# EXPLORATION OF THE REACTIVITY OF SULFUR YLIDES: NOVEL SYNTHESIS OF TETRAHYDROTHIOPHENES AND THIAZOLIDINES

**THESIS SUBMITTED TO**
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**FOR THE DEGREE OF**

**DOCTOR OF PHILOSOPHY**

**IN CHEMISTRY**
**UNDER THE FACULTY OF SCIENCE**

**BY**
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**OCTOBER 2004**

## DECLARATION

I hereby declare that the matter embodied in the thesis entitled **"Exploration of the Reactivity of Sulfur Ylides: Novel Synthesis of Tetrahydrothiophenes and Thiazolidines"** is the result of the investigations carried out by me at the Organic Chemistry Division of Regional Research Laboratory (CSIR), Trivandrum, under the supervision of **Dr. G. Vijay Nair** and the same has not been submitted elsewhere for a degree.

**Smitha M. Nair**

Trivandrum
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## CERTIFICATE

This is to certify that the work embodied in the thesis entitled " **Exploration of the Reactivity of Sulfur Ylides: Novel Synthesis of Tetrahydrothiophenes and Thiazolidines** " has been carried out by **Ms. Smitha M. Nair** under my supervision at the Organic Chemistry Division of the Regional Research Laboratory (CSIR), Trivandrum, and the same has not been submitted elsewhere for any other degree.

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**(Thesis Supervisor)**

Trivandrum
October 2004

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*Smitha M. Nair*

*Trivandrum*
*October 2004*

## CONTENTS

# PREFACE

Organosulfur compounds have received substantial attention in recent years due to their applications in the pharmaceutical industry. Of the various organosulfur compounds, sulfur ylides deserve special mention. Sulfonium and sulfoxonium ylides are now routinely employed in organic synthesis, especially in asymmetric synthesis. Sulfur heterocycles are of great importance as they are structural subunits of many bioactive compounds. In spite of the extensive studies on ylides, their utility in heterocyclic construction remains underexploited.

A systematic investigation of the reactivity of sulfur ylides leading to the synthesis of heterocyclic compounds has been undertaken. The results obtained are presented in the thesis entitled "**Exploration of the Reactivity of Sulfur Ylides: Novel Synthesis of Tetrahydrothiophenes and Thiazolidines.**" The thesis is divided into four chapters.

An introduction to organosulfur chemistry as well as a brief review on sulfur ylides is presented in chapter 1.

The second chapter summarizes our results on the reactions of thietanes with electrophilic carbenes. General information on the experimental procedure is given in this chapter.

The third chapter deals with a facile, completely diastereoselective synthesis of thiazolidines by the reaction of nitrene with thietanes.

The fourth chapter describes a simple synthesis of spirocyclic systems by the 1,3-dipolar cycloaddition of thioformaldehyde S-methylide to activated carbon-carbon double bonds.

It may be noted that each chapter of the thesis is presented as a separate unit, and therefore, figures, schemes and structures are numbered accordingly. Relevant references are given at the end of each chapter.

A summary of the work is given at the end of the thesis.

# ABBREVIATIONS

| | |
|---|---|
| Ac | : acetyl |
| acac | : acetyl acetonate |
| d | : doublet |
| dd | : doublet of doublet |
| DMAD | : dimethyl acetylenedicarboxylate |
| Et | : ethyl |
| ee | : enantiomeric excess |
| g | : gram |
| HMPA | : hexamethylphosphoramide |
| HRMS | : high-resolution mass spectrum |
| Hz | : hertz |
| IR | : infrared |
| *J* | : coupling constant |
| m | : multiplet |
| Me | : methyl |
| mg | : milligram |
| mL | : milliliter |
| mp | : melting point |
| NMR | : nuclear magnetic resonance |
| nOe | : nuclear Overhauser effect |
| Ns | : 2-nitrophenylsulfonyl |
| *o* | : ortho |
| *p* | : para |
| Ph | : phenyl |
| Pr | : n-propyl |
| s | : singlet |
| t | : triplet |
| Tf | : triflyl (trifluoromethanesulfonyl) |
| Ts | : *p*-toluene sulfonyl |
| *tert* | : tertiary |
| $^{t}$Bu | : tertiary butyl |

# CHAPTER 1

# An Introduction to Organosulfur Chemistry and A Brief Review on Sulfur Ylides

## 1.1 Introduction

The thesis focuses on the reactivity of sulfur ylides leading to the construction of substituted tetrahydrothiophenes and thiazolidines. In order to put things in perspective, an introduction to organosulfur chemistry and a brief survey on the chemistry of various sulfur ylides and their rearrangements are given in the following sections.

Sulfur is a versatile element, showing formal oxidation states ranging from -2 to +6, having wide and varied chemistry. It forms weaker bonds to carbon and hydrogen compared to oxygen. Sulfur is less electronegative than oxygen, but possesses electronegativity comparable to that of carbon. It behaves like an electrophile as well as a nucleophile. This makes sulfur compounds versatile in organic synthesis. A large number of sulfur containing compounds have found wide use as therapeutic agents (Figure 1).

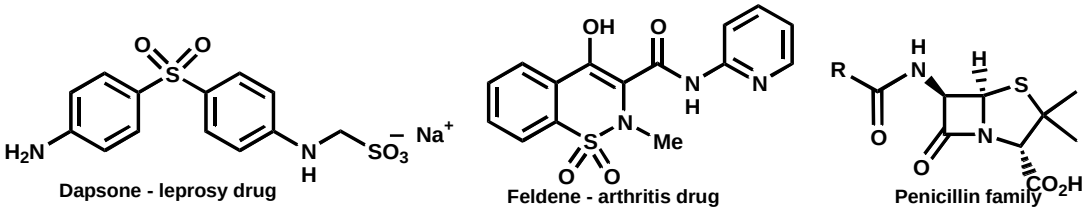



**Figure 1**

Organosulfur compounds can be broadly classified into sulfides, sulfoxides, sulfones and ylides depending on the number of attached atoms on sulfur. The following section comprises of selected examples from each of the above mentioned categories, with special emphasis on sulfur ylides.

## 1.2 Divalent Sulfur Compounds

Thiols, sulfides and thioacetals are classes of compounds belonging to this category (Figure 2).

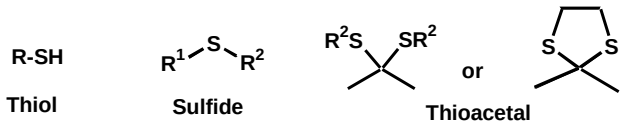
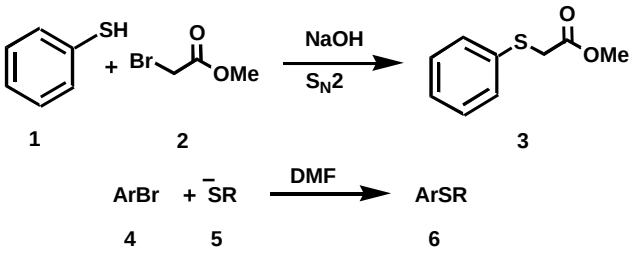



**Figure 2**

### 1.2.1 Thiols

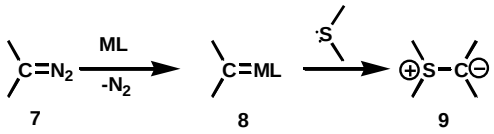
Thiols are divalent sulfur compounds, more acidic than alcohols due to weak sulfur-hydrogen bond (bond strength 364 KJ/mol). Nucleophilic displacement of alkyl halides with reagents such as $H_2S$ or $Na_2S_2O_3$ is a convenient approach for the preparation of aliphatic thiols, whereas the reduction of aryl sulfonyl halides is often the method of choice for the preparation of aromatic thiols. Thiols and their anions (thiolates) are soft nucleophiles, thus thiolates displace halides from alkyl- or aryl halides to form sulfides (Scheme 1).[1,2]




**Scheme 1**

### 1.2.2 Sulfides

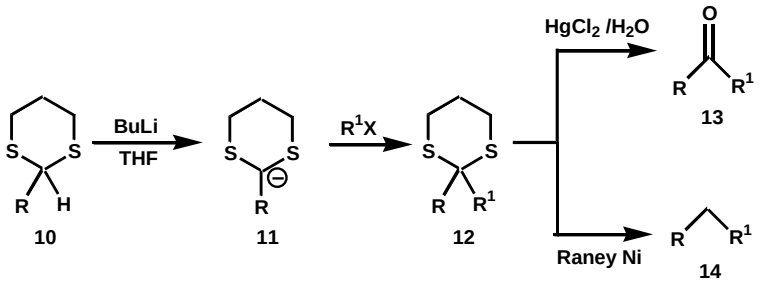
Sulfides are good nucleophiles. They readily form sulfonium salts with alkyl halides, which in turn are precursors to sulfonium ylides. Sulfides react with carbenes to form sulfonium ylides (Scheme 2). Sulfides easily undergo oxidation to sulfoxides and sulfones depending on the reaction conditions and also on the stoichiometry of the oxidant used.




**Scheme 2**

### 1.2.3 Thioacetals

Thioacetals are divalent sulfur compounds. Thiols react with aldehydes or ketones to form thioacetals, which serve as protecting groups for aldehydes and ketones. Dithianes can be prepared by the treatment of aldehydes with dithiols. The two sulfur atoms in dithianes make the adjacent proton much more acidic than that of sulfides. Thus, dithianes can be lithiated $\alpha$ to sulfur using BuLi in THF. The lithiated species **11** can be treated with wide variety of electrophiles to afford substituted aldehydes or ketones **13** on deprotection (Scheme 3).[3] Thus, the polarity at the electrophilic carbon of the aldehyde is reversed (umpolung) making it an acyl anion equivalent. Another useful application of the reaction is the desulfuration of dithianes with Raney nickel, thus allowing the transformation of aldehydes to homologated hydrocarbons **14** (Scheme 3).[4]




**Scheme 3**

## 1.3 Tricoordinated Sulfur Compounds

Sulfonium salts are tricoordinated electrophilic sulfur compounds. Sulfoxides are tricoordinated tetravalent sulfur componds with one lone pair on sulfur (Figure 3).

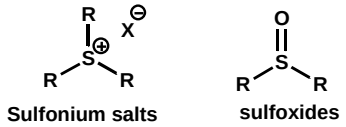
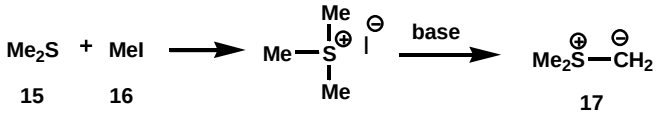



**Figure 3**

### 1.3.1 Sulfonium Salts

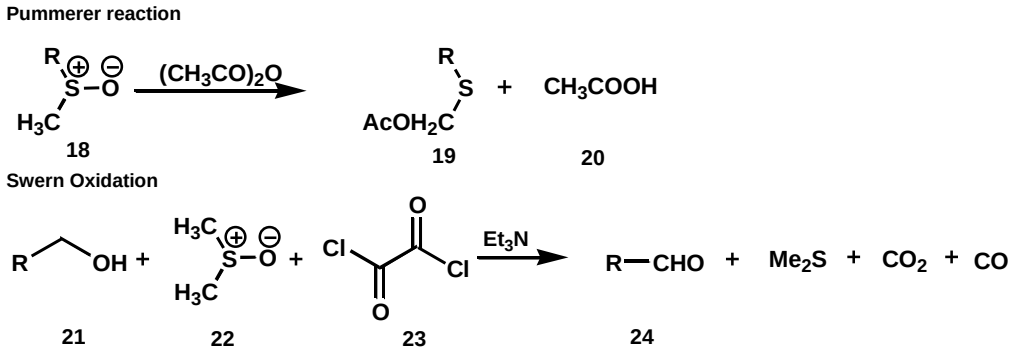
Sulfonium salts are obtained by the alkylation of sulfides. Deprotonation of sulfonium salts yields sulfonium ylides (Scheme 4).[5] These are important intermediates in organic synthesis. Sulfonium ylides react with aldehydes to form epoxides, whereas phosphorus ylides form alkenes. The reactivity profiles of the ylides will be discussed later in this chapter.




**Scheme 4**

### 1.3.2 Sulfoxides

These tricoordinated compounds possess pyramidal structure and can be prepared by the oxidation of sulfides. Sulfoxides on *syn*-*β*-elimination yield alkenes. They are nucleophilic at the oxygen atom and this feature is manifested in a number of reactions as illustrated by the Pummerer reaction[6] and Swern oxidation[7] (Scheme 5).




**Scheme 5**

## 1.4 Tetracoordinated Sulfur Compounds

In tetracoordinated sulfur compounds (Sulfones) all the six valencies of sulfur atom are used for bonding (Figure 4).

**Figure 4**

### 1.4.1 Sulfones

Sulfones are prepared by the oxidation of sulfides or sulfoxides. The sulfonyl group stabilizes anion next to sulfur atom (Figure 5). Thus $\alpha$-metallated sulfones can be prepared by deprotonation using strong bases like butyllithium. These are synthetically useful reagents, known to react with a variety of electrophiles. Another synthetic advantage of sulfones is that the sulfonyl moiety can be reductively removed by metals. The best example of this process is Julia olefination. This is an elimination reaction in which the sulfonyl group in the starting material is lost to form double bond. The reaction proceeds through stepwise mechanism and is regioselective. This reaction forms key step in the synthesis of many biological molecules *e.g.*: sphingosine (Scheme 6).[8]

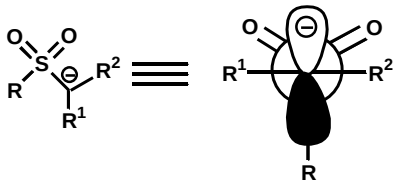
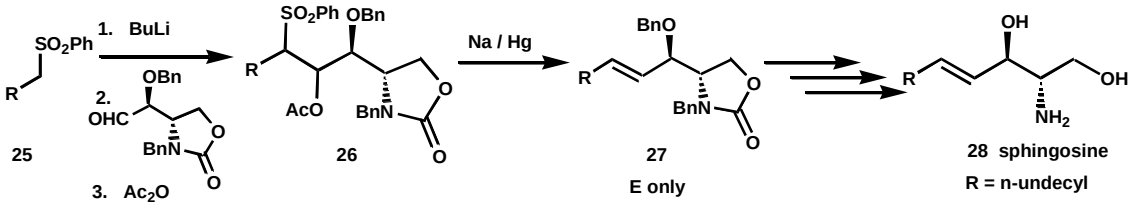


**Figure 5**




**Scheme 6**

## 1.5 Sulfur Yildes

Wittig's discovery of a powerful olefination method[9] involving the reaction of phosphonium ylides and carbonyl compounds evinced considerable interest in the chemistry of sulfur ylides.[10,11] In recent years, sulfur ylides, especially sulfonium and sulfoxonium ylides, have been widely used and accepted as varsatile synthons in organic synthesis.[12,13]

A sulfur ylide can be represented as a negatively charged carbon atom directly bound to a positively charged sulfur atom, or as a ylene as shown in Figure 6.[14] Sulfur ylides act as carbon nucleophiles, and the stability depends on their ability to delocalise the charge density. Thus an electron withdrawing group stabilizes the ylides.[15,16] Other than sulfonium and sulfoxonium ylides, aminosulfoxonium ylides, thiocarbonyl ylides and iminosulfuranes (Figure 7) are also known.[17]

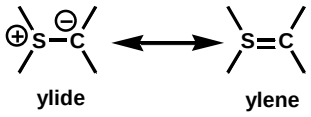



**Figure 6**

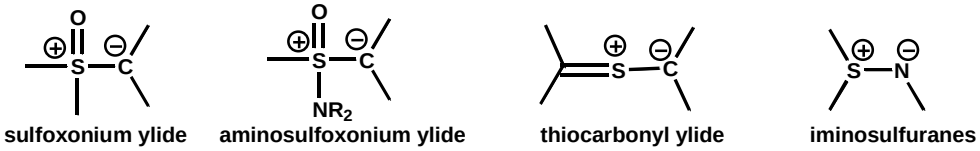
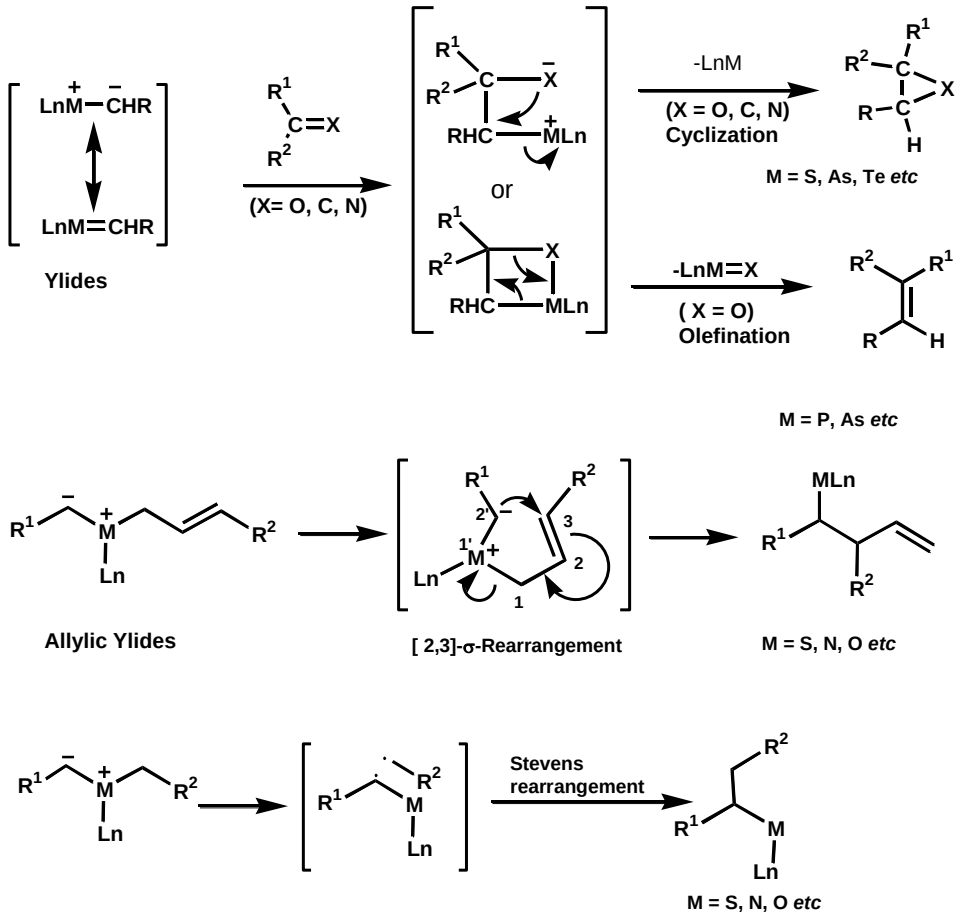



**Figure 7**

### 1.5.1 Sulfonium Ylides

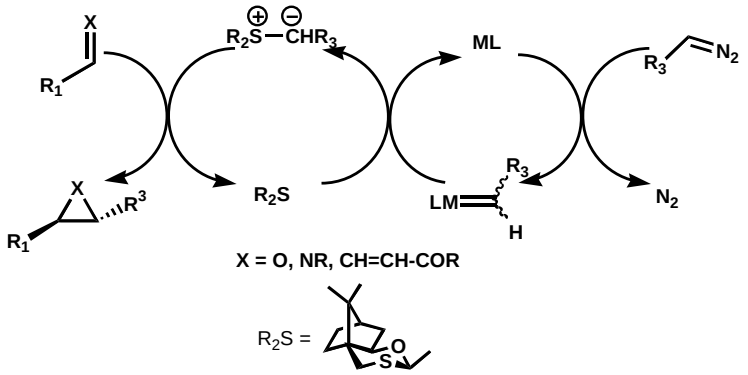
Sulfonium ylides are tricoordinated dipolar sulfur species, prepared by the deprotonation of sulfonium salts. The electrophilic addition of carbenoid species to divalent sulfur compounds is another widely accepted method for the generation of sulfonium ylides.[18] Ylides undergo mainly three types of reactions: olefination, cyclization and rearrangements (Stevens rearrangement, [2,3]-sigmatropic rearrangement), and these are illustrated in Scheme 7.




**Scheme 7**

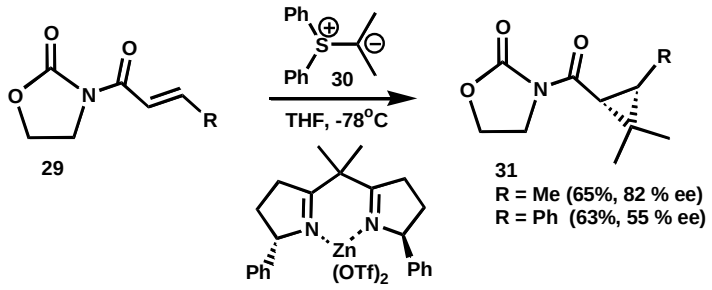
The reactions of sulfonium ylides with C=X functionality (X = O, C or N) have gained wide acceptance in organic synthesis. The nucleophilic addition of the ylides followed by 1,3-elimination results in the formation of cyclopropanes, epoxides and aziridines depending on the X group. Although attempts to use chiral sulfonium ylides[19] for asymmetric epoxidation started as early as 1973, the first successful effort was reported much later, in 1989.[20] Subsequently there has been considerable interest in sulfur ylides, owing to their successful use in asymmetric synthesis.[21-23] Aggarwal and co-workers have reported that optically pure sulfonium ylides react with aldehydes,[24]

imines[25] and $\alpha,\beta$-unsaturated carbonyl[26] compounds to afford enantio-enriched epoxides, aziridines and cyclopropanes respectively (Scheme 8).



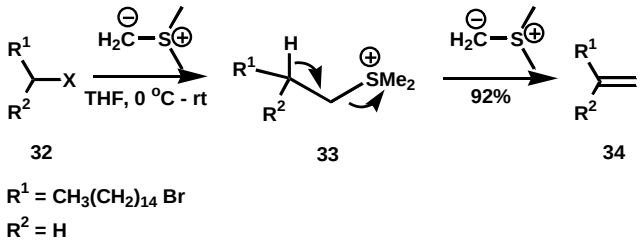

**Scheme 8**

Recently, the first chiral Lewis acid-mediated asymmetric cyclopropanation of a Michael acceptor **29** with sulfonium ylide **30** has been reported (Scheme 9).[27]



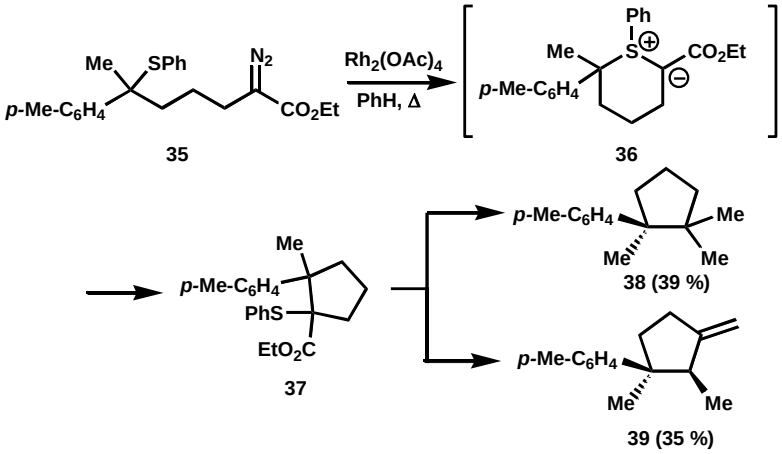

**Scheme 9**

In addition to the cyclization reactions described above, sulfonium ylides are useful reagents for a number of other transformations. Alcaraz and co-workers have reported the one-pot transformation of halides and mesylates to terminal alkenes using excess of sulfonium ylides (Scheme 10).[28]



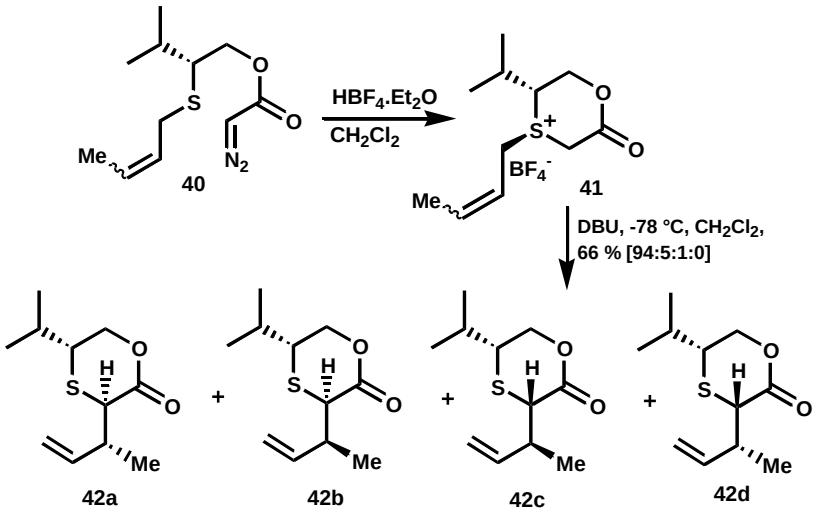

**Scheme 10**

Sulfur ylides, particularly cyclic sulfur ylides, have been used in the synthesis of carbo-[29] and heterocyclic compounds.[30] The generation of a cyclic ylide **36** and its subsequent rearrangement to the cyclopentane **37**, key compound in the synthesis of sesquiterpenes (±)-cuparene **38** and (±)-laurene **39,** has been reported (Scheme 11).[31,32] Kametani and co-workers have reported the synthesis of pyrrolizidine alkaloids applying analogous strategy.[33]



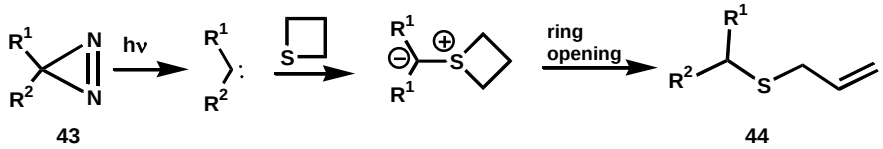

**Scheme 11**

[2,3]-Sigmatropic rearrangements of allylic and benzylic sulfur ylides have been used in the synthesis of cyclic compounds. The use of chiral allylic sulfides in [2,3]-sigmatropic rearrangements resulted in the enantioselective synthesis of cyclic compounds. The synthesis of optically active thioxanones was achieved using the optically pure cyclic sulfur ylide **41** (Scheme 12).[34]



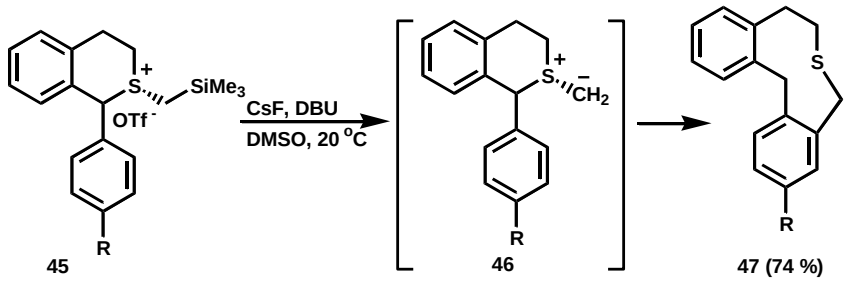

**Scheme 12**

Recently, Romashin *et al*. have reported the reaction of adamantylidene, arylchloro- and phenylcarbenes with trimethylene sulfide and other sulfides generating sulfur ylide intermediates. These ylides, either by H-migration or [2,3]-sigmatropic rearrangement yield sulfides. A representative example is shown below (Scheme 13).[35]



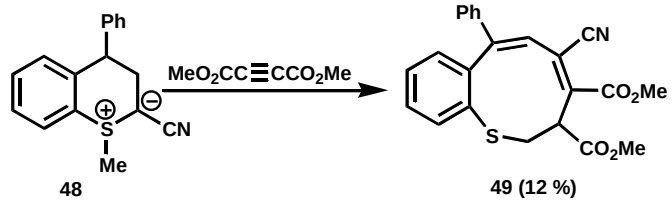

**Scheme 13**

Sulfonium ylides are known to undergo Sommlet-Hauser rearrangement. Thus aryl substituted ylide **46** rearranged to afford 2,5,8,9-tetrahydrodibenzothionine **47** (Scheme 14).[36]




**Scheme 14**

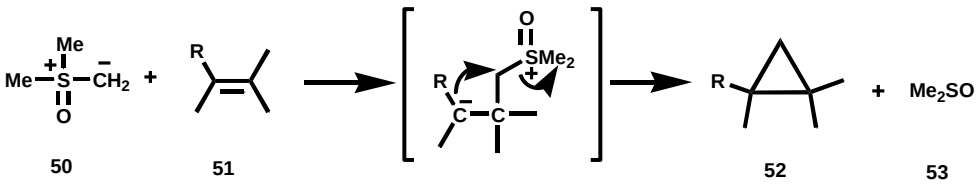
Ring expansion reactions of sulfonium ylides are also well studied; thus the reaction of 2-cyano-*α*-thiochromene ylide **48** with dimethyl acetylenedicarboxylate afforded the ring expansion product **49** in low yield (Scheme 15).[37]




**Scheme 15**

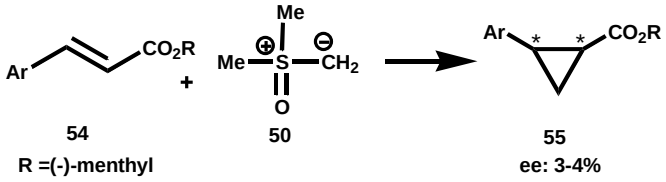
### 1.5.2 Sulfoxonium Ylides

Sulfoxonium ylides were used even before sulfonium ylides in cyclopropanation reactions. Dimethyloxosulfonium methylide was widely used to transfer methylene to activated double bonds.[38-41] The nucleophilic attack of the ylide generates a betaine intermediate; elimination of the sulfoxide from the betaine occurs to afford the cyclopropane (Scheme 16).



