Organic thionitroso compounds

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ORGANIC THIONITROSO COMPOUNDS

by

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DECLARATION

The work described in this thesis was carried out in the Department of Chemistry at the University of Durham between August 1986 and September 1989. All the work is my own, unless stated to the contrary, and it has not been submitted previously for a degree at this or any other University.

Dedicated to my parents.

ACKNOWLEDGEMENTS

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ABSTRACT

ORGANIC THIONITROSO COMPOUNDS

A series of novel N-substituted phthalimide-2-sulphenamides was prepared. The N-aryl analogues were shown to be efficient precursors to thionitrosoarenes. Extension of the methodology to heteroaromatic and acyl derivatives was unsuccessful, with the exception of 3-thionitrosopyridine, the first known thionitrosoheteroarene.

Thionitrosoarenes are shown to be versatile dienophiles and enophiles. Reactions with various substituted dienes proceeded with high stereoselectivity and some regioselectivity to afford 3,6-dihydro-1,2-thiazines. Cycloadditions of thionitrosoarenes generated independently from imidosulphurous chloride precursors showed similar selectivities. The mechanism of cycloaddition is discussed in the light of molecular orbital calculations.

Paul Taylor (October 1989)

ABBREVIATIONS

Ac	Acetyl
Ar	Aryl
Bu	Butyl
Et	Ethyl
Het	Heterocyclic substituent
Me	Methyl
R	Alkyl or general organic substituent
Ph	Phenyl
Tos	Tosyl(4-methylphenylsulphonyl)
Hal	Halogen
Py	Pyridine
Phth	Phthalimide
M	Metal
THF	Tetrahydrofuran
GC	Gas Chromatography
GLC	Gas Liquid Chromatography
IR	Infrared
NMR	Nuclear Magnetic Resonance
ppm	Parts per million
UV	Ultraviolet
mpt.	Melting point
dec	Decomposes
hr.	Hour
min.	Minute
d.e.	Diastereomeric excess
e.e.	Enantiomeric excess
HOMO	Highest occupied molecular orbital
LUMO	Lowest unoccupied molecular orbital

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CHAPTER ONE

INTRODUCTION

1.1 INTRODUCTION

Thionitroso compounds (1) are formally derived from nitroso compounds (2) by replacement of oxygen by sulphur - hence "thionitroso". They are similarly related to sulphur monoxide, S=O, by replacement of oxygen by the R-N= group, thus thionitroso compounds are imides of sulphur monoxide. This introduction will, therefore, begin with a discussion of nitroso analogues and imides of sulphur oxides before progressing to the synthesis and chemistry of thionitroso compounds themselves.

(1) R–N=S (2) R–N=O

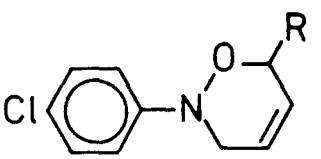
1.2 NITROSO COMPOUNDS

1.2.1 Stable Nitroso Compounds in Diels-Alder Additions

The chemistry of organic nitroso compounds (2) has been widely studied. Their reactivity has been found to be linked to the electronic nature of R, the general trend being that of increasing reactivity with increasing electron-withdrawing R groups. N-Nitroso compounds (nitrosamines), with R = R^1R^2N- and hence an electron rich N=O bond, are, accordingly, stable compounds which have a well developed chemistry[1]. They do not usually, however, undergo [4 + 2] cycloadditions[2] and nitrosamines will not, therefore, be discussed further here. C-Nitroso compounds, where R is aryl or alkyl, have also been extensively studied. [4 + 2] Cycloadditions of nitrosoarenes to a wide range of dienes are known and these reactions have been frequently reviewed[2-5].

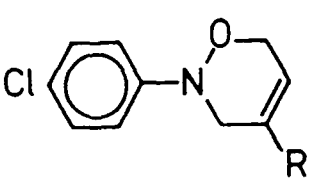
The aforementioned effect of the electronic nature of the N=O bond has been highlighted in kinetic studies of nitrosoarenes[5], which showed that 1-nitro-4-nitrosobenzene reacted with 1,3-cyclohexadiene 3,500 times faster than 1-methoxy-4-nitrosobenzene. The regiochemistry of addition is less well defined, despite rigorous work by Kresze and co-workers, summarised by Boger and Weinreb[5], and is usually explained by a combination of subtle steric and electronic effects, the latter stabilising or destabilising postulated dipolar intermediates. High regioselectivity is generally observed: hence 1-chloro-4-nitrosobenzene reacts with 1-substituted dienes to give, exclusively, 6-substituted N-aryldihydrooxazines (3), and with 2-substituted dienes to give, exclusively, 4-substituted N-aryldihydrooxazines (4)[3]. Nitrosobenzene gives a similar regioselectivity with isoprene (5)[3]. Conversely the 4-carboxyl substituted nitrosobenzene (6) gives exclusively the 5-substituted oxazine with isoprene[6], yet gives the 4-substituted oxazine with the analogous 2-methoxy-1,3-butadiene[7].

(3)



R = OAc, CO_2Me, Ph

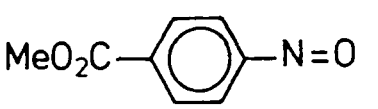
(4)



R = Me, CN, CF_3

(5)

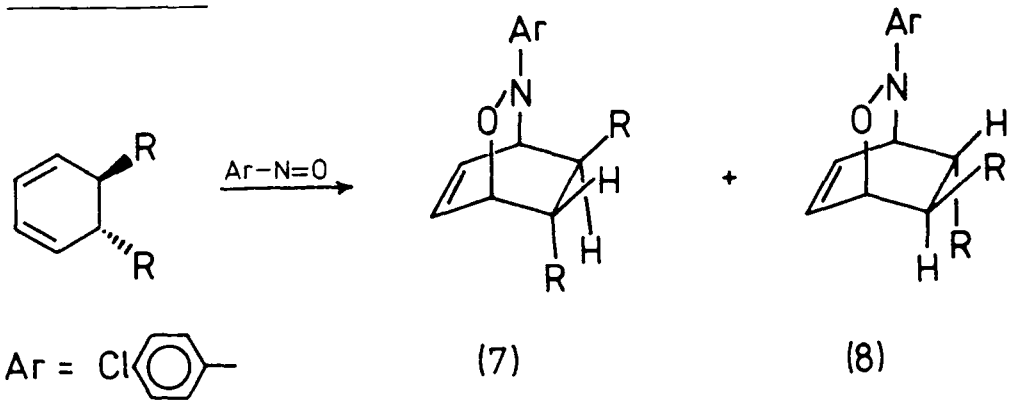
(6)



Simple carbocyclic dienes also undergo [4 + 2] cycloaddition with nitrosoarenes, as expected[3]. Elaboration of the 5 and 6 positions of 1,3-cyclohexadiene was expected to resolve the steric requirements of

the addition in the absence of polar effects in the diene (Scheme 1.1)[8], but instead led to further confusion with R = OAc giving exclusively product (7), but R = $CO_2{}^tBu$ giving a 1:1 mixture of (7) and (8). Nitrosoheteroarenes, with pyridine-based substituents, have also been synthesised and the 4,5-dimethyloxazine obtained, as expected, from the [4 + 2] cycloaddition with 2,3-dimethyl-1,3-butadiene[7].

Scheme 1.1

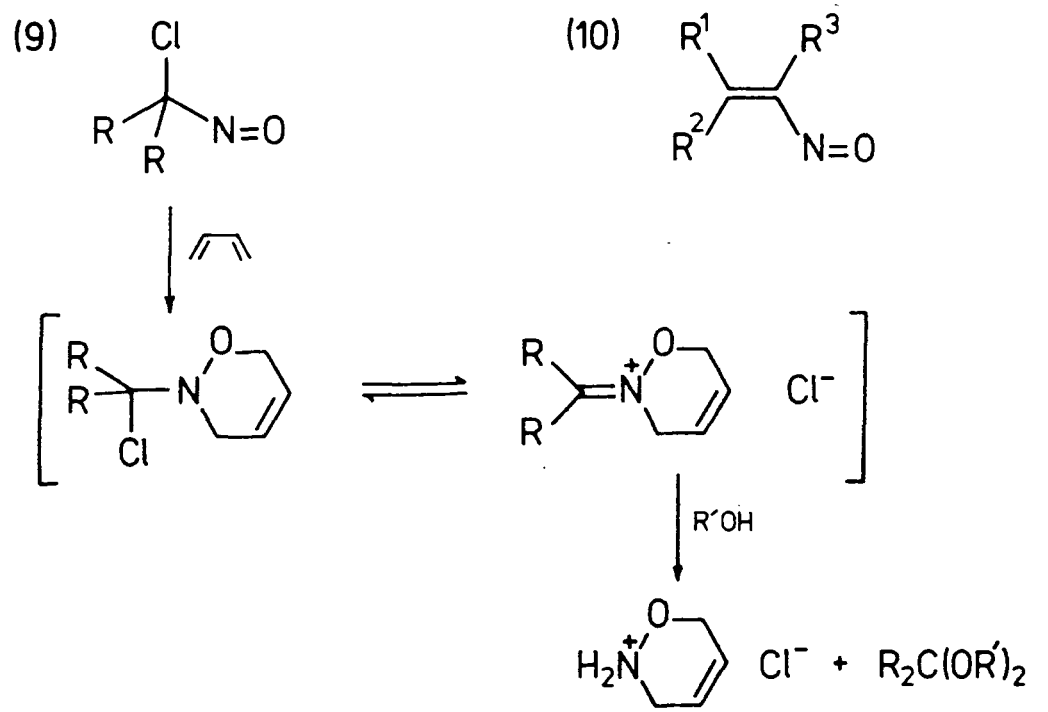


Several nitrosoalkanes have been used as dienophiles, but only the α-chloronitrosoalkanes (9) have been widely studied. They are known to react with 1,3-dienes, as expected, usually followed by solvolysis of the initial adduct, to yield dihydrooxazine hydrochlorides (Scheme 1.2)[4]. Regioselectivity in reactions of (9) with 1- and 2-substituted 1,3-butadienes is, in general, in agreement with that of nitrosobenzene[3], with the exception, characteristically, of isoprene (5) which, unlike 2-phenyl-1,3-butadiene, yields predominantly the 5-substituted oxazine. No satisfactory explanation has been given.

Other examples of reactive nitrosoalkanes are trifluoronitrosomethane, $CF_3N{=}O$, which undergoes rapid [4 + 2] cycloaddition in the manner of other highly electron deficient nitroso compounds[9] (as in Section 1.2.2 below), and vinylnitroso compounds (10). The latter are generated by base-mediated elimination of H-Hal from an α-halooxime[10] and prefer to act as 4π heterodienes unless substituents R^1 and/or R^2

are present, when the usual 2π addition of the N=O bond, rather than the C=C bond, is observed[5].

Scheme 1.2

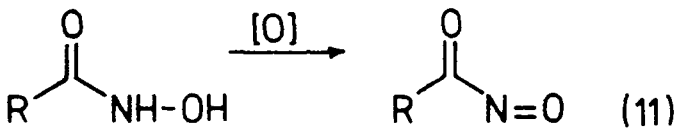


1.2.2 Nitroso Compounds as Reactive Intermediates

As predicted, the highly electron deficient nitroso compounds (11) such as acyl nitroso compounds (R = alkyl)[11], nitrosoformates (R = RO-)[11], nitrosoformamides (R = RNH-)[11] and nitrosoimines (R = ArN=CR-)[12] are unstable and highly dienophilic[11]. Compounds (11) can be generated by oxidation of the corresponding hydroxylamine (Scheme 1.3) and trapped *in situ*, in good yield, with a variety of dienes.

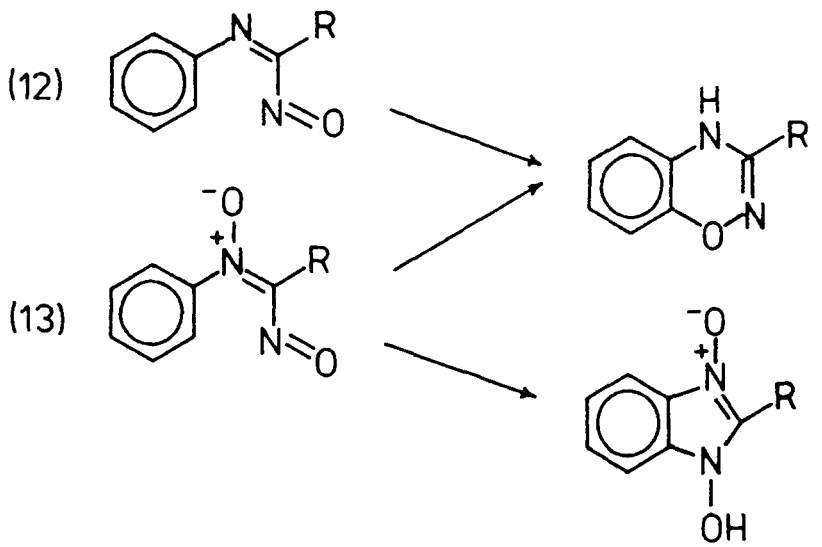
Gilchrist and Rees[12] have used N-aryl-C-nitrosoimines (12) and α-nitrosonitrones (13) (generated as by Minisci *et al.*[13] from nitrosobenzene and nitrile oxides) in intramolecular cycloadditions (Scheme 1.4).

Scheme 1.3



(11)

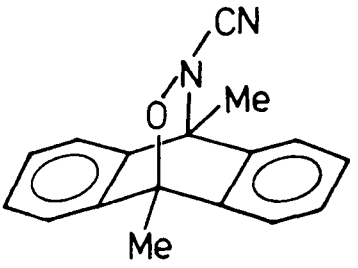
Scheme 1.4



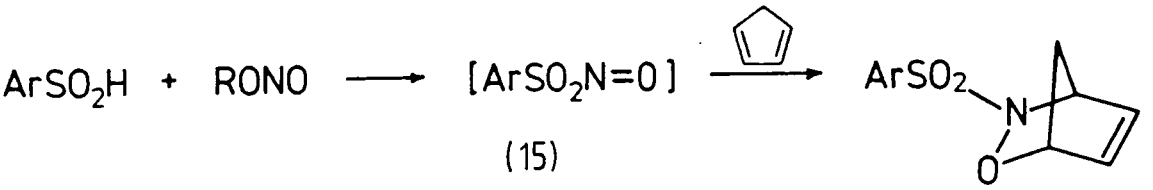
In addition to the above derivatives, Kirby's group reacted nitrosyl chloride and silver cyanide, heterogeneously in chloroform at -20°C [14], to yield nitrosyl cyanide, which was trapped *in situ* by a variety of dienes. Initial trapping of NCNO by 9,10-dimethylanthracene gave adduct (14), which on refluxing in benzene regenerates nitrosyl cyanide, which can then be cleanly trapped by dienes without interference from the nitrosyl chloride/silver cyanide mixture, a method which can be used for most of the other highly reactive nitroso compounds in Kirby's review[11].

Sulphonyl nitroso compounds (15) have been little studied, but can be generated from an alkyl nitrite and a sulphinic acid[15] and have been trapped with cyclopentadiene (Scheme 1.5)[16].

(14)



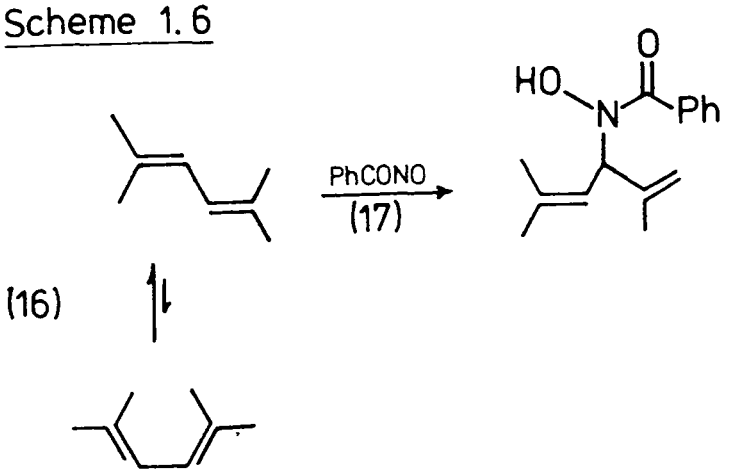
Scheme 1.5



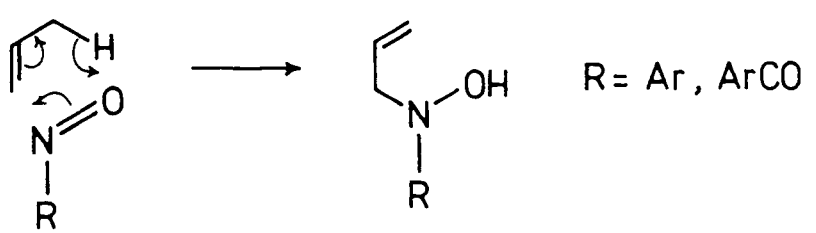
1.2.3 Nitroso Compounds in the Ene Reaction

An alternative to [4 + 2] Diels-Alder addition exists with substituted dienes, *ie.* the ene reaction. This process is, however, relatively slow with nitroso compounds and is hence seen only with dienes which have a high steric barrier associated with the transition to the cisoid conformation required for [4 + 2] addition. For example, 2,5-dimethyl-2,4-hexadiene (16) undergoes an ene reaction with the nitrosobenzoyl compound (17) (Scheme 1.6)[11]. Otherwise the ene reaction is only seen with alkenes, when [4 + 2] addition is, of course, not possible. The products are allylic hydroxylamines (Scheme 1.7)[17].

Scheme 1.6



Scheme 1.7



1.3 IMIDES OF SULPHUR OXIDES

1.3.1 Introduction

(18) $R-N=S=O$ (19) $R^1-N=S=N-R^2$

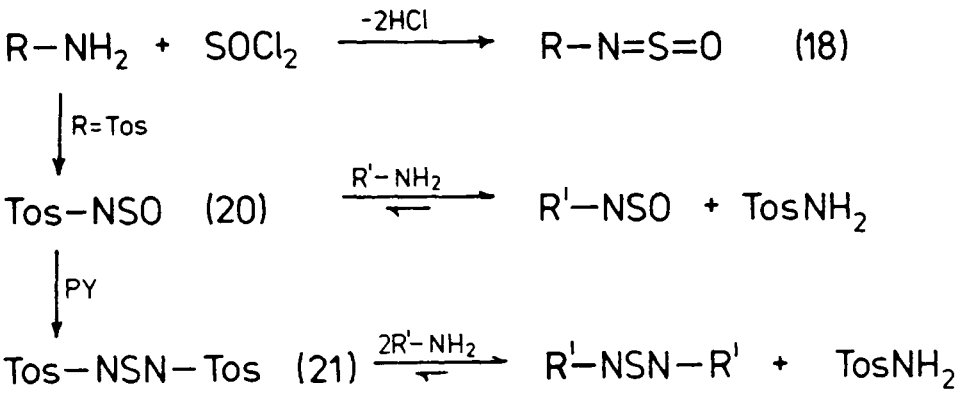
Thionitroso compounds (1) can be considered to be imides of sulphur monoxide. They are, then, related to other sulphur oxides and their imides. Cycloadditions of sulphur dioxide are well known and will be discussed briefly in Chapter 5. Also well studied is the chemistry of N-sulphinylamines (18) and, to a lesser extent, sulphur diimides (19), which are the imides of sulphur dioxide. Cycloadditions of sulphur trioxide and its imides are largely unexplored and, as their reactions may well be non-pericyclic in nature[5], these compounds will not be discussed here.

There are several excellent reviews concerning the synthesis and chemistry of N-sulphinylamines (18) and sulphur diimides (19) by Kresze[2,18] and Weinreb[4,5]. Compounds (18) have been much more widely studied, presumably due to their synthetic availability - sulphur diimides are generally prepared from the corresponding N-sulphinyl compounds. Most N-sulphinylamines can be prepared by reaction of the appropriate amine with thionyl chloride in the presence of base[18]. Otherwise "*trans*-sulphinylation" from the N-sulphinyl derivative of a less basic amine can be used, 4-methylphenyl-N-sulphinylsulphonamide (20) being most commonly used for this purpose[18].

Sulphur diimides can be synthesised directly from amines by several methods[18b], but more usually *via* an analogous "*trans*-imidation" from bis(4-methylphenylsulphonyl)-sulphur diimide (21), which is prepared by

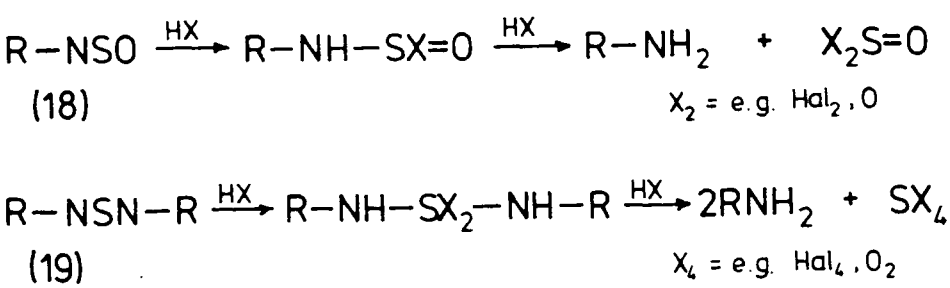
condensation of (20) with, for example, pyridine. The above reactions are summarised in Scheme 1.8.

Scheme 1.8



As with nitroso compounds (2), N-sulphinylamines and sulphur diimides are found to have increasing reactivity (and decreasing stability) with increasing electron demand of the R group (or groups). Besides cycloaddition processes, the chemistry of compounds (18) and (19) is almost entirely associated with addition of HX sequentially across the N-S bond (Scheme 1.9), occurring most readily with electron deficient species which are, therefore, very hydrolytically unstable. These reactions are of limited synthetic use.

Scheme 1.9

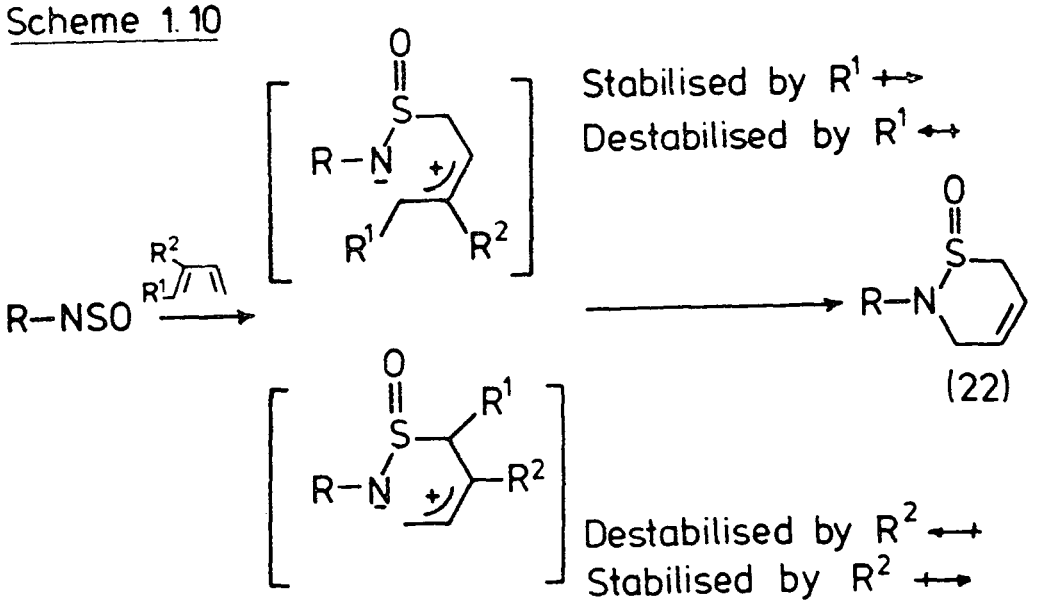


1.3.2 N-Sulphinylamines and Sulphur Diimides in Diels-Alder Reactions

Electron deficient N-sulphinylamines (18) (R = RSO_2- [18], R = perfluoroorgano[19], ROCO- [20] and R = NC- [21]) have been shown to react very readily with a wide variety of dienes. The stereoselectivity [at C(3) and C(6) of the adducts] and regioselectivity of the [4 + 2] cycloaddition have been found to be excellent and, in contrast to nitroso compounds, entirely predictable under "kinetic" conditions. There is also, with these compounds, the complication of the stereochemical orientation of the S-O bond, which has proved to be variable[5].

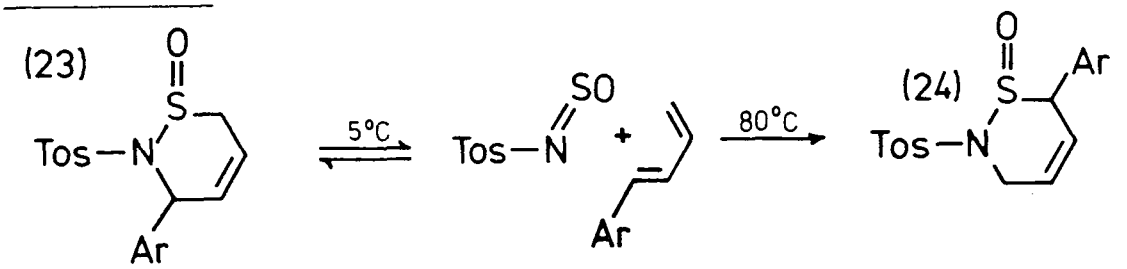
Hence, with an electron demanding substituent, 1-substituted dienes give exclusively 6-substituted 3,6-dihydro-2H-1,2-thiazine 1-oxides (22) whereas with an electron donating substituent, 1-substituted dienes give 3-substituted thiazines, and 2-substituted dienes give 5-substituted thiazines. This has been convincingly rationalised by considering which dipolar intermediate is most stabilised by the substituent (Scheme 1.10)[22].

Scheme 1.10



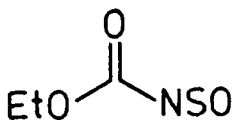
It is clear that the 3-substituted thiazine oxides are kinetic products, as when, for example, 3-aryl-N-tosyl-3,6-dihydrothiazine 1-oxides (23) were heated, rearrangement occurred to give the less sterically crowded thermodynamic products (24), bearing the 6-substituent (Scheme 1.11)[18b]. This must be borne in mind when employing Kresze's transition state stabilisation arguments[22], which only apply at the relatively low temperatures where kinetics dominate.

Scheme 1.11



Although there is general agreement over the stereo- and regioselectivity of addition to RNSO, there has been much debate over the mechanism. The product distributions from reactions of electron deficient (18) with isomeric 2,4-hexadienes, which will be discussed further in Chapter 3, have been used by Mock and Nugent to advocate a non-concerted, stepwise mechanism[23], whereas Hanson and Stockburn have investigated the kinetics of addition of ethyl N-sulphinylcarbamate (25) to 1,1'-bicyclohexenyl and deduced a concerted, pericyclic mechanism[20]. Weinreb has preferred to sit on the fence[24].

(25)



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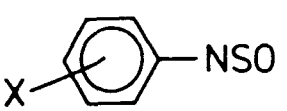


The cycloaddition of N-sulphinylaniline (26, X = H) with 2,3-dimethyl-1,3-butadiene has been known since 1953[25]. Kresze reported that all N-sulphinylanilines gave [4 + 2] cycloadducts with butadiene and dimethylbutadiene, but failed to react with terminally substituted dienes (*eg.* cyclopentadiene, 1,3-cyclohexadiene, 1-acetoxybutadiene and various sorbates) in nearly all cases[18].

Some heteroaromatic analogues have been reported as undergoing [4 + 2] cycloaddition by, for example, the groups of Butler[26] and Hanson[27]. The latter workers found, however, that the sulphinylamines acted as 4π hetero-dienes, behaviour which has also been reported for aniline derivatives (26) in particular cases[28].

N-Sulphinyl derivatives of alkylamines and 1,1-disubstituted hydrazines were, until relatively recently, thought to be unreactive towards cycloaddition. However, it has been discovered by, among others, Weinreb's group[29], that these unreactive sulphinylamines can be activated by Lewis acid catalysts (the best being boron trifluoride etherate) and that these catalysts can also vastly accelerate the rates of the conventional [4 + 2] additions discussed above. The same workers found that similar effects were produced by increased pressure in the system. Stereo- and regio-selectivity was consistent with other N-sulphinylamine cycloadditions but, interestingly, different stereochemistry was found at sulphur using the pressure, rather than Lewis acid, acceleration technique. These findings are all reported in a recent communication by Weinreb[29], but Lewis acid catalysis and a similar idea, *viz.* formation of the methyltetrafluoroborate salt before reaction, had already been used by, among others, Kresze[30a] and Hanson[30b].

The [4 + 2] cycloaddition reactions of sulphur diimides (19) are entirely analogous to those of N-sulphinylamines (18)[5]. Thus the most reactive (19) are the highly electron deficient analogues, *eg.* bis(aryl-

sulphonyl)[31], and, to a lesser extent, the unsymmetrical arylaryl-sulphonyl species. The latter compounds (27) introduce the possibility of addition to either of two different N=S bonds which occurs, in all cases, at the least electron deficient of the bonds[5]. Bis(aryl) and (alkyl) sulphur diimides (19) have been shown to undergo cycloaddition only as their methyl-tetrafluoroborate or -hexachloroantimonate salts, as found for sulphinylamines[32].

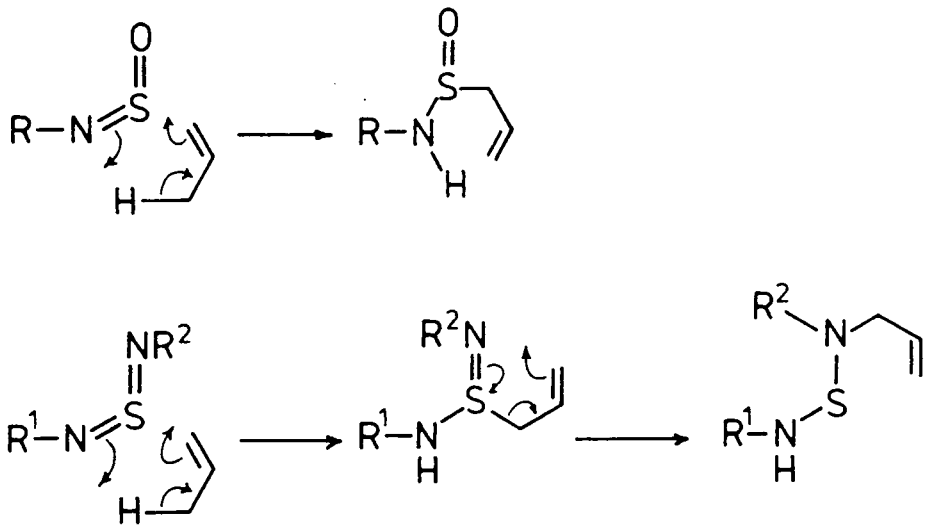
(27) $Ar-N=S=N-SO_2-Ar'$

1.3.3 N-Sulphinylamines and Sulphur Diimides in Ene reactions

N-Sulphinylamines and sulphur diimides, like nitroso compounds, can undergo a range of pericyclic reactions, *ie.* apart from acting as 2π dienophiles in the Diels-Alder sense: the reaction of various sulphinyl-amines as 4π components has already been mentioned.

Both classes of title compounds (18) and (19) have been shown to undergo ene reactions. Compounds (18) react, in the "*cis*" conformation, with a variety of alkenes[33], in a conventional sense. Sulphur diimides (19), as in Diels-Alder additions, have the option of reacting at either N=S bond and once again prefer, exclusively, the least electron deficient of the bonds. The analysis of the course of these reactions was complicated by the subsequent sigmatropic rearrangement of the initial product[34]. Once again these reactions, shown in Scheme 1.12, are favoured by electron demanding R-groups, and all proceed with C-S bond formation.

Scheme 1.12



1.4 THIONITROSO COMPOUNDS

1.4.1 Introduction

(1) R–N=S

Thionitroso compounds (1) have already been introduced as the sulphur analogues of nitroso compounds (2) and as imides of sulphur monoxide, and therefore related to N-sulphinylamines (18) and sulphur diimides (19). Compared to these analogues, thionitroso compounds have received very scant attention: few derivatives are known and their chemistry is poorly developed. The related class of compounds known as nitrile sulphides, $R\text{-}C{\equiv}N^{+}\text{-}S^{-}$, will not be discussed here as they do not have a true N=S double bond; they behave as 4π components in dipolar cycloadditions. Their chemistry has been recently reviewed by Paton[35].

Once again it is convenient to classify the range of R-N=S compounds by the electronic nature of the substituent R. As with nitroso compounds and imides of sulphur dioxide, the most stable, and least reactive, of compounds (1) were predicted to be those with an electron donating group, R, and the most highly unstable and reactive, to be with an electron demanding R group[36].

1.4.2 Thionitrosamines

(28) $R_2N-N=S$ R_2 = (a) Me_2 (b) $+CH_2+_5$ (c) $+CH_2+_6$ (d) Ph_2

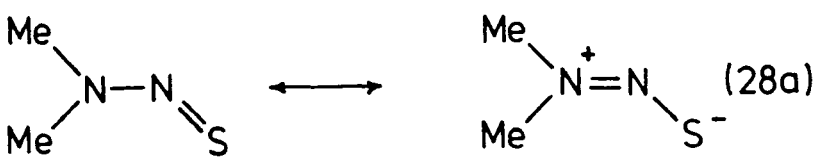
It is not surprising, in light of the above, to find that the first isolated species (1) were N-thionitrosamines (28), discovered by Middleton in 1966[37]. All three derivatives (28a-c) reported, derived from (a) dimethylhydrazine [R = Me], (b) N-aminopiperidine [R_2 = $-(CH_2)_5-$] and (c) N-aminohomopiperidine [R_2 = $-(CH_2)_6-$] were synthesised in low to moderate yields from the respective hydrazine and elemental sulphur, which were stirred together in ether for six days. Derivatives (28a,b) were also prepared by lithium aluminium hydride reduction of the corresponding N-sulphinyl hydrazine, competition with formation of the parent hydrazine causing similarly poor yields. Purification of the uncrystallisable heterocyclic examples (28b,c) was not achieved[1], but N-thionitrosodimethylamine (28a) was obtained pure as a low melting, purple crystalline solid, with many interesting properties.

[1]None of the compounds (28a-c) were stable to distillation.

Compound (28a) was found to be unstable to decomposition except at low temperatures (< $-30^{o}C$) or in dilute, inert solution (*eg.* cyclohexane). The decomposition products were yellow and explosive - appearing to contain dimethylsulphide, sulphur and azides. The decomposition was accelerated by acids (Lewis and protic) but unaffected, surprisingly, by base. In the UV/visible spectrum of (28a), the band assigned to the $n \rightarrow \pi^{*}$ transition showed a remarkable hypsochromic shift on moving from cyclohexane to ethanol as solvent. The opposite change was evident to the naked eye, the solution in a non-polar solvent being purple and in a polar solvent, orange or red (including aqueous solution in which it rapidly decomposes).

Finally, the ^{1}H NMR spectrum showed two distinct singlets for the methyl groups, separated by 23 Hz in D_2O and 38 Hz in CCl_4, a similar effect was seen for the piperidine analogue (28b). All these observations are consistent with a planar structure with hindered rotation around the N-N bond, which is easily explained by a major contribution from the charge separated canonical form (Scheme 1.13) which has both nitrogen atoms in planar, sp^{2}-type environments. This structure explains the distinct methyl signals in the ^{1}H NMR (the two methyl groups being clearly inequivalent in relation to sulphur) and the highly nucleophilic sulphur accounts for the affinity of (28a) for acids and explains the hypsochromic shift (due to hydrogen bonding in polar solvents). These conclusions are reinforced by the similar properties of N-nitrosodimethylamine[37,38].

Scheme 1.13

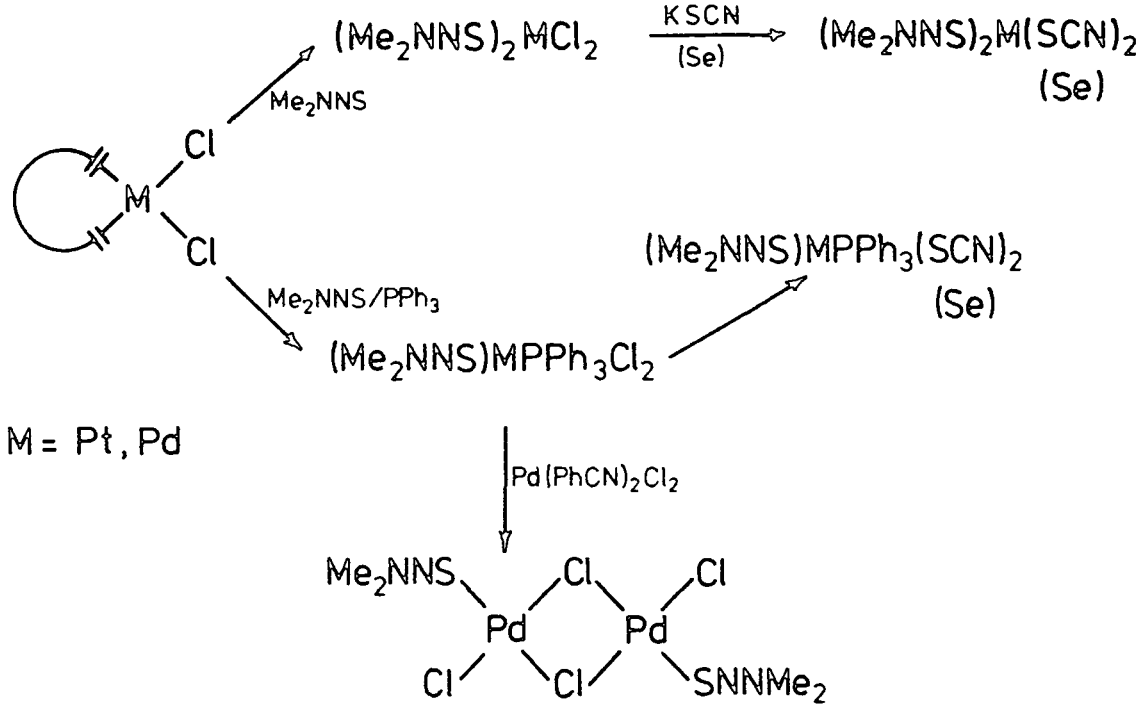


Since the work of Middleton, only one new thionitrosamine has been synthesised, *viz.* 1,1-diphenylthionitrosamine (28d) prepared by Roesky and co-workers from diphenylhydrazine and sulphur monochloride in ether. As with (28b,c) it was not purified. The same group reacted two nitrosamines (28a,d) with chromium pentacarbonyl in tetrahydrofuran (THF) to give the pseudooctahedral $R_2NNSCr(CO)_5$ complexes, for which X-ray structures were obtained[39,40].

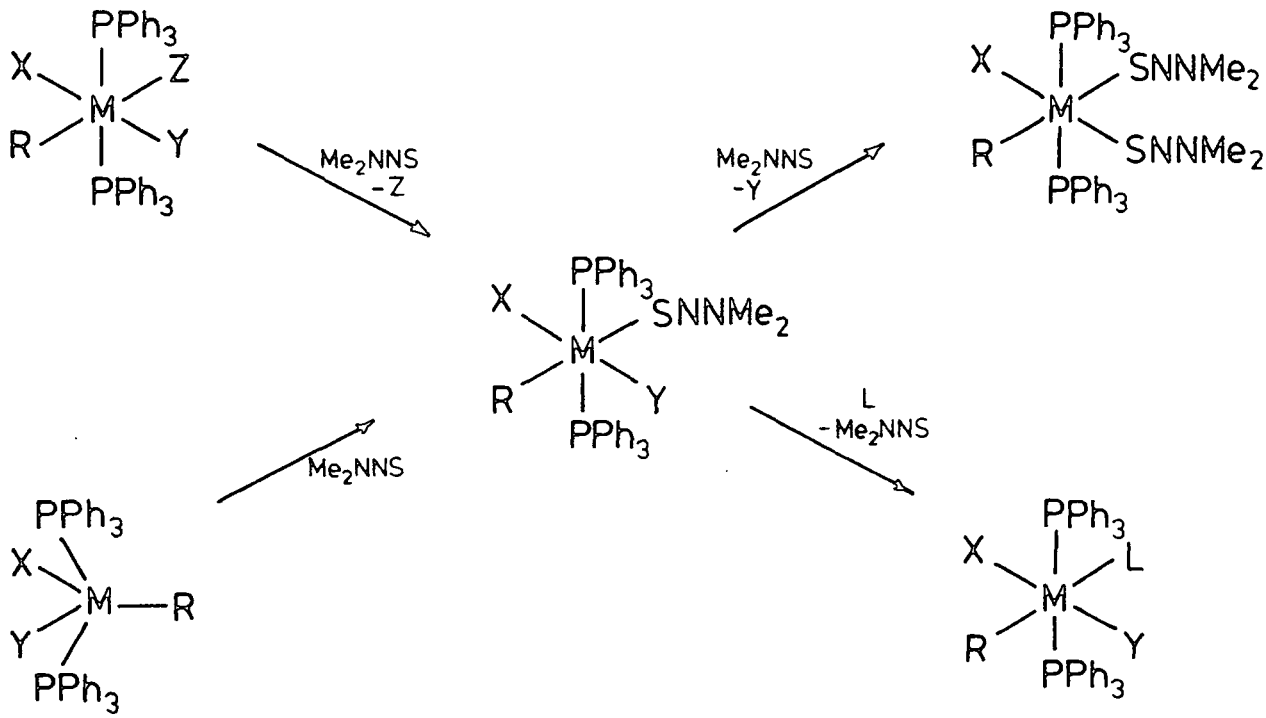
Tresoldi and co-workers discussed, in two papers, the synthesis, reactions and X-ray structures of various platinum and palladium complexes with (28a), bound either once or twice (in which case the *cis* isomer was formed) to the metal[41]. These complexes were synthesised from a dienyl dichloride and reacted with thio- and seleno-cyanates to replace both chloride ligands. Other reactions afforded, for example, bridged structures, and some may have involved species with four thionitroso ligands, $M(SNNMe_2)_4$. These reactions are summarised in Scheme 1.14. In another two papers, Herberhold and Hill utilised thionitrosamine (28a) as a ligand for octahedral ruthenium, osmium and iridium complexes[42]. These complexes were either formed by displacement of a neutral ligand from an 18-electron species or addition to a coordinatively unsaturated 16-electron complex. In some cases a second ligand would be added, again giving the "*cis*" isomer (X-ray evidence). The thionitroso ligands (28a) could be displaced by a carbonyl or isonitrile ligand - these reactions are summarised in Scheme 1.15.

