Dichloromethylation of Nitrobenzene Derivatives via Vicarious Nucleophilic Substitution of Hydrogen with Trichloromethyl Carbanions in Flow

GEORGE ALASTAIR LYALL-BROOKES

Dichloromethylation of Nitrobenzene Derivatives via Vicarious Nucleophilic Substitution of Hydrogen with Trichloromethyl Carbanions in Flow

A thesis submitted for the degree of
MASTER OF SCIENCE

By

George Lyall-Brookes

26/07/2024

Declaration

This thesis is based on work conducted by the author, in the Department of Chemistry at Durham University, during the period October 2022 to September 2023. All the work described in this thesis is original, unless otherwise acknowledged in the text or by reference. None of this work has been submitted for any another degree at this or any other University.

Acknowledgements

I would firstly like to thank my supervisor Professor Ian Baxendale for all of his guidance, knowledge and support over the course of this project, I have thoroughly enjoyed my time in the lab. In a similar vein I would also like to thank Eilish, Linda, Haijing and Diego for all of their advice and for making the lab such a great place to be. Finally, I would like to thank my friends and family for their continued support and encouragement, which has been invaluable throughout the duration of the project.

Abbreviations

δ	chemical shift (NMR spectroscopy)
ν	wavenumber (IR spectroscopy)
~	approximately
°C	degrees Celsius
λ_{max}	the wavelength at which a substance most strongly absorbs photons
α	a carbon directly adjacent to a given functional group
CP	cationic polymerisation
cm^{-1}	inverse centimetre
cm^3	centimetre cubed
CFI	coiled flow invertor
d	doublet (NMR spectroscopy)
dd	doublet of doublets
ddd	doublet of doublets of doublets
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
Conc.	concentrated
equiv.	equivalents
et al.	et alia
FC	Final monomer conversions
FRP	Free radical polymerisation
FT-IR	Fourier-transform infrared
g	grams
GC-MS	gas chromatography-mass spectrometry
$g\ min^{-1}$	grams per minute
$g\ h^{-1}$	grams per hour
h	hours
HMDS	hexamethyldisilazane
HOMO	highest occupied molecular orbital
Hz	Hertz
J	coupling constant (NMR spectroscopy) in Hertz
$Kcal\ mol^{-1}$	kilocalorie per mole

LC-MS	Liquid chromatography-mass spectrometry
Log P	partition coefficient
LUMO	lowest unoccupied molecular orbital
m	medium intensity (IR spectroscopy) or multiplet (NMR spectroscopy)
M	moles per litre
min	minute
mL	millilitres
mL min^{-1}	millilitres per minute
mmol	millimole
mol	moles
mol min^{-1}	moles per minute
m/z	mass-to-charge-ratio
nm	nanometres
NMR	nuclear magnetic resonance
PFA	perfluoroalkoxy
pH	potential of hydrogen
pK_a	dissociation constant
ppm	parts per million
Rt	retention time or residence time
s	strong intensity (IR spectroscopy) or singlet (NMR spectroscopy)
S_NAr	Nucleophilic aromatic substitution
t	triplet (NMR spectroscopy)
t-BuOK	potassium tert-butoxide
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
UV	ultraviolet
VNS	vicarious nucleophilic substitution
w	weak intensity (IR spectroscopy)
w/w	weight for weight

Abstract

In recent years indigo compounds have been adopted across a wide range of applications. Of particular note is their introduction as organic semi-conductors. As this field grows, so does the desire to probe the structure of these compounds, to generate semi-conductors with favourable charge transport properties. One of the strategies employed to achieve this, is the functionalisation of the core indigo structure. This can be executed through the use of functionalised nitro benzaldehyde starting materials, generated via hydrolysis of dichloro methylated intermediates. However, these compounds are often costly to purchase or are not commercially available, as such it would be favourable to establish a procedure for the cost-effective generation of the aldehyde starting materials at scale. Herein we report a procedure for the cost-effective synthesis of the dichloro methylated nitroarene intermediates on a gram scale, through the use of vicarious nucleophilic substitution and flow chemistry, enabling simplified access to a variety of halogenated nitro benzaldehydes. Potentially facilitating the generation, and investigation, of a range of indigo semi-conductors with increased structural diversity.

Contents

1. Introduction

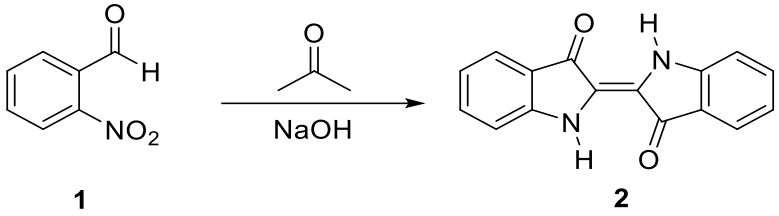
1.1 History of Indigo

All colouring agents, such as indigo, were initially obtained from natural sources such as plants, lichens, insects and molluscs.[1] This process in the case of indigo began, roughly 5000-6000 years ago, across Asia, Africa, Europe and the newly formed Americas.[2] In fact the compound got its name from the Indus Valley in India where much of indigo used in 18th century was shipped to Europe form. This was the sole source of indigo until the end of the 19th century when it became no longer commercially viable to obtain indigo this way. It was at this point of the industrial era of the 1800's that such dyes began to be chemically synthesised.[3] German scientists, namely Adolf Baeyer, began tackling the problem of generating synthetic indigo.

1.2 History of Indigo Synthesis

In 1882 Baeyer successfully achieved this, generating indigo on a laboratory scale, after over 20 years of work dedicated to the problem, followed by determination of the structure the following year. By the start of the 20th century Pfleger and Heumann had expanded upon Baeyer's original method making the synthesis viable on an industrial scale, negating the need for natural isolation. Resulting in the majority of the indigo now used, world-over, coming from synthetic means.[2]

The Baeyer-Drewson synthesis is a simple and elegant reaction and is the modern approach for the generation of indigo on a laboratory scale. The reaction was developed and proposed by Adolf Baeyer in collaboration with Viggo Drewson in 1882.[4] The synthesis simply involves the reaction of *o*-nitrobenzaldehyde **(1)** with acetone in the presence of sodium hydroxide. The reaction proceeds via an initial aldol condensation followed by cyclisation and then finally oxidative dimerization to form the final product, indigo **(2)**.



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Scheme 1: Baeyer-Drewson synthesis of indigo from *o*-nitrobenzaldehyde **(1)** and acetone.[4]

The general structure of the indigo compound **(3)**, a dimeric 3-indolinone, includes a fundamental chromophore consisting of a central C sp^2-C sp^2 bond connecting the two ring systems. Each of these systems contains an electron withdrawing carbonyl oxygen, an aromatic core and NH, electron donating group.[5] The compound possess a deep dark blue colour due to the conjugation of the adjacent double bonds, which also results in the compounds planar structure.[6]

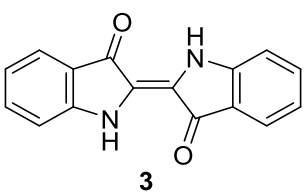

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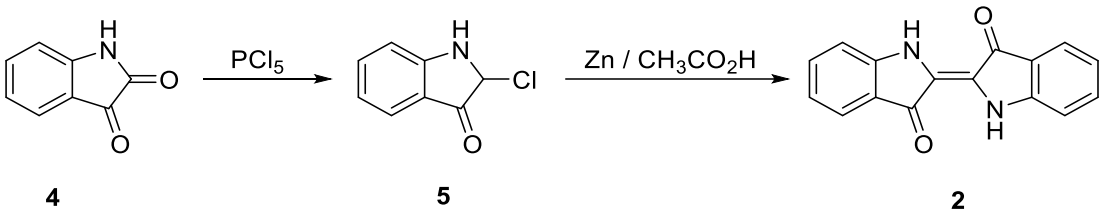
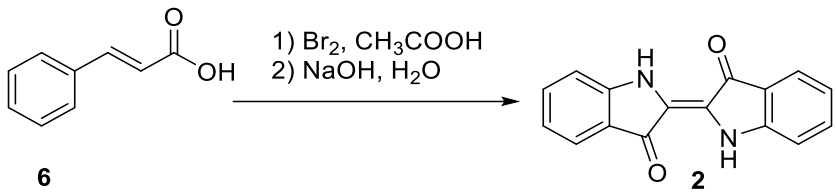
Figure 1: Generic structure of Indigo compounds.

Prior to development of the Baeyer-Drewson method in 1882, Baeyer first developed an alternative method for the synthesis from istatin starting material **(4)** in 1870.



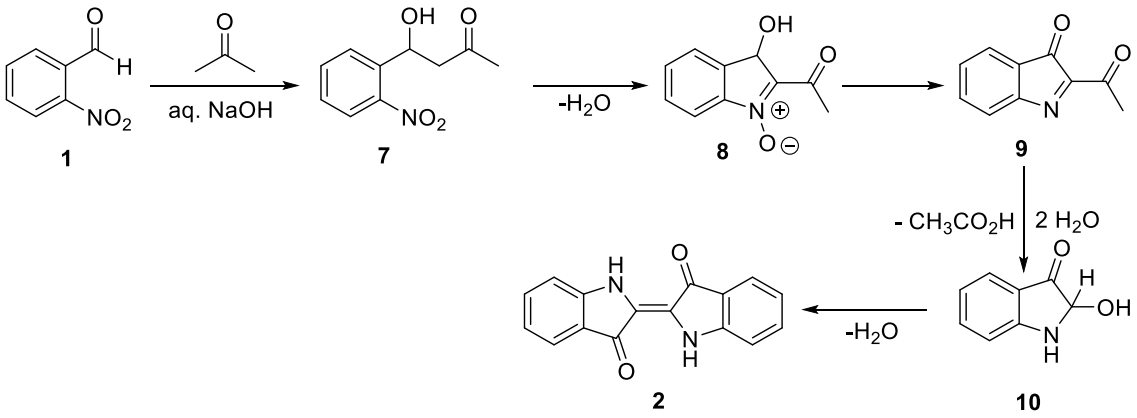
Scheme 2: Indigo synthesis from istatin **(4)** starting material.

This method proved unfeasible for industrial scale up due to the scarcity and high costs associated with the starting material. Over the next 13 years Baeyer continued to work on the problem developing various routes, with varying success. Over this time, Baeyer consulted Heinrich Caro, the head of research as BASF at the time, Caro identified two of Baeyer's proposals that had potential utility in the industrial domain. The first of which being an approach centred on the use of cinnamic acid **(6)**, which upon bromination and treatment with sodium hydroxide would dimerise to form the desired product **(2)**.



Scheme 3: Indigo **(2)** synthesis from cinnamic acid **(6)** starting material.

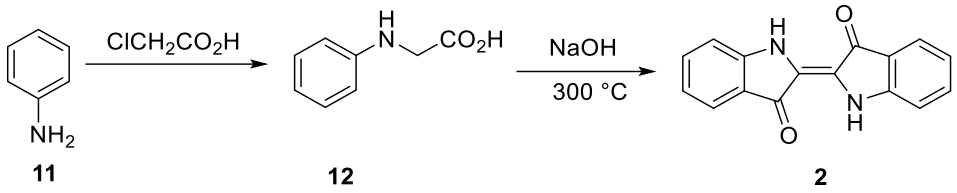
The second identified method known today as the Baeyer-Drewson method which employs *o*-nitrobenzaldehyde **(1)** as a starting material.



Scheme 4: Indigo **(2)** synthesis from *o*-nitrobenzaldehyde **(1)** starting material.

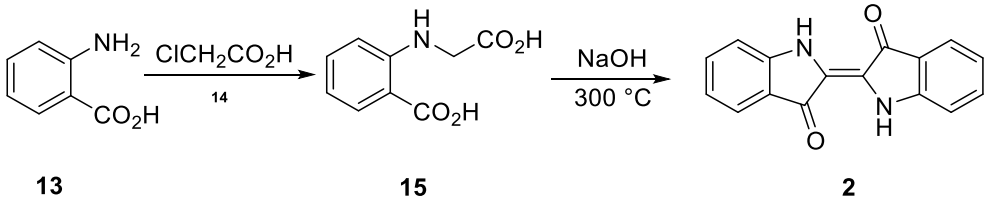
At the time of development, the later method **(Scheme 4)** was impractical due to the difficulty associated with generating the starting material. As such, the former method **(Scheme 3)** was patented by Baeyer and sold to BASF for $100,000. Despite this, the method was never employed on an industrial scale as it lacked economic viability. As such, further development was required before the compounds could be generated at the desired scale.

Another decade past before the next breakthrough in the synthesis of indigo materialised, at this time there were primarily two companies focused on addressing the challenging synthesis, BASF and Hoechst. The two companies combined forces to achieve their shared goal. The breakthrough came via Heumann and the development of a procedure that employed aniline **(11)** as the starting material, which was more readily available than the *o*-nitrobenzaldehye **(1)** required by the Baeyer-Drewson method.



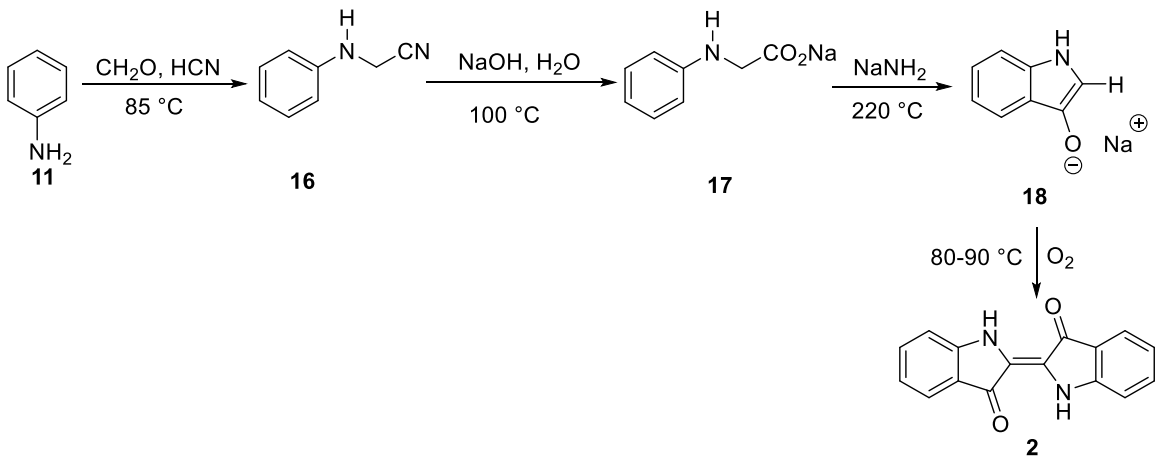
Scheme 5: Indigo synthesis **(2)** from aniline **(11)** starting material.

Despite this breakthrough, the reaction still proved unsatisfactory for the two companies, as the reaction returned poor yields when scaled up. This meant that once again, the reaction was never used on an industrial scale. However, the closely related second variation of this reaction **(Scheme 6)** proved much more fruitful.



Scheme 6: Improved indigo **(2)** synthesis from the chloroacetic acid **(14)** starting material.

Due to the improved success of the reaction both companies began construction of facilities to generate the compound on multi tonne scales. Part way through construction of these facilities, Pfleger discovered the reaction could be further optimised through the introduction of $NaNH_2$ in addition to NaOH in the final step of the transformation. This discovery came with a significant cost to retrofit the factory with the equipment required to enable this step in the reaction, further inflating the cost of the investment made by the companies to 18 million gold marks. In 1897 the first industrial synthesis of Indigo was conducted using this facility; over the next 28 years the method was steadily improved until the optimal method outlined in **Scheme 7**, that is still in use today, was developed. The method utilised aniline **(11)**, formaldehyde and hydrogen cyanide to form the phenylglycine intermediate (**17**) which then cyclises to form the indoxyl (**18**) with the aid of sodium amide.



Scheme 7: Pfleger and Heumann indigo **(2)** synthesis.

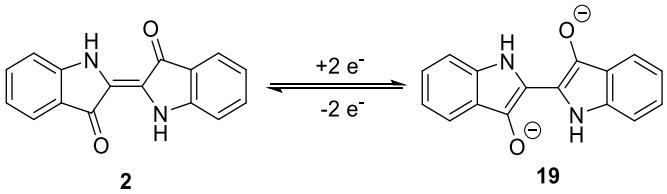
The synthesis of indigo on a large scale is not just limited to the methods outlined thus far in the report. Many procedures have outlined the use of biological pathways to generate the desired indigo compounds. These methods are inherently safer than the corresponding chemical synthesis due to exclusion of aromatic amines **(11)** and cyanide groups **(16)** that are present in the synthetic route proposed by Pfleger and Heumann **(Scheme 7)**. Many of these processes were centred around the work of Ensley *et al.* in 1983 where it was found that recombinant *Escherichia coli* expressing naphthalene dioxygenase from *Psuedomonas putida* PpG7 in rich medium resulted in the formation of indigo.[7]

This work culminated in the development of a commercial method of indigo production using bacterial systems in 1993 by Murdock *et al.*[8] Despite this the biological synthesis of indigo is not a perfect solution for successful synthesis of all indigo related compounds. There are still a variety of challenges associated with such techniques including the instability of many of the enzymes involved, the lack of well characterised enzymes that can be used and, arguably the most limiting of all being, a lack of designability of the enzymes.[9] Meaning it may not be possible to access all the desired derivative compounds.

As such biocatalysis was not used as part of this project. Additionally, neither will the synthetic route proposed by Pfleger and Heumann, due to the prohibitive cost of the equipment required to facilitate the synthesis. Meaning the Baeyer-Drewson method will be adopted to achieve the ultimate goals of the project to prepare indigo derivatives at scale.

1.3 Uses of Indigo

Indigo and its derivatives are of particular importance, due the broad utility of the compounds. Indigo exhibits low acute toxicity allowing the compounds to be widely used in cosmetics, textile, food and printing inks.[10] The structure of the compound also allows the compound to be utilised in a wider range of applications, in particular the two carbonyl groups present in the compound can undergo a redox reaction as shown in **Scheme 8** below, resulting in semiconducting properties which were discovered in the 2010s.[11]



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Scheme 8: Indigo **(2)** redox reaction.

There is much ongoing work to develop high-quality semiconductor films,[12] as indigo molecules possess the desired properties, they are prime evaluation targets. Indeed they have optimal optoelectronic and physicochemical properties to be applied as semiconductor materials in organic field effect transistors.[20]

Organic semi-conductors can display p-type or n-type behaviour. The p-type behaviour is insighted via the introduction of small amounts of trivalent impurities, such as gallium and indium, into the pure semi-conductor introducing large holes. These impurities are known as acceptors, as each atom of the impurity can generate one hole, which can accept one bonded electron. These holes have a positive charge as the three valence electrons on the impurity bind to the four valence electrons on the semiconductor, leaving a one electron deficiency. Meaning the covalent bond cannot be completed, this imbalance is what is known as a hole as can be seen in **Figure 2.**

Due to the large number of atoms contained within a small amount of impurity, millions of holes can be generated via its introduction, it is these holes that are the positive charge carriers. The majority of charge carriers in this type of

semiconductors are the holes, with the minority charge carriers being the electrons. The density of the hole is higher than the density of the electron and the acceptor level lies closer to that of the acceptor level.

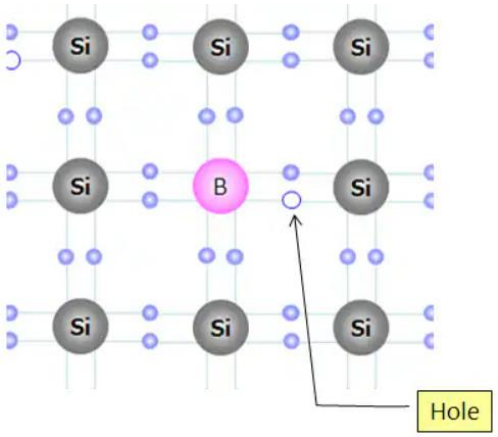


Figure 2: Silicon and boron p-type semiconductor, replicated from "Basic Knowledge of Discrete Semiconductor Device: Chapter 1: Basis of Semiconductors, Toshiba Electronic Devices & Storage Corporation, February 2022 - accessed 15/04/24.[13]

By contrast n-type semiconductors are instead doped with pentavalent impurities such as phosphorus, arsenic or antimony. These impurities are added to increase the number of electrons available for conduction. The impurity forms four covalent bonds with its valent electrons, leaving one remaining valent electron. As such the impurity donates one electron to the n-type semiconductor meaning there are more electrons than holes as can be seen in **Figure 3.**

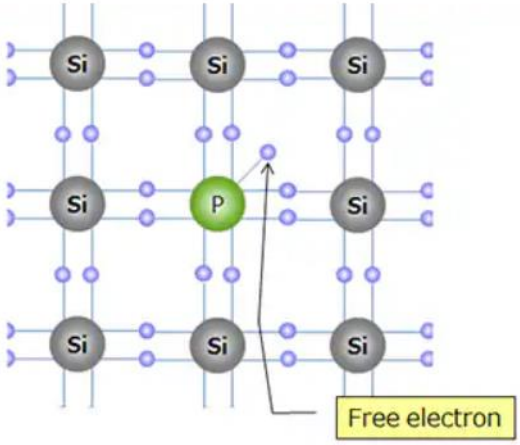


Figure 3: Silicon and phosphorus n-type semiconductor, replicated from "Basic Knowledge of Discrete Semiconductor Device: Chapter 1: Basis of Semiconductors, Toshiba Electronic Devices & Storage Corporation, February 2022 - accessed 15/04/24.[13]

Due to indigo being a particularly good organic semiconductors, it can be used in technology such as solar panels, light-emitting diodes and transistors.[14] Such compounds have also been used in solar cells for more than three decades now with the first cell fabricated by O'Regan and Grätzel in 1991.[15]

Present day solar cells are considered the third generation of solar cells. When sunlight hits the surface of a dye sensitized solar cell, the solar irradiation excites the HOMO electrons into the LUMO of the compound. These electrons are then injected into the conduction band of the metal oxide semiconductor, which is typically non-porous TiO_2. The electrons are then carried towards the working electrode via an external circuit and reaches a load in which work is

performed. This work is delivered in the form of electrical energy. Regeneration of the dye is performed by electrolytes and proceeds via a series of oxidation-reduction processes. Sensitizers should have their LUMO energy level above that of the metal oxide semiconductor conduction band and a HOMO energy level below that of the redox couple of the electrolyte, to achieve the optimal electrochemical cycle.[16] [17]

Many natural dyes, where the term "dye" refers to a compound that can absorb light in the 380-700 nm range, also have potential utility as photo initiators. They are a source of interest as an alternative to metal complexes, providing several benefits including lower costs, greater commercial availability, lower toxicity, better stability/solubility and they can also be extracted with greater ease. As indicated the development of indigo dyes for this purpose are of particular interest.[18]

Indigo derivatives can act as photo initiators in polymerisation.[19] Photo initiators absorb light in the ultraviolet-visible spectral range. The compounds convert this light energy into chemical energy in the form of reactive intermediates, such as free radicals and reactive cations that can then initiate polymerisation. They are used in the cationic polymerization (CP) of epoxides, the free radical polymerization (FRP) of acrylates or the thiol-ene polymerization across differing irradiation sources.[19] Two compounds have been explored in particular, in relation to their photoinitiation affect namely IDG1 **(20)** and IDG 2 **(21)**.

