 127h.

A	**B**	**C**	**D**	**Angle/°**	**A**	**B**	**C**	**D**	**Angle/°**
S2	N	C3	C4	-103.6(2)	C3	C6	C7	C12	-92.7(3)
S2	N	C3	C6	135.12(18)	C4	C3	C6	C7	64.3(3)
O1	S1	C2	S2	-167.43(11)	C5	O5	C4	O6	3.8(3)
O2	S1	C2	S2	-40.63(15)	C5	O5	C4	C3	-173.96(19)
O3	S2	N	C3	-176.01(17)	C6	C3	C4	O5	-143.55(19)

Table C7. Torsion Angles for 127h.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O3	S2	C2	S1	-51.88(16)	C6	C3	C4	O6	38.7(3)
O4	S2	N	C3	-46.1(2)	C6	C7	C8	C9	178.5(2)
O4	S2	C2	S1	178.54(12)	C6	C7	C12	C11	-178.0(2)
N	S2	C2	S1	62.76(15)	C7	C8	C9	C10	-0.3(4)
N	C3	C4	O5	97.8(2)	C8	C7	C12	C11	0.8(3)
N	C3	C4	O6	-79.9(3)	C8	C9	C10	C11	0.6(4)
N	C3	C6	C7	-176.9(2)	C9	C10	C11	C12	-0.2(4)
C1	S1	C2	S2	76.75(15)	C10	C11	C12	C7	-0.5(4)
C2	S2	N	C3	67.3(2)	C12	C7	C8	C9	-0.4(3)
C3	C6	C7	C8	88.4(3)					

Table C8. Hydrogen Atom Coordinates (Å×104) and Isotropic Displacement Parameters (Å2×103) for 127h.

Atom	x	y	z	U(eq)
H	4940(40)	6200(30)	6575(7)	16(7)
H1A	4100(60)	4270(30)	7842(8)	25(8)
H1B	1190(60)	4510(40)	7801(8)	28(8)
H1C	3140(50)	5810(30)	7673(7)	19(7)
H2A	-928.19	4659.67	7118.44	16
H2B	128.09	3714.4	6741.54	16
H3	1803.12	5100.44	5996.57	15
H5A	2730.75	25.58	6364.79	42
H5B	5109.55	379.88	6102.88	42
H5C	5071.28	901.91	6557.77	42
H5D	5876.97	846	6318.83	42
H5E	3498.17	491.7	6580.75	42
H5F	3536.44	-30.33	6125.86	42
H6A	4090.06	7423.97	5749.71	19
H6B	6582.55	6456.94	5839.39	19
H8	1576.18	6597.84	5187.2	22
H9	1487.28	5512.05	4550.71	26
H10	4676.96	3836.58	4325.84	25
H11	7940.34	3211.05	4744.65	23
H12	8003.34	4273.84	5385.51	20

Table C9. Atomic Occupancy for 127h.

Atom	Occupancy	Atom	Occupancy	Atom	Occupancy
H5A	0.77	H5B	0.77	H5C	0.77
H5D	0.23	H5E	0.23	H5F	0.23

D. tert-Butyl 4-methanesulfonylmethanesulfonylpiperazine-1-carboxylate, 127p

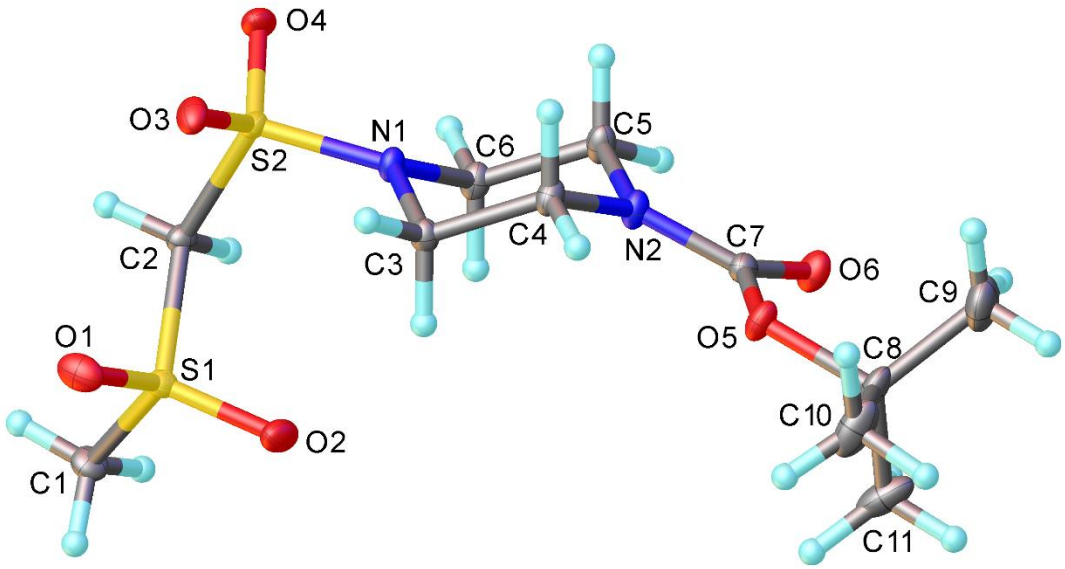

Table D1. Crystal data and structure refinement for 127p.

Identification code	20srv212
Empirical formula	C11H22N2O6S2
Formula weight	342.42
Temperature/K	120
Crystal system	triclinic
Space group	P-1
a/Å	7.9583(2)
b/Å	9.2776(2)
c/Å	11.6097(3)
α/°	68.980(1)
β/°	77.068(1)
γ/°	83.212(1)
Volume/Å3	779.17(5)
Z	2
ρcalcg/cm3	1.460
μ/mm-1	0.369
F(000)	364.0
Crystal size/mm3	0.303 × 0.301 × 0.204
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.708 to 63.98
Index ranges	-11 ≤ h ≤ 11, -13 ≤ k ≤ 13, -17 ≤ l ≤ 17
Reflections collected	16241
Independent reflections	5382 [Rint = 0.0466, Rsigma = 0.0582]
Data/restraints/parameters	5382/0/279
Goodness-of-fit on F2	1.030
Final R indexes [I>=2σ (I)]	R1 = 0.0400, wR2 = 0.0882
Final R indexes [all data]	R1 = 0.0611, wR2 = 0.0978
Largest diff. peak/hole / e Å-3	0.41/-0.51

Table D2. Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å2×103) for 127p. Ueq is defined as 1/3 of of the trace of the orthogonalised UIJ tensor.

Atom	x	y	z	U(eq)
S2	4434.5(5)	7519.3(4)	1042.6(3)	12.45(9)
S1	8188.5(5)	6341.0(4)	774.9(3)	12.84(9)
O4	3538.5(14)	8870.5(12)	1243.6(11)	19.4(2)
O6	2018.7(15)	2566.5(12)	6526.7(10)	18.9(2)
O3	4334.2(14)	7164.7(13)	-36.9(10)	17.6(2)
O5	2218.3(15)	1099.1(12)	5291.3(10)	16.8(2)
O1	8261.2(14)	6230.5(14)	-438.3(11)	21.1(2)
O2	7844.1(14)	4978.0(12)	1870.3(11)	22.7(3)
N1	3770.3(16)	6057.5(13)	2275.9(11)	12.7(2)
N2	2305.4(17)	3670.3(14)	4405.9(11)	15.0(2)
C3	3917.9(19)	4470.5(17)	2242.3(14)	13.5(3)
C7	2167.9(18)	2441.2(16)	5496.7(13)	13.3(3)
C2	6637.1(18)	7824.6(16)	984.4(14)	12.8(3)
C4	2388(2)	3593.7(17)	3155.2(13)	14.4(3)
C1	10107(2)	7112.3(19)	765.7(16)	17.1(3)
C6	3749(2)	6122.0(17)	3524.5(14)	15.2(3)
C5	2227(2)	5228.9(17)	4440.6(15)	16.7(3)
C8	2058(2)	-390.6(17)	6360.4(14)	19.9(3)
C10	2145(3)	-1548(2)	5699.5(18)	30.5(4)
C11	3563(3)	-672(2)	7021(2)	30.7(4)
C9	324(3)	-426(2)	7233.7(19)	32.6(4)

Table D3. Anisotropic Displacement Parameters (Å2×103) for 127p. The Anisotropic displacement factor exponent takes the form: -2π2[h2a*2U11+2hka*b*U12+…].

