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Generation and reactions of thionitroso and thioxophosphine intermediates

Mckelvey, Graham Neil

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GENERATION AND REACTIONS OF THIONITROSO AND THIOXOPHOSPHINE INTERMEDIATES

Graham Neil Mckelvey B.Sc. (Hons)

Department of Chemistry
University of Durham

A Thesis submitted for the degree of Doctor of Philosophy
at the University of Durham ·

September 1995

DECLARATION

The work described in this thesis was carried out in the Department of Chemistry at the University of Durham between October 1992 and September 1995. All the work is my own, unless stated to the contrary, and it has not been submitted for a degree at this or any other University.

Dedicated to my parents.

chemistry /'kemɪstrɪ/ *n.* (*pl.* **-ies**) **1** the study of the elements and the compounds they form and the reactions they undergo.

Oxford English Dictionary.

ACKNOWLEDGEMENTS

ABSTRACT

GENERATION AND REACTIONS OF THIONITROSO AND THIOXOPHOSPHINE INTERMEDIATES

Graham Neil Mckelvey B.Sc. (Hons)
University of Durham (September 1995)

A series of alkylthionitroso compounds have been generated *via* thermal fragmentation of *N*-chlorothio-*N*-trimethylsilylalkylamines and intercepted with dienes to form 1,2-thiazine heterocycles (*via* Diels-Alder reaction) and *N*-alkylsulfenamides (*via* Ene reaction). Both types of product were found to be unstable, decomposing in *ca.* 5h (at 20°C). The reaction of these thionitroso compounds with dienes was temperature dependant, higher temperature (*e.g.* 90°C) favoured the Ene pathway whilst lower temperature (*e.g.* 50°C) favoured the Diels-Alder route.

Thionitroso compounds **125a-e** involving 1,5 and 1,6 S--O or S--S nonbonded interactions were generated and reacted with 2,3-dimethyl-1,3-butadiene to afford 1,2-thiazines **126a-e** *via* Diels-Alder reaction. Compounds **126a-e** exhibited remarkable chemical stability relative to 1,2-thiazines without such a nonbonded interaction. This enhanced stability was thought to arise due to the prevention of ring opening by the aforementioned interaction. Low temperature ^{1}H NMR and Nuclear Overhauser Enhancement spectroscopy provided physical evidence for the existence of the nonbonded interaction in compounds **126**.

Reaction of thionitroso compounds with dienes in the presence of metal fluorides (AgF, CsF, KF) resulted in a promotion of the Diels-Alder reaction at the expense of the Ene reaction. When unsymmetrical dienes (1-methyl-1,3-butadiene, 2-methyl-1,3-butadiene) were used a dramatic increase in the regioselectivity of the cycloaddition reaction was observed.

Arylthioxophosphines have been generated, by magnesium induced dechlorination of arylthiophosphonic dichlorides, and intercepted with unsymmetrical dienes (1-methyl-1,3-butadiene, 2-methyl-1,3-butadiene) to afford 1,2-thiaphosphorin heterocycles. The reactions were found to proceed with complete regioselectivity in favour of the C6 and C5 methyl isomers respectively.

ABBREVIATIONS

Bu   butyl
calc.   calculated
CI   Chemical Impact (ionisation)
DEPT   Distortionless Enhancement by Polarisation Transfer
EI   Electron Impact (ionisation)
Et   ethyl
GC   Gas Chromatography
HOMO   Highest Occupied Molecular Orbital
HRMS   High Resolution Mass Spectroscopy
I.R.   Infrared
LDA   lithium diisopropylamide
LUMO   Lowest Unoccupied Molecular Orbital
*m*CPBA   *meta*-chloroperoxobenzoic acid
Me   methyl
MO   Molecular Orbital
mol   mole
MS   Mass Spectroscopy
NBS   *N*-bromosuccinimide
NOE   Nuclear Overhauser Enhancement
Ph   phenyl
Pr   propyl
R   general alkyl, aryl or heterocyclic substituent as indicated
UV   Ultraviolet
VIS   Visible

CONTENTS

XI

Chapter One

Introduction

Cycloadditions are among the best known and most useful organic reactions. The Diels-Alder reaction generates six-membered rings with remarkable stereoselectivity and regioselectivity and is thus of great synthetic utility.
K. Houk, 1974.

1.1 BACKGROUND

This thesis concerns the generation of *C*-thionitroso and, to a lesser extent, *C*-thioxophosphine compounds, and aspects of their reactions with dienes.

Thionitroso **1** and thioxophosphine **2** compounds are reactive dienophilic species. Both may be generated *in situ* and intercepted with dienes in Diels-Alder (DA) reactions to form heterocycles (Scheme 1.1).
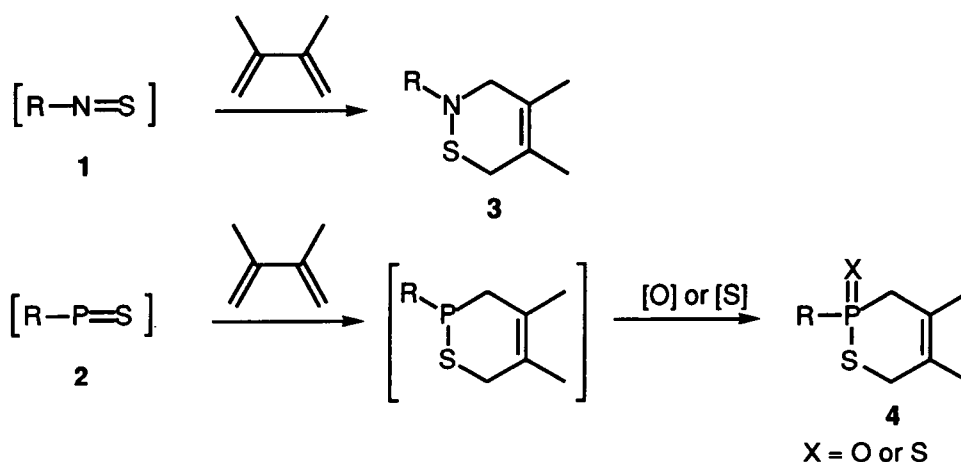
Scheme 1.1

The formation of the 1,2-thiazine **3** and 1,2-thiaphosphorin-2-oxide (or sulfide) **4** heterocycles is taken as evidence for the intermediacy of the free thionitroso and thioxophosphine species, respectively.

This introduction will survey the methods of generation of *C*-thionitroso and *C*-thioxophosphine compounds and the interception of these species to form heterocyclic compounds. Particular attention will be paid to the competition between DA and Ene reactions, and to the regio-isomerism observed when these species are reacted with unsymmetrical dienes. Thioxophosphines will be compared to their thionitroso counterparts.

1.2 *C*-THIONITROSO COMPOUNDS

1.2.1 INTRODUCTION

Thionitroso compounds **1** are closely related to nitroso compounds **5** and *N*-sulfinylamines **6**, and to a lesser extent sulfur diimides **7** (Figure 1.1). The chemistry of nitroso compounds, *N*-sulfinylamines and sulfur diimides is well developed and has been reviewed.[1, 2] The chemistry of thionitroso compounds is not as well advanced; however, reviews are available.[3, 4]

$$R-N=S \quad\quad R-N=O \quad\quad R-N=S=O \quad\quad R-N=S=N-R$$
$$\quad\quad 1 \quad\quad\quad\quad 5 \quad\quad\quad\quad\quad 6 \quad\quad\quad\quad\quad\quad 7$$
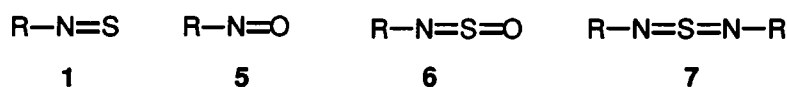
Figure 1.1

C-Thionitroso compounds have been generated by a variety of synthetic approaches. The existence of the free thionitroso species is usually inferred from the isolation of 1,2-thiazine adducts (*e.g.* **3**) upon DA trapping with dienes, or by complexation to a metal centre. Production of sulfur diimides **7** has also been used to infer the existence of thionitroso compounds, as compounds **7** are thought to result from head to tail dimerisation of compounds **3** with concomitant loss of sulfur.

Table 1.1 lists all the *C*-thionitroso (R-N=S) derivatives referred to in this review, and may provide a convenient reference point for the reader.

Table 1.1 List of substituents R in R-N=S

R	R	R	R
1a Ph	**1j** 4-CNC$_6$H$_4$	**1s** Thiazol-2-yl	**1b'** Et
1b 4-ClC$_6$H$_4$	**1k** 2-BrC$_6$H$_4$	**1t** 2,4-di-*t*-Bu-6-MeC$_6$H$_2$	**1c'** CO$_2$Et
1c 4-BrC$_6$H$_4$	**1l** 2-MeC$_6$H$_4$	**1u** 2,4,6-tri-*t*-BuC$_6$H$_2$	**1d'** CO$_2$C$_6$H$_4$
1d 3-NO$_2$C$_6$H$_4$	**1m** 2-CNC$_6$H$_4$	**1v** 2,4,6-TBMC$_6$H$_2$*	**1e'** SO$_2$Ph-4-Me
1e 4-MeC$_6$H$_4$	**1n** 2-Pyridyl	**1w** *i*-Pr	**1f'** 2-NO$_2$C$_6$H$_4$
1f 4-MeOC$_6$H$_4$	**1o** 3-Pyridyl	**1x** *t*-Bu	**1g'** 2-CF$_3$-6-CNC$_6$H$_3$
1g 1-naphthyl	**1p** 4-Pyridyl	**1y** H(CF$_2$)$_2$CH$_2$	**1h'** 3-Br-6-CNC$_6$H$_3$
1h C$_6$F$_5$	**1q** Pyrimidin-2-yl	**1z** H(CF$_2$)$_6$CH$_2$	**1i'** 2,4-di-*t*-Bu-6-CNC$_6$H$_2$
1i 4-NO$_2$C$_6$H$_4$	**1r** Pyrazol-2-yl	**1a'** Me	**1j'** 3-Cl-6-CNC$_6$H$_3$

* 2,4,6-tris[bis(trimethylsilyl)methyl]C$_6$H$_4$

1.2.2 THIONITROSO COMPOUNDS FROM BISAMINE DISULFIDES

1.2.2.1 THERMAL FRAGMENTATION OF *N,N'*-THIODIANILINES

The first evidence for *C*-thionitroso compounds was reported in 1966 by Tavs who proposed that they were intermediates in the thermal decomposition of *N,N'*-thiodianilines.[5] When the *N,N'*-thiodianilines **8a-c** were heated in the presence of excess 2,3-dimethyl-1,3-butadiene, the corresponding 2-aryl-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazines **3a-c** were isolated in 22-41% yield (Scheme 1.2).

R = (a) Ph
    (b) 4-ClC$_6$H$_4$
    (c) 4-BrC$_6$H$_4$
    (d) 3-NO$_2$C$_6$H$_4$
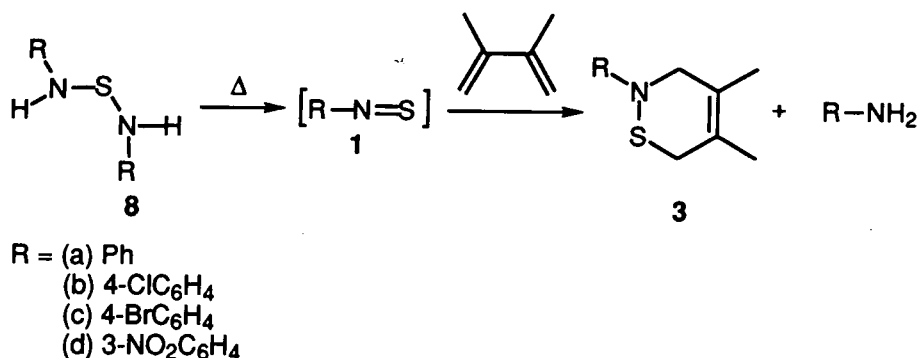
Scheme 1.2

These results were explained by the postulation that the intermediate thionitroso compounds **1a-c** (formed by disproportionation of the *N,N'*-thiodianiline to the parent aniline and a thionitroso compound), were reacting in a [4π + 2π] cycloaddition with the diene.

Davis and Skibo extended the methodology of Tavs to include a derivative with a 3-nitro substituent.[6] These workers also discovered that in the absence of a diene trap thermolysis of *N,N'*-thiodianilines led to almost quantitative conversion to the parent amine, azo compound and sulfur. The presence of azo compound and sulfur was attributed to a head-to-head dimerisation reaction of the thionitroso compound followed by loss of sulfur (Scheme 1.3).[6] More recently, Bryce and Taylor suggested that this type of dimerisation may proceed *via* a head-to-tail mechanism (to produce sulfur diimides **7**) by analogy with dimerisation reactions of thioketones.[7]
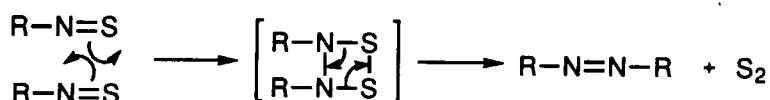
Scheme 1.3

In a reaction similar to the one reported by Tavs,[5] (effectively a thermally-induced proton exchange between nitrogen atoms with concomitant cleavage of an N-S bond in a bisamine disulfide compound), Minami *et al* recognised that thermal decomposition of *N,N'*-diphenyl-*N*-(2-phenyl-*cis*-2-butenoyl)thiobisamine **9** led to thionitroso compound **1a** which could be intercepted in the presence of excess 2,3-dimethyl-1,3-butadiene to yield 1,2-thiazine **3a** as a yellow oil in 35% yield (Scheme 1.4).[8]
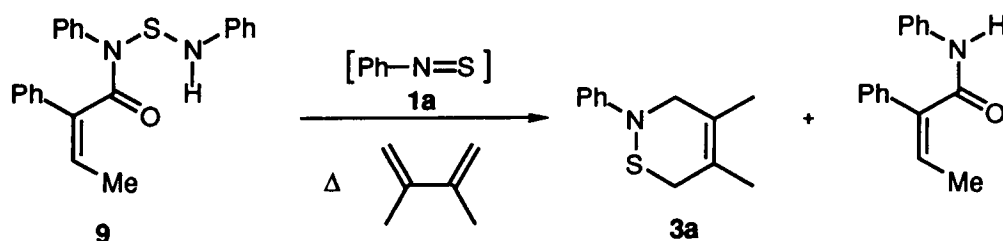
Scheme 1.4

1.2.2.2 FRAGMENTATION OF *N*-(ARYLAMINOTHIO)PHTHALIMIDES

In a modification of the method of Tavs (change of anionic leaving group) Bryce *et al* reported the generation of thionitroso compounds from *N*-(arylaminothio) phthalimides.[7, 9-12] A range of *N*-(arylaminothio)phthalimides **10a-c,e-g** were synthesised, these were easily handled solids that were stable for several months at ambient temperature (*ca*. 15-20°C). Thionitroso compounds **1a-c,e-g** were liberated from the corresponding *N*-(arylaminothio)phthalimides **10a-c,e-g** by treatment with base (Scheme 1.5).[9]

R = (a) Ph
    (b) 4-ClC₆H₄
    (c) 4-BrC₆H₄
    (e) 4-MeC₆H₄
    (f) 4-MeOC₆H₄
    (g) 1-naphthyl
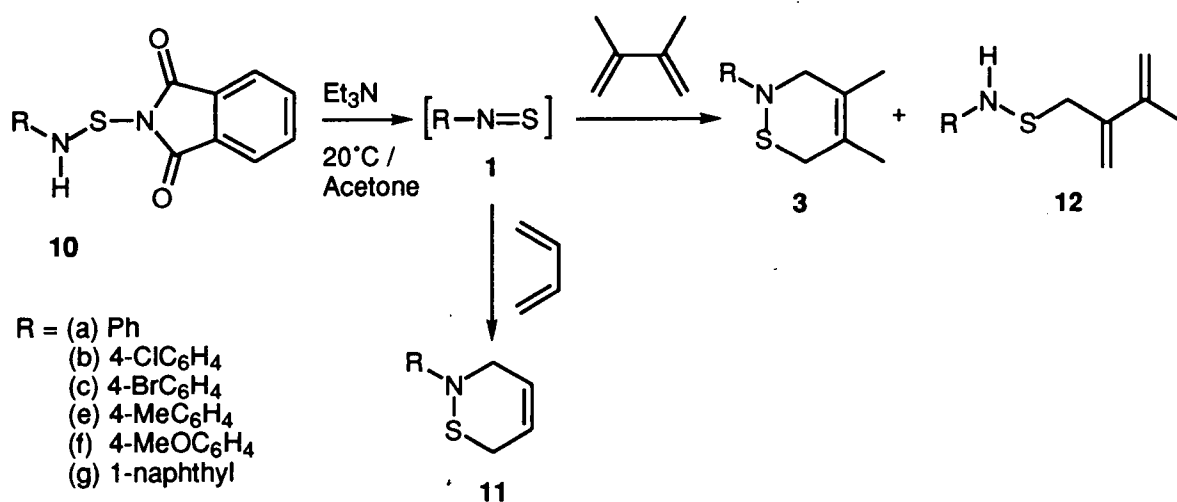
Scheme 1.5

Compounds **1a-c,e-g** were trapped efficiently with both butadiene and 2,3-dimethyl-1,3-butadiene to afford 1,2-thiazines **11a-c,e-g**, and 1,2-thiazines **3a-c,e-g**, respectively, in moderate to high yields (55-75%). Interestingly, when 2,3-dimethyl-1,3-butadiene was used as trap, *N*-aryl-3-methyl-2-methylidene-3-butene-1-sulfenamides **12a-c,e-g** were produced in addition to 1,2-thiazines **3a-c,e-g**. The sulfenamides clearly resulted from Ene reaction with the diene, thus implying that the DA and Ene pathways were in competition. These workers also noted that the nature of the substituent on the aromatic ring of the thionitroso compounds **1a-c,e-g** greatly influenced the ratio of 1,2-thiazine (DA) to sulfenamide (Ene) product observed upon trapping. Electron-releasing substituents favoured the DA product whilst electron-withdrawing substituents favoured the Ene product. The regiochemistry of the Ene reaction in all cases proceeded with C-S bond formation.

Competition between DA and Ene pathways in the reaction of dienes and dienophiles is uncommon, and hence this aspect of thionitroso chemistry is of some interest and is discussed further in Section 1.2.8.

Thionitroso compounds **1c,f** were also reacted with 2-methyl-1,3-butadiene to afford a mixture of regioisomeric 1,2-thiazines **13c,f** and **14c,f** (Scheme 1.6).[9]

$[R-N\!\!=\!\!S]$
1

R = (c) 4-BrC$_6$H$_4$
(f) 4-MeOC$_6$H$_4$

13   **14**   **15**
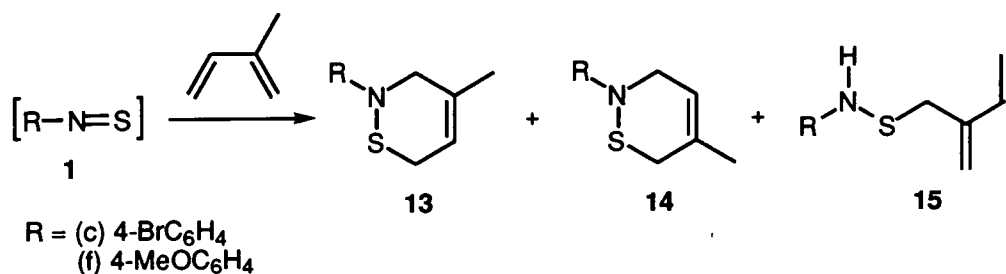
Scheme 1.6

Compounds **13c,f** and **14c,f** were, in both cases, observed in 1 : 3 ratio in the product mixture (along with the expected Ene adduct **15c,f**).[13] Regioisomerism in the trapping reactions of thionitroso compounds is expanded upon in Section 1.2.9.

In a continuation of the work on *N*-(arylaminothio)phthalimides, Bryce and Taylor reported the reaction of thionitroso compounds **1b-c,e-f** with the isomeric (*E,E*) and (*E,Z*)-2,4-hexadienes **16** and **17** to establish the stereochemistry of the cycloaddition reaction (Scheme 1.7).[10]

R = (b) 4-ClC$_6$H$_4$
    (c) 4-BrC$_6$H$_4$
    (e) 4-MeC$_6$H$_4$
    (f) 4-MeOC$_6$H$_4$
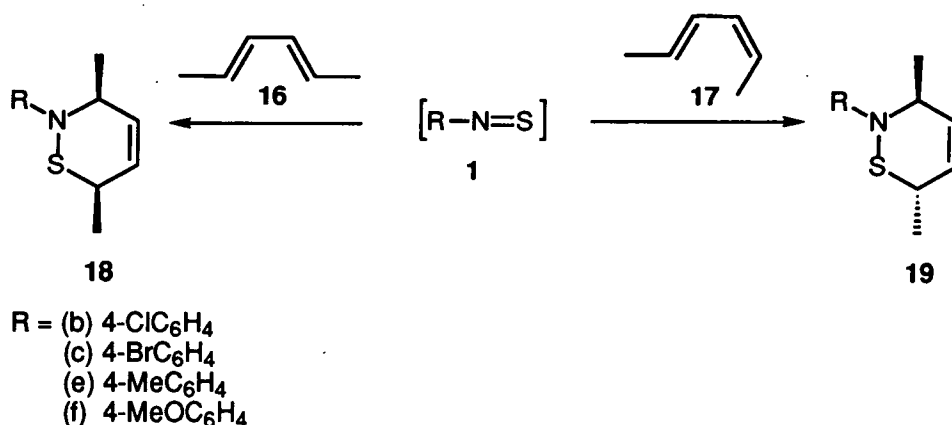
Scheme 1.7

In each case the reactions produced a single stereoisomeric 1,2-thiazine product, **18b-c,e-f** and **19b-c,e-f**, in high yield (*ca.* 70%). The formation of a single stereoisomer supports the view that the <u>free</u> thionitroso compounds **1b-c,e-f** <u>were</u> liberated, and subsequently reacted with the hexadienes **16** and **17** in a concerted [4π + 2π] cycloaddition.

The *N*-(arylaminothio)phthalimide methodology was extended by Bryce *et al* to include thionitrosoarenes **1h-m** and, for the first time, heterocyclic derivatives **1n-s** (Scheme 1.8).[7, 12]

R = (h) C$_6$F$_5$
    (i) 4-NO$_2$C$_6$H$_4$
    (j) 4-NCC$_6$H$_4$
    (k) 2-BrC$_6$H$_4$
    (l) 2-MeC$_6$H$_4$
    (m) 2-NCC$_6$H$_4$
    (n) 2-Pyridyl
    (o) 3-Pyridyl
    (p) 4-Pyridyl
    (q) Pyrimidin-2-yl
    (r) Pyrazol-2-yl
    (s) Thiazol-2-yl

Scheme 1.8

7
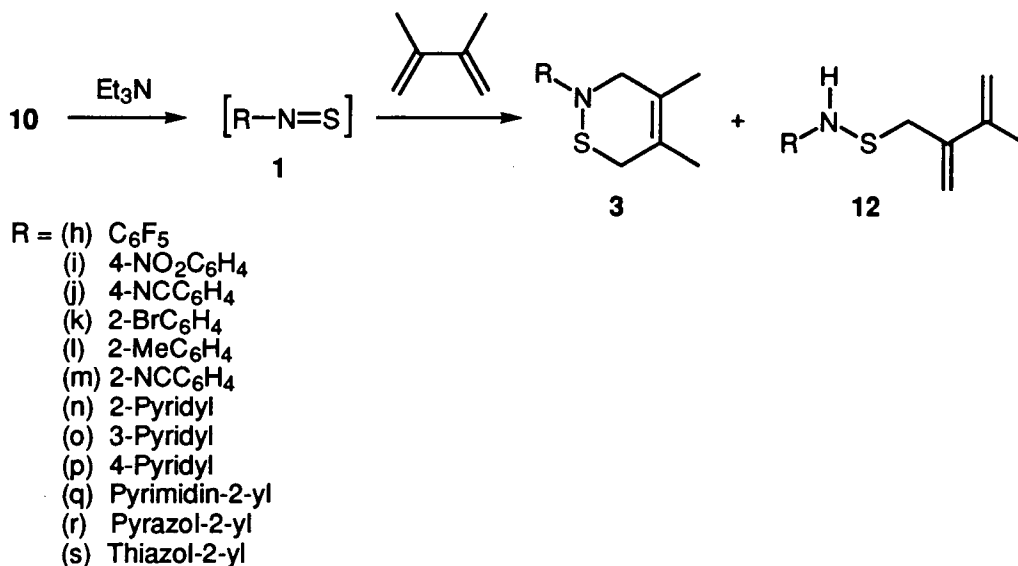
Again it was noted that thionitroso compounds **1** with electron-releasing substituents gave a predominance of the DA adduct **3** in the product mixture, whilst those with electron-withdrawing substituents tended to give a predominance of the Ene adduct **12**. Table 1.2 summarises these effects on the ratio of DA : Ene adduct obtained when a variety of thionitroso compounds **1** were reacted with 2,3-dimethyl-1,3-butadiene.

Table 1.2 Ratio of DA(**3**) : Ene(**12**) adducts obtained upon reaction of R-N=S with 2,3-dimethyl-1,3-butadiene

R	Adduct ratio	
	3 (DA)	**12** (Ene)
1a Ph	55	45
1c 4-BrC$_6$H$_4$	25	75
1e 4-MeC$_6$H$_4$	60	40
1f 4-MeOC$_6$H$_4$	85	15
1g 1-naphthyl	45	55
1i 4-NO$_2$C$_6$H$_4$	20	80
1j 4-CNC$_6$H$_4$	20	80
1k 2-BrC$_6$H$_4$	12	88
1l 2-MeC$_6$H$_4$	35	65
1m 2-CNC$_6$H$_4$	10	90
1n 2-Pyridyl	60	40
1s Thiazol-2-yl	20	80
1h' 3-Br-6-CNC$_6$H$_3$	22	78
1j' 3-Cl-6-CNC$_6$H$_3$	10	90

These observations were rationalised on a 'reactivity - selectivity' basis, and by steric arguments (see Section 1.2.8).

Reaction of thionitroso compounds **1c,e-f** with 2-chloro-1,3-butadiene **20** (to afford the regioisomeric 1,2-thiazines **21c,e-f** and **22c,e-f**) and with 1-methyl-1,3-butadiene **23** (to afford regioisomeric 1,2-thiazines **24c,e-f** and **25c,e-f**), again in moderate to high yields, were also reported by Bryce *et al* (Scheme 1.9).[12]
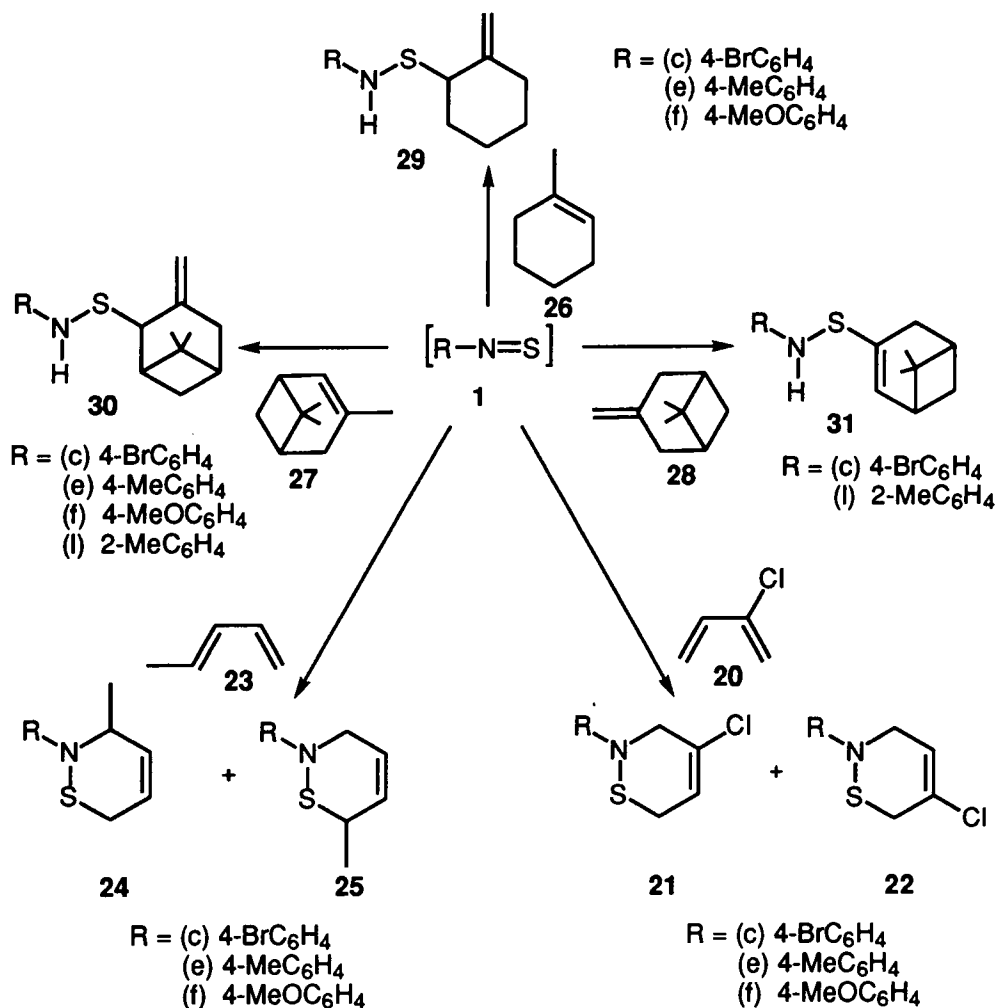
Scheme 1.9

The regioisomerism observed in these cycloaddition reactions is interesting. With 2-chloro-1,3-butadiene **20**, thionitroso compounds **1e-f** showed no regioselectivity (1,2-thiazines **21e-f** and **22e-f** being produced in equal amounts). In contrast, compound **1c** did exhibit regioselectivity as 1,2-thiazines **21c** and **22c** were produced in 2 : 1 ratio. Furthermore, in the reaction of 1-methyl-1,3-butadiene **23** with thionitroso compounds **1c,e-f**, regioselectivity was observed in each case, with 1,2-thiazines **24c,e-f** and **25c,e-f** being produced in 3 : 1, 3 : 1 and 2 : 1 ratios, respectively.

It was concluded from these results that the electronic nature of the substituent on the aromatic ring of the thionitroso species did not influence the regiochemical outcome of the cycloaddition reaction with unsymmetrical dienes. Mechanistic aspects of this are discussed in Section 1.2.9.

Ene reactions of thionitroso compounds were also observed with 1-methylcyclohexene **26**, α-pinene **27** and ß-pinene **28** leading to sulfenamides **29**, **30** and **31**, respectively (Scheme 1.9). The reactions with ß-pinene were the first reported reactions of a thionitroso compound with an exocyclic alkene.[12] As was previously observed, all the Ene reactions proceeded with sole formation of the C-S bond.[7] As the sulfenamides **29**, **30** and **31** were found to be unstable, derivatisation with 2,6-difluorobenzoyl isocyanate **32**, to afford derivatives such as **33**, was used to simplify their analysis. This was the first reported reaction of this type of Ene adduct, although the yields were somewhat low (5-14%) (Scheme 1.10).

32   **30**   **33**

R = (c) 4-BrC$_6$H$_4$
    (e) 4-MeC$_6$H$_4$
    (f) 4-MeOC$_6$H$_4$
    (l) 2-MeC$_6$H$_4$
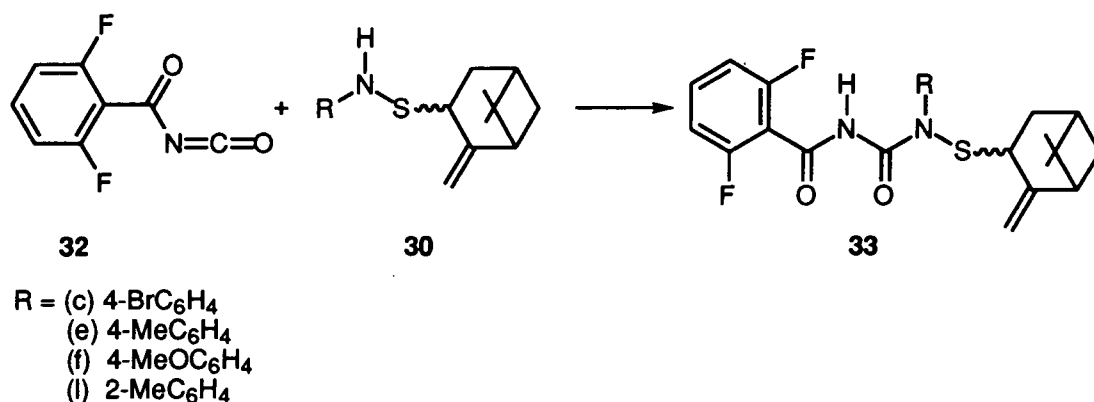
Scheme 1.10

1.2.3 THIONITROSO COMPOUNDS FROM SULFURISED AMINES

1.2.3.1 *N*-THIOSULFINYLANILINE PRECURSORS

In principle, direct reaction of amines with sulfur represents the most efficient route to the formation of thionitroso compounds. Barton and Robson's direct reaction of an amine, 4-(*N*,*N*-dimethylamino)aniline **34**, with a thiolating reagent (phosphorus pentasulfide) did not produce a thionitroso compound, instead a purple crystalline solid was obtained (15% yield), which proved, on analysis, to be 4-(*N*,*N*-dimethylamino)thiosulfinylaniline **35** (Scheme 1.11).[14] This was the first report of a stable *N*-thiosulfinylamine.

34   **35**
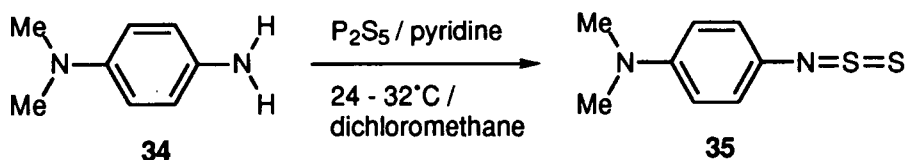
Scheme 1.11

In the same vein Inagaki *et al* have reported desulfurisation of *N*-thiosulfinylanilines **36t-u** to yield sulfur diimides **7t-u** and *N*-sulfinylamines **6t-u** (Scheme 1.12).[15, 16]

$$R-N=S=S \xrightarrow{\substack{\Delta, \, h\sqrt{} \\ \text{or } R_3P}} [R-N=S] \longrightarrow R-N=S=N-R \; + \; R-N=S=O \; + \; RNH_2$$

| **36** | **1** | **7** | **6** |

R = (t) 2,4-di-*t*-Bu-6-MeC$_6$H$_2$
(u) 2,4,6-tri-*t*-BuC$_6$H$_2$
(v) 2,4,6-tris[bis(trimethylsilyl)methyl]C$_6$H$_2$
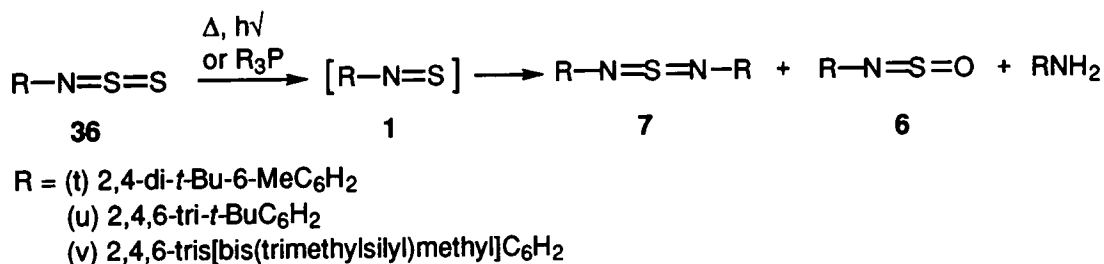
Scheme 1.12

The desulfurisation of compounds **36** was induced thermally, photochemically or by reaction with triphenylphosphine. The reactions were thought to proceed *via* the intermediate thionitroso compounds **1t-u**, which underwent head-to-tail dimerisation followed by loss of sulfur to give sulfur diimides **7t-u** (typically in 20-30% yields). Unno *et al* reported a similar reaction for compound **1v**.[17] Interestingly, compounds **36t-v** were not reported as being unstable; they were probably stabilised kinetically by the very bulky substituents on the nitrogen atom (*cf*. R-P=S species in Section 1.3.5).

1.2.3.2 *N*-ARYLIMINOSULFUR DICHLORIDE PRECURSORS

Sulfur dichloride has also been employed in attempts to generate thionitroso compounds. Bryce and Taylor reported the generation of thionitroso compounds by the action of a mixture of sulfur dichloride and chlorine on amines (Scheme 1.13).[7]

R = (b) 4-ClC$_6$H$_4$
(e) 4-MeC$_6$H$_4$
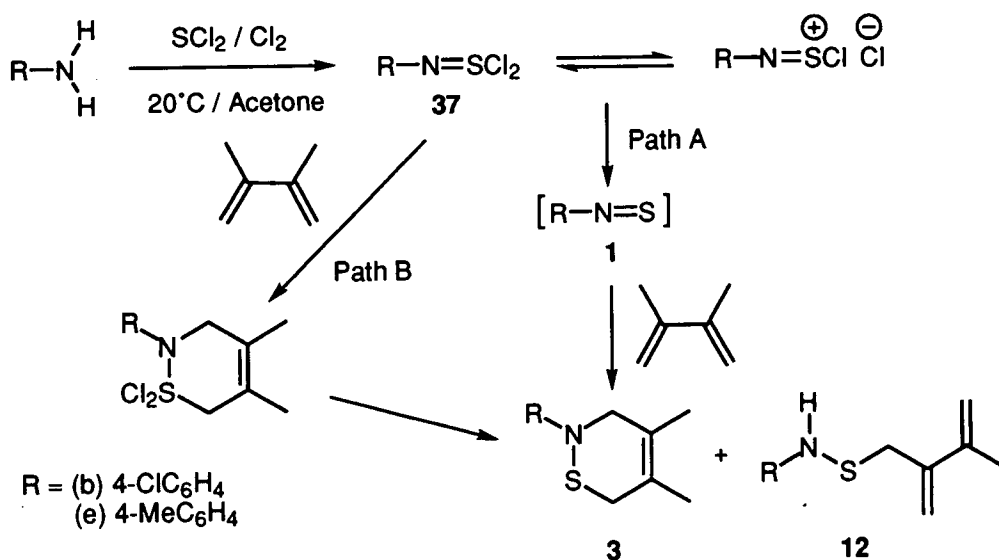
Scheme 1.13

The highly unstable intermediaries in this process were thought to be *N*-aryliminosulfur dichlorides **37**, which had been reported previously.[18] On reaction of compounds **37b,e** with 2,3-dimethyl-1,3-butadiene, both the DA **3b,e**, and the Ene adducts **12b,e** were isolated in *ca.* 70% combined yield. Similar results were observed when *N*-(arylaminothio)phthalimides **10** were used as the precursors, strongly suggesting that the reaction proceeded *via* Path A (by way of thionitroso compounds **1b,e**). However, a discrepancy in the ratio of adducts **3e** and **12e** (there was less Ene adduct) was noted when the results were compared with the *N*-(arylaminothio)phthalimide series of experiments. Thus, the authors could not rule out the possibility that some reaction had occurred *via* Path B, with dechlorination occurring <u>after</u> reaction with the diene.

A more adaptable method for the generation of thionitroso compounds by sulfurising amines was introduced by Mayer *et al.*[19] Reaction of *N,N*-bis(trimethylsilyl)aniline **38** with sulfur dichloride, followed by thermolysis in the presence of excess 2,3-dimethyl-1,3-butadiene, resulted in isolation of DA adduct **3a**, which presumably was formed by way of thionitroso compound **1a** (Scheme 1.14).
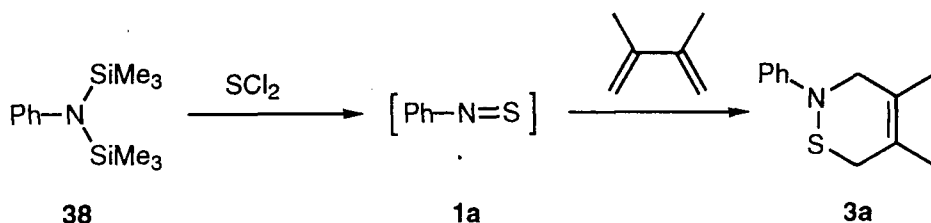
Scheme 1.14

1.2.3.3 FRAGMENTATION OF *N*-CHLOROTHIO-*N*-TRIMETHYLSILYLAMINES

Markovskii *et al* introduced a refinement to the method of Mayer by reacting monosilylated amines **39w-z** with sulfur dichloride in the presence of base to afford *N*-chlorothio-*N*-trimethylsilylalkylamines **40w-z** (Scheme 1.15).* [20, 21]

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* It is possible that the methodology described by Mayer involves formation of *N*-chlorothio-*N*-trimethylsilylamines at some point during the reaction sequence.
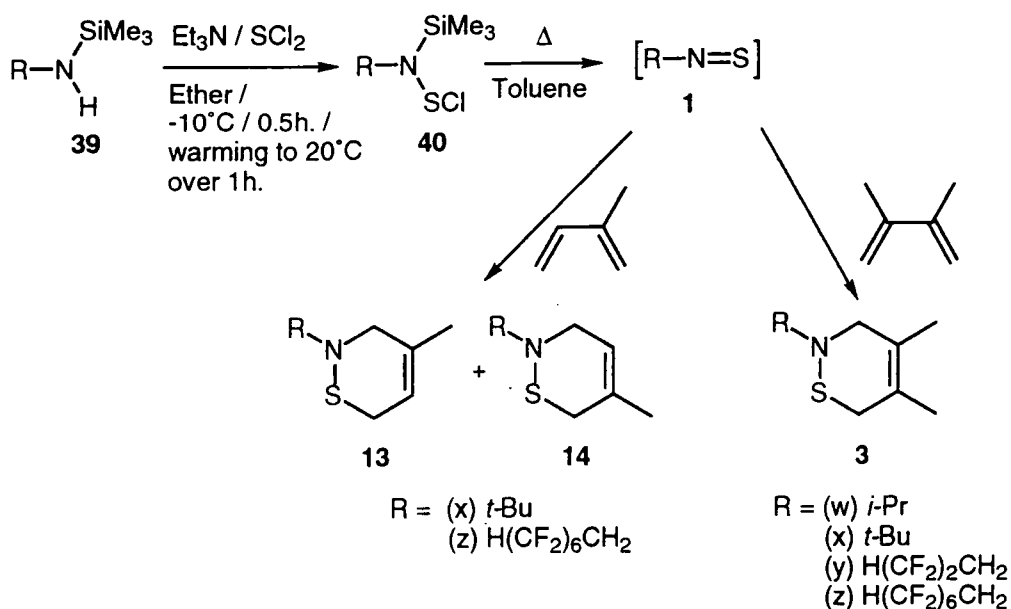
Scheme 1.15

Compounds **40w-z** were described as unstable oils that decomposed slowly at room temperature to a multitude of unidentified polymeric products. However, if compounds **40w-z** were reacted immediately with an excess of 2,3-dimethyl-1,3-butadiene, 1,2-thiazines **3w-z** could be obtained in moderate yields (53-55%), by way of thionitroso compounds **1**. Reaction with 2-methyl-1,3-butadiene produced a mixture of regio-isomeric 1,2-thiazines **13x,z** and **14x,z** in 1 : 4 ratio. Thus the reactions appeared to be highly regioselective (see Section 1.2.9 for further comment on this aspect).

In the absence of a diene trap these authors reported isolation of sulfur diimides and other polymeric products; the observation of sulfur diimides was again indicative of the involvement of thionitroso intermediates (*cf.* the results reported by Inagaki and Unno, Section 1.2.3.1).[15, 16] Markovskii's method worked well for alkylthionitroso compounds. However, this group of workers reported that generation and interception of thionitrosoarenes from *N*-chlorothio-*N*-trimethylsilylarylamines was not possible; instead of the expected 1,2-thiazine products only polymeric material and sulfur diimides were observed. In an extension of this methodology we have now discovered that arylthionitroso compounds can be generated and intercepted from *N*-chlorothio-*N*-trimethylsilylamines using modified conditions.[22] Details of this work form part of this thesis (see Chapter 4).

Unexpectedly neither Mayer nor Markovskii reported the presence of Ene adducts upon trapping with 2,3-dimethyl-1,3-butadiene. Comparison with the work of Bryce *et al*

detailed above would lead one to suspect that these compounds were either highly unstable or had been overlooked.

1.2.3.4 OTHER *N*-SULFURISATION REACTIONS

Bryce has reported the use of piperidine-1-sulfenyl chloride **41** as a sulfur transfer reagent.[23] When diaminonaphthalene **42** was treated with this reagent, sulfur diimide **43** was obtained, possibly by way of bis-thionitroso compound **44** (Scheme 1.16). This is an example of an intramolecular version of the dimerisation reaction exhibited by thionitroso compounds (*cf.* the intermolecular version in for example Scheme 1.12).
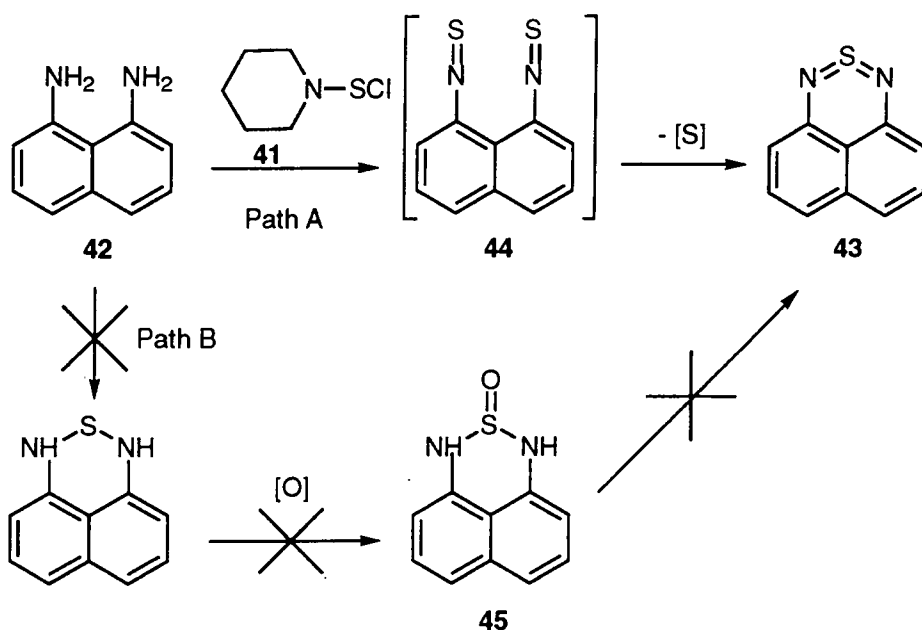
Scheme 1.16

The alternative Path B was ruled out when reaction of an authentic sample of **45** with piperidine-1-sulfenyl chloride **41** under the same conditions failed to produce any sulfur diimide **43**.

1.2.4 THIONITROSO COMPOUNDS FROM YLIDES

1.2.4.1 OXAZIRIDINE PRECURSORS

Generation of thionitroso compounds *via* fragmentation of *S,N*-ylides has been reported by two groups of workers.[24-26] In their work on the reactions of oxaziridines, Hata and

Watanabe described, for the first time, the generation of thionitrosoalkanes **1w,a'-b'** (Scheme 1.17).[24]
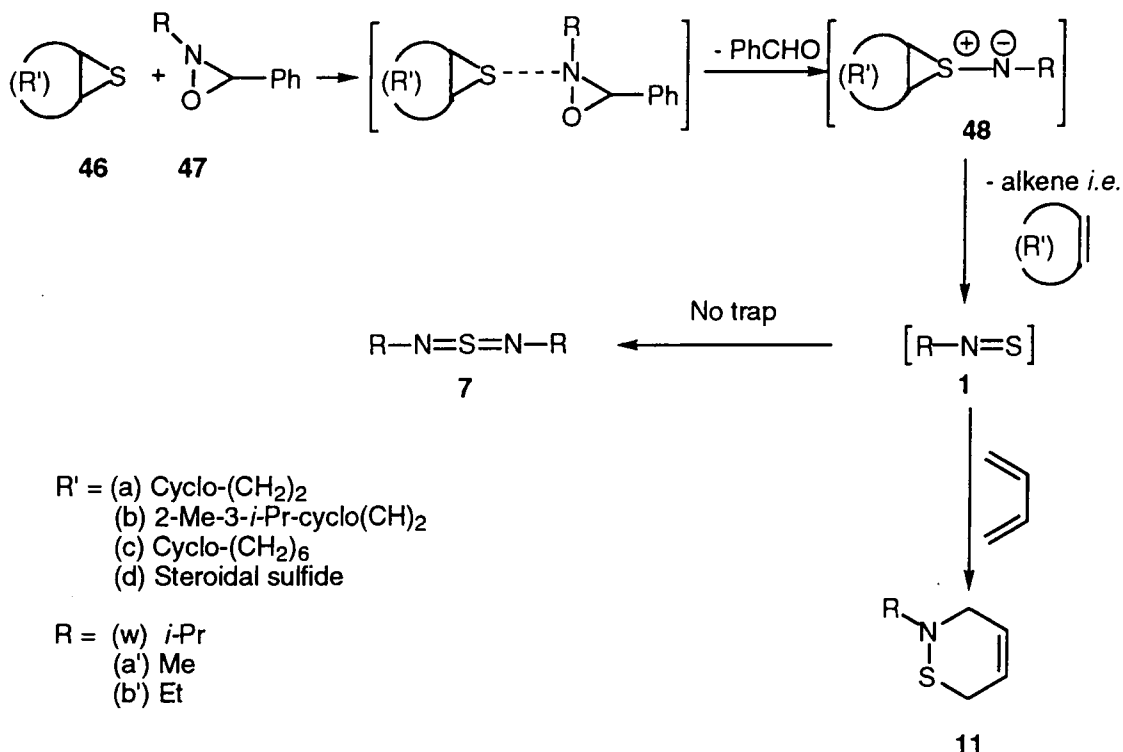
Scheme 1.17

The reaction of episulfides **46a-d** with 2-alkyl-3-phenyloxaziridines **47w,a'-b'** was found to proceed *via* nucleophilic attack of sulfur at nitrogen. The resultant intermediate fragmented with loss of benzaldehyde to give ylides **48** which then underwent further fragmentation by loss of an alkene moiety to give thionitrosoalkanes **1w,a'-b'**. Compounds **1w,a'-b'** were intercepted with butadiene to give 1,2-thiazines **11w,a'-b'***via* DA reaction in 33, 69, and 26% yields, respectively. In the absence of diene trap sulfur diimides **7w,a'-b'** were obtained. Attempts to generate the *t*-Bu derivative failed, this was ascribed to reduced reactivity of the oxaziridine ring to nucleophiles for steric reasons.

Sulfur diimides **7w,a'-b'** were deduced to have resulted from dimerisation of thionitroso compounds **1w,a'-b'**, and from nucleophilic attack of a thionitroso sulfur atom on a molecule of unreacted oxaziridine. This latter seems unlikely in view of MO calculations which show sulfur bearing partial positive charge (thus having reduced nucleophilicity).[21]

1.2.4.2 THIOPHENE *S,N*-YLIDE PRECURSORS

In another reaction involving the fragmentation of ylides Meth-Cohn and van Vuuren described the generation of acyl and sulfonyl thionitroso compounds, the first examples of electron deficient thionitroso species.[25, 26] The inspiration for the methodology was drawn from the chemistry of tetrachlorothiophene 1,1-dioxide **49** which was known to undergo alkene induced DA reaction with synchronous extrusion of sulfur dioxide from the intermediate to give hexahydronaphthalene **50** (Scheme 1.18).
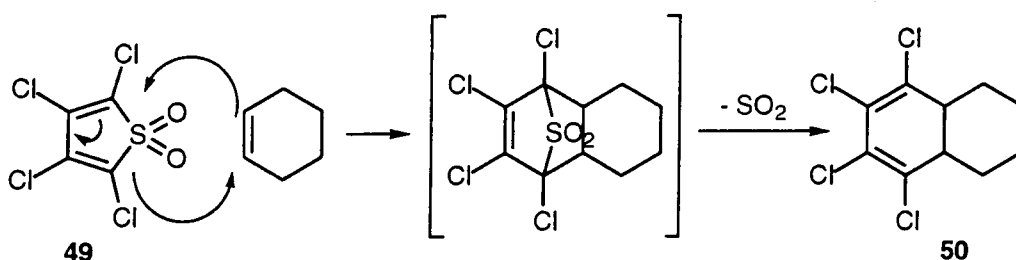
Scheme 1.18

It was reported that the extrusion reaction was not to limited to sulfur dioxide and that the analogous tetrachlorothiophene *S,N*-ylides **51c'-e'** extruded a thionitroso fragment upon similar reaction (Scheme 1.19).

When tetrachlorothiophene *S,N*-ylides **51c'-e'** were reacted with cyclohexene, initial DA reaction resulted in formation of hexahydronaphthalene **50**. Synchronous extrusion of thionitroso compounds **1c'-e'**, followed by Ene reaction with the excess cyclohexene, resulted in a high yield (64-98%) of sulfenamides **52c'-e'** (Scheme 1.19).
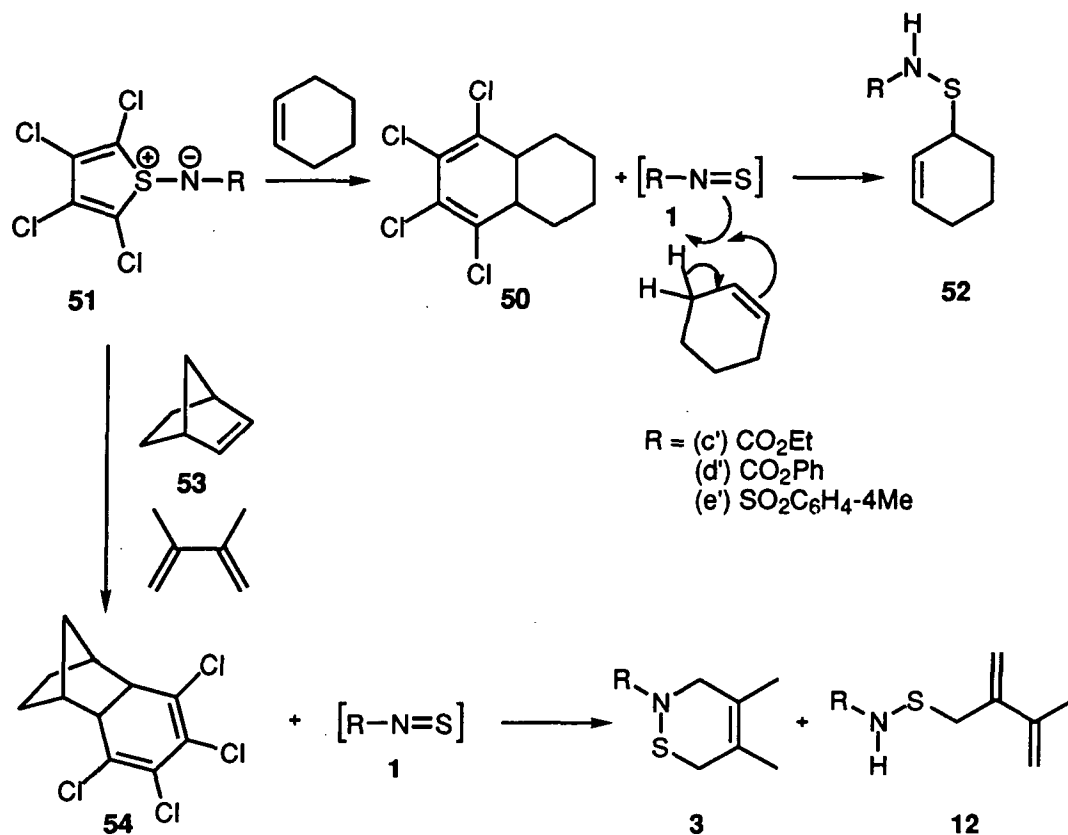
Scheme 1.19

When tetrachlorothiophene *S,N*-ylides **51c'-e'** were reacted with an alkene <u>unable</u> to undergo Ene reaction with the thionitroso fragment, a multitude of uncharacterised products was obtained. However, if such a reaction were performed <u>in the presence of a diene</u>, efficient trapping of the thionitroso compound ensued. Thus, reaction of ylides **51c'-e'** with a mixture of norbornene **53** (an alkene which is unable to undergo Ene reaction as the double bond would be formed at a bridgehead carbon - a process that does not occur due to poor orbital overlap, known as Bredt's Rule) and 2,3-dimethyl-1,3-butadiene was performed. This resulted in the expected adduct **54** from initial DA reaction of the ylide with norbornene, plus thionitroso compounds **1c'-e'**. The thionitroso compounds then underwent both DA and Ene reaction with the 2,3-dimethyl-1,3-butadiene to give 1,2-thiazines **3c'-e'** and sulfenamides **12c'-e'**, respectively. This was the first report of competition between DA and Ene pathways in the cycloaddition reactions of thionitroso compounds.