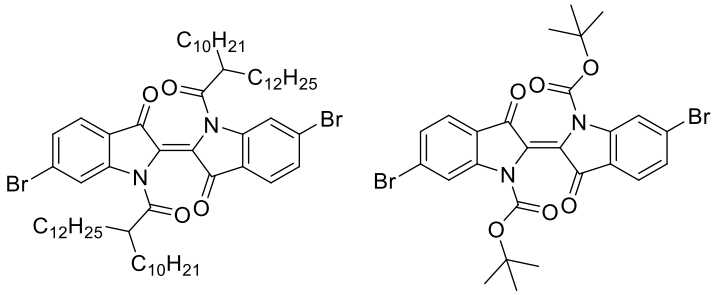


Figure 4: IDG 1 **(20)** and IDG 2 **(21)** compounds used at photoinitiators.[19]

These two compounds have λ_{max} of 591 nm and 543 nm respectively.[19] In the CP of epoxides, good final monomer conversions (FC) were observed for both compounds upon exposure to an LED at 405 nm, with an FC of 52% and 35% for IDG1 **(20)** and IDG2 **(21)** respectively. It was then reported that IDG1 **(20)** had a FC of 37% at 405 nm for the photopolymerization of acrylates.[19]

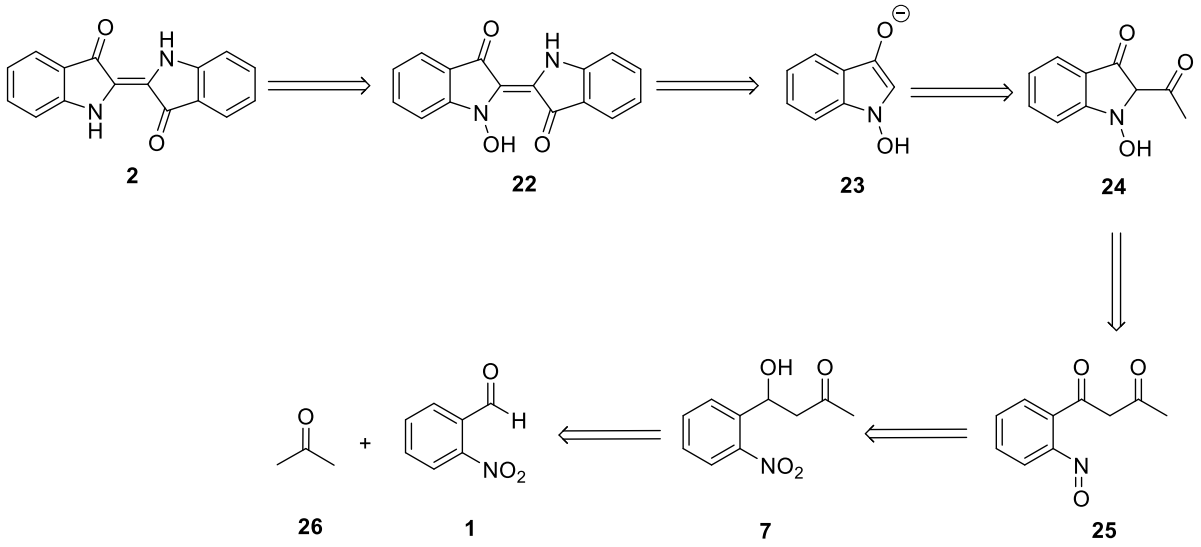
As a result of this widespread utility, chemical functionalisation of the indigo molecule has been attempted with the aim of developing novel indigo molecules with more desirable photochemical properties. The introduction of strong electron-withdrawing groups is one such example, as the HOMO and LUMO energy levels, as well as the crystal structure of indigoids can be significantly altered. These observations could be helpful in the design of new indigoids with superior charge-transport properties and greater ambient stability.[20]

Additionally indigo compounds also have found various medicinal applications. The first reference to indigo, specifically indigo naturalis, in a medicinal context stem from China where doctors discovered it could reduce fever, detoxify the blood, dissolve ecchymoses, and reduce blood temperature.[21] The compound also has anti-inflammatory, antioxidant, antibacterial and immune regulation properties.[22] It has also subsequently been shown to possess an inhibitory effect on various cancers.[23]

1.4 Baeyer-Drewson Indigo Synthesis

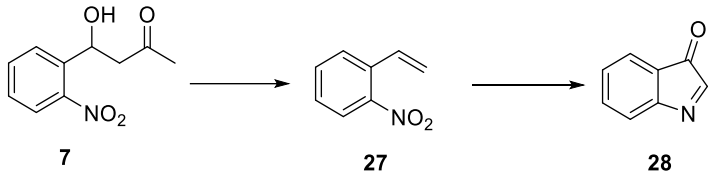
As previously stated, the Baeyer-Drewson indigo synthesis will be central to work conducted as part of this project being a relay to the final indigo compounds of interest. Despite the relative simplicity of the reaction, and over 150

years having elapsed since the development of the reaction, some contention still lingers over the mechanistic steps involved in the synthesis.



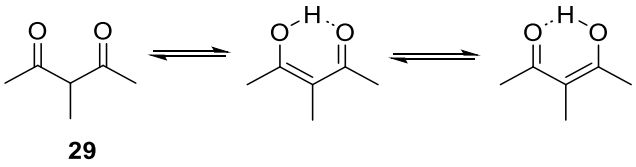
Scheme 9: Retrosynthetic analysis of indigo **(2)**

An early attempt to decipher the reaction mechanism came from Gattermann in the 1954 book "Methods of Organic Chemistry".[24] Gattermann proposed that the condensation of *o*-nitrobenzaldehyde **(1)** with acetone produced a compound, that was given the name *o*-nitrophenyl lactic acid ketone; i.e., 4-hydroxy-4-(2-nitrophenyl)-2-butanone **(7)**. It was then proposed that upon the loss of acetic acid, *o*-nitrostyrene **(27)** was generated and then a "indolone" **(28)** could be formed respectively. With the later dimerising to form the indigo end product **(2)**. [24]



Scheme 10: Gattermann's proposed synthetic route.[24]

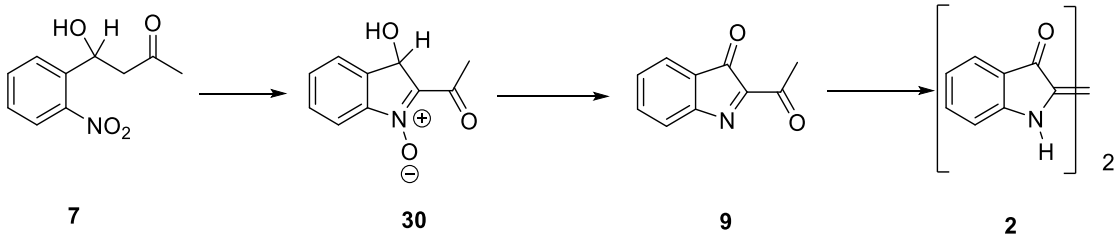
In their 2016 paper, Sánchez-Viesca *et al.* dispute this proposal, stating that the formation of the *o*-nitrostyrene **(27)** is very improbable, due to the lack of a second carbonyl group in the compound. The second carbonyl group is required to stabilise the carbanion generated in the breakdown via the formation of an enolate, as commonly seen in β-diketones **(29) (Scheme 11)**. Due to the omission of the second carbonyl group in 4-hydroxy-4-(2-nitrophenyl)-2-butanone **(7)**, it is likely that any intermediates formed would be unstable and thus unable to proceed via this route.



Scheme 11: Enol formation in β-diketones **(29)**.[25]

Sánchez-Viesca *et al.* also opposed the possibility of the *o*-nitrostyrene **(27)** undergoing dehydration, describing the transformation as impossible.[26] The final indolone, indolenine-3-one **(28)**, is an intermediate found within modern proposals, although the proposed steps that lead to its formation differ greatly.

Romanian researchers Tanasescu and Georgescu presented an alternative sequence for the synthesis, highlighted in **Scheme 12**, that was generally excepted at the time of publication in 1932.[27]



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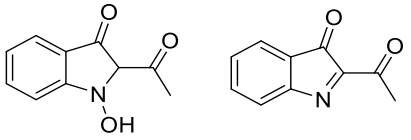
Scheme 12: Tanasescu and Georgescu proposed synthetic route.[27]

Sánchez-Viesca *et al.* once again challenge this proposal, questioning the feasibility of the ring closure proceeding as described. This scepticism stems from the presence of a nitrone intermediate, as these compounds are generated from a reaction between hydroxylamine and a carbonyl compound, not a nitro compound as proposed by the Romanian researchers. This transformation would require the simultaneous reduction of the nitro group, additionally no such transformation involving nitro groups participating in such dehydrations have been highlighted in literature.[26]

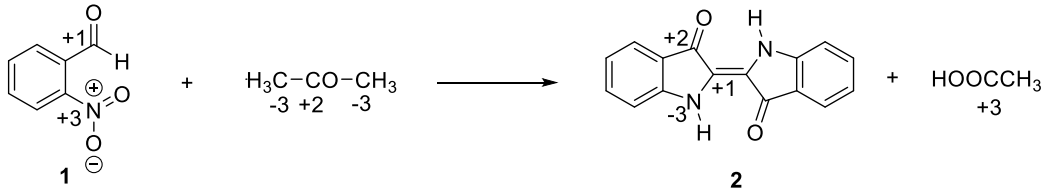
In 1996 Ranganathanin proposed a modern perspective on the reaction, mechanistically displaying what had been previously proposed by Tanasescu and Georgescu over 60 years prior. Ranganathan proposed after *o*-nitrobenzaldehyde **(1)** and acetone undergo the aldol condensation, the resulting product would undergo E1cB elimination in the presence of the hydroxide ion (**Scheme 14**) yielding *o*-nitrosobenzoylacetone **(9)** comparably to previous proposals, where this proposal differed was the proposition of an additional product formation, a saturated indole 1-(*o*-nitrosophenyl)-1,3-butane-dione **(8)**, in addition to the *o*-nitrosobenzoylacetone **(9)**.[28]



8 9

Figure 5: Saturated and unsaturated indole intermediates.[28]

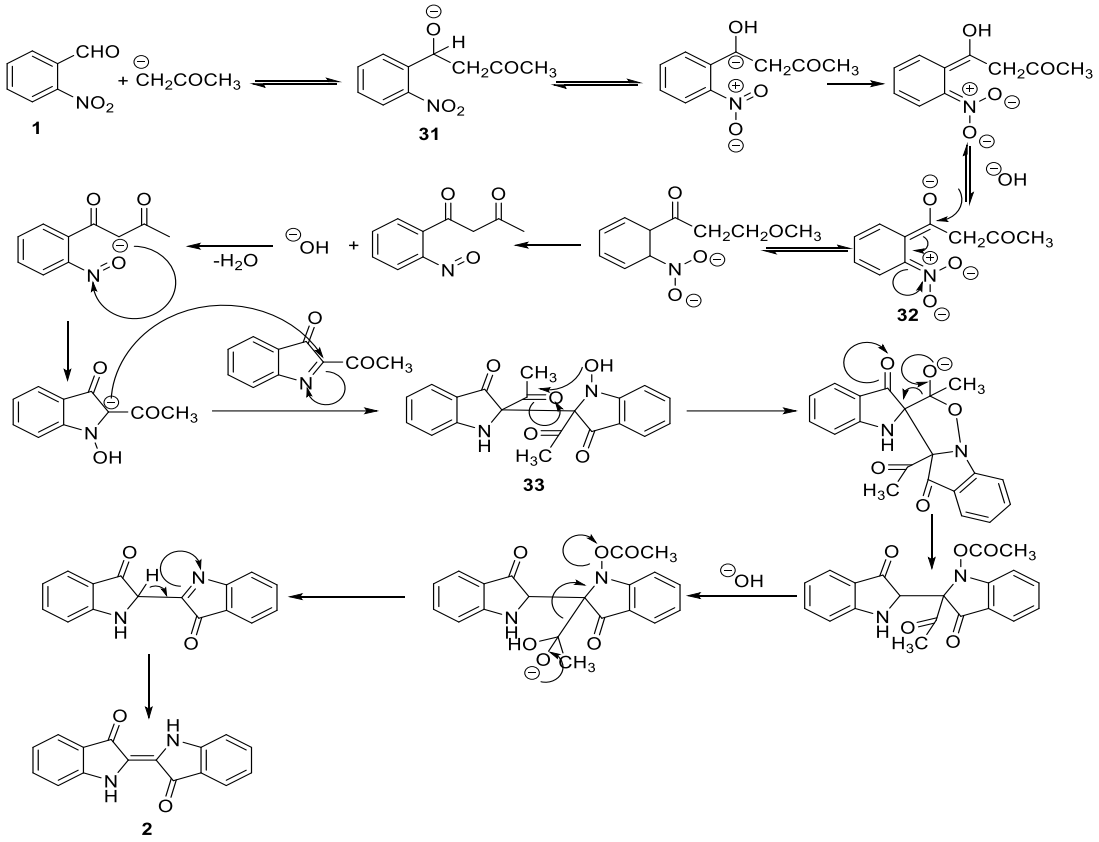
Ranganathan used the oxidation states of the constituent atoms of the organic compounds involved in the reaction to simplify analysis of the transformation, Ranganathan does note this is an overly simplified approach but highlights the potential usefulness of such an approach.[28]



1 2

Scheme 13: Oxidation states of atoms in the formation of indigo **(2)**.[28]

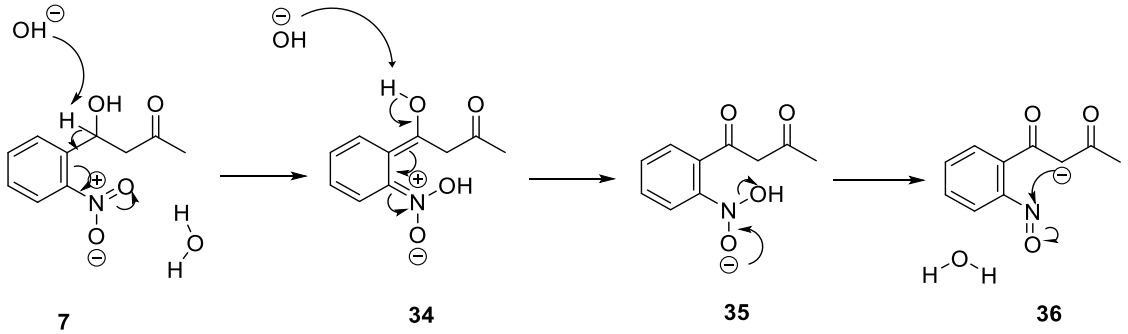
Ranganathan commented on the change in oxidation state of the nitrogen atom, stating that of the six electrons needed for the transformation of NO_2 to NHR (+3 to -3), five have come from acetone and one from the aldehyde group, which is oxidised to form the ketone via a secondary alcohol. Ranganathan then highlighted the transfer of electrons through the proposal of a series of transformation as seen in **Scheme 14**, [28] proposing the reaction proceeded via nucleophilic addition, a hydrogen shift of the alkoxide containing intermediate **(31)**, aromatisation and protonation followed by intramolecular nucleophilic addition prior to the dimerization.



Scheme 14: Indigo synthesis posited by Ranganathan[28]

Although Sánchez-Viesca *et al.* agree as to the generation of the two indole products **(8, 9)**. A source of disagreement with the proposal from Ranganathan, is delaying the elimination of acetic acid until the late stages of the reaction. This results in the formation of a series of highly crowded intermediates, making the later stages of the proposed reaction somewhat improbable.[26]

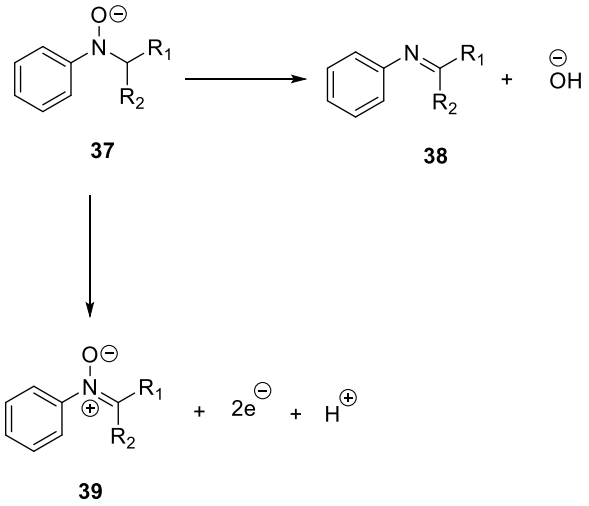
Sánchez-Viesca *et al.* proposed an alternative complete mechanism for the reaction, taking into account the differing viewpoints, known reactivities, experimental data and results from molecular modelling **(Scheme 15)**.[26]



Scheme 15: Oxyamino adduct formation.[26]

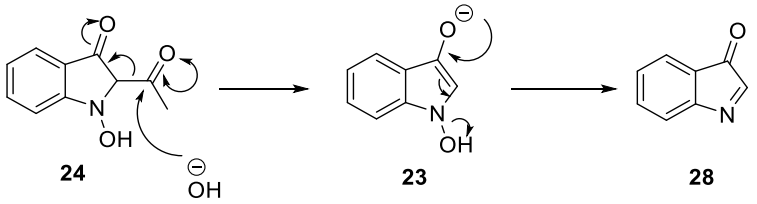
After the initial aldol condensation, the ketol product formed **(7)** contains an acidic benzylic proton due to the proximity to the nitro group and double bond making it is highly susceptible to attack from the hydroxide ion. As such the ketol product **(7)** undergoes oxidation via internal electron transfer via the conjugated system, simultaneously reducing the nitro group to a nitroso via a *o*-semiquinoid nitronate **(35)**. The nitroso group is a good electrophile, reacting with the acidic β-diketone carbon centre, via the Ehrlich-Sachs reaction.[2930]

This reaction occurs between active methylene groups and aromatic nitroso groups. Although, the reaction can be initiated by base, acid or heat, in this case the reaction is base initiated, which is the most typical method of initiation. The hydroxyl anion generates an enolate ion for the reaction to yield the hydroxylamine **(37)**. The adduct formed can be dehydrated to form azo-methine derivatives **(38)** or oxidised to form a nitrone compound **(39)**.



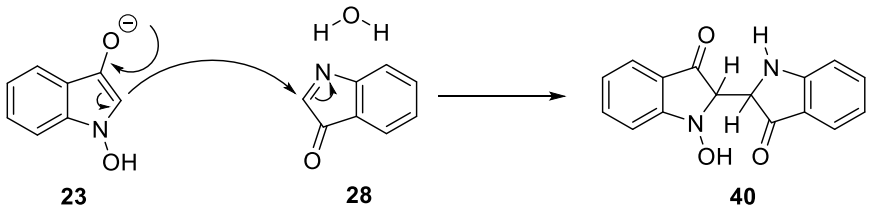
Scheme 16: Azomethine **(38)** derivative and nitrone **(39)** formation.

The external acetyl group is then eliminated, breaking up the β-diketone compound. This generates acetic acid and an enolate, which can then form indolenine-3-one **(28)**.



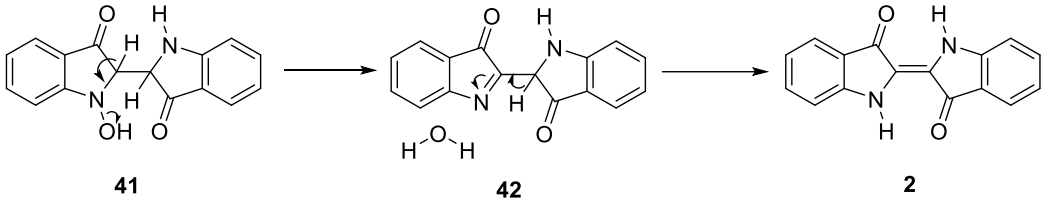
Scheme 17: indolenine-3-one **(28)** formation.[26]

Conjugation between the double bond and the benzene ring, act to stabilise the enolate. Thus, lowering the rate of reaction, which in turn retards the second step of the Ehrlich-Sachs reaction. This allows the formation of the indigo framework via mesomeric effect from the indolenine molecule **(23)**.



Scheme 18: Formation of indigo **(40)** framework[26]

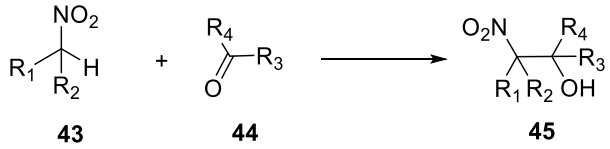
A comparison of the intermediate formed **(23)** in **Scheme 18** with the intermediate **(33)** proposed by Ranganathan highlighted in **Scheme 14**, clearly shows the benefit of eliminating the external carbonyl earlier in the reaction mechanism. Intermediate **(23)** is much less crowded and can readily undergo the final steps in the reaction mechanism to form the vinyl bridge smoothly **(Scheme 19)**.



Scheme 19: Formation of indigo **(2**) from key intermediate **(41)**.[26]

1.5 Comparative Synthetic Routes

Sánchez-Viesca *et al.* then drew comparisons of the above proposal to that of the Henry reaction, a reaction in which the nitro group remains intact throughout the transformation. The Henry reaction is classified as an aldol coupling reaction. The transformation enables the formation of carbon - carbon bonds whilst simultaneously generating β-nitro alcohol functionality **(45)**. [31]

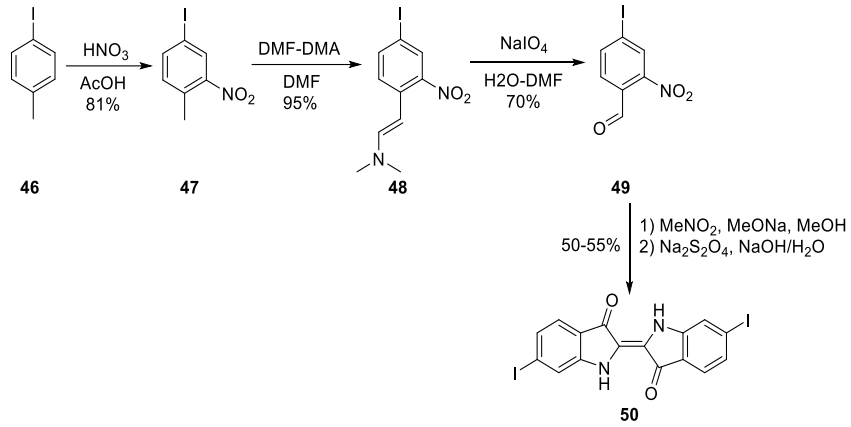


Scheme 20: Henry reaction[32]

In complex synthesis the Henry reaction facilitates the combination of molecular fragments, under mild conditions yielding potentially two asymmetric centres on either side of the newly formed carbon-carbon bond. The reaction can be catalysed or promoted via a range of differing catalysts and conditions, spanning organic bases, inorganic bases, quaternary ammonium salts, protic and aprotic solvents and solventless conditions.[32]The conditions utilised for the reaction are heavily dependent on the functionality present, the solubility of reagents and how readily the nitronate can be generated.

Initial iterations of nitroaldol reactions were promoted via variations of alkoxides or hydroxides in alcoholic or aqueous solvent systems.[32] The strong bases were used to promote reactions between relatively simplistic reagents bearing limited functionality.[32]

Some variation of this approach, namely the Harley-Mason reaction, have been reported in the literature in recent times (2021), with a utilisation of sodium methylate as a means of promotion.[20]

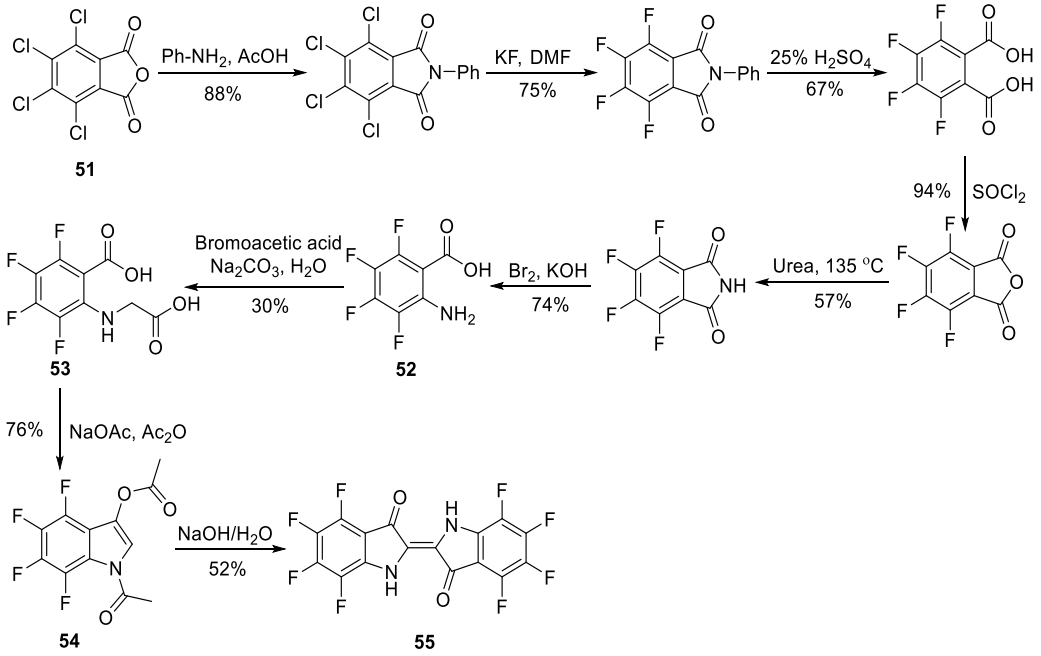


Scheme 21: The synthesis of 6,6' -diiodoindigo **(50)** via the Henry-Mason reaction.[20]

The reaction began with commercially available 4-iodotoluene **(46)** which was firstly nitrated in glacial acetic acid yielding 5-iodo-2-nitrotoluene **(47)**. The resulting compound was then reacted with *N,N'*-dimethylformamide dimethyl acetal and then subsequently oxidized by $NaIO_4$, to yield 4-iodo-2-nitrobenzaldehyde **(49)**. This aldehyde **(49)** underwent a two-step Harley-Mason reaction, yielding the desired indigo product **(50)** in a yield of 53%. The first of these two steps involved the treatment of the 2-nitrobenzaldehyde intermediate **(49)** with nitromethane in the presence of sodium methoxide, which proceeds analogously to the Henry reaction. In the second step a reduction in the presence of sodium dithionite yields the desired product, 6,6'-di-iodoindigo **(50)**.[20]

Klimovich *et al.* have also highlighted alternative approaches for the synthesis of a range of differing indigo derivatives, designed specifically for their potentially superior semi-conductor characteristics. These alternative approaches could not be adopted as part of this body of work due to the limitations of the required starting material but are interesting to highlight as alternative approaches that yield similar compounds.

