Studies of thioaldehydes and dienophilic dithioesters

Thesis submitted to the University of Glasgow
for the degree of Doctor of Philosophy

March 1996

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Acknowledgements

I would like to thank Professor G. W. Kirby for his guidance and help throughout the course of this work. I would also like to thank my husband Douglas and my family for all their support and encouragement.

Finally I gratefully acknowledge financial support from the Loudon Bequest for the duration of this research.

ABSTRACT

Studies have been carried out on the base-mediated elimination reactions of *N*-phthaloyl sulfenamides under various conditions. In particular, ethyl phthalimidosulfanylacetate was treated with triethylamine alone to yield the thioaldehyde, ethyl thioxoacetate, and with 4-dimethylaminopyridine (DMAP) (with or without triethylamine) to yield the dithioester, diethyl 3-thia-2-thioxopentanedioate. The transient, dienophilic products were trapped by Diels-Alder reactions with various dienes. The ratio of thioaldehyde and dithioester adducts were dependent on the amount of DMAP used and also on the reactivity of the diene.

In the absence of any diene, elimination of the phthaloyl sulfenamide led to the polymerisation, catalysed by base, of the transient dienophile. Different types of polymer were formed according to the base used. Triethylamine generated a thioaldehyde polymer while DMAP and combinations of it with other bases led to the dithioester polymer. Depolymerisation was accomplished by the addition of base to the polymers and again the dienophilic intermediates that were generated were captured by dienes to form the corresponding cycloadducts.

The labile dithioester was isolated after immediate addition of acid to the reaction mixture to prevent polymerisation being catalysed by the DMAP. It was isolated in a pure state, after chromatography, as a purple oil. Diels-Alder reactions of this purified dithioester gave the corresponding cycloadducts free from other products.

Elimination reactions were also studied with other β-oxo phthaloyl sulfenamides.

The cycloadduct of ethyl thioxoacetate and anthracene was converted into the corresponding *S*-ethyl sulfonium salt. This reacted with base to form a pair of isomers,

which have been assigned tentative structures. Similarly, the *S*-ethyl sulfonium salt of the cycloadduct of the dithioester and dimethylbutadiene was treated with diazabicyclononane (DBN) to give a cyclopropanecarboxylate identical to that formed from the thioaldehyde cycloadduct.

A known racemic, chiral auxiliary, *trans*-2,5-bis(methoxymethyl)pyrrolidine was prepared and *N*-acylated with chloroacetyl chloride. This chloroacetyl derivative was converted into the corresponding Bunte salt. Base-mediated elimination yielded a chiral thioaldehyde, which was trapped with both cyclopentadiene and cyclohexadiene to yield 4 diastereomers in each case. The cyclopentadiene *endo* adducts were formed in 91% d.e. and the cyclohexadiene *endo* adducts in 75% d.e. In both cases the major *endo* diastereomer was separated from the others by chromatography. The X-ray crystal structure obtained for the major, *endo* cyclohexadiene adduct provided the relative configuration of the chiral centres; the stereoselective formation of this cycloadduct has been rationalised.

Part of this research has been accepted for publication as G. W. Kirby, A. W. Lochead and S. Williamson, *J. Chem. Soc., Perkin Trans. 1*, 1996 (paper 5/07236K).

CONTENTS

CHAPTER ONE

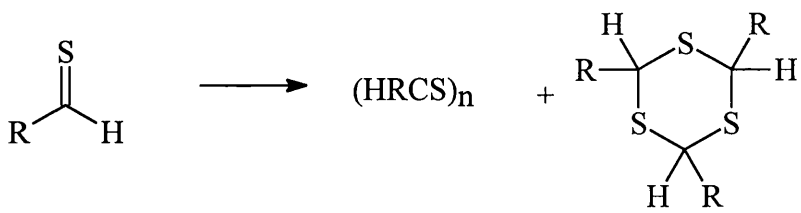
Introduction

1.1 Thioaldehydes

In thiocarbonyl compounds a bivalent sulfur is doubly bonded to carbon by overlap of a 2p orbital of the carbon atom with the 3p orbital of the sulfur. This overlap is less efficient than the 2p-2p overlap of the carbonyl group and therefore thiocarbonyl compounds are more reactive and less stable than their oxygen analogues.

The review of thioaldehyde chemistry presented here is selective and other aspects of the subject can be found in various reviews [1,2,3].

Early attempts to isolate thioketones and thioaldehydes led to the formation of oligomers, polymers and frequently cyclic trimers, which were often stable white solids (Scheme 1) [1,2]. The formation of polymeric material was previously believed to occur spontaneously but it is more likely due to catalysis by protic or Lewis acids. The simplest thioaldehyde, thioformaldehyde is extremely unstable, with a half life of *ca.* 6 min at a pressure of 0.01-0.05 Pa. Thioformaldehyde has, however, been detected in cosmic space, the prolonged existence presumably being due to the interstellar vacuum and large intermolecular distances.

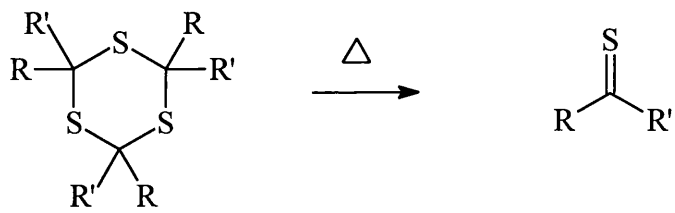


Scheme 1

Modern physicochemical methods have now made it possible to determine the lifetimes and spectroscopic characteristics of such transient compounds [3]. The C=S bond length has been determined to be 1.61 Å which is longer than the C=O bond (1.21 Å in aldehydes or ketones). The free thiocarbonyl group often gives intense colours and the electronic spectra are characterised by three absorption regions due to the $n \rightarrow \pi^*$ transitions in the visible spectrum and the $\pi \rightarrow \pi^*$ and $n \rightarrow \sigma^*$ in the UV region. In the proton NMR spectra of thioaldehydes, the signal of the thioformyl proton is low field within a fairly wide range, δ 9-13.

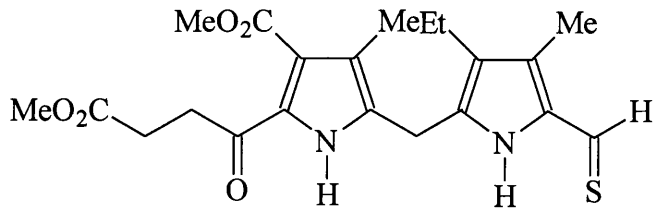
Early attempts to synthesise thioaldehydes involved the direct sulfurisation of the corresponding oxo compound with hydrogen sulfide. Thioketones were prepared by treatment with hydrogen sulfide or phosphorous pentasulfide. The reactions were usually carried out in the presence of an acid catalyst but with limited success. Such treatment often yielded not the thiocarbonyl compound but their cyclic trimers, the corresponding *gem*-dithiols or simply polymeric material. The reaction course depends primarily on the reaction temperature, but also the reaction time and the nature of the solvent.

Thermal cracking of trimers (Scheme 2) occasionally can be accomplished by heating in a vacuum to release the coloured thiocarbonyl compound which trimerises again as it is cooled and condensed. This technique was more successful for thioketones than for thioaldehydes.



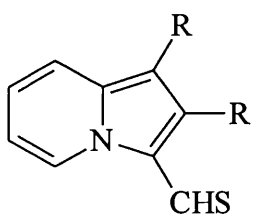
Scheme 2

The first report on a stable thioaldehyde appeared in 1960 where Woodward *et al.*[4] reported the isolation of a thioaldehyde **1** in the total synthesis of chlorophyll a. The stability arises from resonance effects due to conjugation of the thioformyl group with the electron rich pyrrole unit.



1

This report was followed by many more examples, **2**, **3** and **4** of the same type of stabilisation mainly by Reid *et al.* [5-8]. A novel variation of the Vilsmeier-



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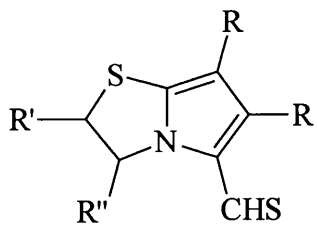

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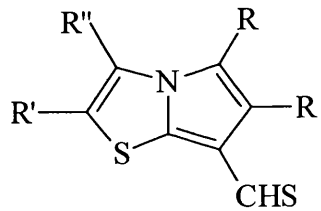
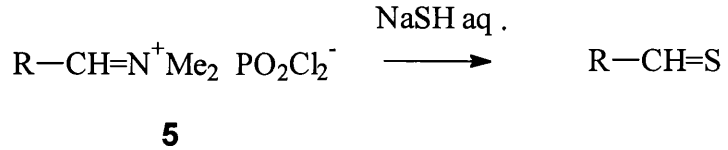


4

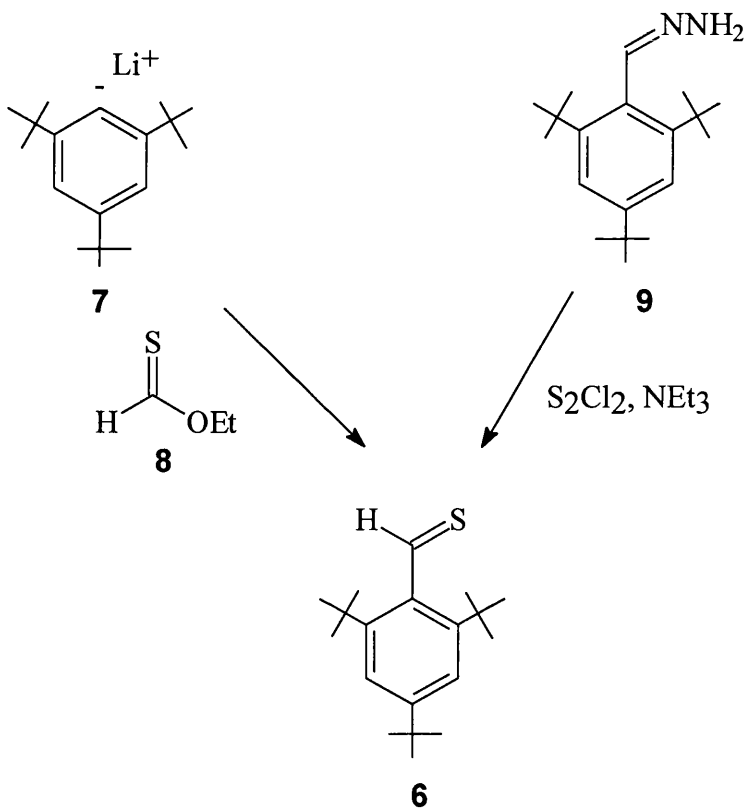
Haack aldehyde synthesis was used in which the Vilsmeier salt **5** was solvolysed with sodium hydrogen sulfide. Nucleophilic attack of a suitable sulfur containing reagent on carbon of the C=X bond led to substitution of the X moiety by sulfur (Scheme 3).



5

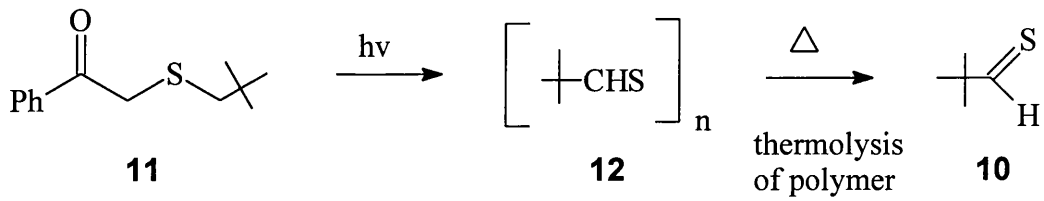
Scheme 3

Then in 1982 Okazaki *et al.* [9] reported the first thioaldehyde, 2,4,6-tri-*t*-butylthiobenzaldehyde **6**, stabilised only by steric effects. It was prepared by treatment of the aryl-lithium salt **7** with ethyl thionoformate **8** or by oxidative sulfurisation of the hydrazone **9** with sulfur monochloride (Scheme 4). Thiobenzaldehyde itself is only stable enough to allow IR data to be obtained at



Scheme 4

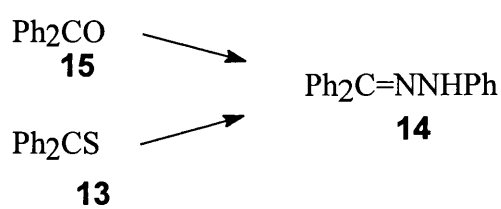
liquid nitrogen temperature. Although resonance effects may still be partly responsible for the stability of the thioaldehyde **6** the formation of 2,2-dimethylpropanethial **10** by Vedejs *et al.* [10,11] in 1983 provides an example of a thioaldehyde stabilised purely by steric effects. It existed for up to 16 h in non-protic solvents. It was prepared by photolysis of the phenacyl sulfide **11** followed by thermolysis of the polymer **12** (Scheme 5).



11 **12** **10**

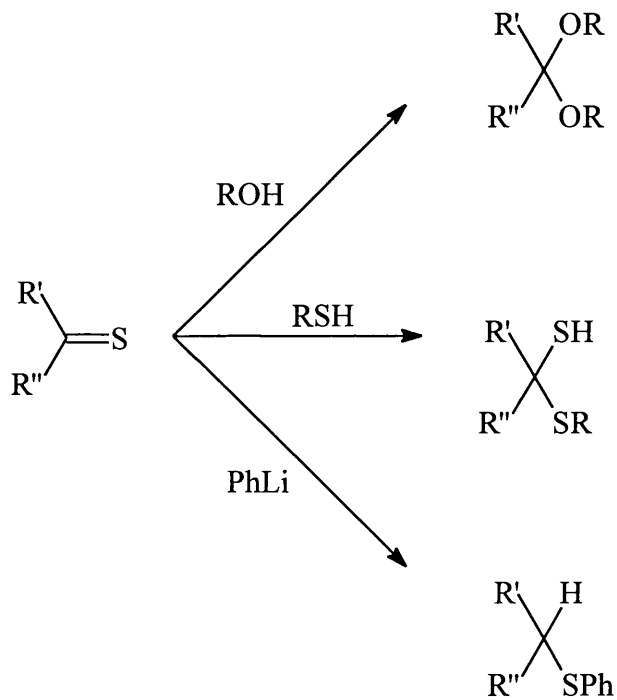
Scheme 5

Most of the studies on the reactivity of the thiono group have been carried out on resonance stabilised compounds. Generally reactions in which the sulfur is removed proceed to give the same products as the oxygen counterparts, but at a much increased rate. The reaction of thiobenzophenone **13** to give the phenylhydrazone **14** proceeds 2000 times faster than for benzophenone **15** (Scheme 6) [12].



Scheme 6

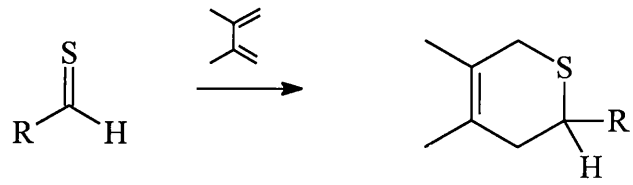
Reduction of thiocarbonyl compounds with sodium borohydride gives the corresponding thiol, again at an increased rate [2,12]. However, the reaction of thiocarbonyl compounds with nucleophiles often differs from that of the carbonyl compounds. While there are many examples of nucleophiles attacking in the normal way at the electrophilic carbon, such as the formation of acetals and dithiohemiacetals, many nucleophiles attack preferentially at the sulfur *i.e.* thiophilic attack. Phenyl-lithium reacts with thioketones to give sulfides (Scheme 7) and oxidation of the sulfur by *m*-chloroperbenzoic acid (MCPBA) leads to the sulfine .



Scheme 7

1.2 Generation of thioaldehydes and their use as dienophiles

It has been known for some time that thiocarbonyl compounds are excellent dienophiles, several orders of magnitude more reactive than their oxygen analogues. Examples of their Diels-Alder reaction (Scheme 8) with dienes has been reported

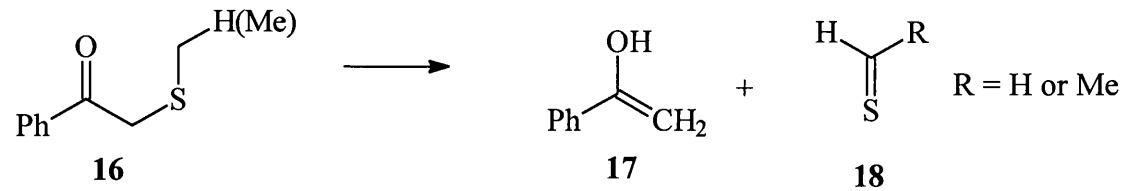


Scheme 8

from every branch of thiocarbonyl chemistry, as described in the 1982 review by Weinreb and Staib [13]. It was soon realised that there was an enormous potential for the trapping of transient thioaldehydes to form cycloadducts before polymerisation could take place. In this way thioaldehydes can be exploited in synthesis providing they are generated and trapped *in situ*. Thioaldehydes having electron withdrawing groups are valuable heterodienophiles in synthesis. The thial π bond is weak and reactive while the steric demands of mono-substituted dienophiles are small and sulfur in the derived cycloadducts may be removed reductively or retained and used to facilitate further transformations.

1.2.1 Photolysis of phenacyl sulfides

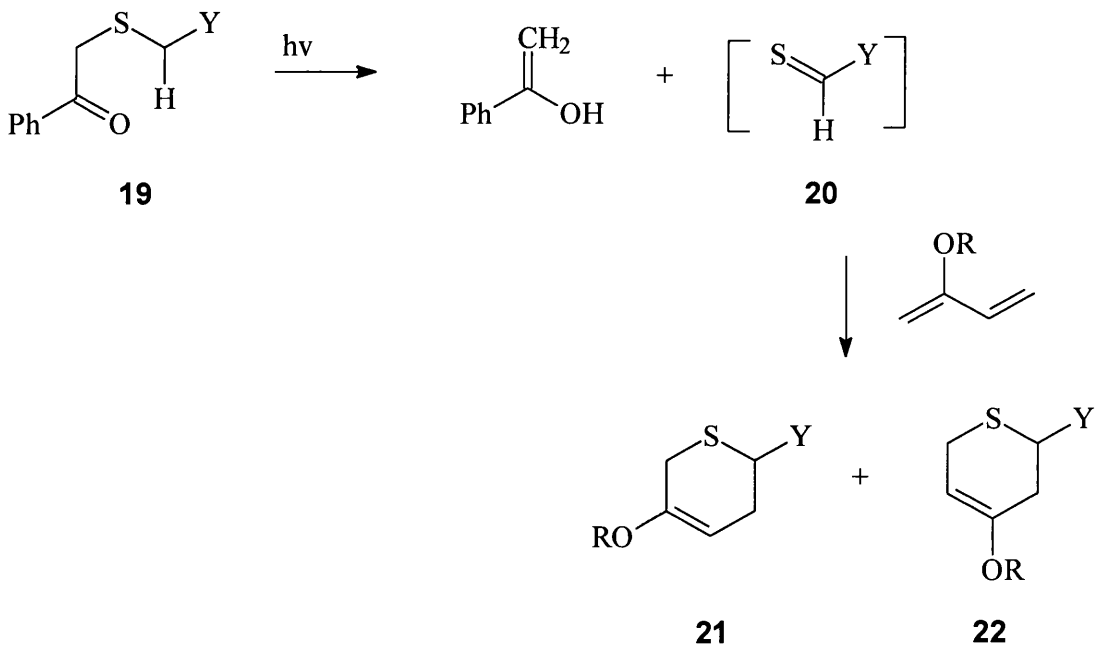
Most of the classical methods of generating thioaldehydes precluded the use of 1,3-dienes and milder methods started to be developed. In 1982 Vedejs *et al.*[14], following an earlier observation by Caserio *et al.*[15,16] reported a mild photochemical method for generating dienophilic thioaldehydes. Caserio *et al.* had observed that phenacyl alkyl sulfides **16** are photolysed by an *intra*molecular Norrish type II process to give the enol of acetophenone **17** and the corresponding thioaldehydes **18** as the primary photo products (Scheme 9). The authors' aim was to study the *intra*molecular



16 **17** **18**

Scheme 9

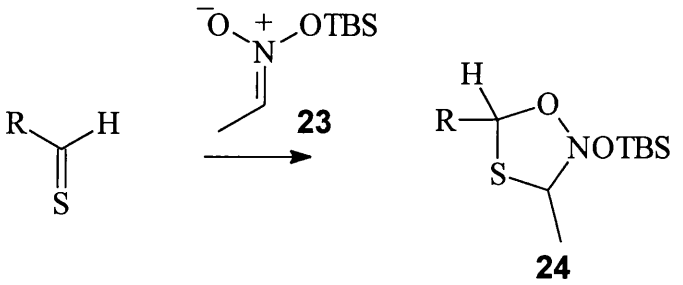
and *inter*molecular mechanisms of the photolysis but they failed to detect any thioaldehyde formation due to rapid polymerisation. Vedejs *et al.* investigated this reaction again and photolyzed a series of phenacyl sulfides **19** in the presence of dienes and found that the intermediate thioaldehydes **20** could be trapped to form the Diels-Alder cycloadducts **21** and **22** (Scheme 10).



19 **20** **21** **22**

Scheme 10

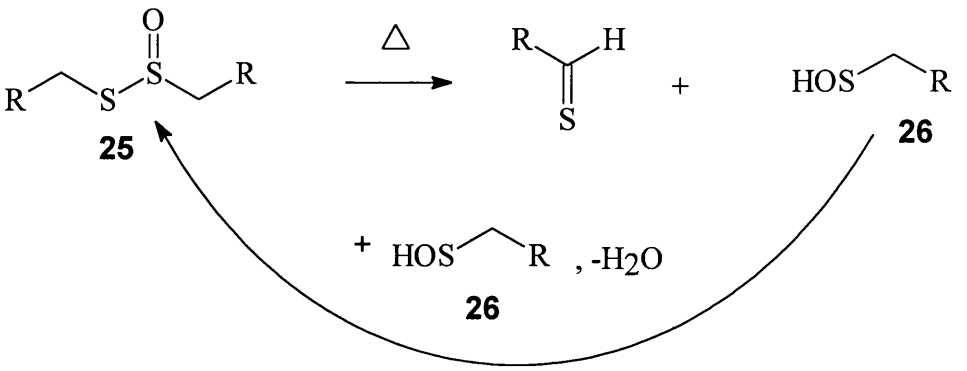
Vedejs *et al.*[17] also showed that the thioaldehydes could be trapped with the *tert*-butyldimethylsilyl nitronate ester **23** to give 1,3-dipolar cycloadducts **24** (Scheme 11).



Scheme 11

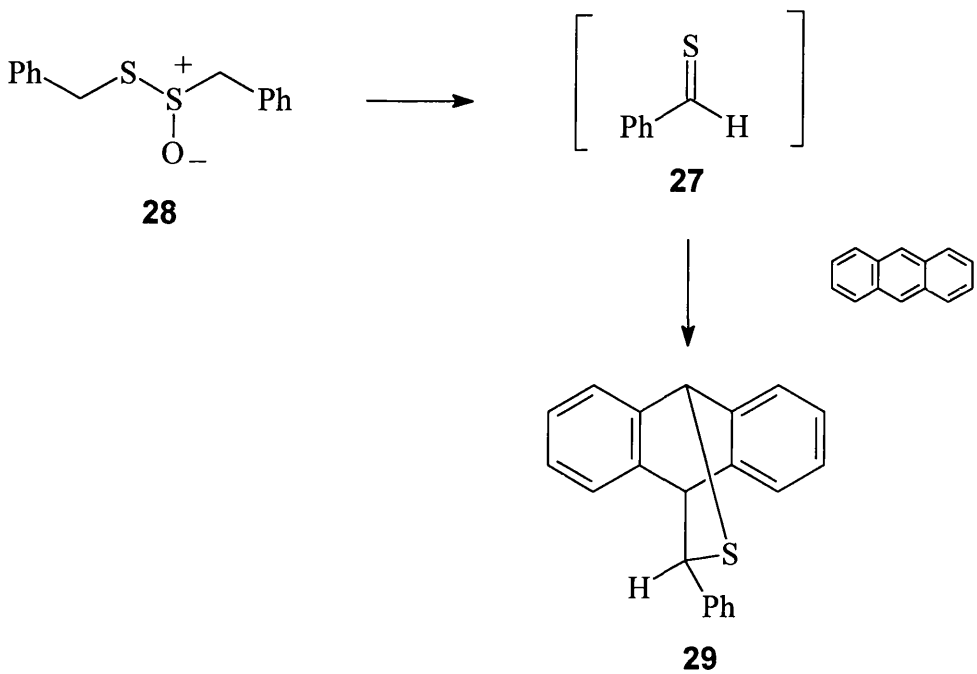
1.2.2 Thermolysis of alkyl thiosulfinates

The photochemical method employed by Vedejs was closely followed by a report by Baldwin and Lopez [18,19], also in 1982 where thioaldehydes were generated by the thermolysis of symmetrical alkyl thiosulfinates **25**. The reaction was originally investigated by Block *et al.* [20,21] and was found to produce the thioaldehydes along with the sulfenic acids **26**. The sulfenic acids then recombine to give thiosulfinates thus all the starting material is converted into thioaldehyde (Scheme 12). Block had been interested in the sulfenic acids and had ignored the thioaldehydes.



Scheme 12

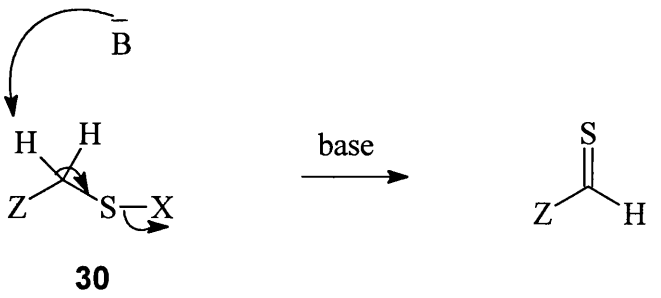
Baldwin and Lopez showed that the thioaldehydes could be trapped with dienes to give the Diels-Alder cycloadducts. Thus thiobenzaldehyde **27** was generated by heating *S*-benzylphenylmethanethiosulfinate **28** in toluene at 100 °C and trapping with anthracene to form the adduct **29** (Scheme 13).



Scheme 13

1.2.3 Base-mediated elimination of sulfenyl derivatives

Soon after these reports appeared on the trapping of transient thioaldehydes, Kirby *et al.* developed a number of methods of generating thioaldehydes under very mild conditions. These reactions involved the 1,2-base-mediated elimination of HX from sulfenyl derivatives **30** where Z was usually an electron withdrawing group, to render the methylene protons acidic enough for mild base elimination, and X a leaving group (Scheme 14). The base used was generally triethylamine.

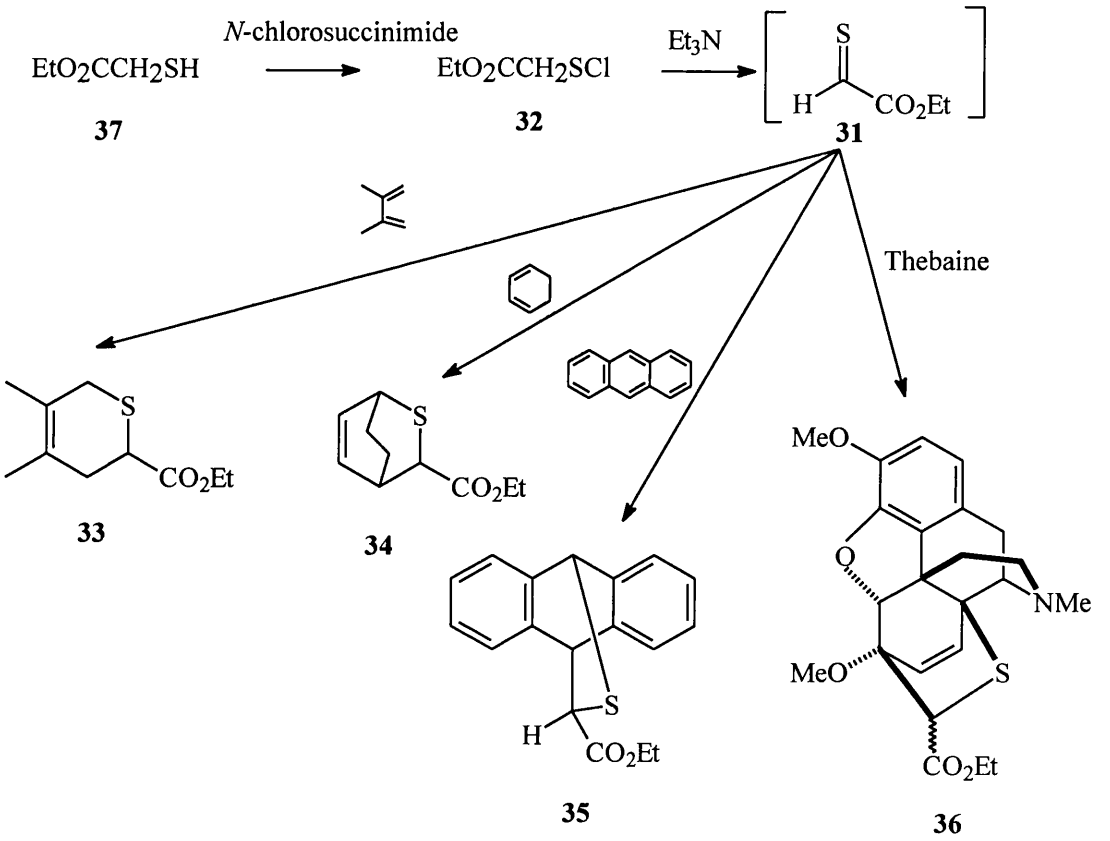


30

Scheme 14

1,2-Elimination of sulfenyl chlorides [22,23]

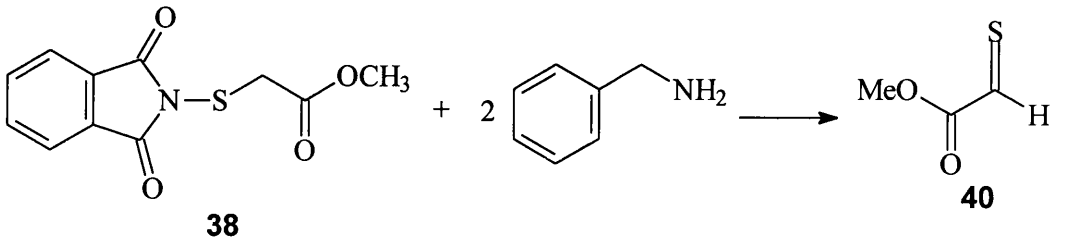
The initial report on the elimination from a sulfenyl derivative to yield a thioaldehyde involved the generation of ethyl thioxoacetate **31** (Scheme 15). The elimination of hydrogen chloride from the sulfenyl chloride **32** yielded the thioaldehyde which was trapped *in situ* with various dienes to produce the corresponding cycloadducts **33-36** (Scheme 15). The sulfenyl chloride could readily be prepared by chlorination of the corresponding thiol, ethyl mercaptoacetate **37**. However, a few problems were encountered when sulfenyl chlorides were used as thioaldehyde precursors. Unwanted products sometimes arose from attack of the sulfenyl chloride on the diene in competition with the elimination to form the thioaldehyde.



Scheme 15

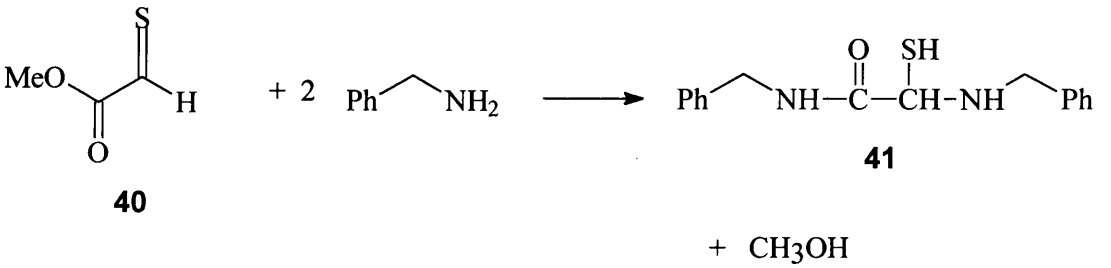
1,2-Elimination of *N*-phthaloyl sulfenamides [24]

While a useful way to generate thioaldehydes, the sulfenyl chloride elimination reaction was limited in its application, as explained above. An alternative method was found however, *viz.* the base-mediated elimination from *N*-phthaloyl sulfenamides. Harpp and Back [25] had reported that treatment of the *N*-phthaloyl sulfenamide **38** with benzylamine generated a mixture of *N*-benzylphthalimide (16%) and the thiooxamide **39** (27%) along with phthalimide (Schemes 16-18). They suggested that this thiooxamide was formed in a complex manner from methyl



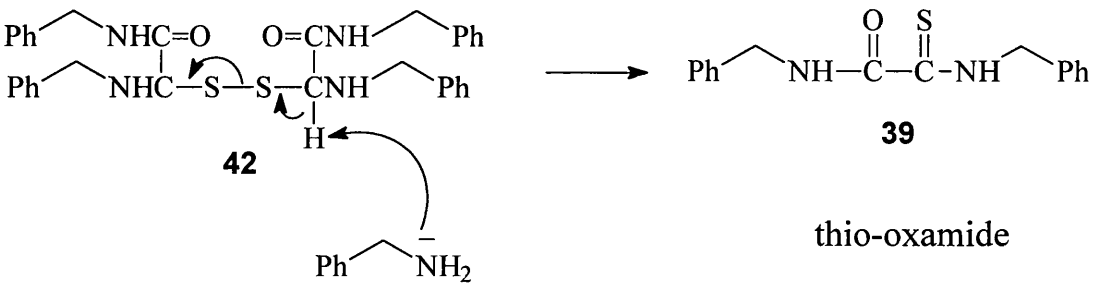
Scheme 16

thioxoacetate **40** generated by base catalysed elimination from the *N*-phthaloyl sulfenamide **38** (Scheme 16). The thioaldehyde **40** probably undergoes attack by the amine, resulting in both amidation and addition to the thione function (Scheme 17).



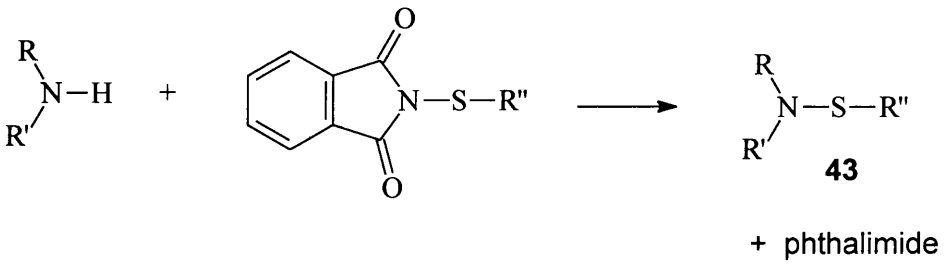
Scheme 17

The resulting thiol **41** may then be oxidised to the corresponding disulfide **42,** which, after elimination with base, would yield the thiooxamide **39** (Scheme 18).



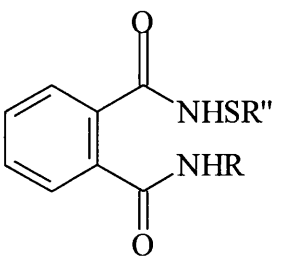
Scheme 18

The reaction of amines with *N*-phthaloyl sulfenamides has been shown generally to be a useful method for the generation of sulfenamides **43** (Scheme 19) [26,27]. An exception to this behaviour appears to be in the reaction of primary amines



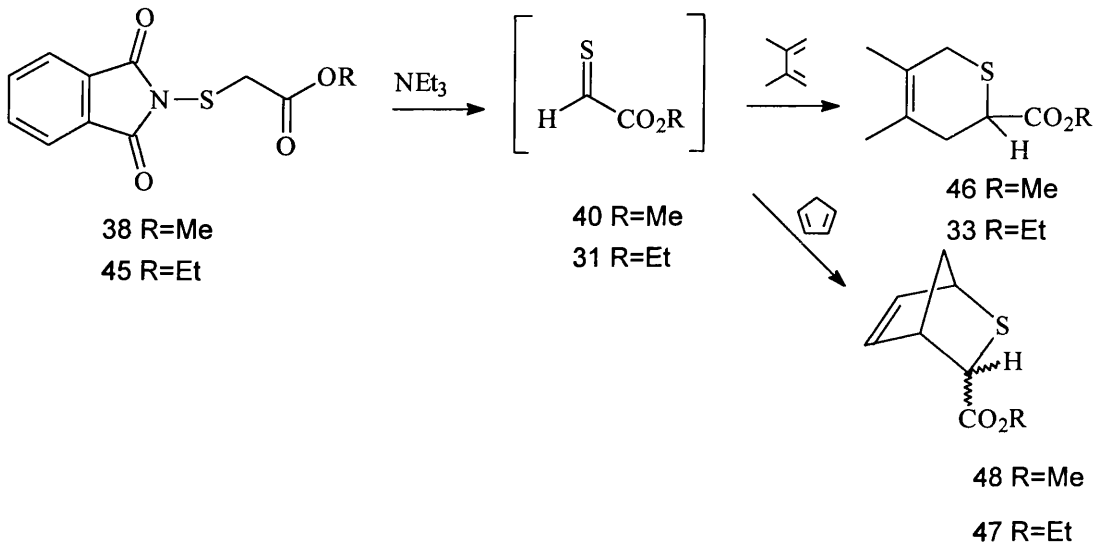
Scheme 19

with *N*-phthaloyl sulfenamides with bulky groups. In this case the nitrogen nucleophile reacts at the carbonyl carbon to give the ring opened product **44**.



44

Kirby and Lochead investigated the reaction of Harpp and Back by treating the *N*-phthaloyl sulfenamides **38** and **45** with triethylamine in the presence of either 2,3-dimethyl-1,3-butadiene or cyclopentadiene and formed excellent yields of the corresponding thioaldehyde cycloadducts **46** and **33** and **48** and **47** respectively (Scheme 20). This method appeared to be superior to the sulfenyl chloride method giving excellent yields since the *N*-phthaloyl sulfenamides themselves did not react with the dienes.

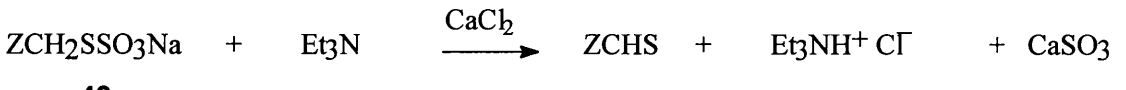


Scheme 20

1,2-Elimination of Bunte salts [28]

It was realised that a general series of thioaldehyde precursors was possible where X is a good leaving group and Z an electron withdrawing group. Thus, the sodium thiosulfate *S*-esters **49** (Bunte salts) were developed as precursors for the thioaldehydes ZCHS, (Scheme 21). The advantage of this method was that Bunte salts are easily prepared from available starting materials, alkyl halides not containing

sulfur by the action of sodium thiosulfate. Again, the Bunte salts do not react directly with the conjugated dienes.



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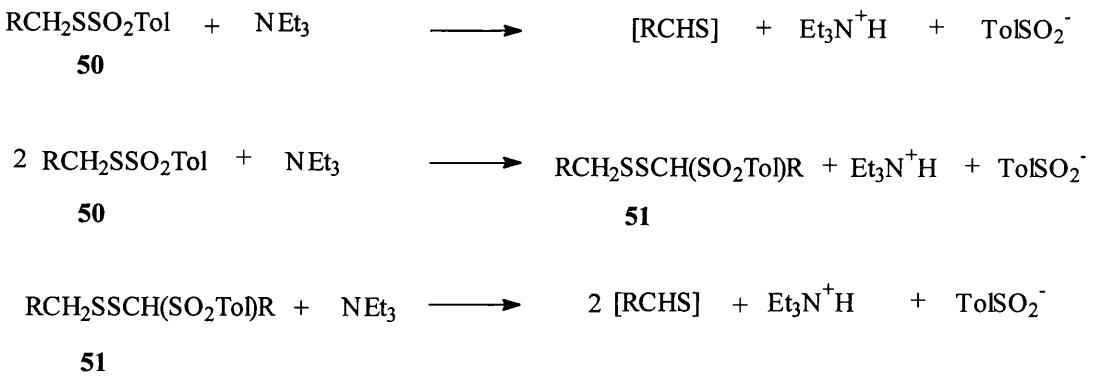
Scheme 21

The elimination again is carried out by triethylamine and the thioaldehydes are efficiently trapped provided that the nucleophilic sulfite dianion is continuously removed as its insoluble calcium salt by calcium chloride present in the reaction mixture.

Fragmentation of toluene-*p*-thiosulfonate *S*-esters [29]

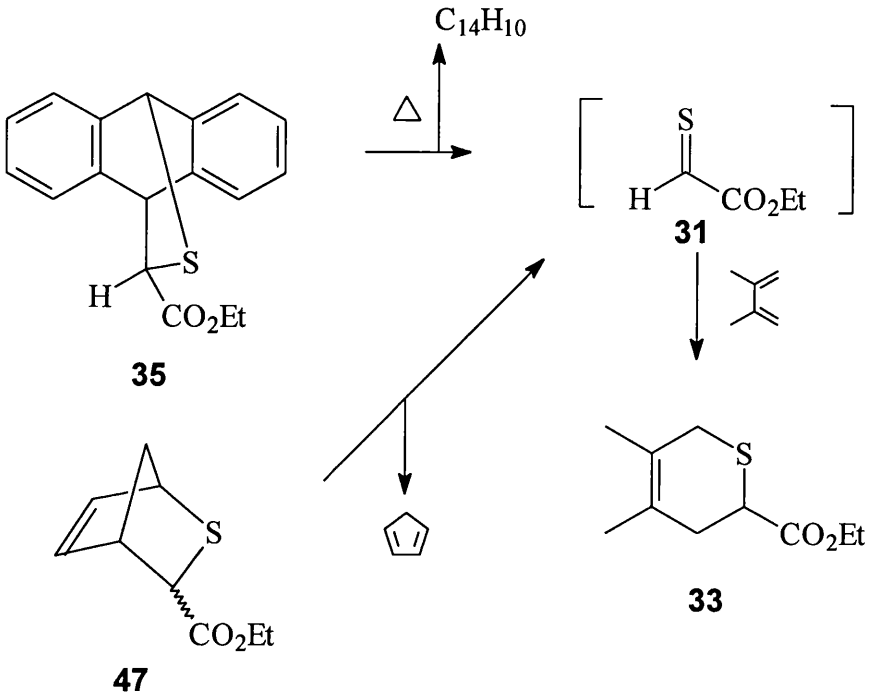
Other classes of thioaldehyde precursors, also developed by Kirby *et al.*, are the thiosulfonate *S*-esters **50** and the derived α-sulfonyl disulfides **51** (Scheme 22). Treatment of **50** with triethylamine gave the corresponding thioaldehydes, which could be trapped by dienes in the presence of calcium chloride. In the absence of the last component, the derivatives **51** were formed, even in the presence of dienes, by attack of toluene-*p*-thiosulfonate on the thioaldehydes. However, these α-sulfonyl disulfides **51**, when treated alone with triethylamine, gave 2 equivalents of thioaldehyde cleanly.



Scheme 22

The foregoing examples of thioaldehyde generation show how readily they can be formed under mild conditions. The reactive species are easily trapped *in situ* as cycloadducts, thus preventing polymerisation.

A useful property of certain thioaldehyde cycloadducts is their ability to undergo a retro Diels-Alder reaction when heated. Thus Bladon *et al.* [23] showed that ethyl thioxoacetate **31** could be generated from the anthracene **35** or cyclopentadiene **47** cycloadducts in toluene at 100-110 °C. The thioaldehyde can be trapped with another diene, for example 2,3-dimethyl-1,3-butadiene, as it is formed to give the cycloadduct **33** (Scheme 23). Kirby and his group first used this method with nitrosocarbonyl dienophiles [30]. Baldwin and Lopez also showed that the anthracene adducts of thiobenzaldehyde **29** could be used as a precursor of the thial.

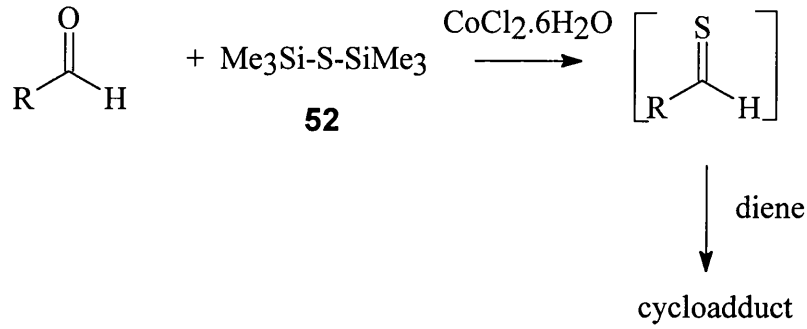


Scheme 23

Following the earlier studies many other methods of thioaldehyde generation have also been developed which are suitable for the trapping of the intermediate thioaldehydes.

1.2.4 Conversion of an aldehyde to a thioaldehyde

Capperucci *et al.* [31] devised a method for directly converting aldehydes into thials which could be trapped *in situ*. Previous methods had generally involved the use of hydrogen sulfide. Treatment of bis(trimethylsilyl) sulfide **52** with a catalytic amount of $CoCl_2 \cdot 6H_2O$ in the presence of aldehydes afforded the corresponding thiocarbonyl compound (Scheme 24). This method was good with aromatic aldehydes and aldehydes bearing an electron withdrawing group. It shows high chemoselectivity in that selective thionation of aldehydes occurs in the presence of other carbonyl groups.



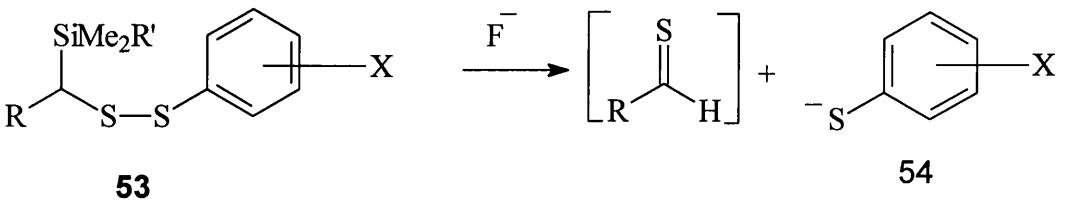
Scheme 24

Other metal salts were found to be unsatisfactory. However, following the idea that in the thionation step a suitable activation of the carbonyl group might favour subsequent attack by nucleophiles such as $Me_3Si\text{-}S\text{-}SiMe_3$, the highly oxophilic agent $CF_3SO_3SiMe_3$ was used as a catalyst for inducing the thionation process. $TfOSiMe_3$ catalysis was found to have a unique effect. The *endo* or the *exo* Diels-Alder cyclohexadiene cycloadduct may be obtained as the predominant diastereomer by simply varying the molar ratio of the sulfurating agent. Thus a 2 : 1 ratio of $(Me_3Si)_2S$: aldehyde gave mainly the *endo* isomer, while a 1 : 1 ratio gave mainly the *exo* isomer.