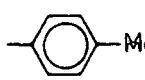
Three important points emerge from the X-ray structures of the various complexes described above. Firstly, the thionitroso ligand is always bound through sulphur in an η^1 fashion. This is unusual in sulphur-nitrogen ligands and is presumably a consequence of the high electron density on sulphur. Secondly, for complexes where the ^1H NMR spectrum could be determined, two distinct methyl signals were observed,

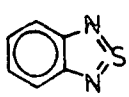
Scheme 1.14



Scheme 1.15



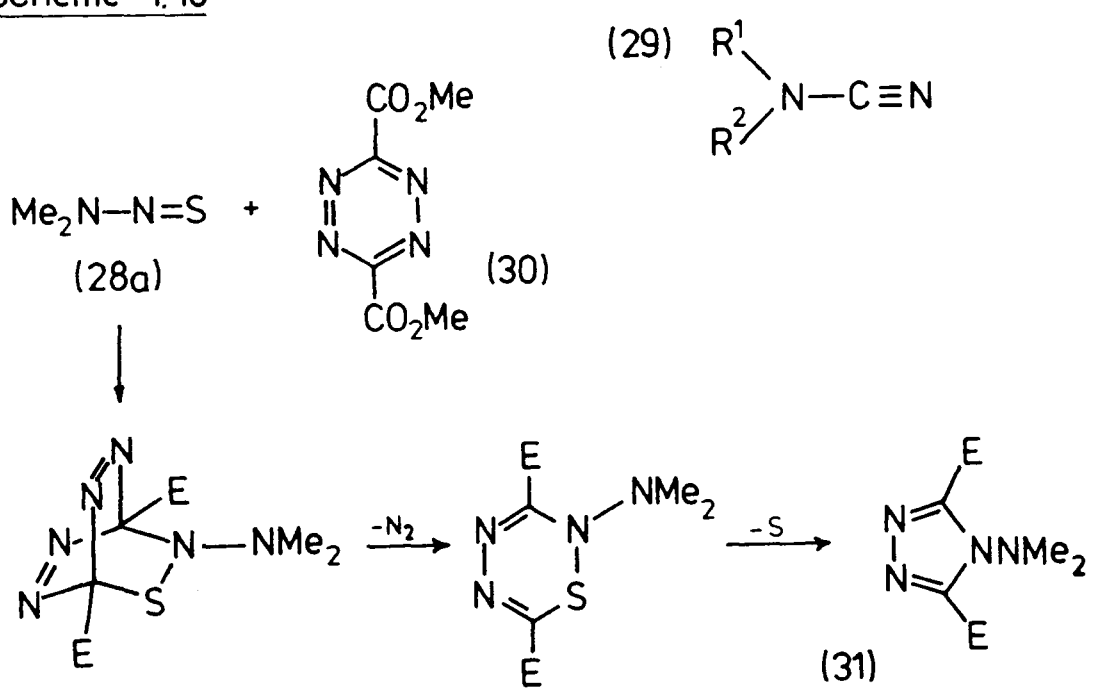
L = CO, RNC; R = H,  ; X, Y = Cl, CO, CS, H_2O;

Z = PPh_3, SO_2,  (Se); M = Ru, Os, Ir.

as in the free ligand. Lastly, the thionitroso ligands, bound in this manner to metals, were found to be much more stable than the free ligand. All these phenomena are, presumably, a result, of the large contribution of the charge separated canonical form (Scheme 1.13) which will clearly be stabilised by coordination to an electron demanding metal centre, thus affirming Middleton's initial conclusions about the electronic and structural nature of thionitrosamines[37].

Only one cycloaddition of these electron rich thionitroso compounds has been reported, by Seitz and Overheu, who showed that thionitrosamines, and their analogues, N,N-dialkylcyanamides (29), underwent "inverse" Diels-Alder addition in the manner of other electron rich C-N bonds, as in hydrazones and oximes[43]. Hence, 1,1-dimethylthionitrosamine (28a) and 3,6-dicarbomethoxy-1,2,4,5-tetrazine (30) reacted under mild conditions to give a substituted 1,2,4-triazole (31), presumably by initial [4 + 2] cycloaddition followed by sequential elimination of dinitrogen and sulphur (Scheme 1.16).

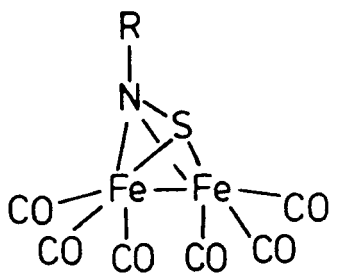
Scheme 1.16



1.4.3 Thionitrosoarenes and Thionitrosoalkanes

The above thionitrosamines (28a-d) are the only thionitroso compounds to have been isolated and characterised, and only the dimethyl derivative (28a) has been prepared in a pure form. The other classes of thionitroso compounds (1), *viz.* aryl, alkyl and electron deficient derivatives, have only been postulated either as transient intermediates - the proof of their existence usually lying in the structures of the products of decomposition or trapping reactions - or as bidentate, bridging ligands in iron carbonyl complexes (32)[44].

(32)



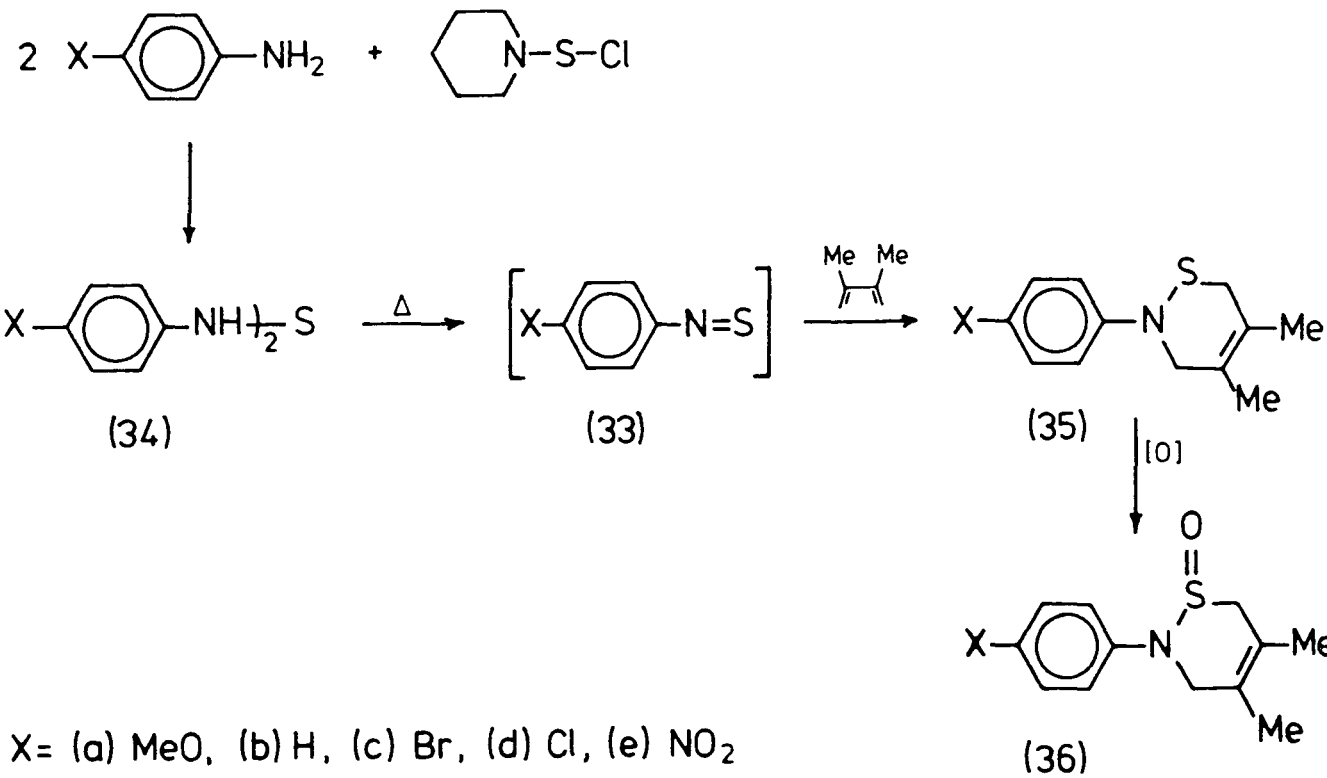
R = ^{t}Bu, Ph

The tertiary butyl and phenyl thionitroso species in compounds (32) were derived from sulphur diimides, not free thionitroso compounds, and the single N-S bond suggests that the free reactive intermediate may never exist in these systems, except in their mass spectra. No X-ray structures were given.

Of the R-N=S species, the first reported were thionitrosoarenes (33) described by Tavs in 1966, who prepared a series of N,N-thiodianilines (34b-e) from the appropriate anilines and piperidine sulphenyl chloride[45]. When compounds (34) were refluxed in excess 2,3-dimethyl-1,3-butadiene, *ca.* 30% yields of N-aryl-4,5-dimethyl-3,6-dihydro-2H-1,2-thiazines (35b-d) were formed when X was H, Br or Cl. No products were reported from the nitro analogue (34e). Thiazines (35b-d) were characterised by IR and ^{1}H NMR spectroscopy, and by perphthalic acid

oxidation to the known thiazine-1-oxides (36b-d) (Scheme 1.17).

Scheme 1.17

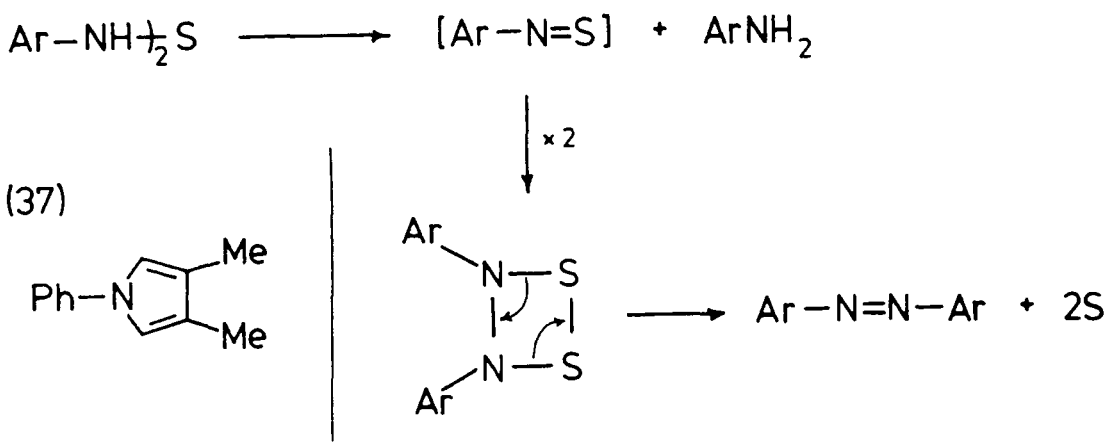


In 1976, Davis and Skibo[46] repeated and extended some of the work of Tavs. Thionitrosoarenes (33a-d) were prepared from the same precursors (34a-d) under slightly milder conditions, *ie.* in benzene at 50°C. 1-Nitro-4-thionitrosobenzene (33e) was, however, only generated on heating compound (34e) in bromobenzene at 120°C for 96 hours. In these reactions no trapping diene was employed, the products being azobenzenes, anilines and sulphur, rationalised by [2 + 2] dimerisation of the intermediates of (33) followed by loss of sulphur (Scheme 1.18). This mechanism was considered reasonable in light of similar reactions of analogues[2]. The transient thionitrosobenzene (33b) was the only example trapped by Davis; the dimethylbutadiene adduct (35b) was

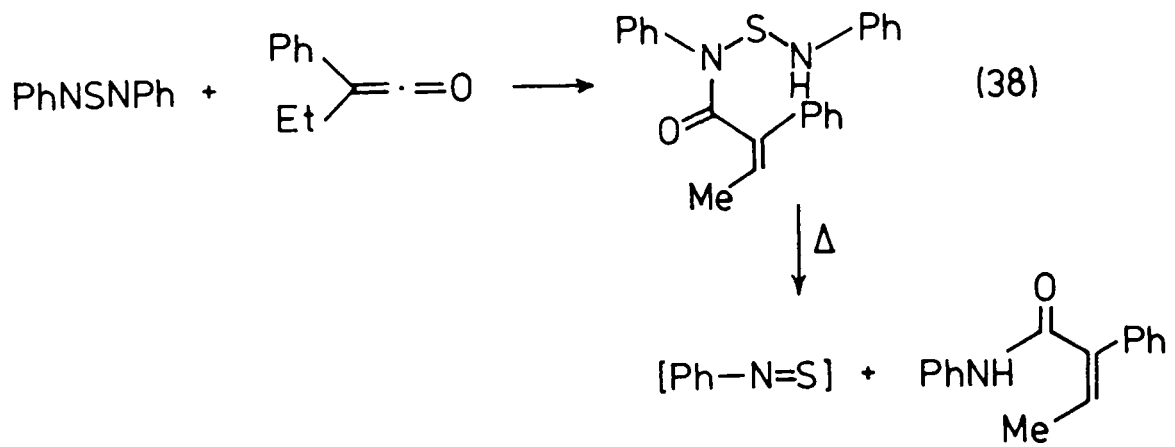
[2]For example, on heating, thiocarbonyl compounds give alkenes with loss of sulphur (ref.47), but this is a very different situation to the combination of two reactive intermediates.

similarly oxidised to the thiazine oxide (36b). Further hydrolysis with potassium hydroxide afforded the pyrrole (37) which was used for characterisation by GLC.

Scheme 1.18



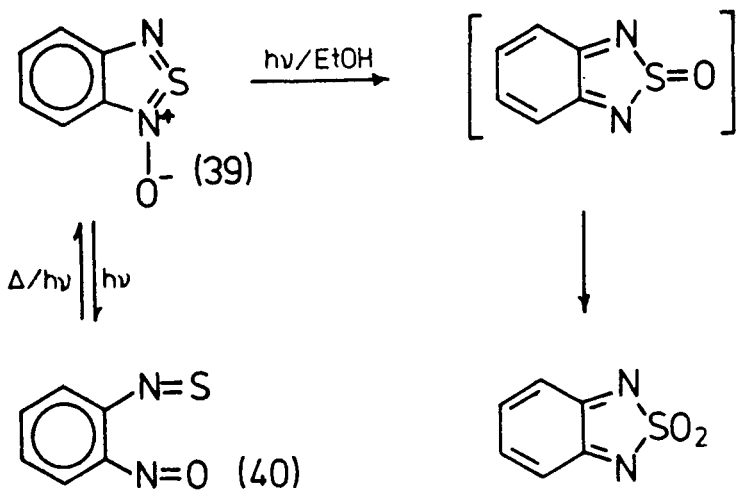
Scheme 1.19



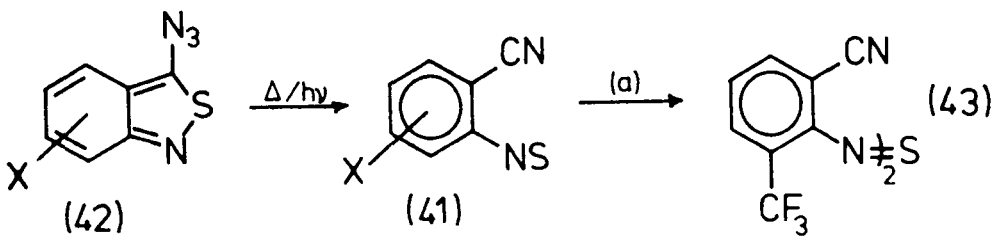
During work on reactions of sulphur diimides (19) with ketenes, Minami's group found that the product of addition of diphenyl sulphur diimide to phenylethylketene (38) fragmented as shown in Scheme 1.19[48]. This rearrangement was formulated as proceeding *via* thionitrosobenzene (33b), eventually forming aniline under the hydrolytic conditions. Indeed, when compound (38) was heated at 140°C in a sealed tube with dimethylbutadiene the dimethylthiazine (35b) was isolated in 35% yield.

The only direct spectroscopic evidence reported for a transient R-N=S species is from the photolysis of benzo(c)-1,2,5-thiadiazole 2-oxide (39) in ethanol. The reversible formation of 1-nitroso-2-thionitrosobenzene (40) (Scheme 1.20) was observed by UV and IR techniques[49].

Scheme 1.20



Scheme 1.21

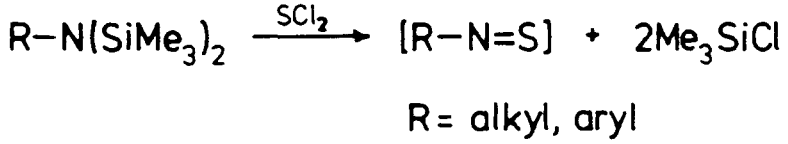


X= (a) 2−CF_3, (b) 3−Br

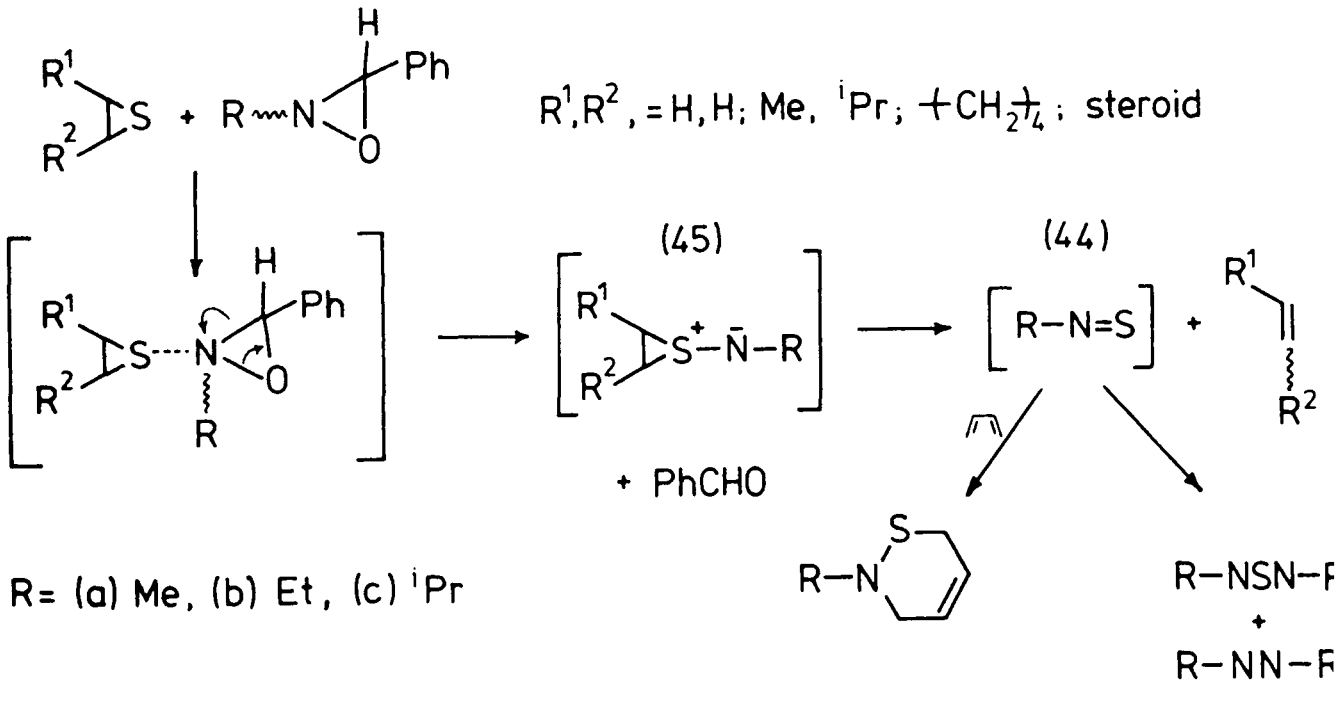
More recently, Joucla and Rees reported a similar route to 2-cyano-thionitrosoarenes (41) by both thermolysis and photolysis of 3-azido-2,1-benzisothiazoles (42), synthesised from the appropriate 3-amino compound (Scheme 1.21)[50]. The trifluoromethyl derivative (42a) was photolysed at room temperature in ether to give the thionitrosoarene

(41a). This intermediate appeared to be rather longer lived than expected and the mass spectrum (m/z 216) was observed. Transformation of (41a) to the corresponding aniline occurred, however, before purification could be achieved (several hours). The unusual stability of this highly electron deficient thionitroso compound may be due to steric hindrance to decomposition pathways - this would certainly be the case for the [2 + 2] dimerisation mechanism postulated by Davis[46]. The intermediate (41a) could be trapped by cyclopentadiene or 1-methoxy-1,3-cyclohexadiene. Thermolysis of (42a) (at 180°C in o-dichlorobenzene) afforded the sulphur diimide (43) and thermolysis of (42b), in refluxing dimethylbutadiene, yielded the expected thiazine (35, X = 5-bromo-2-cyano).

Scheme 1.22



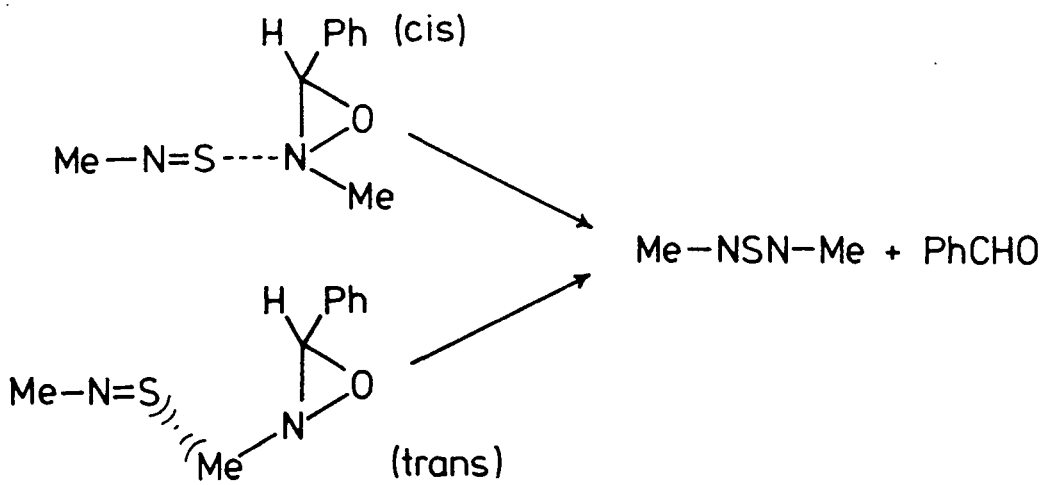
Scheme 1.23



Thionitrosoarenes have also been implied in a few other reactions. In 1976, Mayer's group postulated thionitroso intermediates in the reactions of bis(trimethylsilyl)aniline with sulphur dichloride at low temperature[51], supported later by detection of a dihydrothiazine (35) when dimethylbutadiene was added to the reaction of the aniline derivative (Scheme 1.22)[52]. Thionitrosoalkanes were also considered in this work[51] although they were not trapped.

Hata and Watanabe, however, developed an interesting route to thionitrosoalkanes (44a-c) from the thiirane ylides (45a-c)[53]. The transient species (44) were not detected directly but were trapped with 1,3-butadiene. Compound (44a) in absence of a trap afforded dimethylsulphur diimide and a small amount of azomethane (Scheme 1.23). Apart from providing the first clean route to thionitrosoalkanes and the resulting N-alkylthiazines, this paper contained some interesting new ideas on the fate of the untrapped thionitroso compounds. It was suggested that the azomethane was formed by reaction of two molecules of thionitrosomethane (44a) in the manner advanced by Davis[46], but that the sulphur diimide was formed by reaction of thionitrosomethane with the starting oxaziridine (Scheme 1.24) - perhaps a more likely outcome than dimerisation.

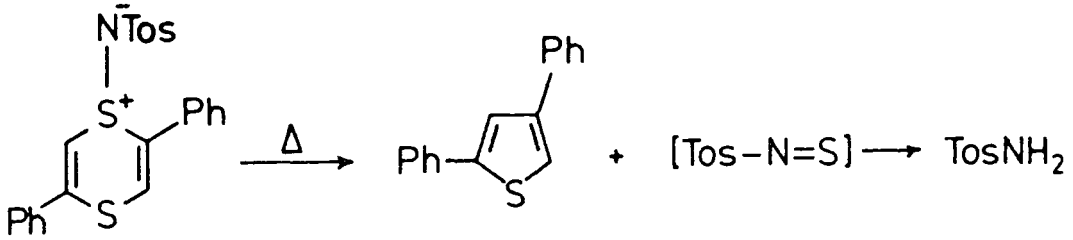
Scheme 1.24



Evidence for this pathway came from the higher yield from the "*trans*" than "*cis*" oxaziridine, as the latter isomer would offer less steric hindrance to sulphur diimide formation. Thionitroso elimination from ylides (45) was found to be a concerted process as the stereochemistry of the precursor episulphide was retained in the resultant alkene. There have been no further reports of trapping of thionitrosoalkanes.

1.4.4 Thionitrosoformates and Thionitrososulphonates

Scheme 1.25

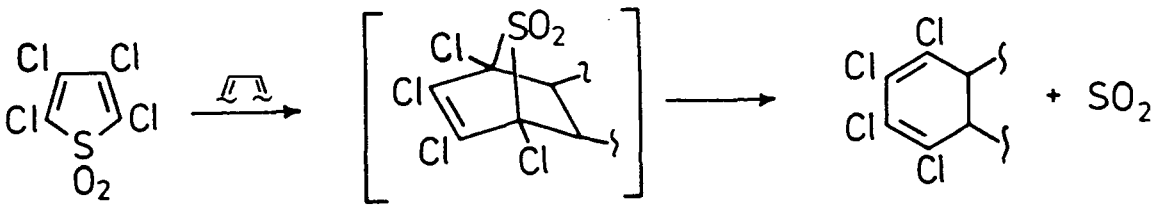


(47) (46)

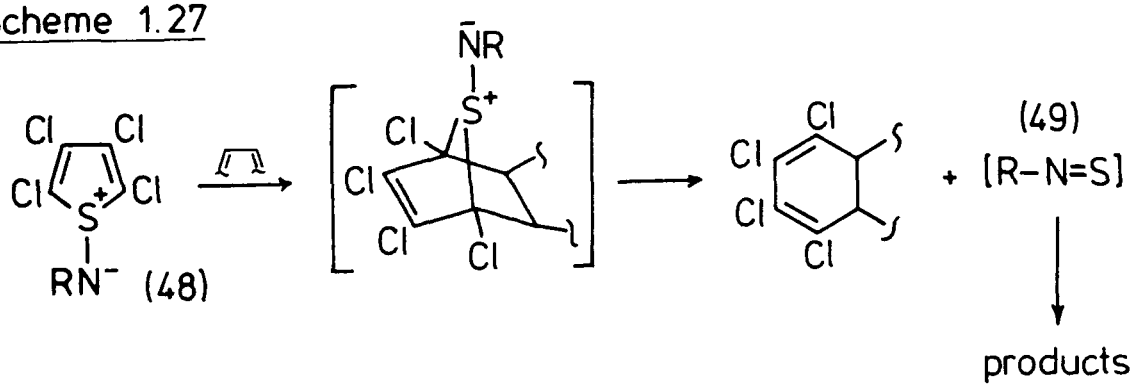
The remaining class of thionitroso compound, namely those with electron withdrawing R groups, are predicted to be very unstable and highly reactive[36]. Apart from one report of the thionitroso derivative of 4-methylphenylsulphonamide (46) as a putative, but untrapped, extrusion product from the dithiin derivative (47) (Scheme 1.25)[54], all the work done in this area is due to Meth-Cohn and co-workers. This group noted that tetrachlorothiophene 1,1-dioxide added readily to electron rich alkenes with concomitant extrusion of sulphur dioxide (Scheme 1.26) and they reasoned that an analogous tetrachlorothiophene S,N-ylide (48) should follow a similar reaction pathway to extrude a thionitroso fragment[55]. The ylides (48) could be easily synthesised from weakly basic amines and hence this methodology provided an ingenious route to the hitherto unknown electron deficient thionitroso

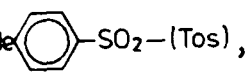
compounds (49) bearing either formyl or sulphonyl substituents [R = (a) Tosyl; (b) EtO_2C-; (c) PhO_2C-] (Scheme 1.27).

Scheme 1.26

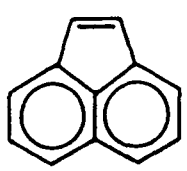


Scheme 1.27



R= (a)  , (b) CO_2Et, (c) CO_2Ph

The ylides (48a-c) were synthesised by direct nitrene attack at the sulphur of tetrachlorothiophene[56]. The nitrene was obtained by simply decomposing the appropriate azide in tetrachlorothiophene solution at 130°C (48b,c) or 150°C (48a).

(50) 

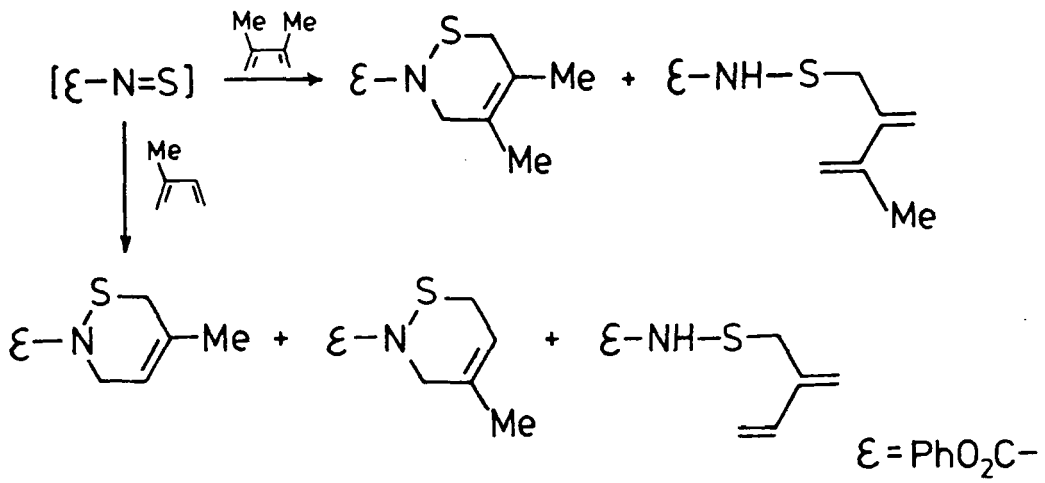
(51) $EtO_2CNH\frac{1}{2}S$

The precursor ylides (48) reacted with a wide variety of alkenes to give the thionitroso intermediates (49), the favoured alkene being acenaphthylene (50) with which reaction was rapid (<1 h. at room temperature) efficient (almost quantitative conversion) and self-indicating, its yellow colour disappearing during reaction[57]. Without a trap all three compounds (49) gave a complex mixture of unidentified

products in dichloromethane but ethylthionitrosoformate (49b) in benzene, toluene or cumene solution formed bis(urethano)sulphide (51). This result was rationalised by considering sulphide (51) as a byproduct of the triplet state of a nitrene or thionitroso species which would be more likely to exist in these solvents than in dichloromethane, which is known to stabilise the singlet state of nitrenes[57].

All three intermediates (49) could be trapped efficiently with dienes. Hence, ethylthionitrosoformate (49b) reacted with 1,3-butadiene and 1,3-cyclohexadiene to give the expected thiazines. When 2,3-dimethyl-1,3-butadiene was used to trap phenylthionitrosoformate (49c), however, a 1:1 mixture of the appropriate thiazine and ene adduct were observed. When isoprene was used the situation became still more complex with a mixture of two regioisomers and an ene adduct in a 1:1:2 ratio. Those reactions are summarised in Scheme 1.28[57].

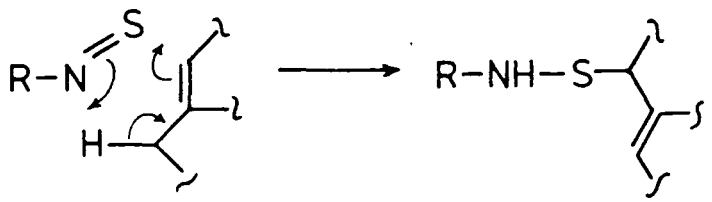
Scheme 1.28



As expected, ene reaction of compounds (49) was not restricted to substituted dienes, and indeed, a range of alkenes underwent this type of addition (Scheme 1.29), the only apparent requirement being two or three hydrogens on the adjacent carbon centre. The alkenes could be used both to generate the thionitroso species (49) [*ie.* in the initial cycloaddition to ylides (48)] and as the trap, but the favoured method was to

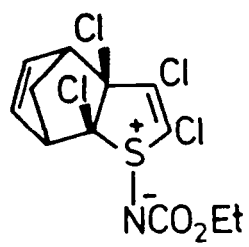
use acenaphthylene for generation of (49) in the presence of the alkene trap. Yields from the latter procedure were excellent. Mechanistic details of these reactions will be discussed in Chapter 3.

Scheme 1.29

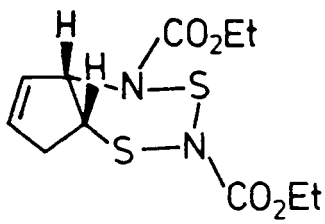


It is noteworthy that cyclopentadiene gave two anomalous reactions under the conditions used above. Firstly, it was found to react with the ylide (48b) as a 4π component to give adduct (52)[56] and secondly, when it did react with the generated ethylthionitrosoformate (49b) it resulted in a most unusual [2 + 2 + 2] adduct (53) as the major product[57].

(52)



(53)



Meth-Cohn's group has attempted to use chiral formate ylides (48) [prepared as (-)-menthyl and (+)-fenchyl esters] to obtain asymmetric induction in the cycloaddition of the resulting chiral thionitroso-formate (49) to dienes[58]. Acenaphthylene addition and extrusion of the chiral intermediate proceeded as expected but, unfortunately, an inseparable mixture of diastereomers was produced. It was concluded that the chiral auxiliary is too far removed from the nitrogen to significantly affect the cycloaddition, due to the main limitation of Meth-Cohn's route - namely the necessity of having a formyl or sulphonyl

group on nitrogen to stabilise the ylide precursor (48).

1.4.5 Conclusion

In conclusion, we have seen that thionitroso compounds are, in general, much less accessible and more reactive than nitroso compounds and imides of sulphur dioxide. This leads to less selectivity and hence mixtures of ene adducts and regioisomeric Diels-Alder adducts in many cases. In these respects R-N=S species (1) are more closely related to an emerging field of reactive intermediate chemistry based on chalcogeno-aldehydes and -ketones (54), many of which are transient species and will be discussed in the remainder of this chapter. As a close relationship lies in their methods of generation, it is convenient to classify the synthetic approaches to thionitroso compounds, as below, in a similar manner to the classification used for compounds (54) (Section 1.5).

Class (1), 1,1-eliminations at sulphur, includes many of the routes to thionitroso compounds, *viz.* Middleton's thionitrosamines[37], Hata and Watanabe's thionitrosoalkanes[53] and Meth-Cohn's thionitroso esters[55].

Class (2), 1,2-elimination across an N-S bond, contains Mayer's silylamine route[51] (best considered as proceeding by addition and subsequent 1,2-elimination from an intermediate silyl sulphenyl chloride). Tavs' [45] and Minami's [48] thionitrosoarenes may have arisen from 1,2-elimination but are probably best considered in Class (3).

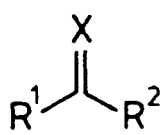
Class (3) includes these thermal fragmentations and also photochemical generation of thionitroso intermediates, as used by Pedersen[49] and Rees[50].

1.5 CHALCOGENO-ALDEHYDES AND CHALCOGENO-KETONES

1.5.1 Introduction

The chalcogen analogues of aldehydes and ketones, *ie.* with sulphur, selenium or tellurium replacing oxygen, are shown below (54). Their chemistry prior to 1984 has been regularly reviewed[59]. Thioketones (54a) will not be discussed here as they are a well known class of compounds with an extensive chemistry. Thioaldehydes (54b), seleno-aldehydes (54d) and selenoketones (54c) will be discussed at some length below, but only in cases where they behave as 2π dienophilic reactive intermediates. Telluroketones are unknown but telluroaldehydes (54f) will be mentioned in Section 1.5.5.

(54)



(a) X= S , R^2= R
(b) X= S, R^2= H
(c) X= Se, R^2= R
(d) X= Se, R^2= H
(e) X= Te, R^2= R
(f) X= Te, R^2= H

In 1974, an astrophysical journal report gave spectroscopic evidence for the presence of thioformaldehyde in interstellar space[60]. Previously reported thioaldehydes were of similarly limited synthetic use being either isolable, stable compounds bearing electron donating groups (of minor chemical interest due to the low reactivity of the C=S bond) or proposed fragments of a multitude of photolytic or thermolytic fragmentations[59]. It is remarkable that only one report of a conventional Diels-Alder cycloaddition to any of compounds (54b-d) had been reported prior to 1980, *ie.* that of thioformaldehyde (from thermolysis of thietane) and cyclopentadiene[61].

The following discussion has been divided according to synthetic approaches to compounds (54b-d), classified in a similar manner to that used for thionitroso compounds. So, firstly 1,1-eliminations will be mentioned, followed by 1,2-eliminations, thermal and photochemical rearrangements and finally a different approach - utilising the so-called "Staudinger Chalcogenation".

1.5.2 1,1-Eliminations

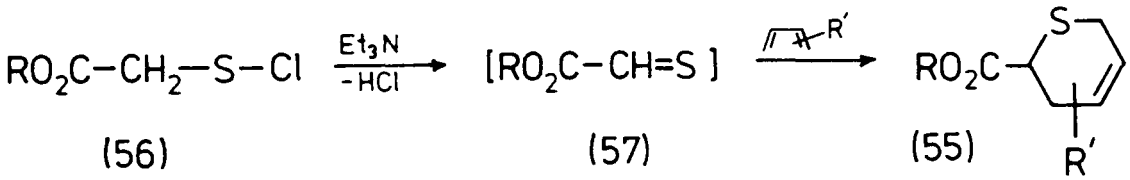
1,1-Eliminations have not been widely used for generation of compounds (54b-d), known examples being of more relevance to Chapter 5.

1.5.3 1,2-Eliminations

Class (2) reactions have been utilised for synthesis of this group of compounds (54b-d) in a number of cases[5]. Kirby recognised that relatively electron deficient thioaldehydes should be excellent dienophiles due to the weak C-S π-bond and low steric demand and that the dihydrothiins (55) resulting from [4 + 2] cycloaddition with dienes should be synthetically useful[62]. Furthermore, an electron withdrawing R group on the α-carbon should not only enhance reactivity but also aid elimination of a proton from that site. Hence, a route involving 1,2-elimination of HCl from the sulphenyl chlorides (56) was proposed, generating thiooxoacetates (57) which could be trapped with various conjugated dienes (Scheme 1.30). Triethylamine elimination of HCl from compounds (56) in the presence of a diene at room temperature, gave the expected dihydrothiins in good yields in many cases. Unfortunately, the competing addition of the precursor sulphenyl chloride directly to the

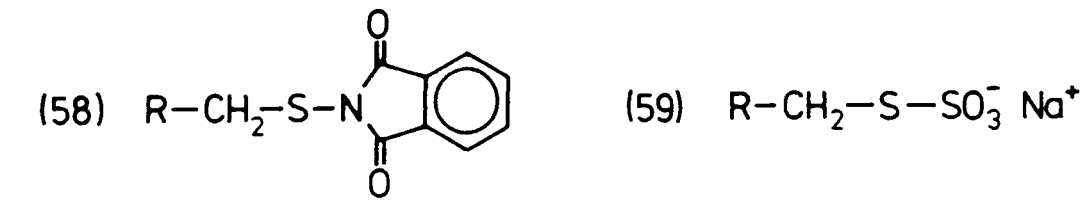
diene was quite significant in some cases, limiting the generality of the method.