Meth-Cohn and van Vuuren noted that the electron-deficient thionitroso compounds **1c'-e'** reacted with 2,3-dimethyl-1,3-butadiene to yield DA and Ene adducts **3c'-e'** and **12c'-e'** in 1 : 1 ratio (*i.e.* a high proportion of Ene adduct was produced). Bryce and Taylor also

found that thionitrosoarenes with electron-withdrawing substituents gave a predominance of Ene adduct with the same diene (Table 1.2).[7] Thus it can be seen that this trend is a general one, even when different methods for the generation of thionitroso compounds are employed.

Meth-Cohn and van Vuuren also reported interception of thionitroso compound **1d'** with 2-methyl-1,3-butadiene (Scheme 1.20).

R = (d') CO$_2$Ph
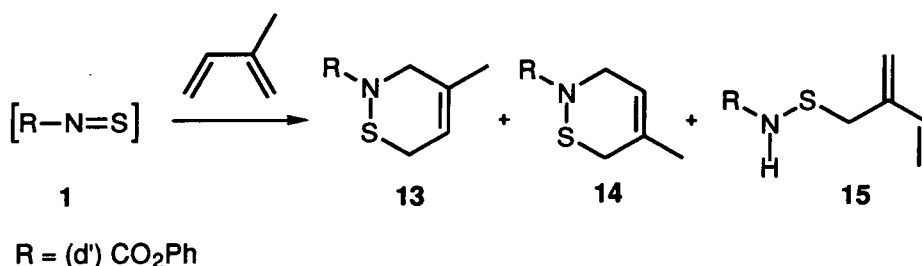
Scheme 1.20

The cycloaddition reaction proceeded *via* both DA and Ene pathways yielding regio-isomeric 1,2-thiazines **13d'** and **14d'**, and sulfenamide **15d'**, respectively. There was no regioselectivity with respect to 1,2-thiazines **13d'** and **14d'**, which were produced in a 1 : 1 ratio. The same authors reported the reaction of compounds **1c'-e'** with a range of alkenes (*e.g.* cyclopentadiene, styrene, 1-hexene) thus proving the versatility of this novel methodology for the generation and interception of electron-deficient thionitroso compounds. When cyclopentadiene was used to intercept compound **1d'** the expected 1,2-thiazine was not observed, instead a [2 + 2 + 2] reaction occurred resulting in the formation of a 1,3,2,4-dithiadiazine in 14% yield.[26]

1.2.5 PHOTOCHEMICAL GENERATION OF THIONITROSO COMPOUNDS

1.2.5.1 BENZO[*C*]-1,2,5-THIADIAZOLE PRECURSORS

Pedersen *et al* were the first to report the photochemical generation of a thionitroso compound.[27] When benzo[*c*]-1,2,5-thiadiazole **55** was subjected to flash photolysis at room temperature, a transient absorption band at 493nm (hexane solvent) was observed which gradually disappeared with concomitant reappearance of starting material (Scheme 1.21).
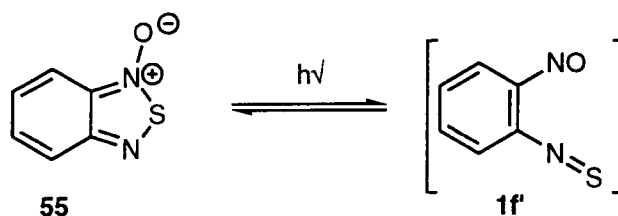
Scheme 1.21

A similar irradiation experiment at low temperature showed transient absorptions at 458 and 485nm from which the authors concluded that the transient species was thionitroso compound **1f'**.

1.2.5.2 3-AZIDO-2,1-BENZISOTHIAZOLE PRECURSORS

The reaction detailed by Pedersen has limited synthetic utility. However, Joucla and Rees subsequently reported a photochemical method for the generation of thionitroso compounds that is applicable to a range of 2-cyanothionitrosoarenes (Scheme 1.22).[28]
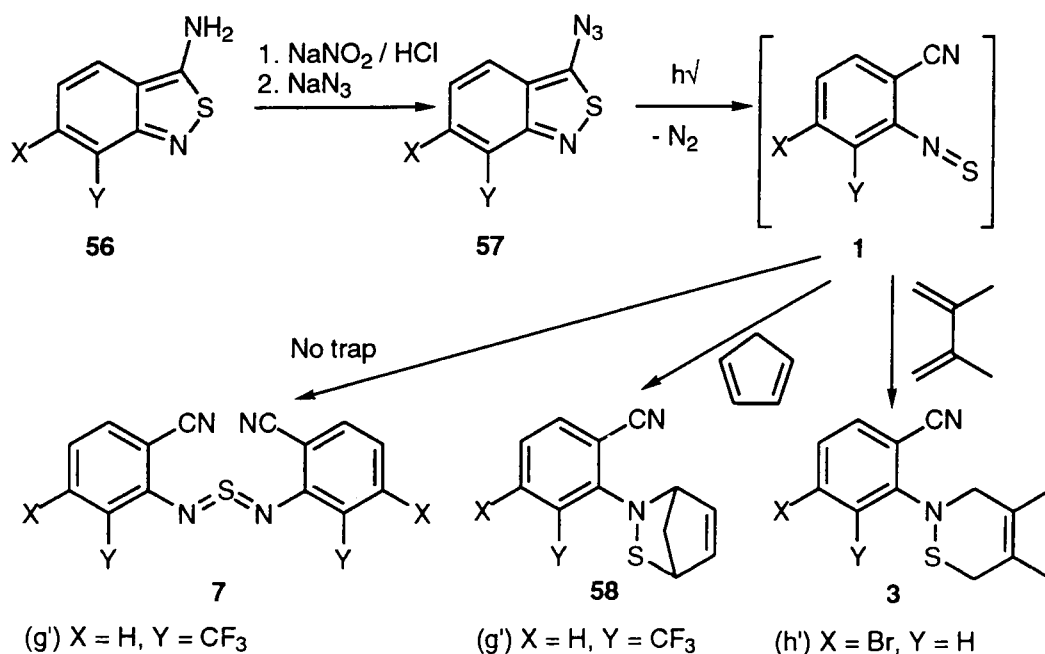
Scheme 1.22

The seminal idea for the methodology came from known ring opening reactions of heterocycles with a carbene or nitrene moiety in the α-position.[29] Joucla and Rees extended this type of reaction to 3-azido-2,1-benzisothiazoles. Thus 3-amino-2,1-benzisothiazoles **56g'-h'** were converted to 3-azido-2,1-benzisothiazoles **57g'-h'** by

sequential treatment with sodium nitrite and sodium azide. Compounds **57g'-h'** thus formed underwent photochemically induced (450 kW Hg lamp) ring opening to yield thionitroso compounds **1g'-h'**. An absorption band at 2220 cm^{-1} (CN) in the I.R. was characteristic of compounds **1g'-h'**.

In the presence of 2,3-dimethyl-1,3-butadiene or cyclopentadiene compounds **1g'-h'** could be intercepted to form 1,2-thiazines **3g'-h'** and **58g'-h'** respectively (yield *ca.* 60% for compounds **58**). These workers are the only ones who note formation of a [4 + 2] DA adduct from reaction of a thionitroso compound and cyclopentadiene. In the absence of a diene trap, compounds **1g'-h'** dimerised to form sulfur diimides **7g'-h'**. In the reaction of compounds **1g'-h'** with 2,3-dimethyl-1,3-butadiene only the DA adduct **3g'-h'** was observed; no Ene product was reported.

Takahashi *et al* extended this route to the generation of thionitroso compound **1i'** by photochemical or thermal fragmentation of a 3-azido-2,1-benzisothiazole **57i'** (Scheme 1.23).[30]
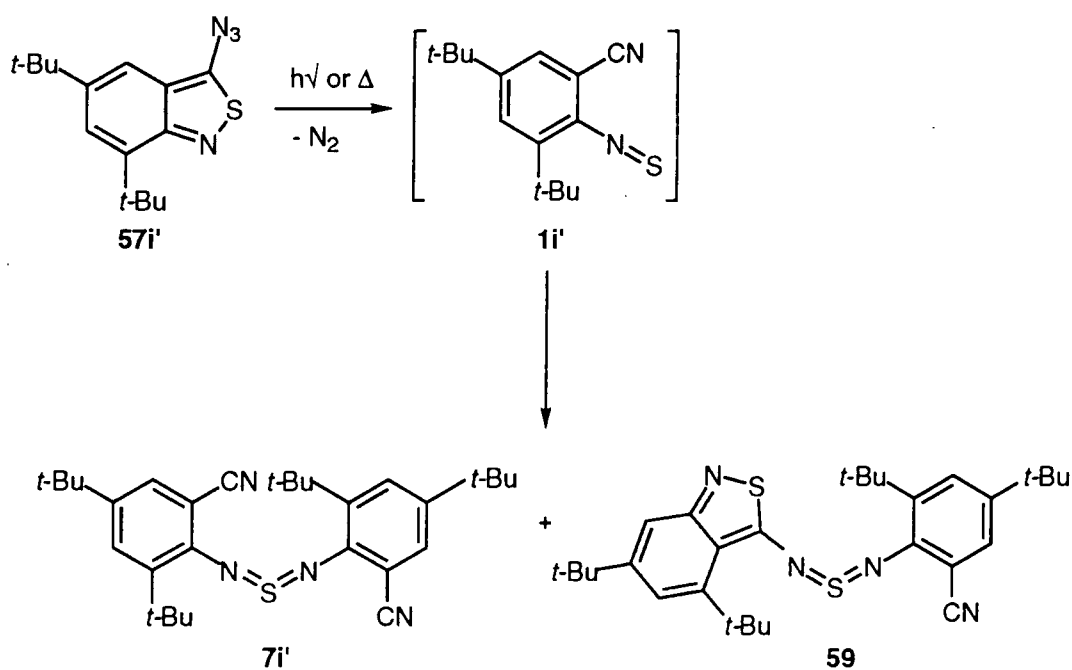
Scheme 1.23

Symmetrical sulfur diimide **7i'** and unsymmetrical sulfur diimide **59** were isolated in the product mixture along with 2,4-di-*t*-butyl-6-cyanoaminobenzene. Compound **7i'** was most likely formed by dimerisation of **1i'**. The authors explained the formation of compound **59** by postulating a 1,3-dipolar reaction between compounds **57i'** and **1i'** to yield an unknown

thiatetrazole intermediate **60** which then decomposed losing nitrogen to yield compound **59** (Scheme 1.24).

R = (i') 2,4-di-*t*-Bu-6-NCC$_6$H$_2$
R'= 2,4-di-*t*-Bu-benzisothiazole
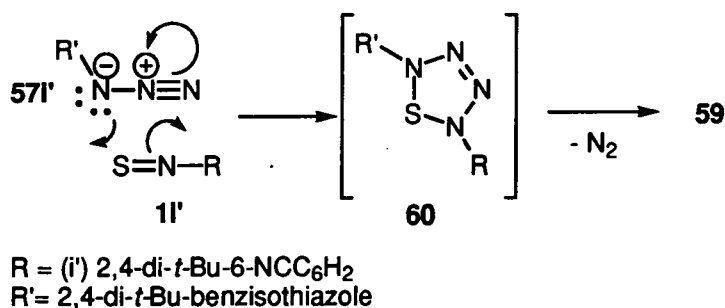
Scheme 1.24

Recognising that such [3 + 2] reactions had not been reported previously, Takahashi *et al* investigated these further by reacting thionitroso compound **1i'** with diazo compounds **61a-c** (Scheme 1.25).
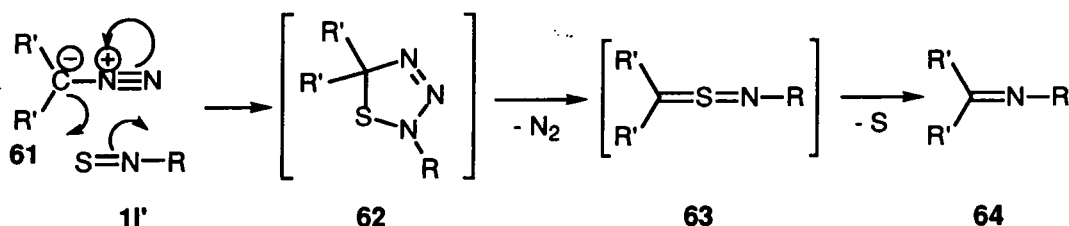
R = (i') 2,4-di-*t*-Bu-6-NCC$_6$H$_2$
R'= (a) Ph
     (b)
     (c)
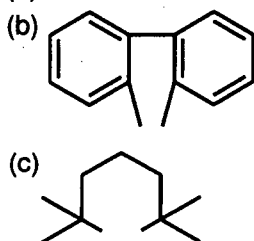
Scheme 1.25

The reactions were considered to proceed *via* [3 + 2] cycloaddition of thionitroso compound **1i'** with an excess of diazo compounds **61a-c**. The initial 1,2,3,4-thiatriazole cycloadducts **62a-c** were not isolable, spontaneous loss of nitrogen yielded thiocarbonylimines **63a-c**. Compounds **63a-b** were usually unstable, decomposing *via* loss of sulfur to yield imines **64a-b**; however, compound **63c** was isolable and was thought to be kinetically stabilised by the steric pressure of the bulky R' group. These workers also reported the reaction of molecular oxygen with compound **1i'** to yield compound **66** (Scheme 1.26).

21
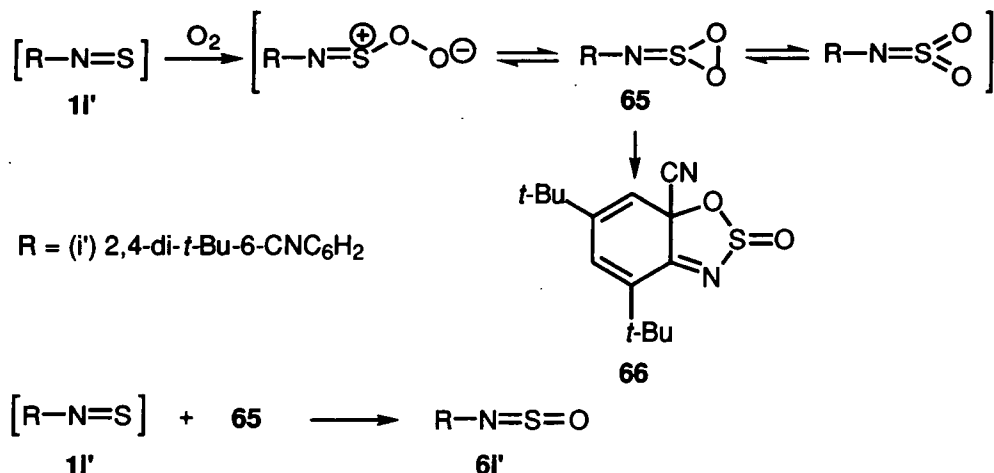
Scheme 1.26

Compounds **7i'** and **59** were amongst the reaction products (formed presumably from dimerisation of **1i'** and [3 + 2] cycloaddition of **1i'** with **57i'**) along with *N*-sulfinylamine **6i'** and oxathiazole **66**. Formation of the latter two compounds was attributed to the action of molecular oxygen on thionitroso compound **1i'** to yield intermediate **65**, which undergoes intramolecular cyclisation forming compound **66**. Formation of compound **6i'** was attributed to the reaction of **65** with thionitroso compound **1i'**.

Compound **57i'** was also reacted with episulfide **67**, affording several products including compounds **7i'**, **59** and *N*-thiosulfinylamine **36i'** (Scheme 1.27).

R = (i') 2,4-di-*t*-Bu-6-NCC₆H₂
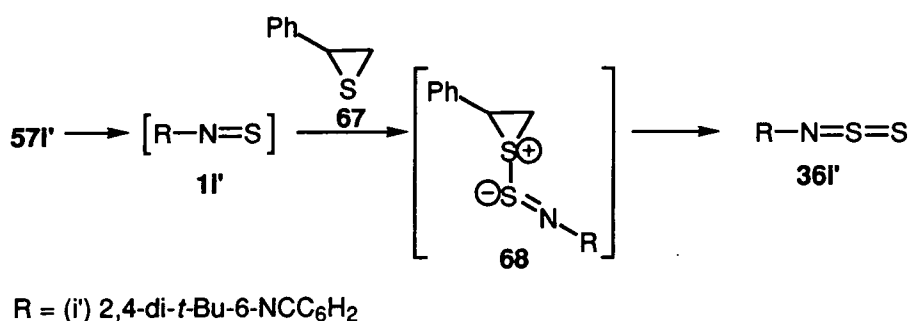
Scheme 1.27

Formation of compound **36i'** was thought to proceed through ylide **68** which would presumably result from nucleophilic attack of **67** on the sulfur atom of thionitroso compound **1i'**. This is a logical sequence as MO calculations show that the sulfur atom of thionitroso compounds has net positive charge (thus being susceptible to nucleophiles),[21] and the reaction is akin to that observed by Hata and Watanabe in the formation of ylides **48** (Section 1.2.4).[24]

In a later publication, Takahashi *et al* reported the thermal fragmentation of compound **57i'** and interception of the resultant thionitroso compound **1i'** with 2,3-dimethyl-1,3-butadiene to afford 1,2-thiazine **3i'** (Scheme 1.28).[31]

$$\textbf{57i'} \xrightarrow{\Delta} [R-N=S] \longrightarrow$$

1i'

R = (i') 2,4-di-*t*-Bu-6-NCC$_6$H$_2$

3i'
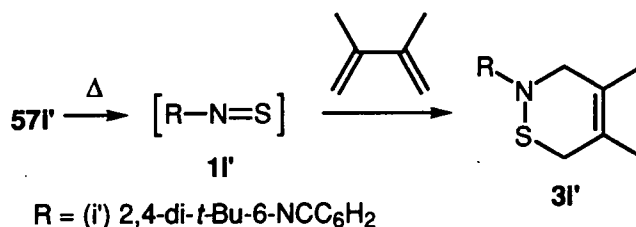
Scheme 1.28

No Ene adduct was mentioned, even though, from our experience, some would be expected.[11] Interestingly, attempted trapping of compound **1i'** with cyclopentadiene failed to produce DA adducts. This is in contrast to the work of Joucla and Rees in which cyclopentadiene was found to be an efficient trap for thionitroso compounds.[28] The reason for the discrepancy may be that different initiation conditions were used (Δ in Takahashi's work and h$\surd$ in Rees' work) although why this should produce the observed effect is unclear.

Bryce and Heaton have reported the generation of thionitroso compounds *via* fragmentation of 3-azido-2,1-benzisothiazoles.[11] In light of earlier work by Bryce *et al* and Joucla and Rees, discrepancies were apparent in the ratio of DA to Ene adducts obtained when thionitroso compounds generated from different precursors were trapped with dienes,[7, 10, 28] (in fact Joucla and Rees did not report the presence of any Ene adduct).Thus, Bryce and Heaton performed experiments designed to probe these discrepancies (Scheme 1.29).
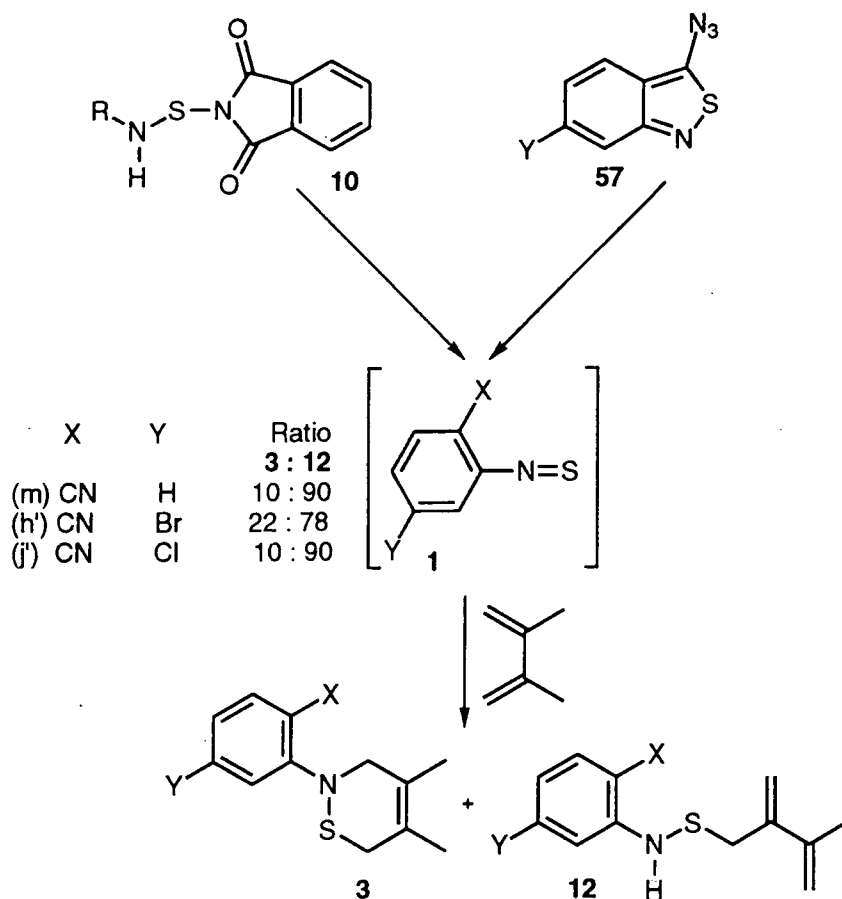
Scheme 1.29

Thionitroso compounds **1m,h',j'** were generated from *N*-(arylaminothio)phthalimide precursors **10m,h',j'** and from 3-azido-2,1-benzisothiazole precursors **57m,h',j'**. Both DA **3m,h',j'** and Ene **12m,h',j'** adducts were observed upon trapping with 2,3-dimethyl-1,3-butadiene, contrary to the observations of Joucla and Rees, who failed to detect the Ene adduct.[28] It was also observed that compound **1m** produced the same ratio of DA : Ene adduct (**3** : **12**, *i.e.* 10 : 90) when generated from either precursor **10m** or **57m**, thus providing strong evidence that the same intermediate, *viz* thionitroso compound **1m**, was involved in each reaction pathway.

1.2.6 SUMMARY- METHODOLOGY EMPLOYED TO ACCESS THIONITROSO COMPOUNDS

Thionitroso compounds have been generated (a) from bisamine disulfides (Section 1.2.2), (b) from sulfurised amines (Section 1.2.3), (c) from ylides (Section 1.2.4) and (d) photochemically from 2,1-benzisothiazoles (Section 1.2.5).

Those methods that have found the most synthetic utility are base-induced fragmentation of *N*-(arylaminothio)phthalimides,[7, 9-12] and thermal decomposition of *N*-chlorothio-*N*-trimethylsilylamines.[20-22]

The other major methods for the synthesis of thionitroso compounds are subject to some limitations. Hata and Watanabe described the generation of alkyl thionitroso compounds from reaction of episulfides with oxaziridines (Section 1.2.4), however, this route cannot tolerate sterically bulky substituents on nitrogen as the oxaziridine ring is made unreactive towards nucleophiles in these cases.[24] Meth-Cohn and van Vuuren reported the synthesis of electron-deficient thionitroso compounds by extrusion from thiophene *S,N*-ylides (Section 1.2.4).[25, 26] It would seem, however, that this method is limited to electron-deficient thionitroso species because those with electron donating substituents lead to a nitrene which is not sufficiently reactive to be attacked by the sulfur of the thiophene. Joucla and Rees first described the synthesis of thionitroso compounds from 3-azido-2,1-benzisothiazoles (Section 1.2.5). This method is clearly limited to derivatives of 2-cyanothionitrosobenzene.

1.2.7 THEORETICAL AND MECHANISTIC ASPECTS OF THIONITROSO CHEMISTRY

The first report concerning computational studies on thionitroso compounds, by Collins and Duke, appeared in 1978.[32] The structure of HNS was optimised and found to be more stable than its isomer H-SN by 107 kJ mol^{-1}. The calculated N-S bond length was 1.5499Å and the H-N-S bond angle 100°. (Also reported was the prediction that FNS was less stable than FSN, a fact which was proved experimentally).

In later more sophisticated work, Wasilewski and Staemmler predicted that H-N=S would show absorptions in the I.R. spectrum at 1231 and 1338cm^{-1} (N=S stretch), and at 3607cm^{-1} (N-H stretch). An N-S bond length of 1.549Å and H-N-S bond angle of 110° was predicted, with an N-S bond order of two, polarised with net negative charge of -0.26 on nitrogen and net positive charge of +0.06 on sulfur.[33] This compares with the N=S stretch for thionitroso compound **1i'** which was measured experimentally by Takahashi *et al* and assigned at 1120 or 1200cm^{-1}.[31] Markovskii *et al* predicted an N-S bond length of 1.491Å, a bond order of 2.00 and charges of -0.11 at nitrogen and +0.03 at sulfur in calculations on H-N=S.[21] Thus the N-S bond was generally predicted to be polarised with net negative charge on nitrogen and positive charge on sulfur.

Schmidt *et al* calculated the π-bond strength of H-N=S to be 176 kJ mol^{-1} (*cf.* N=O 260, P=O 222 and P=S 167 kJ mol^{-1}) thus suggesting that thionitroso compounds would be more reactive than nitroso and oxophosphine compounds, but slightly less reactive than thioxophosphine compounds.[34]

Mehlhorn has performed theoretical studies on H-N=S and *C*-thionitroso compounds (PhN=S and MeN=S). N-S Bond lengths of 1.495Å and 1.505Å (MeN=S and PhN=S respectively) were reported.[35, 36] For H-N=S the N-S bond length was predicted to be in the range 1.552-1.616Å, with an H-N-S bond angle of 110°. The net charge on nitrogen was in the range -0.15 - -0.06 (dependant on the computational method used) and that on sulfur in the range +0.03 - -0.11 with the same proviso. PhN=S was predicted to exhibit weak absorption bands in the UV-VIS spectrum at 1234 and 491nm due to n-π* transitions.

The work of Mehlhorn also suggests that thionitroso compounds will be planar, have a high electron affinity and thus be unstable, and have a small energy gap between the singlet ground state and the triplet first excited state. Electron-withdrawing substituents attached to nitrogen were predicted to lower the energy of the n-π* transition, leading to the possibility that the ground state is actually a triplet in these cases, *i.e.* electron-withdrawing substituents on nitrogen destabilise thionitroso compounds whilst electron-releasing substituents stabilise them. As it is known that thionitroso compounds undergo both DA and Ene reactions, and that Ene reactions are favoured by electron-deficient thionitroso compounds, both Meth-Cohn,[26] and Taylor,[13] alluded to the possibility that the Ene pathway may proceed *via* a biradical pathway (*i.e.* the thionitroso species reacts from the triplet ground state). Meth-Cohn postulated a mechanism involving a biradical that explained the regiospecific C-S bond formation observed with thionitroso compounds **1c'-e'** by analogy with the reactions of oxygen and sulfur monoxide (both of which react from the triplet ground state). Taylor, however, reported that although the Ene reaction may proceed *via* a biradical it is most likely that, just as the DA reaction of compounds **1b-c,e-f** were shown to be concerted (Section 1.2.2.2), it is reasonable to assume that the Ene reaction is also. Taylor also reported that theoretical treatment of the Ene reaction was problematical. It should be noted that compounds **1c'-e'** are considerably more electron deficient than compounds **1b-c,e-f**, thus it is possible that the Ene reaction of compounds **1c'-e'** proceeds *via* a radical pathway whilst Ene reaction of compounds **1b-c,e-f** proceeds in a concerted manner.

In frontier molecular orbital treatments both Taylor,[13] and Markovskii *et al,*[21] report that *C*-thionitroso compounds have LUMO's of lower energy than the LUMO's of both 2-methyl-1,3-butadiene and 2,3-dimethyl-1,3-butadiene. Thus, in the cycloaddition reactions of thionitroso compounds with these dienes, the major interaction will be transfer of electron density from the HOMO of the diene to the LUMO of the thionitroso species, *i.e.* the cycloaddition was predicted to be a normal electron demand DA reaction. Taylor also reported that the cycloaddition reaction most likely proceeds *via* a parallel orientation of thionitroso compound and diene.

Taylor,[13] and Markovskii *et al,*[21] also considered the regiochemical aspects of reaction of thionitroso compounds with 2-methyl-1,3-butadiene. Taylor noted that in the reaction of compounds **1c,f** with 2-methyl-1,3-butadiene to yield the regioisomeric 1,2-thiazines **13c,f** and **14c,f**, the regiochemical outcome predicted was corroborated by experiment (Section 1.2.2.2), *i.e.* predominance of compounds **14c,f** (the C5 methyl isomer). Markovskii *et al* noted that in the reaction of compounds **1x,z** with 2-methyl-1,3-butadiene affording 1,2-thiazines **13x,z** and **14x,z** (Section 1.2.3.3) prediction and experiment were again in agreement.

1.2.8 COMPETITIVE DA AND ENE REACTIONS

Thionitroso compounds are one of only a small number of dienophiles in which the DA and Ene pathways compete in reaction with methylbutadienes. Meth-Cohn and van Vuuren were the first to note this aspect of thionitroso chemistry (Section 1.2.4.2),[25] Bryce *et al* have since expanded this area significantly (Section 1.2.2.2).[7, 9-11, 22]

Concerning other dienophiles behaving in this manner, Gillis and Beck reported the reaction of diethyl azodicarboxylate **69** with 2,3-dimethyl-1,3-butadiene in which both the DA adduct **70** and Ene adduct **71** were produced (Scheme 1.30).[37]

EtO$_2$C—N=N—CO$_2$Et

69

70   +   **71**   **73**
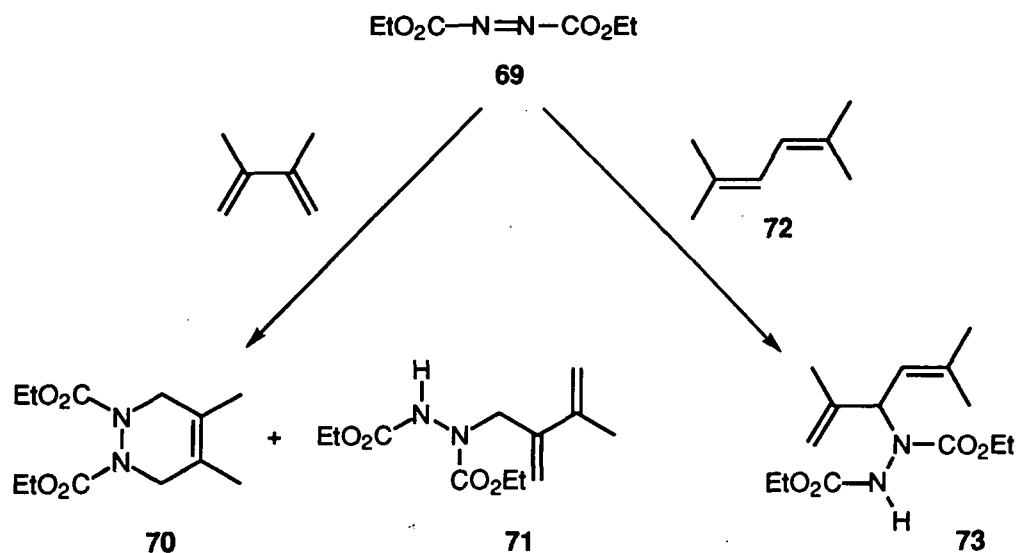
Scheme 1.30

In order to determine the factors influencing which reaction pathway was taken, compound **69** was reacted with 2,5-dimethyl-2,4-hexadiene **72** (a diene which cannot achieve the *s-cis* conformation required for DA reaction due to steric bulk). Compound **73** was isolated and was presumed to have resulted from Ene reaction, thus they concluded that steric factors preventing the diene from achieving the *s-cis* conformation could favour the Ene pathway over the DA.

The geometry of the transition states for both DA and Ene reactions as predicted by Hoffmann are shown in Figure 1.2.[38]

A   **B**
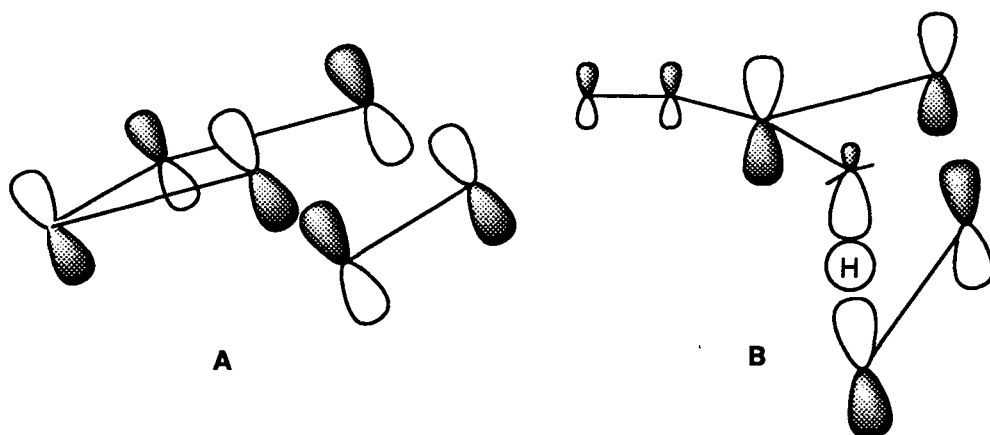
Figure 1.2

The transition state for the DA reaction (**A**) is boat-like involving partial π and partial σ-bonding between the interacting 'p' orbitals, whilst that for the Ene reaction (**B**) adopts a

conformation such that allylic resonance is maximised by having the axis of the breaking C-H bond parallel to the 'p' orbitals of the adjacent double bond.

In the reaction of compound **69** with 2,3-dimethyl-1,3-butadiene neither of the transition states **A** or **B** are disfavoured, but with compound **72** transition state **A** cannot be attained due to steric hindrance, hence the Ene reaction is favoured.

PhS(O)Cl was observed to undergo both Ene and DA reactions by Moiseenkov *et al.*[39] However, Ene reaction occurred at atmospheric pressure in the presence of a Lewis acid, whilst the DA reaction was initiated by high pressure (5 kbar), thus true competition between the DA and Ene pathways was not observed under the same reaction conditions.

Kirby *et al* noted that *C*-nitrosoformamides underwent competing DA and Ene reactions with 2,3-dimethyl-1,3-butadiene.[40] These workers postulated a dipolar transition state to explain the competition between the reaction pathways, arguing that the Ene reaction may be favoured by allylic stabilisation of partial positive charge by the adjacent double bond (Figure 1.3).
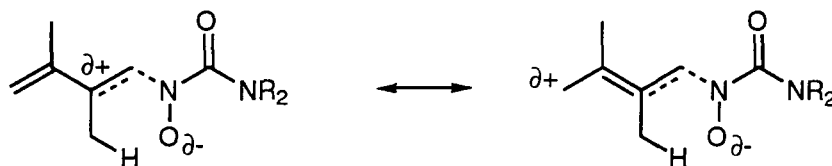
Figure 1.3

Wittig and Dürr reported competition between DA and Ene pathways when the highly reactive benzyne molecule was allowed to react with 2,3-dimethyl-1,3-butadiene.[41] The Ene reaction was seen to be predominant in this case. This result was rationalised using a reactivity-selectivity argument thus: DA reaction requires the diene to adopt the *s-cis* conformation and since this is of higher energy than the *s-trans* conformation, the concentration of *s-trans* diene will be much higher than *s-cis* diene at any given time. Benzyne is a transient species and, once generated, will react almost immediately. At the point of generation of a benzyne molecule the probability that it will encounter a diene molecule in the *s-trans* conformation is much greater than the probability that it will encounter a diene in the *s-cis* conformation, and thus reaction *via* the Ene pathway is statistically more probable.

From the above examples it appears that both steric and electronic factors can affect the outcome when dienophiles participate in competing DA and Ene reactions.

It is now known that competition between the DA and Ene pathways in the reactions of thionitroso compounds with methylbutadienes is strongly influenced by the electronic and steric properties of the substituent on nitrogen. Initial observations by Meth-Cohn and van Vuuren did not reflect this, thionitroso compounds **1c'-e'** produced DA and Ene adducts **3c'-e'** and **12c'-e'** in equal amounts when reacted with 2,3-dimethyl-1,3-butadiene (Section 1.2.4.2).

In later studies by Bryce *et al,* substituted thionitrosoarenes were utilised to probe the factors controlling the preference for a DA or Ene pathway in the reaction of thionitroso compounds **1a,c,e-m** with 2,3-dimethyl-1,3-butadiene.[7, 9-12] From these studies they also found that electronic, steric and solvent parameters affect the outcome of such reactions.

Regarding electronic factors, it was found that thionitrosoarenes bearing electron-donating substituents tended to yield a predominance of DA adduct when reacted with 2,3-dimethyl-1,3-butadiene (Schemes 1.5 and 1.8). Conversely, those bearing electron-withdrawing substituents tended to yield larger amounts of Ene adduct. This observation was rationalised using a reactivity-selectivity argument akin to that used by Wittig and Dürr: thionitrosoarenes bearing electron-donating substituents should be stabilised relative to those bearing electron-withdrawing groups (see Section 1.2.7), and thus should have a higher probability of encountering a diene in the *s-cis* conformation (required for DA reaction) as they will have a longer lifetime than their counterparts with electron-withdrawing substituents. Thus it follows that thionitrosoarenes with electron-donating substituents would give rise to a predominance of DA adduct. Implicit in this argument is the assumption that a thionitrosoarene which encounters a diene in the *s-cis* conformation would <u>preferentially</u> undergo a DA reaction with it, (Ene reaction can occur with both *s-cis* and *s-trans* conformations). No evidence to support this assumption is available.

In order to investigate steric effects, Bryce and Heaton compared trapping reactions of compounds **1c,e,j** and **1k-m** with 2,3-dimethyl-1,3-butadiene (Schemes 1.5 and 1.8, and Table 1.2).[11] It was noted that the thionitrosoarenes with substituents at the 2-position (**1k-m**) produced correspondingly more Ene adduct than their 4-substituted counterparts (**1c,e,j**). As the substituents in both these sets of compounds were identical, electronic effects could be ruled out as the cause of the change in ratio of DA : Ene adduct. Thus the conclusion was drawn that steric hindrance of substituents at the 2-position in

thionitrosoarenes caused these compounds to react preferably *via* the Ene pathway. These observations were rationalised by consideration of the transition state geometries of the DA and Ene reactions (Figure 1.4).
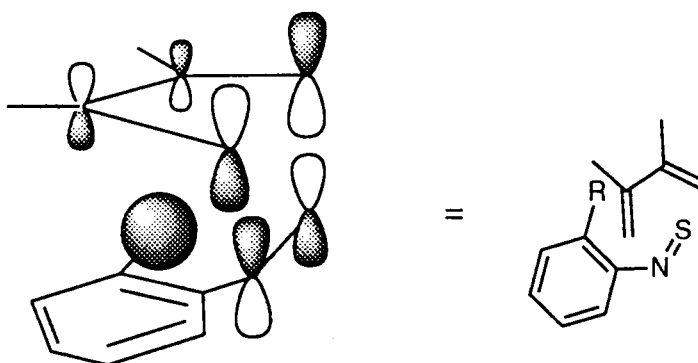
Figure 1.4

It can be seen that if the thionitroso compound approaches the diene in the *endo* mode (achieving maximum orbital overlap) the steric bulk of the substituent R at the 2-position hinders approach of the diene. This is less likely to occur with the 4-substituted derivative (Figure 1.5).
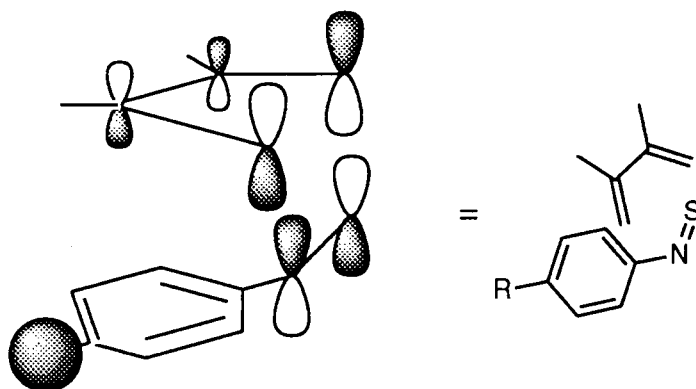
Figure 1.5

Conversely, the transition state for the Ene reaction experiences considerably less steric pressure due to substituents at the 2-position, even in *endo* approach (Figure 1.6).
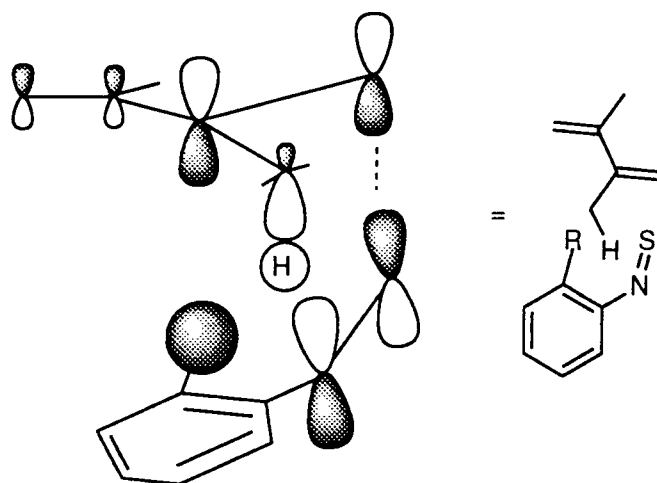
Figure 1.6

Bryce *et al* have also investigated the effect of solvent on the ratio of DA : Ene adducts obtained when thionitrosoarenes were trapped with 2,3-dimethyl-1,3-butadiene.[12] Compounds **1c,e-f** were intercepted with this diene in a variety of solvents (dimethylformamide, acetonitrile, acetone, chloroform and toluene) according to Scheme 1.5. It was noted that formation of the Ene adduct was favoured in more polar solvents. The results were rationalised by postulation of a more polar transition state for the Ene pathway compared with its DA counterpart, hence the former pathway would be favoured in polar solvents which would stabilise any partial charge build-up. (Recall that Kirby suggested that Ene reactions of nitroso compounds proceeded *via* polar transition states, and used this factor to explain the fact that both DA and Ene adducts were produced when these compounds were reacted with dienes).[40]

1.2.9 REGIOCHEMISTRY OF THIONITROSO CYCLOADDITION REACTIONS

The reaction of thionitroso compounds with unsymmetrical dienes, *e.g.* 2-methyl-1,3-butadiene, gives rise to the possibility of regio-isomerism in the product (Scheme 1.31).
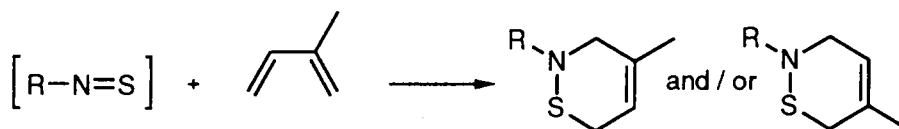
Scheme 1.31

Three groups of workers have reported the reaction of thionitroso compounds with 2-methyl-1,3-butadiene. Meth-Cohn and van Vuuren noted that in the reaction of compound **1d'** with this diene both regio-isomers **13d'** and **14d'** were produced in equal amounts, *i.e.* no regioselectivity was observed (Scheme 1.20).[25]

Markovskii *et al* reacted compounds **1x,z** with 2-methyl-1,3-butadiene and observed both regioisomers **13x,z** and **14x,z** in a 1 : 4 ratio (Scheme 1.15), thus showing a high degree of regioselectivity in these reactions. These workers related the regioselectivity observed to that predicted from consideration of frontier MO's. To summarise, they predicted the largest orbital coefficients at C1 of isoprene (in the HOMO) and at sulfur in the thionitroso compound (in the LUMO). The interaction controlling the regiochemistry of the cycloaddition reaction is between these atoms having the largest coefficients, so these atoms become bonded in the product, and thus the C5 methyl substituted isomer is predominant (Figure 1.7).[21] Carruthers also invokes this type of argument to explain the regiochemistry of DA reactions,[42] as does Houk ,[43] who also reports that electron-deficient dienophiles will have the largest LUMO orbital coefficient on the unsubstituted atom (*i.e.* sulfur in thionitroso compounds), again in agreement with the above.
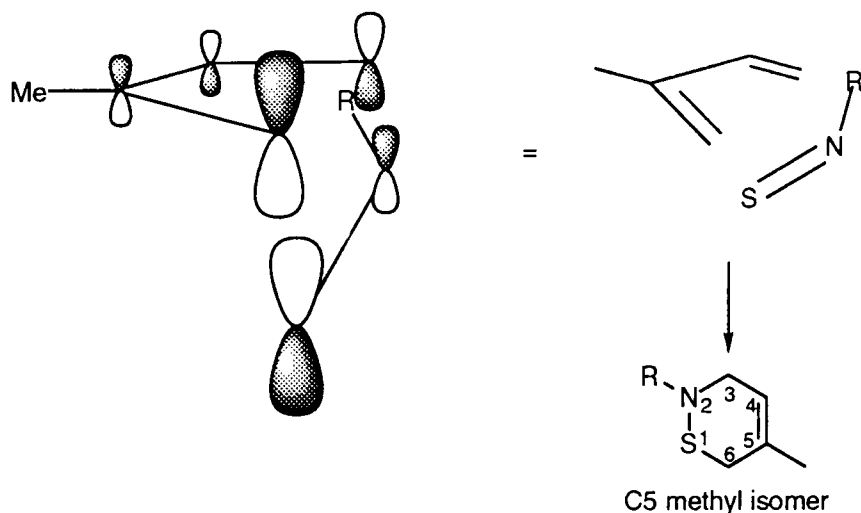
C5 methyl isomer

Figure 1.7

Bryce and Taylor have reported the reaction of thionitrosoarenes **1c,f** with 2-methyl-1,3-butadiene. Again regioselectivity was observed, in both cases the C5 methyl isomers, compounds **14c,f** were produced in three-fold greater quantity than the isomeric C4 methyl compounds **13c,f** (Scheme 1.6).[9] Unlike competition between DA and Ene pathways (Section 1.2.8), the nature of the substituent on the aromatic ring did not appear to exert any influence on the regiochemistry.

Further investigation of the regiochemical aspects of the cycloaddition reactions of thionitroso compounds concerned the reaction of compounds **1c,e-f** with 2-chloro-1,3-butadiene **20**, and 1-methyl-1,3-butadiene **23** (Scheme 1.9).[12] In the reaction with compound **20** both regioisomeric 1,2-thiazine products **21e-f** and **22e-f** were observed in equal amounts, except in the case of compound **1c** where adducts **21c** and **22c** were produced in 2 : 1 ratio, *i.e.* regioselectivity was observed. When compounds **1c,e-f** were reacted with compound **23**, the adducts **24c,e-f** and **25c,e-f** were produced in 3 : 1, 3 : 1 and 2 : 1 ratios, respectively (Scheme 1.9). These observations were rationalised by postulation of a dipolar transition state for the DA cycloaddition reaction. The predominant isomers were then deemed to have resulted from the transition state offering the greater stabilisation of charge (Figure 1.8).
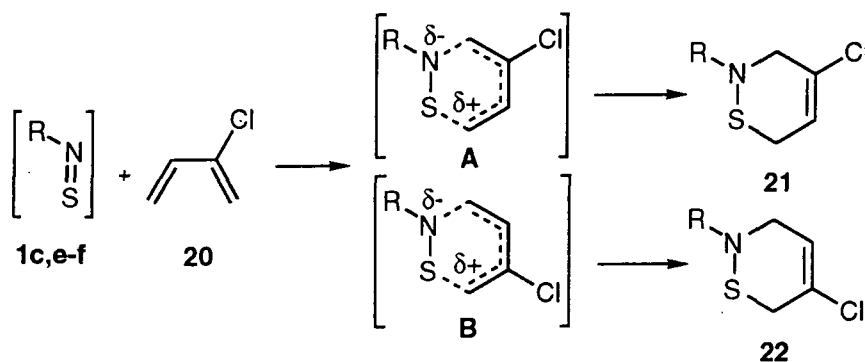
Figure 1.8

Recalling that thionitroso compounds are polarised, with net negative charge on nitrogen and net positive on sulfur, it can be seen in the case of 2-chloro-1,3-butadiene that transition state **B** would be destabilised by the electron-withdrawing chlorine atom relative to transition state **A**, thus explaining the predominance of isomer **21**.

Transition state arguments akin to these have been invoked to explain the regiochemistry of cycloaddition of *N*-sulfinylamines **6**, which were observed to yield only the 5-substituted 1,2-thiazine-1-oxide upon reaction with 2-substituted dienes.[2] The same trend was noted for sulfur diimides **7**. However, the regiochemistry of the cycloaddition reactions of nitroso compounds **5** is not yet well established, and is reported to be dependent on the steric and electronic properties of the substituents in both the nitroso compound and the diene.[2]

1.2.10 METAL COMPLEXES OF *C*-THIONITROSO COMPOUNDS

Only iron complexes of *C*-thionitroso compounds are known, three of these have been reported. Otsuka *et al* reported complexes formed *via* reaction of *N*-sulfinylamine **6a** and sulfur diimide **7a** with iron carbonyl to yield compounds **74** and **75**, respectively (Scheme 1.32).[44]
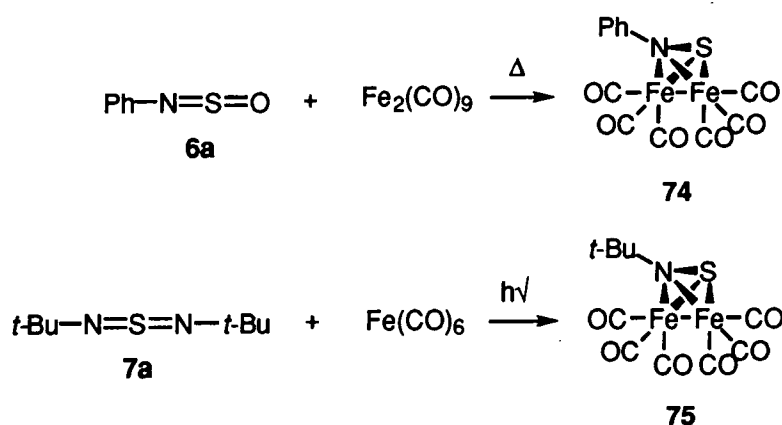
Scheme 1.32

Compounds **74** and **75** were stable at room temperature and their structures were established by spectroscopy; the N-S bond was seen to absorb at 705 - 760 cm^{-1} in the I.R. spectrum. A further complex akin to **74** and **75** was reported by Vrieze *et al*, involving a 4-MePh substituent on nitrogen, and was characterised by X-ray crystal analysis.[45]

1.3 *C*-THIOXOPHOSPHINE COMPOUNDS

1.3.1 INTRODUCTION

C-Thioxophosphines* **2** are the phosphorus analogues of *C*-thionitroso compounds **1** (Figure 1.9).

$$R-N=S \qquad R-P=S$$

1   **2**

Figure 1.9

---

* *Chemical Abstracts* nomenclature. The compounds are referred to in the literature variously as phosphinothioylidenes, phosphinidene sulfides and thioxophosphanes.

As with thionitroso species, most thioxophosphines are reactive intermediates. These species may be generated and trapped *in situ* (*e.g.* with dienes) to form stable cycloadducts from which the structure of the free thioxophosphine is inferred (Scheme 1.33).
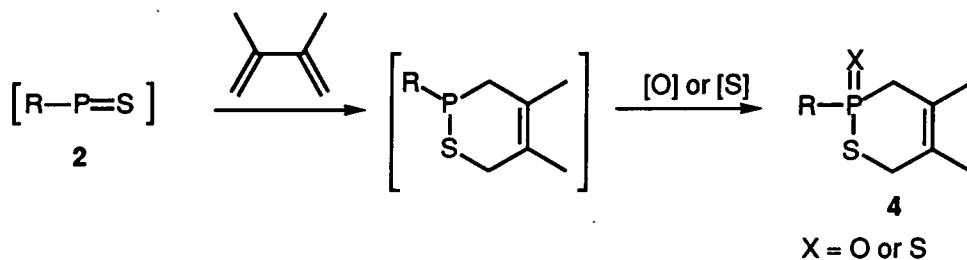
Scheme 1.33

Unlike thionitroso compounds, in the interception of compounds **2** with dienes (*e.g.* 2,3-dimethyl-1,3-butadiene), the primary heterocycle formed (incorporating a trivalent phosphorus atom) is unstable. Under the reaction conditions it is oxidised (by atmospheric oxygen), or thiolated (by excess $RP(S)Cl_2$) to yield a 1,2-thiaphosphorin-2-oxide (or sulfide) **4**.

Methodology for the generation of compounds **2** is scarce, but has been reviewed.[2, 46, 47] This introduction will discuss methods for the generation of *C*-thioxophosphines, and the techniques used to establish their existence, particularly reaction with dienes to form heterocycles such as compounds **4**.

1.3.2 *C*-THIOXOPHOSPHINES FROM THIOPHOSPHONIC DICHLORIDES

In 1971 Inamoto *et al* were the first to report the generation of a *C*-thioxophosphine by magnesium-mediated dechlorination of phenylthiophosphonic dichloride **76a** (Scheme 1.34).[48]
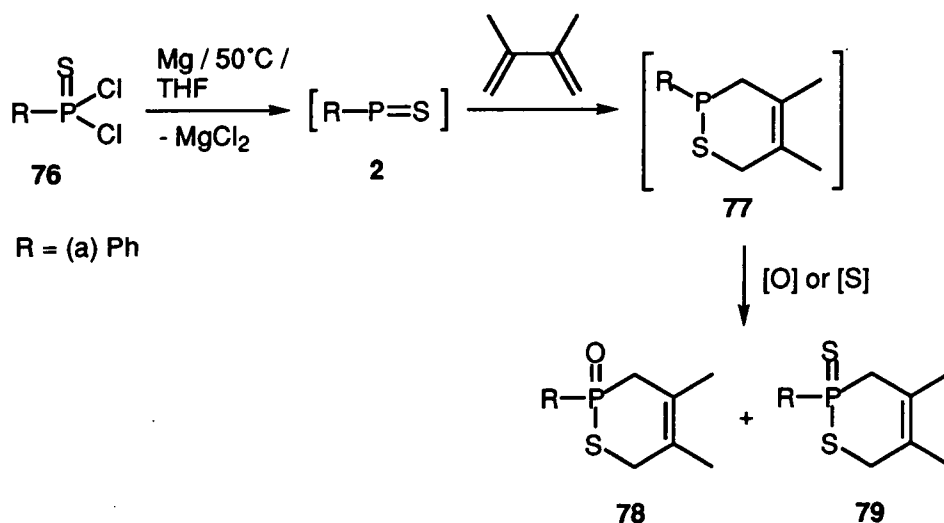
Scheme 1.34

The dechlorination reaction produced phenylthioxophosphine **2a** which, in the presence of 2,3-dimethyl-1,3-butadiene, reacted in a [4π + 2π] DA cycloaddition to yield 1,2-thiaphosphorin **77a**. This reaction is analogous to those of *C*-thionitroso compounds. Compound **77a** was, however, unstable and underwent further reaction to yield a mixture of 2-phenyl-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiaphosphorin-2-oxide **78** and 2-phenyl-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiaphosphorin-2-sulfide **79** in moderate yield (21-22%). In the absence of magnesium no reaction occurred.