1.2.5 Fluoride induced elimination of α-silyldisulfides - 1985

Krafft and Meinke [32] also reported a mild, efficient method of generating thioaldehydes, *viz.* from the silyl disulfides **53** (Scheme 25). The efficiency of cleavage and the stability of the disulfide depended on the stability of the aryl thiolate leaving group **54**, with the 2-nitro and 4-chloro substituted phenyl disulfides being good precursors. Unsubstituted phenyl disulfides required an elevated temperature. Thioaldehydes were generated slowly at room temperature with cesium fluoride or

potassium fluoride but tetrabutylammonium fluoride generated thioaldehydes rapidly at -78 °C.



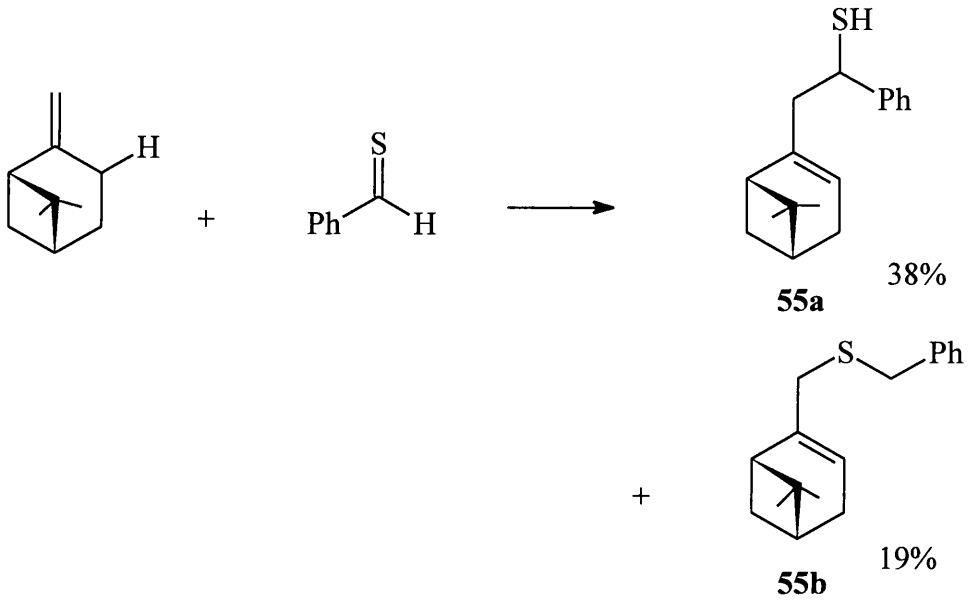
53 **54**

Scheme 25

1.3 Synthetic uses of thioaldehydes

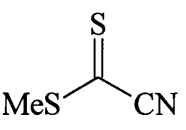
1.3.1 'Ene' reactions

Another useful reaction of thioaldehydes is their ability to undergo the 'ene' reaction. 'Ene' reactions of thioaldehydes may proceed with C-C bond formation to give thiols or with C-S bond formation to give sulfides. Both pathways have been observed for the *inter*molecular 'ene' reactions. In 1983 Baldwin and Lopez [20] reported the *inter*molecular 'ene' reaction between thiobenzaldehyde and β-pinene with the thiol **55a** being produced as the major product in 38% yield while the sulfide **55b** was produced in 19% yield (Scheme 26).

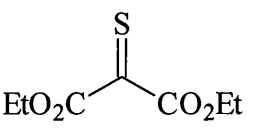


Scheme 26

Kirby *et al.*[23] then showed predominant sulfide formation when ethyl thioxoacetate **31** underwent an *inter*molecular 'ene' reaction with β-pinene. The thiol was formed in 21% yield while the sulfide was formed in 78% yield. Vedejs *et al.* [33] also studied this reaction with methyl thioxoacetate **40** and it was found to react with predominant C-S bond formation. This predominant C-S bond formation resembles the dithioester **56a** and thioketone **56b** which react with β-pinene to give the corresponding sulfides as the sole products.

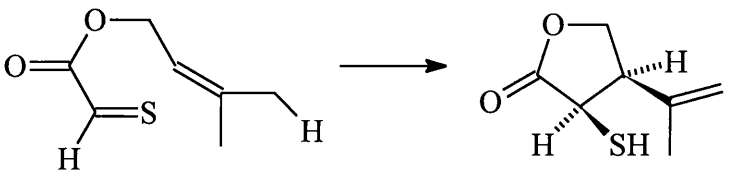


56a



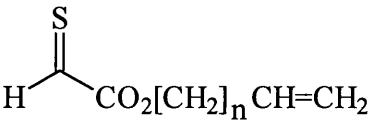
56b

Further studies by Kirby *et al.*[34a] have shown that various allylic and homoallylic thioxoacetic esters underwent *intra*molecular 'ene' reactions. In all cases the enophilic thioaldehyde groups attacked the allylic component of the alkenyl group with C-C bond formation to form α-mercapto lactones *e.g.* **57**, rather than C-S bond



57

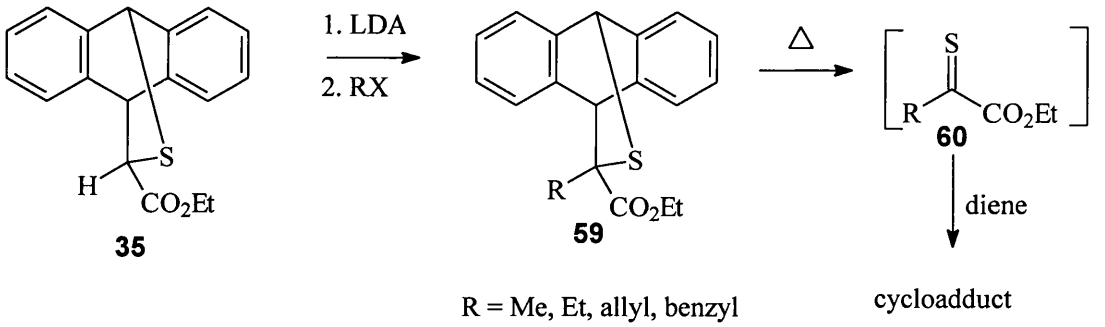
formation to form a sulfide. A further group[34b] of alkenyl thioxoacetates **58** with terminal double bonds, have been formed which also underwent *intra*molecular 'ene' reactions, but this time with C-S bond formation to give a series of thia-alkenolides having 6 to 11 membered rings. The outcome of concerted *intra*molecular 'ene' reactions must depend more on conformational rather than electronic effects.



58

1.3.2 α-Alkylation of thioaldehyde cycloadducts

The Diels-Alder cycloadducts of thioaldehydes have found a variety of uses in synthesis. It is found that the sulfur atom in the ring enhances the acidity of the adjacent proton, enabling it to be removed by base giving the possibility of alkylation at the α position. Kirby *et al.* [35] showed that a variety of α-alkyl substituted thioaldehyde cycloadducts **59** could be formed from the thioaldehyde adducts of anthracene **35** and other dienes. These cycloadducts then underwent retro Diels-Alder reactions to form the thioketones **60** (Scheme 27).

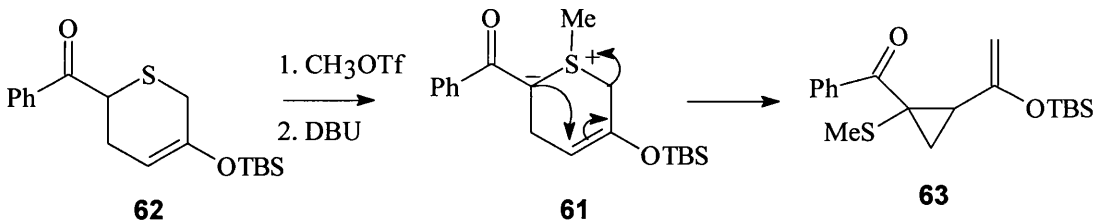


Scheme 27

1.3.3 Rearrangements of thioaldehyde cycloadducts

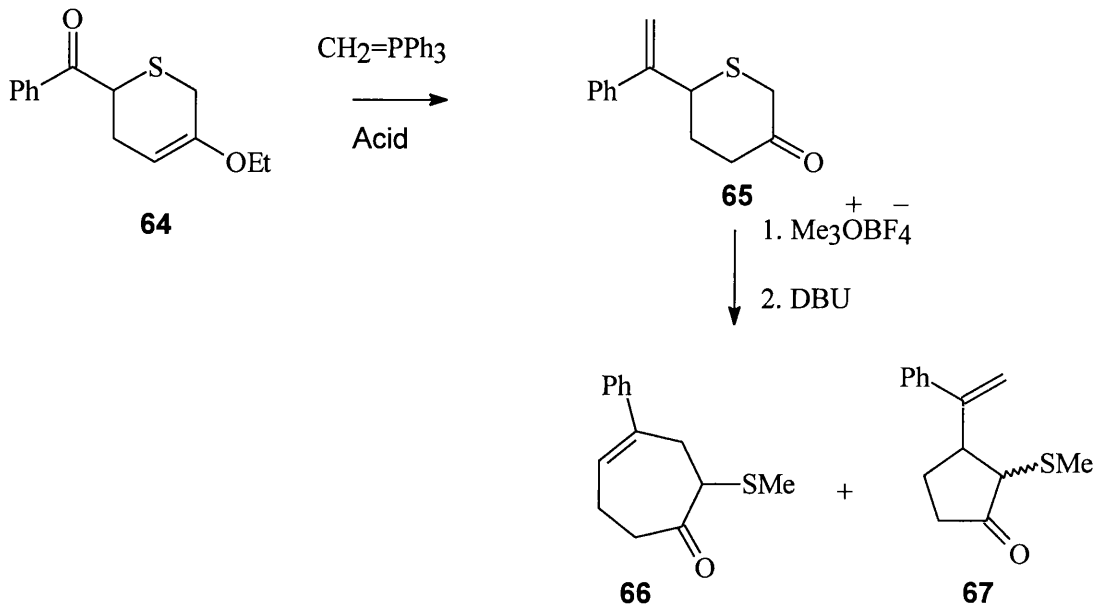
Thioaldehyde cycloadducts have also been shown to undergo a variety of rearrangements and are useful as synthetic precursors to a wide variety of ring systems. Ramberg-Backlund sulfur extrusion has been used to prepare cyclopentane derivatives [36].

Vedejs *et al.* [37] has also shown a variety of other possibilities by first alkylating the sulfur followed by formation of the ylid **61** by abstracting the α proton with a base such as DBU. Such treatment of the thioaldehyde **62** adduct gives a cyclopropane structure **63** after rearrangement (Scheme 28). Conversion of the



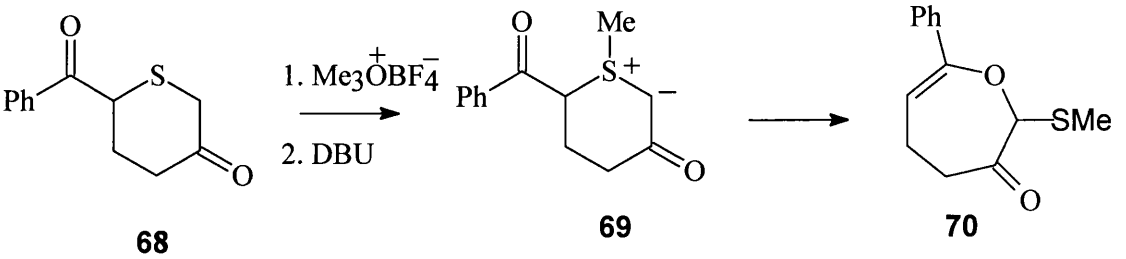
Scheme 28

thioaldehyde adduct **64** into the corresponding ketone **65** followed by treatment as above yielded a ring expansion product, the cycloheptenone **66** together with traces of the cyclopentanone **67**, the Stevens rearranged product (Scheme 29). Similar treatment of the diketone **68** again yielded the ylid intermediate **69** which rearranged



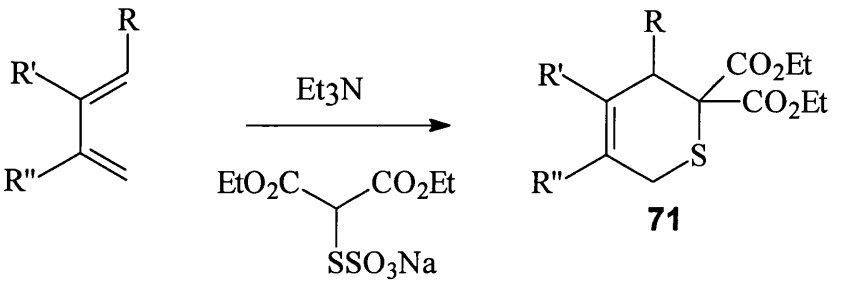
Scheme 29

to the cyclic enol ether **70**. Rearrangement can be viewed as 2,3-shift involving the benzoyl C=O group in the migrating 3 atom component (Scheme 30).



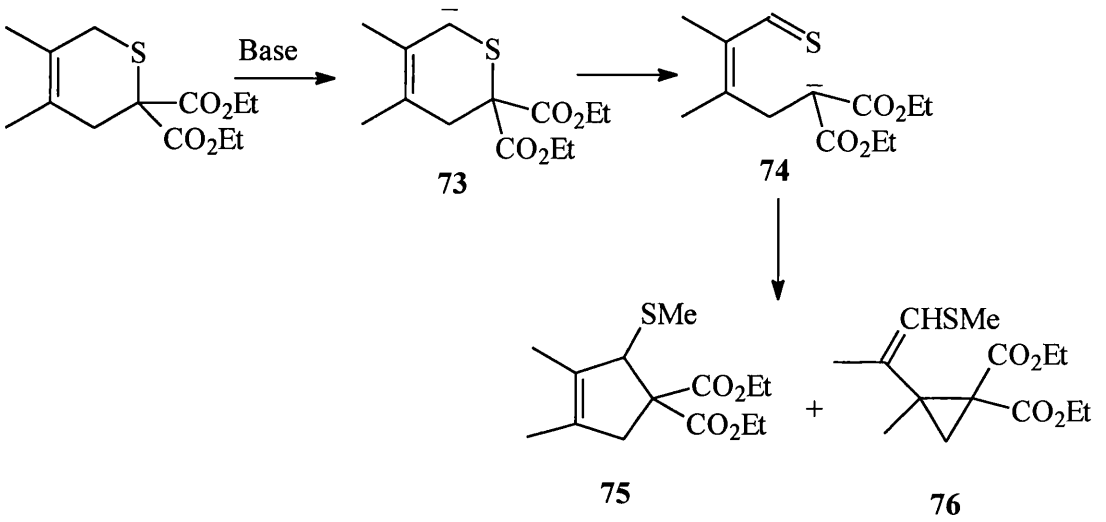
Scheme 30

Larsen [38] also reported a set of carbanion rearrangements to form cyclopentanes and cyclopropanes from the monocyclic cycloadducts of diethyl thioxomalonate **71,** which were prepared from the corresponding Bunte salt **72** and a wide variety of dienes (Scheme 31).



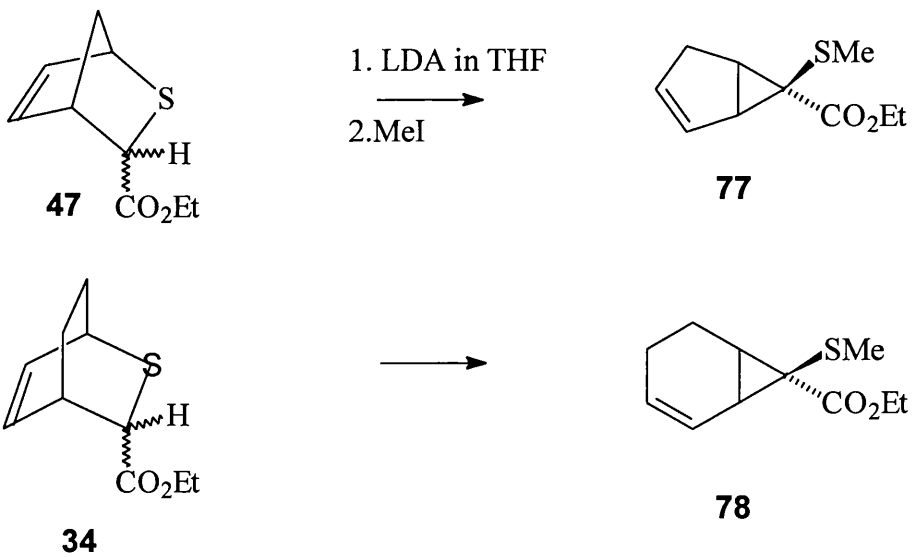
Scheme 31

When the cycloadducts were exposed to either $LiN(Pr^i)_2$ or $KN(SiMe_3)_2$ followed by quenching with methyl iodide a ring contraction occurred leading to cyclopentanes. The first stage involves deprotonation α to the sulfur to give **73** then β-elimination of the more stable malonate carbanion occurs to give **74**. The reactive C=S could then be attacked internally by 1,2-addition to give, after methylation, the cyclopentane **75**. Alternatively, 1,4-addition to the enal system gave the cyclopropane **76** (Scheme 32).



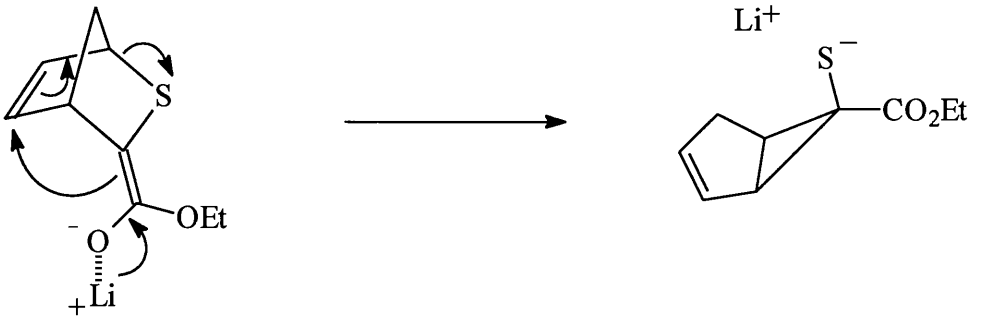
Scheme 32

Kirby *et al.* [35] also carried out some rearrangement reactions. When treated with LDA and methyl iodide, the ethyl thioxoacetate cycloadducts of cyclopentadiene **47** and cyclohexadiene **34** underwent rearrangement and *S*-methylation, rather than *C*-methylation, and afforded the cyclopropanecarboxylates **77** and **78** (Scheme 33).



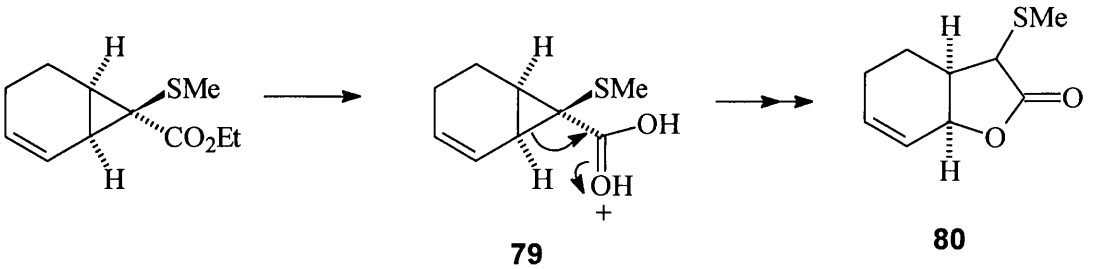
Scheme 33

The formation of the cyclopropanecarboxylate as a single stereoisomer may be explained by a concerted rearrangement (Scheme 34). It was also shown that the



Scheme 34

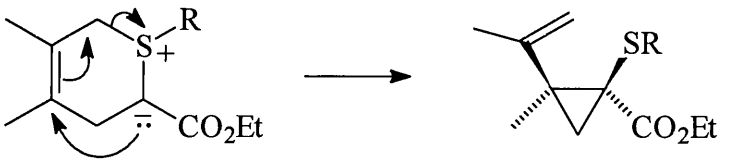
cyclopropanecarboxylic acid corresponding to the ester **78** rearranged slowly in the crystalline state to give the epimeric γ-lactone **80** (Scheme 35). The protonated acid **79** was proposed as an intermediate.



79 **80**

Scheme 35

More examples [35] of rearrangement of the sulfur ylids were also provided. Thioaldehyde cycloadducts were treated with trimethyloxonium tetafluoroborate or triethyloxonium tetrafluoroborate followed by DBN and again substituted, functionalised cyclopropanes **82** were formed stereospecifically (Scheme 36).

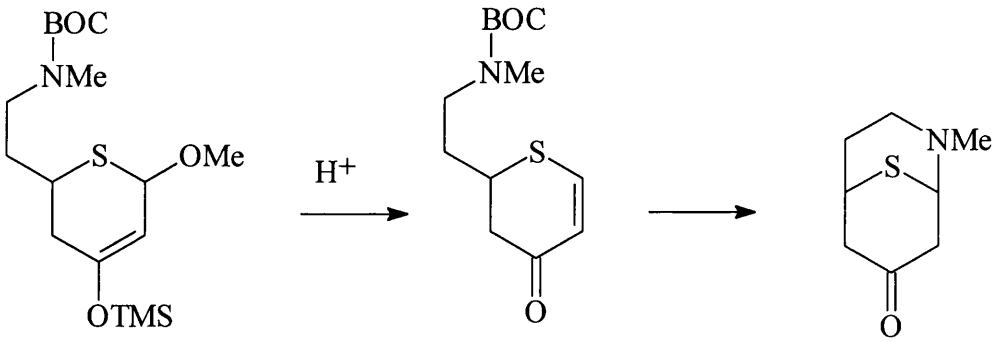


81 **82**

Scheme 36

1.3.4 Ring expansion

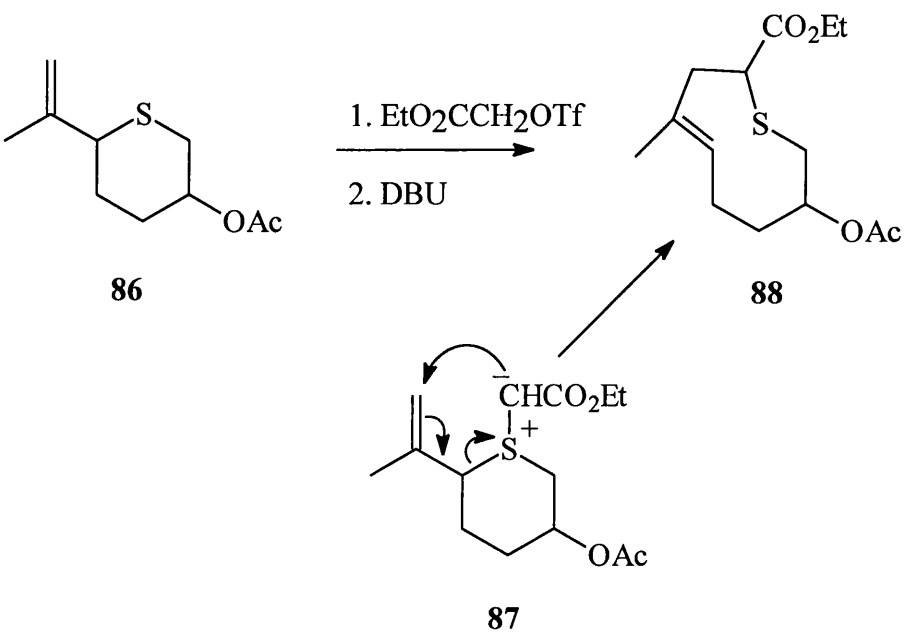
Vedejs *et al.* reported many examples of ring expansion [39,37] and often used 6-membered thioaldehyde cycloadducts as starting materials for subsequent reactions. An example is shown in the αα' bridging process. The thioaldehyde cycloadduct **83** gave the dihydrothiopyrone **84** after mild acid treatment. Then after deprotection, the resulting amine underwent Michael addition to give **85**. The sulfur could then be removed if required to provide a large carboxylic ring (Scheme 37).



83 **84** **85**

Scheme 37

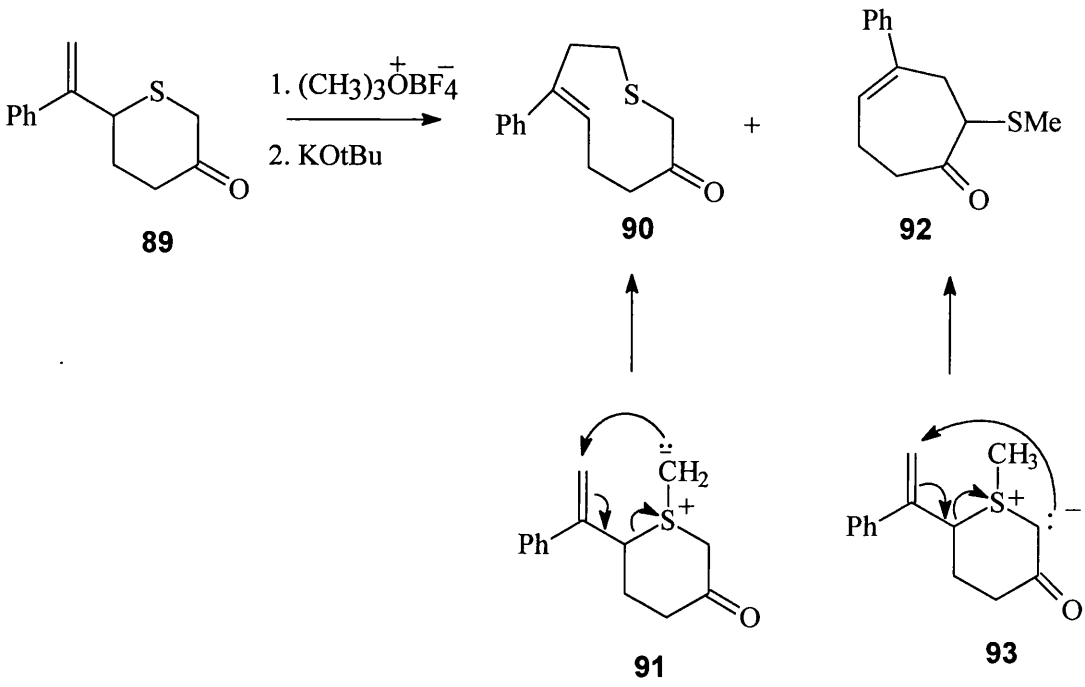
Other examples of ring expansion products were formed *via* the sulfur ylids derived from thioaldehyde cycloadducts. The adduct **86** was treated with a triflate to form a sulfonium ion. Deprotonation with base formed the ylid **87** which then underwent rearrangement to form the 9-membered ring compound **88** (Scheme 38).



86 **88** **87**

Scheme 38

A similar example involved methylation of **89** with trimethyloxonium tetrafluoroborate followed by ylid formation by deprotonation with potassium *t*-butoxide. The deprotonation can occur at two sites and **90** was formed in 32% yield *via* the kinetically favoured methylid **91**, while **92** was formed in 11% yield, by rearrangement of the carbonyl stabilised ylid **93** (Scheme 39).



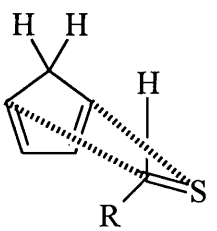
Scheme 39

1.4 Diastereoselectivity in Diels-Alder reactions

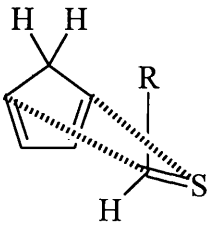
As the foregoing section has shown, the Diels-Alder cycloadducts of thioaldehydes can be utilised in many ways to provide interesting products. Another aspect of the Diels-Alder reaction is its stereoselectivity. It has been shown many times that the reaction of thioaldehydes with cyclopentadiene gives preferentially the *endo* isomer, which is the kinetic product, rather than the more stable *exo* isomer. Thermal equilibration of this mixture gives the *exo* adduct as the major component. The highest kinetic selectivity is observed for thioaldehydes RCHS where R is a bulky alkyl group such as *tert*-butyl or isopropyl. Secondary orbital overlap is apparently a small factor in these reactions. For example α-oxo thioaldehydes react with relatively low *endo* selectivity, therefore steric effects are primarily responsible.

In the transition state leading to *exo* cycloadducts (Scheme 40), the group R of RCHS interacts with the CH_2 group of cyclopentadiene, while in the *endo* transition

state the group R interacts with an sp^2-hybridised centre. As bonding proceeds in the *exo* addition, the separation between the CH_2 group and R increases as the cyclopentadiene becomes bent, and the energy difference between the *endo* and *exo* products is modest. In contrast, the energy difference in an early transition state can be quite large.



ENDO

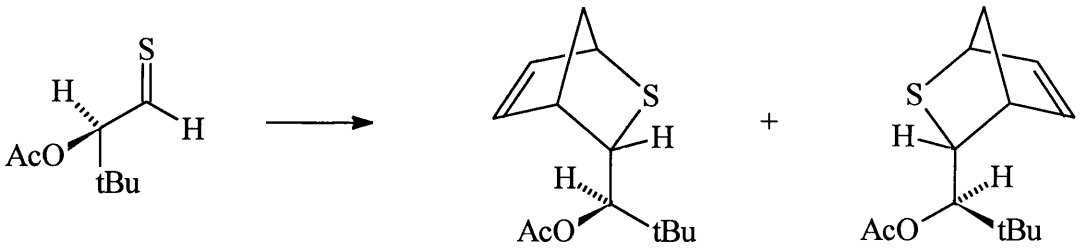


EXO

Scheme 40

Given the many options for removal or modification of the sulfur substituent, useful methodology for control of remote stereochemistry would result if there is a strong bias for a single conformation.

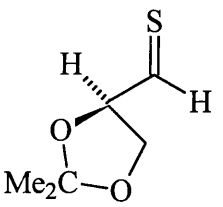
Vedejs *et al.* [40] prepared a series of thioaldehyde precursors having systematically varied substituents α to the eventual thioformyl group. They found that chiral, α-oxygen substituted thioaldehydes react with modest thioformyl face selectivity (Scheme 41). They obtained d.e. values for *endo* adducts, ranging from 30 to 80%. The highest facial selectivity (d.e. = 94% for *endo* adducts) was obtained with the acetonide of thioglyceraldehyde **94**.



82%

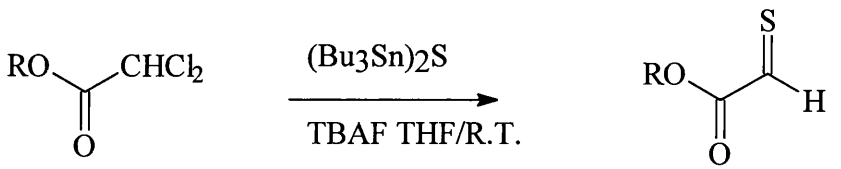
9%

Scheme 41



94

Takahashi *et al.* [41] also reported a study of the asymmetric Diels-Alder reactions of thioaldehydes having an optically active group. They studied the asymmetric induction using some commercially available alcohols. The thioaldehydes **95** were prepared from the corresponding 2,2-dichloroacetates **96** and S^{2-}, which was formed *in situ* by a fluorodestannylation reaction of bis(tributyltin) sulfide with tetrabutylammonium fluoride, TBAF (Scheme 42).

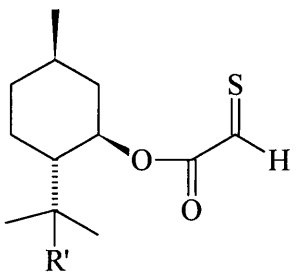


96 **95**

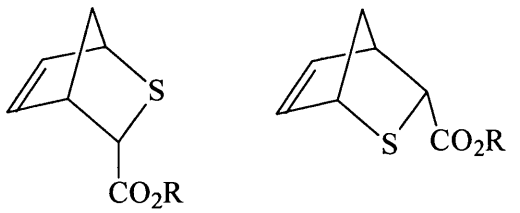
ROH = (1*S*)-*endo*-(-)-borneol
(*S*)-(-)-α-phenylethyl alcohol
(-)-menthol
(-)-8-phenylmenthol

Scheme 42

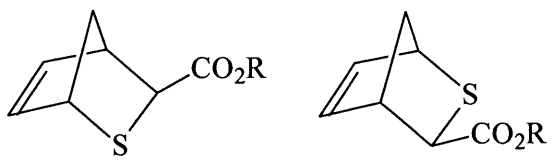
For the series of menthyl derivatives **97** (Scheme 43) it was found that the d.e. of the *endo* cyclopentadiene adducts increased from 14 to 23% when the hydrogen (R') of the isopropyl group was replaced by phenyl. A π-π stacking effect between the phenyl group of the auxiliary and the thiocarbonyl group was suggested as the reason for the increased diastereofacial selection.



97



endo adducts



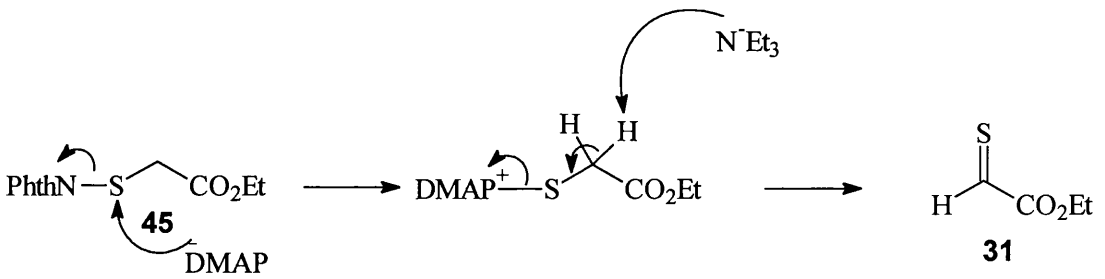
exo adducts

Scheme 43

Various other derivatives **97**, having R' = *p*-XC_6H_4 were then designed. The highest diastereoselectivity for the *endo* adduct (43%) was obtained where R'=*p*-$Bu^tC_6H_4$ and that for the *exo* cycloadducts was highest (58%) where R'=p-FC_6H_4. These results were explained by the steric effects of the *p-tert*-butyl group and the electronic effect of the fluorine atom, respectively.

1.5 Unexpected reactions of thioaldehydes

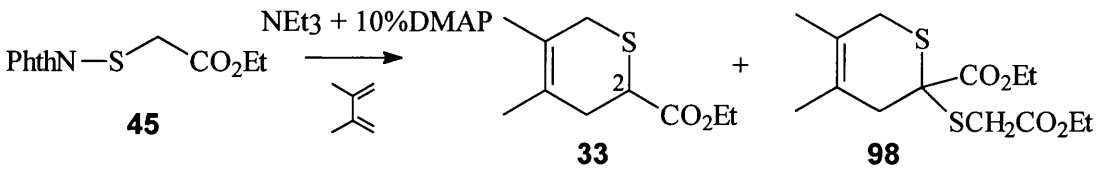
As previously mentioned, ethyl phthalimidosulfanylacetate **45** had been found to be an excellent precursor of ethyl thioxoacetate **31**. Further to this discovery it had been decided that the addition of a small amount of 4-dimethylaminopyridine, DMAP might speed up the reaction by participating in nucleophilic catalysis, as tertiary amines are commonly used for this purpose. DMAP is a powerful nucleophile but a weaker base than triethylamine, so it could attack the sulfur and expel the phthalimido ion. The triethylamine would then deprotonate the resulting quaternary ammonium cation with elimination of the DMAP to generate the thioaldehyde **31** (Scheme 44).



Scheme 44

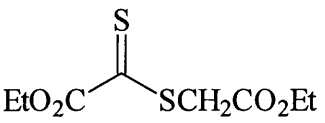
It was found however, that although the addition of DMAP did speed up the reaction the product trapped by the dimethylbutadiene was not simply the thioaldehyde adduct **33**. Instead a mixture of two products was formed, the expected

thioaldehyde cycloadduct **33** together with an α-sulfenylated derivative **98** (Scheme 45) [42].



Scheme 45

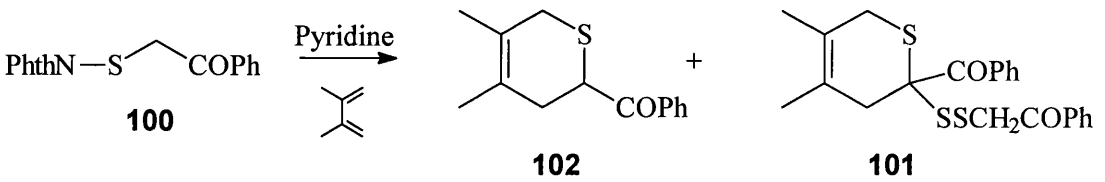
This α-sulfenylated derivative **98** of **33** was thought to have been formed from the dithioester **99**. A pink colour, characteristic of dithioesters, had been observed in the reaction mixture, but the colour was discharged during attempts to isolate the putative intermediate **99**. In a control experiment, it was shown that 2-H of the cycloadduct **33** did not exchange with deuterium in the presence of triethylamine and CD_3OD, nor was deuterium incorporated into the adduct **33** when it was prepared in a reaction mixture containing CD_3OD. Consequently, the abnormal product **98** could not have arisen from the normal adduct **33** by sulfenylation by the precursor **45**.



99

The formation of the unusual cycloadduct **98** is in some respects similar to that observed recently by Capozzi *et al.* [43]. They found that treatment of the *N*-phthaloyl β-oxo sulfenamide **100** with pyridine in the presence of dimethylbutadiene gave a product **101** containing a *disulfide* substituent at the α position of the expected thioaldehyde cycloadduct **102** together with the cycloadduct **102** itself (Scheme 46).

The unexpected structure **101** was determined unambiguously by X-ray crystallography. The reaction with cyclohexadiene gave only the expected thioaldehyde cycloadduct. The origin of the abnormal product **101** was not explained except that it was 'likely due to some oxidative processes which often occur in sulfenamide chemistry'.



100 **102** **101**

Scheme 46

CHAPTER TWO

Preparation and reactions of *N*-phthaloyl sulfenamides

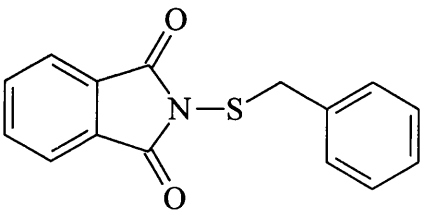
Further studies were required to elucidate the mechanism of formation of Lochead's [42] abnormal product **98**, in particular to confirm or disprove that it arose by cycloaddition of the dithioester **99** on dimethylbutadiene. Again, the origin of the product **101** described by Capozzi *et al.*[43] required clarification. No explanation has been given so far for the formation of these products.

It was therefore necessary to synthesise the *N*-phthaloyl sulfenamides required for these reactions. A number of *N*-phthaloyl sulfenamides were prepared both to continue work already undertaken by Lochead and also to provide precursors for thioaldehydes.

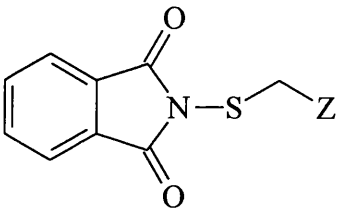
2.1 Preparation of the ester 38 and 45 and benzyl 103 *N*-phthaloyl sulfenamides

2.1.1 *N*-Bromophthalimide method

The first method used to prepare these derivatives was that devised by Buchel and Conte[44] for the preparation of the benzyl derivative **103** and later used by Kirby and Lochead[24] to prepare the methyl **38** and ethyl **45** ester derivatives. This general method involved the reaction of the corresponding disulfide **104** with *N*-bromophthalimide **105** under radical conditions.



103



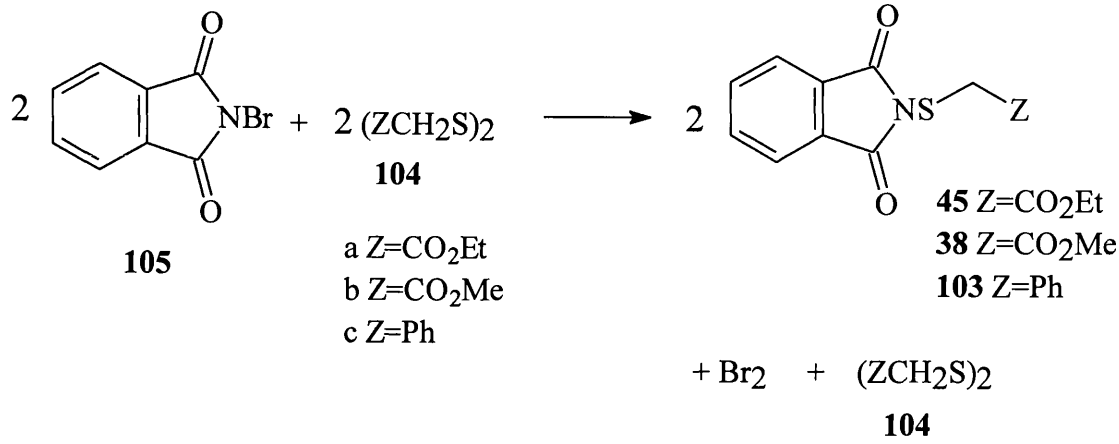
45 Z = CO_2Et

38 Z = CO_2Me

The disulfides **104** were prepared by oxidation of the corresponding thiols with iodine. The oxidation takes place quickly and in excellent yield. Ethyl 2-mercaptoacetate **37** was oxidised to give an oil **104a** whereas phenylmethanethiol gave dibenzyl disulfide **104c**, a white crystalline solid. A sample of the methyl ester disulfide **104b** was already available.

The *N*-bromophthalimide **105** was prepared according to the method of Bredt and Hof [45]. An aqueous solution of phthalimide in sodium hydroxide at 0 °C was added to an aqueous solution of bromine at 0 °C. The precipitate of *N*-bromophthalimide was then recrystallized from ethanol.

The radical reaction was carried out following the literature methods. *N*-Bromophthalimide was heated with benzene containing a catalytic amount of dibenzoyl peroxide (Scheme 47). Bromine was formed immediately when the disulfide **104** was added but dilution of the reaction mixture with hexane precipitated phthalimide rather than the *N*-phthaloyl sulfenamide.



Scheme 47

This general reaction was carried out many times with variations. It was found that bromine could be formed at room temperature without any radical initiator present, but always phthalimide was produced along with some of the desired products. It was thought that a trace of thiol, sometimes present in the disulfides might have been responsible for the previous successes but addition of a trace of thiol produced no change in the reaction pathway. These reactions compare with those of Lochead who found that with some batches of disulfides the yields were substantially lower than before and the reactions were not always reproducible.

It was found that the greatest yield obtainable by this method (15%) (lit.[44] 80%) was for the *N*-phthaloyl sulfenamide **103** derived from dibenzyl disulfide. Only a tiny amount of the methyl **38** (lit.[24] 70%) and ethyl **45** esters (lit.[24] 67%) were formed. The yields were based on the bromophthalimide, since only half the disulfide can be consumed theoretically.

2.1.2 Potassium phthalimide method

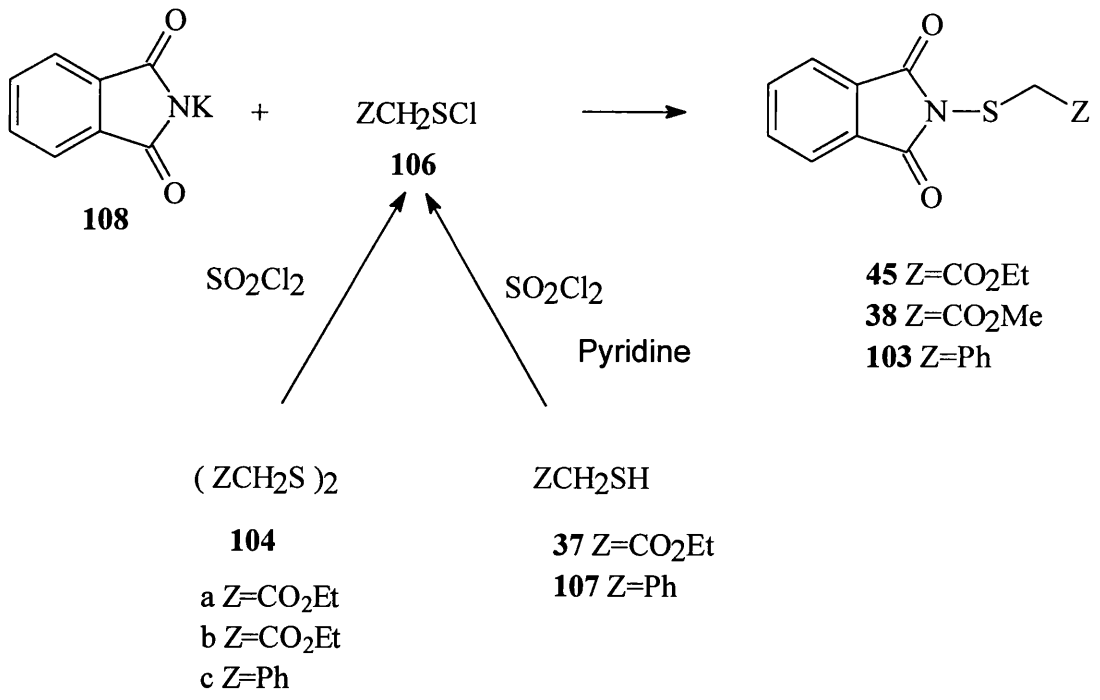
As the method originally used to prepare the *N*-phthaloyl sulfenamides did not appear to be reproducible, another method had to be found. The method of Woulfe

and Miller [46], which had been used to prepare the methyl ester derivative **38** was then investigated.

This method involved the reaction of the sulfenyl chloride **106b**, derived from methyl mercaptoacetate MeO_2CCH_2SH, with potassium phthalimide. The drawback with this method is that potassium phthalimide is insoluble in all appropriate solvents and the reaction must be heterogeneous.

The procedure was carried out as follows for both the ethyl ester **45** and benzyl derivative **103**. The corresponding thiol **37** or **107** and pyridine in carbon tetrachloride were added dropwise to a stirred solution of sulfuryl chloride in carbon tetrachloride at 0 °C. After 20 min the precipitated pyridine hydrochloride was filtered off and 1,2-dichloroethane used to dilute the filtrate containing the sulfenyl chloride **106**. Solid potassium phthalimide **108** was then added with stirring at 0 °C. The yellow colour of the sulfenyl chloride quickly vanished.