Atom	U11	U22	U33	U23	U13	U12
S2	11.13(16)	11.29(16)	12.04(17)	-0.60(12)	-2.51(12)	0.07(12)
S1	10.74(16)	11.93(17)	15.45(18)	-4.13(13)	-2.74(13)	-0.36(12)
O4	16.7(5)	12.5(5)	21.9(6)	-0.9(4)	-0.4(4)	3.5(4)
O6	27.6(6)	16.7(5)	11.6(5)	-4.3(4)	-3.6(4)	-0.1(4)
O3	16.2(5)	23.1(6)	12.0(5)	-2.3(4)	-4.9(4)	-3.5(4)
O5	26.9(6)	10.1(5)	11.8(5)	-1.4(4)	-4.5(4)	-1.5(4)
O1	18.7(5)	28.6(6)	23.0(6)	-17.3(5)	-5.7(5)	2.4(5)
O2	17.1(5)	13.6(5)	28.9(6)	1.4(5)	-2.6(5)	0.2(4)
N1	16.3(6)	9.8(5)	10.8(5)	-2.5(4)	-0.5(5)	-3.0(4)
N2	21.2(6)	11.4(5)	10.9(6)	-2.8(4)	-0.7(5)	-3.4(5)
C3	15.3(7)	12.8(6)	12.3(6)	-5.0(5)	-0.5(5)	-1.9(5)
C7	12.5(6)	12.5(6)	13.2(6)	-3.0(5)	-1.6(5)	-0.4(5)
C2	12.8(6)	10.5(6)	14.9(7)	-3.6(5)	-3.4(5)	-0.7(5)
C4	18.7(7)	12.6(6)	11.5(6)	-2.5(5)	-3.2(5)	-4.3(5)
C1	12.4(7)	20.4(8)	20.3(8)	-7.7(6)	-4.4(6)	-2.6(6)
C6	20.2(7)	13.1(7)	12.5(6)	-4.8(5)	-1.7(6)	-3.2(6)
C5	22.7(8)	11.6(6)	13.7(7)	-4.5(5)	1.3(6)	-1.9(6)
C8	33.5(9)	9.9(6)	13.3(7)	0.1(5)	-5.6(6)	-1.2(6)
C10	56.7(13)	14.0(8)	21.8(9)	-4.0(7)	-11.7(9)	-5.0(8)
C11	48.0(12)	19.2(9)	30.2(10)	-9.5(8)	-23.6(9)	11.9(8)
C9	41.2(12)	23.4(9)	22.5(9)	1.9(7)	2.7(8)	-8.6(8)

Table D4. Bond Lengths for 127p.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S2	O4	1.4347(11)	N1	C3	1.4769(18)
S2	O3	1.4255(11)	N1	C6	1.4684(18)
S2	N1	1.6145(12)	N2	C7	1.3592(18)
S2	C2	1.7911(15)	N2	C4	1.4657(18)
S1	O1	1.4364(11)	N2	C5	1.4545(18)
S1	O2	1.4365(11)	C3	C4	1.518(2)
S1	C2	1.7838(15)	C6	C5	1.521(2)
S1	C1	1.7573(15)	C8	C10	1.516(2)
O6	C7	1.2209(17)	C8	C11	1.511(3)
O5	C7	1.3437(17)	C8	C9	1.515(3)
O5	C8	1.4857(17)			

Table D5. Bond Angles for 127p.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O4	S2	N1	107.04(6)	C7	N2	C5	119.70(12)
O4	S2	C2	103.03(7)	C5	N2	C4	114.59(12)
O3	S2	O4	120.15(7)	N1	C3	C4	108.30(12)
O3	S2	N1	107.95(6)	O6	C7	O5	125.11(13)
O3	S2	C2	108.95(7)	O6	C7	N2	123.26(13)
N1	S2	C2	109.35(7)	O5	C7	N2	111.63(12)
O1	S1	O2	118.60(7)	S1	C2	S2	116.82(8)
O1	S1	C2	109.20(7)	N2	C4	C3	109.68(12)
O1	S1	C1	109.10(7)	N1	C6	C5	108.29(12)
O2	S1	C2	108.23(7)	N2	C5	C6	110.28(12)
O2	S1	C1	109.00(8)	O5	C8	C10	102.09(12)
C1	S1	C2	101.32(7)	O5	C8	C11	110.40(14)
C7	O5	C8	120.52(11)	O5	C8	C9	110.18(14)
C3	N1	S2	121.82(10)	C11	C8	C10	110.33(16)
C6	N1	S2	119.04(9)	C11	C8	C9	113.10(16)
C6	N1	C3	113.68(11)	C9	C8	C10	110.19(16)
C7	N2	C4	125.51(12)				

Table D6. Torsion Angles for 127p. Continued..

A	B	C	D	Angle/°	A	B	C	D	Angle/°
S2	N1	C3	C4	-146.85(11)	C7	O5	C8	C9	61.82(18)
S2	N1	C6	C5	146.61(11)	C7	N2	C4	C3	-129.21(15)
O4	S2	N1	C3	158.17(11)	C7	N2	C5	C6	129.11(14)
O4	S2	N1	C6	-49.57(12)	C2	S2	N1	C3	-90.88(12)
O4	S2	C2	S1	178.70(8)	C2	S2	N1	C6	61.38(12)
O3	S2	N1	C3	27.51(13)	C4	N2	C7	O6	-176.32(14)
O3	S2	N1	C6	179.78(11)	C4	N2	C7	O5	3.7(2)
O3	S2	C2	S1	-52.65(10)	C4	N2	C5	C6	-55.77(17)
O1	S1	C2	S2	64.68(10)	C1	S1	C2	S2	179.71(9)
O2	S1	C2	S2	-65.74(10)	C6	N1	C3	C4	59.53(15)
N1	S2	C2	S1	65.12(10)	C5	N2	C7	O6	-1.8(2)
N1	C3	C4	N2	-54.83(15)	C5	N2	C7	O5	178.25(13)
N1	C6	C5	N2	54.40(16)	C5	N2	C4	C3	56.01(16)

Table D6. Torsion Angles for 127p. Continued..

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C3	N1	C6	C5	-58.97(15)	C8	O5	C7	O6	1.1(2)
C7	O5	C8	C10	178.88(15)	C8	O5	C7	N2	-178.94(12)
C7	O5	C8	C11	-63.81(18)					

Table D7. Hydrogen Atom Coordinates (Å×104) and Isotropic Displacement Parameters (Å2×103) for 127p.

Atom	x	y	z	U(eq)
H6A	3600(20)	7200(20)	3475(16)	14(4)
H3A	3930(20)	4520(20)	1413(17)	18(5)
H5A	1150(20)	5760(20)	4207(16)	14(4)
H6B	4860(20)	5660(20)	3814(16)	15(4)
H3B	5030(20)	3970(20)	2496(16)	18(5)
H1A	10050(20)	7210(20)	1555(18)	24(5)
H2A	6870(20)	8730(20)	300(17)	19(5)
H4A	2500(20)	2520(20)	3212(16)	15(4)
H2B	6710(20)	7940(20)	1744(18)	19(5)
H1B	10230(20)	8050(20)	121(19)	24(5)
H9A	240(30)	230(20)	7700(19)	32(6)
H4B	1310(20)	4040(20)	2874(16)	13(4)
H5B	2230(30)	5180(20)	5300(19)	28(5)
H11A	4700(30)	-660(30)	6410(20)	42(6)
H1C	11030(30)	6390(20)	656(18)	30(5)
H9B	170(30)	-1450(30)	7767(19)	32(6)
H10A	2090(30)	-2580(30)	6320(20)	47(7)
H10B	3200(30)	-1490(20)	5100(20)	35(6)
H9C	-620(30)	-130(30)	6830(20)	41(7)
H10C	1150(30)	-1350(30)	5230(20)	44(7)
H11B	3470(30)	-1610(30)	7660(20)	35(6)
H11C	3630(30)	80(30)	7390(20)	51(7)

E. 1-(4-Methanesulfonylmethanesulfonylpiperazin-1-yl)-2-methylprop-2-en-1-one, 154

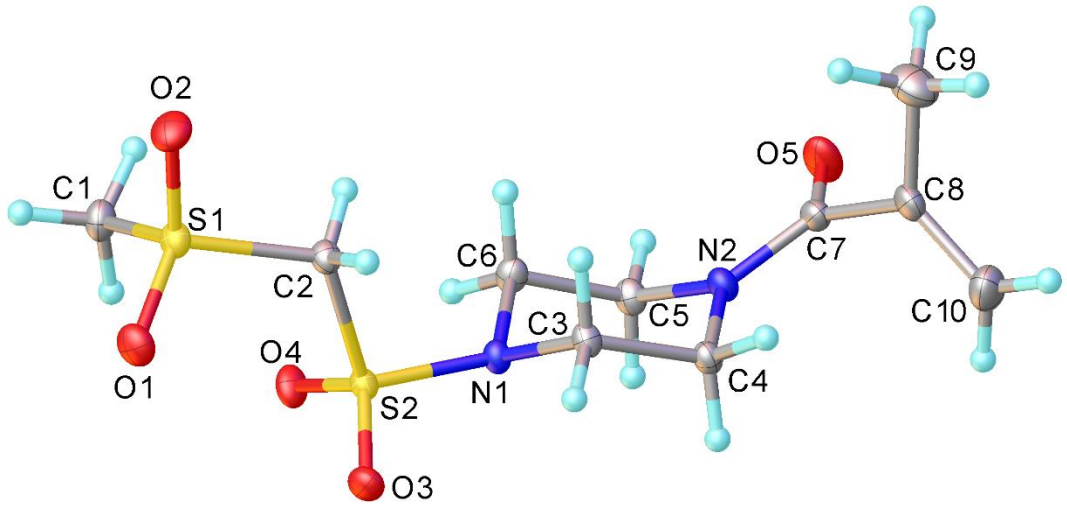

Table E1. Crystal data and structure refinement for 154.