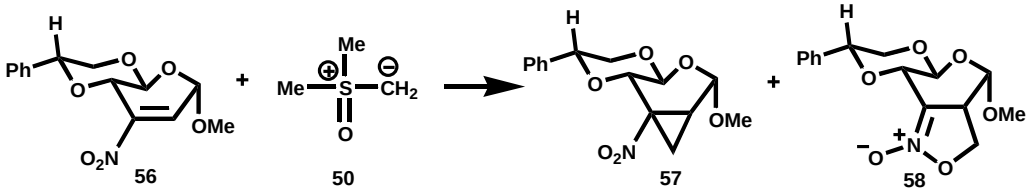

**Scheme 16**

The exploration of asymmetric cyclopropanation reaction using chiral ylide or chiral C=X compounds began in the early 1960s. Nozaki has reported the chiral auxiliary-induced asymmetric cyclopropanation of (-)-menthol derived *α,β*-unsaturated ester **54** with dimethylsulfoxonium methylide. The cyclopropane derivative **55** was obtained in low ee (Scheme 17).[42]



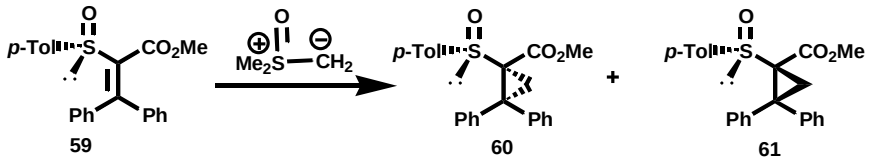

**Scheme 17**

Later, Sakakibara and co-workers have reported the reaction of unsaturated nitro sugar **56** with dimethylsulfoxonium methylide. Both cyclopropane and isoxazoline N-oxide were obtained in this reaction (Scheme 18).[43,44]



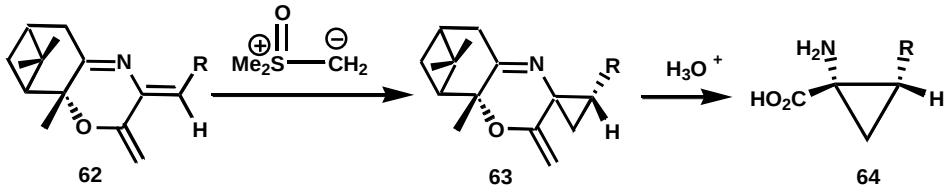

**Scheme 18**

Hamdouchi has reported the first cyclopropanation reaction of chiral vinyl sulfoxide **59** with dimethylsulfoxonium methylide (Scheme 19).[45]



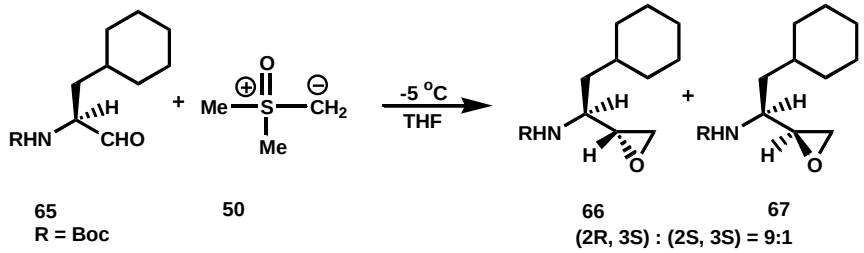

**Scheme 19**

Reaction of (1R,2R,5R)-2-hydroxypinan-3-one based dehydroamino acid derivatives with dimethylsulfoxonium methylide afforded the cyclopropane derivatives as single diastereomers in 45-95% yields (Scheme 20).[46] The cyclopropane derivatives on acid hydrolysis afforded 2-alkyl-1-aminocyclopropane-1-carboxylic acids **64**, a class of biologically important amino acids.




**Scheme 20**

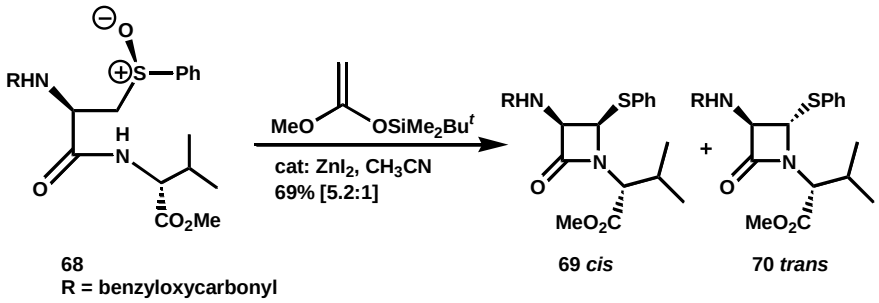
Sulfoxonium ylides are used in asymmetric epoxidation.[47,48] Protected cyclohexyl-L-alaninals on reaction with dimethyl sulfoxonium methylide afforded epoxyamines (Scheme 21)[49] with high stereoselectivity compared to sulfonium ylides.




**Scheme 21**

Asymmetric Pummerer rearrangement of chiral sulfoxides is known in the literature. The reaction proceeds through an ylide–like intermediate, resulting in the

transfer of chirality from the sulfur center to the carbon center. A representative example is given in Scheme 22.[50]



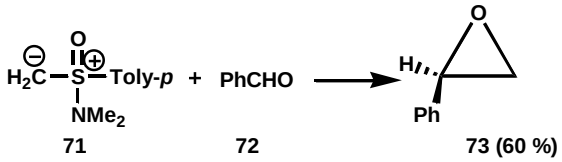

**68**
**R = benzyloxycarbonyl**

**69 *cis*** **70 *trans***

**Scheme 22**

### 1.5.3 Aminosulfoxonium Ylides

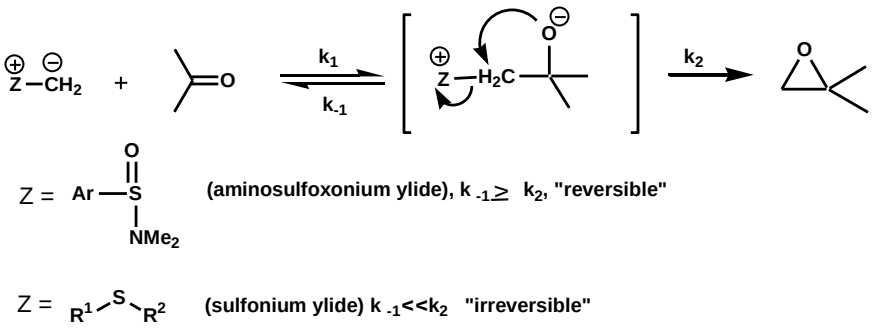
Aminosulfoxonium ylides are dipolar species in which one of the substituents on a sulfonium ylide is replaced by an amino group ($NR_2$). These are also synthetically important reagents for cyclopropanation and epoxidation reactions. Johnson was the first to prepare enantiomerically pure aminosulfoxonium ylide. Aminosulfoxonium ylide **72** when treated with benzaldehyde afforded epoxide **73** in 60% yield, but with low ee (Scheme 23).[51,52] The reversible betaine intermediates formed in the case of aminosulfoxonium ylides were believed to be responsible for the low enantioselectivity (Scheme 24).




**71** **72** **73 (60 %)**

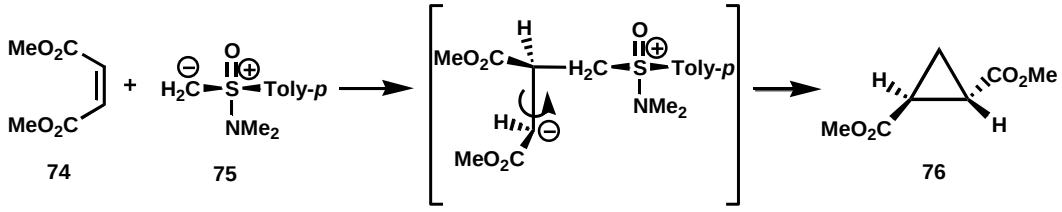
**R, ee : 20%**

**Scheme 23**



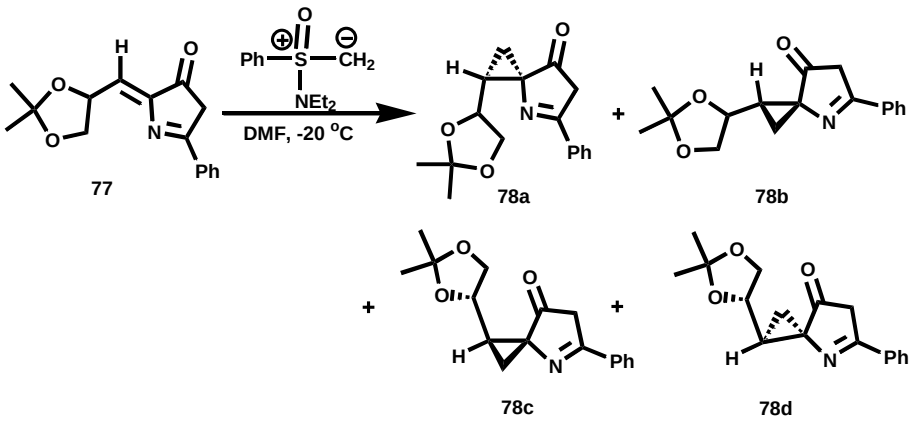

**Scheme 24**

Asymmetric methylene transfer from chiral aminosulfoxonium ylides to $\alpha,\beta$-unsaturated ketones, esters and unsaturated diesters has been reported. Optically active disubstituted cyclopropanes were obtained in moderate yields and up to 35% ee in these reactions. From dimethyl fumarate and dimethyl maleate, the same optically active cyclopropanes were obtained. These results provided evidence for a betaine intermediate in cyclopropanation reaction. The intermediate in the case of dimethyl maleate was believed to have sufficient lifetime to rotate around a single bond, resulting in change in conformation (Scheme 25).[52]



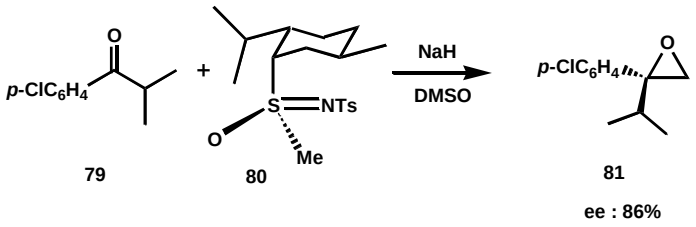

**Scheme 25**

Asymmetric cyclopropanation reaction of chiral oxazolone with aminosulfoxonium ylide has been reported. The reaction afforded mixture of *cis* and *trans* cyclopropanes (Scheme 26).[53]




**Scheme 26**

Although Johnson and co-workers have reported that aminosulfoxonium ylides could be used in asymmetric synthesis, their poor outcome in terms of ee paved way for chiral sulfoximine anions. The first asymmetric methylene transfer from chiral sulfoximine anions to carbon-oxygen double bonds dates back to 1973. Twenty years later Soman and co-workers have reported the reactions of (-)-menthol and (+)-camphor-derived sulfoximines with aldehydes. 2,2-Disubstituted oxiranes were obtained with high enantioselectivity. A representative example is given below (Scheme 27).[54,55] The results point out that the chirality on the carbon substituent is an important factor in determining the outcome of the epoxidation process.




**Scheme 27**

Cyclopropanation reactions of chalcones by chiral sulfoximine anions affording optically active cyclopropanes with high enantioselection have also been reported.[56]

### 1.5.4 Thiocarbonyl Ylides

Thiocarbonyl ylides are sulfur centered 1,3-dipoles in which sulfur atom is flanked by two $sp^2$ carbon atoms. Replacement of one of the carbons by heteroatoms such as $NR_2$, oxygen or sulfur leads to thiocarbonyl S-imides, S-oxides (sulfines) and S-sulfides (thiosulfines) shown in Figure 8. Important contributions to this field were made by Huisgen *et al*.[57] The first reaction involving a thiocarbonyl ylide was reported early in the last century by Staudinger and co-workers who discovered the formation of thiiranes and 1,3-dithiolanes from diazomethane and thiocarbonyl compounds.[58] During the 1960s Schönberg and co-workers also reported similar studies.[59]

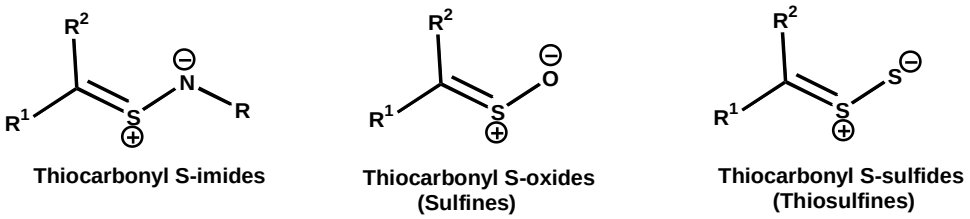
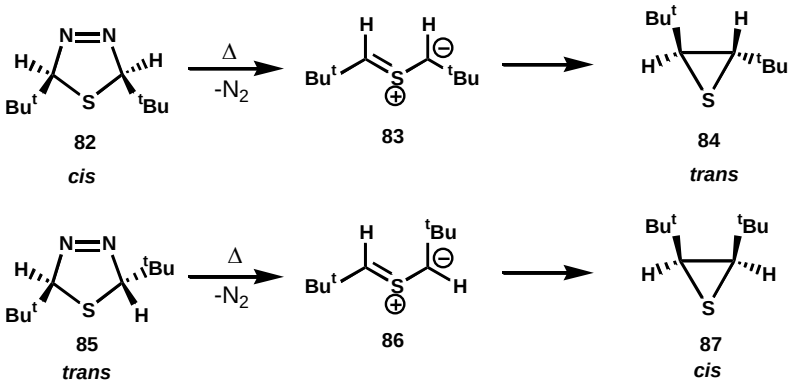



**Figure 8**

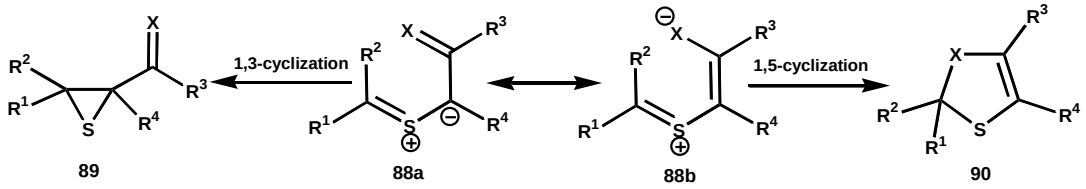
Kellogg and co-workers have reported thiocarbonyl ylides as reactive intermediates[60] which either undergo electrocyclization to give thiiranes or react with suitable dipolarophiles to produce sulfur containing five membered heterocylces. The thermal extrustion of nitrogen from *cis* and *trans* thiadiazoles generates thiocarbonyl ylide with retained configuration. A subsequent thermal conrotatory ring closure yielded *trans* and *cis* thiiranes (Scheme 28), in accordance with the Woodward-Hoffmann rules.




**Scheme 28**

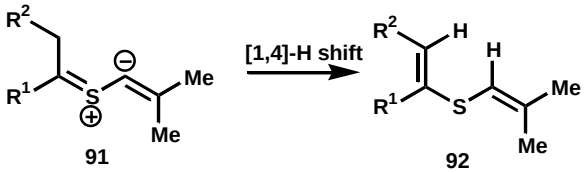
### 1.5.4.1 Chemical Behavior

Thiocarbonyl ylides, which are not push-pull stabilized, in the absence of intercepting reagents, undergo electrocyclic ring closure to give thiiranes **89**. In the case of the ylides with additional π-functionality, 1,5-cyclization is the preferred pathway (Scheme 29).[61-64]



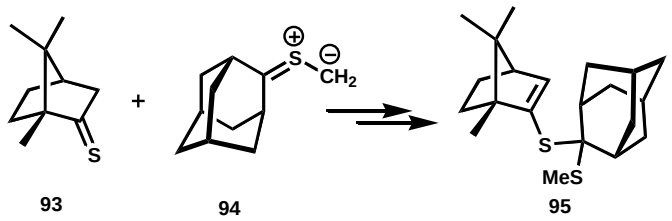

**Scheme 29**

Stang *et al*. have reported the 1,4-hydrogen shift of aliphatic thiocarbonyl ylides **91** to afford vinyl thioethers **92** (Scheme 30).[65]




**Scheme 30**

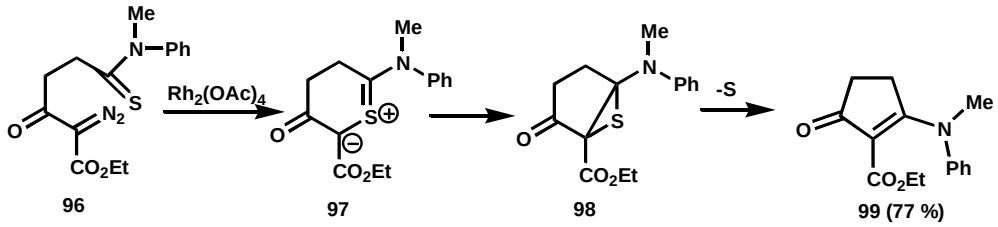
Acidic compounds like thiols and thiophenols are known to add to thiocarbonyl ylides. An illustrative example is given in Scheme 31. Thiocamphor **93** which exists as enethiol in solution adds to adamentanethione S-methylide to yield dithioacetal **95**.[66]




**Scheme 31**

### 1.5.4.2 Three Membered Rings

Thiocarbonyl ylides on 1,3-dipolar electrocyclic ring closure yield thiirane derivatives. Subsequent desulfuration is an efficient procedure for the construction of carbon-carbon double bonds. Danishefsky and co-workers have reported the synthesis of indolizomycin **99** following this protocol (Scheme 32).[67]

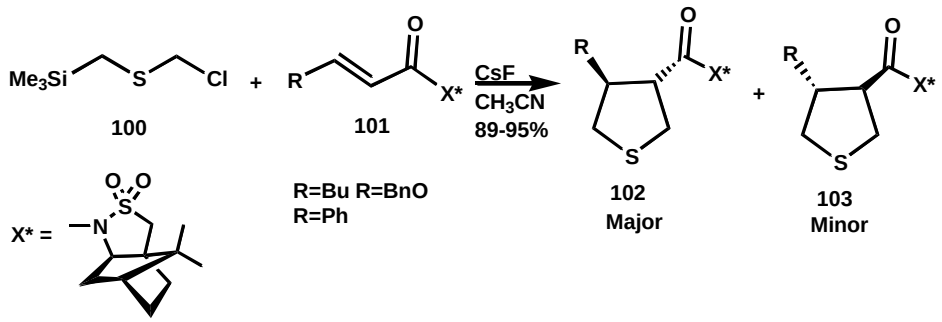



**Scheme 32**

### 1.5.4.3 Five Membered Rings

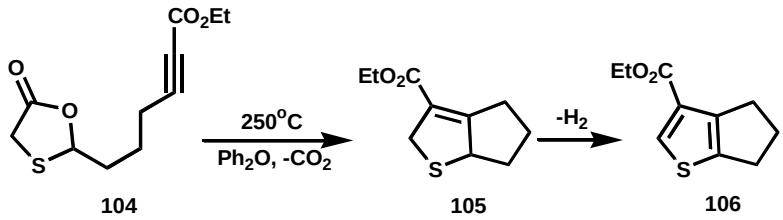
Substituted thiocarbonyl ylides, as well as the parent ylide react with various dipolarophiles to form thiophene derivatives.[68-70] In an attempted synthesis of biotin, a crucial step involves the [3+2] cycloaddition of the suitably substituted thiocarbonyl ylide with maleic or fumaric acid derivatives.[71-73] Karlsson and Högberg have reported the diastereoselective synthesis of tetrahydrothiophene derivatives. The dipolarophiles

bearing (-)-(1S)-2,10-camphorsultam as the chiral auxiliary group yield *trans*-cycloadducts diastereoselectively (Scheme 33).[74]




**Scheme 33**

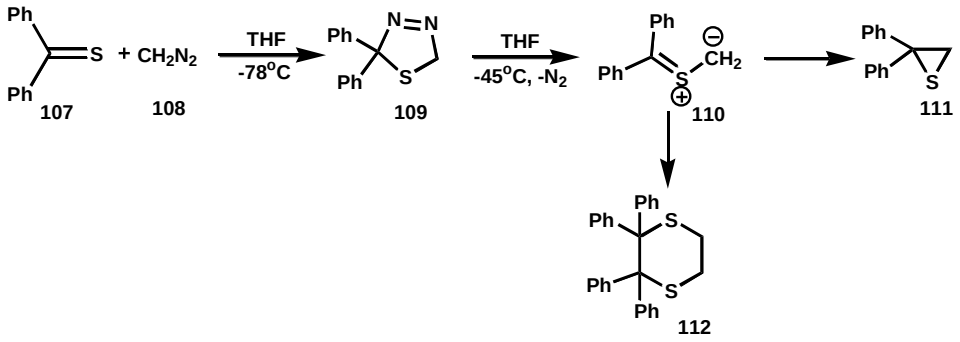
Intramolecular dipolar cycloaddition of thiocarbonyl ylides has been reported. Thus thermal decomposition of 1,3-oxathiolane-5-one **104** afforded fused thiophene derivative *via* a transient thiocarbonyl ylide followed by the [3+2] cycloaddition. 2,5-Dihydrothiophene **105** thus formed, underwent spontaneous oxidation to aromatic thiophene ring (Scheme 34).[75]




**Scheme 34**

### 1.5.4.4 Six Membered Rings

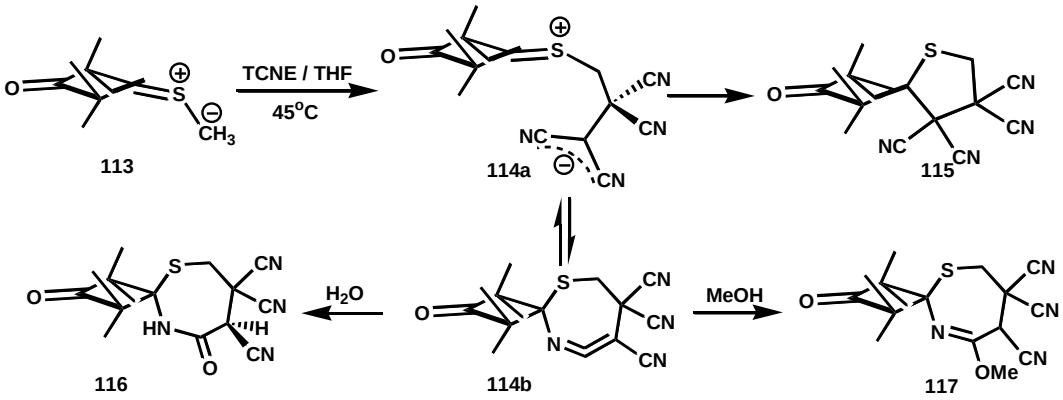
Thiocarbonyl ylides undergo head-to-head dimerization to give sterically crowded 1,4-dithianes. Thus thiobenzophenone S-methylide **110** underwent dimerization to afford 2,2,3,3-tetraphenyl-1,4-dithiane **112** along with **111** (Scheme 35).[76,77]




**Scheme 35**

### 1.5.4.5 Seven Memebered Rings

1,3-dipolar cycloaddition reactions generally follow concerted pathway. Two step mechanism is also possible if the HOMO-LUMO energy difference is high, and with 1,3-dipoles in which there is pronounced steric hindrance at one terminus. Thus cycloaddition between thiocarbonyl ylide **113** and tetracyanoethylene (TCNE) follows a two step pathway. The zwitterion generated has two competitive routes available; a reversible ketene-imine route to a seven membered lactam **116** and an irreversible ring closure to give the thiolane **115** (Scheme 36).[78]

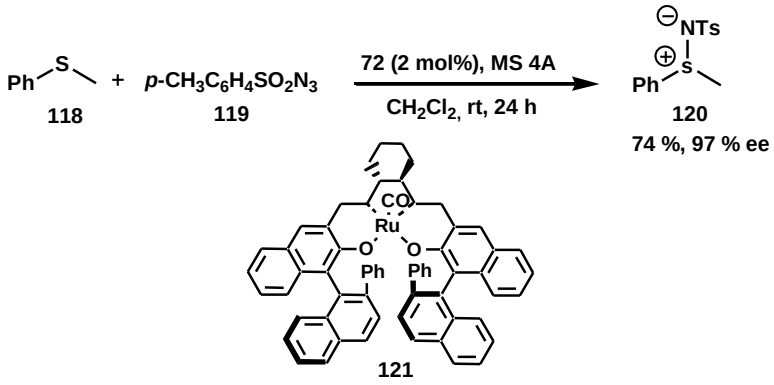



**Scheme 36**

### 1.5.5 Iminosulfurane

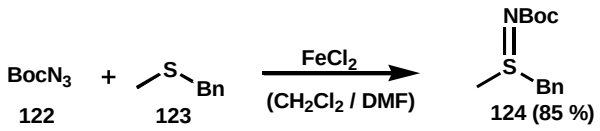
Sulfimides (iminosulfuranes) are nitrogen equivalents of sulfoxides. Optically active sulfoxides are widely used in asymmetric synthesis. In contrast, the use of sulfimides in organic synthesis is rather limited, because of the lack of convenient synthetic methods to access them. The transfer of a nitrene fragment from an alkoxycarbonyl azide to sulfides (thermally or photochemically) is the most common method for the generation of iminosulfurane ylides.[79]

Recently, Murakami and co-workers have reported that Ru (salen) served as an efficient catalyst for sulfimidation;[80] thus sulfimidation of various sulfides with arylsulfonyl azides catalysed by Ru (salen) **121** afforded sulfimides with high enantioselectivity. An example is given below (Scheme 37).



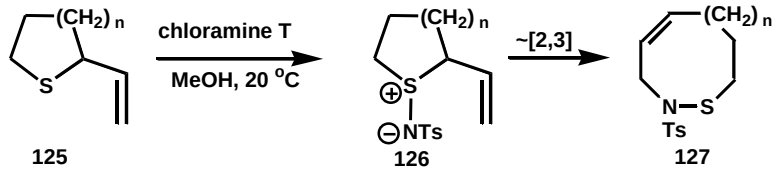

**Scheme 37**

Bach *et al*. have reported the reaction of benzyl methyl sulfide **123** with *t*-butyloxycarbonyl azide ($BocN_3$) **122**. Iron (II)-mediated nitrene transfer from $BocN_3$ to sulfide occurred in DCM: DMF solution to afford sulfimide **124** (Scheme 38).[81]



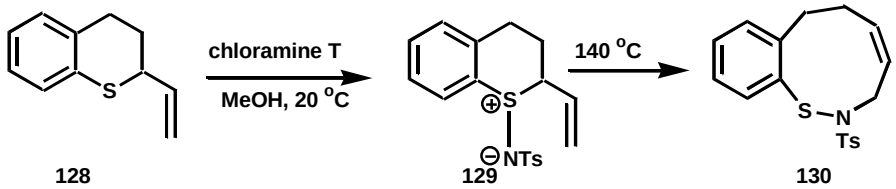

**Scheme 38**

Shashida *et al*. have reported the [2,3]-sigmatropic rearrangement of iminosulfurane ylide. Sulfides reacted with chloramine T in methanol at 20 $^{o}$C to afford the $\alpha$-vinyliminosulfurane ylides. The latter on subsequent [2,3]-sigmatropic rearrangement accompanied by ring expansion afforded the product **127** (Scheme 39).[82]



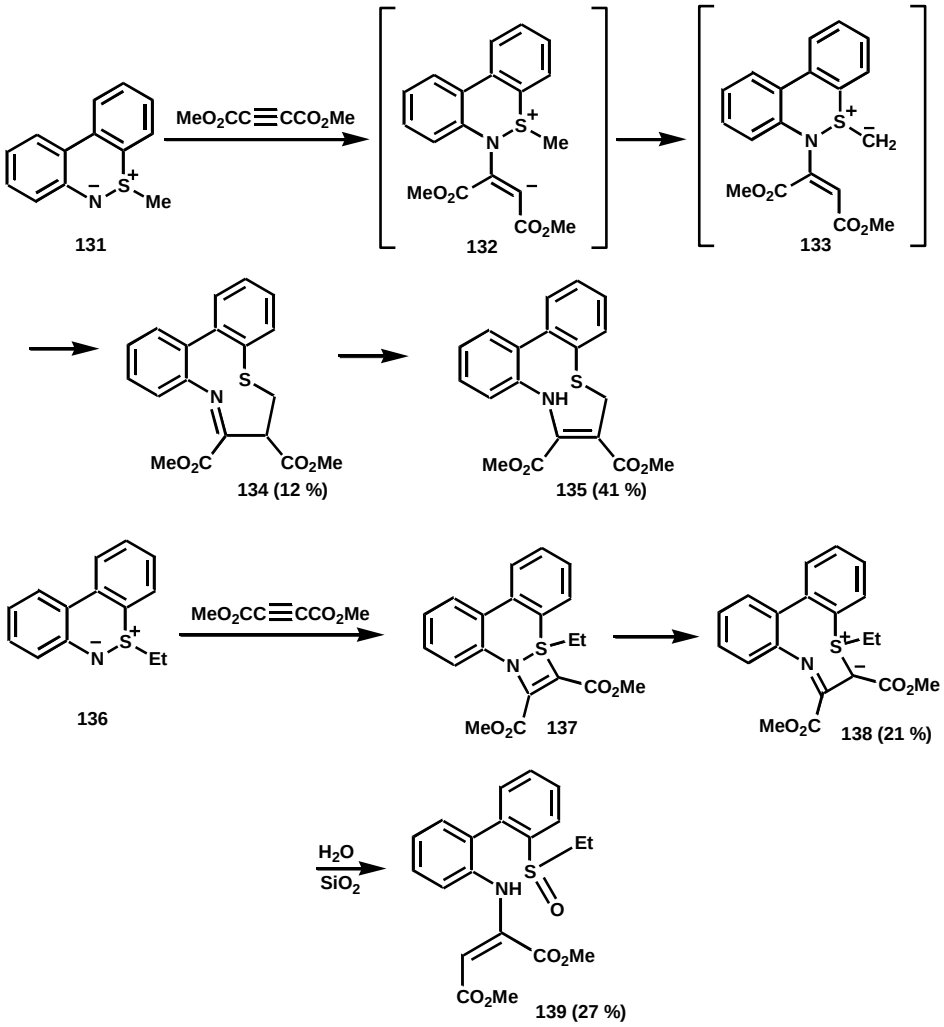

**Scheme 39**

Under the same reaction conditions benzoiminosulfurane **128** rearranged to afford benzothiazonine **130** (Scheme 40).



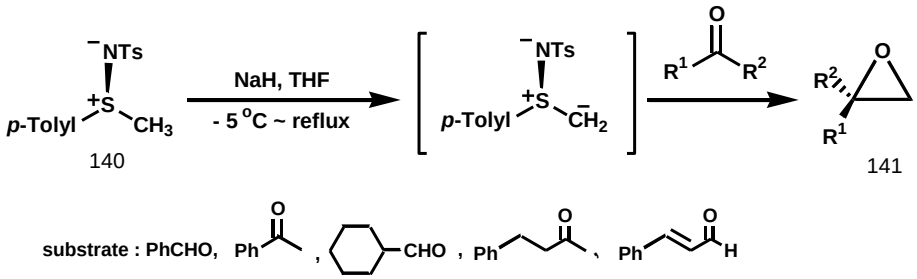

**Scheme 40**

As sulfonium ylides, iminosulfurane ylides also react with activated acetylenes, affording cyclic products. Thus reaction of ylide 9-methyl-9-thia-10-azaphenanthrene **131** with dimethyl acetylenedicarboxylate (DMAD) afforded dibenzothiazonium derivatives **134** and **135** predominantly. The reaction of the ylide 9-ethyl-9-thia-10-azaphenanthrene **136** with DMAD proceeded in a different pathway to afford an isolable ylide, dibenzothiazocine derivative **138** and the biphenyl **139** as the major products (Scheme 41).[83]




**Scheme 41**

The first asymmetric methylene transfer from chiral sulfimides to C=O bonds was recently reported by Taylor *et al*. The reaction of sulfimide **140** with aldehydes and ketones afforded epoxides **141** in 21-70% enantioselectivity (Scheme 42).[84]




**Scheme 42**

## 1.6 Conclusion

It is evident from the literature survey presented above that the sulfur compounds, particularly sulfur ylides, are synthetically important compounds. In spite of the extensive studies in this field, it is clear that much of their reactivity remains to be uncovered. In the following three chapters, our studies on the reactivity profiles of sulfur ylides are presented.