This method appeared to work consistently and continued to work after a few alterations were made to the procedure (Scheme 48). It was found that dichloromethane could be used instead of 1,2-dichloroethane to dilute the sulfenyl chloride solution. Also the original method recommends evaporation of the final filtrate and recrystallisation of the resulting residue to yield the product. It was found, however, that evaporation to low volume and dilution with light petroleum precipitated the product as a light, fluffy, crystalline solid in 50% yield (lit.[46] ~ 50%) which generally required no further purification. It was very important to cool the sulfenyl chloride solution adequately, preferably below 0 °C, before addition of potassium phthalimide. Indeed failure to do so produced an orange colour after initial decolorisation of sulfenyl chloride and gave low yields of impure product. On one occasion the mixture became purple, but the cause of this was never pursued.



Scheme 48

The synthesis of sulfenyl chlorides by halogenation of thiols can also be problematic and does not always proceed as smoothly as indicated by the following schematic equation for the overall reaction.

1. R-SH + Cl_2 → R-SCl + HCl
2. R-SH + R-SCl → R-SS-R + HCl
3. RSSR + Cl_2 → 2R-SCl

Overall:

2R-SH + $2Cl_2$ → 2R-SCl + 2HCl

The halogenation is effected by three partial equations. Firstly the thiol is converted into the desired sulfenyl chloride, which can react in the second phase with unconverted thiol giving disulfide. The third partial reaction represents a disulfide chlorinolysis.

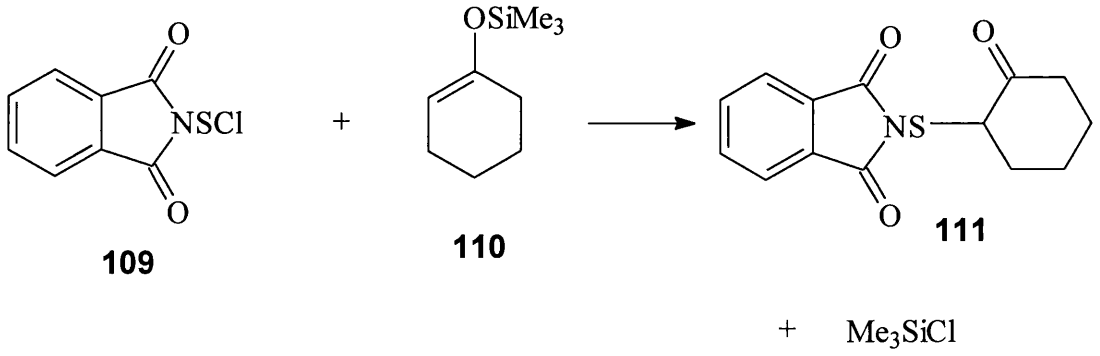
The thiols are converted cleanly into sulfenyl chlorides when added to the chlorinating agent in an inert solvent, in accordance with step 1.

It was found that the chlorinolysis of the corresponding disulfide occurred as easily as that of the thiol and could be carried out at room temperature. The disulfides were prepared as before by oxidation of the thiols. The reaction is carried out without the presence of pyridine thereby giving a sulfenyl chloride solution free from pyridine hydrochloride. *N*-Chlorosuccinimide was also used as a chlorinating agent, for thiols with the sulfenyl chloride solution being decanted from the precipitate of succinimide. Sulfuryl chloride however, was found to be more effective and easier to use as *N*-chlorosuccinimide has to be purified before use.

The reactions with both thiol and disulfide were always successful and therefore seemed to be the desired method by which to prepare the *N*-phthaloyl sulfenamides.

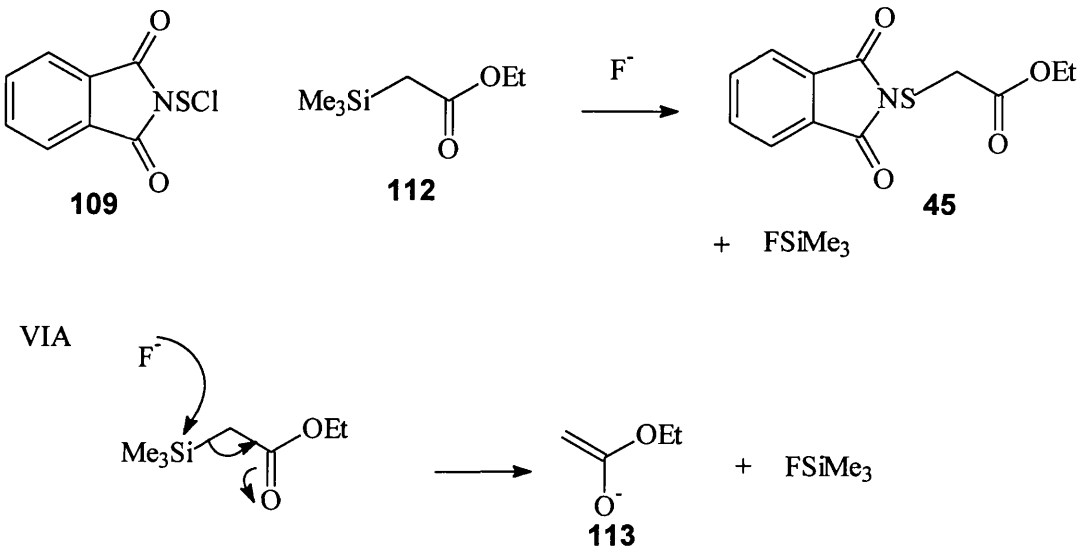
2.1.3 Silicon method

While the sulfenyl chloride method to prepare the *N*-phthaloyl sulfenamides was being studied an alternative method was devised. It was known that the reaction of phthalimidosulfenyl chloride **109** with the trimethylsilyl enol ether **110** derived from cyclohexanone yielded the *N*-phthaloyl sulfenamide **111** in almost quantitative yield [43] (Scheme 49).



Scheme 49

With this in mind it was thought that the same type of process could be applied to the formation of ethyl phthalimidosulfanylacetate **45** with CH_2=C(OEt)OSiMe_3. This O-silylated compound is difficult to make in its pure form and would have to be used as a mixture with the C-silylated isomer **112**. An alternative approach was decided on however, whereby the C-silylated compound **112** would be used instead and fluoride ion induced elimination (with TBAF or CsF) of Me_3Si would provide the enolate **113** required to form the *N*-phthaloyl sulfenamide **45** (Scheme 50).



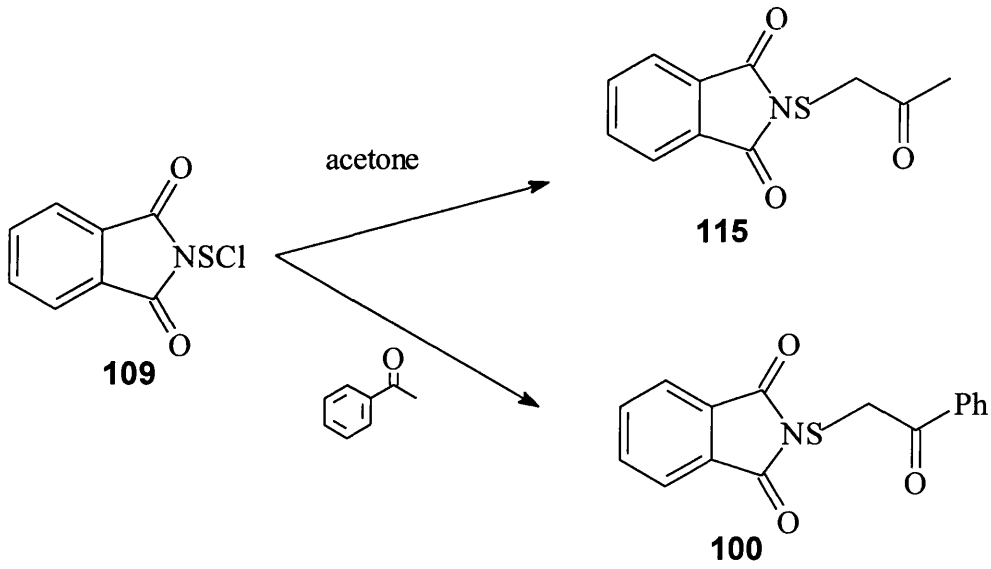
Scheme 50

Ethyl trimethylsilylacetate (ETSA) **112** was prepared from ethyl bromoacetate and chlorotrimethylsilane with zinc under Reformatsky conditions [47]. The reaction proceeds better when a small amount of copper (1) chloride is present. The phthalimidosulfenyl chloride **109** was prepared by the chlorinolysis of *N,N'*-dithiobisphthalimide **114** and will be described in the following section. The reaction to form the phthaloyl sulfenamide **45** was attempted but no product was obtained only phthalimide. This approach was not pursued further however, as the sulfenyl chloride method had proved to be suitable.

2.2 Formation of the *N*-phthaloyl β-oxo sulfenamides 100 and 115

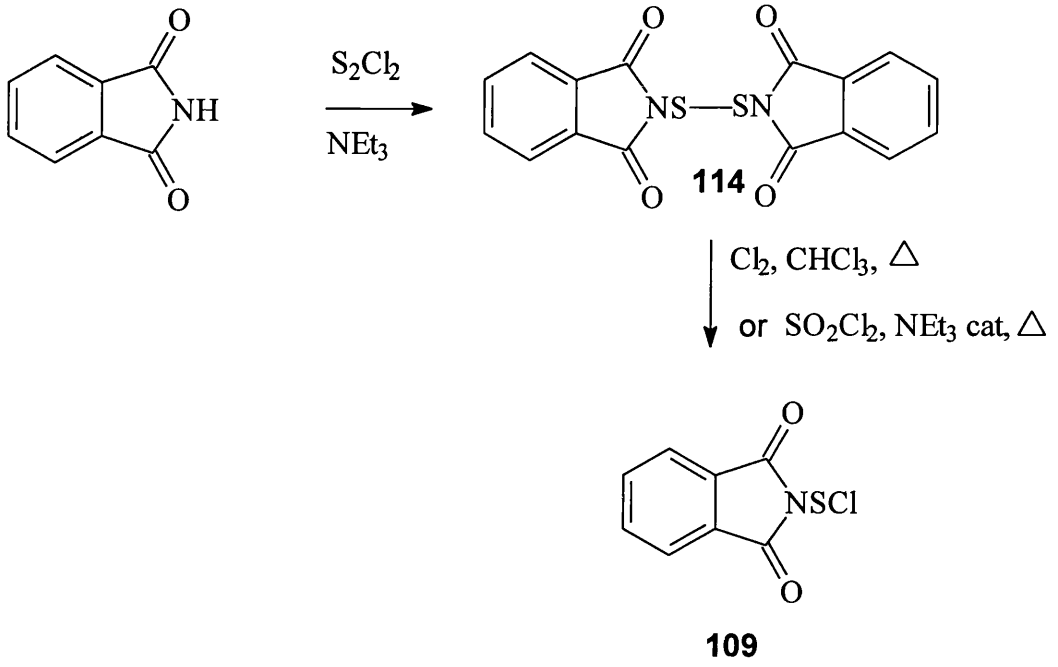
A number of phthaloyl β-oxo sulfenamides have been prepared by Capozzi *et al.* [43] by treating phthalimidosulfenyl chloride **109** with various enolizable ketones, using the ketone as solvent. The methyl **115** and phenyl **100** *N*-phthaloyl β-oxo sulfenamides were prepared following this method.

Phthalimidosulfenyl chloride **109** was dissolved in either acetone or acetophenone at 0 °C. The reaction was complete in less than 30 min and isolation of the phthaloyl sulfenamide was accomplished by diluting the reaction mixture with light petroleum (Scheme 51).



Scheme 51

The preparation of the phthalimidosulfenyl chloride **109** was based on the method of Bombala and Ley [48] by chlorinolysis of *N,N'*-dithiobisphthalimide **114** (Scheme 52). According to the literature method, chlorine gas was passed through a chloroform solution of the disulfide, maintained at 50-60 °C for 4 h. It was much more convenient however, to saturate a cooled mixture of the disulfide with chlorine and then heat under reflux briefly.



Scheme 52

The sulfenyl chloride **109** can also be prepared by refluxing a solution of the disulfide **114** in chloroform with sulfuryl chloride and a catalytic amount of triethylamine. This has been found to be a much more convenient way of preparing the sulfenyl chloride from easily handled reagents.

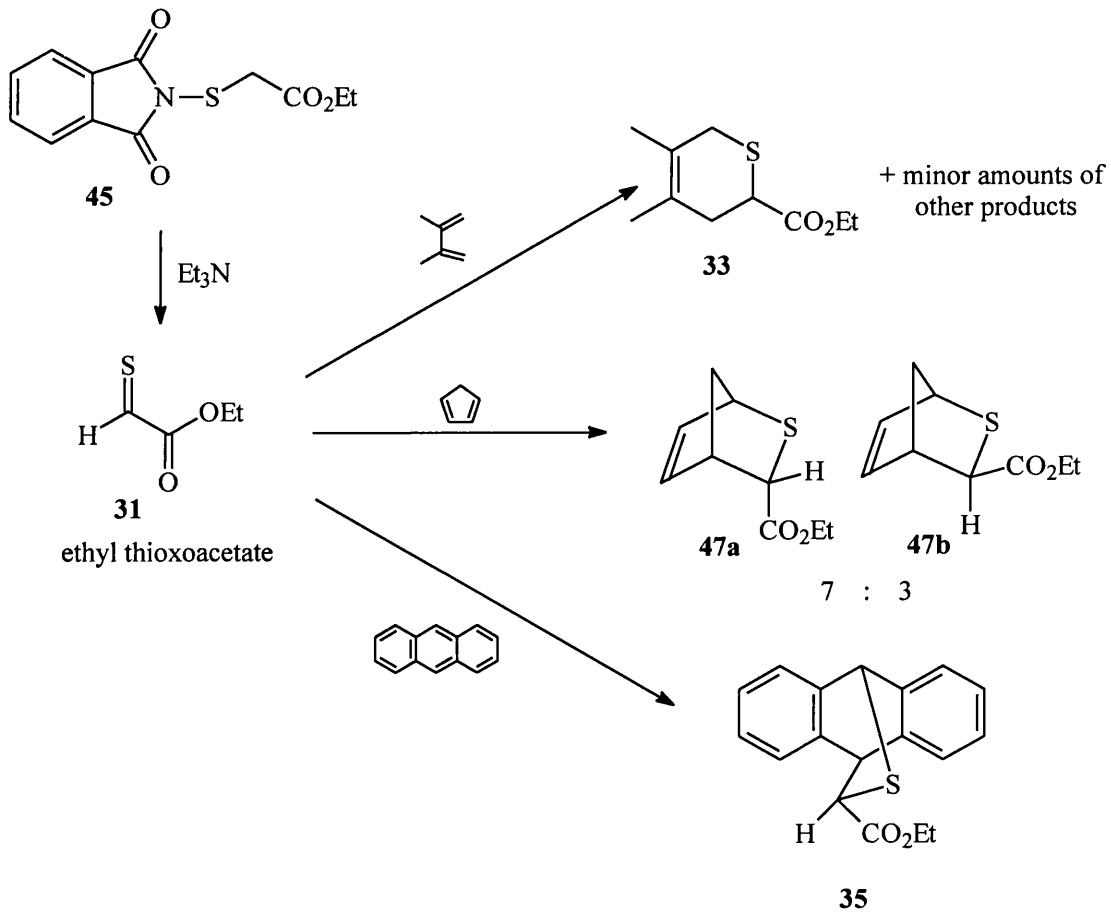
N,N'-Dithiobisphthalimide **114** was prepared by the method of Cava *et al.* [49]. A cooled mixture of phthalimide and triethylamine in THF was treated with sulfur monochloride to form the disulfide (Scheme 52). This method was found to be more successful than an earlier one by Bombala and Ley [48] who treated a suspension of potassium phthalimide in dichloromethane with sulfur monochloride.

2.3 Reactions of ethyl phthalimidosulfanylacetate 45

The *N*-phthaloyl sulfenamides were treated under various conditions with different bases and dienes. The reactions of Lochead and Capozzi were repeated and other combinations investigated.

2.3.1 Cycloadducts from ethyl phthalimidosulfanylacetate 45

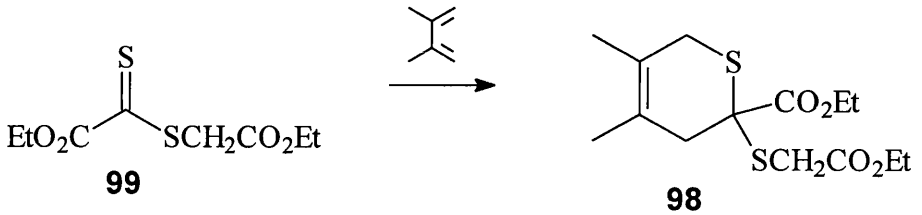
The reactions of Kirby and Lochead were repeated. As previously found, the ethyl ester, **45** when treated with triethylamine, was an excellent precursor of ethyl thioxoacetate **31**, which could be easily trapped with dienes by 2+4 Diels-Alder cycloadditions (Scheme 53). The reaction is carried out at room temperature and phthalimide precipitates out as the reaction proceeds as it is only weakly acidic. Triethylamine therefore, is not consumed during the elimination reaction and may be used in catalytic amounts, but with longer reaction times.



Scheme 53

Kirby and Lochead reported that the cycloadduct **33**, formed by treating the phthaloyl sulfenamide **45** with triethylamine and trapping with dimethylbutadiene was formed in 78% yield. It was found however, after repeating this reaction, that as well as the cycloadduct **33** two other, minor products were formed. At this point the nature of these were unknown.

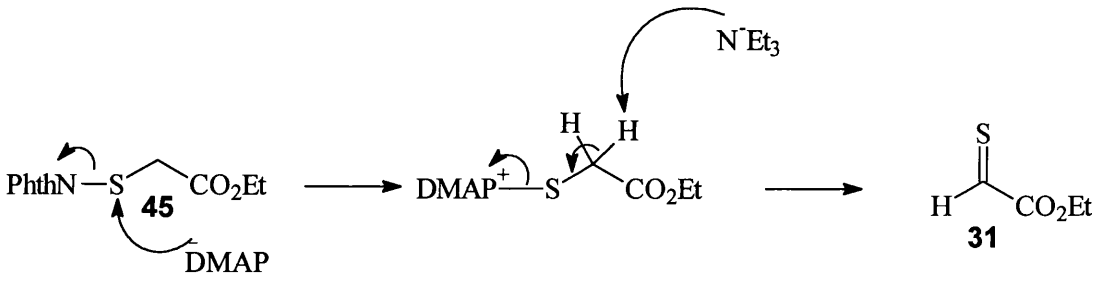
Kirby and Lochead had found that the addition of 0.1 mol equivalent of DMAP to the reaction mixture produced a mixture of two cycloadducts, the normal thioaldehyde cycloadduct **33** and also an α-sulfenylated cycloadduct **98**. This cycloadduct can be thought of as being formed by a 2+4 cycloaddition with the dithioester **99** (Scheme 54).



Scheme 54

This reaction was repeated and it too was found to produce a mixture of three products in good total yield. A transient pink colour, characteristic of dithioesters was observed during the course of the reaction and the 'abnormal' dithioester cycloadduct **98** was formed as the major component of the mixture.

The initial idea of adding DMAP to the reaction was to speed it up by assisting with nucleophilic catalysis (Scheme 44). Tertiary amines are commonly used for this purpose. DMAP would react with the phthaloyl sulfenamide **45** at sulfur as it is a more powerful nucleophile but a weaker base than triethylamine. The triethylamine would then deprotonate the cationic intermediate with elimination of the DMAP to generate the thioaldehyde **31**.

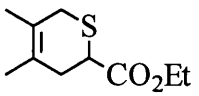
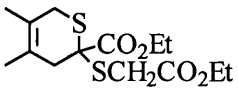


Scheme 44

Upon comparison of the products isolated from these reactions, with or without DMAP, after chromatography, it was found that the same products had been formed under both sets of conditions. The third component of the mixture was found to be the disulfide $(EtO_2CCH_2S)_2$, **104a**.

With triethylamine alone the thioaldehyde adduct **33** was formed as the major component in ~100% yield with traces of the dithioester cycloadduct **98** and disulfide **104a**. The addition of 0.1 mol equivalent of DMAP formed the dithioester cycloadduct as the major product in 86% yield. DMAP alone gave results similar to those with triethylamine and 0.1 mol equivalent of DMAP, *i.e.* the abnormal adduct **98** comprised 94% of the mixture (Table 1). The reaction rate with DMAP alone was also faster than with triethylamine alone (Table 3).

Table 1. Base-mediated elimination of ethyl phthalimidosulfanylacetate **45** in the presence of 2,3-dimethylbuta-1,3-diene (1.2 mol equiv) at room temperature in dichloromethane.

	products (%) [a]		
base (1 mol equiv)	 **33**	 **98**	$(EtO_2CCH_2S)_2$ **104a**
NEt_3	100	Trace	Trace
NEt_3 + 10% DMAP	14	86	Trace
DMAP	6	94	Trace

[a] Yields measured from the ^1H NMR spectra of crude acid and base washed product mixtures; no **45** remained.

DMAP = 4-dimethylaminopyridine

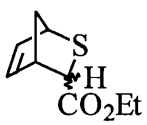
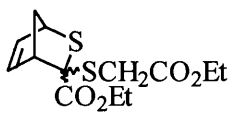
It appears that the addition of just a small amount of DMAP is all that is required to change the course of the reaction and produce a completely different product, when the trapping of the intermediates was accomplished with dimethylbutadiene.

The formation of ethyl thioxoacetate **31** and its trapping with cyclopentadiene was also repeated as reported by Kirby and Lochead (Scheme 53). As found previously, the thioaldehyde cycloadducts **47** were formed in excellent yield as a mixture of isomers with an *endo* : *exo* ratio of 7 : 3. As with the dimethylbutadiene reactions it had been found that the dithioester cycloadducts **116** were formed by the

addition of DMAP. However, larger amounts of DMAP, (1 mol equivalent) were required to form equivalent proportions of the abnormal adducts in the mixture.

Cyclopentadiene is a much more effective trapping agent than dimethylbutadiene and will quickly trap the thioaldehyde before it can undergo any further reaction. With triethylamine alone and trapping with cyclopentadiene the thioaldehyde cycloadduct was formed exclusively in ~100% yield. Addition of 0.1 mol equivalent of DMAP with the triethylamine produced the dithioester cycloadducts as minor products. However, with 1 mol equivalent of DMAP alone, the dithioester cycloadducts were produced as the major component in 73% yield while the thioaldehyde cycloadducts were formed in 27% yield (Table 2). As before the addition of DMAP increased the rate of these reactions .

Table 2. Base-mediated elimination of ethyl phthalimidosulfanylacetate **45** in the presence of cyclopentadiene (2 mol equiv) at room temperature in benzene.

	products (%) [a]	
Base (1 mol equiv)	b  **47**	c  **116**
NEt_3	100	Trace
NEt_3 + 10% DMAP	68	32
DMAP	27	73

[a] Yields measured from the ^1H NMR spectra of crude acid and base-washed product mixtures. No disulfide **104a** was detected.

[b] *endo* : *exo* ~7:3

[c] *endo* : *exo* ~1:1

DMAP = 4-dimethylaminopyridine.

The dithioester cyclopentadiene cycloadducts **116** were also formed as a mixture of isomers in approximately a 1 : 1 *endo* : *exo* ratio. π interactions encourage *endo* formation, which is apparent in the formation of the thioaldehyde cycloadducts. When cycloaddition occurs with the dithioester there is less distinction between the two substituents CO_2Et and SCH_2CO_2Et.

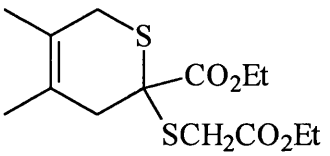
It is not known as yet how the formation of the dithioester cycloadducts occurs. It has been previously shown, by deuterium studies, that exchange of the methylene protons α to the sulfur of ethyl phthalimidosulfanylacetate did not precede the elimination reaction with triethylamine. Also exchange of the methine protons α to sulfur in the cycloadducts did not occur. As expected triethylamine is too weak a base to form significant amounts of carbanions stabilised only by one carbonyl group and one sulfur atom. Very likely, the elimination reaction involves an E2 mechanism. However, the possibility that triethylamine first displaces the phthalimido group by nucleophilic attack on sulfur and then effects elimination of the quaternary ammonium intermediate $Et_3N^+SCH_2CO_2R$ could not be excluded.

The addition of DMAP however, seems to have effected nucleophilic catalysis. As a better nucleophile than triethylamine it is likely to have displaced the phthalimido group thereby easing the elimination reaction, to generate ethyl thioxoacetate **31**. It is thought that the initial process must be formation of the thioaldehyde as the amount of the dithioester cycloadducts is reduced with the more reactive diene, cyclopentadiene. Other products could then be the result of thioaldehyde reactions with the reagents such as DMAP or with itself.

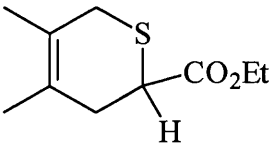
It has also been found that the reaction of the phthaloyl sulfenamide **45** with triethylamine in the presence of anthracene produces the thioaldehyde cycloadduct **35** along with disulfide. No dithioester cycloadducts of anthracene were observed in the presence of DMAP.

2.3.2 ^{1}H NMR and MS spectra of dimethylbutadiene cycloadducts.

The ^{1}H NMR spectrum of the dithioester cycloadduct **98** of dimethylbutadiene has a characteristic AB quartet at δ 3.53 and 3.59, (*J* 15.9 Hz) due to the SCH_2 protons of the side chain, which appears almost like a close doublet. The AB quartet arises from the diastereotopic nature of these protons in a chiral molecule. The corresponding set of protons of the disulfide $(EtO_2CCH_2S)_2$, **104a** gave a singlet at δ 3.59. Both methylene groups in the ring of **98** give clear AB systems whereas in the thioaldehyde cycloadduct **33** they give broad multiplets. The thioaldehyde cycloadduct also shows a characteristic triplet at δ 3.61 (*J* 6.4 Hz) from the α proton.

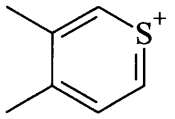


98



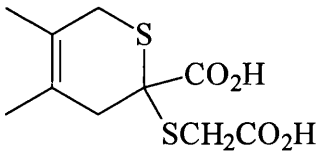
33

In the mass spectrum of the dithioester cycloadduct **98** the molecular ion gave a peak at *m/z* 318.0957 ($C_{14}H_{22}O_4S_2$ requires 318.0954) but is very weak. It appears that the molecule then proceeds to lose the sulfide side chain piece by piece followed by a proton from the ring to give the second most intense peak at *m/z* 198.0703 ($C_{10}H_{14}O_2S$ requires 198.0715). The base peak at *m/z* 125.0402 corresponds to C_7H_9S (requires 125.0425) arising from loss of both substituents and a hydrogen from the molecular ion to give perhaps the aromatic thiapyridinium cation **117**.



117

No molecular ion was observed for the acid **118** derived by hydrolysis of the ester **98** but it was evident that initial loss was of the sulfur side chain to give a peak at *m/z* 171.046 ($C_8H_{11}O_2S$ requires 171.0480) followed by loss of hydrogen to give a peak at *m/z* 170.0391 ($C_8H_{10}O_2S$ requires 170.0401). Again a peak at *m/z* 125.0419 corresponded to loss of both substituents to give the cyclic cation **117**.

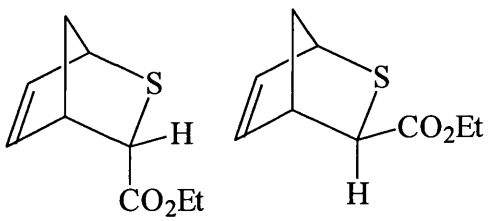


118

Lochead had previously obtained microanalytical data for the acid **118** which showed the presence of only 2 sulfur atoms, not 3.

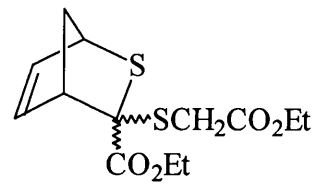
2.3.3 ^{1}H NMR and MS spectra of cyclopentadiene adducts

In the cycloadduct of ethyl thioxoacetate and cyclopentadiene the proton α to the sulfur of the *endo* adduct, **47a** experiences a 4.2 Hz coupling with the adjacent bridgehead proton and gives a doublet. The corresponding proton of the *exo* adduct, **47b** appears as a singlet at higher field due to shielding by the nearby double bond.



47a **47b**

From the ^1H NMR spectra of the dithioester cycloadducts **116** it appears that the adduct with CO_2Et in the *endo* position contributes slightly more than the *exo* CO_2Et adduct to the mixture, *endo*:*exo* = 1.0 : 0.9. The SCH_2 protons of the side chain in the *exo* position (CO_2Et *endo*) gives a very finely split AB quartet which almost appears as a singlet at δ 3.59. This value is consistent with the chemical shifts of the same group in the disulfide **104a** and the dimethylbutadiene adducts **98** at δ 3.59 and δ 3.56 respectively. With the sulfur side chain in the *endo* position the SCH_2 protons resonate at higher field, δ 3.4 due to the shielding effect of the nearby double bond. The signal appears as a distinct AB quartet.



116

The mass spectrum of the dithioester cycloadducts **116** shows the molecular ion at *m/z* 302.0636 ($C_{13}H_{18}O_4S_2$ requires 302.0647). The molecule then appears to undergo a retro Diels-Alder reaction to lose cyclopentadiene giving a major peak at *m/z* 236.0160 ($C_8H_{12}O_4S_2$ requires 236.0177).

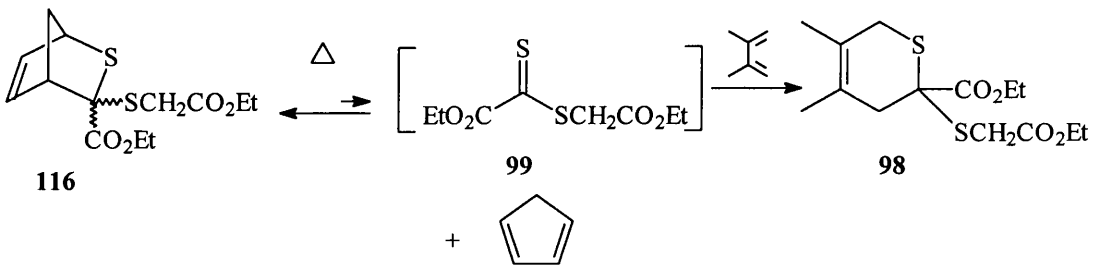
No microanalysis data for the dithioester cycloadducts **116** have been obtained, due to decomposition accompanying distillation, but the spectral analysis (^{13}C NMR, ^1H NMR, IR, MS) strongly confirms the formation of these products.

Similar results have also been reported by Kirby and Trethewey [50] on work concerning the formation of selenoaldehydes. Cycloadducts of dimethylbutadiene, cyclopentadiene and cyclohexadiene formed from the phthalimido and cyanide selenoaldehyde precursors, by base catalysed elimination with triethylamine, were also accompanied by diseleno derivatives. Products of this type were not observed however, when selenosulfate, selenenyl chloride or selenosulfinate precursors were employed, nor were diseleno derivatives of anthracene, 9,10-dimethylanthracene or

thebaine formed in any experiments. Also, the 'abnormal' diseleno adducts were obtained without the use of DMAP.

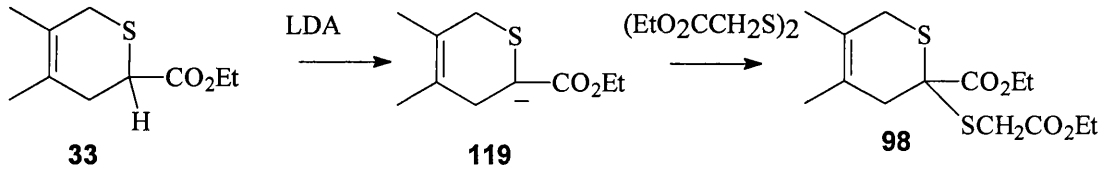
2.3.4 Further cycloadduct formation

The cyclopentadiene dithioester adducts **116** behaved like other cyclopentadiene adducts in that they underwent retro Diels-Alder reactions when heated in refluxing toluene, to generate the dithioester **99** (Scheme 55). The cyclopentadiene adducts **116** were cleanly converted into the dimethylbutadiene adduct **98** when refluxed in toluene containing dimethylbutadiene. A pale pink colour, characteristic for the presence of the dithioester **99** was soon observed but faded as the reaction went to completion. The synthetic utility of this cycloadduct **116** is thus demonstrated as an auxiliary precursor for the reactive dithioester **99**.



Scheme 55

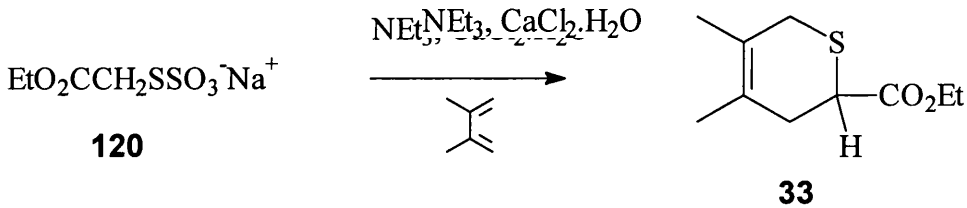
A small amount of the dithioester dimethylbutadiene cycloadduct **98** was also prepared by treatment of the thioaldehyde cycloadduct **33** with LDA, to generate the α anion **119**, followed by sulfanylation by treatment with the corresponding disulfide **104a** (Scheme 56). This experiment served to confirm the structure **98,** since it was unlikely that a disulfide structure analogous to Capozzi's (**101**) would be formed under the conditions.



33 **119** **98**

Scheme 56

Treatment of the Bunte salt $EtO_2CCH_2SSO_3Na$ **120**, prepared from ethyl bromoacetate and sodium thiosulfate, with triethylamine and dimethylbutadiene in refluxing benzene containing calcium chloride as a sulfite ion scavenger, forms the thioaldehyde cycloadduct **33** in good yield (Scheme 57) [28]. However, when this experiment was repeated analysis of the product showed that small amounts of the dithioester cycloadduct **98** were also formed in this system . Addition of 0.1 mol equivalent of DMAP however, did not change the composition of the product mixture.

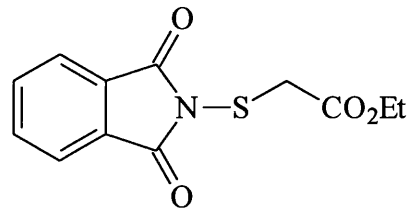


120 **33**

Scheme 57

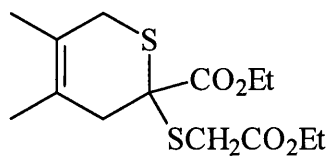
2.3.5 Further base-mediated eliminations of ethyl phthalimidosulfanylacetate

After finding that the addition of a small amount of DMAP to the triethylamine reactions could produce such a dramatic effect, it was interesting to observe how the phthaloyl sulfenamide **45** would react with a different base. Capozzi *et al.* [43] had used pyridine in their reactions and had obtained the disulfide **101**, so it would be interesting to see if any other cycloadducts could be produced using the ester derivative **45**.

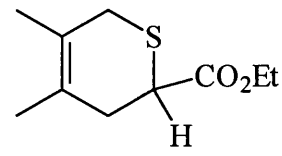


45

The reaction with pyridine, as expected for a weaker base, was slow. It took four days before any precipitate of phthalimide was observed in the reaction mixture, although formation of products occurred (TLC monitoring) before that but only built up slowly. In the presence of dimethylbutadiene all three products **33, 98** and **104a** were formed as before but this time in almost equal proportions. There was no



98

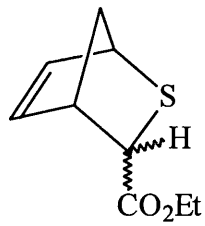


33

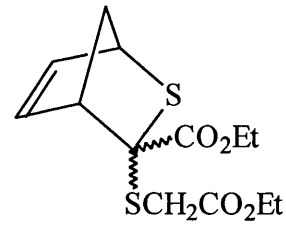
$(EtO_2CCH_2S)_2$

104a

evidence however, that any new cycloadduct had been produced. The reaction with cyclopentadiene was not very successful as the elimination using pyridine was too slow and the diene dimerised again before adducts were formed, but TLC showed the presence of both kinds of cycloadducts **47** and **116**.



47

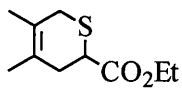
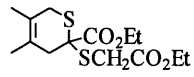


116

The phthaloyl sulfenamide **45** was then treated with triethylamine containing 0.1 mol equivalent of pyridine in the presence of dimethylbutadiene. The reaction rate was dramatically increased with complete precipitation of phthalimide in less than 30 min. This was much faster than when triethylamine was used alone. The presence of a small amount of pyridine must be having a catalytic effect on the reaction, as did DMAP. The product, obtained in good yield, consisted mainly of the normal thioaldehyde cycloadduct **33** with only a small amount of the dithioester cycloadduct **98**. The disulfide **104a** was also present in a significant amount ~ 13%.

The same reaction was conducted with 0.5 mol equivalents of pyridine. Again an enhanced reaction rate was observed and analysis of the mixture this time showed the percentage composition of the disulfide **104a** and the dithioester cycloadduct **98** to have increased (Table 3).

Table 3. Base-mediated elimination of ethyl phthalimidosulfanylacetate **45** in the presence of 2,3-dimethylbuta-1,3-diene (1.2 mol equiv) at room temperature in dichloromethane.

		Product (%) [a]		
Base (1 mol equiv)	rate order [b]	 **33**	 **98**	$(EtO_2CCH_2S)_2$ **104a**
NEt_3	2	100	trace	trace
NEt_3 + 10% DMAP	6	14	86	trace
DMAP	5	6	94	trace
NEt_3 + 10% pyridine	3	84	3	13
NEt_3 + 50% pyridine	4	52	11	37
pyridine	1	29	40	31

[a] Yields measured from the ^1H NMR spectra of crude acid and base washed product mixtures ; no **45** remained.

[b] Order of increasing rate (TLC monitoring) with pyridine the reaction required days and with Et_3N + DMAP, minutes.

DMAP = 4-dimethylaminopyridine.

It is beginning to emerge from these results that different bases must react differently with the phthaloyl sulfenamide **45**. Pyridine and DMAP are both more

nucleophilic than triethylamine and could possibly be reacting differently with the phthaloyl sulfenamide or reacting with the thioaldehyde **31** which is formed .

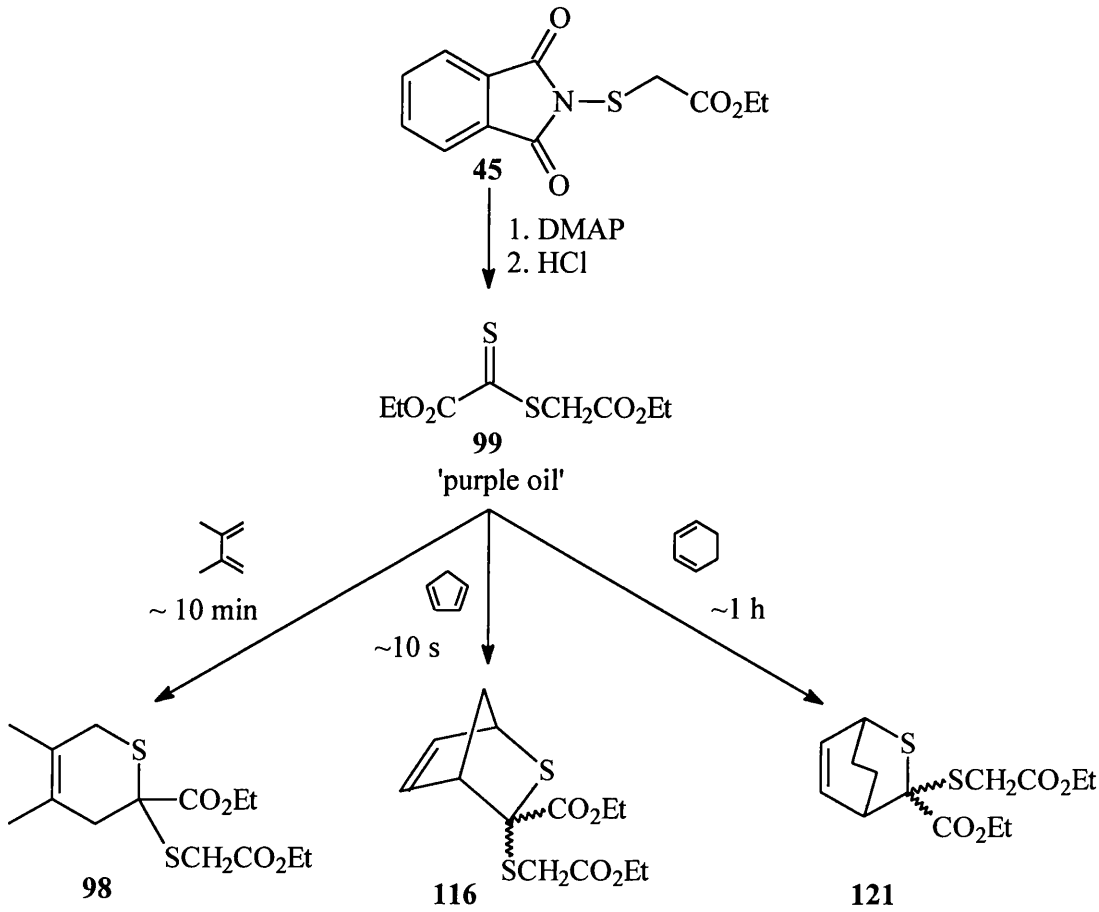
2.4 Isolation and purification of the dienophilic dithioester 99

Although good circumstantial evidence was available (see above) for the formation of the dithioester **99**, as a reactive intermediate trapped *in situ* by dienes, a preliminary attempt at its isolation by Lochead had failed. However, it was observed that the pink colour attributed to **99** persisted in the absence of base and conditions were eventually found for the purification and characterisation of the labile dithioester **99**. Thus, when ethyl phthalimidosulfanylacetate **45** was treated with DMAP alone the mixture rapidly became orange then red and phthalimide began to precipitate out. The mixture was then immediately shaken with dilute hydrochloric acid, to remove the DMAP, and filtered to remove phthalimide (Scheme 58). Evaporation of the solvent then gave a red oil which was immediately chromatographed on silica gel to give the dithioester **99** as a purple oil (56%), λ_{max} (EtOH)/nm 332 (ε 6176 dm^3 mol^{-1} cm^{-1}) and 515 (9.7). These values are typical for dithioesters (see below for an example). The ^1H and ^{13}C NMR [δc 214.8, C=S] spectra and the mass spectrum (accurate mass measurement for M^+ $C_8H_{12}O_4S_2$) confirmed the structure.

The ^1H NMR spectrum showed a singlet for the SCH_2 group at δ 4.09; the high δ value being due to the deshielding effect of the dithioester group. (*cf.* δ 3.59 for SCH_2 in the disulfide **104a**).

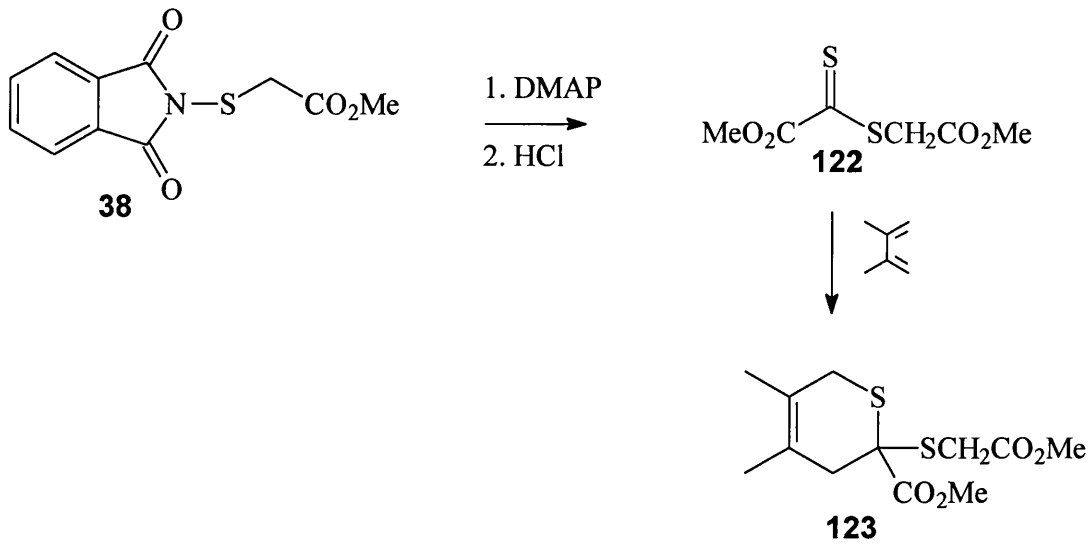
Solutions of the dithioester, taken directly from the chromatography column, were treated separately with dimethylbutadiene, cyclopentadiene and cyclohexadiene (Scheme 58). The purple colour faded as the cycloadditions took place, with the rate of decolorisation dependent upon the reactivity of the diene. Cyclopentadiene reacted fastest followed by dimethylbutadiene while cyclohexadiene was quite slow. This rate order corresponds to that of maleic anhydride with the same dienes [68]. After chromatography the dithioester cycloadducts **98**, **116** and **121** were obtained in good

yield. The crude products themselves however, were free from the thioaldehyde cycloadducts and the disulfide **104a**.



Scheme 58

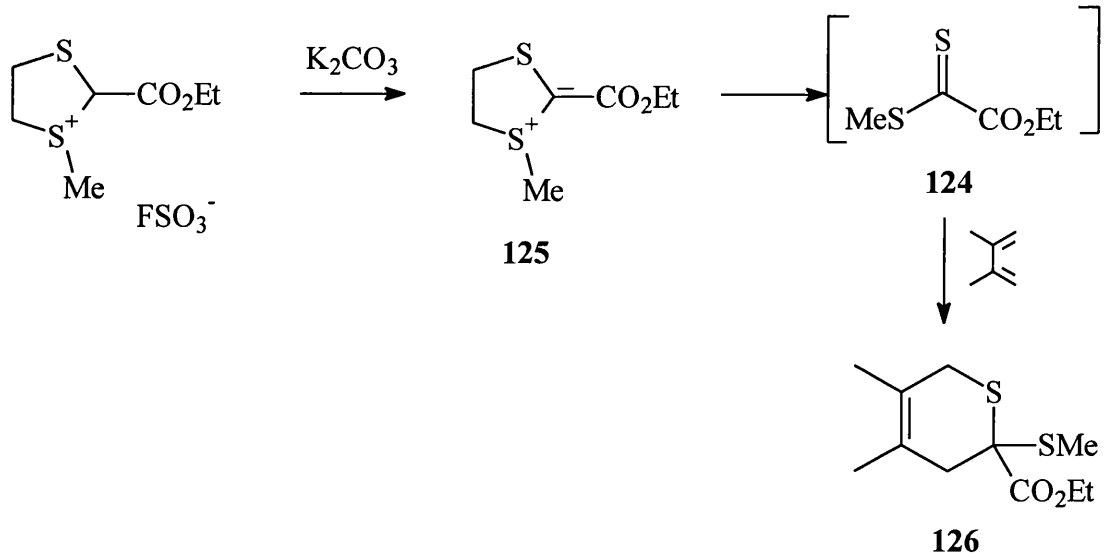
The corresponding methyl ester dithioester **122** was also prepared by treatment of methyl phthalimidosulfanylacetate **38** with DMAP, and the resulting purple oil was treated with dimethylbutadiene to give the methyl ester dithioester cycloadduct **123** (Scheme 59).