Identification code	20srv176
Empirical formula	C10H18N2O5S2
Formula weight	310.38
Temperature/K	120
Crystal system	monoclinic
Space group	P21/n
a/Å	8.8703(2)
b/Å	8.1647(2)
c/Å	18.9384(5)
α/°	90
β/°	90.2180(10)
γ/°	90
Volume/Å3	1371.57(6)
Z	4
ρcalcg/cm3	1.503
μ/mm-1	0.406
F(000)	656.0
Crystal size/mm3	0.339 × 0.22 × 0.201
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.064 to 72.73
Index ranges	-14 ≤ h ≤ 14, -13 ≤ k ≤ 13, -31 ≤ l ≤ 31
Reflections collected	31729
Independent reflections	6375 [Rint = 0.0293, Rsigma = 0.0241]
Data/restraints/parameters	6375/0/245
Goodness-of-fit on F2	1.048
Final R indexes [I>=2σ (I)]	R1 = 0.0290, wR2 = 0.0727
Final R indexes [all data]	R1 = 0.0358, wR2 = 0.0762
Largest diff. peak/hole / e Å-3	0.45/-0.49

Table E2. Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å2×103) for 154. Ueq is defined as 1/3 of of the trace of the orthogonalised UIJ tensor.

Atom	x	y	z	U(eq)
S1	1786.9(2)	11023.7(2)	6339.6(2)	15.84(5)
S2	3633.7(2)	8126.6(2)	5795.4(2)	13.05(5)
O1	3166.8(8)	11926.1(8)	6437.0(4)	22.13(13)
O2	465.9(8)	11912.8(8)	6109.2(4)	23.56(13)
O3	4994.2(7)	8962.3(8)	5619.2(3)	19.64(12)
O4	3502.5(8)	7374.9(8)	6477.9(3)	18.94(12)
O5	844.3(8)	2364.6(10)	3923.3(4)	28.44(16)
N1	3336.3(7)	6699.9(8)	5209.4(3)	13.38(11)
N2	2501.0(8)	4390.0(8)	4177.9(4)	15.18(12)
C1	1344.1(10)	9934.9(11)	7112.1(4)	19.89(15)
C2	2072.3(9)	9491.8(9)	5676.7(4)	14.90(13)
C3	3279.0(9)	7207.0(9)	4458.8(4)	14.46(13)
C4	3540.2(9)	5710.8(10)	3992.4(4)	15.00(13)
C5	2501.9(9)	3951.4(9)	4924.9(4)	16.10(13)
C6	2192.2(9)	5444.8(10)	5377.1(4)	16.13(13)
C7	1657.0(9)	3504.9(11)	3722.8(4)	17.47(14)
C8	1659.1(10)	3952.8(11)	2956.9(5)	19.77(15)
C9	223.1(13)	4703.0(15)	2701.0(6)	31.6(2)
C10	2825.8(13)	3571.6(16)	2551.3(6)	30.7(2)

Table E3. Anisotropic Displacement Parameters (Å2×103) for 154. The Anisotropic displacement factor exponent takes the form: -2π2[h2a*2U11+2hka*b*U12+...].

Atom	U11	U22	U33	U23	U13	U12
S1	19.45(9)	11.76(8)	16.29(9)	-1.60(6)	-0.55(6)	0.84(6)
S2	15.27(8)	11.63(8)	12.22(8)	-0.68(5)	-2.05(6)	-0.01(6)
O1	25.6(3)	16.4(3)	24.4(3)	-2.8(2)	-1.8(2)	-5.5(2)
O2	25.0(3)	19.7(3)	26.0(3)	-0.2(2)	-0.8(2)	8.2(2)
O3	16.4(2)	19.6(3)	22.9(3)	-4.3(2)	-0.8(2)	-4.5(2)
O4	27.8(3)	16.9(3)	12.1(2)	1.1(2)	-3.0(2)	3.0(2)
O5	27.4(3)	31.7(4)	26.2(3)	-6.8(3)	2.6(3)	-17.5(3)
N1	16.6(3)	11.4(2)	12.2(2)	-0.9(2)	0.0(2)	-1.8(2)
N2	16.6(3)	14.1(3)	14.9(3)	-1.4(2)	-1.8(2)	-3.2(2)
C1	25.0(4)	19.6(4)	15.1(3)	-2.3(3)	1.9(3)	-0.9(3)
C2	17.4(3)	13.2(3)	14.2(3)	-0.8(2)	-1.9(2)	1.1(2)
C3	18.2(3)	12.6(3)	12.5(3)	0.3(2)	-1.5(2)	-1.4(2)
C4	16.2(3)	15.4(3)	13.4(3)	-1.7(2)	-0.3(2)	-2.9(2)
C5	20.0(3)	12.4(3)	15.9(3)	-0.1(2)	-0.4(2)	-2.2(2)
C6	18.1(3)	13.7(3)	16.6(3)	-0.8(2)	2.7(2)	-2.9(2)
C7	14.3(3)	19.2(3)	18.9(3)	-6.0(3)	-0.2(2)	-2.2(3)
C8	19.5(3)	21.3(4)	18.5(3)	-6.4(3)	-3.4(3)	-3.5(3)
C9	29.1(5)	31.3(5)	34.4(5)	1.0(4)	-10.6(4)	2.1(4)
C10	29.4(5)	40.7(6)	22.0(4)	-8.4(4)	4.8(4)	-2.7(4)

Table E4. Bond Lengths for 154.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O1	1.4399(7)	N1	C6	1.4776(10)
S1	O2	1.4445(7)	N2	C4	1.4624(10)
S1	C1	1.7576(9)	N2	C5	1.4592(10)
S1	C2	1.7907(8)	N2	C7	1.3493(10)
S2	O3	1.4270(6)	C3	C4	1.5257(11)
S2	O4	1.4358(6)	C5	C6	1.5158(11)
S2	N1	1.6297(7)	C7	C8	1.4959(12)
S2	C2	1.7914(8)	C8	C9	1.4925(14)
O5	C7	1.2380(11)	C8	C10	1.3282(13)
N1	C3	1.4813(10)			

Table E5. Bond Angles for 154.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	S1	O2	118.02(4)	C5	N2	C4	114.58(6)
O1	S1	C1	110.16(4)	C7	N2	C4	126.16(7)
O1	S1	C2	108.96(4)	C7	N2	C5	119.09(7)
O2	S1	C1	108.78(4)	S1	C2	S2	117.25(4)
O2	S1	C2	104.83(4)	N1	C3	C4	109.09(6)
C1	S1	C2	105.24(4)	N2	C4	C3	110.74(6)
O3	S2	O4	119.10(4)	N2	C5	C6	110.55(7)
O3	S2	N1	108.50(4)	N1	C6	C5	108.08(6)
O3	S2	C2	109.10(4)	O5	C7	N2	121.95(8)
O4	S2	N1	107.10(4)	O5	C7	C8	118.95(7)
O4	S2	C2	108.28(4)	N2	C7	C8	119.07(7)
N1	S2	C2	103.66(4)	C9	C8	C7	114.27(8)
C3	N1	S2	117.30(5)	C10	C8	C7	120.49(9)
C6	N1	S2	117.31(5)	C10	C8	C9	125.05(10)
C6	N1	C3	112.27(6)				

Table E6. Torsion Angles for 154.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
S2	N1	C3	C4	160.59(5)	N2	C7	C8	C9	-108.94(9)
S2	N1	C6	C5	-158.93(5)	N2	C7	C8	C10	75.93(12)
O1	S1	C2	S2	53.26(6)	C1	S1	C2	S2	-64.86(6)
O2	S1	C2	S2	-179.53(5)	C2	S2	N1	C3	60.41(6)
O3	S2	N1	C3	-55.47(7)	C2	S2	N1	C6	-77.89(6)
O3	S2	N1	C6	166.23(6)	C3	N1	C6	C5	60.78(8)
O3	S2	C2	S1	-76.37(5)	C4	N2	C5	C6	55.07(9)
O4	S2	N1	C3	174.77(6)	C4	N2	C7	O5	177.33(8)
O4	S2	N1	C6	36.47(7)	C4	N2	C7	C8	-4.95(12)
O4	S2	C2	S1	54.66(6)	C5	N2	C4	C3	-52.94(9)
O5	C7	C8	C9	68.84(11)	C5	N2	C7	O5	2.41(13)
O5	C7	C8	C10	-106.29(11)	C5	N2	C7	C8	-179.87(7)
N1	S2	C2	S1	168.18(4)	C6	N1	C3	C4	-59.11(8)
N1	C3	C4	N2	52.89(8)	C7	N2	C4	C3	131.94(8)
N2	C5	C6	N1	-56.63(8)	C7	N2	C5	C6	-129.44(8)

Table E7. Hydrogen Atom Coordinates (Å×104) and Isotropic Displacement Parameters (Å2×103) for 154.