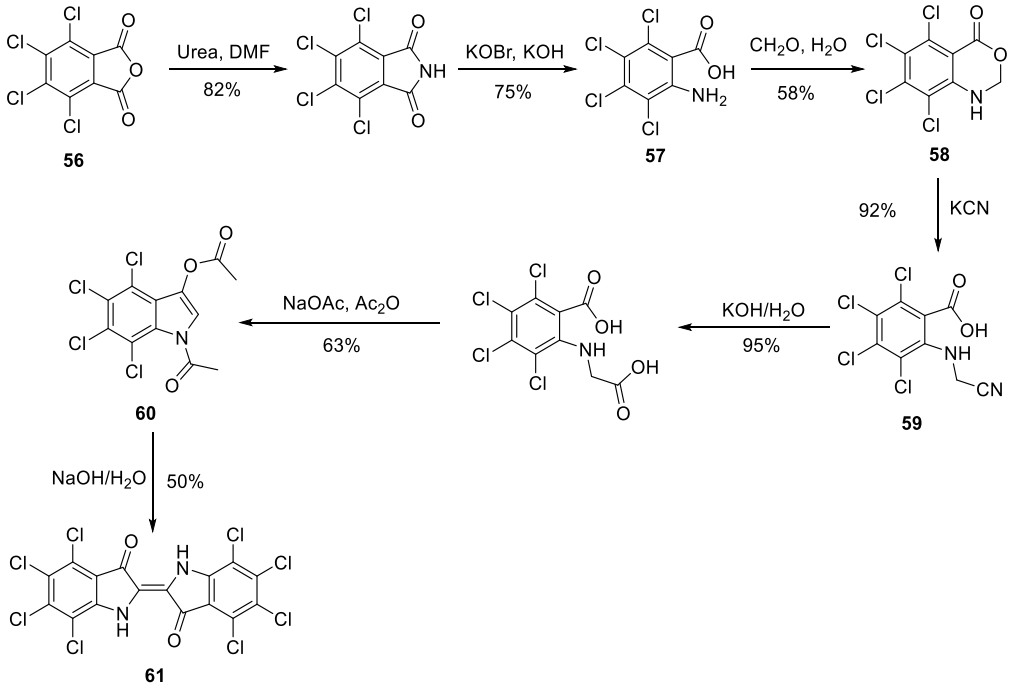
The first approach yielded octafluoroindigo **(55)** via the scheme highlighted in **Scheme 22**. This was a target of particular interest due to proposed benefits of halogen presence in the indigo derivative compounds. Increased ambient stability of n-type OFETs could be observed with compounds containing four fluorine atoms due to the decreased LUMO energy level.[33]



Scheme 22: Synthesis of octafluoroindigo **(55)**.[20]

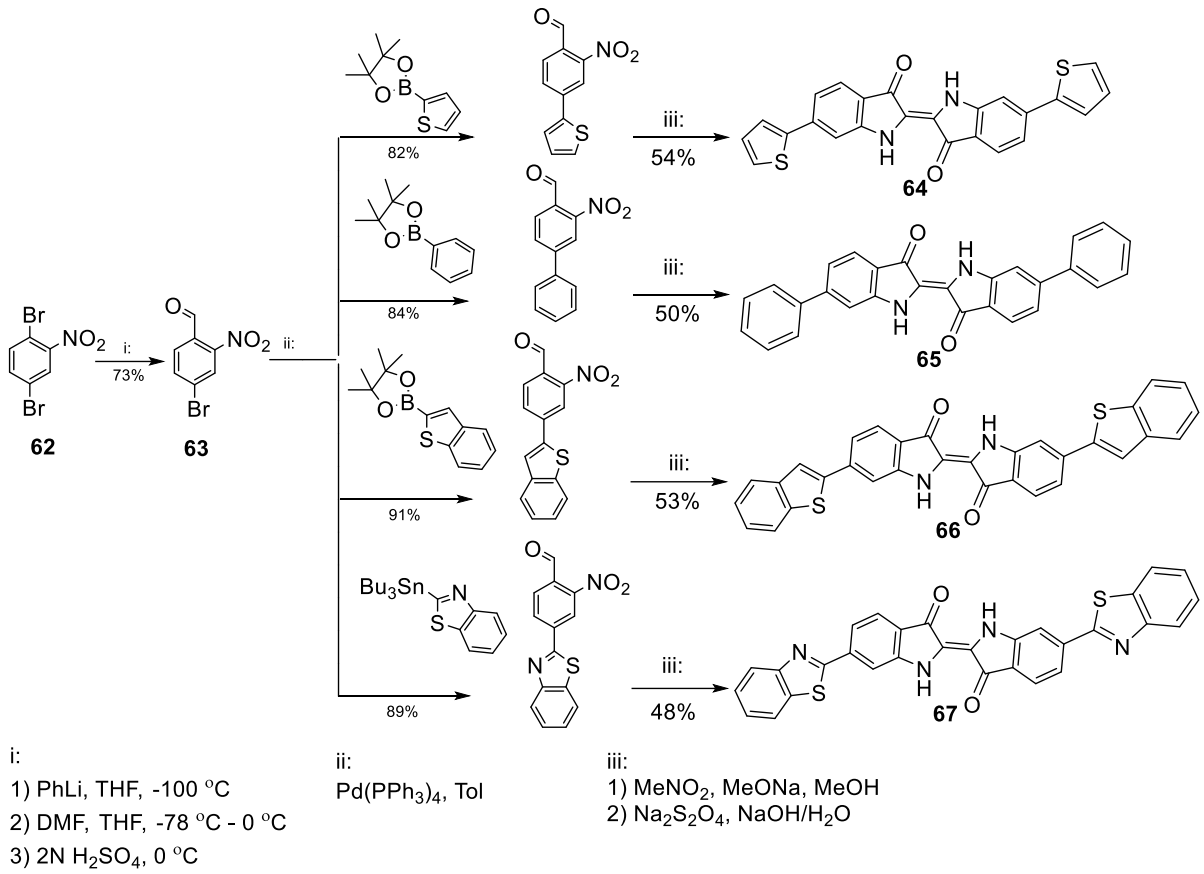
The limiting factor in the synthesis of octaflouroindigo **(55)** was the alkylation of antranilic acid **(52)** with bromoacetic acid, which was limited to a yield of 30% despite extensive attempted reaction optimisation. The desired indigo derivative **(55)** was obtained via an intramolecular Claisen condensation of carboxy aryl glycine **(53)** resulting in the formation of diacetylindoxyle **(54)**, which could then be hydrolysed under alkaline conditions yielding the desired dimer product **(55)**.[20]

Klimovich *et al.* also synthesised the analogous, octachloroindigo **(61)**. This synthesis avoided the limiting alkylation step of the aforementioned transformation **(Scheme 22)**. The antranillic acid **(57)** was treated with formalin leading to the formation of formalide **(58)**, which then underwent a ring opening by potassium cyanide leading to the formation of 2,3,4,5-tetrachloro-6-((cyanomethyl)amino) benzoic acid **(59)**. The tetrachloroindoxyl indigo precursor **(60)** was obtained via an alkaline hydrolysis of the nitrile followed by an intramolecular Claisen condensation.[20]



Scheme 23: Synthesis of octachloroindigo **(61)**[20]

Klimovich *et al.* also highlighted the synthesis of a wider variety of substituted indigo derivatives. These substitutions involved the introduction of phenyl, thienyl, benzothienyl and benzothiazolyl groups at the 6,6'-positions of the indigo compounds **(Scheme 24)**, as it has been highlighted that expansion of the indigo structure via the introduction of phenyl groups, can result in high-performance and air-stable ambipolar semiconductors.[34]



Scheme 24: Synthesis of a variety of substituted indigo derivatives.[33]

1.6 Vicarious Nucleophilic Substitution Chemistry

Despite this apparent utility of the Baeyer-Drewson synthesis for the generation of indigo and its derivatives on a laboratory scale, one limiting factor remains in relation to the generation of indigo derivatives with varying functionalisation. There is a reliance on the availability of suitably substituted aldehyde starting material, with many such compounds proving highly costly to purchase or not being commercially available.

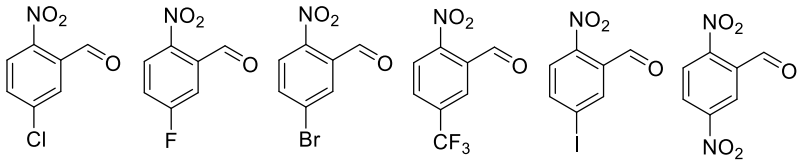


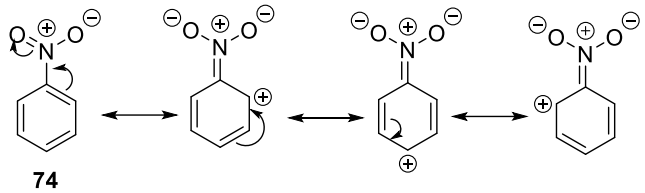
Figure 6: A range of interesting aldehyde starting materials for Indigo synthesis, showing indicative commercial pricing (Sigma-Aldrich, 2022)

As part of this work a method for the generation of such starting materials was conceived. This method would centre on the use of vicarious nucleophilic substitution chemistry.

Vicarious nucleophilic substitution chemistry (VNS chemistry) first appeared in the literature in 1987 when polish chemists, Mieczysław Mąkosza and Jerzy Winiarski[3536] first highlighted the reaction. VNS chemistry is an alternative to

more traditional methods of aromatic functionalisation. VNS reactions with halogenated nitroarene compounds typically proceed at a faster rate than more traditional nucleophilic substitution reactions.

The reaction requires the presence of a strong electron withdrawing group on the benzene ring, which is most commonly a nitro group. This group activates the *ortho* and *para* sites towards nucleophilic attack.



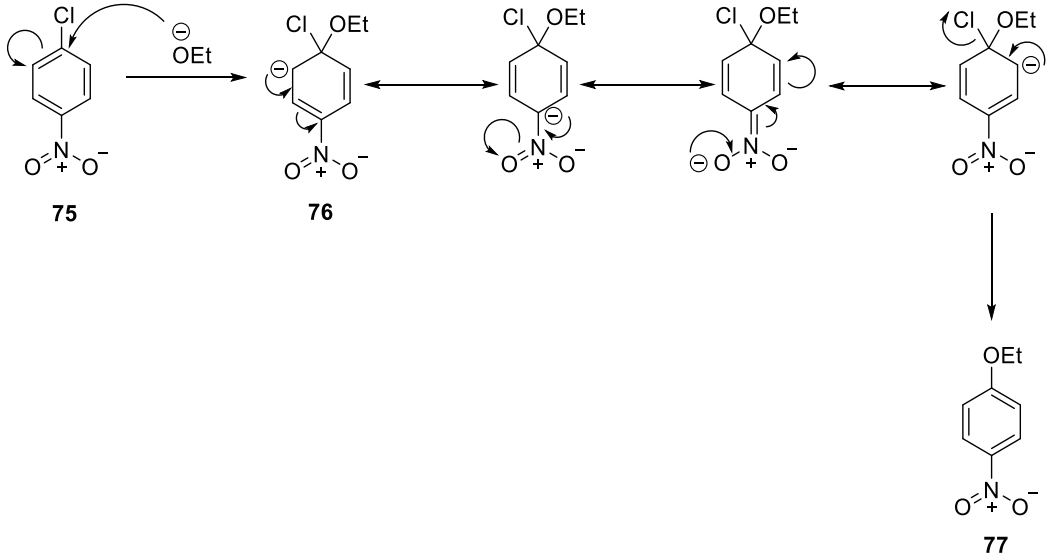
74

Scheme 25: Activation of the *ortho* and *para* position of nitrobenzene **(74)**

The chemistry is also tolerant of additional functional groups present on the ring, such as halogens. The position of these groups has a direct influence on the regiochemistry of the substitution, as the presence of functionality at the *para* site, relative to the nitro group, leads to formation of the *ortho* substituted product alone, whereas when functionality is present at the *ortho* or *meta* position, substitution can occur at both the alternative *ortho* site and the *para* position.

Unlike in the more traditional aromatic substitution methods, such as S_NAr processes, where the leaving group is associated with the electrophile, in VNS chemistry the leaving group is associated with the attacking nucleophile and is typically a halogen which is removed via a base promoted elimination prior to re-aromatisation.

Mąkosza and Winiarski modelled the reaction on the nucleophilic substitution of halogens such as *p*-chloronitrobenzene **(75) (Scheme 26)**. [37]



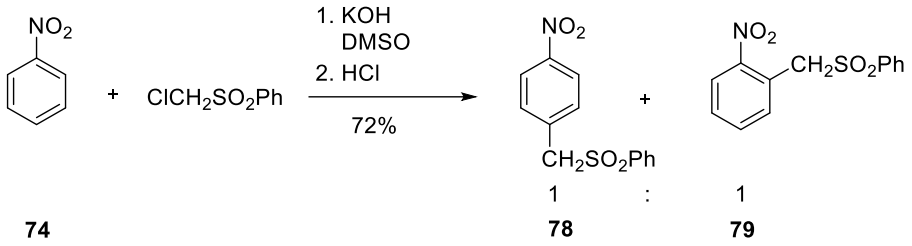
75 **76** **77**

Scheme 26: nucleophilic substitution of p-chloronitrobenzene **(75)**. [37]

As it is the nitro group that facilitates this substitution, it was established that similar addition to the ring carbon atoms bearing a hydrogen could also be possible.[37] Parallels were also drawn to polynitroarenes, as these compounds form relatively stable adducts with a variety of nucleophiles (Meisenheimer complex's). Initially and surprisingly, the addition of nucleophiles to carbons bound to hydrogen occurs at a faster rate than to carbons bound to other substituents, such as halogens.[37] This premise was used to surmise that this would also hold for the majority of mononitroarenes. It was assumed that the first step in the process is the fast and reversible addition of the nucleophile,

to the carbon atoms bound to hydrogen. The resulting adducts formed however, cannot lose the hydride ion resulting in dissociation and a return to the constituent reagents. This then leads to eventual substitution of the halogen instead, via a slower addition to the carbon containing the halogen.

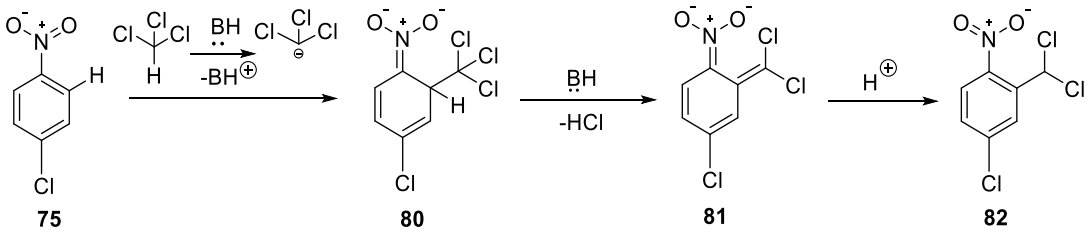
It was therefore determined that it was required to remove the hydride ion from the initial adduct, to successfully obtain the desired product. This however, could not be performed via treatment of the adduct with an external oxidant due to the rapid reversibility of the addition, its low equilibrium constant and the sensitivity of the carbanions to direct oxidation. It was hypothesised that the leaving group associated with the nucleophile, such as chlorine, could be removed from the adduct via a 1,2- hydride shift. A reaction was attempted to confirm whether this was in fact the case. Chloromethyl phenyl sulfone was reacted with nitrobenzene **(71)** in the presence of a strong base **(Scheme 27)**.[38]



Scheme 27: chloromethyl phenyl sulfone reaction with nitrobenzene (**74)** in the presence of potassium hydroxide.[38]

The reaction proceeded with the expected regiochemistry giving *o*- and *p*-nitrobenzyl phenyl sulfones **(78, 79)**.[38] It was however, observed that the leaving group was associated with the carbanion centre in the adduct, acting as a vicarious leaving group which in turn gave rise to the name of the reaction.

Further mechanistic studies were conducted following this discovery, which in turn revealed that the reaction proceeds to the desired product not via a 1,2-hydride shift as initially proposed but instead via a β-elimination of HX. This discovery however, had no impact on the stoichiometry of the reaction as the expected product would still be obtained.[39] As such the general scheme for the process can be outlined, as shown in **Scheme 28**.



Scheme 28: General scheme for a VNS process using chloroform as the nucleophile.

Mąkosza and Winiarski also showed that in the case where a halogen is present in the nitroarene **(75)**, *para* to the nitro group only one product can form, unlike in **Scheme 27**. This is due to the halogen blocking the *para* position, meaning that for substitution to occur at this position an S_NAR type reaction would have to occur. Unwanted S_NAr type reactions can be prevented by employing larger nucleophiles and non-nucleophilic bases such as tert-butoxide or hexamethyldisilane, as such nucleophiles are very slow regarding attack into the *para* position due to steric restraints when a halogen is present.

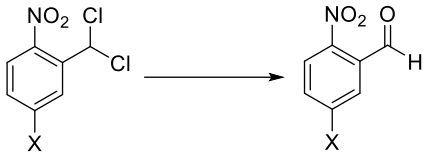
The identity of the base employed in the reaction is critical to its success, in addition to the required size considerations, the base must also be able to generate the carbanion nucleophile and be viable in the elimination step. As a result, Mąkosza and Winiarski proposed that a molar ratio of at least 2:1, base: acid should be employed for the reaction. The importance of the base and the solvent selection were also highlighted, to ensure successful

deprotonation of the nucleophile and efficient β-elimination of the HX from the intermediate adduct. The list of suggested base/solvent combinations consisted of pairs such as KOH, NaOH, *tert*-butoxide, or NaH in Me_2SO, liquid ammonia, or DMF.[35]

Note: In VNS reactions halogens, due to their electronegativity act as an electron withdrawing group via the inductive effect. As such, much like nitro groups, they are also *ortho*, *para* directing. However, as a nitro group has a much greater electron withdrawing affect and because the halogen itself is blocking the *para* position relative to the nitro group, substitution will occur selectively *ortho* relative to the nitro group as shown in **Scheme 28.**

1.7 Generation of Functionalised nitrobenzaldehyde Derivatives

The next stage in the reaction requires the conversion of the dichloro species to an aldehyde via hydrolysis **(Scheme 29)**.

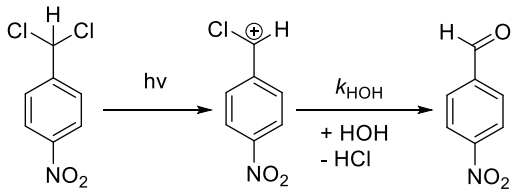


83 **84**

Scheme 29: Hydrolysis of dihalomethylated nitroarenes **(83)** to nitrobenzaldehyde **(84)**.

The current approach for this conversion involves the use of expensive catalysts and long harsh conditions which would not be conducive for larger scale reactions. This transformation can also prove challenging as alkaline conditions cannot be employed and under acidic conditions the reaction proceeds via a carbocationic pathway, which is drastically slowed by the presence of the nitro group.[44] The general procedure employed by Mąkosza and Winiarski is the treatment of the dihalomethylated nitroarenes with $AgClO_4$ in aqueous acetonitrile under heat. Under these conditions 4-chloro-2-(dichloromethyl)-1-nitrobenzene **(82)** was converted to the corresponding aldehyde with a yield of 60% after a 72-hour reaction time. [44]

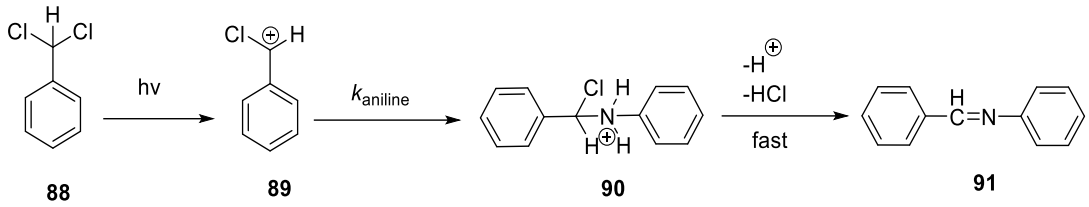
There is however, an alternative approach with potential utility for this transformation, negating the need for both traditional catalysts and the long harsh conditions. Instead relying on photoionization to instigate the hydrolysis to the desired aldehyde intermediate.



85 **86** **87**

Scheme 30: Conversion of dichlorobenzene **(85)** to nitro benzaldehyde **(87)**.[40]

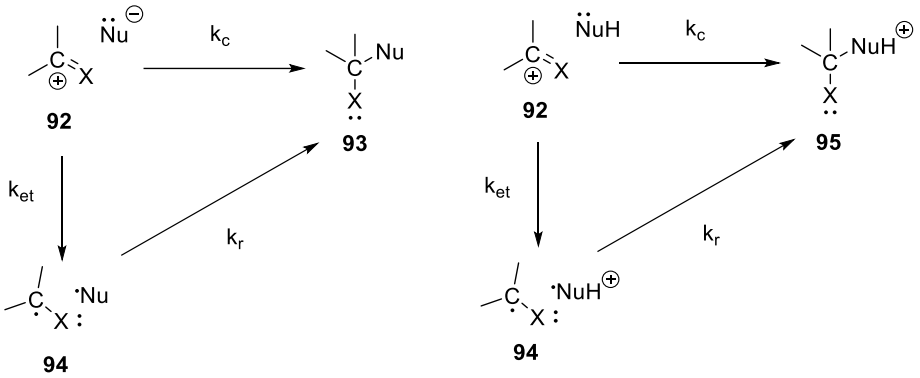
The transformation has been achieved via photoionization of the dichloro species **(85)**, in the presence of pure acetonitrile containing 0.1% of water. Under these conditions an acetonitrile solution containing 1×10^{-4} M of the dichloro species **(85)**, which had not photoionized for 2 years, solvolysed within two and half hours when photolysed with a 200-W mercury lamp, highlighting the potential utility of such an approach.[40] However, the conversion to the benzaldehyde **(87)** was not the intended aim of this work, instead the work was focused on devising a route for the formation of Schiff's bases as highlighted in **Scheme 31**.



Scheme 31: Formation of Schiff's base **(91)** from benzyl-gem-dichloride **(88)** starting material.[40]

The authors found that if aniline **(11**) was present in the reaction mixture, in addition to the acetonitrile, the Schiff's base **(91)** can be selectively formed due to the absence of water-amine hydrogen bonds in acetonitrile, meaning the α chloro benzyl cation **(89)** can be trapped by the aniline **(11)**.[40]

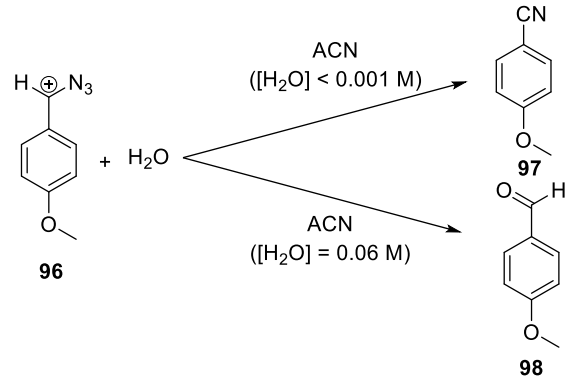
Richard investigated the solvent effects of addition reactions of anionic and neutral nucleophiles to carbocations, with the neutral nucleophile addition relevant in this case. For neutral additions an increase in absolute charge and solvation at the nucleophile site can be observed compared with the comparable anionic addition, as can be seen in **Scheme 32.**[41]



Scheme 32: Anionic (left) and neutral (right) nucleophilic addition to carbocation, where K_{et} (single electron transport pathway), k_c (direct nucleophile addition) and k_r (biradical pathway).[42]

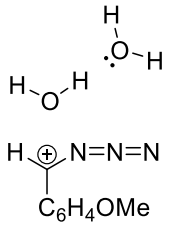
Richard also commented on the trends related to the enthalpy change of neutral addition in the gas phase. The trend focuses on the addition of water to the methyl carbocation and methanol to ethyl and isopropyl carbocations. The corresponding thermochemical data points were -276, -209 and -138 kcal mol^{-1} respectively.[42] Richard posited that this was a result of stabilisation of the carbocation by resonance at the site of addition, with further stabilisation resulting in a more endothermic reaction.

Richard centred discussion of the kinetics of the neutral addition on the reaction of water with α-azido-4-methoxybenzyl carbocation **(96)**. The rate equation for the reaction consists of a second order term, k_B and a 100-fold lager third order term, k_T, in nearly anhydrous acetonitrile ($[H_20] < 0.001$ M).[43] The equation was determined by comparison of the reaction products, from 86% 4-methoxybenzonitrile **(97)**, which forms as a result of a classic Schmidt rearrangement in nearly aqueous solvent, to >97% 4-methoxybenzaldehyde **(98)**, formed as a result of the presence of water in the reaction mixture, at a concentration of 0.06 M. Leading to the addition of the water to the α-azido carbocation **(96)** followed by loss of HN_3 from the α-azidohydrin.



Scheme 33: Reaction of α-azido-4-methoxybenzyl **(96)** with water in nearly anhydrous acetonitrile (top) and acetonitrile containing 0.06M water (bottom)[41]

The explanation was made that formation of oxygen-localized charge is unfavourable in the transition state for the addition of water to the delocalized α-azido carbocation in the organic solvent acetonitrile, meaning that the transition state must be stabilised by a second water molecule via "solvation". This may be a result of hydrogen bonding without formal proton transfer or general base catalysis.[41]



99

Figure 7: Stabilisation of oxygen-localised charge in the transition state of the addition of water to a delocalized α-azido carbocation **(99)** via "solvation".[41]

The approach highlighted by Sanjeev *et al*.[40] could be potentially utilised in the transformation required for the generation of the aldehyde starting material for the final transformation, without the requirement for expensive silver or zinc catalysts and harsh condition.[44]

This would also aid in the automation of the procedure as the source of the photoionization could be incorporated into the system. Leading to the potential of a telescoped or semi-continuous flow process, where the substituted nitrobenzene derivative **(83)** and chloroform could be fed into the system and the aldehyde derivative **(84)** obtained without the need for human intervention. This could be expanded further to generate a fully telescoped flow process for the synthesis of the indigo final product, as the Baeyer-Drewson indigo synthesis is a simple reaction and could be incorporated via the addition of acetone and water into the system.

All though this approach would be advantageous in the generation of functionalised indigo compounds at scale, one obstacle to such an approach may be the requirement of in-line purification/work up. Whilst in-line purification is readily reported on a laboratory scale in the literature, it is seldom reported for reactions at larger scales due to associated issues encountered when volume is increased. Instead, large scale off-line purification techniques are often preferred, which would limit the potential for a large scale fully automated synthetic route, meaning human intervention would still be required.