Scheme 59

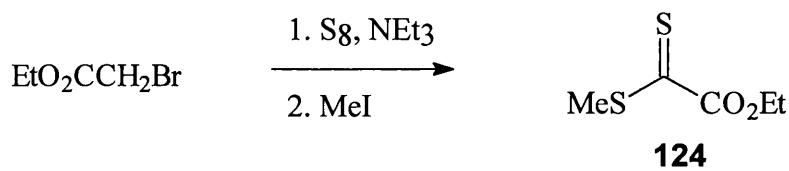
An attempt was then made to prepare the dithioester **99** by an alternative route. Simple dithioesters are familiar, stable compounds and are poor dienophiles. Dithioesters with α carbonyl groups are more unstable and the dienophilic nature of the thiono group is greatly enhanced. They have only occasionally been described in the literature.

Vedejs *et al.* [52] reported the preparation of the dithioester **124,** by a cycloreversion reaction of the ylid **125,** in the presence of dimethylbutadiene and isolated the corresponding Diels-Alder dithioester cycloadduct **126** (Scheme 60). However, they were unable to isolate the intermediate dithioester **124.**



Scheme 60

This same dithioester **124** had been reported earlier [53] as a distillable oil, λ_{max} (CH_2Cl_2)/ nm 332 (ε 8318 dm^3 mol^{-1} cm^{-1}) and 523 (15). The preparation involved treating ethyl bromoacetate with elemental sulfur (S_8) and triethylamine followed by methylation (Scheme 61).



Scheme 61

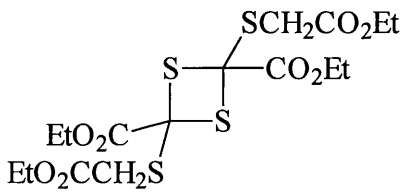
An attempt was therefore made to prepare the dithioester **99** similarly. Ethyl bromoacetate was treated with sulfur and triethylamine. A red colour formed immediately. A second portion of ethyl bromoacetate was then added. However, after work-up the mixture yielded a reddish-brown oil that did not resemble the dithioester or the dithioester polymer. The ^1H NMR spectrum showed a large singlet at δ 3.53

along with two sets of ethoxy signals. The product was unaffected by treatment with triethylamine.

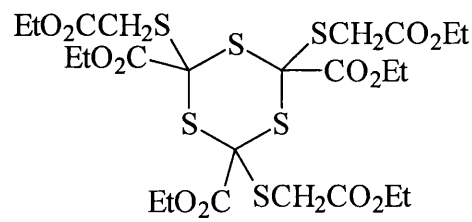
Finally some reactions were carried out to study the polymerisation of the dithioester **99**. The oily dithioester was reasonably stable at room temperature but the stability depended critically upon its purity. Chromatography removed any traces of DMAP which would catalyse the polymerisation.

When the oily dithioester was kept at room temperature the intensity of the characteristic purple colour began to lessen and after 7 days the sample was almost colourless. After this time the ^{1}H NMR spectrum showed that the dithioester monomer had largely disappeared and broad signals showed evidence of polymer formation.

After a further 7 days sharp signals had appeared once again in the ^{1}H NMR spectrum and had largely replaced those of the previous polymer. In particular a singlet at δ 3.79 appeared along with *sharp* ethoxy signals. It is possible that formation of a more stable oligomer has occurred, possibly a dimer **127** or, more likely a trimer **128**.



127



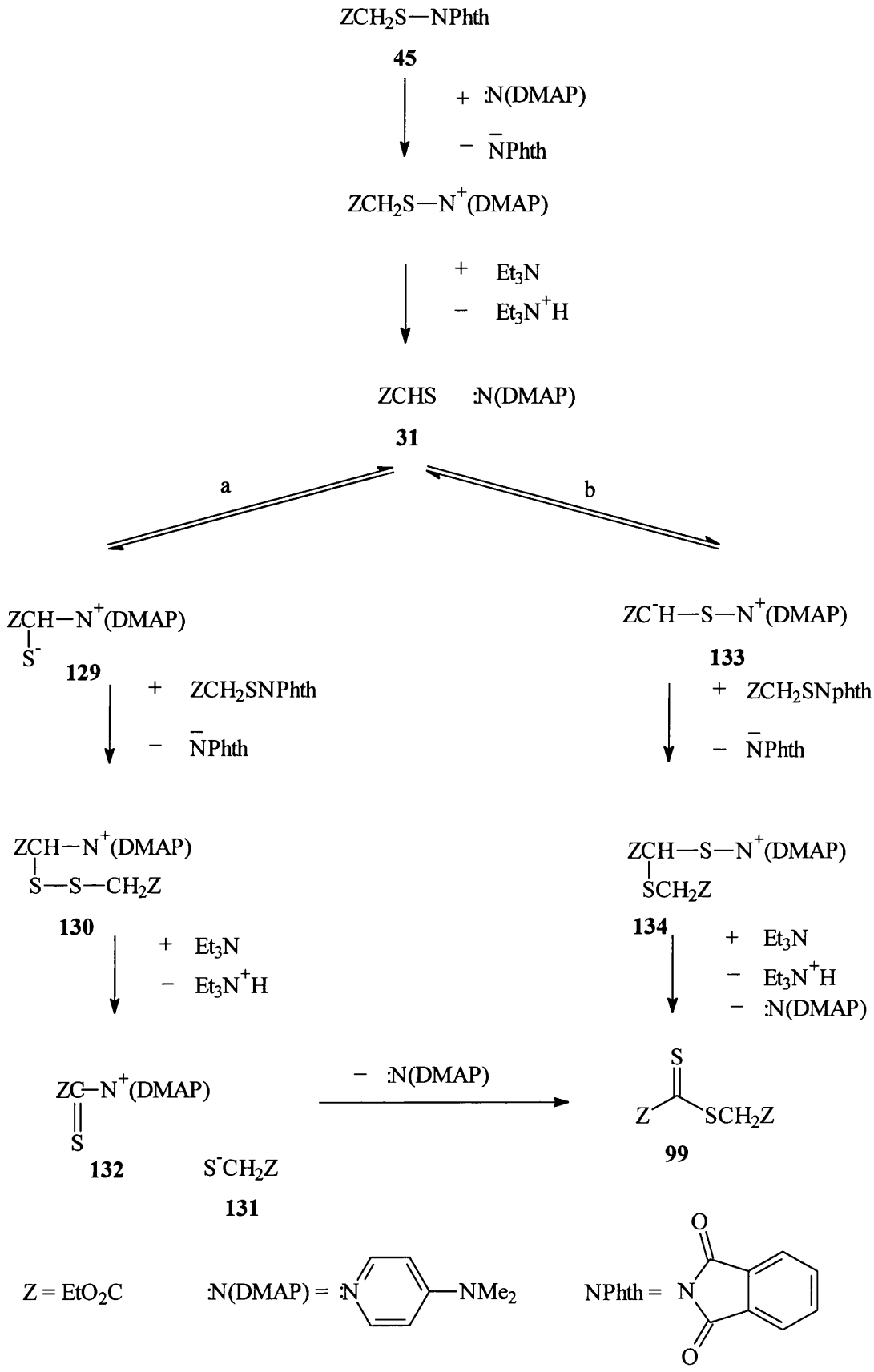
128

The SCH_2 protons could now be seen as a singlet as the sulfide group was no longer directly attached to a chiral centre. However, only the *cis* isomer would give the simple singlet, quartet, triplet pattern observed. The *cis* isomer is perhaps the more stable form having 3 bigger groups equatorial but some *cis/trans* isomer signals would be expected unless there is accidental equivalence of signals in the trimer. In the dithioester cycloadduct **98** the SCH_2 protons are seen as an AB quartet due to

diastereotopic effects. The higher value (δ 3.79) of this signal for the trimer compared to those for the cycloadduct (δ 3.53 and 3.59, ABq) or the disulfide (δ 3.59) may be attributed to the attachment of 2 rather than 1 sulfur atoms.

Treatment of the dithioester **99** with DMAP quickly (< 1 min) formed a dark solution of the polymer. The isolated polymer showed a complex spectrum similar to that obtained by treatment of the phthaloyl sulfenamide **45** with DMAP. Treatment of this polymer with triethylamine and dimethylbutadiene gave the dithioester cycloadduct **98**.

Alternative mechanisms for the formation of the dithioester **99** from ethyl phthalimidosulfanylacetate with DMAP and triethylamine are proposed in Scheme 62.

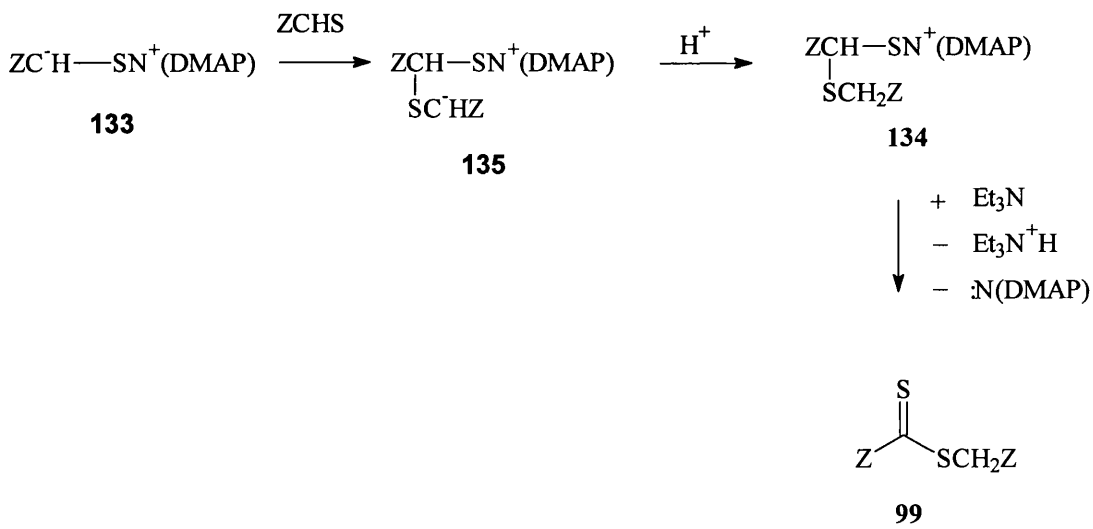

ZCH2S—NPhth
45
+ :N(DMAP)
− NPhth
ZCH2S—N+(DMAP)
+ Et3N
− Et3N+H
ZCHS :N(DMAP)
31
a
b
ZCH—N+(DMAP)
S-
129
+ ZCH2SNPhth
− NPhth
ZC-H—S—N+(DMAP)
133
+ ZCH2SNphth
− NPhth
ZCH—N+(DMAP)
S—S—CH2Z
130
+ Et3N
− Et3N+H
ZCH—S—N+(DMAP)
SCH2Z
134
+ Et3N
− Et3N+H
− :N(DMAP)
ZC—N+(DMAP)
S
132
S-CH2Z
131
− :N(DMAP)
S
Z
SCH2Z
99
Z = EtO2C
:N(DMAP) =
NMe2
NPhth =
O
O

Scheme 62

Nucleophilic catalysis of the formation of ethyl thioxoacetate **31** by DMAP may be followed by carbophilic (path a) or thiophilic (path b) attack of DMAP on the thial group. The carbophilic route allows the reaction of the sulfur anion **129** with the starting material **45** to form the disulfide **130**. Elimination with triethylamine then yields the thiolate **131** which could attack **132** carbophilically to form the dithioester **99**. The disulfide $(ZCH_2S)_2$ which often accompanies the major products might arise by attack of the thiolate **131** on the precursor **45.**

Alternatively, the product **133**, formed by thiophilic attack of the ethyl thioxoacetate **31** and DMAP, could also react with the starting material **45** forming a different intermediate **134** which after undergoing elimination with triethylamine could also yield the dithioester **99**.

It is possible also that the initial product **133**, formed by thiophilic attack of DMAP on ethyl thioxoacetate, then reacts with another molecule of ethyl thioxoacetate **31** to give **135**. Addition of a proton to form **134** followed by elimination with triethylamine could again yield the dithioester **99** (Scheme 63).



Scheme 63

Although it appears from the above mechanisms that the dithioester could be formed in many ways, all that is certain is that it is derived from the thioaldehyde and not directly from the *N*-phthaloyl sulfenamide. Further studies would have to be undertaken however, in order to determine a more definite pathway. Nevertheless it is now possible to prepare solutions of the pure dithioester **99** (and of the corresponding methyl ester) easily from the *N*-phthaloyl sulfenamide **45** and thereby prepare dithioester cycloadducts in high yield. Further, the cyclopentadiene cycloadducts **116** can serve as convenient auxiliary precursors for the dithioester.

2.5 Reactions of ethyl phthalimidosulfanylacetate in the absence of a diene - polymer formation

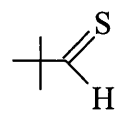
A series of base-mediated elimination reactions of the phthaloyl sulfenamide **45** was again carried out but this time in the absence of a diene to trap the reactive dienophilic intermediates (see Scheme 65 for structures). The thioaldehyde **31** and to a lesser extent the dithioester **99** were susceptible to oligomerisation and polymerisation.

The initial reaction with triethylamine gave an interesting result. When ethyl phthalimidosulfanylacetate **45** was treated with triethylamine in the presence of a diene the time to complete reaction was ~3 h, but when diene was omitted the reaction was complete, *i.e.* the formation of the precipitation of phthalimide was complete, in less than 30 s. In the second case the phthalimide was filtered off and the filtrate washed successively with sodium hydroxide, hydrochloric acid and water then dried and evaporated to yield a yellow, sticky oil.

A set of sharp signals in the ^{1}H NMR spectrum of this polymeric material was attributed to disulfide $(EtO_2CCH_2S)_2$ **104a** . Other broader signals were attributed to the polymer. Thus as well as ethoxy signals there were three clumps of more complicated signals, the largest near δ 3.6 representing about 80% of the proton integral other than that of the ethoxy signals and of the signals for the disulfide **104a**.

Another similar group of smaller intensity (~13%) was observed at δ 4.7 and the third and weakest set around δ 5.0.

According to some literature reports the formation of some disulfide was not unexpected. Vedejs *et al.* [51] reported the formation of disulfides when thioaldehydes were generated in the presence of dienes which were not sufficiently reactive to capture them. Irradiation of the phenacyl sulfide $PhCOCH_2SCH_2C(CH_3)_3$ in the presence of dimethylbutadiene gave a solid polymer (50%) and some dineopentyl disulfide but no Diels-Alder adduct of the thioaldehyde **10**. Vedejs *et al.* also reported



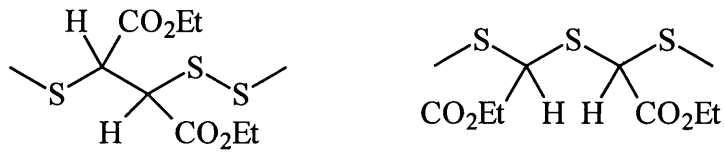
10

that irradiation of $PhCOCH_2SCH_2CO_2CH_3$ without the presence of dienes gives the disulfide $(CH_3O_2CCH_2S)_2$ in 30% yield together with 'complex, non-volatile products'.

It is well known that simple thioaldehydes are very reactive and rapidly form trimers or oligomers. However, Vedejs *et al.* [10] have shown that monomeric thiopivaldehyde **10** can exist in dilute solution for 16-20 h at 20 °C. They found that polymerisation was accelerated by sunlight or impurities. Protic or Lewis acid catalysts caused instantaneous decomposition. Decomposition leads to varying ratios of polymer and trimers as well as uncharacterised amounts of what appears to be soluble oligomers.

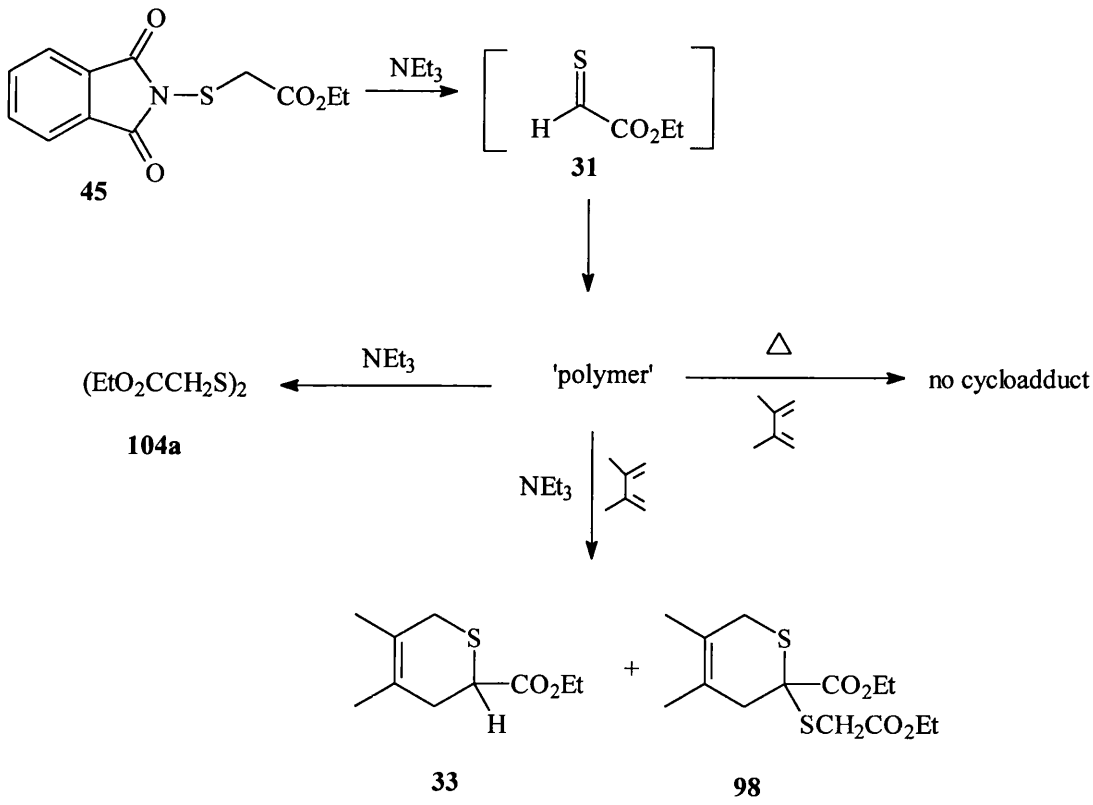
The exact nature of the product formed from the reaction of the phthaloyl sulfenamide **45** with triethylamine has not been determined but is presumed to be some form of oligomer rather than a trimer. The chemical shift, δ 3.6 of the major group of proton signals, other than the ethoxy signals is similar to that of the SCH_2 singlet of the disulfide δ 3.59 and would indicate that only one sulfur atom was attached to the relevant carbon. The other signals at δ 4.7 and δ 5.0 are at lower field

and might indicate the presence of two attached sulfur atoms. The existence of these three sets of signals could indicate various types of linkages in the thioaldehyde polymer, *e.g.* head-to-head or head-to-tail linkages (Scheme 64).



Scheme 64

Surprisingly it was found that when the 'polymer' was treated with triethylamine and dimethylbutadiene the thioaldehyde cycloadduct **33** was produced along with a trace of the dithioester cycloadduct **98** (Scheme 65). Compared to the reaction with the phthaloyl sulfenamide **45**, formation of adducts from the 'polymer' was slow.



Scheme 65

An attempt was made to decompose the 'polymer' by heat alone, but no cycloadducts were formed when the 'polymer' was refluxed with dimethylbutadiene. It appears that base is required to initiate the depolymerisation.

The formation of the thioaldehyde polymer from the phthaloyl sulfenamide **45** was repeated but this time the mixture was filtered immediately after precipitation of phthalimide. The filtrate was immediately washed with hydrochloric acid to remove triethylamine. This time the product consisted of a pale peach oil and the ^{1}H NMR spectrum was similar to that of the previous polymeric material but contained virtually no signals for the disulfide **104a**. Again this polymer depolymerised when treated with triethylamine and dimethylbutadiene giving the thioaldehyde cycloadduct **33** along with some disulfide **104a**. When the isolation of the polymer was long

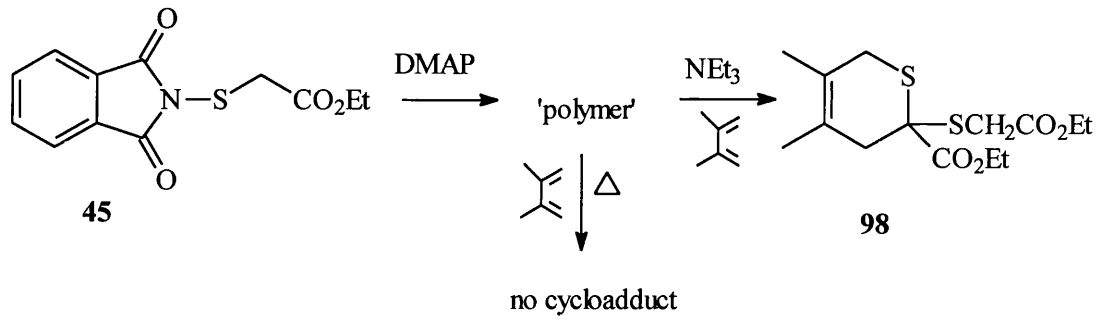
delayed almost all the product was the disulfide **104a** and almost no polymer was obtained.

The thioaldehyde polymer was also depolymerised with DMAP in the presence of dimethylbutadiene. However, only the thioaldehyde cycloadduct **33** was again formed.

Polymers were also formed with other combinations of bases, with reaction rates varying slightly from case to case. The reaction with triethylamine containing 0.1 mol equivalent of DMAP was slightly faster than for triethylamine alone - 15 compared to 30 s. The reaction also produced a transient pink colour which had changed to brown by the end of the reaction. DMAP alone also produced the pink colour, which soon faded but with a slower completion rate of 2 min. The slowest reaction of all was with triethylamine containing 0.1 mol equivalent of pyridine, which took 5 min to produce the phthalimide precipitate.

The ^{1}H NMR spectrum of the reaction products showed that disulfide formed to a much greater extent when DMAP was not included in the initial mixture. Also more complex multiplets could be seen, as well as the ethoxy signals, in the products resulting from the use of DMAP.

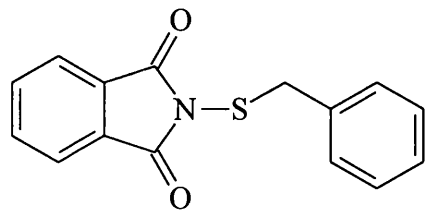
The 'polymer' formed with DMAP, was treated with triethylamine and dimethylbutadiene. The dithioester cycloadduct **98** was formed along with traces of the thioaldehyde cycloadduct **33** and the disulfide **104a** (Scheme 66). It would appear then that different types of 'polymer' are produced depending on the conditions used for thioaldehyde generation. As before, heating the dithioester polymer with dimethylbutadiene alone gave no cycloadduct. The polymerisation of the thioaldehyde and the dithioester and the reverse processes appear to be catalysed by base.



Scheme 66

2.6 Reactions of *N*-phthaloylphenylmethanesulfenamide 103

Since thioaldehyde and dithioester cycloadducts had been formed so quickly using the ester derivatives it was interesting to see how a less reactive phthaloyl sulfenamide would react. The methylene protons of the benzyl derivative **103** are less acidic and not easily removed by base.



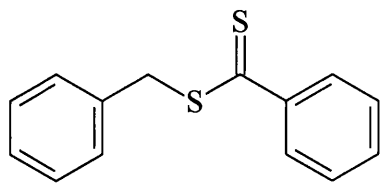
103

When treated with triethylamine and dimethylbutadiene for 1 month at room temperature *N*-phthaloylphenylmethanesulfenamide **103** formed only a small amount of the thioaldehyde cycloadduct **136**. The methylene protons of this *N*-phthaloyl sulfenamide are not very acidic and generally require activation, by for example a nitro group attached to the benzene ring, in order for deprotonation to occur easily with a base such as triethylamine. The more reactive thiobenzaldehyde precursor,

phenylmethanesufenyl chloride $PhCH_2SCl$, **106c** led however, to products formed by the reaction of the sulfenyl chloride with the diene and no thioaldehyde cycloadduct was detected.

Treatment of the phthaloyl sulfenamide **103** with 1 mol equivalent of DMAP in the absence of dimethylbutadiene greatly increased the reaction rate. The mixture slowly turned pink and then red over a few days. After work-up and chromatography a number of fractions were obtained. A tiny amount of a red oil was isolated, the ^1H NMR spectrum of which showed a singlet at δ 4.6 along with aromatic signals. A second fraction was collected which was also a red oil containing a white solid. Although not separable by chromatography on silica or alumina, partial separation could be achieved by careful extraction with hexane. The white solid was identified as dibenzyl disulfide **104c** and was identical to the material obtained by oxidation of benzyl mercaptan. The red oil showed aromatic signals as well as a singlet at δ 3.59. The two components of this fraction were formed in almost equal proportions when DMAP was used as the base. However, treatment with triethylamine containing 10% DMAP gave the disulfide **104c** as the major component.

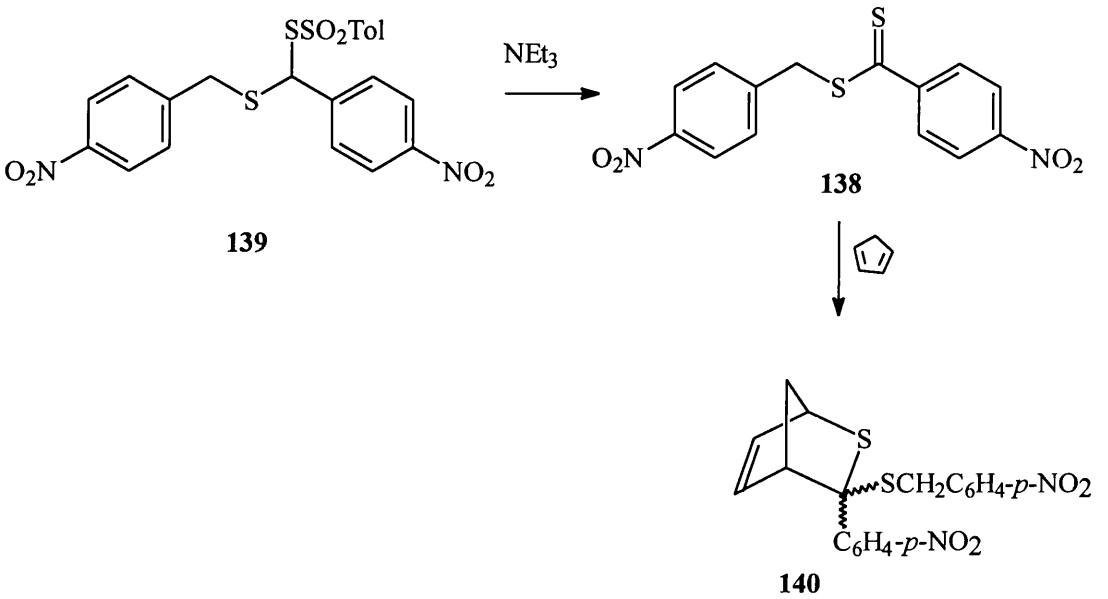
It was thought that the red oil may correspond to the known dithioester benzyl dithiobenzoate **137**, which is a red oil. It is known [54] that thiobenzaldehyde undergoes polymerisation to form the dithioester **137** along with other compounds.



137

The red oil was treated with both dimethylbutadiene and cyclopentadiene but no cycloadducts were formed. Due to its greater stability however, benzyl dithiobenzoate **137** is a poorer dienophile and would not readily react with dienes to form cycloadducts.

Sheldrake [55] had prepared a similar dithioester **138**, as a red crystalline solid, by treatment of the α-sulfenylated thiosulfinate **139** with triethylamine. This had then formed the cycloadducts **140** with cyclopentadiene but decomposed easily back to the dithioester **138** (Scheme 67).

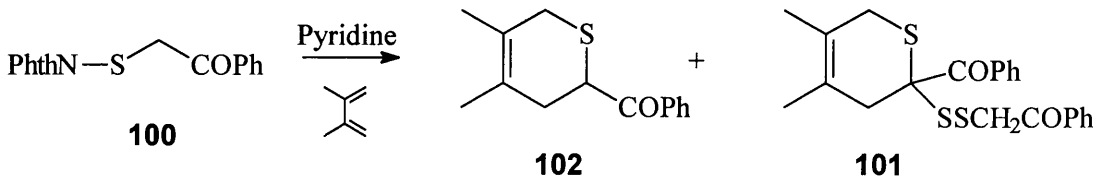


Scheme 67

In another experiment, the phthaloyl sulfenamide **103** was treated with DMAP in the presence of dimethylbutadiene. Two fractions were isolated from the product mixture, neither of which showed incorporation of the diene. The first was the disulfide **104c** but the second was a purple oil, the ^{1}H NMR spectrum of which showed a singlet at δ 4.30 as well as aromatic signals.

2.7 Reactions of the *N*-phthaloyl β-oxo sulfenamides

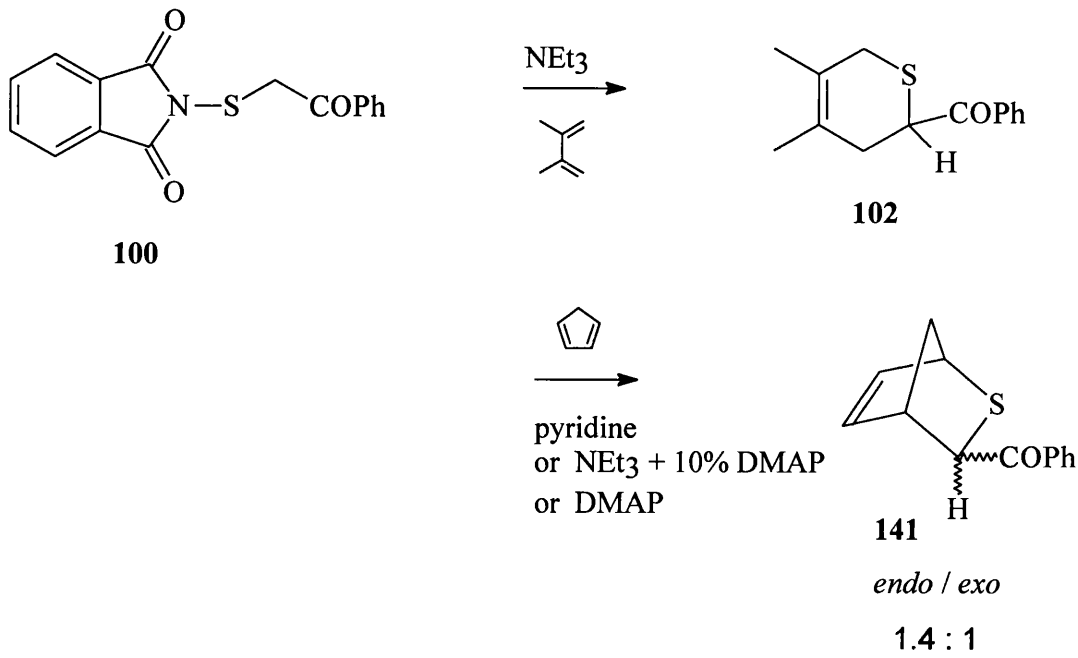
As previously mentioned, the work of the Italian group was to be repeated to compare the formation of their unusual trisulfur cycloadduct **101** with that of the dithioester adducts formed from the esters. Capozzi *et al.* [43] found that the reaction of the phenyl β-oxo derivative **100** with pyridine in the presence of dimethylbutadiene formed two products. The normal thioaldehyde cycloadduct **102** was obtained in 30% yield and the disulfide **101** in 21% yield (Scheme 46).



100 **102** **101**

Scheme 46

The methylene protons of the β-oxo derivatives are more acidic than those of the ester derivatives and are therefore more easily removed by weaker bases such as pyridine. The reaction of **100** with pyridine was repeated with results similar to those in the literature. However, when triethylamine was used in place of pyridine, only the normal thioaldehyde cycloadducts **102** and **141** were obtained from dimethylbutadiene or cyclopentadiene (Scheme 68). The dimethylbutadiene adduct **102** was formed in excellent yield as an orange oil which turned green after a few days at room temperature. The cyclopentadiene adducts **141** were formed in reasonable yield as a mixture of isomers, *endo* : *exo* = 1.4 : 1.



Scheme 68

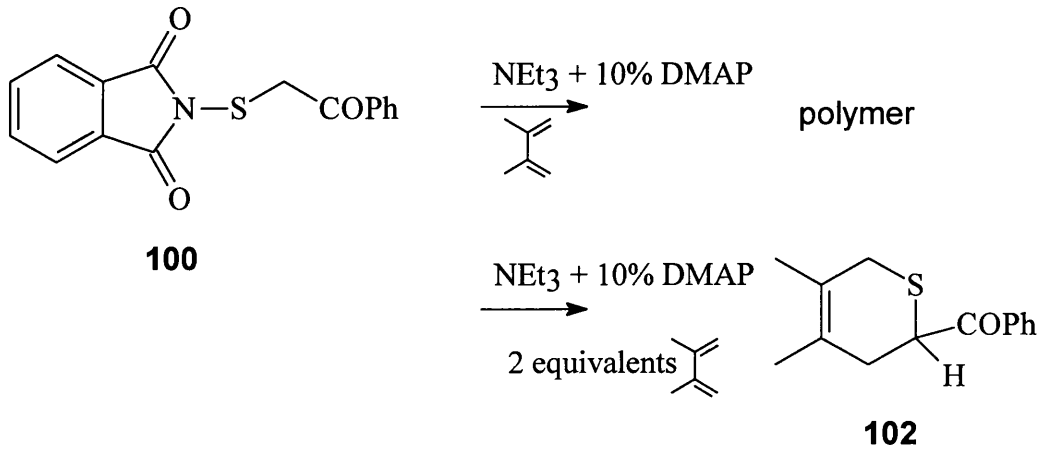
The same thioaldehyde cyclopentadiene adducts **141** were formed when the phthaloyl sulfenamide **100** was treated with pyridine in the presence of the more reactive cyclopentadiene, rather than dimethylbutadiene. There was no sign of a disulfide adduct.

The phthaloyl sulfenamide with 1 mol equivalent of DMAP and cyclopentadiene gave only the thioaldehyde cycloadduct **141**.

It is apparent from these results that thioaldehyde formation must be the initial step of the reaction of the phthaloyl sulfenamide with base. Cyclopentadiene, being a more effective trapping agent than dimethylbutadiene can quickly capture the thioaldehyde before further reactions occur. The thioaldehyde generated might also be more reactive towards cycloaddition thereby explaining the lack of 'abnormal' products with cyclopentadiene.

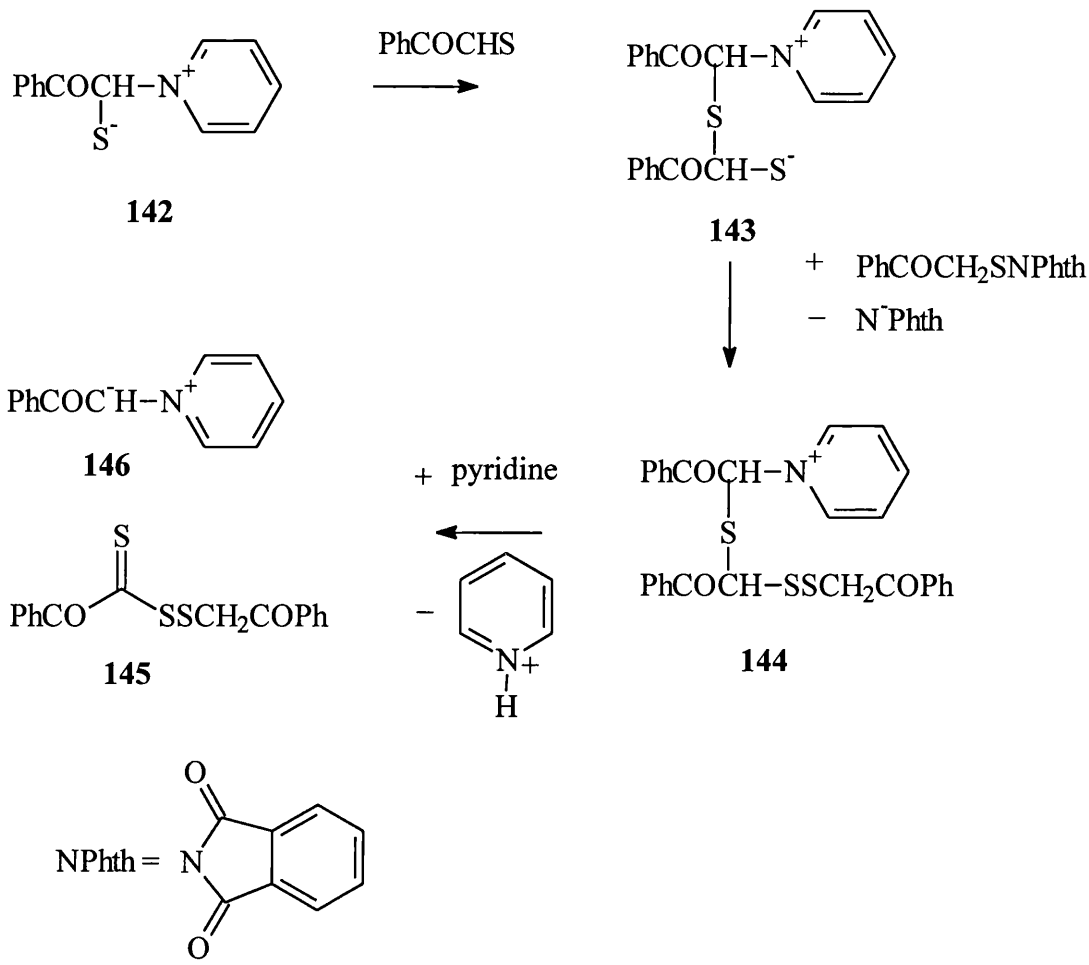
The phthaloyl sulfenamide **100** was also treated with triethylamine containing 0.1 mol equivalent of DMAP in the presence of dimethylbutadiene. Only a very small amount of the cycloadduct **102** was formed, along with other unidentified material which did not resemble a cycloadduct. This same material was later observed from the

reaction of the phthaloyl sulfenamide under the same conditions in the absence of a diene. The greater reactivity must have led to polymer formation when the diene was not sufficiently reactive. With triethylamine and 10% DMAP and an increased concentration of dimethylbutadiene only the thioaldehyde cycloadduct **102** was formed (Scheme 69).



Scheme 69

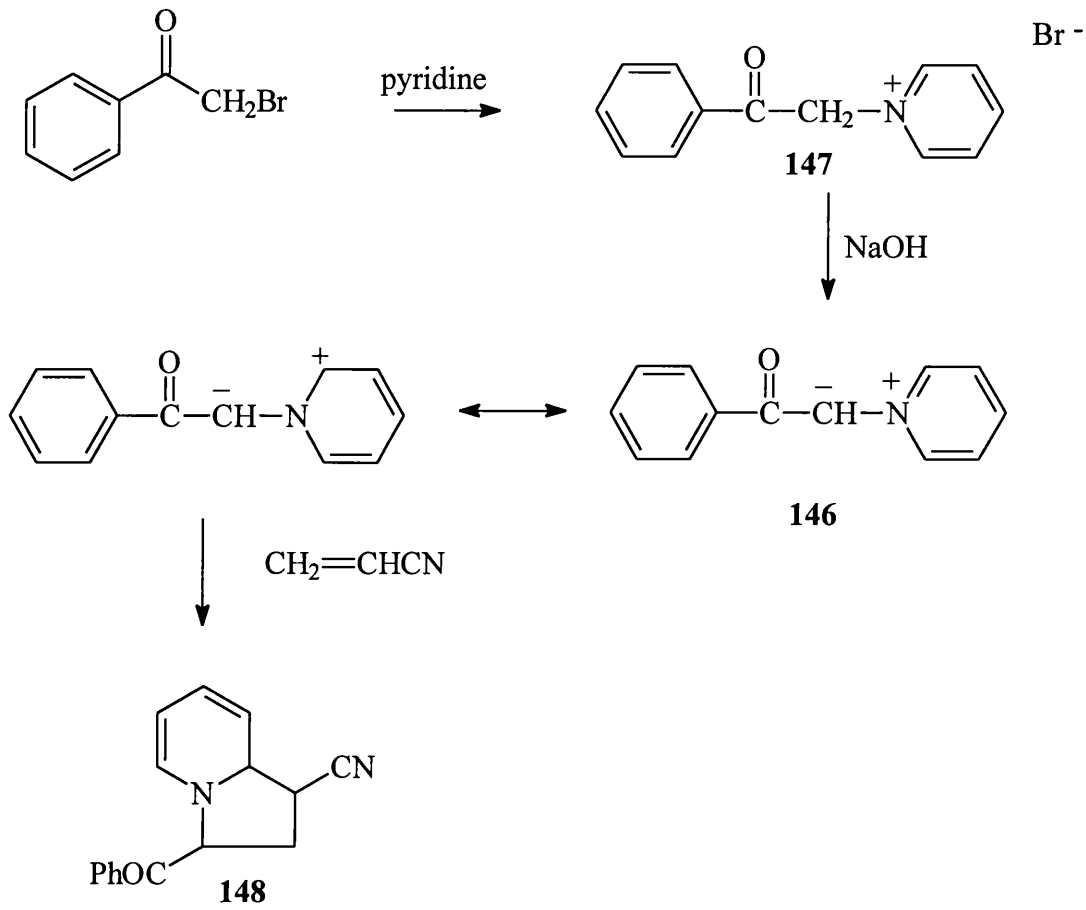
No explanation was provided by Capozzi *et al.* for the formation of the disulfide **101**. Clearly however, 3 molecules of the thioaldehyde precursor **100** must contribute to this product. An extension of the carbophilic route of Scheme 62 could be used to provide a mechanistic explanation (Scheme 70).



Scheme 70

The product **142** formed from the carbophilic attack of pyridine on the thioaldehyde, could then undergo reaction with a second molecule of thioaldehyde to give **143**. Sulfenylation could then occur with the thioaldehyde precursor to give **144**. Fragmentation with more pyridine gives the dienophile **145** along with the stabilised ylid **146**.

If this mechanism were to operate it might be possible to trap *in situ* the ylid **146**. Such compounds are known to undergo 1,3-dipolar cycloadditions. An example was found in the literature [56] whereby the pyridinium salt **147** was used to generate the same ylid **146**, which then underwent cycloaddition with acrylonitrile to form the tetrahydroindolizine **148** (Scheme 71).

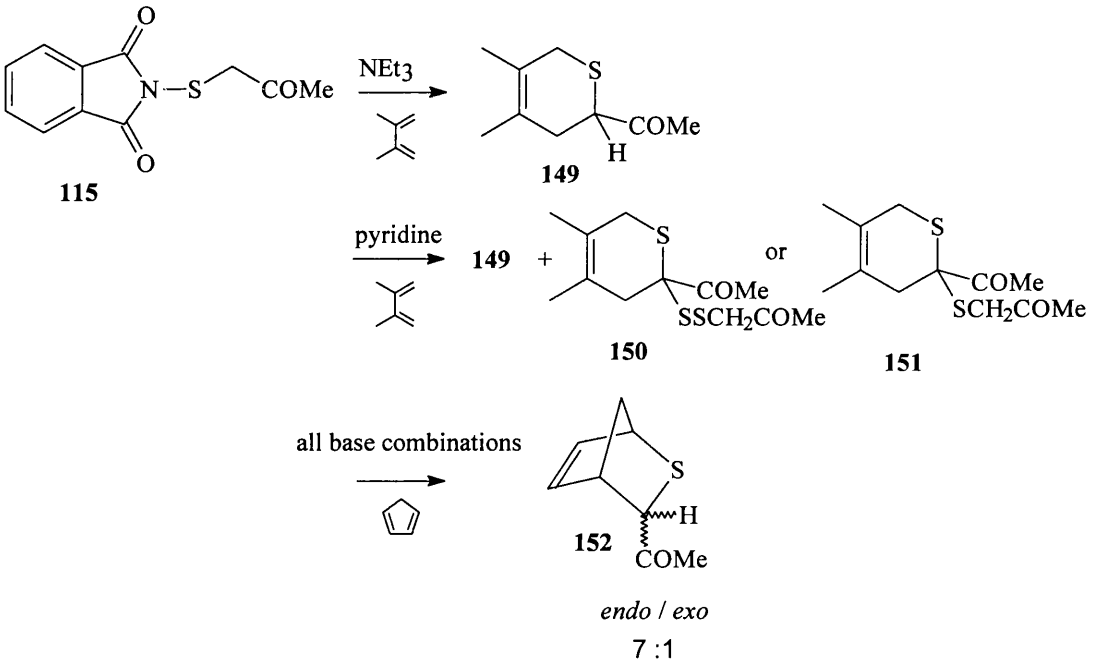


Scheme 71

This same reaction was carried out and the tetrahydroindolizine **148** was formed as an orange solid. An attempt was then made to isolate the ylid **146** from the reaction mixture from the phthaloyl sulfenamide **100** and pyridine. The reaction was carried out as before. The phthalimide was filtered off and the organic filtrate extracted with water. Addition of acrylonitrile and sodium hydroxide produced a yellow colour but work-up only led to a small amount of a yellow oil, possibly pyridine.