Atom	x	y	z	U(eq)
H1A	417(16)	9300(19)	7005(8)	32(4)
H1B	2210(16)	9238(18)	7236(7)	28(3)
H1C	1212(17)	10780(20)	7459(8)	37(4)
H2A	1183(14)	8885(16)	5665(7)	21(3)
H2B	2241(15)	10087(18)	5256(7)	31(4)
H3A	4098(14)	8007(16)	4377(7)	19(3)
H3B	2282(14)	7679(16)	4357(6)	18(3)
H4A	3389(14)	6052(17)	3501(7)	23(3)
H4B	4560(13)	5323(16)	4052(6)	17(3)
H5A	3481(13)	3505(16)	5052(7)	18(3)
H5B	1739(14)	3150(16)	5012(7)	22(3)
H6A	1161(14)	5913(16)	5275(7)	22(3)
H6B	2299(14)	5161(16)	5865(7)	21(3)
H9A	-700(20)	3940(20)	2798(9)	53(5)
H9B	314(17)	4920(20)	2218(8)	37(4)
H9C	28(18)	5760(20)	2949(8)	41(4)
H10A	2833(17)	3820(20)	2062(9)	39(4)
H10B	3689(19)	3060(20)	2731(9)	51(5)

F. 3-(Diethylsulfamoyl)-1,3-dimethanesulfonylpropyl]-N-ethylethanesulfonamido, 178

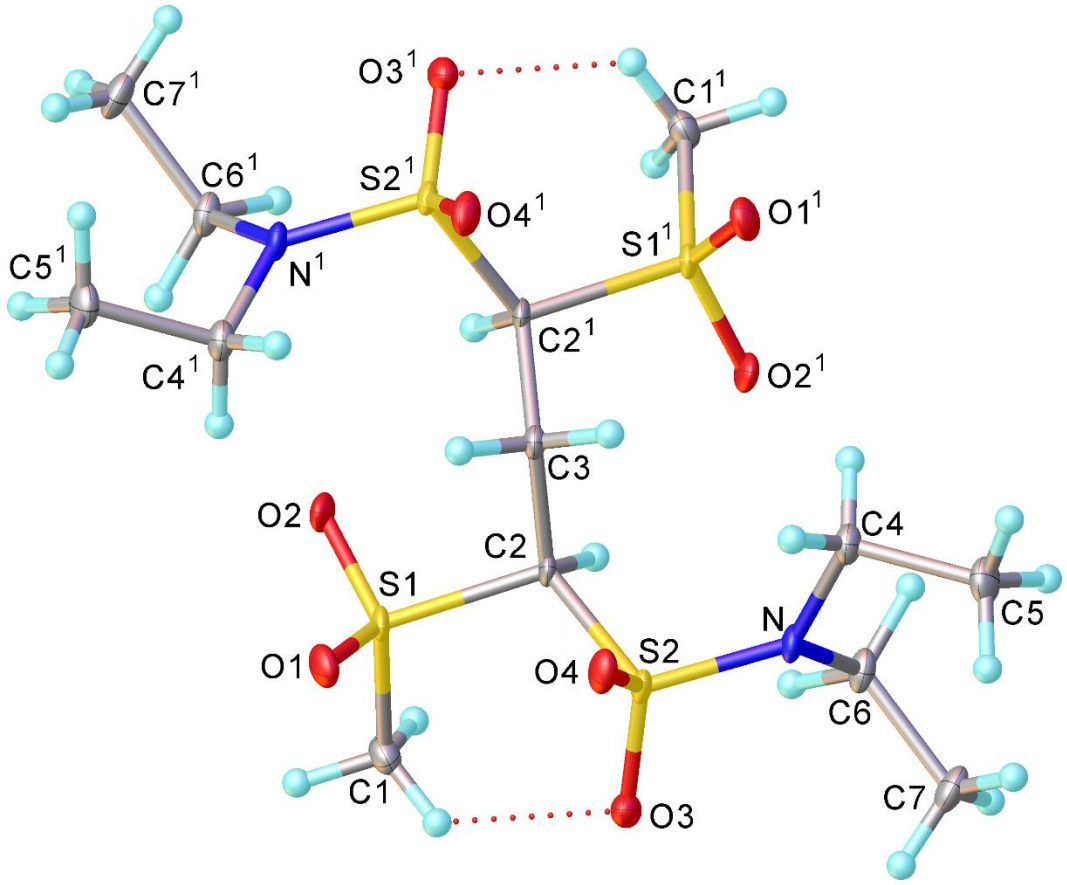

Table F1. Crystal data and structure refinement for 178.

Identification code	20srv137
Empirical formula	C13H30N2O8S4
Formula weight	470.63
Temperature/K	120
Crystal system	monoclinic
Space group	C2/c
a/Å	20.068(7)
b/Å	5.809(2)
c/Å	18.896(6)
α/°	90
β/°	111.155(11)
γ/°	90
Volume/Å3	2054.5(12)
Z	4
ρcalcg/cm3	1.522
μ/mm-1	0.505
F(000)	1000.0
Crystal size/mm3	0.242 × 0.16 × 0.046
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.352 to 59.99
Index ranges	-28 ≤ h ≤ 28, -8 ≤ k ≤ 8, -26 ≤ l ≤ 26

Reflections collected	13893
Independent reflections	2964 [Rint = 0.0572, Rsigma = 0.0519]
Data/restraints/parameters	2964/0/184
Goodness-of-fit on F2	1.058
Final R indexes [I>=2σ (I)]	R1 = 0.0431, wR2 = 0.1003
Final R indexes [all data]	R1 = 0.0607, wR2 = 0.1062
Largest diff. peak/hole / e Å-3	0.71/-0.63

Table F2. Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å2×103) for 178. Ueq is defined as 1/3 of of the trace of the orthogonalised UIJ tensor.

Atom	x	y	z	U(eq)
S1	4573.2(2)	4414.7(9)	3549.0(3)	13.72(13)
S2	6027.0(2)	6705.4(9)	3916.1(3)	13.30(13)
O1	4368.1(7)	6556(2)	3794.8(8)	18.9(3)
O2	4057.9(7)	3272(3)	2905.2(8)	19.6(3)
O3	6191.8(7)	5580(3)	4632.7(7)	18.9(3)
O4	5799.1(7)	9059(3)	3826.3(8)	17.9(3)
N	6707.6(8)	6508(3)	3665.4(9)	13.7(3)
C1	4854.0(11)	2482(4)	4312.6(12)	17.8(4)
C2	5316.3(9)	5030(4)	3239.1(10)	12.5(4)
C3	5000	6418(5)	2500	13.3(5)
C4	6796.8(10)	8074(4)	3089.8(11)	16.1(4)
C5	7567.1(11)	8859(4)	3302.4(13)	20.4(4)
C6	7118.1(10)	4329(4)	3822.5(11)	16.2(4)
C7	7805.8(11)	4511(4)	4511.6(13)	21.1(5)

Table F3. Anisotropic Displacement Parameters (Å2×103) for 178. The Anisotropic displacement factor exponent takes the form: -2π2[h2a*2U11+2hka*b*U12+…].

Atom	U11	U22	U33	U23	U13	U12
S1	5.6(2)	22.5(3)	14.6(2)	0.87(18)	5.56(17)	0.91(17)
S2	5.3(2)	21.1(3)	13.7(2)	-2.62(17)	3.70(16)	-0.35(17)
O1	13.9(7)	24.8(8)	21.7(7)	1.8(6)	10.8(6)	5.5(6)
O2	7.3(6)	33.6(9)	18.0(7)	-0.3(6)	4.7(5)	-5.2(6)
O3	11.1(6)	32.2(9)	13.7(6)	-0.5(6)	4.9(5)	-2.7(6)
O4	10.3(6)	21.3(8)	22.7(7)	-4.2(6)	6.6(6)	2.3(5)
N	5.9(6)	18.3(9)	17.2(8)	0.7(6)	4.6(6)	0.5(6)
C1	15.1(9)	23.9(12)	17.4(9)	2.8(8)	9.6(8)	2.2(8)
C2	4.9(7)	20.3(10)	12.9(8)	-1.3(7)	4.2(7)	0.2(7)
C3	6.6(11)	20.6(15)	13.5(12)	0	4.6(10)	0
C4	9.2(8)	20.4(11)	19.3(9)	-0.1(8)	6.0(7)	-0.9(7)
C5	12.9(9)	24.5(12)	26.2(11)	0.2(9)	9.7(8)	-4.1(8)
C6	8.4(8)	17.1(11)	23.0(10)	-0.6(8)	5.4(7)	1.2(7)
C7	8.5(9)	25.0(13)	25.2(11)	1.7(9)	0.6(8)	0.3(8)

Table F4. Bond Lengths for 178.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O1	1.4390(15)	S2	C2	1.8169(19)
S1	O2	1.4431(14)	N	C4	1.477(3)
S1	C1	1.753(2)	N	C6	1.481(3)
S1	C2	1.8235(19)	C2	C3	1.538(2)
S2	O3	1.4307(14)	C4	C5	1.520(3)
S2	O4	1.4320(16)	C6	C7	1.521(3)
S2	N	1.6031(16)			

Table F5. Bond Angles for 178.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	S1	O2	117.94(9)	N	S2	C2	106.84(9)
O1	S1	C1	109.43(10)	C4	N	S2	121.07(13)
O1	S1	C2	107.25(9)	C4	N	C6	117.87(16)
O2	S1	C1	108.59(10)	C6	N	S2	118.26(14)
O2	S1	C2	103.87(9)	S2	C2	S1	113.83(10)
C1	S1	C2	109.42(10)	C3	C2	S1	106.09(10)
O3	S2	O4	120.21(9)	C3	C2	S2	108.69(14)
O3	S2	N	108.45(8)	C2	C3	C2[1]	116.7(2)
O3	S2	C2	106.03(9)	N	C4	C5	111.84(16)
O4	S2	N	107.63(9)	N	C6	C7	112.29(17)
O4	S2	C2	106.98(9)				