Scheme 1.30



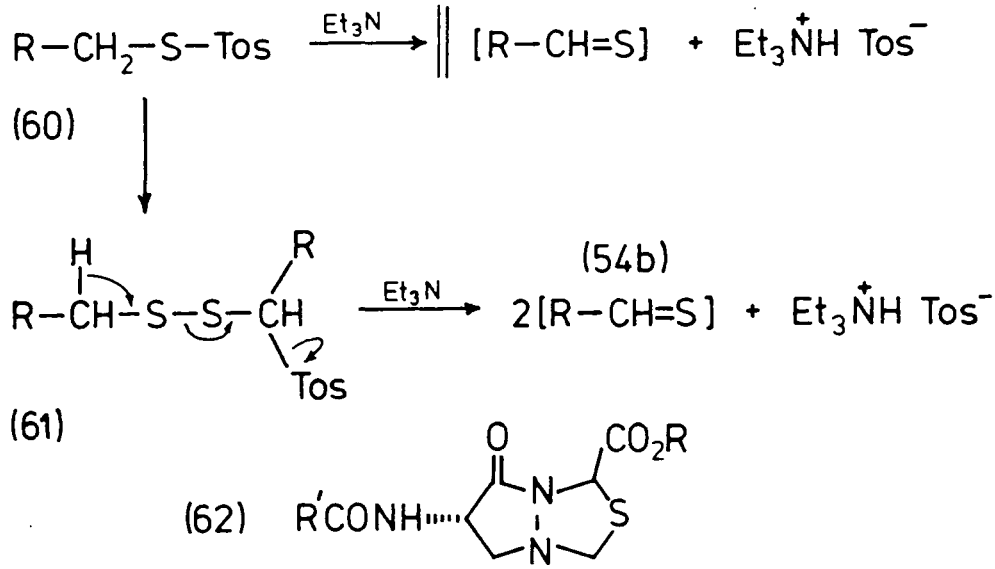
(56) (57) (55)

This problem was quickly solved by Kirby's group by using a phthalimide instead of chloride leaving group, from precursors (58)[63]. The 1,2-elimination proceeded smoothly and high yields of cycloadducts were obtained - cyclopentadiene, 1,3-cyclohexadiene and anthracene could be employed successfully with this modified route.



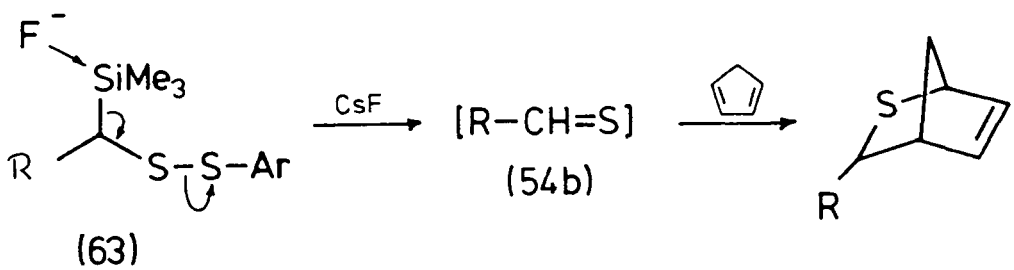
Analogous Bunte salts (59) cleaved on treatment with triethylamine to give thioaldehydes (54b) (R = CO_2Et, PhCO, CN and 4-nitrophenyl)[64]. Thiosulphonates (60) were expected to behave in the same manner, but instead were readily transformed into sulphonyl disulphides (61) which could still be used as thioaldehyde precursors, giving two moles of reactive intermediate from each mole of precursor (61) (Scheme 1.31)[65]. The Kirby phthalimide route has recently been used in a [4 + 2] addition with a 1,3-dipolar pyrazolidinium ylide to give thia-analogues of important antibacterial agents (62)[66].

Scheme 1.31



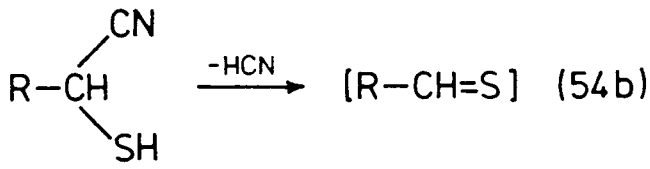
Krafft and Meinke reported a variation on the 1,2-elimination route using fluoride induced eliminations from α-silyldisulphides (63) (Scheme 1.32)[67]. In all cases a mixture of "*endo*" and "*exo*" adducts was found in the cycloaddition to cyclopentadiene - the *endo* isomer predominating. This route, importantly, allowed access to simple, reactive alkyl and aryl thioaldehydes which were not available from Kirby's routes.

Scheme 1.32



All the above 1,2-elimination routes have been in the nitrogen to sulphur sense. A rare example of the reverse is the gas phase dehydrocyanation of thiocyanohydrins to give spectroscopically observed methane- and ethane-thials (Scheme 1.33)[68].

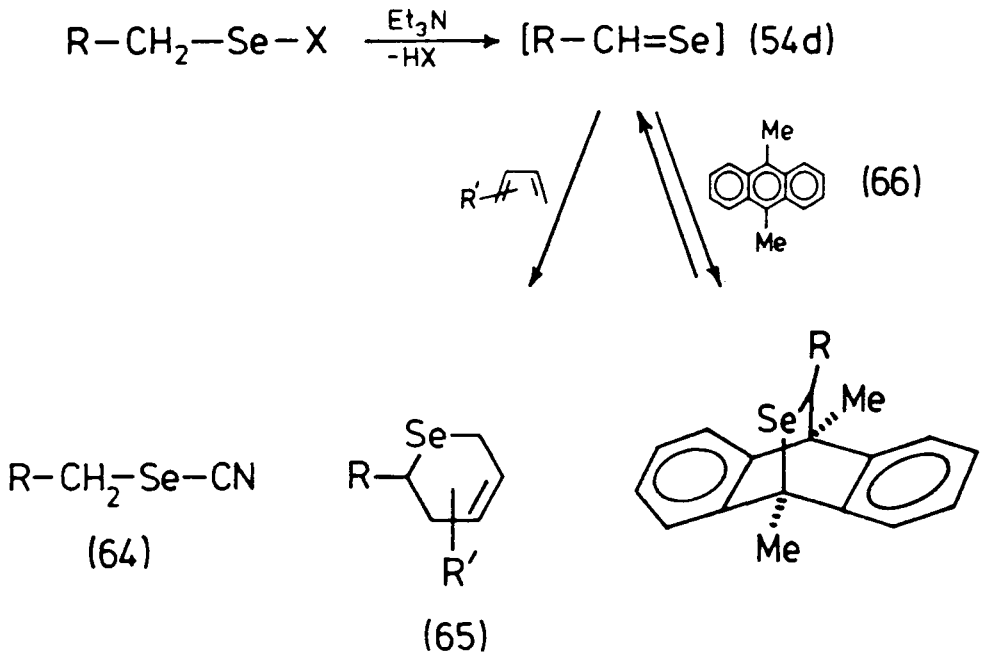
Scheme 1.33



Recent work by the groups of Kirby and of Krafft and Meinke has extended the 1,2-elimination methodology to the generation of selenoaldehydes and -ketones (54c,d). Indeed, until the 1986 communications from these authors[69,70], the only compounds (54c,d) known were, once again, stabilised by electron donating substituents[71] or by coordination to a metal in a similar manner to thionitrosamines[72]. The metal-coordinated species are stabilised against decomposition but are still reactive enough to undergo [4 + 2] cycloaddition reactions with dienes[73] and alkynes[74]. This type of process has also been used with thioaldehydes and selenoketones and clearly has much potential[73,74] - especially as there are interesting changes in stereochemical preferences[75].

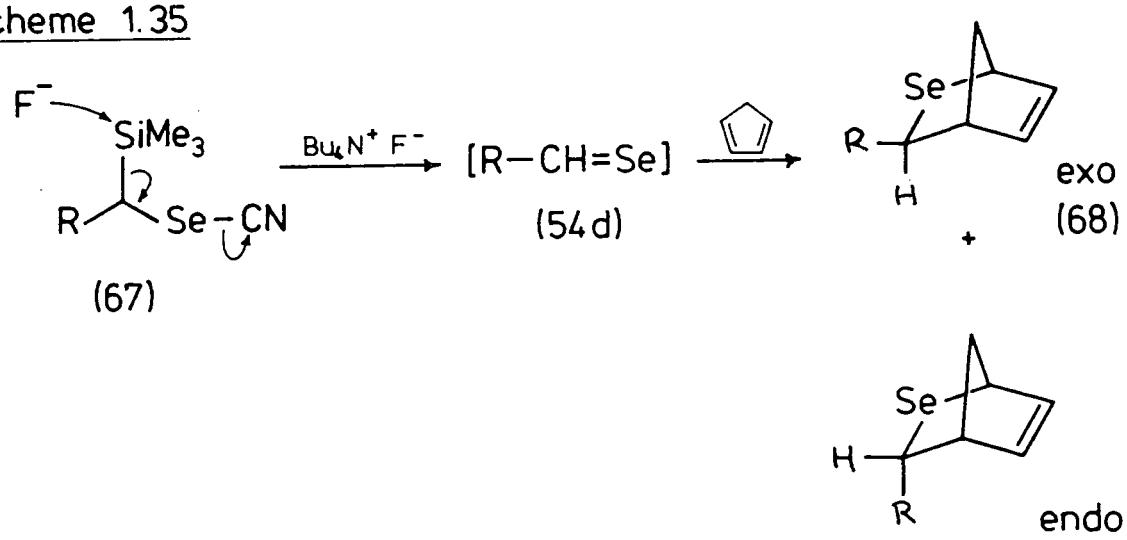
All the routes used by Kirby *et al.* for thioaldehydes have also been used to generate selenoaldehydes (54d) with a similar range of electron withdrawing R groups on the α-carbon[76]. In addition, selenocyanates (64) were successfully utilised, whereas thiocyanates failed as thioaldehyde precursors[76]. The transient selenoaldehydes (54d) could, as expected, be trapped as selenines (65), with the usual dienes, but yields were disappointing from all these routes. The addition to 9,10-dimethylanthracene (66), however, proceeded smoothly and the adduct could be used as a selenoaldehyde transfer reagent (similarly the cyclopentadiene and anthracene adducts) to afford good yields of selenines (65) with dienes which had proved unsatisfactory in direct reactions (Scheme 1.34)[76].

Scheme 1.34



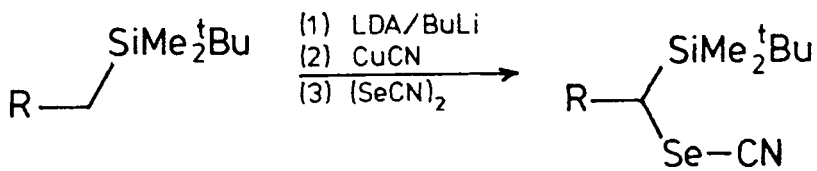
The Meinke and Krafft methodology has also been extended from thio- to seleno-aldehydes. The thiolate leaving group used previously was unsuitable for selenoaldehyde (54d) formation but, in agreement with Kirby's findings[76], these authors reported that α-silylselenocyanates (67) were extremely useful precursors to selenoaldehydes[71]. When stirred with tetrabutylammonium fluoride and cyclopentadiene in dichloromethane, selenanorbornenes (68) were obtained in good yield (Scheme 1.35). Similar results were obtained with other dienes - the only exception was with "poor" dienes and alkyl selenoaldehydes. In this case, the selenals appeared to prefer a polymerisation pathway to cycloaddition. It is interesting that the same conditions were found to give very poor results with α-silylthiocyanates as thioaldehyde precursors[74] - *ie.* both the groups of Kirby and of Krafft and Meinke found that cyanide is a poor leaving group from thiocyanates, but is easily displaced from selenocyanates. This is presumably a manifestation of the greater strength of the C-S bond[76].

Scheme 1.35



Stereo- and regio-chemical preferences in selenoaldehyde addition have been examined[77]. For consistency, Krafft's group extended the fluoride induced elimination route to include generation of electron deficient selenals (54d) (already available by the base induced elimination route[76]) from precursors formed by cyanoselenation of organo-cuprate intermediates (Scheme 1.36)[77]. With cyclic dienes, mixtures of "*endo*" and "*exo*" adducts (Scheme 1.35) were generally found - the observed predominance of *endo* adduct was in agreement with thioaldehyde additions[77].

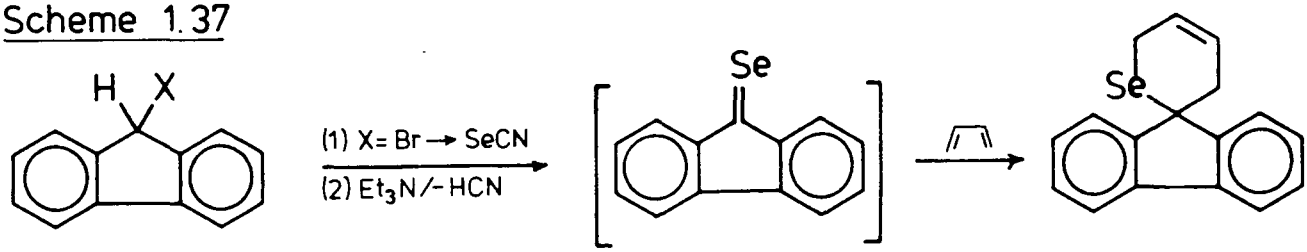
Scheme 1.36



Regioselectivity was determined with electron rich dienes. Electron deficient selenoaldehydes gave the same orientation of addition as their N-sulphinylamine analogues, *ie.* 3- and 5-substituted heterocycles were produced. Electron rich selenoaldehydes gave the opposite

selectivity, as expected, yielding 4- and 6-substituted selenines as the major adducts[77]. [*Nb*. In these examples, the selenoaldehyde derived carbon is assumed to be C(2)]. These phenomena have been rationalised by frontier orbital considerations[77] and could presumably also be explained by the stabilised, charge separated, transition states postulated by Kresze for imides of sulphur dioxide (Section 1.3).

Scheme 1.37



(69)

Meinke and Krafft[78] found that the selenocyanate route was applicable to selenoketone (54c) synthesis. Fluorenyl bromide was refluxed with potassium selenocyanate to give fluorenyl selenocyanate which, on base induced dehydrocyanation, gave selenofluorenone (69) (Scheme 1.37). In trapping reactions of the intermediate (69), 1-substituted dienes gave, exclusively, one regioisomer in the same sense as electron deficient selenals, above (fluorenyl is considered to be an electron withdrawing group). 2-Substituted dienes followed this trend but gave a mixture of regioisomers with the expected predominance of 5-substituted selenine.

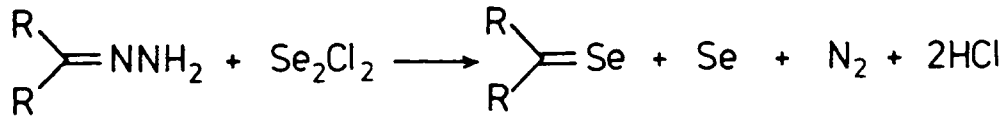
Reaction of selenofluorenone (69) and electron rich selenoaldehydes (54d) with nitrile oxides (*ie*. 1,3-dipoles) afforded exclusively the 1,4,2-oxaselenazole. This anomalous result has been rationalised on steric grounds - the electron deficient fluorenone derivative should have given the opposite selectivity. This is surprising, however, as there seems to be no problem in forming the much more sterically demanding regioisomer found as the only product of addition to

1-substituted dienes.

Meinke and Krafft have since generalised the selenofluorenone synthesis to produce a range of electron deficient selenoketones synthesised simply from the appropriate halide with potassium selenocyanate followed by base induced elimination[79]. Interestingly, regiochemistry was affected by choice of base in some cases.

Simple aryl and alkyl selenoketones (54c) remain elusive, although highly crowded examples have been reported as stable compounds from the reaction of selenium monochloride with hydrazones [or their bis(magnesium bromide) salts] (Scheme 1.38)[80].

Scheme 1.38

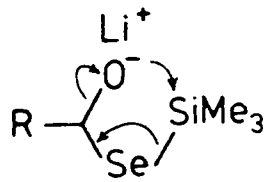


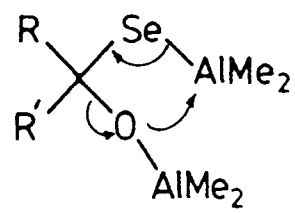
R = e.g. ^{t}Bu

The work of Segi, Murai, Sonoda *et al.* concludes this section. This group have used an addition-elimination process to generate thioaldehydes (54b), selenoaldehydes (54d) and selenoketones (54c) directly from their oxygen analogues. The first two classes were simply formed from aldehydes with bis(trimethylsilyl)-sulphide and -selenide, respectively[81]. The reaction was catalysed by n-butyllithium in close analogy with the Peterson reaction[82] and probably proceeding *via* intermediate (70), the elimination taking place in the reverse sense. This process was used in the first intramolecular selenoaldehyde cycloadditions[83].

The above method was not directly applicable to selenoketone synthesis, but use of bis(dimethylaluminium)selenide was successful. The reaction was uncatalysed and presumed to proceed *via* elimination from a similar intermediate to structure (70), *viz.* (71). Reactive

intermediates (54b-d) bearing a range of alkyl and aryl substituents have been synthesised in this manner and trapped, in nearly all cases, with cyclopentadiene. This exceptionally simple methodology must have great potential providing the silyl reagents do not prove troublesome in handling and in side reactions.

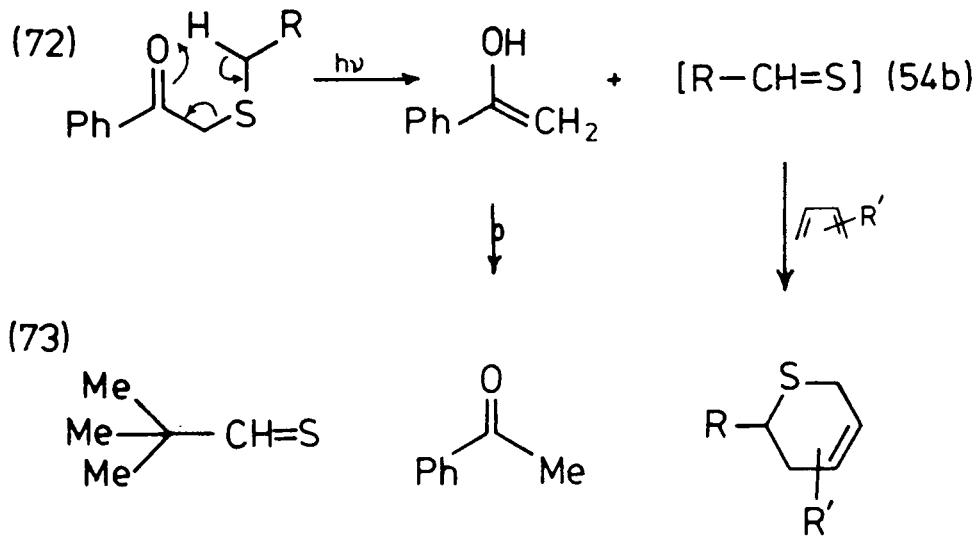
(70) 

(71) 

1.5.4 Photochemical and Thermal Fragmentation

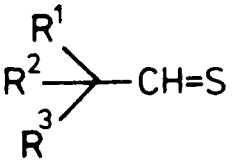
After an early attempt at an elimination route, with limited success, Vedejs *et al.*[85] turned to photochemical generation of thioaldehydes. Phenacyl sulphides (72) bearing electron withdrawing R groups were prepared. Norrish cleavage of compounds (72) occurred on irradiation and resulted in reactive thioaldehydes (54b), which were trapped with dienes in good yield (Scheme 1.39)[86]. Regioselectivity was consistent with that observed by Kirby and by Krafft and Meinke (Section 1.5.3), with the same dependence on the electronic nature of the thioaldehyde substituent[87a]. Successful trapping of aryl and alkyl thials required very pure reagents and a large excess of diene to avoid polymerisation. Interestingly, the same route (Scheme 1.39) could be used to isolate a stable (for 16h. at room temperature) alkyl thioaldehyde, *viz.* 2,2-dimethyl-propanethial (73)[87b].

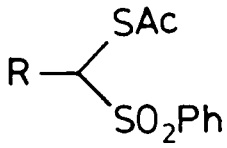
Scheme 1.39



In a summary of his groundwork on photochemically generated thioaldehydes[88], Vedejs concludes that virtually all thioaldehydes are accessible from this route (Scheme 1.39). Furthermore, all electron deficient thioaldehydes will undergo [4 + 2] cycloaddition with a wide range of dienes, including many traditionally "poor" examples. Simple alkyl- and electron rich aryl-derivatives are generally less easy to handle, being trapped only by "good" dienes, *eg.* cyclopentadiene, and being subject to competing reactions with either the acetophenone byproduct or with itself in polymerisations. The predictably reversible regiochemistry allows access to a wide variety of dihydrothiins which are potentially very useful, *eg.* in cytochalasan synthesis[89].

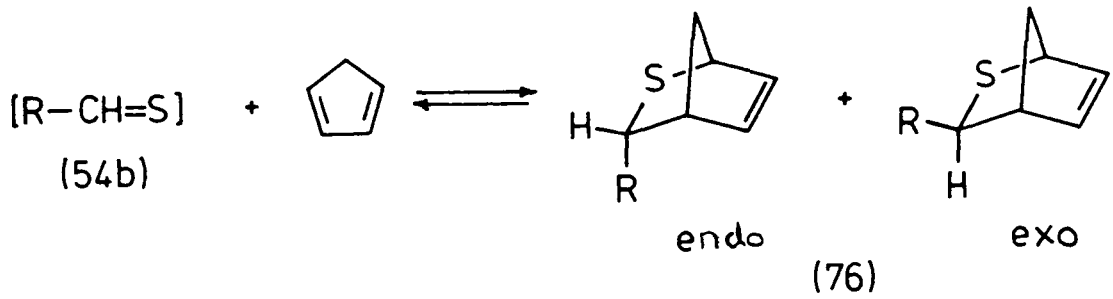
In later, more sophisticated work on the stereochemistry of addition to cyclopentadiene, Vedejs' group found, as did that of Krafft and Meinke[67], a preference for the "*endo*" isomer, especially with α-branched or α,α-doubly branched R groups in thials (74)[90]. With chiral substituents (74, $R^1 \neq R^2 \neq R^3$) some promising enantioselectivity was observed (*ca.* 70% ee. in some cases), α-alkoxy groups gave the best diastereomeric and enantiomeric excesses.

(74) 

(75) 

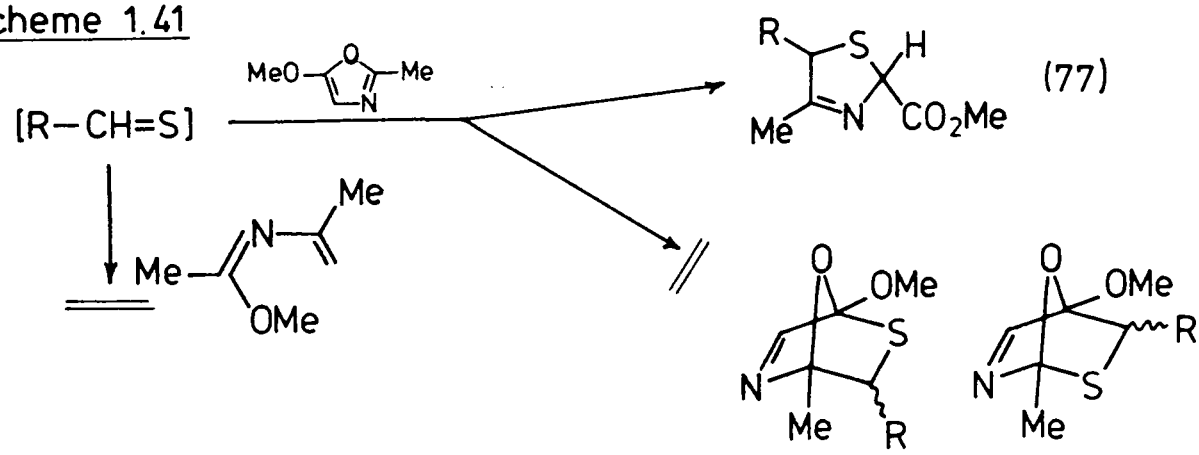
To prove that the above results were a consequence of kinetic control, the same workers used, for comparison, thioaldehydes generated chemically from a modification of Kirby's sulphonyl leaving group methodology, involving diethylamine cleavage of S-acetylthioacetals (75), which gave very similar results[90]. Also, prolonged heating of adducts (76) resulted in isomerisation, by retro Diels-Alder reaction, to thermodynamic products with a very different distribution[90] (Scheme 1.40).

Scheme 1.40



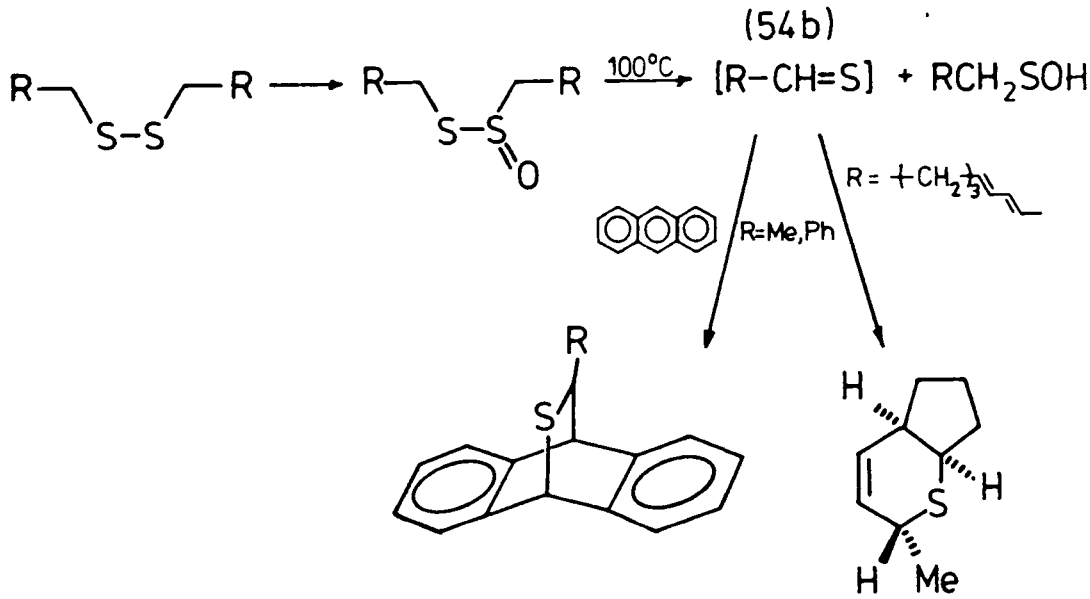
Attempts to use thioaldehyde chemistry to produce cephalosporin analogues by reaction of compounds (54b) with 2-azadienes and 5-alkoxy-oxazoles failed. The latter compounds did react, however, in a [3 + 2] sense, to give thiazolines (77) (*eg.* Scheme 1.41)[91].

Scheme 1.41



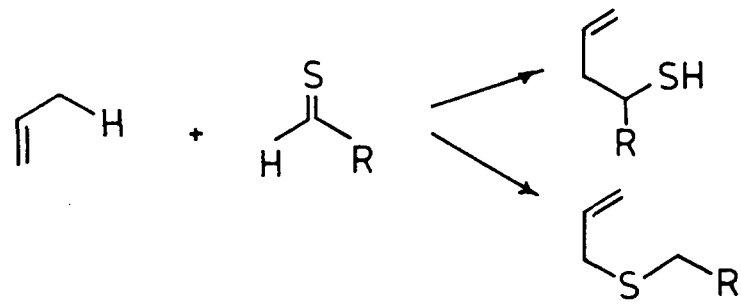
The first thermal generation of thioaldehydes was reported in Baldwin and Lopez's communication on thermolysis of thiosulphinates (Scheme 1.42)[92]. The ethane and benzylthials so formed, were trapped with anthracene and dimethylanthracene, and the adducts could be used, as discussed earlier, to regenerate the intermediates. Later work from this group utilised long chain thiosulphinates in the first intramolecular thioaldehyde cycloadditions (Scheme 1.42)[93] - regioselectivity was as expected.

Scheme 1.42



Baldwin *et al.* also discovered that thioaldehydes (54b) undergo ene reactions - the only example quoted was with pinene[92]. Intramolecular thioaldehyde ene reactions were subsequently investigated by the groups of Kirby[94] and Vedejs[95]. It seems that ene reaction is only seen with more reactive thioaldehydes and never in competition with Diels-Alder addition. Reaction can take place with either C-S or C-C bond formation, the latter pathway being predominant with highly electron poor thials (Scheme 1.43)[94]. Ene reaction of selenocarbonyls is not known.

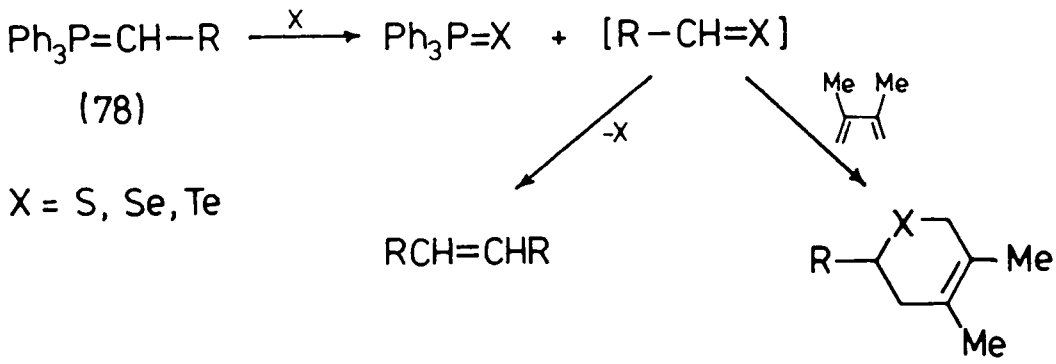
Scheme 1.43



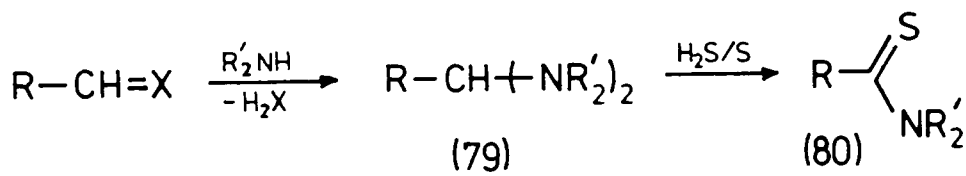
1.5.5 The Staudinger Chalcogenation

The Class (4) synthetic routes lead directly to thio-, seleno- and telluro-aldehydes (54b,d,f) from phosphonium ylides. Wittig reagents (78) reacted with elemental sulphur (or sulphiranes)[96], selenium[97] and activated tellurium[98] to generate the corresponding chalcogenoaldehyde (Scheme 1.44). With no trap, the products of these reactions are symmetrical alkenes (with sulphur this has been known since Staudinger's work early this century[99]). With, for example, dimethylbutadiene as trap, the expected heterocycles are formed (Scheme 1.44).

Scheme 1.44



Scheme 1.45



When the same Japanese workers carried out their reactions in the presence of secondary amines, they found that selenoaldehydes gave bis(dialkylamino)alkanes (79) while thioaldehydes reacted further to yield thioamides (80) (Scheme 1.45)[100].

Chalcogenoketones have not been synthesised by this route.

CHAPTER TWO

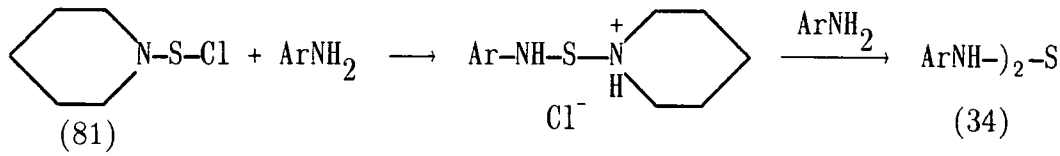
THIOARYLAMINOPHTHALIMIDES - SYNTHETIC TARGETS AND THIONITROSOARENE PRECURSORS

2.1 SYNTHETIC METHODOLOGY TO THIONITROSOARENE PRECURSORS

2.1.1 Review

It is clear from the discussion in Chapter 1 that the most versatile synthetic methodology to reactive intermediates of type RX = Y (nitroso compounds, chalcogeno-aldehydes and -ketones *etc.*) is 1,2-elimination, although photochemical routes have proved equally useful in the case of thioaldehydes. At the outset of our work there was no simple 1,2-elimination route to thionitroso compounds. Of the various classes of thionitroso compounds, we felt that thionitrosoarenes, Ar-N=S, offered the most scope for new studies. Very little was known of their fundamental chemistry and the electronic nature of the N=S bond could, in principle, be finely tuned by varying substituents on the aryl group. The effect this might have on the reactivity patterns attracted our attention. Clearly, we needed to develop a straightforward route to thionitrosoarenes that, hopefully, would also be applicable to other classes of thionitroso compounds.

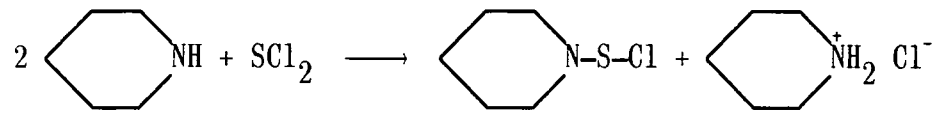
We first appraised the thionitrosoarene precursors which were already known. The work of Rees[50] on photochemical generation from azidobenzisothiazole precursors (42) was not adaptable to 1,2-elimination methodology, and Mayer's route[51] from silylanilines (Scheme 1.22) is never likely to be synthetically useful because of the high reactivity of sulphur dichloride towards potential traps - notably dienes. Minami's precursor (38)[48] was, perhaps, the most obvious candidate for 1,2-elimination processes but these types of compound did not appear readily accessible. This left the thiodianiline precursors (34) used by Tavs[45] and Davis[46] which we felt could be significantly improved if asymmetry could be introduced into the sulphenamide linkage.



(81) (34)

Scheme 2.1

We decided, therefore, to repeat the work of Tavs[45] and Davis[46], who, as discussed earlier, generated thionitrosoarenes from N,N'-thiodiarylamines (34), which were synthesised by addition of piperidine sulphenyl chloride (81) to two equivalents of the appropriate arylamine in ether at -20°C (Scheme 2.1). Piperidine sulphenyl chloride is available from reaction of two moles piperidine (82) with sulphur dichloride in ether[101] (Scheme 2.2).



(82) (81)

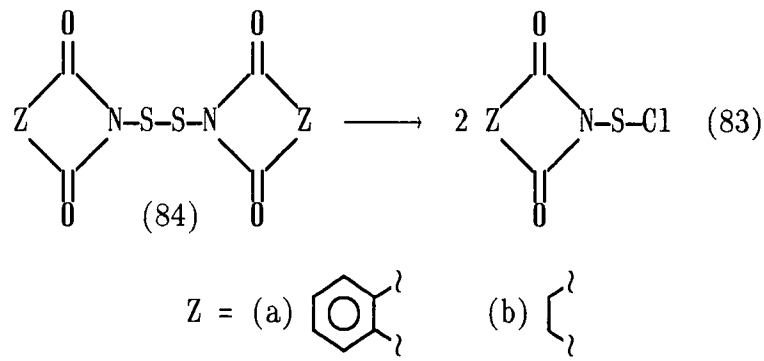
Scheme 2.2

We quickly realised that both compounds (81) and (34) were difficult to handle, the former being a rather hydrolytically sensitive oil which has been known to explode on distillation[46] and the latter being thermally unstable oils or solids; moreover the literature syntheses were not easily repeatable. We therefore sought improvements to this route.

2.1.2 Alternative Reagents for Thiodiamine Synthesis

The first requirement was a readily available sulphenyl chloride which was easy to handle and preferably crystalline. We opted for compounds used by Ley's group as sulphur transfer reagents[102]: phthalimide-N-sulphenyl chloride (83a) and the analogous succinimide-N-

sulphenyl chloride (83b)[1] which are yellow solids prepared by quantitative chlorinolysis of the appropriate dithiobis(imide) (84) in warm chloroform (Scheme 2.3). The phthalimide derivative seemed preferable on grounds of higher yields quoted for its preparation and the slightly better leaving group ability of phthalimide compared with succinimide[103].



Scheme 2.3

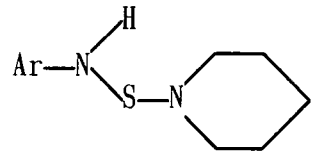
We found repetition of Ley's preparation of (84a) extremely erratic, as did Cava'a group, who developed an alternative, simpler route which we adopted, *viz.* directly from phthalimide and sulphur monochloride with triethylamine in THF[104].

2.1.3 New Thionitrosoarene Precursors

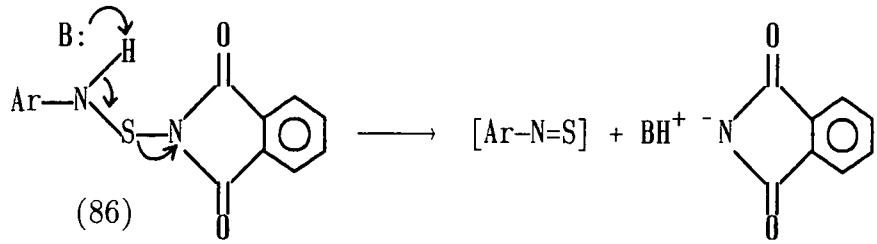
Davis had isolated, as intermediates in the formation of N,N'-thiobis(arylamines) (34), the N,N'-thioarylaminopiperidines (85), by carrying out the thiobis(arylamine) synthesis at -78°C instead of -20°C. These compounds (85) could also be synthesised by addition of sulphenyl chloride (81) to one equivalent of arylamine in ether containing tri-

[1]The following nomenclature has been used throughout (trivial name first): Phthalimide ≡ 1H-Isoindole-1,3(2H)-dione (or its anion); Phthalimide sulphenyl chloride ≡ 1,3-Dihydro-1,3-dioxoisoindole-2-sulphenyl chloride; Thioarylaminophthalimide ≡ N-Aryl-1,3-dihydro-1,3-dioxoisoindole; Succinimde ≡ 2,5-Pyrrolidinedione (or its anion).

ethylamine and were used as thionitrosoarene precursors by thermal decomposition under the same conditions as thiodianilines (34).

(85) 

We became very interested in the unknown phthalimide analogues of (85), namely (86), which seemed ideally designed for a base-induced 1,2-elimination of phthalimide, to give thionitrosoarenes, assisted by the excellent leaving group ability of the phthalimide anion (Scheme 2.4)[2].



(86)

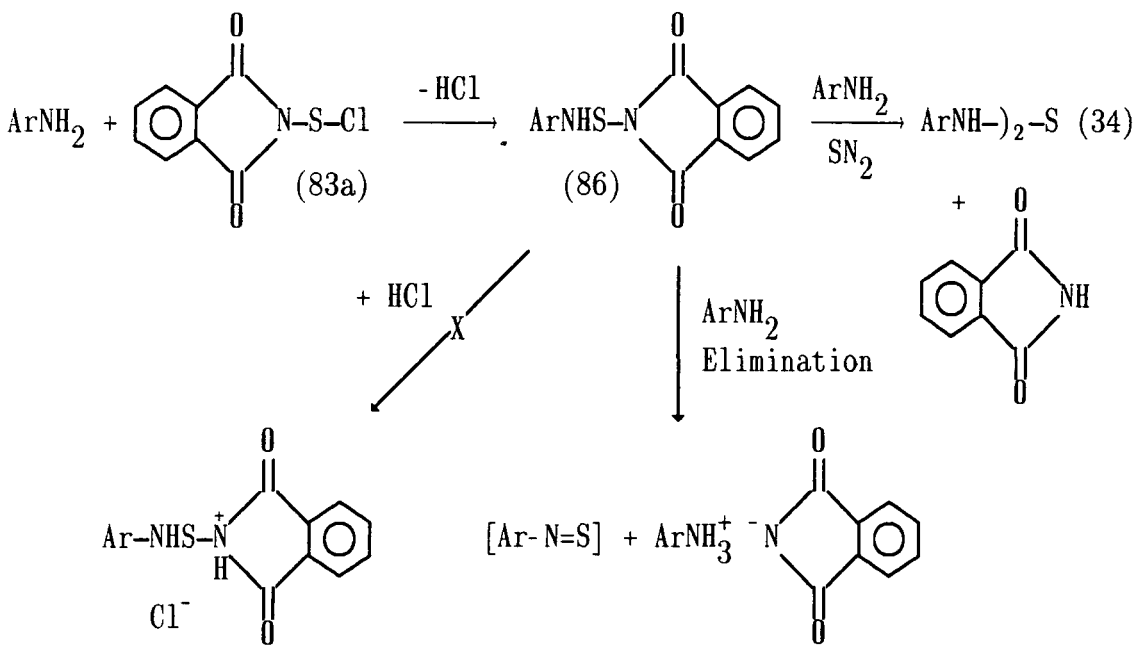
Scheme 2.4

We realised that this adaptation would pose a problem when we considered the mechanism of thiodianiline formation. With piperidine sulphenyl chloride, the hydrogen chloride produced in the first step is required to enhance the leaving group ability of piperidine in the second step (Scheme 2.1). Hence, Davis was able to stop the reaction at the intermediate stage, compound (85), simply by removing the HCl with triethylamine. The unprotonated piperidine was then a very poor leaving group and the second step was thus prevented.

With the weakly basic phthalimide analogue, however, this mechanism does not apply because the hydrogen chloride produced will not protonate the phthalimide nitrogen, but rather the more basic arylamine. Addition

[2]Kirby has noted that these eliminations could proceed *via* initial nucleophilic attack by the base at sulphur (ref. 76), a possibility we cannot discount.

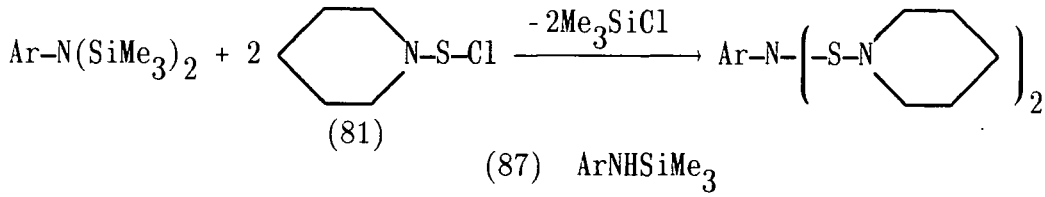
of triethylamine in this case might, therefore, be expected to aid, not hinder, the formation of symmetrical thiodianilines, as the second step can proceed by simple nucleophilic attack, making it difficult to stop the reaction at the intermediate stage. A further complication was the possibility of base-induced 1,2-elimination occurring *in situ* from intermediate (86). This might be expected to proceed readily in the presence of triethylamine and even be induced by the arylamine - the latter situation clearly being unavoidable. The above points are illustrated in Scheme 2.5.