2. Project Aims:

1. Replicate the literature method for the generation of 4-chloro-2-(dichloromethyl)-1-nitrobenzene **(82)**, investigating the repeatability and reproducibility of the published results.
2. Investigate the feasibility of translating the batch procedure to a continuous flow process, for the synthesis of 4-chloro-2-(dichloromethyl)-1-nitrobenzene **(82)**, requiring the development and optimisation of a system and procedure, to generate the compound at a comparable scale to the literature method.
3. Expand the scope of the reaction by establishing whether the chemistry can be translated to a variety of halogenated and non-halogenated nitrobenzene starting materials.
4. Evaluate the scale up of the synthesis to generate the compounds of interest at scale.

Results and Discussion

3. Replication of Literature Method

3.1 Preparation of 4-chloro-2-(dichloromethyl)-1-nitrobenzene (82).

The synthesis of 4-chloro-2-(dichloromethyl)-1-nitrobenzene **(82)** via the use of vicarious nucleophilic chemistry was first reported by Makosza and Owczarczyk in 1989.[44]

The reported experimental procedure was:

To a vigorously stirred solution of potassium *tert*-butoxide (1.44 g, 12 mmol) in a mixture of dry THF (5 mL) and dry DMF (4 mL) cooled at -78 °C under argon, a solution of 1-chloro-4-nitrobenzene **(75)** (0.47 g, 3 mmol) and chloroform (0.59 mL, 0.39 g, 3.30 mmol) in dry DMF (1-2 mL) was added dropwise with a maximum rate whereas the temperature does not exceed -68 °C. The mixture was then stirred at this temperature for 1 min and acidified with acetic acid (1.50 mL) or concentrated hydrochloric acid (2 mL) dissolved in methanol (3 mL). The mixture after reaching room temperature was poured into water (150 mL), and the products were extracted with dichloromethane (3 × 30 mL). The extracts were washed with water (3 × 50 mL) and dried with anhydrous Na_2SO_4, the solvent was evaporated.

This reaction procedure was carried out on a 3 mmol scale and a yield of 94% was reported for the reaction.[44] Replication of this synthesis was a starting point of the work outlined in this report.

3.2 Problems Associated with the Literature Method

Replication and reproducibility of the results outlined in Makosza and Owczarczyk's paper could not be achieved. This may be due to undisclosed parameters such as the rate of addition of reagents and the variation in this parameter that can occur between each reaction. The reaction is, as alluded to, highly exothermic and as such the rate of addition must be managed careful to mitigate any detrimental effect that may result from temperature spikes.

The reaction was therefore carried out at -78 °C to negate this issue as much as possible. However, the reaction was found not to be viable if it exceeds -68 °C, due to the instability of the anions, as such slow addition of the reagents into the basic mixture is required to not exceed this value. Makosza and Owczarczyk note that effective cooling and stirring are essential to mitigate the affect this may have on the reaction. It was also noted that any small variation in such parameters can have a drastic effect on the success of the reaction,[44] an observation we fully agree on. Due to addition rates being dependant on temperature increase, the rate can differ drastically from run to run which can then negatively impact reaction success. Additionally attempted scale up of the reaction proved very challenging, due to the base employed in the reaction.

Initial attempts at replication and scale up of the method outlined by Makosza and Owczarczyk, **(Section 3.1)** are summarised in **Table 1.** The reaction was first carried out on a small 3 mmol scale and as such scalability was not a concern **(Table 1: Entry 1)**. However, upon scaling the reaction to a 15 mmol scale, in line with the desired scale of the reaction, a challenge presents itself **(Table 1: Entry 2,3,4 and 5)**. The base used in the reaction, potassium *tert*-butoxide, presented solubility challenges at this scale, despite its relatively high solubility of 25g 100 mL^{-1} in pure THF. As such the reaction had to be conducted at room temperature to solubilise the base, however this had a detrimental effect on the success of the reaction, due to the issues associate with anion instability.

These two factors meant that the previously outlined method for the synthesis of the dichloro nitrobenzene indigo precursors was not sufficient to generate the required compounds at scale. As can be seen in **Table 1,** where at a 15 mmol scale the maximum percentage conversion that was obtained was an unsatisfactory 55% **(Table 1: Entry 2)**. As such a new method had to be developed and adopted to generate the desired compounds at scale.

Table 1: Attempted replication of the synthesis of 4-chloro-2-(dichloromethyl)-1-nitrobenzene **(82)** via Makosza and Owczarczyk's literature procedure.[44]

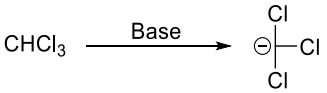
Entry number	**Parameters altered**	**Base**	**1-chloro-4-nitrobenzene sol. composition**	**Solvent system**	**% Conversion (^{1}H NMR)**	**Comment**
1	N/A	Potassium *tert*-butoxide 12 mmol	1-chloro-4-nitrobenzene 3.00 mmol, Chloroform 3.30 mmol, DMF 1-2 mL	THF 5.00 mL, DMF 4.00 mL	84	N/A
2	5x scale up, 15 mmol scale	Potassium *tert*-butoxide 64.16 mmol	1-chloro-4-nitrobenzene 15.00 mmol, Chloroform 15.50 mmol, DMF 5.00-10.00 mL	THF 25.00 mL, DMF 20.00 mL	42	Base solubility issues
3	Conducted at RT, No DMF used in 1-chloro-4-nitrobenzene sol.	Potassium *tert*-butoxide 64.16 mmol	1-chloro-4-nitrobenzene 15.00 mmol, Chloroform 15.50 mmol	THF 25.00 mL, DMF 20.00 mL	0	No base solubility issues observed
4	Conducted at RT, DMF reintroduced	Potassium *tert*-butoxide 64.16 mmol	1-chloro-4-nitrobenzene 15.00 mmol, Chloroform 15.50 mmol, DMF 5.00-10.00 mL	THF 25.00 mL, DMF 20.00 mL	45	No base solubility issues observed
5	Conducted at RT, peristaltic pump used	Potassium *tert*-butoxide	1-chloro-4-nitrobenzene 15.00 mmol, Chloroform	THF 25.00 mL, DMF 20.00 mL	55	No base solubility issues observed

	to deliver 1-chloro-4-nitrobenzene solution at a flow rate of 0.20 mL/min	64.16 mmol	15.50 mmol, DMF 5-10 mL			
6	Conducted as per entry 5, 3 mmol scale	Potassium *tert*-butoxide 12 mmol	1-chloro-4-nitrobenzene 3 mmol, Chloroform 3.30 mmol, DMF 1-2 mL	THF 5 mL, DMF 4 mL	53	Solubility issues observed.

4. Choice of Base

4.1 Alternative Base

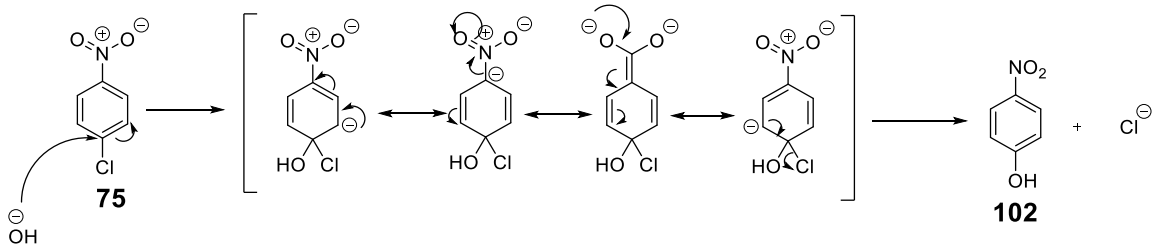
Due to the encountered solubility issues associated with the potassium *tert*-butoxide in the method outlined by Makosza and Owczarczyk [44] when the method was conducted at larger scales, alternative bases had to be explored. The selected base would have to be of sufficient strength to order to promote efficient deprotonation of the nucleophile, chloroform.



100 **101**

Scheme 34: Deprotonation of chloroform **(100)** to generate chloroform anions **(101)**

A suitable base would also have to have sufficient bulk, as smaller, less bulky, bases are able to undergo traditional S_NAr reactions when in the presence of halogen containing compounds. An example of a base that would undergo such a reaction is sodium hydroxide (NaOH). The hydroxide anion would act as a nucleophile attacking at the *ipso* position on the ring, which is activated via the presence of the nitro group *para* to the halogen leaving group.



Scheme 35: Mechanism for S_NAr substitution of 1-chloro-4-nitrobenzene **(75)** with hydroxide anions.

A simple solution would be to employ a solution of potassium *tert*-butoxide dissolved in a solvent, as is commercially available, in the form of a 1 M solution of potassium *tert*-butoxide in THF. The problem however, is the cost associated with the base. A 50 mL bottle of the solution commands a price of £83.80, with two litres of the solution reaching a total of £970 (Price from Merck Chemicals as of 09/07/24). Due to this project's heavy reliance on the base for the

efficient deprotonation, required for a successful reaction, and the anticipated high volume of base that would be required (>2 equivalents required), this option proved economically unviable.

As such a suitable, alternative, base had to be identified. The base that was ultimately carried forward for the remainder of the project was metalated *bis*(trimethylsilyl)amide (HMDS) **(103)**. The anion of HMDS shares the bulky nature of potassium *tert*-butoxide by virtue of the six methyl groups present in the structure **(Figure 8)**.

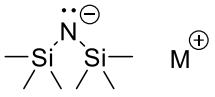


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Figure 8: Structure of bis(trimethylsilyl)amide where M denotes a metal. **(103)**

Due to the size of the compound the base does not undergo S_nAr reactions, but has sufficient strength, to deprotonate chloroform, as its conjugate base has a p*Ka* of ~26 compared with a p*Ka* of ~18 for *tert*-butoxide. HMDS is commercially available as the lithium, sodium or potassium salts. The lithium base is available, as a 1 M solution in THF. The sodium base is available as both a 2 M and 1 M solution and the potassium variant offered in a 20% w/w solution in THF.

The first base tested was the 2 M solution of NaHMDS. This base was employed using analogous conditions/parameters to the method outlined by Makosza and Owczarczyk.[44] The best conversion to the desired product achieved with this base was a quantified NMR conversion of 50%. This modest conversion was likely a result of the reaction mixture freezing at the low temperature of -78 °C halting the reaction. As the base solution used was a 2 M solution, a reduced volume was required to facilitate efficient deprotonation. This in turn meant that the volume of THF present in the reaction mixture was reduced, as the base solution was the sole source of THF in the reaction.

In the reaction THF is present to negate the risk of the reaction mixture freezing, as its freezing point of -108.4 °C is significantly lower than the temperature of the dry-ice acetone bath used in the reaction. Without the presence of the THF in sufficient volume the chloroform and DMF are both susceptible to freezing, as they have freezing points of 63.5 °C and 61 °C respectively. This was noted as being detrimental to the success of the reaction and an alternative base solution had to be found. Issues associated with the temperature and freezing of reaction mixtures will be explored in more detail in **Section 8** of this report.

A new 1 M solution of LiHMDS was next investigated. The base was substituted like for like with the *tert*-BuOK used in the original method[44] whilst the remaining reaction parameters were unchanged. Unlike the previously attempted reaction, no freezing of the reaction mixture was observed and the reaction proceeded for the intended run time (10 minutes) uninhibited. An initial conversion of 73% was achieved. Although still far below the reported yield of 94% achieved by Makosza and Owczarczyk, the conversion provided a solid starting point for reaction optimisation. As such repeatability of the result was investigated. Conversion dropped to 43% on the subsequent run and dropped further again on the following reaction to 30%. This not only indicated a lack of repeatability but also indicated that the lithium base solution may not be suitable for use in the reaction.

In the hopes of achieving reproducibly high conversions, a 1 M solution of NaHMDS was introduced. The solution was used in line with the conditions described in the original method.[44] No freezing was observed and the reaction proceeded for the allocated run time, 10-minutes, without issue. Good conversions were observed, with a conversion of 96% for the initial run followed by a conversion of 90% for the subsequent run. Indicating good repeatable conversions could be achieved using the sodium base. Despite this, the potassium base was still investigated to ensure the potential utility of all commercially available bases were explored.

The potassium base yielded comparatively strong conversion to the sodium base and once again proceeded uninhibited for the intended 10-minute run time. An initial conversion of 67% was observed. However, upon repeat a yield of 99% was achieved, the highest percentage conversion achieved as this stage of the project. Despite the positive outcome, the variance between the conversion of the first and second run was cause for concern regarding repeatability.

4.2 Summary

From the data collected it appeared that the sodium and potassium bases facilitate the most effective conversions. Indicating that the counter ion of the base has a significant effect on the success of the reaction. This is most apparent in the disparity between the conversions observed for the lithium base, compared to that of the potassium and sodium bases. The effect of the counter ion of the base became more apparent as the project progressed and will be discussed further in **Section 2.3.9**. However, at this stage of the project it was still unclear whether the issues with repeatability were solely due to the base used or a culmination of other factors.

The main factor that leads to conversion variation may have been the rate at which the reaction occurs. As detailed in **Section 1.2**, an inherit flaw with the method outlined by Makosza and Owczarczyk[44] is the limitation on the addition rate as to not exceed -68 °C. As the rate of addition is dependent on the temperature response, the time taken for complete addition of the reagents can vary drastically from reaction to reaction which may impact the overall conversion observed.

This is a factor that is independent of the base used and cannot be negated whilst still conducting the reaction as a batch process. As such a flow chemistry approach was introduced in the hopes of achieving greater repeatability, that could facilitate more informed method develop through establishing reliable trends in the data. The lithium base was used in preliminary investigations using a flow reactor, due to the high conversions and repeatability observed when using the base in the batch procedure.

5. Flow Chemistry

5.1 Summary of Flow Chemistry.

The key and commonly reported benefits of flow chemistry are often cited as better mixing, more efficient heat transfer and easy scale up,[45] all of which would prove beneficial in the case of this project. Flow chemistry reactions typically occur within one of three types of reactors: coils, chips or packed bed reactors. The latter is typically used when a heterogeneous catalyst or reagent is required in a transformation within a continuous set up. As the name suggests in packed bed reactors the reactor is loaded with the catalyst/reagent required and the corresponding gas/liquid is passed through the reactor, facilitating the required transformation. As catalysis was not required for the project, logically packed bed reactors had no potential utility and were not explored as part of this work. The remaining two types of reactors: coils and chips both have applications in liquid-liquid systems and as such were both utilised as part of this work.

Chip reactors offer excellent heat transfer properties due to their extremely high surface-to-volume dimensions.[46] Due to the small diameters of the channels in a chip reactor, excellent mixing can also be achieved. However, due to the small diameters, chip reactors also have extremely low throughputs and can more readily experience blockages. These chip reactors are also often costly to manufacture.

Coil reactors are comparatively inexpensive and are widely used in flow synthesis. They are often made from commercially available tubing and as such can be configured as per the requirements of the given transformations. The tubing used typically has an outside diameter of 1/8” or 1/16”, and an internal diameter in the range of 0.01” to

1/16".[45] Due to the increased diameter of the tubing, mixing is generally less effective although this can be negated via the introduction of obstacles such as PTFE static mixers that can distort the flow pattern of a liquid within the reactor to encourage more effective mixing by increasing the interactions between reactants. The temperature of both types of reactors can be easily controlled, by the submergence of the reactor unit in either heating or cooling baths. Alternatively, this can also be achieved by mounting the reactor on a thermostatic unit.[45]

In flow chemistry the reagents and reactants are fed into the reactor via pumps. The rate at which the species are fed into the system can be precisely controlled to ensure uniform conditions are maintained. There are four main types of pumps that are typically used with a flow set up[47] each with particular uses and drawbacks. The first type of pump is a HPLC pump. These pumps are able to deliver a pulseless flow against considerable back pressure ensuring a reproducible flow rate can be maintained. The pumps can operate at pressures up to 1000 bar, accommodating high flow rates. HPLC pumps are susceptible to fouling and blockages when used with certain reagents, as the reagent pumped is in direct contact with the pump system.[45] Syringe pumps are the next class of pumps that are commonly employed in flow chemistry set ups. These pumps fall into two categories, single or dual syringe pumps. Single syringe pumps are the more simplistic. They consist, as the name suggests, of a singular pump unit that delivers a fixed volume into the system. The usefulness of such pumps is limited by this fixed volume, although the size of syringe can be altered, changing the working range of the instrument. Unfortunately, constant uninterrupted flow can't be achieved using this type of pump. By contrast dual syringes, which are paired with solvent/reagent reservoirs and check valves, can provide un-restricted continuous flow.[48] Dual syringes achieve this by the two syringes working independently and conversely of one another. Whilst one pump fills with the reagent or solvent the other pump dispenses it into the system, ensuring a continuous cycle of delivery is maintained. These types of pumps are particularly advantageous due to their high levels of accuracy and precision and the low pulse delivery that can be achieved. However, one downfall of these type of pumps, particularly in the context of this project is an incapability to deal with solids or slurries. This ruled out the use of such pumps as part of this project as slurry formation was ever present throughout the project.

Another class of pump that are better equipped to deal with slurries, are peristaltic pumps. The pumps operate via the use of a circular roller mechanism powered by a motor. This roller mechanism causes compression and relaxation of tubing that surrounds the mechanism. The alternation between compression and relaxation forces fluid from the input to the output. The speed at which this process occurs can be controlled precisely, once calibrated, allowing for accurate flow rate regulation. These pumps also require minimal maintenance as there are no valve or seals on the pump, also making the pump easy to clean. Which is highly beneficial in method development where a high number of runs may be required, or once a method has been established and longer runs may be conducted. A downside of peristaltic pumps is the pulsation present in the fluid flow; this however is only typically problematic at lower flow rates. Meaning this problem is essentially negated as long as a sufficiently high flow rate is employed.

One of the unavoidable downsides of using such a pump is the degradation of the tubing used to connect the inlet and outlet. There are two main factors that affect the rate of degradation of the tubing. The first being simple mechanical wear. Due to the mechanism of the pump this is an inevitability, due to interaction between the tubing and the moving central roller, the tubing become worn over time limiting the lifetime of the tubing. The second factor is dependent on the transformation being carried out, and the solvent/ reagents used to facilitate it. Certain chemicals interact poorly with the tubing, weakening the walls and leading to protruding bulges and micro tears, leaving the tubing unusable. The tubing can be replaced although this incurs a cost, in downtime and budget. Chemical compatibility with the tubing was an issue throughout the project and the problems encountered are summarised in **Section 19.1**.

Gear pumps can also be employed in flow chemistry systems. These pumps operate via the meshing of gears within a sealed cavity case, providing an essentially pulse free-flow, proportional to the speed at which the gears rotate. These pumps are typically relatively cheap, simple and compact. They can be used at high pressure, flow rates and temperature and can handle high viscosity liquids. However, they require an external mass flow controller to control flow rate and also must be operated close to maximum speed in order to maintain performance, limiting the usefulness

of such pumps. In most scenarios these are most beneficial for use at high volume throughputs, and as such are well suited to manufacturing scales.

The final type of pump is a piston pump. These pumps are typically only employed when a reaction is carried out at high pressure. These pumps can handle pressures up to 400 bar. Piston pumps particularly excel when dealing with heavy fluids where a non-pulsating flow is not vital. This pulsation may be problematic, as previously discussed, at low flow rates where precise control is required. These pumps are seldom used outside of the conditions in which they excel, as at lower pressure alternative pumps perform more optimally.

The flow rate of a system is the culmination of the rate at which each of the separate pumps within the system deliver reagents to the reactor. The quicker each of the pumps deliver the reagents, the greater the overall flow rate of the system is. This rate is a key factor in the residence time of the system. The residence time is the time in which a molecule spends within a reactor. The mean residence time of a system can be simply calculated by dividing the reactor volume by the flow rate. The value obtained is often sufficient to inform any optimisation that may be required surrounding this parameter.

At lower flow rates / longer residence times, the way in which fluid moves through the reactor, which is known as the flow pattern, can be discounted as a key reaction parameter. This is due to all flow patterns having equal mass transfer at lower flow rates. However, the throughput from a system is hindered by increasing the residence time of a system as the reactants stay in the reactor for a longer duration. As such a trade-off must be made. At the higher flow rates / shorter residence times the throughput of the reactor can be improved, although flow patterns can now have a inherit impact on the success of a reaction. Consequently, reactor design and structure become vital, the introduction of obstacles within a reactor can be an efficient way to ensure the success of a reaction as these obstacles can enhance liquid-liquid surface areas and heat transfer.[45]

Although molecules do not spend a uniform amount of time in a reactor, a concept known as residence time distribution. Either side of optimum reaction time there will be a certain proportion of molecules that spend longer in the reactor and hence “overreact”, and the inverse is true for molecules that spend less time in the reactor and hence “underreact”. This can prove problematic in highly selective reactions that relying on exact residence times. The adverse effects of this distribution can be negated by employing a longer than required residence time to ensure all molecules have undergone a complete reaction, although this approach does introduce the possibility of unwanted side reaction due to the extended residence time, therefore this strategy works best when the product formed has a high inherent stability.

Precise equipment can also be used to narrow a residence time distribution curve, such as pumps with low variability. Similarly clever reactor design can also be implemented to achieve this such as in the case of Klutz *et al.*,[49] where a coiled flow inverter (CFI) was incorporated into the system. The design was centred around “several straight helix modules, where the tubular reactor is coiled around a coil tube. After each straight helix module, the coil direction is changed by a 90° bend.”[49] The optimised reactor consisted of 27 bends and operated at a flow rate of 3 mL min^{-1} with a mean residence time of 2.6 h. In addition to narrowing the residence time distribution the reactor proved compact and cost effective whilst also being suitable for scale up and for a range of uses. Highlighting the benefits of tackling problems associated with residence time distribution in this manner.

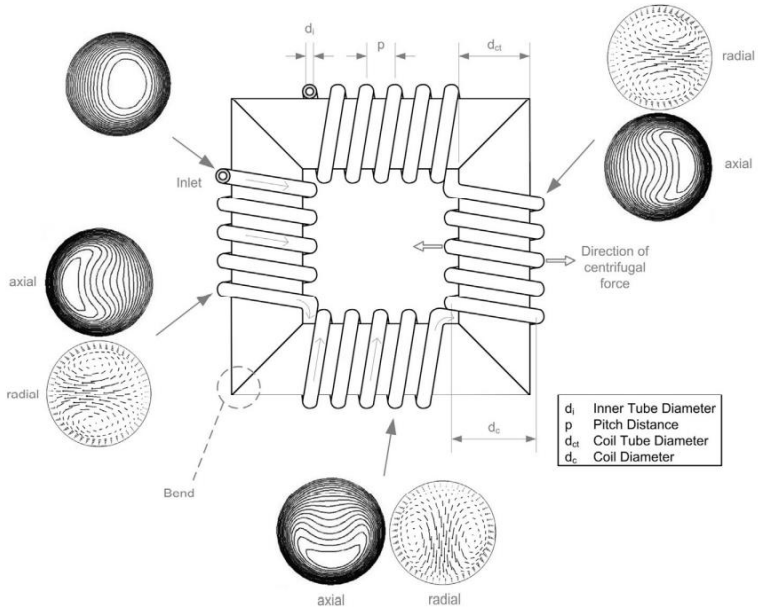


Figure 9: CFI design parameters and corresponding cross-sectional axial velocity profiles showing the effect of centrifugal force – Replicated from Klutz[49]

Once the reaction mixture has passed through the reactor, and the reaction has been quenched, often through the union of an auxiliary flow stream, the material then requires analysis to ascertain the degree of the transformation. Integrated analysis within flow chemistry systems have been widely reported. However, material often requires purification prior to any analysis being conducted. The success and feasibility of such purification can depend on the nature of the material.

Inline purification can be characterised into four categories: extraction/separators, scavengers, chromatography and crystallisation. Inline extracting/separation is typically achieved with either semi permeable membranes or gravity separators. The former is employed when two immiscible liquid-liquid phases, typically an organic and aqueous phase, require separation. Factors such as viscosity, interfacial tension or salt concentration, in the case of aqueous solutions, need to be considered in order for successful use of such a technique. This approach is not typically used as a final purification step and is instead often used to remove spent reagents, unreacted reagents and remaining catalyst. Membrane based liquid-liquid separators also allow for the gradually adjustment of pH to facilitate continuous purification, although the target compound must be ionisable for this approach to work. This approach can prove costly and presents challenges when scaling the reaction.

Aqueous extraction was first referenced in the literature in 1974 by Siraganian, where a gravimetric separator was employed in the extraction of histamine.[50] The Ley group widely expanded the approach, employing a "computerised vision" approach where the interface level between the organic and aqueous layer was observed via a camera connected to a computer programme.[51] The speed in which the two layers separated was key to the success of the approach to ensure complete partition, along with the importance of sufficient separator dimensions in order to overcome surface forces that dominate at smaller scales.[51] Similar approaches have been employed by Maguire *et al.* who used 3D printed separators in the telescoped synthesis of α-diazo-β-keto esters and α-diazo-β-ketosulfones.[52]

The second approach for purification is inline scavengers. This approach works particularly effectively on small scales. Isolation of a pure product can be achieved by using heterogeneous scavengers within in-line packed bed loaded cartridges. To achieve isolation of a pure product various scavengers and immobilised reagents can used in conjunction. These cartridges can however, easily foul meaning they need to be replaced or regenerated frequently.[47] This can prove costly when transformations are scaled due to the amount of material processed. This approach is better suited to removal of minor impurities as opposed to stoichiometric by-products or large excesses of reagents.

As offline purification in these cases often proves more efficient and less costly. Scavengers can be particularly useful in the removal of leached metals or catalytic amounts of homogeneous metal. Once again on larger scales this approach is not typically used as offline purification is generally more fruitful.