Compounds **2a-b** were also shown to undergo insertion reactions with benzil **80** and diethyldisulfide **81** (Scheme 1.35).[49] The isolation of compounds **82a-b** and **83a-b** was taken as evidence for the generation of the free thioxophosphines **2a-b**.
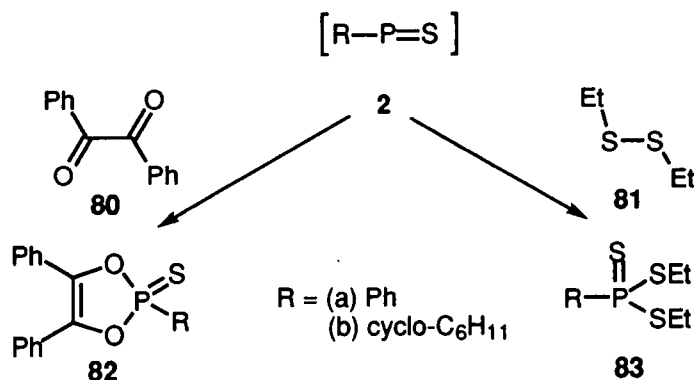
Scheme 1.35

In an extension of their work Inamoto *et al* reported reaction of compound **2a** with tetrahydrofuran, cyclohexadiene and 2,3-diphenyl-1,3-butadiene (Scheme 1.36).[50]
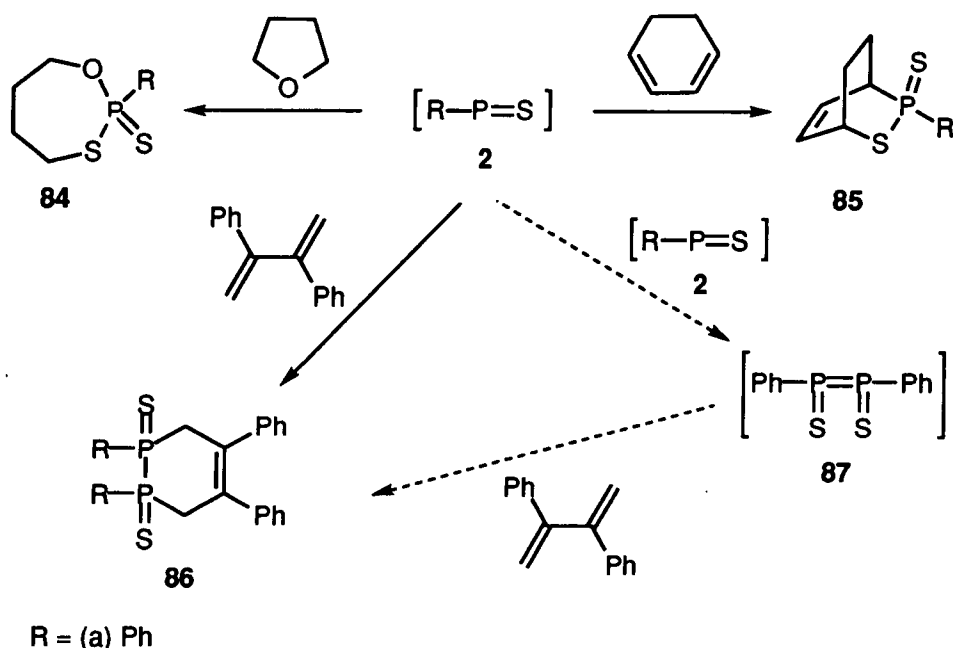
Scheme 1.36

From the reaction with tetrahydrofuran compound **84** was isolated in low yield and was thought to have resulted from insertion of compound **2a** into one of the C-O bonds of tetrahydrofuran (in an extension of this work the same authors reported a similar insertion reaction of **2a** with stilbene oxide).[51] Reaction with cyclohexadiene produced the expected DA adduct **85** in moderate yield; however, reaction with 2,3-diphenyl-1,3-butadiene did not give rise to the expected 1,2-thiaphosphorin, and instead yielded compound **86**. The authors explained this by considering that the diene would be unlikely to adopt the *s-cis* conformation due to steric pressure and they invoked a different mode of reaction in which compound **2a** first dimerised to the reactive intermediate **87** which then reacted with the diene to produce compound **86**. No comment on the mechanism of this last step was made, although a [4π + 2π] cycloaddition is presumably ruled out as this requires the diene to adopt the *s-cis* conformation!

The assertion that free thioxophosphines exist in the dechlorination of thiophosphonic dichlorides has been questioned by Schmidt,[46] who points out that formation of compounds **82** and **83** need not involve a free thioxophosphine. Instead, reaction of magnesium with diethyl disulfide to form magnesium bis(ethanthiolate) which then reacts

with compound **76** to give compound **82**, could explain the observations (the argument is the same for the magnesium salt of benzil to yield **83**).

The objections of Schmidt were placed in new perspective by the work of Lindner *et al* who described the generation and complexation of methylthioxophosphine **2c** (Scheme 1.37).[52]
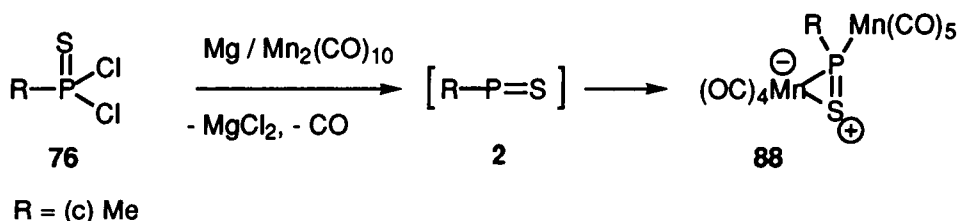
Scheme 1.37

Compound **76c** was dechlorinated with magnesium in the presence of $Mn_2(CO)_{10}$ to yield complex **88** (the structure of which was proved by X-ray crystal analysis) *via* compound **2c**. The mechanism of the reaction was clarified by reaction of compound **76c** with $[Mn(CO)_5]^-$ in the absence of magnesium. This reaction yielded only trace amounts of **88** thus suggesting that nucleophilic attack by the negatively charged manganese atom on intact precursor **76c** did not occur to any great extent. Therefore, this mode of action could be reasonably ruled out in the formation of complex **88**, even in the presence of magnesium. Thus, the reaction was thought to proceed by initial dechlorination of compound **76c** (by magnesium) to afford free **2c** which subsequently reacted with $Mn_2(CO)_{10}$ yielding the observed product. Considering the fact that compound **76c** reacts with magnesium to yield the free thioxophosphine **2c**, it is likely that compounds **76a-b** react in this manner also, and thus the argument of Schmidt is apparently refuted.

1.3.3 C-THIOXOPHOSPHINES FROM 7-PHOSPHANORBORNENE DERIVATIVES

Mathey *et al* were the first to report the generation of a *C*-thioxophosphine by thermal fragmentation of a 7-phosphanorbornene derivative (Scheme 1.38).[53]
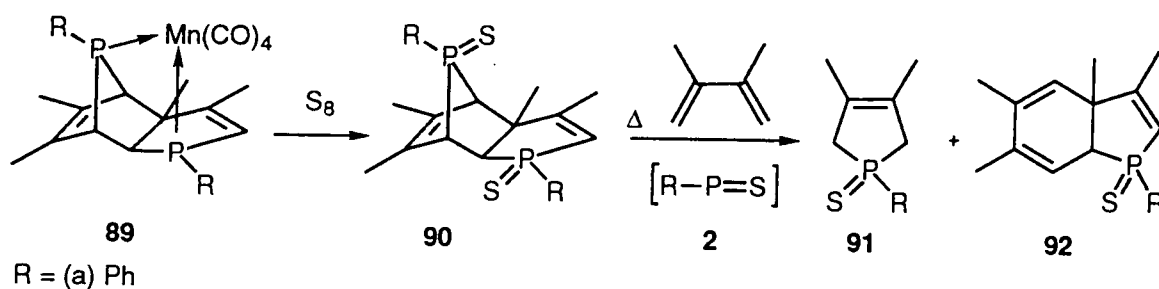
Scheme 1.38

Treatment of complex **89** with elemental sulfur afforded *exo*-dimeric(1-phenyl-3,4-dimethylphosphole sulfide) **90** which, when heated at 150°C for 6h in the presence of 2,3-dimethyl-1,3-butadiene, fragmented *via* extrusion of thioxophosphine **2a**. Compound **2a** reacted with the diene in a [4 + 1] fashion giving phospholene sulfide **91** in 50% yield. Compound **92** was a by-product. The authors noted that, unlike Inamoto *et al* (Section 1.3.2) no [4 + 2] reaction was observed, and because of this, questioned the results of the Japanese workers.

Extrusion of thioxophosphines from 7-phosphanorbornene derivatives has similarities with extrusion of thionitroso compounds from thiophene *S,N*-ylides (Section 1.2.4), both produce reactive intermediates which may be intercepted with dienes and both reactions are made favourable by relief of strain at bridgehead positions.

In an almost identical process Regitz *et al* reported that thermolysis of compound **95** resulted in the extrusion of compound **2a** which could then be intercepted with alcohols to yield compounds **96**. Compounds **95a-b** were synthesised by DA reaction of thioxophosphole **93** and triazolinediones **94a-b**. (Scheme 1.39).[54]
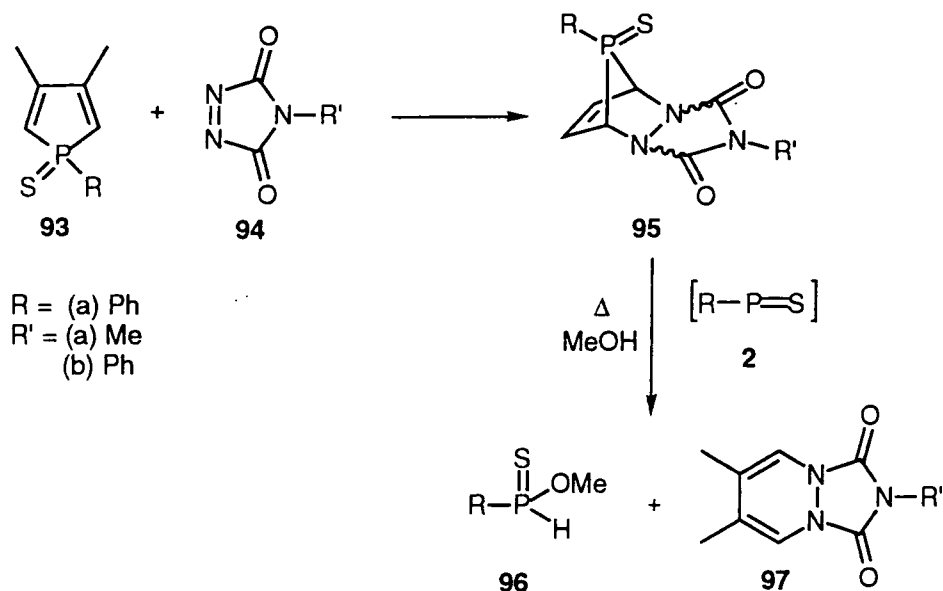
Scheme 1.39

Extrusion of compound **2a** was thought to occur *via* a retro [4 + 1] DA process, the methanol oxygen atom then attacks the phosphorus atom in compound **2a** to afford the ester **96**. Compound **97** was formed as by-product.

Other reports of <u>photochemically</u> induced fragmentation of 7-phosphanorbornene systems exist.[55, 56] That photochemical fragmentation of these systems <u>does not</u> produce free thioxophosphines was demonstrated by Quin *et al.*[57] These workers irradiated compound **95b** in the presence/absence of methanol and observed surprising results (Scheme 1.40).
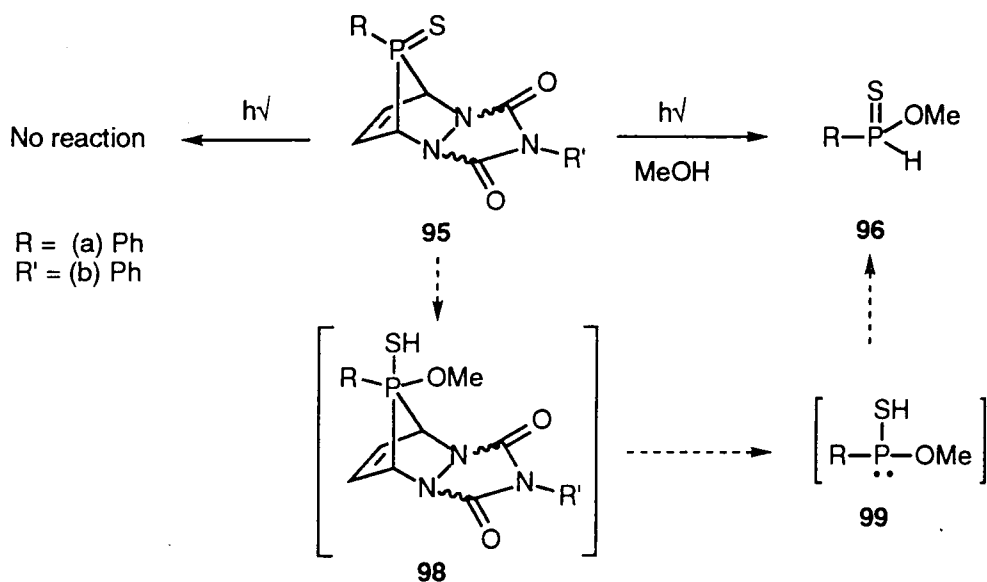
Scheme 1.40

In the presence of methanol compound **96** was obtained, this previously had been presumed to result from attack of methanol on free thioxophosphine **2a**. The experiment in which methanol was omitted produced no reaction, *i.e.* irradiation did not cause fragmentation. In the light of these results Quin *et al* suggested that the formation of compound **96** proceeds through intermediates **98** and **99**.

1.3.4 *C*-THIOXOPHOSPHINES FROM BIS(MERCAPTO)PHOSPHINES

A novel route to *C*-thioxophosphines was reported recently by Harpp *et al.*[58] Compounds **100a,d** were prepared by reaction of the corresponding dichlorophosphine with triphenylmethanethiol. When compounds **100a,d** were reacted with triphenyldibromophosphorane **101** in the presence of a 1,3-diene (2,3-dimethyl-1,3-butadiene, 2,3-diphenyl-1,3-butadiene or cyclohexadiene) DA adducts **79a,d**, **102a** and **85a** respectively, were formed in 10-26% yield (Scheme 1.41).
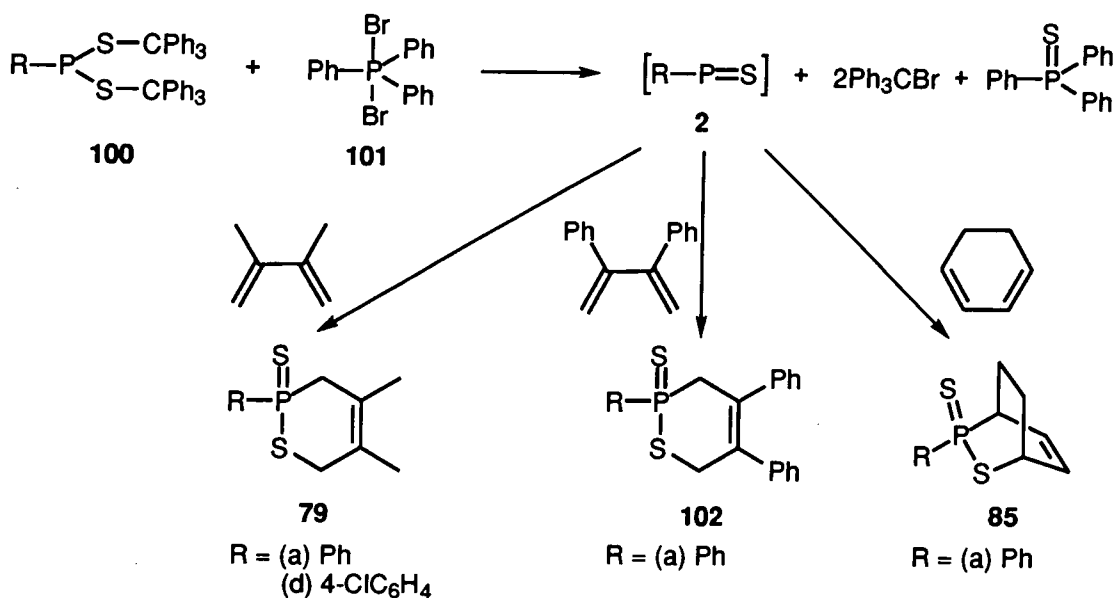
Scheme 1.41

It is interesting to note that [4 + 2] reaction occurred with 2,3-dimethyl-1,3-butadiene, in agreement with Inamoto *et al*, but in contrast to Mathey *et al.*[48, 53] Furthermore, the reaction with 2,3-diphenyl-1,3-butadiene resulted in the expected [4 + 2] DA adduct, in contrast to the observations of Inamoto *et al* who reported isolation of compound **86** (Section 1.3.2).

Harpp *et al* did not discuss the mechanism by which compounds **79a,c, 102a** and **85a** were formed from compound **2**, although the possibility that a dithioxophosphorane may be involved is not discounted. (These compounds are discussed further in Section 1.3.5).

1.3.5 A *C*-THIOXOPHOSPHINE FROM A SELENOXOTHIOXO-PHOSPHORANE

Yoshifuji *et al* have investigated the use of bulky substituents to stabilise a number of reactive phosphorus compounds including a phosphobenzene,[59] a dithioxophosphorane and a diselenoxophosphorane.[60] During further investigations of this kind selenoxothioxo(2,4-di-*t*-butyl-6-dimethylaminophenyl)phosphorane **104** was produced, and this compound was found to undergo deselenation to afford the first stable, isolable *C*-thioxophosphine **105** (Scheme 1.42).[61]
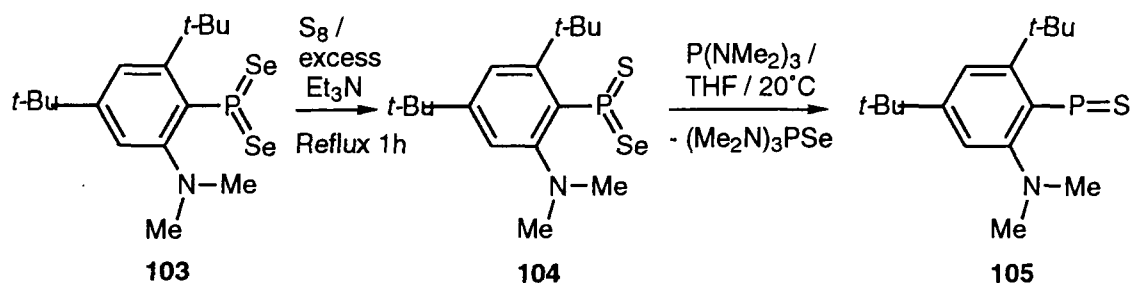
Scheme 1.42

Compound **103** was prepared from the corresponding dichlorophosphine by treatment with lithium naphthalenide to form the diphosphine. This compound was then selenated by reaction with elemental selenium in the presence of base. Reaction of compound **103** with elemental sulfur in the presence of base afforded selenoxothioxophosphorane **104** (15% yield). In a NMR tube-scale reaction, compound **104** was deselenated by treatment with tris(dimethylamino)phosphine to yield thioxophosphine **105** which was stable enough to permit analysis, although it decomposed slowly on storage at room temperature.

The stability of compound **105** was thought to be due to both kinetic stabilisation from the steric bulk of the aromatic substituent, and to a 1,4 interaction between the lone pair electrons on the nitrogen atom and the phosphorus atom (Figure 1.10), although a 1,5 interaction between nitrogen and sulfur is possible, and may be favoured (see Section 3.1.2.2).

105
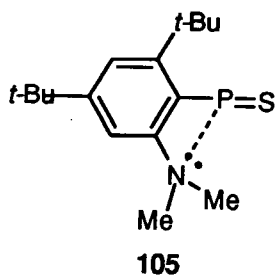
Figure 1.10

Reaction of compound **105** with dienes was not reported, the steric bulk of the substituents on phosphorus would most likely hinder such reactions.

Compound **105** could not be produced by desulfurisation of dithioxo(2,4-di-*t*-butyl-6-dimethylaminophenyl)phosphorane, both sulfur atoms in this molecule being inert to reaction with tris(dimethylamino)phosphine.

Although dithioxophosphoranes with bulky substituents can exist in monomeric form (of general structure **107**), those with less bulky substituents tend to exist in equilibrium with the dimer (phosphonothioic anhydrides, general structure **106**). Lawessons reagent **106** (R = 4-MeOPh) is a typical example (Scheme 1.43).[62]

106   **107**
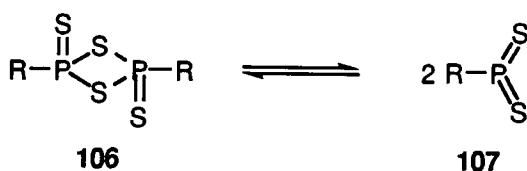
Scheme 1.43

It should be noted that trapping reactions of dithioxophosphoranes with dienes have been reported to give rise to heterocyclic compounds exactly the same as those obtained from trapping thioxophosphines (*e.g.* compound **79a**).[2, 63] Indeed, it has been reported that the dechlorination of compounds **76a-c** with magnesium may at some point involve a dithioxophosphorane.[47] Furthermore, Harpp *et al* do not rule out the involvement of these species in their reactions leading to compounds **79a-c, 85a** and **102a**.[58] Thus, the evidence for the existence of *C*-thioxophosphines in the methodology outlined in Sections 1.3.2 - 1.3.5 is strong, but only in the case of compound **105** (above) can it be definitively stated that a *C*-thioxophosphine was generated.

1.3.6 SUMMARY

Four methods for the generation of *C*-thioxophosphines have been described in the literature, (a) dechlorination of thiophosphonic dichlorides (Section 1.3.2), (b) fragmentation of 7-phosphanorbornene systems (Section 1.3.3), (c) rearrangement of bis(mercapto)phosphines (Section 1.3.4) and (d) deselenation of a selenoxothioxophosphorane (Section 1.3.5).

Methods (a)-(c) rely on reaction with dienes or alcohol to provide evidence for the existence of the reactive intermediate thioxophosphine. Method (d), however, produced the first isolable example of such a species.

1.3.7 THEORETICAL AND REGIOCHEMICAL ASPECTS OF THIOXOPHOSPHINE CHEMISTRY

1.3.7.1 THEORETICAL CONSIDERATIONS

The Pauling electronegativities of phosphorus and sulfur are 2.1 and 2.5 respectively,[64] thus *C*-thioxophosphines would be expected to be polarised with net positive charge on phosphorus and negative on sulfur (*i.e.* the direction of polarisation is reversed compared to thionitroso compounds).

Schoeller and Niecke note that for systems of the R-P=X type the frontier orbitals are subject to influence by the substituent R.[65] This can give rise to two situations, in the first the non-bonding lone pair orbital on phosphorus (designated σ) is the HOMO, and the LUMO is π* of the P=X bond. In this situation the R-P=X system was predicted to dimerise in a [2 + 1] manner, and to react in a [4 + 1] manner with conjugated dienes (Scheme 1.44).
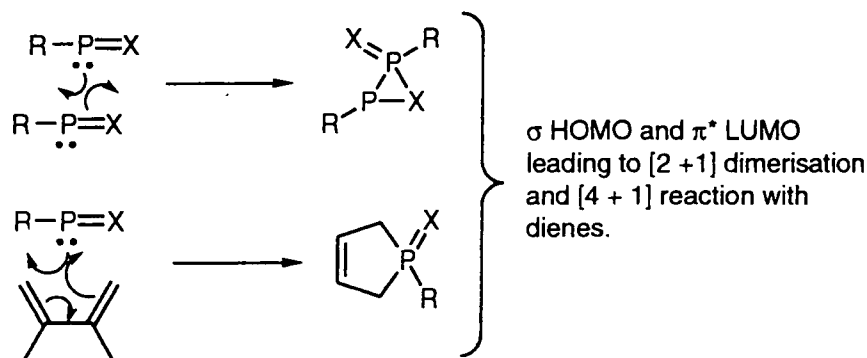
Scheme 1.44

The second situation has the R-P=X π-bond as the HOMO, and the LUMO as π*, in this case the R-P=X system was predicted to undergo [2 + 2] dimerisation reactions, and [4 + 2] reactions with dienes (analogous to thionitroso compounds which were also predicted to undergo [4 + 2] reactions with dienes, Section 1.2.7).

Electron-donating substituents on the phosphorus atom of thioxophosphines were predicted to increase the energy of the π-MO's thus raising them to be HOMO and LUMO, and hence *C*-thioxophosphines would be expected to undergo [4 + 2] reactions with dienes (as most alkyl/aryl groups tend to have slight electron-donating properties).

1.3.7.2 REGIOCHEMICAL CONSIDERATIONS

Reaction of *C*-thioxophosphines with unsymmetrical dienes has not been reported, thus data on the regiochemistry of the cycloaddition reaction is not available. We report aspects of this type of chemistry herein (Chapter 4).

Chapter Two

Alkylthionitroso Compounds

2.1 BENZYLTHIONITROSO COMPOUNDS

2.1.1 INTRODUCTION

The chemistry of thionitroso compounds, especially aryl and heteroaryl derivatives, has been extensively studied within this laboratory (Section 1.2.2.2). However, thionitrosoalkanes (those with an sp^3 carbon bonded to the nitrogen in the N=S moiety) have received less attention. Recently, both Markovskii *et al* (Section 1.2.3.3),[20, 21] and Heaton,[66] demonstrated that this type of compound was accessible *via* thermal decomposition of *N*-trimethylsilyl-*N*-chlorothioalkylamines.

In the trapping of thionitrosoarenes with dienes, Bryce and Taylor found that both DA and Ene reactions occurred. It was noted that the electronic nature of the substituent on the aromatic ring influenced the reaction pathway: electron-withdrawing substituents favoured the Ene pathway, whilst electron-donating substituents favoured the DA route (Section 1.2.2.2).

In later work, Bryce and Heaton demonstrated that the position of the substituent on the aromatic ring also affected the ratio of DA : Ene adducts (Section 1.2.8). Examples of competition between DA and Ene pathways in cycloaddition reactions are rare (Section 1.2.8) and hence this is an area of some interest.

Benzylthionitroso compounds **108** only differ from their thionitrosoarene counterparts (*e.g.* **3a**) (Figure 2.1) in that the former posses a CH$_2$ group between the nitrogen and the aromatic ring.

$$PhCH_2{-}N{=}S \qquad\qquad Ph{-}N{=}S$$

108   **3a**

Figure 2.1

We sought to determine whether thermal decomposition of *N*-trimethylsilyl-*N* -chlorothioalkylamines was a suitable method for the generation of compounds **108**. In tandem with this, we aimed to vary the substituents on the benzene ring of compounds **108** in order to observe the effect on the DA : Ene ratio in the product, to allow a comparison to be drawn with thionitrosoarenes (Section 1.2.2.2).

2.1.2 GENERATION OF BENZYLTHIONITROSO COMPOUNDS AND REACTION WITH 2,3-DIMETHYL-1,3-BUTADIENE

Thionitroso compounds **108a-j** were generated according to the procedure of Markovskii *et al*,[20] by thermally induced fragmentation (70°C, 16h.) of the corresponding *N*-trimethylsilyl-*N*-chlorothiobenzylamines **110a-j** (prepared by treatment of silylamines **109a-j** with sulfur dichloride in the presence of base). Compounds **108a-j** thus formed were intercepted *in situ* with 2,3-dimethyl-1,3-butadiene (Scheme 2.1).

R = (a) Ph
    (b) 4-MeC$_6$H$_4$
    (c) 4-MeOC$_6$H$_4$
    (d) 4-ClC$_6$H$_4$
    (e) 4-FC$_6$H$_4$
    (f) 4-CF$_3$C$_6$H$_4$
    (g) 2-FC$_6$H$_4$
    (h) 2-ClC$_6$H$_4$
    (i) 2-CF$_3$C$_6$H$_4$
    (j) 2-MeOC$_6$H$_4$
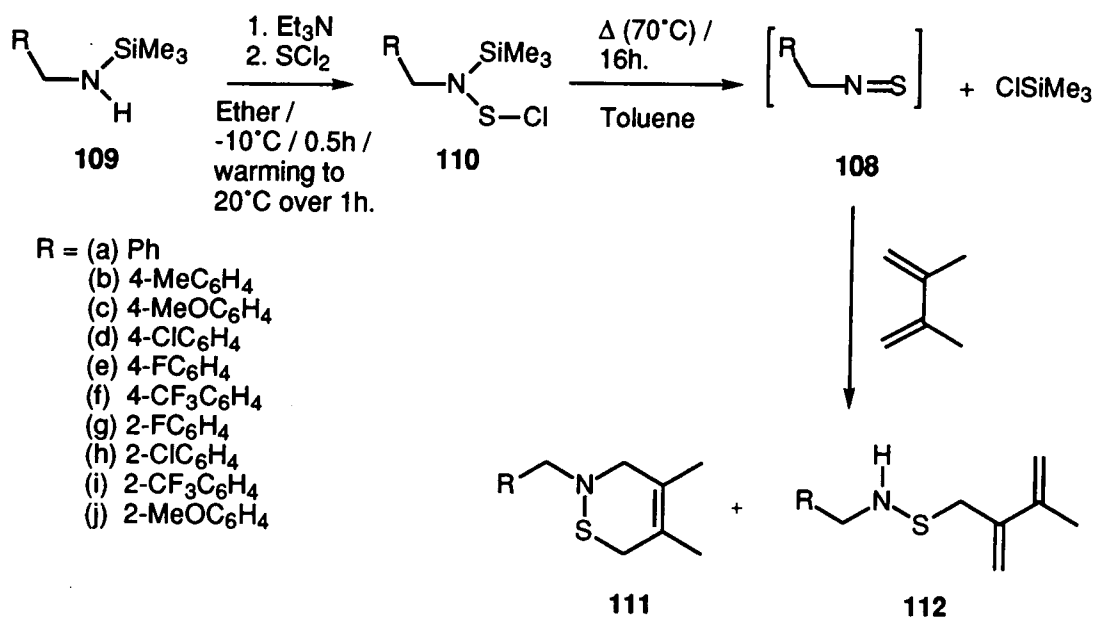
Scheme 2.1

As expected, both the DA **111a-j** and Ene **112a-g,i** adducts were produced as unstable yellow oils in low to moderate yields (5-60%). These materials typically decomposed within 5h at room temperature (NMR evidence). The ratio of adducts was determined by integration of the ^{1}H NMR spectrum of the crude product mixture. The ratios are detailed in Table 2.1. Assignment of the ratios was facilitated by the characteristic resonances of the methylene groups in 1,2-thiazines **111a-j** [slightly broadened singlets typically at δ2.9-3.1 (CH$_2$S) and δ3.3-3.4 (CH$_2$N)], and in sulfenamides **112a-g,i** [slightly broadened singlet at δ3.15-3.25 (CH$_2$S)]. Figure 2.2 shows a typical spectrum and highlights the important diagnostic signals.
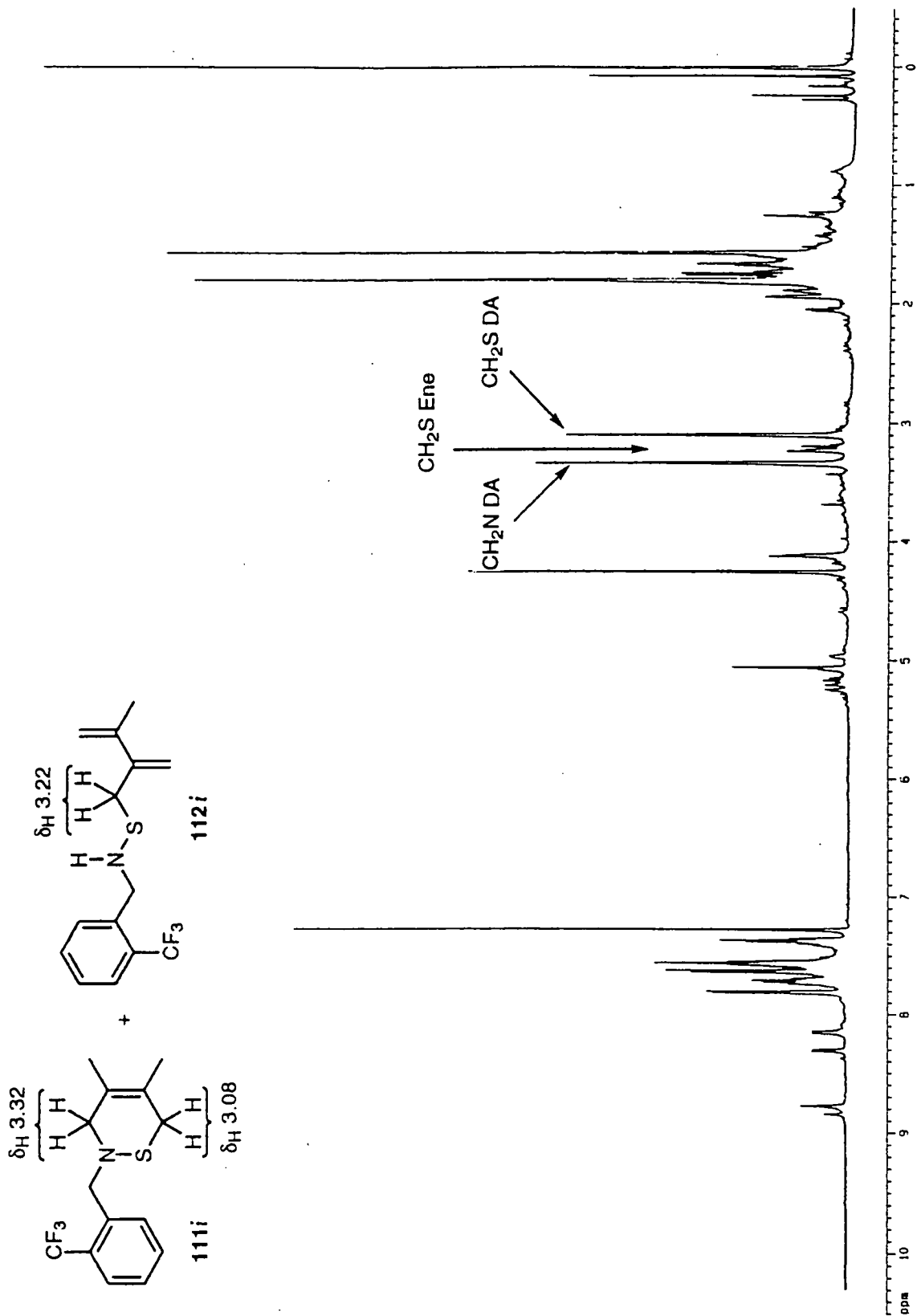
*Figure 2.2 - ¹H NMR Spectrum of adduct mixture **111i** and **112i**, illustrating the characteristic signals observed in the spectra of 1,2-thiazine/sulfenamide mixtures., and highlighting the important diagnostic signals.*

Table 2.1 - Ratio of adducts produced upon reaction of thionitroso compounds **108a-j** with 2,3-dimethyl-1,3-butadiene

Compound	Adduct ratio	
	111 (DA)	**112** (Ene)
108a	1	1
108b	1	1
108c	1	1
108d	1	1
108e	2	1
108f	2	1
108g	4	1
108h	1	0
108i	2	1
108j	1	0

It is clear that for *para* substituted derivatives **108a-d**, the DA : Ene ratio seems independent of the electronic nature of the substituent, (*cf.* **108b** and **108d** which both give a 1:1 ratio despite the former having an electron-donating substituent and the latter an electron-withdrawing one). Compounds **108e-f** represent an exception to the above trend. Here it appears that the very electronegative fluorine atoms cause the DA pathway to be favoured. This is opposite to the observations of Bryce and Taylor with thionitrosoarenes (Section 1.2.2.2).[7]

It has previously been noted that the electronic nature of the substituent on thionitrosoarenes influenced the ratio of DA : Ene adduct in the product. Electron-withdrawing substituents favoured the Ene adduct, whilst electron-donating groups favoured the DA adduct (Section 1.2.8). Excluding compounds **108e-f**, the results of the reactions of *para* substituted benzylthionitroso compounds suggest that the CH_2 unit (*cf.* thionitrosoarenes) insulates the reactive N=S moiety from the electronic influences of the aromatic ring. Thus, as expected, no substituent effect on the DA : Ene ratio was observed. The inconsistency demonstrated by the fluorinated compounds is difficult to rationalise, but may be due to compounds **112e-f** being particularly unstable and decomposing before analysis could be completed.

For the *ortho* substituted compounds **108g-j**, the trend in DA : Ene ratio becomes more complex (Table 2.1). Again, it is clear that the DA adduct is predominant, and that the

electronic nature of the substituent seems unimportant (*cf.* **108h** and **108j**). This contrasts sharply with the results obtained by Heaton in which *ortho* substituted thionitrosoarenes were found to give a predominance of Ene adduct, regardless of the electronic nature of the substituent.[66] Heaton rationalised these observations using transition state arguments, and inferred that the Ene adduct predominated because the transition state leading to it was less sterically crowded than that leading to the DA adduct (Section 1.2.8).[11] The results from the benzylthionitroso compounds **108g-j** suggest that no such steric constraints exist for these compounds, and that a DA pathway therefore occurs preferentially. This may be due to the extra distance between the incoming diene and substituents as well as the conformational flexibility introduced by the extra CH_2 group present in these molecules (Figure 2.3).
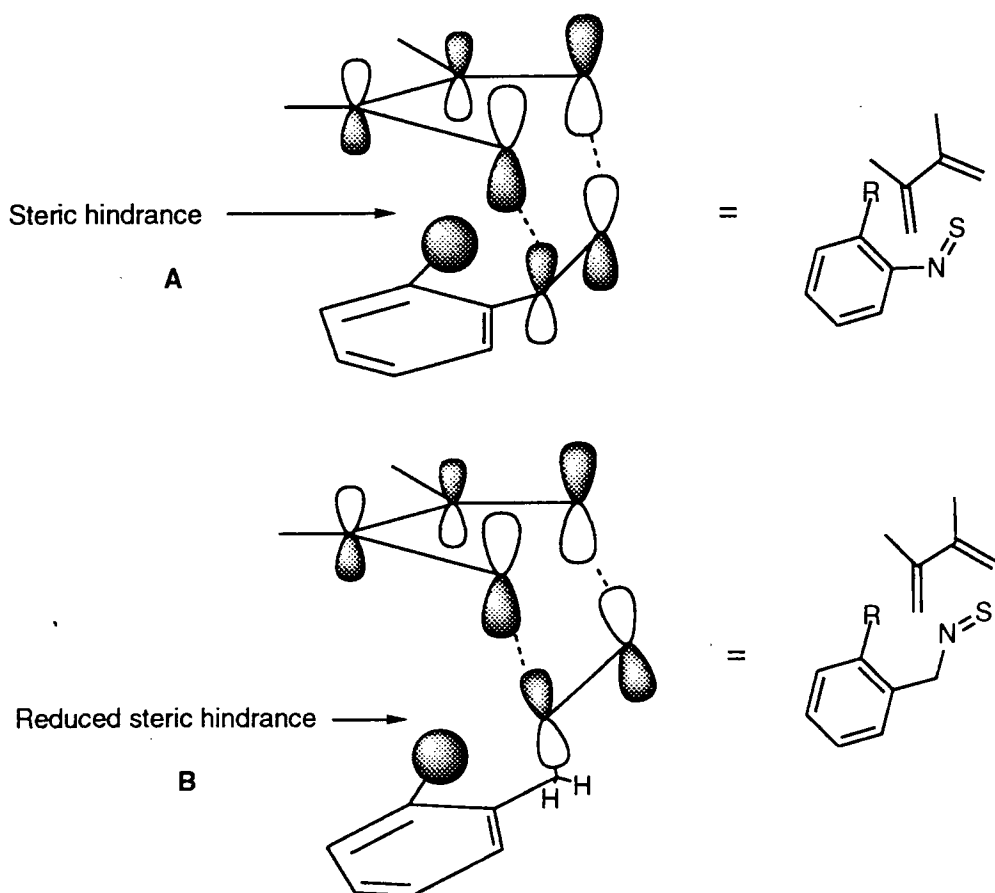
Figure 2.3

In transition state **A** (for thionitrosoarenes) the *ortho* substituent can be seen to hinder the approach of the diene, thus disfavouring the DA pathway. This unfavourable interaction is greatly reduced in transition state **B** (benzylthionitroso).

The fact that compound **108j** (*i.e. ortho*-methoxy substituted) gave only DA adduct is particularly interesting. With this compound there exists the possibility of a favourable six-membered nonbonded interaction between oxygen and sulfur, as illustrated in Figure 2.4.
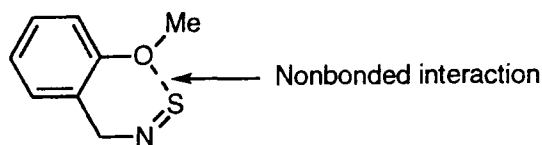
Figure 2.4

The influence that this type of nonbonded interaction in thionitroso compounds has on their reaction with dienes, and other ramifications of this phenomenon, will be discussed in Chapter 3.

2.2 TEMPERATURE VARIATION AND THE TRAPPING OF BENZYLTHIONITROSO COMPOUNDS

2.2.1 INTRODUCTION

Whilst studying the generation and trapping of benzylthionitroso compounds **108a-j** it was noted that variations in the temperature at which the trapping reaction was performed produced a marked effect on the ratio of DA : Ene adducts observed. Previously, Bryce and Heaton had reported an isolated example of this phenomenon in the reaction of compound **1m** with 2,3-dimethyl-1,3-butadiene at 20°C and at 69°C.[11] At the higher temperature, increased levels of the DA adduct **3m** relative to the Ene adduct **12m** were observed. The observation of a temperature effect on the ratio of products with benzylthionitroso compounds prompted us to investigate these species further to clarify the situation.

It has been documented that Ene reactions require greater activation energy than their DA counterparts.[42] It would, therefore, be expected that at higher trapping temperatures, the Ene pathway would be favoured, hence giving a predominance of Ene adduct in the product mixture. Conversely, lower trapping temperatures should produce a predominance of DA adduct.

In our experience, mixtures of DA and Ene adducts in which the Ene adduct predominates tend to be much less stable than those in which the DA adduct is predominant. The Ene adduct is suspected to be particularly unstable, and its decomposition may aid the decomposition of the DA adduct (see Section 3.2 for an expansion of this idea). Thus, if some degree of control over the trapping reaction could be exerted by means of temperature manipulation, it may be possible to eliminate production of the Ene adduct and to produce a readily isolable DA product.

2.2.2 TRAPPING OF BENZYLTHIONITROSO COMPOUNDS AT VARIOUS TEMPERATURES

Benzylthionitroso compound **108b** was chosen as the test system as this produced relatively clean and easily interpretable ^{1}H NMR spectra. The ratio of adducts was assessed from the characteristic resonances due to the methylene groups in 1,2-thiazine **111b** [slightly broadened singlets at $\delta 3.06$ (CH$_2$S) and $\delta 3.32$ (CH$_2$N)], and in the sulfenamide **112b** [slightly broadened singlet at $\delta 3.19$ (CH$_2$S)]. Thionitroso compound **108b** was reacted with 2,3-dimethyl-1,3-butadiene at various temperatures according to Scheme 2.2. The results of the reactions are summarised in Table 2.2.

108

R = (a) Ph
(b) 4-MeC$_6$H$_4$

Δ / X°C / 16h

111 + **112**

Scheme 2.2

54
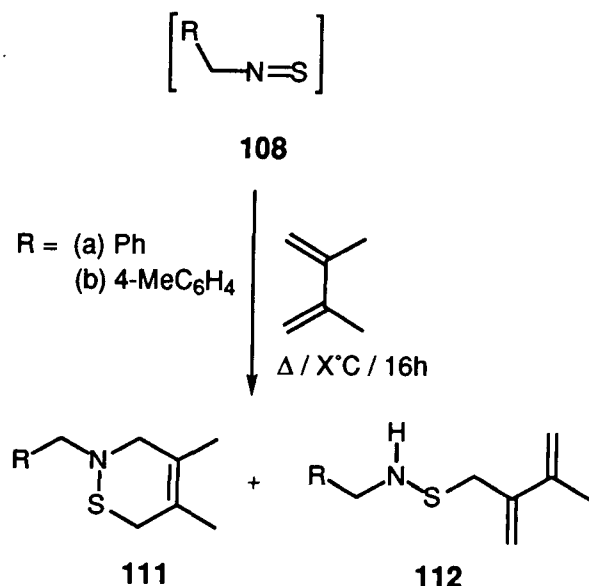
Table 2.2 - Ratio of DA : Ene adducts observed when compound **108b** was reacted at various temperatures with 2,3-dimethyl-1,3-butadiene

Reaction Temperature X°C	Adduct Ratio	
	111b (DA)	**112b** (Ene)
20	1	0
30	1	0
50	1	0
70	1	1
80	1	1
90	1	1
100	1	2

These results show that at low reaction temperature, the Ene adduct **112b** was not produced. Increasing the temperature resulted, however, in a gradual increase in the proportion of Ene adduct in the product, until at the highest attempted temperature the Ene adduct predominated.

To ensure that this was a general effect, a second series of experiments was performed in which thionitroso compound **108a** was reacted with 2,3-dimethyl-1,3-butadiene (Scheme 2.2). The results of these reactions are presented in Table 2.3. The same trend was noted, *i.e.* more Ene adduct **112a** is formed at higher temperature. It was, therefore, concluded that this is a general effect for benzylthionitroso compounds.

Table 2.3 - Ratio of DA : Ene adducts observed when compound **108a** was reacted at various temperatures with 2,3-dimethyl-1,3-butadiene

Reaction Temperature X°C	Adduct Ratio	
	111a (DA)	**112a** (Ene)
20	1	0
40	1	0
60	3	1
70	1	1

To rationalise the results in Tables 2.2 and 2.3, the method of generation of the free thionitroso compound must be taken into consideration, as must its reaction with the diene, including the possibility of retro-reactions. In a DA reaction where both diene and

dienophile are isolable compounds, the observed data would seem to be consistent with the literature.[42] The Ene adduct would be expected to predominate at higher temperature as more energy is available to overcome the higher activation energy of the Ene pathway. However, the thionitroso dienophile is a <u>transient species</u> and hence its mode of generation must first be taken into consideration.

The literature detailing the synthesis of *N*-chlorothio-*N*-trimethylsilylalkylamines states that these compounds decompose slowly at 20°C and rapidly at 100°C.[20] This will affect the equilibrium concentration of thionitroso species in solution at a given temperature (higher concentration at higher temperature). Thus, assuming that concentration of the reactive species does not affect the reaction pathway (DA or Ene), the observed ratios are unlikely to be the result of any precursor effects.

The conformation of the diene must also be taken into account since, in the DA reaction, the diene is required to adopt the higher energy *s-cis* conformation. Since more of this conformer would be present at higher temperatures, this should result in more DA adduct being formed at elevated temperatures. This was clearly not the case, and hence the diene conformation can be disregarded in an explanation of the observed ratios. It is noteworthy that the Ene reaction can occur with either the *s-trans* or *s-cis* diene conformation.

2.2.2.1 RETRO-DA REACTIONS

Finally, the possibility of retro-DA reactions must be considered. If, initially, the thionitroso precursor decomposed quickly at low temperature to release a thionitroso species which subsequently underwent DA reaction, this would result in production of the DA adduct at low temperature. It is, however, possible that as the temperature increases, a retro-DA reaction occurs regenerating the free thionitroso species which, in the presence of the excess diene used in the reaction, undergoes Ene reaction when sufficient activation energy is available at the higher temperature.

The yield of the trapping reaction could provide evidence for retro-reactions. If retro-reactions were occurring, the total yield of adducts should remain constant. This was in fact observed, as the yield of adducts (estimated from the ^{1}H NMR spectra) remained constant at *ca.* 30% when multiple sampling over the duration of a trapping reaction was performed. However, it is possible for the yield to remain constant if the precursor decomposes slowly and the adducts also decompose *via* a non-retro-DA pathway. The

yield could not therefore be used to determine whether retro-DA reactions were occurring in this case, so another method was required.

It was decided to test for retro-DA reactions by looking for 'crossed products' which may arise when a DA adduct produced by trapping a thionitroso compound with a diene is first isolated, then heated <u>with a different diene.</u> This concept is illustrated in Scheme 2.3, in which the thionitroso compound is first trapped with 2,3-dimethyl-1,3-butadiene, the adduct isolated, and then heated with 2-methyl-1,3-butadiene. The presence of the 2-methyl-1,3-butadiene adduct would provide evidence to indicate that retro-DA reactions were occurring.
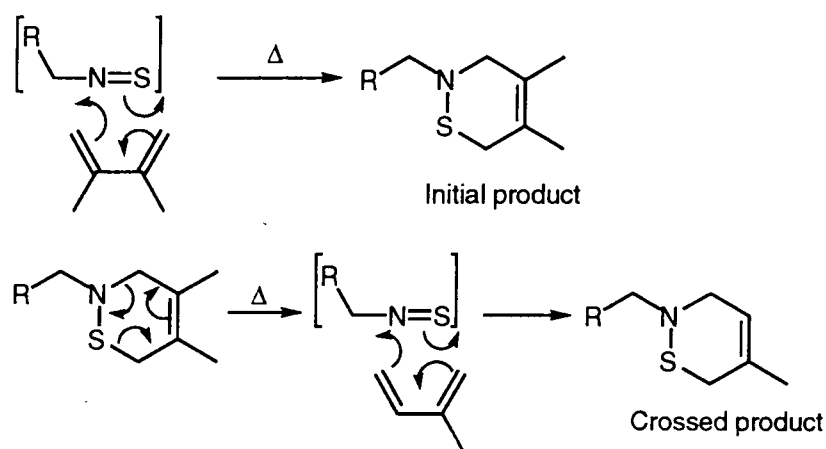
Scheme 2.3

To apply the above to benzylthionitroso compounds, it was first necessary to perform a test reaction to determine whether 2-methyl-1,3-butadiene was a suitable trap, *i.e.* that adducts would form when benzylthionitroso precursors were heated in its presence. Unfortunately, it was found that 2-methyl-1,3-butadiene would not form adducts and thus could not be used in a test such as that described. This problem was overcome by using our previous observation that at low temperature only the DA adduct is formed on reaction with 2,3-dimethyl-1,3-butadiene (Table 2.3). Isolation of the DA adduct by column chromatography, thus removing any residual precursor compound, followed by prolonged heating at a higher temperature (100°C) with 2,3-dimethyl-1,3-butadiene produced some decomposition but significantly, <u>no Ene adduct</u>. This provided evidence that retro-DA processes were not occurring and, therefore, were not involved in the ratio effects. In addition, heating a purified mixture of adducts **111b** and **112b** in the presence of excess 2,3-dimethyl-1,3-butadiene produced a small amount of decomposition but the ratio of adducts remained constant. Thermal decomposition can also, therefore, be reasonably ruled out as the cause of the change in ratio with temperature.

Taking the above points into consideration, it was concluded that the reason for the predominance of the Ene adducts at elevated reaction temperatures was due to there being sufficient energy available to promote this higher energy pathway. This result is entirely in accordance with the literature regarding the reaction of dienophiles with dienes.[42]

2.3 FUNCTIONALISED THIONITROSOALKANES

2.3.1 INTRODUCTION

Having thoroughly investigated benzylthionitroso compounds (Sections 2.1 and 2.2), we sought to extend the existing methodology (thermal fragmentation of *N*-trimethylsilyl-*N*-chlorothioalkylamines) to the synthesis of thionitrosoalkanes containing other functional groups in the alkyl chain attached to nitrogen. Following the work on benzylthionitroso compounds, a logical target compound was 1-thionitroso-2-phenylethane **115** ($PhCH_2CH_2N=S$), which simply contains an extra CH_2 group compared to the benzylthionitroso compounds **108**.

A second area of interest was the synthesis of thionitrosoalkanes in which a chiral sp^3 carbon is attached to the N=S moiety. With this system there exists the possibility of assembly of chirally substituted 1,2-thiazine heterocycles *via* DA reaction with dienes, or production of chiral heterocycles if a prochiral diene is used.[42, 67] This is an area which has been investigated thoroughly for nitroso compounds **5**, and *N*-sulfinylamines **6**,[2] but not for thionitroso compounds. Indeed, only one report by Meth-Cohn *et al* on this aspect of thionitroso compounds has come to our attention.[68] This detailed the reaction of (-)-menthyl and (+)-fenchyl thionitrosoformate esters with *E,E*-hexadiene, yielding an inseparable mixture of diastereoisomers.

Incorporating the above considerations with our desire to study functionalised thionitrosoalkanes, we have investigated the synthesis of chiral thionitroso compounds from the esters of amino acids, and their interception with 2,3-dimethyl-1,3-butadiene.

2.3.2 GENERATION OF FUNCTIONALISED THIONITROSOALKANES

1-Thionitroso-2-phenylethane **115** was generated and intercepted with 2,3-dimethyl-1,3-butadiene to afford a mixture of 1,2-thiazine **116** and sulfenamide **117** (1 : 1 ratio) as an unstable yellow oil in low yield (5%) (Scheme 2.4).
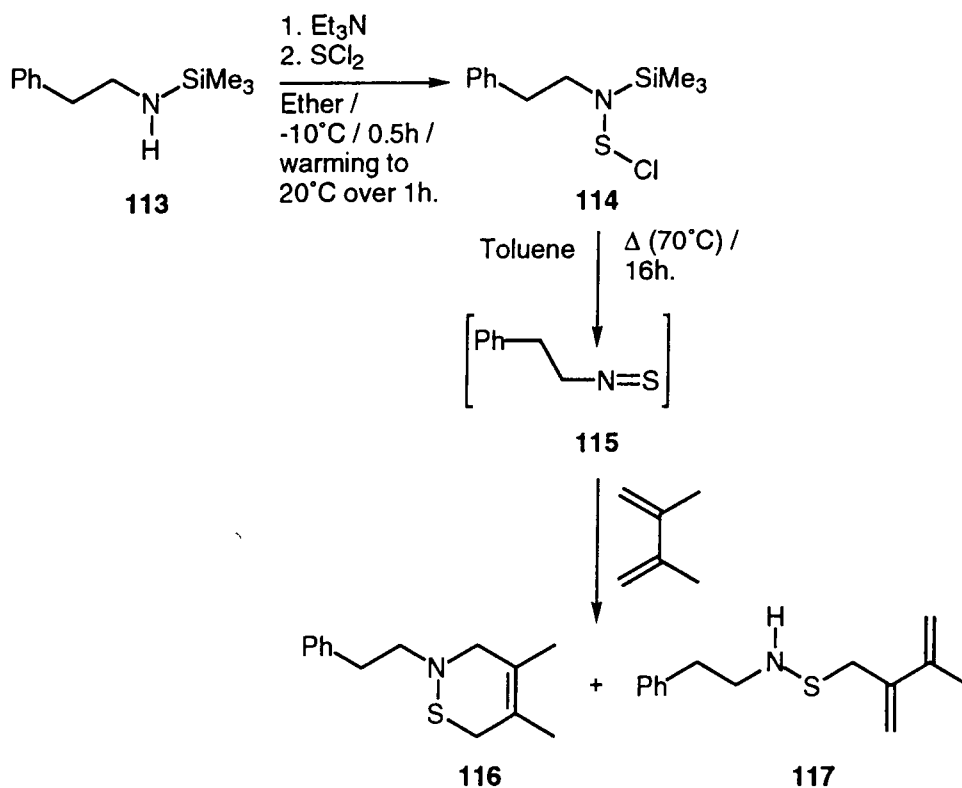
Scheme 2.4

Decomposition of the mixture of compounds **116** and **117** was swift (3h at 20°C, NMR evidence) and this, combined with the low yield meant that overall the reaction was disappointing. On account of this, it was decided to discontinue the work on simple alkyl substituents and to move on to the development of functionalised thionitrosoalkanes.

2.3.2.1 THIONITROSOALKANES FROM AMINO ACID ESTERS

Amino acids represent some of the simplest and most readily available chiral heteroalkylamines, and as such were considered ideal starting materials for our study of heteroalkyl chiral thionitroso compounds. In order to generate thionitrosoalkanes from amines efficiently by fragmentation of *N*-trimethylsilyl-*N*-chlorothioalkylamines, all potentially acidic protons (excluding those on N) must be eliminated, thus simple amino

acids were ruled out. However, removal of the carboxylic acid proton by esterification afforded ideal precursor materials in the form of ethyl esters of amino acids.

Using the method of Marvel and Noyes, ethyl-(2-amino-2-phenyl)ethanoate **118a** was synthesised,[69] ethyl-(2-amino-3-phenyl)propanoate **118b** was liberated from its hydrochloride (as purchased) by treatment with base. Employing a slightly modified version of the synthetic route detailed in Scheme 2.1 (in the synthesis of silylamines **119a-b** triethylamine was used as base in place of butyl lithium, since the latter was found to cause decomposition of amines **118a-b**), thionitroso compounds **121a-b** were generated and intercepted with 2,3-dimethyl-1,3-butadiene (Scheme 2.5).
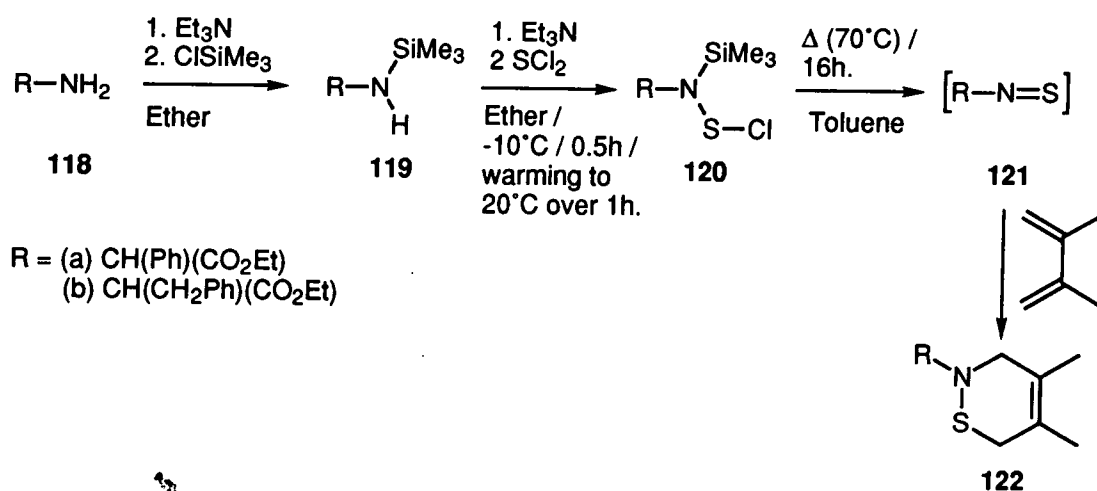
Scheme 2.5

Interestingly, only evidence for the formation of the DA adducts **122a-b** was observed. It is, however, possible that the corresponding Ene adducts had been formed, but were too unstable to detect. Adducts **122a-b** were isolated as yellow oils in low yields (10 - 15%) and seemed particularly unstable, decomposing completely after 3h (at 20°C) to intractable black material. These adducts were by far the most unstable of the 1,2-thiazines thus far mentioned, and due to the rapidity of their decomposition further work on these systems was not deemed profitable.