Scheme 2.5

To obtain (86) in preference to (34) we aimed to accelerate the chlorine elimination without the use of base and hinder both the nucleophilic attack on the sulphur of (86) and deprotonation of the sulphenamide NH in (86). Inspired by Mayer's reaction of a bis(trimethylsilyl)aniline with two moles of piperidine sulphenyl chloride (81) (Scheme 2.6)[52], we reasoned that a mono(trimethylsilyl)arylamine (87) should react readily with the sulphur-chlorine bond of (83a) to give the desired product (86). The silylated aniline is sterically hindered to

both nucleophilic attack at sulphur and sulphenamide deprotonation, thus preventing further reaction of (86).



(81)

(87) ArNHSiMe$_3$

Scheme 2.6

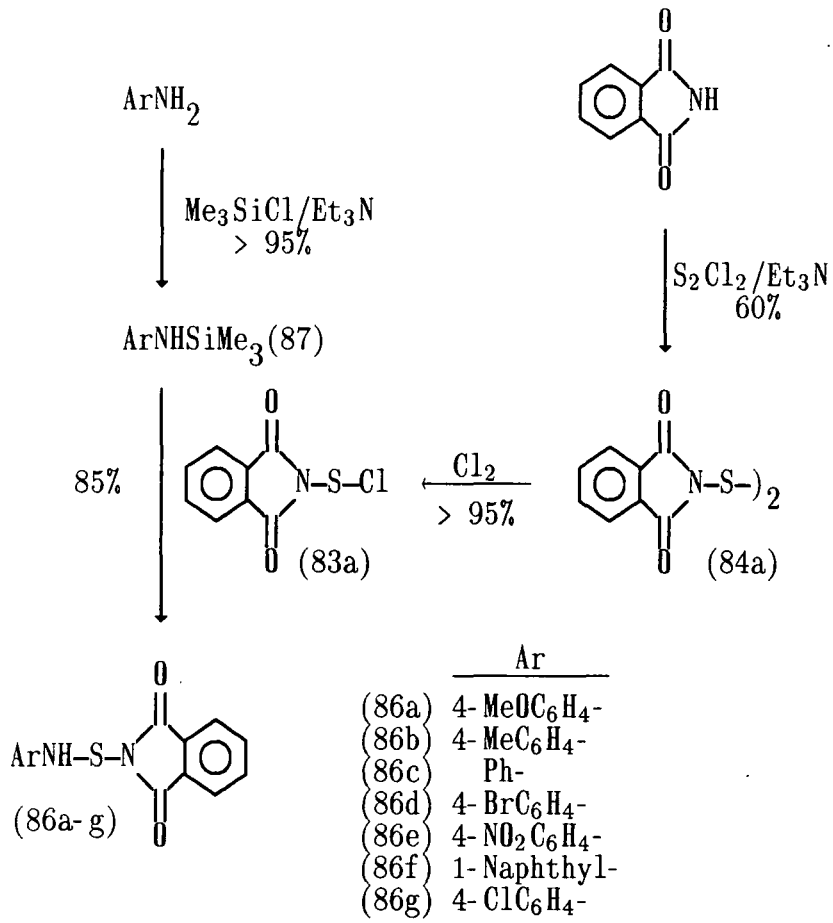
2.1.4 Summary of New Methodology

N,N'-Dithiobis(phthalimide) (84a) was prepared by Cava's route from phthalimide and sulphur monochloride in 60% yield[104]. Chlorinolysis by Ley's procedure gave phthalimide sulphenyl chloride (83a) in near quantitative yield as a yellow crystalline solid[102]. Compound (83a) was most conveniently identified by a small but characteristic downfield shift in the ^{1}H NMR spectrum (7.8 → 8.0 ppm) with respect to the disulphide compound (84a). Compound (83a) is rather moisture-sensitive and was handled and stored in a dry box, although if transferred rapidly in air there was no noticeable hydrolysis.

Preparation of N-trimethylsilylarylamines was trivial: a slight excess of chlorotrimethylsilane was used with triethylamine as base, to afford near quantitative yields of compounds (87) which were sufficiently pure for further reaction.

Finally, one equivalent of (83a) in rigorously dried chloroform was added dropwise to one equivalent of (87) in the same solvent at 0^{o}C with stirring under dry nitrogen. To our delight reaction was complete within ten minutes in nearly all cases, to afford the desired thioaryl-aminophthalimides (86) as pale yellow precipitates. Yields were excellent (typically 85%) and the products needed no further

purification. Our completed synthetic route to thionitrosoarene precursors (86) is shown in Scheme 2.7. Overall yields from arylamines were *ca.* 80%.



Scheme 2.7

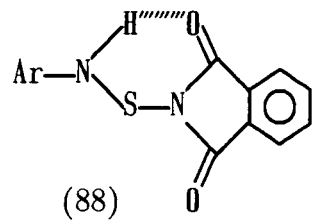
2.1.5 Properties of Thioarylaminophthalimides

Compounds (86a-g) are easily identified by their characteristic IR spectra, *viz.* a strong, sharp sulphenamide band in the 3310-3370 cm^{-1} region and two carbonyl absorptions at 1775-1785 cm^{-1} (strong) and 1720-1730 cm^{-1} (very strong, broad). ^1H NMR spectra are equally characteristic but more difficult to obtain due to the extreme insolubility of many derivatives (86) in deuterochloroform[3]. In all cases except

[3]Use of more polar NMR solvents was unsatisfactory as the chemical shift of the sulphenamide proton moved downfield into the aromatic region.

naphthyl (86f), the phthalimide protons (δ_H 7.9 - 7.7 ppm) are distinct from the other aromatic protons and the sulphenamide proton which resonates at between δ_H 7.1 - 6.2 ppm.

The sharp sulphenamide peaks in both the IR and NMR spectra, together with the strong second carbonyl band in the IR, suggest a considerable degree of intramolecular hydrogen bonding, structure (88); intermolecular hydrogen bonding would not be evident in the highly dilute NMR solutions. This could explain the characteristic insolubility of (86) and also their thermal stability. Compounds (86) are shelf-stable at room temperature for at least one year, whereas the thiodiamines used by Davis are "moderately stable compounds that can be stored for short periods of time without noticeable decomposition" [46].



(88)

2.2 GENERATION AND TRAPPING OF THIONITROSOARENES

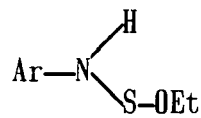
2.2.1 Review and Strategy

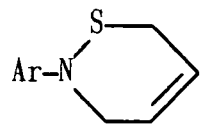
It was clear from literature precedents that there should be no problem trapping thionitrosoarenes, once generated. We chose triethylamine as the base to induce the 1,2-elimination from our precursors (86). With all the analogous precursors to thio- and seleno-aldehydes, where the elimination was base-induced, triethylamine was most commonly employed, although stronger bases were required in some cases. Kirby's phthalimide reagents (58) fragmented smoothly on addition of triethyl-

amine[63], but not if the substituent was alkyl or, importantly, aryl (*ie.* an electron withdrawing group was needed). We hoped, however, that the sulphenamide anion would be sufficiently stabilised for triethylamine to be successful.

Our next decision was choice of solvent. The insolubility of precursors (86) is a distinct advantage as the thionitrosoarene is thus generated in a low, steady-state concentration, which vastly reduces the chances of dimerisation and favours trapping. A polar solvent was required, however, for reaction to proceed at all.

Our first choice of solvent was ethanol: on addition of triethylamine the insoluble precursor (86) was gradually consumed to give a clear yellow solution. However, a major product appeared to arise from nucleophilic substitution at the sulphur of (86) by ethanol, to give an unstable compound tentatively assigned the structure (89) from the ^1H NMR spectrum. We therefore needed a polar, non-nucleophilic solvent and acetone became our solvent of choice for all reactions of (86), except when the precursor (86) was too soluble, when chloroform was used in preference. Ether was also tried as a solvent but to no advantage. Indeed, the convenient self-indicating quality of the procedure was lost in ether due to precipitation of by-products: reactions in acetone and chloroform are judged as complete when the solution becomes clear.

(89) 

(90) 

To test the efficiency of our precursors and trapping procedures it was decided to use the simplest diene, *viz.* 1,3-butadiene, as trap[4].

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[4] 1-Chloro-4-thionitrosobenzene was not used in these experiments as the precursor was synthesised at a later stage for work reported in Chapter 5.

Hence, large excesses of butadiene and triethylamine were condensed under high vacuum into a frozen suspension of precursor (86) in acetone and subsequently stirred at room temperature in a sealed vessel until the suspension became a clear solution. After work-up the 2-aryl-3,6-dihydro-2H-1,2-thiazines (90) were obtained in *ca.* 65% yield. Thiazines (90) are easily purified by chromatography and/or distillation, though rapid bulb-to-bulb distillation under high vacuum was preferable to avoid decomposition.

2.2.2 Properties of 2-Aryl-3,6-Dihydro-2H-1,2-Thiazines

Compounds (90) are yellow oils which often solidify in the freezer. They are very soluble in all common organic solvents and are easily identified by their characteristic NMR spectra in deuterochloroform - the most distinctive features being the two ring methylene groups. The methylene unit adjacent to nitrogen, C(3), is observed at δ_H 4.1 (± 0.1) ppm [2H,m] and δ_C 51 (± 2) ppm, while the CH_2 group adjacent to sulphur, C(6), is at δ_H 3.1 (± 0.1) ppm [2H,m] and δ_C 26 (± 1) ppm. The vinylic protons on C(4) and C(5) are also clear in the ^1H NMR spectra, δ_H 6.3 - 5.8 [2H,m] ppm. The mass spectra of (90) are equally distinctive. Representative NMR and mass spectra for (90d) are included to clarify this discussion (Figures 2.1 and 2.2).

The mass spectrum of (90d) (Figure 2.2), is typical of these thiazines (90) and the fragmentation pattern is of great interest. The major peak in the spectrum, other than the molecular ion (in this case m/e: EI 203; CI 204), is always that of the Ar-N=S species, presumably formed by a retro Diels-Alder process as a result of electron impact. High resolution mass analysis (Table 2.1) confirmed the molecular formula of the postulated thionitrosoarenes providing some spectroscopic

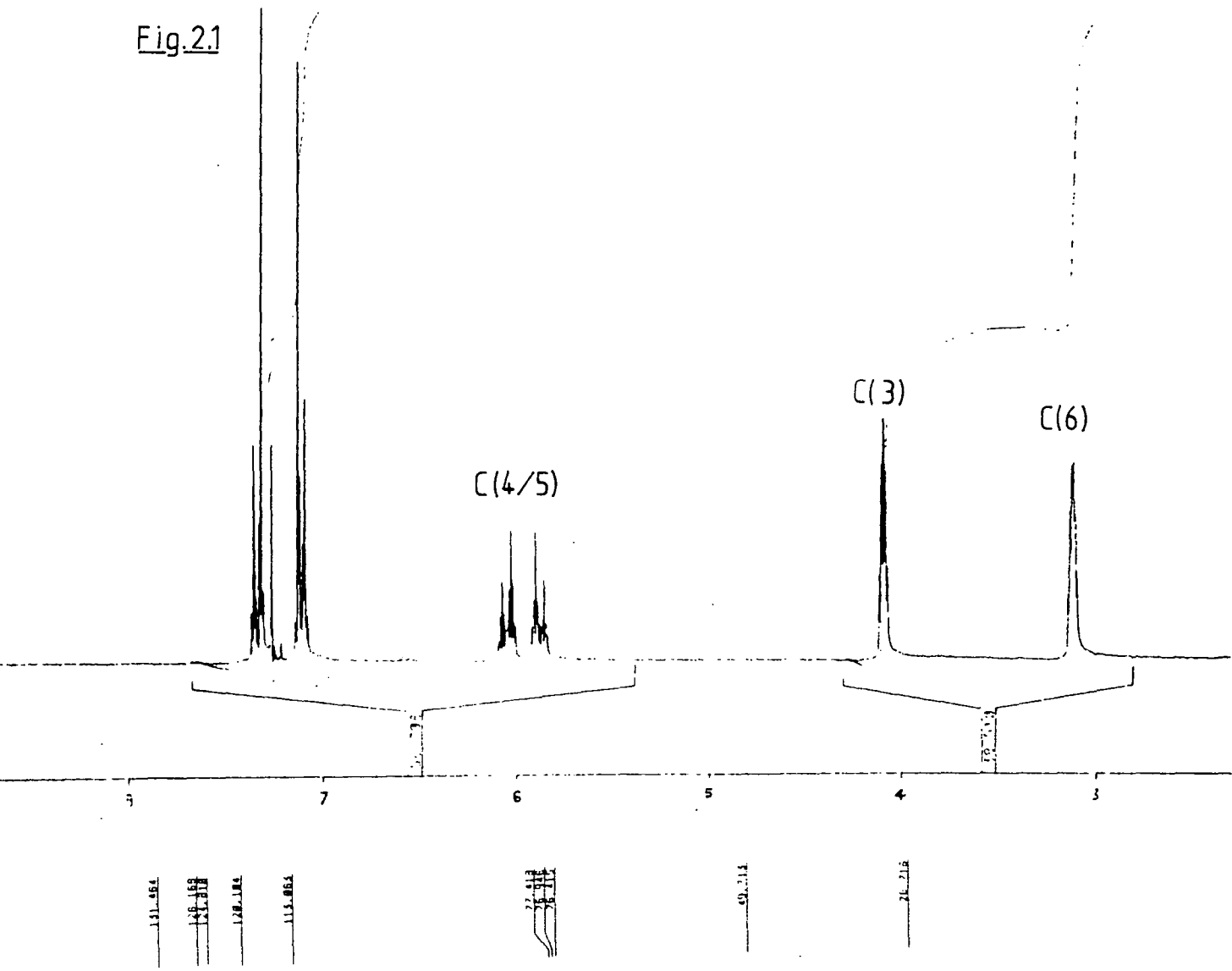
evidence for these transient species. It has been mentioned earlier (Chapter 1) that Rees observed the mass spectrum of the relatively stable 2-cyano-6-trifluoromethylthionitrosobenzene[50].

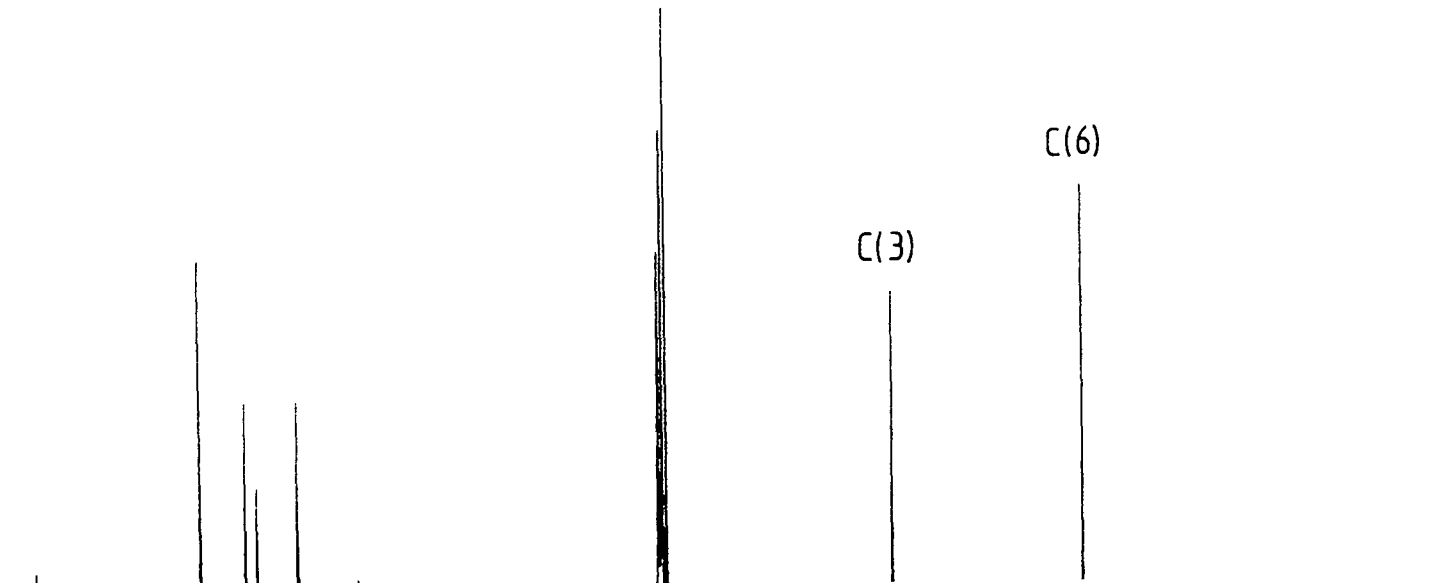
Ar	m/e (found)	m/e (required)
(a) $MeOC_6H_4$-	123.01427	123.01373
(b) MeC_6H_4-	137.02992	137.04082
(c) Ph-	153.02484	153.03639
(d) BrC_6H_4-	200.92478	200.95803
(e) $NO_2C_6H_4$-	167.99934	168.00082
(f) Naphthyl-	173.02992	173.02617

Table 2.1

In conclusion, we have developed a simple 1,2-elimination route to a wide range of substituted thionitrosoarenes and hence 1,2-thiazines, in *ca.* 50% yield, from the appropriate starting arylamine. It is worthy of note that all reagents and solvents used are readily available and cheap.

Fig.2.1





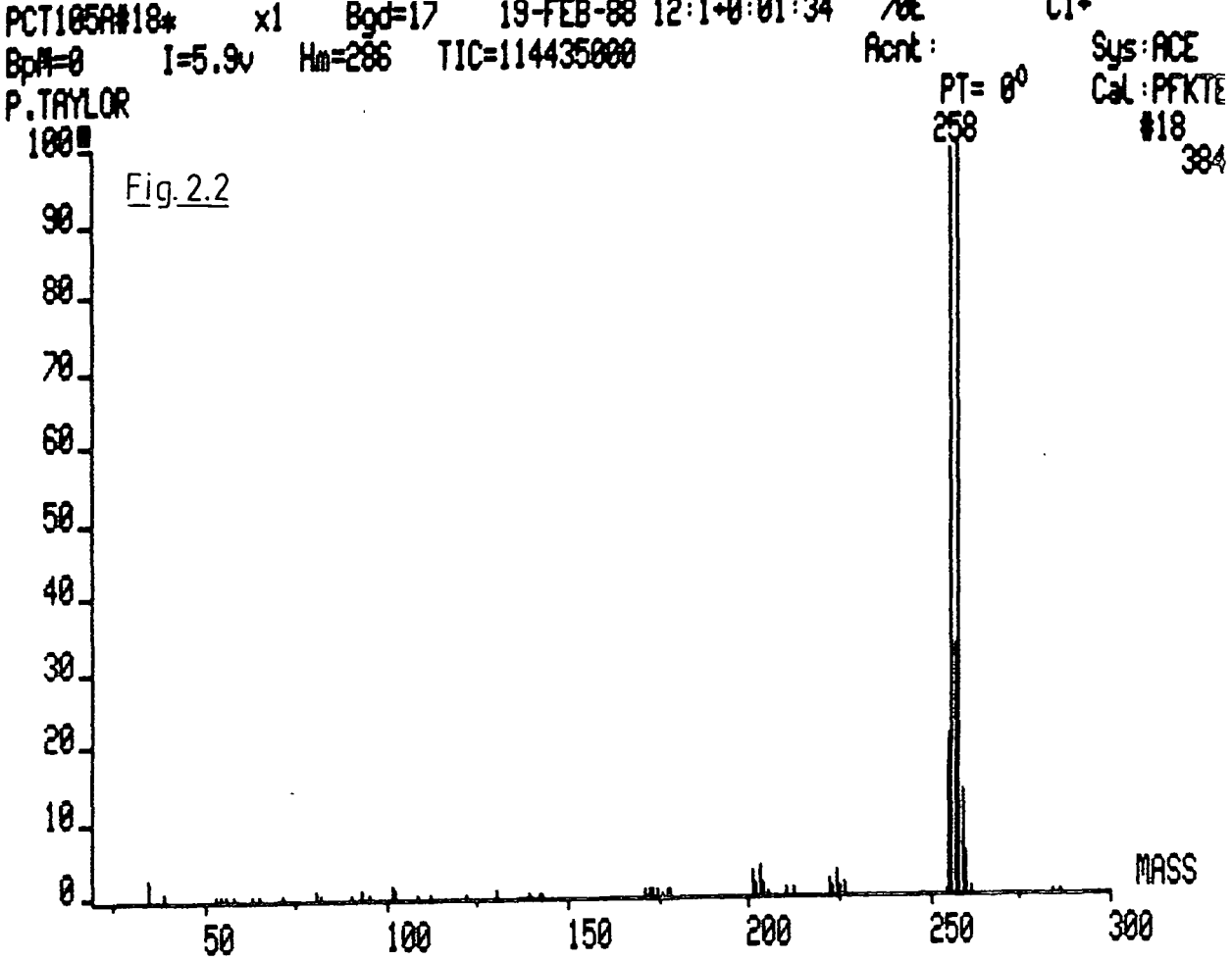
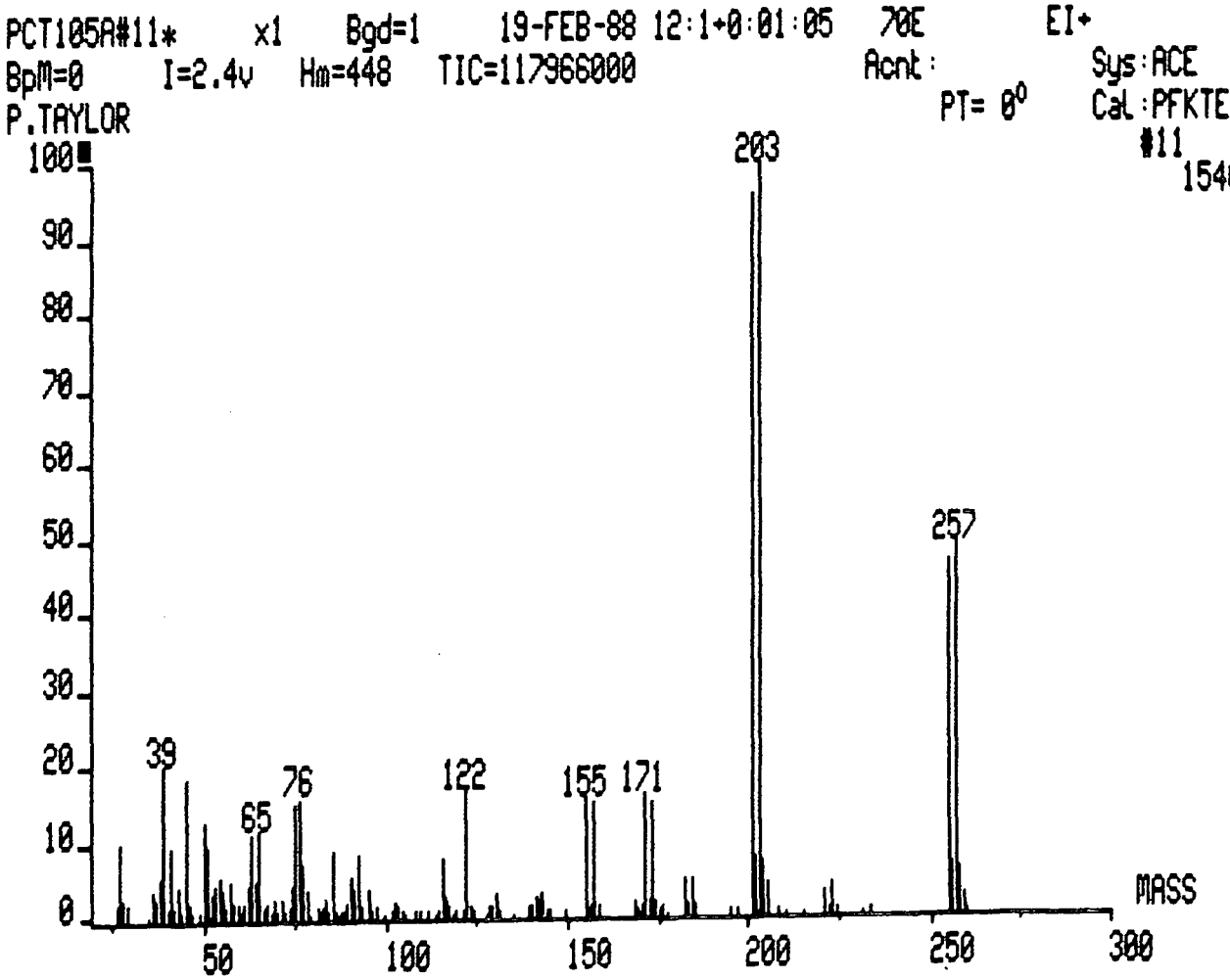

PCT105A#18* x1 Bgd=17 19-FEB-88 12:1+0:01:34 70E CI+
BpM=0 I=5.9v Hm=286 TIC=114435000 Acnt: Sys:ACE
P.TAYLOR PT= 0° CaL:PFKTE
#18
258
384
MASS
50
100
150
200
250
300

Fig. 2.2


PCT105A#11* x1 Bgd=1 19-FEB-88 12:1+0:01:05 70E EI+
BpM=0 I=2.4v Hm=448 TIC=117966000 Acnt: Sys:ACE
P.TAYLOR PT= 0° CaL:PFKTE
#11
203
257
39
65
76
122
155
171
MASS
50
100
150
200
250
300

CHAPTER THREE

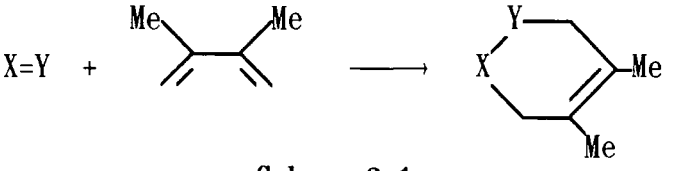
REACTIONS OF THIONITROSOARENES WITH SUBSTITUTED DIENES

3.1 REACTION WITH 2,3-DIMETHYL-1,3-BUTADIENE[1]

3.1.1 Introduction

(91)

Dimethylbutadiene (91) is a widely used, electron rich diene. The majority of the dienophiles discussed in Chapter 1 have been shown to react with (91) to give six-membered heterocycles, as expected (Scheme 3.1).



Scheme 3.1

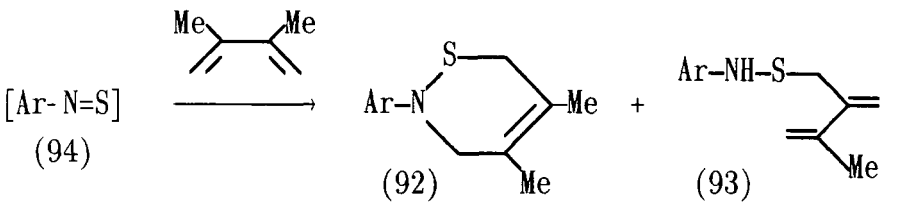
As the diene is symmetrical there is no possibility of regioselectivity in cycloadditions and the question of stereoselectivity does not arise as (91) has no terminal substituent. The only precedent for alternative products from dimethylbutadiene cycloadditions is the competing ene reaction observed by Meth-Cohn's group with thionitroso-formates and -sulphonates[57]. Tavs[45], Davis[46] and Minami[48] reported no ene products from the reaction of diene (91) and thionitrosoarenes.

3.1.2 Results and Discussion

When triethylamine was added in excess to a suspension of precursor (86) and a large excess of diene (91), at room temperature with

[1]Henceforth 2,3-dimethyl-1,3-butadiene will be shortened to dimethylbutadiene.

stirring, reaction proceeded smoothly to give a clear yellow solution. ^{1}H NMR analysis of the crude product mixture[2] showed the presence of the expected 2-aryl-4,5-dimethyl-3,6-dihydro-2H-1,2-thiazines (92) by comparison with the work of Tavs[45]. However, additional vinylic and alkyl protons were clearly observable. By comparison with Meth-Cohn's work[57] we assigned these resonances to the ene product (93). Further analysis of the ^{1}H NMR data revealed that the ratio of Diels-Alder:ene products (92):(93) (as determined by the ratio of integrals) was highly dependent on the nature of the aryl substituent: these ratios are summarised in Table 3.1. This reaction is shown in Scheme 3.2.



Scheme 3.2

(94)	Ar	% (92)	% (93)
(a)	$MeOC_6H_4$-	85	15
(b)	MeC_6H_4-	60	40
(c)	Ph-	55	45
(d)	BrC_6H_4-	25	75
(e)	$NO_2C_6H_4$-	20	80
(f)	1-Naphthyl	45	55

Table 3.1

It is clear from these results that the less reactive, electron rich, thionitrosoarene (94a) gave a predominance of Diels-Alder product (92a). The gradual change to electron poor thionitrosoarenes (94d,e)

[2]For all isomer ratio analysis the solutions were evaporated and the residues stirred with cyclohexane, filtered (removing triethylammonium phthalimide byproduct) and evaporated to give yellow oils.

was accompanied by a complementary change in ratios, until the ene adduct (93) became the major isomer. To our knowledge the only examples of competitive ene and Diels-Alder reactions are with phenylthionitrosoformate[57], benzyne[105] and another reactive intermediate, $PhSO^+$ [106]. Azodicarboxylates (95), which undergo ene additions in preference to Diels-Alder reactions with certain dienes[107], have been shown to give only the Diels-Alder adduct with simple dienes such as dimethylbutadiene (91)[108]. Also, nitroso compounds only give ene in preference to Diels-Alder addition where transition to the cisoid form is highly hindered, as mentioned in Section 1.2.3. This is clearly not the case here.

$$RO_2C\text{-}N{=}N\text{-}CO_2R \quad (95)$$

This lack of precedent and the poor understanding of the ene mechanism (see Section 3.3) has made us reluctant to draw any definite conclusions from these results, though it may be possible to infer stabilisation of charges in the transition states. It is perhaps simpler to employ a reactivity-selectivity rationalisation. Ene reactions can occur when the diene is in either the transoid or cisoid conformation, whereas Diels-Alder reaction can only occur in the latter situation. The thionitrosoarene (94) is therefore likely to encounter many molecules where ene reaction is possible before meeting a cisoid diene[3]. A more reactive thionitrosoarene, being less selective, would therefore give more ene product than a more selective example. This argument does assume a preference for a Diels-Alder, as opposed to ene, pathway, for which we have no evidence.

---

[3] 1,3-Butadiene and isoprene are predicted to contain >95% transoid diene at room temperature. The figure for dimethylbutadiene is not given, but the most stable cisoid form is calculated as being 43^0 out of plane (rotated about the 2,3 bond) - isoprene is 37^0 out of plane - an indication of the difficulty of attaining the planar cisoid conformation (ref.109).

The above explanation is reinforced by the fact that at higher temperatures, as used by Tavs[45], Davis[46] and Minami[48], when there will be considerably more cisoid diene present, no ene products were reported. As with our examples, Meth-Cohn's phenylthionitrosoformate reaction was conducted at ambient temperature[57]. Inference from temperature is, however, likely to be unreliable due to the thermal instability of the ene adducts[57].

The naphthyl analogue (94f) gave slightly more ene product than the electronically similar phenyl analogue (94c). We have rationalised this on the basis of the greater steric demand of the naphthyl substituent disfavouring the more crowded Diels-Alder transition state.

In our hands the Diels-Alder and ene products were inseparable by chromatography[4] or by distillation (due to the thermal sensitivity of the ene adducts). The only exception was the 4-methoxyphenyl analogue (94a) where the small amount of ene adduct present in the products could be removed, but not isolated, by Kugelrohr distillation. The (92)/(93) mixtures could easily be separated from by-products, allowing mass spectral analysis which showed the existence of only one molecular ion (plus the thionitrosoarene peak discussed in Section 2.2.2). This showed that the second product was indeed isomeric with (92) and together with the ^{1}H NMR data we can be confident in assigning the structure (93), though we have been unable to isolate and fully characterise any ene adduct (93).

[4]Including G.C. where the ene product appeared to decompose.

3.2 REACTION WITH ISOPRENE[5]

3.2.1 Introduction

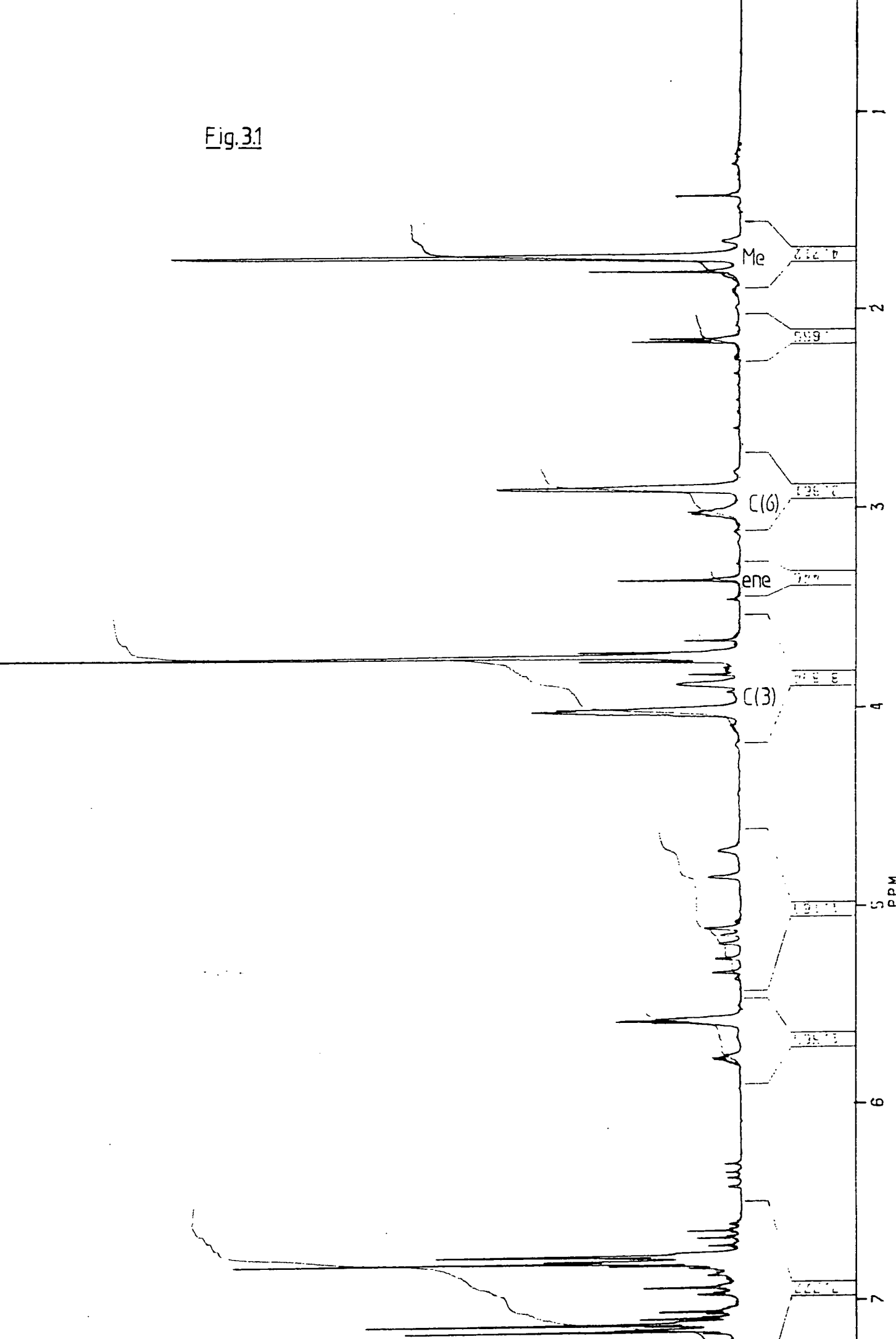
Isoprene is another readily available diene. 1,2-Thiazines resulting from its Diels-Alder addition to thionitrosoarenes (94) have no stereochemistry associated with C(3) or C(6), as with dimethylbutadiene (91), but, unlike that diene, the asymmetry of isoprene allows the possibility of two regioisomeric cycloadducts with the methyl substituent in either the 4 or 5 position. If the thionitrosoarenes were to behave in the fashion of imides of sulphur dioxide or chalcogeno-aldehydes or -ketones (see Chapter 1) we would predict formation of the 5-substituted thiazine from electron deficient dienophiles and the 4-substituted thiazine from electron rich dienophiles. Nitroso analogues were shown to be rather unpredictable[5]. Phenylthionitrosoformate was found to give a 1:1 mixture of Diels-Alder and ene products (as with dimethylbutadiene) the Diels-Alder adducts being a mixture of 4- and 5- substituted thiazines[57]. Reaction of thionitrosoarenes with isoprene has not been reported.

3.2.2 Results and Discussion

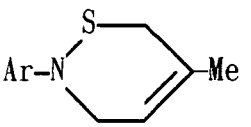
The reaction of isoprene (5) with thionitrosobenzenes was investigated using an electron rich (94a) and electron deficient (94d) example, under similar conditions to those used with dimethylbutadiene. Mixtures of isomers were formed which were analysed by their ^{1}H NMR spectra. Firstly, the spectrum of the adducts of (94a) (Figure 3.1) was studied. By comparison with spectra of dimethylbutadiene adduct

[5]Isoprene is an acceptable IUPAC name for 2-methyl-1,3-butadiene.

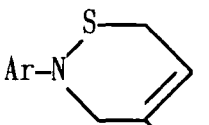
Fig.3.1



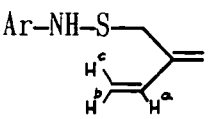
mixtures, it was immediately apparent that both Diels-Alder and ene products were present. The observed spectrum was therefore assumed to be due to a mixture of the two regioisomers (96a) and (97a) and the ene adduct (98a). The methyl, methoxy and aromatic resonances in the spectrum overlapped and so were of no use in distinguishing between the isomers. Two distinct signals were seen, however, in both the thiazine CH_2S, and thiazine CH_2N regions, as a major and minor peak, in a 3:1 ratio (from integrals) in each case. The CH_2S of the ene adduct (98a) gave a characteristic singlet at 3.4 ppm.



(96)



(97)



(98)

The problem was clearly how to assign the two sets of similar resonances to the two regioisomers. This was achieved by comparison with the ^1H NMR spectra of the adducts of 1-methoxy-4-thionitrosobenzene (94a) with butadiene and with dimethylbutadiene. For the 5-substituted thiazine (96a) the methylene group adjacent to sulphur is similar to that in the dimethylbutadiene adduct (*ie.* with a methyl group on the α-carbon) and the methylene group adjacent to nitrogen is analogous to that in the butadiene adduct (*ie.* with no methyl group on the α-carbon). Conversely, the 4-substituted thiazine (97a) has a "butadiene adduct-like" CH_2S and a "dimethylbutadiene adduct-like" CH_2N. The ring methylene signals in the butadiene adduct are seen downfield of those in the dimethylbutadiene adduct, hence it is reasonable to assume that the resonances at higher chemical shift (δ_H 4.0 and 3.0 ppm) are from methylene groups with no substituent on the α-carbon and those further upfield (δ_H 3.9 and 2.9 ppm) are from methylene groups with a substituent on the α-carbon. Similar arguments can be applied, with

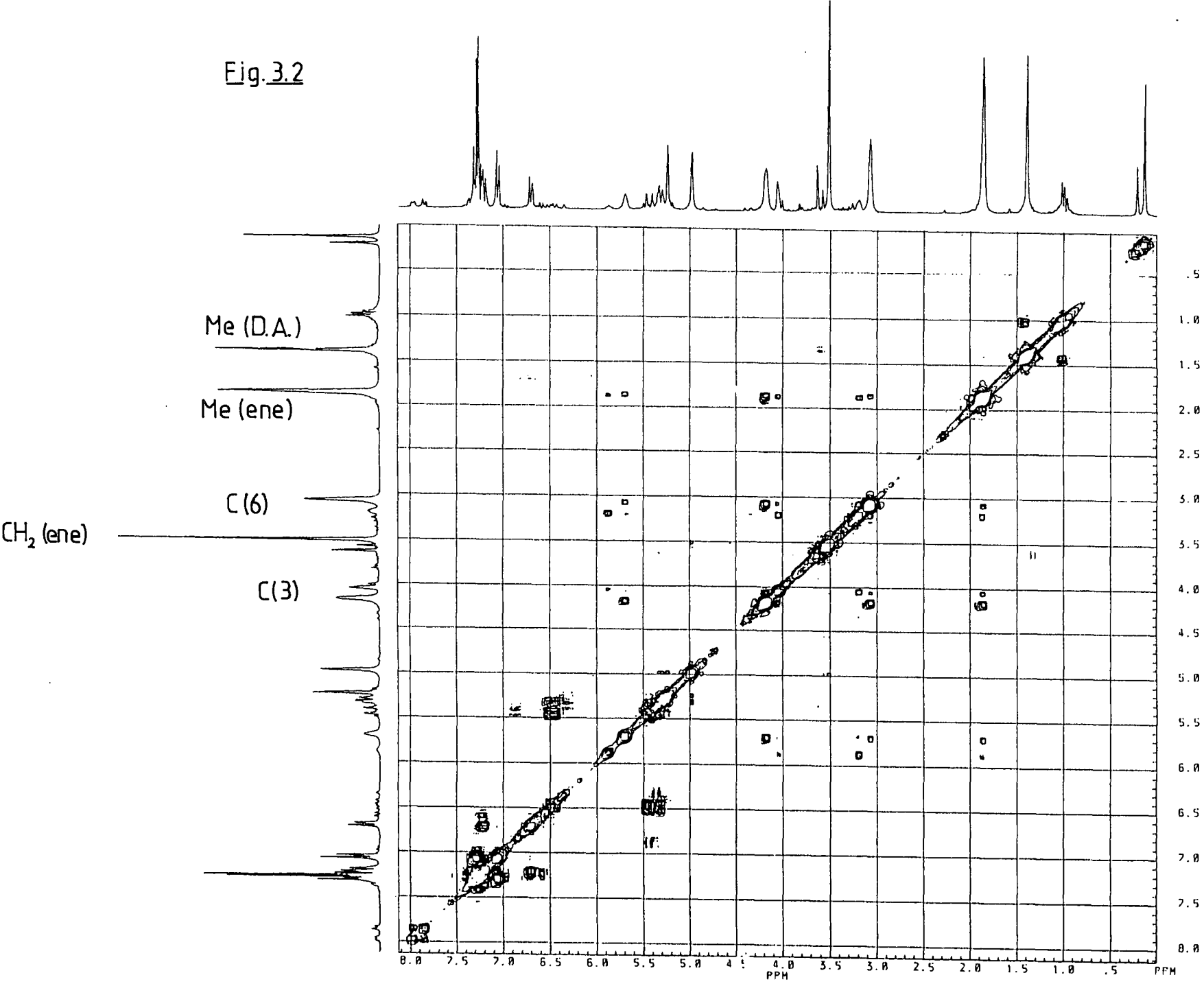
success, to the ^{13}C NMR spectra, leading to the conclusion that the major isomer has a "butadiene adduct-like" CH_2N and a "dimethylbutadiene adduct-like" CH_2S, *ie.* structure (96a). Similarly the minor isomer can be shown to be structure (97a). The highly coupled vinylic protons of the thiazines were easily distinguished from those of the ene adduct.