[1]1-X,+Y,1/2-Z

Table F6. Torsion Angles for 178.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
S1	C2	C3	C2[1]	-86.45(10)	O4	S2	N	C4	-29.17(16)
S2	N	C4	C5	139.21(16)	O4	S2	N	C6	170.21(13)
S2	N	C6	C7	-101.98(18)	O4	S2	C2	S1	-79.72(12)
S2	C2	C3	C2[1]	150.76(12)	O4	S2	C2	C3	38.27(13)
O1	S1	C2	S2	49.54(13)	N	S2	C2	S1	165.24(10)
O1	S1	C2	C3	-69.93(15)	N	S2	C2	C3	-76.78(13)
O2	S1	C2	S2	175.12(10)	C1	S1	C2	S2	-69.07(14)
O2	S1	C2	C3	55.66(16)	C1	S1	C2	C3	171.46(15)
O3	S2	N	C4	-160.66(14)	C2	S2	N	C4	85.44(16)
O3	S2	N	C6	38.71(16)	C2	S2	N	C6	-75.18(15)
O3	S2	C2	S1	49.71(13)	C4	N	C6	C7	96.8(2)
O3	S2	C2	C3	167.69(11)	C6	N	C4	C5	-60.1(2)

[1]1-X,+Y,1/2-Z

Table F7. Hydrogen Atom Coordinates (Å×104) and Isotropic Displacement Parameters (Å2×103) for 178.

Atom	x	y	z	U(eq)
H1A	5252(13)	3070(40)	4703(14)	26(7)

Table F7. Hydrogen Atom Coordinates (Å×104) and Isotropic Displacement Parameters (Å2×103) for 178.

Atom	x	y	z	U(eq)
H1B	4936(15)	1160(50)	4114(16)	44(9)
H1C	4460(13)	2370(40)	4473(13)	22(6)
H2	5533(11)	3590(40)	3165(11)	14(6)
H3	4633(11)	7440(40)	2549(11)	12(5)
H4A	6503(11)	9370(40)	3062(11)	8(5)
H4B	6642(13)	7300(40)	2605(14)	23(6)
H5A	7571(14)	10050(50)	2949(14)	32(7)
H5B	7880(12)	7600(40)	3291(12)	17(6)
H5C	7753(13)	9620(40)	3813(14)	31(7)
H6A	7200(12)	3960(40)	3339(12)	15(5)
H6B	6786(12)	3130(40)	3902(12)	16(6)
H7A	8098(13)	5670(40)	4440(12)	19(6)
H7B	8027(14)	3050(50)	4578(14)	30(7)
H7C	7701(13)	4860(40)	4951(14)	26(6)

G. 1-(4-{1,3-Dimethanesulfonyl-3-[4-(2-methylprop-2-enoyl)piperazin-1-ylsulfonyl]propanesulfonyl}piperazin-1-yl)-2-methylprop-2-en-1-one, 181

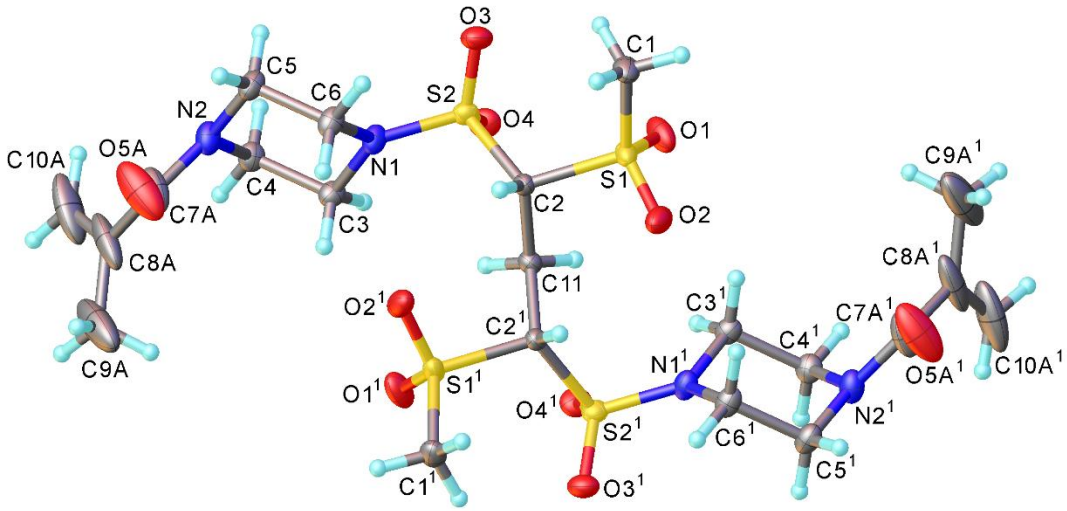

Table G1. Crystal data and structure refinement for 181.

Identification code	20srv211
Empirical formula	C21H36N4O10S4
Formula weight	632.78
Temperature/K	120
Crystal system	monoclinic
Space group	C2/c
a/Å	20.2163(4)
b/Å	5.72920(10)
c/Å	25.6503(5)
α/°	90
β/°	106.3480(10)
γ/°	90
Volume/Å3	2850.79(9)
Z	4
ρcalcg/cm3	1.474
μ/mm-1	0.392
F(000)	1336.0
Crystal size/mm3	0.12 × 0.094 × 0.073
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.2 to 64.06
Index ranges	-29 ≤ h ≤ 30, -8 ≤ k ≤ 8, -38 ≤ l ≤ 38
Reflections collected	28746
Independent reflections	4964 [Rint = 0.0463, Rsigma = 0.0355]
Data/restraints/parameters	4964/71/237
Goodness-of-fit on F2	1.040
Final R indexes [I>=2σ (I)]	R1 = 0.0399, wR2 = 0.0940
Final R indexes [all data]	R1 = 0.0553, wR2 = 0.1011
Largest diff. peak/hole / e Å-3	0.40/-0.32

Table G2. Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å2×103) for 181. Ueq is defined as 1/3 of of the trace of the orthogonalised UIJ tensor.

Atom	x	y	z	U(eq)
S1	4284.5(2)	4495.3(7)	1565.4(2)	22.12(9)
S2	3617.0(2)	2313.0(6)	2380.1(2)	19.86(8)
O1	4188.2(7)	2282(2)	1292.4(5)	35.0(3)
O2	4907.2(6)	5781(2)	1594.1(5)	31.9(3)
O3	3007.8(5)	3456(2)	2058.3(4)	27.4(2)
O4	3733.0(6)	-113.9(19)	2297.6(5)	26.5(2)
N1	3654.8(7)	2652(2)	3006.6(5)	21.3(2)
N2	3310.7(7)	2624(2)	3986.7(5)	25.6(3)
C1	3577.8(8)	6311(3)	1278.5(6)	27.1(3)
C2	4337.1(7)	3931(2)	2273.3(5)	17.1(2)
C3	4025.5(7)	1060(2)	3442.6(6)	21.0(3)
C4	3551.3(8)	480(2)	3793.9(6)	22.5(3)
C5	2956.0(8)	4192(3)	3551.3(6)	24.8(3)
C6	3423.1(8)	4835(2)	3202.7(6)	22.9(3)
C11	5000	2508(3)	2500	18.2(3)
O5A	3624(2)	5648(5)	4567.4(11)	68.9(14)
C7A	3644(3)	3549(6)	4481.3(14)	40.7(9)
C8A	3977(4)	1935(9)	4937.3(17)	62.8(17)
C9A	4669(3)	2684(13)	5272.7(17)	90(2)
C10A	3624(4)	157(9)	5049.6(18)	81(2)
O5B	2968(5)	4816(10)	4601(2)	103(3)
C7B	3267(4)	3122(10)	4501(2)	49.0(16)
C8B	3567(4)	1383(12)	4936(2)	43.1(13)
C9B	3046(4)	-57(9)	5095(2)	49.4(15)
C10B	4232(4)	1261(15)	5174(3)	55.6(17)

Table G3. Anisotropic Displacement Parameters (Å2×103) for 181. The Anisotropic displacement factor exponent takes the form: -2π2[h2a*2U11+2hka*b*U12+...].