A similar set of reactions was performed with the methyl β-oxo derivative **115**. No base eliminations to form thioaldehydes had previously been carried out with

this phthaloyl sulfenamide by Capozzi *et al.*[43]. As expected, the results were very similar for the two β-oxo phthaloyl sulfenamides. Treatment of **115** with triethylamine and dimethylbutadiene gave the thioaldehyde adduct **149** in good yield. Changing the base to pyridine, in this case an 'abnormal' adduct was formed as well as the thioaldehyde cycloadduct (Scheme 72). The ^{1}H NMR spectrum of this 'abnormal' adduct **150** or **151** showed the same pattern as that for the trisulfur adduct **101**, whose structure had been determined by X-ray analysis, and shown to have a disulfide side chain. The ^{1}H NMR spectrum showed a broad singlet and two AB systems for

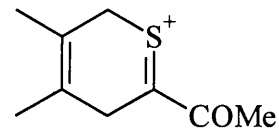


Scheme 72

protons other than the methyl protons. The broad singlet has the lowest chemical shift, δ 2.71 while the AB system at δ 3.16 (*J* 15.5 Hz) accounted for the protons α to sulfur in the ring. The sharper AB system, which appeared almost as a doublet, δ 3.46 (J_{AB} 14.4 Hz was reasonably attributed to $SSCH_2$. Capozzi had assigned a broad AB

quartet at δ 3.16 to the $SSCH_2$ group of his phenyl compound **101** but this seems unreasonable as the value is too low. Also it is apparent from other work that the same type of protons appear as very sharp peaks. In general the chemical shifts observed in the methyl adduct are lower than those of the phenyl adduct but follow the same pattern. The values for the ^{13}C NMR spectra were similar.

The mass spectrum of this product was not very useful, as was found for that of the phenyl compound **101**. No molecular ion was observed and the only information obtained was a peak at *m/z* 215.0568 ($C_{10}H_{15}OS_2$ requires 215.0565) which might correspond to loss of COMe from a product containing a sulfide **151** rather than a disulfide **150** side chain. Also there was a peak at *m/z* 169.0679 ($C_9H_{13}OS$ requires 169.0687) which may correspond to **153,** which might have arisen from a product with either a sulfide or disulfide side chain.



153

This 'abnormal' adduct seemed to decompose more readily than the other adducts and could not be obtained in a completely pure state by chromatography. It could be obtained as a yellow almost crystalline solid but was more commonly isolated as an oil.

The reaction with triethylamine containing 0.1 mol equivalent of DMAP in the presence of dimethylbutadiene also led to a mixture of two products, in poor yield, the thioaldehyde cycloadduct **149** and another product. The 'abnormal' adduct this time was different from that obtained using pyridine, according to the ^1H NMR spectrum. Again the mass spectrum was not very useful as the peaks were all very small relative to the base peak. If the adduct contained only a single sulfur side chain then the peak at *m/z* 258 corresponds to its molecular ion, but the intensity of this peak

was only 0.2 %. The only other information is a peak at *m/z* 169 which might represent the ion **153**. The ^{1}H NMR spectrum indicated a different structure from that obtained before. The usual methyl signals are present but also a sharp set of peaks at δ 2.56 and δ 2.57 possibly a doublet or an AB quartet. A singlet was also present at δ 3.43, possibly due to SCH_2, along with some smaller broader peaks. The spectrum does not bear much resemblance to that of the ethyl ester dithioester adduct **98** where the SCH_2 was an AB quartet and other ring protons were broad AB systems. However, the methyl signals must indicate some sort of 'abnormal' adduct.

As with the phenyl derivative **100,** reactions with DMAP and cyclopentadiene led only to the thioaldehyde cycloadducts **152** (Scheme 72).

2.8 Conclusions

In conclusion, ethyl phthalimidosulfanylacetate has been shown to be an efficient precursor of both ethyl thioxoacetate **31** and also the dithioester diethyl 3-thia-2-thioxopentanedioate, **98** depending on the conditions chosen for the elimination.

The dithioester cyclopentadiene cycloadducts **116** have been shown to serve as a clean source of the dithioester **98**. Also the dithioester itself can be isolated for use in further reactions. The mechanism of the formation of this dithioester cannot be completely explained at present, except that much evidence indicates that it is formed from the thioaldehyde rather than directly from the phthaloyl sulfenamide **45**.

Other elimination reactions with β-oxo derivatives show that their main use is as thioaldehyde precursors.

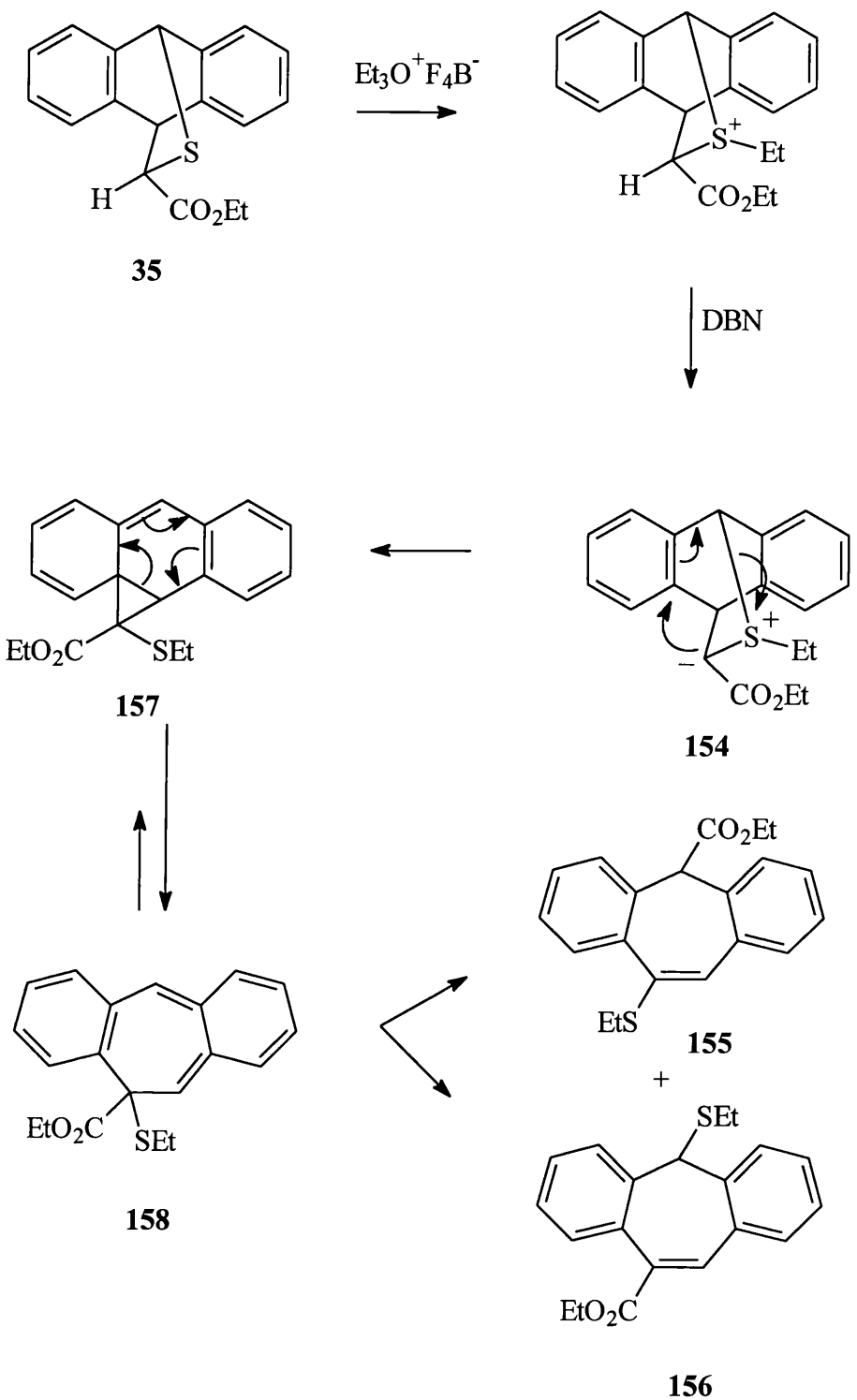
CHAPTER THREE

S-Alkylation and rearrangement of cycloadducts.

3.1 *S*-Alkylation and rearrangement of the cycloadduct 35 of ethyl thioxoacetate and anthracene

It has previously been shown that thioaldehyde cycloadducts can be alkylated at sulfur by reagents such as a trialkyloxonium tetrafluoroborate. The resulting sulfonium salt can then be treated with base to abstract the acidic proton α to the sulfur cation leading to subsequent rearrangement of the sulfur ylid.

Rahman [57] had shown that the anthracene cycloadduct **35** of ethyl thioxoacetate **31** underwent such a rearrangement when treated successively with triethyloxonium tetrafluoroborate and then diazabicyclononene (DBN) (Scheme 73). He found that rearrangement of the ylid **154** led to a mixture of two isomers which were thought to be **155** and **156**. The rearrangement was thought to have occurred through the cyclopropane derivative **157**. Disrotary ring opening then could lead to the intermediate structure **158** which might undergo a 1,5-migration of either the ethylthio group to yield **156** or the ethoxycarbonyl group to yield **155**. Rahman obtained the isomers as a yellow gum which could not be separated by chromatography into the individual components.



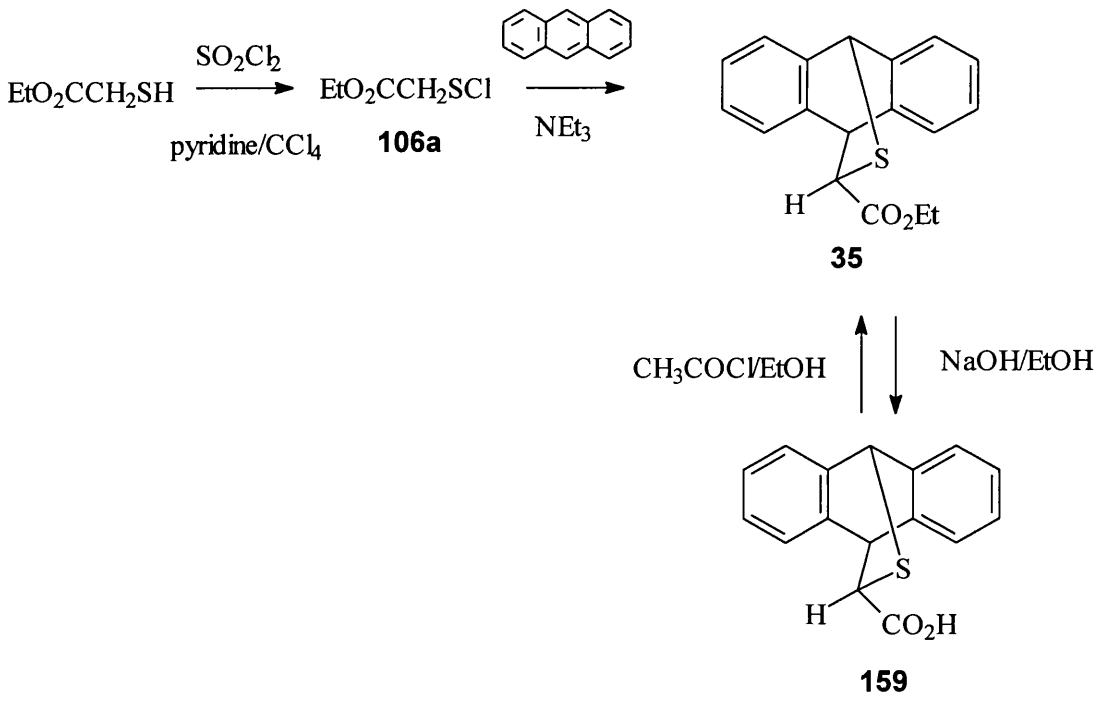
35 **157** **154** **158** **155** **156**

Scheme 73

3.1.1 Further work

It was decided to repeat this work in an attempt to separate the products and clarify their structures **155** and **156**. An element of doubt had been present due to the chemical shift of the protons on the non-benzoid double bond. These gave singlets at δ 8.06 and 8.26. A low field singlet might be expected for the proton α to the ester group, but that α to the ethylthio was expected to be much less deshielded.

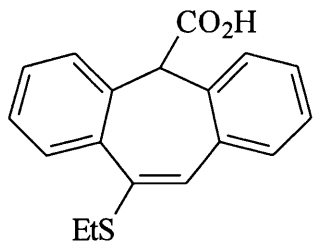
The anthracene cycloadduct **35** was prepared following the method of Kirby and Choi [33] (Scheme 74). The ester was then converted into the acid **159** to allow purification by easy removal of the excess of anthracene. This acid was then esterified to provide the cycloadduct **35**. Triethyloxonium tetrafluoroborate was prepared following the method of Meerwein [58], from boron trifluoride etherate and epichlorohydrin.



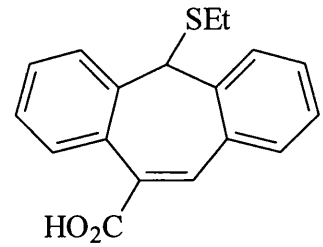
Scheme 74

Treatment of the anthracene adduct **35** with the oxonium salt followed by DBN gave the mixture of isomers **155** and **156,** as reported, as a pale yellow gum (90%). Chromatography of this gum led to a pale yellow oil which began to solidify after standing at room temperature for a few hours. It was then found that careful washing with ether could yield a white solid m.p. 80-82 °C. Both the yellow gum and the white solid gave the same proton NMR spectrum and attempted recrystallisation of the white solid caused it to revert to the gum. No separation was obtained by chromatography and the ratio of isomers (major:minor = 3.7 : 1) remained constant in both the gummy and the solid states.

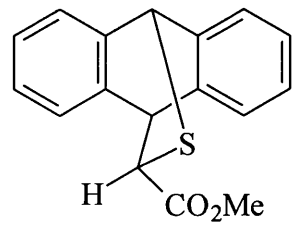
Treatment of the isomer mixture with sodium hydroxide in ethanol gave the corresponding acid derivatives **160** and **161**. Again the ratio of the isomers remained unchanged as measured by ^1H NMR spectroscopy and the signals were all further downfield than in the esters.



160



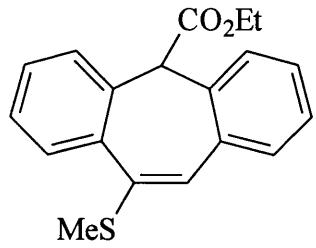
161



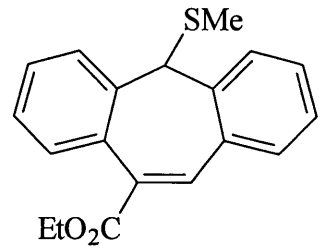
35b

Two other variations were then prepared. The anthracene methyl ester **35b**, prepared from the acid **159** by treatment with acetyl chloride and methanol, was treated with both triethyloxonium tetrafluoroborate and trimethyloxonium

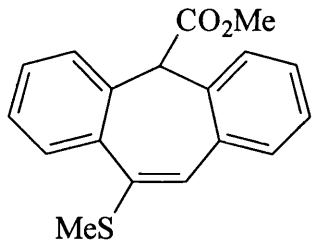
tetrafluoroborate to yield a further two sets of isomers **162** and **163** (major:minor = 3.1:1) and **164** and **165** (major:minor = 3.6:1) (tentative structures).



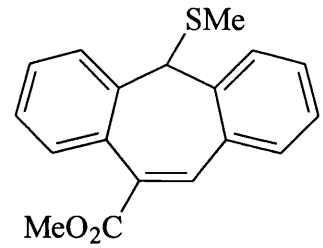
162



163



164



165

Unfortunately, these isomers also formed yellow gums which showed no separation on TLC. As before careful washing with diethyl ether yielded white solids with relatively sharp melting points, having ^{1}H NMR spectra identical to those of the gum. The ratio of isomers in both these new sets were similar to those of the original set. A small amount of **162** and **163** was recrystallised but the ratio of isomers remained unchanged, *ie.* no separation had occurred on crystallisation.

It was thought that maybe the pairs of isomers might be interconverting in solution. The relatively sharp melting point of the solid and the recrystallised sample also seemed unlikely if a mixture of isomers was present. A high temperature (60 °C) ^{1}H NMR spectrum was run on the *S*-methylated ethyl ester derivatives **162** and **163** in an attempt to increase the rate of conversion if this was occurring. The ratio of

isomers in this case was 3.1:1. If interchange is rapid enough then the peaks would broaden and coalesce. However, no change was observed in the comparison of the normal and high temperature ^1H NMR spectra.

Rahman had assigned the enol thioether **155** to the minor component of the mixture, but there was no real evidence for this. In all cases the minor isomer showed a signal for the vinyl proton more downfield than for the major isomer. The signals of the *S*-alkyl group were more downfield in the minor isomer (Tables 4, 5 and 6) .

Table 4. Comparison of chemical shifts of the C=CH protons in the rearrangement products.

	chemical shift (δ ; $CDCl_3$)	
Rearrangement product	minor isomer	major isomer
SEt, CO_2Et :**155** and **156**	8.26	8.06
SMe,CO_2Et :**162** and **163**	8.25	8.04
SMe,CO_2Me:**164** and **165**	8.27	8.06
SEt,CO_2H:**159** and **160**	8.45	8.27

Table 5. Comparison of chemical shifts of the *S*-alkyl group in the rearrangement products

	chemical shift (δ ; $CDCl_3$)	
Rearrangement product	minor isomer	major isomer
SEt, CO_2Et:**155** and **156**	1.16, 2.46	1.08, 2.28
SMe,CO_2Et:**162** and **163**	2.08	1.88
SMe,CO_2Me:**164** and **165**	2.07	1.88
SEt,CO_2H:**159** and **160**	1.24, 2.53	2.33, 1.13

Table 6. Comparison of chemical shifts of the saturated carbon ring proton in the rearrangement products.

	chemical shift (δ ; $CDCl_3$)	
Rearrangement product	minor isomer	major isomer
SEt, CO_2Et:**155** and **156**	4.47	5.14
SMe,CO_2Et:**162** and **163**	4.45	5.04
SMe,CO_2Me:**164** and **165**	4.37	5.04
SEt,CO_2H:**159** and **160**	4.50	5.17

It is difficult from these data to determine precisely which tentative structure corresponds to that of the major or minor component.

The ^1H NMR spectra of the *S*-methylated ethyl esters **162** and **163** were also run in benzene. The *S*-methyl signals now had similar chemical shifts and the vinyl proton signals also moved much closer (Table 7).

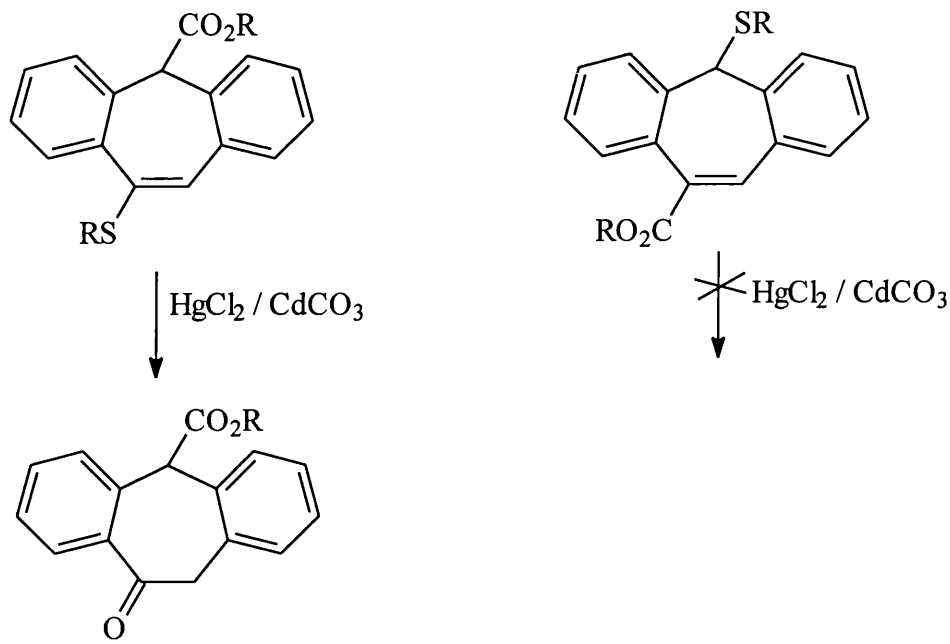
Table 7. Comparison of chemical shifts, in deuterochloroform and benzene, of the major and minor isomers of the rearrangement products **162** and **163**.

	major isomer		minor isomer	
protons	$CDCl_3$	Benzene	$CDCl_3$	Benzene
C=CH	8.04	8.34	8.25	8.40
Ring	5.04	4.90	4.45	4.43
S-methyl	1.88	1.61	2.08	1.60

An attempt was made to separate of the isomers **162** and **163** by HPLC, but only one peak was observed with both silica and reverse-phase columns.

3.1.2 Attempted chemical separation of the rearrangement products

As physical separation of the isomers was unsuccessful an attempt was made to separate them by chemical means. It was thought that it might be possible to convert the enol thioether group of one of the isomers into a keto group. The other isomer containing the *S*-alkyl group on the saturated carbon would remain unchanged (Scheme 75).



Scheme 75

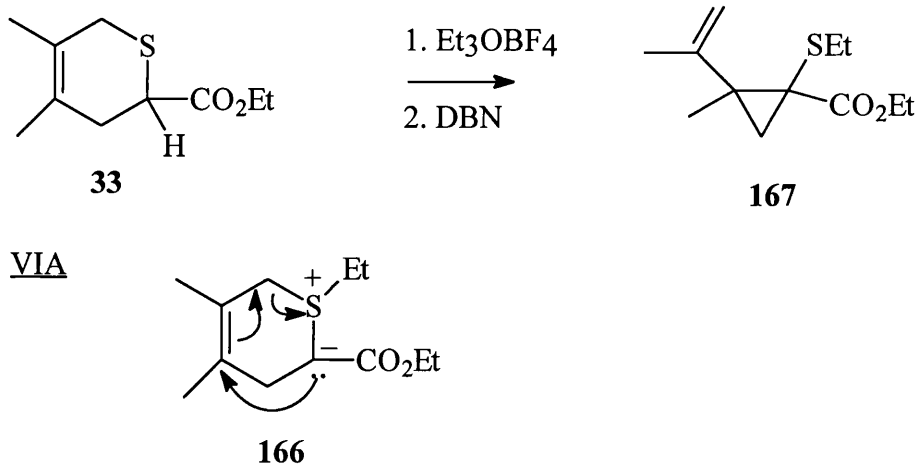
Examples were found in the literature [59,60] of the hydrolysis of enol thioethers with mercuric chloride in acetonitrile and water. Examples of the hydrolysis of thioacetals used mercuric chloride in acetone in the presence of cadmium carbonate. It was decided to combine these two approaches as the resulting ketone would be highly enolizable and the cadmium carbonate would maintain neutral conditions avoiding possible aldol reactions occurring.

Thus the reaction with each mixture **155** and **156**, **162** and **163** and **164** and **165** was carried out in acetonitrile and water, containing cadmium carbonate and mercuric chloride at room temperature. All three sets of isomers were treated in turn under these conditions and in all cases both isomers appeared to have reacted. There was no evidence of one isomer being left unchanged. Again on TLC there appeared only one spot although the ^{1}H NMR spectra again appeared to show two products in each case.

Both of the *S*-alkyl groups must have reacted with the mercuric chloride. The mass spectra, with accurate mass measurement of ions showed that the *S*-alkyl group was replaced by a hydroxy group in each case. The products formed by treatment of the *S*-methyl, ethyl esters **162** and **163** and the *S*-ethyl, ethyl esters **155** and **156** were identical. No other steps were taken however, to clarify the nature of these rearrangement products.

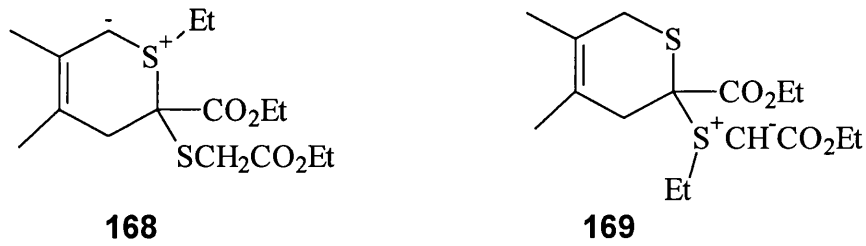
3.2 *S*-Alkylation and rearrangement of the dimethylbutadiene dithioester cycloadduct **98**

Kirby *et al.* [35] showed that the thioaldehyde cycloadduct **33**, when *S*-alkylated with triethyloxonium tetrafluoroborate followed by abstraction of the α proton with DBN, gave an ylid intermediate **166** which rearranged to give the cyclopropane **167** (Scheme 76).



Scheme 76

It was decided to treat the cycloadduct **98** of the dithioester and dimethylbutadiene in the same way. Either sulfur might be preferentially alkylated. Deprotonation α to the positive sulfur would give the alternative ylids **168** and **169**.

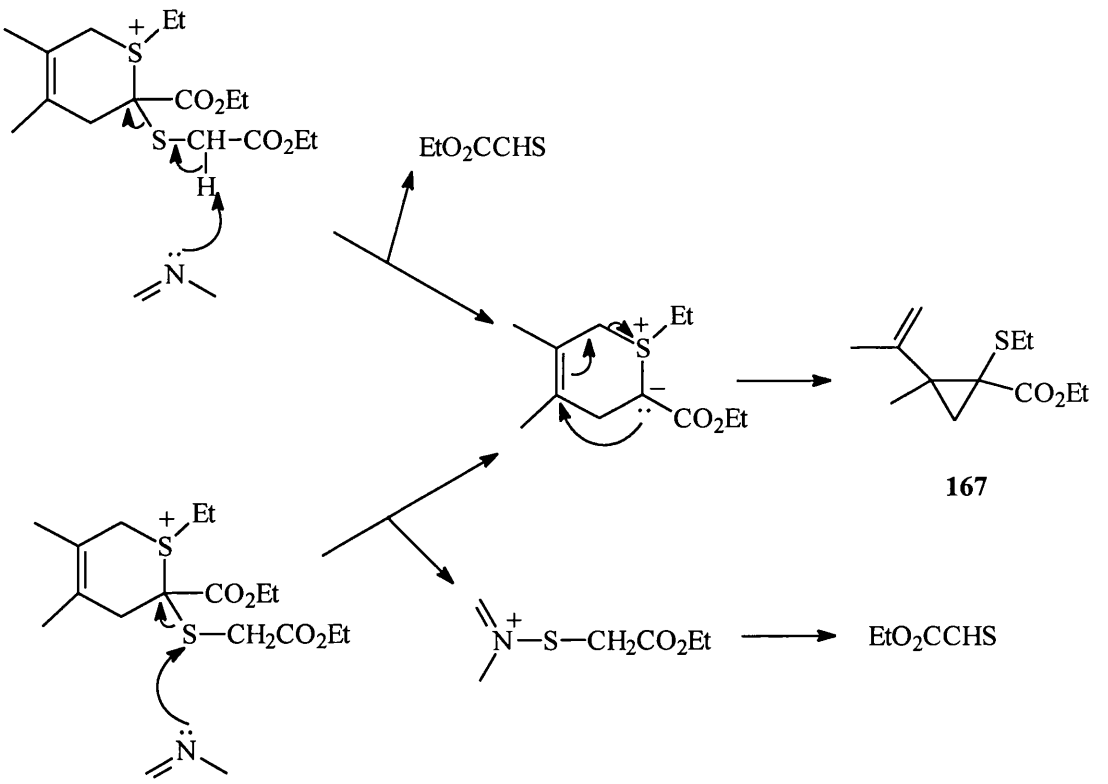


168 **169**

The dithioester cycloadduct **98** was thus treated with an excess of triethyloxonium tetrafluoroborate, followed by DBN. A red colour developed when the base was added and after work-up an oil was obtained in good yield. The TLC of this crude product showed two new spots. The ^{1}H NMR spectrum of this crude mixture corresponded to that of a mixture of the disulfide $(EtO_2CCH_2S)_2$, **104a** and the cyclopropane **167**, which had been obtained earlier from the dimethylbutadiene thioaldehyde cycloadduct **33**. The ^{13}C NMR spectrum corresponded exactly to that

expected for this mixture, and molecular ions were found for both components in the mass spectrum.

Apparently therefore, *S*-alkylation had occurred at the sulfur in the ring rather than in the side chain. The dithioester cycloadduct must then have lost its sulfide side chain at some other stage in the reaction sequence thus enabling it to behave like the thioaldehyde cycloadduct. The simplest interpretation of this result involves base-mediated loss (stepwise or concerted) of the sulfide side chain either as ethyl thioxoacetate **31** or by nucleophilic attack on sulfur. However, the formation of substantial amounts of the disulfide **104a** suggests that the process is more complex, although this disulfide might have arisen from the thioaldehyde by-product (Scheme 77).

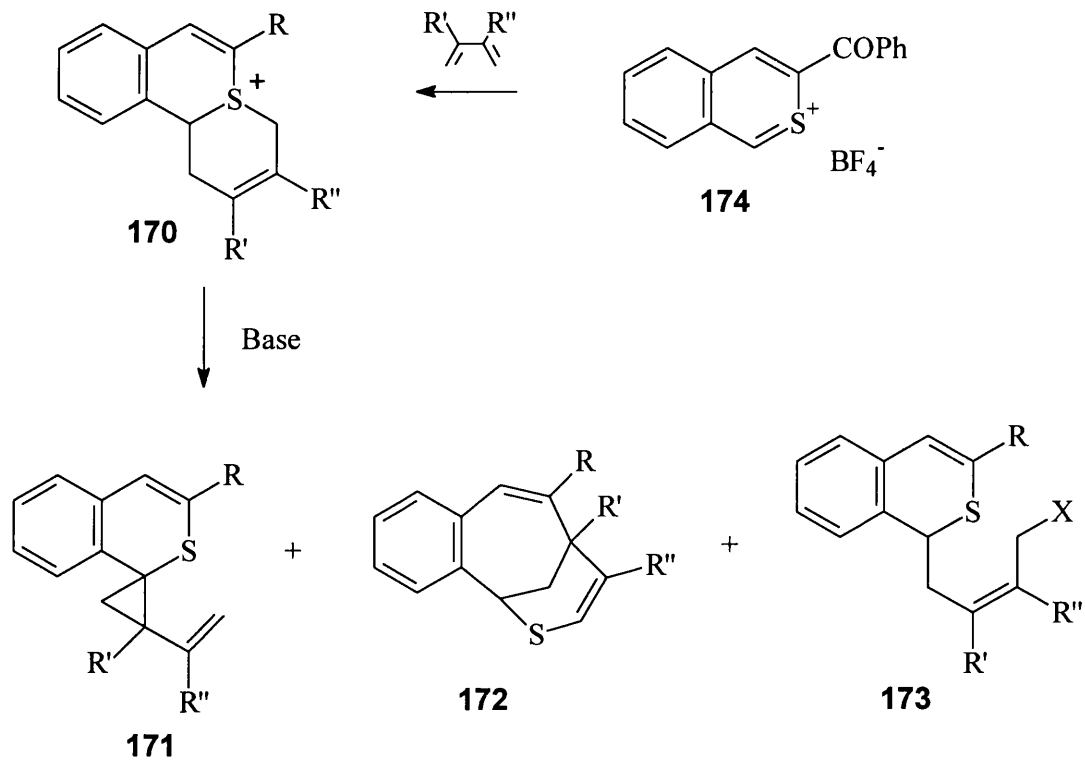


Scheme 77

Minor amounts of other products were also formed as observed by ^1H NMR spectroscopy. Two other tiny quartets were present near the position for the SCH_2Me quartet. These products might have arisen from alkylation at the other sulfur atom, or perhaps from alkylation at both sulfurs. However, they are both very minor products.

Similar treatment of the dithioester cycloadduct of cyclopentadiene **116** led to an uncharacterised, dark mixture. Even the first stage, treatment with triethyloxonium tetrafluoroborate gave a dark solution.

Similar studies have been carried out by another group [61]. Treatment of the cycloadduct **170** with base gave 3 types of rearrangement products **171**, **172** and **173**. **171** and **172** correspond to the 2 possible positions of deprotonation of the sulfonium salt **170** while **173** was formed by an S_N2 attack by X^- (Scheme 78). The



Scheme 78

cycloadducts were formed by cycloaddition of the 2-benzothiopyrylium salt **174** and a range of dienes [62]. The ratios of the products were dependent on the base used for deprotonation *e.g.* **173** was only formed with Et_3N, Et_2NH or O^-Ac and not with LDA, NaH or K_2CO_3.

3.3 Conclusions

S-Alkylation then base-mediated rearrangement of methyl and ethyl thioxoacetate cycloadducts of anthracene **35** and **35b** has provided three pairs of isomers. The structures, however, still cannot be proven and neither physical nor chemical separation has been successful so far. However, separation by preferential cleavage of the C-S bond of one of the isomers is still a possibility providing that the correct conditions can be found.

Similar treatment of the cycloadduct **98** of the dithioester **99** and dimethylbutadiene has shown that, despite many possible alternative routes, the rearrangement occurs to form the same product as that from the thioaldehyde cycloadduct **33**.

CHAPTER FOUR

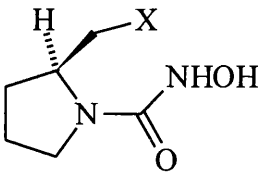
Synthesis of (±)-*trans*-2,5-bis(methoxymethyl)pyrrolidine and its use as a thioaldehyde chiral auxiliary

Thioaldehydes have now become popular heterodienophiles because of their high reactivity, and efficient synthetic methods to capture them have been developed. However, little work has been reported on asymmetric cycloaddditon of thioaldehydes having a chiral auxiliary.

Vedejs *et al.* [40] reported the diastereoselective Diels-Alder reaction of racemic α-alkoxy thioaldehydes with cyclopentadiene, obtaining d.e. values ranging from 30 to 80%. Further Takahashi *et al.* [41] reported the Diels-Alder reaction of optically active α-alkoxycarbonyl thioaldehydes with cyclopentadiene, which proceeded with moderate diastereomeric excesses (d.e. of *endo* adducts = 12 to 43%). Some *endo* adducts were isolated in optically pure form.

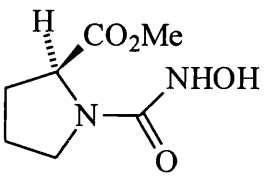
This is an important new area and we planned further investigations. Thus a route was sought to prepare a thioaldehyde containing a potentially effective chiral auxiliary. It had been noted that α-oxo thioaldehydes RCO-CSH were of similar shape and size to carbamoylnitroso compounds RCO-NO, both of which exist as transient dienophiles.

The group of Streith [63] had reported diastereomeric excesses ranging from 52%-68% in the reaction of cyclohexadiene with carbamoylnitroso compounds formed by the oxidation of the hydroxamic acids **175a-d** derived from L-proline. The selectivity was thought to result from the presence of two reacting conformations around the C-N bond **176** and **177**. However, Gouverneur and Ghosez [64] observed

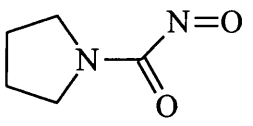


175

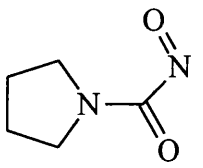
a X = OH
b X = OMe
c X = NHPh



175d

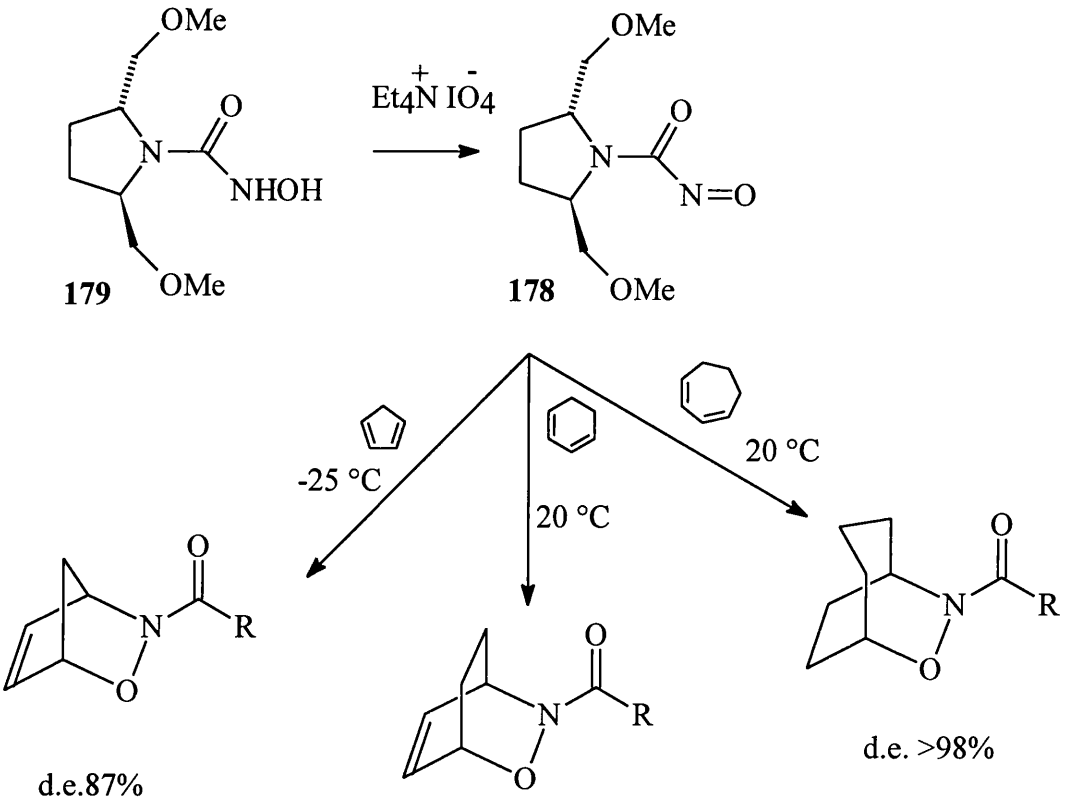


176



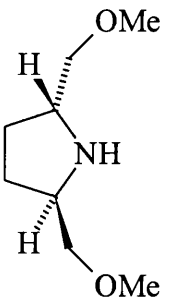
177

that much higher diastereoselectivities could be obtained with a carbamoylnitroso compound **178** derived from a disubstituted pyrrolidine **179** possessing C_2 symmetry (Scheme 79). The starting material for the hydroxamic acid **179**, the carbamoylnitroso precursor, was (2*R*,5*R*)-bis(methoxymethyl)pyrrolidine **180**.



Scheme 79

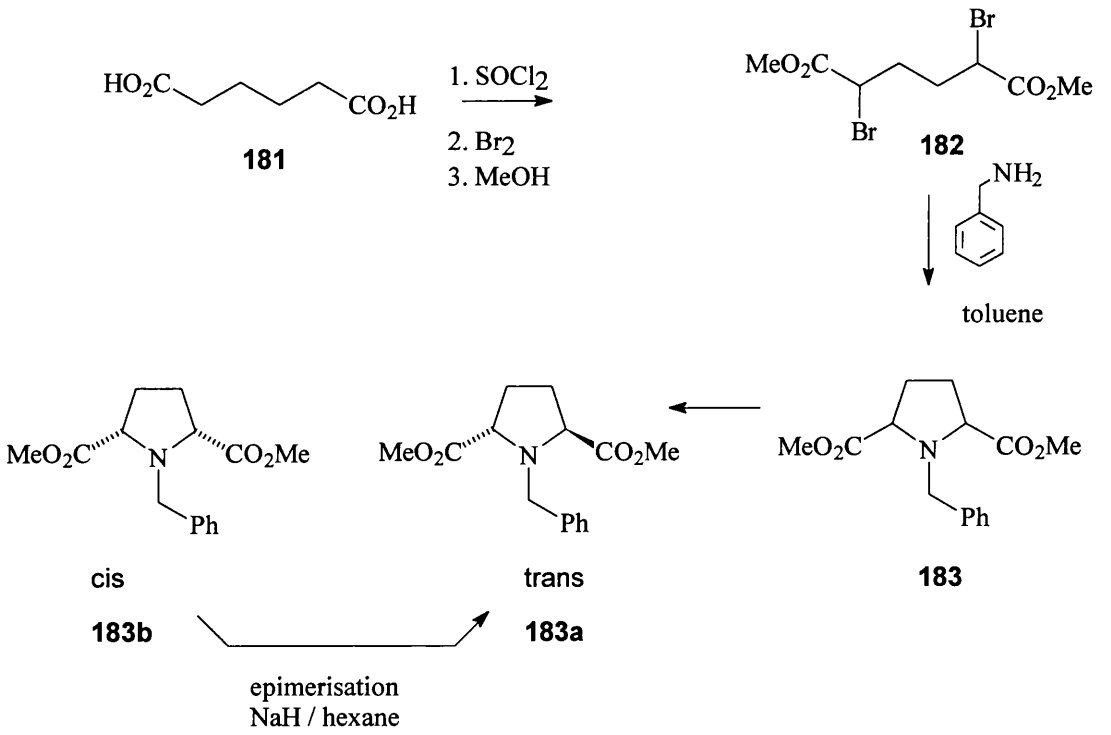
It was decided to synthesise this auxiliary **180** and then try to form the corresponding thioaldehyde, which could undergo Diels-Alder reactions. As this auxiliary had been shown to be effective with the carbamoylnitroso compounds it was likely that similar results could be obtained with a thioaldehyde.



180

4.1 Preparation of *trans*-2,5-bis(methoxymethyl)pyrrolidine 180.

The experimental procedure was obtained from Ghosez [65] and the auxiliary was prepared as follows. Adipic acid **181** was treated with thionyl chloride to form the corresponding acid chloride which was then brominated. Treatment with methanol then gave the dibromodiester **182**. Treatment of this diester with benzylamine gave the *N*-benzyl diester **183** as a mixture of *trans* and *cis* isomers **183a** and **183b** (Scheme 80).



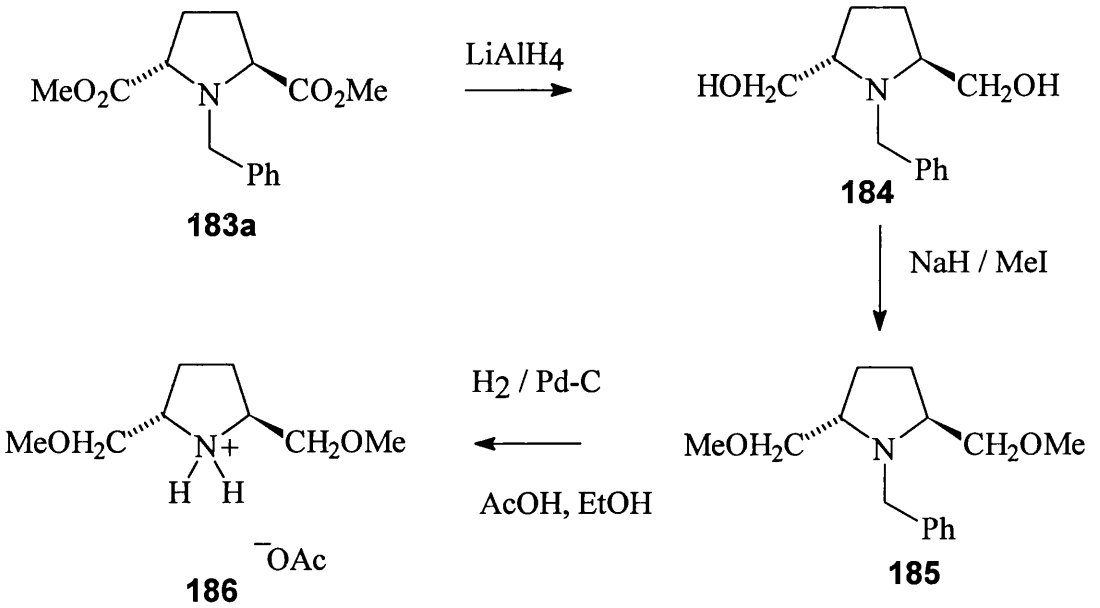
Scheme 80

The isomers were separated by column chromatography on silica gel, although the preparation had recommended HPLC. The unwanted *cis* isomer **183b** was epimerised by treatment with sodium hydride to give largely the *trans* isomer.

At this stage the desired *trans* diester **183a** could be hydrolysed to form the racemic *trans* diacid. The acid was resolved by Ghosez *et al.* as the d-ephedrine salt

which was recrystallised and esterified to give the (*S*,*S*) diester. Resolution with l-ephedrine gave the (*R*,*R*) diester. It was decided however, to omit the resolution step and carry out further transformations with the racemic diester as the final results would be unchanged other than by the formation of racemic, diastereoisomeric products.

The racemic diester **183a** was then reduced to the diol **184** by treatment with lithium aluminium hydride. After further treatment with sodium hydride and methyl iodide the diol was converted into the methyl ether **185**. The benzyl protecting group was then removed by hydrogenolysis with palladium on carbon catalyst (Scheme 81).



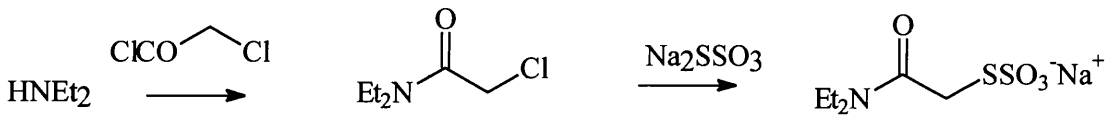
Scheme 81

Acetic acid had been used in the hydrogenolysis and the product was isolated as its acetate salt **186**. Ghosez *et al.*[65] then prepared the hydrochloride salt by saturation with hydrogen chloride gas but the acetate form was used for further transformations in the present investigations.

4.2 Preparation of Bunte salts as thioaldehyde precursors

4.2.1 Preparation of the diethylamido Bunte salt 188

As the chiral auxiliary was time-consuming to prepare it was decided first to investigate a model. This avoided unnecessary waste of the auxiliary when developing the Bunte salt preparation. Thus diethylamine was easily converted into the chloroacetamide **187** by treatment with chloroacetyl chloride. The Bunte salt **188** was formed, as described earlier [28], by treatment with sodium thiosulfate (Scheme 82). Although only isolated as a gum, the salt **188** was suitable for further transformations.