The ^1H NMR signals due to the thiazine ring in the products of addition to 1-bromo-4-thionitrosobenzene (94d) are almost identical to those described above. Assigning these to the two regioisomers (96d) and (97d) was, therefore, trivial. The remaining signals were assigned to the ene adduct (98d) by comparison with the dimethylbutadiene adduct (93d) and reinforced by examination of the coupling constants of the vinylic protons. The small resonances due to adduct (98a) in the products from (94a) were then assigned with confidence.

Confirmation that the three sets of signals were due to three different isomers came from the coupling constant driven ^1H-^1H shift correlation spectrum (COSY) of the products of addition of 1-bromo-4-thionitrosobenzene (94d) and isoprene (Figure 3.2). Simplistically, the off-diagonal elements correspond to coupling of protons which are close in space and in fixed relative positions - in our case corresponding to the same ring or conjugated system. It is clear that all the resonances assigned to the thiazine sub-structure of the major isomer (96d) are coupled to each other and similarly in the minor isomer (97d). The remaining vinylic signals are all coupled to each other, consistent with the conjugated ene adduct (98d), but to nothing else, the CH_2S in the ene product (3.5 ppm) being independent of the other protons in this acyclic structure.

Periodate oxidation[110] of the mixture of isomers (96-98,d) to the known thiazine-1-oxides (99,100d) and unknown sulphoxide (101d) further confirmed the assignments of the thiazines (96-7,d) by comparison with

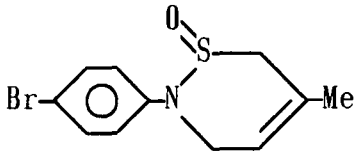
Fig. 3.2


Me (D.A.)
Me (ene)
C(6)
CH_2 (ene)
C(3)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
PPM
.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
PPM

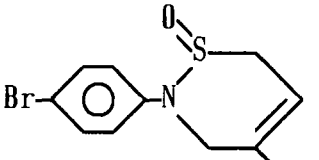
known ^1H NMR spectra.

	Ar	% (96)	% (97)	% (98)
(a)	$MeOC_6H_4$-	65	22	13
(d)	BrC_6H_4-	25	8	67

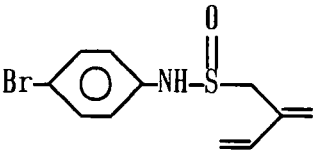
Table 3.2



(99)



(100)



(101)

The results, summarised in Table 3.2, show that in both cases a 3:1 mixture of 5- : 4-substituted thiazines was produced from Diels-Alder addition and that the ene adduct was the major product from reaction of (94d) but the minor product from (94a).

The trend in ratios of Diels-Alder to ene products is in full agreement with the trend found with dimethylbutadiene, but for both compounds (94a,d) the amount of ene adduct (98a,d) is slightly less when isoprene is the diene [13% compared with 15% for (94a) and 66% compared with 75% for (94d)]. The lower percentage of ene product may be explained simply as a statistical effect, there being only one, not two, of the methyl groups necessary for ene reaction. Alternatively, the phenomenon may be the result of the greater ease of transition to the cisoid conformation (which favours Diels-Alder addition) associated with the single substituent.

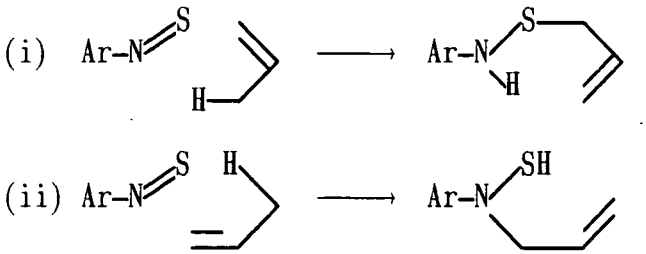
The fact that regioselectivity of isoprene addition is not dependent on the electronic nature of the aryl substituent suggests that inductive effects are not responsible for the predominance of the 5-substituted thiazine (96) - this may simply be due to steric interactions placing the methyl group away from the bulky N-aryl substituent.

The isomer mixtures were, once again, inseparable, but as was the case with the products of dimethylbutadiene addition, the ene adduct could be removed, by distillation, from the isoprene adducts of 1-methoxy-4-thionitrosobenzene (94a). Analysis confirmed the thiazine structures of the two remaining regioisomers (96,97a).

3.3 REACTION WITH ALKENES

3.3.1 Introduction

Having been unable to isolate the proposed ene adducts of the dienes in Sections 3.1 and 3.2, we decided to confirm the novel enophilic behaviour of thionitrosoarenes by using substituted alkenes as traps. The ene reaction could feasibly proceed with either (i) C-S bond formation or (ii) C-N bond formation (Scheme 3.3).

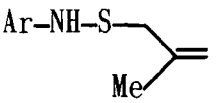


Scheme 3.3

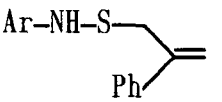
It has been shown (Chapter 1) that nitroso compounds react by path (ii)[17], imides of sulphur dioxide by path (i)[33,34], and thio- and seleno- aldehydes by both[92,94,95], but favouring path (i) with electron deficient examples[94]. All Meth-Cohn's examples proceed, as we have postulated for reactions in Sections 3.1 and 3.2, by path (i) - *ie.* with C-S bond formation[57].

3.3.2 Results and Discussion

Thionitrosoarenes (94a,f) were trapped with 2-methylpropene (isobutene) and 2-phenylpropene (*α*-methylstyrene) under the experimental conditions used with butadiene and dimethylbutadiene respectively. The products, (102) and (103) respectively, were yellow oils which were unstable to distillation. Products (102a,103a) were also unstable to chromatography and could not be fully purified, adducts (102f,103f) were, however, sufficiently stable on silica to allow analytical samples to be obtained. It was necessary to store all the products (102,103) in the freezer though some decomposition was still apparent within weeks.



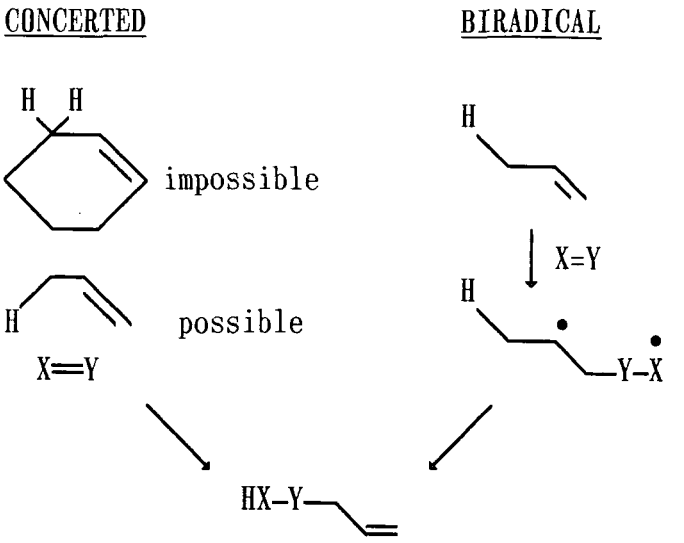
(102)



(103)

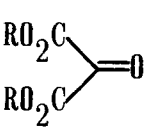
Ene reaction only appeared possible with methyl substituted alkenes. Cyclohexene, which reacted smoothly with thionitroso-formates and -sulphonates[57], gave no observable ene adduct with thionitrosoarenes (94a,f). Thaler and Franzus found that diethylazodicarboxylate (95, R = Et) reacted faster with primary than secondary hydrogens[111]. That ene reaction of thionitrosoarenes had indeed occurred with C-S bond formation was evident from the amine band in the I.R. spectra (*ca.* 3370 cm^{-1}) - the structures were confirmed by ^{1}H and ^{13}C NMR spectra.

The mechanism of the ene reaction has been subject to much discussion. Hoffmann concluded, in his seminal 1969 review, that reaction could be either concerted or stepwise biradical[112]. The former pathway was thought to be preferred, but where the correct geometry for a concerted transition state is unattainable, *eg.* with cyclohexene, the biradical route is necessary (Scheme 3.4).



Scheme 3.4

Kinetic isotope-effect data for ene addition of mesoxalic esters (104) to allylbenzene (105) suggested that reaction proceeded *via* an initial [2 + 2] complex with a subsequent pseudo-pericyclic process which includes the C-H bond cleavage[113]. A closer analogue, ene reaction of pentafluoronitrosobenzene (106), has been judged, again using kinetic isotope-effects, to proceed *via* an aziridinium oxide intermediate - this rate determining process again being followed by a fast pseudo-pericyclic C-H bond breaking step (Scheme 3.5)[114]. This pathway would not lead to the observed regioisomer in the case of thionitrosoarenes as it proceeds with C-N bond formation. The required intermediate here would be a thiirane S,N-ylide (45) - a possibility which will be discussed in Chapter 5.



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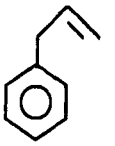
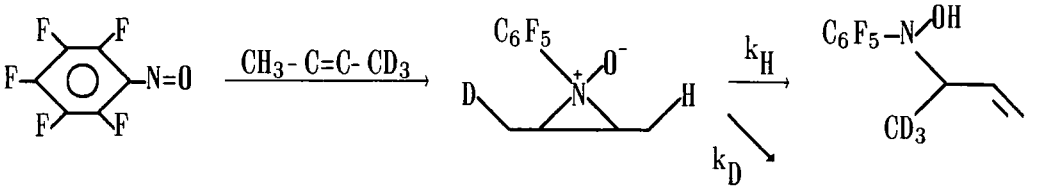
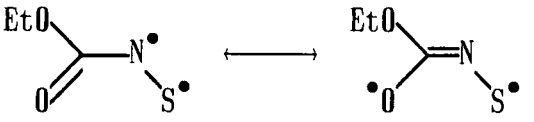
(105) 



Scheme 3.5

Meth-Cohn has suggested that the surprising *peri* selectivity for ene alongside Diels-Alder reaction of thionitroso compounds may be a result of their triplet-state reactivity. The possibility of stabilisation of this biradical form by the adjacent formate group is shown in Scheme 3.6[57]. Molecular orbital representations of ene reactions are discussed briefly in Section 3.6.



Scheme 3.6

The only comment we are able to make from our limited observations on ene activity is that if these reactions do proceed by a stepwise pathway, it is surprising that no adduct was observed with cyclohexene - this observation being more consistent with a pericyclic mechanism ([4 + 2] or initial [2 + 2]). There is clearly a need for more experimental observation in this area.

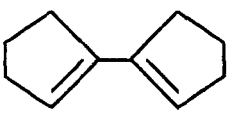
3.4 REACTION WITH BICYCLIC TETRASUBSTITUTED DIENES

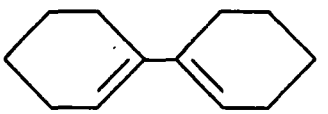
3.4.1 Introduction

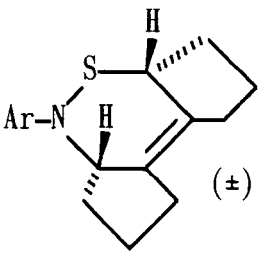
The bicyclic dienes, 1,1'-bicyclopentenyl (107) and 1,1'-bicyclohexenyl (108) are predicted to be excellent dienes, as they are effectively tetra-alkyl substituted[20]. The highly substituted 1,2-thia-

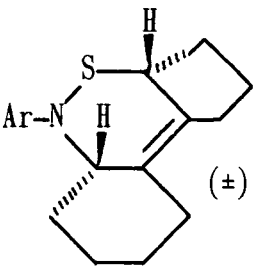
zines resulting from addition of dienes (107) and (108) to thionitroso-arenes have two chiral centres at C(3) and C(6). Prior to our work there were no reports of reaction of thionitroso compounds (1) with bicyclic dienes. Indeed, the only heterodienophiles which have, to our knowledge, been reported as undergoing cycloaddition with a bicyclic diene are N-sulphinylaniline and N-sulphinylethylcarbamate, which Hanson's group showed gave only the expected 'syn' products, as confirmed by an X-ray structure of the bicyclohexenyl adduct of the former sulphinylamine[20,30b].

Ene reaction could, in principle, compete with the Diels-Alder addition but this has never been observed with dienes (107) and (108) and considering the close analogue with cyclohexene, which gave no ene adducts with thionitrosoarenes, we expected only the 'syn' 1,2-thiazines (109) and (110).

(107) 

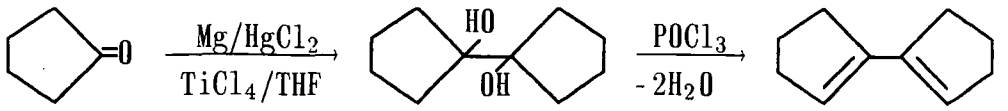
(108) 

(109) 

(110) 

3.4.2 Results and Discussion

Bicyclopentenyl (107) and bicyclohexenyl (108) were synthesised by Corey's modified McMurray pinacol coupling reaction, of cyclopentanone and cyclohexanone respectively, with subsequent $POCl_3$ dehydration (Scheme 3.7)[115].



(107)

Scheme 3.7

Reaction of dienes (107), (108) and 1-methoxy-4-thionitrosobenzene (94a) were carried out under the experimental conditions used with dimethylbutadiene. The products of both reactions appeared, from ^{1}H and ^{13}C NMR data, to be single stereoisomeric products (d.e. >95%) which were assigned the 'syn' structures (109) and (110).

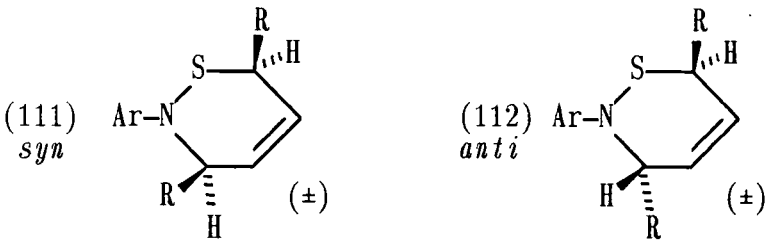
Perhaps the most important conclusion from these results is not the formation of the expected stereoisomers, but the fact that thionitrosoarenes will add to such highly substituted dienes. This suggests that steric effects in other dienes would be unlikely to interfere with reactions of thionitrosoarenes.

3.5 REACTIONS WITH 1,4-DISUBSTITUTED DIENES

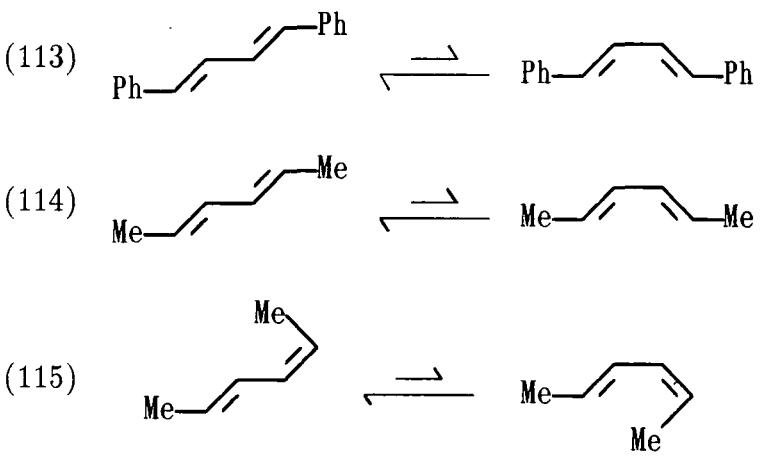
3.5.1 Introduction

Symmetrical 1,4-substituted dienes offer no possibility of regiochemistry in their cycloadditions. However, the resulting substituents at C(3) and C(6) of the 1,2-thiazine ring will have a stereochemical relationship giving either the 'syn' (111) or 'anti' (112) structures. 1,4-Diphenyl-1,3-butadiene (113) is known to be a poor diene as the conjugation between the two benzene rings is lost during Diels-Alder reactions[5]. The 1,4-dimethyl analogues (*ie.* 2,4-hexadienes) are, in contrast, 'good' dienes due to their two alkyl substituents. These hexadienes were suitable for stereochemical investigations due to the availability of the (E,E) and (E,Z) isomers, (114) and (115) respectively.

If reaction of diene (114) with thionitrosoarenes was to proceed in a concerted fashion, we would expect exclusively the 'syn' product (111), whereas diene (115) would give the 'anti' structure (112).



R = Ph, Me

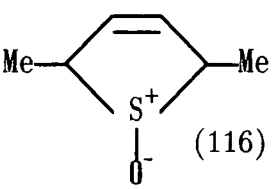


The additions of various heterodienophiles to these two isomeric hexadienes (114,115) have provided interesting results. Mock and Nugent[23] and Weinreb[24] found that N-sulphinylamines (18) and sulphur diimides (19) added to the hexadienes with complete retention of stereochemistry with regard to the methyl groups[6]. Their results were somewhat confused by the unpredictable stereochemistry at sulphur: this problem is, of course, absent in thionitrosoarene adducts. The ^{1}H NMR spectra of the products of addition of two nitrosoarenes to 2,4-hexadienes have been reported, but no attention was given to the stereochemistry of addition - indeed the configuration of the diene was not

[6]The highly hindered (Z,Z)-2,4-hexadiene, which cannot adopt a planar cisoid conformation gave a 1:1 mixture of 'syn' and 'anti' products - the addition is clearly forced to proceed by a stepwise mechanism.

specified[116].

To our knowledge, reactions of chalcogeno-carbonyl compounds and 2,4-hexadienes have not been reported, but some other thionitroso analogues have given noteworthy results. Thermally generated triplet sulphur monoxide, S=O, reacts, not surprisingly, by a biradical stepwise pathway to give a mixture of diastereoisomers with both (E,E)- and (E,Z)-hexadiene[117]. The products [2,5-dimethyl-2,5-dihydrothiophene 1-oxides (116)] are formally due to chelotropic reaction with the sulphur centre as a 2π component and will be mentioned again in Chapter 5, but the important point is that at this temperature (115°C), internal rotation of the biradical intermediate is likely to occur within the timescale of the reaction, leading to loss of stereoselectivity. One complication was that the hexadienes were found to isomerise during the reaction, while a similar silylene (SiH_2) addition to (E,E)-2,4-hexadiene appeared to proceed with no isomerisation of the diene under pyrolytic conditions (420°C), albeit on a much shorter timescale[118]. The isomerisation during the sulphur monoxide reaction is best explained by the reversibility of the first addition, the so-formed biradical being able to rotate before the diene is regenerated.



(116)

The addition of singlet oxygen to the two 2,4-hexadienes (114,115) was also complicated by isomerisation, which was shown, conclusively, to be induced by the dienophile[119].

3.5.2 Results and Discussion

1-Methoxy-4-thionitrosobenzene (94a), generated under our usual conditions, reacted with an excess of 1,4-diphenyl-1,3-butadiene (113) to give a single product (^{1}H NMR, ^{13}C NMR, mpt.) in 60% yield and in >99% diastereomeric excess (d.e.). The product was assumed to have the 'syn' structure (111) as the steric barriers to any (E,Z)-diphenyl-butadiene [the necessary precursor to a single 'anti' product (112)] attaining the cisoid conformation would be prohibitive.

Thionitrosoarenes (94a,d) reacted with (E,E)-2,4-hexadiene (114) to give exclusively the 'syn' products (111, R = Me) (70% yield, >98% d.e.) as judged by ^{1}H and ^{13}C NMR data, and assuming the impossibility of complete inversion of stereochemistry. No ene adduct was observed.

Thionitrosoarenes (94a,b,d,g) reacted with (E,Z)-2,4-hexadiene (115) under similar conditions to give the 'anti' products (112, R = Me). In all cases these expected adducts were accompanied by a second product with ^{1}H and ^{13}C NMR resonances corresponding to those seen in the spectra of the products (111, R = Me) of the (E,E)-hexadiene addition, above. The ratios of the 'anti' and 'syn' products are shown in Table 3.3 and appear to be dependent on the electronic nature of the aryl substituent - the purest 'anti' diastereomers we were able to synthesise were the 4-bromophenyl and 4-chlorophenyl derivatives (112d,g, R = Me) which had diastereomeric excesses of *ca.* 90%. Again there was no apparent ene adduct.

	Ar	ANTI %(112)	SYN %(111)
(a)	$MeOC_6H_4$-	50	50
(b)	MeC_6H_4-	70	30
(d)	BrC_6H_4-	90	10
(g)	ClC_6H_4-	90	10

Table 3.3

Isomer ratios were determined primarily from the integrals of the methyl signals in the ^{1}H NMR spectrum (confirmed by comparison of peak heights in the ^{13}C NMR spectrum). These appeared, in all cases, as four distinct doublets between δ_H ($CDCl_3$) 1.0 and 1.5 ppm. It is reasonable to assume that the two doublets with higher chemical shifts are from the methyl groups on the 3-position, due to the greater deshielding effect of Ar-N compared with S. We can at least be confident that these two doublets are from methyl groups in similar ring positions, as their coupling constants are very similar [*eg.* (111,112a) 6.64, 6.72 Hz] and distinctly different from the two higher field doublets [7.21, 7.18 Hz]. It is simple to assign the whole spectrum by comparison with the spectra of the pure adducts (111) obtained previously, chemical shifts and coupling constants for all resonances due to the 'syn' isomer are identical in the pure form and in the mixture.

Confirmation of the ^{1}H NMR assignments for the 'syn' structures (111a,d) was provided by Nuclear Overhauser Effect (NOE) difference experiments. Significant NOE differences (≥ 5%) are shown in Figure 3.3 for compounds (111a,d, R = Me). It is clear that these effects (which occur between protons in close proximity) are entirely in agreement with our assigned structures.

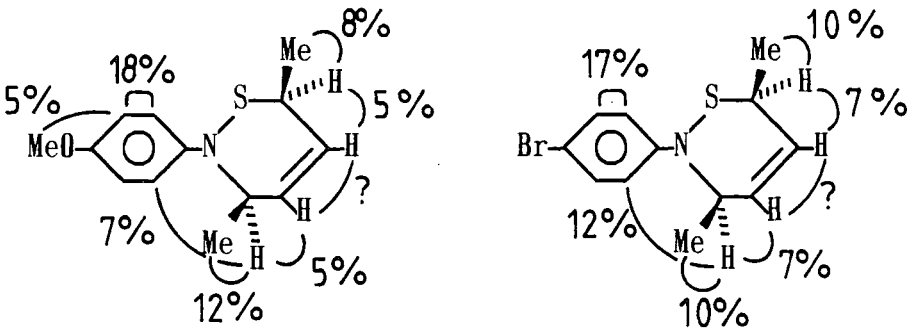


Figure 3.3

N.B. The resonances for protons on C(4) and C(5) are too close in chemical shift for an accurate value to be obtained.

Conclusive proof that the stereochemistry of the adduct (111a, R = Me) is indeed 'syn' was provided by a two dimensional ^{1}H NMR spectrum (COSY) of this adduct (Figure 3.4). This spectrum showed coupling between H(a) and H(b) (See Figure 3.5) but not between H(a) and H(d), H(b) and H(c) or H(c) and H(d), entirely consistent with a 'syn' structure with the methyl groups, as expected, in the equatorial positions. No realistic conformation of the 'anti' product (112) could allow protons H(a) and H(b) into such close proximity.

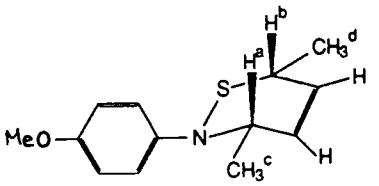
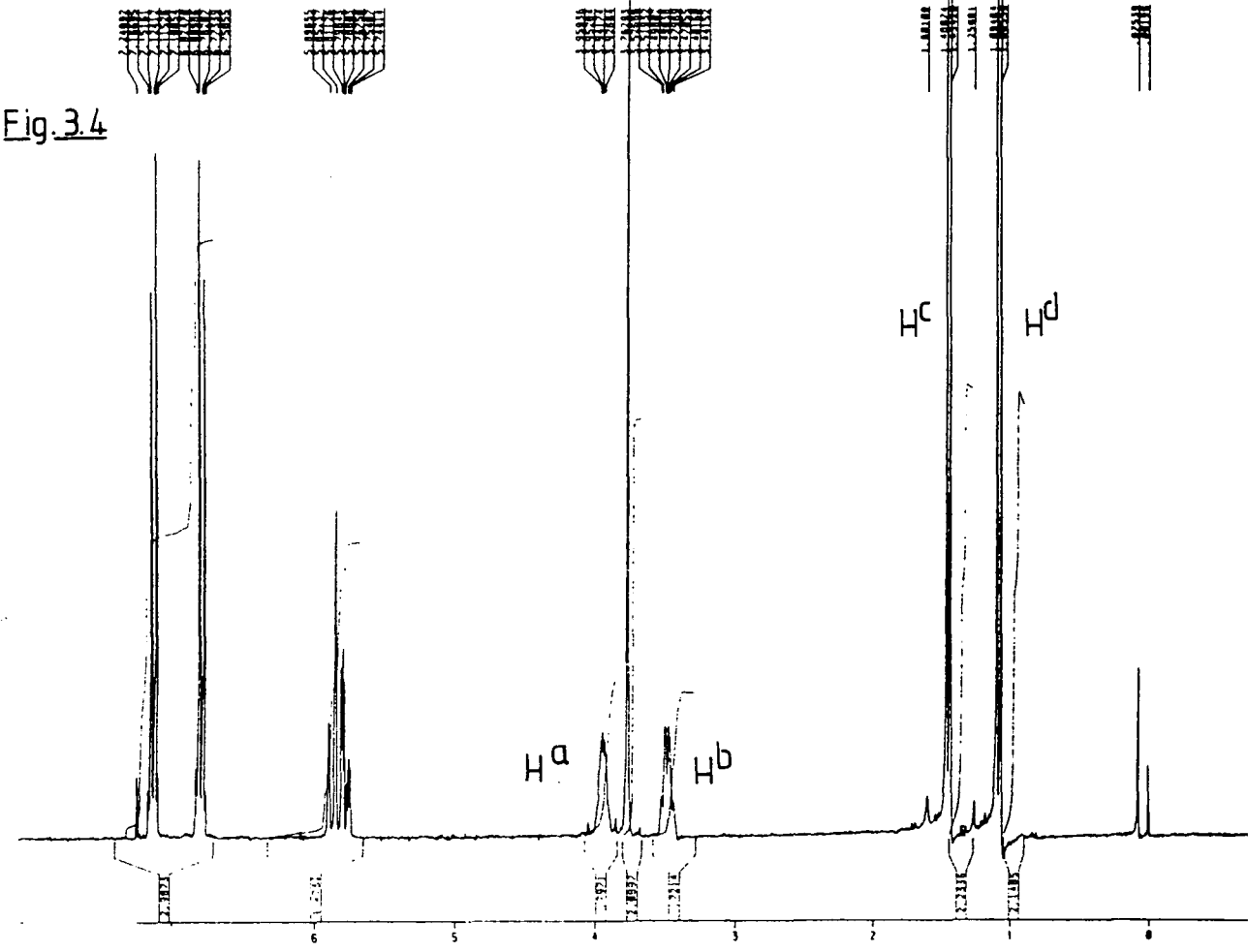
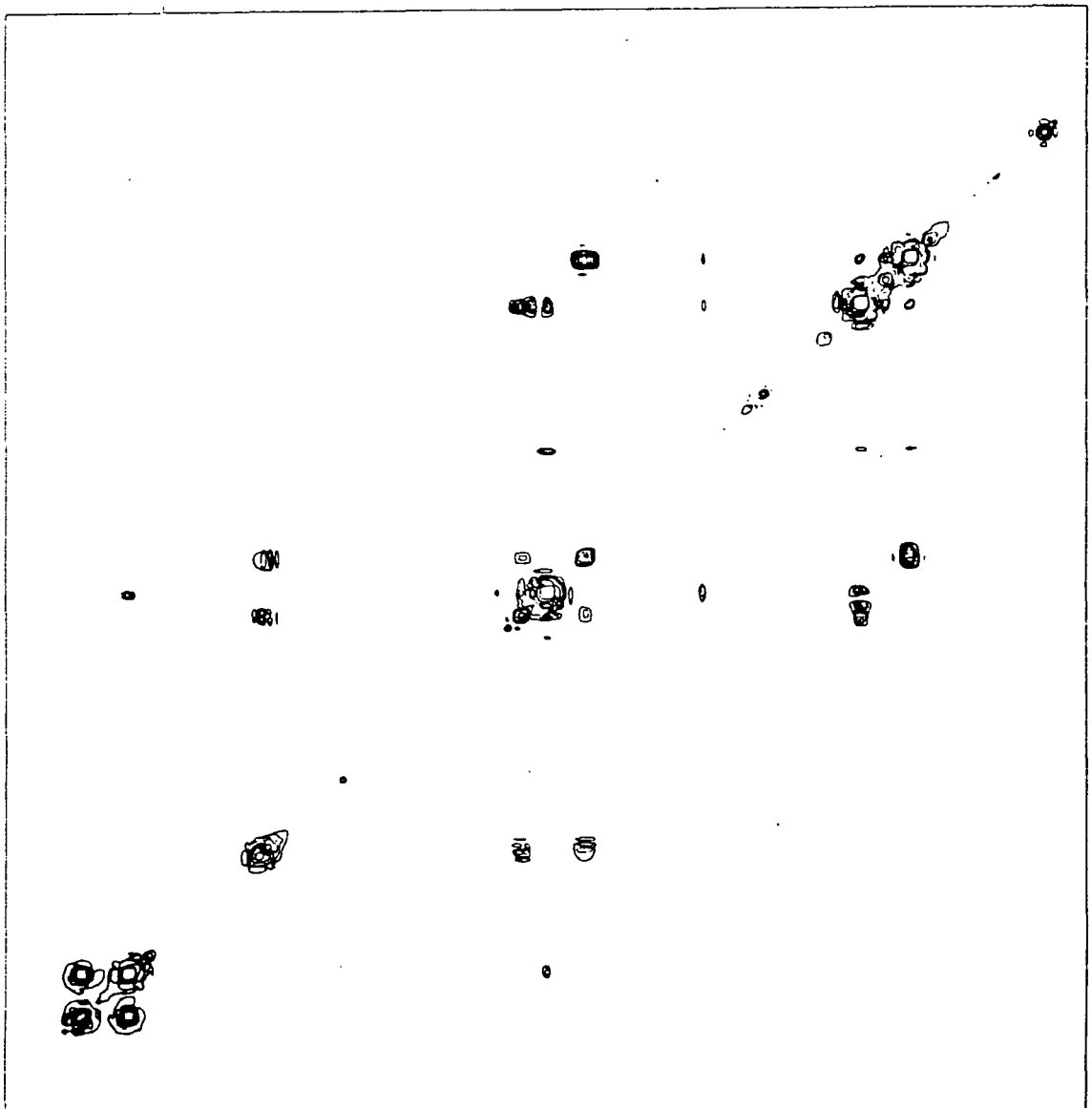


Figure 3.5

We felt that the unexpected results from addition of thionitroso-arenes to (E,Z)-hexadiene could be rationalised in three ways, *ie.* due to isomerisation of (i) starting materials, (ii) intermediates or (iii) products. The last possibility was easily eliminated by heating product mixtures (overnight in refluxing chloroform) when no changes in ^{1}H NMR spectra were observed. For isomerisation to occur in intermediates, (ii), a stepwise (biradical or charge-separated) pathway, with internal rotation of the molecule occurring during reaction, is necessary. This seemed an unlikely explanation as the most probable result of this type of mechanism would be a 1:1 mixture of isomers in all cases (as with SO[117]). Furthermore, two mechanisms would then be required - one for the (E,E) - and one for the (E,Z)-diene: concerted in the former case and stepwise in the latter.

Fig. 3.4





The other possibility, (i), the presence of an impurity of (E,E)-diene in the (E,Z)-diene, seemed most likely. The presence of even a few percent of (E,E)-diene would be sufficient to explain our results, due to the large excess (35 equivs.) of diene used in the reactions (unfortunately cycloaddition did not proceed satisfactorily with smaller excesses).

To decide between mechanisms (i) and (ii), thionitrosoarenes (94a,d) were generated in the presence of a 1:1 mixture of (E,E)- and (E,Z)-2,4-hexadienes (114,115). 1-Methoxy-4-thionitrosobenzene (94a) gave a remarkable result in that only the 'syn' product (111) was observed (>96% d.e.). 1-Bromo-4-thionitrosobenzene gave a mixture of 'syn' and 'anti' products but showed similar selectivity, affording the 'syn' adduct in 80% d.e. These results were particularly informative as the marked preference for reaction with the (E,E)-diene is strongly suggestive of a concerted mechanism. A stepwise mechanism does not require initial transition to the cisoid conformation and is therefore little influenced by steric effects. A similar competition experiment with sulphur monoxide showed only a 1.6:1 increase in reactivity from (E,Z)- to (E,E)-2,4-hexadiene[117]: our results represent a >97:1 increase with the methoxy compound (94a) and a 9:1 increase with the bromo compound (94d). In addition, these results show that a small amount of (E,E)-diene contaminating the (E,Z)-diene would indeed give the observed isomer mixtures, as discussed above.

We are unsure of the origin of the impurity of (E,E)-diene. It may be present in the reagent as purchased, or be generated during the reaction (as with SO[117] and $^1O_2$ [119]). G.C. analysis of the reagent showed the presence of *ca.* 10% (E,E)-hexadiene but this may be due to isomerisation on chromatography. It should be noted, however, that diene isomerisation cannot be induced by the dienophile if a concerted

mechanism is occurring - *ie.* a reversible first stage of a stepwise mechanism is required.

The relationship between electronic nature and product distribution (Table 3.3) has been rationalised, once again, on a reactivity-selectivity basis. The least reactive, electron rich, thionitrosoarenes are more selective, preferring to react with the small amount of (E,E)-diene present, to give significant amounts of 'syn' adducts (111); whereas the reactive, electron deficient, thionitrosoarenes are relatively indiscriminate, giving predominantly 'anti' products (112) as expected statistically.

We have thus established that thionitrosoarenes react with 1,4-substituted dienes with retention of stereochemistry, and probably by a concerted mechanism. Competition experiments have suggested a reactivity-selectivity relationship to the electronic nature of the aryl substituent. The lack of ene products was, at first, surprising, as the dienes (114,115) possess a methyl substituent. However, when possible transition states are compared with those of the close analogue 2,3-dimethylbutadiene, which does give ene adducts, it is clear that with any likely mechanism (concerted or stepwise anionic, cationic or biradical) the transition states with hexadienes are much less stabilised than those with 2,3-dimethylbutadiene. For example, in a concerted process the forming double bond is not conjugated in the (E,E)-hexadiene case, whereas conjugation is retained with 2,3-dimethylbutadiene, and a biradical is not allylically stabilised with a hexadiene as it is with 2,3-dimethylbutadiene (similarly an intermediate anion or cation). These points are illustrated in Figure 3.6.

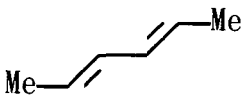
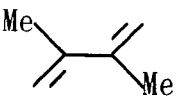
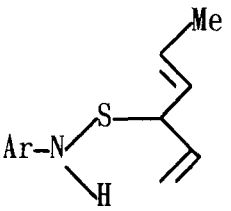
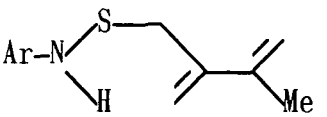
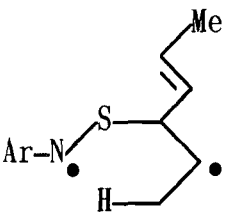
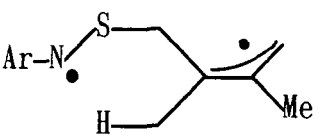
(E,E)-HEXADIENE	2,3-DIMETHYLBUTADIENE
	
Concerted	Concerted
	
Non-conjugated product	Conjugated product
Stepwise Biradical	Stepwise Biradical
	
Non-stabilised intermediate	Allylically stabilised intermediate

Figure 3.6

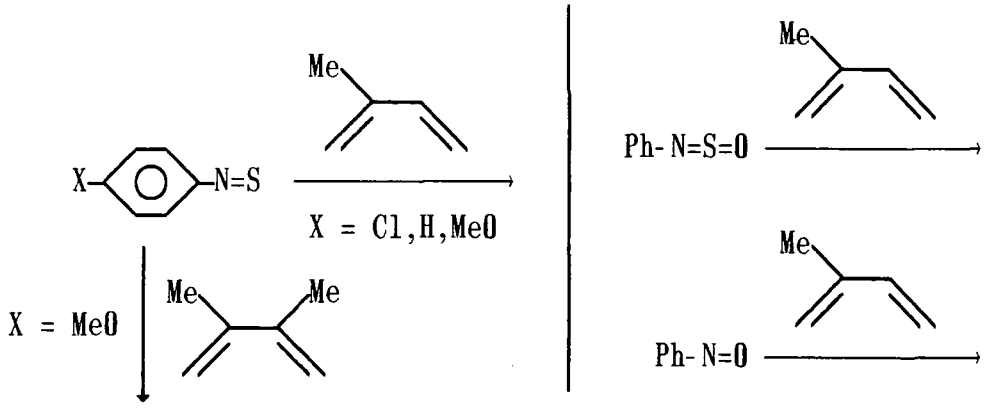
3.6 MNDO CALCULATIONS

3.6.1 Introduction

Molecular orbital calculations have been performed for the dienes and dienophiles shown in Scheme 3.8 using the MNDO (Modified Neglect of Diatomic Differential Overlap) method, as introduced by Dewar and Thiel in 1977[120]. The calculations were carried out by the group of Dr. P. Hanson at the University of York, and the results have been used in a second order perturbation treatment to calculate stabilisation energies, E, for Diels-Alder pericyclic transition states:

(a) where the planes of the reactants are parallel and separated by 2Å;

(b) where the planes of the reactants are 2Å apart at sulphur and 2.5Å apart at nitrogen.



Scheme 3.8

What follows in Section 3.6.2 is a comparison of prediction and experimental observation.

3.6.2 Discussion

Nine points of interest arising from the MNDO calculations are described below.

(1) For both transition state geometries, (a) and (b), the order of reactivities of the dienophiles is according to the magnitude of the stabilisation obtained, *viz.*

$$ClC_6H_4NS > PhNS > MeOC_6H_4NS > PhNSO$$

In every case, except for parallel alignment of PhNSO and isoprene, the regiochemistry predicted agrees with observation.

(2) The total stabilisation energy, E, can be subdivided into the part arising from transfer of electron density from the occupied orbitals of the diene to the unoccupied orbitals of the dienophile and, conversely, the part due to electron transfer from the occupied orbitals of the dienophile to the unoccupied orbitals of the diene. For all the dienophiles studied, the first of these contributions, *viz.* electron transfer to the dienophile, is the greater; *ie.* all the dienophiles are of 'normal electron demand'. However, the percentage, δ, of the stabilisation, E, which arises from net electron transfer from diene to dienophile varies both with the dienophile and with the assumed transition state geometry. This point is illustrated in Table 3.4, with isoprene as the diene.

DIENOPHILE	(94g)		(94c)		(94a)		PhNSO	
REGIOISOMER‡	Major	Minor	Major	Minor	Major	Minor	Major	Minor
Parallel Orientation (C-N = 2Å)	19.8	20.0	16.9	17.0	14.2	14.4	8.4	8.4
Non-Parallel (C-N = 2.5Å)	11.9	12.8	8.1	9.2	4.4	5.4	7.1	8.4

Table 3.4: *δ values for the dienophiles ClC_6H_4NS (94g), PhNS (94c), $MeOC_6H_4NS$ (94a) and PhNSO; ‡Major = 5-methylthiazine (96), Minor = 4-methylthiazine (97).*

For parallel orientation, δ falls across the table, predicting a complementary fall in reactivity - as is observed. For non-parallel orientation, δ falls similarly for Ar-N=S (94) but δ for (94a) is significantly less than for PhNSO, predicting PhNSO to be more reactive towards isoprene than compound (94a). As this is not the case, it appears that parallel orientation is a better model of the actual transition state.