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# Chapter 2

## Synthesis of Highly Substituted Tetrahydrothiophene Derivatives *via* Sulfonium Ylides Derived from Thietanes.

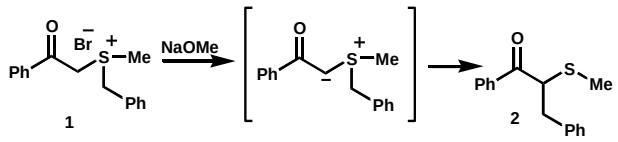
### 2.1 Introduction

Heterocycles have assumed great importance by virtue of their incorporation in most biologically active natural and synthetic organic molecules.[1] Heterocyclic construction usually involves reactions like hetero Diels-Alder reactions,[2] Huisgen 1,3-dipolar cycloadditions,[3] radical reactions,[4] Lewis acid induced cyclizations,[5] and sigmatropic rearrangements.[6]

Sulfonium ylide rearrangement reactions[7,8] play a key role in the synthesis of sulfur containing heterocycles. These may be classified as [1,2]-Stevens rearrangement, [2,3]-sigmatropic rearrangement, Sommelet-Hauser rearrangement and Pummerer rearrangement. In the following sections, these reactions are briefly described with illustrative examples of each category. This is followed by a detailed discussion of our work with sulfonium ylides generated from thietanes.

### 2.2 [1,2]-Stevens Rearrangement

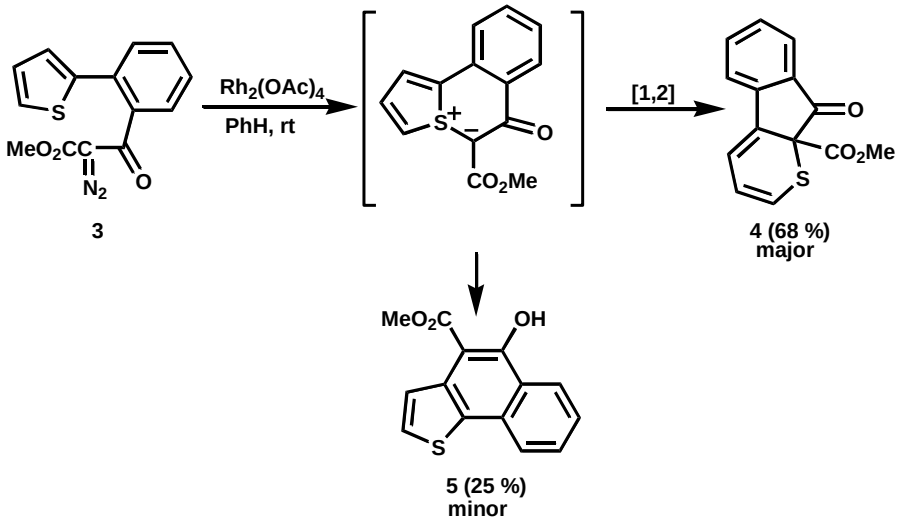
The [1,2]-Stevens rearrangement, one of the early known ylide rearrangements was discovered in 1928 (Scheme 1).[9] This reaction has been studied by various groups and has found application in penicillin chemistry,[10a] in the synthesis of pyrrolizidine alkaloids,[10b] antibiotics,[10c] sugar chemistry[10d] and also in the synthesis of (-)-epilupinine.[10e]




**Scheme 1**

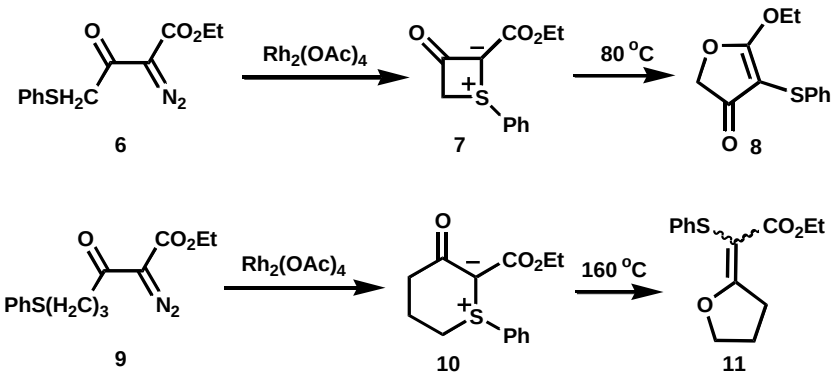
## 2.2.1 Cyclization of Diazosulfides *via* Sulfonium Ylide

Reaction of carbenes with sulfides results in the formation of sulfonium ylides. This reaction has been shown to work intramolecularly also. Thus intramolecular cyclization of diazosulfides under the action of transition metal compounds (predominantly Rh or Cu) affords cyclic sulfonium ylides.[11] This type of cyclization processes are often complicated by C-H insertion reactions of carbenes. Thus Rh(II) catalyzed decomposition of **3** leads to the [1,2]-rearrangement product **4** along with C-H insertion product **5** (Scheme 2).[12]




**Scheme 2**

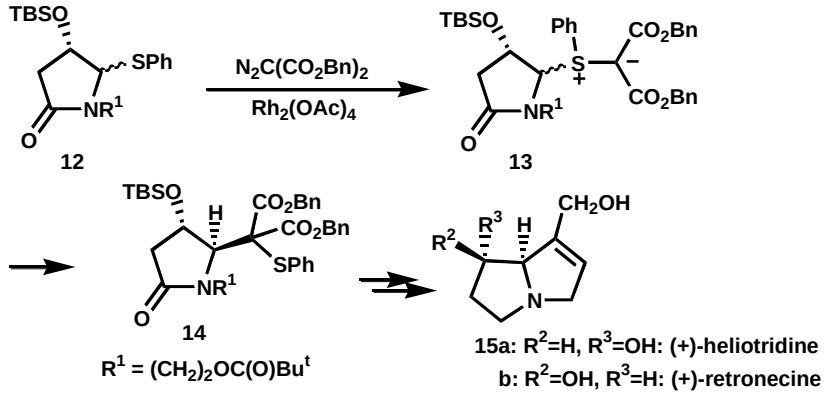
The intramolecular reaction of diazosulfides allows the convenient generation of four to seven membered cyclic sulfonium ylides. Moody and Davis have reported the thermal rearrangement of such cyclic ylides leading to heterocyclic compounds.[13] Thus four and six membered *S*-phenyl-substituted sulfur ylides **7** and **10**, which in turn were generated from diazosulfides on heating, underwent [1,4]-rearrangement to form dihydro and tetrahydrofuran derivatives **8** and **11** respectively (Scheme 3).[13b]




**Scheme 3**

## 2.2.2 Stereoselective Synthesis of Alkaloids

The intramolecular reaction strategy leading to the generation of sulfur ylides and their thermal rearrangement has been successfully employed in the synthesis of carbocyclic natural compounds[14] and pyrrolizidine alkaloids.[15] [1,2]-Rearrangements are known to proceed with high stereoselectivity, and these have been utilized in the stereoselective synthesis of alkaloids (+)-heliotridine **15a** and (+)-retronecine **15b** (Scheme 4).[10b]

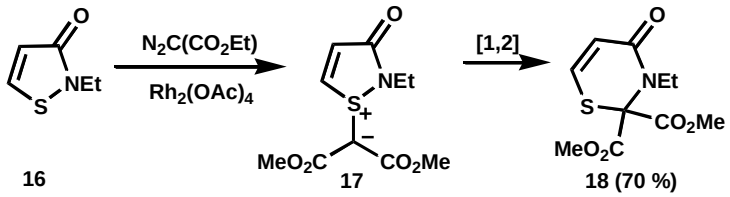



**Scheme 4**

## 2.2.3 Carbene Insertion into S-N Bond

Crow and co-workers have reported that 2,3-dihydroisothiazol-3-one on reaction with diazomalonate catalyzed by $Rh_2(OAc)_4$ affords stabilized cyclic ylide **17**. The latter

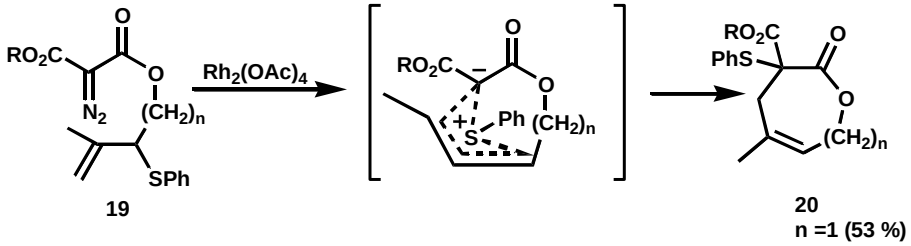
undergoes [1,2]-rearrangement resulting in the formation of 3,4-dihydro-1,3-thiazin-4(2H)-one **18** (Scheme 5).[16]




**Scheme 5**

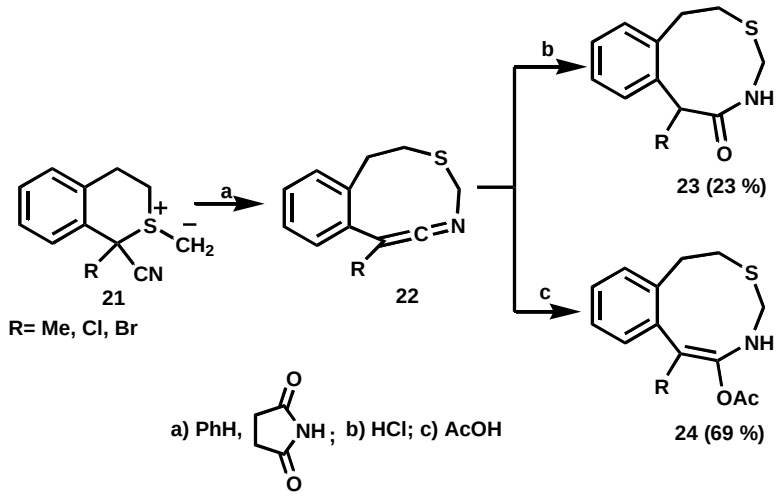
## 2.3 [2,3]-Sigmatropic Rearrangement

Baldwin was the first to study [2,3]-sigmatropic rearrangement of sulfonium ylides.[17] Such rearrangements involving allylic and benzylic sulfur ylides have been widely used in the synthesis of cyclic compounds.[18] Substituted five to eight membered lactones were prepared by the [2,3]-sigmatropic rearrangement of the corresponding allylic sulfonium ylides (Scheme 6).[19]




**Scheme 6**

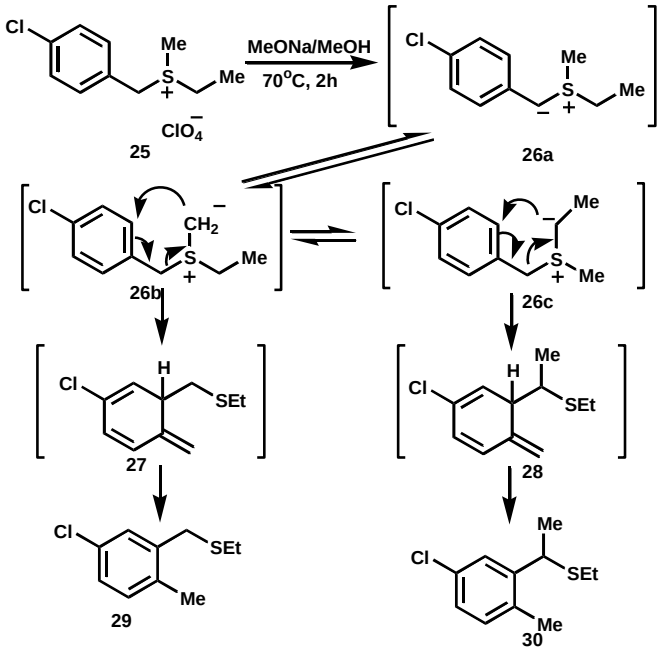
Another promising synthetic application of [2,3]-sigmatropic rearrangement was the ring expansion of cyclic sulfur ylides.[20] Kataoka and co-workers have reported the reaction of 1-cyanoisothiochroman ylide **21** with succinimide. The reaction afforded ketenimine **22**, which gave amides **23** or enol acetates **24** upon acid hydrolysis (Scheme 7).[21]




**Scheme 7**

## 2.4 Sommelet-Hauser Rearrangement

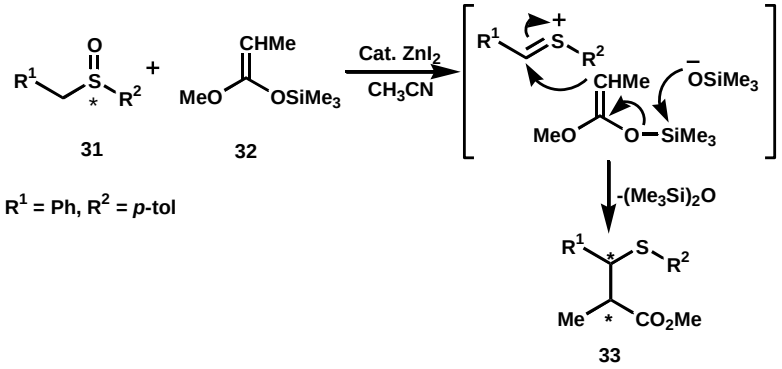
Sommelet-Hauser rearrangement, a well documented reaction of ylides, was discovered in 1937.[22] Later Campbell and Darwish reported the asymmetric version of this rearrangement using chiral sulfonium salt.[23] Of the three sulfonium ylides generated, **26b** and **26c** underwent intramolecular rearrangement to **29** and **30** respectively in the ratio 1:4.2 (Scheme 8). Very high diastereoselectivity in the Sommelet-Hauser rearrangement of dibenzyl sulfide complexes of rhenium Lewis acid has been reported recently.[24]




**Scheme 8**

## 2.5 Pummerer Rearrangement

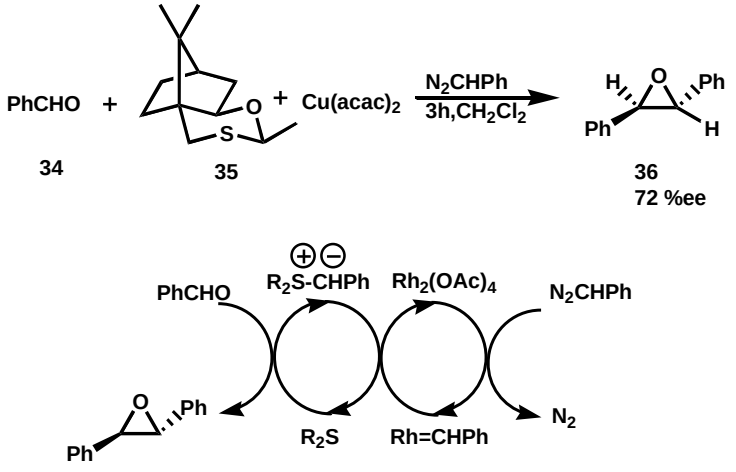
The sulfoxide-based Pummerer rearrangement discovered in 1909 proceeds *via* ylide like intermediate.[25] Kita and co-workers have reported an interesting variation of the Pummerer rearrangement. The reaction of chiral sulfoxide with *O*-silylated ketene acetals catalyzed by $ZnI_2$ afforded $\beta$-sulfur substituted ether, with two newly formed chiral centers (Scheme 9).[26] Great improvement in selectivity (higher than 80%) was achieved by this modified procedure.




**Scheme 9**

## 2.6 Chiral Sulfonium Ylides

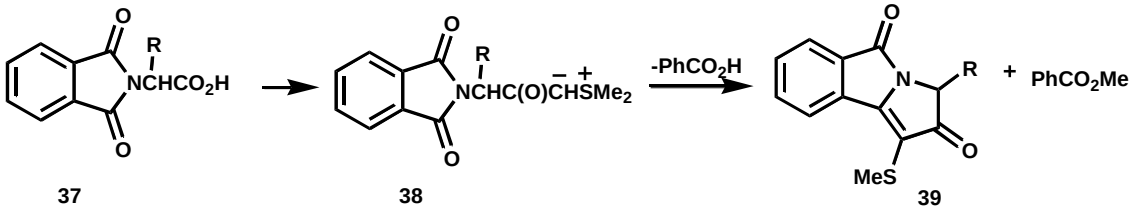
The ease of preparation and versatility of chiral sulfonium ylides made them useful in organic synthesis especially for asymmetric epoxidation,[27] cyclopropanation,[28] aziridination[29] and olefination.[30] The first successful use of chiral sulfonium ylide for asymmetric epoxidation dates back to 1989.[31] More recently, Aggarwal and co-workers have reported very high asymmetric induction in epoxidation by thioacetal **35**. In this process sulfonium ylide was generated *in situ* from chiral sulfides and phenyl diazomethane, catalyzed by rhodium acetate (Scheme 10).[32] This successful catalytic epoxidation process has been extended for cyclopropanation and aziridination by substituting the aldehyde by *α,β*-unsaturated carbonyl compounds and *N*-sulfonylimines respectively.




**Scheme 10**

## 2.7 Other Rearrangements

Intramolecular cyclization of phthalimido-substituted sulfur ylides is a promising approach for the synthesis of analogs of alkaloids.[33] Thus *N*-phthaloyl-*α*–amino acid **37** was converted to the corresponding sulfonium salt,[34] followed by deprotonation to afford the stabilized ylide **38**. The latter on heating in toluene with an equimolar amount of benzoic acid afforded methylthio-substituted pyrrolizine **39 (**Scheme 11).[35]



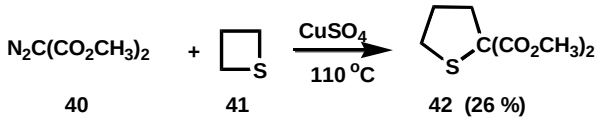

**Scheme 11**

## 2.8 Thietanes

Thietanes are four membered heterocyclic compounds containing one sulfur atom in the ring. They are highly reactive species, thus making them more attractive than the open-chain sulfides. Even though Lilienfeld in 1911 obtained 3-hydroxythietane,[37] Grishkevich was the first who isolated and identified thietane and some of its analogs.[38]

It may be mentioned that thietane derivatives have found important applications as insecticides.[39] The earliest and most general method for the synthesis of thietanes involved the reaction of 1,3-dihaloalkanes with alkali sulfides[40] or hydrosulfides.[41]

Copper catalyzed thermal reaction of diazomalonate with parent thietane **41** to afford tetrahydrothiophene **42** in low yields has been reported by Ando *et al.* (Scheme 12).[42]




**Scheme 12**

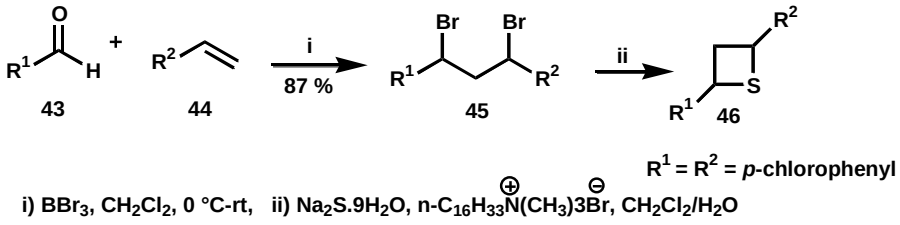
## 2.9 Background to The Present Work

It is clear from the literature survey presented above that, in spite of the substantial amount of work in the area of sulfonium ylides,[7] generation of ylides from thietanes and their chemistry has remained practically univestigated, except for an isolated report (vide supra). Ylides derived from oxetanes, the oxygen analogs of thietanes, however, have been studied in detail by various groups.[36] In view of this, it was of interest to investigate

the reactivity of thietanes with electrophilic carbenes. The results of our investigations carried out in this direction are discussed below.

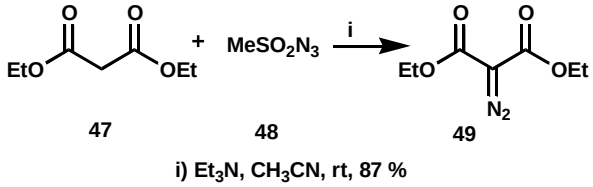
## 2.10 Results and Discussion

The thietanes required for our investigations were prepared from the corresponding 1,3-dibromides and sodium sulphide nonahydrate[43]. The 1,3-dibromides in turn were prepared following a literature procedure.[44] A typical reaction is presented in Scheme 13. Detailed experimental procedure for the preparation of thietane derivatives are given in section **2.14.1** of this chapter**.**




**Scheme 13**

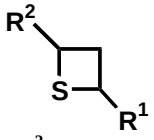
The diazo compounds were prepared from the corresponding active methylene compounds using Regitz[45] diazotization protocol, as illustrated in the Scheme 14.




**Scheme14**

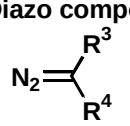
The thietanes and diazo compounds selected for our studies are listed below (Figure 1).

**Thietanes**



**46** $R^1 = R^2 =$ ***p*-Cl phenyl**
**53** $R^1 = R^2 =$ **phenyl**
**54** $R^1 = R^2 =$ ***p*-$CH_3$ phenyl**
**55** $R^1 =$ ***p*-Cl phenyl**, $R^2 =$ **phenyl**
**56** $R^1 =$ ***p*-$CH_3$ phenyl**, $R^2 =$ **phenyl**
**57** $R^1 =$ **phenyl**, $R^2 =$ ***p*-$NO_2$ phenyl**
**58** $R^1 =$ ***p*-$CH_3$ phenyl**, $R^2 =$ ***p*-Cl phenyl**
**77** $R^1 =$ **phenyl**, $R^2 =$ **H**
**80** $R^1 =$ ***p*-Cl phenyl**, $R^2 =$ **H**
**81** $R^1 =$ **m-Cl phenyl**, $R^2 =$ **H**
**82** $R^1 =$ **m- $NO_2$ phenyl**, $R^2 =$ **H**
**87** $R^1 =$ ***n*-hexyl**, $R^2 =$ **H**

**Diazo compounds**

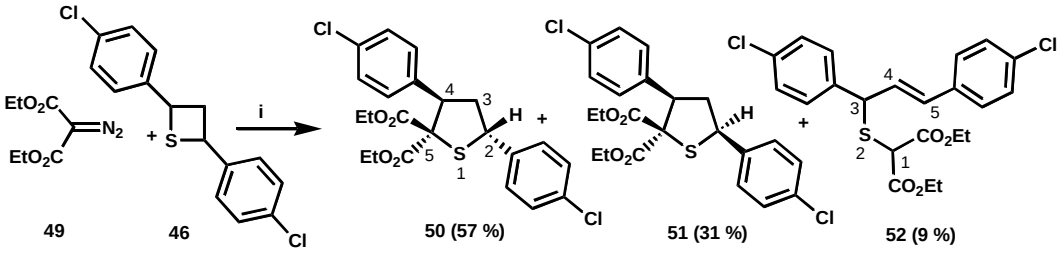


**49** $R^3 = R^4 = CO_2Et$
**89** $R^3 =$ **H**, $R^4 = COPh$
**92** $R^3 =$ **H**, $R^4 = CO_2Et$
**93** $R^3 = R^4 = SO_2Ph$
**94** $R^3 = R^4 = COPh$
**95** $R^3 = R^4 = COCH_3$
**96** $R^3 = R^4 =$ **1,3-Cyclohexanedione**
**97** $R^3 = R^4 =$ **5,5-dimethyl 1,3-Cyclohexanedione**

**Figure 1**

## 2.11 Reactions of Thietanes with Diethyl Diazomalonate

Our studies were initiated by exposing a solution of diastereomeric mixture of 2,4-bis-(4-chlorophenyl)thietane **46** (*cis:trans* ratio 1:2.2, determined by HPLC analysis) in benzene to dicarboethoxycarbene, generated by the Rh(II) catalyzed decomposition of diethyl diazomalonate. A slow but facile reaction occurred to afford a diastereomeric mixture of tetrahydrothiophenes **50** in 57 % and **51** in 31 % yields along with the allyl thioether **52** in 9 % yield (Scheme 15).




i) $Rh_2(OAc)_4$, benzene, Argon, 80 $^oC$, 16 h,

**Scheme 15**

The structures of compounds **50**, **51** and **52** were elucidated by spectroscopic data. The IR spectrum of *trans*-**50**, displayed absorption at 1745 $cm^{-1}$ characteristic of the ester carbonyl. In the $^{1}H$ NMR spectrum (Figure 2), benzylic protons resonated at $\delta$ 4.24 as a multiplet and at $\delta$ 4.70 as a triplet. The methylene protons at C-3 were discernible as a multiplet centered at $\delta$ 2.63. In the $^{13}C$ NMR spectrum (Figure 3), signals due to benzylic carbons were observed at $\delta$ 51.2 and 52.7. The signals due to the ester carbonyls were visible at $\delta$ 167.6 and 169.9. All the other signals were also in accordance with the assigned structure. Finally, the configuration of the major diastereomer was ascertained to be *trans* by single crystal X-ray analysis (Figure 4).

The IR spectrum of the *cis*-**51** displayed a strong absorption at 1739 $cm^{-1}$ typical of the ester carbonyl functionality. In the $^{1}H$ NMR spectrum (Figure 5), benzylic proton on C-4 resonated as a multiplet centered at $\delta$ 4.20, while the benzylic proton on C-2 furnished a doublet of doublet at $\delta$ 4.61 ($J$ = 5.2 Hz) . The methylene protons at C-3 were discernible as separate signals at δ 2.82 (uneven quartet) and at $\delta$ 2.48 as a multiplet. In the $^{13}C$ NMR spectrum, signals due to the ester carbonyls were visible at $\delta$ 169.1 and 169.8. All the other signals were also in accordance with the assigned structure.

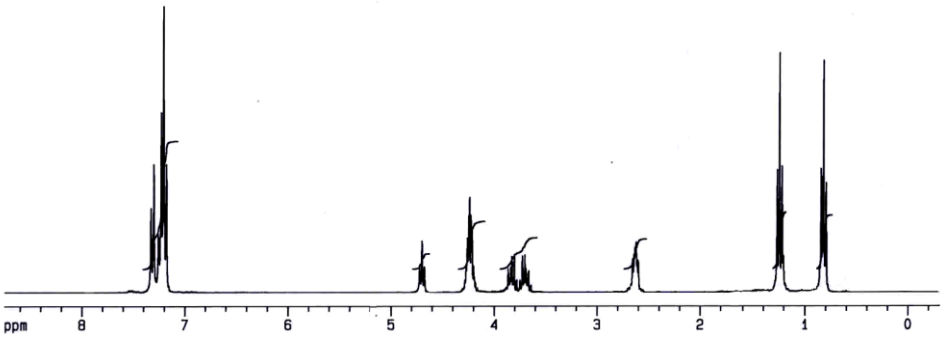



**Figure 2. $^{1}H$ NMR spectrum of 50**

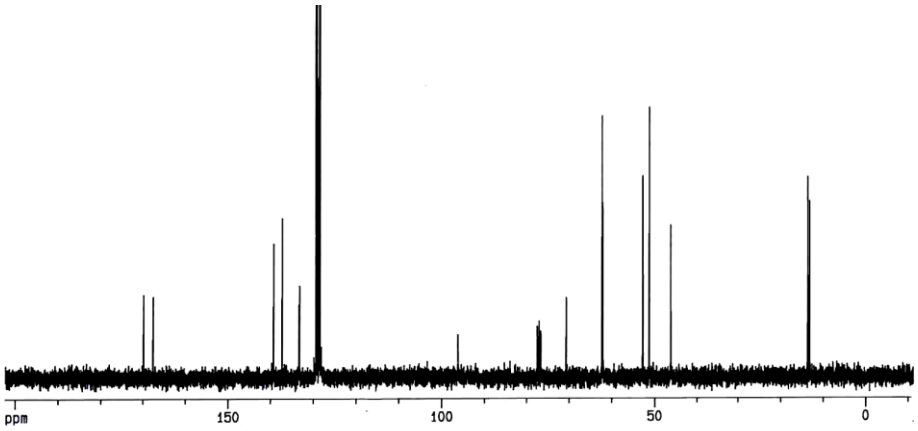



**Figure 3. $^{13}$C NMR spectrum of 50**

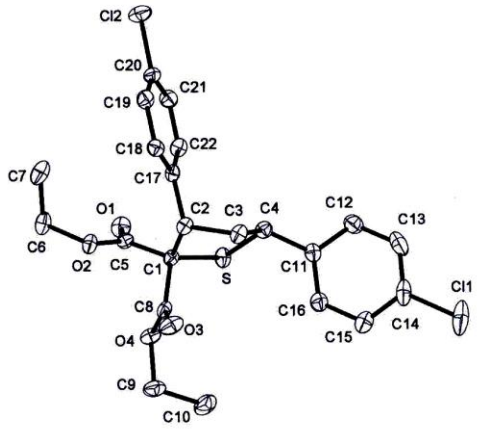



**Figure 4. X-ray crystal structure of *trans*-50**

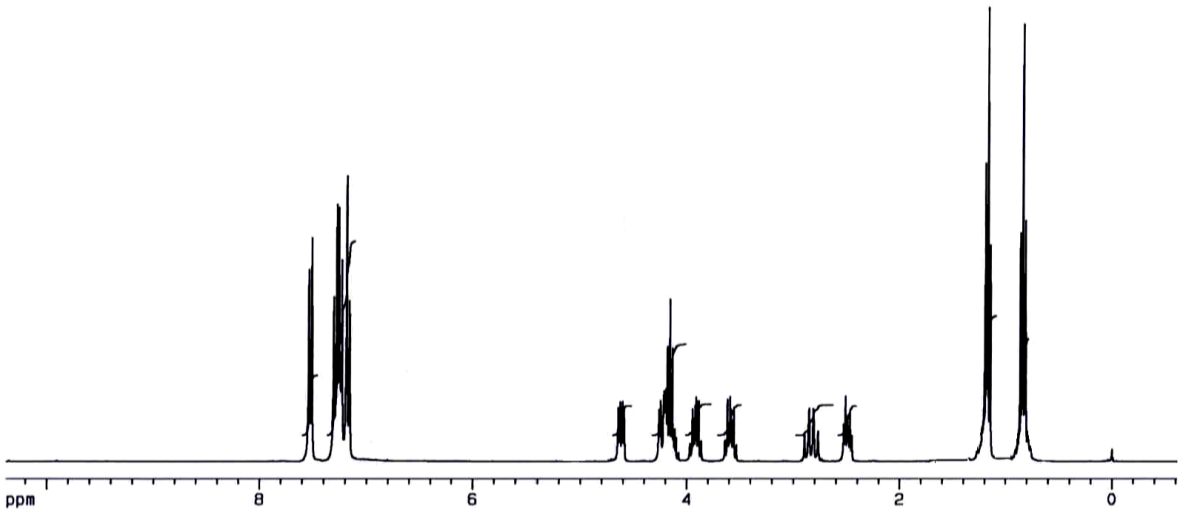
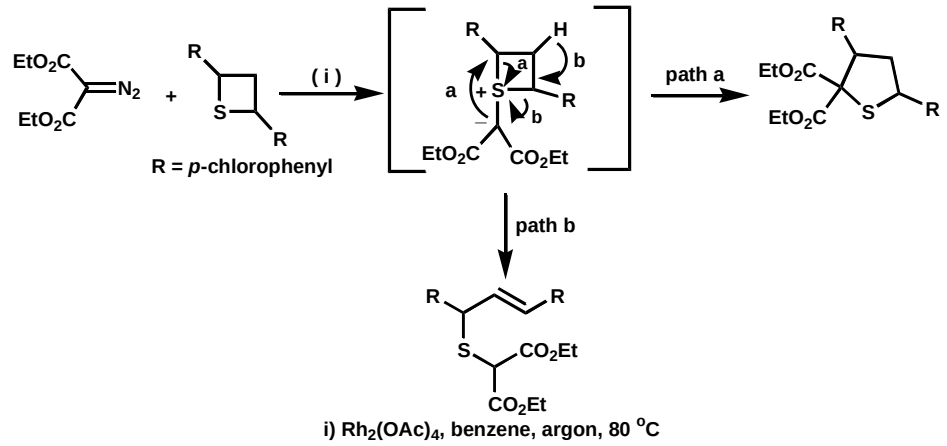



**Figure 5. $^{1}$H NMR spectrum of 51**

The IR spectrum of the allyl thioether **52** exhibited a strong band at 1740 $cm^{-1}$ characteristic of ester functionality. In the $^{1}$H NMR spectrum, methine proton at C-1 resonated as a singlet at $\delta$ 3.95, the methine proton at C-3 appeared at $\delta$ 4.81 as a doublet ($J$ = 8.8 Hz), and the olefinic protons on C-4 and C-5 were discernible at δ 6.29 as a doublet of doublet ($J$ = 8.8 Hz) and at $\delta$ 6.43 as a doublet ($J$ = 15.7 Hz) respectively. In the $^{13}$C NMR spectrum, the signals of the ester carbonyls were discernible at $\delta$ 166.5 and 166.7. All the other signals were also in agreement with the proposed structure.