Similar to scavengers, catch and release methods of purification can also be implemented in flow systems. This approach involves the trapping of the desired compound onto a solid phase media within a heterogeneous matrix cartridge, followed by the release of the pure form of the compound, typically consisting of a change in solvent, pH or ionic strength. This approach has similar limitations to the use of scavengers, in addition to the potential retention of undesired compounds within the cartridge due to similar functionalities being present.[47] This approach does have utility when paired with biocatalysts, as the trapping cartridge can be used downstream from the biocatalytic process trapping the pure product whilst the unused reagents can be recirculated in a closed loop system as shown by De Vitis *et al.*[53]

Purification via chromatography is one of the most commonly employed methods of purification within traditional batch chemistry. Contrastingly this is not the case within flow systems, as flow reactions that incorporate in-line chromatography are scarce. Despite this scarcity both normal and reverse phase chromatography is possible within a continuous flow set up. An example of the use of chromatography within a continuous flow set up can be seen in the recently reported use of puriFlash® systems.[54,55]This system act as a scale up preparative HPLC and operates via the use of two sample loops. The first of which loads the material and the second injects onto the column. This process is repeated in an alternating fashion to perform a type of continuous purification.

Despite the broad compatibility of this approach due to the use of SiO_2 as a stationary phase, this approach does encounter some limitations. Issues can arise from the need to overcome solvent incompatibility, column fouling, removal of particulates and the rapid elution of highly polar compounds.[47]Additionally inline chromatography is not suitable for reactions with a mean residence time of less than one minute as the two-loop system cannot process such a high throughput of material, very dilute solutions also cannot be processed in this manner along with co-polar species due to the similarity in the retention on the column. Inline chromatography also losses viability at scales greater than 100 g which is problematic for reaction scale up.

5.2 Flow Set Up

A three-pump system was required to facilitate the desired transformation to form the dichloro nitrobenzene indigo precursors. Vapourtec SF-10 peristaltic pumps were used initially. These pumps can operate at flow rates ranging from 0.02 mL min^{-1} to 10 mL min^{-1}. Prior to any kind of method development or trial runs it was apparent that the optimal flow rate would fall within this range and as such these pumps would be sufficient for the reaction. These pumps can also tolerate the presence of light slurries, which as the project progressed would prove vital. Additionally, the pumps can also operate at pressures up to 10 bar, which was predicted to be sufficiently high, as all reagents used within the reaction are in the majority liquid phase limiting the potential for pressure build up.

The three pumps were each connected to a differing reagent via a metal needle submerged with the solutions connected to standard PFA tubing with an internal diameter of 1/32” and an outer diameter of 1/16” delivering the reagents to the pump. The first pump was connected to the base solution, which in all cases was a HMDS base in THF. The second pump was connected to the nitrobenzene derivative in DMF, in some runs THF was also incorporated into this solution. The final pump was connected to an acidic quench solution which across all runs was made up of a variation of acetic acid or hydrochloric acid and methanol.

Connected to the outlet of the pump was more PFA tubing that transported the reagents towards the reactor. Prior to the reagents entering the reactor the two fluid streams were mixed. This was initially achieved with the use of a “T” mixer, although as the project progressed this was exchanged for a “Y” mixer. The “T” mixer used was commercially available and was purchased from Upchurch Scientific® this mixer was made of FEP plastic, 1/4”-28 Flat-Bottom, for

1/16" OD. The “Y” mixer was made as per the required specifications for the project. The “Y” mixer had dimensions of two 1/4” – 28 UNF inlets, an internal diameter of 3 mm and an outlet of 5/16”.

Once the two reagents had mixed, they were fed into a reactor. Initially a commercially available 2 mL Uniqsis chip reactor was employed however, as the project progressed this was altered to a 20 mL coil reactor. This reactor was custom built from commercially available PFA tubing with an external diameter of 1/8” and an internal diameter of 1/16”. PTFE static mixers were also utilised within the coil, to increase mixing efficiency. The entire reactor was submerged in a dry ice/acetone bath to ensure the reactor remained at -78 °C. The reaction mixture was then transported out of the reactor by more commercially available PFA tubing with an internal diameter of 1/32” and an outer diameter of 1/16”. The reaction mixture then passed through a T mixer where the third pump introduced the quench solution. This quenched solution was collected in a collection flask and worked up offline as per the procedure outline in **Section 3.1**.

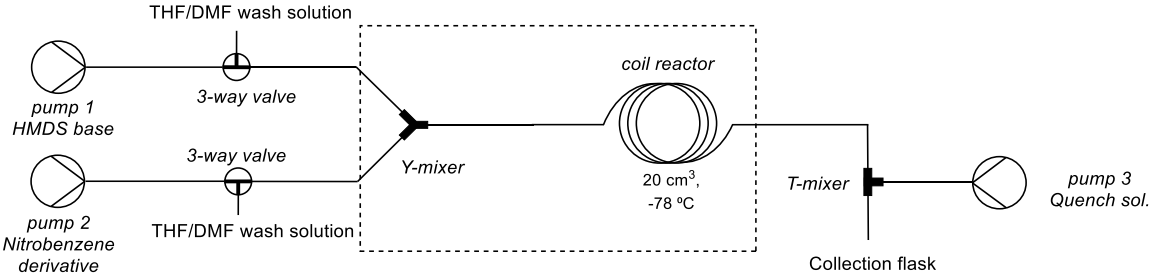


Figure 10: General schematic representation of the flow system.

6. Overview of Reaction Monitoring

6.1 Unsuitable Methods for Reaction Monitoring

Thin layer chromatography (TLC) would have been a useful tool for reaction monitoring, through a comparison of the obtained Rf values of the starting material and the product of the reaction. However, for this to be a viable option there has to be a noticeable difference between the two corresponding materials on the TLC plate. This was unfortunately not the case in this transformation. The starting material and the desired product had effectively identical Rf values, rendering the use of TLC futile. This would also prove an issue in the purification of the compounds as is discussed in **Section 13** of this report.

A range of solvent compositions were explored in the hopes of achieving two distinguishable species on the plate. For example: 95:5, hexane: toluene; 70:30, hexane: chloroform; 80:20, hexane: chloroform; 100, chloroform; 50:50, hexane: chloroform; 95:5, hexane: chloroform; 90:10, hexane: ethyl acetate; 100, hexane; 95:5, toluene: acetonitrile; 100, toluene. Separation between the two spots of interest was insufficient across all ten solvent systems. 100% hexane showed some potential, although it still lacked any diagnostic utility.

Mass spectrometry was also investigated for its diagnostic potential. Both liquid and gas chromatography were considered. LC-MS was trailed first, following a 10-minute run with 1-chloro-4-nitrobenzne **(75)** as the starting material. An aliquot of the reaction mixture was taken and dissolved in methanol and analysed via low-resolution liquid chromatography mass spectrometry. The starting material could be observed in the sample at a retention time of 1.12 minutes, and a m/z of 156.09 and 158.06 corresponding to the two isotopes of the chlorine within the starting material, indicating that complete conversion had not been achieved. As the starting material would not be present if complete conversion had taken place, due to it being the limiting reagent within the reaction. At a retention time of 2.26 minutes a new peak was observed with the expected mass of the dichloro methyl substituted product **(82)** at a

m/z of 238.18 and 240.12 in a ~1: 095 ratio, once again corresponding to the two most common isotopic arrangements of the desired product. High-resolution accurate mass spectroscopy was then conducted in the hopes of ascertaining the identity of the intended product. However, neither the starting material or the desired product could be observed in the accurate mass analysis.

GC-MS was then explored as an alternative analysis. An aliquot of the reaction mixture was taken and dissolved in, dichloromethane. GC-MS confirmed the presence of the desired product **(82)** which was corroborated via NMR analysis. Indicating that GC-MS could be used for the detection of the compounds of interest, which was key in the characterisation of the compounds that will be discussed in **Sections 14-21**. This method was only used to detect the presence of the compounds and not to provide information regarding percentage conversion of the reaction. It would have been possible to establish conversion in a semi quantitative manner through the use of calibration with an internal standard of the desired product and determination of the response factor of the system. However, due to time commitment associated with developing such a method, this was not explored within this project.

6.2 Method of Reaction Monitoring Used

It was found that NMR spectroscopy was suitable for the semi-quantitative monitoring of the transformation. Samples were initially dissolved in d_6-chloroform, although it was found that d_6-DMSO was a more solubilising solvent and as such was employed for all further analysis.

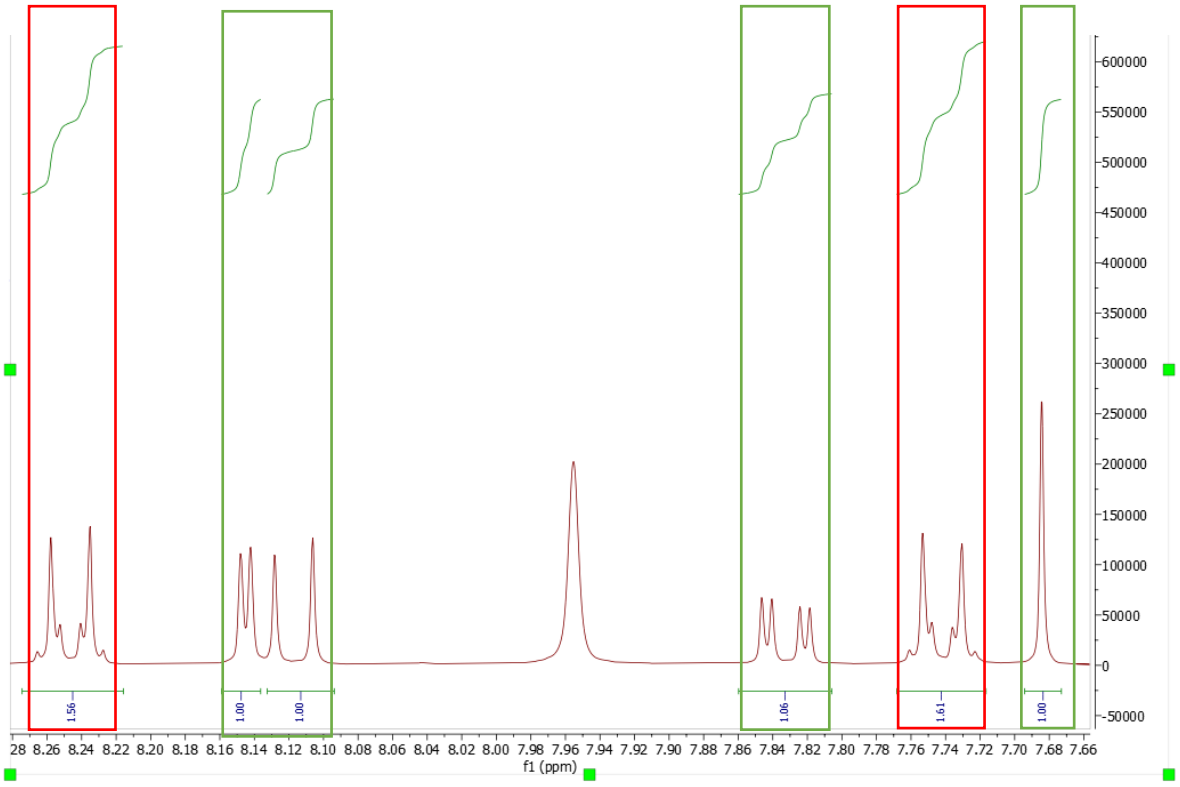


Figure 11: 4-chloro-2-(dichloromethyl)-1-nitrobenzene **(82)** ^{1}H NMR spectrum (highlighted in green) with the presence of 1-chloro-4-nitrobenzene **(75)** starting material (highlighted in red)

As can be seen in **Figure 11** the peaks that correspond to the 1-chloro-4-nitrobenzene starting material **(75)** can be observed at 8.25 and 7.74 ppm. Each of these peaks correspond to two protons due to the symmetrical nature of the starting material. The peaks that correspond to the product are: 8.15, 8.12, 7.83 and 7.68 ppm all of which correspond to a singular proton.

^{1}H NMR was used to determine the success of all reactions conducted as part of this project. NMR spectroscopy can be made quantitative with the introduction of an internal standard to allow determination of the yield. 1,3,5-

trimethoxybenzene was used as the internal standard for this method as it was soluble in d_6-DMSO and has no interfering peaks with the product. The yield can be calculated as such:

$$n_p = \frac{(\frac{I_p}{N_p})}{(\frac{I_{is}}{N_{is}})}$$

Equation 1: Determination of the moles of the product (n_p) where N_p is the no. of protons of the corresponding peak of product, N_{is} the no. of protons of the corresponding peak of internal standard, I_p is the integral of the corresponding peak of product and I_{is} is the integral of the corresponding peak of internal standard.

$$\text{NMR yield } \% = \left(\frac{\text{moles of product}}{\text{initial moles of limiting reagent}}\right) \times 100$$

Equation 2: NMR percentage yield calculation.

$$\text{Yield } \% = \text{Mass of reaction mixture} \times \text{NMR yield}$$

Equation 3: Percentage yield calculation

7. Initial reactions

7.1 Initial Flow System Configuration.

As discussed in **Section 3.2** a three-pump system was used throughout the project. A 1 M LiHMDS in THF solution was employed as the base in the reaction and was delivered at a flow rate of 1 mL min^{-1}. A mass of 15.46 g 1-chloro-4-nitrobenzene **(75)**, 19.32 mL of chloroform and 180.68 mL of DMF, was used as a feed solution at a flow rate of 0.25 mL min^{-1} and the quench solution of acetic acid was delivered at a flow rate of 0.30 mL min^{-1}. Meaning that the reaction was carried out at a flow rate of 1.25 mL min^{-1}. A 2 mL Uniqsis glass chip reactor was used, resulting in a mean residence time of 1.36 min. The reactor was submerged in a dry ice acetone bath to maintain a temperature of -78 °C.

7.2 Initial Success and Problems Encountered

Under these initial conditions the desired product was successfully synthesised. Identification of the starting material from the resulting NMR spectrum proved challenging due to baseline noise indicating near 100% conversion to the desired compound had been achieved. This result instilled confidence that the previously reported batch method could be successfully translated to flow. However, the reaction could only proceed for a few minutes before exceeding the maximum operating pressure, of 10 bar. This was due to the formation of blockages within the small channels of the reactor chip. These blockages were observed due to the slurry like consistency of the reaction mixture.

Following the premature conclusion of the reaction, the reactor required extensive cleaning to remove any remanence of the reaction mixture. A bleach solution was used to clear the blockages. The reactor was then washed with various solvents to ensure all of the bleach solution was removed to prevent future contamination.

It was deemed that the glass chip reactor, although allowing proof of principle, would not be suitable for the reaction moving forward, as it was not viable to conduct such extensive cleaning after every short run. Additionally, as the reaction could not proceed uninhibited for any length of time, method development would prove nearly impossible as no useful data could be established from the system in this configuration. Finally, as the reaction mixture appeared to be a fine slurry like consistency, no matter how the reaction procedure was optimised the small channels of a reactor chip would remain impractical for carrying out this reaction.

8. Reaction Optimisation

8.1 The Introduction of a Coil Reactor

Due to the reasoning outlined in **Section 7.2**, a coil reactor was introduced in the hopes of negating any problems associated with blockages forming within the reactor. A 3.20 mL coil, with an external diameter of 1/8" and an internal diameter of 1/16", was first introduced, all other parameters remained the same. Each reaction was conducted in triplicate to investigate the repeatability of the results obtained. The initial run returned a conversion of 75%. This reduced conversion was partially to be expected due to the inferior mixing and temperature control that results from the transition from a small channel reactor chip to a larger diameter flow coil reactor. Blockages were still observed in the run; however, the reaction could proceed for a longer duration, reaching a ten-minute mark before the maximum pressure of the pump was exceeded. Across the next two runs the reaction once again proceeded for 10 minutes prior to the pressure limit being exceeded. Conversion differed slightly across the three runs ranging from the 75% observed initially to 56% and 55% across the two subsequent runs. This could be perhaps due to the non-uniform way in which the reactor blocks leading to variation in the way in which mixing occurs.

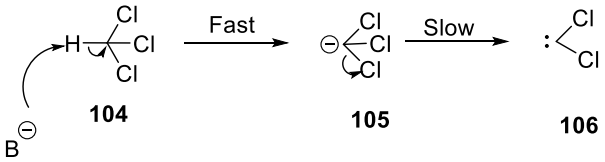
A new reaction design was employed using the same coil reactor, the flow rates across all three pumps were doubled (LiHMDS solution: 2 mL min^{-1}, 1-chloro-4-nitrobenzene **(75)** solution: 0.50 mL min^{-1}, acetic acid solution: 0.6 mL min^{-1}, residence time: 1.17 min.) in the hopes that the resulting increase in flow rate would prevent the aggregation of solid precipitate within the reactor. This proved to be the case and the reaction proceeded for the full duration of the intended run (20 minutes), small pressure spikes were still observed although. There was only minimal solid build up observed on the walls of the tubing following completion of the reaction.

Although the reaction proceeded uninhibited, conversion was adversely affected by the increase in the flow rate. A modest conversion of only 24% was observed. This drop in conversion was perhaps due to the decrease in residence time from 2.34 minutes under the previous conditions to 1.17 minutes. This may have led to the reactants having insufficient time to react prior to leaving the reactor, resulting in unreacted material remaining. Additionally, due to the inferior mixing capabilities of coil reactors there may have not been sufficient interactions between the two reagents to facilitate a reaction, prior to leaving the reactor, once again resulting in unreacted material remaining. It is likely a combination of these two factors that resulted in the lower conversion observed.

As such the size of the coil reactor used was increased again to a 20 mL reactor. It was hoped by increasing the residence time of the reaction, that the amount of unreacted material could be minimised improving the overall conversion. Due to the increased diameter of the reactor, mixing efficiency was further reduced. To negate this, PTFE static mixers were added to the reactor, providing improved in-line mixing of the two reagent flow streams. The 1-chloro-4-nitrobenzene **(75)** solution was also diluted ten-fold by taking a 25 mL aliquot and diluting it to 250 mL with DMF. This was undertaken in the hopes of reducing the amount of precipitation observed, making the system less susceptible to pressure spikes. The first run that was conducted under the new conditions, proceeded for the full duration of the intended run (10 minutes) and returned perfect conversion to the desired product.

8.2 Temperature Alterations

As it appeared that optimal conditions had been found, further work was then conducted to investigate whether the reaction could be conducted at higher temperatures. As the aim of project was to generate the compounds of interest at scale, considerations were taken throughout the project as to how the proposed synthetic approach would translate to larger scale synthesis. One parameter that was a particular concern was the cryogenic temperature at which the reaction was operated. Makosza and Owczarczyk conducted the original batch procedure at -78 °C in the hopes of preventing the formation of the dichlorocarbene species **(106)** following the deprotonation of chloroform **(104)**, as trihalomethyl carbanions **(105)** are known for their instability due to their dissociation to dihalocarbenes **(Scheme 36)**.[56]



Scheme 36: Formation of di-chlorocarbenes **(106)** via alpha elimination, where B^- represents a base.

Makosza and Owczarczyk proposed the reaction was carried out at low temperatures due to the increased stability of intermediates at such temperatures. This also provides a cooling affect to combat the strong exothermic nature of the reaction.[44] It was reported that the rate of addition in the batch reaction should be at a rate that ensures the reaction temperature does not exceed -68 °C. As a result, it was thought that the reaction temperature could perhaps be increased, as through the implementation of flow chemistry, greater control of temperature could be achieved, negating the need to carefully control the exothermic nature of the reaction, in addition to the possibility of quicker reaction times, due to the continuous processing approach, preventing the formation of the carbene species.

Increasing the temperature would be particularly useful for the scale up of the procedure. As the use of dry ice/ acetone baths is not particularly conducive to long run times, due to the need to maintain a constant temperature. Alternatively, there are some examples of purpose-built reactors, with cryogenic freezers, that can maintain a temperature of -78 °C. However, examples of such reactors are scare and laboratories that have such instruments are scarcer. Additionally, such reactors are very energy intensive, meaning any process that uses such instruments prove costly. As such it would be optimal to run the reaction at higher temperature to facilitate more effective scale up.

The reaction was first attempted at room temperature as it would be beneficial if no temperature control was required. All other parameters remained constant. The reaction ran for 20 minutes without any blockages or pressure spikes. However, only starting material was detected in the NMR spectrum. As such, lower temperatures were subsequently explored, the reaction was carried out at temperatures of both -20 and -40 °C.

At both -20 and -40 °C the reaction only proceeded for ~2-3 minutes before the maximum pressure for the system was exceeded. Both reactions were repeated three times to ensure that the pressure spike observed were not a result of an unrelated blockage within the system. Across all six runs at the two different temperatures the same result was observed, with the system exceeding the pressure limit following less than 3 minutes of run time. It was found that the pressure spikes observed were a result of a build-up of solid precipitate within the system. It is unclear whether this was a result of the temperature at which the reaction was conducted, the result of another variable or a culmination. However, as the desired compound was not observed in the resulting NMR spectra of the recovered materials, focus was drawn away from modification of the temperature. In conclusion, it appears that the temperature cannot be raised below the -78 °C outlined in the original method, without inhibiting the success of the reaction, although the optimal temperature for the reaction, in flow, may fall outside of the window investigated as part of this work (40-78 °C). As such, further experimental investigation is required to provide certainty surrounding the optimal temperature.

8.3 Precipitation / Freezing Challenges

8.3.1 Installation of a Y-piece Mixer

After investigating the primary source of blockages within the system it became apparent that solid precipitate was building up firstly in the flat interconnecting zone of the "T" piece where the two reagent streams converge prior to entering the reactor. As such a "Y" piece mixer was introduced. Due to the structure of the new mixer, it was hoped that it would ensure the continuous movement of the two streams and any solid particulates within them. The new mixer worked as intended, preventing the build-up of solid material at the point at which the two reagents meet. The first run conducted with the new mixer was performed at -78 °C under the same parameters as listed above. The reaction proceeded for the full duration of the intended run with a conversion of 61%, although pressure spikes were observed, they did not exceed 7 bar of pressure. It was clear that the introduction of the new mixer had minimised solid build up, however it was also clear that the introduction of this mixer alone would not solve all the problems observed thus far in the project.

8.3.2 Dilution of nitroarene Solution

With the "Y"-piece mixer now installed continued optimisation of the reaction could be more freely conducted without critical solid build up within the system. As such the solvent ratios within the reaction were investigated to determine the impact that manipulating them could achieve.

Firstly, the flow rate of the base was reduced from 2 mL min^{-1} to 1.50 mL min^{-1}. The nitroarene stock solution used was also altered, making the solution less dilute, 0.14 mmol mL^{-1}, a fourfold dilution was implemented as opposed to the previously employed ten-fold dilution. This resulted in 3 equivalents of the base being used.

Due to the decrease in the flow rate of the base solution, the volume of THF present in the reaction was also decreased. The reaction exceeded the pressure limit almost immediately causing the reactor to stop. However, unlike previous runs the cause of the pressure spike did not appear to be a result of the build-up due to precipitate and instead appeared to be a result of the freezing of the reaction mixture within the coil. The reaction was attempted again under the same conditions and parameters. The result was replicated, the pressure spiked almost immediately and this once again appeared to be a result of the reaction mixture freezing.

The reaction was then attempted at room temperature using the same solvent ratios to investigate whether the freezing of the reaction mixture was in fact the cause of the pressure spikes. The reaction proceeded throughout the allocated duration of the run (10 minutes) without any pressure spikes, somewhat suggesting the freezing of the reaction material was responsible for the pressure spikes previously observed. Although this was not conclusive evidence as temperature also has an effect of the general viscosity of the reaction mixture, which will inevitably contribute to the pressure observed within the system. As expected only starting material was observed in the resulting NMR spectrum of the crude reaction upon analysis.

In the hopes of conclusively confirming the freezing hypothesis, the undiluted stock solution was used for the reaction. This reduced the equivalence of the base used down to 1.5 equivalents, as well as decreasing the amount of DMF used in the reaction. It is hoped by decreasing the amount of DMF, which in turn improves the ratio of THF:DMF, this would prevent the freezing of the reaction mixture as discussed in **Section 4.1**. This undiluted stock solution had previously led to precipitate build up however, it was thought that the introduction of the Y-mixer may help to overcome this issue. This did not prove to be the case. The pressure exceeded the maximum limit causing the reaction to cease within a comparable time frame to when the T mixer was used. It was clear that this pressure spike had been caused by the build-up of solid particulates as opposed to the DMF in the reaction mixture freezing. As the blockage could be removed by pumping cleaning solution through the system without removing the reactor from the dry ice/ acetone bath. Once again somewhat confirming the idea that the solvent ratio is vital to the success of the reaction.

As diluting the solution four and ten-fold had proved unsuccessful, the stock solution was then diluted with THF. As it was thought that through dilution there would be a less solid build up and through the use of THF the freezing would not be a problem. Surprisingly once again the pressure of the system exceeded the maximum limit, due to the build of solid precipitate. Following the completion of this run the system was flushed completely with THF alone, to investigate whether the cleaning solution used was inadvertently affecting the success of the reaction. Following this the reaction was repeated, once again using the THF diluted nitroarene solution. This proved equally unsuccessful, ruling out any contribution from the cleaning solution to the problems encountered. It also confirmed that simple dilution of the nitroarene solution in isolation was not a viable approach for reaction optimisation.

8.3.3 Further Solution Dilution

As diluting the nitroarene solution alone had not been successful it was thought that introducing a similar dilution for the base may prove more fruitful. 100 mL of the lithium base was diluted to 250 mL with THF and the nitroarene solution diluted with THF, as described above, was used once again. This alteration to the procedure appeared to make little to no change to the outcome of the reaction. Extensive cleaning of all of the components within the system was conducted and the reaction was reattempted, however, as anticipated, this once again did not change the outcome, and the reaction was once again cut short in a comparable manner.