(3) The total stabilisation, E, can also be subdivided into the parts arising from interaction of N and S with the respective C atoms to which they have become bonded and the part arising from cross-interaction. For parallel orientation the C-N and C-S contributions are similar, *ca.* 39%, but for non-parallel orientation (C-N = 2.5Å, C-S = 2.0Å) the greater part arises, as expected, from the C-S interaction (*ca.* 68%) as opposed to the C-N interaction (*ca.* 13%). These proportions are essentially constant across the range of Ar-NS dienophiles.

(4) Combining the findings in (2) and (3), it is clear that as similar non-parallel geometries are predicted to have similar extents of C-S and C-N bonding (the former being five times greater) the values of δ in Table 3.4 are directly comparable. As the value of δ for the 4-chloro derivative (94g) is nearly three times greater than that for the 4-methoxy derivative (94a), and as the energies represented by δ are greater than the difference in E between (94a) and (94g), it seems that the 4-chloro case is predicted to attain significantly more stabilisation in the non-parallel transition state than the 4-methoxy case.

(5) As preference for a non-parallel transition state is indicative of a stepwise mechanism, it seems reasonable to infer that if any thionitrosoarenes (94) were to exhibit a switch of mechanism from concerted to stepwise (which could feasibly occur in a solvent of suitable polarity) it would be the most electron deficient - as exemplified by the 4-chloro derivative (94g). If the observed loss of stereochemistry on addition to (E,Z)-hexadiene had been due to a stepwise mechanism, this treatment would have predicted lowest diastereomeric excesses with electron deficient thionitrosoarenes (*eg.* 94g), the opposite to our observations.

(6) Calculations for 1-methoxy-4-thionitrosobenzene (94a) and dimethylbutadiene give stabilisations for the two geometries considered which are less than with isoprene, but this may be an artefact of considering only the true π-orbitals and not those with weak π character which arise by virtue of the methyl substituents. The value of δ is the same for the two dienes in parallel orientations, but δ for dimethylbutadiene in non-parallel orientation is slightly greater than with isoprene (4.6 *vs.* 4.4%). This treatment does not appear to predict any marked preference for Diels-Alder addition between the dienes - the reason for the higher proportions of ene adduct with dimethylbutadiene must lie elsewhere. Unfortunately, the 'ene' transition state proved troublesome in attempted modelling.

(7) We have considered the possibility of either a pericyclic or stepwise path to ene-product. Fukui *et al.* reasoned that no ene reactions should be considered as simply pericyclic, despite the orbital phases matching[121]. This is because the coefficient of the

hydrogen s-orbital is so small that no effective overlap is possible, a situation exacerbated in Ar-N=S systems as the coefficient on nitrogen (which becomes bonded to the hydrogen in question) is also very small (Figure 3.7).

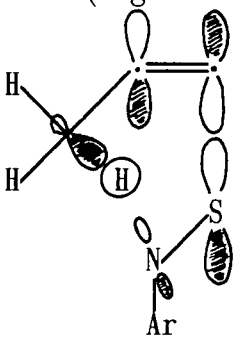
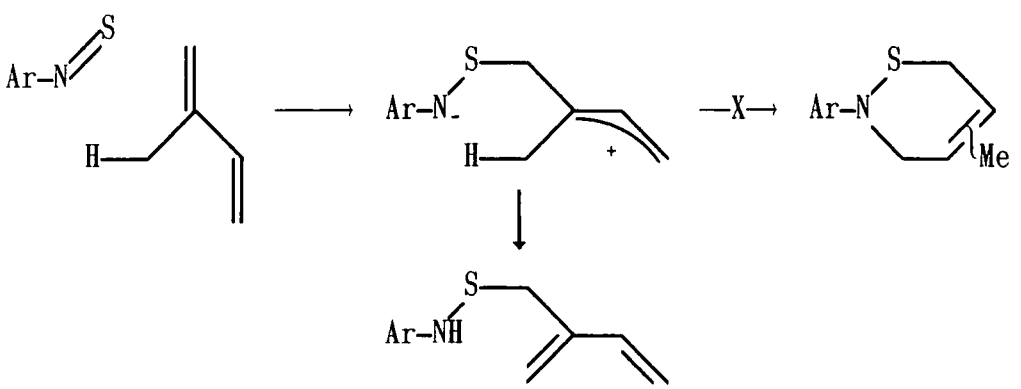


Figure 3.7: *Pericyclic "ene" transition state showing good C-S overlap and poor N-H overlap.*

Fukui suggests that ene reactions, in general, go *via* transfer of electron density from the HOMO of one partner to the LUMO of the other and thence to the LUMO of the σ bond to hydrogen. This gives a dipolar character to the concerted ene transition state which, in the extreme, could be represented by a charge separated intermediate (Scheme 3.9), identical for that during an electrophilic Diels-Alder mechanism.

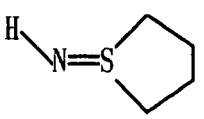


Scheme 3.9

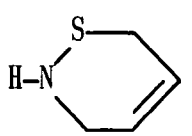
As we have shown that addition to 2,4-hexadienes is probably concerted, and it is therefore likely that all Diels-Alder additions of Ar-NS are concerted (*ie.* the reactions do not appear

to proceed *via* an electrophilic mechanism), it seems unlikely that formation of the dipole (117) is a feasible route to ene adduct when it does not lead to Diels-Alder adduct. Furthermore, we have seen that ene reaction also proceeds readily with non-conjugated alkenes which cannot form allylically stabilised cationic intermediates. A concerted ene mechanism, as postulated by Fukui[121] therefore seems most reasonable.

(8) It was noted that there were certain resemblances between the frontier and immediately adjacent orbitals of Ph-NS and SO_2. Both have a σ-HOMO and both have a highest occupied π-orbital which has a large coefficient on one atom and a near zero coefficient on the other (*NB.* in SO_2 it is sulphur which has the zero coefficient whereas in Ph-NS it is nitrogen - so the parallel is not perfect). Furthermore, both have subjacent occupied π-orbitals and a lowest unoccupied π-orbital with insubstantial coefficients. It seemed feasible, therefore, to consider a chelotropic reaction pathway (see Section 5.2.4) with initial reaction at the sulphur centre, followed by rearrangement. Calculations on model cycloadducts (118) and (119) showed that this pathway was possible as the postulated 5-membered intermediate (118) is predicted to be considerably less thermodynamically stable than thiazine (119) (+ 82.8 and + 17.8 kcal mol^{-1}, respectively). Work described in Section 5.2.4, however, discounted this possibility.



(118)



(119)

(9) If Ph-N=O is substituted for Ph-N=S in the above treatment [points (2)-(5) above], the predicted regioselectivity is entirely wrong. It seems likely, and indeed reasonable, that the explanation for this anomaly is simply that Ph-N=O needs to approach the diene (a) more closely and (b) with the opposite non-parallel alignment (Figure 3.8).

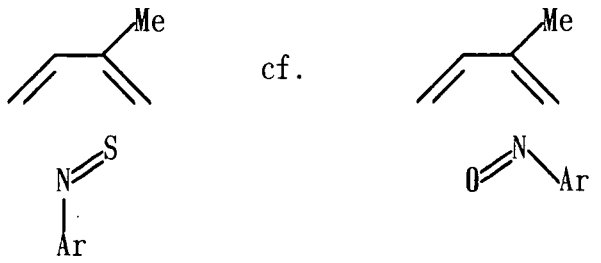


Figure 3.8

In conclusion, we have shown that thionitrosoarenes cycloadd to a wide variety of substituted dienes with retention of stereochemistry and some regioselectivity. We consider a concerted mechanism of cycloaddition to be most likely.

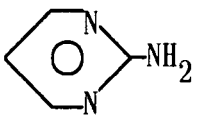
CHAPTER FOUR

SYNTHETIC METHODOLOGY TO ELECTRON DEFICIENT THIONITROSO COMPOUNDS

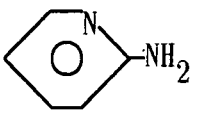
4.1 THIONITROSOPYRIDINES

4.1.1 Introduction

Thionitroso compounds bearing heterocyclic substituents had not, to our knowledge, been reported prior to this thesis. We felt that our synthetic strategy should be readily adaptable to this area, especially to derivatives of heteroaromatic amines. The N-sulphinyl derivatives of various amino pyridines were discussed in Chapter 1, the most notable points being the high reactivity of these compounds and the tendency for them to behave as 4π heterodienes[27], in contrast to the conventional dienophilic nature of N-sulphinylamines. We therefore investigated synthetic routes to a series of thionitrosopyridines with the nitrogen atom in each of the 2-, 3- and 4-positions of the ring.



(120)



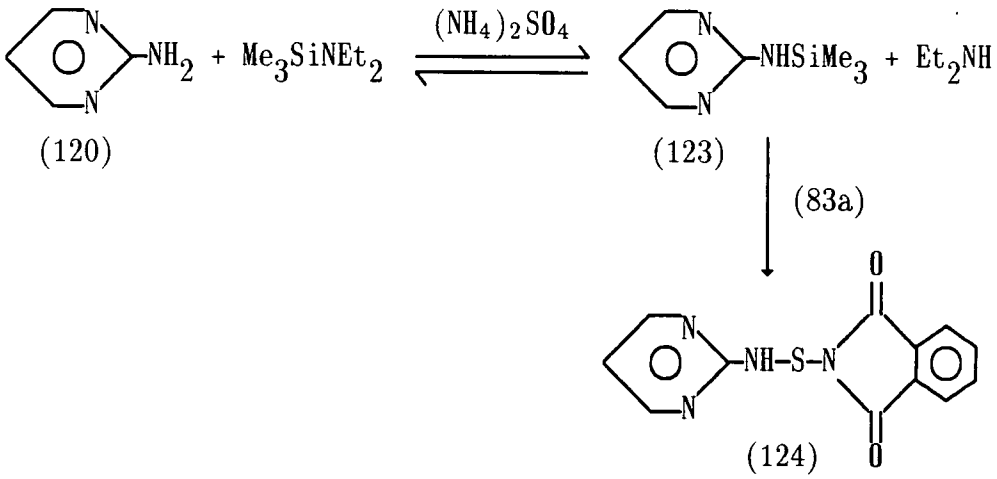
(121)

For the first of these cases we used the 2-aminopyrimidine (120), rather than the 2-aminopyridine (121), derivative. The precedent from the R-NSO analogues suggested the possibility of some interesting reactivity with all these derivatives.

4.1.2 2-Aminopyrimidine Derivatives

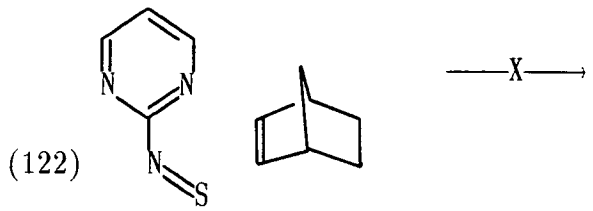
The application of our usual methodology to generation of 2-thionitrosopyrimidine (122) met with an immediate problem. Synthesis of 1,1,1-trimethyl-2-(2-pyrimidyl)silazane (123) could not be achieved using chlorotrimethylsilane, as in Section 2.1. Instead we adopted a

literature preparation of compound (123) utilising the ammonium sulphate catalysed equilibrium of 2-aminopyrimidine (120) and trimethylsilyl-diethylamine (TMSDEA)[122] (Scheme 4.1). The diethylamine byproduct is removed from the equilibrium by distillation.



Scheme 4.1

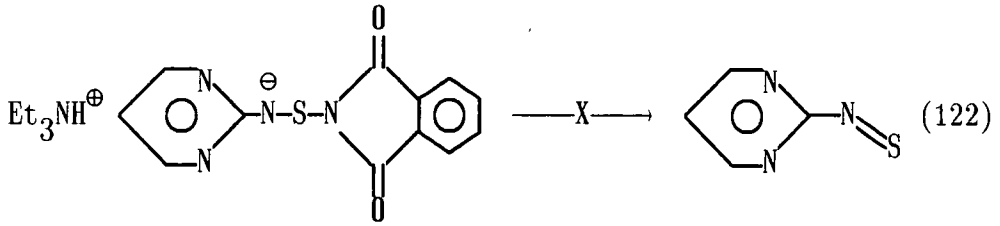
Reaction of the silylamine (123) with phthalimide sulphenyl chloride (83a) proceeded smoothly to give pure product (124), in good yield. Unfortunately, attempts to generate 2-thionitrosopyrimidine (122) from this precursor under the usual conditions were largely unsuccessful. Only trace amounts of thiazines (<5%) could be detected by ^{1}H NMR in reaction mixtures containing butadiene or isoprene. More electron rich dienes (*eg.* 2,3-dimethoxy-1,3-butadiene) which might have been expected to be reactive towards electron deficient thionitroso compounds gave no observable thiazine products. As the N-sulphinyl-aminopyrimidine analogue was known to undergo cycloadditions as a 4π component with reactive alkenes[27], we attempted to mimic this process using our thionitroso analogue and norbornene, again with no success (Scheme 4.2).



(122)

Scheme 4.2

The reason for the failure of precursor (124) as a source of thionitrosopyrimidine is unclear. It is possible that the highly stabilised anion formed initially is reluctant to eliminate phthalimide to give a thionitrosoarene which would be so highly reactive (due to the electron demanding substituent) (Scheme 4.3).

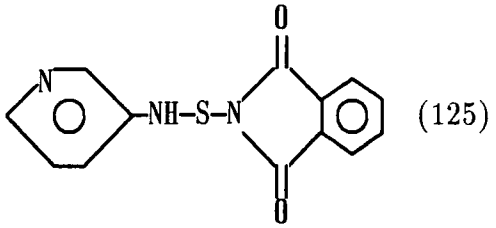


(122)

Scheme 4.3

4.1.3 3-Aminopyridine Derivatives

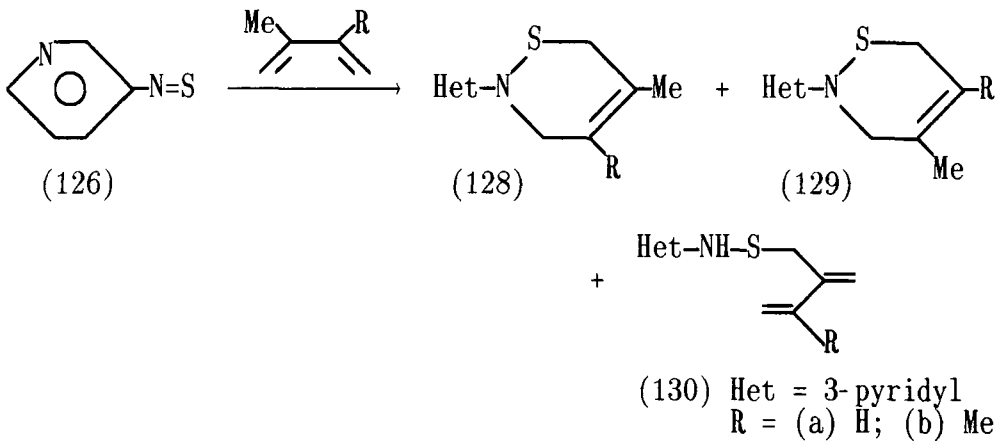
3-Aminopyridine , which has no conjugation from the electron demanding ring nitrogen to the amino group, is thus a more basic amine than the 2- or 4-substituted analogues. This fact allowed us to synthesise precursor (125) by the usual method (Section 2.1), *ie.* using chlorotrimethylsilane as the silylating agent.



(125)

In contrast to the 2-aminopyrimidine analogue (Section 4.1.2), compound (125) proved to be a good source of the first known thio-

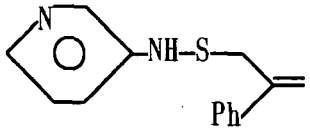
nitrosoheteroarene, *viz.* 3-thionitrosopyridine (126), which was successfully trapped with a number of dienes in the usual manner. As well as the simple butadiene adduct (127), we were successful in trapping intermediate (126) with isoprene and dimethylbutadiene, to afford product mixtures (128-130a) and (129-130b) respectively (Scheme 4.4).



Scheme 4.4: *NB. Compounds (128b) and (129b) are equivalent.*

Interestingly the isomer ratios from these reactions were very similar to those found with 1-bromo-4-thionitrosobenzene (94d). 1,4-Diphenylbutadiene also gave an adduct with (126), but this could only be obtained in low yield (*ca.* 15%) and not completely pure.

The first ene reaction of a thionitrosoheteroarene was also performed, using α-methylstyrene as trap and affording the unstable adduct (131) in 45% yield.



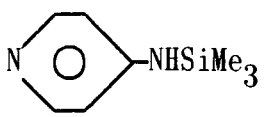
(131)

It appears that 3-thionitrosopyridine (126) behaves in all respects (synthetically and in reactions) as an electron deficient thionitrosoarene such as 1-bromo-4-thionitrosobenzene (94d). This is in good agreement with the N-sulphinylaminopyridine series, where the 3-amino-

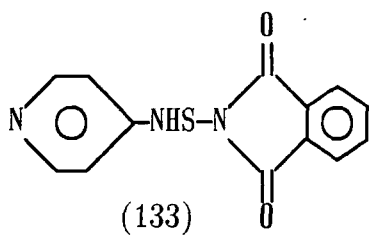
pyridine derivative is the only member which can easily be isolated and handled in the manner of its simple aryl analogues[27].

4.1.4 4-Aminopyridine Derivatives

As expected, this very weakly basic amine required an alternative to chlorotrimethylsilane as silylating agent. Hence 1,1,1-trimethyl-2-(4-pyridyl)silazane (132) was prepared both by a literature route employing hexamethyldisilazane (HMDS)[123] and, in a much more satisfactory manner, by adaptation of the route used for silylation of 2-aminopyrimidine (Section 4.1.2). The second step in the synthesis, *viz.* reaction with sulphenyl chloride (83a), failed, however, to yield the desired product (133). The resulting mixture appeared to consist of a multitude of other pyridine- and phthalimide- containing products, which remain uncharacterised.



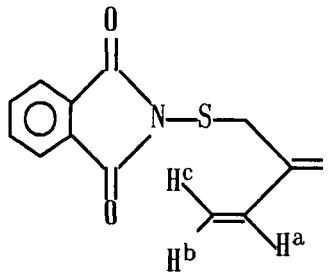
(132)



(133)

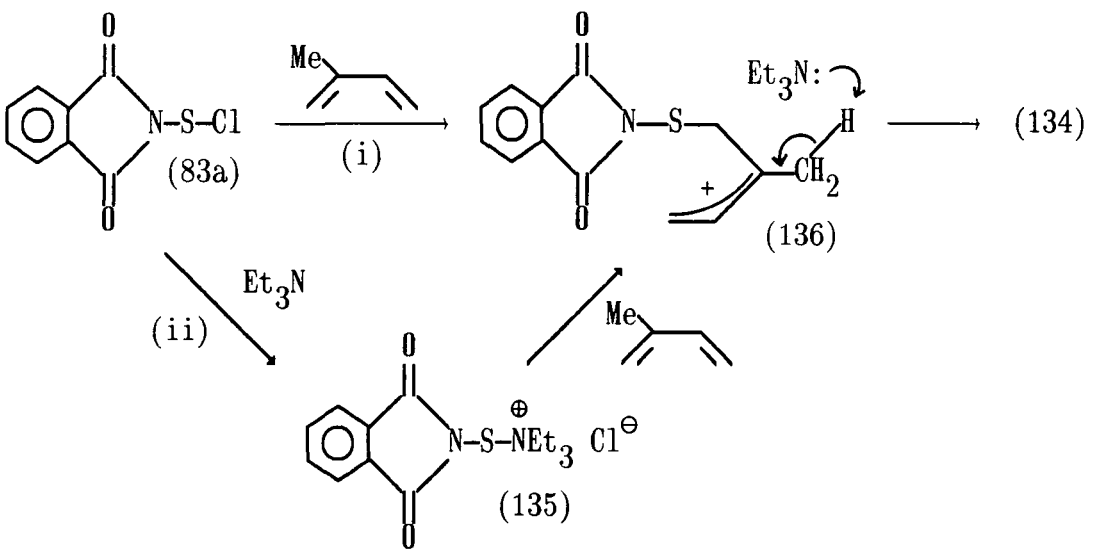
We were concerned that the precursor (133) may have been formed, but that the basic ring nitrogen of any of the pyridine species present would be likely to cause deprotonation *in situ*. The only way to avoid this problem appeared to be to attempt, rather optimistically, to carry out the synthesis in the presence of both triethylamine and a diene, in the hope that the reaction sequence from silylamine to thiazine might proceed in one pot. When this procedure was used, with isoprene as trap, no thiazines or ene adducts were observed. We did, however, find an unexpected diene containing product (15% yield) which, after careful

analysis (IR, ^{1}H NMR, ^{13}C NMR and mass spectra) was assigned structure (134). This compound is a shelf-stable, white, crystalline solid. As there is no aminopyridine residue in product (134) we carried out the reaction with no silylamine (132) present when compound (134) was not formed (TLC).



(134)

The mechanism shown in Scheme 4.5, [path (i)], is a possible explanation for the observed course of reaction. However, Kirby's group only observed addition of their, more reactive, alkyl sulphenyl chlorides to dienes in certain cases (not isoprene) under similar conditions[62]. We feel that the less reactive phthalimide sulphenyl chloride (83a) is unlikely to add directly to isoprene.



Scheme 4.5

We have, therefore, postulated the mechanism shown as path (ii) in Scheme 4.5. This would proceed with initial nucleophilic displacement

of the chloride of (83a) by triethylamine followed by electrophilic attack of the ionic intermediate (135) on isoprene - the sulphur centre being a much more powerful electrophile in compound (135) than in the sulphenyl chloride (83a). Elimination of a proton from the more highly stabilised allyl cation (136)[1] would lead to the observed product (134). This rationalisation is reinforced by the observation of a colour change (from yellow to orange) when triethylamine is added to a chloroform solution containing only phthalimide sulphenyl chloride (83a). Attempts to isolate the postulated intermediate (135) failed. The function of the silylaminopyridine may be simply as a base for the final deprotonation or, more subtly, as a scavenger of the chloride produced, *via* formation of chlorotrimethylsilane.

4.2 ACYLTHIONITROSO COMPOUNDS

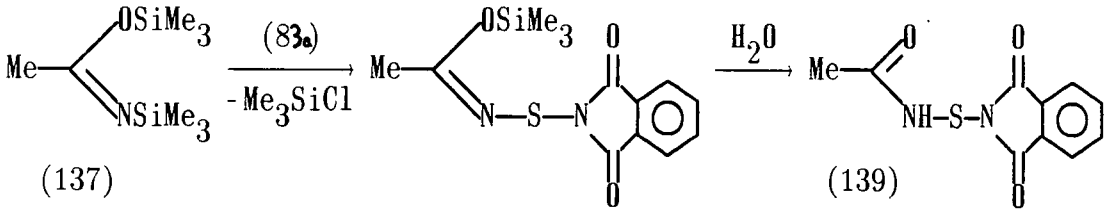
4.2.1 Introduction and Methodology

As Meth-Cohn's group had previously investigated the chemistry of thionitroso-formates and -sulphonates[57], we decided to attempt to extend our methodology to a different class of highly electron deficient thionitroso compounds, *viz.* acylthionitroso compounds. The ready availability of bis(trimethylsilyl)acetamide (BTMSA) (137) made thionitrosocarbonylmethane (138) an attractive target.

We proposed to react BTMSA with one equivalent of phthalimide sulphenyl chloride (83a). Reaction with the N-silyl, as opposed to O-silyl, group should be favoured due to the greater strength of the

[1]Attack at the 4-position, rather than the 1-position, of isoprene would result in the methyl group being on the central, as opposed to the terminal, carbon atom of the allyl cation. An electron donating substituent in this position provides virtually no stabilisation as the LUMO has a zero coefficient on the central carbon atom.

Si-O bond as compared with the Si-N bond[124]. Simple hydrolysis of the remaining silyl group was expected to yield the desired precursor (139) (Scheme 4.6).

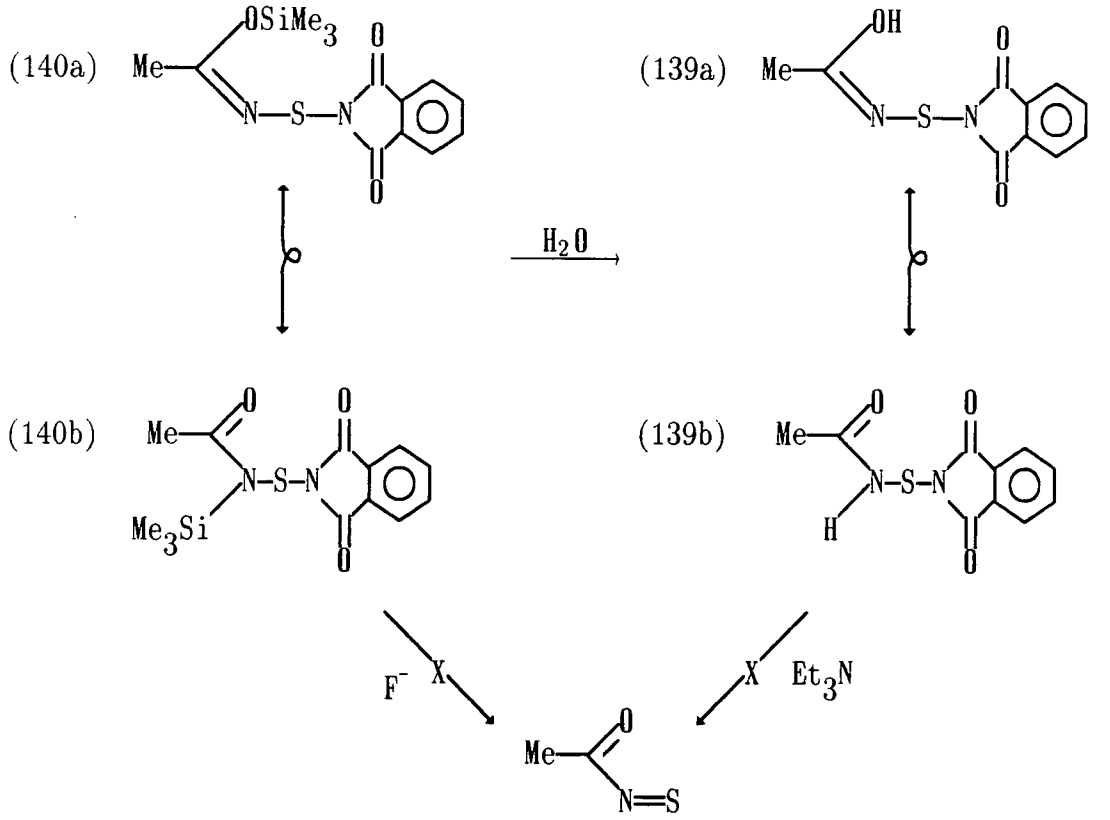


Scheme 4.6

4.2.2 Attempted Synthesis of Thionitrosocarbonylmethane

Reaction of BTMSA (137) and one equivalent of sulphenyl chloride (83a) resulted in an interesting mixture of two tautomeric monosilylated compounds (140a,b). The ^{1}H NMR spectrum showed two methyl singlets at δ_H ($CDCl_3$) 1.9 and 2.6 ppm. The higher-field resonance was close to that observed for BTMSA (137) whereas the lower-field resonance was similar to that seen for acetamide. These resonances were therefore assigned to the O-silylated (140a) and N-silylated (140b) forms, respectively. The two tautomers appeared to exist in approximately a 1:1 ratio (by ^{1}H NMR integration).

This mixture was easily converted to the desired sulphenamide (139) by hydrolysis in wet chloroform (Scheme 4.7). Precursor (139) also showed signs of tautomerism in the ^{1}H NMR spectrum. Unlike their silylated analogues, tautomers (139a,b) seemed to be exchanging in deuterochloroform solution at room temperature. The ^{1}H NMR spectrum showed two very broad singlets for the NH/OH proton and methyl group [δ_H ($CDCl_3$) 7.4 and 2.5 ppm, respectively]. This is clearly a reflection of the greater mobility of the proton as compared with the bulky trimethylsilyl group.



(138)

Scheme 4.7

Unfortunately, all attempts to generate the acylthionitroso compound (138) from precursor (139) with triethylamine were unsuccessful. Furthermore, attempted fluoride ion induced elimination of the silyl and phthalimide groups from the silylated precursor (140), using tetramethylammonium fluoride, also failed (Scheme 4.7). The explanation for this failure is, perhaps, similar to that proposed in Section 4.1.2 for the 2-aminopyrimidine derivatives, ie. that the anion formed initially is far too stable to allow subsequent formation of such a highly reactive thionitroso compound.

It seems that the methodology used for simple thionitrosoarenes is not generally applicable to electron deficient analogues. We have, however, succeeded in generating the first known thionitrosoheteroarene, *viz.* 3-thionitrosopyridine.

CHAPTER FIVE

OTHER APPROACHES TO THIONITROSOARENES

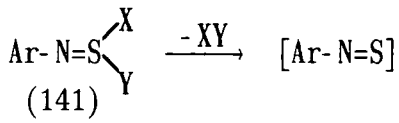
5.1 INTRODUCTION

The work presented in Chapters 2 - 4 of this thesis concerns thionitroso compounds generated *via* 1,2-eliminations - Class (2) of the various methodologies discussed in Chapter 1. Although Class (1) approaches, *viz.* 1,1-eliminations, have proved successful with many other types of thionitroso compounds, they have not previously been used as a route to thionitrosoarenes (94). Our work on this area is presented in Section 5.2. Class (3) syntheses have been most generally used, previously, to generate thionitrosoarenes and are not developed further here. Class (4) reactions, *viz.* Staudinger Chalcogenations, have, conversely, never been used in synthesis of any thionitroso compounds. This approach is considered very briefly in Section 5.3.

5.2 1,1-ELIMINATION ROUTES TO THIONITROSOARENES

5.2.1 Introduction

Thionitrosoarenes (94) should, in principle, be available by reductive 1,1-eliminations from precursors (141) (Scheme 5.1).



Scheme 5.1

We decided to investigate the cases where XY represents =O (Section 5.2.2), Cl_2 (Section 5.2.3) and $-CH_2-CH=CH-CH_2-$ (Section 5.2.4), below.

5.2.2 1,1-Elimination from N-Sulphinylamines

Reductive elimination of oxygen from N-sulphinylamines was used by Middleton to prepare two thionitrosamines (28a,b)[37]. It was mentioned earlier, however, that over-reduction to the parent hydrazine was a significant problem (Scheme 5.2). This reaction is clearly even less likely to stop at the desired thionitroso compound if it is a reactive intermediate and we were, therefore, rather pessimistic about this approach to thionitrosoarenes.

$$R_2N\text{-}NSO \xrightarrow{LiAlH_4} \underset{(28)}{R_2N\text{-}N{=}S} \xrightarrow{LiAlH_4} R_2N\text{-}NH_2$$

Scheme 5.2

Phosphines, R_3P, were chosen as the deoxygenation reagents. The reaction of N-sulphinylaniline with boiling triethylphosphite, $(EtO)_3P$, has been known for some years and results in a mixture of phosphates (Scheme 5.3)[125]. These conditions (*ie.* boiling triethylphosphite) were clearly too vigorous for our purposes, making the highly nucleophilic tris(dialkylamino)phosphines, $(R_2N)_3P$, the reagents of choice.

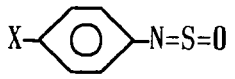
$$Ph\text{-}NSO + 3\ P(OEt)_3 \longrightarrow PhN{=}P(OEt)_3 + OP(OEt)_3 + SP(OEt)_3$$

Scheme 5.3

Hence N-sulphinylaniline (142a) and N-sulphinylanisidine (142b) were mixed with hexamethylphosphoroustriamide (HMPT) (143) and dimethylbutadiene in various solvents and at various temperatures (20 - 80°C)[1]. Excluding the reaction of N-sulphinylaniline (142a) in acetone (see below) no noticeable reaction occurred (TLC) and incorporation of the

[1] N-sulphinylanilines will not cycloadd to dimethylbutadiene under these conditions (ref. 18).

diene was not observed (^{1}H NMR) in any of these reactions.

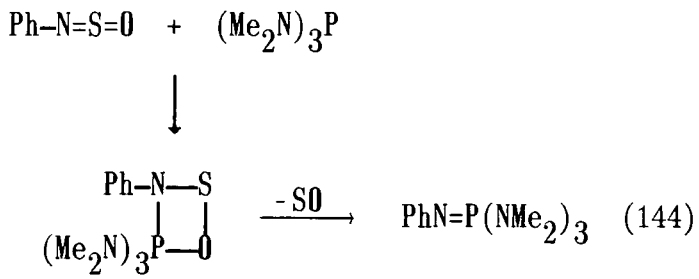


(142) X = (a) H
(b) MeO

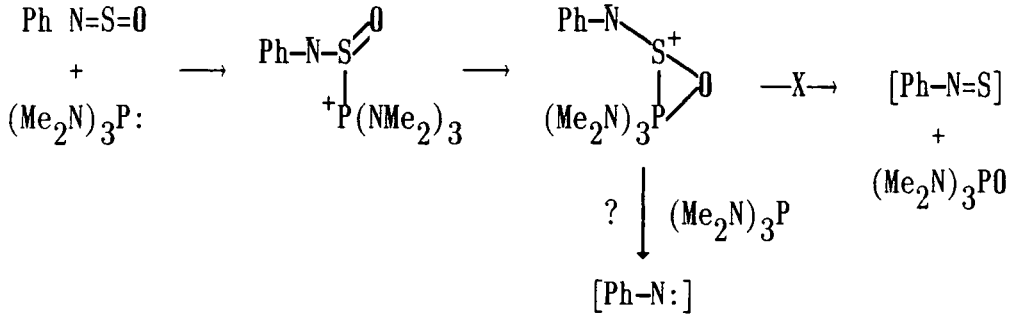
$(Me_2N)_3P$

(143)

The reaction of compound (142a) and HMPT (143) in acetone gave a different result. The major non-phosphine product was aniline (IR, ^{1}H NMR, *ca.* 70%) but it is not clear how this product could arise. The two likely mechanisms are shown in Scheme 5.4.



Mechanism (i)



Mechanism (ii)

Scheme 5.4

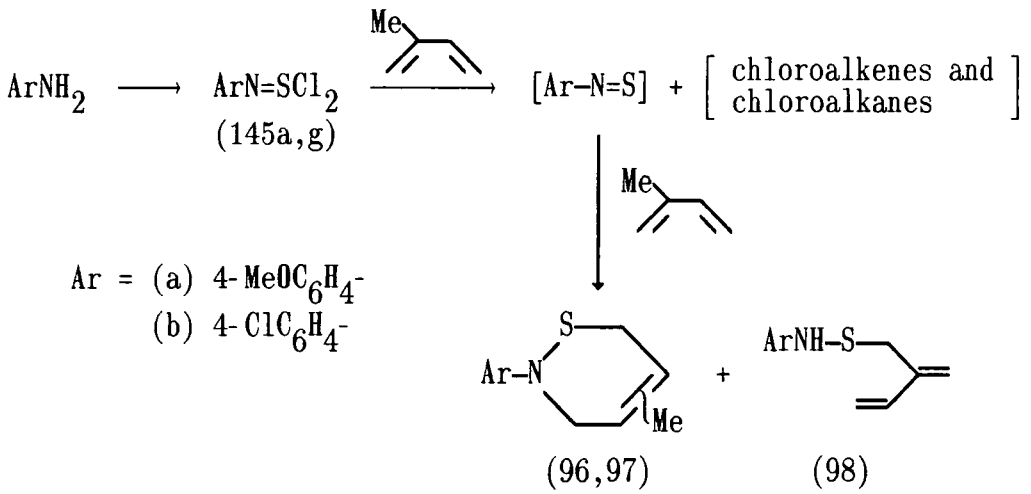
Mechanism (i), *viz.* nucleophilic attack with subsequent SO elimination[126], would lead not to aniline but to a phosphinimine (144). Mechanism (ii), *viz.* nucleophilic attack at sulphur, would be the necessary pathway to a thionitrosoarene. It is perhaps feasible, however, that this could lead to a nitrene intermediate, which would

inevitably result in aniline formation.

It was apparent from these initial studies that this route gave either no reaction or, as anticipated, over-reduction, and we therefore abandoned N-sulphinylarylamines as thionitrosoarene precursors.

5.2.3 1,1-Elimination from N-Arylimidosulphurous Chlorides

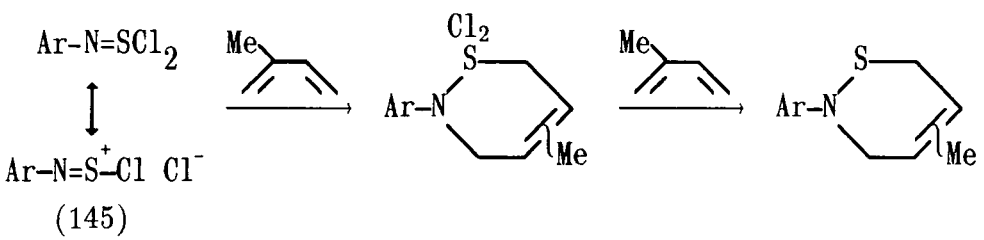
To our knowledge the title compounds, Ar-N=SCl_2 (145), have not previously been considered as thionitroso precursors. We felt, however, that due to the instability of compounds (145)[127] relative to their N-sulphinylaniline analogues, the XY elimination should proceed with much greater ease than the deoxygenation of compounds (142) and under conditions which would not remove the sulphur atom. We were further attracted to the potential precursors (145) as it became evident that dienes could be employed both as traps for the transient thionitrosoarenes and as the dechlorinating agent needed to generate them. Isoprene was chosen as diene to allow comparisons of regio- and ene selectivities with those discussed in Chapter 3. Our proposed methodology is outlined in Scheme 5.5.



Scheme 5.5

The imidosulphurous chloride derivatives of 4-chloro- and 4-methoxy- aniline were prepared as unstable waxy substances by chlorinolysis of a chloroform solution of the appropriate aniline and sulphur dichloride. Addition of isoprene to compounds (145) dissolved in acetone resulted in slow fading of the deep orange colour to give a clear, almost colourless solution. After workup, the products were analysed by their ^{1}H NMR spectra.

The regioselectivity of addition appeared to be essentially identical to that found with thionitrosoarenes generated from phthalimide precursors (Section 3.2), *ie.* the 5-substituted thiazine predominated over the 4-substituted isomer in a 3:1 ratio approximately. The proportion of ene adduct in the products from the 4-methoxy derivative (94a) was, as in Section 3.2, very small. We had, however, expected the products from the 4-chloro derivative (94g) to contain largely ene adduct due to the electron withdrawing substituent. In fact, although there was more ene adduct from this derivative (94g) than from the former (94a) (as expected), the Diels-Alder adducts predominated in a 2:1 ratio. This anomaly may be due to competing initial cycloaddition to the imidosulphurous chloride precursor (145g), followed by dechlorination of the cycloadduct as the second step, thus leading to a larger than predicted proportion of thiazines in the product (Scheme 5.6).



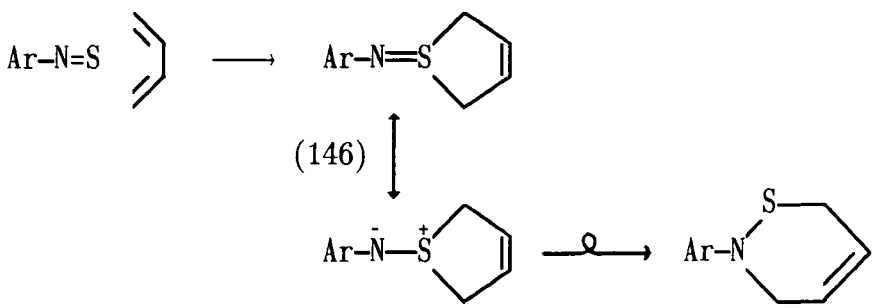
Scheme 5.6

Complications may arise from the possibility of a large ionic contribution to compounds (145) (Scheme 5.6). The ionic form will clearly be much more likely to exist with the electron donating methoxyphenyl substituent, making direct comparison with the chlorophenyl analogue (145g) dangerous.

This route to thionitrosoarenes (94), and the resulting adducts, appears to be exceptionally clean - all byproducts are volatile chloroalkenes and -alkanes, but the difficulties involved in synthesis and handling of the very hydrolytically sensitive imidosulphurous chloride precursors (145), present, unfortunately, a major drawback to this methodology.

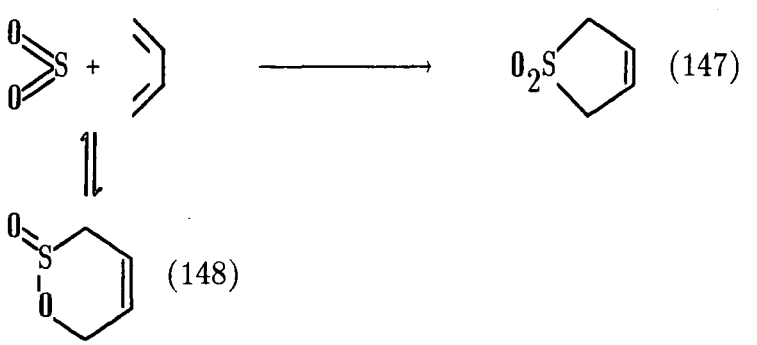
5.2.4 1,1-Elimination from 2,5-Dihydrothiophene S,N-ylides

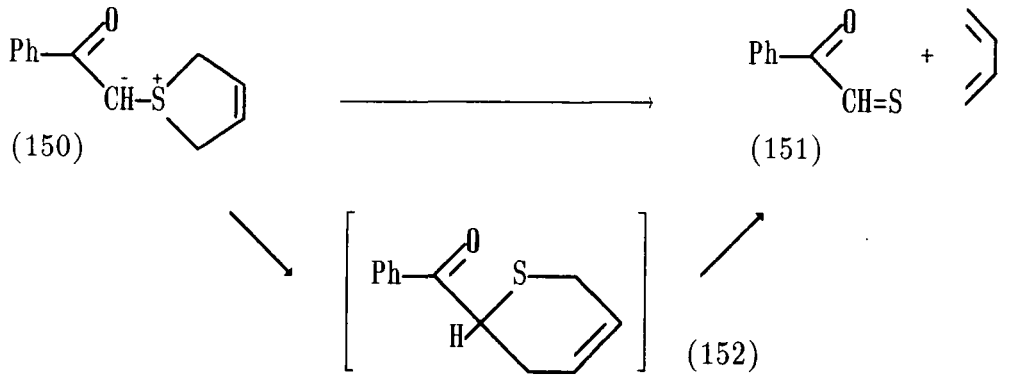
1,1-Elimination of butadiene from the 2,5-dihydrothiophene S,N-ylides (146), was of interest for a number of reasons. The MNDO calculations described in Section 3.6 suggested the possibility of a chelotropic reaction pathway to 1,2-thiazines, involving a five-membered intermediate which is, in fact, ylide (146). If this mechanism (Scheme 5.7) does occur, then an independent synthesis of the S,N-ylide (146) should also lead to spontaneous rearrangement to the thiazine at room temperature.