## Mechanistic Considerations

A mechanistic rationalization for the formation of the products can be presented as follows. The reaction can be viewed as occurring by the initial formation of the sulfonium ylide by the reaction of thietane with the carbene, which in turn is generated by the Rh(II) catalyzed reaction of diazocompound. The Stevens rearrangement indicated by pathway *a* leads to the tetrahydrothiophene. It is reasonable to assume that the open chain compound arises *via* an intramolecular *β*-elimination process, identified by pathway *b*[43] (Scheme 16).

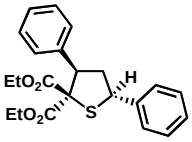
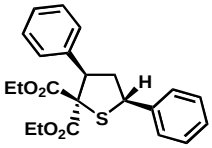
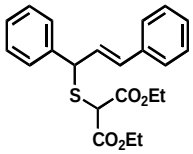
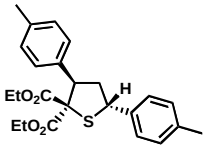
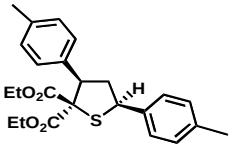
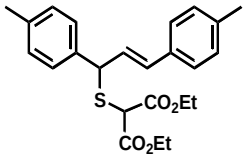
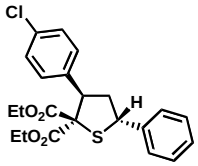
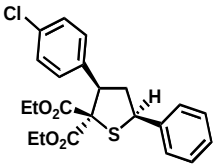
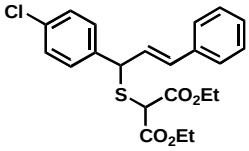
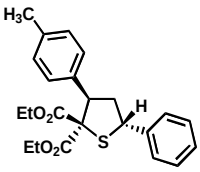
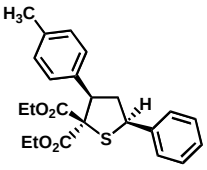
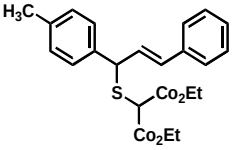
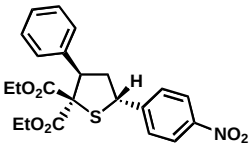
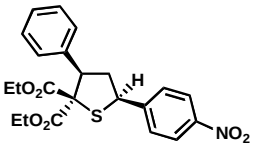
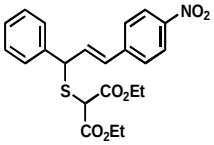
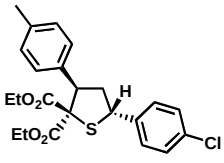
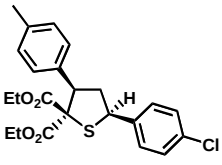
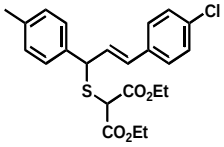



**Scheme 16**

The diastereoselectivity of the reaction can be rationalized as follows. The amount of the *cis* tetrahydrothiophene derivative formed in the reaction closely corresponds to the proportion of the *cis* thietane in the diastereomeric mixture of starting materials. Similarly the *trans* tetrahydrothiophene derivative and the allyl thioether together correspond to the proportion of the *trans* thietane in the mixture. The presumption that the allyl thioether is formed from the *trans* thietane is mechanistically sound and reasonable. With this analysis we can conclude that the diastereoselectivity of the reaction is high.

Similar reactivity pattern was observed with other 2,4-diaryl thietanes **53-58**, which furnished the corresponding tetrahydrothiophenes in good yields along with the allyl thioethers. The results obtained are presented in Table 1.

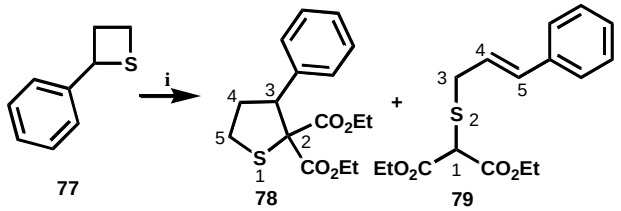
**Table 1**

| Entry | Thietane | *Trans* Product | *Cis* Product | Allyl thioether |
|---|---|---|---|---|
| **1** | **53** |  **59** (54 %) |  **60** (31 %) |  **61** (11 %) |
| **2** | **54** |  **62** (50 %) |  **63** (24 %) |  **64** (18 %) |
| **3** | **55** |  **65a** (38 %) |  **66a** (32 %) |  **67** (14 %) |
| **4** | **56** |  **68a** (32 %) |  **69a** (26 %) |  **70** (17 %) |
| **5** | **57** |  **71** (36 %) |  **72** (18 %) |  **73** (38 %) |
| **6** | **58** |  **74** (36 %) |  **75** (32 %) |  **76** (12 %) |

**Reaction Conditions: i)Diethyl diazomalonate, $Rh_2(OAc)_4$, benzene, Argon, 80 $^oC$, 16 h**
**Isolated yield in parentheses**

In the case of thietanes **55** and **56,** in addition to the cyclized products (**65a**, **66a**, **68a** and **69a**) small amounts of regioisomeric products (**65b**, **66b**, **68b** and **69b)** arising from the alternative 1,2-rearrangement were also isolated (the experimental details along with data are given in the experimental section of this chapter). But with thietanes **49** and **50** the reaction afforded regioselectively single diastereomeric pairs of products.

Similar reaction pattern was observed in the reaction of monosubstituted thietanes and diethyl diazomalonate. Thus 2-phenylthietane **77** on treatment with diethyl diazomalonate and a catalytic amount of $Rh_2(OAc)_4$ in benzene under refluxing conditions furnished the tetrahydrothiophene derivative **78** in 69 % yield and the allyl thioether **79** in 10 % yield (Scheme 17).




**77** **78** **79**

**i) Diethyl diazomalonate, $Rh_2(OAc)_4$, benzene, argon, 80 °C**, 16 h

**Scheme 17**

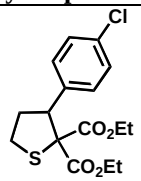
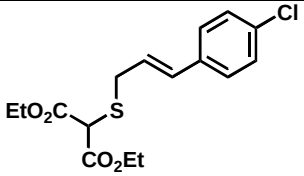
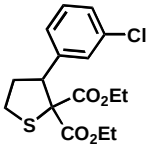
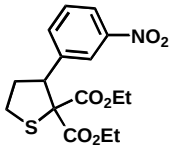
As usual, the structures of the products were elucidated by spectroscopic data. In the vibrational spectrum of the compound **78**, the peak at 1738 $cm^{-1}$ was attributed to the ester carbonyl absorption. In the $^1H$ NMR spectrum, the signal due to benzylic proton at C-3 was found to overlap with the signals of methylene protons of one of the ester groups, thus displaying a multiplet centered at $\delta$ 4.19. The other ester methylene protons appeared as multiplets centered at $\delta$ 3.62 and 3.84. In the $^{13}C$ NMR spectrum, signals of the ester carbonyls were observed at $\delta$ 168.6 and 169.8. All the other signals were also in accordance with the assigned structure.

In the case of compound **79,** the peak at 1738 $cm^{-1}$ in IR spectrum was attributed to the ester carbonyl absorption. In the $^1H$ NMR spectrum, the methine proton at C-1 appeared as a singlet at $\delta$ 4.13 and the methylene protons at C-3 resonated as a doublet at

$\delta$ 3.50 ($J$ = 7.4 Hz). The olefinic proton at C-5 appeared as a doublet at $\delta$ 6.52 ($J$ = 15.8 Hz) and the one at C-4 was discernible as a multiplet centered at $\delta$ 6.16. In the $^{13}$C NMR spectrum, the ester carbonyl groups displayed peaks at $\delta$ 168.5 and at 168.7. All the other signals were also in good agreement with the assigned structure.

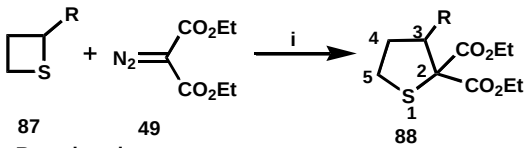
Other 2-aryl-substituted thietanes also exhibited similar reactivity profile and the results are summarized in Table 2.

**Table 2**

| Entry | Thietane | Cyclic product | Allylthioether |
|---|---|---|---|
| **1** | **80** |  **83** (65 %) |  **84** (9 %) |
| **2** | **81** |  **85** (65 %) | **(0 )** |
| **3** | **82** |  **86** (65 %) | **(0)** |

**Reaction Conditions: i) $Rh_2(OAc)_4$, benzene, Argon, 80 $^oC$, 16 h**
**Isolated yield in parentheses**

The reaction was applicable to alkyl substituted thietanes also; 2-*n*-hexyl thietane **87** when treated with the carbene generated by the Rh(II) catalyzed decomposition of diethyl diazomalonate furnished tetrahydrothiophene **88** in good yield (Scheme 18).



**87** **49** **88**

**R = *n*-hexyl**

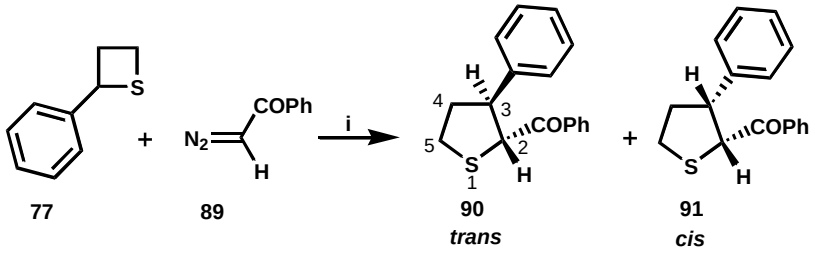
**i) $Rh_2(OAc)_4$, benzene, argon, 80 $^oC$, 16 h, 60 %**

**Scheme 18**

The product **88** was purified by column chromatography and characterized on the basis of spectroscopic data. In the IR spectrum, the strong absorption at 1737 $cm^{-1}$ was typical of the ester carbonyl. In the $^{1}H$ NMR spectrum, resonance signals for the methylenes of the ester groups appeared around $\delta$ 4.28. The signal due to the methyl of the 2-*n*-hexyl chain appeared as a multiplet centered at $\delta$ 0.97. The methine proton at C-3 appeared as a multiplet centered at $\delta$ 2.17, and the methylene protons adjacent to the sulfur atom appeared as a multiplet centered at $\delta$ 3.35. In the $^{13}C$ NMR spectrum, the ester carbonyl groups displayed peak at $\delta$ 163.7. All the other signals were also in good agreement with the proposed structure.

## 2.12 Reactions of Thietanes with Various Diazo Compounds

In view of the success with diethyl diazomalonate, it was reasonable to extend the reaction to a variety of other diazocompounds: symmetrical, unsymmetrical and cyclic. In a typical reaction, 2-phenylthietane was treated with benzoyl diazomethane and catalytic amount of Cu(II) acetylacetonate* in refluxing benzene under argon for 16 hours. The reaction afforded isomeric mixture of tetrahydrothiophenes in the ratio 3.2:1 in 63 % yield (Scheme 19).




**77** **89** **90** ***trans*** **91** ***cis***

**i) $Cu(acac)_2$, benzene, argon, 80 $^{o}$C,16 h, 63 %, 3.2:1**

**Scheme 19**

* It may be mentioned that although the reaction occurred with $Rh_2(OAc)_4$ as the catalyst, $Cu(acac)_2$ gave better results with diazo compounds other than diethyl diazomalonate.

As usual, the products were characterized using conventional spectroscopic methods. In the $^{1}$H NMR spectrum of **90** and **91** (Figure 6), the proton at C-2 of **90** resonated at $\delta$ 4.75, whereas the corresponding proton of the *cis* compound **91** was discernible at $\delta$ 4.67. The benzylic proton at C-3 resonated as a multiplet at $\delta$ 4.09. The methylene protons at C-4 displayed their signals as separate multiplets at $\delta$ 2.37 and $\delta$ 2.60. In the $^{13}$C NMR spectrum, the carbonyl group displayed peak at $\delta$ 195.7. All the other signals were also in good agreement with the proposed structure.

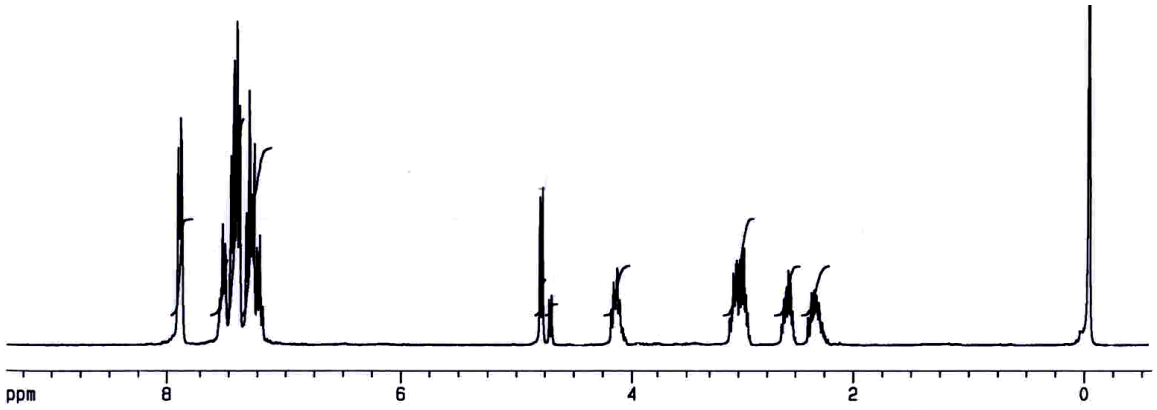



**Figure 6. $^{1}$H NMR spectrum of mixture of isomers (90 and 91)**

The stereochemistry of the major isomer **90** was assigned by nOe difference spectroscopic studies undertaken in $CDCl_3$ solution at 500 MHz (Figure 7). The presence of $H_1/H_3$ nOe cross peaks indicates that they are on the same side of the tetrahydrothiophene ring; $H_2/H_6$ cross peaks also support their presence on the same side of the thiophene ring. The $H_1/H_d$, $H_3/H_d$ and $H_5/H_d$ nOe confirmed that the protons $H_1$, $H_3$ and $H_5$ are on the same side of the ring, whereas $H_2$, $H_4$ and $H_6$ are on the opposite side. The intraring vicinal couplings $^{3}J_{1\text{-}2}$ = 6.5Hz, $^{3}J_{2\text{-}3}$ = 9.4Hz, $^{3}J_{2\text{-}4}$ = 6.1Hz, $^{3}J_{3\text{-}5}$ = 6.4Hz, $^{3}J_{3\text{-}6}$ = 9.1Hz, $^{3}J_{4\text{-}5}$ = 4.4Hz and $^{3}J_{4\text{-}6}$ = 5.7Hz all support the assigned structure. Thus it was concluded that the major isomer obtained was the *trans* compound.

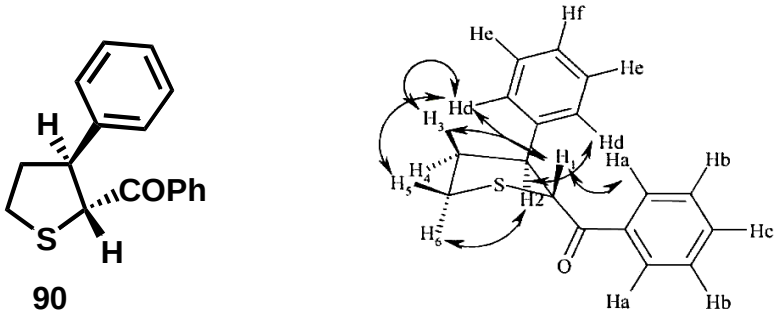
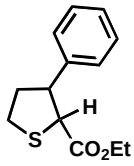
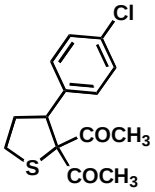
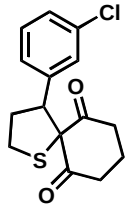
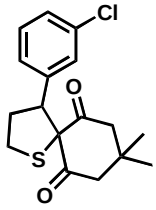



**Figure 7. nOe cross-peaks present in the spectrum of 90**

Analogous reactivity was observed with other diazo compounds and the results obtained are summarized in Table 3.

**Table 3**

| Entry | Thietane | Diazocompound | Cyclic product | Yields(%)[a] |
|---|---|---|---|---|
| **1** | **77** | **92** |  **98** | **55%** |
| **2** | **77** | **93** | No reaction | |
| **3** | **77** | **94** | No reaction | |
| **4** | **80** | **95** |  **99** | **80%** |
| **5** | **81** | **96** |  **100** | **48%** |
| **6** | **81** | **97** |  **101** | **52%** |

**Reaction Conditions: i) Cu (II) acetylacetonate, benzene, argon, 80 $^{o}$C, 16 h**
**[a]Isolated yield**

## 2.13 Conclusion

In conclusion, our studies have uncovered a facile method for the synthesis of highly substituted tetrahydrothiophene derivatives. It is conceivable that this reaction

protocol can be extended using chiral catalysts for the enantiospecific ring expansion of thietanes to tetrahydrothiophenes.

## 2.14 Experimental Details

**General:** Melting points were recorded on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300 ($^1$H) and 75 ($^{13}$C) MHz respectively on a Bruker Avance DPX-300 MHz NMR spectrometer. Chemical shifts ($\delta$) are reported relative to TMS ($^1$H) and $CDCl_3$ ($^{13}$C) as the internal standards. Coupling constant ($J$) is reported in Hertz (Hz). High resolution mass spectra were recorded under EI/HRMS (at 5000 resolution) using JEOL JMS 600H mass spectrometer. IR spectra were recorded on a Nicolet Impact 400D FT-IR spectrophotometer. Analytical HPLC was performed on a Shimadzu High Pressure Liquid Chromatograph ($\lambda$=254 nm) using 60:50 methanol-water mixture as the eluent at a flow rate of 1mL/minute. Elemental analyses were performed on a Perkin Elmer-2400 Elemental Analyzer. Commercial grade solvents were distilled prior to use. Analytical thin layer chromatography was performed on glass plates coated with silica gel containing calcium sulfate as binder. Gravity column chromatography was performed using 100-200 mesh silica gel and mixtures of hexane and ethyl acetate were used for elution.

### 2.14.1 General Procedure For The Preparation of Thietane Derivatives

A solution of the 1,3-dibromide (2.8 mmol) in dichloromethane (15mL) was added to a solution of sodium sulphide nonahydrate (2.8 mmol) in 15mL water. To this was added hexadecyltrimethylammonium bromide (20 % solution). The mixture was stirred rapidly till the complete consumption of the starting material was confirmed by TLC. The organic layer was separated and washed with water and dried over anhydrous sodium sulfate. Removal of the solvent on a rotary evaporator gave the crude product,[43] which was purified by column chromatography using petroleum ether as the solvent. The thietane derivatives **46, 53-58** were obtained as inseparable diastereomeric mixtures. The

ratio of thietanes **46** and **53** were found to be *cis: trans* as 1:2.2 and 1:2.4 respectively by HPLC analysis.

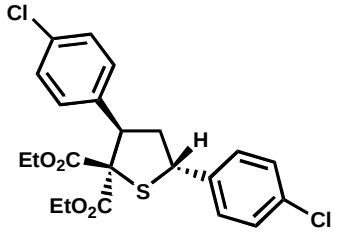
## 2.14.2 General Procedure For The Rh(II) or Cu(II) Catalyzed Reaction of Thietanes

A mixture of thietane, diethyl diazomalonate and 2 mol% of $Rh_2(OAc)_4$ or Cu(II) was refluxed in 5 mL of dry benzene under an argon atmosphere for 16 h. The solvent was then removed under vacuum and the residue was subjected to silica gel column chromatography using (95:5) hexane-ethyl acetate mixture furnished the products.

***Diethyl (E)-3,5-bis(4-chlorophenyl)tetrahydrothiophene-2,2-dicarboxylate 50, Diethyl (Z)-3,5-bis(4-chlorophenyl)tetrahydrothiophene-2,2-dicarboxylate 51***

***and Diethyl{[(2E)-1,3-di-4-chlorophenylprop-2enyl]thio}malonate 52***

The diastereomeric mixture of 2,4-bis(4-chlorophenyl)thietane **46** (100 mg, 0.339 mmol) and diethyl diazomalonate (76 mg, 0.407 mmol) were reacted and the reaction mixture was processed as described in the general procedure to afford products **50** (88 mg, 57 %), **51** (48 mg, 31 %) and **52** (14 mg, 9 %).




***trans*- 50**

**m.p:** 84-86$^{o}$C, Colorless crystalline solid.

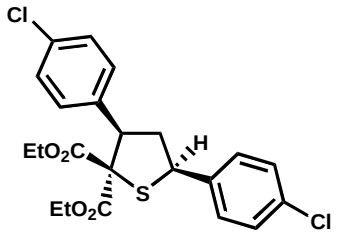
**IR** (KBr) $\nu_{max}$**:** 2981, 1745, 1574, 1491, 1258, 1201, 1093, 1041, 958, 825, 720, 622, 560 $cm^{-1}$.

**$^{1}$H NMR:** $\delta$ 0.87 ( t, 3H, $J$ = 7.1Hz, $OCH_2C\underline{H}_3$), 1.31 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.60-2.66 (m, 2H, $C\underline{H}_2$), 3.67-3.87 (m, 2H, $OC\underline{H}_2CH_3$), 4.21-4.28 ( m, 3H, ArC<u>H</u>, $OC\underline{H}_2CH_3$), 4.70 (t, 1H, $J$ = 7.1 Hz, SC<u>H</u>Ar), 7.13-7.55 (m, 8H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 13.5, 13.9, 46.2, 51.2, 52.7, 62.0, 62.2, 70.6, 128.2, 128.5, 128.7, 129.1, 129.4,

133.3, 133.4, 137.4, 167.6, 169.9.

Anal. Calcd for $C_{22}H_{22}O_4SCl_2$: C, 58.28; H, 4.89; S, 7.07. Found. C, 57.99; H, 4.86; S, 7.44.




***cis*-51**

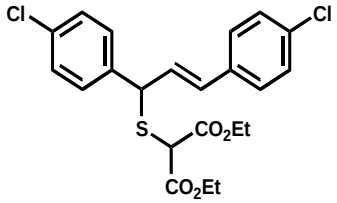
Pale yellow viscous liquid.

**IR** (Neat) $\nu_{max}$**:** 2887, 1739, 1594, 1491, 1260, 1115, 1050, 927, 813, 727, 636, 555 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 0.83 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.16 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.45-2.51 (m, 1H, $C\underline{H}_2$), 2.80-2.84 (uneven q, 1H, $C\underline{H}_2$), 3.54-3.60 (m, 1H, $OC\underline{H}_2CH_3$), 3.87-3.93 (m, 1H, $OC\underline{H}_2CH_3$), 4.12-4.25 (m, 3H, $CH_2C\underline{H}Ar$, $OC\underline{H}_2CH_3$), 4.61(dd, 1H, $J$ = 5.2 Hz, 11.5 Hz, $SC\underline{H}Ar$), 7.16-7.30 (m, 6H, $Ar\underline{H}$), 7.81 (d, 2H, $J$ = 7.2 Hz, $Ar\underline{H}$).

**$^{13}$C NMR:** $\delta$ 13.5, 13.9, 44.7, 50.2, 53.1, 62.1, 62.2, 69.1, 128.3, 128.8, 129.5, 130.0, 133.6, 133.6, 135.4, 138.4, 169.1, 169.8.

**HRMS** (E1): *m/z* Calcd for $C_{22}H_{22}O_4SCl_2$ [$M^+$]: 452.0616. Found: 452.0637.




**52**

Pale yellow viscous liquid

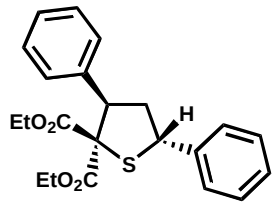
**IR** (Neat) $\nu_{max}$**:** 2980, 1740, 1579, 1491, 1253, 1150, 1093, 927, 821, 725, 627, 508 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 1.19 ( m, 6H, $OCH_2C\underline{H}_3$ ) 3.95 (s, 1H, $C\underline{H}(CO_2Et)_2$ ), 4.1 (m, 4H, $OC\underline{H}_2CH_3$), 4.81 (d, 1H, $J$ = 8.8 Hz, $SC\underline{H}Ar$), 6.29 (dd, 1H, $J$ = 8.8 Hz, $J$ = 15.6 Hz, $C\underline{H}$=CHAr), 6.43 (d, 1H, $J$ = 15.7 Hz, CH=$C\underline{H}Ar$), 7.19-7.31 (m, 8H, $Ar\underline{H}$).

**$^{13}$C NMR:** $\delta$ 14.0, 14.0, 51.9, 52.5, 62.1, 62.2, 126.7, 127.9, 128.7, 130.0, 129.5, 131.3, 133.8, 133.8, 134.9, 136.2, 137.8, 139.0, 166.5, 166.7.

***Diethyl (E)-3,5-diphenyl)tetrahydrothiophene-2,2-dicarboxylate 59, Diethyl (Z)-3,5-diphenyl)tetrahydrothiophene-2,2-dicarboxylate 60 and Diethyl{[(2E)-1,3-diphenylprop-2enyl]thio}malonate 61***

The diastereomeric mixture of 2,4-diphenylthietane **53** (100 mg, 0.442 mmol) and diethyl diazomalonate (99 mg, 0.531 mmol) were reacted and the reaction mixture was processed as described in the general procedure to afford products **59** (92 mg, 54 %), **60** (53 mg, 31 %) and **61** (19 mg, 11 %).




***trans*-59**

Pale yellow viscous liquid

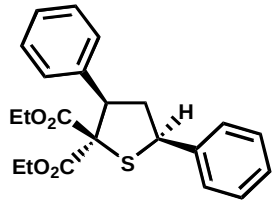
**IR** (Neat) $\nu_{max}$**:** 2986, 1742, 1574, 1498, 1253, 1201, 1091, 1031, 974, 865, 740, 606, 529 cm$^{-1}$.

**$^{1}$H NMR:** $\delta$ 0.79 (t, 3H, $J$ = 7.1Hz, $OCH_2C\underline{H}_3$), 1.3 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.67-2.84 (m, 2H, $C\underline{H}_2$ ), 3.68-3.90 (m, 2H, $OC\underline{H}_2CH_3$), 4.27-4.39 (m, 3H, ArC<u>H</u>, $OC\underline{H}_2CH_3$), 4.85 (t, 1H, $J$ = 7.2 Hz, SC<u>H</u>Ar), 7.20-7.64 (m, 10H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 13.4, 14.0, 46.5, 52.1, 53.8, 61.8, 62.0, 71.0, 127.4, 127.9, 128.2, 128.4, 128.5, 128.6, 128.7, 139.4, 167.9, 170.1.

Pale yellow viscous liquid

**IR** (Neat) $\nu_{max}$**:** 2981, 1738, 1574, 1490, 1253, 1201, 1105, 1031, 968, 860, 720, 614, 534 cm$^{-1}$.



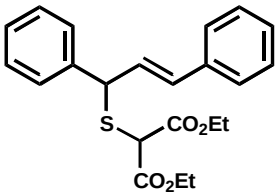

***cis*-60**

**$^{1}$H NMR:** $\delta$ 0.84 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.23 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.56-2.63 (m, 1H, $C\underline{H}_2$), 3.00 (uneven q, 1H, $C\underline{H}_2$), 3.52-3.63 (m, 1H, $OC\underline{H}_2CH_3$), 3.88-3.99 (m, 1H, $OC\underline{H}_2CH_3$), 4.15-4.28 (m, 1H, $OC\underline{H}_2CH_3$), 4.36 (dd, 1H, $J$ = 4.8 Hz, 13.7 Hz, $CH_2C\underline{H}Ar$), 4.69-4.75 (dd, 1H, $J$ = 5.2 Hz, 11.5 Hz, $SC\underline{H}Ar$), 7.44-7.19 (m, 8H, $Ar\underline{H}$), 7.66 (d, 2H, $J$ = 7.2 Hz, $Ar\underline{H}$).

**$^{13}$C NMR:** $\delta$ 13.5, 14.0, 45.1, 51.2, 53.8, 61.5, 61.8, 69.4, 127.58, 127.8, 128.1, 128.2, 128.4, 128.7, 128.7, 137.4, 140.0, 169.4, 169.7.

Pale yellow viscous liquid

**IR** (Neat) $\nu_{max}$**:** 2980, 1739, 1573, 1491, 1254, 1201, 1093, 1041, 968, 825, 723, 624, 564 $cm^{-1}$.



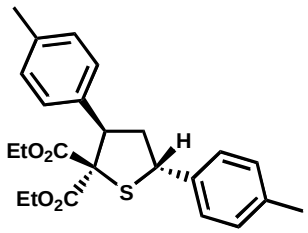

**61**

**$^{1}$H NMR:** $\delta$ 1.20-1.31 (m, 6H, $OCH_2C\underline{H}_3$) 3.89 (s, 1H, $C\underline{H}(CO_2Et)_2$), 4.08-4.25 (m, 4H, $OC\underline{H}_2CH_3$), 4.89 (d, 1H, $J$ = 9.0 Hz, $SC\underline{H}Ar$), 6.38 (dd, 1H, $J$ = 9 Hz, $J$ = 15.7 Hz, $C\underline{H}$=CHAr), 6.56 (d, 1H, $J$ = 15.6 Hz CH=$C\underline{H}Ar$), 7.27-7.45 (m, 10H, $Ar\underline{H}$).

**$^{13}$C NMR:** $\delta$ 14.0, 14.1, 51.9, 52.5, 62.2, 126.8, 127.1, 128.7, 129.0, 129.5, 131.4, 133.8, 133.9, 135.0, 136.2, 137.8, 139.0, 166.5, 166.7.

***Diethyl (E)-3,5-bis(4-methylphenyl)tetrahydrothiophene-2,2-dicarboxylate 62, Diethyl (Z)-3,5-bis(4-methylphenyl)tetrahydrothiophene-2,2-dicarboxylate 63 and Diethyl{[(2E)-1,3-di-4-methylphenylprop-2enyl]thio}malonate 64***

The diastereomeric mixture of 2,4-bis(4-methylphenyl)thietane **54** (100 mg, 0.394 mmol) and diethyl diazomalonate (88 mg, 0.472 mmol) were reacted and the reaction mixture was processed as described in the general procedure to afford products **62** (81 mg, 50 %), **63** (39 mg, 24 %) and **64** (29 mg, 18 %).




***trans*-62**

Pale yellow viscous liquid.