8.3.4 Solvent Ratio Alterations

The ratios of the reagents were then altered to better reflect both the ratio of base to substrate and the ratio of DMF to THF used in the original method. The 1M sodium base was pumped at a flow rate of 1.25 mL min^{-1} and the 1-chloro-4-nitrobenzene **(75)** solution was pumped at a flow rate of 1 mL min^{-1}, meaning the system had a total flow rate of 2.25 mL min^{-1} and a mean residence time of 8.89 minutes. The composition of the nitroarene solution was also altered in order reflect this change in approach. The solution contained (1-chloro-4-nitrobenzene (9.85 g, 62.50 mmol), chloroform (6.10 mL, 72.05 mmol) and DMF (93.90 mL)) **(Table 2: Entry 1)**. Under these conditions the reaction mixture froze and prevented a reaction. These conditions acted as a starting point for the subsequent investigation into the optimal solvent ratio.

The solvent ratio of the 1-chloro-4-nitrobenzene **(75)** solution was altered from 100% in the aforementioned run to 90:10, DMF: THF **(Table 2: Entry 2)**. This change resulted in no change of the outcome from the reaction. As such the THF content was increased further to 20% **(Table 2: Entry 3)**. Once again, the reaction proved unsuccessful due to the reaction mixture freezing. However, the reaction proceeded for a noticeably longer duration than the previous attempt proceeding for ~5 minutes, indicating that increasing the volume of THF was the correct approach to take.

From this initial trend, the amount of THF used in the reaction was further increased to a ratio of 70:30, DMF: THF **(Table 2: Entry 4)**. There was no observable blockages or evidence of the reaction mixture freezing within the initial intended ten-minute run time. As such the reaction was left to run until all of the nitroarene solution had been used up. The reaction ran for 78 minutes, the pressure remained at zero throughout baring a slight peak at the ~65-minute mark where the pressure reached a peak of 0.3 bar. The resulting reaction mixture was collected in 13-minute intervals and worked up as per the standard procedure. In the resulting NMR spectra for the 6 aliquots collected only starting material could be observed. Meaning that despite the run proceeding uninhibited for extended periods of time under these conditions, conversion to the desired product still couldn't be achieved.

In the hopes of achieving both an uninhibited and successful run, the volume of THF used was further increased to investigate whether this ratio would prove more effective than the 70:30 ratio. A 60: 40 ratio was employed **(Table 2: Entry 5)**. However, this caused the system to exceed the maximum pressure within 6 minutes of run time due to the presence of solid build up within the reactor. It appeared that the 70:30 ratio was therefore optimal for avoiding the reaction mixture both freezing and for solid formation. As lowering the THF content further would result in freezing of the reaction mixture and reducing the volume of DMF would result in the formation of solid build up, due to the more solubilising nature of the solvent.

Surprisingly the subsequent runs appeared to contradict this, as when the reaction was repeated using the 70:30 ratio, freezing of the reaction mixture was observed causing a premature end to the reaction **(Table 2: Entries 6-8)**. The flow rate of all of the pumps within the system were doubled, whilst maintaining this solvent ratio, in the hopes that reducing residence time may limit the freezing of the reaction mixture, as the material would spend less time within the cooled reactor **(Table 2: Entry 9)**. This proved not to be the case and only reduced the time taken for the reaction to cease. Additionally, the volume of chloroform was also increased to investigate the effect this may have on the freezing point of the reaction mixture **(Table 2: Entry 11)**. Once again, the reaction mixture froze, indicating that the chloroform content of the solution was not a contributing factor to the freezing point of the solution.

Table 2: Summary of solvent ratio investigation

Entry	DMF vol. (mL)	THF vol. (mL)	Chloroform vol. (mL)	Solvent ratio	% conversion (^{1}H NMR)	Time Proceeded (min)	Cause of reaction termination	Comment
1	93.90	0.00	6.10	100:0	0	0	Freezing	N/A
2	84.51	9.40	6.10	90:10	0	~2	Freezing	N/A
3	74.96	18.78	6.10	80:20	0	~5	Freezing	N/A
4	65.73	28.17	6.10	70:30	0	78	N/A	N/A
5	56.22	37.48	6.10	60:40	0	6	Solid Formation	N/A
6	65.73	28.17	6.10	70:30	0	6	Freezing	N/A
7	65.73	28.17	6.10	70:30	0	~2	Freezing	N/A
8	65.73	28.17	6.10	70:30	0	~2	Freezing	N/A
9	65.73	28.17	6.10	70:30	0	0	Freezing	Flow rate doubled
10	61.04	32.87	6.10	65:35	0	0	Solid Formation	Flow rate returned to original
11	61.46	28.17	12.20	70:30	0	0	Freezing	N/A

8.3.5 Introduction of Antifreeze

In an attempt to prevent the freezing, the addition of further solvents to the reaction mixture was then explored, to investigate whether they could be used as an antifreeze, possibly negating the need for higher THF content. The classic example of such an approach is the introduction of sodium chloride into water, the addition of the sodium chloride depresses the freezing point to -21 °C. It was hoped that a similar approach in the project would prove fruitful. *tert*-butanol was employed as the antifreeze agent. The solvent has a melting point of 25-26 °C, however it was hoped that when added to the solution it would depress the freezing point to a suitable level. A volume of 7.18 mL of the *t*ert-butanol was added to the nitroarene solution. The reaction was run using both the 70:30 DMF:THF ratio (60.70 mL DMF, 26.02 mL THF) and the 60:40 DMF:THF ratio (52.03 mL DMF, 37.56 mL). Under the former conditions the reaction mixture froze after ~5 minutes in a comparable manner to when the *tert*-butanol was not used. Under the later conditions the pressure exceeded the maximum limit due again to the build of solid within the reactor, comparable to when the antifreeze agent was not used. Indicating that the use of the *t*ert-butanol provides no benefit to the reaction.

8.3.6 Introduction of Sodium Base

It was anecdotally reported that lithium-based reagents can prove problematic within flow chemistry set ups, causing a multitude of problems often related to blockages within the system. As such the lithium base was swapped out for

NaHMDS to investigate whether this would influence the success of the reaction. The flow rate of the base remained unchanged at a flow rate of 1.25 mL min^{-1}, as did the flow rate of the 1-chloro-4-nitrobenzene **(75)** solution at a flow rate of 1 mL min^{-1} (this solution was made up of 1-chloro-4-nitrobenzene **(75)** (4.92 g, 31.25 mmol), chloroform (6.10 mL, 73.05 mmol), DMF (61.04 mL), THF (32.87 mL)). The quench solution was also unchanged from the previous runs and was delivered at a flow rate of 0.25 mL min^{-1} **(Table 3: Entry 1)**. The reaction proceeded for 30 minutes with the pressure remaining consistently ~0.6 bar for the majority of the run. When the pressure did spike, it did so in a manner consistent with the build-up of precipitate, followed by the blockage clearing and the pressure returning to normal. Three 10-minute aliquots of the resulting reaction mixture were taken and worked up as per the standard procedure as outlined in **Section 3.1**. The resulting NMR spectra showed no sign of the desired compound, only indicating the presence of starting material. Increasing the flow rate of the acid quench solution to 1 mL min^{-1} also had no effect on the result of the reaction under these conditions **(Table 3: Entries 2-4)**

Table 3: Summary of runs conducted with NaHMDS

Entry	1-chloro-4-nitrobenzene (g, mmol)	Chloroform (mL, mmol)	DMF: THF (mL)	Acid	Acid flow rate mL (min^{-1})	Pressure (Bar)	Run time (min)	Comment
1	4.92, 31.25	6.10, 73.05	61.04: 32.87	10% acetic acid in methanol	0.25	~0.6	30.00	No product formed
2	4.92, 31.25	6.10, 73.05	61.04: 32.87	10% acetic acid in methanol	1	~0.3	20.00	No product formed
3	4.92, 31.25	6.10, 73.05	61.04: 32.87	10% acetic acid in methanol	1	~0.6	~2.00	Solid build up at the acid line caused the reaction to cease
4	4.92, 31.25	6.10, 73.05	61.04: 32.87	10% acetic acid in methanol	1	~0.6	~2.00	Solid build up at the acid line caused the reaction to cease

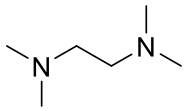
8.3.7 Acid Quench Solution Alterations

With an increase in the flow rate of the acid quench line unforeseen problems arose. Using the conditions outline in **section 8.3.5** the reaction was ran with acetic acid as the quench solution delivered at a flow rate of 1 mL min^{-1}. The reaction proceeded for ~4.50 minutes before the pressure spiked exceeding the maximum pressure of the system. However, unlike previous runs, the pressure spike was not caused by solid build up or freezing of the reaction mixture

within the reactor but was instead a result of precipitation at the acid output line. In the hopes of rectifying this, the acid solution was swapped out for an alternative solution of 10% conc. (32 wt.% in H_2O) hydrochloric acid dissolved in methanol, in line with the alternative solution outlined in the original procedure.[44] The reaction preceded uninhibited throughout the entirety of the intended run time however the desired product was still not formed.

8.3.8 Use of TMEDA as an Additive (107)

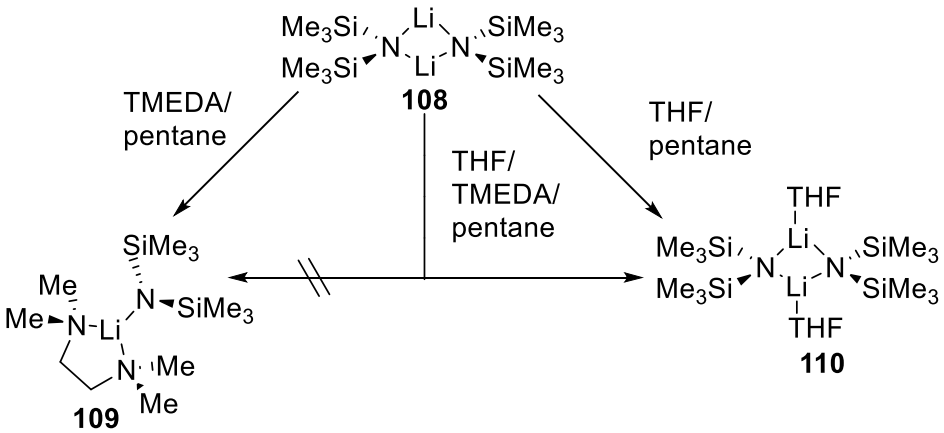
TMEDA (tetramethylethylenediamine) **(107)** is a bidentate ligand, it forms stable organometallic complexes that are soluble in organic solvents. TMEDA also has an affinity for lithium ions hence the potential utility as part of this project.



107

Figure 12: Structure of TMEDA **(107)**

It was hoped that the introduction of TMEDA **(107)** into the reaction mixture may act to "mop up" the disassociated lithium counterions which, under the previously employed conditions, may have been responsible or contributing to the solid build up observed. TMEDA **(107)** (7.63 mL) was added to the 1-chloro-4-nitrobenzene **(75)** solution along with 1-chloro-4-nitrobenzene **(75)** (1.48 g), chloroform (7.63 ml), DMF (59.62 mL), THF (25.55 mL) at a flow rate of 2.50 mL min^{-1}. The introduction of the TMEDA **(107)** had no effect on the success of the reaction as the pressure exceeded the limit within mere seconds of the reaction commencing. This may be due to the presence of THF in the reaction mixture as it has been shown to outcompete TMEDA **(107)** in lithium complex formation in other organolithium reactions.[57]



Scheme 37: Lithium complexes formed with LiHMDS in the presence of 5 equiv. of THF and TMEDA **(107)**, replicated from Collum[57]

In the presence of 5 equiv. of THF, LiHMDS exclusively forms the dimer **110**, whereas in the presence of 5 equiv. of TMEDA **(107)**, **109** is exclusively formed. In the presence of equimolar quantities of both THF and TMEDA **(107)** **110** is exclusively formed, indicating that THF outcompetes the TMEDA **(107)** when in equal quantities of the two are present. As such, this explains the lack of impact of the TMEDA **(107)** introduction in the reaction mixture, as THF is far in excess, meaning it will readily outcompete the TMEDA **(107)** in complex formation.

As the TMEDA **(107)** had no impact on the success of the reaction when the lithium base was employed, the reaction was attempted with the potassium base. The reaction was carried out under identical conditions and parameters, baring the switch of base. Although TMEDA **(107)** may not have as strong an affinity to potassium ions as it does for lithium ions, the ligand should still operate in a comparable manner. The reaction proceeded for the full duration of

the intended run, a large pressure spike was observed during the run although the pressure did not exceed 10 bar and returned to ~0.6 bar of pressure where it remained for the remainder of the run. Despite proceeding for the full intended duration, the desired product was not generated and only the starting material could be observed in the resulting NMR spectrum.

8.3.9 Use of KHMDS as a Base

Following the attempted runs with TMEDA **(107)** it became evident that under identical conditions the potassium base was more conducive to a successful reaction than the lithium base. As such the potassium base was exclusively used moving forward with the project. The other reagents used were once again adjusted to better reflect the original literature batch procedure **(Table 4: Entry 1).**[44] This ensured that the chloroform was in a 25% molar excess.

Notably this reaction was conducted with no THF in the nitroarene solution in the hopes that the reaction mixture would remain in solution due to the higher volume of the more solubilising DMF. Once again, the reaction proceeded for the intended duration, without exceeding 1 bar of pressure throughout the run. Two 5-minute aliquots were taken and worked up as per the standard procedure outlined in **Section 3.1**. The resulting NMR spectra revealed that only the starting material was present in the first spectrum whereas the desired product could be observed in the second. However, the observed conversion was only 12% meaning that further optimisation was required.

The solutions were then altered to better reflect the compositions used to achieve the most optimal conversion thus far **(Table 4: Entry 2)** although this did not generate the desired product. A ten-fold dilution of this solution **(Table 4: Entry 3)** also did not change the success of the reaction and 0% conversion was observed.

The conditions that yielded the 12% conversion were returned to **(Table 4: Entry 4)**. The run time was extended to investigate whether conversion would improve once the system entered steady state, which is typically defined as when 2.5 times the reactor volume has been processed. Surprisingly the conversion did not improve but instead dropped to 0%, once again meaning that only the starting material could be seen in the resulting NMR spectrum.

Table 4: Summary of runs conducted with KHMDS.

Entry	1-chloro-4-nitrobenzne (g, mmol)	Chloroform (mL, mmol)	DMF (mL)	Flow rate (mL min^{-1})	Acid solution	Acid solution flow rate (mL min^{-1})	% Conversion (^{1}H NMR)	Comment
1	0.74, 4.70	3.82,47.67	46.19	2.50	10% 32% hydrochloric acid in methanol	1.00	12	Pressure < 1 bar
2	3.89, 24.69	4.83, 60.28	45.17	2.00	10% 32% hydrochloric acid in methanol	2.00	0	Pressure < 1 bar
3	0.20, 1.27	0.24, 2.30	50.23	2.50	10% 32% hydrochloric acid in methanol	1.00	0	No pressure

4	2.96, 18.79	15.26, 190.46	184.74	2.50	10% 32% hydrochloric acid in methanol	1.00	0	No Pressure, 20 min, run time

8.3.10 Control of Temperature at the Point of Mixing

Upon assessment of the current system configuration a potential source of poor conversions was identified. The "Y"-piece mixer, where the two reagent streams converge, had to this point not been fully submerged within the dry ice acetone bath. Meaning that the two reagent streams were meeting at room temperature as opposed to -78 °C. It had already been established that the reaction is highly temperature dependant, due to the instability of the chloroform anion. This design feature was rectified, by ensuring the mixer and a section of the proceeding tubing was completely submerged.

As such we tested the solution compositions first outlined in **Section 8.3.9 (Table 4: Entry 1)**. An issue was encounter immediately. Due to the temperature of the mixer the DMF containing solution immediately froze upon interacting with the mixer, causing the reactor to fail. The previously optimised 70:30 DMF: THF solution (DMF (32.33 mL) and THF (13.86 mL)) was then introduced to negate this problem, which proved somewhat successful, as the freezing problem was negated, although the desired compound was still not obtained. The solution to this problem entailed mixing the two reagent streams prior to the mixer being submerged within the bath. This ensured that a sufficient volume of THF was present in the reaction mixture to prevent freezing. Although, it took both this change and a further change to the concentration of the acid quench solution before the desired compound was generated again.

The concentration of the acid solution was increased from a 10% hydrochloric acid solution to a 67% acid solution. This was achieved by diluting 80.00 mL of conc. hydrochloric acid in 120.00 mL of methanol. This changed yielded the desired product at a conversion of 20%. Following this result the mass of the 1-chloro-4-nitrobenzene **(75)** in the solution was doubled to 1.58 g, whilst the remaining constituents of the solution remained unchanged. Once again two sequential 5-minute aliquots were taken. The first of which indicated a conversion of 9%, whilst the second aliquot indicated a conversion of 92%. The run was repeated to establish the repeatability of this result. Upon repeat a conversion of 75% was achieved, although lower than the previous conversion, this result remained a significant improvement upon the previously obtained results.

8.3.11 Flow Rate Alterations

Efforts turned to increasing conversion. The approach taken was to increase the flow rate of the system which in turn decreases the mean residence time. It was apparent that without a rapid quench within a suitable time frame the reaction tended to revert to the starting material. As such, it was thought that it may be beneficial to increase the flow rate as it would ensure that the reaction was completed and quench more rapidly. The flow rates were increased to 3.00 mL min^{-1} on the base line, 3.75 mL min^{-1} for the nitroarene solution and 3.00 mL min^{-1} for the acid quench solution. Meaning the residence time for the reaction was reduced to 2.58 minutes. Across the full run, a near quantitative conversion of 99% was observed.

The flow rates were further increased to 4-, 5- and 4- mL min^{-1} respectively across the three pumps, which additionally reduces the residence time to 2.22 minutes. This would be beneficial as the overall throughput of the system would be improved, a parameter often used to determine the efficiency of the system. However, such flow rates appeared to be too high for the pumps to operate consistently at, despite the fact that the SF-10 Vapourtec pumps can operate at flow rates up to 10 mL min^{-1}. The slurry like nature of the reaction mixture meant that this was not possible. Indeed, following this run the tubing connecting the inlet and the outlet on the pump split, likely the result of the high pressure associated with operating at such a high flow with a slurry like reaction mixture. As such the flow rates were returned to 3-, 3.75- and 3-mL min^{-1} across the three pumps.

8.4 Summary of Reactor Design

After optimisation it was determined that the optimal flow configuration consisted of a three-pump system, with the first pump delivering KHMDS at a flow rate of 3 mL min^{-1}. The base was used as it was of comparative strength to the *tert*-butoxide used in the batch procedure and to the alternative hexamethyldisilane bases, whilst also proving the most solubilising preventing the build-up of solid. The second pump delivering a solution of 1-chloro-4-nitrobenzene **(75)** (1.58 g), chloroform (4 mL) and DMF (46 mL) at a flow rate of 3.75 mL min^{-1}. The third pump contained, 80:120, hydrochloric acid: methanol at a flow rate of 3 mL min^{-1}, as this ensured that the solution was of sufficient strength to effectively quench the reaction mixture and avoided the pitfall of precipitation that was observed when employing acetic acid. The reaction was conducted at a temperature of -78 °C to prevent the formation of the dichlorocarbene's from the unstable chloroform anions, that form at higher temperatures.

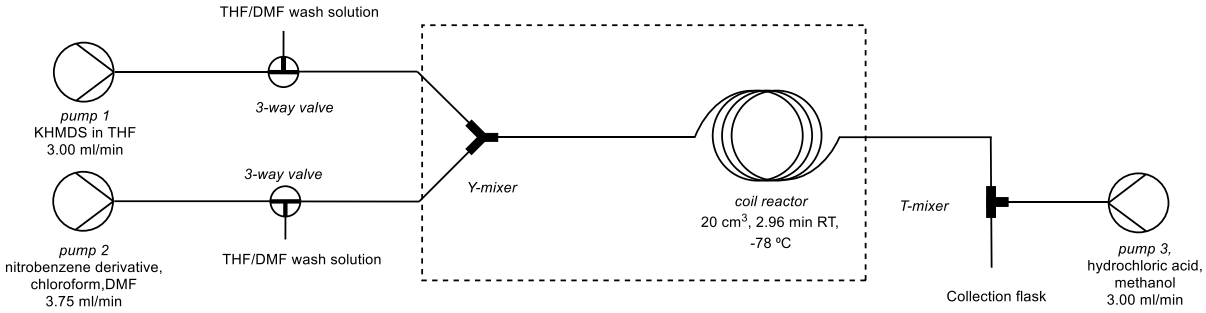


Figure 13: Schematic outline of the flow system employed

9. Scale Up

9.1 Solution Scale Up

Due to the nature of flow chemistry the reaction can proceed, continuously, until the reagents are spent. Meaning for the scale up of a flow procedure a sufficient volume of each of the reagents must be present prior to commencing the run. As such, the nitroarene solution in particular required scaling up to facilitate a longer run time.

Initially all of the components of the solution were simply scaled up by a factor of two resulting in 100 mL stock solutions. However, when the reaction was attempted, the introduction of this solution had a detrimental effect on the success of the reaction. The best yield that could be achieved using the solution was 71%. The pressure of the system was also noticeable increased on runs conducted with this solution, not enough, on shorter 5-10-minute runs, to exceed the pressure limit but would likely prove problematic over longer runs.

Upon investigation it was discovered that if the volume of chloroform used was kept low, the reaction would proceed with no issues and returned good conversions (97%). This stock solution consisted of 3.15 g of 1-chloro-4-nitrobenzene **(75)**, 3.65 mL of chloroform and 96.35 mL of DMF. It is likely that the improvement in the conversion observed was a result of the adjusted chloroform concentration, as it has been shown previously that the chloroform concentration can have a drastic effect on the success of the reaction. Whereas the reduction of pressure within the system is instead likely a result of the increased volume of DMF and the solubilising effect the solvent has on the reaction mixture.

As more than 100.00 mL of solution would be required to facilitate a 1 hour run time, the solution had to be scaled up further. The volume of the solution was increased to 200.00 mL, although the mass of 1-chloro-4-nitrobenzene **(75)** was unchanged at 3.15 g, due to concerns over solid build up, 7.31 mL of chloroform and 192.69 mL of DMF were used to make up this solution. This solution performed comparatively well achieving a conversion of 99%. This result was reproducible over four 10-minute repeat runs and was thus employed to conduct a 1-hour run.

To achieve this the configuration of the system remained unchanged, a three-pump system was still employed delivering the solution at the same flow rates. Six 10-minute aliquots were taken throughout the run. Across all six aliquots the observed conversions were poor, with a maximum conversion of only 47%.

The reaction was repeated to ensure that this was not anomalous data. After ~5.00 minutes of run time the pressure exceeded the limit for unknown reasons. The coil was removed from the dry ice bath and heated in the hopes of rectifying the issue. The coil was resubmerged and the run recommenced. Three 20-minute aliquots were taken from the run. The first aliquot displayed similarly poor conversion to the previously conducted experiment with an observed conversion of 47%. However, this was somewhat expected considering the interruption to the run and the subsequent removal from the bath. In contrast the second and third aliquots taken displayed excellent conversions of 99% across the corresponding 40.00 minutes window.

Now that a suitable conversion had been observed across an extended period of 40 minutes it was clear that the reaction could be successfully scaled up using flow chemistry. Despite this success the throughput of the reaction was still comparatively low due to the mass of the 1-chloro-4-nitrobenzene **(75)** being used, as it is the limiting reagent in the reaction. A 1 hour run time under these conditions, outlined above, would only return 5.41 g of the desired product if quantitative conversion was achieved. A more suitable return for the reaction would be ~10.00 g of the desired product. As such the mass of the 1-chloro-4-nitrobenzene **(75)** was increased in the reaction mixture.

9.2 Throughput Improvement

A stock solution comprising of 1-chloro-4-nitrobenzene **(75)** (6.30 g, 0.20 M), chloroform (7.31 ml, 1.71 mmol min^{-1}) and DMF (192.69 mL) was prepared, whilst the remaining solutions and parameters were kept consistent with previous successful runs. The reaction was intended to run for 60 minutes; however, the pressure exceeded the limit due to the build-up of solid precipitate within the reactor after 40 minutes of run time. Two 20-minute aliquots were still obtained and analysed via NMR spectroscopy. The first of the two aliquots had a conversion of 83%, with the later having a slightly lower conversion of 79%. The two conversions observed were both significantly lower than the 99% conversion that had been observed when a lower concentration of 1-chloro-4-nitrobenzene **(75)** was used. This, paired with the returning issue of solid precipitate build up, indicated that the concentration of the nitrobenzene derivative used for the run was too high. A trade-off would have to be made surrounding the concentration of the 1-chloro-4-nitrobenzene **(74)** used, to ensure sufficient throughput was achieved, whilst avoiding the build-up of solid precipitate associated with the use of a higher concentration.

As such a slightly decreased concentration of 1-chloro-4-nitrobenzene **(75)** was employed. The concentration of the 1-chloro-4-nitrobenzene **(75)** was lowered to 0.19 M (5.83 g) which upon a perfect yield would return 10.00 g of the desired product. The solution once again contained 7.31 mL chloroform (1.71 mmol min^{-1}) and 192.69 mL DMF. The flow rate was unchanged along with the remaining parameters. The reaction proceeded uninhibited for the full 60 minutes and did not exceed a pressure of 1.1 bar throughout the whole run. Three, 20-minute aliquots were obtained and analysed. Conversions of >90% were observed across all three of the aliquots with specific conversions of 91, 93 and 91% observed respectively.