2.4 CONCLUSIONS

Benzylthionitroso compounds **108a-j** were generated by thermal fragmentation of *N*-trimethylsilyl-*N*-chlorothioalkylamines **110a-j**. Interception of compounds **108a-j** with 2,3-dimethyl-1,3-butadiene afforded mixtures of *N*-benzyl-1,2-thiazines **111a-j** and sulfenamides **112a-g,i**. These product mixtures were unstable, typically decomposing after 5h (at 20°C) even under an inert atmosphere (Ar).

Excluding fluorinated derivatives **108e-f**, the electronic nature of the substituent on the aromatic ring in benzylthionitroso compounds **108** did not appear to influence the ratio of DA : Ene adducts produced on reaction with 2,3-dimethyl-1,3-butadiene. These results were expected since the benzyl methylene group insulates the N=S moiety from the electronic influences of the aromatic ring. In strong contrast to the above, substituent electronic effects in thionitrosoarenes greatly influenced this ratio, as would be expected since the N=S moiety is attached directly to the aromatic ring in these compounds (Sections 1.2.2.2 and 1.2.8).

The ratio of DA : Ene adducts formed when thionitroso compounds **108a,b** were reacted with 2,3-dimethyl-1,3-butadiene was temperature-dependent. Low temperature favoured production of the DA adduct **111**, whereas high temperature favoured formation of the Ene adduct **112**, a result which is in accordance with expectations from the literature.[42] This study provides the first example of the control of DA : Ene ratio by temperature in thionitroso trapping reactions and as such offers the possibility of the synthesis of pure 1,2-thiazines. This is of interest since, in our experience, the pure 1,2-thiazines tend to be more stable than 1,2-thiazine/sulfenamide mixtures.

Chapter Three

Synthesis and Properties of Stable

1,2-Thiazines

3.1 HETEROALKYL SUBSTITUTED THIONITROSO COMPOUNDS

3.1.1 INTRODUCTION

In Chapter 2 we showed how we have developed the existing methodology to the synthesis and trapping of thionitrosoalkanes. In Section 2.3.2 it was demonstrated that adducts **116** and **117** were obtained when compound **115** was intercepted with 2,3-dimethyl-1,3-butadiene. These adducts were, however, produced in low yields and found to be unstable. In Section 2.3.2.1 we also demonstrated that 1,2-thiazines **122a-b** could be produced from amino acid esters (*via* thionitroso compounds **121a-b**), but again were very unstable and produced in low yield (Figure 3.1).
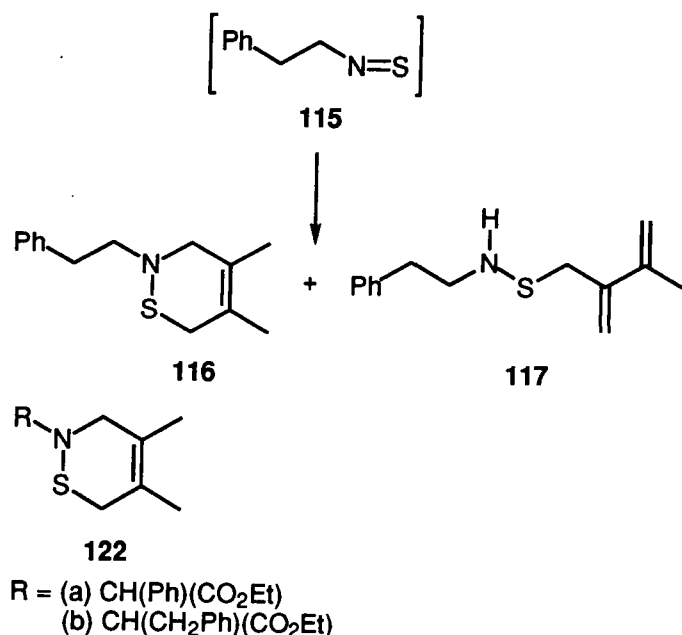
Figure 3.1

We wished to continue our studies into the generation of heteroalkyl substituted thionitroso compounds and reasoned, from our experience with the above derivatives, that in order to obtain cycloadducts which were relatively more stable, a chemically inert heteroalkyl functionality was required. The ether functionality is well known for its inertness, being cleaved only in the presence of strong acid,[70] so from this standpoint we investigated the generation and interception of thionitroso compounds incorporating an ether functionality.

3.1.2 ETHER AND THIOETHER FUNCTIONALISED THIONITROSOALKANES

Thionitroso compounds **125a-e** were generated and intercepted with 2,3-dimethyl-1,3-butadiene to afford 1,2-thiazine adducts **126a-e** as yellow oils (after column chromatography). Once pure, compounds **126a-e** were stable in air for <u>a number of months</u> at 20°C (Scheme 3.1).

Compound 126	Yield %
R = (a) PhOCH$_2$CH$_2$	45
(b) PhOCH$_2$CH(Me)	40
(c) PhSCH$_2$CH$_2$	40
(d) MeSCH$_2$CH$_2$CH$_2$	20
(e) 2-MeSC$_6$H$_4$	40
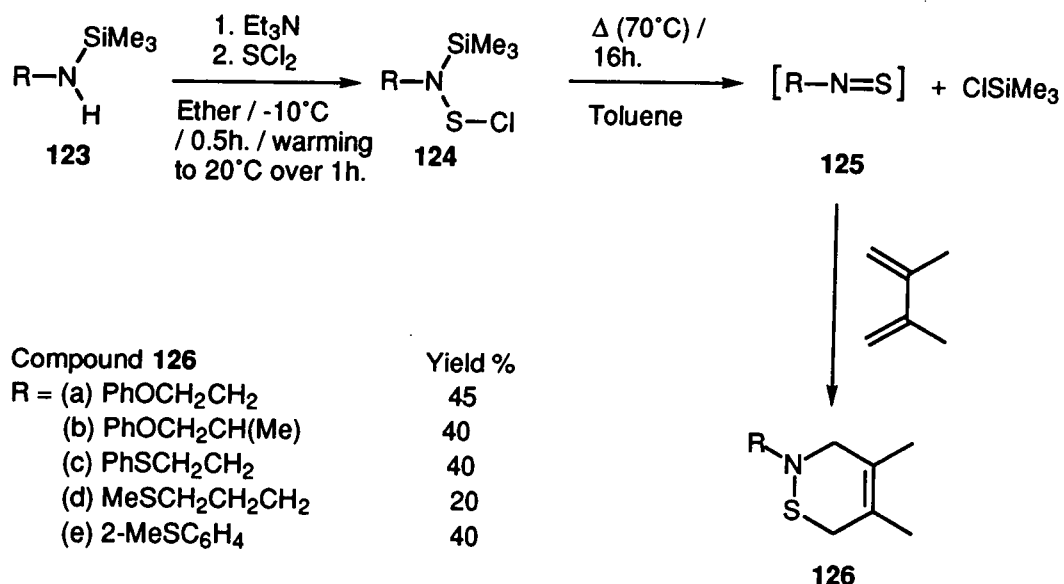
Scheme 3.1

There are two noteworthy facets of this work to be considered. Firstly, reaction of compounds **125a-d** with 2,3-dimethyl-1,3-butadiene produced only the 1,2-thiazine adducts **126a-d** (**125e** was the exception and did give a small amount of Ene adduct). This result is in contrast with the observations on the thionitroso compounds detailed in Chapter 2. Secondly, the remarkable stability of compounds **126a-e**, once pure, contrasts markedly with the 1,2-thiazine adducts detailed in Chapter 2 and with previous 1,2-thiazines synthesised within this laboratory.[13, 66] The reason for these observations may be the involvement of S--O and S--S nonbonded interactions in both the thionitroso compounds **125a-e**, and in 1,2-thiazines **126a-e**, an idea which will be expanded upon later in this thesis.

That an Ene adduct was produced from the reaction of compound **125e** with 2,3-dimethyl-1,3-butadiene is not surprising. Compound **125e** is a thionitrosoarene with an S-methyl group in the 2-position. Based on the work of Bryce and Heaton (Section 1.2.8), it would be expected, in the absence of the nonbonded interaction, to produce predominantly Ene

adduct due to steric hindrance inhibiting formation of the DA adduct. Although compound **125e** is not in the same class as **125a-d** (*i.e.* not a thionitrosoalkane), it has been included at this juncture as an example of another structure capable of intramolecular nonbonded interaction.

3.1.2.1 THE ABSENCE OF ENE ADDUCT

In view of the fact that no Ene adduct had been produced when thionitroso compounds **125a-d** were trapped with 2,3-dimethyl-1,3-butadiene (Scheme 3.1), we tested whether or not a free thionitroso compound was actually involved in the reaction sequence. This would allow us to rule this out as a cause of the lack of Ene product.

By analogy with the work of Bryce and Taylor on thionitrosoarenes (Section 1.2.2.2),[10] we sought to use a reaction with (*E,E*)-2,4-hexadiene **16** to provide evidence for the existence of free thionitroso compound **125a** (Scheme 3.2).

125a 16   **127**   **128**   and / or   **129**

                                                                Syn   *Anti*

                                                A mixture of *syn* and
                                                anti would not be obtained
                                                from a concerted reaction
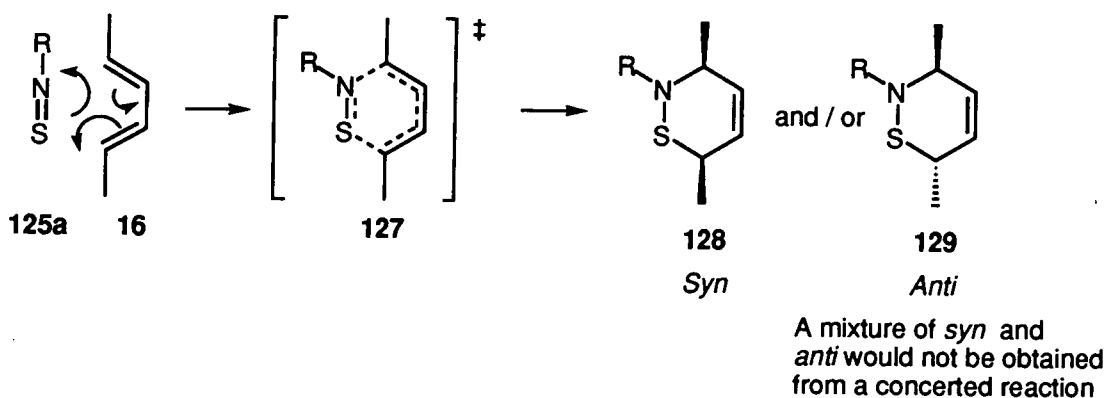
Scheme 3.2

If a concerted DA reaction occurs between **125a** and **16** (represented by transition state structure **127** in which simultaneous bond fission and formation occurs), only the product in which the methyl groups are *syn,* can be formed. [Note that compound **128** would in fact be a mixture of diastereomers (as would compound **129**) due to the stereochemistry associated with the nitrogen atom]. Generation of free thionitroso compound **125a** is a prerequisite for the occurrence of a concerted reaction. If the reaction is not concerted, the possibility of a mixture of products **128** and **129** exists. Thus the observation of a single isomer in this type of experiment is taken as evidence for a concerted reaction, and would also be evidence for the generation of a free thionitroso compound. It should be noted, however, that this argument contains a pitfall: this being the possibility of non-concerted stereospecific reaction occurring to give a single isomeric product **128** without

involvement of compound **125a**. Indeed, such a scenario for *N*-sulfinylamines **6** has been documented by Boger and Weinreb.[2] Thus, in drawing conclusions from this type of experiment, we assumed that a pure *syn* product would indicate involvement of a free thionitroso compound.

Compound **125a** was generated (in the same manner as detailed in Scheme 3.1) and intercepted with (*E,E*)-2,4-hexadiene **16** (Scheme 3.3).

R = a) PhOCH₂CH₂   **128**
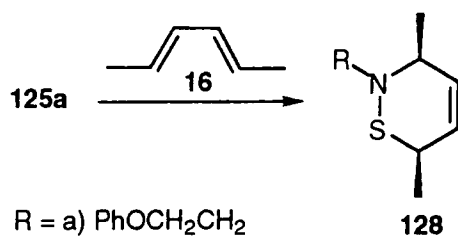
Scheme 3.3

Only a single isomer, **128a**, was observed, thus indicating that a concerted reaction had occurred and therefore the involvement of free thionitroso compound **125a** is implicated. That the product of the reaction detailed in Scheme 3.3 was a pure *syn* isomer was determined initially from the ^{1}H NMR spectrum (Figure 3.2), and was confirmed by a ^{13}C DEPT spectrum (Figure 3.3).

It can thus be concluded that the lack of Ene adduct was not due to a change in the mechanism of fragmentation of compound **124a** to **125a**, as reaction with (*E,E*)-2,4-hexadiene proceeded in a manner analogous to that observed by Bryce and Taylor with thionitrosoarenes.[10]

The lack of Ene reactivity in compounds **125a-d** can be rationalised in terms of a stabilising nonbonded interaction (Figure 3.4).
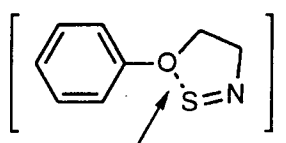
Nonbonded interaction

125a

Figure 3.4
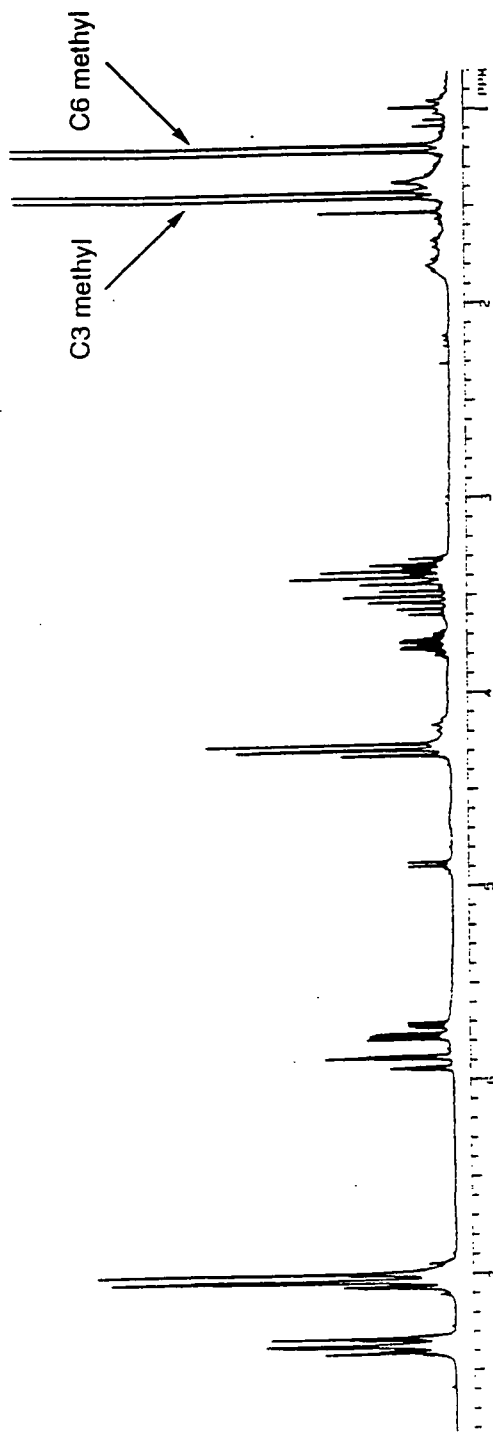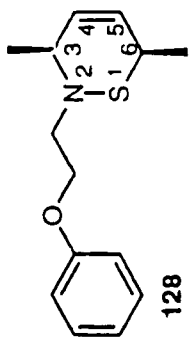
*Figure 3.2 - ¹H NMR Spectrum of compound **128** showing, from the number of methyl group signals, that this compound was a single isomer.*
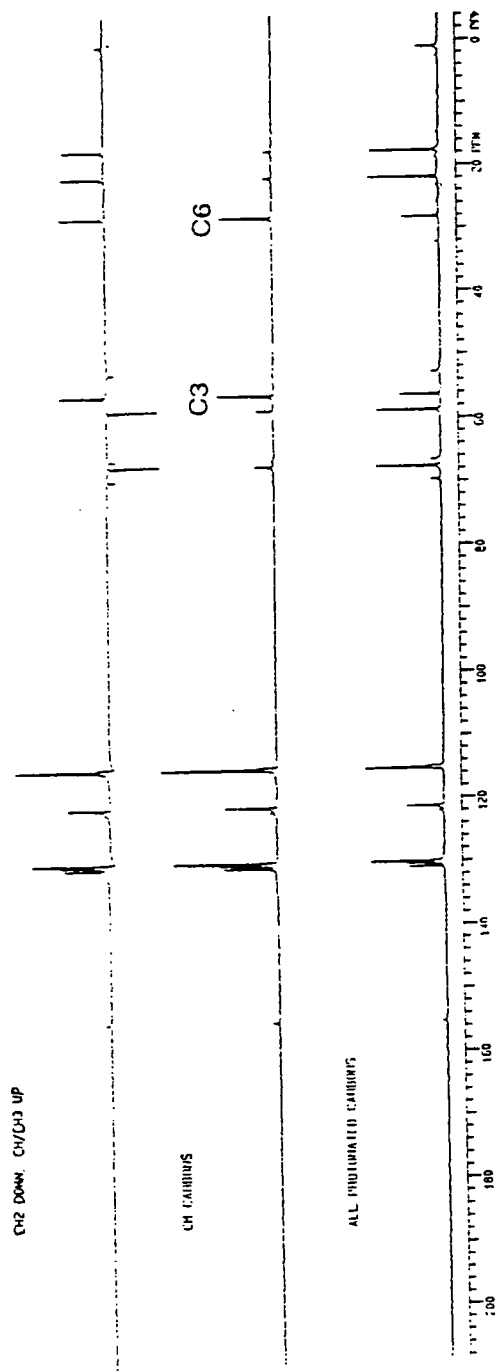
*Figure 3.3 - ¹³C DEPT Spectrum of compound **128**.*

67

Such a nonbonded interaction would stabilise the electron-deficient thionitroso moiety by increasing the electron density in the thionitroso moiety. This being the case, one can then use the arguments of Taylor to explain the lack of Ene reactivity (Section 1.2.8). These state that thionitroso compounds with electron-donating substituents would be stabilised (relative to those with electron-withdrawing substituents), *i.e.* they would have a longer lifetime. For this reason, they would be more likely to encounter a diene molecule in the *s-cis* conformation and thus undergo a DA reaction to give a 1,2-thiazine. This line of reasoning can also be applied to thionitroso compounds stabilised by a nonbonded interaction; therefore, it should be expected that the DA adduct would be favoured in reaction of compounds **125a-d** with dienes, as was observed. It should be recognised that the same proviso used by Taylor applies here also, *i.e.* the assumption that a thionitroso compound encountering a diene in the *s-cis* conformation reacts preferentially *via* the DA pathway. No evidence to support this assumption was gathered here, or by Taylor.

A second possible explanation for the absence of Ene adduct concerns the effect of the nonbonded interaction on the polarity of the thionitroso moiety (in which sulfur has net positive charge, see Section 1.2.7). It has been noted previously that the Ene reaction is favoured when polar solvents are employed.[66] This suggests that the Ene pathway would be favoured by increasing the polarity of the thionitroso moiety, and, conversely, would be disfavoured by decreasing the polarity. It can be seen that the posited nonbonded interaction would decrease the polarity of the thionitroso moiety (by donating electron-density onto the sulfur atom), and thus would disfavour the Ene pathway, as observed.

3.1.2.2 STABILITY OF COMPOUNDS **126a-e**

Compounds **126a-e** showed remarkable stability. In our experience, the adduct mixtures produced *via* the trapping of thionitroso compounds have usually shown limited stability (typically total decomposition occurred in 3 - 48h on standing at ambient temperature). Compounds **126a-e** were stable for at least 2 months (monitored by ^{1}H NMR spectroscopy), and adduct **126b** showed no significant decomposition after 9 months when stored in $CDCl_3$ at 4°C. Further, it was noted that it was possible to produce chromatographically pure products, a situation that proved impossible to achieve with compounds **111a-j** in our hands. Figure 3.5 shows the ^{1}H NMR spectrum of adduct **126a** which clearly illustrates this fact.

The enhanced stability of compounds **126a-e** (probably due to protection of the thiazine sulfur atom from nucleophilic attack) may be due to intramolecular S--O and S--S
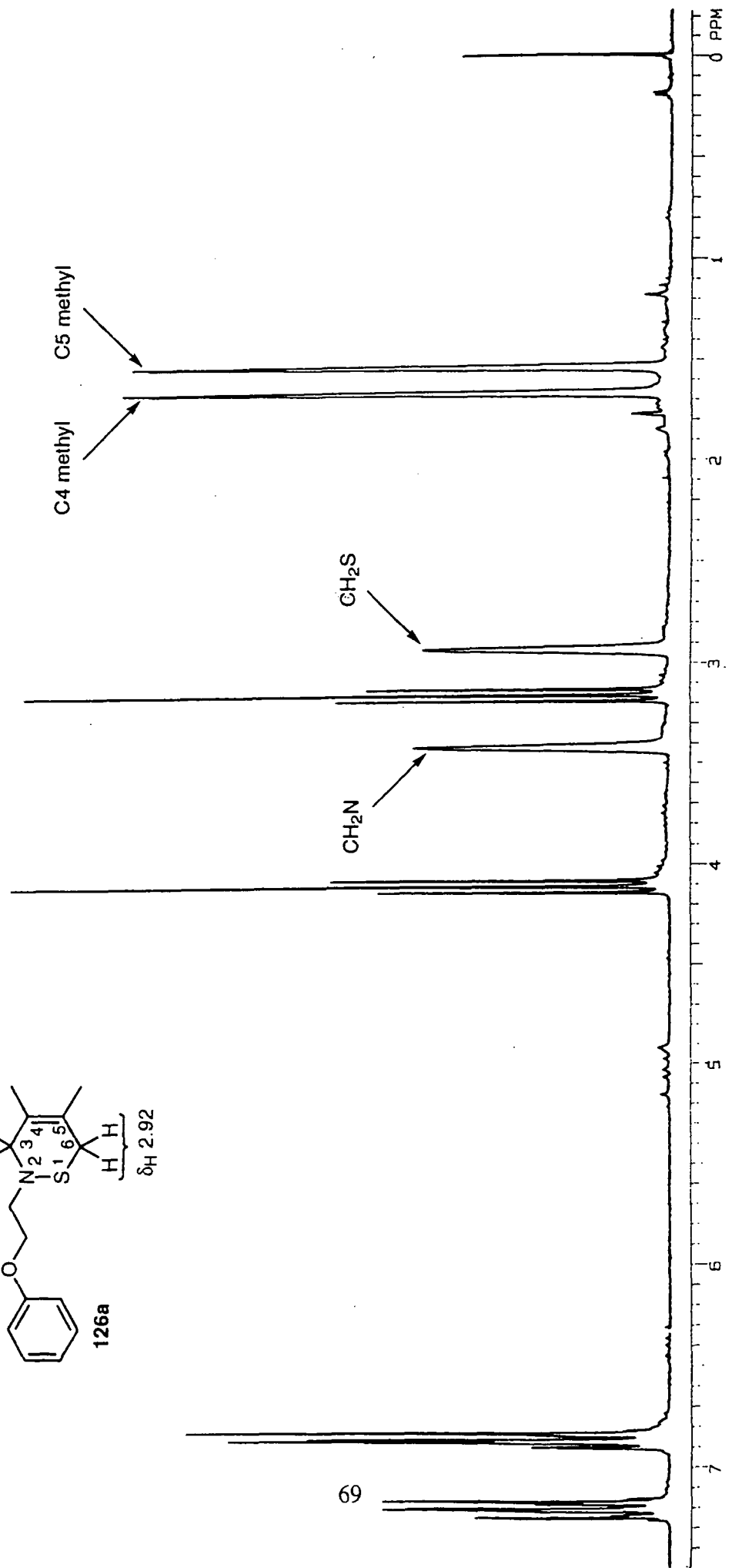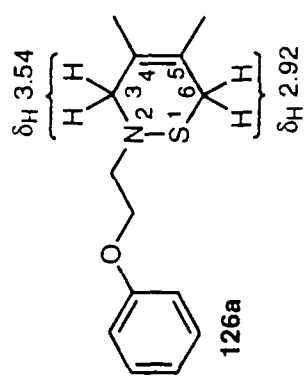
*Figure 3.5 - ¹H NMR Spectrum of compound **126a** illustrating that this type of compound could be obtained spectroscopically pure, and highlighting the slightly broadened signals due to protons in the 1,2-thiazine ring.*

nonbonded interactions (reduced susceptibility of sulfur to nucleophiles due to nonbonded interactions has previously been noted).[71] This type of interaction (sometimes referred to as close contact) is well documented,[71, 72] one of the earliest examples being methyl-2-nitrobenzenesulfenate **130** (Figure 3.6).[71]

130
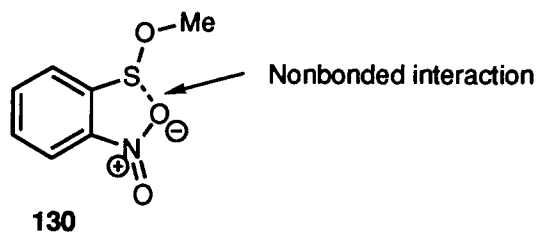
Figure 3.6

The S--O internuclear distance in compound **130** was found to be 2.44Å by X-ray crystallography, which is significantly less than the van der Waals distance of 3.25Å but greater than the S-O single bond length of *ca*. 1.6Å. Although 1,3 1,4 and 1,5 S--O nonbonded interactions (3, 4 and 5 atoms in the pseudo-ring, respectively) have been observed crystallographically (Cambridge Crystallographic Data Base, and detailed in reference 71), the most favoured and most abundant is the 1,5 interaction in compounds of general structure **131** (Figure 3.7).

| 131 | 132 | 133 |
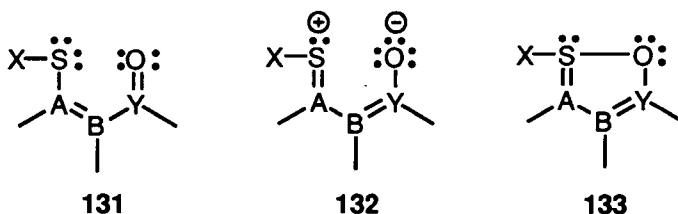
Figure 3.7

In compounds of general structure **131**, both electrostatic and covalent interaction (shown diagramatically by limiting structures **132** and **133**, respectively) can be maximised. The optimum geometry for a 1,5 S--O nonbonded interaction displays an X-S--O bond angle of 180°, *i.e.* it is linear.[71] Obviously in compounds **126a-e** the electrostatic interaction will be predominant, and the X-S--O angle will be less than 180°, thus the nonbonded interaction will be somewhat weaker than in the ideal case. In orbital terms, the X-S--O systems (in structures **131**) can be considered as a delocalised σ-system with a three centre-four electron bond in analogy with hypervalent sulfur species. For comparative purposes Figure 3.8 details other types of sulfur-oxygen interactions.

S=O	S-O	S···O	S--O	S / O
1.40 - 1.49Å	1.56 - 1.65Å	1.65 - 2.25Å	2.03 - ~ 3.25Å	3.10 - 3.60Å
Covalent bond	Covalent bond	Hypervalent bond	Nonbonded interaction	Van der Waals distance

Figure 3.8

It has been noted that nucleophilic attack on the sulfur atom of divalent sulfur compounds occurs in-plane and along a line extended from either covalent bond to sulfur (Figure 3.9).[72]
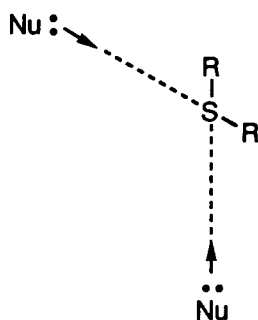
Figure 3.9

Hence it can be seen that if nonbonded interactions were occurring in compounds **126a-e**, the approach of nucleophiles would be severely hindered due to unfavourable steric interactions and reduction of the partial positive charge on sulfur. We suggest that this is responsible for the stability of these compounds (Figure 3.10).
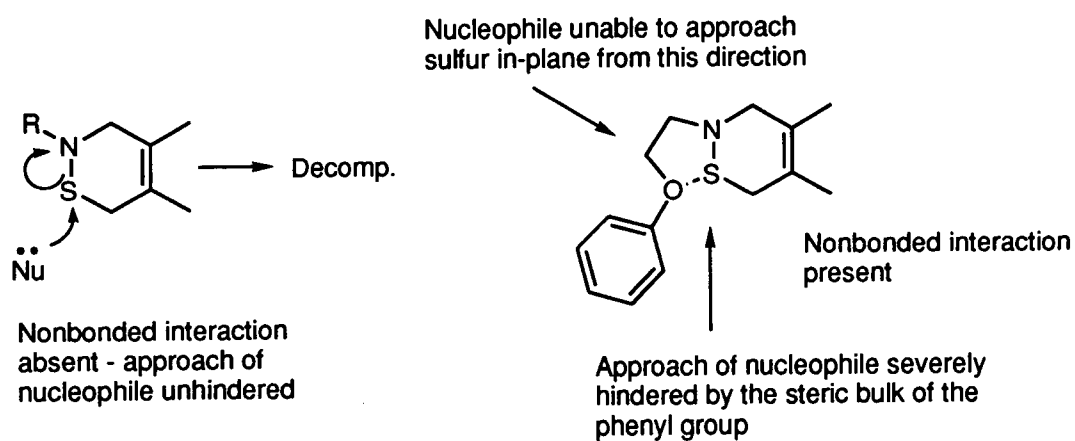
Figure 3.10

Interestingly, there are no reports of crystal structures of compounds involving an intramolecular 1,6 S--O or S--S nonbonded interaction. The stability of compound **126d** may therefore be a physical consequence of a rare 1,6 S--S interaction. Further experimental evidence for nonbonded interactions in compounds **126a-e** is presented in Sections 3.2 and 3.3.

3.1.2.3 THE EFFECT OF NONBONDED INTERACTIONS ON THE REGIOCHEMISTRY OF THIONITROSO CYCLOADDITION REACTIONS

Nonbonded interactions in compounds **125a-d** have been postulated as the cause of the lack of Ene reactivity of these compounds when reacted with 2,3-dimethyl-1,3-butadiene (Section 3.1.2.1). It was suspected that nonbonded interactions would also affect the regiochemistry of the cycloaddition reactions of these compounds with unsymmetrical dienes. An experiment to explore this was undertaken (Scheme 3.4).

$$[R-N=S]$$
125

R = (b) PhOCH$_2$CH(Me)   **134**
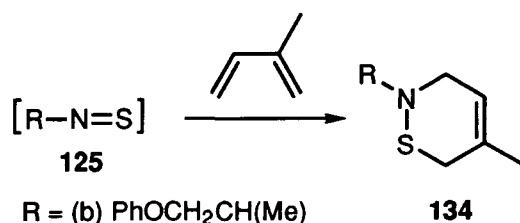
Scheme 3.4

Upon reaction of compound **125b** with 2-methyl-1,3-butadiene a single regioisomeric adduct with the methyl group at C5 (compound **134b**) was produced (10% yield). It can be seen, therefore, that compound **125b** reacts with this diene with complete regioselectivity. This result contrasts markedly with the analogous reactions of thionitrosoarenes in which only partial regioselectivity was observed (Section 1.2.9). The explanation for the regioselectivity observed in the reaction of compound **125b** may be steric since the transition state leading to the C5 isomer has the diene methyl group furthest away from the substituents on nitrogen. This does not, however, explain the role of the nonbonded interaction. Further studies on the regiochemistry of thionitroso cycloaddition reactions are presented in Chapter 4.

3.1.2.4 LIMITATIONS OF THE METHODOLOGY

In our search for amines that would potentially lead to 1,2-thiazines stabilised by nonbonded interactions, we discovered that the methodology detailed in Scheme 3.1 was unsuitable for the production of certain thionitroso compounds (Scheme 3.5).

R = (a) 2-MeOC$_6$H$_4$
(b) 2-PhOC$_6$H$_4$
(c) 2-NO$_2$C$_6$H$_4$
(d) 2,4,6-tri-BrC$_6$H$_2$OCH$_2$CH$_2$
(e) CH$_2$=CHCH$_2$
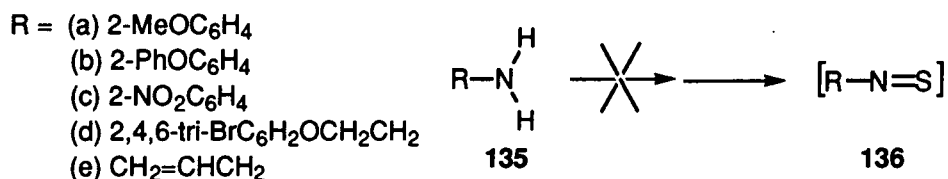
Scheme 3.5

Both 2-methoxyaniline **135a** and 2-phenoxyaniline **135b** decomposed upon addition of base, most probably due to the fact that the anion corresponding to loss of Me$^+$ or Ph$^+$ would be resonance stabilised. In our hands, addition of the trimethylsilyl group to 2-nitroaniline **135c** failed, this was presumably due to steric pressure from the nitro group disfavouring addition of this bulky species. 2,4,6-Tribromophenoxyethylamine **135d** was hitherto unknown, and was synthesised according to Scheme 3.6.
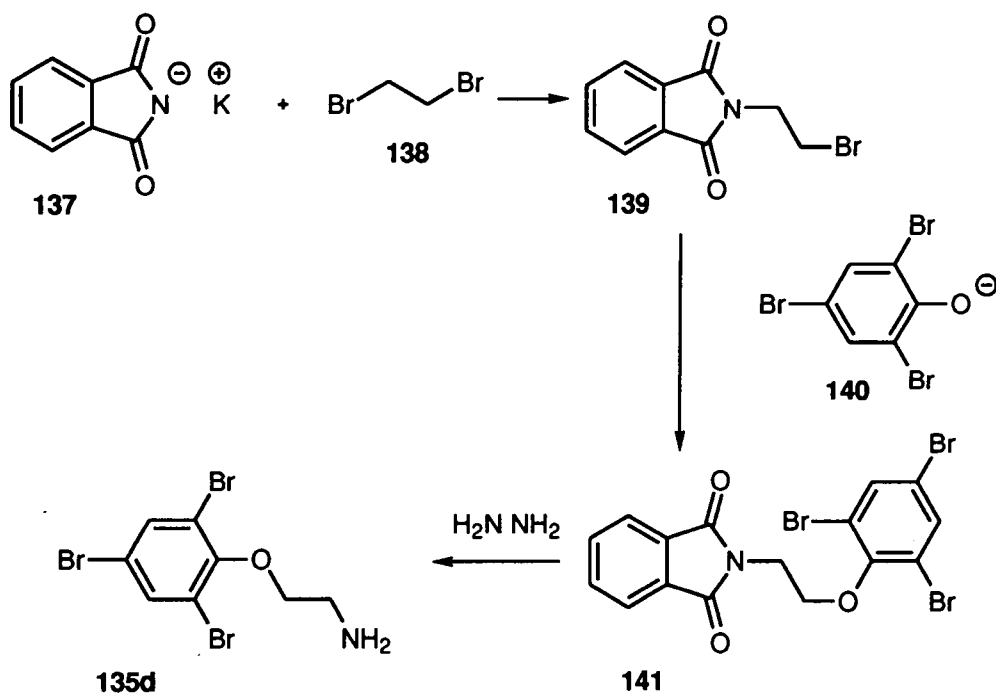
Scheme 3.6

It was hoped that generation and interception of a thionitroso compound derived from compound **135d** would produce a stable 1,2-thiazine which, because of the bulky bromine

atoms, would also be crystalline (no crystal structure of a free, 1,2-thiazine exists although a crystal structure for a 1,2-thiazine complexed to a transition metal has been obtained in our laboratory).[73] Unfortunately a thionitroso compound could not be generated from compound **135d**, probably due to the extreme insolubility of this compound.

The attempt to prepare and intercept a thionitroso compound from 2-propenamine (**135e**) was in order to observe any stabilising effect due to interaction of the 'p' orbitals of the π-system with the 'd' orbitals of the sulfur atom. The reason for the failure of this reaction was probably due to reaction of sulfur dichloride with the double bond, possibly causing polymerisation.

3.2 RING CHEMISTRY OF 1,2-THIAZINES

3.2.1 INTRODUCTION

Having synthesised a series of stable 1,2-thiazines **126a-e**, we sought to investigate their chemistry and compare it with the chemistry of some unstabilised 1,2-thiazines. We hoped that some chemical inertness of compounds **126a-e** would provide additional evidence for the proposed nonbonded interaction. This work represents the first systematic study of the chemistry of this heterocycle.

It was suspected that 1,2-thiazines would decompose *via* cleavage of the relatively weak N-S bond (*cf.* bond strengths N-S 192, C-S 218, and C-N 222 kJ mol^{-1}).[74] Decomposition may be spontaneous, but nucleophilic attack at sulfur would greatly facilitate the process (Scheme 3.7).
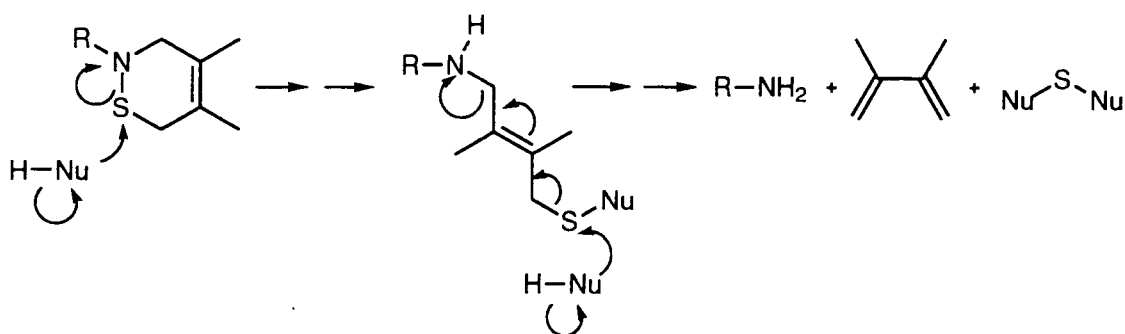
Scheme 3.7

Scheme 3.7 shows how a 1,2-thiazine could decompose when attacked by a nucleophile. Analogous 1,2-dihydrooxazine and 1,2-thiazine-1-oxide heterocycles have been shown to react by this and other routes.[1, 75]

We have addressed three areas in relation to the ring chemistry of 1,2-thiazines; (a) reaction with nucleophiles, (b) chemistry of the double bond and (c) attempted generation of anions at the C6 position of the 1,2-thiazine ring.

3.2.2 REACTION OF NUCLEOPHILES WITH 1,2-THIAZINES

Scheme 3.7 showed how nucleophilic attack at sulfur may cause decomposition of 1,2-thiazines and Figure 3.10 demonstrated how 1,2-thiazines could be made inert to nucleophilic attack by the introduction of a nonbonded interaction. We sought to provide evidence for the nonbonded interaction by comparison of the reactivity of 1,2-thiazines both with and without the possibility of such interactions.

1,2-Thiazines **3e** and **126a** were therefore reacted with a series of nucleophiles according to Scheme 3.8.

Compound	R			
126a	$PhOCH_2CH_2$		H_2O	No reaction **126a** and **3e**
3e	$4\text{-}MeC_6H_4$			
			HCl	No reaction **126a** Decomp.* **3e**
			NaOH	No reaction **126a** Partial decomp.* **3e**
			MeS^-Na^+	Partial decomp.* **3e** (Reaction not performed on **126a**)
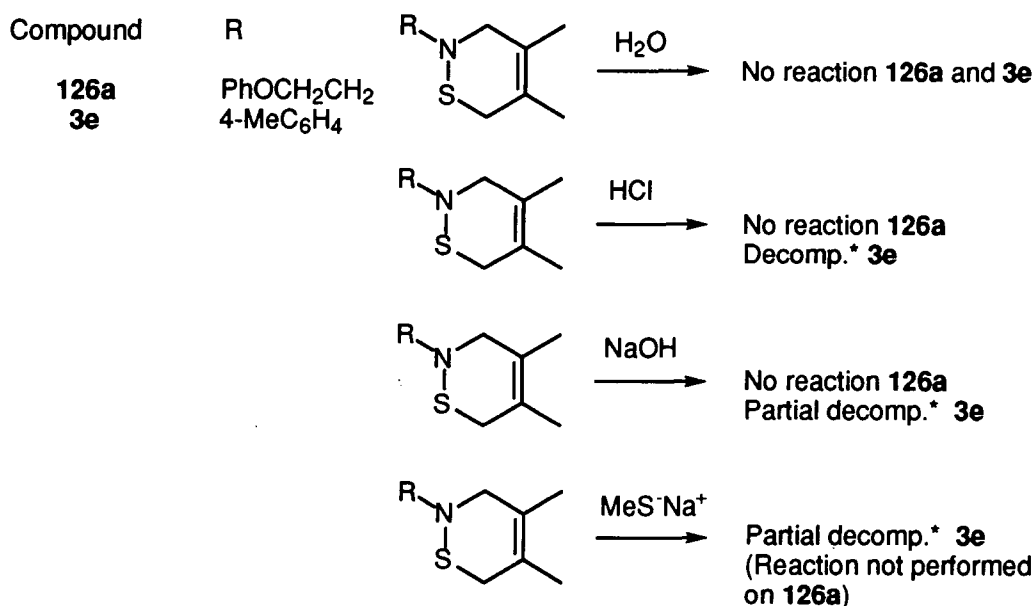
* = Reaction product not identifiable by ^1H NMR or MS

Scheme 3.8

It is clear from the results of the above reactions that 1,2-thiazine **126a** was less reactive than compound **3e**. Since **126a** is the compound with the possibility of a 1,5 S--O

nonbonded interaction, these results suggest that this interaction is occurring and is responsible for the enhanced stability.

It was disappointing that no ring opened product could be isolated from the above reactions, especially those of **126a**. However, when the reactions were analysed, only extensive decomposition to azo compounds and a multitude of other species (^{1}H NMR and MS data) which proved to be inseparable by column chromatography, was evident.

3.2.3 1,2-THIAZINE DOUBLE BOND CHEMISTRY

Although the double bond in compounds **3e** and **126a** is *tetra* substituted (and hence the least reactive of C=C bonds) we wished to obtain a comprehensive view of the chemistry of 1,2-thiazines, and thus an investigation into the reactions of the double bond in these species was deemed pertinent (Scheme 3.9).

Compound	R
126a	PhOCH$_2$CH$_2$
3e	4-MeC$_6$H$_4$

Br$_2$ ⟶ Decomp.* **126a** and **3e**

HBr ⟶ No reaction **126a** / Decomp.* **3e**

NBS ⟶ Decomp.* **126a**

mCPBA ⟶ No reaction **126a**

3e mCPBA ⟶ **142** + **143**

* = Reaction product not identifiable by ^{1}H NMR or MS

R = 4-MeC$_6$H$_4$
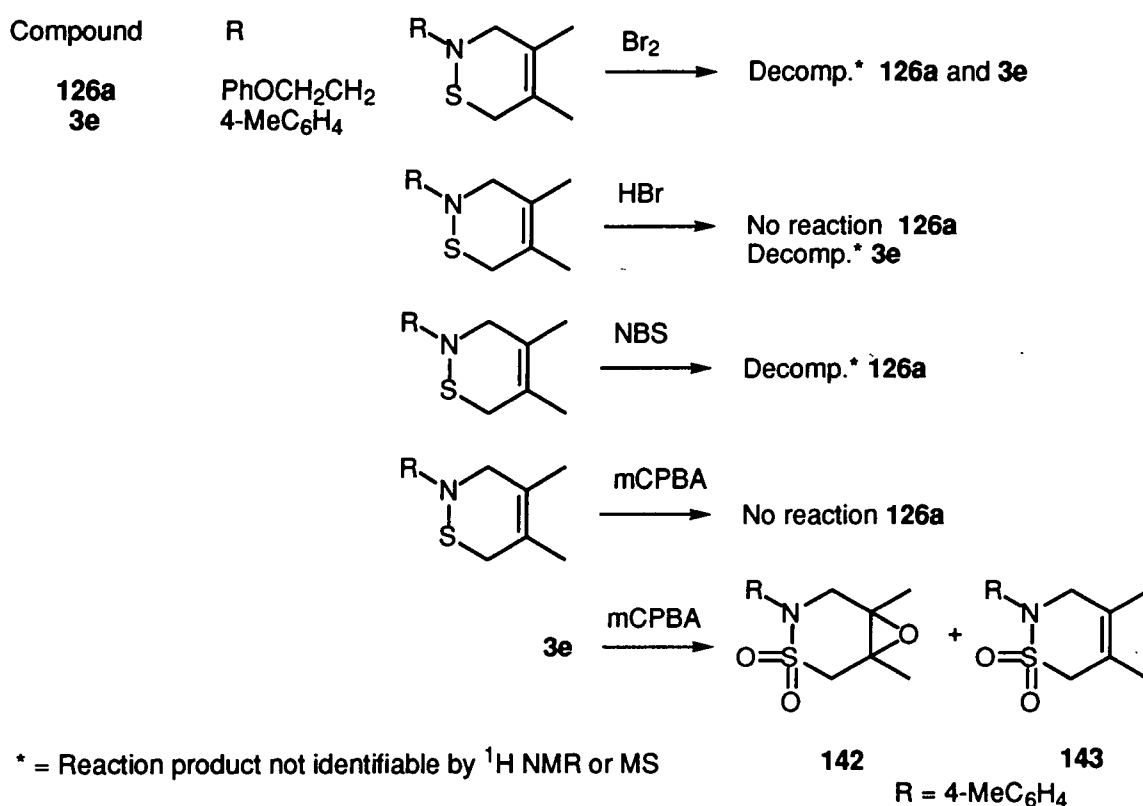
Scheme 3.9

Again, it can be seen that compound **126a** was the least reactive of those studied, as would be expected. Noteworthy was the reaction with hydrogen bromide (*cf.* reaction with hydrochloric acid in Scheme 3.8); compound **3e** decomposed (possibly *via* nucleophilic

attack at sulfur), whereas compound **126a** was inert under these conditions. Secondly, the reaction with *meta*-chloroperoxybenzoic acid should be highlighted as this demonstrated the lack of reactivity of compound **126a** at sulfur which is most likely caused by the nonbonded interaction presumed present in this system (compound **3e** was prone to oxidation, as expected from previous work by Tavs).[5] A further noteworthy point was the fact that elemental bromine and *N*-bromosuccinimide both decomposed compound **126a**, thus suggesting that this compound may be unstable to radicals (compound **3e** was not treated with NBS). Excluding the oxidation reaction, it was not possible to isolate any products from the above reactions and extensive decomposition of the ring system was again evident.

3.2.4 1,2-THIAZINE ANION CHEMISTRY

As the sulfur atom is able to expand its valency beyond the octet, stabilisation of negative charge on adjacent atoms by resonance into vacant 'd' orbitals is possible.[72] Considering this, we reasoned that formation of the anion at C6 in the 1,2-thiazine ring was a possibility (Scheme 3.10).
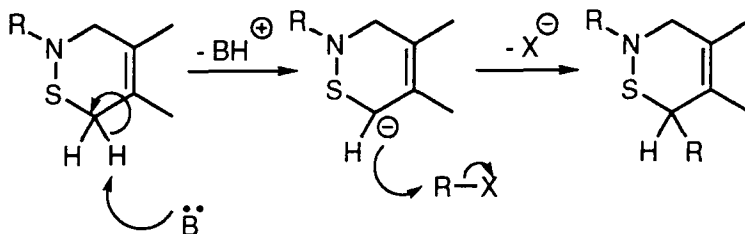
Scheme 3.10

Addition of a suitable electrophile, *e.g.* an alkyl halide, would result in a C6 substituted 1,2-thiazine (Scheme 3.10). Weinreb *et al* have shown that the analogous 1,2-thiazine-1-oxides undergo exactly this kind of reaction.[76]

Upon consideration of the results presented in Section 3.2.2, we realised that 1,2-thiazine heterocycles which were not stabilised by a nonbonded interaction were very susceptible to decomposition (presumably due to nucleophilic attack at sulfur). Generation of anions at carbon involves the use of a strong base, and most of these bases act as strong nucleophiles. Hence the initial exploration into the anion chemistry of 1,2-thiazines was performed on stabilised 1,2-thiazines to minimise the chance of ring opening. Compounds **126b-c** were, therefore, reacted with *n*-butyl lithium at low temperature, and subsequently quenched with methyl iodide according to Scheme 3.11.

R = (b) PhOCH₂CH(Me)
    (c) PhSCH₂CH₂

1. BuLi / -78°C
2. MeI

THF

126   **144**
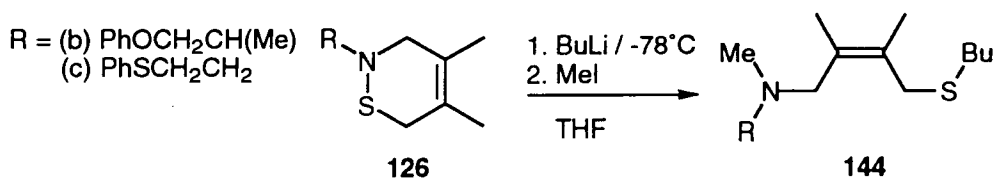
Scheme 3.11

However, instead of obtaining a C6 substituted 1,2-thiazine, the ring opened products, *N*-alkyl-*N*-methyl-4-butylthio-2,3-dimethyl-2-butenamines **144b-c**, were obtained (as yellow oils in 20-42% yield). Under similar conditions, Weinreb *et al* noted, for the analogous 1,2-thiazine-1-oxides, that *N*-alkyl substituted derivatives yielded C6 substituted products whilst *N*-aryl substituted derivatives gave ring opened products,[76] (reaction of compound **3e** under the conditions detailed in Scheme 3.11 produced a multitude of uncharacterised products).

The appearance of signals characteristic for compounds **144b-c** in the ^{1}H and ^{13}C NMR spectra (2.20-2.26ppm for NC$\underline{H}_3$ and 18.0-22.0ppm for N$\underline{C}$H₃, respectively) as well as a shift from 1735 cm^{-1} to 1730 cm^{-1} of the C=C bond in the I.R. spectra (caused by relief of strain due to ring opening),[77] provided the information required for product identification. The ^{13}C DEPT technique was employed to confirm the peak assignments. Compounds **144b-c** were probably formed by nucleophilic attack of *n*-butyl lithium at sulfur followed by nucleophilic attack by the transient negatively charged nitrogen atom on methyl iodide (Scheme 3.12).
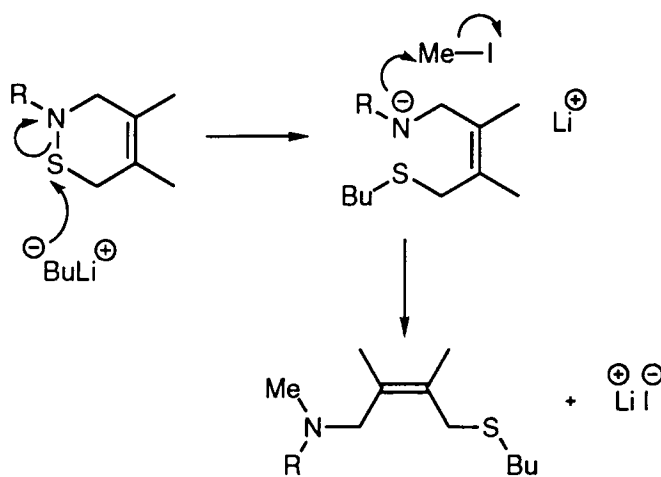
Scheme 3.12

In order to determine whether a strong nucleophile was needed to induce the reaction, a subsequent experiment in which the *n*-butyl lithium was replaced by lithium

diisopropylamide (LDA, a non-nucleophilic strong base) was performed, no reaction was observed under these conditions, suggesting that the ring opening reaction does require the presence of a strong nucleophile.

It was thus concluded that anions could not be generated at C6 of the 1,2-thiazines **126b-c**. However, the ring-opened products **144b-c** were produced when a strong nucleophilic base was used in an attempt to generate the anions. This work provides the first examples of ring opening reactions of 1,2-thiazines, and is also the first synthesis of the highly functionalised alkenes **144b-c**.

In addition, it can be seen that although the nonbonded interaction in compounds **126a-e** provides a degree of chemical stability, if severe reaction conditions are used the interaction can be disrupted.

3.3 ^{1}H NMR STUDIES ON 1,2-THIAZINES

3.3.1 INTRODUCTION

As we were able to obtain compounds **126a-e** in a pure state, and had developed methodology which allowed us to access other 1,2-thiazines virtually free from impurities (Chapter 4), the first detailed ^{1}H NMR studies on both stabilised and non-stabilised 1,2-thiazines was made possible.

The ^{1}H NMR spectrum of all the 1,2-thiazine heterocycles mentioned in this work produced characteristic signals for the methylene protons on C3 and C6 (Figure 3.11).
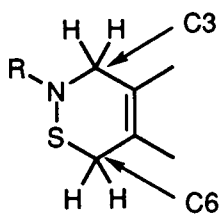
Figure 3.11

Both sets of protons produced broad singlets at ambient temperature in the range 2.8-4.1 ppm (C3), and 2.7-3.5 ppm (C6). These diagnostic signals were utilised in the ^{1}H NMR experiments detailed below.

3.3.2 VARIABLE TEMPERATURE ^{1}H NMR SPECTROSCOPY

3.3.2.1 INTRODUCTION

The application of dynamic NMR spectroscopy to organic chemistry is widespread and is the subject of excellent reviews by both Oki,[78] and Kemp.[79] Variable temperature ^{1}H NMR spectroscopy can be used to obtain a variety of information including identification of exchange phenomenon (*i.e.* where molecular motion causes the environment of a proton to change).[78, 79]

Dynamic processes in a molecule which effectively change the chemical environment of a proton cause signal broadening in the ^{1}H NMR spectrum; this is due to the fact that the spectrometer detects a time-averaged signal for all the environments which the proton passes through. For example, chair-chair interconversion in cyclohexanes causes the environments of protons H_A and H_B to change rapidly (Figure 3.12).
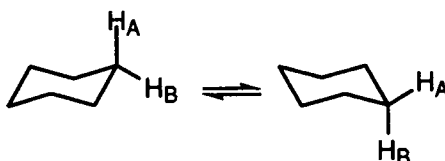
Figure 3.12

At ambient temperature the signals for H_A and H_B are indistinguishable since the interconversion rate between the two chair forms is much higher than the rate at which the spectrometer is able to detect the protons in their individual sites. Lowering the temperature slows the rate of interconversion, this causes the signal for the two protons to coalesce (*i.e.* disappear into the baseline). If the temperature is lowered sufficiently (-60°C in the case of cyclohexane) the signals for H_A and H_B decoalesce (*i.e.* reappear from the baseline) as two individual signals. This latter effect is due to the fact that at this reduced temperature the chair-chair interconversion rate has been slowed to a rate which is less than that at which the spectrometer can detect a signal. Thus the two protons can be detected in different environments and therefore give separate signals.

In 1,2-thiazines, the situation is more complex as a combination of ring flexing and inversion about nitrogen are responsible for broadening the methylene signals adjacent to nitrogen and sulfur (Figure 3.13). Unsaturated heterocycles tend to adopt a flatter, pseudo-chair conformation, but interconversion still occurs.
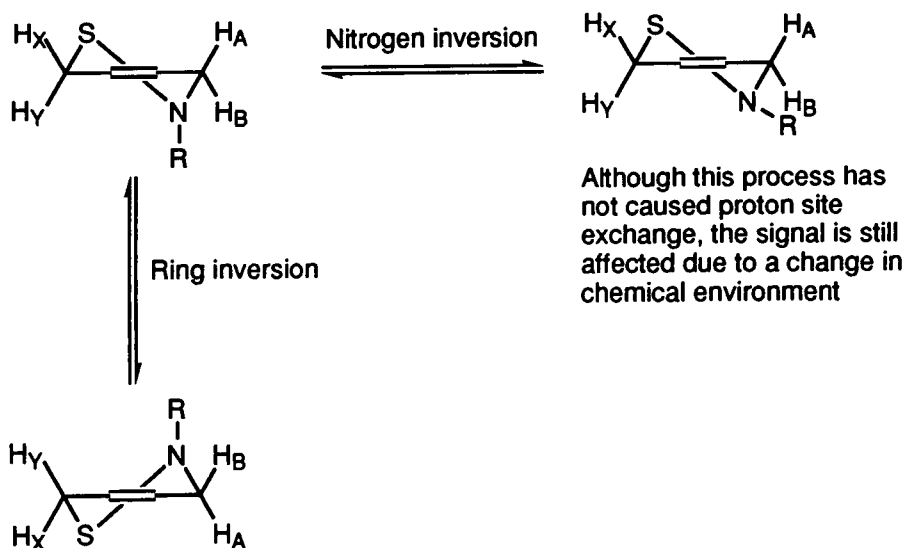
Figure 3.13

If the above processes responsible for ring flexing were to be slowed down, it may be possible to resolve the signals for the protons as they would be chemically dissimilar ($H_A \neq H_B$ and $H_X \neq H_Y$). Further, the resolved signals should appear as doublets since the C3 protons would split each other, as would those at C6, *i.e.* both would appear as *AB* systems.