**IR** (neat) $\nu_{max}$**:** 2986, 1741, 1594, 1491, 1248, 1198, 1087, 1036, 958, 865, 725, 632, 575 $cm^{-1}$.

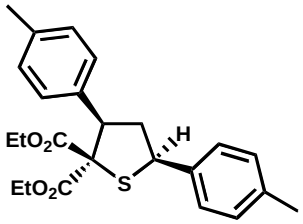
**$^1$H NMR:** $\delta$ 0.82 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.27 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.31 (s, 6H, $C\underline{H}_3$), 2.59-2.81 (m, 2H, $C\underline{H}_2$), 3.72-3.89 (m, 2H, $OC\underline{H}_2CH_3$ ), 4.28-4.34 (m, 3H, ArC$\underline{H}$, $OC\underline{H}_2CH_3$), 4.81 (t, 1H, $J$ = 7 Hz, SC$\underline{H}$Ar), 7.07-7.21 (m, 4H, Ar$\underline{H}$), 7.32 (d, 2H, $J$ = 8 Hz, Ar$\underline{H}$), 7.53 (d, 2H, $J$ = 8 Hz, Ar$\underline{H}$).

**$^{13}$C NMR:** $\delta$ 13.5, 13.9, 21.1, 21.1, 46.7, 51.7, 53.3, 62.0, 62.1, 70.6, 128.0, 128.8, 129.3, 129.6, 133.3, 137.0, 137.2, 137.7, 139.6, 167.8, 170.2.

Pale yellow viscous liquid.

**IR** (KBr) $\nu_{max}$**:** 2991, 1739, 1579, 1491, 1263, 1169, 1093, 1046, 979, 813, 725, 637, 575 $cm^{-1}$.

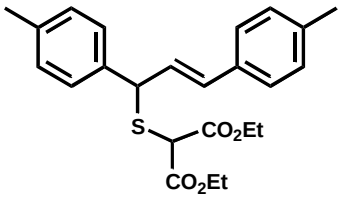
**$^1$H NMR:** $\delta$ 0.88 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.23 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.30 (s, 3H, $CH_3$), 2.35 (s, 3H, $CH_3$), 2.52-2.56 (m, 1H, $C\underline{H}_2$ ), 2.96 (uneven q, 1H, $C\underline{H}_2$), 3.59-3.65 (m, 1H, $OC\underline{H}_2CH_3$ ), 3.91-3.98 ( m, 1H, $OC\underline{H}_2CH_3$), 4.19-




***cis*-63**

4.24 ( m, 2H, OC$\underline{H}_2$CH$_3$), 4.30 (dd, 1H, *J* = 4.7 Hz, 13.7 Hz, CH$_2$C$\underline{H}$Ar ), 4.69 (dd, 1H, *J* = 5.2 Hz, 11.4 Hz, SC$\underline{H}$Ar), 7.06 (d, 2H, *J* = 8 Hz, Ar$\underline{H}$), 7.14 (d, 2H, *J* = 7.9 Hz, Ar$\underline{H}$) 7.29 (d, 2H, *J* = 8 Hz, Ar$\underline{H}$) 7.53 (d, 2H, *J* = 8 Hz, Ar$\underline{H}$).

**$^{13}$C NMR:** $\delta$ 13.5, 13.9, 21.0, 21.1, 45.0, 50.9, 53.6, 61.7, 61.8, 69.7, 127.5, 127.8, 128.2, 128.5, 128.6, 129.3, 134.1, 136.7, 137.3, 140.0, 169.3, 169.7.




**64**

Pale yellow viscous liquid.

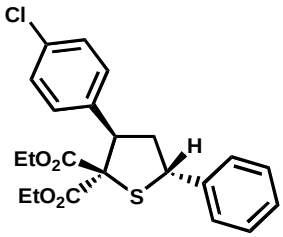
**IR** (Neat) $\nu_{max}$**:** 2990, 1740, 1571, 1494, 1248, 1211, 1091, 1051, 954, 823, 725, 632, 567 cm$^{-1}$.

**$^{1}$H NMR:** $\delta$ 1.21-1.31 (m, 6H, OCH$_2$C$\underline{H}_3$), 2.33 (s, 6H, C$\underline{H}_3$), 4.06 (s, 1H, C$\underline{H}$(CO$_2$Et)$_2$), 4.14-4.25 (m, 4H, OC$\underline{H}_2$CH$_3$), 4.84 (d, 1H, *J* = 9 Hz, SC$\underline{H}$Ar), 6.34-6.53 (m, 2H, C$\underline{H}$=C$\underline{H}$Ar), 7.08-7.32 (m, 8H, Ar$\underline{H}$).

**$^{13}$C NMR:** $\delta$ 13.5, 14.0, 21.1, 21.2, 51.7, 53.3, 61.8, 62.1, 127.7, 127.9, 128.5, 128.7, 129.3, 129.6, 133.3, 137.0, 137.2, 137.7, 139.6, 166.4, 166.6.

***Diethyl(E)-3-(4-chlorophenyl)-5-phenyltetrahydrothiophene-2,2-dicarboxylate 65a, Diethyl(E)-5-(4-chlorophenyl)-3-phenyltetrahydrothiophene-2,2-dicarboxylate 65b, Diethyl(Z)-3-(4-chlorophenyl)-5-phenyltetrahydrothiophene-2,2-dicarboxylate 66a, Diethyl(Z)-5-(4-chlorophenyl)-3-phenyltetrahydrothiophene-2,2-dicarboxylate 66b and Diethyl{[(2E)-1-(4-chlorophenyl)-3-phenylprop-2enyl]thio}malonate 67***

The diastereomeric mixture of 2-(4-chlorophenyl)-4-phenylthietane **55** (100 mg, 0.383 mmol) and diethyl diazomalonate (86 mg, 0.461 mmol) were reacted and the reaction mixture was processed as described in the general procedure to afford products **65a** (61 mg, 38 %), **65b** (10 mg, 6 %), **66a** (51 mg, 32 %), **66b** (5 mg, 3 %) and **67** (22 mg, 14 % ).



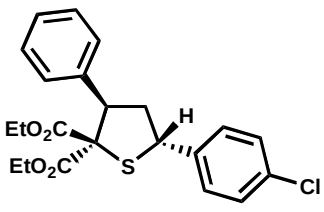

***trans*-65a**

Pale yellow viscous liquid.

**IR** (Neat) $\nu_{max}$**:** 2980, 1743, 1571, 1489, 1248, 1203, 1093, 1046, 948, 826, 723, 627, 558 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 0.87 (t, 3H, $J$ = 7.1Hz, $OCH_2C\underline{H}_3$), 1.3 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.69-2.76 (m, 2H, $C\underline{H}_2$), 3.74-3.88 (m, 2H, $OC\underline{H}_2CH_3$), 4.27-4.36 (m, 3H, ArC<u>H</u>, $OC\underline{H}_2CH_3$), 4.85 (t, 1H, $J$ = 7.1 Hz, SC<u>H</u>Ar), 7.21-7.44 (m, 9H, Ar<u>H</u>).

**$^{13}$C NMR**: $\delta$ 13.5, 14.0, 46.7, 51.7, 53.1, 62.0, 70.5, 127.7, 128.0, 128.7, 129.1, 129.3, 129.6, 133.3, 137.2, 137.7, 139.6, 167.9, 170.2.



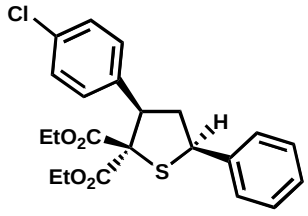

***trans*-65b**

Pale yellow viscous liquid.

**IR** (Neat) $\nu_{max}$**:** 2981, 1743, 1574, 1491, 1250, 1201, 1093, 1044, 951, 825, 720, 625, 560, $cm^{-1}$.

**$^1$H NMR:** $\delta$ 0.79 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.30 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.69-2.76 (m, 2H, $C\underline{H}_2$), 3.74-3.88 (m, 2H, $OC\underline{H}_2CH_3$), 4.27-4.36 (m, 3H, ArC<u>H</u>, $OC\underline{H}_2CH_3$), 4.85 (t, 1H, $J$ = 7.1 Hz, SC<u>H</u>Ar), 7.21-7.44 (m, 9H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 13.6, 14.0, 46.7, 51.7, 53.3, 62.1, 70.6, 127.7, 128.0, 128.7, 129.1, 129.3, 129.6, 133.3, 137.2, 137.7, 139.6, 167.9, 170.2.



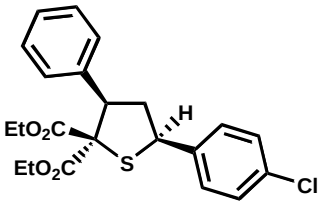

***cis*-66a**

Pale yellow viscous liquid.

**IR** (Neat) $\nu_{max}$**:** 2983, 1739, 1574, 1491, 1258, 1198, 1091, 1051, 948, 851, 728, 625, 568, cm$^{-1}$.

**$^{1}$H NMR:** $\delta$ 0.91 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.23 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.53-2.6 (m, 1H, $C\underline{H}_2$ ), 2.95 (uneven q, 1H, $C\underline{H}_2$), 3.58-3.68 (m, 1H, $OC\underline{H}_2CH_3$), 3.95-4.01 (m, 1H, $OC\underline{H}_2CH_3$), 4.21-4.34 (m, 3H, $OC\underline{H}_2CH_3$, $CH_2C\underline{H}$Ar), 4.74 (dd, 1H, $J$ = 5.2 Hz, 11.3 Hz, SC<u>H</u>Ar), 7.23-7.4 (m, 7H, Ar<u>H</u>), 7.59-7.66 (m, 2H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 13.5, 14.0, 44.9, 50.4, 53.1, 61.9, 69.0, 127.7, 127.9, 128.3, 128.6, 128.8, 129.6, 130.0, 133.6, 135.7, 139.7, 169.2, 169.7.




***cis*-66b**

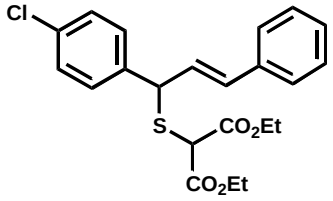
Pale yellow viscous liquid.

**IR** (Neat) $\nu_{max}$: 2981, 1739, 1574, 1490, 1259, 1200, 1096, 1049, 950, 851, 729, 627, 570 cm$^{-1}$.

**$^{1}$H NMR:** $\delta$ 0.83 (t, 3H, $J$ =7.1 Hz, $OCH_2C\underline{H}_3$), 1.23 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.53-2.6 (m, 1H, $C\underline{H}_2$ ), 2.95 (uneven q, 1H, $C\underline{H}_2$ ), 3.58-3.68 (m, 1H, $OC\underline{H}_2CH_3$), 3.95-4.01 (m, 1H, $OC\underline{H}_2CH_3$),

4.21-4.34 ( m, 3H, OC<u>H</u>$_2$CH$_3$, CH$_2$C<u>H</u>Ar), 4.74 ( dd, 1H, *J* = 5.2 Hz, 11.3 Hz, SC<u>H</u>Ar), 7.23-7.4 (m, 7H, Ar<u>H</u>), 7.59-7.66 (m, 2H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 13.6, 14.0, 45.0, 51.1, 53.8, 62.0, 72.8, 127.7, 127.9, 128.3, 128.6, 128.8, 129.6, 130.0, 133.6, 135.7, 139.7, 169.2, 169.7.




**67**

Pale yellow viscous liquid.

**IR** (Neat) $\nu_{max}$: 2983, 1740, 1578, 1488, 1248, 1201, 1083, 1051, 968, 828, 727, 621, 569 cm$^{-1}$.

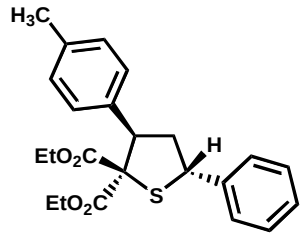
**$^{1}$H NMR:** $\delta$ 1.22-1.33 (m, 6H, OCH$_2$C<u>H</u>$_3$), 4.05 (s, 1H, C<u>H</u>(CO$_2$Et)$_2$), 4.14-4.25 (m, 4H, OC<u>H</u>$_2$CH$_3$), 4.88 (d, 1H, *J* = 8.9 Hz, SC<u>H</u>Ar) 6.34 (dd, 1H, *J* = 8.9 Hz, *J* = 15.7 Hz, C<u>H</u>=CHAr), 6.51(d, 1H, *J* = 15.6 Hz, CH=C<u>H</u>Ar), 7.23-7.43 (m, 9H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 14, 14.0, 51.9, 52.5, 62,1, 62.2, 126.7, 127.9, 128.1, 128.7, 128.9, 130.0, 129.1, 129.5, 131.3, 133.8, 134.9, 139.0, 166.5, 166.7.

***Diethyl(E)-3-(4-methylphenyl)-5-phenyltetrahydrothiophene-2,2-dicarboxylate <u>68a</u>, Diethyl(E)-5-(4-methylphenyl)-3-phenyltetrahydrothiophene-2,2-dicarboxylate <u>68b</u>, Diethyl(Z)-3-(4-methylphenyl)-5-phenyltetrahydrothiophene-2,2-dicarboxylate <u>69a</u>, Diethyl(Z)-5-(4-methylphenyl)-3-phenyltetrahydrothiophene-2,2-dicarboxylate <u>69b</u> and Diethyl{[(2E)-1-(4-methylphenyl)-3-phenylprop-2enyl]thio}malonate <u>70</u>***

The diastereomeric mixture of 2(4-methylphenyl)-4-phenylthietane **56** (100 mg, 0.417 mmol) and diethyl diazomalonate (92 mg, 0.499 mmol) were reacted and the reaction mixture was processed as described in the general procedure to afford products

**68a** (53 mg, 32 %), **68b** (6 mg, 4 %), **69a** (43 mg, 26 %), **69b** (3 mg, 2 %) and **70**(28 mg, 17 %).



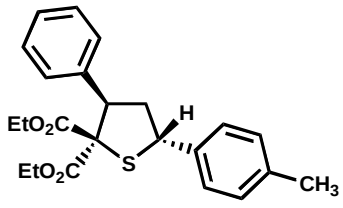

***trans*-68a**

Pale yellow viscous liquid.

**IR** (Neat) $\nu_{max}$: 2983, 1745, 1596, 1491, 1248, 1195, 1093, 1039, 958, 875, 760, 620, 561 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 0.79 (t, 3H, $J$ = 7.1Hz, $OCH_2C\underline{H}_3$), 1.29 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.34 (s, 3H, $C\underline{H}_3$), 2.67-2.75 (m, 2H, $C\underline{H}_2$), 3.73-3.87 (m, 2H, $OC\underline{H}_2CH_3$), 4.26-4.36 (m, 3H, ArC<u>H</u>, $OC\underline{H}_2CH_3$), 4.84 (t, 1H, $J$ = 7.8 Hz, SC<u>H</u>Ar), 7.09 (d, 2H, $J$ = 7.5 Hz, Ar<u>H</u> ), 7.19-7.45 (m, 7H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 13.4, 14.0, 21.0, 46.5, 51.9, 53.6, 61.8, 71.0, 127.4, 127.9, 128.2, 128.5, 129.2, 136.3, 136.9, 137.0, 137.9, 141.0, 167.9, 170.19.




***trans*-68b**

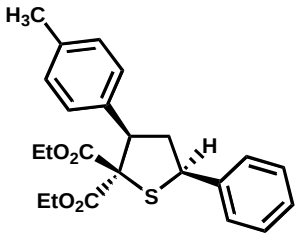
Pale yellow viscous liquid.

**IR** (Neat) $\nu_{max}$: 2982, 1745, 1595, 1489, 1247, 1196, 1091, 1038, 956, 876, 762, 618, 563 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 0.79 ( t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.29 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.31 (s, 3H, $C\underline{H}_3$), 2.67-2.75 (m, 2H, $C\underline{H}_2$), 3.73-3.87 (m, 2H, $OC\underline{H}_2CH_3$), 4.26-4.36 (m, 3H, ArC<u>H</u>, $OC\underline{H}_2CH_3$), 4.84 (t, 1H, $J$ = 7.8 Hz, SC<u>H</u>Ar), 7.09 (d, 2H, $J$ = 7.5 Hz, Ar<u>H</u> ), 7.19-7.45 (m, 7H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 13.5, 14.1, 21.0, 46.6, 52.2, 53.6, 62.0,

71.0, 127.4, 127.9, 128.2, 128.6, 129.2, 136.3, 136.9, 137.9, 141.0, 167.9, 170.2.




***cis*-69a**

Pale yellow viscous liquid.

**IR** (Neat) $\nu_{max}$: 2983, 1738, 1594, 1491, 1249, 1198, 1091, 1039, 948, 819, 728, 625, 578 $cm^{-1}$.

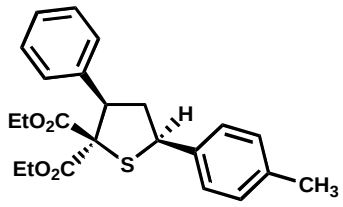
**$^{1}$H NMR:** $\delta$ 0.84 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.23 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.29 (s, 3H, $C\underline{H}_3$), 2.54-2.58 (m, 1H, $C\underline{H}_2$), 2.98 (uneven q, 1H, $C\underline{H}_2$), 3.52-3.68 (m, 1H, $OC\underline{H}_2CH_3$), 3.89-3.98 ( m, 1H, $OC\underline{H}_2CH_3$), 4.16-4.37 (m, 3H, $OC\underline{H}_2CH_3$, $CH_2C\underline{H}Ar$), 4.73 (dd, 1H, $J$ = 5 Hz, $J$ = 11 Hz, $SC\underline{H}Ar$), 7.06 (d, 1H, $J$ = 7.8 Hz, $Ar\underline{H}$), 7.15 (d, 1H, $J$ = 7.8 Hz, $Ar\underline{H}$), 7.21-7.36 (m, 2H, $Ar\underline{H}$), 7.40-7.43 (m, 3H, $Ar\underline{H}$), 7.53 (d, 1H, $J$ = 7.8 Hz, $Ar\underline{H}$), 7.65 (d, 1H, $J$ = 7.2 Hz, $Ar\underline{H}$).

**$^{13}$C NMR:** $\delta$ 13.5, 14.0, 21.1, 45.0, 51.0, 53.6, 61.7, 69.7, 127.5, 127.8, 128.2, 128.6, 128.7, 129.3, 134.1, 136.8, 137.4, 140.1, 169.3, 169.8.

Pale yellow viscous liquid.

**IR** (Neat) $\nu_{max}$: 2983, 1738, 1594, 1491, 1249, 1198, 1091, 1039, 948, 819, 728, 625, 578 $cm^{-1}$.

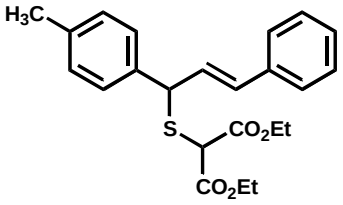
**$^{1}$H NMR:** $\delta$ 0.84 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.23 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.34 (s, 3H, $CH_3$), 2.54-2.58 (m, 1H, $C\underline{H}_2$), 2.98 (uneven q, 1H,




***cis*-69b**

C$\underline{H}_2$), 3.52-3.68 (m, 1H, OC$\underline{H}_2$CH$_3$), 3.89-3.98 ( m, 1H, OC$\underline{H}_2$CH$_3$), 4.16-4.37 ( m, 3H, OC$\underline{H}_2$CH$_3$, CH$_2$C$\underline{H}$Ar), 4.73 (dd, 1H, *J* = 5 Hz, *J* = 11Hz, SC$\underline{H}$Ar), 7.06 (d, 1H, *J* = 7.8 Hz, Ar$\underline{H}$), 7.15 (d, 1H, *J* = 7.8 Hz, Ar$\underline{H}$), 7.21-7.36 (m, 2H, Ar$\underline{H}$), 7.40-7.43 (m, 3H, Ar$\underline{H}$), 7.53 (d, 1H, *J* = 7.8 Hz, Ar$\underline{H}$), 7.65 (d, 1H, *J* = 7.2 Hz, Ar$\underline{H}$).

**$^{13}$C NMR:** $\delta$ 13.5, 14.0, 21.2, 45.0, 51.1, 53.7, 61.8, 69.7, 127.5, 127.8, 128.2, 128.6, 128.7, 129.3, 134.1, 136.8, 137.1, 137.4, 169.4, 169.8.




**70**

Pale yellow viscous liquid.

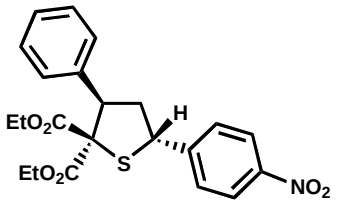
**IR** (Neat) $\nu_{max}$: 2991, 1740, 1602, 1498, 1249, 1204, 1091, 1039, 978, 849, 728, 645, 570 cm$^{-1}$.

**$^{1}$H NMR**: $\delta$ 1.22-1.31 (m, 6H, OCH$_2$C$\underline{H}_3$), 2.33 (s, 3H, C$\underline{H}_3$), 4.07 (s, 1H, C$\underline{H}$(CO$_2$Et)$_2$), 4.08-4.22 (m, 4H, OC$\underline{H}_2$CH$_3$), 4.88 (d, 1H, *J* = 9 Hz, SC$\underline{H}$Ar), 6.34 (dd, 1H, *J* = 8.8 Hz , *J* = 15.7 Hz, C$\underline{H}$=CHAr ), 6.53 (d, 1H, *J* = 15.6 Hz, CH=C$\underline{H}$Ar), 7.08-7.44 (m, 9H, ArH).

**$^{13}$C NMR:** $\delta$ 14.0, 14.0, 51.9, 52.5, 62.2, 62.2, 126.7, 127.8, 128.5, 128.9, 131.3, 133.7, 133.8, 134.9, 136.2, 137.8, 139.0, 166.4, 166.7.

***Diethyl(E)-5-(4-nitrophenyl)-3-phenyltetrahydrothiophene-2,2-dicarboxylate 71, Diethyl(Z)-5-(4-methylphenyl)-3-phenyltetrahydrothiophene-2,2-dicarboxylate 72 and Diethyl{[(2E)- 3-(4-nitrophenyl)-1-phenylprop-2enyl]thio}malonate 73***

The diastereomeric mixture of 2-(4-nitrophenyl)-4-phenylthietane **57** (100 mg, 0.369 mmol) and diethyl diazomalonate (82 mg, 0.443 mmol) were reacted and the reaction mixture was processed as described in the general procedure to afford products **71** (57 mg, 36 %), **72** (29 mg, 18 %) and **73** (60 mg, 38 %).



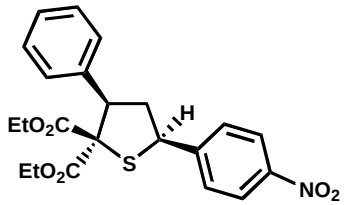

***trans*-71**

Pale yellow viscous liquid.

**IR** (Neat) $\nu_{max}$: 2981, 1745, 1605, 1522, 1446, 1344, 1187, 1041, 958, 855, 760, 612, 565 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 0.86 ( t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.31 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.72-2.87 (m, 2H, $C\underline{H}_2$), 3.73-3.96 (m, 2H, $OC\underline{H}_2CH_3$), 4.29-4.36 ( m, 3H, ArC<u>H</u>, $OC\underline{H}_2CH_3$), 4.82 (t, 1H, $J$ = 7.1 Hz, SC<u>H</u>Ar), 7.24-7.39 (m, 5H, Ar<u>H</u>), 7.66 (d, 2H, $J$ = 8.6 Hz), 8.16 (d, 2H, $J$ = 8.6 Hz).

**$^{13}$C NMR:** $\delta$ 13.4, 13.9, 45.9, 51.3, 52.9, 62.0, 62.3, 70.4, 123.5, 127.7, 128.5, 128.8, 129.1, 129.8, 138.7, 140.4, 146.6, 147.3, 167.5, 169.6.




***cis*-72**

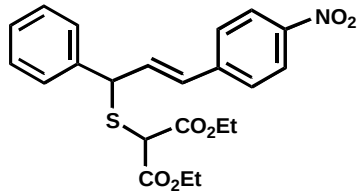
Yellow viscous liquid.

**IR** (Neat) $\nu_{max}$: 2975, 1739, 1600, 1522, 1442, 1341, 1198, 1036, 958, 860, 760, 612, 562 $cm^{-1}$.

. **$^1$H NMR:** $\delta$ 0.94 ( t, 3H, $J$ =7.1 Hz, $OCH_2C\underline{H}_3$), 1.25 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.59-2.67 (m, 1H, $C\underline{H}_2$), 3.01( uneven q, 1H, $C\underline{H}_2$), 3.54-3.69 (m, 1H, $OC\underline{H}_2CH_3$), 3.95-4.06 (m, 1H, $OC\underline{H}_2CH_3$), 4.16-4.32 (m, 3H, $CH_2C\underline{H}Ar$, $OC\underline{H}_2CH_3$), 4.40( dd, 1H, $J$ = 5.1 Hz, 11.2 Hz, SC<u>H</u>Ar), 7.27-7.38 (m,

3H, ArH), 7.62-7.65 (m, 4H, ArH), 8.13 (d, 2H, *J* = 7.4 Hz, ArH).

**$^{13}$C NMR:** $\delta$ 13.9, 14.1, 44.8, 51.2, 53.3, 62.1, 62.2, 69.0, 123.1, 123.9, 128.1, 128.7, 129.2, 129.8, 139.3, 144.8, 147. 5, 169.0, 169.3.




**73**

Pale yellow viscous liquid.

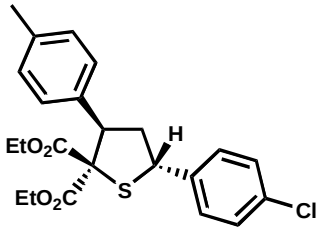
**IR** (Neat) $\nu_{max}$: 2981, 1740, 1600, 1522, 1441, 1346, 1131, 1031, 968, 855, 750, 612, 535 cm$^{-1}$.

**$^{1}$H NMR:** $\delta$ 1.25-1.35 ( m, 6H, $OCH_2CH_3$ ), 4.11 (s, 1H, $CH(CO_2Et)_2$), 4.15-4.25 (m, 4H, $OCH_2CH_3$), 5.03 (d, 1H, *J* = 8.9 Hz, SCHAr), 6.32 (dd, 1H, *J* = 8.9 Hz, *J* = 15.7 Hz, CH=CHAr), 6.59 (d, 1H, *J* = 15.6 Hz, CH=CHAr), 7.28-7.41 (m, 5H, ArH), 7.63 (d, 2H, *J* = 8.7 Hz), 8.21 (d, 2H, *J* = 8.7 Hz).

**$^{13}$C NMR:** $\delta$ 13.9, 14.0, 51.0, 51.6, 61.0, 62.3, 124.0, 126.2, 126.7, 128.0, 128.4, 128.7, 129.0, 133.9, 135.7, 146.5, 147.5, 166.1, 166.4.

***Diethyl(E)-5-(4-chlorophenyl)-3-(4-methylphenyl)tetrahydrothiophene-2,2-dicarboxylate 74, Diethyl(Z)-5-(4-chlorophenyl)-3-(4-methylphenyl)tetrahydrothiophene-2,2-dicarboxylate 75 and Diethyl{[(2E)-3-(4-chlorophenyl)-1-(4-methylphenyl)prop-2enyl]thio}malonate 76***

The diastereomeric mixture of 2-(4-chlorophenyl)-4-(4-methylphenyl)thietane **58** (100 mg, 0.364 mmol) and diethyl diazomalonate (81 mg, 0.437 mmol) were reacted and the reaction mixture was processed as described in the general procedure to afford products **74** (56 mg, 36 %), **75** (50 mg, 32 %) and **76** (19 mg, 12 %).



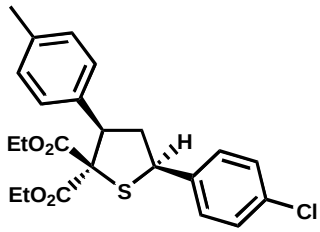

***trans*-74**

Pale yellow viscous liquid.

**IR** (Neat) $\nu_{max}$: 2986, 1745, 1595, 1486, 1253, 1196, 1093, 1041, 956, 874, 732, 638, 563 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 0.87 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.29 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.31 (s, 1H, $C\underline{H}_3$), 2.64-2.75 (m, 2H, $C\underline{H}_2$), 3.76-3.89 (m, 2H, $OC\underline{H}_2CH_3$), 4.26-4.35 (m, 3H, ArC<u>H</u>, $OC\underline{H}_2CH_3$), 4.77 (t, 1H, $J$ = 7.1 Hz, SC<u>H</u>Ar), 7.04-7.40 (m, 8H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 13.5, 14.0, 21.1, 46.7, 51.7, 53.3, 62.0, 62.1, 70.6, 128.0, 128.8, 129.3, 129.6, 133.3, 137.0, 137.2, 137.7, 139.6, 167.8, 170.2.




***cis*-75**

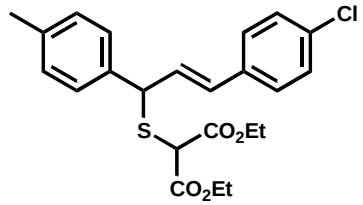
Pale yellow viscous liquid.

**IR** (Neat) $\nu_{max}$: 2981, 1738, 1579, 1491, 1253, 1193, 1091, 1036, 951, 824, 742, 698, 575 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 0.91 (t, 3H, $J$ =7.1 Hz, $OCH_2C\underline{H}_3$), 1.23 (t, 3H, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.34 (s, 1H, $C\underline{H}_3$), 2.50-2.56 (m, 1H, $C\underline{H}_2$), 2.86-2.99 (uneven q, 1H, $C\underline{H}_2$), 3.61-3.67 (m, 1H, $OC\underline{H}_2CH_3$), 3.93-3.99 (m, 1H, $OC\underline{H}_2CH_3$), 4.19-4.33 (m, 3H, $CH_2C\underline{H}$Ar, $OC\underline{H}_2CH_3$), 4.69 (dd, 1H, $J$ = 5.2 Hz, $J$ = 11.5 Hz, SC<u>H</u>Ar), 7.04-7.61 (m, 8H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 13.5, 14.0, 21.1, 44.8, 50.3, 53.4, 61.8, 61.9, 69.0, 127.9, 128.0, 128.4, 128.8, 129.4, 130.0,

133.5, 134.9, 135.8, 136.6, 137.2, 138.8, 169.1, 169.7.




**76**

Yellow viscous liquid

**IR** (Neat) $\nu_{max}$**:** 2979, 1740, 1601, 1481, 1248, 1196, 1031, 966, 876, 731, 618, 563 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 1.26-1.37 (m, 6H, $OCH_2C\underline{H}_3$), 2.33 (s, 3H, $C\underline{H}_3$), 4.06 (s, 1H, $C\underline{H}(CO_2Et)_2$), 4.19-4.24 (m, 4H, $OC\underline{H}_2CH_3$), 4.85 (d, 1H, $J$ = 9 Hz, $SC\underline{H}Ar$), 6.25 (dd, 1H, $J$ =8.9 Hz, $J$ = 15.7 Hz, $C\underline{H}$=CHAr), 6.5 (d, 1H, $J$ = 15.6 Hz, CH=$C\underline{H}$Ar), 7.09-7.39 (m, 8H, Ar$\underline{H}$).

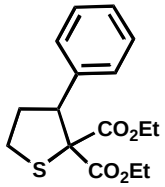
**$^{13}$C NMR:** $\delta$ 13.6, 14.0, 21.1, 51.7, 53.3, 61.9, 62.1, 127.7, 128.0, 128.5, 129.1, 129.6, 133.3, 137.0, 137.2, 137.7, 139.6, 166.4, 166.6.