Atom	U11	U22	U33	U23	U13	U12
S1	20.99(17)	30.73(19)	14.87(15)	1.61(13)	5.44(12)	7.63(13)
S2	16.36(15)	20.93(16)	21.64(16)	-1.52(12)	4.27(12)	-2.74(12)
O1	44.2(7)	38.8(7)	19.6(5)	-7.2(5)	5.1(5)	13.7(5)
O2	22.3(5)	49.2(7)	25.9(5)	13.8(5)	9.6(4)	4.7(5)
O3	17.5(5)	33.6(6)	28.2(5)	2.6(5)	1.8(4)	-0.9(4)
O4	26.8(5)	20.9(5)	30.7(6)	-7.0(4)	6.1(5)	-5.1(4)
N1	25.9(6)	17.8(5)	23.4(6)	3.8(4)	11.9(5)	3.2(4)
N2	34.6(7)	21.5(6)	24.2(6)	3.0(5)	13.8(5)	3.8(5)
C1	24.0(7)	35.5(8)	20.8(6)	6.0(6)	4.8(6)	9.6(6)
C2	15.7(6)	20.7(6)	14.7(5)	-1.4(5)	3.8(5)	-0.1(5)
C3	20.9(6)	18.3(6)	24.5(6)	2.9(5)	7.6(5)	1.8(5)
C4	27.0(7)	17.1(6)	24.5(7)	2.4(5)	9.2(6)	-0.2(5)
C5	25.3(7)	23.3(7)	29.4(7)	5.1(6)	13.9(6)	3.9(5)
C6	26.3(7)	17.1(6)	28.8(7)	3.8(5)	13.6(6)	3.5(5)
C11	18.0(8)	19.4(9)	16.2(8)	0	3.1(7)	0
O5A	126(3)	31.5(13)	35.5(14)	-7.2(10)	0.4(17)	23.7(16)
C7A	70(3)	29.4(16)	25.1(14)	2.1(11)	16.8(17)	15.7(17)
C8A	109(5)	61(3)	17.5(16)	4.8(17)	17(2)	48(3)
C9A	105(4)	125(5)	29.1(19)	-15(3)	1(2)	68(4)

Table G3. Anisotropic Displacement Parameters (Å2×103) for 181. The Anisotropic displacement factor exponent takes the form: -2π2[h2a*2U11+2hka*b*U12+...].

Atom	U11	U22	U33	U23	U13	U12
C10A	165(8)	54(3)	30.4(19)	17.5(19)	37(3)	42(3)
O5B	204(8)	68(3)	60(3)	20(2)	78(4)	78(5)
C7B	87(5)	38(3)	32(2)	1(2)	32(3)	19(3)
C8B	66(4)	45(3)	21(2)	1(2)	18(2)	16(3)
C9B	69(4)	37(3)	34(2)	1(2)	2(3)	-3(2)
C10B	70(4)	72(5)	32(3)	-4(3)	26(3)	13(4)

Table G4. Bond Lengths for 181.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O1	1.4353(13)	O5A	C7B	1.605(8)
S1	O2	1.4424(12)	C7A	C8A	1.494(5)
S1	C1	1.7530(15)	C7A	O5B	1.652(7)
S1	C2	1.8176(13)	C7A	C7B	0.816(7)
S2	O3	1.4335(11)	C7A	C8B	1.740(8)
S2	O4	1.4356(11)	C8A	C9A	1.484(8)
S2	N1	1.5989(13)	C8A	C10A	1.322(8)
S2	C2	1.8106(14)	C8A	C7B	1.694(9)
N1	C3	1.4737(18)	C8A	C8B	0.886(8)
N1	C6	1.4730(18)	C8A	C10B	0.779(7)
N2	C4	1.4579(19)	C9A	C10B	1.177(10)
N2	C5	1.4551(19)	C10A	C8B	0.757(7)
N2	C7A	1.365(4)	C10A	C9B	1.214(9)
N2	C7B	1.377(5)	C10A	C10B	1.338(10)
C2	C11	1.5364(17)	O5B	C7B	1.209(6)
C3	C4	1.526(2)	C7B	C8B	1.491(8)
C5	C6	1.517(2)	C8B	C9B	1.483(9)
O5A	C7A	1.225(4)	C8B	C10B	1.312(9)
O5A	O5B	1.435(8)			

Table G5. Bond Angles for 181. Continued...

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	S1	O2	118.20(8)	C8B	C8A	C10A	33.3(5)
O1	S1	C1	109.68(8)	C8B	C8A	C7B	61.5(6)
O1	S1	C2	106.98(7)	C10B	C8A	C7A	166.0(11)
O2	S1	C1	108.36(8)	C10B	C8A	C9A	52.0(8)
O2	S1	C2	103.60(6)	C10B	C8A	C10A	74.1(8)
C1	S1	C2	109.67(7)	C10B	C8A	C7B	164.7(9)
O3	S2	O4	120.46(7)	C10B	C8A	C8B	103.7(9)
O3	S2	N1	108.28(7)	C10B	C9A	C8A	31.4(4)
O3	S2	C2	106.03(6)	C8A	C10A	C10B	34.1(4)
O4	S2	N1	107.58(7)	C8B	C10A	C8A	40.0(6)
O4	S2	C2	107.58(7)	C8B	C10A	C9B	94.8(9)
N1	S2	C2	106.08(6)	C8B	C10A	C10B	71.5(8)
C3	N1	S2	123.91(10)	C9B	C10A	C8A	133.8(6)
C6	N1	S2	121.09(10)	C9B	C10A	C10B	150.4(6)
C6	N1	C3	114.13(12)	O5A	O5B	C7A	46.1(3)

Table G5. Bond Angles for 181. Continued…

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C5	N2	C4	113.52(12)	C7B	O5B	O5A	74.2(5)
C7A	N2	C4	121.16(19)	C7B	O5B	C7A	28.1(4)
C7A	N2	C5	118.79(18)	N2	C7B	O5A	98.0(4)
C7A	N2	C7B	34.6(3)	N2	C7B	C8A	106.2(4)
C7B	N2	C4	128.1(3)	N2	C7B	C8B	117.2(4)
C7B	N2	C5	117.2(3)	O5A	C7B	C8A	91.1(5)
S2	C2	S1	114.76(7)	C7A	C7B	N2	71.9(5)
C11	C2	S1	105.78(7)	C7A	C7B	O5A	48.4(5)
C11	C2	S2	108.89(10)	C7A	C7B	C8A	61.9(6)
N1	C3	C4	108.24(11)	C7A	C7B	O5B	107.7(8)
N2	C4	C3	110.00(12)	C7A	C7B	C8B	93.3(7)
N2	C5	C6	110.37(12)	O5B	C7B	N2	122.7(5)
N1	C6	C5	107.80(12)	O5B	C7B	O5A	59.4(5)
C2	C11	C2[1]	115.89(16)	O5B	C7B	C8A	124.3(6)
C7A	O5A	O5B	76.3(3)	O5B	C7B	C8B	120.0(5)
C7A	O5A	C7B	29.9(3)	C8B	C7B	O5A	116.6(6)
O5B	O5A	C7B	46.5(3)	C8B	C7B	C8A	31.5(3)
N2	C7A	C8A	118.9(3)	C8A	C8B	C7A	59.2(6)
N2	C7A	O5B	97.2(4)	C8A	C8B	C7B	87.0(7)
N2	C7A	C8B	103.4(3)	C8A	C8B	C9B	159.1(8)
O5A	C7A	N2	121.0(3)	C8A	C8B	C10B	35.3(5)
O5A	C7A	C8A	119.8(3)	C10A	C8B	C7A	152.5(8)
O5A	C7A	O5B	57.6(3)	C10A	C8B	C8A	106.8(10)
O5A	C7A	C8B	124.4(4)	C10A	C8B	C7B	153.3(9)
C8A	C7A	O5B	109.9(3)	C10A	C8B	C9B	54.6(8)
C8A	C7A	C8B	30.6(3)	C10A	C8B	C10B	75.3(8)
O5B	C7A	C8B	87.3(3)	C7B	C8B	C7A	27.9(3)
C7B	C7A	N2	73.5(5)	C9B	C8B	C7A	141.8(5)
C7B	C7A	O5A	101.8(6)	C9B	C8B	C7B	113.9(6)
C7B	C7A	C8A	89.3(6)	C10B	C8B	C7A	94.4(6)
C7B	C7A	O5B	44.2(5)	C10B	C8B	C7B	122.1(8)
C7B	C7A	C8B	58.8(5)	C10B	C8B	C9B	123.8(7)
C7A	C8A	C7B	28.8(3)	C10A	C9B	C8B	30.6(3)
C9A	C8A	C7A	114.7(5)	C8A	C10B	C9A	96.6(11)
C9A	C8A	C7B	138.8(5)	C8A	C10B	C10A	71.8(7)
C10A	C8A	C7A	119.7(6)	C8A	C10B	C8B	41.0(6)
C10A	C8A	C9A	125.1(5)	C9A	C10B	C10A	164.3(8)
C10A	C8A	C7B	92.5(6)	C9A	C10B	C8B	132.2(9)
C8B	C8A	C7A	90.2(7)	C8B	C10B	C10A	33.2(3)
C8B	C8A	C9A	146.4(7)				

[1]1-X,+Y,1/2-Z

Table G6. Torsion Angles for 181. Continued..

A	B	C	D	Angle/°	A	B	C	D	Angle/°
S1	C2	C1[1]	C2[1]	87.64(7)	C8A	C10A	C10B	C9A	44(2)
S2	N1	C3	C4	-132.47(11)	C8A	C10A	C10B	C8B	18.5(7)
S2	N1	C6	C5	131.79(12)	C8A	C7B	C8B	C7A	-5.0(7)
S2	C2	C1[1]	C2[1]	-148.53(9)	C8A	C7B	C8B	C10A	-123(2)
O1	S1	C2	S2	-54.43(10)	C8A	C7B	C8B	C9B	179.2(9)
O1	S1	C2	C1[1]	65.63(11)	C8A	C7B	C8B	C10B	3.0(5)

Table G6. Torsion Angles for 181. Continued..