The foregoing outlines the expected behaviour of 1,2-thiazines. We sought to compare the ^{1}H NMR spectra of 1,2-thiazines involving the supposed nonbonded interactions with those from 1,2-thiazines without such an interaction. The *raison d'être* for this was the postulation that the nonbonded interaction would slow the ring flexing processes. Thus, the temperature at which the methylene signals coalesced in 1,2-thiazines containing a nonbonded interaction would be <u>higher</u> than in analogues without the nonbonded interaction. If this effect were observed, it would provide physical evidence for the nonbonded interaction (in addition to the chemical evidence presented in Section 3.2).

A quantitative treatment of the variable temperature ^{1}H NMR behaviour of 1,2-thiazines involving calculations of rates of inversion *etc.* was deemed outside the scope of this thesis. However, now that these compounds can be accessed pure with relative synthetic ease, there is scope for more specialist studies of this kind in future.

3.3.2.2 ^{1}H NMR SPECTROSCOPY OF COMPOUNDS 3k' AND 126a AT LOW
TEMPERATURE

Compound **3k'** was chosen to provide the benchmark ^{1}H NMR spectra, as it was the most stable of the 1,2-thiazines not incorporating the nonbonded interaction (presumably the steric bulk of the phenyl groups increases its stability).[17, 59-61]
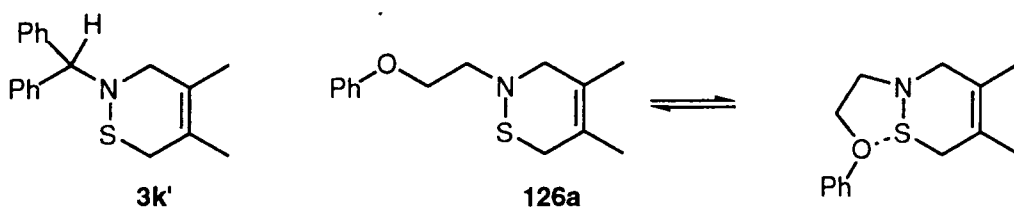
Figure 3.14

The ^{1}H NMR spectrum of compound **3k'** was recorded at 20°C and -50°C in CDCl$_3$ (Figure 3.15). The signal for the CH$_2$S protons appears at δ2.96-3.01, (the slight change in chemical shift is due to referencing and does not affect the experiment) and the signal for the CH$_2$N protons appears at δ3.45-3.50.

The CH$_2$S peak was observed to coalesce further than the CH$_2$N signal in the spectrum recorded at -50°C. This suggests that the ring flexing on the sulfur side of the 1,2-thiazine ring is slower than at the nitrogen side. The logical rationalisation for this observation is that on the nitrogen side of the ring both ring flexing and inversion about nitrogen are responsible for broadening the signal due to the CH$_2$N protons. Conversely, on the sulfur side of the ring, inversion about nitrogen will have a minimal effect on the CH$_2$S protons, hence these would be expected to coalesce at higher temperature, as observed.

The ^{1}H NMR spectrum of compound **126a** was recorded between 20°C and -90°C in 20°C increments in CD$_2$Cl$_2$ (Figure 3.16). The signal for the CH$_2$S and CH$_2$N protons appear at δ3.05 and δ3.46, respectively. The CH$_2$S peak was again seen to coalesce to a larger extent than the CH$_2$N, as expected. Comparison of the spectrum of compound **3k'** at -50°C with that of compound **126a** at -50°C shows that the CH$_2$S signal in the latter has coalesced to a greater extent. This indicates that the sulfur side of compound **126a** was less flexible (slower inversion) than the same area in compound **3k'**. This would be expected if S--O nonbonded interactions were causing the inversion at sulfur to be slowed down.
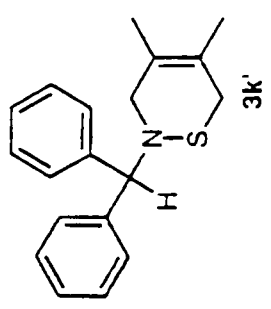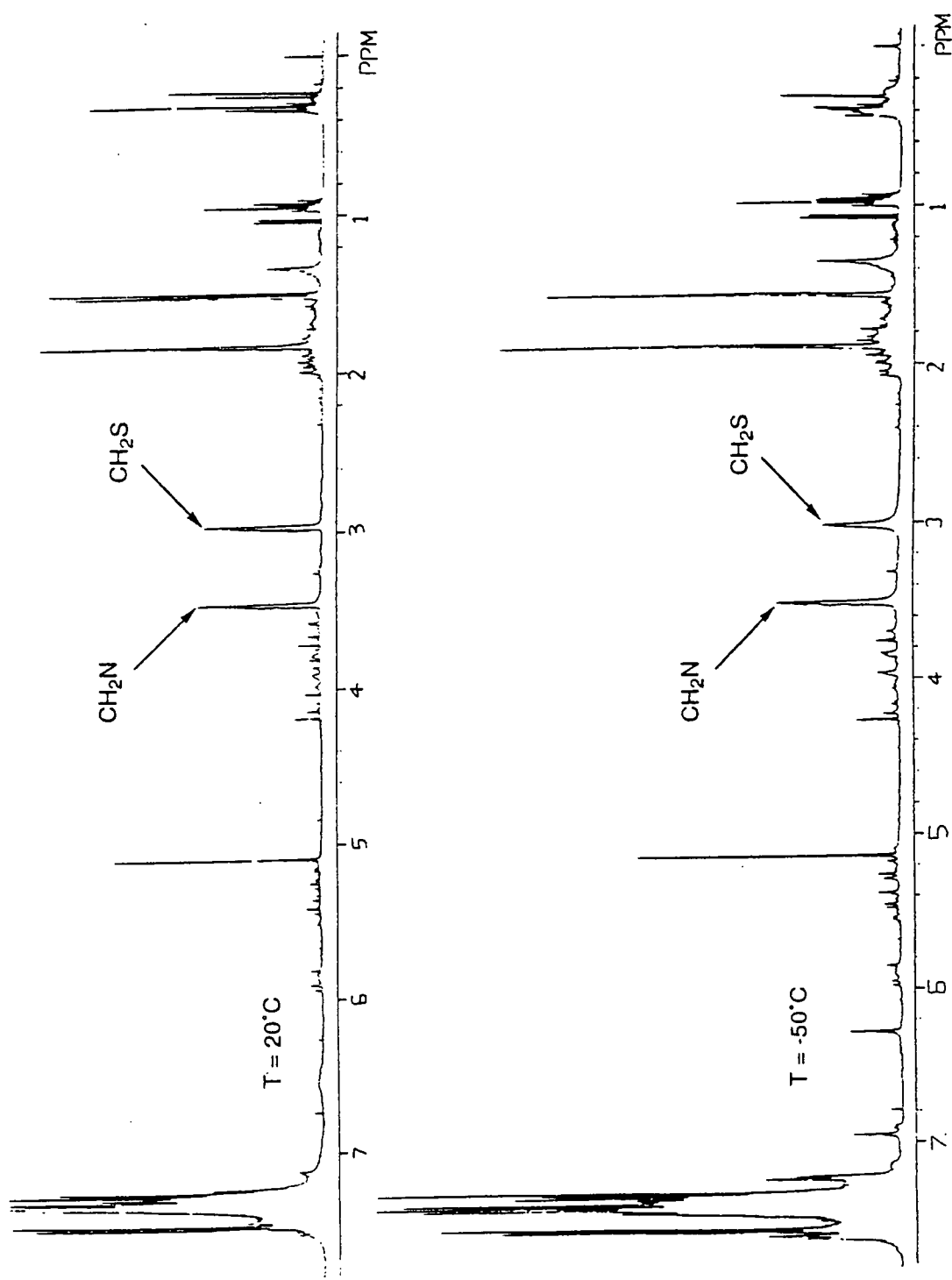
Figure 3.15 - ^1H NMR Spectra of compound 3k' at 20°C and -50°C showing partial coalescence of the CH$_2$S signal at -50°C.

T = Temperature

83
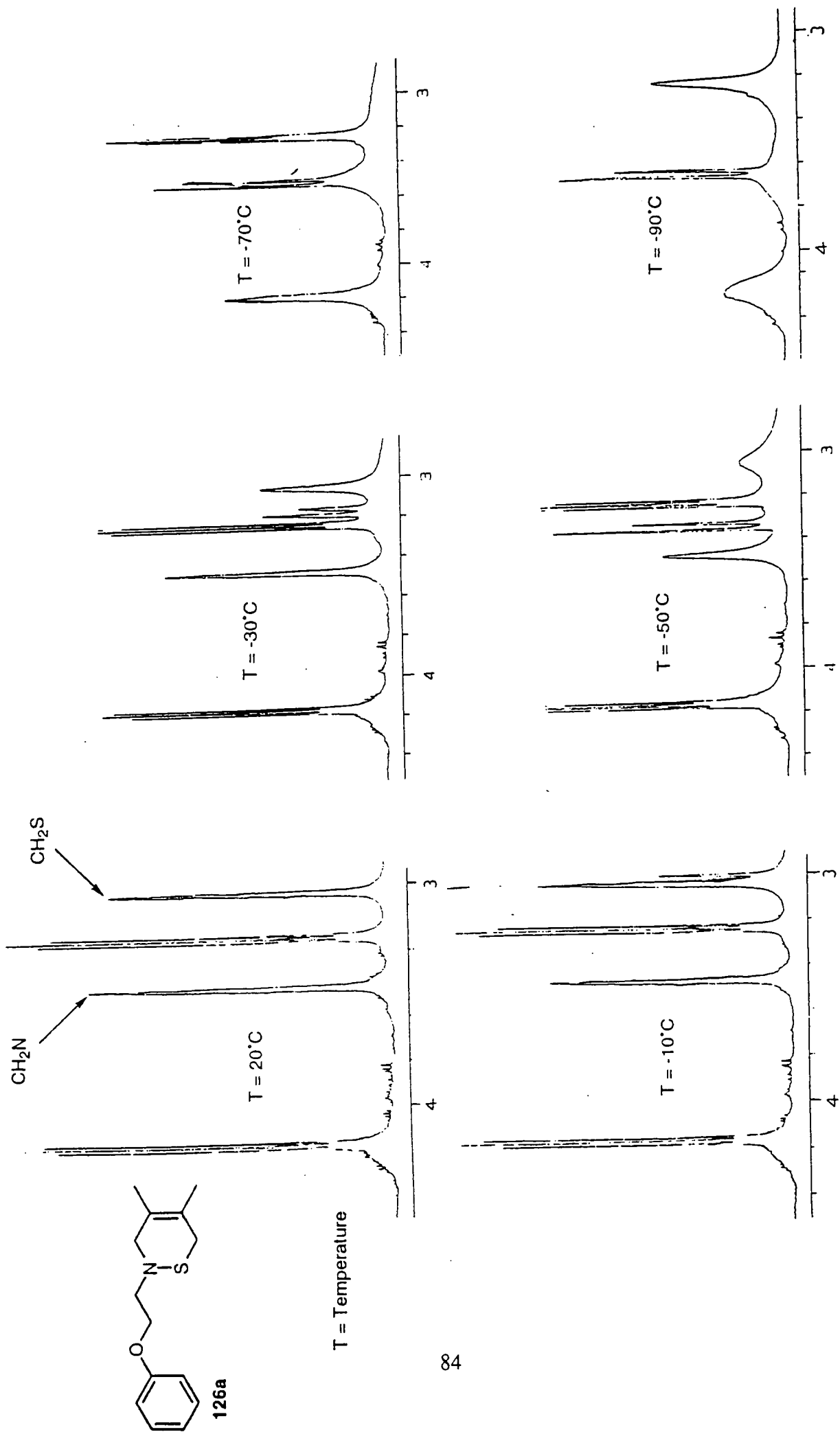
Figure 3.16 - ¹H NMR Spectra of compound **126a** between 20°C and -90°C demonstrating the coalescence of the CH₂S and CH₂N signals.

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The spectra of compound **126a** at -70 and -90°C show both the CH$_2$S and CH$_2$N peaks to be fully coalesced. At this temperature the molecular motions causing the signal broadening have been slowed to such a rate that they cause the protons to change environment at approximately the same rate as the spectrometer detects them. This causes the signal to become infinitely broad, hence it disappears into the baseline.

At the lower temperatures (-70 and -90°C), the triplet signal due to a CH$_2$ group in the alkyl chain attached to nitrogen can be seen to overlap the coalesced CH$_2$S and CH$_2$N signals (this occurs because chemical shifts are not fully temperature independent). As a consequence of this, it was not possible to observe the decoalescence of the methylene signals to form *AB* doublets. In order to observe this effect, a 1,2-thiazine involving a nonbonded interaction, but without signals near to those of the CH$_2$S and CH$_2$N protons was required.

3.3.2.3 ^{1}H NMR SPECTROSCOPY OF COMPOUND **126e** AT LOW TEMPERATURE

Compound **126e** has the possibility of an S--S nonbonded interaction (Figure 3.17), and the ^{1}H NMR spectrum does not contain any signals near to those of the CH$_2$S and CH$_2$N protons.
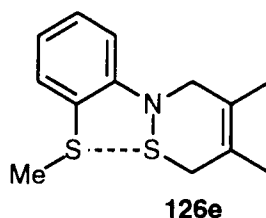
126e

Figure 3.17

With this compound, we hoped to observe the coalescence and decoalescence of the CH$_2$S and CH$_2$N signals unimpeded by interference from other signals close-by.

The ^{1}H NMR spectrum of compound **126e** was recorded between 20°C and -90°C in 20°C increments in CD$_2$Cl$_2$ (Figure 3.18). The signal for the CH$_2$S protons appears at δ2.92, and the signal for the CH$_2$N protons at δ3.80. The CH$_2$S peak was again seen to coalesce faster than the CH$_2$N peak, as expected.

The spectrum at -50°C shows both CH$_2$S and CH$_2$N signals fully coalesced. The spectra at -70°C and -90°C show the signals decoalescing. At the lowest temperatures studied the

85
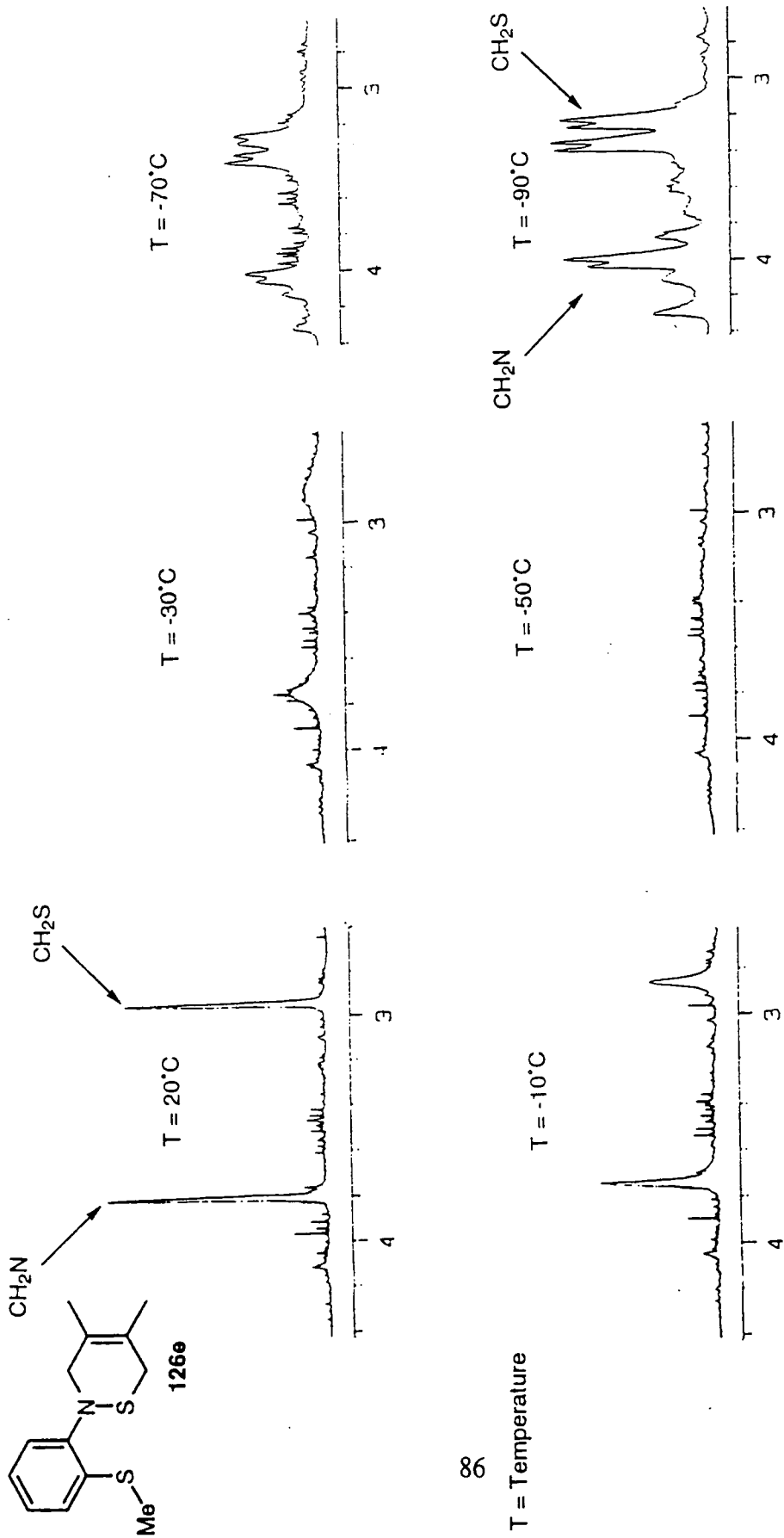
Figure 3.18 - ¹H NMR Spectra of compound **126e** between 20°C and -90°C demonstrating the coalescence and decoalescence of the CH₂S and CH₂N signals.

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CH_2S signal appears as two doublets at δ3.23 and δ3.35, *i.e.* an *AB* system, indicating that the dynamic processes causing signal broadening were occurring at a rate less than that at which the individual protons in the methylene groups were detected. The CH_2S protons are in chemically inequivalent environments (one axial and one equatorial in the 1,2-thiazine ring) hence both are coupled to each other and they appear as two doublets. The CH_2N signal appears as a distorted quartet centred on δ4.00 but is, in fact, an incompletely resolved pair of doublets. This indicates that the protons in the methylene group on the nitrogen side of the ring are subject to more rapid change in chemical environment (and thus have been slowed to a lesser extent at this temperature) than those at the sulfur side (as expected from the observations made previously on compounds **3k'** and **126a**).

Interestingly, when the -70°C spectrum of compound **126e** was run in d_6-acetone, both the CH_2S and CH_2N signals remained fully coalesced (compared with the spectrum in CD_2Cl_2 in which the signals had begun to decoalesce at -70°C). It is possible that this effect was caused by the oxygen atom in the acetone disrupting the S--S nonbonded interaction. The effect of this disruption would be that the dynamic processes causing signal broadening would not be slowed by the S--S interaction, thus the signal for the protons would decoalesce at a lower temperature in acetone, as observed. Solvent effects such as this are commonplace in dynamic NMR spectroscopy.[78]

Overall, the low temperature ^{1}H NMR data indicates the occurrence of a nonbonded interaction at sulfur. Additionally, compounds **3k'**, **126a** and **126e** were shown to behave in a manner analogous to cyclohexane, as expected.

3.3.3 NUCLEAR OVERHAUSER ENHANCEMENT SPECTROSCOPY

3.3.3.1 INTRODUCTION

The nuclear Overhauser enhancement (NOE) technique is used in ^{1}H NMR spectroscopy to identify protons which are in close proximity in space.[77] The effect arises from the fact that magnetic nuclei, as well as interacting through bonds, can also interact through space. This through-space interaction does not lead to coupling, but it can be revealed when one of the interacting nuclei is irradiated at its resonance frequency, as this in turn causes the signal for the other interacting nucleus to become enhanced. The NOE effect only operates over short distances (2-4Å between interacting nuclei) and falls off as the inverse sixth power of the distance apart (r^{-6}) of the nuclei.

NOE difference spectra are obtained by computerised subtraction of the normal ^{1}H spectrum from that in which the signal for a proton is irradiated at its resonance frequency. This has the effect of removing all the signals that have not been enhanced (*i.e.* are not due to protons which are close in space to the proton irradiated). Thus, the remaining signals will be due to protons which are in close proximity to the one that was irradiated, and hence information regarding proximities can be obtained. It was hoped to employ this technique to elicit information in relation to two 1,2-thiazine compounds produced during the course of this work.

3.3.3.2 NOE DIFFERENCE SPECTROSCOPY ON COMPOUND 126e

The low temperature ^{1}H NMR spectroscopy performed on compound **126e** indicated the presence of an S--S nonbonded interaction. Molecular modelling shows that for this interaction to occur, the molecule must adopt a near planar conformation which, in turn, causes the proton attached to carbon C6' on the benzene ring to be in close proximity to the CH$_2$N protons for a greater amount of time than that which would occur simply due to free rotation of the aromatic ring (Figure 3.19)
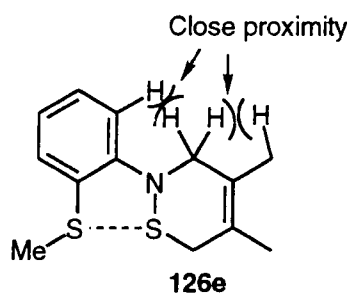
Figure 3.19

To determine whether the protons were actually close in space an NOE difference spectrum of compound **126e** in CDCl$_3$ was obtained in which the signal due to the CH$_2$N protons at δ3.80 was irradiated (Figure 3.20). One of the aromatic protons (most likely the proton attached to C6') was enhanced suggesting that it is in close proximity to the CH$_2$N protons, and providing further evidence for the S--S nonbonded interaction. Interestingly, the signal due to the protons in the C4 methyl group of the 1,2-thiazine ring can also be seen to be enhanced, and to approximately the same extent as the aromatic proton. This suggests that both these sets of protons are close to the CH$_2$N protons, as would be expected. The observed signal enhancement was small, and due to the difficulty in performing NOE spectra (sample preparation and spectrometer operating environment
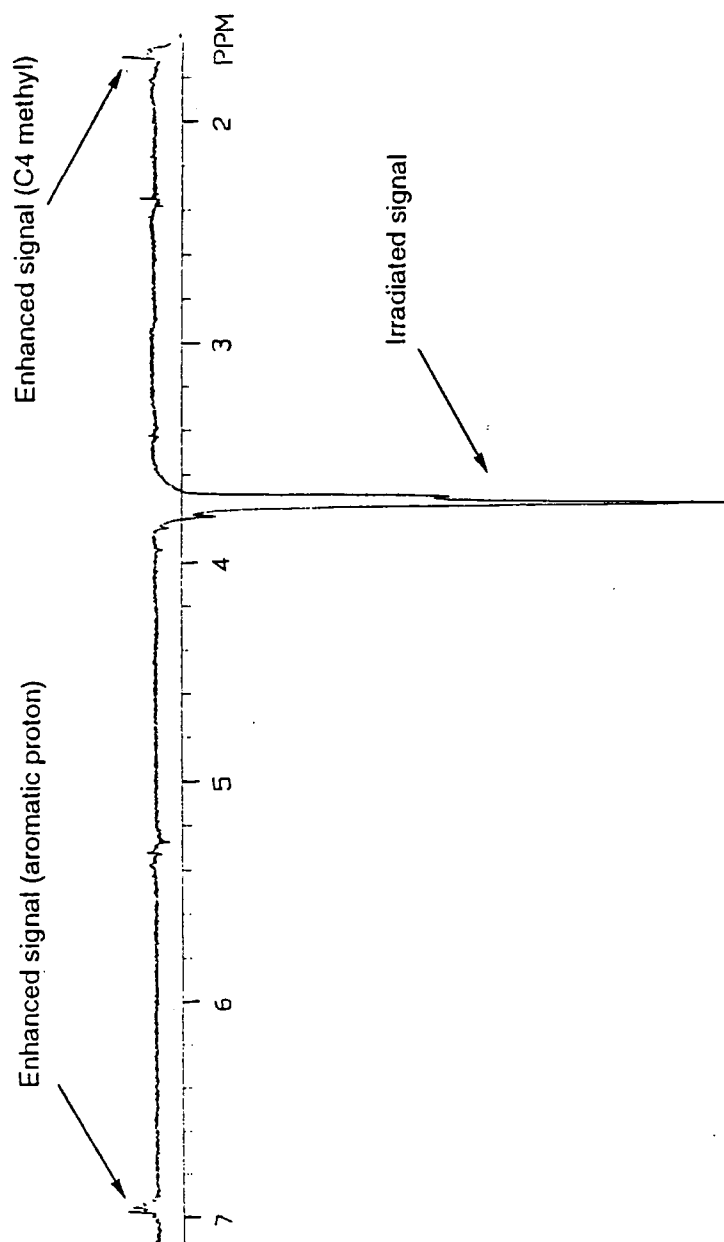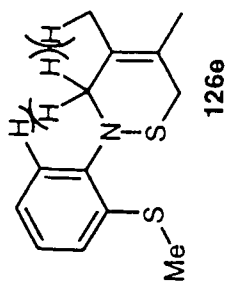
Figure 3.20 - NOE Difference spectrum of compound **126e** showing enhancement of an aromatic proton signal when the signal for CH$_2$N was irradiated.

must be rigorously controlled), this evidence alone was insufficient to confirm the presence of an S--S interaction. However, considered along with the low temperature observations and chemical studies, the evidence for such an interaction in this type of 1,2-thiazine is compelling.

3.3.3.3 NOE DIFFERENCE SPECTROSCOPY ON COMPOUND 31'

The ^1H NMR spectrum of compound **31'** (Figure 3.21) was unusual in that the CH_2S and CH_2N signals were not broad singlets (as was typical in other 1,2-thiazines), rather they appeared as four doublets at $\delta2.57, 3.03, 3.25$ and 3.53, with each doublet being assigned to one proton (Figure 3.22).
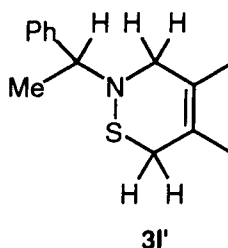
Figure 3..22

It appeared that these signals were due to two *AB* systems, this could be caused by the conformation of the molecule being locked on the NMR time scale at ambient temperature, (exactly as for compound **126e** at -70 and -90°C), thus enabling the individual protons to be detected. Alternatively, as the protons are made diastereotopic by the chiral substituent on nitrogen, this may cause them to be magnetically inequivalent. Either way, as this phenomenon was occurring at room temperature, it was possible to use an NOE difference experiment to determine which protons in **31'** were in close proximity.

A series of NOE difference spectra of compound **31'** were obtained in $CDCl_3$, the signals at $\delta2.57, 3.03, 3.25$ and 3.53 were irradiated in turn and the effect on the remainder of the spectrum observed (Figure 3.23). The information obtained from these spectra is summarised in Table 3.1.
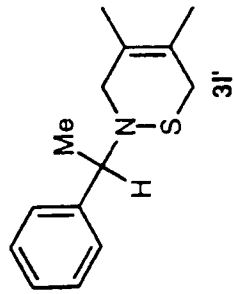
Figure 3.21- *1H NMR Spectrum of compound 31' at 20°C illustrating the unusual
signal pattern for the CH₂S and CH₂N protons.*
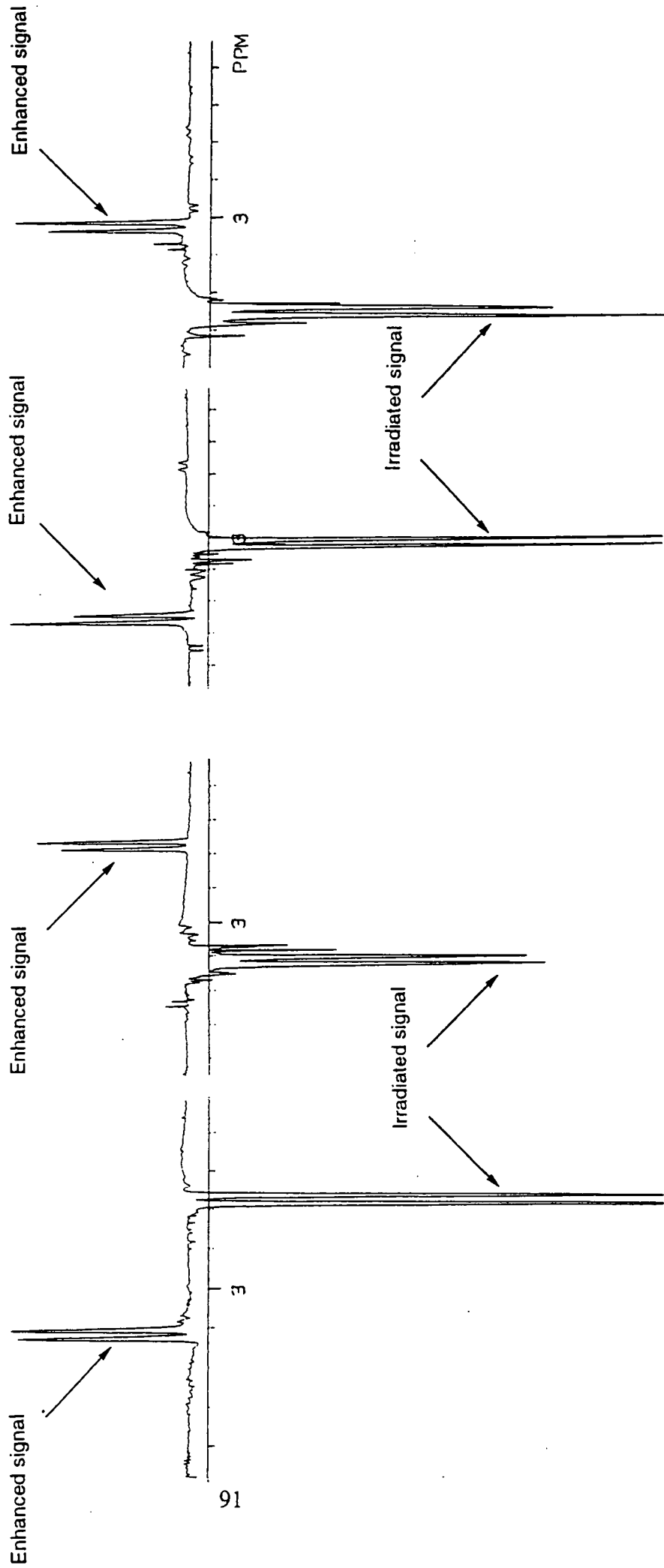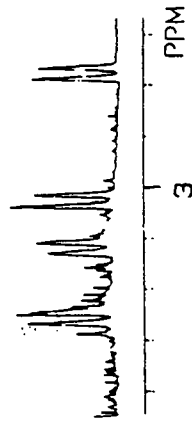
Figure 3.23- *A series of NOE difference spectra of compound 31' showing that the
CH₂S and CH₂N protons were AB systems.*

Table 3.1 Conclusions drawn from the NOE difference spectra of compound **3l'**

Irradiated Peak δ	Enhanced Peak δ	Conclusion
2.57	3.25	Protons at δ2.57 and δ3.25 in close proximity
3.03	3.53	Protons at δ3.03 and δ3.53 in close proximity
3.25	2.57	Protons at δ3.25 and δ2.57 in close proximity
3.53	3.03	Protons at δ3.53 and δ3.03 in close proximity

The results in Table 3.1 show that the proton at δ2.57 is in close proximity to the proton at δ3.25, *i.e.* both are attached to the same carbon atom (C6) and form an *AB* system. Additionally, the proton at δ3.03 was found to be in close proximity to the proton at δ3.53, therefore, both of these are attached to the same carbon atom (C3) and form a second *AB* system.

Molecular modelling has shown that compound **3l'** can adopt a conformation in which the 'p' orbitals of the double bond can interact with the 'p' orbitals of the benzene ring; an approximate illustration of this is shown in Figure 3.24.

The methyl groups have been removed from the double bond for clarity.
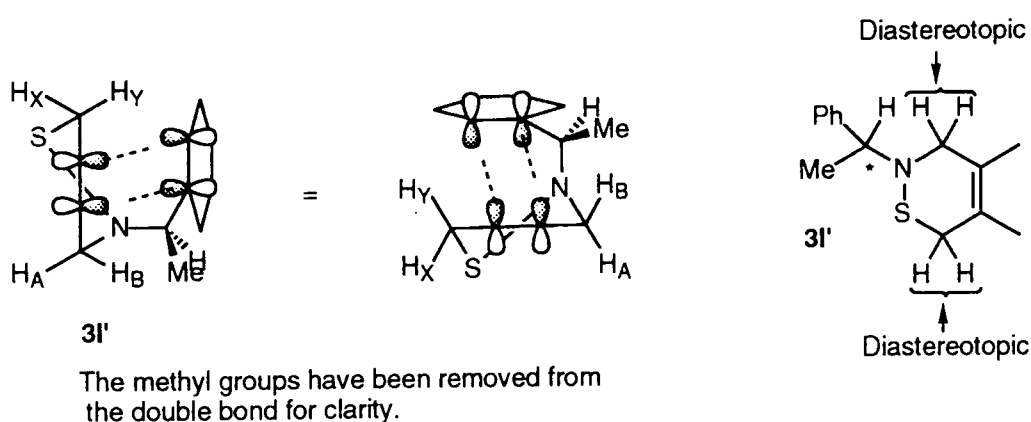
Figure 3.24

Such a conformation would prevent both ring and nitrogen inversion due to steric pressure, and may explain the unusual ^{1}H NMR spectrum of compound **3l'**. However, if the ring conformation were locked, the 1,2-thiazine nitrogen atom effectively becomes a chiral centre, thus a diastereoisomeric mixture (instead of simply a racemic mixture) is produced. This being the case, it would be expected that different signals in both the ^{1}H and ^{13}C NMR spectra would be observed for the atoms in each diastereomer (for instance, if all the atoms were different one would expect to observe twice as many signals). This in fact <u>was not observed</u>, thus it is unlikely that the unusual splitting pattern exhibited by the methylene protons in this molecule was a result of conformational locking.

A more plausible explanation for the unusual splitting pattern stems from the fact that the asymmetric substituent on the nitrogen atom of this compound renders the protons in both methylene groups diastereotopic (Figure 3.24). As such they are magnetically inequivalent and therefore resonate at different frequencies, thus producing the unusual splitting pattern. This phenomenon is well documented in texts on asymmetric synthesis.[80] It is noteworthy that diastereotopic protons are not always magnetically inequivalent, and therefore simply incorporating a chiral substituent on the nitrogen atom of 1,2-thiazines need not necessarily produce a complex spectrum. Compound **126b** has a chiral substituent attached to nitrogen, but in this case the CH_2N protons are equivalent (and as such appear as a singlet in the ^{1}H NMR spectrum).

3.4 CONCLUSIONS

Thermal fragmentation of compounds **124a-e** enabled thionitroso compounds **125a-e** to be generated. Compounds **125a-e** were intercepted with 2,3-dimethyl-1,3-butadiene to afford 1,2-thiazines **126a-e**.

Compounds **126a-e** showed remarkable stability compared to other 1,2-thiazines of which we had experience. The reason for the enhanced stability was thought to be 1,5 S--O and S--S nonbonded interactions preventing the decomposition of these compounds by nucleophile-induced ring opening.

Unexpectedly, reaction of compounds **125a-d** with 2,3-dimethyl-1,3-butadiene did not give rise to Ene adduct. This observation was rationalised on the basis of the enhanced stability of these compounds due to the posited nonbonded interactions. As a consequence

of this enhanced stability, compounds **125a-d** are more likely to encounter a diene in the *s-cis* conformation enabling them to undergo a DA reaction, the Ene pathway is, therefore, disfavoured.

The chemistry of selected 1,2-thiazines which could contain a nonbonded interaction was compared with that of 1,2-thiazines without such an interaction. From these studies it was observed that the former were considerably less reactive, thus providing persuasive chemical evidence for the existence of a nonbonded interaction. As part of the chemical studies performed, we discovered the first example of a ring opening reaction of this type of 1,2-thiazine. This reaction was initiated by a nucleophilic base (butyl lithium) and the products, highly functionalised alkenes **143b-c**, were themselves new materials.

Variable temperature ¹H NMR spectroscopy, and NOE difference spectroscopy, were performed on 1,2-thiazines involving the putative nonbonded interactions. These studies provided compelling physical evidence for the existence of such an interaction. They also demonstrated that these 1,2-thiazines behaved in a manner analogous to cyclohexane, as expected.

A series of novel 1,2-thiazines **126a-e** were synthesised and studied thoroughly. These studies provided compelling chemical and physical evidence to suggest that nonbonded interactions occur in compounds **126a-e**, and it is most likely these interactions that are responsible for the stability of this interesting class of heterocycles. There is now scope for future work in this area involving the use of hetero-functionalised dienes that could be used to access highly functionalised heterocycles of this type, and in turn it may be possible to utilise these compounds to synthesise, by ring opening, more highly functionalised alkenes.

Chapter Four

Regiochemistry of Thionitroso and

Thioxophosphine Cycloaddition

Reactions

4.1 AZOMETHINE YLIDES AS TRAPS FOR THIONITROSO COMPOUNDS

4.1.1 INTRODUCTION

Thionitroso compounds have been shown to act as 2π components in $[4\pi + 2\pi]$ cycloadditions with dienes (Chapters 1-3). We were also interested in the possibility of thionitroso compounds acting as the 2π component in $[4\pi + 2\pi]$ cycloadditions with 1,3-dipolar species (*i.e.* acting as dipolarophiles), in order to generate novel heterocyclic systems. 1,3-Dipolar species have 4π electrons associated with three atoms, one of which is a heteroatom and hence this type of reaction can be referred to as a [3 + 2] cycloaddition, indicating the number of atoms involved in the cycloaddition reaction. The term [3 + 2] cycloaddition will be employed herein.

Takahashi *et al* have postulated a [3 + 2] reaction between a thionitroso compound and an azide, and have investigated the reaction of a thionitroso compound with diazo compounds (Section 1.2.5.2), and with molecular oxygen.[30] Their results were, however, disappointing in terms of the synthesis of new heterocycles since only one example was isolated (compound **66**).

Considering the previous work on [3 + 2] reactions of thionitroso compounds, we were interested in investigating the dipolarophilic potential of thionitroso compounds in order to generate new five membered heterocycles. We thus sought to employ a previously unused 1,3-dipole which could be generated under relatively mild conditions (an important factor when one considers the unstable nature of the thionitroso precursor compounds with which we had been working) in our investigations. Therefore we chose to study the reaction of thionitroso compounds with unstabilised azomethine ylides.

4.1.2 REACTION OF THIONITROSO COMPOUNDS WITH UNSTABILISED AZOMETHINE YLIDES

Azomethine ylide **146** was synthesised (using the method described by Padwa and Chen) by treatment of *N*-benzyl-*N*-cyanomethyl-*N*-trimethylsilylmethylamine **145** with one equivalent of silver (I) fluoride.[81] In the same vessel, one equivalent of thionitroso precursor compound **40** was concomitantly dechlorinated and desilylated by a second equivalent of silver (I) fluoride to yield the thionitroso compounds **1*** (Scheme 4.1).

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* Generation of thionitroso compounds in the presence of silver (I) fluoride is dealt with in Section 4.2.
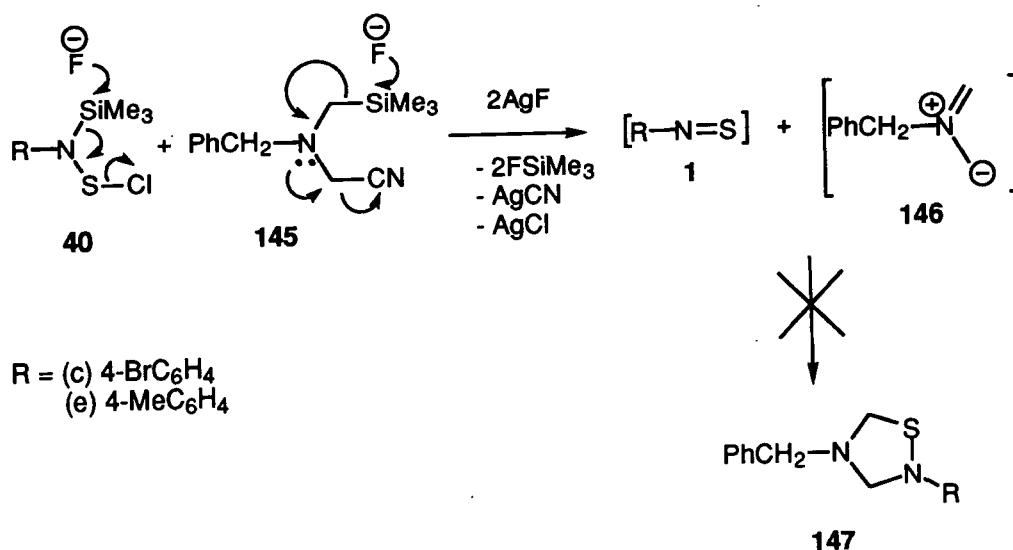
Scheme 4.1

It was hoped that compounds **1** and **146** would be liberated simultaneously *in situ* and react in a [3 + 2] manner to afford 2-aryl-4-benzyl-1,2,4-thiadiazines **147c,e**. However, this was not observed with either derivative **1c** or **1e**. In each case, compound **145** was recovered unchanged together with a number of other compounds including azo compounds and sulfur (which are characteristic of reaction of compounds **40c,e** in the absence of a trap as dimerisation and loss of sulfur occurs, Section 1.2.3.3).

From these observations we concluded that compounds **40c,e** probably fragmented at a much higher rate than compounds **145** (thus compounds **1c,e** were liberated and dimerised before there was any **146** present). We knew from our experience in the trapping of thionitroso compounds that a large excess of diene (typically 5-10 equivalents) was required in order for the reactions to yield 1,2-thiazine adduct. We, therefore, reasoned that the reactions with the azomethine ylide failed to produce heterocyclic product **147** since the reactive species was not present in large enough excess, if at all. Clearly, it is unlikely that such a large excess of azomethine ylide could be obtained in solution, even if a large excess of its precursor **145** was used initially as the ylide itself is a highly reactive species and would thus react soon after it was generated. Taking this problem into account, and the fact that we had observed some interesting results in the reaction of thionitroso compounds with dienes in the presence of silver (I) fluoride, investigation into [3 + 2] reactions involving thionitroso compounds was curtailed.

4.2 METAL FLUORIDES IN THE GENERATION OF THIONITROSO COMPOUNDS

4.2.1 INTRODUCTION

Prior to our investigations into the [3 + 2] reactions of thionitroso compounds (Section 4.1), it was necessary to determine whether thionitroso precursor compounds **40c,e** fragmented, in the presence of silver (I) fluoride, to afford thionitroso compounds **1c,e** (the silver (I) fluoride was required to produce the azomethine ylide). Therefore compound **40c** was treated with one equivalent of silver (I) fluoride in the presence of excess 2,3-dimethyl-1,3-butadiene.* The results of this reaction were very surprising. Thionitroso compounds were generated [as a 1,2-thiazine (**3c**) was isolated], however, there was almost complete suppression of the Ene reaction as a result of which the 1,2-thiazine could be obtained cleanly in high yield. We decided that this unusual phenomenon was worthy of further investigation.

4.2.2 THE INFLUENCE OF METAL FLUORIDES ON THE GENERATION OF THIONITROSO COMPOUNDS

4.2.2.1 SILVER (I) FLUORIDE

Compounds **40c,e,k'-l'** were treated with one equivalent of silver (I) fluoride in the presence of an excess of 2,3-dimethyl-1,3-butadiene (Scheme 4.2). Compounds **1c,e,l'** had been reported previously by Taylor,[13] and Heaton, [66] and were used to allow a comparison to be made, whereas compound **1k'** was a new derivative.

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* Initial work performed by Dr. A. Chesney, a postdoctoral colleague within this laboratory.
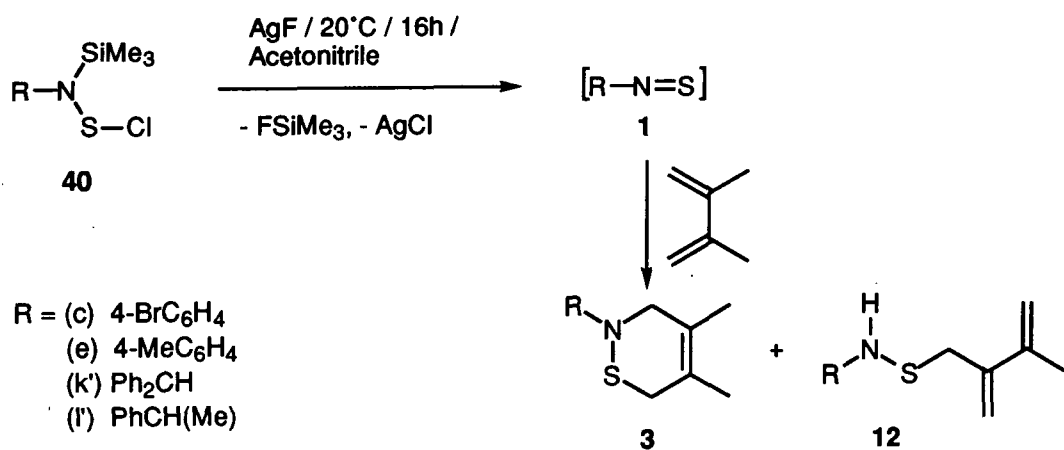
Scheme 4.2

The results of these reactions are summarised in Table 4.1.

Table 4.1 Generation of thionitroso compounds **1c,e,k',l'** and their reaction with 2,3-dimethyl-1,3-butadiene in the presence of silver (I) fluoride

Compound	Adduct ratio (by NMR)		Yield[†] %
	3 (DA)	**12** (Ene)	
1c	>95 (25)	<5 (75)	87 (50)
1e	>95 (60)	<5 (40)	78 (55)
1k'	100	0	24
1l'	100 (92)	0 (8)	30 (20)

Notes.

1. † = Combined yield of adducts **3** and **12**.

2. Bracketed figures detail the observations of Taylor,[13] and Heaton,[66] for the same derivatives generated in the absence of silver (I) fluoride.

The results summarised in Table 4.1 highlight a number of important points. Firstly, it can be seen that thionitrosoarenes (*i.e.* **1c,e**) can be produced *via* fragmentation of compounds **40** in the presence of silver (I) fluoride (indeed, the silver (I) fluoride may even induce the reaction). In their seminal paper describing this methodology, Markovskii *et al* reported that thionitrosoarenes could not be generated thermally from these compounds.[20] We have noted elsewhere that, contrary to their report, thionitrosoarenes can be generated by thermal fragmentation of compounds **40**.[22] We have now discovered that by utilisation of silver (I) fluoride, thionitrosoarenes can be accessed from compounds **40** under relatively

mild conditions, and may be intercepted to afford 1,2-thiazines in high yield, with minimum contamination from the Ene adduct.

To ensure that free thionitroso intermediates were being liberated from compounds **40c,e** in the presence of silver (I) fluoride, reaction in the presence of excess *E,E*-hexadiene was performed,* a single isomeric product was obtained, consistent with the involvement of free thionitroso species (in analogy with similar reactions detailed in Section 3.1.2.1 aimed at proving the concerted nature of thionitroso cycloaddition reactions).

Table 4.1 also shows that reaction of thionitroso compounds **1c,e,l'** with 2,3-dimethyl-1,3-butadiene in the presence of silver (I) fluoride produced a greatly reduced amount of Ene adduct **12c,e,l'** compared to reaction in the absence of silver (I) fluoride. This suggests that the silver (I) fluoride was responsible for the suppression of the Ene reaction. Additionally the results for compounds **1c,e** indicate that the electronic nature of the substituent on the aromatic ring no longer influenced the ratio of DA : Ene adduct when the reactions were conducted in the presence of silver (I) fluoride (in the absence of silver (I) fluoride, the ratio was found to be strongly influenced by this factor, see Chapter 1). We decided to investigate other fluorides to determine whether these effects were general.

4.2.2.2 CAESIUM AND POTASSIUM FLUORIDES

In addition to silver (I) fluoride, caesium fluoride has also been utilised to generate azomethine ylides.[82] We thus sought to investigate the effect of caesium fluoride (and, in addition, potassium fluoride) on the chemistry of thionitroso compounds. Compounds **40c,e** were thus reacted with excess 2,3-dimethyl-1,3-butadiene in the presence of one equivalent of metal fluoride according to Scheme 4.3.

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* Dr. A. Chesney, University of Durham. Unpublished results.
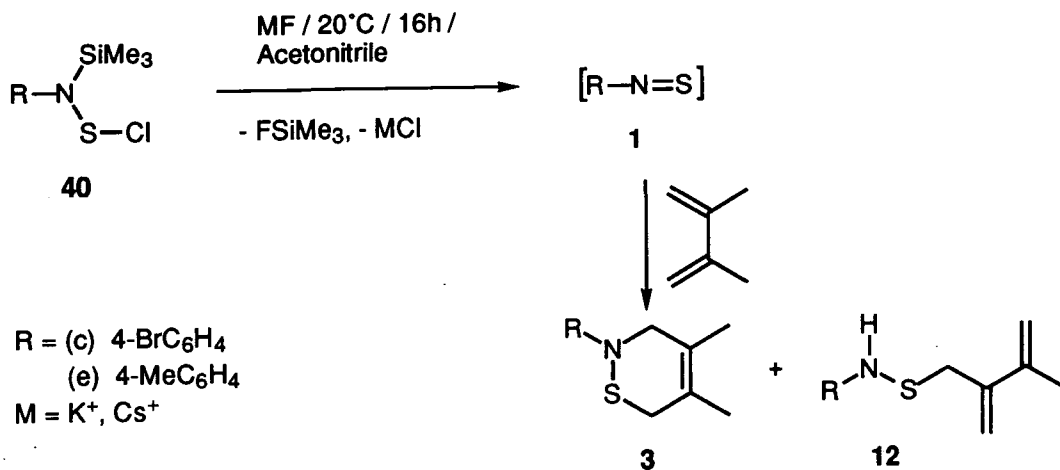
Scheme 4.3

The results of these reactions are presented in Table 4.2.

Table 4.2 Generation of thionitroso compounds **1c,e** and reaction with 2,3-dimethyl-1,3-butadiene in the presence of metal fluorides

Compound	Metal (M)	Adduct ratio (by NMR)		Yield[†] %
		3 (DA)	12 (Ene)	
1c	Cs	>95	<5	40
	K	>95	<5	73
1e	Cs	>95	<5	82

Note.

1. † = Combined yield of adducts **3** and **12**.

These results clearly demonstrate that reaction of thionitroso compounds **1c,e** with 2,3-dimethyl-1,3-butadiene in the presence of caesium and potassium fluorides resulted in a predominance of the DA adducts **3**, as was the case with silver (I) fluoride. Again the electronic nature of the substituent on the aromatic ring did not appear to influence the ratio of DA : Ene adduct in these reactions, consistent with results obtained in the presence of silver (I) fluoride.

The results presented in Tables 4.1 and 4.2 lucidly demonstrate that thionitroso compounds can be produced *via* fragmentation of compounds **40** in the presence of a variety of metal fluorides. Thionitroso compounds generated in the presence of metal

fluorides tended to react with the 2,3-dimethyl-1,3-butadiene trap predominantly by a DA pathway. This is in sharp contrast with earlier results from this laboratory for reaction of the same compounds with the same diene (bracketed figures, Table 4.1), in the absence of metal fluorides.

To ensure that the Ene adduct was not simply being decomposed by the metal fluorides present, a mixture of adducts **3** and **12** was treated with the metal fluoride. At no point was a change in ratio observed. Secondly, a comparison of the yields in Table 4.1 (with those in brackets) suggests that the reaction simply proceeds mostly by the DA pathway.

4.2.2.3 RATIONALISATION OF RESULTS

In Section 1.2.8 it was noted that steric, electronic and solvent factors affected the ratio of DA : Ene adducts obtained on reaction of thionitroso compounds with dienes. These factors must first be considered, in the light of the results listed in Tables 4.1 and 4.2, to determine whether these, as opposed to the presence of metal fluorides, were responsible for the increased DA selectivity. Steric effects can be disregarded immediately as firstly we have concentrated on 4-substituted thionitrosoarenes, and secondly any unfavourable steric interactions usually favour the Ene pathway, which is opposite to what was observed (see Tables 4.1 and 4.2). Solvent effects can also be summarily dealt with since it has been shown that polar solvents tend to favour the Ene pathway. Our reactions were conducted in acetonitrile, which would normally favour the Ene reaction, again contrary to our observations. Thus electronic effects remain as the most likely reason for the enhancement of the DA pathway. We have already discounted the electronic effect of the thionitroso substituent as being responsible for our observations, hence we suspected that the metal cation in the mixture was somehow influencing the reaction pathway.

It is possible that the metal cations (Ag^+, Cs^+, K^+) influence the reaction pathway by interaction with the thionitroso moiety. The fluoride anion was assumed to be associated with silicon as $FSiMe_3$ since the presence of an organic source of fluoride anion (tertiary butyl ammonium fluoride), in the reaction of compound **40c** with 2,3-dimethyl-1,3-butadiene produced no effect on the ratio of DA : Ene adducts obtained (when compared to thermal fragmentation of **40c**). Additionally, reaction in the presence of other Lewis acids (boron trifluoride and aluminium trichloride) did not affect the DA : Ene ratio.

An analogy between our observations and those found in the literature may now be drawn, since it has been noted that Lewis acids increase the rate of DA reactions (although they

also increase the rate of the Ene reaction).[83] This is caused by formation of a salt with the dienophile, the salt then acts as the dienophile in the cycloaddition reaction. Salt formation lowers the energy of the dienophile LUMO, thus bringing this orbital closer in energy to the diene HOMO and hence increasing the rate of the reaction (the rate of a normal electron-demand cycloaddition reaction increases as the energy levels of the dienophile LUMO and the diene HOMO are brought closer).

A similar scenario can be envisaged in which the nitrogen atom of the thionitroso moiety donates electron-density onto the metal cation (recall that thionitroso compounds are polarised with net negative charge on nitrogen, Section 1.2.7), *i.e.* the metal acts as a Lewis acid. If this is assumed to be the case, then the rate of both the DA and Ene reactions of thionitroso compounds should be increased in the presence of metal fluorides. To explain our observations fully, we must also assume that the rate of the DA reaction was increased to a greater extent relative to the rate of the Ene reaction, an assumption for which we can offer no further evidence. There is also the possibility that the increased preference for the DA pathway in the presence of metal cations is due to complex formation between the metal and diene increasing the proportion of diene present in the *s-cis* conformation. There is precedence for this in the literature, where metals (and, especially relevant here, silver) are known to form complexes with 1,3-butadiene, the most stable of which involves the *s-cis* diene conformer.[84]

4.2.3 INFLUENCE OF SILVER (I) FLUORIDE ON THE REGIOCHEMISTRY OF CYCLOADDITION

4.2.3.1 INTRODUCTION

We were interested in the mechanism of the cycloaddition reaction of thionitroso compounds with dienes in the presence of silver (I) fluoride. By reaction with an unsymmetrical diene (2-methyl-1,3-butadiene) we hoped to gain mechanistic insight into this process. Reaction of thionitroso compounds with 2-methyl-1,3-butadiene leads potentially to a mixture of regioisomeric 1,2-thiazine products with the methyl group at position C4 or C5 (Scheme 4.4). In previous work, both Bryce and Taylor,[9] and Markovskii *et al*,[21] noted that the C5 methyl isomer was predominant (Section 1.2.9).
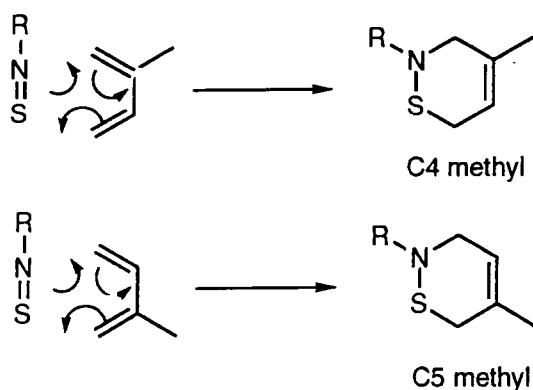
Scheme 4.4

Simple MO theory can be used to predict the predominance of the C5 methyl isomer as regioselectivity is thought to be controlled by frontier MO interactions.[83] Cycloaddition of thionitroso compounds with dienes is considered to be of normal electron-demand, *i.e.* the major interaction is transfer of electron density from the HOMO of the diene to the LUMO of the thionitroso dienophile.[13, 21] The relative sizes of the orbital coefficients in the HOMO of 2-methyl-1,3-butadiene have been calculated and are illustrated in Figure 4.1.[83]
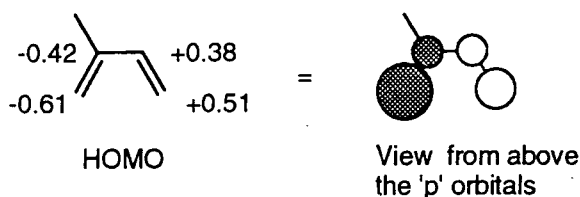
Figure 4.1

The nitrogen atom of thionitroso compounds bears a net negative charge, therefore the orbital coefficient on nitrogen in the HOMO is the largest. Consequently, the orbital coefficient on sulfur is largest in the LUMO (Figure 4.2). Markovskii *et al* have performed calculations confirming this, (they found that increasing the electron withdrawing nature of R increases the size of the orbital coefficient on sulfur in the LUMO).[21]
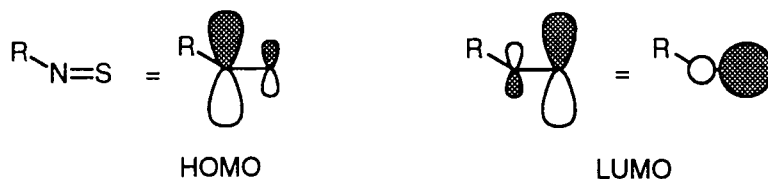
Figure 4.2

The regioselectivity of the cycloaddition reactions of thionitroso compounds can be explained in terms of the above orbital theory as it has been shown that interaction of the atoms with the largest coefficients in the diene HOMO and dienophile LUMO is energetically favourable (Figure 4.3).[83]

C5 methyl isomer - predicted
as the major isomer by MO theory
and observed as the major isomer
experimentally.[9, 21]
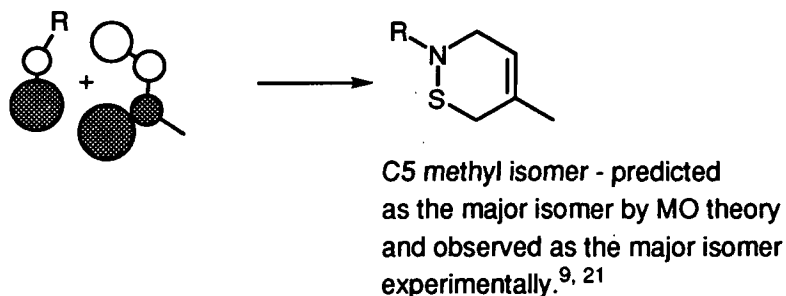
Figure 4.3

4.2.3.2 REACTION OF THIONITROSO COMPOUNDS WITH 2-METHYL-1,3-BUTADIENE IN THE PRESENCE OF SILVER (I) FLUORIDE

Thionitroso compounds **1c,e-f** were generated from compounds **40** in the presence of one equivalent of silver (I) fluoride and excess 2-methyl-1,3-butadiene (Scheme 4.5).