***Diethyl 3-phenyltetrahydrothiophene-2,2-dicarboxylate 78 and Diethyl {[(2E)-3-phenylprop-2-enyl]thio}malonate 79***

A solution of 2-phenylthietane **77** (100 mg, 0.666 mmol) and diethyl diazomalonate (149 mg, 0.799 mmol) were reacted and the reaction mixture was processed as described in the general procedure to afford products **78** (140 mg, 69 %) and **79** (14 mg, 10 %) as a pale yellow viscous liquids.

**IR** (Neat) $\nu_{max}$**:** 1738, 1656, 1457, 1360, 1228, 1178, 994, 723 $cm^{-1}$.

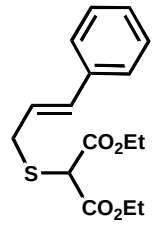
**$^1$H NMR:** $\delta$ 0.78 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7.1 Hz), 1.25 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7.1 Hz), 2.53-2.58 (m, 2H, $C\underline{H}_2$ ), 3.03-3.17 (m, 2H, $C\underline{H}_2$), 3.60- 3.64 (m,




**78**

1H, OC<u>H</u>$_2$CH$_3$), 3.87 -3.81 (m, 1H, OC<u>H</u>$_2$CH$_3$), 4.14-4.27 (m, 3H, OC<u>H</u>$_2$CH$_3$, C<u>H</u>Ar), 7.18-7.28 (m, 3H, Ar<u>H</u>), 7.39 (d, 2H, Ar<u>H</u>, *J* = 8.1Hz).

**$^{13}$C NMR:** $\delta$ 13.4, 13.8, 31.0, 36.8, 53.7, 61.7, 69.3, 127.3, 128.3, 130.3, 131.2, 131.4, 138.6, 168.6, 169.8.




**79**

**IR** (Neat) $\nu_{max}$**:** 2982, 1742, 1602, 1448, 1368, 1301, 1144, 967, 861, 752, 699 cm$^{-1}$.

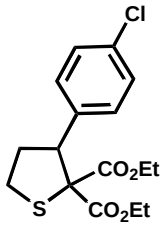
**$^{1}$H NMR:** $\delta$ 1.22-1.34 (m, 6H, OCH$_2$C<u>H</u>$_3$), 3.50 (d, 2H, SC<u>H</u>$_2$, *J* = 7.4 Hz), 4.13 (s, 1H, C<u>H</u>(CO$_2$Et)$_2$), 4.17-4.25 (m, 4H, OC<u>H</u>$_2$CH$_3$ ), 6.11-6.21 (m, 1H, CH$_2$C<u>H</u>), 6.52 (d, 1H, *J* = 15.8 Hz, C<u>H</u>Ar), 7.20-7.41 (m, 5H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 13.4, 13.8, 30.9, 53.7, 61.7, 61.8, 69.3, 127.3, 128.3, 130.1, 131.2, 131.5, 138.5, 168.5, 168.7.

***Diethyl 3-(4-chlorophenyl)tetrahydrothiophene-2,2-dicarboxylate <u>83</u> and Diethyl {[(2E)-3-(4-chlorophenyl)prop-2-enyl]thio}malonate <u>84</u>***

A solution of 2-(4-chlorophenyl)thietane **80** (100 mg, 0.384 mmol) and diethyl diazomalonate (86 mg, 0.461 mmol) were reacted and the reaction mixture was processed as described in the general procedure to afford products **83** (104 mg, 65 %) and **84** (14 mg, 9 %) as a pale yellow viscous liquids.

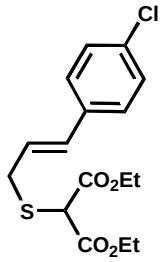
**IR** (Neat) $\nu_{max}$**:** 1745, 1656, 1461, 1367, 1248, 1162, 987, 739 cm$^{-1}$.




**83**

**$^1$H NMR:** $\delta$ 0.86 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7.1 Hz), 1.25 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7.1 Hz), 2.51-2.55 (m, 2H, $C\underline{H}_2$ ), 3.06-3.11 (m, 2H, $C\underline{H}_2$), 3.63- 3.69 (m, 1H, $OC\underline{H}_2CH_3$), 3.86 -3.9 (m, 1H, $OC\underline{H}_2CH_3$), 4.08-4.11 (m, 1H, C<u>H</u>Ar), 4.18-4.25 (m, 2H, $OC\underline{H}_2CH_3$), 7.22-7.34 (m, 4H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 13.5, 13.9, 30.8, 36.8, 53.1, 61.9, 62.4, 128.4, 129.8, 133.5, 137.1, 168.9, 169.9.




**84**

**IR** (Neat) $\nu_{max}$**:** 2980, 1745, 1600, 1448, 1364, 1305, 1143, 965, 864, 757, 690 $cm^{-1}$.

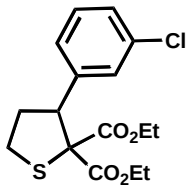
**$^1$H NMR:** $\delta$ 1.24-1.34 (m, 6H, $OCH_2C\underline{H}_3$), 3.6 (d, 2H, $SC\underline{H}_2$, $J$ = 7.4 Hz), 4.14 (s, 1H, $C\underline{H}(CO_2Et)_2$), 4.18-4.28 (m, 4H, $OC\underline{H}_2CH_3$), 6.11-6.24 (m, 1H, CH2CH), 6.51 (d, 1H, $J$ = 15.8 Hz, C<u>H</u>Ar), 7.23-7.42 (m, 5H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 13.5, 13.9, 31.0, 37.0, 61.7, 61.9, 127.3, 128.8, 130.2, 131.2, 131.5, 138.6, 168.6, 168.8.

***Diethyl 3-(3-chlorophenyl)tetrahydrothiophene-2,2-dicarboxylate* <u>85</u>**

A solution of 2-(3-chlorophenyl)thietane **81** (100 mg, 0.384 mmol) and diethyl diazomalonate (86 mg, 0.461 mmol) were reacted and the reaction mixture was processed as described in the general procedure to afford products **85** (104mg, 65 %) as a pale yellow viscous liquid.

**IR** (Neat) $\nu_{max}$**:** 1743, 1651, 1468, 1360, 1234,




**85**

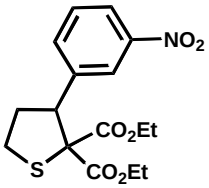
1165, 988, 743 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 0.86 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7.1 Hz), 1.3 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7 Hz), 2.54-2.58 (m, 2H, $C\underline{H}_2$ ), 3.07-3.13 (m, 2H, $C\underline{H}_2$), 3.67- 3.73 (m, 1H, $OC\underline{H}_2CH_3$), 3.87 -3.93 (m, 1H, $OC\underline{H}_2CH_3$), 4.07-4.12 (m, 1H, C<u>H</u>Ar), 4.23-4.29 (m, 2H, $OC\underline{H}_2CH_3$), 7.28-7.35 (m, 4H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 13.5, 14.0, 30.9, 36.8, 61.9, 62.0, 128.3, 129.7, 133.4, 137.1, 168.7, 168.9.

***Diethyl 3-(3-nitropheny)ltetrahydrothiophene-2,2-dicarboxylate* <u>86</u>**

A solution of 2-(4-nitrophenyl)thietane **82** (100 mg, 0.503 mmol) and diethyl diazomalonate (112 mg, 0.604 mmol) were reacted and the reaction mixture was processed as described in the general procedure to afford products **86** (116 mg, 65 %) as a pale yellow viscous liquid.




**86**

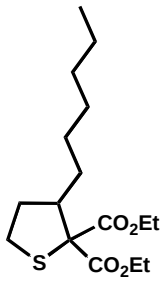
**IR** (Neat) $\nu_{max}$**:** 1747, 1652, 1467, 1362, 1238, 1168, 998, 733 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 0.89 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7.2 Hz), 1.27 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7.1 Hz), 2.61-2.67 (m, 2H, $C\underline{H}_2$ ), 3.15 (t, 2H, $C\underline{H}_2$, $J$ = 6.6 Hz), 3.67- 3.73 (m, 1H, $OC\underline{H}_2CH_3$), 3.89 -3.95 (m, 1H, $OC\underline{H}_2CH_3$), 4.19-4.28 (m, 3H, $OC\underline{H}_2CH_3$, C<u>H</u>Ar), 7.49 (t, 1H, Ar<u>H</u>, $J$ = 8 Hz), 7.79 (d, 1H, Ar<u>H</u>, $J$ = 7.7 Hz), 8.1-8.13 (m, 1H, Ar<u>H</u>), 8.24 (s, 1H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 13.8, 14.2, 30.6, 36.3, 53.2, 62.1, 68.9, 123.3, 129.0, 134.7, 140.6, 148.0, 168.2, 169.3.

***Diethyl 3-n-hexyltetrahydrothiophene-2,2-dicarboxylate* 88**

A solution of 2-*n*-hexylthietane **87** (100 mg, 0.633 mmol) and diethyl diazomalonate (141 mg, 0.759 mmol) were reacted and the reaction mixture was processed as described in the general procedure to afford product **88** (120 mg, 60 %) as a pale yellow viscous liquid.




**88**

**IR** (Neat) $\nu_{max}$**:** 2953, 1737, 160`, 1467, 1367, 1198, 1098, 838, 768, 668 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 0.89-0.98 (m, 3H, C<u>H</u>$_3$), 1.5-1.28 (m, 16H, aliphatic protons, OCH$_2$C<u>H</u>$_3$), 2.15-2.19 (m, 1H, CC<u>H</u>), 2.75-2.79 (m, 2H, CHC<u>H</u>$_2$), 3.31-3.4 (m, 2H, SC<u>H</u>$_2$), 4.13-4.34 (m, 4H, OC<u>H</u>$_2$CH$_3$).

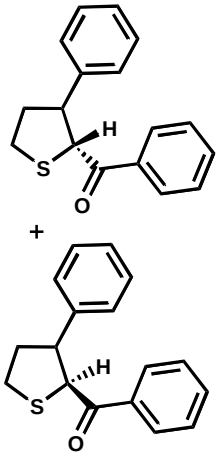
**$^{13}$C NMR:** $\delta$ 14, 14.1, 26.0, 28.4, 29.2, 29.8, 31.7, 31.9, 35.9, 41.2, 62.1, 62.4, 63.0, 163.7.

***2-Benzoyl-3-phenyltetrahydrothiophene* 90 *and* 91**

A solution of 2-phenylthietane **77** (100 mg, 0.666 mmol) and benzoyl diazomethane (130 mg, 0.799 mmol) were reacted and the reaction mixture was processed as described in the general procedure to afford isomeric mixture of products **90** and **91** (119 mg, 63 %) in the ratio 3.2:1 as a pale yellow solid.

**IR** (KBr) $\nu_{max}$**:** 2944, 1745, 1459, 1245, 1118, 1009, 905, 867, 734 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 2.33-2.40 (m, 1.31H, C<u>H</u>$_2$), 2.57-2.64 (m, 1.31H, C<u>H</u>$_2$ ), 3.00-3.10 (m, 2.63H, SC<u>H</u>$_2$), 4.03-4.15 (m, 1.31H, C<u>H</u>Ar), 4.67 (d, 0.31H, SC<u>H</u>CHAr, $J$ = 6.7 Hz), 4.75 (d, 1H, SC<u>H</u> CHAr, $J$ = 6.5 Hz), 7.17-7.31 (m, 4H, Ar<u>H</u> ), 7.37-7.45 (m, 5.3H, ArH), 7.5-7.54 (m, 1.31H, Ar<u>H</u>), 7.88-7.91



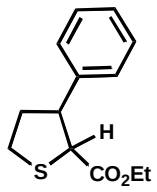
**90+91**

(m, 2.63H, ArH).

**$^{13}$C NMR:** $\delta$ 32.8, 35.9, 39.6, 48.8, 55.3, 126.9, 127.5, 128.7, 129.2, 131.8, 133.2, 136.0, 136.1, 141.8, 195.7.

***Ethyl 3-phenyltetrahydrothiophene-2-carboxylate* <u>98</u>**

A solution of 2-phenylthietane **77** (100 mg, 0.666 mmol) and ethyl diazoacetate (91 mg, 0.799 mmol) were reacted and the reaction mixture was processed as described in the general procedure to afford product **98** (87 mg, 55 %) as a pale yellow viscous liquids.



**98**

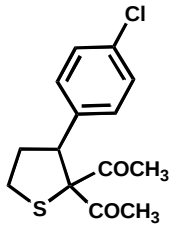
**IR** (Neat) $\nu_{max}$**:** 2934, 1742, 1598, 1448, 1367, 1268, 1178, 1023, 758, 698 cm$^{-1}$.

**$^{1}$H NMR:** $\delta$ 1.23 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7.1 Hz), 2.22-2.29 (m, 1H, $C\underline{H}_2CHAr$ ), 2.51-2.56 (m, 1H, $C\underline{H}_2CHAr$), 2.94-2.99 (m, 1H, $SC\underline{H}_2$), 3.06- 3.15 (m, 1H, $SC\underline{H}_2$), 3.69-3.77 (m, 1H, $C\underline{H}Ar$), 3.93 (d, 1H, $SC\underline{H}CO_2Et$, $J$ = 8.5 Hz ), 4.11-4.19 (m, 2H, $OC\underline{H}_2CH_3$), 7.2-7.45 (m, 5H, $Ar\underline{H}$).

**$^{13}$C NMR:** $\delta$ 14.1, 32.0, 39.4, 50.7, 53.2, 61.2, 127.2, 128.7, 129.0, 129.6, 131.9, 132.9, 172.8.

***2-Diacetyl-3-(4-chlorophenyl)tetrahydrothiophene 99***

A solution of 2-(3-chlorophenyl)thietane **72** (100 mg, 0.384 mmol) and diazoacetylacetone (58 mg, 0.461 mmol) were reacted and the reaction mixture was processed as described in the general procedure to afford products **99** (110 mg, 80 %) as a pale yellow viscous liquid.




**99**

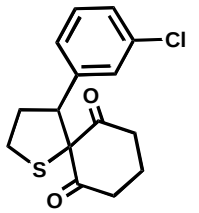
**IR** (Neat) $\nu_{max}$**:** 2856, 1702, 1597, 1472, 1353, 1193, 1088, 898, 783, 699 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 1.92 (s, 3H, COC$\underline{H}_3$), 2.22 (s, 3H, COC$\underline{H}_3$), 2.27-2.35 (m, 1H, C$\underline{H}_2$CHAr ), 2.49-2.55 (m, 1H, C$\underline{H}_2$CHAr), 2.98-3.07 (m, 2H, SC$\underline{H}_2$), 4.32-4.36 (m, 1H, C$\underline{H}$Ar), 7.32-7.49 (m, 4H, Ar$\underline{H}$).

**$^{13}$C NMR:** $\delta$ 27.1, 29.3, 31.2, 37.6, 50.5, 126.4, 127.6, 128.4, 129.9, 141.4, 199.3, 202.6.

***4-Phenyl-1-thiaspiro[4.5]decane-6,10-dione 100***

A solution of 2-(4-chlorophenyl)thietane **81** (100 mg, 0.384 mmol) and diazocyclohexane 1,3-dione (64 mg, 0.461 mmol) were reacted and the reaction mixture was processed as described in the general procedure to afford product **100** (68 mg, 48 %) as a pale yellow solid.




**100**

m.p: 96-98 °C

**IR** (KBr) $\nu_{max}$**:** 2945, 1731, 1499, 1236, 1087, 1009, 911, 834, 736 $cm^{-1}$.

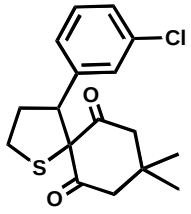
**$^1$H NMR:** $\delta$ 1.65-1.71 (m, 1H, C$\underline{H}_2$), 1.97-2.04 (m, 1H, C$\underline{H}_2$), 2.17-2.21 (m, 1H, C$\underline{H}_2$ ), 2.53-2.6 (m, 2H, C$\underline{H}_2$), 2.71-2.81 (m, 2H, C$\underline{H}_2$), 3.06-3.25 (m, 3H, C$\underline{H}_2$), 4.21-4.27 (m, 1H, C$\underline{H}$Ar), 7.16-7.28 (m, 4H, Ar$\underline{H}$).

**$^{13}$C NMR:** $\delta$ 16.4, 32.7, 35.4, 38.5, 39.0, 49.3, 70.8, 128.0, 130.5, 203.8, 204.6.

HRMS (EI) Calcd for $C_{15}H_{15}O_2ClS$: 294.0481. Found: 294.0495.

***4-(3-Chlorophenyl)-8,8-dimethyl-1-thiaspiro[4.5]decane-6,10-dione 101***

A solution of 2-(3-chlorophenyl)thietane **81** (100 mg, 0.384 mmol) and 2-diazo-5,5-dimethyl cyclohexane-1,3-dione **97** (76 mg, 460 mmol) were reacted and the reaction mixture was processed as described in the general procedure to afford product **101** (62 mg, 52 %) as a pale yellow solid.




**101**

m.p: 121-123 °C

**IR** (KBr) $\nu_{max}$**:** 2950, 1725, 1495, 1237, 1087, 1009, 913, 843, 798, 689 cm$^{-1}$.

**$^{1}$H NMR:** $\delta$ 1.27 (s, 3H, $CH_3$), 1.31 (s, 3H, $CH_3$), 2.03-2.08 (m, 2H, C$\underline{H}_2$), 2.30-2.32 (m, 1H, C$\underline{H}_2$), 2.57-2.75 (m, 3H, C$\underline{H}_2$), 3.12-3.24 (m, 2H, C$\underline{H}_2$), 4.26-4.30 (m, 1H, C$\underline{H}$Ar), 7.14-7.25 (m, 2H, Ar$\underline{H}$), 7.38-7.41 (m, 2H, Ar$\underline{H}$).

**$^{13}$C NMR:** $\delta$ 28.3, 28.6, 32.7, 35.4, 38.5, 39.0, 49.3, 71.4, 128.5, 130.6, 138.4, 200.7, 201.5.

## 2.15 References

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# CHAPTER 3

# The Reaction of Nitrene with Thietanes: A Facile Diastereoselective Synthesis of Substituted 1,2-Thiazolidines *via* Sulfonium Ylides

## 3.1 Introduction

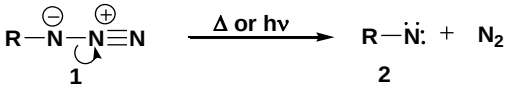
Nitrogen atom transfer reactions mediated by nitrenes, catalyzed by transition-metal complexes, have become a very appealing methodology for the synthesis of nitrogen derivatives in recent years. Thus, nitrenes have gained much importance in organic synthesis. They react with nucleophiles like sulfides to generate sulfimides, nitrogen analogs of sulfonium ylides. The [1,2]-Stevens rearrangement of sulfimides leading to the synthesis of thiazolidines constitutes the focal theme of this chapter.

## 3.2 Nitrenes

Nitrenes are neutral electron deficient species that contain monovalent nitrogen atom surrounded by a sextet of electrons. These are nitrogen analogs of carbenes. Though nitrenes can be generated in both singlet and triplet states, in the ground state, most nitrenes exist in triplet state.[1]

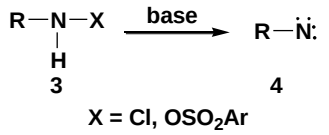
### 3.2.1 Methods for Nitrene Generation

Several methods are available in the literature for the generation of nitrenes, and the general ones are discussed below. The most common method for generating nitrene intermediate is by the thermolysis or photolysis of azides (Scheme 1).[2]



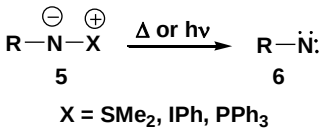

**Scheme 1**

Chloramine derivatives and aminooxosulfonyl derivatives on reaction with a base give rise to nitrenes (Scheme 2).[1]



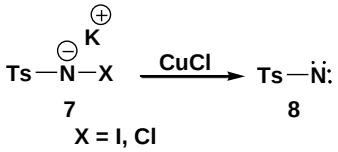

**Scheme 2**

Of the various precursors for the generation of nitrenes, ylides have become popular in recent years. These on thermolysis or photolysis generate nitrenes. The I-N ylide, *N*-tosyliminoaryliodinane is widely used for nitrene generation (Scheme 3).[3]




**Scheme 3**

Chloramine-T is also a useful and inexpensive precursor for nitrene generation (Scheme 4).[4]



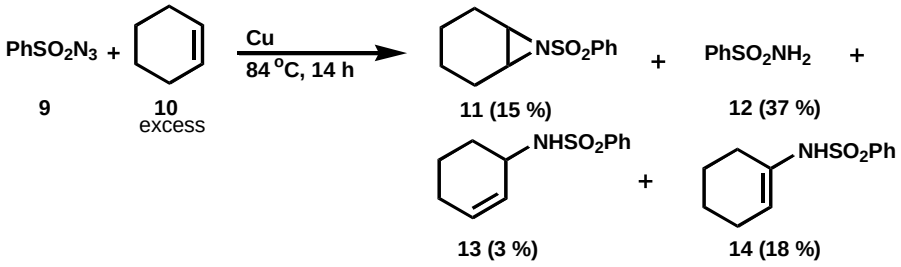

**Scheme 4**

## 3.2.2 Reactivity Profiles of Nitrenes

Nitrene reactions can be broadly classified into four categories *viz*., aziridination reactions, C-H insertion reactions, rearrangement reactions and ylide chemistry. Selected examples from each category mentioned above are discussed in the following sections.

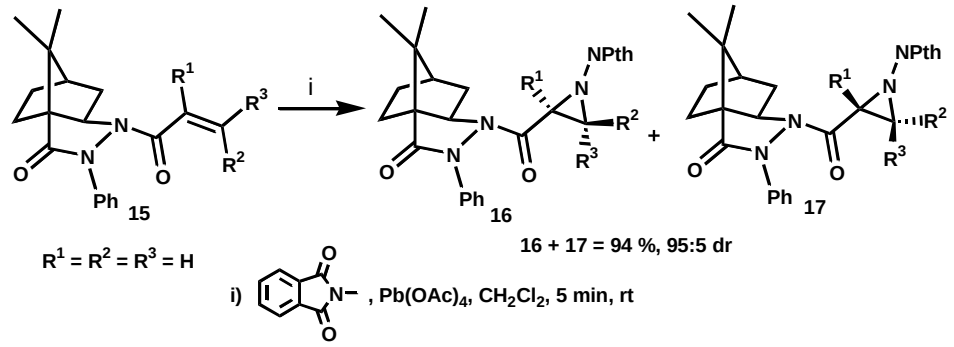
### 3.2.2.1 Aziridination

The synthesis of small, strained, highly reactive ring systems like aziridines are of great interest; they are important synthetic intermediates in the preparation of pharmaceuticals and agrochemicals.[5] The photochemical or metal-catalyzed reaction of azides is the earliest and generally accepted method for the synthesis of aziridines. The first metal-catalyzed nitrogen atom transfer reaction was reported by Kwart and Kahn.[6] An illustrative example is given below (Scheme 5).



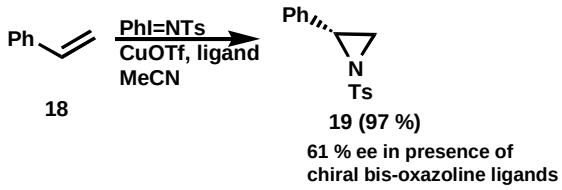

**Scheme 5**

Lead tetraacetate-induced aziridination of olefins with *N*-amino derivatives is a valuable synthetic transformation, but its application is hampered by the requirement of large amounts of the oxidizing agent. Very recently, Yang has reported a highly diastereoselective aziridination of chiral camphor *N*-enoylpyrazolidinones with *N*-aminophthalimides by oxidation with $Pb(OAc)_4$ (Scheme 6).[7]



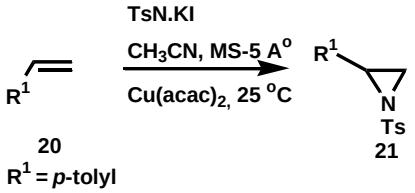

**Scheme 6**

Hypervalent, stabilized compounds like RI=NR[1] have been reported to serve as convenient aziridination reagents. The reaction of *N*-(*p*-tolylsulfonyl)imino]phenyliodinane with styrene afforded the aziridine in 61% ee in the presence of a chiral catalyst (Scheme 7).[8]



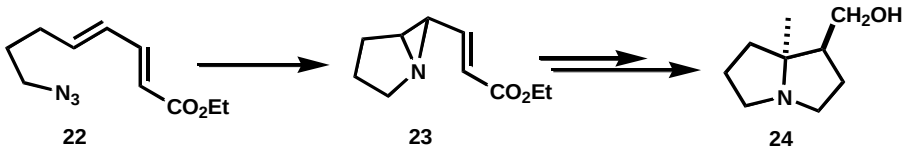

**Scheme 7**

Recently, Sain and Jain have reported *N*-iodo-*N*-potassio-*p*-toluenesulfonamide as a cheap and efficient nitrene source for the aziridination of alkenes. 4-Methylstyrene **20** on reaction with TsN.KI in the presence of catalytic amount of $Cu(acac)_2$ afforded the aziridine in 80% yield (Scheme 8).[4]



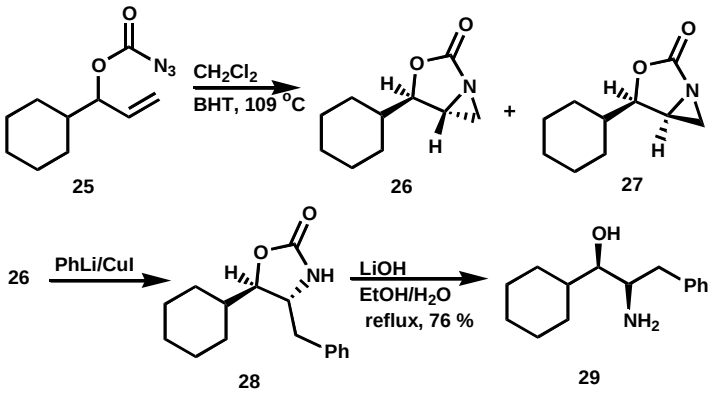

**Scheme 8**

Intramolecular aziridination reaction of azides is also well studied and this has been used in the synthesis of biologically active heterocycles like pyrrolizine derivative **24** (Scheme 9).[9]



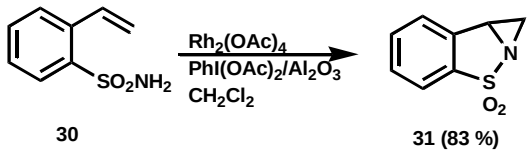

**Scheme 9**

Bergmeier has reported a facile synthesis of vicinal amino alcohols *via* a tandem intramolecular aziridination mediated by acylnitrene. An illustrative example is given in scheme 10.[10]




**Scheme 10**

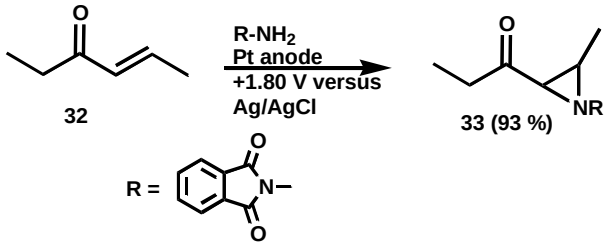
Direct intramolecular aziridination reaction involving sulfonamide **30** catalyzed by $Rh_2(OAc)_4$ with $PhI(OAc)_2$ and $Al_2O_3$ afforded aziridine **31** in excellent yield (Scheme 11).[11]




**30** **31 (83 %)**

**Scheme 11**

Electrochemical lead-mediated aziridination of alkenes using *N*-amino phthalimide as the nitrogen source has also been reported. Very recently, this procedure was modified by Hilt for the aziridination of functionalized alkenes by the direct electrochemical method under metal-free conditions.[12] A representative example is given in scheme 12.

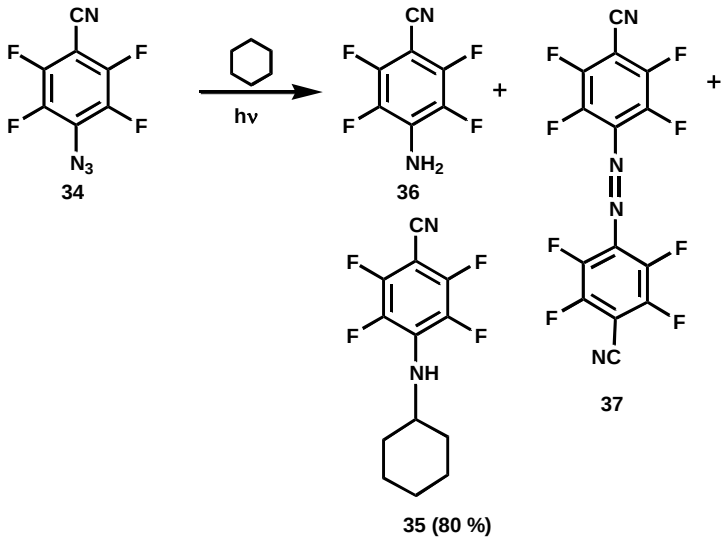



**32** **33 (93 %)**

**Scheme 12**

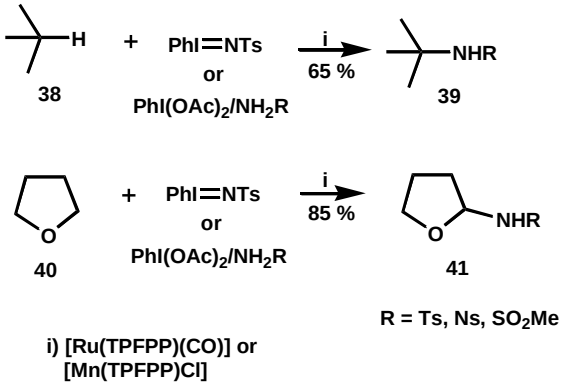
## 3.2.2.2 Insertion into C-H Bonds

C-H insertion of nitrenes is a well-studied reaction. Singlet nitrenes can undergo direct insertion into a carbon-hydrogen bond. Extensive investigations in this area have established this as an efficient method for the functionalization of unactivated C-H bonds. Photolysis of 4-azido-tertafluorobenzonitrile **34** with cyclohexane afforded the nitrene-inserted product **35** in 80 % yield along with small amounts of **36** and **37** (Scheme 13).[13]



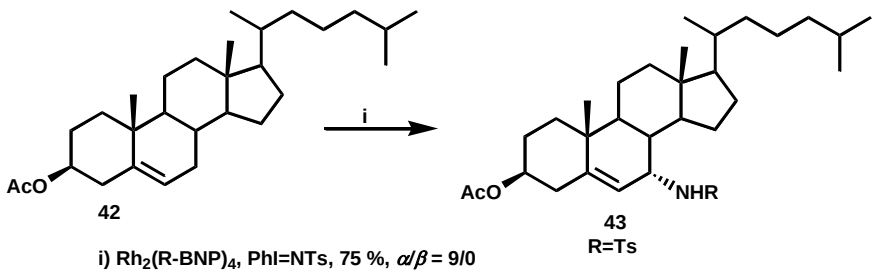

**Scheme 13**

Amidation of a variety of hydrocarbons catalyzed by ruthenium and manganese meso-tetrakis(pentafluorophenyl)porphyrins afforded *N*-substituted amides in very high yields. In the case of tetrahydrofuran, insertion occurs selectively at the C-H bond $\alpha$- to oxygen (Scheme 14).[14]



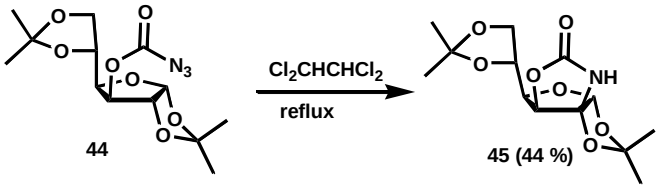

**Scheme 14**

Recently, excellent regio- and $\alpha$-selectivity has been reported for the intermolecular rhodium-catalyzed amidation of cholesteryl acetate (Scheme 15).[11]




**Scheme 15**

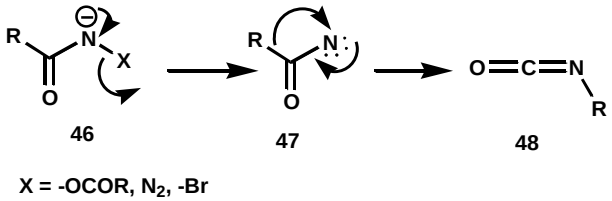
Banks *et al*. have reported the synthesis of enantiomerically pure 1,3-oxazin-2-ones *via* the nitrene insertion into C-H bonds of sugars.[15a] Recently, nitrene insertion at C-2 of diacetone-D-glucose **44** by intramolecular pathway has also been reported (Scheme 16).[15b]




**Scheme 16**

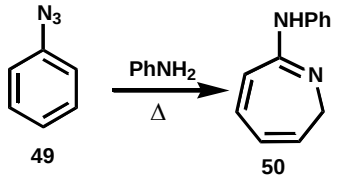
## 3.2.2.3 Rearrangements

Well-known reactions like Lossen rearrangement, Curtius rearrangement and Hofmann rearrangement are considered to occur *via* the intermediacy of nitrene as represented in scheme 17.[16]




**Scheme 17**

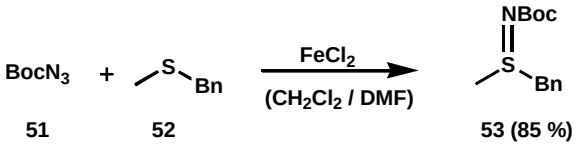
Aryl azides are known to yield ring expansion products *via* a nitrene intermediate (Scheme 18). Very recently, Platz and coworkers have reported the rearrangement of naphthylnitrenes to cyclic ketenimines and cyclic nitrile ylides.[17]




**Scheme 18**

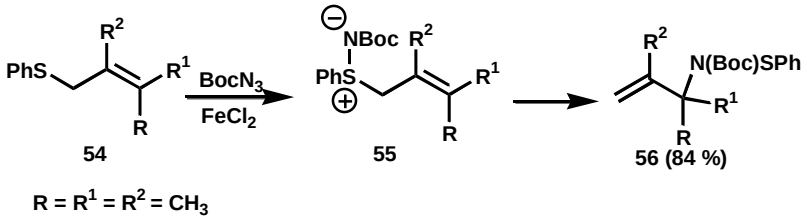
### 3.2.2.4 Ylide Chemistry

Nitrenes, being electrophilic species, react with nucleophiles to generate ylides. As early as 1971, Ando had reported the formation of sulfur ylides, *viz.*, sulfimides by the reaction of nitrenes and divalent sulfur compounds.[18a] Recently Bach *et al*. reported the iron (II)-mediated nitrene transfer from $BocN_3$ to sulfide to afford sulfimide (Scheme 19).[18b] Aryl sulfonyl azides serve as good nitrene precursors for the synthesis of sulfimides in excellent yield.