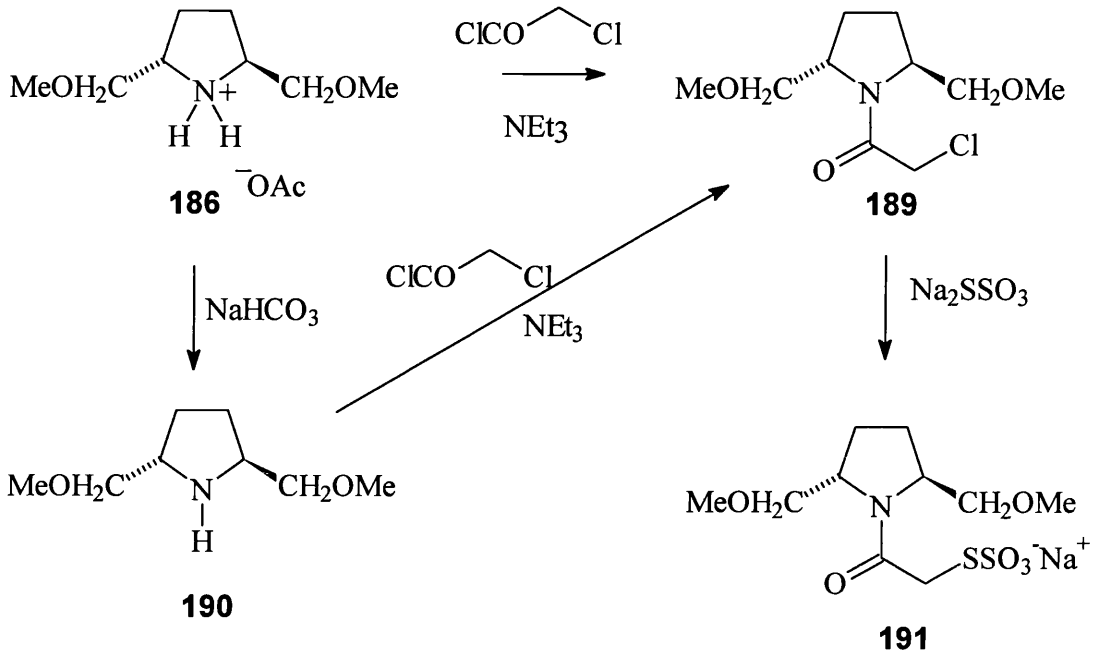


187 **188**

Scheme 82

4.2.2 Preparation of the *trans*-2,5-bis(methoxymethyl)pyrrolidine Bunte salt 191

The corresponding chloroacetamide **189** was formed as above by treatment with chloroacetyl chloride. The acetate salt **186** was converted into the free amine **190** by adding aqueous sodium hydrogen carbonate to the salt and extracting into an organic solvent. Treatment with chloroacetyl chloride and triethylamine then yielded the chloroacetamide **189**. It was found to be easier however, to form the chloroacetate (95%) directly from the acetate salt **186** by treating with 2 mol equivalents of triethylamine followed by 1 mol equivalent of chloroacetyl chloride. Treatment with sodium thiosulfate then provided the Bunte salt **191** again as a gum (82%) (Scheme 83).

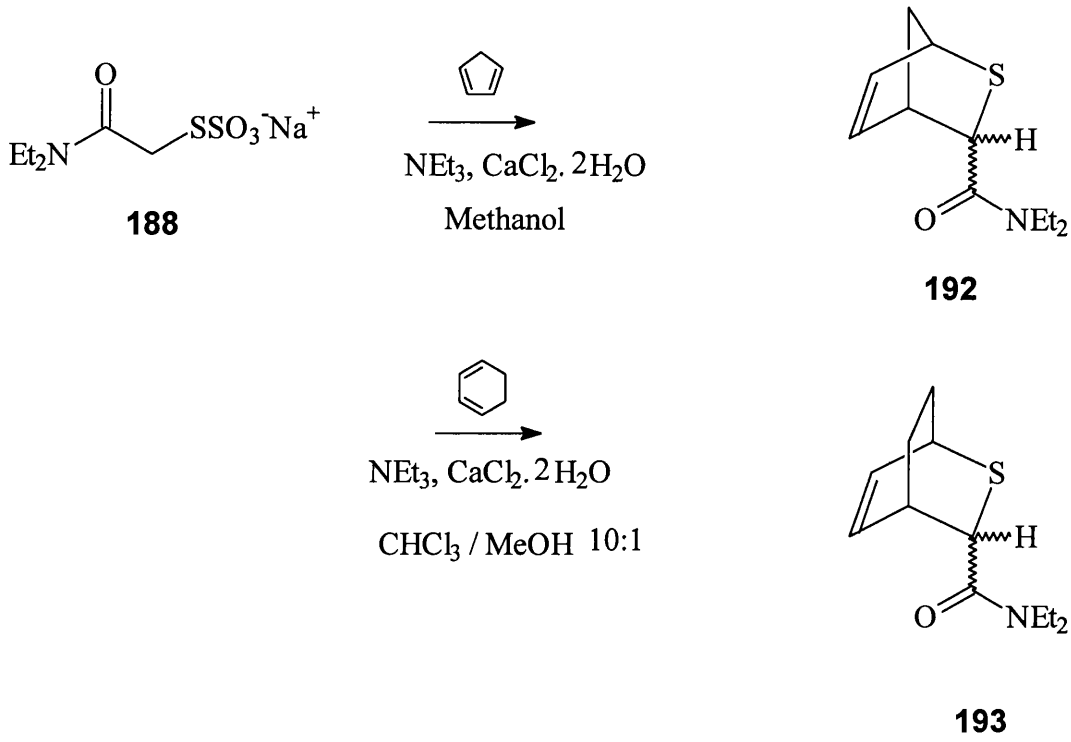


Scheme 83

4.3 Cycloadduct formation

4.3.1 Formation of cycloadducts from the diethylamido Bunte salt 188

Again the model Bunte salt **188** was used to establish conditions for the generation of the thioaldehyde and capture by an appropriate diene. Following previous conditions, the Bunte salt **188** was treated with triethylamine and cyclopentadiene in methanol containing calcium chloride dihydrate at room temperature (Scheme 84). The calcium chloride is used to remove the sulfite dianion, which is liberated from the elimination as its insoluble calcium salt and thus prevent it reacting nucleophilically with the thioaldehyde. Under these conditions the cycloadducts **192** were formed easily in good yield.



Scheme 84

However, with cyclohexadiene as the trapping agent and methanol as the solvent no cycloadduct was obtained. Cyclohexadiene is not as efficient at trapping as cyclopentadiene, *i.e.* the cyclohexadiene is unable to trap the thioaldehyde quickly enough to prevent polymerisation.

Previously it had been found [28] when generating ethyl thioxoacetate **31** from the corresponding Bunte salt **118** that cycloadduct formation was easily accomplished in methanol at room temperature when trapping with cyclopentadiene. However, changing the diene to dimethylbutadiene gave lower yields and acceptable yields were only obtained in a less polar solvent system. Heating at reflux was then required because elimination is slower in less polar solvents. By applying these findings to the present case, the cyclohexadiene cycloadducts **193** were formed in acceptable yield (44%) in chloroform-methanol (10:1) as the solvent system at room temperature

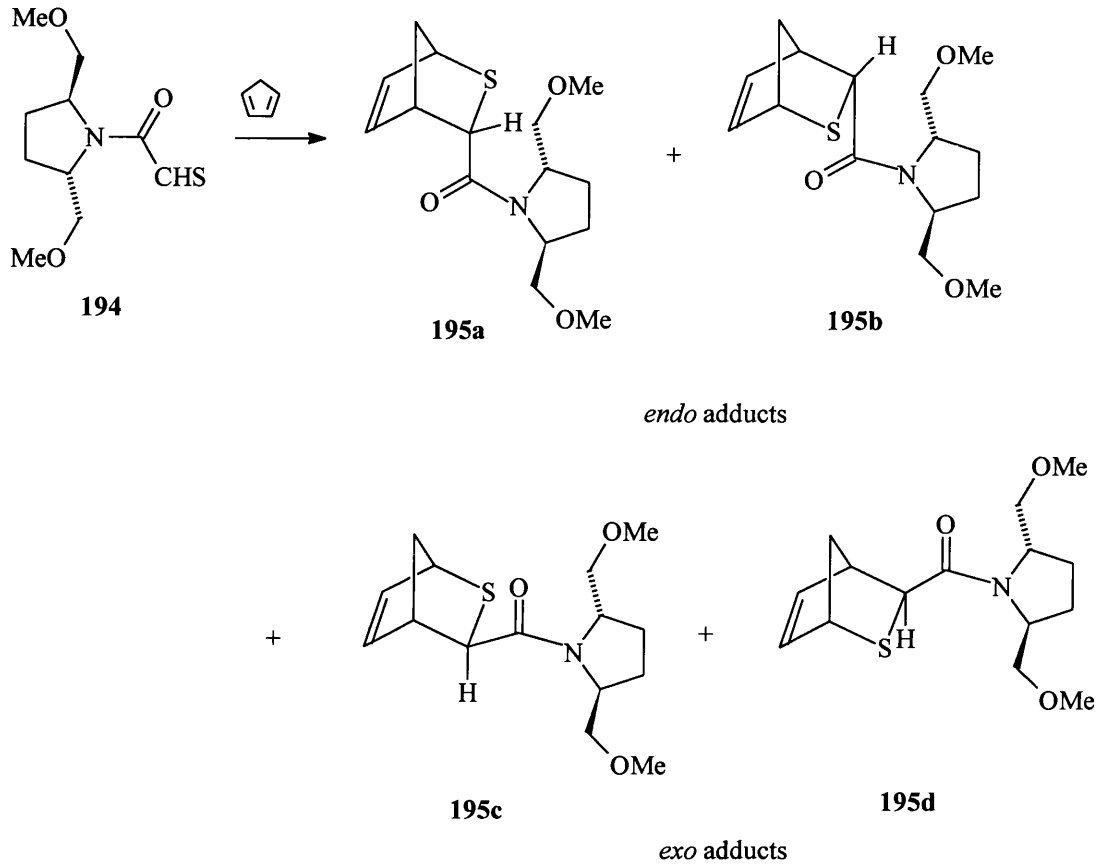
overnight (Scheme 84). A compromise had to be established for the ratio of the two solvents. In chloroform alone the reaction might work well but the sulfite dianion generated would not be removed since calcium chloride is insoluble in chloroform. Addition of a small amount of methanol allows enough calcium chloride to dissolve and after precipitation of calcium sulfite the methanol can then dissolve further calcium chloride. The sulfite can therefore always be removed as long as the reaction is slow enough. The addition of more methanol allows the reaction to proceed more quickly but lowers the yield.

4.3.2 Formation of cycloadducts from the *trans*-2,5-bis(methoxymethyl) pyrrolidine Bunte salt 191

Now that the conditions for the Diels-Alder cycloadditions had been established the cyclopentadiene and cyclohexadiene cycloadducts of the thioaldehyde containing the auxiliary could be prepared.

Formation of the cyclopentadiene cycloadducts 194

Treatment of the racemic Bunte salt **191** with triethylamine quickly gave the corresponding, racemic thioaldehyde **194** at room temperature which was trapped with cyclopentadiene in the presence of calcium chloride dihydrate. The cycloadducts **195a-d** were formed as racemic mixtures and all 4 diastereomers were formed, as judged by the ^{1}H NMR spectrum of the mixture (Scheme 85).



Scheme 85

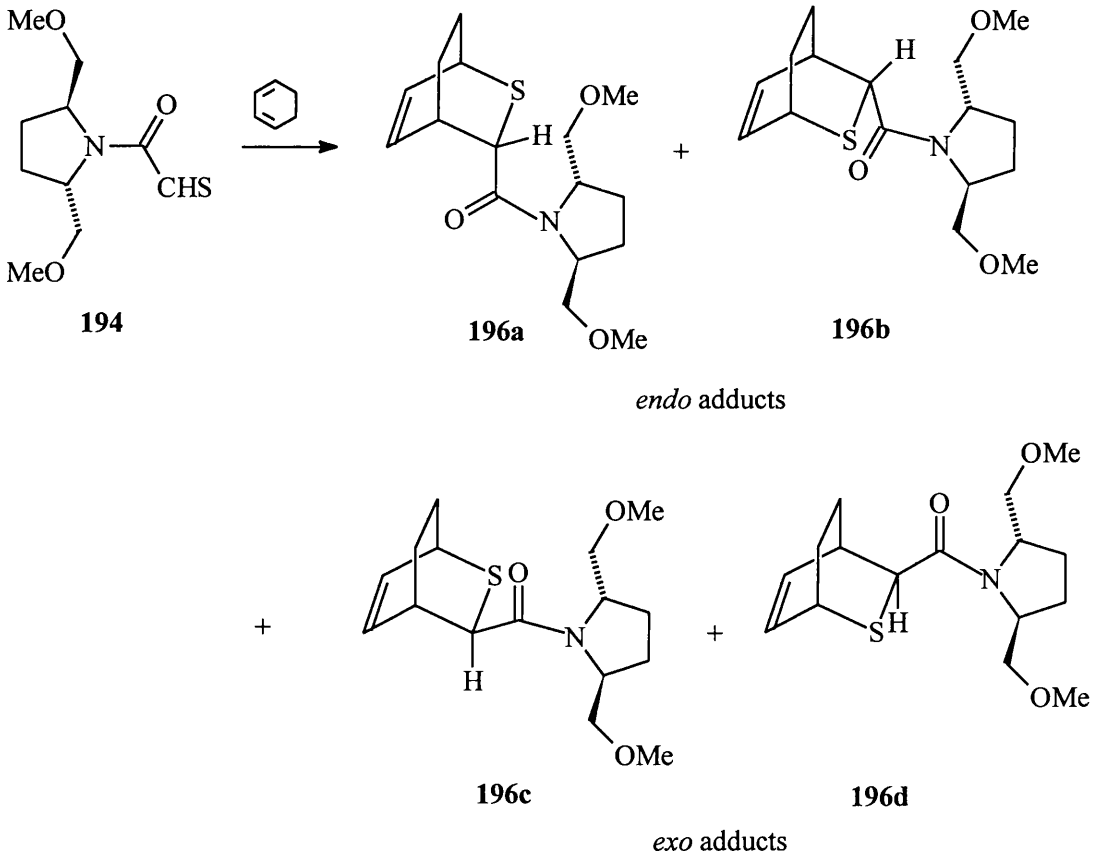
The observed *endo* : *exo* ratio, **(195a + 195b)** : **(195c + 195d)**, was 2.4:1. The *endo* and *exo* adducts were formed with diastereomeric enrichments (d.e.s) of 91 and 89%, respectively.

It was found that the major, *endo* adduct of the set of 4 was isolated from all other adducts by chromatography. Although a racemic auxiliary had been used, it showed that an optically pure cycloadduct could easily be obtained from the resolved material. The relative configuration **195a** or **195b** of this major diastereomer could not be determined however, as the adducts were only obtained as oils and crystallisation attempts were unsuccessful.

HPLC of the remaining mixture, containing the major *exo* isomer along with the minor *endo* and *exo* isomers, was also carried out. With a silica column 3 peaks were observed corresponding to the 3 isomers.

Formation of the cyclohexadiene adducts 196

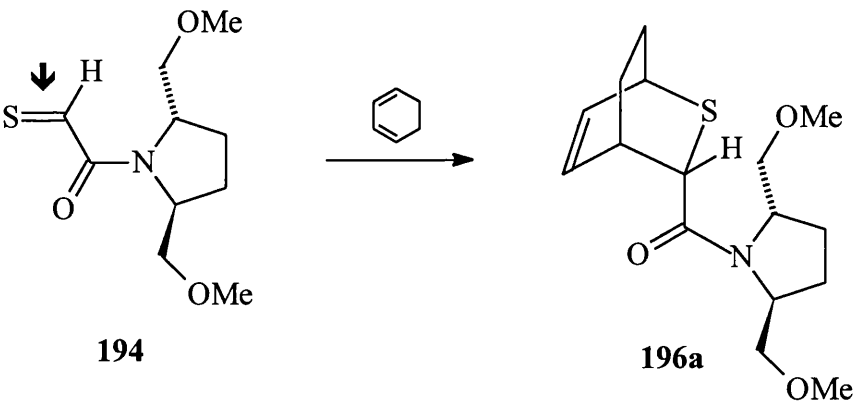
The corresponding cyclohexadiene cycloadducts **196** (Scheme 86) were also formed in the solvent system which was found to be most effective for the diethylamido Bunte salt. Thus the racemic pyrrolidine Bunte salt **191** was treated with triethylamine in chloroform-methanol (10:1) and stirred at room temperature for 3 h .



Scheme 86

This time the observed *endo* : *exo* ratio (**196a** + **196b**) : (**196c** + **196d**) was 10.5:1. The *endo* adducts were formed with a d.e of 75%. This is what would be expected as the cyclohexadiene is known to give larger *endo* : *exo* ratios than cyclopentadiene *e.g.* for ethyl thioxoacetate EtO_2CCHS the values are 88:12 for cyclohexadiene and 7:3 for cyclopentadiene.

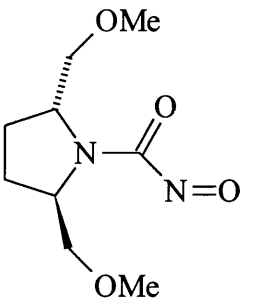
Only three of the diastereomers were identified by ^1H NMR spectroscopy. However, the amount of the minor *exo* component would be very small and difficult to detect. As before the major *endo* adduct was completely separated from the others by chromatography. It was obtained as a white solid which was recrystallised from hexane-ethyl acetate, m.p. 97-98 °C. An X-ray crystal structure was obtained (Figure 1) and the relative configuration of this racemic form **196a** was determined. The bond lengths and angles are given in Tables 8 and 9, in the Experimental Section. Thus the major adduct had the structure **196a** expected for the addition to the less hindered face of the thioaldehyde in the conformation **194** (Scheme 87), *i.e.* the diene should approach the thial group from the face (see bold arrow in structure **194**) opposite to that of the adjacent methoxymethyl group.



194 **196a**

Scheme 87

Ghosez and Gouverneur explained their results with the nitroso dienophile in terms of the structure **178** having a *cisoid* nitrosocarbonyl group. Presumably, the



178

transoid CONO system, preferred on the grounds of dipole-dipole repulsion, would experience a severe steric interaction between the nitroso oxygen and the pyrrolidine ring. If this interpretation is correct then the COCHS system should certainly be *cisoid,* as shown in **194,** because the steric effect would be larger and the dipole-dipole repulsion less. Ghosez and Gouverneur's observed d.e. (>98 %) with cyclohexadiene was larger than ours. Their d.e. with cyclopentadiene (87%) was similar but their experiment had been carried out at low temperature (-20 °C).

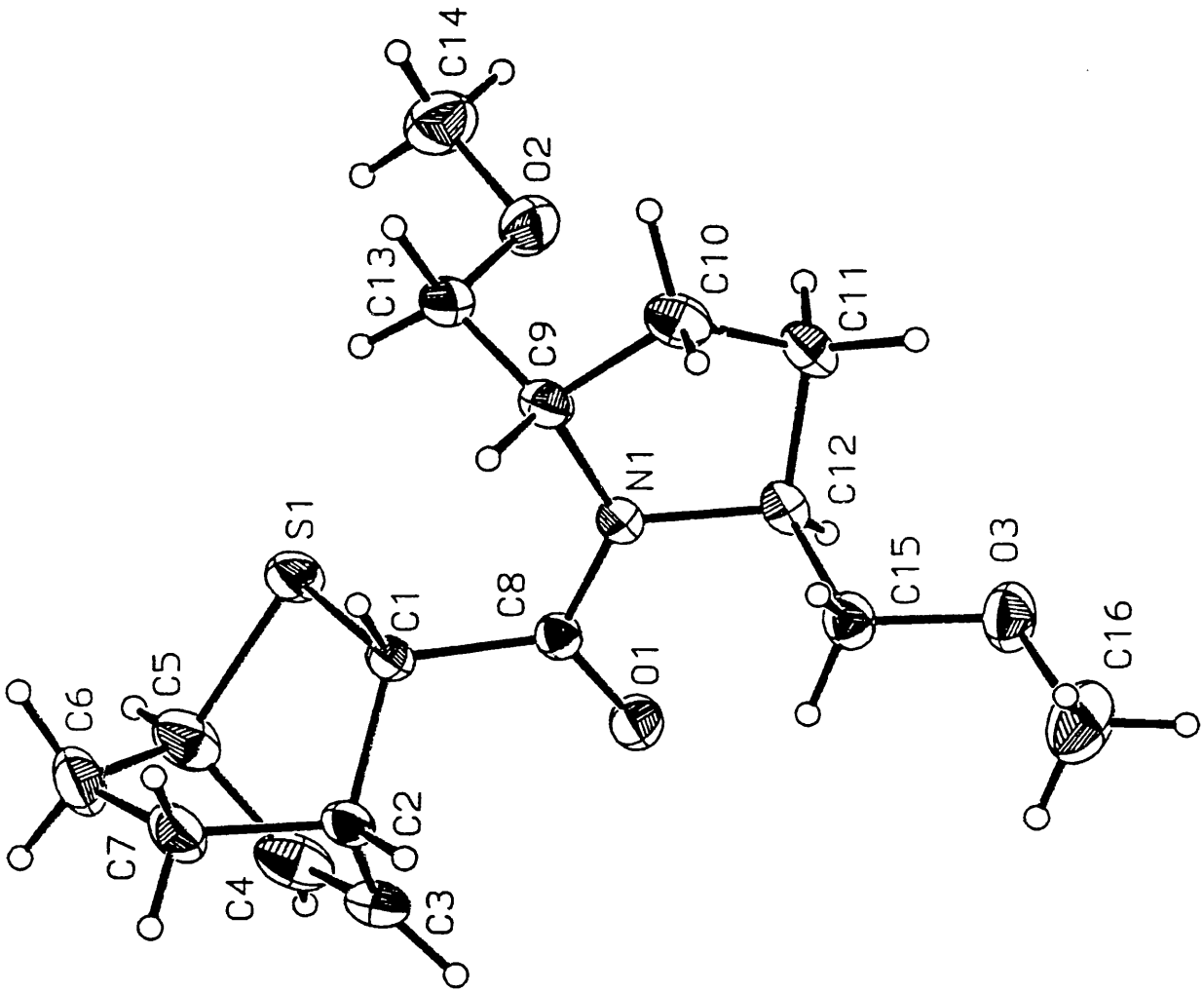


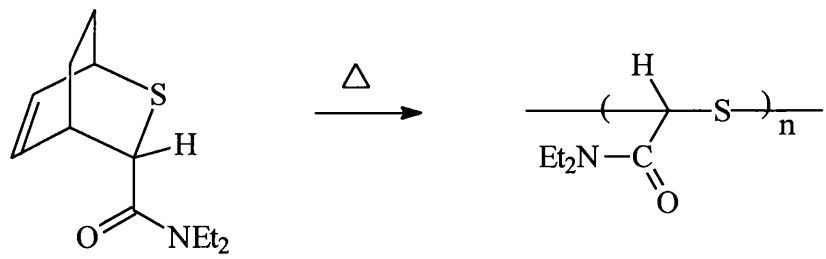
Figure 1. X-ray crystal structure of the major *endo* cyclohexadiene cycloadduct **196a**

4.4 Attempted cleavage of the amide auxiliary

To be of value in synthesis the chiral auxiliary, as well as inducing stereoselectivity, must be removable at the end of the process. It was hoped that the foregoing pyrrolidine adducts would be hydrolysable, thus giving the carboxylic acid.

4.4.1 Treatment with sodium hydroxide

Routes to hydrolysis were sought using the diethylamido cycloadduct as this was easily prepared and many attempts might be needed as amides are not readily hydrolysed. The first, obvious method was treatment with aqueous hydroxide. Thus the cyclohexadiene adduct **193** was stirred in sodium hydroxide for 2 days. As expected no change had occurred. Refluxing however, gave material which was thought to be a thioaldehyde polymer **197** (Scheme 88). Presumably the higher temperature had induced the retro Diels-Alder reaction.



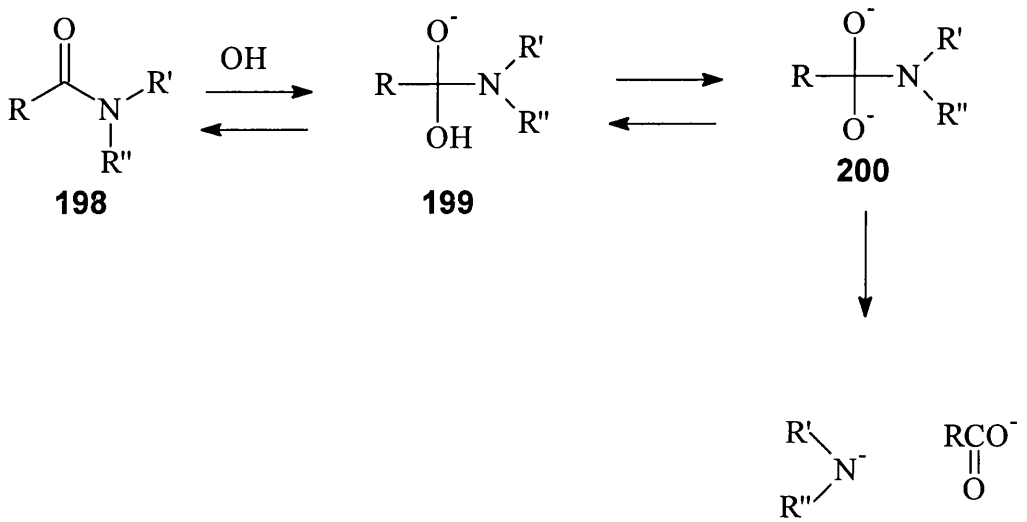
193 **197**

Scheme 88

4.4.2 Treatment with potassium *tert*-butoxide

A room temperature method employing potassium *tert*-butoxide was investigated [66]. The addition of a hydroxide ion to an amide of the general formula **198** should produce **199**. The thermodynamically preferred route for the breakdown of this however, involves loss of a hydroxide and leads back to the amide. Therefore, if

the hydroxylic proton could be removed by a second strong base, **200** should be generated. Cleavage with loss of amide anion would generate the thermodynamically more stable carboxylate directly (Scheme 89). In general, with potassium *tert*-butoxide this amide cleavage can be accomplished at room temperature. The reactions were carried out using ~6 equivalents of potassium *tert*-butoxide and 2 equivalents of water in ether. The reaction of the water with the potassium *tert*-butoxide generates finely divided, essentially anhydrous, potassium hydroxide and *tert*-butyl alcohol. The strongly nucleophilic and poorly solvated hydroxide should add to the amide. Conversion to the dianion, which should then cleave easily, could then be accomplished by the excess of potassium *tert*-butoxide.

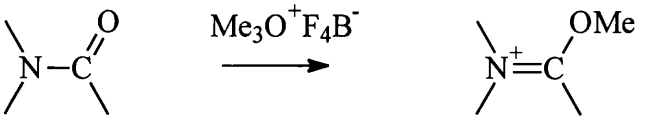


Scheme 89

This procedure with the cyclopentadiene diethylamido cycloadduct **192** led to a brown oil which did not resemble the carboxylic acid. The amine portion, diethylamine, is volatile and would not have been detected.

Another hydrolysis method using trimethyloxonium tetrafluoroborate was attempted. It was hoped that the amide group would be methylated, on oxygen, rather

than the sulfur. Hydrolysis of the resulting imino ether **201** should occur under mild conditions (Scheme 90). Again however, another unidentified brown oil was obtained.



201

Scheme 90

Although the amide auxiliary has not been successfully cleaved it should be possible and other methods could still be attempted, including treatment with aqueous sodium periodate [67] although this might attack S to form S^{+}-O^{-}. Enzymic hydrolysis is also possible, especially because of the structural resemblance of the pyrrolidine amide and a proline peptide.

4.5 Conclusions

In conclusion, *trans*-2,5-bis(methoxymethyl)pyrrolidine has been shown to be reasonably successful as a thioaldehyde auxiliary, particularly in inducing high diastereoselectivity (*endo* d.e. = 91%) when the thioaldehyde is trapped with cyclopentadiene. Trapping with cyclohexadiene was less successful, giving reasonable diastereoselectivity for the *endo* isomers (d.e. = 75%). The major adducts however, were easily separated from other diastereomers thus providing a single diastereomer.

Although the racemic auxiliary had been used, optically active products could be obtained by resolving the auxiliary at an earlier stage in the synthesis.

With the successful X-ray structure analysis of the cyclohexadiene adduct, a route has been established to a particular cycloadduct configuration. Providing the auxiliary can be removed, functionalisation of the α substituent can provide a useful route to other chiral products.

CHAPTER FIVE

Experimental Section

General methods

^{1}H NMR spectra were obtained at 90 MHz with a Perkin-Elmer R-32 spectrometer and at 200 MHz with a Bruker WP200 SY spectrometer. Generally, deuteriochloroform was used as solvent with tetramethylsilane as an internal standard. ^{13}C NMR spectra were obtained at 50.3 MHz with a Bruker WP200 SY spectrometer. All proton chemical shifts are quoted to the nearest 0.01 ppm. Carbon chemical shifts are quoted to the nearest 0.1 ppm.

Mass spectra were obtained by EI at 70 eV with an AEI MS9 instrument. IR spectra were recorded on either a Perkin-Elmer 580 or 257 spectrometer. M.p.s were determined on a Kofler, hot-stage microscope.

Analytical TLC was carried out on precoated Merck Kieselgel GF_{254} plates of thickness 0.25 mm. Spots were viewed under an ultra-violet lamp and developed by iodine vapour. Column chromatography employed TLC grade silica with reduced pressure to assist flow.

Solutions in organic solvents were dried over $MgSO_4$ and organic solvents were generally evaporated on a Buchi Rotavapor with slight heating.

5.1 Preparation and reactions of *N*-phthaloyl sulfenamides

5.1.1 Attempted preparation of *N*-phthaloyl sulfenamides under radical conditions

The initial method used to prepare the ester *N*-phthaloyl sulfenamides was that previously used by Lochead [24] and originally devised by Buchel and Conte [44] for the

preparation of the benzyl derivative. The method involves the reaction of *N*-bromophthalimide with the appropriate disulfide under radical conditions.

Preparation of *N*-bromophthalimide 105

N-Bromophthalimide **105** was prepared according to the method of Bredt and Hof [45]. Phthalimide (5 g, 34 mmol) was dissolved in aqueous sodium hydroxide solution (1.6 g in 65 ml water, 40 mmol) and cooled to 0 °C. This solution was then added to a cooled (0 °C) solution of bromine (5.44 g, 34 mmol) in water (25 ml). Immediately a white precipitate formed which was filtered off. Recrystallisation from ethanol gives white crystals of N-*bromophthalimide* **105**, m.p. 190-200 °C (lit.[45] 180 °C) (2.48 g, 32.3%).

Preparation of the disulfides 104a-c

Ethyl 2-mercaptoacetate **37** (6.0 g, 50 mmol) in ethanol (100 ml) was added slowly with stirring at room temperature to iodine (6.35 g, 25 mmol) in aqueous potassium iodide (100 ml). Oxidation was complete when the potassium iodide solution became colourless. Dichloromethane (160 ml) was added and the mixture was washed with aqueous sodium sulfite to remove any excess of iodine, then with water and then dried and evaporated to give the disulfide **104a** as a clear oil in quantitative yield.

δ_H(200 MHz; $CDCl_3$) 1.30 (t, J=7.1Hz, OCH_2*Me*), 3.59 (s, SCH_2) and 4.22 (q, J=7.1Hz, O*C*H_2Me).

Dibenzyl disulfide **104c** was obtained in the same way from benzyl mercaptan **107** (6.2 g, 50 mmol). In this case the oxidation step gave a precipitate in the solution. *Dibenzyl disulfide* **104c** was obtained as white crystals by recrystallisation of the white solid from hexane, m.p. 69-72 °C.

δ_H (200 MHz; $CDCl_3$) 3.54 (s, SCH_2) and 7.16-7.32 (m, ArH).

Radical reaction of *N*-bromophthalimide 105 and the disulfide 104

An attempt was made to prepare ethyl phthalimidosulfanylacetate **45** based on the method previously used by Lochead. The ethyl ester disulfide **104a** (2.1g, 8.85 mmol) was added slowly to a refluxing solution of *N*-bromophthalimide **105** (2g, 8.85 mmol) in benzene (20 ml) containing a catalytic amount of dibenzoyl peroxide as a radical initiator. An orange colour was observed soon after addition, indicating the formation of bromine. The mixture was refluxed for a further hour after which time some solid was present. Addition of hexane to the cooled mixture led to the precipitation of more solid. Filtration gave a yellow solid which was recrystallised from ethanol to give white, needle-like crystals (0.71 g), m.p. 238 °C. This melting point corresponds to that of phthalimide.

The reaction mixture formed bromine in the absence of dibenzoyl peroxide as it did at room temperature, but phthalimide was always produced. The reaction was carried out many times but only a tiny amount of the *N*-phthaloyl sulfenamide **45** was formed.

The above reaction was also carried out with the methyl ester disulfide **104b** and also benzyl disulfide **104c**. Again the reactions were not very successful, with the benzyl derivative giving the best yield.

5.1.2 Preparation of *N*-phthaloyl sulfenamides via the sulfenyl chlorides

The *N*-phthaloyl sulfenamides were successfully prepared based on a method by Woulfe and Miller [46].

Ethyl phthalimidosulfanylacetate 45

A mixture of ethyl 2-mercaptoacetate **37** (12.02 g, 100 mmol) and pyridine (7.91 g, 100 mmol) in carbon tetrachloride (10 ml) was added slowly with stirring to sulfuryl chloride (13.5 g, 100 mmol) in carbon tetrachloride at -10 °C. A yellow colour indicating the formation of the sulfenyl chloride **106a** quickly developed as the

addition continued. Sulfur dioxide was liberated and a precipitate of pyridine hydrochloride formed. The solution was stirred for a further 10 min. The yellow solution was then decanted, diluted with dichloromethane (200 ml) and cooled to -10 °C. Potassium phthalimide **108** (20 g, 108 mmol) was added with vigorous stirring. The yellow colour quickly began to fade and had disappeared completely after *ca.* 5 min.

Any unreacted potassium phthalimide and potassium chloride were then filtered off and the filtrate evaporated to low volume. The phthaloyl sulfenamide was then obtained by the addition of light petroleum (b.p. 40-60 °C) . The white, fluffy solid precipitate was filtered off and washed with more light petroleum to give *ethyl phthalimidosulfanylacetate* **45** (17.9 g, 67.5%), m.p. 76-82 °C (lit.[24] 76-82 °C) which required no further purification.

ν_{max} (KBr)/cm^{-1} 1715, 1740 and 1785 (weak);

δ_H (200 MHz; $CDCl_3$) 1.20 (t, J=7.1 Hz $OCH_2\mathit{CH_3}$), 3.52 (s, SCH_2), 4.14 (q, J=7.1Hz $O\mathit{CH_2}CH_3$), 7.78-7.84 (m, ArH) and 7.90-7.97 (m, ArH);

m/z 265 (M^+).

The *N*-phthaloyl sulfenamide **45** was also prepared starting from the disulfide. Thus the sulfenyl chloride **106a** was prepared by the addition of disulfide **104a** (1 g, 4.2 mmol) in carbon tetrachloride (1 ml) to sulfuryl chloride (0.57 g, 4.2 mmol) in carbon tetrachloride (4 ml) with stirring at room temperature. A yellow colour slowly began to form. After 20 min the solution was diluted with dichloromethane followed by the addition of potassium phthalimide **108**. Work-up as before gave *ethyl phthalimidosulfanylacetate* **45** (0.70 g, 32%).

Methyl phthalimidosulfanylacetate 38

Prepared as above from the disulfide **104b** (2 g, 9.5 mmol) to give *methyl phthalimidosulfanylacetate* **38** as a white solid (0.49 g, 21 %), m.p. 125 °C (lit.[24] 125-130 °C).

ν_{max} (KBr)/ cm^{-1} 1715, 1740 and 1785 (weak);

δ_H (90 MHz; $CDCl_3$) 3.54 (s, SCH_2), 3.73 (s, OMe) and 7.72-8.03 (m, ArH);

m/z 251 (M^+).

N-Phthaloylphenylmethanesulfenamide 103

The *N*-phthaloyl sulfenamide was prepared from both the thiol and the disulfide. Thus, benzyl mercaptan **107** (6.2 g, 50 mmol) was treated as before with the sulfuryl chloride to form the sulfenyl chloride **106c**. However, a pink colour developed after addition of the potassium phthalimide **108** and a poor yield of N-*phthaloylphenylmethanesulfenamide* **103** was obtained (1.41 g, 10.5%) m.p. 160 °C (lit.[44] 167-168).

δ_H (200 MHz, $CDCl_3$) 4.12 (s, SCH_2), 7.20-7.30 (m, ArH_6) and 7.72-7.95 (m, ArH_4);

m\z 269 (M+).

The *N*-phthaloyl sulfenamide **103** was prepared more successfully from the disulfide. Thus dibenzyl disulfide **104c** (1.8 g, 7.3 mmol) gave a reasonable yield of N-*phthaloylphenylmethanesulfenamide* **103** (4.0 g).

5.1.3 Attempted preparation of ethyl phthalimidosulfanylacetate 45 via ethyl trimethylsilylacetate 112.

An attempt was made to prepare the phthaloyl sulfenamide **45** by fluoride induced reaction of ethyl trimethylsilylacetate (ETSA) and phthalimidosulfenyl chloride **109**.

ETSA was prepared following an organic synthesis procedure [47]. Thus zinc (19.5 g, 0.3 mol washed with acid followed by acetone and dried) and copper (1) chloride (2.98 g, 30 mmol) in ether (30 ml) and benzene (100 ml) were refluxed for 30 min. The heating was then removed and chlorotrimethylsilane (21.8 g, 0.2 mol) and ethyl bromoacetate (36.8 g, 0.22 mol) in ether (18 ml) and benzene (70 ml) were added dropwise at a rate sufficient to maintain a gentle reflux for a further hour. After

cooling hydrochloric acid (60 ml, 5M) was added slowly with stirring. The liquid, mainly organic layer was washed twice with sodium bicarbonate, water and then dried and evaporated to give *ethyl trimethylsilylacetate* **112** as a clear oil (8.4 g, 26.3%). Further product was obtained by extracting the remaining aqueous portion with ether to give a yellow liquid (2.11 g).

δ_H (90 MHz; $CDCl_3$) 0.00 (s, $SiMe_3$), 1.15 (t, J=7.1Hz, OCH_2Me), 1.82 (s, $SiCH_2$) and 3.95 (q, OCH_2Me).

The phthalimidosulfenyl chloride **109** was prepared by chlorination of N,N'-dithiobisphthalimide **114** and will be described in the following section.

Phthalimidosulfenyl chloride **109** (0.5 g, 2.34 mmol) was dissolved in THF containing caesium fluoride (0.37 g, 2.44 mmol). ETSA **112** (0.35 g, 2.18 mmol) was added and the mixture stirred at room temperature. After an hour more solid was present in the mixture and was identified as phthalimide.

A mixture of phthalimidosulfenyl chloride **109** (0.5 g, 2.34 mmol) and ETSA **112** (0.37 g, 2.34 mmol) in THF (2 ml) was then added to tetrabutylammonium fluoride (2.3 ml, 1M sol in THF, 2.34 mmol) with stirring at room temperature. Immediately upon addition a red colour developed and the mixture was evaporated to give a red oil which solidified. The residue was dissolved in dichloromethane then washed with hydrochloric acid. Addition of hexane gave a precipitate m.p. 240 °C. and was found to be phthalimide.

5.1.4 Preparation of *N*-phthaloyl β-oxo sulfenamides.

The phenyl and methyl *N*-phthaloyl sulfenamides were prepared following the method of Capozzi *et al.* [43], whereby phthalimidosulfenyl chloride was treated with an enolizable ketone.

Phthalimidosulfenyl chloride 109 [48,49]

Sulfur monochloride (12.29 g, 91.0 mmol) was added to a cooled mixture of recrystallised phthalimide (26.8 g, 0.18 mol) and triethylamine (18.34 g, 0.18 mol) in

THF (180 ml) with stirring. After 45 min water (500 ml) was added to the brownish mixture and the solids were filtered off and dried to give a white solid (35.65 g). This crude product was recrystallised from chloroform-methanol (300 ml:150 ml) to give the white crystalline N,N'-*dithiobisphthalimide* **114** (24.02 g, 74%) m.p. 228 °C (lit.[49] 225 °C).

Chlorine gas was passed into a mixture of the disulfide **114** (58 g, 0.16 mol) in chloroform (600 ml) with stirring at -10 °C for 1.25 h until the mixture was saturated. The mixture was then refluxed briefly for 5 min and the disulfide all dissolved. After allowing to cool any precipitated solid was filtered off and the filtrate evaporated to give the *phthalimidosulfenyl chloride* **109** as a yellow solid (33.5 g, 48%) m.p. 115-117 °C. (lit.[48] 115-117 °C).

δ_H (90 MHz, $CDCl_3$) 7.82-8.10 (m, ArH).

Phthalimidosulfenyl chloride could also be prepared by treatment of the disulfide **114** with sulfuryl chloride. Thus sulfuryl chloride (3.78 g, 28 mmol) was added to a refluxing mixture of the disulfide (5 g, 14 mmol) in chloroform (20 ml). Slowly a yellow colour developed. After refluxing for 4 h any remaining solid was filtered off after allowing to cool. The filtrate was evaporated to give the sulfenyl chloride **109** as a yellow solid (2.7 g, 45%).

This reaction was also found to occur more rapidly with the addition of a catalytic amount of pyridine or triethylamine.

_N_-phthaloylbenzoylmethanesulfenamide 100 [43]

Phthalimidosulfenyl chloride **109** (1.3 g, 6.0 mmol) was added to acetophenone (30 ml) while cooling to *ca.* 0 °C (cooling to much causes acetophenone to solidify). The mixture was stirred for 15 min after which time the yellow colour of the sulfenyl chloride had gone. Addition of light petroleum gave a white precipitate which was filtered off. The solid was washed with more light petroleum to remove

last traces of acetophenone to give N-*phthaloylbenzoylmethanesulfenamide* **100** (91.3 g, 76%), m.p. 143-145 °C (lit.[43] 143-145 °C).

δ_H (200 MHz; $CDCl_3$) 4.27 (s, SCH_2), 7.41-7.62 (m, ArH) and 7.76-7.93(m, ArH).

N-Phthaloylacetylmethanesulfenamide 115 [43]

Phthalimidosulfenyl chloride **109** (1.3 g, 6 mmol) was added to acetone (30 ml) at 0 °C. The yellow colour quickly disappeared. After stirring for 15 min addition of light petroleum gave a white precipitate which was filtered off and dried to give N-*phthaloylacetylmethanesulfenamide* **115** (0.57 g, 43%) m.p. 149-150 °C (lit.[43] 149-150 °C).

δ_H (200 MHz; $CDCl_3$) 2.47 (s, Me), 3.57 (s, SCH_2) and 7.76-7.97 (m, ArH);

m\z 235 (M^+).

5.1.5 Treatment of ethyl phthalimidosulfanylacetate 45 with various bases in the presence of 2,3-dimethyl-1,3-butadiene.

Ethyl 3,6-dihydro-4,5-dimethyl-2H-thiin-2-carboxylate 33 and the corresponding acid - treatment with triethylamine

Triethylamine (0.10 g, 1 mmol) in dichloromethane (1 ml) was added slowly to ethyl phthalimidosulfanylacetate **45** (265 mg, 1 mmol) and dimethylbutadiene (0.10 g, 1.2 mmol) in dichloromethane (10 ml) with stirring at room temperature. Phthalimide began to precipitate out after 10 min and was filtered off after 30 min. The filtrate was washed with sodium hydroxide (1M), hydrochloric acid (1M) and water, then dried and evaporated to give a yellow oil (0.17 g).

This crude mixture was almost entirely the thioaldehyde cycloadduct **33** but contained traces of the dithioester cycloadduct **98** and the disulfide **104a** which were identified by TLC. Chromatography (hexane-ethyl acetate, 4:1) of the oil gave pure *ethyl* 3,6-*dihydro*-4,5-*dimethyl*-2H-*thiin*-2-*carboxylate* **33** as an almost colourless oil.

δ_H (200 MHz; $CDCl_3$) 1.28 (t, *J*=7.1Hz, OCH_2Me), 1.71 (brs, 4-and 5- Me), 2.46 (m, 3-H_2), 3.09 (m, 6-H_2), 3.62 (t, *J*=6.5Hz, 2-H) and 4.19 (q, *J*=7.1Hz, OCH_2Me);

δ_C (50.3 MHz; $CDCl_3$) 13.9 (OCH_2Me), 19.8 and 19.1 (2×Me), 30.3 (C-3), 34.0 (C-6), 40.8 (C-2), 60.9 (OCH_2Me), 125.4 and 122.8 (C-4 and C-5) and 171.4 (C=O).

The ester **33** (0.39 g) in ethanol (1 ml) was added to sodium hydroxide (4 ml, 1M) and the mixture was stirred overnight at room temperature. After evaporation to low volume, addition of hydrochloric acid (1M) yielded a white precipitate. After filtration the precipitate was washed with small amount of ethanol to give the carboxylic acid (0.19 g) which was then recrystallised from light petroleum m.p. 97-98 ° C (lit.[23] 97-98 °C).

δ_H (90 MHz; $CDCl_3$) 1.72 (brs, 4- and 5- Me), 2.49 (m, 3-H_2), 3.09 (m, 6-H_2), 3.62 (t, *J*=6Hz, 2-H) and 8.35 (brs, OH);

m/z 172 (M^+).

Ethyl 2-(ethoxycarbonylmethylsulfanyl)-4,5-dimethyl-3,6-dihydro-2H-thiine-2-carboxylate 98 and the corresponding acid - treatment with DMAP

DMAP (0.12 g, 1 mmol) in dichloromethane (2 ml) was added to ethyl phthalimidosulfanylacetate **45** (265 mg, 1 mmol) and dimethylbutadiene (0.10 g, 1.2 mmol) in dichloromethane (10 ml) with stirring at room temperature. The mixture turned yellow as the base was added . A red colour formed after addition of the base and a precipitate appeared after *ca.* 30 s. The colour then began to fade leaving an almost colourless solution. Work-up as for the ester **33** gave a yellow oil (0.11 g). This crude product consisted almost entirely of the dithioester cycloadduct **98** and was contaminated only by a very small amount of the thioaldehyde cycloadduct **33** and just a trace of the disulfide **104a**.

Ethyl 2-(ethoxycarbonylmethylsulfanyl)-4,5-dimethyl-3,6-dihydro-2H-thiine-2-carboxylate **98** (85 mg, 54%) was obtained as an almost colourless oil by chromatography (hexane-ethyl acetate, 4:1).

Found : M^+, 318.0957. $C_{14}H_{22}O_4S_2$ requires *M*, 318.0954;

ν_{max} (liq. film)/ cm^{-1} 1730 and 1734;

δ_H(200 MHz; $CDCl_3$) 1.27 and 1.30 (2×t, *J*=7.1Hz, 2×OCH_2*Me*), 1.70 and 1.73 (2× brs, 2×Me), 2.47 and 2.89 (ABq, J_{AB}=18.1Hz, 3-H_2), 2.79 and 3.39 (ABq, J_{AB}=17Hz, 6-H_2), 3.53 and 3.59 (ABq, J_{AB}=15.9Hz, SCH_2) and 4.16 and 4.22 (2×t, *J*=7.1Hz, 2×O*CH*$_2$Me);

δ_C (50.3 MHz; $CDCl_3$) 14.0 and 14.2 (2×OCH_2*Me*), 19.2 and 20.1 (2×Me), 30.4 (C-3), 33.8 (C-6), 40.3 (SCH_2), 58.1 (C-2), 61.4 and 62.2 (2×O*CH*$_2$Me), 122.2 and 124.3 (C-4 and C-5) and 169.8 and 179.0 (C=O).

Hydrolysis of the dithioester cycloadduct **98** as described previously for **33** gave the dicarboxylic acid as a white solid m.p. 172-174 ° C.