R = (c) 4-BrC$_6$H$_4$
(e) 4-MeC$_6$H$_4$
(f) 4-MeOC$_6$H$_4$
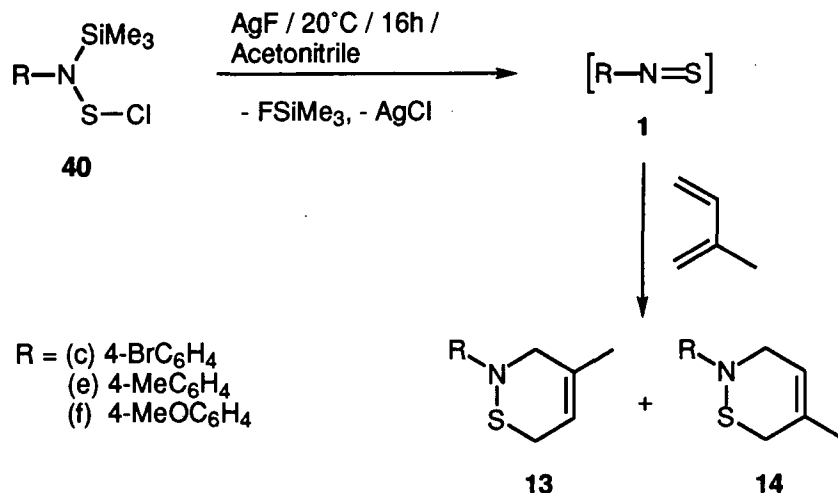
Scheme 4.5

The results of these reactions are presented in Table 4.3.

Table 4.3 Generation of thionitroso compounds **1c,e-f** and their reaction with 2-methyl-1,3-butadiene in the presence of silver (I) fluoride

Compound	Adduct ratio (by NMR)		Yield[†] %
	13	**14**	
1c	1 (1)	> 14 (3)	20 (65)
1e	1	> 14	40
1f	1 (1)	> 14 (3)	42 (60)

Notes.

1. † = Combined yield of adducts **13** and **14**.

2. Bracketed figures detail the observations of Taylor for the trapping of these thionitroso compounds without silver (I) fluoride, and the yield quoted is that of both regioisomeric 1,2-thiazines plus Ene adduct.[13]

Inspection of Scheme 4.5 reveals that the presence of silver (I) fluoride suppresses the Ene reaction completely. This is in accordance with our earlier results with 2,3-dimethyl-1,3-butadiene and is presumably for similar reasons.

Analysis of the isomer mixture **13** and **14** was accomplished by use of ^{1}H NMR spectroscopy, the method being identical to that employed by Taylor.[13] To summarise, this method involved comparison of the chemical shift of the CH_2S and CH_2N protons in the spectra of butadiene (**11**) and 2,3-dimethyl-1,3-butadiene (**3**) adducts with those in the spectra of isomer mixtures **13** and **14** (Figure 4.4).
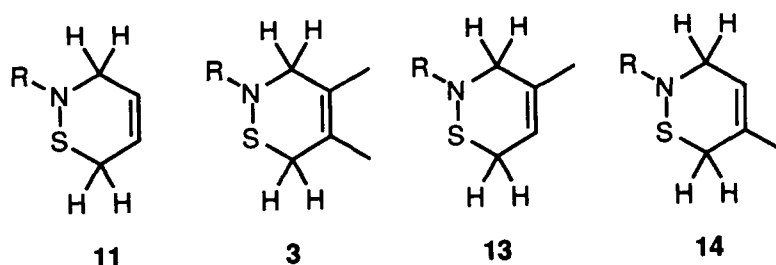
Figure 4.4

Thus compound **14** can be seen to have a CH_2N akin to that in compound **11** and a CH_2S akin to that in compound **3**. As an illustrative example of this, Figures 4.5 and 4.6 show the ^{1}H and ^{13}C NMR spectra of mixture **13e** and **14e**.

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Figure 4.5 - ¹H NMR Spectrum of adduct mixture 13e and 14e showing that compound 14e was the major isomer.

13e
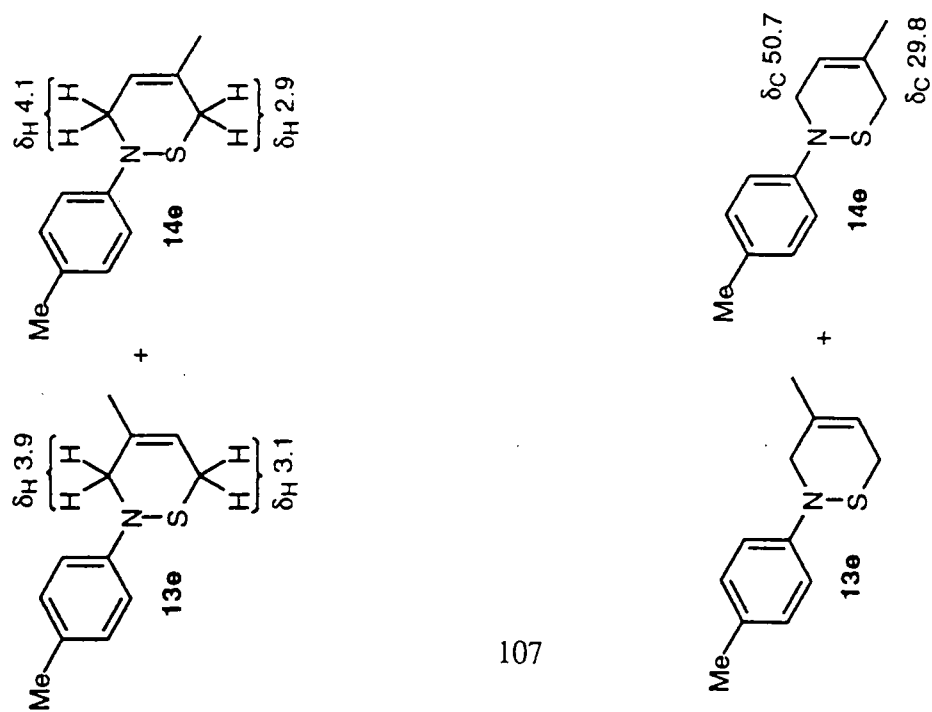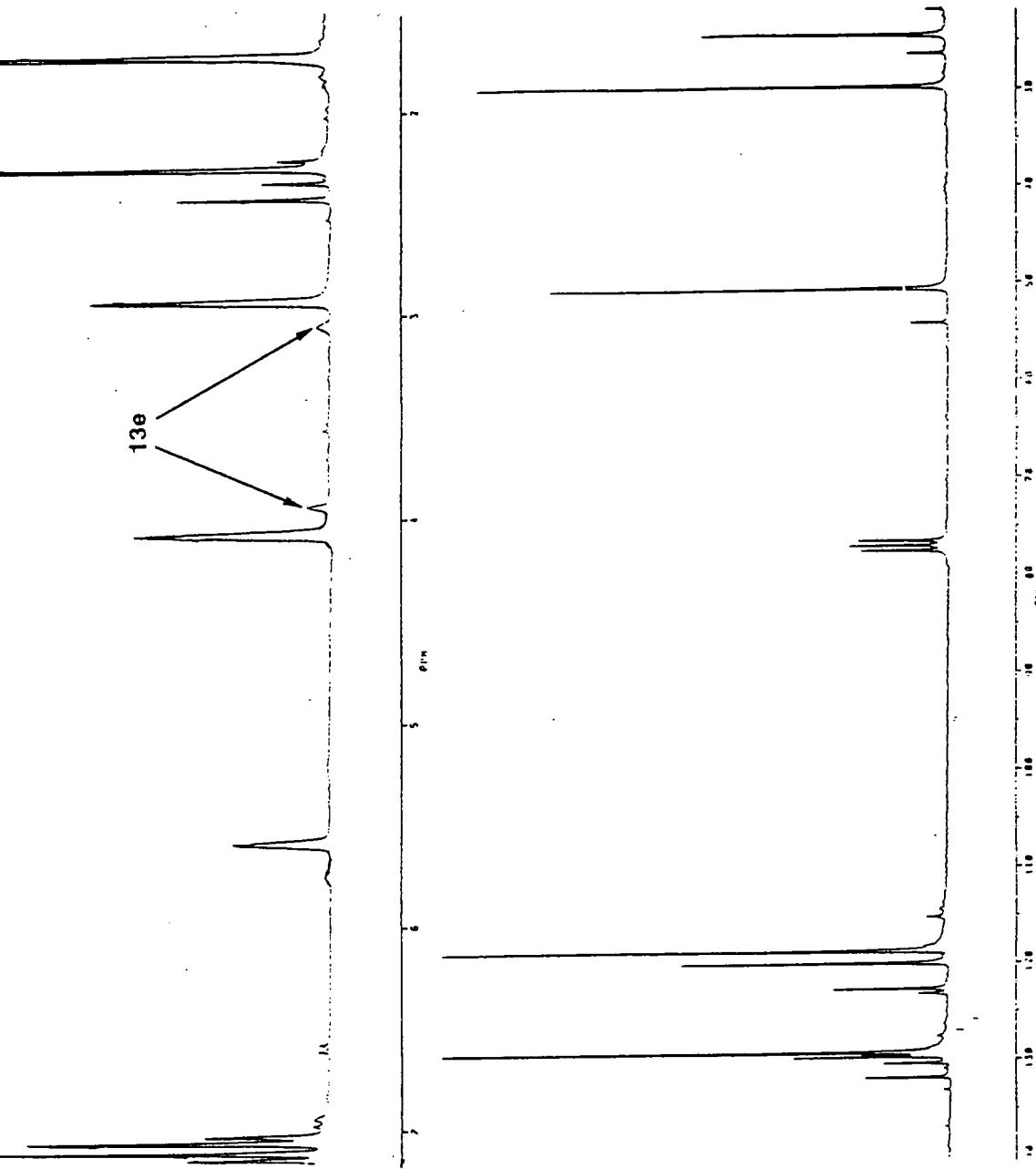
Figure 4.6 - ¹³C NMR Spectrum of adduct mixture 13e and 14e.

δ_H 4.1

δ_H 2.9

14e

Me

δ_H 3.9

δ_H 3.1

13e

Me

+

δ_C 50.7

δ_C 29.8

14e

Me

13e

Me

+

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Figure 4.7 shows the chemical shifts assigned to the methylene protons of compounds **3e** and **11e** by Taylor.[13] Also shown are the assignments made by us to the methylene protons in compounds **13e** and **14e** after inspection of the spectra in Figures 4.5 and 4.6.
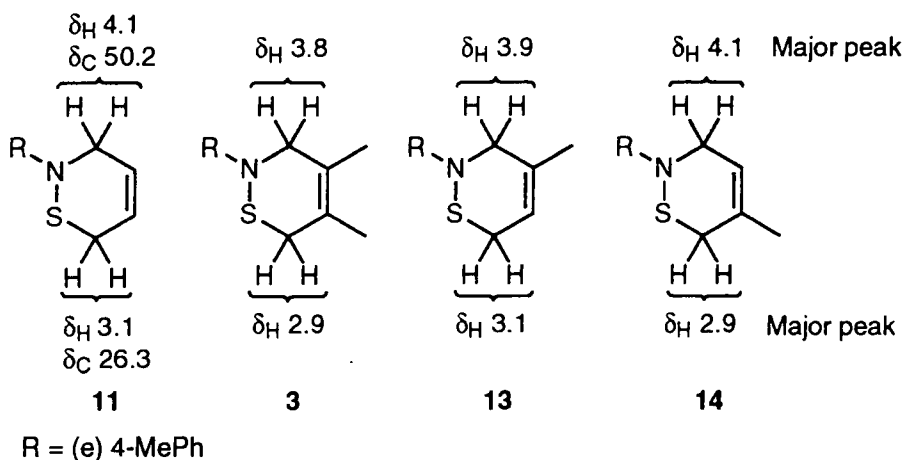
Figure 4.7

From Figure 4.5 it can be seen that the major peaks were at $\delta 2.9$ and $\delta 4.1$, and the minor peaks were at $\delta 3.9$ and $\delta 3.1$. Comparison of these chemical shifts with those for structures **11e** and **3e** assigned by Taylor (Figure 4.7) show that the major peaks correspond to isomer **14e**. Figure 4.6 also illustrates the presence of a major and minor isomer, with the peak at $\delta 50.7$ being assigned to C3 in **14e**, in analogy with the assignment of C3 in **11e** by Taylor ($\delta 50.2$).

It has been demonstrated (see Table 4.3) that the presence of silver (I) fluoride in the reaction of thionitroso compounds with 2-methyl-1,3-butadiene causes an increase in the amount of C5 methyl isomer (compounds **14**) produced. The figures in brackets indicate the observations for the analogous reaction in the absence of silver (I) fluoride. Thus, the cycloaddition reaction exhibited enhanced regioselectivity in the presence of silver (I) fluoride.

In Section 4.2, in order to explain the enhancement of the DA pathway, we assumed that the metal cation became associated with the thionitroso compound and perturbed the LUMO in the same manner as a Lewis acid. We can now build on this idea since the same association of the metal and the thionitroso compound will occur in reactions with 2-methyl-1,3-butadiene (since only the diene has been changed, this is unlikely to affect interaction between the thionitroso compound and the metal cation). Thus we propose that the association of the thionitroso compound and the metal cation causes the enhanced

regioselectivity. This idea is entirely compatible with the literature; for example, Fleming notes that cycloaddition reactions carried out in the presence of a Lewis acid are usually more regioselective.[83]

To rationalise our observation that silver (I) fluoride caused enhanced regioselectivity, we have assumed that the silver (I) cation becomes associated with the nitrogen atom of the thionitroso compound. The association of metal cation and thionitroso compound affects the orbital coefficients of the thionitroso compound, the nitrogen is effectively made more electronegative, thus in the HOMO the coefficient on nitrogen becomes even larger. It follows therefore that in the LUMO, the coefficient on sulfur is correspondingly larger and thus the driving force for the production of the C5 methyl isomer is also correspondingly larger (compared to reaction in the absence of silver (I) fluoride). This concept is illustrated pictorially in Figure 4.8.
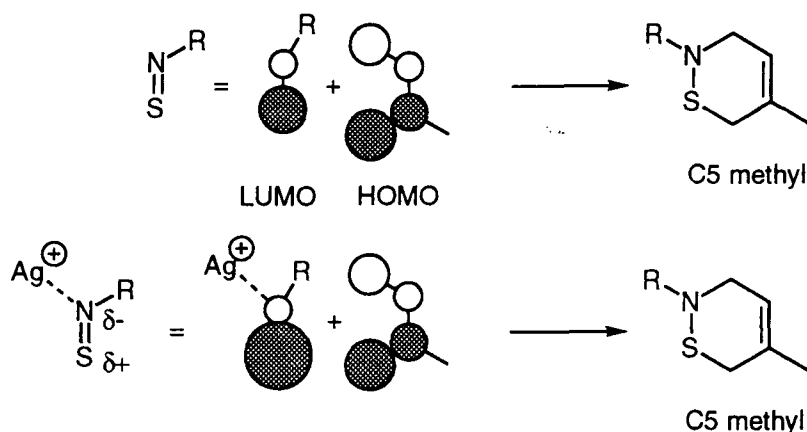
Association of the silver (I) cation with the nitrogen atom produces a larger coefficient on the sulfur atom in the LUMO, thus providing a relatively stronger driving force for C5 methyl product.

Figure 4.8

4.2.3.3 REACTION OF THIONITROSO COMPOUNDS WITH 1-METHYL-1,3-BUTADIENE IN THE PRESENCE OF SILVER (I) FLUORIDE

In order to establish whether silver (I) fluoride produced similar enhancements in regioselectivity when thionitroso compounds were reacted with other unsymmetrical dienes, we investigated reactions involving 1-methyl-1,3-butadiene. Thus, thionitroso compounds **1c,f** were generated from compounds **40c,f** in the presence of one equivalent of silver (I) fluoride and excess 1-methyl-1,3-butadiene according to Scheme 4.6.
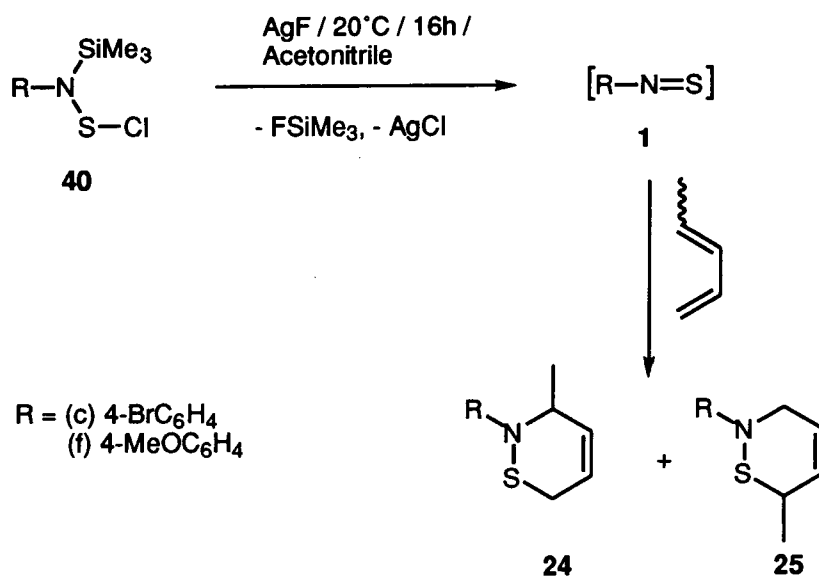
Scheme 4.6

The results of these reactions are summarised in Table 4.4.

Table 4.4 Generation of thionitroso compounds **1c,f** and their reaction with 1-methyl-1,3-butadiene in the presence of silver (I) fluoride

Compound	Adduct ratio (by NMR)		Yield[†] %
	24	**25**	
1c	>9 (2)	1 (1)	40 (70)
1f	>9 (3)	1 (1)	30 (70)

Notes.

1. † = Combined isolated yield of adducts **24** and **25**.

2. Bracketed figures detail the observations of Heaton for the trapping of these thionitroso compounds in the absence of silver (I) fluoride (yields estimated from ^{1}H NMR spectra).[66]

The ratio of compounds **24** and **25** in the product mixture was assessed from integration of the protons in the methyl groups at C3 and C6 in the 1,2-thiazine ring. Assignment of these chemical shifts was by direct comparison with the results of Heaton.[66] Carbon-13 spectra were also obtained, and DEPT was used to confirm the predominance of a single isomer. Figure 4.9 shows the DEPT spectrum of a mixture containing **24c** and **25c**, due to
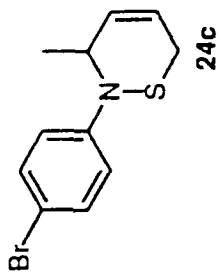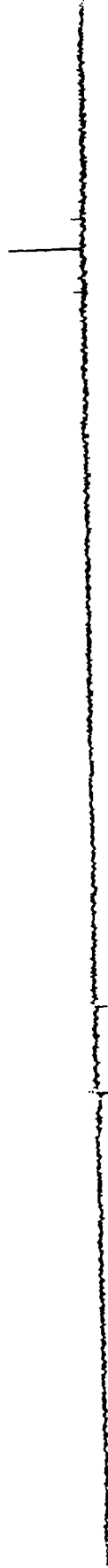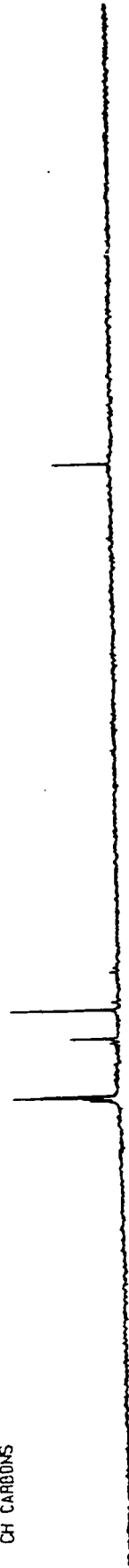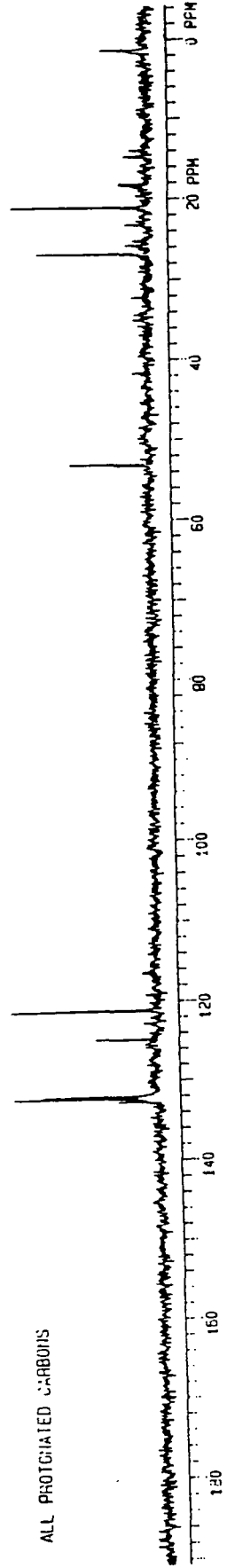
Figure 4.9 - 13C DEPT Spectrum of adduct mixture 24c and 25c showing only the peaks due to compound 24c and thus indicating that this was the major isomer.

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the very small amounts of **25c** present, and the relative insensitivity of ^{13}C spectroscopy (compared to ^{1}H spectroscopy), only the peaks assignable to compound **24c** appear.

The results collated in Table 4.4 show that the C3 isomer was predominant in reactions conducted in the absence of silver (I) fluoride (bracketed figures). In the presence of silver (I) fluoride the amount of this isomer was greatly increased, *i.e.* enhanced regioselectivity was observed in these reactions, as was the case in analogous reactions with 2-methyl-1,3-butadiene noted previously. The relative sizes of the terminal coefficients in the HOMO of 1-methyl-1,3-butadiene have been predicted,[83] and are shown in Figure 4.10.
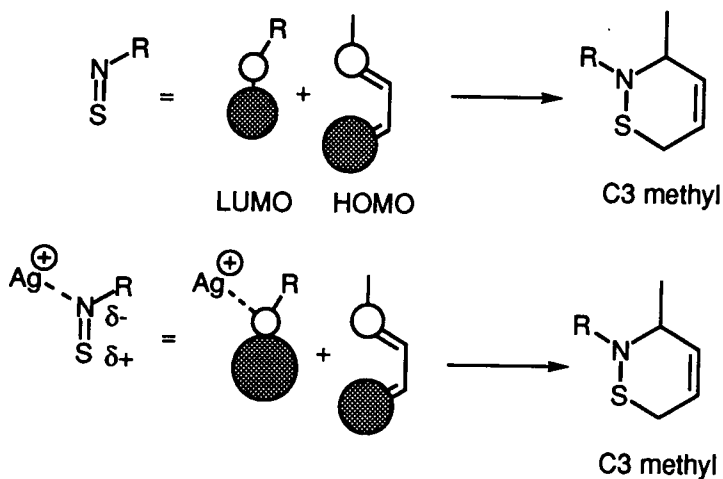
Again, association of the silver (I) cation with the nitrogen atom causes an increase in the size of the orbital coefficient on the sulfur atom in the LUMO, this in turn produces a stronger driving force for production of the C3 isomer.

Figure 4.10

To explain the observed regiochemistry (Table 4.4) we assumed, as before, that the silver (I) cation was associated with the nitrogen atom of the thionitroso species thus affecting the LUMO of the thionitroso compound in the same manner. Figure 4.10 shows how this effect enhances production of the C3 methyl product.

The results presented in Tables 4.3 and 4.4 demonstrate that the cycloaddition reactions of thionitroso compounds with unsymmetrical dienes exhibit enhanced regioselectivity when performed in the presence of silver (I) fluoride. This effect was general for the dienes studied, and was independent of the electronic nature of the thionitroso substituent. Furthermore, we have found that our results may be rationalised in accordance with the MO data described in the literature.[83] This study provides important insights as to the role of silver (I) fluoride (and by analogy caesium and potassium fluorides) in the generation

of thionitroso compounds, and suggests that the metal cation becomes bound to the free
thionitroso moiety during the reaction sequence.

4.3 A SHORTER ROUTE TO THIONITROSO COMPOUNDS

4.3.1 INTRODUCTION

In Section 4.2, we demonstrated how compounds **40** could be fragmented in the presence
of metal fluorides to afford thionitroso compounds (indeed, we alluded to the idea that the
metal fluoride may even induce the fragmentation of compounds **40**). Potassium fluoride
is also known for its ability to scavenge hydrohalides,[85] and it was this property which we
sought to exploit in the generation of thionitroso compounds.

We reasoned that if an amine were treated with sulfur dichloride in the presence of a base,
the resultant *N*-chlorothioamine (if formed) should be able to undergo loss of hydrogen
chloride (a hydrohalide) when treated with potassium fluoride. A thionitroso compound
would thus be liberated, which should in turn be intercepted with a diene as usual.

Our motivation in attempting to develop a shorter route to thionitroso species stemmed
from difficulties encountered in addition of the trimethylsilyl group to amines containing
very bulky substituents, where steric hindrance prevented such a reaction. We wished to
access thionitroso compounds incorporating bulky substituents not accessible by existing
methodology, as there was the possibility that 1,2-thiazine adducts of such species would
be crystalline and thus lend themselves to full structural analysis.

The reaction of sulfur dichloride with amines represents possibly the simplest method
with the potential to access thionitroso compounds. One will not be surprised, therefore, to
learn that several reports of such a reaction appear in the literature pertaining to
thionitroso compounds. Boger and Weinreb note that the reaction of sulfur dichloride with
amines affords sulfur diimides,[2] as do Davis and Skibo.[6] Bryce *et al* also note this fact,
and speculate involvement of a thionitroso compound at some point in the reaction
sequence, although they also note that this method has not proved synthetically useful
with respect to the generation of thionitroso compounds.[3]

Justification for the idea that treatment of amines with sulfur dichloride would yield *N*-chlorothioamines is available in the literature, Burgess and Penton employed such a reaction to produce compound **149** (Scheme 4.7).[86]
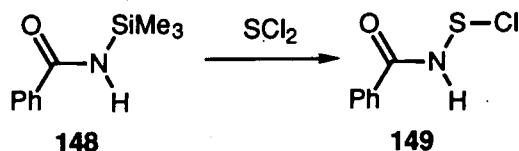
Scheme 4.7

4.3.2 THIONITROSO COMPOUNDS FROM *N*-CHLOROTHIOAMINES

Compounds **150k,k',m'** were produced by treatment of the corresponding amine with one equivalent of sulfur dichloride in the presence of one equivalent of triethylamine. These compounds were then dehydrochlorinated by treatment with a slight excess (*ca*.1.1 eq.) of potassium fluoride in the presence of excess 2,3-dimethyl-1,3-butadiene to afford a mixture of compounds **3** and **12** (Scheme 4.8). In the absence of potassium fluoride compounds **3** and **12** were not observed, instead an intractable black residue was obtained.

$$R = (k) \quad 2\text{-BrC}_6\text{H}_4$$
$$(k') \quad \text{Ph}_2\text{CH}$$
$$(m') \quad \text{Ph}_3\text{C}$$
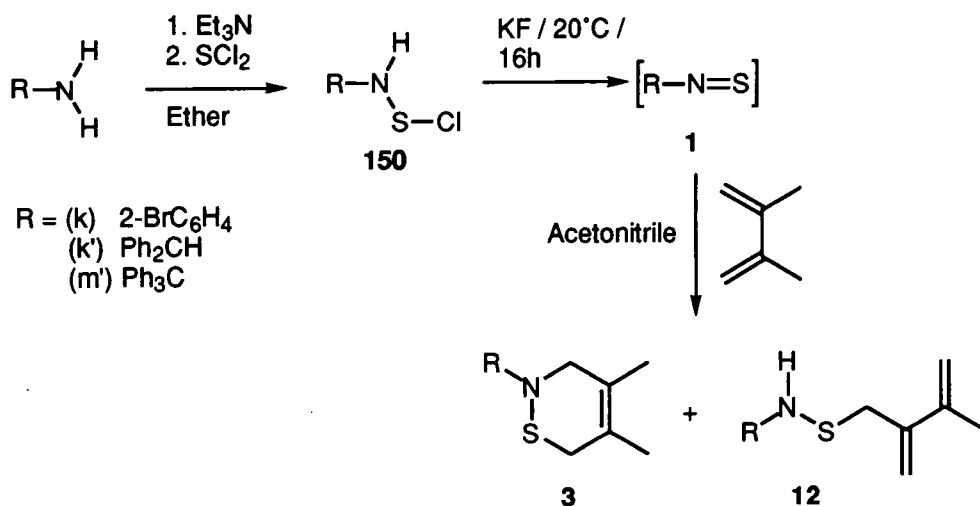
Scheme 4.8

The results of these reactions are listed in Table 4.5

Table 4.5 Potassium fluoride-induced generation of thionitroso compounds **1k,k',m'** from compounds **150** and their reaction with 2,3-dimethyl-1,3-butadiene

Compound	Adduct ratio (by NMR)		Yield %
	3 (DA)	12 (Ene)	
1k	>95	<5	30
1k'	100	0	30
1m'	100	0	32

Compounds **150** were highly unstable red/yellow oils which had to be used immediately after preparation in order for this methodology to be successful. Their structure was assigned from the I.R. spectrum in which the disappearance of one of the amine stretching absorptions at $3450cm^{-1}$ suggested that the chlorothio group was in place. Further analysis was not possible due to their extreme instability.

The fact that DA adducts **3k,k',m'** and Ene adduct **12k** were observed, suggests that thionitroso compounds **1k,k',m'** were produced. As expected, in the presence of a metal cation, the Ene pathway was highly disfavoured (see Section 4.2).

We have thus discovered a new method for the generation of thionitroso compounds. This method can be used when sterically very demanding amines are being employed. As an example, compound **1m'** was accessible *via* this method whereas previously this compound was inaccessible as it was not possible to add the trimethylsilyl group to the amine. Unfortunately, in spite of the bulky substituents, compound **3m'** was not crystalline. Overall, this new method for the generation of thionitroso compounds is very simple, quick, and utilises inexpensive reagents. On the negative side, compounds **150** proved to be highly unstable and difficult to manipulate.

In an extension of the new methodology, it was demonstrated that both silver and caesium fluoride could also be employed to liberate thionitroso compounds from *N*-chlorothioamines.[73]

4.3.2.1 A THIONITROSO COMPOUND FROM THIOACETAMIDE

We had been interested for some time in the generation of a thionitroso compound from thioacetamide **151** as this would provide scope for the introduction of a 1,4 S--S nonbonded interaction in its cycloaddition product. Having recognised that our new

methodology might allow access to this species, we attempted to generate it according to Scheme 4.9.
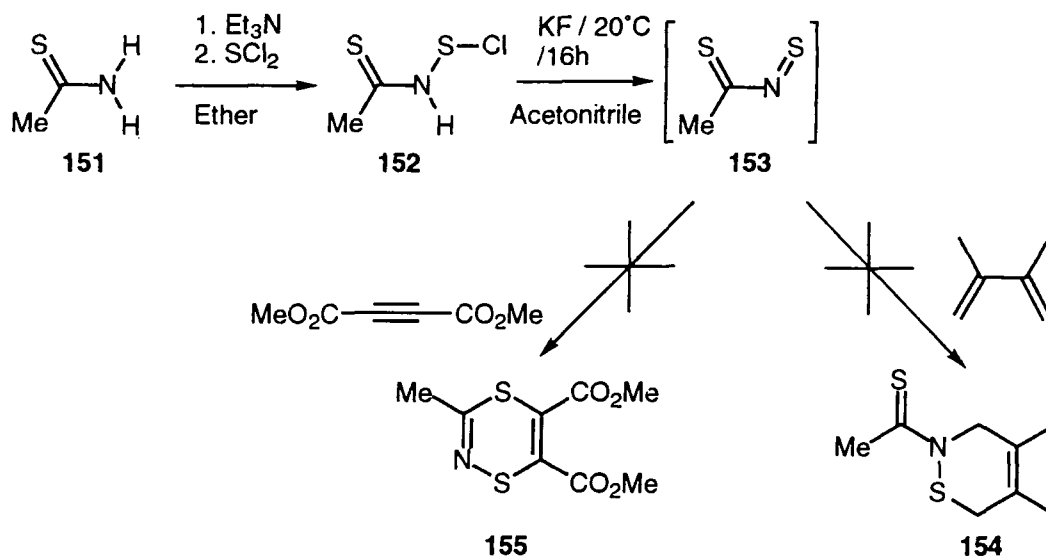
Scheme 4.9

It could not be ascertained with certainty that compound **152** was formed (the I.R. data was inconclusive). We did not, however, observe the production of compound **154** upon reaction in the presence of 2,3-dimethyl-1,3-butadiene. We also recognised the possibility that, if formed, compound **153** may act as a 4π hetero-diene. Thus we attempted a reaction in the presence of dimethylacetylene dicarboxylate. Formation of compound **155** however, was not observed. We thus concluded that the methodology employed was probably not suitable for the generation of compound **153**.

4.4 GENERATION AND REACTIONS OF *C*-THIOXOPHOSPHINES

4.4.1 INTRODUCTION

C-Thioxophosphines are the phosphorus analogues of *C*-thionitroso compounds. Like their thionitroso counterparts, most thioxophosphines are reactive intermediates. Dienes have been used to intercept these species with the resultant formation of 1,2-thiaphosphorin heterocycles (Section 1.3).[48, 50, 53, 58]

We were interested in the regiochemistry of the cycloaddition reactions of thioxophosphines with dienes, and wished to compare this aspect of their chemistry with

that of thionitroso compounds (detailed in Section 4.2). In order to make our comparisons as relevant as possible, we chose to investigate the reactions of phenylthioxophosphines. No reports of the reaction of phenylthioxophosphines with unsymmetrical dienes were found during a search of the Chemical Abstracts data base upto the end of 1994.

4.4.2 SYNTHESIS OF PHENYLTHIOPHOSPHONIC DICHLORIDES

The title compounds serve as direct precursors to phenylthioxophosphines and were synthesised from the parent benzenes **156a-c** by means of a Friedel-Crafts reaction with phosphorus trichloride, followed by *in situ* thiolation with elemental sulfur (Scheme 4.10).[87]

$$R-\langle\text{benzene}\rangle-X + 3PCl_3 \xrightarrow[\text{2. } S_8]{\text{1. AlCl}_3 \text{ / reflux}} R-\overset{\overset{\text{S}}{\|}}{P}\overset{\cdots\text{Cl}}{\underset{\text{Cl}}{}}$$

156
(a) R = X = H
(b) R = Me, X = H
(c) R = Cl, X = H

76
R = (a) Ph
    (d) 4-MeC$_6$H$_4$
    (e) 4-ClC$_6$H$_4$
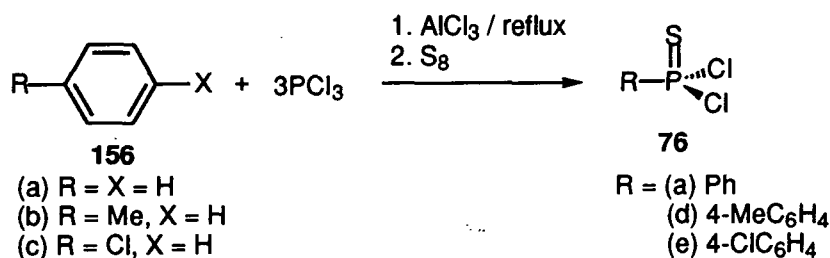
Scheme 4.10

Compounds **76a,d-e** were obtained in high yield (50 -70%) as colourless oils having an acrid odour, and were stable for a number of weeks at 4°C.

4.4.3 REACTION OF PHENYLTHIOXOPHOSPHINES WITH 2-METHYL-1,3-BUTADIENE

Compounds **76a,d-e** were dechlorinated with magnesium (as described by Inamoto *et al*),[48] to afford thioxophosphine intermediates **2a,d-e**, which were intercepted with an excess of 2-methyl-1,3-butadiene (Scheme 4.11).
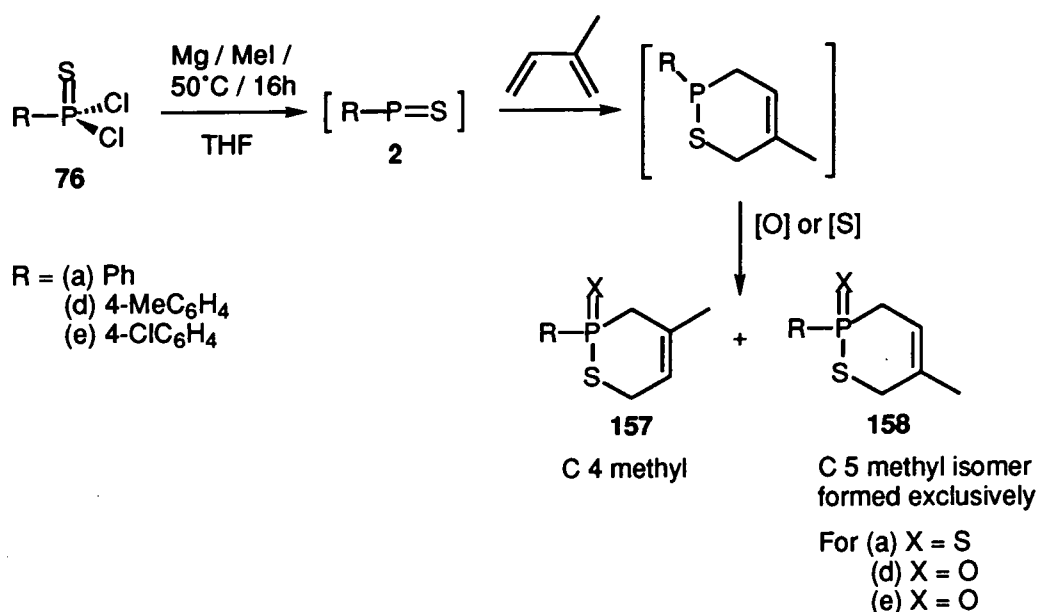
Scheme 4.11

The results of these reactions are summarised in Table 4.6.

Table 4.6 Reaction of thioxophosphine compounds **2a,d-e** with 2-methyl-1,3-butadiene

Compound	Adduct ratio (by NMR)		Yield %
	157	158	
2a	0	1	10
2d	0	1	17
2e	0	1	20

Scheme 4.11 shows how reaction of compounds **2a,d-e** with 2-methyl-1,3-butadiene could have produced both regioisomeric adducts **157** and **158**. Table 4.6 reveals that only compounds **158a,d-e** were observed, *i.e.* the cycloaddition reaction between the thioxophosphines and the diene proceeded with complete regioselectivity in favour of the C5 methyl isomer. No evidence for the formation of Ene adduct was observed. These results contrast markedly with those obtained for thionitroso compounds where only partial regioselectivity was seen, and production of an Ene adduct was in most instances also evident.[9]

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Exactly which isomer had been produced (**157** or **158**, Scheme 4.11) was ascertained from the ¹H NMR spectra by comparison with the literature spectrum for compound **78a**. Figure 4.11 illustrates how this was achieved.

δ_H 1.97, d, $^4J_{PCCCH}$ = 5 Hz

Coupling to P expected

δ_H 1.77, s, not coupled to P
Literature compound.

Coupling to P not observed
Compounds under investigation.
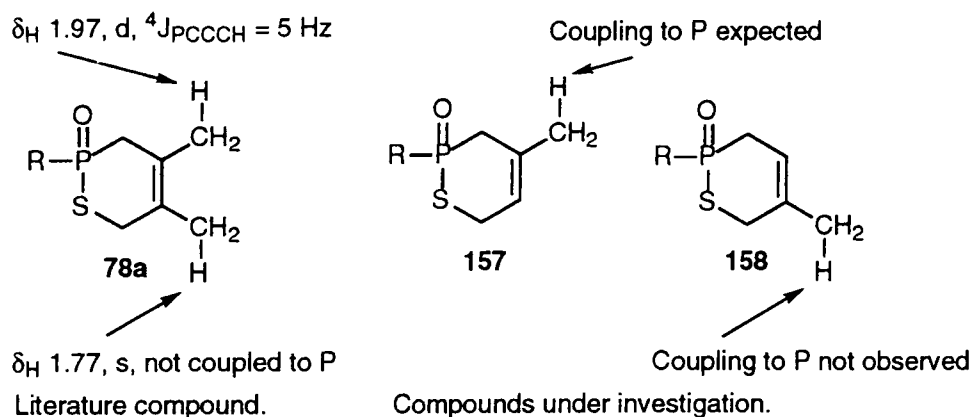
Figure 4.11

Structure **78a** shows the assignments detailed in the literature.[50] The protons of the C4 methyl group were split into a doublet by coupling to phosphorus, whilst those on C5 remained a singlet. It was, therefore, straightforward to analyse the products of the reactions detailed in Scheme 4.11, in each case the methyl group appeared as a singlet, and could thus be assigned to the C5 methyl structures **158**. Further evidence for the production of a single isomer in each case was provided by ³¹P NMR (only a single peak was observed), and ¹³C NMR (by use of a DEPT experiment). The DEPT experiment was performed to simplify the normal ¹³C NMR spectrum, and in addition revealed a large ¹J$_{CP}$ coupling (in the region of 50Hz) present in the signal for C3 of each of compounds **158a,d-e**. Figures 4.12 - 4.14 show the ¹H, ³¹P and ¹³C DEPT NMR spectra respectively of compound **158e** and serve to illustrate the above points.

4.4.3.1 RATIONALISATION OF RESULTS

Thioxophosphines **2a,d-e** reacted with 2-methyl-1,3-butadiene with complete regioselectivity to yield the C5 methyl isomers **158a,d-e**. In this respect, they exhibit similar behaviour to their thionitroso counterparts, which also gave predominantly the C5 methyl isomer (Section 4.2). The thioxophosphines, however, showed enhanced regioselectivity in this respect. Secondly, the electronic nature of the substituent on the aromatic ring did not affect the regioselectivity, again analogous to thionitroso compounds.
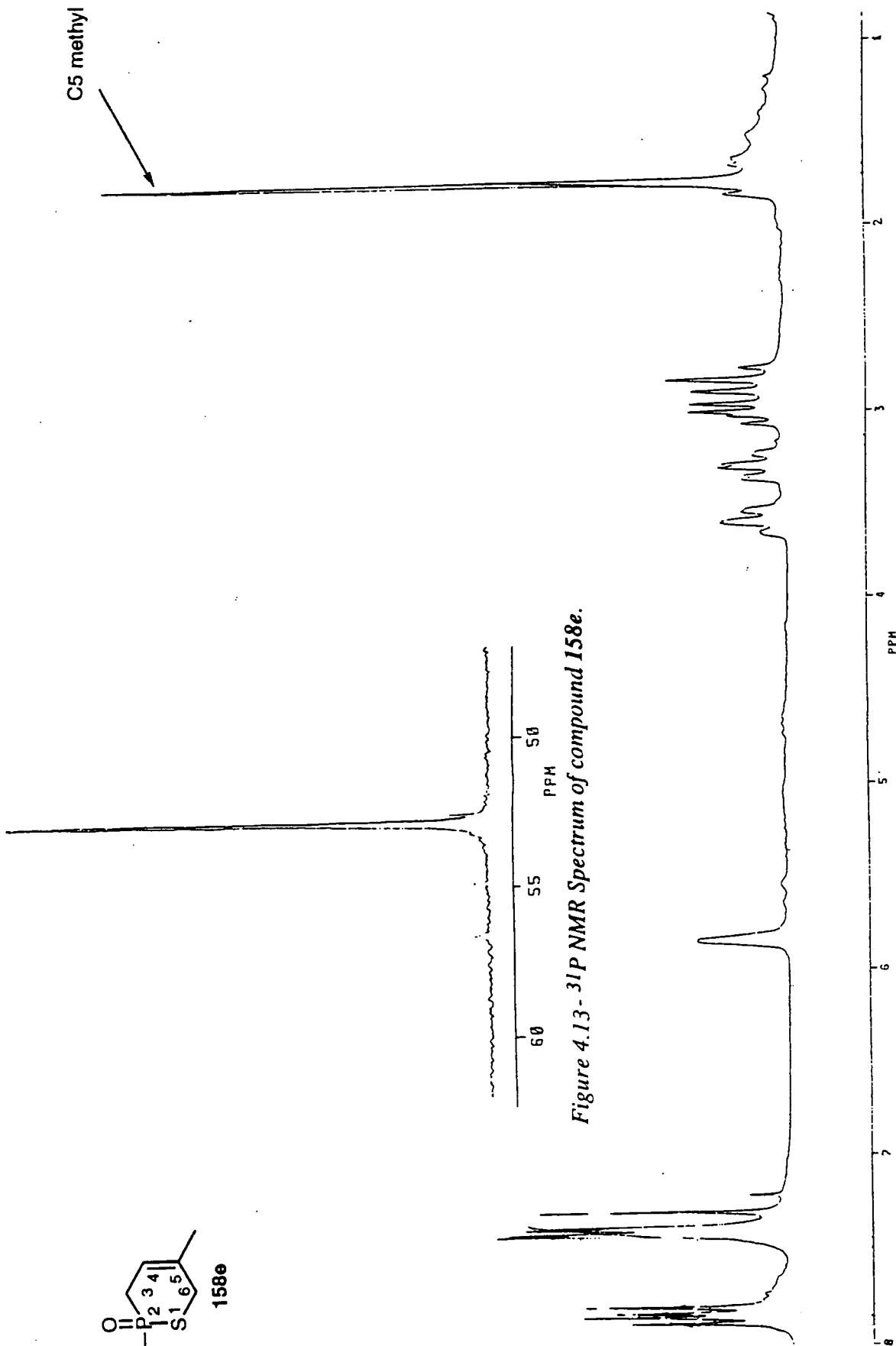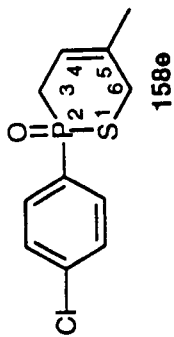
Figure 4.13 - *31P NMR Spectrum of compound 158e.*

Figure 4.12 - *1H NMR Spectrum of compound 158e indicating the presence of a single isomer with the methyl group at C5.*

120
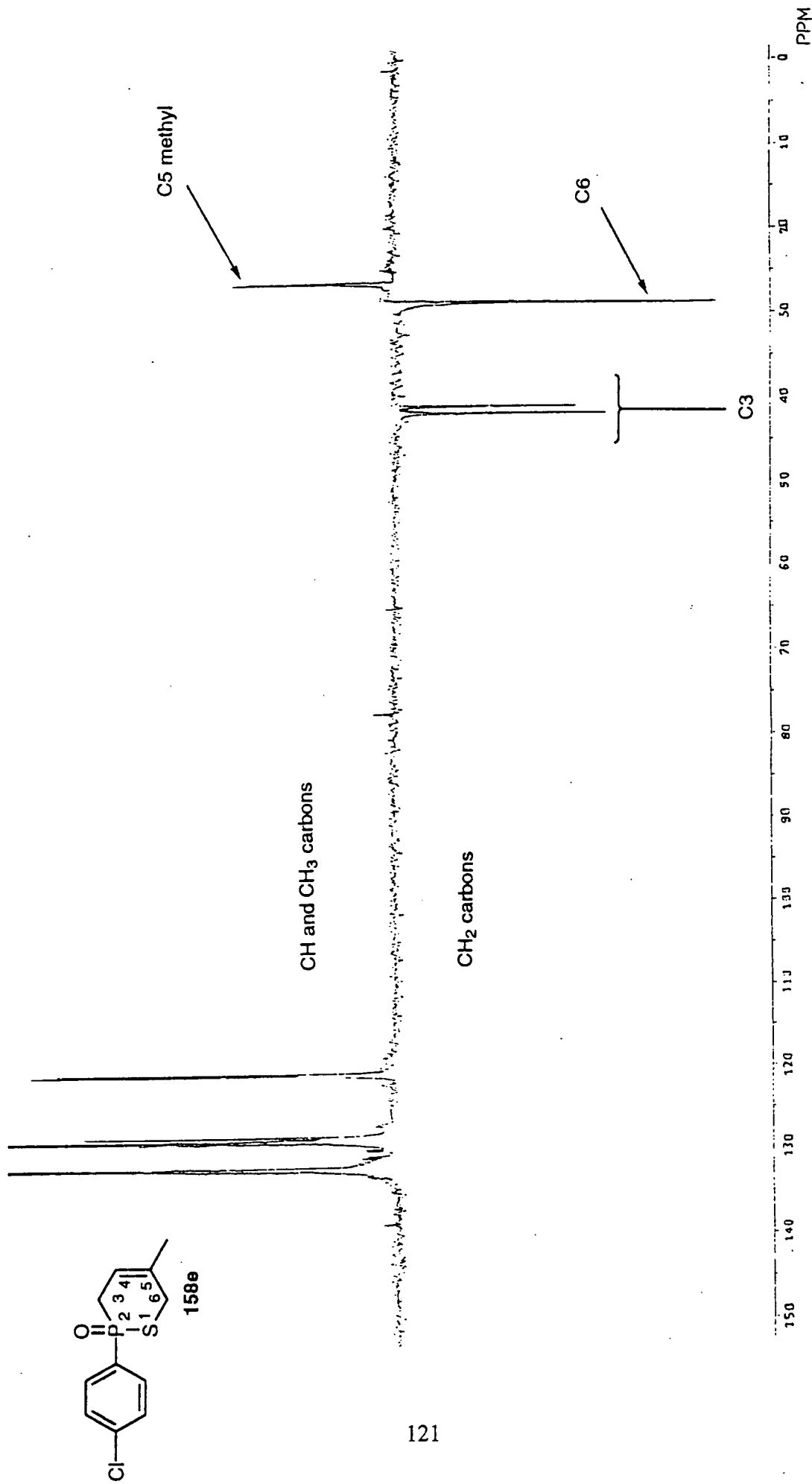
Figure 4.14 - 13C DEPT Spectrum of compound **158e** showing the presence of a single isomer with the methyl group at C5, and highlighting the $^1J_{CP}$ coupling of the C3 signal.

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In attempting to rationalise the thioxophosphine results with arguments similar to those used to explain the thionitroso observations (Section 4.2), we must first assume that a concerted reaction between compounds **2** and the diene occurred (the only evidence we can offer for this being reaction of compound **2a** with *trans* 1-methyl-1,3-butadiene which yielded a single isomer, see Section 4.4.4). With the above assumption in mind, a rationalisation in orbital terms can be attempted.

Regioselectivity in thionitroso compounds could be explained in terms of the relative sizes of the orbital coefficients in the diene HOMO and dienophile LUMO. Thionitroso compounds are polarised with a negative charge on nitrogen, which ultimately causes the orbital coefficient on the sulfur atom in the LUMO to be large (the regiochemistry is then controlled by interaction of the largest coefficients in the diene HOMO and dienophile LUMO, Section 4.2.3). Based on Pauling electronegativities, thioxophosphines would also be expected to be polarised, but in the opposite direction to thionitroso compounds, *i.e.* sulfur net negative (Pauling electronegativities: N = 3.0, S = 2.5, P = 2.1).[74] Therefore, the orbital coefficient on the sulfur atom in the LUMO of thioxophosphines will be small. This leads to the prediction that the C4 methyl isomer would be the major product in a cycloaddition reaction with 2-methyl-1,3-butadiene (Figure 4.15).

LUMO   HOMO

C4 methyl predicted, contrary to experimental results
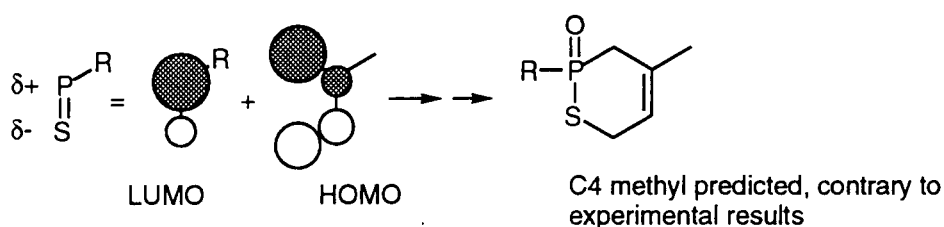
Figure 4.15

Thus, orbital considerations predict the C4 isomer as the major product, which is opposite to our experimental observations. A rationalisation on steric grounds must, therefore, be considered to explain formation of the C5 methyl isomer (Bryce and Taylor employed steric arguments to explain the formation of the C5 methyl isomer in the reactions of thionitroso compounds).[9] The fact that steric effects appear to override orbital considerations is not surprising, since it is acknowledged that this is one of the major factors not accounted for by simple MO theory.[83] Therefore, the fact that only the C5 methyl isomer was observed when thioxophosphines **2a,d-e** were reacted with 2-methyl-1,3-butadiene can be rationalised on steric grounds thus: the C2 methyl substituent of the diene and the phenyl substituent on phosphorus become oriented in the transition state such that unfavourable steric interactions between the two are minimised. It is obvious

that the transition state leading to the C5 methyl isomer would be favoured on these grounds over that leading to the C4 isomer.

To determine whether there were any trends in the regioselectivity of thioxophosphine cycloaddition reactions, we investigated reaction of these compounds with 1-methyl-1,3-butadiene.