Scheme 5.7

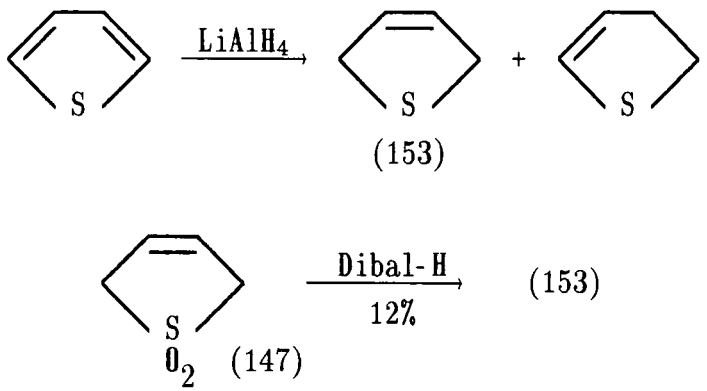
This predicted course of reaction had precedent in analogous systems. The reaction of butadiene with SO_2 to give butadiene sulphone [2,5-dihydrothiophene 1,1-dioxide (147)] is well known. Adduct (147) is, however, the 'thermodynamic' product, the initial 'kinetic' product being the six-membered Diels-Alder adduct (148) which very readily undergoes retro-Diels-Alder reaction[128]. MNDO calculations for dihydrothiophene S,N-ylides predicted the reverse situation, *ie.* the thiazine is likely to be the more thermodynamically stable product (Section 3.6). The addition of sulphur monoxide, SO, to dienes has been discussed previously (Section 3.5). Once again the products are dihydrothiophene derivatives, *viz.* 1-oxides (149)[117], although these reactions proceed *via* a stepwise biradical pathway, so again the parallel is not perfect. The 2,5-dihydrothiophene S,C-ylide (150) is thought to fragment thermally to give butadiene and a thioaldehyde (151), possibly *via* the thiopyran (152)[129]. This mechanism has not, however, been fully investigated. The reactions of the above thionitroso analogues are summarised in Scheme 5.8.





Scheme 5.8

It was, therefore, of great interest to attempt the synthesis of the unknown S,N analogues (146) of these compounds. 2,5-Dihydrothiophene (153) can be prepared by lithium aluminium hydride reduction of thiophene[130], but this procedure involves a difficult distillation to separate the desired product (153) from its isomer (Scheme 5.9). We consequently adopted the low yielding, but clean and repeatable, synthesis devised by Gardner *et al.*[131], utilising Dibal-H reduction of butadiene sulphone (147) (Scheme 5.9).

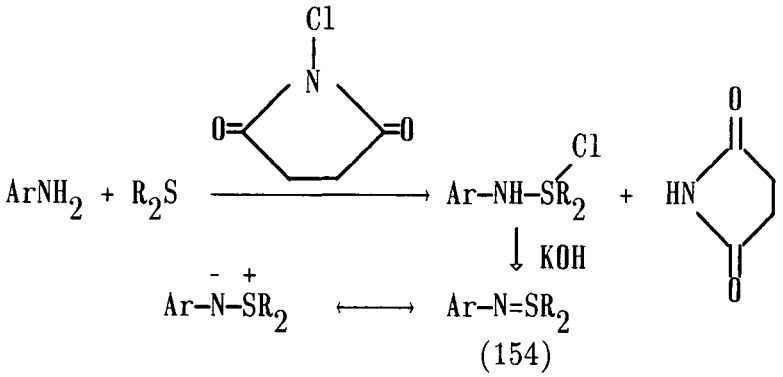


Scheme 5.9

The procedure used by Claus *et al.*[132] to prepare arylsulphilimines (154) of various sulphides (Scheme 5.10) appeared suitable for the synthesis of compounds (146), although we proposed to use a tertiary amine base (DBU[2]) in place of potassium hydroxide to avoid deprotonating

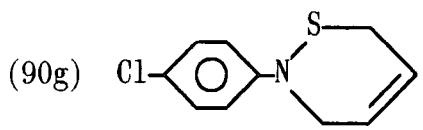
[2]DBU ≡ 1,8-Diazabicyclo-[5.4.0]-undec-7-ene.

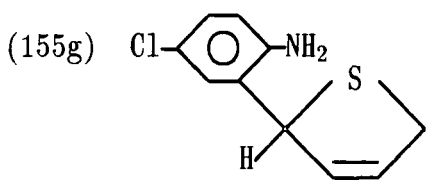
the acidic allylic sites of the dihydrothiophene ring.



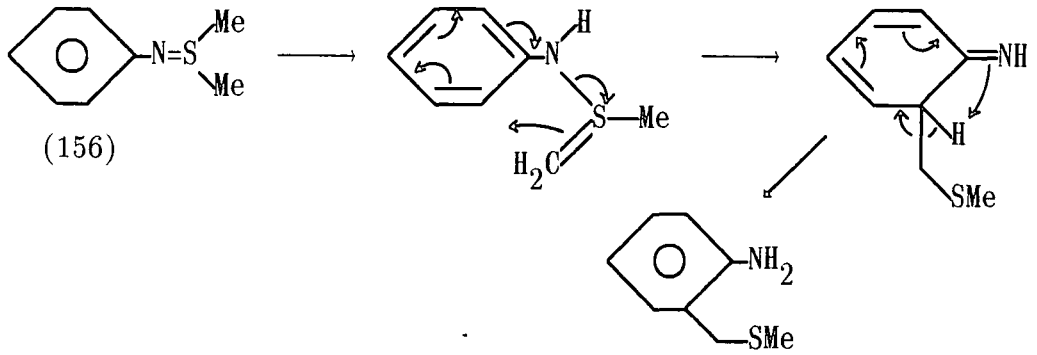
Scheme 5.10

The first arylamine we reacted with dihydrothiophene was 4-chloroaniline. Reaction proceeded as expected to give a yellow solid in 45% yield. On standing for a few hours, however, this product transformed quantitatively into a white crystalline solid. The IR spectrum of the white solid showed a primary amine functionality and the ^{1}H NMR spectrum indicated the loss of one of the aromatic protons. We suspected, therefore, that rearrangement of the initial sulphilimine (146g) had occurred. It was evident that no 1,2-thiazine (90g) was present and all the analytical data indicated structure (155g) as being correct.

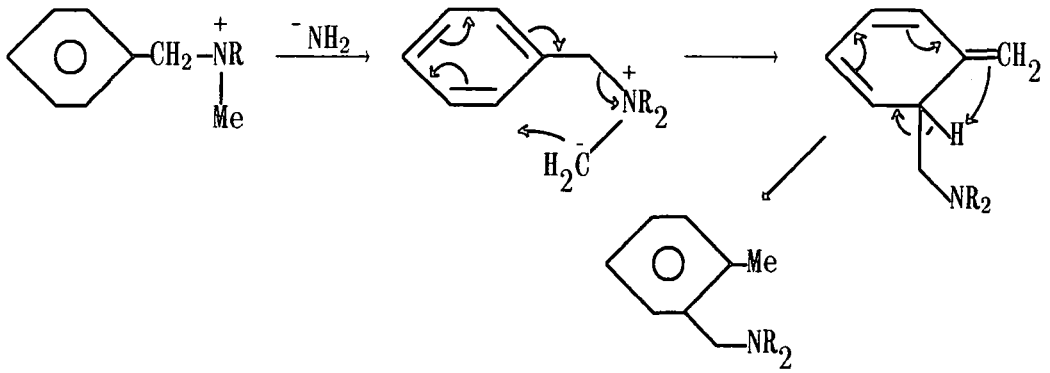




This result is consistent with the analogous, base induced, rearrangement of S,S-dimethylsulphilimines (156)[133] (Scheme 5.11). This is, in turn, comparable with the Sommelet-Hauser Rearrangement of benzylquaternaryammonium salts (Scheme 5.12)[134].

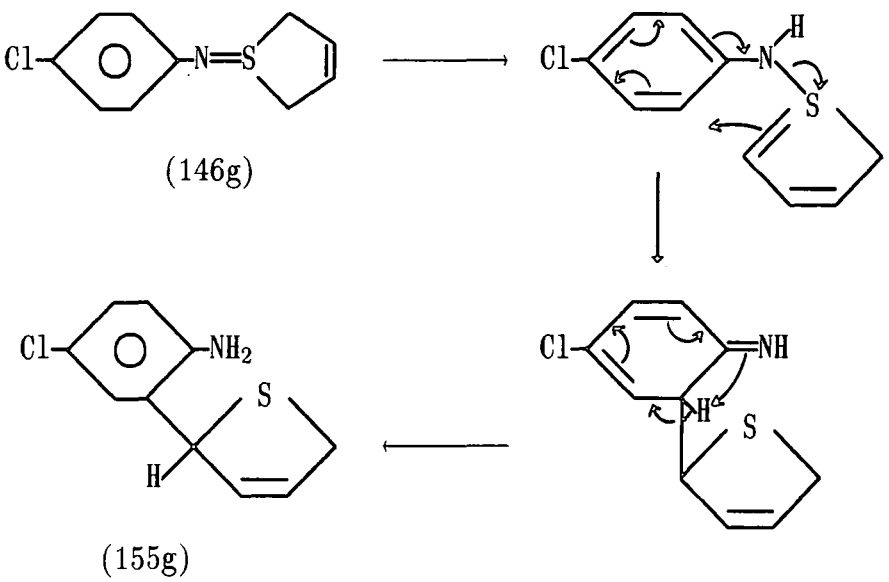


Scheme 5.11



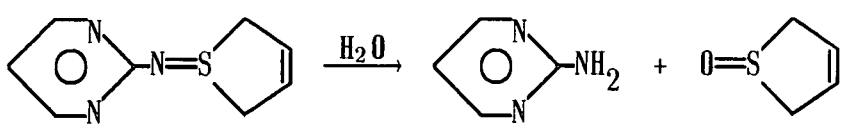
Scheme 5.12

It is reasonable that this reaction should proceed in such a facile manner in the 2,5-dihydrothiophene case when, as has already been noted, the ease of hydrogen abstraction from the 2 and 5 positions is considered. This would result in a doubly stabilised allyl radical or anion allowing the mechanism in Scheme 5.13 to proceed very readily.

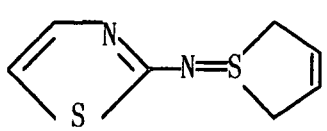


Scheme 5.13

As there was no trace of thiazine (90g) in the products of the reaction described above, we had successfully proved that the cyclo-addition of thionitrosoarenes does not proceed *via* a 5-membered intermediate (further evidence was the lack of the rearranged products, *eg.* (155g), in any reactions of thionitrosoarenes with dienes). Nevertheless we aimed to synthesise an arylamine/dihydrothiophene ylide which was stable at room temperature to investigate the possibility of conversion to the thiazine at higher temperatures or by photochemical reaction. It was clearly necessary to block the ortho positions. We felt that 2,6-dimethylaniline would create steric problems and hence we opted for the 2-aminopyrimidine derivative (157). Synthesis of (157) appeared to proceed smoothly but the products did not appear to contain either the desired ylide (157) or a thiazine derivative (90). Further investigation showed the major products to be 2-aminopyrimidine and the known 2,5-dihydrothiophene 1-oxide (158)[135] (identified by IR and ^{1}H NMR spectra). This indicated that the sulphilimine (157) had indeed formed, but that it had reacted further, by hydrolysis (Scheme 5.14). We have not succeeded in isolating the extremely moisture sensitive sulphilimine. This result was consistent with the observation of Rees and Gilchrist that the dimethylsulphilimine of 2-aminopyrimidine was not isolable for the same reason[136].



(157) (158)

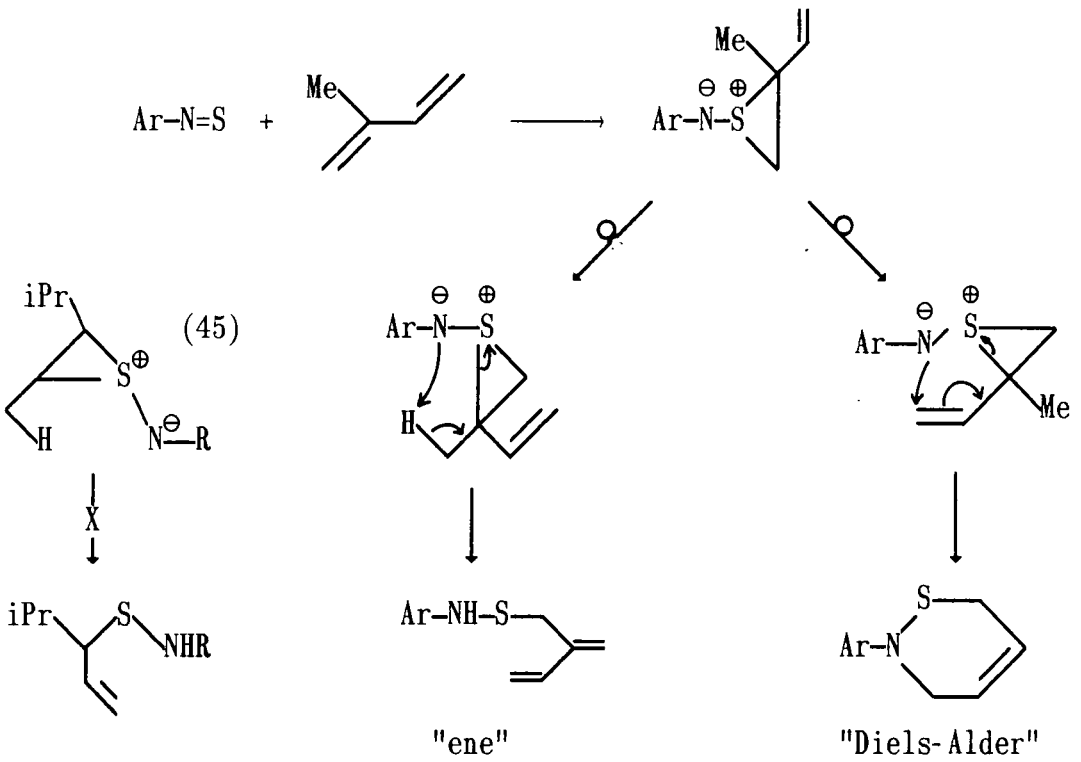


(159)

Scheme 5.14

This result (Scheme 5.14) is further evidence that rearrangement of dihydrothiophene S,N-ylides to 1,2-thiazines does not occur at room temperature. It is noteworthy that this procedure represents a simple method of selectively oxidising a sulphide to a sulphoxide (and not to the sulphone), which may prove to be quite general.

Attempts to synthesise the 2-amino-1,3-thiazole analogue (159) failed, but we are confident that we have eliminated the 5-membered dihydrothiophene as a possible intermediate in thiazine formation. It is still feasible, however, that the reactions of thionitrosoarenes (94) could proceed *via* chelotropic addition, but in a [2 + 2] sense (*eg.* Scheme 5.15), as suggested as a possible ene mechanism[113] (Section 3.3).



Scheme 5.15

If this is the case, however, Hata and Watanbabe's thionitrosoalkane precursors (45) would have been expected to have given rise to ene product (Scheme 5.15), which was not observed[53]. It would be necessary to synthesise an aryl derivative of thiirane ylide (45) to completely

rule out this possibility.

5.3 STAUDINGER CHALCOGENATIONS

In Section 1.5.5 the reactions of Wittig reagents with sulphur, selenium and tellurium to produce chalcogenoaldehydes were discussed. It seemed reasonable to attempt the nitrogen analogues of these reactions to produce chalcogenonitroso compounds, as shown in Scheme 5.16.

$$Ph\text{–}N{=}PPh_3 \xrightarrow[Y=S,Se]{Y} [Ph\text{–}N{=}Y] + Ph_3P{=}Y$$

Refluxing the commercially-available tetraphenylphosphinimine (160) with elemental sulphur or selenium in toluene containing dimethylbutadiene did not, unfortunately, yield any thiazine products. In fact, little change was apparent. This approach to chalcogenonitroso compounds was, therefore, abandoned. It is possible, however, that under the correct conditions these reactions could occur and provide an extremely simple route to thionitroso and the hitherto unknown selenonitroso compounds.

In conclusion, we have developed a novel 1,1-elimination route to thionitrosoarenes. Attempts at a similar 1,1-elimination of butadiene led to some interesting results, of mechanistic and synthetic significance.

CHAPTER SIX

EXPERIMENTAL

6.1 INTRODUCTION - GENERAL METHODS

Throughout, dry nitrogen refers to nitrogen passed through phosphorus pentoxide. Solvents were used distilled from the appropriate drying agent: diethyl ether (sodium/benzophenone); THF (potassium); chloroform and dichloromethane (phosphorus pentoxide); acetone (anhydrous potassium carbonate); triethylamine (3Å molecular sieves).

Melting points were obtained on a Kofler hot stage microscope apparatus and are uncorrected.

Infrared spectra were recorded as thin films or KBr discs on a Perkin-Elmer 577 spectrophotometer.

Proton and carbon NMR spectra were recorded on a Bruker AC 250 spectrometer (250.13 and 62.90 MHz, respectively). Chemical shifts are quoted in ppm. TMS was the internal standard for all solutions.

Mass spectra were obtained on a VG 7070E spectrometer and were recorded in either EI or CI mode. In the CI mode ammonia was employed as the impingent gas. High resolution masses were measured in the EI mode.

Column chromatography on silica refers to gravity chromatography on Merck silica gel (70 - 230 mesh).

Kugelrohr distillations were carried out on a Büchi GKR-51 apparatus.

6.2 EXPERIMENTAL PROCEDURES (CHAPTER 2)

6.2.1 Experimental for Section 2.1

N,N'-Dithiobis(phthalimide) (84a) - was prepared following a slightly modified version of Cava's procedure[104]. Hence, a stirring suspension

of phthalimide (29g, 0.20 mol) in a mixture of triethylamine (27 ml, 0.20 mol) and freshly distilled THF (300 ml) was cooled to $0^{o}C$. Sulphur monochloride (8 ml, 0.20 mol) was added dropwise over 2 mins. with vigorous stirring. Stirring was continued at room temperature for a further 1 hr. The mixture was poured into water (300 ml) and stirred for a further 10 mins., then filtered. The precipitate was washed with ether (30 ml) and then recrystallised from 3:1 chloroform-methanol to yield (84a) as white crystals (21g, 60%). MPt. 223-225^{o}C (lit.[104] 228^{o}C).

Phthalimide sulphenyl chloride (83a) - was prepared by the literature procedure[102] for chlorinolysis of dithiobis(phthalimide) (84a), in quantitative yield. ^{1}H NMR ($CDCl_3$) δ_H: 8.0 (m) ppm [lit.[102] 8.0 ppm, (84a) 7.8 ppm].

N-Trimethylsilylarylamines (87a-g) - A stirring solution of arylamine (20 mmol) and triethylamine (3 ml, 22 mmol) dissolved in freshly distilled ether (100 ml) was cooled to $0^{o}C$ under dry nitrogen. Chlorotrimethylsilane (2.8 ml, 22 mmol) was added dropwise over 5 mins. and stirring was continued for a further 1 hr.[1] at room temperature. The precipitate of triethylamine hydrochloride was removed by filtration under dry nitrogen and the filtrate was evaporated under dry conditions to afford crude (87a-g) as solids or high boiling point oils in > 95% yield. The crude products (87a-g) were, in all cases, pure enough for further reaction. If required, purification could be achieved by distillation at high vacuum. ^{1}H NMR δ_H ($CDCl_3$): *ca.* 3.4 (1H,s,broad,

[1] 72 hrs. for (87e).

NH), 0.2 (9H,s,Me_3Si) ppm[2]. This procedure was used to synthesise the following known compounds:

(87a) 2-(4-methoxyphenyl)-1,1,1-trimethylsilazane;

(87b) 1,1,1-trimethyl-2-(4-methylphenyl)silazane;

(87c) 1,1,1-trimethyl-2-phenylsilazane;

(87d) 2-(4-bromophenyl)-1,1,1-trimethylsilazane;

(87e) 1,1,1-trimethyl-2-(4-nitrophenyl)silazane;

(87f) 1,1,1-trimethyl-2-(1-naphthyl)silazane;

(87g) 2-(4-chlorophenyl)-1,1,1-trimethylsilazane.

Thioarylaminophthalimides (86a-g), *eg.* ***N-(1-naphthyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide (86f)*** - To a stirring solution of N-trimethylsilylnaphthylamine (87f) (2.4g, 11.1 mmol) dissolved in freshly distilled chloroform (25 ml) under dry nitrogen, was added phthalimide sulphenyl chloride (83a) (2.4g, 11.1 mmol) dissolved in freshly distilled chloroform (25 ml), dropwise over 5 mins. A precipitate quickly formed and stirring was continued for 1 hr. The precipitate was collected by filtration and dried, to afford (86f) as a pale yellow solid (2.5g, 70%). Analysis found: C, 67.5; H, 3.9; N, 8.4; required for $C_{18}H_{12}N_2O_2S$: C, 67.5; H, 3.8; N, 8.7%; MS m/e (EI): 320 (M^+).

All compounds (86a-g) were prepared by this procedure. Yields, melting points and IR and ^1H NMR spectra are recorded in Table 6.1. The other analogues prepared were:

(86a) N-(4-methoxyphenyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide;

(86b) N-(4-methylphenyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide;

(86c) N-phenyl-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide;

---

[2]Resonances for the aryl substituent were essentially unchanged from starting materials.

(86d) N-(4-bromophenyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide;

(86e) N-(4-nitrophenyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide;

(86f) N-(4-chlorophenyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide.

6.2.2 Experimental for Section 2.2

2-Aryl-3,6-dihydro-2H-1,2-thiazines (90a-f) - A suspension of thioaryl-aminophthalimide (86) (0.7 mmol) dissolved in freshly distilled acetone[3] (50ml) was cooled to liquid nitrogen temperature. 1,3-Butadiene (1g, 18 mmol) and triethylamine (2 ml, 14 mmol) were condensed onto the frozen suspension under high vacuum. This mixture, in a sealed vessel, was allowed to warm to room temperature with stirring. Stirring was continued until the suspension had become a clear yellow solution (3 - 72 hrs.). The residue from evaporation was column chromatographed (silica column, 20 x 4 cm) eluting with 1:1 cyclohexane-dichloromethane to afford a yellow oil which was distilled (Kugelrohr 150 - 180°C, 0.01 mbar) to afford (90a-f) as yellow oils. Yields and analytical data for the following compounds are recorded in Table 6.2:

(90a) 2-(4-methoxyphenyl)-3,6-dihydro-2H-1,2-thiazine;

(90b) 2-(4-methylphenyl)-3,6-dihydro-2H-1,2-thiazine;

(90c) 2-phenyl-3,6-dihydro-2H-1,2-thiazine;

(90d) 2-(4-bromophenyl)-3,6-dihydro-2H-1,2-thiazine;

(90e) 2-(4-nitrophenyl)-3,6-dihydro-2H-1,2-thiazine;

(90f) 2-(1-naphthyl)-3,6-dihydro-2H-1,2-thiazine.

---

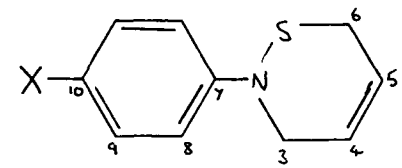
[3]Chloroform was used as solvent for (90e).

Table 6.1. Properties of N-(arylaminothio)phthalimides (86)

Compound Formula	Yield (%)/mpt (^{o}C)	ν_{max} (cm^{-1})	δ_H (ppm $CDCl_3$, 250 MHz)	
(86a)	85	3300(NH)	7.9-7.7	(4H,m,P)[a]
$C_{15}H_{12}N_2O_3S$	182-184	1780(CO)	7.3-6.8	(4H,m,Ar)[b]
		1720(CO)	6.20	(1H,s,NH)
			3.75	(3H,s,OMe)
(86b)	>95	3310(NH)	7.9-7.7	(4H,m,P)
$C_{15}H_{12}N_2O_2S$	194-196	1775(CO)	7.25-7.05	(4H,m,Ar)
		1720(CO)	6.26	(1H,s,NH)
			2.25	(3H,s,Me)
(86c)	85	3340(NH)	7.9-7.7	(4H,m,P)
$C_{14}H_{10}N_2O_2S$	189-192	1780(CO)	7.4-6.9	(5H,m,Ar)
		1730(CO)	6.38	(1H,s,NH)
(86d)	>95	3320(NH)	7.9-7.7	(4H,m,P)
$C_{14}H_9BrN_2O_2S$	162-164(dec)	1775(CO)	7.4-7.2	(4H,m,Ar)
		1720(CO)	6.32	(1H,s,NH)
(86e)	85	3320(NH)	8.2-8.1	and
$C_{14}H_9N_3O_4S$	166-168	1780(CO)	7.5-7.4	(4H,A,B,Ar)
		1725(CO)	8.0-7.7	(4H,m,P)
			6.73	(1H,s,NH)
(86f)	70	3370(NH)	8.1-7.4	(11H,m,Ar+P)
$C_{18}H_{12}N_2O_2S$	143-145	1785(CO)	7.02	(1H,s,NH)
		1730(CO)		
(86g)	65	3320(NH)	8.0-7.7	(4H,m,P)
$C_{14}H_9ClN_2O_2S$	165-166	1780(CO)	7.3-7.1	(4H,m,Ar)
		1725(CO)	6.28	(1H,s,NH)

[a] P refers to hydrogen atoms on the phthalimide ring.
[b] Ar refers to hydrogen atoms on the substituent Ar in formula (86).

Table 6.2. Properties of Butadiene Adducts (90)



Adduct Mol. Formula	M⁺ [Found] (Req.)	Yield[a] %	m/e M⁺ (Ar-N=S)	ν_{max}/cm^{-1}	$\delta_H(CDCl_3/250\ MHz)$	$\delta_C(CDCl_3)$ (δ/ppm)
(90a) $C_{11}H_{13}NOS$	[207.0880] (207.0718)	65	207 (153)	1645(C=C)	7.25-6.75 (4H,m,Ar) 6.1 -5.8 (2H,m,2xCH) 4.0 (2H,m,CH_2N) 3.76 (3H,s,MeO) 3.0 (2H,m,CH_2S)	154.5(C_{10}) 145.3(C_7) 126.6/125.0(C_4/C_5) 120.6(C_8) 113.9(C_9) 55.6(CH_3) 50.7(C_3) 25.8(C_6)
(90b) $C_{11}H_{13}NS$	[191.0438] (191.0769)	75	191 (137)	1645(C=C)	7.15-7.0 (4H,m,Ar) 6.1 -5.8 (2H,m,2xCH) 4.1 (2H,m,CH_2N) 3.1 (2H,m,CH_2S) 2.28 (3H,s,CH_3)	149.0(C_7) 129.3(C_9/C_{10}) 126.6/124.9(C_4/C_5) 118.8(C_3) 50.2(C_8) 26.3(C_6) 20.5(CH_3)
(90c) $C_{10}H_{11}NS$	[177.0606] (177.0612)	65	177 (123)	1645(C=C)	7.3 -6.6 (5H,m,Ar) 6.1 -5.8 (2H,m,2xCH) 4.0 (2H,m,CH_2N) 3.0 (2H,m,CH_2S)	151.5(C_7) 128.7(C_9) 126.6/124.8(C_4/C_5) 120.8(C_{10}) 116.5(C_8) 49.8(C_3) 26.7(C_6)
(90d) $C_{10}H_{10}BrNS$	[254.9856] (254.9717)	75	255/7 (201/3)	1645(C=C)	7.75-7.05 (4H,m,Ar) 6.1 -5.8 (2H,m,2xCH) 4.1 (2H,m,CH_2N) 3.1 (2H,m,CH_2S)	150.5(C_7) 131.5(C_9) 126.2/124.8(C_4/C_5) 120.1(C_8) 113.1(C_{10}) 49.7(C_3) 26.7(C_6)
(90e) $C_{10}H_{10}N_2O_2S$	[222.0482] (222:0463)	50	222 (168)	1490(NO_2) 1330(NO_2)	8.1 -8.0 7.2 -7.1 (4H,m,Ar) 6.05-5.75 (2H,m,2xCH) 4.1 (2H,m,CH_2N) 3.2 (2H,m,CH_2S)	156.1(C_7) 140.0(C_{10}) 126.3 125.4 ($C_4/C_5/C_9$) 124.0 115.9(C_8) 49.2(C_3) 26.7(C_6)
(90f) $C_{14}H_{13}NS$	[227.0736] (227.0769)	55	227 (173)	1650(C=C)	8.3 -7.2 (7H,m,Ar) 6.3 -6.0 (2H,m,2xCH) 4.2 (2H,broad s,CH_2N) 3.1 (2H,broad s,CH_2S)	150-115 (many peaks) 53.2(C_3) 25.6(C_6)

[a] Yield is for spectroscopically pure material isolated after distillation.

6.3 EXPERIMENTAL PROCEDURES (CHAPTER 3)

6.3.1 Experimental for Section 3.1

Adducts of thionitrosoarenes (94a-f) with 2,3-dimethyl-1,3-butadiene (92a-f, 93a-f) - To a stirring suspension of thioarylaminophthalimide (86) (0.5 mmol) dissolved in freshly distilled acetone (50 ml)[4] under dry nitrogen, was added, sequentially, dimethylbutadiene (1 ml, 9 mmol) and triethylamine (2 ml, 14 mmol). Stirring was continued at room temperature until the suspension became a clear solution (3 - 72 hrs.). After evaporation the residue was stirred vigorously with cyclohexane (50 ml) for 30 mins. Precipitated triethylammonium phthalimide was removed by filtration and the filtrate was evaporated to afford crude (92a-f, 93a-f) as yellow oils. ^{1}H NMR spectra of these crude mixtures were used to assess isomer ratios (Table 3.1). Separation of the mixtures of adducts (92a-f, 93a-f) from all other products was achieved by column chromatography (silica column, 20 x 4 cm) eluting with 1:1 cyclohexane-dichloromethane to afford yellow oils. Distillation of the mixture (92, 93a) (Kugelrohr, 155^{o}C, 0.03 mbar) afforded pure (92a) as a yellow oil (60 mg, 50%). Analysis found: C, 65.0; H, 7.2; N, 5.5; required for $C_{13}H_{17}NOS$: C, 66.3; H, 7.3; N, 6.0%; high resolution MS found: 235.1041 (required: 235.1031); MS m/e (EI): 235 (M^+), 153 (ArNS); (CI): 236, 154; IR ν_{max} (neat): 1245, 1045 (C-O-C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ_H: 7.1-6.75 (4H,m,Ar), 3.87 (2H,m,CH_2N), 3.79 (3H,s,CH_3O), 2.90 (2H,m,CH_2S), 1.71 (6H,s,2xCH_3); ^{13}C NMR ($CDCl_3$) δ_C: 154.4, 145.4, 124.8, 124.2, 120.5, 113.9, 55.8/55.5 (CH_3O,CH_2N), 30.2 (CH_2S), 19.8 (CH_3), 16.9 (CH_3) ppm. Yields and ^{1}H NMR data for the chromatographed isomer

[4]Acetone (10 ml) was used for (94a) and chloroform (50 ml) for (94e).

Table 6.3. Properties of Diels Alder Products (92) and Ene Products (93) from Dimethylbutadiene Addition to Thionitrosoarenes (94)

Phthalimide Precursor (86)	Combined Yield of Adducts (92) + (93)[a]	Isomer ratio[b]	$\delta_H(CDCl_3)$ (excluding aromatics)[c]	
(86a)	65%	(92a)(85%)	3.8	(2H,m,CH_2N)
			3.7	(3H,s,CH_3O)
			2.9	(2H,m,CH_2S)
			1.7	(6H,s,2xCH_3)
		(93a)(15%)	5.2-4.5	(5H,m,2x=CH_2+NH)
			3.7	(3H,s,CH_3O)
			3.4	(2H,s,CH_2S)
			1.9	(3H,s,CH_3)
(86b)	55%	(92b)(60%)	3.8	(2H,m,CH_2N)
			2.9	(2H,m,CH_2S)
			2.2	(3H,s,CH_3Ar)
			1.7	(6H,s,2xCH_3)
		(93b) 40%	5.1-4.5	(5H,m,2x=CH_2+NH)
			3.4	(2H,s,CH_2S)
			2.2	(3H,s,CH_3Ar)
			1.9	(3H,s,CH_3)
(86c)	55%	(92c)(55%)	3.9	(2H,m,CH_2N)
			2.9	(2H,m,CH_2S)
			1.7	(6H,s,2xCH_3)
		(93c)(45%)	5.2-4.6	(5H,m,2x=CH_2+NH)
			3.4	(2H,s,CH_2S)
			1.9	(3H,s,CH_3)
(86d)	50%	(92d)(25%)	3.9	(2H,m,CH_2N)
			2.9	(2H,m,CH_2S)
			1.7	(6H,s,2xCH_3)
		(93d)(75%)	5.5-4.6	(5H,m,2x=CH_2+NH)
			3.4	(2H,s,CH_2S)
			1.9	(3H,s,CH_3)
(86e)	45%	(92e) 20%	4.0	(2H,m,CH_2N)
			3.0	(2H,m,CH_2S)
			1.7	(6H,s,2xCH_3)
		(93e) 80%	5.3-4.7	(5H,m,2x=CH_2+NH)
			3.4	(2H,s,CH_2S)
			1.9	(3H,s,CH_3)
(86f)	65%	(92f) 45%	3.9	(2H,m,CH_2N)
			2.9	(2H,m,CH_2S)
			1.8	(6H,s,2xCH_3)
		(93f) 55%	5.6-4.6	(5H,m,2x=CH_2+NH)
			3.5	(2H,s,CH_2S)
			1.9	(3H,s,CH_3)

[a] The yield quoted is for the mixture of adducts, nmr spectroscopically pure, after column chromatography and/or bulb-to-bulb distillation.

[b] Based on ^1H n.m.r. analysis of the crude reaction mixture.

[c] Aromatics essentially similar to parent anilines.

mixtures (92a-f,93a-f) are recorded in Table 6.3 for the following compounds:

(92a) 2-(4-methoxyphenyl)-4,5-dimethyl-3,6-dihydro-2H-1,2-thiazine;

(92b) 4,5-dimethyl-2-(4-methylphenyl)-3,6-dihydro-2H-1,2-thiazine;

(92c) 4,5-dimethyl-2-phenyl-3,6-dihydro-2H-1,2-thiazine;

(92d) 2-(4-bromophenyl)-4,5-dimethyl-3,6-dihydro-2H-1,2-thiazine;

(92e) 4,5-dimethyl-2-(4-nitrophenyl)-3,6-dihydro-2H-1,2-thiazine;

(92f) 4,5-dimethyl-2-(1-naphthyl)-3,6-dihydro-2H-1,2-thiazine;

(93a) N-(4-methoxyphenyl)-3-methyl-2-methylidene-3-butene-1-sulphenamide;

(93b) 3-methyl-2-methylidene-N-(4-methylphenyl)-3-butene-1-sulphenamide;

(93c) 3-methyl-2-methylidene-N-phenyl-3-butene-1-sulphenamide;

(93d) N-(4-bromophenyl)-3-methyl-2-methylidene-3-butene-1-sulphenamide;

(93e) 3-methyl-2-methylidene-N-(4-nitrophenyl)-3-butene-1-sulphenamide;

(93f) 3-methyl-2-methylidene-N-(1-naphthyl)-3-butene-1-sulphenamide.

6.3.2 Experimental for Section 3.2

Adducts of thionitrosoarenes (94a,d) with 2-methyl-1,3-butadiene (isoprene) (96-98a,d) - were prepared analogously to (92,93a,d) (Section 6.3.1) using the same quantity of starting material (86a,d), triethylamine and solvent, but with isoprene (1 ml, 10 mmol) in place of dimethylbutadiene. Isomer ratios (Table 3.3) were assessed in a similar manner to (92,93) and the mixture of regioisomeric thiazines (96,97a) was isolated by distillation as for (92a). Analysis found: C, 65.2; H, 6.8; N, 5.9; required for $C_{12}H_{15}NOS$: C, 65.1; H, 6.8; N, 6.3%; MS m/e (EI): 221 (M^+), 153 (ArNS); (CI): 222, 154. Yields and ^1H NMR data for the following compounds are recorded in Table 6.4:

(96a) 2-(4-methoxyphenyl)-5-methyl-3,6-dihydro-2H-1,2-thiazine;

(96d) 2-(4-bromophenyl)-5-methyl-3,6-dihydro-2H-1,2-thiazine;

PHTHALIMIDE PRECURSOR (86)	(86a)	(86d)
Combined Yield of Adducts (96-98)[a]	60%	65%
δH ($CDCl_3$) (excluding aromatics)[c]	(96a) (65%)[b]	(96d) (25%)[b]
	5.6 (1H,m,=CH) 4.0 (2H,m,CH_2N) 3.7 (3H,s,CH_3O) 2.9 (2H,m,CH_2S) 1.75 (3H,s,CH_3)	5.6 (1H,m,=CH) 4.05 (2H,m,CH_2N) 2.95 (2H,m,CH_2S) 1.72 (3H,s,CH_3)
	(97a) (22%)	(97d) (8%)
	5.8 (1H,m,=CH) 3.9 (2H,m,CH_2N) 3.7 (3H,s,CH_3O) 3.0 (2H,m,CH_2S) 1.75 (3H,s,CH_3)	5.8 (1H,m,=CH) 3.9 (2H,m,CH_2N) 3.05 (2H,m,CH_2S) 1.72 (3H,s,CH_3)
	(98a) (13%)	(98d) (67%)
	6.35 (1H,dd,H_a) J_{ac} 16.9Hz J_{ab} 10.2Hz 5.30 (1H,d,H_c) J_{ac} 16.9Hz 5.16 (1H,d,H_b) J_{ab} 10.2Hz 5.10 (1H,s,=CH) 4.84 (1H,s,=CH) 4.7 (1H,s,NH) 3.73 (3H,s,CH_3O) 3.36 (2H,s,CH_2S)	6.35 (1H,dd,H_a) J_{ac} 17.7Hz J_{ab} 10.8Hz 5.30 (1H,d,H_c) J_{ac} 17.8Hz 5.18 (1H,d,H_b) J_{ab} 10.9Hz 5.11 (1H,s,=CH) 4.90 (1H,s,NH) 4.85 (1H,s,=CH) 3.38 (2H,s,CH_2S)

Table 6.4: *Properties of Diels Alder Products (96,97) and Ene Products (98) from Isoprene Addition to Thionitrosoarenes (94);* [a,b,c] *footnotes as for Table 6.3.*

(97a) 2-(4-methoxyphenyl)-4-methyl-3,6-dihydro-2H-1,2-thiazine;

(97d) 2-(4-bromophenyl)-4-methyl-3,6-dihydro-2H-1,2-thiazine;

(98a) N-(4-methoxyphenyl)-2-methylidene-3-butene-1-sulphenamide;

(98d) N-(4-bromophenyl)-2-methylidene-3-butene-1-sulphenamide.