δ_H (200 MHz, $(CD_3)_2CO$) 1.70-1.71 (brs, 2×Me), 2.43 and 2.84 (br ABq, J_{AB}=18Hz, 3-H_2), 2.89 and 3.41 (br ABq, J_{AB}=17Hz, 6-H_2), 3.59 and 3.63 (ABq, J_{AB}=15.7Hz, SCH_2), 10.06 (br s, OH);

m/z 172 (M^+- SCH_2CO_2H).

Treatment with triethylamine and 10% DMAP

Ethyl phthalimidosulfanylacetate **45** was treated as before with triethylamine (0.10 g, 1 mmol), and DMAP (0.12 g, 0.1 mmol). The mixture turned yellow as the base was added, more quickly than with DMAP alone and had darkened to reddish/orange after the final addition of base. Phthalimide began to precipitate out after *ca.* 5 min. After 30 min mixture was worked up as before to give the crude product as an orange oil (0.12 g). The major component of the mixture was the dithioester cycloadduct **98** which comprised of 86% of the mixture according to the ^{1}H NMR spectrum. The thioaldehyde cycloadduct **33** was present as 14% along with a small amount of the disulfide **104a**. Only a trace of polymeric material was detected.

Treatment with triethylamine and 10% pyridine

Ethyl phthalimidosulfanylacetate **45** was treated as before with triethylamine (0.10 g, 1 mmol) and pyridine (8.0 mg, 0.1 mmol) . A yellow colour developed as

base was added which darkened as addition continued. Work-up gave an orange oil (0.12 g). This crude mixture consisted of the thioaldehyde cycloadduct **33** as the major product at 84% along with only a small amount of the dithioester cycloadduct **98**, 3%. However, more of the disulfide **104a** was formed than previously at 13%.

Treatment with triethylamine and 50% pyridine

Ethyl phthalimidosulfanylacetate **45** was treated as before with triethylamine (0.10 g, 1 mmol) and pyridine (0.04 g, 0.5 mmol). Again a yellow colour developed which darkened to orange as addition continued. The precipitate formed quickly after the final addition of base and work-up gave an orange oil (0.10 g). This contained almost equal amounts of the thioaldehyde cycloadduct **33** and the disulfide **104a**, 52% and 37% respectively. The dithioester cycloadduct **98** was also present in greater amount than before, 11% and a small amount of polymeric material was also detected.

Treatment with pyridine

Ethyl phthalimidosulfanylacetate **45** was treated as before with pyridine (0.16 g, 2 mmol). No colour developed as base was added but a yellow colour developed after a few days. A precipitate formed after 4 days. The mixture was worked up after a week to give an orange oil (0.13 g) which consisted of almost equal amounts of all three components - the thioaldehyde cycloadduct **33**, 29%, the dithioester cycloadduct **98**, 40% and the disulfide **104a,** 31%.

5.1.6 Treatment of ethyl phthalimidosulfanylacetate 45 with various bases in the presence of cyclopentadiene

Ethyl *exo* and *endo*-2-thiabicyclo[2.2.1]hept-5-ene-3-carboxylate 47 - treatment with triethylamine

Triethylamine (0.41 g, 4 mmol) was added slowly to ethyl phthalimidosulfanylacetate **45** (1.0 g, 3,78 mmol) and cyclopentadiene (0.5 g, 7.56

mmol) in benzene (25 ml). The mixture remained colourless and phthalimide had precipitated out after stirring for 1 h at room temperature. The precipitate was filtered off and the filtrate washed with sodium hydroxide (1M), hydrochloric acid (1M) and water, then dried and evaporated to leave a clear oil (0.61 g). This crude product contained the thioaldehyde cycloadducts **47** as a mixture of isomers contaminated by only a trace of the dithioester cycloadducts **116**, as observed by TLC. The isomers *endo* : *exo* = 7:3 were separated by chromatography (hexane-ethyl acetate, 4:1) to give colourless oils.

Ethyl 3-endo-2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-*carboxylate* **47a** (0.38g, 55%)
δ_H (200 MHz; $CDCl_3$) 1.25 (t, *J*=7.1Hz, OCH_2Me), 1.59-1.68 (m, 7-H_2), 3.75 (m, 4-H), 4.08 (m, 1-H), 4.14 (q, *J*=7.1Hz, OCH_2Me), 4.42 (d, *J*=3.9Hz, 3-H), 5.88 (dd, *J*=3 and 5.4Hz, 5-H) and 6.43 (dd, *J*=2.9 and 5.4Hz, 6-H).

Ethyl 3-exo-2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-*carboxylate* **47b** (0.16g, 23%)
δ_H (200 MHz; $CDCl_3$) 1.28 (t, *J*=7.2Hz, OCH_2Me), 1.68 (d, *J*=9.9, 7-H), 1.90 (d, *J*=9.5Hz, 7-H), 3.29 (s, 3-H), 3.53 (brs, 4-H), 4.1 (brs, 1-H), 4.22 (q, *J*=7.2Hz, OCH_2Me), 5.95 (dd, *J*=3.2 and 5.4Hz, 5-H) and 6.38 (dd, *J*=2.79 and 5.4Hz, 6-H).

Ethyl 3-*endo* and 3-*exo*-(ethoxycarbonylmethylsulfanyl)-2-thiabicyclo[2.2.1]hept-5-ene-3-carboxylate 116 and the corresponding acids - treatment with DMAP

DMAP (0.46 g, 3.78 mmol) in benzene was added to ethyl phthalimidosulfanylacetate **45** (1.0 g, 3.77 mmol) in benzene (25 ml) containing cyclopentadiene (500 mg, 7.58 mmol) with stirring at room temperature. The mixture turned yellow and a precipitate soon began to form. Work-up as before for **47** yielded a yellow oil (0.58 g) containing 73% of the dithioester cycloadducts **116** and 27% of the thioaldehyde cycloadducts **47**. The cycloadducts were separated by chromatography although the *endo* and *exo* isomers of the dithioester cycloadducts could not be obtained separately and were analysed as a mixture. *Ethyl* 3-endo *and* 3-

exo-*(ethoxycarbonylmethylsulfanyl)*-2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-*carboxylate* **116**, *endo* : *exo* = 1.0:0.9 were isolated as an almost colourless oil (61%).

Found M^+, 302.0636. $C_{13}H_{18}O_4S_2$ requires *M*, 302.0647;

ν_{max} (liq. film)/ cm^{-1} 1732.

Endo adduct (*endo*-3-CO_2Et)

δ_H (200 MHz; $CDCl_3$) 1.28 or 1.29 (t, *J*=7.1Hz, Me), 1.30 or 1.33 (t, *J*=7.2Hz, Me), 1.75 (br d, *J*=9.8Hz, 7-H), 1.95 (dt, *J*=9.8, 2.2Hz, 7-H), 3.59 and 3.60 (ABq, J_{AB}=15Hz, SCH_2), 3.68 (m, 1- or 4-H), 4.08 (m, 4- or 1-H), 4.09-4.33 (m, OCH_2), 5.96 (dd, *J*=5.4 and 3.1Hz, 5- or 6-H) and 6.56 (dd, 5.4 and 2.8Hz, 6- or 5-H).

Exo adduct (*exo*-3-CO_2Et)

δ_H (200 MHz; $CDCl_3$) 1.28 or 1.29 (t, *J*=7.1Hz, *Me),* 1.30 or 1.33 (t, *J*=7.2Hz, Me), 1.87 (dt, *J*=9.6 and 2.3Hz, 7-H), 2.36 (br d, *J*=9.6Hz, 7-H), 3.39 and 3.42 (ABq, J_{AB}=15.3Hz, SCH_2), 3.90 (m, 1- or 4-H), 4.09-4.33 (m, OCH_2 and 4- or 1-H), 6.17 (dd, *J*=5.4, 3.3Hz, 5- or 6-H) and 6.42 (dd, *J*=5.4, 2.9Hz, 6- or 5-H).

The ^{13}C NMR spectrum was analysed as a mixture of isomers.

δ_C (50.3 MHz; $CDCl_3$) 14.0 and 14.1 (4×OCH_2*Me*), 35.3 and 35.3 (2×C-7), 50.0 and 52.2 (SCH_2), 51.8 and 53.3, 53.4 and 54.0 (C-4 and C-1), 61.5, 62.0 and 62.4 (4× O*C*H_2Me), 69.8 and 71.1 (C-3), 132.5 and 132.9 (C-5), 137.1 and 141.0 (C-6) and 169.4, 169.5, 169.9 and 171.0 (C=O).

The esters **116** were converted to the acids as before by treatment with ethanolic sodium hydroxide, to give a white solid *endo* : *exo* = 3:1, m.p. 136-139 °C. Found: M^+, 246.0038. $C_9H_{10}O_4S_2$ requires *M*, 246.0020.

Endo adduct

δ_H (200 MHz; $CDCl_3$) 1.81 (dt, *J*=9.5, 2.25Hz, 7-H), 2.32 (d, *J*=9.52Hz, 7-H), 3.55 and 3.74 (ABq, J_{AB}=15.4Hz, SCH_2), 3.69 (brs, 4-H), 4.12 (brs, 1-H), 5.97 (dd, *J*=5.34, 3.2Hz, 5-H) and 6.6 (dd, *J*=5.4, 2.7Hz, 6-H).

Exo adduct

δ_H (200 MHz; $CDCl_3$) 1.73 (d, *J*=9.7Hz, 7-H), 1.91 (dt, J=9.7, 2.2Hz, 7-H), 3.39 and 3.52 (ABq, J_{AB}=15.2Hz, SCH_2), 3.87 (brs, 4-H), 4.24 (brs, 1-H), 6.22 (dd, *J*=5.9, 3.2Hz, 5-H) and 6.38 (dd, *J*=5.36, 2.8Hz, 6-H).

Treatment with triethylamine and 10% DMAP

Ethyl phthalimidosulfanylacetate **45** was treated as before with triethylamine (0.41 g, 4 mmol) and DMAP (0.05 g, 0.4 mmol) dissolved in a little benzene. The mixture slowly turned yellow and precipitate began to form. Work-up as before after 1 h gave a yellow oil (0.53 g) which contained both types of cycloadducts. The thioaldehyde cycloadducts **47** were the major products at 68% and the dithioester adducts **116** at 32%.

Treatment with pyridine

Ethyl phthalimidosulfanylacetate **45** was treated as before with pyridine (0.59 g, 7.56 mmol). No immediate reaction occurred and work-up after 10 days gave an orange oil (0.22 g) which contained cyclopentadiene dimer as the major product. Small amounts of both types of adducts were also detected by TLC.

5.1.7 Retro Diels-Alder reaction of the dithioester cyclopentadiene cycloadducts 116 and trapping of the intermediate dithioester 99 with dimethylbutadiene

The cyclopentadiene dithioester cycloadducts **116** (0.15 g, 0.5 mmol) were refluxed in toluene (5 ml) containing dimethylbutadiene (0.08 g, 1 mmol). A pale pink

colour was soon observed which passed quickly. Refluxing was continued for 4 h and evaporation of the solvent gave the dimethylbutadiene adduct **98** in quantitative yield with no trace of the cyclopentadiene dimer.

5.1.8 Treatment of ethyl phthalimidosulfanylacetate with various bases in the presence of cyclohexadiene.

Ethyl 3-*endo* and 3-*exo*-2-thiabicyclo[2.2.2]oct-5-ene-3-carboxylate 34 - treatment with triethylamine

Triethylamine (0.10 g, 1 mmol) was added to ethyl phthalimidosulfanylacetate **45** (265 mg, 1 mmol) in dichloromethane (10 ml) containing cyclohexadiene (96 mg, 1.2 mmol). The solution slowly began to turn yellow and TLC after 5 min showed a cycloadduct beginning to form. The mixture had darkened after leaving overnight but no precipitate had formed. The mixture was then washed with sodium hydroxide (1M), hydrochloric acid (1M) and water then dried and evaporated to give a dark oil (0.13 g). The ^{1}H NMR spectrum showed the oil to consist of a mixture of the thioaldehyde cycloadducts **34** with *endo* : *exo* = 6:1 along with a very small amount of the disulfide **104a**. Chromatography (hexane-ethyl acetate, 4:1) gave the adducts as almost colourless oils.

Ethyl 3-endo-2-*thiabicyclo*[2.2.2]*oct*-5-*ene*-3-*carboxylate* **34a** (0.1 g, 51%)

δ_H (200 MHz; $CDCl_3$) 1.24 (t, *J*=7.1Hz, OCH_2*Me*), 1.45-1.76 and 2.02-2.10 (2×m, CH_2CH_2), 3.36 (m, CH), 3.49 (m, CH), 4.01 (d, *J*=2.89Hz, 3-H), 4.13 (q, *J*=7.1Hz with fine splitting, O*CH*$_2$Me), 6.23 (t, *J*=7.5Hz, 5-H) and 6.63 (t, J=7.5Hz, 6-H).

Ethyl 3-*endo* and 3-*exo*-(ethoxycarbonylmethylsulfanyl)-2-thiabicyclo[2.2.2]oct-5-ene-3-carboxylate 121 and the corresponding acids - treatment with DMAP

The above reaction was repeated and ethyl phthalimidosulfanylacetate **45** was treated with DMAP (0.46 g, 3.77 mmol). The reaction mixture darkened immediately as base was added and a precipitate formed quickly. During work-up much coloured

material was extracted into the aqueous layer to leave an orange oil (0.27 g) containing the dithioester cycloadducts **121** as the major product. Chromatography (hexane-ethyl acetate, 4:1) gave *ethyl* 3-endo *and* 3-exo-*(ethoxycarbonylmethylsulfanyl)-2-thiabicyclo*[2.2.2]*oct-5-ene-3-carboxylate* **121** as a clear oil which consisted of a mixture of isomers with *endo:exo* = 9:4. The isomers could not be separated and were analysed as a mixture. The ^{1}H NMR spectrum showed many overlapping multiplets, including those, near δ 1.30 and 4.20, expected for the ethoxy groups. The *endo* and *exo* isomers could be easily distinguished however, in the ^{13}C NMR spectrum due to the different intensities of each isomer.

Found : M^{+}, 316.0781. $C_{14}H_{20}O_4S_2$ requires *M*, 316.0803

δ_H (200 MHz; $CDCl_3$) 3.41 (s, SCH_2, *endo*), 6.31 (t, *J*=7.2Hz, 5- or 6-H *endo*), 6.36 (t, *J*=7.1, 5- or 6-H, *exo*), 6.50 (t, *J*=7.1Hz, 6- or 5-H, *exo*) and (t, *J*=7.5Hz, 6- or 5-H, *endo*);

Endo adduct **121a**

δ_C (50.3 MHz; $CDCl_3$) 14.0 and 14.1 (OCH_2*Me*), 18.9, 28.6 and 34.25 (CH_2CH_2), (SCH_2), 35.6, 37.0 (CH), 61.6 and 61.7 (*OCH_2*Me), 65.6 (C-3), 133.0 and 136.32 (C-5 and C-6) and 169.5, 170.7 (CO).

Exo adduct **121b**

δ_C (50.3 MHz; $CDCl_3$) 14.0 and 14.1 (OCH_2*Me*), 20.6, 28.8 and 34.2 (CH_2CH_2), 35.8 and 37.3 (CH), 61.5 and 62.1 (*OCH_2*Me), 66.7 (C-3), 131.8 and 132.2 (C-5 and C-6) and 169.3 and 169.6 (C=O).

The mixture of isomers **121** was converted to the acid as before with *endo:exo* = 3:1. The acids were characterised as a mixture.

Found : M^{+}, 260.0150. $C_{10}H_{12}O_4S_2$ requires *M*, 260.0177.

δ_H (200 MHz; $CDCl_3$) 1.19-1.74 and 2.55-2.66 (3×m, CH_2CH_2), 3.37 (m, CH,), 3.40 (s, SCH_2, *exo*), 3.45 (s with splitting, SCH_2, *endo*), 3.52-3.66 (m, CH,), 6.31

(t, *J*=7.4Hz, 5-H *endo*), 6.37 (t, *J*=7.4Hz, 5-H *exo*), 6.48 (t, J=7.4Hz, 6-H *exo*) and 6.63 (t, J=7.4Hz, 6-H *endo*).

5.1.9 Treatment of the Bunte salt 120 with various bases in the presence of dimethylbutadiene

Preparation of the Bunte salt 120

Ethyl bromoacetate (15 g, 0.09 mol) and sodium thiosulfate pentahydrate (24 g, 95.0 mmol) were heated in ethanol-water (1:1, 300 ml) to boiling for *ca.* 5 min. The mixture was then evaporated to dryness and the residue was extracted with boiling ethanol (200 ml). The extract was filtered to remove the insoluble sodium bromide. The Bunte salt **120** (65%) m.p. 153-157 °C crystallised out from the filtrate.

δ_H (90 MHz; D_2O, Bu^tOH δ 1.29 as standard) 1.31 (t, J=7 Hz, Me), 3.98 (s, CH_2) and 4.25 (q, *J*=7Hz, CH_2Me).

Treatment with triethylamine

Triethylamine (0.51 g, 5 mmol) was added dropwise to a refluxing mixture of the Bunte salt **120** (0.88 g, 4 mmol), calcium chloride dihydrate (0.59 g, 4 mmol), and dimethylbutadiene (0.41 g, 5 mmol) in ethanol (5 ml) and benzene (10 ml). Refluxing was continued for 3 h. Hydrochloric acid (15 ml, 1M) was then added and the layers were separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with sodium hydroxide (1M) and water then dried and evaporated to leave an orange oil (0.69 g) which contained the thioaldehyde cycloadduct **33** as 77% of the mixture and the dithioester adduct **98**, 7% along with the disulfide **104a** at 16 %.

Treatment with triethylamine and 10% DMAP

The above reaction was repeated adding a mixture of triethylamine (0.51 g, 5 mmol) and DMAP (0.06 g, 0.5 mmol) dissolved in a little benzene. Work-up gave an

orange oil (0.59 g). This contained the products in proportions similar to before with the thioaldehyde cycloadduct **33** the major product at 78%, the dithioester cycloadduct **98**, 9% and the disulfide **104a**, 13%.

5.1.10 Isolation and purification of the dienophilic dithioester 99

Diethyl 3-thia-2-thioxopentanedioate 99

DMAP (0.92 g, 7.55 mmol) dissolved in a little dichloromethane was added to ethyl phthalimdosulfanylacetate **45** (2 g, 7.55 mmol) in dichloromethane (50 ml). The mixture turned from orange to red as the base was added. Hydrochloric acid was added immediately upon formation of the precipitate to prevent further reaction with DMAP. After filtration the layers were separated and the acid layer extracted with dichloromethane. Combined organic solutions were washed with water then dried and evaporated to give a reddish oil. The oil was immediately purified by chromatography (hexane-ethyl acetate, 4:1) to give a purple solution. The solvent was not evaporated and the solution divided into 4 equal portions.

First portion - Evaporation of the solvent gave the dithioester, *diethyl* 3-*thia*-2-*thioxopentanedioate* **99** as a purple oil (0.124 g, 56%).

Found : M^+, 236.0159 $C_8H_{12}O_4S_2$ requires *M*, 236.0141;

ν_{max} (liq. film)/ cm^{-1} 1260, 1367, 1736 and 2982;

λ_{max} (EtOH) / nm 232 (ε 6176 $dm^3mol^{-1}cm^{-1}$), 515 (ε 9.7).

δ_H (200 MHz; $CDCl_3$) 1.29 (t, *J*=7.1Hz, $SCH_2CO_2CH_2\mathit{Me}$), 1.41 (t, *J*=7.1Hz, $OCH_2\mathit{Me}$), 4.08 (s, SCH_2), 4.21 (q, *J*=7.1Hz, $SCH_2CO_2\mathit{CH_2}Me$) and 4.39 (q, *J*=7.1Hz, $O\mathit{CH_2}Me$);

δ_C (50.3 MHz; $CDCl_3$) 13.9 and 14.0 ($OCH_2\mathit{Me}$), 38.2 (SCH_2), 62.1 and 63.6 ($O\mathit{CH_2}Me$), 159.3 ($CH_2\mathit{C}$=O), 166.2 (CS*C*=O) and 214.8 (CS).

Second portion - cyclopentadiene (0.25 g, 3.77 mmol) was added to the dithioester **99** solution. The colour had disappeared after 2 min. Evaporation and chromatography of the clear residue gave the pure cyclopentadiene adducts **116** (0.15 g, 87%).

third portion - Dimethylbutadiene (0.31 g, 3.77 mmol) was added. The colour had disappeared after 40 min. Evaporation and chromatography of the clear residue gave the pure cycloadduct **98** (0.15 g, 88%).

Fourth portion - cyclohexadiene (0.30 g, 3.77 mmol) was added. The purple colour had not completely disappeared even after leaving overnight. Evaporation and chromatography of the residue gave the cyclohexadiene cycloadducts **121** (0.11 g, 67%) contaminated by a small amount of the dithioester **99**.

Dimethyl 3-thia-2-thioxopentanedioate 122 and methyl 2-(methoxycarbonylmethylsulfanyl)-4,5-dimethyl-3,6-dihydro-2H-thiine-2-carboxylate 123.

The corresponding methyl ester dithioester was prepared similarly from methyl phthalimidosulfanylacetate. *Dimethyl* 3-*thia*-2-*thioxopentanedioate* **122** was isolated after chromatography as a purple oil.

δ_H (200 MHz; $CDCl_3$) 3.76 (s, SCH_2CO_2Me), 3.95 (s, $CSCO_2Me$) and 4.11 (s, SCH_2).

Addition of dimethylbutadiene to a solution of the purple dithioester **122** in dichloromethane gave a colourless solution after *ca.* 30 min and the dithioester cycloadduct, *methyl* 2-*(methoxycarbonylmethylsulfanyl)*-4,5-*dimethyl*-3,6-*dihydro*-2H-*thiine*-2-*carboxylate* **123** was isolated as a clear oil.

δ_H (200 MHz; $CDCl_3$) 1.72 (J=7.3 Hz, 2×Me), 2.49 and 2.79 (ABq, J_{AB}=18Hz, 3-H), 2.91 and 3.37 (ABq, J_{AB}=18Hz, 6-H), 3.52 and 3.64 (ABq, J_{AB}=16.2Hz, SCH_2), 3.72 (s, OMe) and 3.78 (s, OMe).

Attempted preparation of the dithioester 99 by an alternative route

An attempt was made to prepare the dithioester **99** based on a method by Thiel *et al.*[53]. Ethyl bromoacetate (8.35 g, 0.05 mol) was added to a mixture of sulfur, S_8 (3.2 g, 0.15 mol) and triethylamine (15.3 g, 0.15 mol) in DMSO (50 ml) with stirring at room temperature. Immediately a red colour developed. After stirring for 2 h the mixture had turned much darker. A second portion of ethyl bromoacetate (9.18 g, 0.055 mol) was added and the reaction mixture became very warm and was cooled in an ice bath with stirring for 10 min. The mixture was extracted with dichloromethane and the extracts washed with aqueous sodium bicarbonate to remove DMSO then dried and evaporated to leave a reddish oil (7.5 g). The ^{1}H NMR spectrum showed a large singlet δ 3.53 along with two sets of quartets and triplets in the ethoxy regions but this did not correspond to the dithioester.

Polymer formation from the dithioester 99

The neat dithioester **99** was kept for 1 week at room temperature, in the absence of base, after which time the purple colour had almost gone. The signals in the ^{1}H NMR spectrum showed the monomer had been replaced by broad multiplets previously shown by the polymer.

After a further week, the now completely colourless mixture of oil and solid gave strong sharp signals, as well as much lower intensity broad and sharp signals. It would appear that the polymeric material has been converted to simpler structures, possibly dimers or trimers.

δ_H (200 MHz; $CDCl_3$) 1.30 and 1.41 (2×t, *J*=7.1Hz, Me), 3.79 (s, SCH_2) and 4.22 and 4.41 (2×q, *J*=7.1Hz, OCH_2).

Treatment of the dithioester 99 with DMAP

Addition of DMAP (0.06 g, 0.47 mmol) to a solution of the dithioester **99** (0.11 g, 0.47 mmol) in dichloromethane (5 ml) produced a red colour which quickly

turned orange/brown. The mixture was washed with hydrochloric acid (1M) and water then dried and evaporated to give a dark oil (0.1 g). The ^{1}H NMR spectrum showed a complex spectrum similar to that obtained by the treatment of ethyl phthalimidosulfanylacetate **45** with DMAP in the absence of diene.

Treatment of this polymer with triethylamine in the presence of dimethylbutadiene gave the dithioester cycloadduct **98** with minor amounts of the disulfide **104a** and a trace of the thioaldehyde cycloadduct **33**.

5.1.11 Polymer formation from ethyl phthalimidosulfanylacetate 45 and reverse reaction

Polymer formation using triethylamine and the reverse reactions

Triethylamine (0.19 g, 1.88 mmol) was added to ethyl phthalimidosulfanylacetate **45** (0.5 g, 1.88 mmol) in dichloromethane (10 ml) with stirring at room temperature. The colour darkened as the base was added and a precipitate formed *ca.* 15 s after final addition of base. This was a very dramatic increase in the reaction rate caused by the absence of diene. The phthalimide was filtered off and the filtrate washed with sodium hydroxide (1M), hydrochloric acid (1M) and water then dried and evaporated to give an orange oil (0.17 g). The ^{1}H NMR spectrum showed a large proportion of this to be the disulfide **104a** δ_H (200 MHz; $CDCl_3$) 1.30 (t, *J*=7.1Hz, $OCH_2\mathit{Me}$), 3.59 (s, SCH_2) and 4.22 (q, *J*=7.1Hz, OCH_2Me).

The spectrum also showed 3 areas of more complicated signals along with ethoxy signals. The largest was situated around δ 3.68 and corresponded to about 80% of the proton intensity of a thioaldehyde polymer other than the ethoxy signals. A smaller area situated at δ 3.60 corresponded to about 13% and the final group was present at δ 5.0.

Dimethylbutadiene (1.09 g, 13 mmol) was added to a mixture of the polymeric material (0.17 g) in chloroform (20 ml) and refluxed for 3 h. On evaporation only a trace of the thioaldehyde cycloadduct **33** was detected.

Triethylamine (0.1 g, 0.96 mmol) was then added to a mixture of the polymeric material (0.11 g) in dichloromethane (10 ml) containing dimethylbutadiene (0.09 g, 1.1 mmol) and left for 2 days at room temperature. Evaporation gave an orange oil (0.13 g) and the ^{1}H NMR spectrum showed this oil to contain the thioaldehyde cycloadduct **33** while the original disulfide **104a** remained unchanged. There was also a very small amount of the dithioester cycloadduct **98**.

Polymer formation without the disulfide 104a contaminant

Triethylamine (0.96 g, 9.43 mmol) was added to ethyl phthalimidosulfanylacetate **45** (2.5 g, 9.43 mmol) in dichloromethane (50 ml). The mixture was filtered immediately after formation of the precipitate and the filtrate was immediately washed with hydrochloric acid (1M) to prevent further reaction. It was further washed with sodium hydroxide and water then dried and evaporated to give a pale peach oil (1.03 g). The ^{1}H NMR spectrum was similar to the previous polymeric material but contained virtually no disulfide **104a**.

The polymer was treated with triethylamine and dimethylbutadiene. Again leaving for 1 day led to the formation of the thioaldehyde cycloadduct **33** along with some disulfide presumably formed by allowing the polymer to come into contact with the base.

DMAP (0.25 g, 2.1 mmol) was then added to the polymer (0.25 g, 2.11 mmol if derived from the thioaldehyde) in dichloromethane (5 ml) containing dimethylbutadiene (0.35 g, 4.22 mmol). Evaporation of the mixture after 1 day gave an oil (0.28 g) which showed products similar to that formed by the triethylamine with no greater amount of the dithioester cycloadduct **98**.

Polymer Formation Using DMAP and reverse reactions

DMAP (0.23 g, 1.88 mmol) dissolved in a little dichloromethane was added to ethyl phthalimidosulfanylacetate **45** (0.5 g, 1.88 mmol) in dichloromethane (10 ml) with stirring at room temperature. A pink colour developed and precipitate appeared after *ca.* 30 s. The colour had completely vanished after *ca.* 2 min. Work-up as before gave an orange oil (0.12 g). The ^{1}H NMR spectrum showed a collection of signals δ 3.4-3.85 along with complicated ethoxy signals and a less intense collection at δ 4.8-5.0. The disulfide **104a** was formed only as a minor impurity.

Triethylamine (0.09 g, 0.85 mmol) was added to the polymer (0.1 g, 0.42 mmol if derived from the dithioester **99**) in dichloromethane (10 ml) containing dimethylbutadiene (0.07 g, 0.85 mmol). After leaving overnight evaporation gave an oil which contained the dithioester cycloadduct **98** as the major product. Some of the disulfide **104a** was also present along with a trace of the thioaldehyde cycloadduct **33**.

5.1.12 Treatment of *N*-phthaloylphenylmethanesulfenamide 103 with various bases in the presence of dimethylbutadiene

Treatment with triethylamine

Triethylamine (0.18 g, 1.75 mmol) was added to the *N*-phthaloyl sulfenamide **103** (0.44 g, 1.63 mmol) in benzene (15 ml) containing dimethylbutadiene (0.14 g, 1.75 mmol) with stirring at room temperature. A precipitate had formed after 3 weeks and a new product was detected by TLC. The precipitate was filtered off and the solvent evaporated. Chromatography (hexane-ethyl acetate, 4:1) yielded an oil (0.11 g) which turned green after 2 days. It appeared to be the thioaldehyde cycloadduct.

Treatment with DMAP in the absence of diene

DMAP (0.45 g, 3.7 mmol) in a little dichloromethane was added to the *N*-phthaloyl sulfenamide **103** (1 g, 3.7 mmol) in dichloromethane (10 ml) with stirring at

room temperature. A pink colour slowly began to develop and remained as precipitate formed. After 2 days the mixture was washed with sodium hydroxide, hydrochloric acid and water then dried and evaporated to give a red oil (0.50 g) which was separated by chromatography to yield a number of fractions. The first fraction was a red oil (17 mg).

δ_H (90 MHz; $CDCl_3$) 4.6 (s), 7.3-7.5 (ArH) and 8.0-8.1 (ArH).

The second fraction was isolated as a red oil containing a white solid (0.33 g). These two components were partially separated by careful extraction with hexane. The white solid was identified as dibenzyl disulfide **104c** and was identical to material prepared by oxidation of benzyl mercaptan **107**.

δ_H (200 MHz; $CDCl_3$) 3.54 (s, SCH_2) and 7.10-7.32 (m, ArH).

δ_C (50.3 MHz; $CDCl_3$) 43.3 (SCH_2), 127.6, 128.6 and 129.6 (CHAr) and 137.5 (CAr).

m/z M^+ (246).

The red oil in this fraction may correspond to the known dithioester **137**.

δ_H (200 MHz; $CDCl_3$) 3.99 (s, SCH_2) and 7.16-7.34 (m, ArH).

δ_C (50.3 MHz; $CDCl_3$) 43.2 (SCH_2), 127.6, 128.5 and 129.5 (CHAr) and 136.6 (C).

Treatment of **103** with DBN led entirely to dibenzyl disulfide **104c**.

When the phthaloyl sulfenamide **103** was treated with DMAP and dimethylbutadiene two fractions were isolated. The first was the disulfide **104c** and the second was a purple oil.

δ_H (200 MHz; $CDCl_3$) 4.30 (s), 7.20-7.41 and 7.76-7.98 (m, ArH)

5.1.13 Treatment of *N*-phthaloylbenzoylmethanesulfenamide 100 with various bases in the presence of dimethylbutadiene

Preparation of the disulfide 101- treatment with pyridine

Pyridine (1.58 g, 2 mmol) was added to the *N*-phthaloyl sulfenamide **100** (0.23 g, 0.77 mmol) in dichloromethane (5 ml) with stirring at room temperature. A white solid formed after 3 h. The mixture was then washed with sodium hydroxide,

hydrochloric acid and water then dried and evaporated to leave an orange oil (0.09 g) which contained a 1:1 mixture of cycloadducts by analysis of the ^{1}H NMR spectrum. Chromatography (hexane-ethyl acetate, 4:1) gave the thioaldehyde cycloadduct **102** (0.18 g) as an almost colourless oil and the disulfide **101** (58 mg) as a pale yellow solid which was recrystallised from acetone to give a white solid m.p. 114-116°C. (lit.[43] 114-116 °C) .

δ_H (200 MHz; $CDCl_3$) 1.78 (s, Me) 1.84 (s, Me), 2.93 (brs, CH_2), 2.99 and 3.33 (ABq, J_{AB}=15.4Hz, CH_2) and 3.89 and 3.92 (ABq, J_{AB}=14.9Hz, $SSCH_2$).

δ_C (50.3 MHz; $CDCl_3$) 18.8 and 20.3 (2Me), 32.3(C3), 38.8 (C6), 45.0 ($SSCH_2$), 65.9 (C2), 125.3 (CAr), 127.7 (CAr), 128.0, 128.5, 128.6, 130.3, 132.9 and 133.5 (6CHAr) and 134.7 and 135.1 (CO).

2-benzoyl-3,6-dihydro-4,5-dimethyl-2H-thiine 102 - treatment with triethylamine

Triethylamine (0.17 g, 1.68 mmol) was added to the *N*-phthaloyl sulfenamide **100** (0.5 g, 1.68 mmol) in dichloromethane (10 ml) containing dimethylbutadiene (0.16g, 2 mmol) with stirring at room temperature. A precipitate had formed after 3 h and the mixture was worked up as before to give a yellow oil (0.42 g) which was purified by chromatography to give 2-*benzoyl*-3,6-*dihydro*-4,5-*dimethyl*-2H-*thiine* **102** (0.36 g, 93%) as an almost colourless oil.

δ_H (200 MHz; $CDCl_3$) 1.73 (s, 2Me), 2.47 (m, CH_2CH), 2.98 (brs, CH_2S), 4.49 (t, *J*=5.6Hz, $CHCH_2$), 7.43 (m, ArH) and 7.96 (m, ArH).

Treatment with triethylamine and 10% DMAP

The above reaction was repeated and the *N*-phthaloyl sulfenamide **100** was treated with triethylamine (0.17 g, 1.68 mmol) and DMAP (0.02 g, 0.17 mol). The mixture immediately turned bright yellow then pink followed by orange. After work-up as before a yellow oil was obtained (0.14 g) which did not contain any cycloadducts (^{1}H NMR spectrum analysis) and was thought to be polymeric material.

However, using excess diene (0.32 g, 4 mmol) led to the formation of the thioaldehyde cycloadduct **102**.

Treatment of the *N*-phthaloyl sulfenamide **100** with DMAP also led to polymeric material and the same product was obtained by treatment with base in the absence of diene.

5.1.14 Treatment of *N*-phthaloylbenzoylmethanesulfenamide 100 with various bases in the presence of cyclopentadiene.

3-*endo* and 3-*exo*-3-benzoyl-2-thiabicyclo[2.2.1]hept-5-ene 141 - treatment with triethylamine

Triethylamine (0.20 g, 2 mmol) was added to the *N*-phthaloyl sulfenamide **100** in dichloromethane (10 ml) containing cyclopentadiene (0.26 g, 4 mmol) with stirring at room temperature. After 3 h the mixture was worked up by washing with sodium hydroxide, hydrochloric acid and water then dried and evaporated to give an orange oil which was purified by chromatography to give 3-endo and 3-exo-3-*benzoyl*-2-*thiabicyclo*[2.2.1]*hept*-5-*ene* **141** (0.2 g, 56%) as an almost colourless oil *endo* : *exo* = 1.4 : 1, which were characterised as a mixture.

δ_H (200 MHz; $CDCl_3$) 1.75 (m, 7H *endo* and *exo*), 1.84 and 1.89 (2brs, 7H *exo*), 3.64 (brs, 4H *exo*), 3.75 (m, 4H *endo*), 4.03 (brs, 1H *endo*), 4.03 (s, 3H *exo*), 4.11 (brs, 1H *exo*), 5.09 (d, *J*=3.5Hz, 3H *endo*), 6.06 (dd, *J*=3.23 and 5.42 Hz, 5H *exo*), 6.13 (dd, *J*=5.36 and 3.06 Hz, 5H *endo*), 6.35 (dd, *J*=5.43 and 2.92 Hz, 6H *endo*), 6.44 (dd, *J*=5.43,2.80 Hz, 6H *exo*), 7.46 (m, ArH *endo* and *exo*) and 7.91 (m, ArH *endo* and *exo*).

Treatment of the *N*-phthaloyl sulfenamide **100** with other base combinations, triethylamine and DMAP, DMAP or pyridine all yielded only the thioaldehyde cycloadduct **141** when trapping with cyclopentadiene.

5.1.15 Attempted capture of a possible by-product 146

An attempt was made to capture a possible by-product which may have been formed when the *N*-phthaloyl sulfenamide **100** was treated with pyridine.

Preparation and capture of the ylid 146 by known methodology

Bromine (13.4 g, 84 mmol) was added gradually to a solution of acetophenone (10.08 g, 84 mmol) in anhydrous ether (10 ml) containing aluminium chloride (0.1 g, 0.75 mmol) with cooling in ice. Initial bromine disappeared after *ca.* 5 min, then additional bromine was taken up quickly. Ether and dissolved HBr are then removed under a current of nitrogen, and after washing with light petroleum and water, 1:1 almost white crystals of phenacyl bromide were obtained (9.92 g, 60%).

Pyridine (0.79 g, 10.04 mmol) was added to the phenacyl bromide (2 g, 10.04 mmol) in chloroform (10 ml). After *ca.* 30 min the mixture contained a white precipitate and TLC showed no starting material to be present. The solid was filtered off and combined with more solid which crystallised from the filtrate to give *N*-phenacylpyridinium bromide **147** (1.05 g, 81%).

Acrylonitrile (0.29 g, 5.55 mmol) followed by sodium hydroxide (115 mg in 15 ml of water) were added to the pyridinium salt **147** (1 g, 3.6 mmol) dissolved in water and acetonitrile (68 ml : 4 ml). Immediately a yellow colour developed and after 30 min the indolizidine **148** had precipitated out as an orange solid (0.46 g, 51%) which was filtered off.

δ_H (90 MHz; $CDCl_3$) 2.32 (m, CH_2), 3.28 (m, CHCN), 4.63 (m, NCH), 4.80 (m, CHCOPh), 5.15 and 6.02 (2×m, allylic H), 7.45 (m, CHAr) and 7.90 (m, CHAr).

The *N*-phthaloyl sulfenamide **100** was treated with pyridine and dimethylbutadiene as before. The precipitate was filtered off and the organic filtrate extracted with water (10 ml). Acetonitrile (0.5 ml) was added to the aqueous extract followed by acrylonitrile (0.04 g, 0.76 mmol) and sodium hydroxide (0.5 ml, 1M). The mixture turned yellow and after leaving overnight, extracted with

dichloromethane. The yellow colour remained in the aqueous layer. However, evaporation of the organic layer gave only a small amount of yellow oil, possibly pyridine.

5.1.16 Treatment of *N*-phthaloylacetylmethanesulfenamide 115 with various bases in the presence of dimethylbutadiene.

2-acetyl-3,6-dihydro-4,5-dimethyl-2H-thiin 149 - treatment with triethylamine

Triethylamine (0.27 g, 2.68 mmol) was added to the *N*-phthaloyl sulfenamide **115** (0.68 g, 2.68 mmol) in dichloromethane (15 ml) containing dimethylbutadiene (0.25 g, 3.0 mmol). A yellow colour formed immediately, which turned darker as the reaction proceeded. After 3 h the mixture was worked up to leave a yellow oil with much of the dark material being removed by the alkaline wash. The crude product was purified by chromatography (hexane-ethyl acetate, 4:1) to give 2-*acetyl*-3,6-*dihydro*-4,5-*dimethyl*-2H-*thiin* **149** as an almost colourless oil (0.37 g, 82%).

δ_H (200 MHz; $CDCl_3$) 1.71 (s, 2Me), 2.33 (s, COMe), 2.35 (brs, 3-H_2), 2.95 (brs, 6-H_2) and 3.59 (t, J=5.4Hz, 2-H).

Treatment with triethylamine and 10% DMAP

The *N*-phthaloyl sulfenamide **115** was treated, as before, with triethylamine (0.27 g, 2.68 mmol) and DMAP (0.03 g, 0.27 mmol). The precipitate quickly formed and the colour quickly darkened from yellow to orange/red. Work-up as before after 10 min gave a yellow oil (0.22 g) which contained a mixture of two products which were separated by chromatography. The first fraction was the thioaldehyde cycloadduct **149** but the second also resembled a cycloadduct and might possibly be a type of 'abnormal' cycloadduct.

δ_H (200 MHz; $CDCl_3$) 1.71 (s, Me), 1.74 (s, Me), 2.23 (s, COMe), 2.40 (s, COMe), 2.57 (d, J=1.86Hz, SCH_2), 2.81 and 3.29 (ABq, J_{AB}=17Hz, CH_2), 2.42 and 2.76 (ABq, J_{AB}=17Hz, CH_2) and 3.43 (s).

Treatment with DMAP alone however, led to a complex mixture of unidentified products.

Treatment with pyridine

Pyridine (0.42 g, 5.36 mmol) was added to the *N*-phthaloyl sulfenamide **115** (0.68 g, 2.68 mmol) in dichloromethane (20 ml) containing dimethylbutadiene (0.25 g, 3 mmol). After 3 h the yellow solution containing solid was worked up as before to leave a yellow oil (0.35 g) containing two products which were separated by chromatography (hexane-ethyl acetate, 4:1). The first product was isolated as a yellow oil (0.05 g) and was identified as the thioaldehyde cycloadduct **149**. The second fraction was also isolated as a yellow oil (0.14 g) and was again thought to be some sort of 'abnormal' cycloadduct.

If *M* =$C_{12}H_{18}O_2S_2$, found : M^+-COMe, 215.0568. $C_{10}H_{15}OS_2$ requires *M*, 215.0565.

δ_H (200 MHz; $CDCl_3$) 1.77 (s, 2Me), 2.27 (s, COMe), 2.39(s, COMe), 2.71 (brs, CH_2), 2.93 and 3.41 (ABq, J_{AB}=16Hz, CH_2) and 3.41 and 3.51 (ABq, J_{AB}=14.4Hz, SCH_2).

δ_C (50.3 MHz; $CDCl_3$) 19.0 and 20.2 (Me), 24.9 and 28.2 (COMe), 30.7 (CH_2), 36.3 (CH_2), 47.96 (SCH_2), 66.5 (C), 123.6 and 125.4 (*C*Me) and 201.1 and 202.1 (CO).

5.1.17 Treatment of *N*-phthaloylacetylmethanesulfenamide 115 with various bases in the presence of cyclopentadiene

3-*endo* and 3-*exo*-3-acetyl-2-thiabicyclo[2.2.1]hept-5-ene 152 - treatment with triethylamine.

Triethylamine (0.14 g, 1.33 mmol) was added to the *N*-phthaloyl sulfenamide **115** (0.25 g, 1.48 mmol) in benzene (10 ml) containing cyclopentadiene (0.12 g, 1.48 mmol) with stirring at room temperature. The precipitate began to form after 15 min and after leaving overnight the mixture was washed with sodium hydroxide, hydrochloric acid and water then dried and evaporated to leave an orange oil (0.11 g).

The oil contained 3-endo and 3-exo-3-*acetyl*-2-*thiabicyclo*[2.2.1]*hept*-5-*ene* **152**, as the only products, *endo*:*exo* =7:1 which were characterised as a mixture although separate isomers were identified in the ^{1}H NMR spectrum.

Endo isomer **152a**

δ_H (200 MHz; $CDCl_3$) 1.61-1.81 (m, 7-H_2), 2.13 (s, COMe), 3.74 (brs, 4-H), 4.11 (brs, 1-H), 4.42 (d, *J*=3.8Hz, 3-H), 5.86 (dd, *J*=5.46, 3.1 Hz, 5-H) and 6.42 (dd, *J*=5.45, 2.9 Hz, 6-H).

Exo isomer **152b**

δ_H (200 MHz; $CDCl_3$) 1.61-1.81 (m, 7-H_2), 2.30 (s, COMe), 3.41 (s, 3-H), 3.54 (brs, 4-H), 4.12 (brs, 1-H), 5.99 (dd, *J*=5.45, 3.2Hz, 5-H) and 6.39 (dd, *J*=5.4, 3.0 Hz, 6-H).

Treatment of the *N*-phthaloyl sulfenamide **115** with other bases and trapping with cyclopentadiene led only to the thioaldehyde cycloadduct **152** being formed. However, treatment with DMAP led to a small trace of a second cycloadduct which was detected by ^{1}H NMR spectroscopy.

5.2 *S*-Alkylation and rearrangement of cycloadducts

5.2.1 *S*-Alkylation and rearrangement of thioaldehyde anthracene cycloadducts

Ethyl 9,10-dihydro-10,9-(epithiomethano)-anthracene-12-carboxylate 35 and the corresponding acid 159

The ethyl thioxoacetate anthracene cycloadduct **35** was prepared from the corresponding sulfenyl chloride **106a** based on the method of Kirby and Choi [33]. Ethyl mercaptoacetate **37** (3.0 g, 25 mmol) and pyridine (1.98 g, 25 mmol) in carbon tetrachloride (3 ml) were added slowly with stirring to a solution of sulfuryl chloride (3.37 g, 25 mmol) in carbon tetrachloride (25 ml) at -10 °C. The yellow colour of the sulfenyl chloride quickly developed and the precipitate of pyridine hydrochloride was filtered off after 10 min. The sulfenyl chloride solution was added slowly to a refluxing mixture of anthracene (8.9 g, 50 mmol) and triethylamine (2.55 g, 25 mmol) in chloroform (120 ml). A red colour developed as the sulfenyl chloride was added and the nature of this is unknown. Refluxing was continued for a further 10 min and the mixture allowed to cool. Excess anthracene crystallised out and was filtered off. The filtrate was then washed with HCl and water then dried and evaporated to give the crude anthracene ester **35**. The ester at this stage could be purified by chromatography but was difficult to obtain without contamination by anthracene and was therefore immediately converted to the acid **159**. The residue was mixed with ethanol-1M NaOH (1:1, 150 ml) and stirred overnight at room temperature. The mixture was then evaporated to remove the organic solvent and excess anthracene was removed by washing 5 times with dichloromethane. The aqueous layer was then acidified with HCl and 9,10-*dihydro*-10,9-*(epithiomethano)-anthracene*-12-*carboxylic acid* **159** precipitated out as a white solid (2.79 g, 42%).

δ_H (200 MHz; $CDCl_3$) 4.16 (d, *J*=2.8Hz, SCH), 5.07 (d, *J*=2.7Hz, 10-H), 5.18 (s, 9-H), 6.05 (brs, OH) and 7.10-7.44 (m, ArH).