4.4.4 REACTION OF PHENYLTHIOXOPHOSPHINES WITH 1-METHYL-1,3-BUTADIENE

Compounds **76a,d-e** were dechlorinated with magnesium, in the presence of excess *cis/trans* 1-methyl-1,3-butadiene, to afford thioxophosphine intermediates **2a,d-e** which were intercepted by the diene *via* DA reaction (Scheme 4.12).
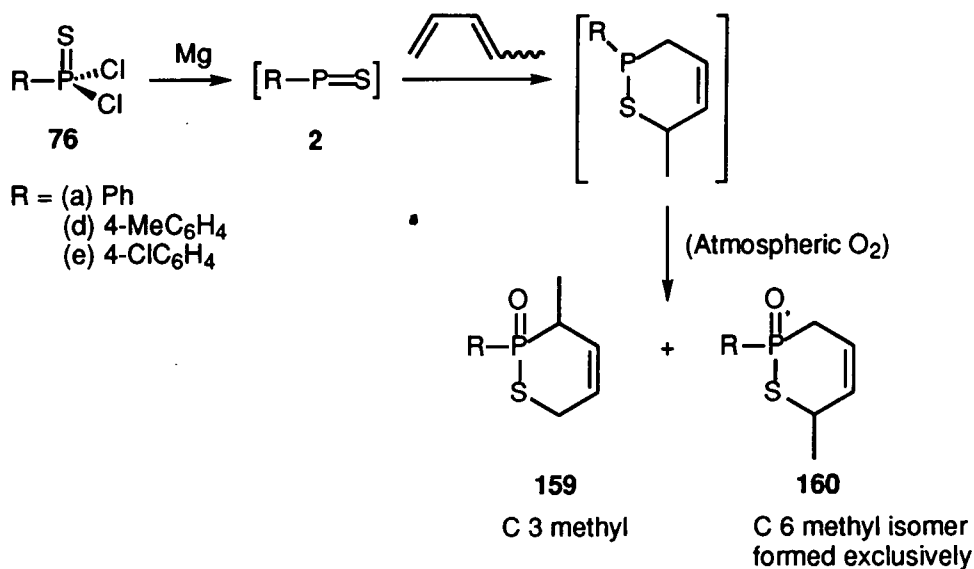
Scheme 4.12

The results of these reactions are correlated in Table 4.7

Compound	Adduct ratio (by NMR)		Yield %
	159	**160**	
2a	0	1	20
2d	0	1	20
2e	0	1	10

As can be seen from Table 4.7, the reaction of thioxophosphines **2a,d-e** proceeded with exclusive formation of compounds **160a,d-e** (the C6 methyl isomer). These observations can be rationalised by the steric arguments employed previously. Thus, it can be seen that the transition state leading to the formation of compounds **160** would be strongly favoured over that leading to the formation of compounds **159**, since the latter would involve unfavourable steric interaction between the C1 methyl substituent of the diene and the phenyl substituents on phosphorus. Incidentally, the formation of compounds **160** is, in this case, consistent with orbital considerations (Figure 4.16).
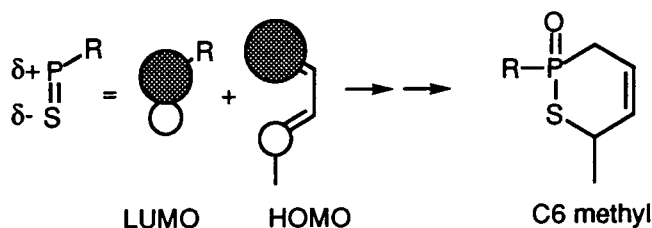
Figure 4.16

4.4.4.1 ASSIGNMENT OF SPECTRA

Scheme 4.12 shows that cycloaddition of thioxophosphines **2** with *cis/trans* 1-methyl-1,3-butadiene could have produced a mixture of compounds **159** and **160**. Table 4.7 shows that only compounds **160** were produced. This fact was deduced from the NMR spectra in the following manner.

It should be noted that a *cis/trans* mixture of 1-methyl-1,3-butadiene was utilised as the thioxophosphine trap in the reactions detailed in Scheme 4.12 (this was more economical than employment of either pure isomer since a large excess of the diene was used). This resulted in highly complex NMR spectra for the product of the cycloaddition reactions. Using the analysis of the product produced when compound **2a** was reacted with *cis/trans*

1-methyl-1,3-butadiene as an illustrative example, the following was observed. In the ^{1}H NMR spectrum, two doublet signals with fine coupling were present due to methyl groups, the ^{31}P spectrum contained two peaks, and the ^{13}C NMR DEPT spectrum was complex (see Figures 4.17 - 4.19). The appearance of the spectra could have been due either to a mixture of compounds **159a** and **160a**, or by there being two isomers of the same compound brought about by the use of a *cis/trans* diene mixture (Figure 4.20).
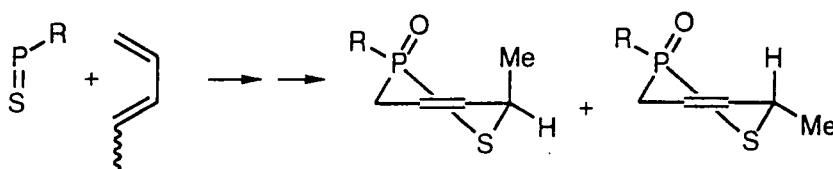
The conformation of the 1,2-thiaphosphorin ring is locked, so in the above structures the methyl groups are inequivalent.

Figure 4.20

We resolved this problem by recognising that only a single isomer (*i.e.* methyl axial or equatorial, but not both) could be formed from a concerted reaction between compound **2a** and a single isomer of the diene. Thus, if reaction between **2a** and a single isomer of the diene produced simplified spectra then this would constitute evidence that the isomeric mixture of dienes produced an isomeric mixture of products as shown in Figure 4.20. Obviously, if a mixture of compounds **159** and **160** was being produced, the reaction products would have been unaffected by this change in the isomeric composition of the diene, and their spectra would remain unchanged.

Compound **2a** was thus reacted with *trans* 1-methyl-1,3-butadiene in exactly the same manner as before (Scheme 4.12). When the product of this reaction was analysed, the spectra were considerably simplified and could be assigned as compound **160a** (Figures 4.21 and 4.22 show the salient sections of the ^{1}H and ^{13}C spectra with the single C6 methyl group at δ1.54 and δ21.5 respectively). This experiment proves that only the C6 methyl isomers **160a,d-e** were produced in the original reactions with *cis/trans* 1-methyl-1,3-butadiene (Scheme 4.12), and that the spectra were complex because a mixture of isomers in which the methyl group at C6 is axial and equatorial was formed due to reaction with the isomeric diene. This result also demonstrates that the ring conformation of compounds **160a,d-e** is effectively locked on the NMR time scale (since the axial and equatorial methyl groups appear as separate signals).
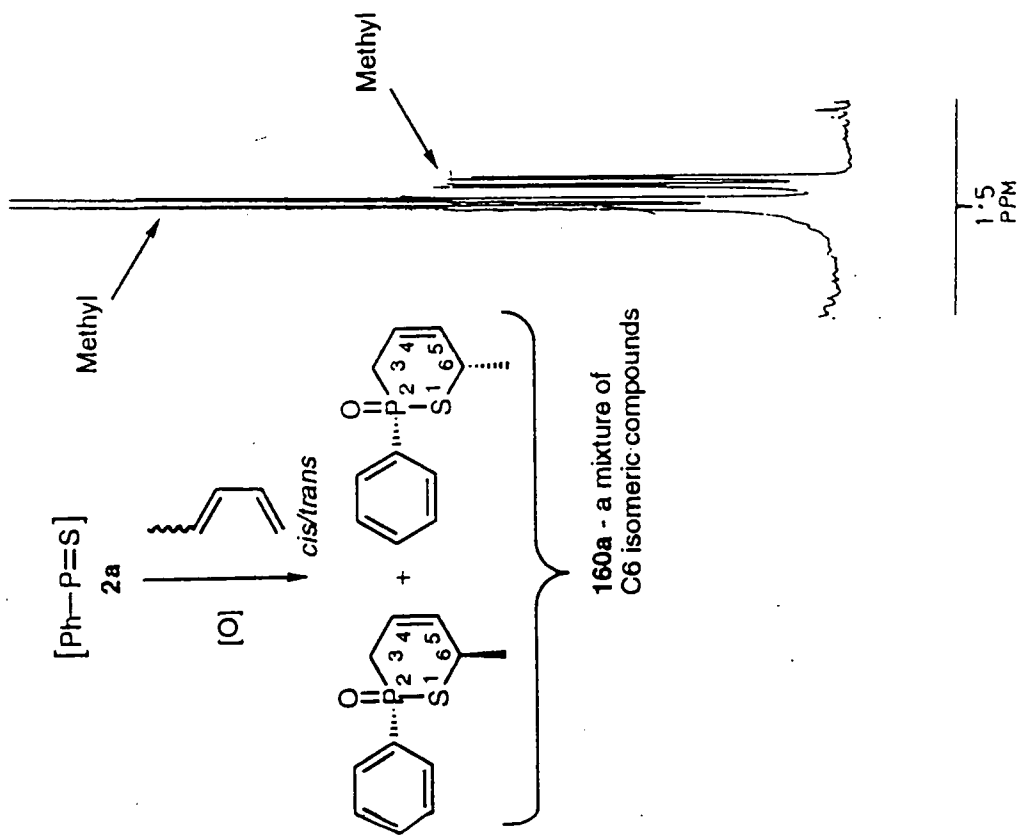
Figure 4.17 - ^1H NMR Spectrum.

Figure 4.18 - ^{31}P NMR Spectrum.
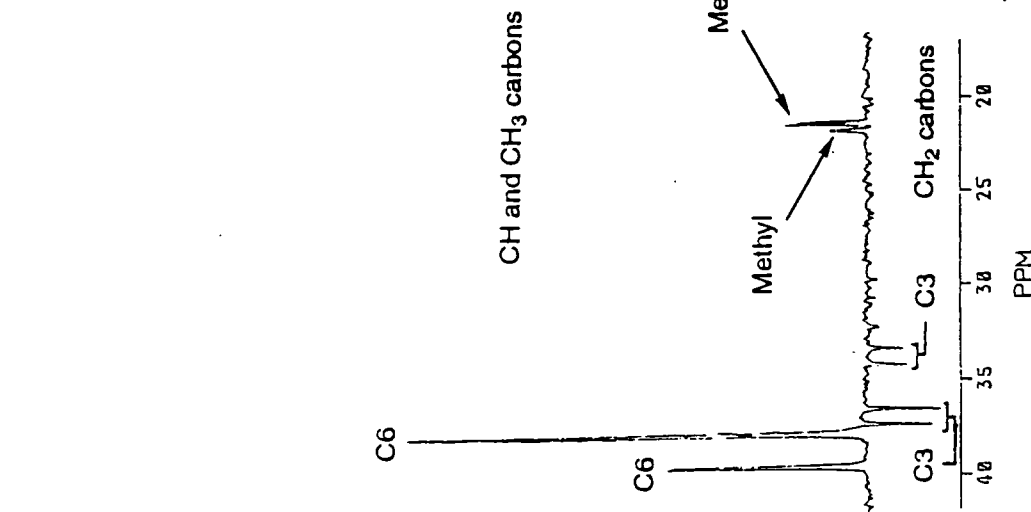
Figure 4.19 - ^{13}C DEPT Spectrum.

Figures 4.17 - 4.19 - Illustrate the salient features of the ^1H, ^{31}P and ^{13}C DEPT spectra of the product obtained via reaction of compound 2a with cis/trans 1-methyl-

1,3-butadiene, and indicate that a mixture of isomers were formed.

C6 methyl

20

PPM

Figure 4.22 - ^{13}C NMR Spectrum.

C6 methyl

15

PPM
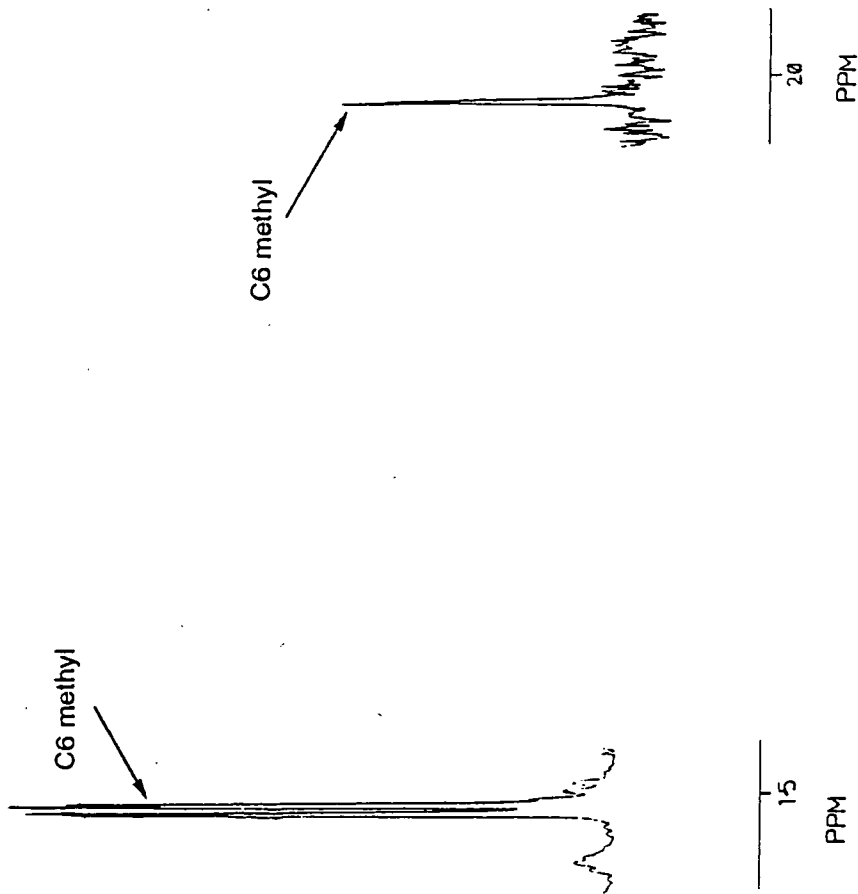
Figure 4.21 - ^1H NMR Spectrum.
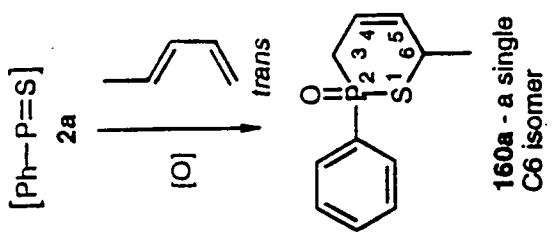
Figures 4.21 - 4.22 - Illustrate the salient features of the ^1H and ^{13}C spectra of the product obtained via reaction of compound 2a with <u>trans</u> 1-methyl-1,3-butadiene, and enable the product to be assigned structure 160a.

[Ph–P=S]
2a

trans

[O]

O=P

2 3
1 4
S 5
6

160a - a single
C6 isomer

127

4.5 NONBONDED INTERACTIONS AND THIOXOPHOSPHINES

4.5.1 INTRODUCTION

Chapter 3 details our studies on nonbonded interactions in thionitroso chemistry. We reasoned that it may be possible to utilise similar nonbonded interactions to provide further evidence for the intermediacy of free thioxophosphines.

Consider the reaction sequence for the trapping of thioxophosphines (Scheme 4.13).

Intermediate 1,2-thiaphosphorin   **78**
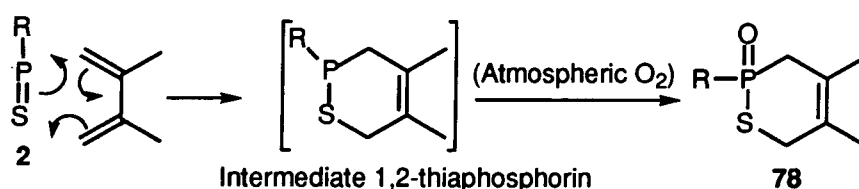
Scheme 4.13

It is believed that the reaction sequence proceeds *via* an intermediate 1,2-thiaphosphorin heterocycle (in which the phosphorus atom is tricoordinate), this species becomes oxidised under the reaction conditions to afford the 1,2-thiaphosphorin-2-oxide **78**.[50] The intermediacy of a free thioxophosphine **2** is inferred by postulating a [4π + 2π] reaction between it and the diene, to afford the initial transient heterocycle.

It is possible that a nonbonded interaction would stabilise the transient 1,2-thiaphosphorin heterocycle, thus preventing oxidation and providing direct evidence of a [4π + 2π] reaction and, therefore, further evidence for the existence of free thioxophosphines **2** (Scheme 4.14).

X = O or S   Nonbonded interaction
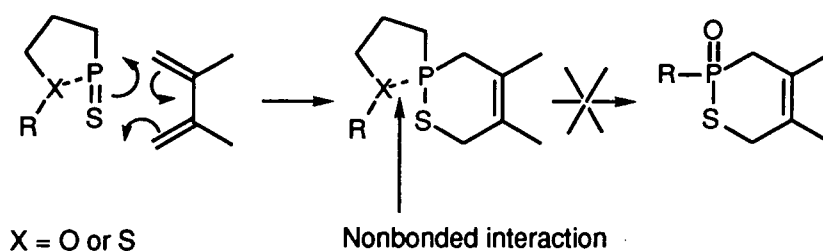
Scheme 4.14

methylene groups would maximise the chance of success as this offers the possibility of either a five-membered ring interaction at phosphorus, or a six-membered ring interaction at sulfur (Figure 4.23).

5-membered ring nonbonded
interaction at phosphorus

6-membered ring nonbonded
interaction at sulfur
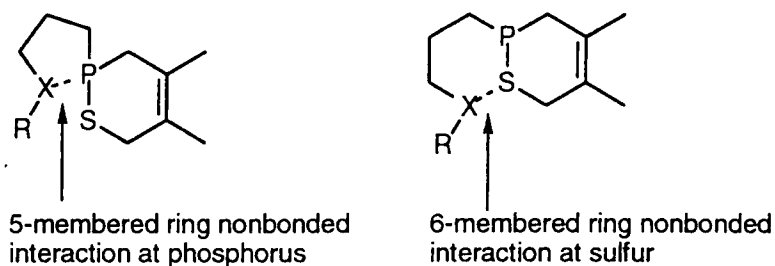
Figure 4.23

4.5.2 SYNTHESIS OF ALKYLTHIOPHOSPHONIC DICHLORIDES

Alkylthiophosphonic dichlorides **161a-b** were identified as suitable precursors. Scheme 4.15 shows a possible retrosynthetic pathway which we devised in order to incorporate readily available and inexpensive starting materials.

X = (a) O
    (b) S
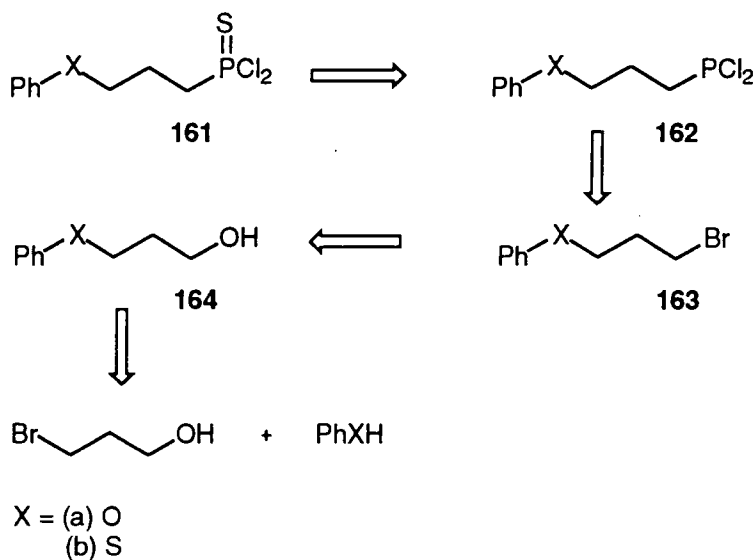
Scheme 4.15

Compounds **163a-b** and **164a-b** were synthesised according to Scheme 4.16.
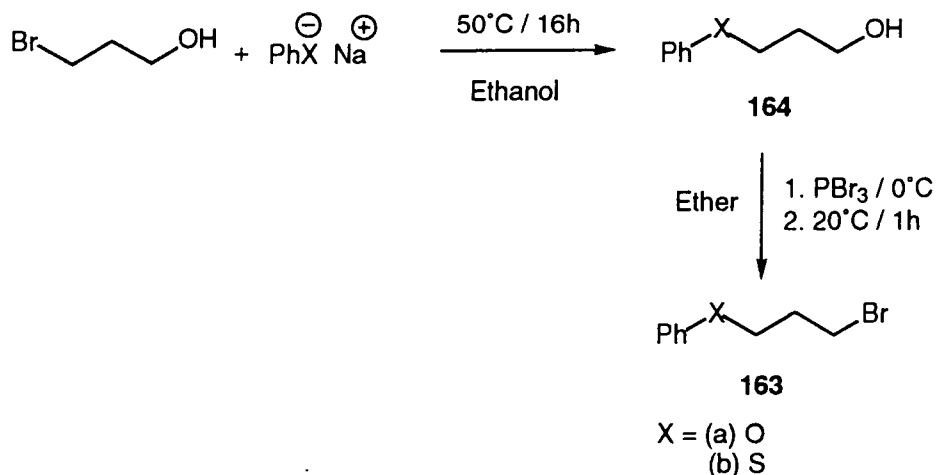
Scheme 4.16

The results of these reactions are listed in Table 4.8.

Table 4.8 Synthesis of compounds **163a-b** and **164a-b**

X	Yield % 163	Yield % 164
O	61	71
S	71	88

Compounds **163a-b** and **164a-b** were obtained as stable clear liquids in good yield. However, due to time constraints the investigation into nonbonded interactions in the chemistry of thioxophosphines was not progressed beyond this point. Had time permitted, we had intended to access compounds **162** by converting compounds **163** into their corresponding Grignard reagents and then reacting with phosphorus trichloride. Assuming that compounds **162** could be synthesised in this manner, we had intended to convert them to compounds **161** by reaction with thiophosphoryl chloride [P(S)Cl₃]. Both of the above are literature procedures.[88]

4.6 CONCLUSIONS

Reactions between an azomethine ylide and thionitroso compounds were investigated, but all were unsuccessful. The reason for this was believed to be a high rate of fragmentation of the thionitroso precursor compounds compared to the fragmentation rate of the azomethine ylide precursor compounds. This had the effect of releasing thionitroso compounds into solution (which presumably dimerised) before any azomethine ylide had been released.

Thionitroso compounds may be generated by fragmentation of *N*-chlorothio-*N*-trimethylsilylamines **40** in the presence of metal fluorides. When thionitroso compounds were reacted with dienes in the presence of metal fluorides, the DA pathway was promoted at the expense of the Ene pathway. This observation was rationalised by postulating an interaction between the metal cation and the thionitroso compound. This interaction was thought to affect the thionitroso compound LUMO in the same manner as a Lewis acid, *i.e.* the LUMO energy was lowered. This resulted in an increase in the rate of the DA reaction (as the diene HOMO and thionitroso LUMO would be brought closer in energy) relative to the rate of the Ene reaction.

In the presence of metal fluorides, the reaction of thionitroso compounds with unsymmetrical dienes (1-methyl-1,3-butadiene and 2-methyl-1,3-butadiene) exhibited a dramatic increase in the regioselectivity. This effect was rationalised by postulating an interaction between the metal cation and the thionitroso nitrogen atom. The metal was assumed to exert an influence on the orbital coefficients of the thionitroso LUMO such that the coefficient on sulfur became larger. As a result of this, there was an increased driving force for production of the major isomer. This rationalisation was entirely consistent with the literature.[83]

A new method for the generation of thionitroso compounds was developed in which potassium fluoride was used to liberate thionitroso compounds by dehydrochlorination of *N*-chlorothioamines **150**. This method is both rapid and utilises simple reagents, it can also tolerate sterically demanding substituents on the nitrogen atom of the thionitroso compound. In this respect it proved to be the only method by which triphenylmethylthionitroso compound **1m'** could be made. The disadvantage of the method lies in the fact that compounds **150** were highly unstable and required rapid and expert manipulation in order for the methodology to be successful.

We have studied the reaction of thioxophosphines with unsymmetrical dienes (1-methyl-1,3-butadiene and 2-methyl-1,3-butadiene), and found that these reactions proceeded with complete regioselectivity. We rationalised our observations in this respect by reasoning that the observed isomer was that whose transition state incurred the least steric interaction between the methyl group of the diene and the substituent on the phosphorus atom of the thioxophosphine.

We initiated a study on nonbonded interactions in the area of thioxophosphine chemistry, and, in preliminary work the necessary precursor compounds **163a-b** and **164a-b** were successfully synthesised. Unfortunately, due to time constraints, our studies were curtailed at this point. However, this is an interesting and unexplored aspect of the chemistry of thioxophosphine intermediates, and there is scope for future work. In principle, the synthesis of compounds **161** and **162** from compounds **163** can be accomplished utilising known literature reactions.[88] Assuming these reactions can be accomplished successfully, it would be interesting to determine whether 1,2-thiaphosphorin heterocycles in which the tricoordinate phosphorus atom is stabilised by the putative nonbonded interaction can be obtained.

Chapter Five

Experimental Procedures and

Analytical Data

5.1 GENERAL PROCEDURES

All operations were carried out under an inert atmosphere (N_2 or Ar, dried by passing through a tower containing P_2O_5) unless otherwise stated. All glassware was dried at 140°C for 12h before use. Solvents were dried by refluxing over an appropriate drying agent prior to use, *i.e.* ether and THF over Na/benzophenone, toluene over lithium aluminium hydride, and acetonitrile over calcium hydride.

Proton NMR spectra were recorded on Brüker AC250 (250.13 MHz), Varian VXR200 (200.06 MHz), and Varian XM400 (399.96 MHz) instruments at ambient temperature in $CDCl_3$ unless otherwise stated. Throughout this work the methylene protons adjacent to nitrogen in 1,2-thiazines are referred to as CH_2N and those adjacent to sulfur as CH_2S. In the Ene adduct the methylene group attached to S is referred to as CH_2S. Where the possibility of ambiguity exists between the methylenes adjacent to sulfur in the 1,2-thiazine and Ene adducts, the methylene group in the Ene adduct is referred to as CH_2S Ene. Carbon-13 and ^{31}P NMR spectra were recorded on the same instruments at 62.90 MHz and 101.26 MHz respectively, in $CDCl_3$ unless otherwise stated. Chemical shifts are quoted in parts per million (ppm) relative to tetramethylsilane (H & C), and 85% H_3PO_3 (P).

Mass spectra were recorded on a VG Analytical 7070E spectrometer employing He as carrier gas. Gas Chromatography coupled with Mass Spectrometry (GCMS) was performed on a Hewlett Packard 5890 Series 2 GC coupled to a VG Trio 1000 mass spectrometer incorporating a 25m x 0.2mm column with a 0.33μm film of methyl silicone as the stationary phase. Mass spectra were recorded in EI and CI mode, where CI mode was used this has been indicated. In CI mode ammonia was employed as the carrier gas.

I.R. spectra were recorded on a Perkin Elmer 1720X F.T. I.R. spectrophotometer as thin films (neat) on rock salt plates.

Column chromatography refers to gravity chromatography on either alumina (Merck, activity 1), or silica (Sorbisil C60, 40-60H), as indicated.

5.2 EXPERIMENTAL PROCEDURES FOR CHAPTER 2

5.2.1 EXPERIMENTAL FOR SECTION 2.1.2

N-Trimethylsilylbenzylamines 109a-j

These compounds were prepared according to a slightly modified literature procedure.[13] Thus, the corresponding amine (8mmol) was taken up in diethyl ether (50ml), and the mixture cooled to 0°C. *n*-Butyl lithium (5.3ml, 8mmol) was added dropwise with stirring, upon completion of addition the mixture was stirred at 0°C for 15mins. Chlorotrimethylsilane (1.1ml, 8mmol) was added dropwise, formation of a white precipitate (lithium chloride) was almost instantaneous. The mixture was then stirred for 16h whilst allowing to warm to ambient temperature. Removal of the precipitate of lithium chloride by filtration under an inert atmosphere, followed by removal of the solvent *in vacuo* afforded the title compounds as stable colourless oils. The conversion was quantitative (I.R. evidence, disappearance of a N-H stretching absorption at *ca.* 3400 cm^{-1}), and the compounds did not require any further purification. If required, purification could be achieved by bulb-to-bulb distillation under high vacuum (Kugelrohr apparatus), typically affording the silylamines in high yield (80-90%).

N-Chlorothio-*N*-trimethylsilylbenzylamines 110a-j

The procedure of Markovskii *et al* was used to synthesise these compounds.[20] Hence, to a stirring solution of the corresponding silylamine (6mmol) at -10°C was added triethylamine (0.85ml, 6mmol), followed by dropwise addition of sulfur dichloride (0.4ml, 6mmol). A yellow/white precipitate of triethylamine hydrochloride formed soon after addition of the sulfur dichloride. The resultant mixture was stirred at -10°C for 0.5h, then allowed to warm to ambient temperature over a period of 1h. The precipitate of triethylamine hydrochloride was removed by pressure filtration (sequentially through No.1 and No.3 sinters) under an inert atmosphere to afford an ethereal solution of compounds **110a-j**. Removal of the ether *in vacuo* yielded the title compounds as highly unstable red/yellow oils with a penetrating odour. The conversion was again quantitative (I.R. evidence, disappearance of a N-H stretching absorption at *ca.* 3430 cm^{-1}), and the compounds were used in the next step without further purification. Indeed, due to the extreme instability of compounds **110a-j**, further analysis was not possible, and it was necessary to perform the next step of the reaction sequence within 0.5h of having produced these compounds, otherwise decomposition occurred.

Adducts of benzylthionitroso compounds (108a-j) with 2,3-dimethyl-1,3-butadiene

To the corresponding *N*-chlorothio-*N*-trimethylsilylbenzylamine **110** (3mmol) was added toluene (50ml) and 2,3-dimethyl-1,3-butadiene (5ml, 0.04mol). The resultant mixture was stirred at 70°C for 16h, upon cooling and removal of the toluene *in vacuo* (1mm Hg), a crude mixture of compounds **111** and **112** was obtained. The ratio of DA adduct **111** to Ene adduct **112** was assessed by integration of the ^{1}H NMR spectrum of the crude product mixture <u>as rapidly as possible</u>. Further purification was made difficult by the speed at which these compounds decomposed [total decomposition after 5h at 20°C being typical (NMR data)]. It was not possible to obtain ^{13}C NMR, elemental analysis or high resolution mass spectra of these compounds due to their instability.

The crude mixtures were subjected to column chromatography (alumina/hexane), this had the effect of significantly cleaning the adduct mixtures (to give yellow oils with a pungent odour), although they still remained impure and decomposed after about 8h. The DA adduct <u>could not</u> be separated from the Ene adduct by column chromatography.

Analytical data for compounds **111a-j** and **112a-g,i** are presented below.

2-Benzyl-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazine 111a

Yield[(a)] 10%; δ_H 1.74 (3H, s, CH$_3$), 1.77 (3H, s, CH$_3$), 3.05 (2H, s, CH$_2$S), 3.32 (2H, s, CH$_2$N), 3.99 (2H, s, CH$_2$), 7.10-7.40 (5H, m, aromatics); MS *m/z* : 219 (M$^+$), (C$_{13}$H$_{17}$NS).

2-(4-Methylbenzyl)-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazine 111b

Yield[(a)] 15%; δ_H 1.57 (3H, s, CH$_3$), 1.77 (3H, s, CH$_3$), 2.45 (3H, s, CH$_3$), 3.06 (2H, s, CH$_2$S), 3.32 (2H, s, CH$_2$N), 4.00 (2H, s, CH$_2$), 7.20-7.60 (4H, m, aromatics)); MS *m/z* : 233 (M$^+$), (C$_{14}$H$_{19}$NS).

2-(4-Methoxybenzyl)-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazine 111c

Yield[(a)] 15%; δ_H 1.75 (3H, s, CH$_3$), 1.80 (3H, s, CH$_3$), 3.05 (2H, s, CH$_2$S), 3.32 (2H, s, CH$_2$N), 3.90 (3H, s, CH$_3$O), 3.95 (2H, s, CH$_2$), 6.80-7.60 (4H, m, aromatics); MS *m/z* : 249 (M$^+$), (C$_{14}$H$_{19}$NOS), 121 (100%, *p*-MeOPhCH$_2$$^+$).

2-(4-Chlorobenzyl)-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazine 111d

Yield[(a)] 20%; δ_H 1.57 (3H, s, CH$_3$), 1.72 (3H, s, CH$_3$), 3.06 (2H, s, CH$_2$S), 3.31 (2H, s, CH$_2$N), 4.01 (2H, s, CH$_2$), 7.20-7.60 (4H, m, aromatics); MS (CI) *m/z* : 254 (M$^+$+ 1, ^{35}Cl), (C$_{13}$H$_{16}$ClNS + H), 142 (100%, *p*-ClPhCH$_2$NH$_2$$^+$).

2-(4-Fluorobenzyl)-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazine 111e

Yield[a] 20%; δ_H 1.56 (3H, s, CH$_3$), 1.70 (3H, s, CH$_3$), 3.04 (2H, s, CH$_2$S), 3.30 (2H, s, CH$_2$N), 3.99 (2H, s, CH$_2$), 6.96-7.30 (4H, m, aromatics); MS *m/z* : 237 (M$^+$), (C$_{13}$H$_{16}$FNS), 109 (100%, *p*-FPhCH$_2$$^+$).

2-(4-Trifluoromethylbenzyl)-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazine 111f

Yield[a] 30%; δ_H 1.58 (3H, s, CH$_3$), 1.71 (3H, s, CH$_3$), 3.08 (2H, s, CH$_2$S), 3.34 (2H, s, CH$_2$N), 4.10 (2H, s, CH$_2$), 7.20-8.00 (4H, m, aromatics); MS *m/z* : 287 (M$^+$), (C$_{14}$H$_{16}$F$_3$NS), 287 (100%, M$^+$).

2-(2-Fluorobenzyl)-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazine 111g

Yield[a] 35%; δ_H 1.63 (3H, s, CH$_3$), 1.79 (3H, s, CH$_3$), 3.10 (2H, s, CH$_2$S), 3.42 (2H, s, CH$_2$N), 4.14 (2H, s, CH$_2$), 7.00-7.40 (4H, m, aromatics); MS *m/z* : 237 (M$^+$), (C$_{13}$H$_{16}$FNS), 109 (100%, *p*-FPhCH$_2$$^+$).

2-(2-Chlorobenzyl)-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazine 111h

Yield[a] 15%; δ_H 1.59 (3H, s, CH$_3$), 1.79 (3H, s, CH$_3$), 3.06 (2H, s, CH$_2$S), 3.36 (2H, s, CH$_2$N), 4.18 (2H, s, CH$_2$), 7.15-7.45 (4H, m, aromatics); MS *m/z* : 253 (M$^+$, ^{35}Cl), (C$_{13}$H$_{16}$ClNS + H), 125 (100%, *o*-ClPhCH$_2$$^+$).

2-(2-Trifluoromethylbenzyl)-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazine 111i

Yield[a] 60%; δ_H 1.57 (3H, s, CH$_3$), 1.79 (3H, s, CH$_3$), 3.08 (2H, s, CH$_2$S), 3.32 (2H, s, CH$_2$N), 4.24 (2H, s, CH$_2$), 7.30-7.80 (4H, m, aromatics); MS *m/z* : 287 (M$^+$), (C$_{14}$H$_{16}$F$_3$NS), 159 (100%, *o*-CF$_3$PhCH$_2$$^+$).

2-(2-Methoxybenzyl)-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazine 111j

Yield[a] 20%; δ_H 1.58 (3H, s, CH$_3$), 1.79 (3H, s, CH$_3$), 3.08 (2H, s, CH$_2$S), 3.29 (2H, s, CH$_2$N), 3.77 (3H, s, CH$_3$O), 4.07 (2H, s, CH$_2$), 6.80-7.40 (4H, m, aromatics); MS *m/z* : 249 (M$^+$), (C$_{14}$H$_{19}$NOS), 121 (100%, *o*-MeOPhCH$_2$$^+$).

N-(Benzyl)-3-methyl-2-methylidene-3-butene-1-sulfenamide 112a

Yield[a] 5%; δ_H 1.84 (3H, s, CH$_3$), 3.19 (2H, s, CH$_2$S), 4.90-5.00 (5H, m, 2 x CH$_2$ + NH), 7.10-7.40 (5H, m, aromatics); MS *m/z* : 219 (M$^+$), (C$_{13}$H$_{17}$NS).

N-(4-Methylbenzyl)-3-methyl-2-methylidene-3-butene-1-sulfenamide 112b

Yield[a] 15%; δ_H 1.78 (3H, s, CH$_3$), 3.19 (2H, s, CH$_2$S), 4.75 (5H, s, 2 x CH$_2$ + NH), 7.10-7.40 (5H, m, aromatics); MS *m/z* : 233 (M$^+$), (C$_{14}$H$_{19}$NS).

N-(4-Methoxybenzyl)-3-methyl-2-methylidene-3-butene-1-sulfenamide 112c

Yield[a] 15%; δ_H 1.85 (3H, s, CH_3), 3.19 (2H, s, CH_2S), 3.90 (3H, s, CH_3O), 3.95 (2H, s, CH_2), 4.78 (5H, s, 2 x CH_2 + NH), 6.80-7.60 (4H, m, aromatics); MS *m/z* : 249 (M^+), ($C_{14}H_{19}NOS$).

N-(4-Chlorobenzyl)-3-methyl-2-methylidene-3-butene-1-sulfenamide 112d

Yield[a] 15%; δ_H 1.78 (3H, s, CH_3), 3.22 (2H, s, CH_2S), 4.00 (2H, s, CH_2), 4.70-5.20 (5H, m, 2 x CH_2 + NH), 7.20-7.60 (4H, m, aromatics). MS (CI) *m/z* : 254 (M^+ + 1), ($C_{13}H_{16}ClNS$ + H), 142 (100%, *p*-$ClPhNH_2^+$).

N-(4-Fluorobenzyl)-3-methyl-2-methylidene-3-butene-1-sulfenamide 112e

Yield[a] 20%; δ_H 1.81 (3H, s, CH_3), 3.19 (2H, s, CH_2S), 3.99 (2H, s, CH_2), 4.99-5.22 (5H, m, 2 x CH_2 + NH), 6.96-7.30 (4H, m, aromatics); MS *m/z* : 237 (M^+), ($C_{13}H_{16}FNS$).

N-(4-Trifluoromethylbenzyl)-3-methyl-2-methylidene-3-butene-1-sulfenamide 112f

Yield[a] 20%; δ_H 1.74 (3H, s, CH_3), 3.22 (2H, s, CH_2S), 4.09 (2H, s, CH_2), 5.00-5.10 (5H, m, 2 x CH_2 + NH), 7.30-7.60 (4H, m, aromatics); MS *m/z* : 287 (M^+), ($C_{14}H_{16}F_3NS$), 159 (100%, *o*-$CF_3PhCH_2^+$).

N-(2-Fluorobenzyl)-3-methyl-2-methylidene-3-butene-1-sulfenamide 112g

Yield[a] 5%; δ_H 1.86 (3H, s, CH_3), 3.22 (2H, s, CH_2S), 4.14 (2H, s, CH_2), 4.90-5.40 (5H, m, 2 x CH_2 + NH), 7.00-7.40 (4H,m,aromatics); MS *m/z* : 237 (M^+), ($C_{13}H_{16}FNS$).

N-(2-Trifluoromethylbenzyl)-3-methyl-2-methylidene-3-butene-1-sulfenamide 112i

Yield[a] 15%; δ_H 1.75 (3H, s, CH_3), 3.21 (2H, s, CH_2S), 4.10 (2H, s, CH_2), 5.00-5.10 (5H, m, 2 x CH_2 + NH), 7.20-8.00 (4H, m, aromatics); MS *m/z* : 287 (M^+), ($C_{14}H_{16}F_3NS$).

Note.

(a) Yield estimated from the ^{1}H NMR spectrum of crude product mixtures by integration of the CH_2S and CH_2N signals, and comparing with the integration of the aromatic protons [this was shown to be a viable method for assessing yields by isolation of an adduct mixture (111i and 112i) and comparing the isolated yield with that estimated from the NMR spectrum].

5.2.2 EXPERIMENTAL FOR SECTION 2.2.2

N-Trimethylsilylbenzylamines 109a-b

These compounds were prepared in the manner described in Section 5.2.1.

N-Chlorothio-*N*-trimethylsilylbenzylamines 110a-b

These compounds were prepared in the manner described in Section 5.2.1.

Reaction of benzylthionitroso compounds 108a and 108b with 2,3-dimethyl-1,3-butadiene at various temperatures

To the corresponding *N*-chlorothio-*N*-trimethylsilylbenzylamine **110** (3mmol) was added toluene (50ml) and 2,3-dimethyl-1,3-butadiene (5ml, 0.04mol). The reaction mixture was then stirred at the temperatures stated in Tables 2.1-2.2 for 16h. Upon cooling and removal of the toluene *in vacuo* (1mm Hg) the ratio of adducts was assessed by integration of the ^{1}H NMR spectrum of the crude product mixture, as before. Analytical data for the adducts was identical to that detailed in Section 5.2.1.

5.2.2.1 EXPERIMENTAL FOR SECTION 2.2.2.1

Reaction of (4-Methylbenzyl)thionitroso compound 108b with 2-methyl-1,3-butadiene

To *N*-chlorothio-*N*-trimethylsilyl(4-methylbenzyl)amine **110b** (3mmol) was added toluene (50ml) and 2-methyl-1,3-butadiene (5ml, 0.04mol). The reaction mixture was then stirred at 70°C for 16h. Upon cooling and removal of the toluene *in vacuo* (1mm Hg) the ^{1}H NMR spectrum showed that no DA or Ene adducts had formed.

Test for retro DA reaction by heating adduct mixture 111b and 112b with 2,3-dimethyl-1,3-butadiene

The adduct mixture (1mmol) was isolated by column chromatography (alumina/hexane). To this was added toluene (50ml) and 2,3-dimethyl-1,3-butadiene (5ml, 0.04mol). The mixture was then heated at 100°C for 16h. Upon cooling and removal of the toluene *in vacuo* (1mm Hg) the ^{1}H NMR spectrum showed that no change in the ratio of DA : Ene adducts had occurred.

5.2.3 EXPERIMENTAL FOR SECTION 2.3.2

N-Trimethylsilylphenethylamine 113

This compound was prepared analogously to the *N*-trimethylsilylamines in Section 5.2.1.

N-Chlorothio-*N*-trimethylsilylphenethylamine 114

This compound was prepared analogously to the *N*-chlorothio-*N*-trimethylsilylamines in Section 5.2.1.

Adducts of phenethylthionitroso compound 115 with 2,3-dimethyl-1,3-butadiene

This reaction was carried out employing a procedure analogous to that detailed in Section 5.2.1, using *N*-chlorothio-*N*-trimethylsilylphenethylamine 114 as the thionitroso precursor.

Analytical data for compounds 116 and 117 are presented below.

2-(Phenethyl)-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazine 116

Yield$^{(a)}$ 5%; $\delta_H^{(b)}$ 1.67 (3H, s, CH_3), 1.73 (3H, s, CH_3), 2.95-3.44 (8H, m, $CH_2S + CH_2N$ + 2 x CH_2), 7.20-7.30 (5H, m, aromatics); MS (CI) *m/z* : 234 (M^++ 1), ($C_{14}H_{19}NS$), 122 ($PhCH_2CH_2NH_3^+$).

N-(Phenethyl)-3-methyl-2-methylidene-3-butene-1-sulfenamide 117

Yield$^{(a)}$ 5%; $\delta_H^{(b)}$ 1.82 (3H, s, CH_3), 2.95-3.44 (6H, m, CH_2S + 2 x CH_2), 4.20-4.23 (5H, m, 2 x CH_2 + NH), 7.20-7.30 (5H, m, aromatics); MS (CI) *m/z* : 234 (M^+ + 1), ($C_{14}H_{19}NS$).

Notes.
(a) Yield estimated from the ^1H NMR spectrum of the crude product mixture.
(b) Poorly resolved spectrum and low yield, combined with overlapping signals in the ^1H NMR spectrum, may be the source of error in peak assignment and integrals.

5.2.3.1 EXPERIMENTAL FOR SECTION 2.3.2.1

Synthesis of Ethyl-(2-amino-2-phenyl)ethanoate 118a

This compound was manufactured by a literature procedure.[69] Hence, 2-amino-2-phenylethanoic acid (3.92g,0.026mol) was added to absolute ethanol (140ml) and $HCl_{(g)}$ (excess) was passed into solution until the acid dissolved completely (after about 5 mins).

The reaction mixture was then heated for 3h at 110°C. After cooling, the ethanol was removed *in vacuo* and the residue was taken up in water (50ml). This solution was neutralised with ammonium hydroxide. The aqueous layer was then extracted with benzene (3 x 30ml) which was separated and dried over magnesium sulfate. Removal of the benzene *in vacuo* followed by vacuum distillation yielded 1.66g (40%, lit.[69] 60%) of compound **118a** bp_{10} 160-162°C (lit.[69] bp_5 114-115°C) as a colorless oil; δ_H 1.22 (3H, t, CH_3, J_{HH} = 8.7Hz), 1.91 (2H, s, NH_2), 4.18 (2H, q, CH_2, J_{HH} = 8.7Hz), 4.61 (1H, s, CH), 7.30-7.45 (5H, m, aromatics); I.R. ν_{max} cm^{-1} 3450, 3400 (NH), 3030, 2900 (CH), 1720 (C=O), 1610 (C=C); MS *m/z* : 106 (100%, $PhCHNH_2^+$), no M^+.

Synthesis of Ethyl-(2-amino-3-phenyl)propanoate 118b
This compound was liberated from its hydrochloride (as purchased) by neutralisation of an aqueous solution with 2M NaOH followed by extraction into ethyl acetate.

N-Trimethylsilylamines 119a-b
These compounds were prepared analogously to the N-trimethylsilylamines in Section 5.2.1, except that triethylamine was employed as base in place of n-butyl lithium.

N-Chlorothio-N-trimethylsilylamines 120a-b
These compounds were prepared analogously to the N-chlorothio-N-trimethylsilylamines in Section 5.2.1.

Adducts of thionitrosoalkanes 121a-b with 2,3-dimethyl-1,3-butadiene
These reactions were carried out employing a procedure analogous to that detailed in Section 5.2.1, utilising compounds **120a-b** as the thionitroso precursors.

Analytical data for compounds **122a-b** are presented below. These compounds were extremely unstable, typically decompositing after 3h at 20°C.

2-(1-Ethoxycarbonyl-1-phenylmethyl)-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazine 122a
Yield[(a)] 10%; δ_H 1.25 (3H, t, CH_3, J_{HH}= 8.7Hz), 1.48 (3H, s, CH_3), 1.59 (3H, s, CH_3), 3.20 (2H, s, CH_2S), 3.44 (2H, s, CH_2N), 4.18 (2H, q, CH_2, J_{HH} = 8.7Hz), 4.70 (1H, s, CH), 7.20-7.50 (5H, m, aromatics); MS *m/z* : not obtainable due to instability.

2-(1-Ethoxycarbonyl-1-benzylmethyl)-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazine 122b
Yield[(a)] 15%; δ_H 1.26 (3H, t, CH_3, J_{HH} = 6.6Hz), 1.58 (3H, s, CH_3), 1.71 (3H, s, CH_3),

3.00 (2H, br s, CH$_2$S), 3.20 (2H, br s, CH$_2$N), 3.95-4.20 (3H, m, CH + CH$_2$), 4.40 (2H, q, CH$_2$, J_{HH} = 6.6Hz) 7.20-7.50 (5H, m, aromatics); MS *m/z* : 305 (M$^+$), (C$_{17}$H$_{23}$NO$_2$S).

Note.

(a) Yield estimated from the ^{1}H NMR spectrum of the crude product mixture.

5.3 EXPERIMENTAL PROCEDURES FOR CHAPTER 3

5.3.1 EXPERIMENTAL FOR SECTION 3.1.2

N-Trimethylsilylamines 123a-e

These compounds were prepared analogously to the *N*-trimethylsilylamines in Section 5.2.1, except that triethylamine was employed as base in place of *n*-butyl lithium.

N-Chlorothio-*N*-trimethylsilylamines 124a-e

These compounds were prepared analogously to the *N*-chlorothio-*N*-trimethylsilylamines in Section 5.2.1.

Adducts of thionitroso compounds 125a-e with 2,3-dimethyl-1,3-butadiene

These reactions were carried out employing a procedure analogous to that detailed in Section 5.2.1, utilising compounds **124a-e** as the thionitroso precursors.

Column chromatography (alumina/hexane) of the crude product mixture afforded compounds **126a-e** as yellow oils in a pure state.

Analytical data for compounds **126a-e** are presented below.

Figure 5.1 shows the convention used in the assignment of ^{13}C NMR resonances in the 1,2-thiazine ring.
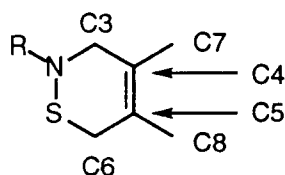
Figure 5.1

High resolution mass spectrometry was employed for accurate analysis of the adducts as all were oils and tended to produce inaccurate elemental analysis. It was found that salts of the adducts **126a-b** (hydrochloride, hydrobromide and oxalate) were unstable and hence unsuitable for elemental analysis. All isolated yields were calculated with reference to starting amine and thus represent the final yield after 3 steps.

2-(2-Phenoxyethyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine 126a

Yield[a] 45%; δ_H 1.54 (3H, s, CH_3), 1.68 (3H, s, CH_3), 2.94 (2H, br s, CH_2S), 3.16 (2H, t, CH_2, J_{HH} = 6.1Hz), 3.46 (2H, br s, CH_2N), 4.11 (2H, t, CH_2, J_{HH} = 6.1Hz), 6.83-7.25 (5H, m, aromatics); δ_C 17.4 (C8), 19.7 (C7), 27.1 (C6), 55.9 (C3), 59.3 (CH_2), 66.6 (CH_2), 122.2 (C5), 124.3 (C4), 114.6, 120.7, 129.4, 158.8; I.R. ν_{max} cm^{-1} 3030, 2950 (CH), 1600 (C=C); MS *m/z* : 249 (M^+), 142 (100%, $PhOCH_2^+$), HRMS: found 249.11771, calc. 249.118736 ($C_{14}H_{19}NOS$).

2-(1-Methyl-2-phenoxyethyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine 126b

Yield[a] 40%; δ_H 1.27 (3H, d, CH_3, J_{HH} = 5.6Hz), 1.62 (3H, s, CH_3), 1.69 (3H, s, CH_3), 2.95 (2H, br q, CH_2S, J_{HH} (AB) = 18Hz), 3.42 (1H, st, CH, J_{HH} = 5.6Hz), 3.54 (2H, br s, CH_2N), 3.80-4.19 (2H, m, CH_2), 6.87-7.31 (5H, m, aromatics); δ_C 17.5 (C8), 17.8 (C7), 20.2 (CH_3), 31.5 (C6), 56.5 (C3), 60.4 (CH), 71.5 (CH_2), 123.8 (C5), 125.9 (C4), 115.1, 121.2, 130.0, 160.0; I.R. ν_{max} cm^{-1} 3030, 2972, 2928 (CH), 1735 (C=C of thiazine), 1599, 1586 (C=C), 1243 (C-O); MS *m/z* : 263 (M^+), 156 (100%, M^+ - $PhOCH_2$), HRMS: found 263.09969, calc. 263.13439 ($C_{15}H_{21}NOS$).

2-(2-Thiophenoxyethyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine 126c

Yield[a] 40%; δ_H 1.55 (3H, s, CH_3), 1.68 (3H, s, CH_3), 2.90 (2H, br s, CH_2S), 3.04 (2H, t, CH_2, J_{HH} = 8.8Hz), 3.17 (2H, t, CH_2, J_{HH} = 8.8Hz), 3.39 (2H, br s, CH_2N), 7.10-7.30 (5H, m, aromatics); δ_C 17.2 (C8), 18.6 (C7), 26.7 (C6), 32.1 (CH_2), 55.6 (C3), 59.1 (CH_2), 122.0 (C5), 124.0 (C4), 125.6, 125.8, 128.7, 153.6; MS *m/z* : 265 (M^+), HRMS: found 265.09457, calc. 265.09589 ($C_{14}H_{19}NS_2$).

2-(3-Thiomethoxypropyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine 126d

Yield[a] 20%; δ_H 1.59 (3H, s, CH_3), 1.75 (3H, s, CH_3), 1.80-1.90 (5H, m, CH_2 + CH_3), 2.56 (2H, t, CH_2, J_{HH} = 7.5Hz), 2.89 (2H, t, CH_2, J_{HH} = 7.5Hz), 2.95 (2H, br s, CH_2S), 3.39 (2H, br s, CH_2N); 14.9 (CH_3), 16.6 (C8), 18.2 (C7), 30.7 (C6), 31.0 (CH_2), 54.4 (CH_2), 58.1 (C3), 67.5 (CH_2), 128.0 (C5), 130.2 (C4); MS *m/z* : HRMS: found 217.09589, calc. 217.09578 ($C_{10}H_{19}NS_2$).

2-(2-Thiomethoxyphenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine 126e

Yield[a] 40%; δ_H 1.72 (3H, s, CH$_3$), 1.82 (3H, s, CH$_3$), 2.42 (3H, s, CH$_3$), 2.92 (2H, br s, CH$_2$S), 3.80 (2H, br s, CH$_2$N), 6.92-7.18 (4H, m, aromatics); δ_C 15.2 (C8), 16.6 (C7), 19.9 (CH$_3$), 29.9 (C6), 57.6 (C3), 125.9 (C5), 127.1 (C4), 120.6, 122.1, 124.2, 124.9, 125.1, 149.1; MS *m/z* : 251 (M$^+$), HRMS: found 251.08020, calc. 251.06460 (C$_{13}$H$_{17}$NS$_2$).

Note.

(a) Isolated yield (from the amine, over 3 steps) for chromatographically pure material.

5.3.1.1 EXPERIMENTAL FOR SECTION 3.1.2.1

Adduct of thionitrosoalkane 125a with (*E,E*)-2,4-hexadiene

This reaction was carried out according to the analogous procedure detailed in Section 5.3.1 for reaction with 2,3-dimethyl-1,3-butadiene, except that (*E,E*)-2,4-hexadiene was used as the diene. Compound **128a** was obtained from the crude reaction mixture by column chromatography (alumina/hexane) as a yellow oil in a pure state.

Analytical data for compound **128a** are presented below.

2-(2-Phenoxyethyl)-3,6-dimethyl-3,6-dihydro-2*H*-1,2-thiazine 128a

Yield 20%; δ_H 1.20 (3H, d, CH$_3$, J_{HH} = 6.7Hz), 1.43 (3H, d, CH$_3$, J_{HH} = 6.7Hz), 3.30-3.50 (3H, m, CHS + CH$_2$), 3.75 (1H, m, CHN), 4.29 (2H, t, CH$_2$, J_{HH} = 6.5Hz), 5.70-5.95 (2H, m, vinylics), 6.90-7.40 (5H, m, aromatics); δ_C 18.1 (CH$_3$), 20.3 (CH$_3$), 27.0 (C6), 55.5 (C3), 58.0 (CH$_2$), 66.5 (CH$_2$), 129.5 (C5), 130.0 (C4), 114.0, 120.0, 129.0; I.R. v_{max} cm^{-1} 3030, 2965, 2925 (C-H), 1600 (C=C); MS *m/z* : 249 (M$^+$), HRMS: found 249.11831, calc. 249.11874 (C$_{14}$H$_{19}$NOS).

5.3.1.2 EXPERIMENTAL FOR SECTION 3.1.2.3

Adduct of thionitrosoalkane 125b with 2-methyl-1,3-butadiene

This reaction was carried out according to the analogous procedure detailed in Section 5.3.1 for reaction with 2,3-dimethyl-1,3-butadiene, except that 2-methyl-1,3-butadiene was used as the diene. Compound **134b** was obtained from the crude reaction mixture by column chromatography (alumina/hexane) as a yellow oil in a pure state.

Analytical data for compound **134b** are presented below.

2-(1-Methyl-2-phenoxyethyl)-5-methyl-3,6-dihydro-2*H*-1,2-thiazine 134b

Yield 10%; δ_H 1.28 (3H, d, CH$_3$, J_{HH} = 6.8Hz), 1.71 (3H, br s, CH$_3$), 2.92 (2H, br q, CH$_2$S, J_{HH} (AB) = 12Hz), 3.46 (1H, st, CH, J_{HH} = 6.8Hz), 3.69 (2H, br s, CH$_2$N), 3.81-4.16 (2H, m, CH$_2$), 5.51 (1H, m, vinylic), 6.89-7.31 (5H, m, aromatics); δ_C 17.0 (CH$_3$), 24.8 (CH$_3$), 30.1 (C6), 51.2 (C3), 60.1 (CH), 71.0 (CH$_2$), 114.5, 120.7, 121.0 (C4), 129.4, 130.5 (C5), 158.8; MS *m/z* : 249 (M$^+$), 142 (100%, M$^+$ - PhOCH$_2$), HRMS: found 249.11843, calc. 249.11874 (C$_{14}$H$_{19}$NOS).

5.3.1.3 EXPERIMENTAL FOR SECTION 3.1.2.4

Attempted generation of thionitroso compounds 136a-e

These reactions were carried out according to the procedure detailed in Section 5.2.1, the salient features of each reaction are summarised below.

o-Methoxythionitrosobenzene 136a and o-Phenoxythionitrosobenzene 136b

The amines **135a-b** were observed to decompose at the silylation step upon addition of the *n*-butyl lithium base, thus preventing further progress.

o-Nitrothionitrosobenzene 136c

The trimethylsilyl group could not be added to amine **135c**.

2-(2,4,6-Tribromophenoxy)thionitrosoethane 136d

Silylation and chlorothiolation of 2-(2,4,6-tribromophenoxy)ethylamine **135d** could not be carried out in diethyl ether due to insolubility. It was possible to perform these reactions using chloroform solvent, but insolubility was still problematical. No adducts corresponding to the trapping of the thionitroso compound with 2,3-dimethyl-1,3-butadiene were observed when attempted generation of thionitroso compound **136d** was performed.