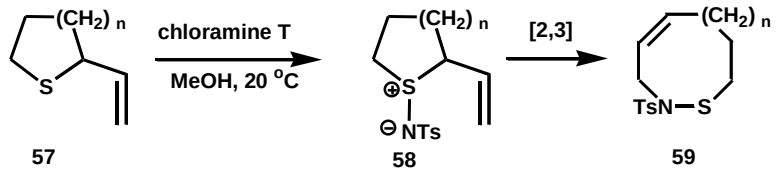

**Scheme 19**

Fe(II) catalyzed reaction of nitrenes with allyl sulfides **54**, afforded $\alpha$-branched *N-tert*-butyloxycarbonyl (Boc)-protected *N*-Allylamines **56** *via* [2,3]-sigmatropic rearrangement (Scheme 20).[19]




**Scheme 20**

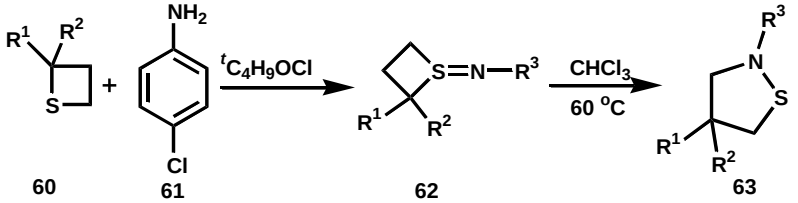
Sashida *et al*. have reported the [2,3]-sigmatropic rearrangement of $\alpha$-vinyliminosulfurane ylides **58** formed by the reaction of chloramine T with sulfides **57** (Scheme 21).[20]




57 58 59

**Scheme 21**

The thietane **60** has been reported to react with aniline and *tert*-butyl hypochlorite to form *N*-aryl-1,2-thiazolidines **63** *via* the thermal ring enlargement of thietane-1-*N*-arylimides (Scheme 22).[21] Presumably the reaction involves a nitrene intermediate.




60 61 62 63

$R^1$ = H, $R^2$ = $R^3$ = *p*-chlorophenyl

**Scheme 22**

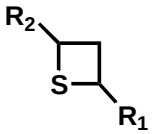
## 3.3 Present Work

In the context of our studies on sulfonium ylides generated from thietanes (Chapter 2), it was perceived that the latter would easily form ylides with nitrenes and these would undergo Stevens rearrangement to deliver thiazolidine derivatives. It is worthy of note that except for an isolated report of a limited study (*vide supra*, Scheme 22), there has not been any work in this area. We have now studied the reaction in some detail and results including the stereochemical implications of the reaction are discussed below.

## 3.4 Results and Discussion

The thietanes selected for our studies are given in Figure 1. These were prepared from the corresponding 1,3-dibromides following a literature procedure[22]. An illustrative example is given in chapter 2, Scheme 13 and the detailed experimental procedure is given in section **2.14.1** of chapter 2.

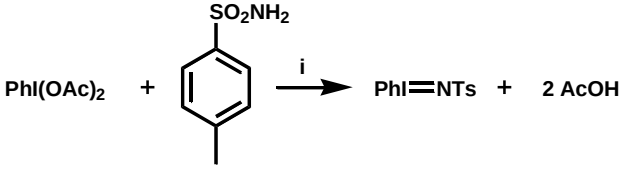
**Thietanes**




| | | | |
|---|---|---|---|
| **67** | **$R_1$= *p*-$CH_3$ phenyl, $R_2$= *p*-Cl phenyl** | **79** | **$R_1$= p-Cl phenyl, $R_2$= H** |
| **69** | **$R_1$=$R_2$= phenyl** | **81** | **$R_1$= phenyl, $R_2$= H** |
| **70** | **$R_1$=$R_2$= *p*-Cl phenyl** | **82** | **$R_1$= *p*-fluorophenyl, $R_2$= H** |
| **71** | **$R_1$= $R_2$= p-Cl phenyl** | **83** | **$R_1$= m-Cl phenyl, $R_2$= H** |
| **75** | **$R_1$= *p*-Cl phenyl,$R_2$= phenyl** | **87** | **$R_1$= *n*-hexyl, $R_2$= H** |

**Figure 1**

The I-N ylide, [N-(*p*-toly tolylsulfonyl)imino]phenyliodinane was prepared from (diacetoxyiodo)benzene and *p*-toluenesulfonamide (Scheme 23).[23]

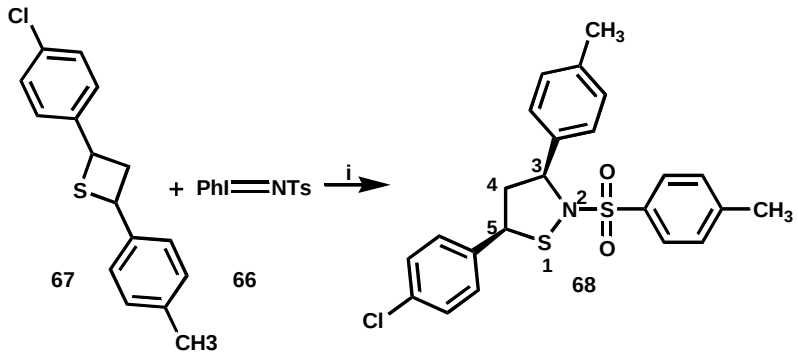



**i) KOH, methanol, 10 °C**

**Scheme 23**

## 3.4.1 Reaction of *p*-Toluenesulfonyl Nitrene with 2,4-Diarylthietanes

Our studies were initiated by heating 2-(4-chlorophenyl)-4(4-methylphenyl)thietane **67** with [*N*-(p-tolylsulfonyl)imino]phenyliodinane **66** in benzene in the presence of a catalytic amount of $Cu(acac)_2$. A facile reaction occurred to afford the thiazolidine derivative **68** in 76 % yield (Scheme 24). Interestingly, only a single isomer was obtained. Unreacted thietane **67** was recovered.




**i) Cu(acac)$_2$, benzene, 80 $^{o}$C, argon, 10 min**

**Scheme 24**

The structure of the product **68** was established by spectroscopic methods. In the IR spectrum, the sulfonyl group showed absorption bands at 1345 and 1159 cm$^{-1}$. In the $^{1}$H NMR spectrum (Figure 2), C-4 methylene protons appeared as multiplets centered at $\delta$ 2.90 and $\delta$ 2.45. The signal due to the benzylic protons on C-3 appeared at $\delta$ 5.21 as a triplet ($J$ = 7.5 Hz) and the C-5 benzylic proton was discernible as a doublet of doublet at $\delta$ 3.89 ($J$ = 6 Hz, $J$ = 10.6 Hz). In the $^{13}$C NMR spectrum (Figure 3), resonance signals of the benzylic carbons C-3 and C-5 were seen at $\delta$ 68.3 and $\delta$ 55.0 respectively. Finally, the structure assigned was confirmed unequivocally by single crystal X-ray analysis (Figure 4).

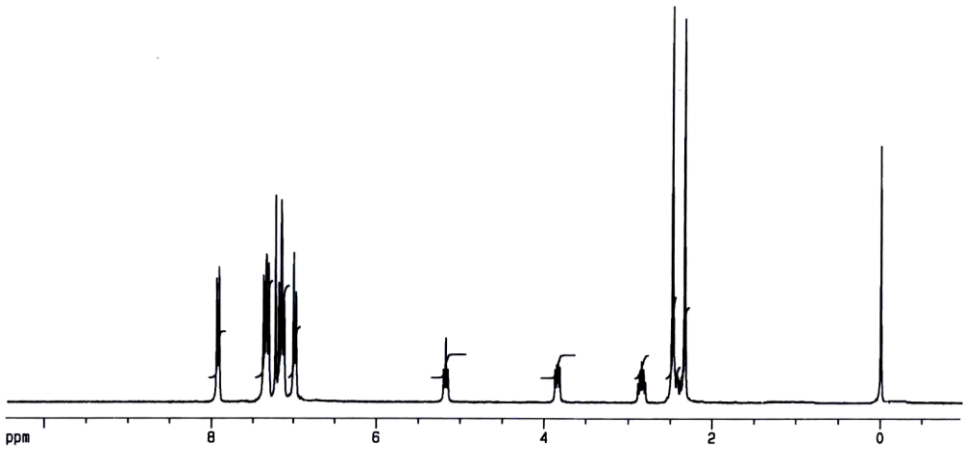



**Figure 2. $^{1}$H NMR spectrum of 68**

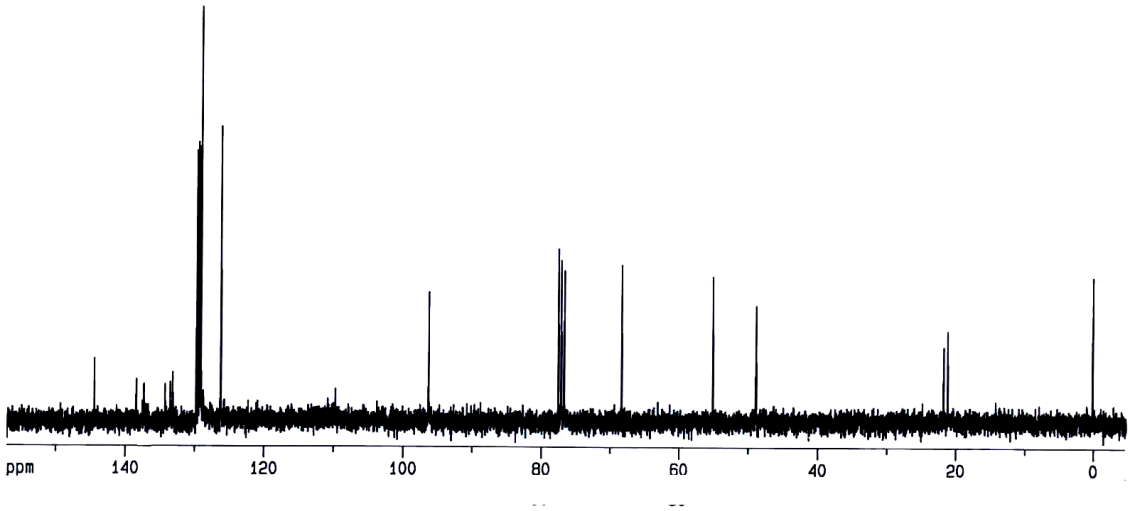



**Figure 3. $^{13}$C NMR spectrum of 68**

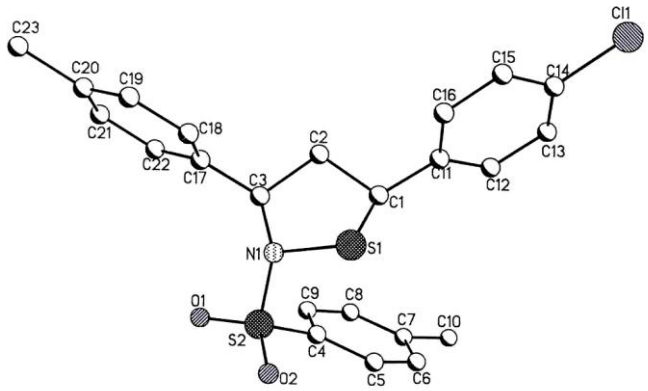
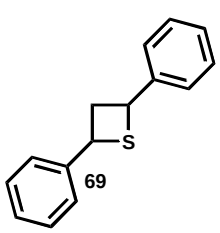
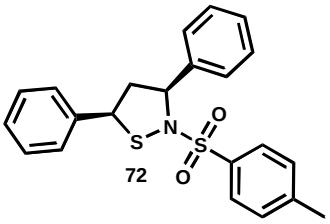
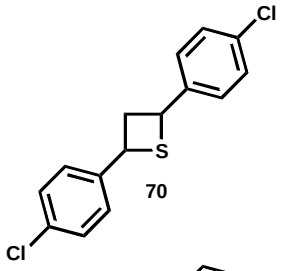
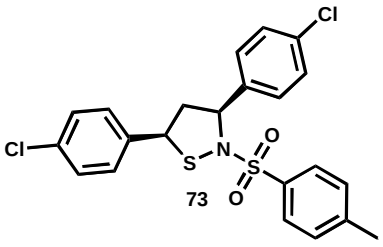
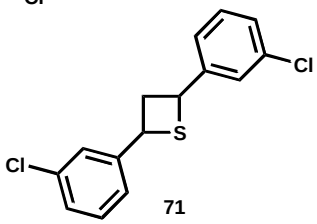
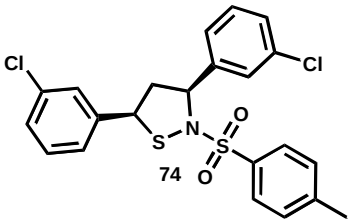



**Figure 4. X-ray structure of 68**

The experiment was repeated under a variety of conditions by changing the experimental parameters. But in all cases the only product obtained was the one derived from the cis isomer.

Similar reactivity was observed with other thietanes **69-71** and adducts **72-74** were obtained in high yields, and with complete diastereoselectivity. The results are given in Table 1.

**Table 1**

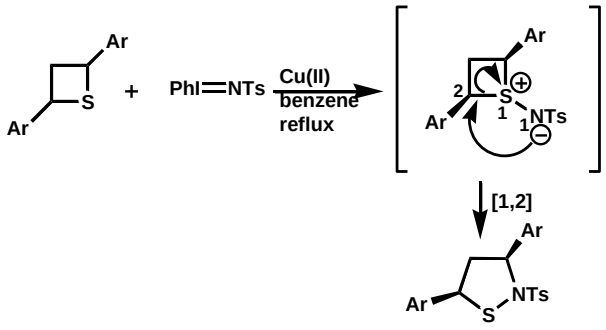
| Entry | Thietanes | Product | Yield[a] (%) |
|---|---|---|---|
| 1 |  69 |  72 | 73 |
| 2 |  70 |  73 | 72 |
| 3 |  71 |  74 | 75 |

**Reaction Conditions: PhI=NTs, $Cu(acac)_2$, benzene, 80 $^oC$, argon, 10 min**

**[a]isolated yield**

## 3.4.2 Mechanistic Considerations

A mechanistic rationale for the reaction of nitrene with thietanes leading to thiazolidines can be presented along the following lines. The thietanes used in our studies are *cis/trans* isomers as determined by HPLC and $^1$H NMR data (vide infra). It appears that from this diastereomeric mixture of thietanes the *cis* isomer selectively reacts with the nitrenoid to form the ylide intermediate (sulfimide). The latter on [1,2]-rearrangement yields the product (Scheme 25).




**Scheme 25**

The selectivity observed in the reaction was further confirmed by the HPLC analysis. The *cis:trans* ratio of the diastereomers in 2,4-bis(3-chlorophenyl)thietane **71** was found to be 1.9:1 (Figure 5A). The reaction of **71** with the nitrene (Table 1, Entry-3) afforded **74** in 75 % yield. When the recovered thietane **71** was subjected to HPLC analysis, it was found to be *cis:trans* mixture in the ratio 0.5:1 (Figure 5B). This confirms that the *cis* isomer preferentially reacted with the nitrene to afford the product.

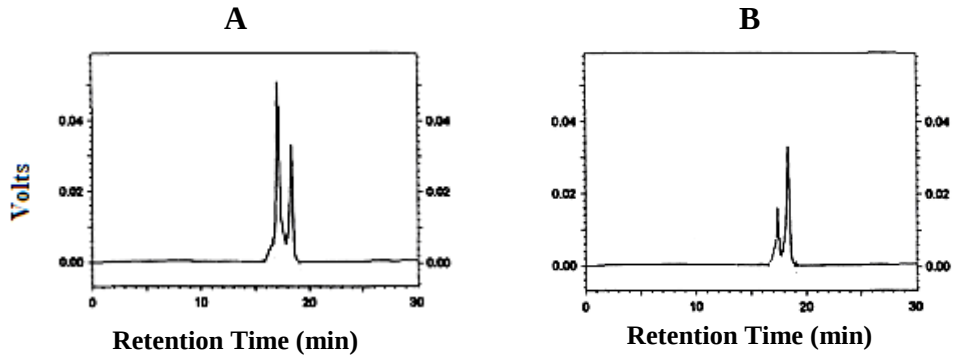
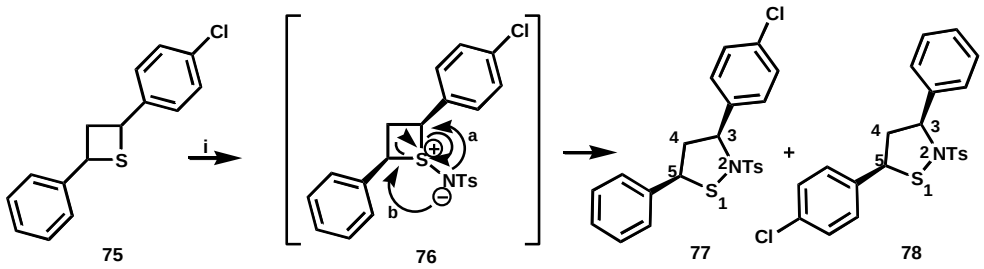



**Figure 5. HPLC traces of 71 in methanol before and after the reaction.**

Reaction of 2-(4-chlorophenyl)-4-phenylthietane **75** with (N-(p-tolylsulfonyl)imino)phenyliodinane in presence of catalytic amount of Cu(II) afforded thiazolidines **77** and **78** in 71 % yield as an inseparable mixture in the ratio 2:1.

Rearrangement of the intermediate sulfimide **76** *via* path a and path b will account for the formation of **77** and **78** respectively (Scheme 26).



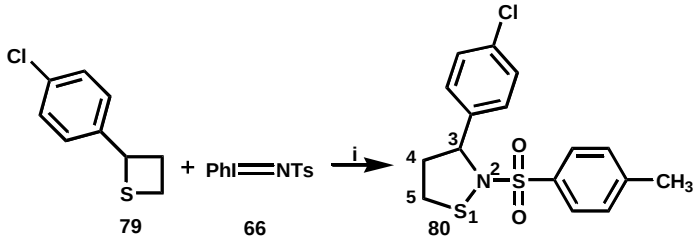

i) PhI=NTs, $Cu(acac)_2$, benzene, argon, 80 °C, 10 min

**Scheme 26**

As usual, characterization of the product was accomplished using conventional spectroscopic methods. In the $^1$H NMR spectrum of **77** and **78** the methylene protons at C-4 appeared as two multiplets centered at $\delta$ 2.43 and $\delta$ 2.95. The benzylic proton at C-3 was discernible as a multiplet centered at δ 5.22 and the C-5 proton signal appeared as a multiplet centered at $\delta$ 3.85. In the $^{13}$C NMR spectrum, the signals at $\delta$ 55.0 and $\delta$ 67.8 were assigned to benzylic carbons C-5 and C-3 respectively. All the other signals were also consistent with the proposed structure.

## 3.5 Reaction of Nitrene with Monosubstituted Thietanes

Prompted by the interesting results obtained with disubstituted thietanes, we extended the reaction of nitrene to monosubstituted thietanes. Thus Cu(II) catalyzed reaction of 2-(4-chlorophenyl)thietane **79** with (*N*-(p-tolylsulfonyl)imino)phenyliodinane afforded the thiazolidine **80** in 67 % yield (Scheme 27).




79 66 80

i) $Cu(acac)_2$, benzene, 80 °C, argon, 10 min

**Scheme 27**

The product was purified by column chromatography and its structure was ascertained on the basis of spectroscopic data. In the IR spectrum of **80**, the sulfonyl group absorbed at 1345 and 1159 $cm^{-1}$. In the $^{1}H$ NMR spectrum (Figure 6), resonance signals due to C-4 methylene protons appeared as multiplets centered at $\delta$ 2.30 and 2.15. The methylene protons at C-5 displayed their signals as multiplets centered at $\delta$ 2.63 and 2.85. The benzylic proton signal was discernible at $\delta$ 5.18 as an uneven triplet. In the $^{13}C$ NMR spectrum (Figure 7), the resonance signal of the benzylic carbon was observed at δ 66.7. All the other signals also were in agreement with the assigned structure.

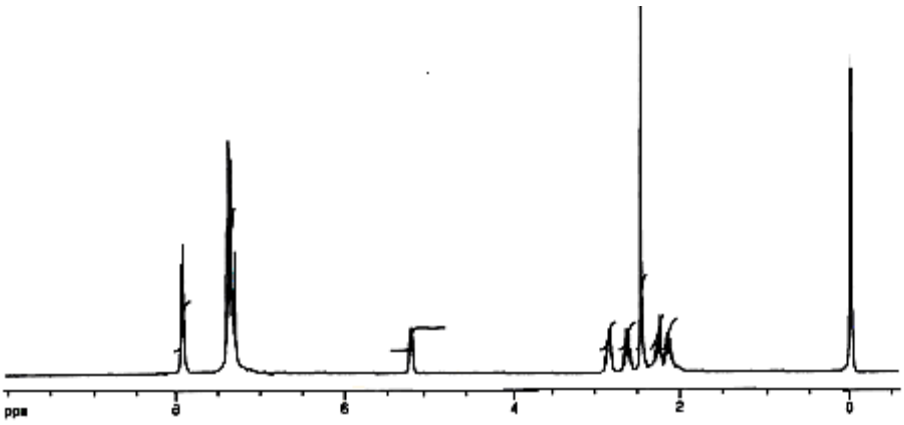



**Figure 6. $^{1}H$ NMR spectrum of 80**

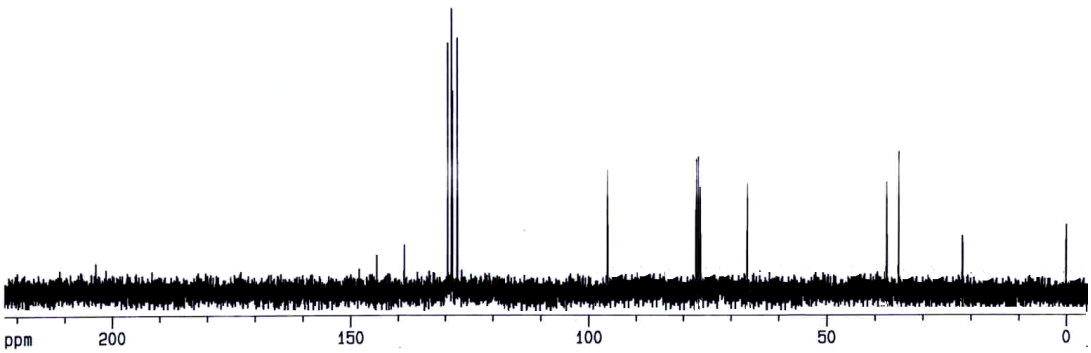
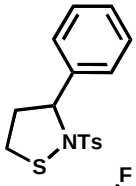
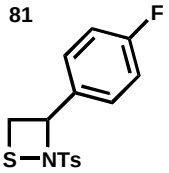
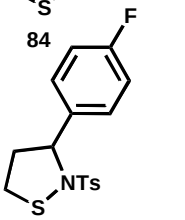
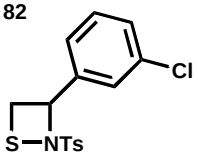
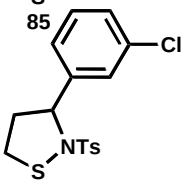



**Figure 7. $^{13}C$ NMR spectrum of 80**

Similar reaction occured with other monosubstituted thietanes **81-83** to afford the expected thiazolidines **84-86** in good yields (Table 2).

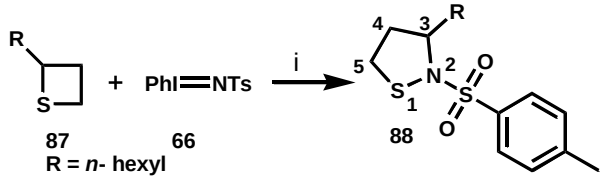
**Table 2**

| Entry | Thietanes | Products | Yields (%)[a] |
|---|---|---|---|
| 1 |  81 |  84 | 63 |
| 2 |  82 |  85 | 60 |
| 3 |  83 |  86 | 56 |

**Reagents and conditions: PhI=NTs, $Cu(acac)_2$, benzene, argon, 10 min**

**[a]isolated yield**

In a subsequent experiment, 2-*n*-hexylthietane **87** on reaction with PhI=NTs, in the presence of catalytic amount of $Cu(acac)_2$ afforded the product **88** in 54 % yield (Scheme 28).




87 66 88

R = *n*- hexyl

**i) $Cu(acac)_2$, benzene, 80 $^oC$, 10 min**

**Scheme 28**

The product **88** was separated by column chromatography and characterized using spectroscopic techniques. In the IR spectrum, the sulfonyl group absorbed at 1347 $cm^{-1}$ and 1160 $cm^{-1}$. In the $^1H$ NMR spectrum, the methyl protons on the phenyl ring resonated as a singlet at δ 2.45. The methine proton at C-3 resonated at $\delta$ 4.10 as an uneven triplet.

In the $^{13}C$ NMR spectrum, resonance signal due to C-3 carbon was observed at $\delta$ 66.6. All the other signals were also in agreement with the assigned structure.

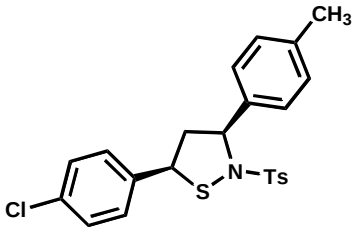
## 3.6 Conclusion

In conclusion, we have uncovered a facile reaction of (N-(p-tolylsulfonyl)imino)phenyliodinane with thietanes leading to a completely diastereoselective synthesis of thiazolidine derivatives. Our studies reveal that PhI=NTs is a convenient nitrene precursor. The experimental simplicity makes these reactions especially noteworthy.

## 3.7 Experimental Details

***5-(4-chlorophenyl)-2-[(4-methylphenyl)sulfonyl]-5- (4-methylphenyl)isothiazolidine* 68**

A diastereomeric mixture of 2-(4-chlorophenyl)-4(4-methylphenyl)thietane **67** (100 mg, 0.42 mmol), PhI=NTs (31 mg, 0.083 mmol) and 2 mol% of Cu $(acac)_2$ in 2 mL of dry benzene was refluxed under an argon atmosphere for 10 minutes. The solvent was then removed under vacuum. The residue on chromatographic separation on silica gel using 95:5 hexane-ethyl acetate solvent mixture, afforded 82 mg of the unreacted **67**. Further elution using 90:10 hexane-ethyl acetate solvent mixture afforded 26 mg of **68** (76 %) as a white crystalline solid.




**68**

mp: 124-126 °C

**IR** (KBr) $\nu_{max}$**:** 1645, 1491, 1406, 1345, 1159, 1084, 1001, 936, 821 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 2.36 (s, 3H, ArC<u>H</u>$_3$), 2.44-2.45 (m, 1H, C<u>H</u>$_2$), 2.50 (s, 3H, C<u>H</u>$_3$), 2.83-2.92 (m, 1H, C<u>H</u>$_2$), 3.89 (dd, 1H, SC<u>H</u>Ar, $J$ = 6 Hz, $J$ = 10.6 Hz), 5.21 (t, 1H, C<u>H</u>Ar, $J$ = 7.5Hz), 7.19 (d, 2H, Ar<u>H</u>, $J$ = 8.4 Hz), 7.19-7.40 ( m, 8H, Ar<u>H</u>), 7.94 (d, 2H, Ar<u>H</u>, $J$ = 8.2Hz).

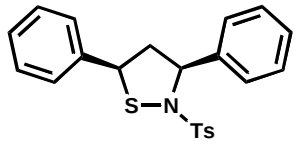
**$^{13}$C NMR:** $\delta$ 21.2, 21.8, 48.8, 55.0, 68.3, 126.1, 128.7, 129.0, 129.2, 129.7, 133.1, 133.4, 134.2, 137.3, 138.4,

144.5.

HRMS (EI) Calcd for $C_{23}H_{22}ClNO_2S_2$: 444.0103. Found: 443.9886.