6.3.3 Experimental for Section 3.3

Adducts of thionitrosoarenes (94a,f) with 2-methylpropene (isobutene) (102a,f) - were prepared analogously to (90a,f) (Section 6.2.2) using the same quantity of starting material (86a,f), triethylamine and solvent, but with isobutene (1g, 18 mmol) in place of butadiene. The resulting solutions were evaporated and the residues stirred vigorously with cyclohexane, filtered and evaporated as with (92,93). Compound (102a) was unstable to both distillation and chromatography and could not be purified further. Compound (102f) was column chromatographed as for (90f), but could not be distilled. Properties and analytical data for the following compounds are recorded in Table 6.5:

(102a) N-(4-methoxyphenyl)-2-methyl-2-propene-1-sulphenamide

(102f) 2-methyl-N-(1-naphthyl)-2-propene-1-sulphenamide

Adducts of thionitrosoarenes (94a,f) with 2-phenylpropene (α-methylstyrene) (103a,f) - were prepared analogously to (92,93a,f) (Section 6.3.1) using the same quantity of starting material (86a,f), triethylamine and solvent, but with α-methylstyrene (1 ml, 8 mmol) in place of dimethylbutadiene. After cyclohexane extraction, (103a) was pumped under high vacuum at room temperature to remove excess α-methylstyrene but, as with (102a), further purification was not possible due to instability to chromatography and distillation. Compound (103f) could be purified by column chromatography (silica column, 20 x 4 cm)

ADDUCT MOL. FORMULA	M^+ [FOUND] (Reqd.)	YIELD %	m/e M^+ ArNS	ν(max) cm^{-1}	250 MHz δH ($CDCl_3$) (ppm)	δC ($CDCl_3$) (ppm)
(102a) $C_{11}H_{15}NOS$	[209.0839] (209.0874)	65‡	209 153		7.0-6.7(4H,m,Ar) 4.84(1H,s,=CH) 4.66(1H,s,NH) 4.56(1H,s,=CH) 3.74(3H,s,CH_3O) 3.12(2H,s,CH_2S) 1.86(3H,s,CH_3)	
(102f) $C_{14}H_{15}NS$	[229.1013] (229.0925)	45	229 173	3360(NH)	7.9-7.25(7H,m,Ar) 5.16(1H,s,NH) 4.80(1H,m,=CH) 4.43(1H,m,=CH) 3.23(2H,s,CH_2S) 1.91(3H,s,CH_3)	44.4(CH_2S) 21.2(CH_3)
(103a) $C_{16}H_{17}NOS$	[271.1020] (271.1031)	65‡	271 153		7.4-6.7(9H,m,Ar) 5.40(1H,s,=CH) 4.89(1H,s,NH) 4.65(1H,s,=CH) 3.71(3H,s,CH_3O) 3.59(2H,s,CH_2S)	
(103f) $C_{19}H_{17}NS$	[291.1068] (291.1082)	45	291 173	3380(NH) 1620(C=C)	7.85-7.3(12H,m,Ar) 5.50(1H,s,NH) 5.38(1H,s,=CH) 4.79(1H,m,=CH) 3.75(2H,s,CH_2S)	41.8(CH_2S)

Table 6.5: *Ene Adducts of Thionitrosoarenes (94) and Alkenes;* ‡*Crude Yield.*

eluting first with cyclohexane to remove excess α-methylstyrene, then with 1:1 cyclohexane-dichloromethane, but was unstable to distillation. Properties and analytical data for the following compounds are recorded in Table 6.5:

(103a) N-(4-methoxyphenyl)-2-phenyl-2-propene-1-sulphenamide

(103f) N-(1-naphthyl)-2-phenyl-2-propene-1-sulphenamide

6.3.4 Experimental for Section 3.4

1,1'-Bicyclopentenyl (107) - was prepared from cyclopentanone in two steps. 1,1'-Bicyclopentyl-1,1'-diol was prepared by the literature method[115a] and subsequently dehydrated with $POCl_3$[115b] to afford (107) as a pale yellow liquid in 55% yield (for two steps, lit.[115] 80%). BPt. 36°C (0.6 mbar) (lit.[115b] 31°C, 0.1 mbar).

1,1'-Bicyclohexenyl (108) - was prepared from cyclohexanone analogously to (107) in 65% yield (lit.[115] 88%). BPt. 70°C (0.6 mbar) (lit.[115b] 68°C, 0.5 mbar).

(3a,RS,5a,SR)-5-(4-Methoxyphenyl)-1,2,3,3a,5a,6,7,8-octahydro-5H-4-thia-5-aza-as-indacene (109a) - was prepared analogously to (92,93a), using the same quantity of starting material (86a), triethylamine and solvent, but with bicyclopentenyl (107) (1g, 7.5 mmol) in place of dimethylbutadiene. The resulting solution was evaporated and column chromatographed (silica column, 20 x 4 cm) eluting first with cyclohexane to recover excess (107), then with 1:1 cyclohexane-dichloromethane to afford (109a) as a yellow oil which was distilled (Kugelrohr, 180°C, 0.01 mbar), if necessary, to afford (109a) as a yellow oil in 75% yield. High resolution MS found: 287.1304 (required for $C_{17}H_{21}NOS$: 287.1344);

MS m/e (EI): 287 (M^+), 153 (ArNS); (CI): 288, 154; IR ν_{max} (neat): 1245, 1035 (C-O-C) cm^{-1}; ^1H NMR ($CDCl_3$) δ_H: 7.1-6.7 (4H,m,Ar), 3.7 (4H,m,CHN + CH_3O), 3.3 (1H,m,CHS), 2.3 (4H,m,CH_2(3)+CH_2(6)), 2.1-1.1 (8H,m,4xCH_2); ^{13}C NMR ($CDCl_3$) δ_C: 154.1, 146.9, 137.5, 133.5, 120.1, 114.2, 63.8 (CHN), 55.6 (CH_3O), 40.2 (CHS), 31.1, 30.2, 28.6, 26.2, 23.6, 19.8 ppm.

(8a,RS,10a,SR)-10-(4-Methoxyphenyl)-1,2,3,4,5,6,7,8,8a,10a-decahydro-10H-9-thia-10-azaphenanthrene (110a) - was prepared by exact analogy with (109a) with bicyclohexenyl (108) (1.2g, 7.5 mmol) in place of bicyclopentenyl. Chromatography and distillation under the same conditions afforded (110a) as a yellow oil in 75% yield. High resolution MS found: 315.1657 (required for $C_{19}H_{25}NOS$: 315.1657); IR ν_{max} (neat): 1245, 1035 (C-O-C) cm^{-1}; ^1H NMR ($CDCl_3$) δ_H: 7.1-6.7 (4H,m,Ar), 3.76 (3H,s,CH_3O), 3.6 (1H,m,CHN), 3.4 (1H,m,CHS), 2.9 (2H,m,CH_2(1)), 2.2-1.1 (14H,m,7xCH_2); ^{13}C NMR ($CDCl_3$) δ_C: 154.3, 147.0, 132.8, 129.1, 120.7, 113.7, 63.0 (CHN), 55.3 (CH_3O), 37.5 (CHS), 35.0, 30.7, 28.8, 28.7, 28.1, 26.8, 26.1, 25.2 ppm.

(3RS,6SR)-2-(4-Methoxyphenyl)-3,6-diphenyl-3,6-dihydro-2H-1,2-thiazine (111a, R=Ph) - was prepared and purified by exact analogy with (109a) using 1,4-diphenyl-1,3-butadiene (0.5g, 2 mmol) in place of bicyclopentenyl (107). Excess diene was recovered by the same method and further elution afforded (111a, R=Ph) as a white solid in 60% yield, mpt. 71-72°C. Analysis found: C, 76.2; H, 5.8; N, 2.7; required for $C_{23}H_{19}NOS$: C, 77.3; H, 5.4; N, 3.9%; high resolution MS found: 359.1768 (required: 359.1344); MS m/e (EI): 359 (M^+), 153 (ArNS); (CI): 360, 154; IR ν_{max} (neat): 1645 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ_H: 7.5-7.1 (14H,m,Ar), 6.4-6.2 (2H,m,2x =CH), 5.0 (1H,m,CHN), 4.6 (1H,m,CHS), 3.74 (3H,s,CH_3O);

^{13}C NMR ($CDCl_3$) δ_C: 155-114 (many resonances), 60.1 (CHN), 55.6 (CH_3O), 41.2 (CHS) ppm.

Adducts of thionitrosoarenes (94a,d) with (E,E)-2,4-hexadiene (111a,d, R=Me) - were prepared, purified and analysed by exact analogy with (92,93a,d), using (E,E)-2,4-hexadiene (1 ml, 9 mmol) in place of dimethylbutadiene to afford (111a, R=Me) as a white solid (mpt. 26-28^oC) and (111d, R=Me) as a yellow oil. Yields and analytical data for the following compounds are recorded in Table 6.6:

(111a, R=Me)
(3RS,6SR)-2-(4-methoxyphenyl)-3,6-dimethyl-3,6-dihydro-2H-1,2-thiazine;

(111d, R=Me)
(3RS,6SR)-2-(4-bromophenyl)-3,6-dimethyl-3,6-dihydro-2H-1,2-thiazine.

Adducts of thionitrosoarenes (94a,b,d,g) with (E,Z)-2,4-hexadiene (112a,b,d,g, R=Me) - were prepared analogously to (92,93a,b,d,g), using the same quantity of starting material (86), triethylamine and solvent, but using (E,Z)-2,4-hexadiene (1 ml, 9 mmol) in place of dimethylbutadiene. Isomer ratios (Table 3.3) were assessed in the same manner. Crude (112a,b,d,g, R=Me) were yellow oils which were not purified further. Crude yields, diastereomeric excesses and ^1H NMR data for the following compounds are recorded in Table 6.7 :

(112a, R=Me)
(3RS,6RS)-2-(4-methoxyphenyl)-3,6-dimethyl-3,6-dihydro-2H-1,2-thiazine;

(112b, R=Me)
(3RS,6RS)-3,6-dimethyl-2-(4-methylphenyl)-3,6-dihydro-2H-1,2-thiazine;

(112d, R=Me)
(3RS,6RS)-2-(4-bromophenyl)-3,6-dimethyl-3,6-dihydro-2H-1,2-thiazine;

(112g, R=Me)
(3RS,6RS)-2-(4-chlorophenyl)-3,6-dimethyl-3,6-dihydro-2H-1,2-thiazine.

ADDUCT MOL.FORMULA	(111a, R=Me) $C_{13}H_{17}NOS$	(111d, R=Me) $C_{12}H_{14}BrNS$
M^+ [Found] (Required)	[235.0996] (235.1031)	[282.9968] (283.0030)
YIELD %	70	70
m/e M^+ ArNS	235 153	283/285 201/203
ν(max)/cm^{-1}	1640 (C=C)	1640 (C=C)
δH ($CDCl_3$) (250 MHz) (ppm)	7.2-6.7 (4H,m,Ar) 5.9-5.7 (2H,m,2x=CH) 3.9 (1H,m,CH N) 3.76 (3H,s,CH_3O) 3.5 (1H,m,CHS) 1.44 (3H,d,CH_3-C(3)) J = 6.64 Hz 1.08 (3H,d,CH_3-C(6)) J = 7.18 Hz	7.4-7.0 (4H,m,Ar) 5.9-5.6 (2H,m,2x=CH) 4.05 (1H,m,CHN) 3.55 (1H,m,CHS) 1.45 (3H,d,CH_3-C(3)) J = 6.64 Hz 1.09 (3H,d,CH_3-C(6)) J = 7.16 Hz
δC ($CDCl_3$)	154.5 146.7 131.4 131.0 121.0 113.8 55.5 (CH_3O) 52.9 (CH_2N) 30.6 (CH_2S) 21.0 (CH_3) 16.0 (CH_3)	151.0 131.5 130.8 120.0 112.7 52.2 (CH_2N) 32.2 (CH_2S) 20.3 (CH_3) 16.1 (CH_3)

Table 6.6

ADDUCT	% YIELD	D.E.	δH ($CDCl_3$/250 MHz) /ppm
(112a, R=Me)	70	0%	7.3-6.7 (4H,m,Ar) 6.0-5.75 (2H,m,2x=CH) 4.14 (1H,m,CHN) 3.75 (3H,s,CH_3O) 2.94 (1H,m,CHS) 1.38 (3H,d,CH_3-C(3)) J=6.62 Hz 1.24 (3H,d,CH_3-C(6)) J=7.09 Hz
(112b, R=Me)	75	40%	7.3-6.8 (4H,m,Ar) 6.1-5.7 (2H,m,2x=CH) 4.20 (1H,m,CHN) 2.92 (1H,m,CHS) 2.26 (3H,s,Me) 1.40 (3H,d,CH_3-C(3)) J=6.62 Hz 1.30 (3H,d,CH_3-C(6)) J=7.10 Hz
(112d, R=Me)	65	80%	7.35-7.05 (4H,m,Ar) 6.05-5.65 (2H,m,2x=CH) 4.20 (1H,m,CHN) 2.97 (1H,m,CHS) 1.40 (3H,d,CH_3-C(3)) J=6.79 Hz 1.31 (3H,d,CH_3-C(6)) J=7.14 Hz
(112g, R=Me)	65	80%	7.15 (4H,m,Ar) 6.0-5.7 (2H,m,2x=CH) 4.20 (1H,m,CHN) 2.97 (1H,m,CHS) 1.41 (3H,d,CH_3-C(3)) J=6.62 Hz 1.32 (3H,d,CH_3-C(6)) J=7.04 Hz

Table 6.7

6.4 EXPERIMENTAL PROCEDURES (CHAPTER 4)

6.4.1 Experimental for Section 4.1

1,1,1-Trimethyl-2-(2-pyrimidyl)-silazane (N-trimethylsilyl-2-amino-pyrimidine) (123) - was prepared by the literature procedure[122] from 2-aminopyrimidine (2g, 21 mmol) in 90% yield. BPt. 150°C (*ca.* 30 mm Hg) (lit.[122] 88°C, 9 mm Hg).

N-(2-Pyrimidyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide (124) - was prepared analogously to (86f) (Section 6.2) from (123) (2.8g, 17 mmol) and (83a) (3.9g, 17 mmol) which afforded (124) as a white precipitate (4.3g, 85%), mpt. 187-188°C. Analysis found: C, 52.4; H, 2.8; N, 20.5; required for $C_{12}H_8N_4O_2S$: C, 52.9; H, 3.0; N, 20.6%; IR ν_{max} (KBr): 3120 (NH), 1780, 1735 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ_H (py = pyrimidyl; phth = phthalimide): 8.65 (2H,d,py,J=5.0 Hz), 8.48 (1H,s,NH), 7.84 (4H,m,phth), 6.93 (1H,t,py,J=5.0 Hz) ppm.

1,1,1-Trimethyl-2-(3-pyri dyl)-silazane (N-trimethylsilyl-3-amino-pyrimidine - was prepared analogously to (87a-g) in quantitative yield (crude).

N-(3-Pyri dyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide (125) - was prepared analogously to (86f) in 60% yield, mpt. 130-132°C (dec). IR ν_{max} (KBr): 3140 (NH), 1790, 1730 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ_H (py = 3-pyridyl; phth = phthalimide): 8.30 (1H,m,py), 8.17 (1H,m,py), 7.85 (4H,m,phth), 7.34 (1H,m,py), 6.80 (1H,s,py), 2.2 (3H,s,broad,NH+H_2O) ppm.

2-(3-Pyridyl)-3,6-dihydro-2H-1,2-thiazine (127) - was prepared analogously to (90a-f) (Section 6.2) in 60% yield, dist. 170°C (0.01 mbar). High resolution MS found: 178.0735 (required for $C_9H_{10}N_2S$: 178.0565); MS m/e (EI): 178 (M^+), 124 (ArNS); (CI): 179, 125; IR ν_{max} (neat): 1640 (weak,C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ_H (py = 3-pyridyl): 8.53 (1H,m,py), 8.14 (1H,m,py), 7.56 (1H,m,py), 7.16 (1H,m,py), 5.97 (2H,m, 2x =CH), 4.13 (2H,m,CH_2N), 3.13 (2H,m,CH_2S); ^{13}C NMR ($CDCl_3$) δ_C: 147.2, 141.6, 140.6, 126.0, 125.3, 124.8, 123.1, 49.3 (CH_2N), 26.8 (CH_2S) ppm.

Adducts of 3-thionitrosopyridine with isoprene (128a-130a) - were prepared analogously to (96-98) (Section 6.3) and isomer ratios were analysed in a similar manner. ^1H NMR data for the following isomers is given below:

(128a) 5-methyl-2-(3-pyridyl)-3,6-dihydro-2H-1,2-thiazine;

(129a) 4-methyl-2-(3-pyridyl)-3,6-dihydro-2H-1,2-thiazine;

(130a) 2-methylidene-N-(3-pyridyl)-3-butene-1-sulphenamide.

^1H NMR ($CDCl_3$) δ_H: 8.6-7.1 (m,Ar,all adducts);

(128a): 5.6 (1H,m,=CH), 4.1 (2H,s,CH_2N), 3.0 (2H,s,CH_2S), 1.75 (3H,s,CH_3);

(129a): 5.8 (1H,m,=CH), 3.9 (2H,s,CH_2N), 3.1 (2H,s,CH_2S), 1.75 (3H,s,CH_3);

(130a): 6.36 (1H,dd,H^a,J=17.7,10.8 Hz), 5.33 (1H,d,H^c,J=17.6 Hz), 5.20 (1H,d,H^b,J=10.6 Hz), 5.19 (1H,s,NH), 5.12 (1H,s,=CH), 4.89 (1H,s,=CH), 3.43 (2H,s,CH_2S) ppm.

Adducts of 3-thionitrosopyridine with dimethylbutadiene (129b-130b) - were prepared analogously to (92-93) (Section 6.3) and isomer ratios were analysed in a similar manner. ^1H NMR data for the following

isomers is given below:

(129b) 4,5-dimethyl-2-(3-pyridyl)-3,6-dihydro-2H-1,2-thiazine;

(130b) 3-methyl-2-methylidene-N-(3-pyridyl)-3-butene-1-sulphenamide.

^{1}H NMR ($CDCl_3$) δ_H: 8.5 - 7.1 (m,Ar,both adducts);

(129b): 3.95 (2H,s,CH_2N), 2.96 (2H,s,CH_2S), 1.72 (6H,s,2xCH_3);

(130b): 5.23 (1H,s,NH), 5.16 (2H,s,2x =CH), 5.11 (1H,s,=CH), 4.87 (1H,s,=CH), 3.49 (2H,s,CH_2S) ppm.

2-Phenyl-N-(3-pyridyl)-2-propene-1-sulphenamide (131) - was prepared analogously to (103a,f) (Section 6.3) in 45% yield. High resolution MS found: 242.0855 (required for $C_{14}H_{14}N_2S$: 242.0878); MS m/e (EI): 243 (M^++1); (CI): 243, 154; IR ν_{max} (neat): 3430 (NH), 1620 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ_H (py = 3-pyridyl): 8.24 (1H,d,py,J=2.8 Hz), 8.09 (1H,m, py), 7.5-7.3 (6H,m,Ar), 7.13 (1H,dd,py,J=4.6 Hz), 5.42 (1H,s,=CH), 5.08 (1H,s,NH), 4.95 (1H,s,=CH), 3.68 (2H,s,CH_2S); ^{13}C NMR ($CDCl_3$) δ_C: 143-116 (many resonances), 42.3 (CH_2S) ppm.

1,1,1-Trimethyl-2-(4-pyrimidyl)-silazane (N-trimethylsilyl-4-amino-pyrimidine (132) - was prepared analogously to (123) from 4-amino-pyridine (2g, 21 mmol) in >95% yield. BPt. 180°C (*ca.* 30 mm Hg) (lit.[123] not given).

2-(2-Methylidene-3-butenethio)-1H-isoindole-1,3(2H)-dione (134) - To a stirring solution of (132) (0.6g, 3.6 mmol), isoprene (5 ml, 50 mmol) and triethylamine (2 ml, 14 mmol) dissolved in freshly distilled chloroform (10 ml) under dry nitrogen was added, dropwise, (83a) (0.8g, 3.7 mmol) dissolved in chloroform (20 ml). The mixture was stirred overnight at room temperature, then column chromatographed (silica

column, 20 x 4 cm) eluting with dichloromethane. The first fraction afforded (134) as a white solid (150 mg, 15%), mpt. 120-125°C. Analysis found: C, 62.6; H, 4.7; N, 5.1; required for $C_{13}H_{11}NO_2S$: C, 63.6; H, 4.5; N, 5.7%; High resolution MS found: 245.0476 (required: 245.0511); IR ν_{max} (KBr): 1785, 1740, 1715 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ_H: 7.83 (4H, m,Ar), 6.33 (1H,dd,H^a,J=17.6,10.9 Hz), 5.47 (1H,d,H^c,J=17.6 Hz), 5.24 (1H,d,H^b,J=10.9 Hz), 5.04 (1H,s,=CH), 4.98 (1H,s,=CH), 3.70 (2H,s,CH_2S); ^{13}C NMR ($CDCl_3$) δ_C: 167.0, 138.6, 134.8, 133.5, 131.0, 122.8, 119.1, 114.6, 38.3 (CH_2S) ppm.

6.4.2 Experimental for Section 4.2

***N*-Acetyl-*N*-trimethylsilyl-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide (140)** - A stirring solution of (83a) (0.5g, 2.3 mmol) dissolved in freshly distilled chloroform was cooled to 0°C under dry nitrogen. Bis(trimethylsilyl)acetamide (137) (0.6 ml, 2.4 mmol) was added dropwise causing the yellow solution to become completely clear. Evaporation under dry conditions afforded a white solid (0.85g, 97%) consisting of two tautomers (140a) and (140b). ^1H NMR ($CDCl_3$) δ_H: 7.75 (4H,m,Ar), 2.60 (1.5H,s,MeC=O), 1.92 (1.5H,s,MeC=N), 0.30 (4.5H,s,Me_3Si), 0.25 (4.5H,s,Me_3Si) ppm.

***N*-Acetyl-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide (139)** - To a stirring solution of (140) (0.85g, 2.3 mmol) dissolved in chloroform (25 ml) at room temperature was added water (0.5 ml). Stirring was continued, vigorously, for 1 hr. The solution was evaporated and the residue dried under high vacuum to afford (139) as a white solid (0.62g, 96%), mpt. 160-165°C. Analysis found: C, 50.1; H, 3.4; N, 11.5; required for $C_{10}H_8N_2O_3S$: C, 50.8; H, 3.4; N, 11.9%; MS m/e (CI^-): 325;

IR ν_{max} (KBr): 3300 (NH), 1795, 1745, 1695 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ_H: 7.89 (4H,m,Ar), 7.4 (1H,s,broad,NH/OH), 2.5 (3H,s,broad,CH_3) ppm.

6.5 EXPERIMENTAL PROCEDURES (CHAPTER 5)

6.5.1 Experimental for Section 5.2.3

N-Arylimidosulphurous chlorides (145a,g) - Through a solution of arylamine (1 mmol) and sulphur dichloride (0.125g, 1.2 mmol) dissolved in freshly distilled chloroform was bubbled chlorine gas for 1 hr. at room temperature under dry nitrogen. The resulting solution was evaporated under dry conditions to give waxy yellow solids assumed to be compounds (145a,g). These were found to be very air- and moisture-sensitive and were therefore used immediately for further reaction.

Reaction of N-arylimidosulphurous chlorides (145a,g) with isoprene - To a stirring solution of crude (145a,g), from above, dissolved in freshly distilled acetone (50 ml) under dry nitrogen was added isoprene (2 ml, 20 mmol). The solution was stirred for 48 hrs. at room temperature. The deep orange colour faded leaving an almost colourless solution which was evaporated to give a residue which was stirred vigorously with cyclohexane (50 ml) and then filtered. The filtrate was evaporated to afford yellow oils identified as mixtures of compounds (96-98a,g), in both cases, by comparison of the ^1H NMR spectra with those of mixtures prepared independently by the procedure described in Section 6.3.2. Overall yields were *ca.* 70%.

6.5.2 Experimental for Section 5.2.4

2,5-Dihydrothiophene (153) - was prepared by the procedure of Gardner *et al.*[131] from 2,5-dihydrothiophene 1,1-dioxide (butadiene sulphone) (7.5g). Compound (153) was obtained as a clear liquid (600 mg, 11%, lit.[131] 12%). BPt. 120-122°C (lit.[131] 122°C).

2-(2-Amino-5-chlorophenyl)-2,5-dihydrothiophene (155g) - was prepared by a modified version of that used by Claus *et al.* to prepare sulphilimines[132]. Hence, a stirring solution of (153) (100 mg, 1.2 mmol) and 4-chloroaniline (150 mg, 1.2 mmol) dissolved in freshly distilled dichloromethane (5 ml) was cooled to -20°C under dry nitrogen. N-Chlorosuccinimide (155 mg, 1.2 mmol) dissolved in dichloromethane (5 ml) was added dropwise over 20 mins. Stirring was continued for 1 hr. as the solution warmed to room temperature, a white precipitate forming. DBU (360 μl, 2 equivs.) was added and the suspension immediately cleared to give a pale yellow solution. This solution was column chromatographed (silica column, 20 x 4 cm) eluting with dichloromethane. The first fraction contained small amounts of yellow products which contained only aniline residues (^{1}H NMR). The second fraction appeared to contain two compounds (^{1}H NMR) one of which was presumed to be the sulphilimine (154g). On standing (*ca.* 24 hrs.) the yellow solid became white[5]. Recrystallisation from 3:1 petroleum ether/diethyl ether afforded white crystals (115 mg, 45%) of (155g), mpt. 100-102°C. Analysis found: C, 56.0; H, 4.7; N, 6.1; required for $C_{10}H_{10}ClNS$: C, 56.7; H, 4.8; N, 6.6%; high resolution MS found: 211.0031 (required: 211.0222); MS m/e (EI): 211 (M^+); (CI): 212; IR ν_{max} (KBr): 3400, 3300 (NH_2) cm^{-1}; ^{1}H NMR

[5]On one occasion the yellow sulphilimine was not observed, the white product (155g) being formed immediately.

($CDCl_3$) δ_H: 7.03 (2H,m,Ar), 6.60 (1H,d, Ar,J=8.15 Hz), 5.98 (2H,m,2x =CH), 5.38 (1H,m,CH), 3.93 (2H,m,CH_2), 3.9 (2H,s,broad,NH_2); ^{13}C NMR ($CDCl_3$) δ_C: 143.1, 131.2, 130.1, 128.2 (2 coincident), 127.5, 123.3, 117.7, 55.0 (CH), 39.6 (CH_2) ppm.

2,5-Dihydrothiophene 1-oxide (158) - was prepared by a modified version of the procedure used for (155g), above. Hence, to a stirring solution of (153) (100 mg, 1.2 mmol) and 2-aminopyrimidine (110 mg, 1.2 mmol) dissolved in freshly distilled dichloromethane (5 ml), under dry nitrogen, was added, at room temperature, a solution of N-chlorosuccinimide (155 mg, 1.2 mmol) dissolved in dichloromethane, dropwise over 20 mins. Stirring was continued for 96 hrs., then DBU (190 μl, 1.1 equiv.) was added, the suspension becoming a clear yellow solution. Column chromatography (silica column, 20 x 4 cm) eluting with ethyl acetate yielded first succinimide and then 2-aminopyrimidine. Elution with methanol yielded a third fraction which appeared bright yellow on the column. The methanol fractions were combined and evaporated. Dichloromethane (*ca.* 100 ml) was added and the mixture stirred for 30 mins. A solid residue was removed by filtration and the filtrate evaporated to give (158) as a pale yellow oil (60 mg, 50%). IR ν_{max} (neat): 1020, (S=O) cm^{-1} (lit.[135] 1020 cm^{-1}); ^1H NMR ($CDCl_3$) δ_H: 5.96 (2H,s), 3.64 (4H,dd,J=17 Hz) [lit.[135] 6.02 (2H,s), 3.58 (4H,dd,J=17 Hz)] ppm.

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APPENDICES

COLLOQUIA, CONFERENCES AND PUBLICATIONS

RESEARCH COLLOQUIA, SEMINARS, LECTURES AND CONFERENCES ORGANISED BY THE DEPARTMENT OF CHEMISTRY

DURING THE PERIOD: 1986-1987

* ALLEN, Prof. Sir G. (Unilever Research) Biotechnology and the Future of the Chemical Industry	13th November 1986
BARTSCH, Dr. B. (University of Sussex) Low Co-ordinated Phosphorus Compounds	6th May 1987
BLACKBURN, Dr. M. (University of Sheffield) Phosphonates as Analogues of Biological Phosphate Esters	27th May 1987
* BORDWELL, Prof. F.G.(Northeastern University,USA) Carbon Anions, Radicals, Radical Anions and Radical Cations	9th March 1987
CANNING, Dr. N.D.S. (University of Durham) Surface Adsorption Studies of Relevance to Heterogeneous Ammonia Synthesis	26th November 1986
CANNON, Dr. R.D. (University of East Anglia) Electron Transfer in Polynuclear Complexes	11th March 1987
CLEGG, Dr. W. (University of Newcastle-upon-Tyne) Carboxylate Complexes of Zinc; Charting a Structural Jungle	28th January 1987
DÖPP, Prof. D. (University of Duisburg) Cyclo-additions and Cyclo-reversions Involving Captodative Alkenes	5th November 1986
DORFMÜLLER, Prof. T. (University of Bielefeld) Rotational Dynamics in Liquids and Polymers	8th December 1986
GOODGER, Dr. E.M. (Cranfield Inst.Technology) Alternative Fuels for Transport	12th March 1987
GREENWOOD, Prof. N.N. (University of Leeds) Glorious Gaffes in Chemistry	16th October 1986
HARMER, Dr. M. (I.C.I. Chemicals & Polymer Group) The Role of Organometallics in Advanced Materials	7th May 1987
HUBBERSTEY, Dr. P. (University of Nottingham) Demonstration Lecture on Various Aspects of Alkali Metal Chemistry	5th February 1987
HUDSON, Prof. R.F. (University of Kent) Aspects of Organophosphorus Chemistry	17th March 1987

HUDSON, Prof. R.F. (University of Kent) — 18th March 1987
Homolytic Rearrangements of Free Radical Stability

JARMAN, Dr. M. (Institute of Cancer Research) — 19th February 1987
The Design of Anti Cancer Drugs

KRESPAN, Dr. C. (E.I. Dupont de Nemours) — 26th June 1987
Nickel(0) and Iron(0) as Reagents in Organofluorine Chemistry

* KROTO, Prof. H.W. (University of Sussex) — 23rd October 1986
Chemistry in Stars, between Stars and in the Laboratory

* LEY, Prof. S.V. (Imperial College) — 5th March 1987
Fact and Fantasy in Organic Synthesis

MILLER, Dr. J. (Dupont Central Research, USA) — 3rd December 1986
Molecular Ferromagnets; Chemistry and Physical Properties

MILNE/CHRISTIE, Dr.A./Mr.S.(International Paints) — 20th November 1986
Chemical Serendipity: A Real Life Case Study

NEWMAN, Dr. R. (University of Oxford) — 4th March 1987
Change and Decay: A Carbon-13 CP/MAS NMR Study of humification and Coalification Processes

OTTEWILL, Prof. R.H. (University of Bristol) — 22nd January 1987
Colloid Science a Challenging Subject

PASYNKIEWICZ, Prof. S. (Technical Univ.,Warsaw) — 11th May 1987
Thermal Decomposition of Methyl Copper and its Reactions with Trialkylaluminium

ROBERTS, Prof. S.M. (University of Exeter) — 24th June 1987
Synthesis of Novel Antiviral Agents

RODGERS, Dr. P.J. (I.C.I. Billingham) — 12th February 1987
Industrial Polymers from Bacteria

* SCROWSTON, Dr. R.M. (University of Hull) — 6th November 1986
From Myth and Magic to Modern Medicine

SHEPHERD, Dr. T. (University of Durham) — 11th February 1987
Pteridine Natural Products; Synthesis and Use in Chemotherapy

THOMSON, Prof. A. (University of East Anglia) — 4th February 1987
Metalloproteins and Magneto-optics

WILLIAMS, Prof. R.L. (Metropolitan Police Forensic Science) — 27th November 1987
Science and Crime

WONG, Prof.E.H. (University of New Hampshire,USA) 29th October 1986
Coordination Chemistry of P-O-P Ligands

WONG, Prof.E.H. (University of New Hampshire,USA) 17th February 1987
Symmetrical Shapes from Molecules to Art and Nature

DURING THE PERIOD: 1987-1988

* BAILEY, Dr. P.D. (University of York) November 1987
Oncogenes

BIRCHALL, Prof. D. (I.C.I. Advanced Materials) 25th April 1988
Environment Chemistry of Aluminium

* BORER, Dr. K. (University of Durham Industrial Research Laboratories) 18th February 1988
The Brighton Bomb - (A Forensic Science View)

BOSSONS, L. (Durham Chemistry Teachers' Centre) 16th March 1988
GCSE Practical Assessment

* BUTLER, Dr. A.R. (University of St.Andrews) 5th November 1987
Chinese Alchemy

* CAIRNS-SMITH, Dr. A. (Glasgow University) 28th January 1988
Clay Minerals and the Origin of Life

DAVIDSON, Dr. J. (Herriot-Watt University) November 1987
Metal Promoted Oligomerisation Reactions of Alkynes

GRAHAM, Prof. W.A.G. (University of Alberta, Canada) 3rd March 1988
Rhodium and Iridium Complexes in the Activation of Carbon-Hydrogen Bonds

* GRAY, Prof. G.W. (University of Hull) 22nd October 1987
Liquid Crystals and their Applications

HARTSHORN, Prof. M.P. (University of Canterbury, New Zealand) 7th April 1988
Aspects of Ipso-Nitration

* HOWARD, Dr. J. (I.C.I. Wilton) 3rd December 1987
Chemistry of Non-Equilibrium Processes

JONES, Dr. M.E. (Durham Chemistry Teachers' Centre) 29th June 1988
GCSE Chemistry Post-mortem

JONES, Dr. M.E. (Durham Chemistry Teachers' Centre) 6th July 1988
GCE Chemistry A-Level Post-mortem

*	KOCH, Prof. H.F. (Ithaca College, U.S.A.) Does the E2 Mechanism Occur in Solution ?	7th March 1988
	LACEY, Mr. (Durham Chemistry Teacher's Centre) Double Award Science	9th February 1988
*	LUDMAN, Dr. C.J. (Durham University) Explosives	10th December 1987
	McDONALD, Dr. W.A. (I.C.I. Wilton) Liquid Crystal Polymers	11th May 1988
	MAJORAL, Prof. J.-P. (Université Paul Sabatier) Stabilisation by Complexation of Short-Lived Phosphorus Species	8th June 1988
	MAPLETOFT, Mrs. M. (Durham Chemistry Teachers' Centre) Salters' Chemistry	4th November 1987
	NIETO DE CASTRO, Prof. C.A. (University of Lisbon and Imperial College) Transport Properties of Non-Polar Fluids	18th April 1988
*	OLAH, Prof. G.A. (University of Southern California) New Aspects of Hydrocarbon Chemistry	29th June 1988
	PALMER, Dr. F. (University of Nottingham) Luminescence (Demonstration Lecture)	21st January 1988
	PINES, Prof. A. (University of California, Berkeley, U.S.A.) Some Magnetic Moments	28th April 1988
	RICHARDSON, Dr. R. (University of Bristol) X-Ray Diffraction from Spread Monolayers	27th April 1988
	ROBERTS, Mrs. E. (SATRO Officer for Sunderland) Talk - Durham Chemistry Teachers' Centre - "Links between Industry and Schools"	13th April 1988
	ROBINSON, Dr. J.A. (University of Southampton) Aspects of Antibiotic Biosynthesis	27th April 1988
*	ROSE, van Mrs. S. (Geological Museum) Chemistry of Volcanoes	29th October 1987
*	SAMMES, Prof. P.G. (Smith, Kline and French) Chemical Aspects of Drug Development	19th December 1987
	SEEBACH, Prof. D. (E.T.H. Zurich) From Synthetic Methods to Mechanistic Insight	12th November 1987
	SODEAU, Dr. J. (University of East Anglia) Durham Chemistry Teachers's Centre: "Spray Cans, Smog and Society"	11th May 1988

SWART, Mr. R.M. (I.C.I.) — 16th December 1987
The Interaction of Chemicals with Lipid Bilayers

TURNER, Prof. J.J. (University of Nottingham) — 11th February 1988
Catching Organometallic Intermediates

* UNDERHILL, Prof. A. (University of Bangor) — 25th February 1988
Molecular Electronics

WILLIAMS, Dr. D.H. (University of Cambridge) — 26th November 1987
Molecular Recognition

WINTER, Dr. M.J. (University of Sheffield) — 15th October 1987
Pyrotechnics (Demonstration Lecture)

DURING THE PERIOD: 1988-1989

ASHMAN, Mr. A. (Durham Chemistry Teachers' Centre) — 3rd May 1989
The Chemical Aspects of the National Curriculum

AVEYARD, Dr. R. (University of Hull) — 15th March 1989
Surfactants at your Surface

AYLETT, Prof. B.J. (Queen Mary College, London) — 16th February 1989
Silicon-Based Chips: The Chemists Contribution

* BALDWIN, Prof. J.E. (Oxford University) — 9th February 1989
Recent Advances in the Bioorganic Chemistry of Penicillin Biosynthesis

BALDWIN & WALKER, Drs. R.R. and R.W. (Hull University) — 24th November 1988
Combustion: Some Burning Problems

BOLLEN, Mr. F. (Durham Chemistry Teachers' Centre) — 18th October 1988
Lecture about the use of SATIS in the classroom

* BUTLER, Dr. A.R. (St. Andrews University) — 15th February 1989
Cancer in Linxiam: The Chemical Dimension

CADOGAN, Prof. J.I.G., (British Petroleum) — 10th November 1988
From Pure Science to Profit

* CASEY, Dr. M. (University of Salford) — 20th April 1989
Sulphoxides in Stereoselective Synthesis

WALTERS & CRESSEY, Mr. D. and T. (Durham Chemistry Teachers' Centre) — 1st February 1989
GCSA Chemistry 1988: "A Coroner's Report"

* CRICH, Dr. D. (University College London) Some Novel Uses of Free Radicals in Organic Synthesis	27th April 1989
DINGWALL, Dr. J. (Ciba Geigy) Phosphorus-containing Amino Acids: Biologically Active Natural and Unnatural Products	18th October 1988
ERRINGTON, Dr. R.J. (University of Newcastle-upon-Tyne) Polymetalate Assembly in Organic Solvents	1st March 1989
FREY, Dr. J. (Southampton University) Spectroscopy of the Reaction Path: Photodissociation Raman Spectra of NOCl	11th May 1989
HALL, Prof. L.D. (Addenbrooke's Hospital, Cambridge) NMR - A Window to the Human Body	2nd February 1989
HARDGROVE, Dr. G. (St. Olaf College, U.S.A.) Polymers in the Physical Chemistry Laboratory	December 1988
HARWOOD, Dr. L. (Oxford University) Synthetic Approaches to Phorbols Via Intramolecular Furan Diels-Alder Reactions: Chemistry under Pressure	25th January 1988
JÄGER, Dr. C. (Friedrich-Schiller University GDR) NMR Investigations of Fast Ion Conductors of the NASICOM Type	9th December 1988
JENNINGS, Prof. R.R. (Warwick University) Chemistry of the Masses	26th January 1989
JOHNSON, Dr. B.F.G. (Cambridge University) The Binary Carbonyls	23rd February 1989
JONES, Dr. M.E. (Durham Chemistry Teachers' Centre) Discussion Session on the National Curriculum	14th June 1989
JONES, Dr. M.E. (Durham Chemistry Teachers' Centre) GCSE and A Level Chemistry 1989	28th June 1989
LUDMAN, Dr. C.J. (Durham University) The Energetics of Explosives	18th October 1988
MACDOUGALL, Dr. G. (Edinburgh University) Vibrational Spectroscopy of Model Catalytic Systems	22nd February 1989
* MARKO, Dr. I. (Sheffield University) Catalytic Asymmetric Osmylation of Olefins	9th March 1989

McLAUCHLAN, Dr. K.A. (University of Oxford) — 16th November 1988
The Effect of Magnetic Fields on Chemical Reactions

* MOODY, Dr. C.J. (Imperial College) — 17th May 1989
Reactive Intermediates in Heterocyclic Synthesis

MORTIMER, Dr. C. (Durham Chemistry Teachers' Centre) — 14th December 1989
The Hindenberg Disaster - an Excuse for Some Experiments

NICHOLLS, Dr. D. (Durham Chemistry Teachers' Centre) — 11th July 1989
Demo: "Liquid Air"

* PAETZOLD, Prof. P. (Aachen) — 23rd May 1989
Iminoboranes XB≡NR: Inorganic Acetylenes ?

* PAGE, Dr. P.C.B. (University of Liverpool) — 3rd May 1989
Stereocontrol of Organic Reactions Using 1,3-dithiane-1-oxides

POLA, Prof. J. (Czechoslovak Academy of Sciences) — 15th June 1989
Carbon Dioxide Laser Induced Chemical Reactions - New Pathways in Gas-Phase Chemistry

* REES, Prof. C.W. (Imperial College London) — 27th October 1988
Some Very Heterocyclic Compounds

REVELL, Mr. P. (Durham Chemistry Teachers' Centre) — 14th March 1989
Implementing Broad and Balanced Science 11-16

SCHMUTZLER, Prof. R. (Technische Universitat Braunschweig) — 6th October 1988
Fluorophosphines Revisited - New Contributions to an Old Theme

* SCHROCK, Prof. R.R. (M.I.T.) — 13th February 1989
Recent Advances in Living Metathesis

* SINGH, Dr. G. (Teeside Polytechnic) — 9th November 1988
Towards Third Generation Anti-Leukaemics

SNAITH, Dr. R. (Cambridge University) — 1st December 1988
Egyptian Mummies: What, Where, Why and How ?

STIBR, Dr. R. (Czechoslovak Academy of Sciences) — 16th May 1989
Recent Developments in the Chemistry of Intermediate-Sited Carboranes

VON RAGUE SCHLEYER, Prof. P. (Universitat Erlangen Nurnberg) — 21st October 1988
The Fruitful Interplay Between Calculational and Experimental Chemistry

WELLS, Prof. P.B. (Hull University) 10th May, 1989
Catalyst Characterisation and Activity

* - Indicates Colloquia attended by the author.

CONFERENCES ATTENDED

1. **R.S.C. Graduate Symposium**, University of Durham, 27th March, 1987.
2. **R.S.C. Graduate Symposium**, University of Durham, 19th April, 1988.
3. R.S.C. Heterocyclic Chemistry Group, Postgraduate Heterocyclic Symposium, University of Nottingham, July 1988.

   Poster presented by the author: "*Efficient Generation of Thionitrosoarenes by Fragmentation of N-(Arylaminothio)phthalimides*".
4. **R.S.C. Perkin Division, North East Regional Meeting**, University of York, 16th December, 1988.
5. **R.S.C. Graduate Symposium**, University of Durham, 12th April, 1989.
6. **R.S.C. Heterocyclic Chemistry Group, Ninth Lakeland Heterocyclic Symposium**, Grasmere, 4th - 8th May, 1989.

PUBLICATIONS

1. M.R. Bryce and P.C. Taylor, *J.C.S.Chem., Commun.*, 1988, 950.
2. M.R. Bryce and P.C. Taylor, *Tetrahedron Lett.*, 1989, 30, 3835.