Thionitroso-2-propene 136e

Upon addition of sulfur dichloride to the silylamine, an immediate production of a black colouration was observed. Removal of the ether solvent afforded an intractable viscous material which prevented further progress.

2-(2,4,6-Tribromophenoxy)ethylamine 135d

N-[2-(2,4,6-Tribromophenoxy)ethyl]phthalimide **141** (2.06g, 4.0mmol) was dissolved in ethanol (50ml) and hydrazine hydrate (1ml, 0.02mol) was added dropwise. The resultant mixture was refluxed for 3h, cooled, then 2M HCl (30ml) was added. The mixture was then refluxed for a further 1h. After cooling, the precipitate of 2-(2,4,6-tribromophenoxy) ethylamine hydrochloride was filtered off. To the precipitate 2M NaOH (50ml) was added and the mixture stirred for 0.5h after which the aqueous phase was extracted with diethyl ether (3 x 50ml). The organic phase was washed with brine (30ml) and water (30ml). After separation, the organic phase was dried over magnesium sulfate and the solvent removed *in vacuo* to afford 2-(2,4,6-tribromophenoxy) ethylamine as a white solid (1.10g, 73%), which was used without further purification; mpt 192-193°C; δ_H 1.56 (2H, s, NH$_2$), 3.13 (2H, t, CH$_2$, J_{HH} = 6.0Hz), 4.04 (2H, t, CH$_2$, J_{HH} = 6.0Hz), 7.65 (2H, s, aromatics); δ_C 42.3 (CH$_2$), 75.7 (CH$_2$), 117.4, 118.9, 135.1, 152.6; I.R. v_{max} cm^{-1} 3400, 3350 (NH$_2$), 3030, 2950 (CH), 1600 (C=C); MS m/z : 373 (M$^+$, ^{79}Br), HRMS: found 372.81460 (^{79}Br) calc. 372.81360 (C$_8$H$_8$Br$_3$NO).

N-[2-(2,4,6-Tribromophenoxy)ethyl]phthalimide 141

To a solution of sodium-2,4,6-tribromophenoxide **140** (containing 0.04mol) in DMF (80ml) was added N-(2-bromoethyl)phthalimide **139** (10.0g, 0.04mol), the resultant mixture was stirred at 100°C for 16h. After cooling, water was added until no further precipitate formed. The liquid was decanted from the precipitate, then the precipitate was heated in ethanol for 0.5h at 60°C. Filtration of the cooled reaction mixture afforded N-[2-(2,4,6-tribromophenoxy)ethyl]phthalimide **141** (8.30g, 41%) as a pale tan powder; mpt 133-134°C; δ_H 4.16 (2H, t, CH$_2$, J_{HH} = 4.3Hz), 4.30 (2H, t, CH$_2$, J_{HH} = 4.7Hz), 7.80 (2H, s, aromatics), 7.78-7.90 (4H, m, aromatics); δ_C 38.2 (CH$_2$), 70.7 (CH$_2$), 118.4, 119.5, 123.7, 133.1, 135.9, 152.9, 168.6, 206.0; Analysis : (Found C, 38.0; H, 1.9; N, 2.8; Br, 45.7%; required for C$_{16}$H$_{10}$Br$_3$NO$_3$ C, 38.1; H, 2.0; N, 2.8; Br, 47.5%).

N -(2-Bromoethyl)phthalimide 139

This compound was prepared according to a literature procedure.[89] Compound **139** was obtained as a white solid spectroscopically pure (24.74g, 88%, lit.[89] 72.3%), Mpt 68-69°C (lit.[89] 73-75°C).

5.3.2 EXPERIMENTAL FOR SECTION 3.2.2

Reaction of 1,2-thiazines 126a and 3e with H_2O

The corresponding 1,2-thiazine (0.045mmol) was taken up in THF (5ml), this solution was added to water (5ml) and the mixture stirred for 1h, (the THF serves to make the water and the 1,2-thiazine miscible). Upon completion of stirring the THF was removed *in vacuo* (1mm Hg) to leave an imiscible oil/water mixture which was then extracted with chloroform (3 x 5ml). After separation of the organic layer and drying over magnesium sulfate the chloroform was removed *in vacuo* to yield a crude product which was analysed.

Found : both compounds **126a** and **3e** remained unchanged.

Reaction of 1,2-thiazines 126a and 3e with $HCl_{(aq)}$

The corresponding 1,2-thiazine (0.045mmol) was taken up in THF (5ml), this solution was added to 2M HCl (5ml) and the mixture stirred for 1h, (the THF serves to make the aqueous phase and the 1,2-thiazine miscible). Upon completion of stirring, the THF was removed *in vacuo* (1mm Hg) to leave an imiscible emulsion which was then extracted with chloroform (3 x 5ml). After separation of the organic layer and drying over magnesium sulfate, the chloroform was removed *in vacuo* to yield a crude product which was analysed.

Found : **126a** remained unchanged, **3e** decomposed.[a]

Reaction of 1,2-thiazines 126a and 3e with $NaOH_{(aq)}$

The corresponding 1,2-thiazine (0.59mmol) was taken up in THF (5ml), this solution was added to 2M NaOH (5ml) and the mixture stirred for 1h, (the THF serves to make the aqueous phase and the 1,2-thiazine miscible). Upon completion of stirring, the THF was removed *in vacuo* (1mm Hg) to leave an imiscible emulsion which was then extracted with chloroform (3 x 5ml). After separation of the organic layer and drying over magnesium sulfate, the chloroform was removed *in vacuo* to yield a crude product which was analysed.

Found : **126a** remained unchanged, **3e** partial decomposition.[b]

Reaction of 1,2-thiazine 3e with sodium thiomethoxide

Compound **3e** (0.13g, 0.59mmol) was dissolved in dichloromethane (30ml) and to this solution sodium thiomethoxide (0.04g, 0.59mmol) was added. The mixture was stirred at 20°C for 14h. Upon completion of stirring, methanol (10ml) was added to the solution and the mixture stirred for 0.5h. Removal of the volatile materials *in vacuo* followed by

column chromatography (alumina/hexane) afforded the crude product which was analysed.

Found : partial decomposition.[b]

Notes.

(a) Decomposed means that the product of the reaction contained no unreacted starting material and could not be identified by ^{1}H NMR and MS (even after work-up by chromatography, if possible). Usually a multitude of compounds were produced, amines, azo compounds and sulfur amongst them.

(b) Partial decomposition indicates that not all the starting material had reacted, but that which did had decomposed to an unidentifiable mixture.

5.3.3 EXPERIMENTAL FOR SECTION 3.2.3

Reaction of 1,2-thiazines 126a and 3e with Br$_2$

The corresponding 1,2-thiazine (1.8mmol) was dissolved in carbon tetrachloride (30ml) and the mixture cooled to -20°C. Bromine (0.1ml, 1.8mmol) was added dropwise and the mixture was stirred for 2h whilst allowing to come to 20°C. The carbon tetrachloride was removed *in vacuo* (1mm Hg) and the crude residue analysed.

Found : both compounds 126a and 3e decomposed.

Reaction of 1,2-thiazines 126a and 3e with HBr

The corresponding 1,2-thiazine (1.8mmol) was dissolved in diethyl ether (30ml) and the mixture cooled to 0°C. HBr (0.47g, 1.8mmol) (30% w/w solution of HBr in acetic acid) was added dropwise to the stirring mixture in the dark. Upon completion of addition the mixture was allowed to come to 20°C over 3h. The mixture was then washed with aqueous potassium hydrogen carbonate (3 x 15ml) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded the crude product.

Found : 126a remained unchanged, 3e decomposed.

Reaction of 1,2-thiazine 126a with N-bromosuccinimide (NBS)

Compound 126a (0.22g, 0.87mmol) was dissolved in carbon tetrachloride (15ml) and NBS (0.16g, 0.87mmol) was added. The resultant mixture was stirred at 20°C for 16h. Removal of the solids by filtration followed by removal of the solvent *in vacuo* afforded a crude black residue. Column chromatography (alumina using gradient elution from hexane, hexane : dichloromethane (1 : 1), to pure dichloromethane) afforded a dark oil.

Found : decomposed.

Reaction of 1,2-thiazines 126a and 3e with *m*-chloroperoxybenzoic acid (mCPBA)

The corresponding 1,2-thiazine (0.84mmol) was dissolved in dichloromethane (30ml) and cooled to 0°C. mCPBA (1.7mmol, 2eq.) was added followed by potassium hydrogen carbonate (0.18g, 1.7mmol) and the mixture stirred for 2h whilst allowing to come to 20°C. For adduct **3e** the colour was seen to change from yellow/orange to deep red then back to orange over the course of the reaction. After 2h the mixture was washed with potassium hydrogen carbonate (2 x 20ml) and the organic phase dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded the product.

Found : **126a** remained unchanged, **3e** afforded a 3 : 1 mixture of compounds **142** and **143** in combined yield of 80% (addition of excess mCPBA produced only compound **142**, attempts to oxidise compound **3e** with periodate caused decomposition).

Analytical data for compounds **142** and **143** are presented below.

2-(4-Methylphenyl)-4,5-dimethyl-4,5-epoxy-3,6-dihydro-*2H*-1,2-thiazine-1,1-dioxide 142

Yield 60%; δ_H 1.31 (3H, s, CH_3), 1.45 (3H, s, CH_3), 2.25 (3H, s, CH_3), 3.28 (2H, q, CH_2S, J_{HH} (AB) = 14Hz), 3.99 (2H, q, CH_2N, J_{HH} (AB) = 16Hz), 6.85-8.12 (4H, m, aromatics); MS *m/z* : 267 (M$^+$), ($C_{13}H_{17}NO_3S$).

2-(4-Methylphenyl)-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazine-1,1-dioxide 143

Yield 20%; δ_H 1.67 (3H, s, CH_3), 1.70 (3H, s, CH_3), 2.23 (3H, s, CH_3), 3.45 (2H, br s, CH_2S), 4.10 (2H, br s, CH_2N), 6.85-8.12 (4H, m, aromatics); MS *m/z* : 251 (M$^+$), ($C_{13}H_{17}NO_2S$).

5.3.4 EXPERIMENTAL FOR SECTION 3.2.4

Reaction of 1,2-thiazines 126b-c with *n*-butyl lithium and methyl iodide

The corresponding 1,2-thiazine (2.4mmol) was dissolved in THF (10ml) and the mixture cooled to -78°C. *n*-Butyl lithium (3ml, 4.8mmol, 1.6M in hexane) was added dropwise, a colour change from yellow to deep red accompanied the addition. Upon completion of addition the mixture was stirred at -78°C for 5mins, then methyl iodide (0.3ml, 4.8mmol) was added dropwise. A colour change from deep red to pale orange was observed. After stirring for a further 0.5h at -78°C the reaction was allowed to come to 20°C over 2h. When stirring was complete the excess base was removed by quenching with distilled water (2ml). The water was decanted from the mixture and extracted with dichloromethane (2 x 3ml), the organic layer was then combined with the original THF

solution. Removal of the THF and dichloromethane *in vacuo* afforded a yellow oil. Column chromatography (alumina/dichloromethane) afforded a pale yellow oil which was stable in air but decomposed on heating.

Analytical data for compounds **144b-c** are presented below.

_N_-Methyl-_N_-(1-methyl-2-phenoxyethyl)-4-butylthio-2,3-dimethyl-2-butenamine 144b
Yield 42%; δ_H 0.90 (3H, t, CH_3, J_{HH} = 6.2Hz), 1.14 (3H, d, CH_3, J_{HH} = 6.2Hz), 1.20-1.60 (4H, m, 2 x CH_2), 1.74 (3H, s, CH_3), 1.79 (3H, s, CH_3), 2.26 (3H, br s, NCH_3), 2.43 (2H, t, CH_2, J_{HH} = 7.5Hz), 3.17 (3H, m, CH + CH_2), 3.39 (2H, br s, CH_2), 3.80-4.10 (2H, m, CH_2), 6.90-7.40 (5H, m, aromatics); δ_C 12.0, 13.7, 18.0, 18.8, 22.1 (CH_3N), 30.1, 31.8 (CH_2S), 31.9, 37.2, 55.9 (CH_2N), 69.6, 114.5, 120.8 (C3 butene), 121.0 (C2 butene), 129.4; I.R. ν_{max} cm^{-1} 3030, 2958, 2928 (CH), 1730 (C=C of butene), 1599, 1586 (C=C), 1243 (C-O); MS (CI) *m/z* : 336 (M^+ + 1), 336 (100%, M^+ + 1); HRMS: found 335.22820, calc. 335.22829 ($C_{20}H_{33}NOS$).

_N_-Methyl-_N_-(2-thiophenoxyethyl)-4-butylthio-2,3-dimethyl-2-butenamine 144c
Yield 20%; δ_H 0.90 (3H, t, CH_3, J_{HH} = 7.5Hz), 1.21-1.54 (4H, m, 2 x CH_2), 1.72 (3H, s, CH_3), 1.80 (3H, s, CH_3), 2.20 (3H, br s, NCH_3), 2.57 (2H, t, CH_2, J_{HH} = 7.5Hz), 2.96 (2H, br s, CH_2), 3.01 (2H, t, CH_2, J_{HH} = 7.5Hz), 3.23 (2H, br s, CH_2), 3.50 (2H, t, J_{HH} = 7.5Hz), 7.26-7.34 (5H, m, aromatics); δ_C 13.1, 14.5, 17.3, 18.0 (CH_3N), 21.5, 31.1, 31.4, 35.0 (CH_2S), 41.5, 55.6 (CH_2N), 59.4, 120.8 (C3 butene), 121.6 (C2 butene), 125.2, 128.3, 129.4, 136.2; MS (CI) *m/z* : 338 (M^+ + 1), 338 (100%, M^+ + 1); HRMS: found 338.15737, calc. 338.19762 ($C_{19}H_{31}S_2$ + H).

5.3.5 SYNTHESIS OF STARTING MATERIALS

The following details the synthesis of materials which were required in the course of our investigations which could not be obtained from chemical suppliers.

2-Thiophenoxyethylamine - parent amine of thionitroso compound 125c
This compound was prepared by a simple procedure such that thiophenol (5.0ml, 0.049mol) was dissolved in acetonitrile (150ml) and cooled to 0°C with stirring. To the stirring solution was added sodium (1.12g, 0.049mol) portionwise. The mixture was allowed to come to 20°C over 1h and stirring continued until the sodium had dissolved (3h). Bromoethylamine hydrobromide (10.0g, 0.049mol) was then added portionwise and the resultant mixture stirred at 50°C for 16h. After this time the acetonitrile was removed

in vacuo (1mm Hg) and the remaining solid residue was taken up in 2M HCl (60ml). The aqueous mixture was washed with dichloromethane (3 x 30ml) to remove unreacted organic material, then the aqueous phase was made basic by addition of 2M NaOH. The resultant aqueous mixture was then extracted with dichloromethane (3 x 50ml) and the organic phase separated and dried over magnesium sulfate. Removal of the dichloromethane *in vacuo* afforded 2-thiophenoxyethylamine as a colorless oil (5.90g, 82%) that was unstable to heat, and was used without further purification; δ_H 1.55 (2H, s, NH_2), 2.68-2.88 (4H, m, 2 x CH_2), 7.00-7.25 (5H, m, aromatics); δ_C 37.6 (CH_2), 40.5 (CH_2), 125.4, 128.6, 129.3, 135.4; I.R. ν_{max} cm^{-1} 3365, 3290 (NH_2), 3070, 2920, 2860 (CH), 1600 (C=C); MS *m/z* : 153 (M$^+$), HRMS: found 153.05587, calc. 153.06122 ($C_8H_{11}NS$).

5.3.6 EXPERIMENTAL FOR SECTION 3.3

5.3.6.1 REDUCED TEMPERATURE ^{1}H NMR SPECTROSCOPY

The spectra were obtained on a Varian XM400 spectrometer with acquisition parameters as follows; Frequency 399.964 MHz; Spectral width 5000.0 Hz; Acquisition time 3.744 s; Relaxation delay 0.000 s; Pulse width 3.2 µs; Repetitions 64.

For compound **3k'** spectra were recorded at 20°C and -50°C in CDCl$_3$.

For compounds **126a** and **126e** spectra were recorded at 20°, -10°, -30°, -50°, -70° and -90°C in CD$_2$Cl$_2$.

5.3.6.2 NUCLEAR OVERHAUSER ENHANCEMENT SPECTROSCOPY

The spectra for compounds **126e** and **3l'** were obtained on a Varian XM400 spectrometer in CDCl$_3$ at 20°C with acquisition parameters as follows; Frequency 399.964 MHz; Spectral width 10000.0 Hz; Acquisition time 3.744 s; Relaxation delay 0.100 s; Pulse width 9.8 µs; Repetitions 256; Line broadening 0.3 Hz.

5.4 EXPERIMENTAL PROCEDURES FOR CHAPTER 4

5.4.1 EXPERIMENTAL FOR SECTION 4.1.2.

N-Benzyl-N-cyanomethyl-N-trimethylsilylmethylamine 145

This compound was prepared according to a literature procedure.[90] Yield 88% (lit.[90] 53%); δ_H 0.09 (9H, s, 3 x CH_3), 2.13 (2H, s, CH_2), 3.33 (2H, s, CH_2), 3.56 (2H, s, CH_2), 7.26-7.28 (5H, m, aromatics); [lit.[90] δ_H 0.10 (9H, s, 3 x CH_3), 2.00 (2H, s, CH_2), 3.78 (2H, s, CH_2), 7.28 (5H, s, aromatics)].

N-Chlorothio-N-trimethylsilylamines 40c,e

These compounds were prepared analogously to the N-chlorothio-N-trimethylsilylamines in Section 5.2.1.

Reaction of thionitroso compounds 1c,e with azomethine ylide 146

To the corresponding N-chlorothio-N-trimethylsilylbenzylamine **40c,e** (3mmol) was added sequentially acetonitrile (50ml), N-benzyl-N-cyanomethyl-N-trimethylsilylmethylamine **145** (0.7g, 3mmol), and silver (I) fluoride (0.8g, 6mmol). The resultant mixture was stirred in the dark [silver (I) fluoride is light sensitive] for 16h. Removal of the solvent *in vacuo* followed by extraction into hexane and filtration [to remove the combined precipitates of silver (I) chloride and silver (I) cyanide] afforded the products of the reaction in hexane. Upon removal of the hexane *in vacuo* compound **145** was recovered unchanged (*ca.* 80%) along with a number of other compounds amongst which were sulfur and diazoarenes. No evidence for the formation of 1,2,4-thiadiazines **147c,e** was found.

5.4.2 EXPERIMENTAL FOR SECTION 4.2.2

5.4.2.1 EXPERIMENTAL FOR SECTION 4.2.2.1.

N-Chlorothio-N-trimethylsilylamines 40c,e,k'-l'

These compounds were prepared analogously to the N-chlorothio-N-trimethylsilylamines in Section 5.2.1.

Adducts of thionitroso compounds 1c,e,k'-l' with 2,3-dimethyl-1,3-butadiene in the presence of silver (I) fluoride

To the corresponding *N*-chlorothio-*N*-trimethylsilylbenzylamine **40** (3mmol) was added sequentially acetonitrile (50ml), 2,3-dimethyl-1,3-butadiene (5ml, 0.04mol), and silver (I) fluoride (0.4g, 3mmol, which had been dried by heating to 50°C for 1h under 1mmHg vacuum). The reaction mixture was then stirred <u>in the dark</u> at 20°C for 16h. The silver (I) chloride formed during the reaction was removed by filtration, and the acetonitrile solvent was removed *in vacuo* (1mm Hg). The ratio of adducts was assessed by integration of the ^{1}H NMR spectrum of the crude product mixture <u>as rapidly as possible</u>. Purification could be effected by taking up the remaining residue (produced upon removal of the acetonitrile) in hexane (10ml) and immediately subjecting it to column chromatography (alumina/hexane). Removal of the solvent *in vacuo* afforded the products as yellow oils with an unpleasant odour which were stable for about 2 days at 20°C.

Analytical data for compounds **3c,e,k'-l'** and **12c,e** are presented below. Yields are quoted with respect to starting amine.

2-(4-Bromophenyl)-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazine 3c

Yield[a] 87% (lit.[13] 50%); δ_H[b] 1.72 (6H, s, 2 x CH$_3$), 2.96 (2H, br s, CH$_2$S), 3.92 (2H, br s, CH$_2$N), 7.03-7.34 (4H, m, aromatics); δ_C 17.0 (CH$_3$), 19.6 (CH$_3$), 30.6 (C6), 54.7 (C3), 112.9, 120.2, 124.2 (C5), 124.6 (C4), 131.5, 150.4.

2-(4-Methylphenyl)-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazine 3e

Yield[a] 78% (lit.[13] 55%); δ_H[b] 1.70 (6H, s, 2 x CH$_3$), 2.25 (3H, s, CH$_3$), 2.90 (2H, br s, CH$_2$S), 3.90 (2H, br s, CH$_2$N), 7.10-7.90 (4H, m, aromatics); δ_C 16.9 (CH$_3$), 19.6 (CH$_3$), 20.5 (CH$_3$), 30.6 (C6), 55.1 (C3), 118.7, 122.7, 124.0, 124.8, (C5) 129.2 (C4), 129.4, 148.9.

2-(Diphenylmethyl)-4,5-dimethyl-3,6-dihydro-*2H*-1,2-thiazine 3k'

Yield[a] 24%; δ_H 1.51 (3H, s, CH$_3$), 1.84 (3H, s, CH$_3$), 2.96 (2H, br s, CH$_2$S), 3.45 (2H, br s, CH$_2$N), 5.10 (1H, s, CH), 7.20-7.60 (10H, m, aromatics); δ_C 17.9 (CH$_3$), 20.2 (CH$_3$), 28.5 (C6), 56.5 (C3), 72.6 (CH), 122.9 (C5), 124.7 (C4), 127.7, 128.1, 128.6, 129.0, 143.7, 143.9; MS *m/z* : 295 (M$^+$), 167 (100%, Ph$_2$CH$^+$), HRMS: found 295.13264, calc. 295.13947 (C$_{19}$H$_{21}$NS).

±2-(1-Methylbenzyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine 3l'

Yield[a] 30% (lit.[66] 20%); δ_H[c] 1.55 (3H, s, CH$_3$), 1.59 (3H, d, CH$_3$, J_{HH} = 7.4Hz), 1.79 (3H, s, CH$_3$), 2.57 and 3.25 (2H, dd, CH$_2$S, J_{HH} (AB) = 16.4Hz), 3.03 and 3.53 (2H, dd, CH$_2$N, J_{HH} (AB) = 17.6Hz), 4.02 (1H, q, CH, J_{HH} = 7.4Hz), 7.20-7.35 (5H, m, aromatics); δ_C 17.5 (CH$_3$), 19.7 (CH$_3$), 23.2 (CH$_3$), 28.4 (C6), 56.0 (C3), 62.0 (CH), 122.6 (C5), 124.6 (C4), 126.3, 127.2, 128.4, 145.0; MS (CI) *m/z* : 234 (M$^+$ + 1), (C$_{14}$H$_{19}$NS), 122 (100%, PhCH(CH$_3$)$^+$).

Notes.

(a) Isolated yield (over 3 steps) for chromatographically pure material.

(b) Data consistent with the literature.[13]

(c) Data consistent with the literature except in the assignment of the CH$_2$S and CH$_2$N signals, here the literature was proved incorrect (by an NOE experiment detailed in Section 3.3.3.3).[66]

N-(4-Bromophenyl)-3-methyl-2-methylidene-3-butene-1-sulfenamide 12c[a]

δ_H[b] 3.38 (2H, s, CH$_2$S), 4.90-5.10 (5H, m, 2 x CH$_2$ + NH).

N-(4-Methylphenyl)-3-methyl-2-methylidene-3-butene-1-sulfenamide 12e[a]

δ_H[b] 3.40 (2H, s, CH$_2$S), 4.95-5.10 (5H, m, 2 x CH$_2$ + NH).

Notes.

(a) Due to the very low concentration of these compounds their presence could be detected only in the ^{1}H NMR spectrum.

(b) Data consistent with the literature.[13]

5.4.2.2 EXPERIMENTAL FOR SECTION 4.2.2.2.

The experiments involving caesium fluoride and potassium fluoride were carried out exactly as described in Section 5.4.2.1 except that caesium or potassium fluorides (dried as before) were used in place of silver (I) fluoride. Analysis of compounds **3c,e** and **12c,e** was exactly as described in Section 5.4.2.1.

5.4.3 EXPERIMENTAL FOR SECTION 4.2.3

5.4.3.1 EXPERIMENTAL FOR SECTION 4.2.3.2

N-Chlorothio-N-trimethylsilylamines 40c,e-f

These compounds were prepared analogously to the N-chlorothio-N-trimethylsilylamines in Section 5.2.1.

Adducts of thionitroso compounds 1c,e-f with 2-methyl-1,3-butadiene in the presence of silver (I) fluoride

These reactions were carried out employing a procedure analogous to that detailed in Section 5.4.2.1, utilising compounds **40c,e-f** as the thionitroso precursors, and 2-methyl-1,3-butadiene as the trap.

Analytical data for compounds **13c,e-f** and **14c,e-f** are presented below.

2-(4-Bromophenyl)-4-methyl-3,6-dihydro-2H-1,2-thiazine 13c[a]

δ_H[b] 3.10 (2H, br s, CH$_2$S), 3.96 (2H, br s, CH$_2$N). 5.72 (1H, br s, CH).

2-(4-Methylphenyl)-4-methyl-3,6-dihydro-2H-1,2-thiazine 13e[a]

δ_H 1.66 (3H, s, CH$_3$), 3.10 (2H, br s, CH$_2$S), 3.95 (2H, br s, CH$_2$N).

2-(4-Methoxyphenyl)-4-methyl-3,6-dihydro-2H-1,2-thiazine 13f[a]

δ_H[b] 3.02 (2H, br s, CH$_2$S), 3.98 (2H, br s, CH$_2$N). 5.80 (1H, br s, CH).

Notes.

(a) Due to the very low concentration of these compounds their presence could be detected only in the ^{1}H NMR spectrum.

(b) Data consistent with the literature.[13]

2-(4-Bromophenyl)-5-methyl-3,6-dihydro-2H-1,2-thiazine 14c

Yield[a] 20% (lit.[13] 65%); δ_H[b] 1.72 (3H, s, CH$_3$), 2.93 (2H, br s, CH$_2$S), 4.07 (2H, br s, CH$_2$N). 5.59 (1H, br s, CH), 7.02-7.48 (4H, m, aromatics).

2-(4-Methylphenyl)-5-methyl-3,6-dihydro-2H-1,2-thiazine 14e

Yield[a] 40%; δ_H 1.72 (3H, s, CH$_3$), 2.27 (3H, s, CH$_3$), 2.92 (2H, br s, CH$_2$S), 4.06 (2H, br s, CH$_2$N), 5.58 (1H, s, CH), 7.01-7.13 (4H, m, aromatics); δ_C 20.4 (CH$_3$), 24.5 (CH$_3$),

29.8 (C6), 50.7 (C3), 118.7, 120.0 (C4), 122.7 (C5), 129.4, 131.7, 148.9; MS *m/z* : 205 (M$^+$), 137 (100%, 4-MePhNS$^+$), HRMS: found 205.09106, calc. 205.09252 (C$_{12}$H$_{15}$NS).

2-(4-Methoxyphenyl)-5-methyl-3,6-dihydro-*2H*-1,2-thiazine 14f

Yield[a] 42% (lit.[13] 60%); δ_H[b] 1.75 (3H, s, CH$_3$), 2.92 (2H, br s, CH$_2$S), 3.77 (3H, s, CH$_3$), 4.03 (2H, br s, CH$_2$N), 5.60 (1H, br s, CH), 6.77-7.26 (4H, m, aromatics).

Notes.

(a) Isolated yield (over 3 steps) for chromatographically pure material.

(b) Data consistent with the literature.[13]

5.4.3.2 EXPERIMENTAL FOR SECTION 4.2.3.3

N-Chlorothio-*N*-trimethylsilylamines 40c,f

These compounds were prepared analogously to the *N*-chlorothio-*N*-trimethylsilylamines in Section 5.2.1.

Adducts of thionitroso compounds 1c,f with *cis/trans* 1-methyl-1,3-butadiene in the presence of silver (I) fluoride

These reactions were carried out employing a procedure analogous to that detailed in Section 5.4.2.1, utilising compounds **40c,f** as the thionitroso precursors, and *cis/trans* 1-methyl-1,3-butadiene as the trap.

Analytical data for compounds **24c,f** and **25c,f** are presented below.

(3-*RS*)-2-(4-Bromophenyl)-3-methyl-3,6-dihydro-*2H*-1,2-thiazine 24c[a]

Yield[a] 40% (lit.[66] 70%); δ_H[b] 1.48 (3H, d, CH$_3$, J_{HH} = 7.9Hz), 2.42 and 2.51 (2H, dd, CH$_2$S, J_{HH} (AB) = 6.98Hz), 4.00-4.05 (1H, m, CHN), 5.70-6.10 (2H, m, CH), 7.07-7.35 (4H, m, aromatics); δ_C 19.6 (CH$_3$), 25.4 (C6), 51.7 (C3), 112.2, 119.7, 123.4 (C5), 123.5 (C4), 130.7, 150.1; MS (CI) *m/z* : 271 (M$^+$+ 1, ^{81}Br), (C$_{11}$H$_{11}$BrNS), 173 (100%, 4-BrPhNH$_2^+$, ^{81}Br).

(3-*RS*)-2-(4-Methoxyphenyl)-3-methyl-3,6-dihydro-*2H*-1,2-thiazine 24f[a]

Yield[a] 30% (lit.[66] 70%); δ_H[b] 1.45 (3H, d, CH$_3$, J_{HH} = 7.2Hz), 2.38 and 2.46 (2H, dd, CH$_2$S, J_{HH} (AB) = 6.38Hz), 3.74-3.80 (1H, m, CHN), 3.82 (3H, s, CH$_3$O), 5.80-6.10 (2H, m, CH), 6.80-7.20 (4H, m, aromatics); δ_C 21.0 (CH$_3$), 24.9 (C6), 53.2 (C3), 55.0 (CH$_3$O), 114.0, 121.5, 124.3 (C5), 124.7 (C4), 131.9, 139.9.

Notes.

(a) Isolated yield (over 3 steps) for chromatographically pure material.

(b) Data consistent with the literature.[66]

(6-*RS*)-2-(4-Bromophenyl)-6-methyl-3,6-dihydro-2*H*-1,2-thiazine 25c[a]

δ_H 1.20 (3H, d, CH$_3$, J_{HH} = 7.9Hz).

(6-*RS*)-2-(4-Methoxyphenyl)-6-methyl-3,6-dihydro-2*H*-1,2-thiazine 25f[a]

δ_H 1.20 (3H, d, CH$_3$, J_{HH} = 7.2Hz).

Note.

(a) Due to the very low concentration of these compounds their presence could be detected only in the ^{1}H NMR spectrum.

5.4.4 EXPERIMENTAL FOR SECTION 4.3.2

N-Chlorothioamines 150k,k',m'

The corresponding amine was taken up in diethyl ether (50ml) and the mixture cooled to -10°C. Triethylamine (0.42ml, 3mmol) was added, followed by dropwise addition of sulfur dichloride (0.21ml, 3mmol). A white precipitate of triethylamine hydrochloride formed almost immediately on addition of the sulfur dichloride. When all the sulfur dichloride had been added, the temperature was brought to 20°C over 0.5h. Removal of the precipitate of triethylamine hydrochloride (*via* pressure filtration through a sinter under Ar), followed by removal of the solvent *in vacuo*, afforded the products as unstable red/yellow oils that were used immediately without further purification due to their instability. (These compounds must be used in the next step within 0.5h of being prepared).

Generation of thionitroso compounds 1k,k',m' from compounds 150, and their subsequent interception with 2,3-dimethyl-1,3-butadiene

The corresponding N-chlorothioamine **150** (3mmol) was taken up in acetonitrile (30ml), 2,3-dimethyl-1,3-butadiene (5ml, excess) and anhydrous potassium fluoride (0.2g, 3mmol) were added sequentially and the resultant mixture stirred at 20°C for 16h. After this period the solvent was removed *in vacuo* to afford a crude residue, this was taken up in hexane (15ml) and subjected to column chromatography (alumina/hexane) to afford the products.

Analytical data for compounds **3k,m'** and **12k** are presented below (data for **3k'** may be found in Section 5.4.2.1)

2-(2-Bromophenyl)-4,5-dimethyl-3,6-dihydro-2H-1,2-thiazine 3k

Yield[a] 30% (lit.[66] 66%); δ_H[b] 1.71 (3H, s, CH$_3$), 1.76 (3H, s, CH$_3$), 2.92 (2H, br s, CH$_2$S), 3.81 (2H, br s, CH$_2$N), 6.90-7.60 (4H, m, aromatics); δ_C 17.9 (CH$_3$), 20.0 (CH$_3$), 30.0 (C6), 57.5 (C3), 113.9, 122.2 (C5), 125.3 (C4), 127.5, 128.5, 132.6, 143.1.

2-(Triphenylmethyl)-4,5-dimethyl-3,6-dihydro-2H-1,2-thiazine 3m'

Yield 24%; δ_H 1.40 (3H, s, CH$_3$), 1.45 (3H, s, CH$_3$), 2.69 (2H, br s, CH$_2$S), 3.42 (2H, br s, CH$_2$N), 7.00-7.60 (15H, m, aromatics); δ_C 17.9 (CH$_3$), 19.5 (CH$_3$), 33.8 (C6), 54.0 (C3), 79.0 (4° C aliphatic), 122.9 (C5), 126.0 (C4), 126.3, 126.7, 127.0, 127.4, 127.8, 128.8, 129.0, 129.2, 143.6; MS (CI) m/z : 244 (Ph$_3$C$^+$ + H), no M$^+$ observed due to the high stability of the daughter fragment at m/z 244 .

N-(2-Bromophenyl)-3-methyl-2-methylidene-3-butene-1-sulfenamide 12k[c]

δ_H 3.35 (2H, br s, CH$_2$S).

Notes.

(a) Isolated yield (over 3 steps).

(b) Data consistent with the literature.[66]

(c) Due to the very low concentration of this compound, only the CH$_2$S signal could be assigned with certainty.

5.4.4.1 EXPERIMENTAL FOR SECTION 4.3.2.1

N-(Chlorothio)thioacetamide 152

This compound was prepared analogously to the *N*-chlorothioamines in Section 5.4.4. The evidence for the formation of this compound [disappearance of a N-H stretching absorption in the I.R. spectrum (compared to the parent amine **151**)] was inconclusive.

Reaction of compound 152 with 2,3-dimethyl-1,3-butadiene

This reaction was performed in an identical manner to the analogous reactions detailed in Section 5.4.4. A multitude of uncharacterised products was obtained, no evidence for the formation of DA adduct **154** was obtained.

Reaction of compound 152 with dimethylacetylene dicarboxylate

This reaction was performed in an identical manner to the analogous reactions detailed in Section 5.4.4 when 2,3-dimethyl-1,3-butadiene was employed as trap. When dimethylacetylene dicarboxylate was used in place of 2,3-dimethyl-1,3-butadiene, a multitude of uncharacterised products was obtained, with no evidence for the formation of DA adduct **155**.

5.4.5 EXPERIMENTAL FOR SECTION 4.4.2

Synthesis of phenylthiophosphonic dichlorides 76a,d-e

These compounds were prepared according to a literature procedure.[87] Hence, benzene (11.5ml, 0.13mol) and phosphorus trichloride (34.0ml, 0.39mol) were stirred together at 20°C for 10mins, then aluminium trichloride (17.3g, 0.13mol) was added piecemeal. Upon completion of addition, the mixture was refluxed for 3h then cooled to 30°C at which point sulfur (4.2g, 0.13mol) was added in small aliquots (CAUTION - explosion resulted when all the sulfur was added at once). The mixture was heated at 80°C for 3mins, cooled, and the excess phosphorus trichloride removed *in vacuo*. The remaining residue was quenched in ice (400g) and the aqueous layer extracted with 40-60° petrol (3 x 100ml). Removal of the petrol *in vacuo* followed by fractional distillation afforded compound **76a** as a clear liquid with an acrid odour.

Compounds **76d** and **76e** were prepared as above, employing methylbenzene and chlorobenzene in place of benzene, respectively.

Analytical data for compounds **76a,d-e** are presented below.

Phenylthiophosphonic dichloride 76a

Yield 69.2% (lit.[87] 73.9%); Bp$_{0.7}$ 81-82°C (lit.[87] Bp$_{2-3}$ 95-110°C,); δ_H 7.45-7.65 (3H, m, aromatics), 8.05-8.20 (2H, m, aromatics); δ_P 74.8; MS *m/z* : 210 (M$^+$, ^{35}Cl), (C$_6$H$_5$Cl$_2$PS), 210 (100%, M$^+$).

4-Methylphenylthiophosphonic dichloride 76d[a]

Yield 62% (lit.[87] not quoted); Bp$_{0.03}$ 82-84°C (lit.[87] Bp$_2$ 118-121°C); δ_H 2.45 (6H, s, 2 x CH$_3$), 7.30-7.50 (4H, m, aromatics), 7.80-8.10 (4H, m, aromatics); δ_P 76.6, 76.8; GCMS chromatogram shows a 60 : 40 mixture of 4-methyl and 2-methyl isomers, MS *m/z* : 224 (M$^+$, ^{35}Cl), (C$_7$H$_7$Cl$_2$PS), 224 (100%, M$^+$).

Note.

(a) The initial product of the reaction consisted of a mixture of mono and di-aryl substituted phosphorus chlorides, and also a mixture of *ortho* and *para* methyl isomers. It was possible to remove the disubstituted product by distillation, however, the 4-methylphenylthiophosphonic dichloride could not be separated from the 2-methylphenylthiophosphonic dichloride isomer by distillation. The use of a mixture of isomers was, however, acceptable for our purposes.

4-Chlorophenylthiophosphonic dichloride 76e

Yield 50% (lit.[87] not quoted); Bp$_3$ 156-160°C (lit.[87] not quoted); δ_H 7.50-7.57 (2H, m, aromatics), 7.98-8.12 (2H, m, aromatics); δ_P 72.3; MS *m/z* : 244 (M$^+$, ^{35}Cl), (C$_6$H$_4$Cl$_2$PS), 143 (100%, 4-ClPhPH$^+$).

5.4.6 EXPERIMENTAL FOR SECTION 4.4.3

Reaction of thioxophosphines 2a,d-e with 2-methyl-1,3-butadiene

The method of Inamoto *et al* was employed, [50] incorporating slight modifications. Hence, magnesium (35 mesh dried under Ar, 0.34g, 0.014mol) was added to THF (20ml) and stirring begun. To the stirring mixture 2-methyl-1,3-butadiene (5ml, 0.04mol) was added, followed by the appropriate dichloride **76** (0.014mol) and iodomethane (3 drops, catalytic amount). The resultant mixture was stirred at 50°C for 16h. The mixture was then cooled and the magnesium chloride precipitate removed by filtration under Ar. The THF solvent was removed from the filtrate *in vacuo* and the remaining residue was extracted with chloroform (3 x 15ml). The chloroform extract was washed with distilled water (3 x 10ml) and dried over magnesium sulfate. Removal of the chloroform *in vacuo* followed by chromatography (silica with pure benzene, then benzene : dichloromethane (1 : 1), then pure dichloromethane), afforded the products **158a,d-e** as viscous clear oils with a pungent odour, from benzene. The products were stable at 20°C for at least two weeks. Numerous uncharacterised products eluted in the dichloromethane phase, thus explaining the low yield of compounds **158a,d-e**.

Analytical data for compounds **158a,d-e** are presented below.

Figure 5.2 shows the convention used in the assignment of ^{13}C NMR resonances in the 1,2-thiaphosphorin ring.

X = O or S
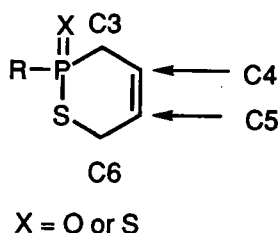
Figure 5.2

2-Phenyl-5-methyl-3,6-dihydro-2H-1,2-thiaphosphorin-2-sulfide 158a

Yield 10%; δ_H 1.85 (3H, s, CH3), 2.77-3.78 (4H, m, 2 x CH2), 5.94-5.97 (1H, m, CH), 7.48-7.92 (5H, m, aromatics); δ_C 26.0 (d, CH3, J_{CP} = 12.6Hz), 28.2 (C6), 40.8 (d, C3, J_{CP} = 50.8Hz), 120.3 (d, C4, J_{CP} = 14.2Hz), 128.3, 128.5, 130.4, 130.6, 131.9, 132.2; δ_P 53.3; MS (CI) *m/z* : 241 (M$^+$ + 1), 241 (100%, M$^+$ + 1), HRMS : 240.01180, calc. 240.01180 ($C_{11}H_{13}PS_2$).

2-(4-Methylphenyl)-5-methyl-3,6-dihydro-2H-1,2-thiaphosphorin-2-oxide 158d[a]

Yield 17%; δ_H 1.83 (6H, s, 2 x CH3), 2.51 (6H, s, 2 x CH3), 2.89-3.77 (8H, m, 4 x CH2), 5.96-5.97 (2H, m, 2 x CH), 7.37-8.00 (8H, m, aromatics); δ_C 22.0 (2 x CH3), 26.7 (d, 2 x CH3, J_{CP} = 9.5Hz), 42.6 (d, 2 x C3, J_{CP} = 50.0Hz), 120.9 (d, 2 x C4, J_{CP} = 12.5Hz), 128.1, 129.0, 129.9, 131.2, 131.4, 133.4, 143.3; δ_P 52.8, 53.1; MS *m/z* : HRMS found : 238.05420, calc. 238.05813 ($C_{12}H_{15}OPS$).

Note.

(a) The analytical data are consistent with a 60 : 40 mixture of the 4-methylphenyl and 2-methylphenyl isomers carried over from precursor compound **76d**, as expected.

2-(4-Chlorophenyl)-5-methyl-3,6-dihydro-2H-1,2-thiaphosphorin-2-oxide 158e

Yield 20%; δ_H 1.76 (3H, s, CH3), 2.76-3.60 (4H, m, 2 x CH2), 5.83-5.84 (1H, m, CH), 7.37-7.88 (4H, m, aromatics); δ_C 28.1 (d, CH3, J_{CP} = 9.3Hz), 28.5 (C6), 41.2 (d, C3, J_{CP} = 50.8Hz), 120.9 (d, CH, J_{CP} = 12.5Hz), 128.7, 129.0, 132.2, 132.4, 133.0, 138.0; δ_P 53.0; MS *m/z* : 258 (M$^+$, ^{35}Cl), 190 (100%, 4-ClPhPOS$^+$), HRMS : 258.00321, calc. 258.00350 ($C_{11}H_{12}ClOPS$).

5.4.7 EXPERIMENTAL FOR SECTION 4.4.4

Reaction of thioxophosphines 2a,d-e with *cis/trans* 1-methyl-1,3-butadiene
A procedure identical to that described for the analogous reactions in Section 5.4.6 was employed, except that *cis/trans* 1-methyl-1,3-butadiene was used in place of 2-methyl-1,3-butadiene.

Analytical data for compounds **160a,d-e** are presented below.

2-Phenyl-6-methyl-3,6-dihydro-*2H*-1,2-thiaphosphorin-2-oxide 160a
Yield 20%; $\delta_H^{(a)}$ 1.36 (3H, dd, CH3, J_{HH} = 7.2Hz, J_{PH} = 2.3Hz), 1.45 (3H, dd, CH3, J_{HH} = 7.2Hz, J_{PH} = 2.2Hz), 2.61-3.40 (4H, m, 2 x CH2), 4.07-4.11 (2H, m, 2 x CH), 5.72-5.93 (4H, m, 4 x CH), 7.34-7.99 (10H, m, aromatics); $\delta_C^{(a)}$ 21.3 (d, CH3, J_{CP} = 7.4Hz), 21.7 (d, CH3, J_{CP} = 6.0Hz), 33.7 (d, C3, J_{CP} = 53.5Hz), 36.8 (d, C3, J_{CP} = 51.5Hz), 37.9 (C6), 39.6 (C6), 123.1-123.5 (m, 2 x C4), 128.4, 128.6, 128.9, 129.4, 130.1, 131.4, 131.9, 132.3, 132.9, 133.1, 134.4; $\delta_P^{(a)}$ 50.0, 56.0; MS *m/z* : HRMS$^{(b)}$ found : 224.04260, calc. 224.04247 ($C_{11}H_{13}PS$).

Notes.
(a) The analysis is consistent with a 2 : 1 mixture of isomers in which the methyl group at C6 is both axial and equatorial. This was caused by trapping with a mixture of *cis* and *trans* 1-methyl-1,3-butadiene.
(b) No M$^+$ was observed for this compound, hence high resolution MS was performed on the daughter fragment corresponding to loss of oxygen from M$^+$.

2-(4-Methylphenyl)-6-methyl-3,6-dihydro-*2H*-1,2-thiaphosphorin-2-oxide 160d
Yield 20%; $\delta_H^{(a)}$ 1.36 (6H, dd, CH3, J_{HH} = 7.4Hz, J_{PH} = 2.1Hz), 1.44 (6H, dd, CH3, J_{HH} = 7.2Hz, J_{PH} = 2.2Hz), 2.30 (6H, s, CH3) 2.50-3.20 (4H, m, 2 x CH2), 4.00-4.20 (2H, m, 2 x CH), 5.70-6.00 (4H, m, 4 x CH), 7.17-7.85 (10H, m, aromatics); $\delta_C^{(a)}$ 21.5 (d, CH3, J_{CP} = 8.0Hz), 21.9 (d, CH3, J_{CP} = 7.0Hz), 30.4 (d, C3, J_{CP} = 59.0Hz), 33.8 (d, C3, J_{CP} = 53.0Hz), 37.0 (d, C3, J_{CP} = 51.6Hz), 36.8 (d, C3, J_{CP} = 51.6Hz), 37.6 (C6), 39.5 (C6), 123.4 (m, 4 x C4), 128.4, 129.0, 129.2, 129.3, 129.8, 130.2, 130.5, 130.7, 131.0, 131.4, 131.7, 132.7, 133.9, 134.2, 138.0, 142.0; $\delta_P^{(a)}$ 49.6, 50.1, 55.2, 55.8; MS *m/z* : HRMS found : 238.05712, calc. 238.05813 ($C_{12}H_{15}OPS$).

Notes.

(a) The analysis is consistent with a 2 : 1 mixture of isomers in which the methyl group at C6 is both axial and equatorial. This was caused by trapping with a mixture of *cis* and *trans* 1-methyl-1,3-butadiene. Recalling that this compound is, in addition, a mixture of 60 : 40 *para* : *ortho* methyl isomers, then there are a total of four inseparable isomers in this mixture, hence the complexity of the analysis.

2-(4-Chlorophenyl)-6-methyl-3,6-dihydro-2*H*-1,2-thiaphosphorin-2-oxide 160e

Yield 10%; δ_H[a] 1.42 (3H, dd, CH$_3$, J_{HH} = 4.7Hz, J_{PH} = 2.3Hz), 1.49 (3H, dd, CH$_3$, J_{HH} = 7.2Hz, J_{PH} = 2.1Hz), 2.64-3.24 (4H, m, 2 x CH$_2$), 4.02-4.17 (2H, m, 2 x CH), 5.82-5.94 (4H, m, 4 x CH), 7.36-7.92 (10H, m, aromatics); δ_C[a] 21.3 (d, CH$_3$, J_{CP} = 8.4Hz), 21.8 (d, CH$_3$, J_{CP} = 9.0Hz), 34.8 (d, C3, J_{CP} = 54.7Hz), 37.1 (d, C3, J_{CP} = 54.7Hz), 38.1 (C6), 39.7 (C6), 123.0 (d, C4, J_{CP} = 9.0Hz), 123.4 (d, C4, J_{CP} = 9.5Hz), 128.3, 128.7, 131.4, 131.6, 132.3, 132.7, 132.9, 133.2, 134.8. 135.0; δ_P[a] 49.0, 56.0; MS *m/z* : HRMS (^{35}Cl) found : 258.01001, calc. 258.00350 (C$_{11}$H$_{13}$ClOPS).

Notes.

(a) The analysis is consistent with a 2 : 1 mixture of isomers in which the methyl group at C6 is both axial and equatorial. This was caused by trapping with a mixture of *cis* and *trans* 1-methyl-1,3-butadiene.

5.4.7.1 EXPERIMENTAL FOR SECTION 4.4.4.1

Reaction of thioxophosphine 2a with *trans* 1-methy-1,3-butadiene

A procedure identical to that described for the analogous reactions in Section 5.4.7 was employed, except that *trans* 1-methyl-1,3-butadiene was used in place of *cis/trans* 1-methyl-1,3-butadiene.

Analytical data for a single isomer (C6 methyl group axial or equatorial) of compound **160a** are presented below.

2-Phenyl-6-methyl-3,6-dihydro-2*H*-1,2-thiaphosphorin-2-oxide 160a

Yield 20%; δ_H 1.54 (3H, dd, CH$_3$, J_{HH} = 7.2Hz, J_{PH} = 2.2Hz), 2.61-3.40 (2H, m, CH$_2$S), 4.07-4.11 (1H, m, CH), 5.72-5.93 (2H, m, CH vinylic), 7.34-7.99 (5H, m, aromatics); δ_C 21.5 (d, CH$_3$, J_{CP} = 7.4Hz), 30.5 (d, C3, J_{CP} = 56.6Hz), 37.9 (C6), 123.1-123.5 (C4), 128.4, 128.6, 128.9, 129.4, 130.1, 131.4, 131.9, 132.3, 132.9, 133.1, 134.4; δ_P 55.9; MS *m/z* : HRMS[a] found : 224.04260, calc. 224.04247 (C$_{11}$H$_{13}$PS).

Note.

(a) No M^+ was observed for this compound, hence high resolution MS was performed on the daughter fragment corresponding to loss of oxygen from M^+.

5.4.8 EXPERIMENTAL FOR SECTION 4.5.2

Synthesis of 3-phenoxypropanol 164a and 3-thiophenoxypropanol 164b

Sodium phenoxide (6.7g, 0.057mol) was dissolved in ethanol (150ml) and to this solution was added 3-bromopropanol (8.0g, 0.057mol). The resultant mixture was stirred at 50°C for 16h. After cooling, the ethanol was removed *in vacuo* and the remaining oily residue was taken up in diethyl ether (150ml). This solution was washed with water (3 x 50ml) and dried over magnesium sulfate. Removal of the diethyl ether *in vacuo* afforded compound **164a**, which required no further purification. Compound **164b** was synthesised in the same manner with sodium thiophenoxide in place of sodium phenoxide.

Analytical data for compounds **164a-b** are presented below.

3-Phenoxypropanol 164a

Yield 71%; Bp$_2$ 50-52°C (lit.[91] Bp$_{760}$ 248-250°C,); δ_H 2.03 (2H, quin., CH$_2$, J_{HH} = 5.9Hz), 2.15 (1H, br s, OH), 3.85 (2H, t, CH$_2$, J_{HH} = 5.9Hz), 4.11 (2H, t, CH$_2$, J_{HH} = 5.9Hz), 7.10-7.50 (5H, m, aromatics).

3-Thiophenoxypropanol 164b

Yield 88%; δ_H 1.85 (2H, quin., CH$_2$, J_{HH} = 6.25Hz), 2.50 (1H, br s, OH), 3.00 (2H, t, CH$_2$, J_{HH} = 6.25Hz), 3.71 (2H, t, CH$_2$, J_{HH} = 6.25Hz), 7.10-7.50 (5H, m, aromatics); MS *m/z* : 168 (M^+), 110 (100%, PhSH$^+$).

Synthesis of 3-phenoxy-1-bromopropane 163a and 3-thiophenoxy-1-bromopropane 163b

These compounds were produced by a simple procedure. Thus for compound **163a**, diethyl ether (100ml) and 3-phenoxypropanol (5.4g, 0.035mol) were cooled to 0°C with stirring. Phosphorus tribromide (3.5ml, 0.035mol) was added dropwise, stirring was continued at 0°C for a further 10mins, then for 1h at 20°C. The solvent was removed *in vacuo* and the remaining residue taken up in dichloromethane (70ml). This solution was washed with water (3 x 70ml) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded compound **163a**, which required no further purification.

Compound **163b** was prepared in an analogous manner with 3-thiophenoxypropanol in place of 3-phenoxypropanol.

Preliminary analytical data for compounds **163a-b** are presented below, due to time constraints full analytical data could not be obtained. Note that both compounds were unstable to distillation.

3-Phenoxy-1-bromopropane 163a
Yield 61%; δ_H 2.27 (2H, quin., CH_2, J_{HH} = 6.00Hz), 3.56 (2H, t, CH_2, J_{HH} = 6.40Hz), 4.10 (2H, t, CH_2, J_{HH} = 5.6Hz), 6.80-7.30 (5H, m, aromatics).

3-Thiophenoxy-1-bromopropane 163b
Yield 71%; δ_H 2.07 (2H, quin., CH_2, J_{HH} = 6.80Hz), 3.00 (2H, t, CH_2, J_{HH} = 6.80Hz), 3.45 (2H, t, CH_2, J_{HH} = 6.3Hz), 7.10-7.30 (5H, m, aromatics).

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Appendix One

Publications and Presentations

A 1.1 PUBLICATION

M. R. Bryce, A. Chesney, J. N. Heaton, **G. N. Mckelvey** and M. Anderson, *Tetrahedron Lett.*, 1994, **35**, 5275.

A 1.2 PRESENTATION

Poster: "The use of Thionitroso Species in the Synthesis of 1,2-Thiazines," presented at the 6th Symposium on the Latest Trends in Organic Synthesis, Sept. 22-Oct. 2, 1994, at the Virginia Polytechnic Institute and State University, Blacksburg, VA, U.S.A.

Appendix Two

Research Colloquia, Seminars

and Lectures

A 2.1 COLLOQUIA, LECTURES AND SEMINARS ATTENDED

1992 - 1993 (August 1 - July 31)

1992

October 29   Dr. J. Emsley, Imperial College, London
              The Shocking History of Phosphorus

November 5   Dr. C. J. Ludman, University of Durham
              Explosions, A Demonstration Lecture

November 11   Prof. D. Robins, Glasgow University
              Pyrrolizidine Alkaloids : Biological Activity, Biosynthesis and Benefits

1993

January 21   Prof. L. Hall, Cambridge
              NMR - Window to the Human Body

January 27   Dr. W. Kerr, University of Strathclyde
              Development of the Pauson-Khand Annulation Reaction : Organocobalt
              Mediated Synthesis of Natural and Unnatural Products

January 28   Prof. J. Mann, University of Reading
              Murder, Magic and Medicine

February 10   Dr. D. Gillies, University of Surrey
              NMR and Molecular Motion in Solution

February 11   Prof. S. Knox, Bristol University
              The Tilden Lecture Organic Chemistry at Polynuclear Metal Centres

February 18   Dr. I. Fraser, ICI Wilton
              Reactive Processing of Composite Materials

March 11   Dr. R. A. Y. Jones, University of East Anglia
              The Chemistry of Wine Making

March 17   Dr. R. J. K. Taylor, University of East Anglia
              Adventures in Natural Product Synthesis

1993 - 1994 (August 1 - July 31)

<u>1993</u>

October 27   Dr. R.A.L. Jones, Cavendish Laboratory, Cambridge
              Perambulating Polymers

November 25   Dr. R.P. Wayne, University of Oxford
              The Origin and Evolution of the Atmosphere

December 1   Prof. M.A. McKervey, Queen's University, Belfast
              Synthesis and Applications of Chemically Modified Calixarenes

December 8   Prof. O. Meth-Cohn, University of Sunderland
              Friedel's Folly Revisited - A Super Way to Fused Pyridines

<u>1994</u>

February 9   Prof. D. Young, University of Sussex
              Chemical and Biological Studies on the Coenzyme Tetrahydrofolic Acid

March 2   Dr. C. Hunter, University of Sheffield
              Noncovalent Interactions between Aromatic Molecules

March 10   Prof. S.V. Ley, University of Cambridge
              New Methods for Organic Synthesis

1994 - 1995 (August 1 - July 31)

<u>1994</u>

October 19   Prof. N. Bartlett, University of California
              Some Aspects of Ag(II) and Ag(III) Chemistry

November 10 Dr M. Block, Zeneca Pharmaceuticals, Macclesfield
             Large Scale Manufacture of the Thromboxane Antagonist Synthase
             Inhibitor ZD 1542

November 16 Prof. M. Page, University of Huddersfield
             Four Membered Rings and b-Lactamase

<u>1995</u>

March 1   Dr M. Rosseinsky, Oxford University
             Fullerene Intercalation Chemistry

March 8   Nikki Chesters, Wayne Devonport & Penelope Herbertson, University of
             Durham 1995 Graduate Seminar Series

May 3   Prof. E. W. Randall, Queen Mary and Westfield College
             New Perspectives in NMR Imaging

May 10   George Bates, Steve Carss, Martyn Coles, University of Durham
             1995 Graduate Seminar Series

May 17   Graham McKelvey, Richard Towns & Tim Thompson, University of
             Durham 1995 Graduate Seminar Series