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O2	S1	C2	S2	179.97(8)	C8A	C8B	C9B	C10A	-30.2(19)
O2	S1	C2	C1[1]	-59.97(11)	C8A	C8B	C10B	C9A	36.3(10)
O3	S2	N1	C3	155.25(11)	C8A	C8B	C10B	C10A	-152.7(11)
O3	S2	N1	C6	-36.05(13)	C9A	C8A	C10A	C8B	141.6(10)
O3	S2	C2	S1	-49.11(9)	C9A	C8A	C10A	C9B	126.6(8)
O3	S2	C2	C1[1]	-167.44(8)	C9A	C8A	C10A	C10B	-10.4(6)
O4	S2	N1	C3	23.59(13)	C9A	C8A	C7B	N2	99.2(6)
O4	S2	N1	C6	-167.71(11)	C9A	C8A	C7B	O5A	0.5(6)
O4	S2	C2	S1	81.00(9)	C9A	C8A	C7B	C7A	40.7(8)
O4	S2	C2	C1[1]	-37.33(10)	C9A	C8A	C7B	O5B	-52.3(10)
N1	S2	C2	S1	-164.10(7)	C9A	C8A	C7B	C8B	-144.9(9)
N1	S2	C2	C1[1]	77.58(9)	C9A	C8A	C8B	C7A	139.5(13)
N1	C3	C4	N2	-54.54(15)	C9A	C8A	C8B	C10A	-66.5(15)
N2	C5	C6	N1	55.63(16)	C9A	C8A	C8B	C7B	136.8(11)
N2	C7A	C8A	C9A	137.6(4)	C9A	C8A	C8B	C9B	-41(3)
N2	C7A	C8A	C10A	-49.6(6)	C9A	C8A	C8B	C10B	-38.9(10)
N2	C7A	C8A	C7B	-70.7(6)	C9A	C8A	C10B	C10A	169.1(6)
N2	C7A	C8A	C8B	-65.7(7)	C9A	C8A	C10B	C8B	153.8(7)
N2	C7A	C8A	C10B	121(3)	C10A	C8A	C9A	C10B	12.8(7)
N2	C7A	O5B	O5A	-122.4(3)	C10A	C8A	C7B	N2	-103.3(5)
N2	C7A	O5B	C7B	57.3(7)	C10A	C8A	C7B	O5A	158.0(3)
N2	C7A	C7B	O5A	-119.2(3)	C10A	C8A	C7B	C7A	-161.8(6)
N2	C7A	C7B	C8A	120.5(3)	C10A	C8A	C7B	O5B	105.1(8)
N2	C7A	C7B	O5B	-119.5(5)	C10A	C8A	C7B	C8B	12.5(5)
N2	C7A	C7B	C8B	117.6(4)	C10A	C8A	C8B	C7A	-154.0(7)
N2	C7A	C8B	C8A	124.9(6)	C10A	C8A	C8B	C7B	-156.7(9)
N2	C7A	C8B	C10A	60(2)	C10A	C8A	C8B	C9B	25.3(16)
N2	C7A	C8B	C7B	-60.9(6)	C10A	C8A	C8B	C10B	27.6(11)
N2	C7A	C8B	C9B	-54.8(8)	C10A	C8A	C10B	C9A	-169.1(6)
N2	C7A	C8B	C10B	125.8(4)	C10A	C8A	C10B	C8B	-15.3(7)
N2	C7B	C8B	C7A	71.3(6)	C10A	C8B	C10B	C8A	152.7(11)
N2	C7B	C8B	C8A	76.3(8)	C10A	C8B	C10B	C9A	-171.0(9)
N2	C7B	C8B	C10A	-46(2)	O5B	O5A	C7A	N2	77.9(5)
N2	C7B	C8B	C9B	-104.5(7)	O5B	O5A	C7A	C8A	-95.8(5)
N2	C7B	C8B	C10B	79.2(9)	O5B	O5A	C7A	C7B	0.2(6)
C1	S1	C2	S2	64.47(10)	O5B	O5A	C7A	C8B	-59.9(5)
C1	S1	C2	C1[1]	-175.47(10)	O5B	O5A	C7B	N2	123.4(6)
C2	S2	N1	C3	-91.31(12)	O5B	O5A	C7B	C7A	-179.7(8)
C2	S2	N1	C6	77.39(12)	O5B	O5A	C7B	C8A	-130.1(5)
C3	N1	C6	C5	-58.47(16)	O5B	O5A	C7B	C8B	-110.7(6)
C4	N2	C5	C6	-57.89(17)	O5B	C7A	C8A	C9A	-111.8(5)
C4	N2	C7A	O5A	152.8(4)	O5B	C7A	C8A	C10A	61.0(6)
C4	N2	C7A	C8A	-33.4(5)	O5B	C7A	C8A	C7B	39.9(5)
C4	N2	C7A	O5B	-150.9(3)	O5B	C7A	C8A	C8B	44.9(7)
C4	N2	C7A	C7B	-113.1(5)	O5B	C7A	C8A	C10B	-129(3)
C4	N2	C7A	C8B	-61.9(4)	O5B	C7A	C7B	N2	119.5(5)
C4	N2	C7B	O5A	132.5(3)	O5B	C7A	C7B	O5A	0.3(7)
C4	N2	C7B	C7A	91.3(6)	O5B	C7A	C7B	C8A	-120.0(5)
C4	N2	C7B	C8A	38.9(7)	O5B	C7A	C7B	C8B	-123.0(7)
C4	N2	C7B	O5B	-168.9(7)	O5B	C7A	C8B	C8A	-138.4(6)
C4	N2	C7B	C8B	7.0(9)	O5B	C7A	C8B	C10A	156(2)
C5	N2	C4	C3	57.08(17)	O5B	C7A	C8B	C7B	35.8(6)
C5	N2	C7A	O5A	3.0(6)	O5B	C7A	C8B	C9B	42.0(8)
C5	N2	C7A	C8A	176.8(4)	O5B	C7A	C8B	C10B	-137.4(5)

Table G6. Torsion Angles for 181. Continued..

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C5	N2	C7A	O5B	59.3(3)	O5B	C7B	C8B	C7A	-112.7(11)
C5	N2	C7A	C7B	97.0(5)	O5B	C7B	C8B	C8A	-107.7(9)
C5	N2	C7A	C8B	148.3(3)	O5B	C7B	C8B	C10A	130(2)
C5	N2	C7B	O5A	-60.8(5)	O5B	C7B	C8B	C9B	71.5(10)
C5	N2	C7B	C7A	-102.0(5)	O5B	C7B	C8B	C10B	-104.7(9)
C5	N2	C7B	C8A	-154.3(3)	C7B	N2	C4	C3	-135.8(5)
C5	N2	C7B	O5B	-2.2(10)	C7B	N2	C5	C6	133.5(4)
C5	N2	C7B	C8B	173.8(5)	C7B	N2	C7A	O5A	-94.0(7)
C6	N1	C3	C4	58.12(15)	C7B	N2	C7A	C8A	79.8(6)
O5A	C7A	C8A	C9A	-48.5(6)	C7B	N2	C7A	O5B	-37.7(5)
O5A	C7A	C8A	C10A	124.2(5)	C7B	N2	C7A	C8B	51.2(5)
O5A	C7A	C8A	C7B	103.2(7)	C7B	O5A	C7A	N2	77.7(7)
O5A	C7A	C8A	C8B	108.1(7)	C7B	O5A	C7A	C8A	-96.0(7)
O5A	C7A	C8A	C10B	-65(3)	C7B	O5A	C7A	O5B	-0.2(6)
O5A	C7A	O5B	C7B	179.7(8)	C7B	O5A	C7A	C8B	-60.1(6)
O5A	C7A	C7B	N2	119.2(3)	C7B	O5A	O5B	C7A	0.2(4)
O5A	C7A	C7B	C8A	-120.3(4)	C7B	C7A	C8A	C9A	-151.7(6)
O5A	C7A	C7B	O5B	-0.3(7)	C7B	C7A	C8A	C10A	21.0(7)
O5A	C7A	C7B	C8B	-123.3(4)	C7B	C7A	C8A	C8B	5.0(7)
O5A	C7A	C8B	C8A	-91.4(7)	C7B	C7A	C8A	C10B	-169(3)
O5A	C7A	C8B	C10A	-156.7(19)	C7B	C7A	O5B	O5A	-179.7(8)
O5A	C7A	C8B	C7B	82.8(7)	C7B	C7A	C8B	C8A	-174.2(8)
O5A	C7A	C8B	C9B	89.0(9)	C7B	C7A	C8B	C10A	120(2)
O5A	C7A	C8B	C10B	-90.5(6)	C7B	C7A	C8B	C9B	6.2(9)
O5A	O5B	C7B	N2	-79.2(7)	C7B	C7A	C8B	C10B	-173.3(7)
O5A	O5B	C7B	C7A	0.2(6)	C7B	C8A	C9A	C10B	164.8(9)
O5A	O5B	C7B	C8A	67.9(6)	C7B	C8A	C10A	C8B	-20.4(8)
O5A	O5B	C7B	C8B	104.9(7)	C7B	C8A	C10A	C9B	-35.4(7)
O5A	C7B	C8B	C7A	-44.3(6)	C7B	C8A	C10A	C10B	-172.4(7)
O5A	C7B	C8B	C8A	-39.4(7)	C7B	C8A	C8B	C7A	2.7(4)
O5A	C7B	C8B	C10A	-161.9(19)	C7B	C8A	C8B	C10A	156.7(9)
O5A	C7B	C8B	C9B	139.8(5)	C7B	C8A	C8B	C9B	-178(2)
O5A	C7B	C8B	C10B	-36.4(7)	C7B	C8A	C8B	C10B	-175.7(7)
C7A	N2	C4	C3	-94.2(3)	C7B	C8A	C10B	C9A	-139(3)
C7A	N2	C5	C6	94.1(3)	C7B	C8A	C10B	C10A	30(3)
C7A	N2	C7B	O5A	41.2(4)	C7B	C8A	C10B	C8B	15(3)
C7A	N2	C7B	C8A	-52.3(5)	C7B	C8B	C9B	C10A	152.1(9)
C7A	N2	C7B	O5B	99.8(10)	C7B	C8B	C10B	C8A	-5.1(8)
C7A	N2	C7B	C8B	-84.2(8)	C7B	C8B	C10B	C9A	31.2(11)
C7A	O5A	O5B	C7B	-0.2(4)	C7B	C8B	C10B	C10A	-157.8(9)
C7A	O5A	C7B	N2	-56.9(5)	C8B	C7A	C8A	C9A	-156.7(7)
C7A	O5A	C7B	C8A	49.6(5)	C8B	C7A	C8A	C10A	16.1(5)
C7A	O5A	C7B	O5B	179.7(8)	C8B	C7A	C8A	C7B	-5.0(7)
C7A	O5A	C7B	C8B	69.0(7)	C8B	C7A	C8A	C10B	-173(3)
C7A	C8A	C9A	C10B	-174.9(8)	C8B	C7A	O5B	O5A	134.4(4)
C7A	C8A	C10A	C8B	-30.3(8)	C8B	C7A	O5B	C7B	-45.9(7)
C7A	C8A	C10A	C9B	-45.3(8)	C8B	C7A	C7B	N2	-117.6(4)
C7A	C8A	C10A	C10B	177.6(8)	C8B	C7A	C7B	O5A	123.3(4)
C7A	C8A	C7B	N2	58.5(5)	C8B	C7A	C7B	C8A	2.9(4)
C7A	C8A	C7B	O5A	-40.2(5)	C8B	C7A	C7B	O5B	123.0(7)
C7A	C8A	C7B	O5B	-93.1(10)	C8B	C8A	C9A	C10B	50.7(13)
C7A	C8A	C7B	C8B	174.4(8)	C8B	C8A	C10A	C9B	-15.0(10)
C7A	C8A	C8B	C10A	154.0(7)	C8B	C8A	C10A	C10B	-152.1(11)
C7A	C8A	C8B	C7B	-2.7(4)	C8B	C8A	C7B	N2	-115.9(7)