The acid was then converted back to the ester. The acid **159** (2.79 g, 10.4 mmol) was stirred overnight with ethanolic HCl (200 ml 0.1M from acetyl chloride

1.57 g in ethanol 200 ml). Some ester precipitates out from the solution and evaporation to low volume allows *ethyl* 9,10-*dihydro*-10,9-(epi*thiomethano)-anthracene*-12-*carboxylate* **35** to be collected by filtration in good yield (2.76 g, 90% from acid).

δ_H (200 MHz; $CDCl_3$) 1.17 (t, *J*=7.1Hz, OCH_2*Me*), 4.08 and 4.06 (2q, *J*=7.1Hz, OCH_2Me), 4.10 (d, *J*=2.6Hz, SCH), 5.06 (d, *J*=2.6Hz, 10-H), 5.12 (s, 9-H) and 7.10-7.4 (m, ArH).

The anthracene cycloadduct **35** could also be prepared using ethyl phthalimidosulfanylacetate **45** as the thioaldehyde precursor. A solution of ethyl phthalimidosulfanylacetate **45** (1.23 g, 4.64 mmol) in chloroform (5 ml) was added slowly to a refluxing mixture of anthracene (1.65 g, 9,28 mmol) and triethylamine (0.47 g, 4.64 mmol) in chloroform (60 ml). A slight orange colour began to form as addition began and had darkened by the end of addition. It was not however, as dark as with the sulfenyl chloride **106a**. After refluxing for a further 10 min work-up as before gave the acid **159** in similar yield.

The methyl ester **35b** could also be prepared from the acid as follows. The acid **159** (0.54 g, 2 mmol) was stirred overnight with methanolic HCl (40 ml 0.1M from acetyl chloride 0.31 g in methanol 40 ml). Work-up as before gives *methyl* 9,10-*dihydro*-10,9-(epi*thiomethano)-anthracene*-12-*carboxylate* **35b** as a white solid (0.49g, 86%).

δ_H (200 MHz; $CDCl_3$) 3.61 (s, OMe), 4.12 (d, *J*=2.65Hz, SCH), 5.07 (d, *J*=2.6Hz, 10-H), 5.13 (s, 9-H) and 7.10-7.41 (m, ArH).

Formation of 155 and 156 - *S*-ethylation and rearrangement of the ethyl ester anthracene cycloadduct 35

Triethyloxonium tetrafluoroborate was prepared based on the method of Meerwein [58]. Epichlorohydrin (14 g, 0.15 mol) was added dropwise to boron trifluoride etherate (28.4 g, 0.2 mol) in anhydrous ether (50 ml) at a rate sufficient to

maintain boiling. Refluxing was continued for a further hour. After allowing to stand at room temperature overnight a solid had formed. The crystalline oxonium salt was filtered off under argon to prevent reaction with atmospheric moisture and then washed with ether. *Triethyloxonium tetrafluoroborate* was obtained as a slightly dark hygroscopic solid (16.5 g, 57%). The salt however, did not keep well in the crystalline form even under argon and was better stored as a solution in dichloromethane.

The reaction was carried out following the method of Rahman [57]. The anthracene cycloadduct **35** (2.14 g, 7.23 mmol) and triethyloxonium tetrafluoroborate (1.50 g, 7.28 mmol) were stirred at room temperature in dry dichloromethane (50 ml) for 2 h. The mixture was then evaporated and the residue dissolved in dry acetonitrile (10 ml) with stirring at 0 °C under nitrogen. 1,5 Diazabicyclo[4.3.0]non-5-ene, DBN (0.93 g, 7.50 mmol) was then added dropwise. The mixture turned yellow with each drop but the colour disappeared again. After half of the DBN had been added the colour persisted and after 2 h the colour had gone. Water (35 ml) was then added and the mixture extracted with ether (3 × 50 ml). The extracts were washed with HCl and water then dried and evaporated to give a pale yellow partially crystalline residue (2.09 g). Chromatography yielded a pale yellow oil (1.63 g, 70%) which turned to a sticky solid after a few hours. A white solid was obtained by triturating carefully with ether. The product readily reverts back to the sticky state but once dry solid is obtained it is relatively stable. Careful recrystallisation of the white solid from light petroleum (40-60 °C) and ethyl acetate gave a white crystalline solid m.p. 80-82 °C.

The ^{1}H NMR spectrum of all forms of the product were identical and showed a mixture of isomers **155** and **156** *ca.* 3.7 : 1 and these could not be separated by chromatography. Only on spot was observed with TLC.

Minor isomer - δ_H (200 MHz; $CDCl_3$) 1.16 (t, *J*=7.4Hz, SCH_2*Me*), 1.37 (t, *J*=7.1Hz, CO_2CH_2*Me*), 2.46 (q, *J*=7.4Hz, S*CH*$_2$Me), 4.36 (q, *J*=7.1Hz, CO_2*CH*$_2$Me), 4.47 (s, *CH*CO_2Et), 7.10-7.75 (m, ArH) and 8.26 (s, C=CH).

Major isomer - δ_H (200 MHz; $CDCl_3$) 1.08 (t, *J*=7.4Hz, SCH_2Me), 1.34 (t, *J*=7.1Hz, CO_2CH_2Me), 2.28 (q, *J*=7.4Hz, SCH_2Me), 4.36 (q, *J*=7.1Hz, CO_2CH_2Me), 5.14 (s, $CHCO_2Et$), 7.10-7.75 (m, ArH) and 8.06 (s, C=CH).

Minor isomer - δ_C (50.3 MHz; $CDCl_3$) 14.3 (SCH_2Me), 14.4 (OCH_2Me), 25.9 (SCH_2), 49.5 (CH), 61.5 (OCH_2Me), 123.8, 124.2, 125.6, 126.2, 126.9, 128.9, 129.1 and 130.3 (CHAr), 131.4 and 140.4 (C) and 167.6 (CO).

Major isomer - δ_C (50.3 MHz; $CDCl_3$) 14.4 (SCH_2Me), 14.5 (OCH_2Me), 26.7 (SCH_2), 56.2 (CH), 61.3 (OCH_2Me), 126.6, 127.3, 128.3, 128.4, 128.8, 129.95, 130.7 and 131.6 (CHAr), 131.8, 132.8 and 133.5 (CAr), 138.2 (CH), 140.6 and 141.3 (C) and 168.1 (CO).

The isomers **155** and **156** were converted to the acids **160** and **161** by treatment with 1M NaOH in ethanol. The ratio of isomers remained unchanged.

Major isomer - δ_H (200 MHz; $CDCl_3$) 1.13 (t, *J*=7.4Hz, SCH_2Me), 2.33 (q, *J*=7.4Hz, SCH_2Me), 5.17 (s, CH), 7.24-7.77 (m, ArH) and 8.27 (s, C=CH).

Minor isomer - δ_H (200 MHz; $CDCl_3$) 1.24 (t, *J*=7.4Hz, SCH_2Me), 2.53 (q, *J*=7.4Hz, SCH_2Me), 4.50 (s, CH), 7.24-7.77 (m, ArH) and 8.45 (s, C=CH);

m/z 296 (M^+).

Formation of 162 and 163 - *S*-methylation and rearrangement of the ethyl ester anthracene cycloadduct 35

The anthracene cycloadduct **35** (1 g, 3.38 mmol) was treated with trimethyloxonium tetrafluoroborate (0.5 g, 3.38 mmol) to form the methylated product. Treatment with DBN and work-up as before gave a yellow oily mixture (1.02 g, 97%). Chromatography gave a yellow oil which partially solidified after leaving for a few days. Again the ^1H NMR spectrum appeared to show a mixture of two isomers although no separation was observed by TLC. A small amount of white powder was

obtained by careful trituration with ether m.p. 92-94 °C. Careful recrystallisation yielded **162** and **163** as a white crystalline solid m.p. 94-95 °C (light petroleum-ether).

Found : M^+, 310.1028. $C_{19}H_{18}O_2S$ requires *M*, 310.1028;

ν_{max} (KBr)/cm^{-1} 1691;

Major isomer - δ_H (200 MHz; $CDCl_3$) 1.40 (t, *J*=7.1Hz, CO_2CH_2*Me*), 1.88 (s, SMe), 4.39 (q, *J*=7.1Hz, CO_2*CH*$_2$Me), 5.04 (s, CH), 7.17-7.54 (m, ArH) and 8.04 (s, C=CH);

δ_C (50.3 MHz; $CDCl_3$) 14.3 (OCH_2*Me*), 16.1 (SMe), 58.1 (CH), 61.3 (O*CH*$_2$Me), 126.7-131.6 (CAr), 133.3 and 132.7 (C), 138.0 (C=*C*H), 140.1 and 140.7 (C) and 168.1 (CO);

Minor isomer - δ_H (200 MHz; $CDCl_3$) 1.42 (t, *J*=7.1Hz, CO_2CH_2*Me*), 2.08 (s, SMe), 4.41 (q, *J*=7.1Hz, CO_2*CH*$_2$Me), 4.45 (s, CH), 7.17-7.54 (m, ArH), 7.71 (m, ArH) and 8.25 (s, C=CH);

δ_C (50.3 MHz; $CDCl_3$) 14.3 (OCH_2*Me*), 15.5 (SMe), 52.0 (CH), 61.5 (O*CH*$_2$Me), 123.5-130.6 (CAr), 131.6, 132.8 and 133.2 (C), 138.4 (C=*C*H), 140.0 (C) and 167.5 (CO).

The ^1H NMR spectrum was run at high temperature (333 K) in an attempt to show if interconversion of isomers was occurring but no difference was observed in the spectra.

The ^1H NMR spectrum run in benzene showed various shifts.

Major isomer - δ_H (200 MHz; Benzene D_6) 1.02 (t, *J*=7.1Hz, CO_2CH_2*Me*), 1.61 (s, SMe), 4.15 (q, *J*=7.1Hz, CO_2*CH*$_2$Me), 4.90 (s, CH), 6.84-7.11 (m, ArH), 7.71 (m, ArH) and 8.34 (s, C=CH).

Minor isomer - δ_H (200 MHz; Benzene D_6) 1.04 (t, *J*=7.1Hz, CO_2CH_2*Me*), 1.60 (s, SMe), 4.15 (q, *J*=7.1Hz, CO_2*CH*$_2$Me), 4.43 (s, CH), 6.84-7.11 (m, ArH), 7.86 (dd, *J*=15.0, 7.9Hz, ArH) and 8.40 (s, C=CH).

When HPLC was carried out using the mixture of isomers, on both silica and reverse phase HPLC columns, only one signal was observed.

Silica column - Particle size 5 μ, 25 cm; flow rate 1.1 ml / min; solvent hexane-isopropanol, 9:1. Signal at 3.23 min.

Reverse phase column - Particle size 5 μ, 25 cm; flow rate 0.5 ml / min; solvent methanol-water, 1:1. Signal at 6.34 min.

Formation of 164 and 165 - *S*-methylation and rearrangement of the methyl ester anthracene cycloadduct 35b

The methyl ester anthracene cycloadduct **35b** (0.4 g, 1.42 mmol) was treated with trimethyloxonium tetrafluoroborate (0.24 g, 1.6 mmol) in dichloromethane (20 ml) to give the methylated product. Treatment with DBN (0.18 g, 1.5 mmol) and work-up as before gave **164** and **165** as a yellow gummy solid (0.44g, 100%). Again the ^1H NMR spectrum appeared to show a mixture of isomers 3.6:1 with no separation however, on TLC.

Found : M^+ 296.0860. $C_{18}H_{16}O_2S$ requires *M*, 296.0871;

ν_{max} (KBr) / cm^{-1} 1708;

Major isomer - δ_H (200 MHz; $CDCl_3$) 1.88 (s, SMe), 3.93 (s, OMe), 5.04 (s, CH), 7.18-7.53 (m, ArH) and 8.06 (s, C=CH);

δ_C (50.3 MHz; $CDCl_3$) 16.1 (SMe), 52.4 (OMe), 58.1 (CH), 126.8, 127.4, 128.6, 128.7, 128.8, 129.9, 130.6 and 131.7 (CHAr), 132.6 and 133.0 (C), 138.4 (C=*C*H), 140.2 (C) and 168.7 (CO).

Minor isomer - δ_H (200 MHz; $CDCl_3$) 2.07 (s, SMe), 3.94 (s, OMe), 4.37 (s, CH), 7.18-7.53 (m, ArH), 7.72 (d, *J*=7.8Hz, ArH) and 8.27 (s, C=CH).

δ_C (50.3 MHz; $CDCl_3$) 15.6 (SMe),52.0 (CH), 52.5 (OMe), 123.5-130.9 (CHAr), 138.8 (C=*C*H) and 168.2 (CO).

5.2.2 Treatment of the rearrangement products with mercuric chloride

Mercuric chloride (0.21 g, 0.76 mmol) in acetonitrile-water (3:1, 5 ml) was added to the *S*-ethylated ethyl ester isomers **155** and **156** (0.12 g, 0.38 mmol) in acetonitrile-water (3:1, 5 ml) containing cadmium carbonate (0.25 g, 1.5 mmol) with stirring under nitrogen. The cadmium carbonate removes any acid which could cause condensation of ketones thereby maintaining neutral conditions. After stirring overnight the TLC showed the ester had gone and a new spot was observed at lower Rf. The mixture was filtered and extracted 3 times with dichloromethane. The organic extracts were washed with HCl and water then dried and evaporated to leave a yellow oil which formed a gum after chromatography (0.102 g). Only one spot was observed by TLC implying that both isomers had reacted with possible replacement of the SEt with OH as implied by MS. The ^{1}H NMR spectrum appeared to show two components in almost equal proportions although the signals corresponding to each component could not be distinguished.

Found : M^+ 280.1099. $C_{18}H_{16}O_3$ requires *M*, 280.1100;

δ_H (200 MHz; $CDCl_3$) 1.36 and 1.37 (2×t, *J*=7.1Hz, OCH_2Me), 4.33 and 4.36 (2×q, *J*=7.1Hz, OCH_2Me), 5.04 (s), 5.06 (s), 7.17-7.55 (m, ArH), 7.74-8.13 (m, ArH), 8.17 (s) and 8.18 (s).

δ_C (50.3 MHz; $CDCl_3$) 14.3 and 61.5 (OCH_2Me), 76.4 (CH), 121.4-131.0 (CAr), 141.1-141.5 (C) and 160.7 (CO).

Treatment of 162 and 163 with mercuric chloride

Mercuric chloride (0.15 g, 0.55 mmol) in acetonitrile-water (3:1, 4 ml) was added to the isomers **162** and **163** (60 mg, 0.19 mmol) in acetonitrile-water (3:1, 4 ml) containing cadmium carbonate. The mixture was stirred overnight then worked up as before to give a yellow gum after chromatography (46 mg, 86%). The ^{1}H NMR spectrum appeared to show two components, again probably due to cleavage of the *S*-alkyl group, which could not be separated.

Found : M^+ 280.1090. $C_{18}H_{16}O_3$ requires *M*, 280.1100;

ν_{max} (liq. film) /cm^{-1} 910, 1611, 1712, 2253 and 3491;

δ_H (200 MHz; $CDCl_3$) 1.36 (t, *J*=6.9Hz, OCH_2*Me*), 1.37 (t, *J*=7.1Hz, OCH_2*Me*), 4.34 (q, *J*=7.1Hz, O*CH*$_2$Me), 4.36 (q, *J*=7.0Hz, O*CH*$_2$Me), 5.04 (s, CH), 5.05 (s, CH), 7.17-7.58 (m, ArH), 7.74-8.13 (m, ArH), 8.16 (s, C=CH) and 8.18 (s, C=CH).

Treatment of 164 and 165 with mercuric chloride.

Mercuric chloride (0.76 g, 2.8 mmol) in acetonitrile-water (3:1, 4 ml) was added to the isomers **164** and **165** (0.417 g, 1.41 mmol) in acetonitrile-water (3:1, 30 ml) containing cadmium carbonate (0.97 g, 5.6 mmol). After stirring for 3 h the mixture was worked up as before to give a yellow foam after chromatography (0.274 g, 73%). m.p. 95-100 °C.

Found : M^+ 266.0939. $C_{17}H_{14}O_3$ requires *M*, 266.0943;

ν_{max} (KBr)/cm^{-1} 1716 and 3433;

δ_H (200 MHz; $CDCl_3$) 3.83 (s, OMe), 5.05 (s, CH), 5.06 (s, CH), 7.17-7.52 (m, ArH), 7.66-8.11 (m, ArH), 8.16 (s, C=CH) and 8.18 (s, C=CH);

δ_C (50.3 MHz; $CDCl_3$) 52.5 (OMe), 76.5 (CH), 121.5, 121 7, 122.0 and 122.2 (CH), 126.1 and 126.5 (CH), 129.0, 129.2, 129.3, 129.5 and 129.6 (CH), 130.6 (CH), 130.7 and 130.9 (C), 132.0 and 132.1 (C), 138.9 and 139.0 (CH), 141.1, 141.2, 141.4 and 141.6 (C) and 167.6 and 167.7 (CO).

5.2.3 *S*-Alkylation and rearrangement of the dimethylbutadiene dithioester cycloadduct 98

The dithioester, dimethylbutadiene cycloadduct **98** (0.09 g, 0.28 mmol) was dissolved in dichloromethane (10 ml). Triethyloxonium tetrafluoroborate (0.4 ml, 2M solution in dichloromethane, 1.0 mmol) was added with stirring at room temperature. After 1.5 h the solvent was evaporated and the residue was dissolved in acetonitrile (2 ml) with cooling to 0 °C under nitrogen. DBN (0.16 g, 1.3 mmol) was added slowly. As base was added the clear mixture turned orange / red and after 1.5 h the colour had

darkened more. Water (50 ml) was added and the mixture extracted with ether (3×30 ml). The ether extracts were washed with HCl and water then dried and evaporated to leave a reddish oil (0.1 g). The ^{1}H NMR spectrum of this crude product showed both the cyclopropane and the disulfide **104a**. Chromatography yielded the *ethylthiocyclopropanecarboxylate* **167** as an oil along with traces of other minor products.

δ_H (200 MHz; $CDCl_3$) 1.22 (s, 2-Me), 1.22 (t, *J*=7.7Hz, SCH_2*Me*), 1.30 (t, *J*=7.1Hz, OCH_2*Me*), 1.35 and 1.75 (ABq, J_{AB}=5.2Hz, 3-H_2), 1.83 (s, vinyl-Me), 2.57 (q, *J*=7.5Hz, S*CH*$_2$Me), 4.23 and 4.24 (2×q, *J*=7.1Hz, O*CH*$_2$Me), 4.85 (brs, C=C*H*$_2$) and 4.94 (quintet, *J*=1.5Hz, C=C*H*$_2$);

δ_C (50.3 MHz; $CDCl_3$) 15.1, 15.5, 20.0 and 21.1 (4×Me), 27.1 and 27.3 (2×CH_2), 37.3 and 37.9 (C-1 and C-2), 61.4 (OCH_2), 113.5 (C=*C*H_2), 145.8 (*C*=CH_2) and 171.9 (C=O).

m/z M^+ 228.

5.3 Synthesis of (±)-*trans*-2,5-bis(methoxymethyl)pyrrolidine and its use as a chiral auxiliary

5.3.1 Preparation of (±)-*trans*-2,5-bis(methoxymethyl)pyrrolidine 173

The auxiliary was prepared following the method of Ghosez *et al.*[65].

(±) and meso-Dimethyl α, δ- dibromoadipate 182

A mixture of adipic acid **181** (50 g, 0.34 mol) and thionyl chloride (99 g, 0.83 mol) was heated at 60 °C with stirring until a solution was effected. Excess thionyl chloride was then removed by distillation to leave the crude acid chloride as a pale yellow liquid. Bromine (125 g, 0.78 mol) was added as quickly as it would react at 60 °C ~ 24 h. The resulting mixture was then added slowly to methanol (250 ml) with cooling (-10 °C). The mixture was stirred overnight at room temperature . A white precipitate formed and was filtered off to give pure (±) and meso-*dimethyl*-α, δ-*dibromoadipate* **182** (30.32 g). Water (250 ml) was added to the filtrate and two layers formed. The top layer was extracted with dichloromethane (3 × 150 ml) and the organic extracts combined with the oily bottom layer. The resulting solution was washed with sodium hydrogen sulfite, sodium hydrogen carbonate and water then dried and evaporated to give the crude dibromodiester **182** as an orange oil (58.35 g). It was found however, that slight evaporation of the methanol yielded more of the precipitate and was a cleaner way to obtain the dibromodiester.

δ_H (200 MHz; $CDCl_3$) 1.98-2.17 and 2.21-2.40 (2×m, CH_2CH_2), 3.80 (s, OMe) and 4.27-4.31 (m, BrCH).

***Trans*-Dimethyl *N*-benzylpyrrolidine-2,5-dicarboxylate 183a**

Benzylamine (31.9 g, 0.297 mol) was added over a period of 4 h at room temperature to a vigorously stirred solution of the dibromodiester **182** (30.3 g, 0.09 mol) in toluene (50 ml). The mixture was then heated for 2 h at 80 °C. After cooling to room temperature the crystals of benzylamine hydrobromide were filtered off and washed with toluene. The combined toluene solutions were extracted with water 5 times and then dried and evaporated to give the crude diester as a mixture of *cis* and

trans isomers (20.07 g). The isomers were separated by chromatography (hexane-ethyl acetate, 4:1), to give cis and trans *dimethyl* N-*benzylpyrrolidine*-2,5-*dicarboxylate* **183**.

Cis-N-*benzylpyrrolidine*-2,5-*dicarboxylate* **183b**

δ_H (200 MHz; $CDCl_3$) 2.01-2.11 (m, CH_2CH_2), 3.38-3.48 (m, 2NCH), 3.58 (s, 2OMe), 3.92 (s, NCH_2) and 7.19-7.34 (m, ArH).

Trans-N-*benzylpyrrolidine*-2,5-*dicarboxylate* **183a**

δ_H (200 MHz; $CDCl_3$) 1.84-2.02 and 2.20-2.42 (m, CH_2CH_2), 3.64 (s, 2OMe), 3.80-3.86 (m, 2NCH), 3.79-3.96 (ABq, J_{AB}=12.9Hz, NCH_2) and 7.19-7.34 (m, ArH).

Epimerisation of the *cis* isomer 183b

A solution of the *cis* diester **183b** (10 g, 36.1 mmol) in hexane (10 ml) containing methanol (0.2 ml) was added dropwise to a suspension of sodium hydride (1.73 g of a 60% suspension in mineral oil, 43.4 mmol) in hexane (40 ml). After stirring overnight at room temperature under nitrogen, a little methanol was added and two layers formed. The top layer was separated and the bottom layer was extracted twice with hexane. The combined solutions were evaporated to give a *trans*:*cis* mixture 5:1 which was separated as before by chromatography to yield more of the *trans* diester **183a** (3.15 g).

(*S,S*) and (*R,R*) *N*-Benzyl-*trans*-2,5-bis(pyrrolidine)methanol 184

A solution of the diester **183a** (10 g, 36.0 mmol) in dry THF (50 ml) was added to a suspension of lithium aluminium hydride (2.22 g, 55 mmol) in dry THF (200 ml) with vigorous stirring at room temperature under nitrogen. After stirring overnight the mixture was cooled (-20 °C) and water (2.2 ml) was added slowly. Stirring was continued for a further 10 min followed by addition of NaOH (4M, 2.2 ml) with stirring for a further 10 min. Finally addition of water (9 ml) and stirring for an hour gave a precipitate which was removed by filtration through Celite and was washed with hot THF. The THF was evaporated and the residue treated in brine (45

ml). The resulting solution was extracted with ether (4 × 50 ml). The combined ether extracts were dried and evaporated to leave *(*S,S*) and (*R,R*)* N-*benzyl*-trans-2,5-*bis(pyrrolidine)methanol* **184**, the diol, as a yellow oil (7.45 g, 96.3%) which was sufficiently pure for further transformation.

δ_H (200 MHz; $CDCl_3$) 1.67-1.83 and 1.86-2.13 (2×m, CH_2CH_2), 3.13 (brs, 2×NCH), 3.40-3.56 (m, 2×CH_2OH), 3.82 (s, $PhCH_2$) and 7.16-7.31 (m, ArH).

(*S,S*) and (*R,R*) *N*-Benzyl-*trans*-2,5-bis(methoxymethyl)pyrrolidine 185

A solution of the diol **184** (7.23 g, 32.7 mmol) in dry THF (100 ml) at 0 °C was treated by small portions of sodium hydride (3.27 g 60% in mineral oil, 81.8 mmol). After stirring for 1 h at room temperature methyl iodide (14.42 g, 0.1 mol) was added dropwise. After stirring overnight at room temperature the THF was evaporated and the residue taken up in dichloromethane (60 ml) and the solution was extracted with brine (50 ml) at 0 °C. The aqueous layer was washed with dichloromethane 3 times and the combined organic extracts were dried and evaporated to give the crude ether which was purified by chromatography to give *(*S,S*)* and *(*R,R*)* N-*benzyl*-trans-2,5-*bis(methoxymethyl)pyrrolidine* **185** as a colourless oil (5.4 g, 66%).

δ_H (200 MHz; $CDCl_3$) 1.60-1.77 and 1.87-2.08 (2×m, CH_2CH_2), 3.16-3.39 (m, 2× NCH and 2×CH_2OMe), 3.27 (s, 2×OMe), 3.88 and 3.99 (ABq, J_{AB}=14.3 Hz, $PhCH_2$) and 7.16-7.39 (m, ArH).

Racemic (±)-*trans*-2,5-bis(methoxymethyl)pyrrolidinium acetate 186

A mixture of the ether **185** (5.3 g, 22 mmol in ethanol 960 ml) and acetic acid (2.5 ml, 42.6 mmol) and palladium on carbon (10% wt, 1 g) was hydrogenated at room temperature under 70 psi hydrogen pressure for 22 h, although most of the gas uptake occurred in the first 5 min. The catalyst was removed by filtration through Celite and was washed with ethanol. The solvent was removed to leave (±)-trans-2,5-*bis (methoxymethyl)pyrrolidinium acetate* **186** (4.86 g, 95.9%) as an oil.

δ_H (200 MHz; $CDCl_3$) 1.68-1.93 and 2.0-2.15 (2×m, CH_2CH_2), 2.00 (s, COMe), 3.36 (s, 2×OMe), 3.56-3.58 (m, CH_2OMe), 3.80 (m, 2×NCH) and 10.79 (brs, NH_2).

Racemic (±)-2,5-*trans*-bis(methoxymethyl)pyrrolidine 190

The acetate **186** was converted into the free amine **190** by the addition of sodium hydrogen carbonate followed by extraction into an organic solvent. The acetate form however, was suitable for further transformations.

δ_H (200 MHz; $CDCl_3$) 1.35-1.53 and 1.79-1.98 (2×m, CH_2CH_2), 2.60 (s, NH), 3.0-3.33 (m, CH_2OMe), 3.36 (s, CH_2OMe) and 3.38-3.43 (m, NCH).

5.3.2 Preparation of the diethyl amino Bunte salt 188

Chloroacetyl chloride (2.19 g, 19.36 mmol) was added slowly to diethylamine (1.42 g, 19.36 mmol) in dichloromethane (25 ml) with cooling. After stirring for 1 h the mixture was washed with water and HCl then dried and evaporated to give the chloroacetamide **187** as a yellow oil (1.44 g, 50%).

δ_H (200 MHz; $CDCl_3$) 1.15 and 1.25 (2×t, J=7.1Hz, Me),3.39 and 3.40 (2×q, J=7.1Hz, CH_2Me) and 4.10 (s, CH_2).

Sodium thiosulfate pentahydrate (1.66 g, 6.68 mmol) was dissolved in ethanol-water (1:1, 50 ml) and the amide **187** (1.0 g, 6.68 mmol) was added. The mixture was heated at reflux for 2 min and then allowed to cool. Removal of the solvent left a gummy residue which was extracted with boiling ethanol, to remove the Bunte salt and leave the sodium chloride in solution. Evaporation of the ethanol extract gave the Bunte salt **188** as a sticky gum.

δ_H (200 MHz; $CDCl_3$) 1.09 (t, J=7.1Hz, Me), 3.71 (q, J=7.1Hz, CH_2Me) and 4.03 (brs, CH_2).

5.3.3 Treatment of the diethylamino Bunte salt 188 with triethylamine and trapping the thioaldehyde with various dienes

3-*endo* and 3-*exo* diethylamido 2-thiabicyclo[2.2.1]hept-5-ene 192 - trapping with cyclopentadiene

Triethylamine (0.12 g, 1.2 mmol) was added to the Bunte salt **188** (0.25 g, 1.0 mmol) in methanol (5 ml) containing calcium chloride dihydrate (0.29g, 2.0 mmol) and cyclopentadiene (0.40 g, 5.0 mmol) with stirring at room temperature. After 3 h dilute HCl was added and the mixture extracted twice with chloroform. The organic extracts were washed with HCl, NaOH and water then dried and evaporated to leave a yellow oil which contained a mixture of isomers, *endo* : *exo* = 2.8:1. Purification by chromatography (hexane-ethyl acetate, 1:1) gave 3-endo *and* 3-exo *diethylamido* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene* **192** as a colourless oil (0.16 g, 76%). They were not separated by chromatography.

Endo isomer **192a** - δ_H (200 MHz; $CDCl_3$) 1.08 and 1.21 (2×t, *J*=7.1Hz, Me), 1.60-1.74 (m, 7-H), 3.32 (q, *J*=7.1Hz, CH_2Me), 3.68 (brs, 4-H), 4.05 (brs, 1-H), 4.41 (d, *J*=3.43Hz, 3-H), 6.27 (m, 5-H) and 6.42 (m, 6-H).

Exo isomer **192b** - δ_H (200 MHz; $CDCl_3$) 1.14 and 1.18 (2×t, *J*=7.1Hz, Me), 1.67-1.72 (m, 7-H), 2.06 (d, *J*=9.37Hz, 7-H), 3.34 (q, CH_2Me), 3.51 (m, 4-H), 4.13 (brs, 1-H), 6.00 (m, 5-H) and 6.26 (m, 6-H).

3-*endo* and 3-*exo* diethylamido -2-thiabicyclo[2.2.2]oct-5-ene 193 - trapping with cyclohexadiene

Triethylamine (0.12 g, 1.2 mmol) was added to the Bunte salt **188** (0.25 g, 1 mmol) in chloroform-methanol (5 ml:0.5 ml) containing calcium chloride dihydrate (0.29 g, 2 mmol) and cyclohexadiene (0.40 g, 5 mmol) with stirring at room temperature. The mixture slowly turned yellow and after stirring overnight worked up as before to give an orange oil which was purified by chromatography (hexane-ethyl acetate, 1:1) to give a pale yellow oil (0.10 g, 44%) which contained almost entirely 3-endo *diethylamido-2-thiabicyclo*[2.2.2]*oct*-5-*ene* **193a**.

Endo adduct **193a**- δ_H (200 MHz; $CDCl_3$) 1.07 and 1.19 (2×t, *J*=7.1Hz, Me), 1.45-1.56, 1.64-1.81 and 2.04-2.17 (3×m, CH_2CH_2), 3.28 (q, *J*=7Hz, CH_2Me), 3.40-3.54 (m, 1-H and 4-H), 4.07 (d, *J*=2.4Hz, 3-H) and 6.53 and 6.54 (2×q, 5-H and 6-H).

5.3.4 Preparation of (±)-2,5-*trans*-bis(methoxymethyl)pyrrolidine Bunte salt 191

Triethylamine (0.20 g, 2 mmol) was added to a solution of the acetate **186** (0.22 g, 1 mmol) in dichloromethane (25 ml). The mixture was cooled (-20 °C) and chloroacetyl chloride (0.11 g, 1 mmol) was added slowly with stirring. After 1 h the mixture was washed with water to remove salt. The organic layer was dried and evaporated to leave an orange oil which was chromatographed (hexane-ethyl acetate, 1:1) to give the chloroacetamide **189** as a pale yellow oil (0.22 g, 95%).

δ_H (200 MHz; $CDCl_3$) 1.72-1.80 and 1.94-2.26 (2×m, CH_2CH_2), 3.33 (s, OMe), 3.44-3.62 (m, NCH) and 4.11-4.33 (ABq, J_{AB}=12.4Hz, $COCH_2$).

The amide **189** (0.81 g, 3.45 mmol) and sodium thiosulfate pentahydrate (0.86 g, 3.45 mmol) were heated in ethanol-water (20 ml, 1:1), until refluxing for 5 min. The mixture was evaporated to dryness and the residue extracted with boiling ethanol. Evaporation of the ethanol gave (±)-2,5-trans-*bis(methoxymethyl)pyrrolidine Bunte salt* **191** as a sticky pale yellow gum (0.98 g, 82%).

δ_H (200 MHz; $CDCl_3$) 1.78-2.20 (m, CH_2CH_2), 3.34 (s, OMe), 3.60-3.75 (m, CH_2OMe), 3.89 (brs), 4.06 (brs,) and 4.14-4.25 (m).

5.3.5 Treatment of the 2,5-*trans*-bis(methoxymethyl)pyrrolidine Bunte salt 191 with triethylamine and trapping the thioaldehydes with various dienes

3-*endo* and 3-*exo*-2,5-*trans*-bis(methoxymethyl)-α-oxo-pyrrolidine-2-thiabicyclo[2.2.1] hept-5-ene 195 -Trapping with cyclopentadiene

Triethylamine (0.07 g, 0.72 mmol) was added to the Bunte salt **191** (0.24 g, 0.72 mmol) in methanol (4 ml) containing calcium chloride dihydrate (0.21 g, 1.44 mmol) and cyclopentadiene (0.24 g, 3.58 mmol) with stirring at room temperature. After 3 h HCl was added and the mixture extracted twice with chloroform. The

chloroform extracts were washed with NaOH, HCl and water then dried and evaporated to leave a yellow oil which was purified by chromatography (hexane-ethyl acetate, 1:1) to give *3*-endo and 3-exo-2,5-trans-*bis(methoxymethyl)*-α-*oxo-pyrrolidine*-2-*thiabicyclo*[2.2.1] *hept*-5-*ene* **195** as a colourless oil (0.15 g, 73%) containing a mixture of 4 racemic diastereomers. Further careful chromatography allowed the *endo* and *exo* isomers to be separated. The major *endo* diastereomer was isolated alone but the major *exo* diastereomer contained the minor *endo* and *exo* diastereomers.

The *endo*:*exo* ratio was 2.4:1. The d.e. value of the *endo* adducts was 91% while that of the *exo* adducts was 89%.

Major *endo* adduct

Found : M^+ 297.1396. $C_{15}H_{23}NO_3S$ requires *M*, 297.1398;

ν_{max} (liq. film)/cm^{-1} 2930 and 1644;

δ_H (200 MHz; $CDCl_3$) 1.65 (brs, 7-H_2), 1.88-1.99 and 2.06-2.25 (2×m, CH_2CH_2), 3.33 (s, OMe), 3.36 (s, OMe), 3.43-3.46 (m, CH_2OMe), 3.61 (brs, 4H), 4.12 (brs, 1H), 4.17-4.30 (m, NCH), 4.67 (d, *J*=3.58Hz, 3H), 5.81-5.83 (ABq, J_{AB}=3.1Hz, 5H) and 6.50-6.53 (ABq, J_{AB}=2.94Hz, 6H);

δ_C(50.3 MHz; $CDCl_3$) 25.2 and 27.6 (CH_2), 49.9 and 51.2 (C4 and C1), 51.9 (C7), 53.5 (C3), 57.2 and 58.0 (NCH), 58.8 and 59.1 (OMe), 71.5 and 74.3 (CH_2OMe), 130.4 and 137.2 (C5 and C6) and 169.8 (CO).

Major *exo* adduct

δ_H (200 MHz; $CDCl_3$) 1.64 (dt, *J*=9.23, 1.97 Hz, 7-H), 1.77-2.23 (m, CH_2CH_2), 2.42 (d, *J*=9.24Hz, 7-H), 3.31 (s, OMe), 3.35 (s, OMe), 3.44 (s, 3H), 3.48-3.62 (m, CH_2OMe), 4.04-4.14 (m, NCH), 4.18 (brs, CH), 4.69 (m, CH), 5.99 (dd, *J*=6.2 and 3.2 Hz, 5-H) and 6.41 (dd, *J*-5.4, 2.8 Hz, 6H).

δ_C (50.3 MHz; $CDCl_3$) 25.3 and 27.5 ($2CH_2$), 48.7 (C4), 48.9 (C1), 50.6 (C7), 52.0 (C3), 57.7 and 58.3 (NCH), 59.0 and 59.1 (OMe), 71.7 and 74.0 (CH_2OMe), 133.4 and 138.7 (C5 and C6) and 172.5 (CO).

Minor *endo* adduct

δ_H (200 MHz; $CDCl_3$) 4.69 (d, *J*=3.4 Hz, 3H), 6.22 (dd, *J*=5.4, 3.0Hz, 5H) and 6.45 (dd, *J*=5.9, 3.0Hz, 6H).

δ_C (50.3 MHz; $CDCl_3$) 25.2 and 27.1 ($2CH_2$), 49.1 and 51.4 (C4 and C1), 51.7 (C7), 53.6 (C3), 57.0 (NCH), 59.3 (OMe), 70.7 and 74.9 (CH_2OMe), 134.1 and 136.3 (C5 and C6) and 170.1 (CO).

Minor *exo* adduct

δ_H (200 MHz; $CDCl_3$) 6.38 (dd, *J*=6, 2.75 Hz, 6H).

The signals were further separated by using different solvents.

Major *exo* adduct

δ_H (200 MHz; $CDCl_3$:benzeneD_6,1:1) 1.55 (dt, *J*=11.25, 2.06Hz, 7H), 1.76-2.1 (m, CH_2CH_2), 2.49 (d, *J*=9.23Hz), 3.15 (s, OMe), 3.26 (s, OMe), 3.32 (s, 3H), 3.95 (m, 4H), 4.25 (m, 1H), 5.78 (dd,), 6.25 (dd,).

δ_H (200 MHz; benzeneD_6) 1.51 (dt, *J*=9.0, 2.0Hz, 1H), 1.65-1.79 (m, CH_2CH_2), 2.02 (d, *J*=7.58Hz, 1H), 3.03 (s, OMe), 3.16 (s, OMe), 5.60 (dd, *J*=5.35, 3.2 Hz, 5H), 6.12 (dd, *J*=5.38, 2.79Hz, 6H).

Minor *endo* adduct

δ_H (200 MHz; benzeneD_6) 4.81 (d, *J*=3.3Hz, 3H), 6.26 (dd, *J*=5.34, 3.0Hz, 5H), 6.59 (dd, *J*= , 3.4Hz, 6H).

HPLC showed separation of the fraction containing the *exo* isomers and the minor *endo* isomer. 3 peaks were observed using a silica column at 8.85, 9.51 and

10.60 min (25 cm silica column, particle size 5 μ, flow rate 1.1 ml / min, solvent hexane-isopropanol, 9:1)

3-*endo* and 3-*exo*-2,5-*trans*-bis(methoxymethyl)α-oxo-pyrrolidine-2-thiabicyclo[2.2.2] oct-5-ene 196 - Treatment with cyclohexadiene

Triethylamine (0.12 g, 1.2 mmol) was added to the Bunte salt **191** (0.34 g, 1.0 mmol) in chloroform-methanol (5.5 ml, 10:1) containing partially dissolved calcium chloride dihydrate (0.29 g, 2.0 mmol) and cyclohexadiene (0.40 g, 5.0 mmol) with stirring at room temperature. A precipitate quickly began to form. After 3 h HCl was added and the mixture extracted twice with chloroform. The chloroform extracts were washed with NaOH and water then dried and evaporated to leave an orange oil (0.32 g) which contained a mixture of racemic diastereomers. Chromatography (hexane-ethyl acetate, 1:1) gave the major *endo* diastereomer *3*-endo-2,5-trans-*bis(methoxymethyl)α-oxo-pyrrolidine-2-thiabicyclo*[2.2.2]*oct-5-ene* **196a** as a white solid (0.15 g) m.p. 97-98 °C (hexane-ethyl acetate). A satisfactory X-Ray crystal structure was also obtained (Figure 1 and Tables 8 and 9). A yellow oil (0.03 g) was also obtained which contained the minor *endo* diastereomer **196b** along with the major *exo* diastereomer. The minor *exo* diastereomer was undetected.

The *endo*:*exo* ratio was 10.5:1 and the d.e. value of the *endo* adducts was 75%.

Major *endo* adduct **196a**

Found : M^+ 311.1559. $C_{16}H_{25}NO_3S$ requires *M*, 311.1555;

ν_{max} (KBr)/cm^{-1} 1630;

δ_H (200 MHz; $CDCl_3$) 1.42-1.51, 1.63-1.77 and 1.86-2.17 (3×m, 2×CH_2CH_2), 3.09 (m, 4H), 3.33 (s, OMe), 3.35 (s, OMe), 3.46 (m, OCH_2Me), 3.54 (m, 1H), 4.10 (m, NCH), 4.29 (d, *J*=2.4Hz, 3H), 6.19 (t, *J*=7.5Hz, 5H) and 6.67 (t, *J*=7.5Hz, 6H).

Minor *endo* adduct **196b**

δ_H (200 MHz; $CDCl_3$) 3.30 (s, OMe), 3.36 (s, OMe), 4.40 (d, *J*=2.27Hz, 3H), 6.47 (t, *J*=7.5Hz, 5H) and 6.60 (t, *J*=7.5Hz, 6H).

Major exo adduct

δ_H (200 MHz; $CDCl_3$) 3.30 (s, OMe), 3.33 (s, OMe), 6.38 (t, *J*=7.5Hz, 5H) and 6.60 (t, *J*=7.5Hz, 6H).

The diastereomers were seen more clearly by changing the solvent and running at higher frequency.

Minor *endo* adduct **196b**- δ_H (350 MHz; $CDCl_3$:benzeneD_6,1:1) 3.09 (s, OMe), 3.17 (s, OMe), 4.40 (d, *J*=1.29, 3H), 6.50 (t, *J*=3.5Hz, 5H) and 6.56 (t, *J*=3.5Hz, 6H).

Major *exo* adduct - δ_H (350 MHz; $CDCl_3$:benzeneD_6,1:1) 3.03 (s, OMe), 3.18 (s, OMe), 6.18 (t, 6H) and 6.40 (t, 7H).

The bond lengths and angles of **196a** were determined by X-ray structure analysis (Tables 8 and 9).

Table 8. Bond lengths of the major endo cyclohexadiene cycloadduct **196a**.

Bond	**Bond length [A]**
S(1) - C(5)	1.839(3)
S(1) - C(1)	1.835(2)
O(1) - C(8)	1.228(3)
O(2) - C(13)	1.410(3)
O(2) - C(14)	1.412(4)
O(3) - C(15)	1.404(3)
O(3) - C(16)	1.402(4)

N(1) -C(8)	1.354(3)
N(1) - C(12)	1.473(3)
N(1) - C(9)	1.486(3)
C(1) - C(8)	1.522(3)
C(1) - C(2)	1.550(3)
C(2) - C(3)	1.499(4)
C(2) - C(7)	1.539(3)
C(3) - C(4)	1.324(5)
C(4) - C(5)	1.471(5)
C(5) - C(6)	1.544(5)
C(6) - C(7)	1.535(4)
C(9) - C(13)	1.503(4)
C(9) - C(10)	1.536(30
C(10) - C(11)	1.517(4)
C(11) - C(12)	1.519(4)
C(12) - C(15)	1.522(3)

Table 9. Bond angles of the major *endo* cyclohexadiene cycloadduct **196a**.

angle	value[deg]
C(5) - S(1) - C(1)	97.03(11)
C(13) - O(2) - C(14)	112.3(2)
C(15) - O(3) - C(16)	111.8(3)
C(8) - N(1) - C(12)	118.9(2)
C(8) - N(1) - C(9)	128.8(2)
C(12) - N(1) - C(9)	112.1(2)
C(8) - C(1) - C(2)	112.1(2)

C(8) - C(1) - S(1)	109.85(14)
C(2) - C(1) - S(1)	109.22(14)
C(3) - C(2) - C(7)	108.9(2)
C(3) - C(2) - C(1)	111.8(2)
C(7) - C(2) - C(1)	107.8(2)
C(4) - C(3) - C(2)	115.3(3)
C(3) - C(4) - C(5)	115.5(3)
C(4) - C(5) - C(6)	110.5(3)
C(4) - C(5) - S(1)	108.7(2)
C(6) - C(5) - S(1)	107.9(2)
C(7) - C(6) - C(5)	108.9(2)
C(6) - C(7) - C(2)	111.4(2)
O(1) - C(8) - N(1)	120.7(2)
O(1) - C(8) - C(1)	121.1(2)
N(1) - C(8) - C(1)	118.1(2)
N(1) - C(9) - C(13)	114.9(2)
N(1) - C(9) - C(10)	103.0(2)
C(13) - C(9) - C(10)	111.7(2)
C(11) - C(10) - C(9)	105.1(2)
C(10) - C(11) - C(12)	103.8(2)
N(1) - C(12) - C(11)	103.2(2)
N(1) - C(12) - C(15)	109.7(2)
C(11) - C(12) - C(15)	112.7(2)
O(2) - C(13) - C(9)	110.7(2)
O(3) - C(15) - C(12)	107.6(2)

5.3.6 Attempted hydrolysis of the amide linkage

Treatment with sodium hydroxide

The diethyl cyclohexadiene amide cycloadduct **193** was stirred in ethanol-NaOH (1M) for 2 days. No change was observed by TLC so the mixture was refluxed for 4 h. TLC showed starting material to be disappearing. The mixture was then washed with dichloromethane then dried and evaporated to give some unreacted amide. The remaining aqueous portion was then acidified and extracted with ether. The ether extracts were dried and evaporated to give a pale yellow oil which appeared to be a thioaldehyde polymer presumably formed by the retro Diels-Alder reaction of the cycloadduct induced by the higher temperature of the attempted hydrolysis.

δ_H (200 MHz; $CDCl_3$) 1.21 and 1.27 (2×t, J=7.1Hz, Me), 3.46 and 3.64 (2×q, J=7.1Hz, CH_2Me) and 6.38 (brs, CH).

Treatment with potassium *tert*-butoxide

The amide **192** (0.11 g, 0.51 mmol) was dissolved in ether (5 ml) containing water (18.4 mg, 1.02 mmol). Potassium *tert*-butoxide (0.34 g, 3 mmol) was then added with vigorous stirring at room temperature. After stirring overnight TLC (hexane-ethyl acetate, 1:1) showed the amide had largely gone and there was a spot on the base line. The reaction mixture was cooled and water was added. The layers were separated and the aqueous, alkaline layer was evaporated to low volume. HCl (5M) was added slowly until the mixture was slightly acidic giving a slightly cloudy mixture which was extracted twice with ether. The ether extracts were dried and evaporated to give a brown oil (47 mg). The ^{1}H NMR spectrum of this oil did not resemble that of the acid, derived by hydrolysis, of the cycloadduct of ethyl thioxoacetate and cyclopentadiene.

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