9.3 Conversion Improvement

The concentration of the 1-chloro-4-nitrobenzene **(75)** used was then lowered further in the hopes of improving the conversion beyond the ~92%. The concentration was dropped to 0.16 M (5.00 g) which would result in a maximum yield of 8.59 g of the desired product. Once again, all other parameters were kept constant. This alteration to the concentration of the nitroarene compound used had little effect on the overall success of the reaction. Like the previous attempt the pressure throughout the entirety of the run didn't exceed 1.1 bar of pressure and across the three aliquots, which were once again taken, the observed conversions were within experimental error at 92, 91 and

91%. Indicating that the concentration of 1-chloro-4-nitrobenzene **(75)** does not markedly affect the conversion of the reaction observed, meaning the higher concentration should be used as this will result in a greater throughput.

Following on from this result further work was conducted in the hopes of improving the conversion of the reaction. The flow rate was the next parameter adjusted to evaluate its impact. The flow rate of both the nitroarene solution and the base were both reduced, whereas the acid solution was kept at the same flow rate, as reducing this solution would have a detrimental effect on the success of the reaction, due to decreasing the efficiency of the reaction quench. The nitroarene solution flow rate was reduced to 2.78 mL min^{-1} whilst the base flow rate was reduced to 3.47 mL min^{-1} maintaining the relative stoichiometry of the reaction. A longer mean residence time would mean more time prior to quenching for the two reagent streams to interact and react. Across a shorter 10-minute run time, two five-minute aliquots were taken and analysed both of which gave conversions of 99%, indicating the success of this approach.

9.4 Substrate Scope

To highlight the utility of the optimised process a substrate scope investigation was conducted. Six compounds were included in this substrate scope: 1-bromo-4-nitrobenzene, 1-fluoro-4-nitrobenzene, 1-iodo-4-nitrobenzene, 1-trifluoromethyl-4-nitrobenzene, 2,4-dinitrobenzene and nitrobenzene. All of the compounds were run under comparable conditions to the 1-chloro-4-nitrobenzene **(75)** process. Flow rates of 2.78 mL min^{-1}, 3.47 mL min^{-1} and 3.00 mL min^{-1} were employed across the three pumps. The nitrobenzene derivative solutions consisted of 15.70 mmol of the nitrobenzene derivative, 27.27 mmol of the chloroform and 96.35 mL of DMF. The base and the acid solutions were also kept consistent across all runs. Conversion to the desired dichloro methylated products across a 10-minute run time was comparatively successful to 1-chloro-4-nitrobenzene **(74)** process, with percentage conversions ranging from 86 – 97%.

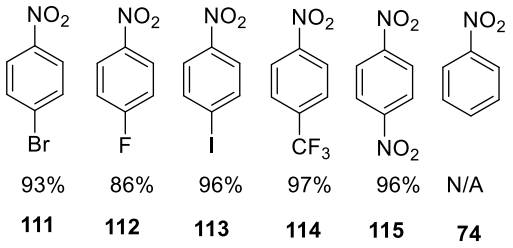


Figure 14: Substrate scope compounds with corresponding % conversions determined via ^{1}H NMR.

10. Purification

10.1 Literature Purification

In the original publication from Mąkosza and Owczarczyk [44] column chromatography was employed, followed by recrystallisation to obtain pure compounds. Column chromatography was first used to remove any residual DMF solvent that could not be removed via the work up procedure outline in **Section 1.1**, or via rotary evaporation. The resulting solid was then recrystalised to remove any remaining impurities or unreacted starting material. Recrystallisation conditions were not outlined for the compounds of interest within this project, however conditions were outline for the nitroquinoline and nitroisoquinoline heterocycle compounds within the data set, with ethanol used as the solvent of choice for the recrystallisation.

10.2 Initial Column Chromatography

Column chromatography was initially investigated in order to establish whether recrystallisation was required to obtain pure product or whether column chromatography could be employed in isolation to achieve this.

A solution of 4-chloro-2-(dichloromethyl)-1-nitrobenzene **(82)** was used to investigate the potential purification sequence. 18.10 g of the crude reaction mixture (92% conversion to 4-chloro-2-(dichloromethyl)-1-nitrobenzene **(82)**) was loaded to 250 g of silica. A solvent system of 50:50, hexane: chloroform was used as the eluent. A mass of 12.10 g of product containing mixture was retained and both starting material and DMF remained present in the sample (0.08: 1: 1.66: 0.09, starting material: product: DMF: chloroform). A 1.00 g aliquot from the 12.10 g isolated material was then taken and columned again. 20.00 g of silica was used and the same solvent composition was employed. This time the full 1.00 g of reaction mixture was recovered with no material being lost on the column. Despite this improved retention, unreacted starting material, DMF and residual chloroform all remained present in the reaction mixture (0.08: 1: 0.38: 0.09, starting material: product: DMF: chloroform). In the hopes of removing the unwanted components of the reaction the reaction mixture was columned for a third time. The same 1.00 g of reaction mixture was loaded onto 25.00 g of silica, with same solvent composition used once again. Like the previous attempt the full 1.00 g of loaded material was recovered. However, unlike the previous attempt all of the residual DMF was removed, although some residual chloroform still remained. Unreacted starting material was also still present (0.9: 1: 0.07, starting material: product: chloroform) in the sample which is to be expected considering the similarity of the structure of the product and starting material and the effect this has on the corresponding polarities. With 1-chloro-4-nitrobenzene **(75)** having a LogP value of 2.40 compared to a value of 3.47 for the product. The reaction mixture remained a liquid following the chromatography, unlike in the originally outlined procedure where Mąkosza and Owczarczyk describe the product being a solid residue at this stage of the purification.[44]

10.3 Alternative Approach to Solvent Removal

Purifying the reaction mixture via column chromatography was deemed an ineffective method for purification of the compounds. Additionally at scale this approach would not be feasible. As such an alternative approach was required. Samples were placed on a high vacuum to remove the residual solvent and to prepare them for subsequent purification.

This proved highly effective and removed all solvent present in the sample. In the case of all derivatives synthesised this approach was employed. Samples were placed on the high vacuum for times ranging from 2 hours to overnight (~14 hours), with the former appearing to be of sufficient time to achieve the desired removal. The mass of the reaction mixture did not drop further when left under vacuum for longer durations, such as overnight, indicating that the desired product is not volatile and as such cannot be lost via evaporation.

10.4 Recrystallisation

As ethanol was the solvent of choice for the recrystallisation of the nitroquinoline and nitroisoquinoline heterocycles in the original data set, it was used as a starting point. Boiling ethanol was added to two aliquots of the reaction mixture. One was placed in the freezer overnight whilst the other was left at room temperature for the same duration. No crystals could be observed in either sample with both forming miscible solutions.

Alternative solvents were then explored to determine their potential utility. The first of which was hexane which much like ethanol formed a miscible solution with no crystal formation. The same was true for toluene which also formed a miscible solution upon cooling. Recrystallisation with chloroform was also attempted and like aforementioned solvents, this was once again unsuccessful.

10.5 Preparative Plates

The use of preparative TLC plates was also investigated. A screen of optimal solvent systems was conducted using thin layer chromatography plates.

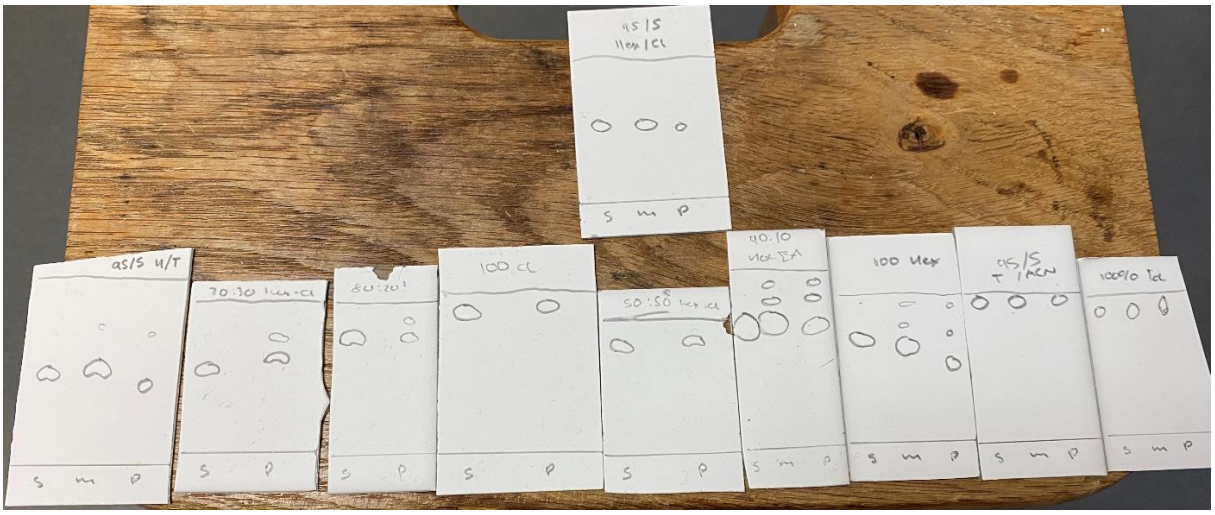


Figure 15: TLC plates from solvent system testing, where s corresponds to the starting material, p corresponds to the product and m corresponding to a mix of the two. Solvent compositions from right to left: 95:5 hexane: Toluene, 70:30 Hexane: Chloroform, 80:20 Hexane: Chloroform, 100 Chloroform, (Bottom) 50:50 Hexane: Chloroform, (Top) 95:5 Hexane: Chloroform, 90:10 Hexane: Ethyl Acetate, 100 Hexane, 95:5 Toluene: Acetonitrile, 100 Toluene.

From this screen it was determined that 95:5, hexane: chloroform, would be an optimal starting point. A sample of the crude product to be purified was dissolved in diethyl ether and loaded onto the plate. Upon inspection two bands could be observed under UV light following elution. The two bands were located directly on top of each other. The silica corresponding to each of the bands was scrapped off the plate and washed with 95:5 Hexane: Chloroform.

TLC analysis of the resulting solutions was conducted in order to determine which band contained the compound of interest. Each band was split into 3 fractions. All three fractions from the bottom band indicated the presence of the compound of interest, with one of the three fractions from the bottom band also indicating the presence of the desired compound. As such both solutions were analysed via NMR spectroscopy.

The bottom band, when analysed, consisted of primarily the compound of interest however, some impurities were still visible in the NMR spectrum. Whereas the inverse was true for the top band, with the majority of the peaks in the spectra corresponding to impurities with small traces of the compound of interest present. It is though that this is due to the close proximity of the two bands and the possible cross contamination as a result. As such the solvent composition was altered in the hopes of widening the separation observed between the two bands.

A solvent composition of 90:10, hexane: chloroform was employed. A large separation was observed between the two bands. When TLC analysis was conducted on the three fractions collected from both bands, the compound of interest only appeared in the fractions corresponding to the bottom band, as expected. However, upon NMR analysis of the bottom layer, impurities were still apparent in the spectrum.

In a final attempt to achieve the desired purification via this method, the solvent composition was again altered to investigate the effect on separation. This time the chloroform concentration was lowered to 2.5%. This alteration led to three separate, clearly defined, bands present on the plate as opposed to the two bands present under the previous two conditions. The spot, on the TLC plate, corresponding to the desired product was present in all of the fractions from both the middle and bottom band and was absent from the fractions collected from the top band. In the NMR spectra for both the middle and bottom fraction the peaks corresponding to the compound of interest were the prominent feature, despite the impurities still being present. The impurities present decreased proportionally with the height of the corresponding band on the plate. With the most impurities and minimal product seen in the top band.

Aligning with the trend observed across all three solvent compositions. As none of the conditions attempted could achieve the desired separation required for the purification of the compounds alternative methods had to be explored.

10.6 Preparative HPLC

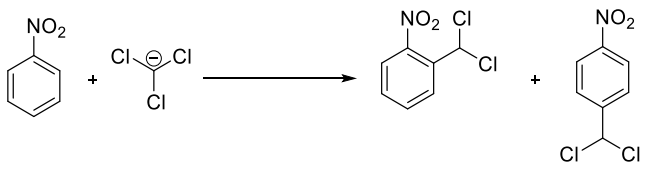
As the preparative plates had shown the most potential in achieving the desired purification, preparative HPLC was a logical next step due to the selectivity of the technique and the ability to closely monitor the correlation between the peaks of interest and the fractions collected via a UV detector. Samples were prepared by diluting 120.00 mg of reaction mixture in ~10.00 mL of 50:50, water: acetonitrile. The system used a reverse phase column with a 5.00 mL sample loop. After a 5-minute equilibration time the instrument was ran for 10.00 minutes on a gradient starting at 70:30, water: acetonitrile, with the ratio of acetonitrile gradually increasing to 100% acetonitrile at ~8.00 minutes. There were two main peaks observed via the UV detector, the two peaks were well resolved and the corresponding fractions were collected in separate vials.

Of the two peaks observed, the later eluting peak had a significantly larger peak area. When this observation was paired with the calculated conversions, of all of the synthesised compounds, which indicated a much larger mass of desired product compared to the starting material, the assumption was made that the later eluting peak corresponded to the compound of interest. As such, all of the fractions that corresponded to this peak were combined and the solvent removed. The resulting yellow oil was weighed and a sample dissolved in d_6-DMSO for NMR analysis. The assumption proved correct and the desired product was identified in the NMR spectra without the presence of the impurities.

This approach was employed for all seven of the synthesised samples. For the bromo, iodo, chloro and di-nitro derivative this approach was sufficient and all compounds could be separated from any impurities present in the crude mixture. This however, was not the case for the remaining three compounds, the CF_3, fluoro and nitrobenzene derivatives. This was most apparent in the fluoro derivative as it was clear by the UV spectra alone that the desired separation had not been achieved as the two peaks were co-eluting.

Although, the same co-elution could not be seen in the UV spectra for the CF_3 derivative a similar issue presented itself. Upon NMR analysis, following the same sample preparation procedure listed above, trace impurities were still visible in the spectra. Although, to a noticeably less significant extent than in the crude material, the presence of such impurities was still not acceptable for the purpose of obtaining a pure sample. It is thought that these two compounds in particular may be problematic due to the presence of the fluorine atoms, making the compounds comparatively more lipophilic meaning, as the column is reverse phase, these compounds may be retained for longer than the rest of the compounds in the data set.

The problem observed with the nitro benzene derivative differed from both of the fluorine containing compounds. The UV spectra observed was comparable to any of the four compounds that were successfully purified. A peak with a small peak area would elute first with good resolution to the peak with the larger peak area that would elute slightly later. It was thought that the two peaks in this case may correspond to the two regioisomers that could form in the reaction between nitrobenzene and the chloroform anion, rather than the starting material and desired product relationship that had presented itself amongst the other derivatives.



74 **105** **116** **117**

Scheme 38: Regio isomers generated from the vicarious nucleophilic substitution of nitrobenzene **(74)** with chloroform anions **(105)**.

As such all the fractions corresponding to each of the two peaks were collected and combined into two samples. The resulting samples were analysed via NMR spectroscopy. Contrary to the expectation the NMR spectrum for the smaller, first eluting peak, had no indication as to the presence of either regio isomer. Surprisingly there was also no indication as to the presence of staring material either in the spectrum. Unsurprisingly considering the previous spectra upon NMR analysis of the larger, later eluting peak, both regio isomers were visible. As such further work was required in order to ascertain whether the two regio isomers could be separated.

A normal phase column was used in the hopes of separating the two compounds however, this proved unsuccessfully and ultimately the two regio isomers could not be separated within the time constraints of this project. Although with the dedication of further time the separation of the two regio isomers may be possible.

The mass recovery observed across all the compounds was the poor. 120 mg of each of compounds were loaded onto the column and a mass recovery of 34.20 mg was not exceeded for any of the derivatives.

Table 5: Mass recovery from preparative HPLC of functionalised dichloromethyl nitrobenzene derivatives.

Compound	Mass recovered (mg)	% mass recovered
4-chloro-2-(dichloromethyl)-1-nitrobenzene **(84)**	13.10	11
2-(dichloromethyl)-4-fluoro-1-nitrobenzene **(119)**	N/A	N/A
2-(dichloromethyl)-4-iodo-1-nitrobenzene **(120)**	34.20	29
4-bromo-2-(dichloromethyl)-1-nitrobenzene **(118)**	7.20	6
2-(dichloromethyl)-1-nitro-4-(trifluoromethyl)benzene **(121)**	9.40	8
2-(dichloromethyl)-1,4-dinitrobenzene **(122)**	2.50	2
1-(dichloromethyl)-2-nitrobenzene **(116)** / 1-(dichloromethyl)-4-nitrobenzene **(117)**	2.10	2

This proved unproblematic across the majority of the derivatives as enough material was retained in order to perform the required characterisation of the compound to confirm structures. However, for both the fluorine containing derivatives this proved detrimental to the purification and characterisation of the compounds as is detailed below.

Work was conducted to ascertain where material was being lost within the process. The lower-than-expected yield of the reaction will obviously be a large contributing factor to the poor mass recovery. Although, if an approximate average yield of 30% is applied to all of the compounds a mass recovery of 36 mg would still be expected. As can be seen in **Table 5** all of the compounds, excluding the iodo derivative, fall sort of this figure. Indicating a further loss of mass within the purification process.

The HPLC instrument allows for the collection of every noteworthy peak within a run, with each peak collected in a corresponding vial. These samples were then analysed by TLC, to determine whether any of the fractions collected outside of the fraction of interest contained a large concentration of relevant material. The TLC plate was examined under UV light to observe any relevant spots on the plate. No spots could be observed on the plate, suggesting that there is no large concentration of relevant material within any of the alternative fractions. However, the lack of visible

spots on the plate could also be explained by extensive dilutions of any relevant material. There is also the possibility that the mass may be distributed across numerous fractions, meaning the cumulative concentration of relevant material across said fraction may have been insufficient to generate visible spots on the TLC plate, although this would be unlikely as it would be expected that due to the structural similarity of any compound present, a similar retention time would be observed.

There is also a possibility that the mass is instead lost during sample preparation. This is feasible as the reaction mixture is only sparingly soluble in water, and as the sample is dissolved in ~50:50, water: acetonitrile, there is a potential for issues of solubility. The samples were required to be prepared in this manner to avoid immediately flushing through the column, as the make-up of the sample should closely match that of the starting conditions of the system it will be run with. Due to the sensitive nature of the HPLC instrument all samples were also required to be filtered to negate any issues that may be incurred as a result of blockages, caused by solid particulates, within the system or damage/soiling of the column. This paired with potential solubility issues may lead to loss of material in filtration prior to the samples being loaded into the system.

As under the original solvent gradient the semi-pure CF_3 derivative could be observed via NMR despite the presence of impurities, whereas under these new conditions that was no longer the case, it was thought that the solvent used and the ratio of these solvents, may be having a negative effect on the mass recoveries. To investigate this a new solvent composition was employed for both sample preparation and for the gradient used. Thus 120.00 mg of the compounds were dissolved in ~10 mL of 50:50, methanol: water, with the gradient starting on 70:30, water: methanol, steadily increasing to 100% methanol at ~8 minutes. Once again, the resulting NMR spectrum showed no visible peaks corresponding to the compound. Due to the presence of water in the sample preparation again the possibility of sample loss through insolubility can't be ruled out, as the compound was similarly soluble in this solvent composition as it was in the acetonitrile: water solution.

10.7 Summary

In summary reverse phase preparative HPLC is a suitable method for purification of the majority of the compounds in the data set. Four of the seven compounds could be purified with ease under this method. With the method also capable of purifying the two regio isomers of the nitrobenzene derivative together, only faltering at the separation of the regio isomers. It is, however not a suitable method for the purification of the two fluorine containing compounds within the data set and an alternative approach would have to be developed and employed for the purification of these compounds. The reasoning for the poor mass recoveries for this method are still unknown however, for the four compounds that this method was successful in purifying this is a redundant issue as enough material could be recovered to conduct the required characterisation and quantification. However, as this reaction is part of a three-step synthesis of the functionalised indigo compounds purification at this stage of the synthesis would likely not be required. As it could be conducted after the next stage of the reaction, where due to the more evident structural differences between the aldehyde material that is generated in the next step of the reaction and the starting material, a simpler purification technique may be possible such as recrystallisation or column chromatography. Thus, negating any challenges encountered with the purification of the compounds synthesised as part of this project.

11. Experimental

11.1 Chemicals

All chemicals used were purchased from Sigma-Aldrich™, Alfa Aesar™, Fluorochem™ or abcr™ and were used without further purification.

11.2 NMR Spectrometer

The NMR spectra were recorded on a Bruker 400 Ultrashield (^{1}H NMR at 400 MHz; ^{13}C NMR at 101 MHz; ^{19}F NMR at 376 MHz) at a temperature of 297 K. Commercially available deuterated dimethylsulfoxide (d_6-DMSO) was used as a solvent for all samples. Coupling constants were measured to the nearest 0.1 Hz. The multiplicity of the signals are indicated by: singlet - s, doublet - d, triplet - t, multiplet - m, doublet of doublets – dd, doublet of doublets of doublets – ddd.

Yields were determined via quantitative ^{1}H NMR. 1,3,5-trimethoxybenzene was used as an internal standard across all the synthesised samples, as the relevant peak in the internal standard would not co-elute with any of the relevant product peaks. All samples were prepared in d_6-DMSO. Conversions were also determined via ^{1}H NMR spectroscopy.

11.3 IR spectrometer

IR spectra were recorded neat on a Perkin-Elmer Paragon 1000 FT-IR spectrometer fitted with a Diamond attenuated total reflection (ATR) accessory (Golden Gate). Assigned peaks are reported in wavenumbers (cm^{-1}), peaks were assigned the following abbreviations regarding their appearance: s (strong, signal >70% of strongest signal), m (moderate, signal between 40-70% of the strongest signal), w (weak, signal < 40% of the broadest signal).

11.4 GC-MS

Low Resolution GC-MS analysis was conducted using a Shimadzu QP2010-Ultra equipped with a Rxi-5Sil MS column (0.15 µm × 10 m × 0.15 mm) in EI mode with Helium carrier (0.41mL/min flow rate). The gradient oven temperature ranged from 50 °C to 300 °C in 5 minutes, with an injection volume of 0.5 µL and a 25:1 Split: Splitless ratio.

11.5 Chromatography

TLC chromatography was conducted on Merck™ TLC silicon dioxide 60 F254 plates with glass backing, with detection via UV absorption. Solvents were purchased from Sigma-Aldrich™.

Preparative chromatography was conducted on Supelco Z265829 Preparative TLC plates, layer thickness 1000 µm, with detection via UV absorption.

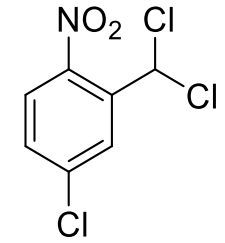
Preparative HPLC was conducted on a InterChim PuriFlash 450 system equipped with a Waters XBridge C18 (19 x100mm, 5um) column, eluting with an acetonitrile gradient.

11.6 Elemental Analysis

Elemental analysis (C, H and N) was conducted on an Exeter Analytical CE-440 Elemental Analyser. Calibration was conducted with 4-bromobenzoic acid.

12 4-chloro-2-(dichloromethyl)-1-nitrobenzene (82)

12.1 Method



Chemical formula: $C_7H_4Cl_3NO_2$
Exact mass: 238.93

Using SF-10 Vapourtec pumps a solution containing potassium hexamethyl disilazide 10% w/w in THF (stream 1, 2.78 mL min^{-1}) was combined with a solution of 1-chloro-4-nitrobenzene **(75)** (2.50 g/5.21 g, 15.86 mmol/33.07 mmol) dissolved in chloroform (3.65 mL/12.24 mL, 27.27 mmol/152.77 mmol) and dimethyl formamide (96.44 mL/387.76 mL) (stream 2, 3.47 mL min^{-1}) using a "Y"-mixer. The resulting mixture was directed through a PFA coil reactor (20 mL, -78 °C, 3.12 min residence time) fitted with a PTFE static mixer. The resulting mixture was quenched with a solution of 32% hydrochloric acid (80 mL) diluted with (120 mL) methanol (stream 3, 3 mL min^{-1}). The collected solution was then diluted with 150 mL of deionised water and washed with dichloromethane (3 × 30 mL) followed by deionised water (3 × 50 mL). The solvent was removed *in vacuo* giving the desired crude product as a brown mixture.

12.2 Data

10-minute run time: Yield: 42%, 100% conversion, Productivity: 0.055 g min^{-1}

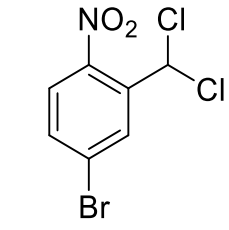
60-minute run time: Yield: 45%, 100% conversion, Productivity: 0.055 g min^{-1}

^{1}H NMR (400 MHz, d_6-DMSO) δ 8.16 (d, *J* = 2.3 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 7.85 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.69 (s, 1H).^{13}C NMR (101 MHz, d_6-DMSO) δ 144.8 (C), 139.5 (C), 136.1 (C), 132.0 (CH), 129.5 (CH), 127.5 (CH), 66.9 (CH). ν_{max}/cm^{-1} 3103.53w (CH), 1524.34s (CH), 1336.09s (NO), 1110.29m (CH), 725.05s (CH). Rt = 4.41 min., m/z 238.90.

Measured: 35.11% carbon, 1.74% hydrogen, 5.64% nitrogen.
Expected: 34.96% carbon, 1.68% hydrogen, 5.82% nitrogen.
Difference: 0.15% carbon, 0.06% hydrogen, -0.18% nitrogen.