Table G6. Torsion Angles for 181. Continued..

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C7A	C8A	C8B	C9B	179(100)	C8B	C8A	C7B	O5A	145.4(6)
C7A	C8A	C8B	C10B	-178.4(8)	C8B	C8A	C7B	C7A	-174.4(8)
C7A	C8A	C10B	C9A	19(3)	C8B	C8A	C7B	O5B	92.6(9)
C7A	C8A	C10B	C10A	-171(3)	C8B	C8A	C10B	C9A	-153.8(7)
C7A	C8A	C10B	C8B	173(3)	C8B	C8A	C10B	C10A	15.3(6)
C7A	O5B	C7B	N2	-79.5(8)	C8B	C10A	C10B	C8A	-18.5(7)
C7A	O5B	C7B	O5A	-0.2(6)	C8B	C10A	C10B	C9A	25(3)
C7A	O5B	C7B	C8A	67.6(9)	C9B	C10A	C8B	C7A	-136.2(18)
C7A	O5B	C7B	C8B	104.7(11)	C9B	C10A	C8B	C8A	169.2(7)
C7A	C7B	C8B	C8A	5.0(7)	C9B	C10A	C8B	C7B	-72(2)
C7A	C7B	C8B	C10A	-118(2)	C9B	C10A	C8B	C10B	153.1(5)
C7A	C7B	C8B	C9B	-175.8(6)	C9B	C10A	C10B	C8A	-84.3(14)
C7A	C7B	C8B	C10B	7.9(8)	C9B	C10A	C10B	C9A	-40(4)
C7A	C8B	C9B	C10A	148.9(11)	C9B	C10A	C10B	C8B	-65.8(14)
C7A	C8B	C10B	C8A	-1.4(7)	C9B	C8B	C10B	C8A	179.0(11)
C7A	C8B	C10B	C9A	34.9(9)	C9B	C8B	C10B	C9A	-144.7(8)
C7A	C8B	C10B	C10A	-154.1(7)	C9B	C8B	C10B	C10A	26.3(6)
C8A	C7A	O5B	O5A	113.3(4)	C10B	C8A	C10A	C8B	152.1(11)
C8A	C7A	O5B	C7B	-67.0(8)	C10B	C8A	C10A	C9B	137.1(8)
C8A	C7A	C7B	N2	-120.5(3)	C10B	C8A	C7B	N2	-132(3)
C8A	C7A	C7B	O5A	120.3(4)	C10B	C8A	C7B	O5A	129(3)
C8A	C7A	C7B	O5B	120.0(5)	C10B	C8A	C7B	C7A	170(3)
C8A	C7A	C7B	C8B	-2.9(4)	C10B	C8A	C7B	O5B	76(3)
C8A	C7A	C8B	C10A	-65.3(19)	C10B	C8A	C7B	C8B	-16(3)
C8A	C7A	C8B	C7B	174.2(8)	C10B	C8A	C8B	C7A	178.4(8)
C8A	C7A	C8B	C9B	-179.6(11)	C10B	C8A	C8B	C10A	-27.6(11)
C8A	C7A	C8B	C10B	0.9(5)	C10B	C8A	C8B	C7B	175.7(7)
C8A	C9A	C10B	C10A	-41(2)	C10B	C8A	C8B	C9B	-2(2)
C8A	C9A	C10B	C8B	-23.0(6)	C10B	C10A	C8B	C7A	70.6(19)
C8A	C10A	C8B	C7A	54.6(17)	C10B	C10A	C8B	C8A	16.1(6)
C8A	C10A	C8B	C7B	118(2)	C10B	C10A	C8B	C7B	135(2)
C8A	C10A	C8B	C9B	-169.2(7)	C10B	C10A	C8B	C9B	-153.1(5)
C8A	C10A	C8B	C10B	-16.1(6)	C10B	C10A	C9B	C8B	60.2(13)
C8A	C10A	C9B	C8B	9.6(6)	C10B	C8B	C9B	C10A	-31.8(7)

[1]1-X,+Y,1/2-Z

Table G7. Hydrogen Atom Coordinates (Å×104) and Isotropic Displacement Parameters (Å2×103) for 181. Continued..

Atom	x	y	z	U(eq)
H1A	3620.75	7754.78	1490.28	45(4)
H1B	3150.96	5507.29	1281.35	45(4)
H1C	3566.28	6685.69	903.27	45(4)
H2	4334(9)	5360(30)	2432(7)	21(4)
H3A	4451.84	1815.51	3665.98	25
H3B	4154.99	-385.72	3284.17	25
H4A	3151.66	-433.38	3578.98	27
H4B	3803.42	-479.53	4107.94	27
H5A	2816	5624.83	3708.32	30
H5B	2534.53	3425.04	3323.62	30
H6A	3169.21	5806.26	2891.44	27
H6B	3824.82	5735.16	3419.18	27

Table G7. Hydrogen Atom Coordinates (Å×104) and Isotropic Displacement Parameters (Å2×103) for 181. Continued..

Atom	x	y	z	U(eq)
H11	5064(9)	1460(30)	2228(7)	19(4)
H9A1	4995.61	2644.67	5053.77	78(9)
H9A2	4828.29	1627.78	5583.46	78(9)
H9A3	4639.62	4277.4	5403.24	78(9)
H10A	3811.84	-753.96	5366.26	97
H11A	3183.24	-211.66	4813.56	97
H9B1	2739.33	963.08	5227.41	65(11)
H9B2	3279.32	-1144.74	5382.68	65(11)
H9B3	2774.61	-939.74	4779.39	65(11)
H10B	4403.52	202.74	5466.19	67
H11B	4541.52	2230.14	5054.59	67

Table G8. Atomic Occupancy for 181.

Atom	Occupancy	Atom	Occupancy	Atom	Occupancy
O5A	0.591(5)	C7A	0.591(5)	C8A	0.591(5)
C9A	0.591(5)	H9A1	0.591(5)	H9A2	0.591(5)
H9A3	0.591(5)	C10A	0.591(5)	H10A	0.591(5)
H11A	0.591(5)	O5B	0.409(5)	C7B	0.409(5)
C8B	0.409(5)	C9B	0.409(5)	H9B1	0.409(5)
H9B2	0.409(5)	H9B3	0.409(5)	C10B	0.409(5)
H10B	0.409(5)	H11B	0.409(5)		