13 4-bromo-2-(dichloromethyl)-1-nitrobenzene (118)

13.1 Method



Chemical formula: $C_7H_4BrCl_2NO_2$
Exact mass: 282.88

Using SF-10 vapourtec pumps a solution containing potassium hexamethyl disilazide 10% w/w in THF (stream 1, 2.78 mL min^{-1}) was combined with a solution of 1-bromo-4-nitrobenzene **(111)** (3.20 g, 15.84 mmol) dissolved in chloroform (3.65 mL, 27.27 mmol) and dimethyl formamide (96.44 mL) (stream 2, 3.47 mL min^{-1}) using a "Y"-mixer. The resulting mixture was directed through a PFA coil reactor (20 mL, -78 °C, 3.12 min residence time) fitted with a PTFE static mixer. The resulting mixture was quenched with a solution of 32% hydrochloric acid (80 mL) diluted with 120 mL methanol (stream 3, 3.00 mL/min). The collected solution was then diluted with 150 mL of deionised water and washed with dichloromethane (3 × 30 mL) followed by deionised water (3 × 50 mL). The solvent was removed *in vacuo* giving the desired crude product as a brown mixture.

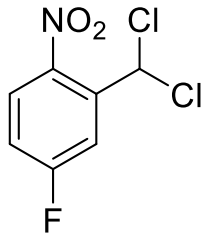
13.2 Data

Yield: 30%, observed conversion: 93%, Productivity: 0.047 g min^{-1}. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.16 (d, *J* = 2.3 Hz, 1H), 8.12 (d, *J* = 8.9 Hz, 1H), 7.84 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.69 (s, 1H).^{13}C NMR (101 MHz, d_6-DMSO) δ 144.8 (C), 139.5 (C), 136.1 (C), 132.0 (CH), 129.5 (CH), 127.5 (CH), 66.9 (CH). ν_{max}/cm^{-1} 2980.74w (CH), 1523.11s (CH), 1337.90s (NO), 1097.40m (CH), 722.33s (CH). Rt = 4.63 min., m/z 282.90.

Measured: 30.40% carbon, 1.62% hydrogen, 4.93% nitrogen.
Expected: 29.51% carbon, 1.42% hydrogen, 4.92% nitrogen.
Difference: 0.89% carbon, 0.20% hydrogen, 0.010% nitrogen.

14 2-(dichloromethyl)-4-fluoro-1-nitrobenzene (119)

14.1 Method



Chemical formula: $C_7H_4Cl_2FNO_2$
Exact mass: 222.96

Using SF-10 vapourtec pumps a solution containing potassium hexamethyl disilazide 10% w/w in THF (stream 1, 2.78 mL min^{-1}) was combined with a solution of 1-fluoro-4-nitrobenzene **(112)** (2.24 g, 15.88 mmol) dissolved in chloroform (3.65 mL, 27.27 mmol) and dimethyl formamide (96.44 mL) (stream 2, 3.47 mL min^{-1}) using a "Y"-mixer. The resulting mixture was directed through a PFA coil reactor (20 mL, -78 °C, 3.12 min residence time) fitted with a PTFE static mixer. The resulting mixture was quenched with a solution of 32% hydrochloric acid (80 mL) diluted with 120 mL methanol (stream 3, 3.00 mL min^{-1}). The collected solution was then diluted with 150 mL of deionised water and washed with dichloromethane (3 × 30 mL) followed by deionised water (3 × 50 mL). The solvent was removed *in vacuo* giving the desired crude product as a brown mixture.

14.2 Data

Yield: 30%, observed conversion: 86%, Productivity: 0.037 g min^{-1}. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.20 (dd, *J* = 9.1, 5.0 Hz, 1H), 7.99 (dd, *J* = 9.4, 2.8 Hz, 1H), 7.71 (d, *J* = 1.2 Hz, 1H), 7.62 (ddd, *J* = 9.2, 7.5, 2.8 Hz, 1H).

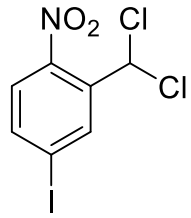
Crude NMR spectrum used due to the inability to generate a quantifiable NMR spectrum following preparative HPLC.

Due to the inability to obtain a pure spectrum the ^{13}C NMR analysis was unusable due to the number of co-eluting peaks.

^{19}F NMR (376 MHz, d_6-DMSO) δ -101.99. Rt = 5.18 min, m/z 223.10.

15 2-(dichloromethyl)-4-iodo-1-nitrobenzene (120)

15.1 Method



Chemical formula: $C_7H_4Cl_2INO_2$
Exact mass: 330.87

Using SF-10 Vapourtec pumps a solution containing potassium hexamethyl disilazide 10% w/w in THF (stream 1, 2.78 mL min^{-1}) was combined with a solution of 1-iodo-4-nitrobenzene **(113)** (3.95 g, 15.86 mmol) dissolved in chloroform (3.65 mL, 27.27 mmol) and dimethyl formamide (96.44 mL) (stream 2, 3.47 mL min^{-1}) using a "Y"-mixer. The resulting mixture was directed through a PFA coil reactor (20 mL, -78 ^{o}C, 3.12 min residence time) fitted with a PTFE static mixer. The resulting mixture was quenched with a solution of 32% hydrochloric acid (80 mL) diluted with 120 mL methanol (stream 3, 3.00 mL min^{-1}). The collected solution was then diluted with 150.00 mL of deionised water and washed with dichloromethane (3 × 30.00 mL) followed by deionised water (3 × 50.00 mL). The solvent was removed *in vacuo* giving the desired crude product as a brown mixture.

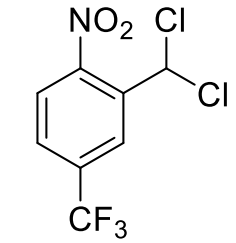
15.2 Data

Yield: 21%, observed conversion 96%, Productivity: 0.038 g min^{-1}. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.41 (d, *J* = 1.9 Hz, 1H), 8.13 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.64 (s, 1H). ^{13}C NMR (101 MHz, d_6-DMSO) δ 145.7 (C), 140.8 (C), 138.1 (C), 135.3 (CH), 126.8 (CH), 103.1 (CH), 66.8 (CH). ν_{max}/cm^{-1} 3093.75w (CH), 1521.99s (CH), 1338.12s (NO), 1175.21m (CH), 719.18s (CH). Rt = 4.91 min., m/z 330.90.

Measured: 27.50% carbon, 1.39% hydrogen, 4.44% nitrogen.
Expected: 25.33 carbon, 1.21% hydrogen, 4.22% nitrogen.
Difference: 2.17% carbon, 0.18% hydrogen, 0.22% nitrogen.

16 2-(dichloromethyl)-1-nitro-4-(trifluoromethyl)benzene (121)

16.1 Method



Chemical formula: C8H4Cl2F3NO2
Exact mass: 272.96

Using SF-10 Vapourtec pumps a solution containing potassium hexamethyl disilazide 10% w/w in THF (stream 1, 2.78 mL min^{-1}) was combined with a solution of 1-nitro-4-(trifluoromethyl)benzene **(114)** (3.03 g, 15.85 mmol) dissolved in chloroform (3.65 mL, 27.27 mmol) and dimethyl formamide (96.35 mL) (stream 2, 3.47 mL min^{-1}) using a "Y"-mixer. The resulting mixture was directed through a PFA coil reactor (20 mL, -78 ^{o}C, 3.12 min residence time) fitted with a PTFE static mixer. The resulting mixture was quenched with a solution of 32% hydrochloric acid (80 mL) diluted with 120 mL methanol (stream 3, 3.00 mL min^{-1}). The collected solution was then diluted with 150 mL of deionised water and washed with dichloromethane (3 × 30 mL) followed by deionised water (3 × 50 mL). The solvent was removed *in vacuo* giving the desired crude product as a brown mixture.

16.2 Data

Yield: 26%, observed conversion: 97%, Productivity: 0.040 g min^{-1}. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.16 (d, *J* = 2.3 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 7.85 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.69 (s, 1H).

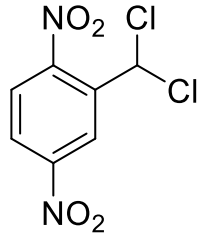
A pure ^{1}H NMR spectrum could not be obtained however no coeluting peaks were observed in the crude spectra.

Due to the inability to obtain a pure spectrum the ^{13}C NMR analysis was unusable due to the number of co-eluting peaks.

^{19}F NMR (376 MHz, d_6-DMSO) δ -61.88. Rt = 4.67 min., m/z 273.95.

17 2-(dichloromethyl)-1,4-dinitrobenzene (122)

17.1 Method



Chemical formula: $C_7H_4Cl_2N_2O_4$
Exact mass: 249.95

Using SF-10 Vapourtec pumps a solution containing potassium hexamethyl disilazide 10% w/w in THF (stream 1, 2.78 mL min^{-1}) was combined with a solution of 1,4-dinitrobenzene **(115)** (2.67 g, 15.88 mmol) dissolved in chloroform (3.65 mL, 27.27 mmol) and dimethyl formamide (96.35 mL) (stream 2, 3.47 mL min^{-1}) using a "Y"-mixer. The resulting mixture was directed through a PFA coil reactor (20 mL, -78 ^{o}C, 3.12 min residence time) fitted with a PTFE static mixer. The resulting mixture was quenched with a solution of 32% hydrochloric acid (80.00 mL) diluted with 120 mL methanol (stream 3, 3.00 mL min^{-1}). The collected solution was then diluted with 150 mL of deionised water and washed with dichloromethane (3 × 30 mL) followed by deionised water (3 × 50 mL). The solvent was removed *in vacuo* giving the desired crude product as a brown mixture.

17.2 Data

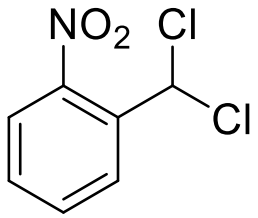
Yield: 41%, observed conversion 96%, Productivity: 0.057 g min^{-1}. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.37 – 8.31 (m, 2H), 7.95 – 7.90 (m, 2H), 7.68 (s, 1H). ^{13}C NMR (101 MHz, d_6-DMSO) δ 148.6 (C), 146.8 (C), 128.2 (CH), 124.8 (CH), 70.6 (CH).

Only four of the expected six aromatic signals can be observed, this may be due to the low concentration of the sample meaning the remaining two signals were lost in the noise.

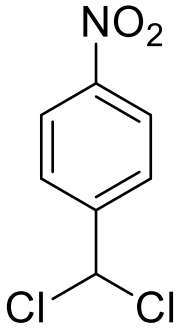
ν_{max}/cm^{-1} 3104.30w (CH), 1524.57s (CH), 1337.29s (CH), 1110.69m (CH), 727.99s (CH). Rt = 4.52 min., m/z 249.80.

18 1-(dichloromethyl)-2-nitrobenzene (116), 1-(dichloromethyl)-4-nitrobenzene (117)

18.1 Method



Chemical formula: $C_7H_5Cl_2NO_2$
Exact mass: 204.97



Chemical formula: $C_7H_5Cl_2NO_2$
Exact mass: 204.97

Using SF-10 vapourtec pumps a solution containing potassium hexamethyl disilazide 10% w/w in THF (stream 1, 2.78 mL min^{-1}) was combined with a solution of nitrobenzene **(74)** (1.95 g, 15.84 mmol) dissolved in chloroform (3.65 mL, 27.27 mmol) and dimethyl formamide (96.35 mL) (stream 2, 3.47 mL min^{-1}) using a "Y"-mixer. The resulting mixture was directed through a PFA coil reactor (20 mL, -78 °C, 3.12 min residence time) fitted with a PTFE static mixer. The resulting mixture was quenched with a solution of 32% hydrochloric acid (80 mL) diluted with 120 mL methanol (stream 3, 3.00 mL min^{-1}). The collected solution was then diluted with 150 mL of deionised water and washed with dichloromethane (3 × 30 mL) followed by deionised water (3 × 50 mL). The solvent was removed in vacuo giving the desired crude product as a brown mixture.

18.2 Data

Both possible regio isomers co-eluted and as a result correctly assigning peaks to the corresponding compound proved challenging.

1-(dichloromethyl)-2-nitrobenzene (**116**)

Yield: 9%, Productivity: 0.011 g min^{-1}. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.18 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.06 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.74 (ddd, *J* = 8.2, 7.4, 1.4 Hz, 1H). ^{13}C NMR (101 MHz, d_6-DMSO) δ 142.6 (C), 135.8 (C), 135.0 (CH), 130.3 (CH), 125.1 (CH), 124.8 (CH), 67.7 (CH). Rt = 4.49 min., m/z 205.90.

1-(dichloromethyl)-4-nitrobenzene (**117**)

Yield: 5%, Productivity: 0.053 g min^{-1}. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.37 – 8.30 (m, 2H), 7.69 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (101 MHz, d_6-DMSO) δ 146.9 (C), 145.6 (C), 126.1 (CH), 123.8 (CH), 70.6 (CH). Rt = 4.49 min., m/z 205.90.

^{1}H NMR: The remaining signal for both isomers co elutes at ~7.9 ppm meaning the two peaks cannot be deciphered from one another.

Ratio of Regio isomers: 1.4:1, 1-(dichloromethyl)-2-nitrobenzene (**116**): 1-(dichloromethyl)-4-nitrobenzene (**117**)

19 Yield and Conversion Disparity

19.1 Cause of Disparity

As can be in **Section 11-17** a large disparity between the conversions and the yields across all of the synthesised products was observed. The cause of such a disparity was not immediately evident. Various potential explanations for this were explored.

It was initially thought that that the loss of the desired product may be due to the volatility of the compounds. To investigate this, a sample was placed under high vacuum for an extended duration with the mass measured periodically. However, the compound mass was stable and so this was not the cause of the disparity.

It was then posited that degradation may have been contributing to the loss of mass. As quantitative analysis of the samples was not conducted immediately following synthesis, degradation may have occurred between identification of complete conversion and determination of the yield. To probe this possibility a sample synthesised ~2 months prior to this investigation was directly compared to a compound generated on the day of testing. Both samples were dissolved in d_6-DMSO and quantitative NMR was run, once again with 1,3,5-trimethoxybenzene as the internal standard. Both samples had conversions of 100% and based upon the quantitative analysis both samples also had comparatively poor yields. There was no difference in the yields observed between the two samples, being ~30%. Indicating that the compounds were not degrading over time and as such this was not the source of the disparity between the two values.

The method of yield determination was next called into question. As up to this stage the assumption was made that the quantitative yield calculations were returning the correct value. This was tested, to determine whether a calculation error had been made. For this investigation 1,4-dinitrobenzene **(115)** was used as an alternative internal standard as its corresponding peak does not overlap with any of the peaks within the sample and it is soluble in d_6-

DMSO. Calculation of the quantitative yield with the alternative internal standard return comparable results, validating the previously collected data and ruling out calculation error as the source of the disparity between yield and conversion.

It was finally thought that the compounds may be polymerising, as can occur in the indigo compounds generated from the precursors synthesised as part of this work.[58] However, this was swiftly ruled out as the source of the disparity through the use of mass spectrometry. All sampled were analysed via GC-MS, there was no indication across all of the samples as to the presence of compounds with a mass to charge ratio indicative of a polymerised product. Indicating, once again, that this was not the cause of the disparity between the two values.

19.2 Alteration of the Extraction Solvent

Having exhausted many of the potential causes for the unexplained variance between the yield and conversion. Further work was conducted, and it was discovered that upon alteration of the extraction solvent, used in the work up procedure, the observed yield could be drastically improved to fall in line with the expected yields for the reactions.

The extraction solvents that were being employed consisted of, a combination of dichloromethane (3 × 30 mL) and water (3 × 50 mL) as outlined in the original batch procedure.[44] Under this extraction procedure it was estimated that that a maximum mass recovery of 25-35% was being achieved, leading to the poor final yields observed across all of the synthesised compounds. The extraction solvent was altered to ethyl acetate (3 × 50 mL) which resulted in drastically improved mass recovery and in turn yields, as illustrated with the 4-chloro-2-(dichloromethyl)-1-nitrobenzene compound **(84)** where a 93% yield, determined once again via quantitative NMR, was achieved via employing this new extraction strategy. This yield is comparable to the batch process where a yield of 94% was reported.

20 Implications of Work

20.1 Summary of Work Conducted

As highlighted by the 93% yield outlined above **(section 19.2)**, an effective procedure for the generation of di-chloromethyl substituted indigo precursors has been developed. The reaction proceeds to completion giving the desired compounds in good conversion. The reaction can proceed throughout the duration of the run time with little to no impact on the pressure observed within the system, with the pressure not exceeding 2 bar of pressure throughout the duration of a one hour run time. The ability to run the reaction for extended run times of up to an hour, although there is no indication that the reaction could not be run for longer durations, means that the compounds can be generated on a large laboratory scale.

The productivity of the reaction at this scale was demonstrated through the generation of 15.70 g of the chlorine containing precursor with a 91% conversion, with a maximum theoretical yield of 10.00 g hour $^{-1}$. Although due to the reaction behaving comparably over both ten minute and hour long runs, it stands to reason that upon lowering the flow rates to 2.78 ml min^{-1} and 3.47 ml min $^{-1}$ for the base and reagent lines respectively, an hour-long run could be achieved with 100% conversion, ~93% yield and a max theoretical yield of 9.25 g hour^{-1}. Although this would have to be determined experimentally prior to making such a claim. The reaction worked well across all of the substituted compounds returning good conversions across the board.

Baring the expected regioselectivity issues observed when the reaction was conducted with the nitrobenzene starting material, due to the lack of a functional group para to the nitro functionality blocking substitution at that position, all other compounds displayed good regioselectivity generating a mono substituted product in the desired position, ortho to the nitro group.

Similar trends were observed in this work, as were found by Míjkosza and Owczarczyk[44], the nitro benzene **(74**) and fluorine containing compounds, of the 1-fluoro-4-nitrobenzene **(112)** and 1-nitro-4-(trifluoromethyl)benzene **(114)**, performed poorly in the reaction in comparison to the other functionalised starting material. Míjkosza and Owczarczyk posited that fluorine para to the nitro group deactivates the nitroarene towards nucleophilic substitution, as a result of more efficient conjugation to the nitro group through the ring, due to a good correlation of the p orbital size.[44] The fact that this is also observed in the flow procedure indicates that the deactivating effect of fluorine on nitroarenes towards nucleophilic substitution, cannot be overcome through the implementation of flow chemistry.

One additional point to note as mentioned in **Section 5.1** is the degradation of the equipment as a result of the chemistry involved in the method. The Vapourtec compatibility manual[59] indicates that potassium hydroxide (concentrated), which is most comparable to the base employed in the reaction, is compatible with the tubing of the pump, but does reduce the lifetime of the tubing. This proved to be true for the reaction outlined in this work. Over time the base would weaken the tubing resulting in alterations to the flow rate and the generation of micro tears. To mitigate this the tubing had had to be periodically changed out to ensure the pumps maintained optimal performance. As one may expect this effect was exacerbated when longer run times were attempted meaning the tubing would have to be replaced more frequently. This is a factor that would need to be considered if this method was to be used on a larger scale.

20.2 Wider Potential Applications of Work

The primary area of research that may benefit from this work is the generation of organic semi-conductors. As in many cases the effect of introducing certain functionalities into the indigo compounds cannot be predicted and can only be determined through experimentation. As such the methodology developed as part of this project may assist in conducting such work in the future. The process appears tolerant of various functionalities para to the nitro group, allowing for the generation of various functionalised indigo derivatives, at a scale that could facilitate investigation of the effects the introduced functionalities may have on the semi conducting properties of the resulting indigo compounds.

21 Future Work

21.1 Short Term Potential Work

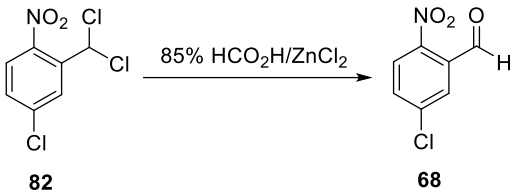
To confirm the conclusion that the methodology developed is suitable for all of the functionalised derivatives it is pertinent to investigate the affect that the alteration of extraction solvent, employed for the chloro derivative **(82)**, will have on the remaining compounds. Extrapolating from the data collected throughout the duration of the project one would expect that the compounds would behave comparatively to one another.

Additionally, the scope of the chemistry could also be expanded, to include a wider range of functional groups *para* to the nitro group in the nitroarene starting material. This would be useful to conduct as it would further highlight the utility of the approach developed. Expanding the reaction scope could also be extended to the nucleophile used. Although the use of chloroform and its corresponding anion has shown to be highly successfully in undergoing the required VNS mechanism, there is a push to reduce the volume of chloroform used in all aspects of chemistry due to the environmental consequences of its use. As such alternatives could be explored with ammonia being one such solvent that has the potential to behave comparatively.

21.2 Longer Term Potential Work

Once it has been established that high yields can be obtained for all of the compounds, attention should then turn to generating the corresponding functionalised indigo aldehydes. This could be initially attempted by employing the

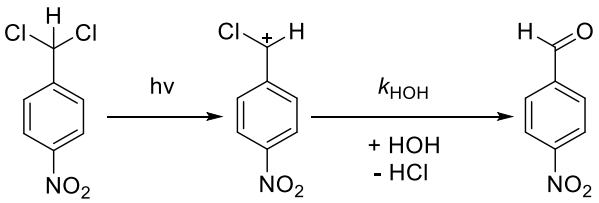
approach Míjkosza and Owczarczyk outlined in the same paper as the batch procedure.[44] The second step of the three-stage synthesis, to generate the final indigo compounds, is the hydrolysis of the dihalide intermediate formed via vicarious nucleophilic substitution chemistry, as outlined as part of this work. To facilitate the transformation of the di-chloro methyl derivative to the required aldehyde containing intermediate 85% formic acid in the presence of a zinc (II) chloride catalyst was employed, which returned a 60% yield over a 72-hour reaction time.[44]



82 **68**

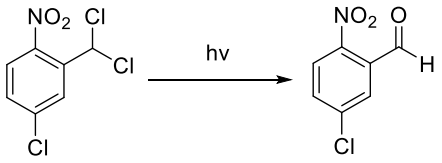
Scheme 39: Hydrolysis of 4-chloro-2-(dichloromethyl)-1-nitrobenzene **(82)** to 5-chloro-2-nitrobenzaldehyde **(68)**.[44]

As mentioned in **section 1.7** there is potential to expand upon the work conducted by Sanjeev *et al*.[40] It would be logical to divert attention to this approach following completion of the zinc catalysed reaction **(Scheme 39)**. This work would involve the utilisation of photochemistry to facilitate the required transformation. It is hoped that the chemistry outlined could be repurposed, as Sanjeev *et al*. have previously highlighted that this approach can be used to induce the required transformation with somewhat comparable compounds, the structural similarity of the compound used by Sanjeev *et al.* and the required compound for this project can be seen in **Scheme 40 and 41**. It is also hoped that the implementation of flow could further improve upon the currently outlined procedure. Reducing the time in which the transformation takes to occur whilst simultaneously improving the process efficiency.



85 **86** **87**

Scheme 40: Conversion of dichloro nitrobenzene **(85)** to nitro benzaldehyde **(87)**.[40]



82 **68**

Scheme 41: The required photochemical transformation of 4-chloro-2-(dichloromethyl)-1-nitrobenzene **(82)** to 5-chloro-2-nitrobenzaldehyde **(68)**.

Once the aldehyde intermediates have been synthesised successfully, the final stage of the indigo synthesis can take place. The Bayer-Drewson indigo synthesis is well precedented in the literature and should prove unproblematic. The aim of this facet of the work would be to simply highlight the ability to telescope the synthesis of the desired compounds from the functionalised nitrobenzene starting materials, on a gram scale.

21.3 Highly Speculative Potential Work

One of the areas of flow chemistry that remains a challenge is the true telescoping of multi-step synthesis. The obvious benefits of such approaches are evident, a fully continuous process requires no human intervention aside from stop/start commands. This can make the process less time intensive, as tasks such as purification and reaction mixture manipulation do not have to be completed manually and are instead completed autonomously. However idyllic such a system sounds, the design from both a chemical and engineering standpoint, can prove challenging at best and impossible at worst.

Of the three stages of the proposed synthesis of the indigo compounds all would likely be possible to complete in flow in isolation. The first stage has already been highlighted to be successful as outlined in this report. The second, photochemical step in the synthesis, would in theory be particular conductive to a flow chemistry approach, provided the transformation behaves as expected. Then the final stage would likely proceed via the use of a simple two pump system. Despite all three stages likely working very successfully in flow, the challenge arises from the seamless, autonomous transition from one stage of the synthesis to the next. Purification, to remove spent and unreacted reagents, solvent manipulations, to mitigate solvent incompatibilities, and a multitude of other factors all have to be considered and addressed prior to configuring any true telescoped procedure.

The main challenge that is often encountered in such a procedure is the methods in which purification is conducted. Although many techniques for inline purification have been detailed in the literature and implemented in various processes, ranging from inline SiO_2 purification, extractions/separations, scavengers, crystallisations/trituration's and catch and release strategies. The same problem typically persists in all instances. Once the scale of the reaction surpasses a certain threshold, the volume of liquid, the chosen purification technique can hold/process, quickly becomes the limiting factor.

This has led to industry, where the scales are typically greater, adopting strategies such as large-scale aqueous quenches and extractions along with azeotropic distillations, resulting in more semi-continuous processes as opposed to truly telescoped procedures. That being said, in specific cases a telescoped procedure can work at larger scales although such approaches are typically not utilised unless absolutely necessary such as in the case of hazardous chemistry like azide chemistry, where many of the intermediates are particularly difficult to handle due to their explosive nature, or fluorination chemistry where reagents are particularly toxic.

As such it may prove that implementing the full three stage synthesis required for the generation of the functionalised indigo compounds in a telescoped manner may be overcomplicating the synthesis. Requiring both elaborate engineering approaches and challenging chemistry. This can only be established upon attempts to develop such a system. In such a case a logical and satisfactory conclusion to this body of work would be the generation of the desired compounds at a gram scale, with good productivity, functional group toleration and yield.

22 References

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