***2-[(4-methylphenyl)sulfonyl]-3,5-diphenylisothiazolidine 72***

A diastereomeric mixture of 2,4-diphenylthietane **69** (100 mg, 0.44 mmol), PhI=NTs (33 mg, 0.086 mmol) and 2 mol% of $Cu(acac)_2$ in 2 mL of dry benzene was refluxed under an argon atmosphere for 10 minutes. The solvent was then removed under vacuum. The residue on chromatographic separation on silica gel using 95:5 hexane-ethyl acetate solvent mixture, afforded 80 mg of unreacted **69**. Further elution using 90:10 hexane-ethyl acetate solvent mixture afforded 23 mg of **72** (73 %) as a white crystalline solid.




**72**

mp: 114-116 °C

**IR** (KBr) $\nu_{max}$**:** 1643, 1490, 1409, 1345, 1158, 1089, 1010, 937, 821 $cm^{-1}$.

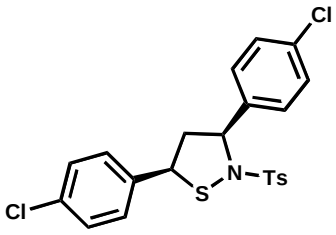
**$^1$H NMR:** $\delta$ 2.43-2.50 (m, 1H, C$\underline{H}_2$), 2.51 (s, 3H, C$\underline{H}_3$), 2.87-2.91 (m, 1H, C$\underline{H}_2$), 3.84 (dd, 1H, SC$\underline{H}$Ar, *J* = 5.9 Hz, *J* = 10.7 Hz), 5.22 (t, 1H, C$\underline{H}$Ar, *J* = 7.6 Hz), 7.08 (d, 2H, Ar$\underline{H}$, *J* = 8.4 Hz), 7.22-7.41 ( m, 10H, Ar$\underline{H}$), 7.94 (d, 2H, Ar$\underline{H}$, *J* = 8.2 Hz).

**$^{13}$C NMR:** $\delta$ 21.8, 48.8, 55.1, 67.5, 127.4, 128.7, 129.1, 129.2, 129.3, 129.4, 129.7, 139.9, 144.7.

***3,5-bis(4-chlorophenyl)-2-[(4-methylphenyl)sulfonyl]isothiazolidine 73***

A diastereomeric mixture of 2,4-bis(4-chlorophenyl)thietane **70** (100 mg, 0.34 mmol), PhI=NTs (25 mg, 0.067 mmol) and 2 mol% of $Cu(acac)_2$ in 2 mL of dry benzene was refluxed under an argon atmosphere for 10 minutes. The solvent was then removed under vacuum. The residue on chromatographic separation on silica gel using 95:5 hexane-ethyl acetate solvent mixture, afforded 82 mg of unreacted **70**. Further elution

using 90:10 hexane-ethyl acetate solvent mixture afforded 23 mg of **73** (72 %) as a white crystalline solid.




**73**

mp: 146-148 °C

**IR** (KBr) $\nu_{max}$**:** 1647, 1492, 1407, 1347, 1163, 1088, 1003, 938, 823 $cm^{-1}$.

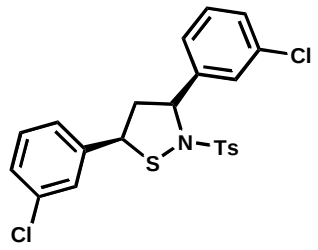
**$^1$H NMR:** $\delta$ 2.40-2.44 (m, 1H, C<u>H</u>$_2$), 2.51 (s, 3H, C<u>H</u>$_3$), 2.86-2.94 (m, 1H, C<u>H</u>$_2$), 3.89 (dd, 1H, SC<u>H</u>Ar, $J$ = 5.9Hz, $J$ = 10.7 Hz), 5.21 (t, 1H, C<u>H</u>Ar, $J$ = 7.5 Hz), 7.03 (d, 2H, Ar<u>H</u>, $J$ = 8.4 Hz), 7.2-7.41 ( m, 8H, Ar<u>H</u>), 7.93 (d, 2H, Ar<u>H</u>, $J$ = 8.2 Hz).

**$^{13}$C NMR:** $\delta$ 21.8, 48.8, 55.1, 67.6, 127.6, 128.7, 129.0, 129.1, 129.2, 129.4, 129.7, 139.9, 144.8.

HRMS (EI) Calcd for $C_{22}H_{19}Cl_2NO_2S_2$: 463.0234. Found: 463.0022.

***3,5-bis(3-chlorophenyl)-2-[(4-methylphenyl)sulfonyl]isothiazolidine <u>74</u>***

A diastereomeric mixture of 2,4-bis(3-chlorophenyl)thietane **71** (100 mg, 0.34 mmol), PhI=NTs (25 mg, 0.067 mmol) and 2 mol% of $Cu(acac)_2$ in 2 mL of dry benzene was refluxed under an argon atmosphere for 10 minutes. The solvent was then removed under vacuum. The residue on chromatographic separation on silica gel using 95:5 hexane-ethyl acetate solvent mixture, afforded 81 mg of unreacted **71**. Further elution using 90:10 hexane-ethyl acetate solvent mixture afforded 24 mg of **74** (75 %) as a colourless viscous liquid.




**74**

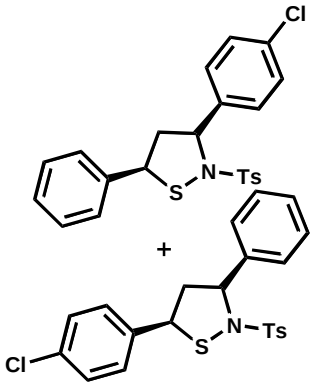
**IR** (Neat) $\nu_{max}$**:** 1640, 1490, 1401, 1346, 1162, 1089, 1002, 937, 821 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 2.42-2.44 (m, 1H, C<u>H</u>$_2$), 2.51 (s, 3H, C<u>H</u>$_3$), 2.88-2.92 (m, 1H, C<u>H</u>$_2$), 3.90 (dd, 1H, SC<u>H</u>Ar, $J$ = 5.9Hz, $J$ = 10.6 Hz), 5.21 (t, 1H, C<u>H</u>Ar, $J$ = 7.5 Hz), 7.03 (d, 2H, Ar<u>H</u>, $J$ = 8.4 Hz), 7.25-7.48 ( m, 8H, Ar<u>H</u>), 7.94 (d, 2H, Ar<u>H</u>, $J$ = 8.2 Hz)

**$^{13}$C NMR:** $\delta$ 21.7, 48.8, 55.2, 67.5, 127.6, 128.8, 129.2, 129.3, 129.3, 129.5, 129.7, 139.7, 144.7.

***3-(4-chlorophenyl)-2-[(4-methylphenyl)sulfonyl]-5-phenylisothiazolidine 77 and 5-(4-chlorophenyl)-2-[(4-methylphenyl)sulfonyl]-3-phenylisothiazolidine 78***

A diastereomeric mixture of 2-(4-chlorophenyl)-4-phenylthietane **75** (100 mg, 0.38 mmol), PhI=NTs (29 mg, 0.077 mmol) and 2 mol% of $Cu(acac)_2$ in 2 mL of dry benzene was refluxed under an argon atmosphere for 10 minutes. The solvent was then removed under vacuum. The residue when subjected to chromatography on a silica column using 95:5 hexane-ethyl acetate solvent mixture, afforded 82 mg of unreacted **75**. Further elution using 90:10 hexane-ethyl acetate solvent mixture afforded 20 mg of **77** and **78** (71 %).




**77+78**

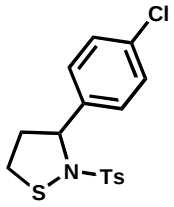
**IR** (KBr) $\nu_{max}$**:** 1645, 1491, 1407, 1344, 1158, 1081, 1007, 937, 822 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 2.40-2.44 (m, 1H, C$\underline{H}_2$), 2.51 (s, 3H, C$\underline{H}_3$), 2.86-2.95 (m, 1H, C$\underline{H}_2$), 3.81-3.92 (m, 1H, SC$\underline{H}$Ar), 5.16-5.28 (m, 1H, C$\underline{H}$Ar), 7.01 (d, 2H, Ar$\underline{H}$, $J$ = 8.5 Hz), 7.18-7.47 ( m, 9H, Ar$\underline{H}$), 7.94 (d, 2H, Ar$\underline{H}$, $J$ = 8.2 Hz)

**$^{13}$C NMR:** $\delta$ 21.7, 48.8, 55.0, 67.8, 126.1, 127.6, 127.8, 128.4, 128.7, 128.9, 129.4, 129.5, 129.6, 133.3, 141.4, 144.6.

***3-(4-chlorophenyl)-2-[(4-methylphenyl)sulfonyl]isothiazolidine 80***

2-(4-chlorophenyl)thietane **79** (100 mg, 0.54 mmol), PhI=NTs (41 mg, 0.108 mmol) and 2 mol% of $Cu(acac)_2$ in 2 mL of dry benzene was refluxed under an argon atmosphere for 10 minutes. The solvent was then removed under vacuum. The residue when subjected to chromatography on a silica column using 95:5 hexane-ethyl acetate solvent mixture, afforded 87 mg of unreacted **79**. Further elution using 90:10 hexane-ethyl acetate solvent mixture afforded 30 mg of **80** (67 %) as a white crystalline solid.




**80**

mp: 94-96 °C

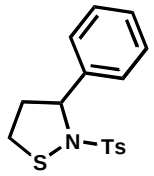
**IR** (KBr) $\nu_{max}$**:** 1681, 1572, 1451, 1345, 1159, 1091, 901 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 2.10-2.19 (m, 1H, C<u>H</u>$_2$), 2.26-2.34 (m, 1H, C<u>H</u>$_2$), 2.47 (s, 3H, C<u>H</u>$_3$), 2.60-2.66 (m, 1H, SC<u>H</u>$_2$), 2.81-2.88 (m, 1H, SC<u>H</u>$_2$), 5.18 (uneven triplet, 1H, NC<u>H</u>Ar), 7.26-7.35 (m, 6H, Ar<u>H</u>,), 7.88 (d, 2H, Ar<u>H</u>, $J$ = 8.1 Hz).

**$^{13}$C NMR:** $\delta$ 21.7, 35.1, 37.6, 66.7, 127.7, 128.6, 128.7, 128.9, 129.7, 138.7, 144.5.

### *2-[(4-methylphenyl)sulfonyl]-3-phenylisothiazolidine* <u>84</u>

2-phenylthietane **81** (100 mg, 0.66 mmol), PhI=NTs (50 mg, 0.13 mmol) and 2 mol% of $Cu(acac)_2$ in 2 mL of dry benzene was refluxed under an argon atmosphere for 10 minutes. The solvent was then removed under vacuum. The residue when subjected to chromatography on a silica column using 95:5 hexane-ethyl acetate solvent mixture, afforded 86 mg of unreacted **81**. Further elution using 90:10 hexane-ethyl acetate solvent mixture afforded 27 mg of **84** (63 %) as a white crystalline solid.




**84**

mp: 90-92 °C

**IR** (KBr) $\nu_{max}$**:** 1682, 1572, 1452, 1344, 1160, 1093, 903, 818 $cm^{-1}$.

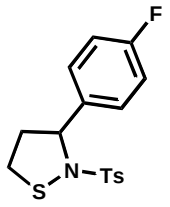
**$^1$H NMR:** $\delta$ 2.09-2.18 (m, 1H, C<u>H</u>$_2$), 2.30-2.36 (m, 1H, C<u>H</u>$_2$), 2.47 (s, 3H, C<u>H</u>$_3$), 2.62-2.70 (m, 1H, SC<u>H</u>$_2$), 2.70-2.89 (m, 1H, SC<u>H</u>$_2$), 5.26 (uneven triplet, 1H, NC<u>H</u>Ar), 7.28-7.41 (m, 7H, Ar<u>H</u>), 7.90 (d, 2H, Ar<u>H</u>, $J$ = 8.2 Hz).

**$^{13}$C NMR:** $\delta$ 21.7, 35.1, 37.6, 66.8, 128.0, 128.2, 128.7, 128. 8, 128.9, 129.7, 138.8, 144.6.

HRMS (EI) Calcd for $C_{16}H_{17}NO_2S_2$: 319.0701. Found: 319.0740.

***3-(4-flurophenyl)-2-[(4-methylphenyl)sulfonyl]isothiazolidine* 85**

2-(4-fluorophenyl)thietane **82** (100 mg, 0.595 mmol), PhI=NTs (44 mg, 0.119 mmol) and 2 mol% of $Cu(acac)_2$ in 2 mL of dry benzene was refluxed under an argon atmosphere for 10 minutes. The solvent was then removed under vacuum. The residue when subjected to chromatography on a silica column using 95:5 hexane-ethyl acetate solvent mixture, afforded 87 mg of unreacted **82**. Further elution using 90:10 hexane-ethyl acetate solvent mixture afforded 24 mg of **85** (60 %) as a colourless viscous liquid.




**85**

**IR** (Neat) $\nu_{max}$**:** 1682, 1570, 1449, 1348, 1158, 1093, 902, 818 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 2.14-2.20 (m, 1H, C<u>H</u>$_2$), 2.30-2.36 (m, 1H, C<u>H</u>$_2$), 2.48 (s, 3H, C<u>H</u>$_3$), 2.60-2.68 (m, 1H, SC<u>H</u>$_2$), 2.81-2.89 (m, 1H, SC<u>H</u>$_2$), 5.22 (uneven triplet, 1H, NC<u>H</u>Ar), 7.27-7.36 (m, 6H, Ar<u>H</u>), 7.90 (d, 2H, Ar<u>H</u>, $J$ = 8.1 Hz).

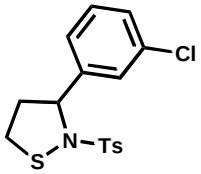
**$^{13}$C NMR:** $\delta$ 21.7, 35.1, 37.6, 66.8, 127.7, 128.7, 128.8, 128.9, 129.7, 138.7, 144.5, 158.0, 164.4.

***3-(3-chlorophenyl)-2-[(4-methylphenyl)sulfonyl]isothiazolidine* 86**

2-(3-chlorophenyl)thietane **83** (100 mg, 0.54 mmol), PhI=NTs (41 mg, 0.108 mmol) and 2 mol% of $Cu(acac)_2$ in 2 mL of dry benzene was refluxed under an argon atmosphere for 10 minutes. The solvent was then removed under vacuum. The residue when subjected to chromatography on a silica column using 95:5 hexane-ethyl acetate solvent mixture, afforded 87 mg of unreacted **83**. Further elution using 90:10 hexane-ethyl acetate solvent mixture afforded 24 mg of **86** (56 %) as a white crystalline solid.

**IR** (KBr) $\nu_{max}$**:** 1668, 1597, 1427, 1343, 1163, 1083, 898, 799 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 2.26-2.30 (m, 1H, C<u>H</u>$_2$), 2.35-2.43 (m, 1H, C<u>H</u>$_2$), 2.47 (s, 3H, C<u>H</u>$_3$), 2.62-2.67 (m, 1H, SC<u>H</u>$_2$), 2.81-2.87 (m, 1H, SC<u>H</u>$_2$), 5.18 (uneven t, 1H, NC<u>H</u>Ar), 7.25-7.36




**86**

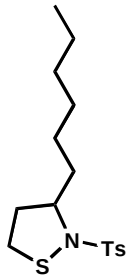
mp: 96-98 °C

(m, 6H, Ar<u>H</u>), 7.89 (d, 2H, Ar<u>H</u>, *J* = 8.1 Hz).

**$^{13}$C NMR:** $\delta$ 21.7, 35.1, 37.6, 66.8, 127.6, 128.5, 128.7, 128.9, 129.6, 138.7, 144.5.

***2-[(4-methylphenyl)sulfonyl]-3-hexylisothiazolidine* <u>88</u>**

2-*n*-hexylthietane **87** (100 mg, 0.636 mmol), PhI=NTs (48 mg, 0.127 mmol) and 2 mol% of $Cu(acac)_2$ in 2 mL of dry benzene was refluxed under an argon atmosphere for 10 minutes. The solvent was then removed under vacuum. The residue when subjected to chromatography on a silica column using 95:5 hexane-ethyl acetate solvent mixture, afforded 87 mg of unreacted **87**. Further elution using 90:10 hexane-ethyl acetate solvent mixture afforded 22 mg of **88** (54 %) as a colourless viscous liquid.




**88**

**IR** (Neat) $\nu_{max}$**:** 1665, 1596, 1432, 1347, 1160, 1088, 901, 808 $cm^{-1}$.

**$^{1}$H NMR:** $\delta$ 0.89 (t, 3H, C<u>H</u>$_3$, J = 6.1Hz), 1.25-1.30 (m, 6H, alkyl C<u>H</u>$_2$), 1.59-1.61 (m, 2H, alkyl C<u>H</u>$_2$), 2.0 -2.10 (m, 2H, C<u>H</u>$_2$), 2.30-2.34 (m, 2H, CHC<u>H</u>$_2$), 2.45 (s, 3H, C<u>H</u>$_3$), 2.78-3.0 (m, 2H, SC<u>H</u>$_2$), 4.10 (uneven triplet, 1H, NC<u>H</u>), 7.30 (d, 2H, Ar<u>H</u>, *J* = 8.1 Hz), 7.79 (d, 2H, Ar<u>H</u>, *J* = 8.3Hz).

**$^{13}$C NMR:** $\delta$ 14.2, 21.7, 22.8, 29.1, 31.5, 31.9, 32.6, 39.8, 66.6, 127.2, 127.9, 129.7, 133.2, 144.9.

## 3.8 References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# CHAPTER 4

# Thiocarbonyl Ylide: Synthon for Substituted Tetrahydrothiophene Derivatives

## 4.1 Introduction

1,3-Dipolar cycloaddition reactions which constitute a powerful tool for heterocyclic construction, were developed by the monumental efforts of Huisgen and co-workers.[1] These reactions are bimolecular in nature and involve the addition of a 1,3-dipole to a multiple π-bond system. The highly stereoselective and regioselective manner of addition is advantageous in the synthesis of natural products.[2] Thiocarbonyl ylides are reactive intermediates which can be depicted in three different ways *viz*., 1,3-dipole **1a**, biradical **1b** or even as a tetravalent sulfur species[3] **1c**. In this section the available information on the general methods of preparation of thiocarbonyl ylides and their cycloaddition to various dipolarophiles is given as a prelude to our studies on the parent thiocarbonyl ylide which forms the subject matter of this chapter.

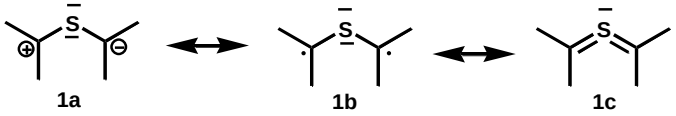
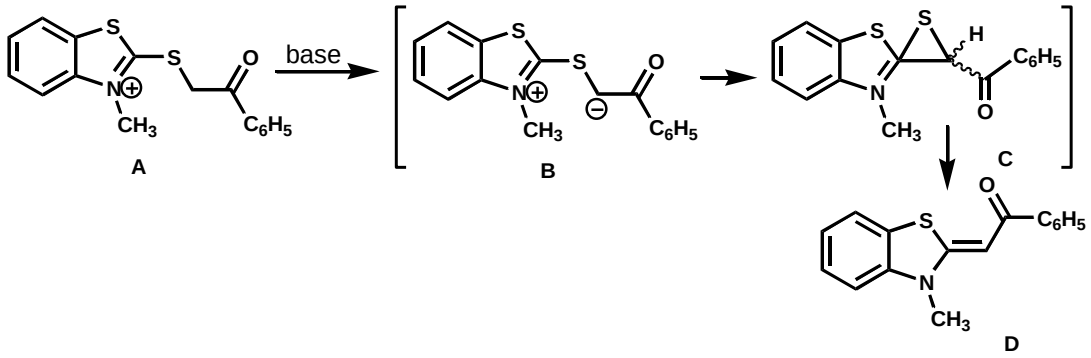



**Figure 1**

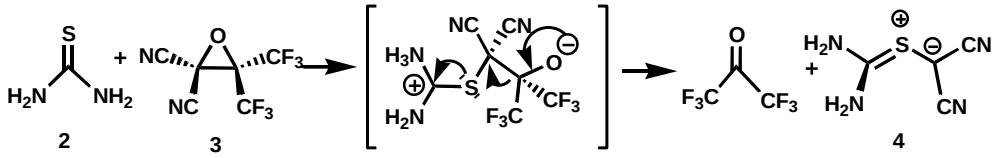
## 4.2 Generation of Thiocarbonyl Ylides

Knott was the first to establish the structure of thiocarbonyl ylide. He generated a highly unstable thiocarbonyl ylide **B**, by the deprotonation of a quaternized benzothiazole, which collapsed to thiirane and on subsequent desulfuration afforded the unsaturated thiazole derivative (Scheme 1).[4]



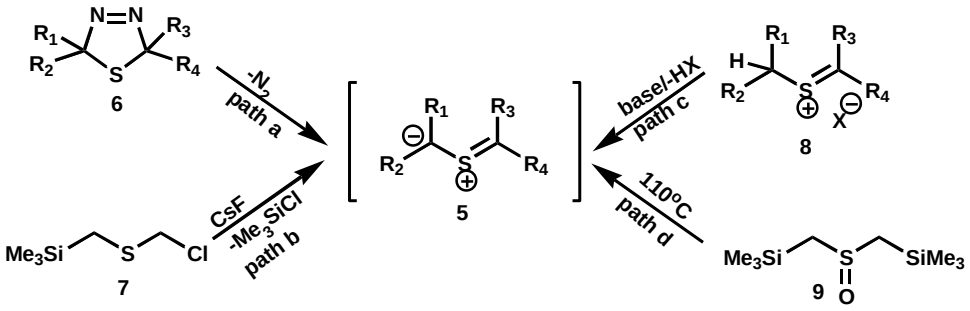

**Scheme 1**

Later, Middleton synthesised a very stable thiocarbonyl ylide **4** by the reaction of thiourea with oxirane **3**. Usually the reaction of thiourea with oxiranes affords thiiranes; however in this reaction, due to the unusual electronic properties of the oxirane, cleavage of the C-C bond intercedes to afford the stable ylide **4** (Scheme 2).[5]




**Scheme 2**

In general, thiocarbonyl ylides are highly reactive, short lived species which can be generated *in situ* by several methods (Scheme 3). These include the thermal decomposition of 1,3,4-thiadiazolines **6** (path a)[8], CsF catalyzed elimination of trimethylsilylchloride from chloromethyl trimethylsilylmethyl sulfide **7** (path b)[9], deprotonation of sulfenium salts **8** (path c)[10] and also the thermal decomposition of bis(trimethylsilylmethyl) sulfoxide **9** (path d).[11] Flash vacuum pyrolysis of 1,3-oxathiolan-5-ones is another accepted method for the ylide generation.[12]



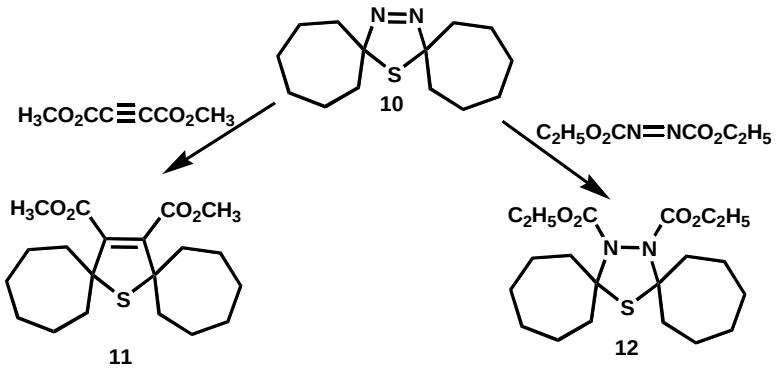

**Scheme 3**

Among these methods, the most flexible and general route for the generation of the ylide is from 1,3,4-thiadiazoline which smoothly releases nitrogen on thermolysis, generating the ylide *in situ* (path a). This method is well developed for the generation of substituted ylides.

## 4.3.1 Thiadiazolines

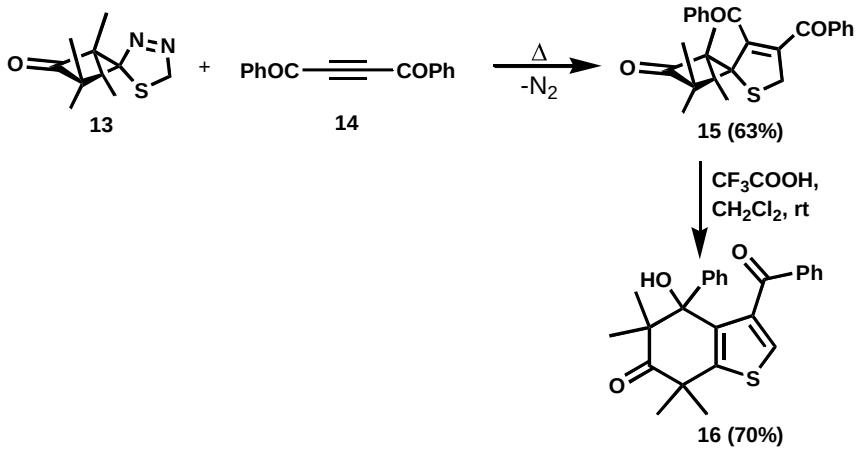
1,3,4-Thiadiazolines, precursors for thiocarbonyl ylides, decompose to ylides which undergo addition reactions with a wide variety of dipolarophiles.[13-15] They are known to collapse to give episulfides on nitrogen extrustion.[16] These synthetically important molecules are prepared from the corresponding aldehydes or ketones, hydrazine and hydrogen sulfide, which condenses spontaneously at -20 $^{o}$C.[17]

Kellogg and co-workers have reported the cycloaddition reactions of the ylide generated form cycloheptyl substituted thiadiazoline **10** with dimethyl acetylenedicarboxylate (DMAD) and diethyl azodicarboxylate (Scheme 4).[13]




**Scheme 4**

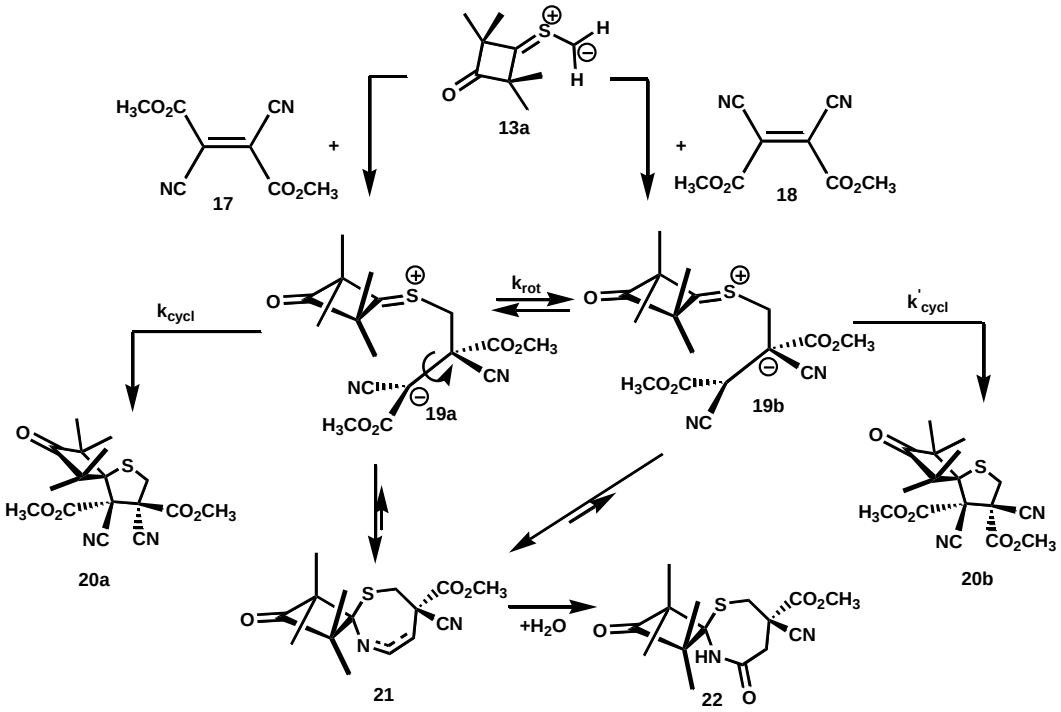
Mlostoń et al. have reported that 2,2,4,4-tetramethyl-3-thioxocyclobutanone S-methylide **13** on thermolysis underwent cycloaddition with **14** to afford the spiroadduct **15**. Under acidic conditions, the spirocyclic product **15** isomerizes *via* opening of the cyclobutanone ring followed by aromatization of the five-membered ring to yield thiophene derivative **16** (Scheme 5).[18]




**Scheme 5**

Recently, cycloaddition of sterically hindered thiocarbonyl ylide **13a** with electrophilic *cis/trans* isomeric dipolarophiles have been reported.[19] Dimethyl 2,3-dicyanofumarate **17** and dimethyl 2,3-dicyanomaleate **18** were used as dipolarophiles.

Huisgen proposed a non-concerted pathway for these reactions. The stereochemical integrity is still preserved in the reaction (Scheme 6).

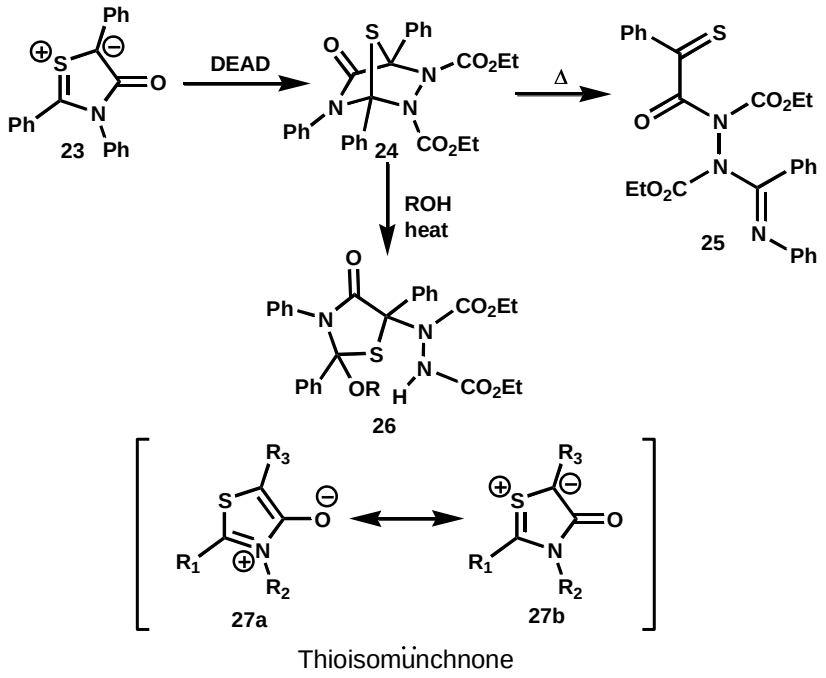


**Scheme 6**

## 4.3.2 Thioisomünchnones

Thioisomünchnones are compounds containing a thiazole ring with two inherent mesoionic systems. A representative example is shown in Scheme 6. Each of these mesoionic rings is a masked 1,3-dipole. Thioisomünchnones thus possess a thiocarbonyl ylide dipole. These compounds have attracted attention because of their ease of preparation, interesting physical properties and the propensity of their thiocarbonyl ylide dipole to undergo dipolar cycloaddition. Thioisomünchnones have been trapped by various dipolarophiles like dimethyl maleate, fumarate, N-phenylmaleimide, maleic anhydride, methyl vinyl ketone, acrylonitrile, *etc* resulting in complex heterocyclic ring systems.[20-22] They even undergo cycloadditon with nitrogen-containing dipolarophiles like diethyl azodicarboxylate (DEAD) (Scheme 7).[23] Heating of the cycloadduct **24**

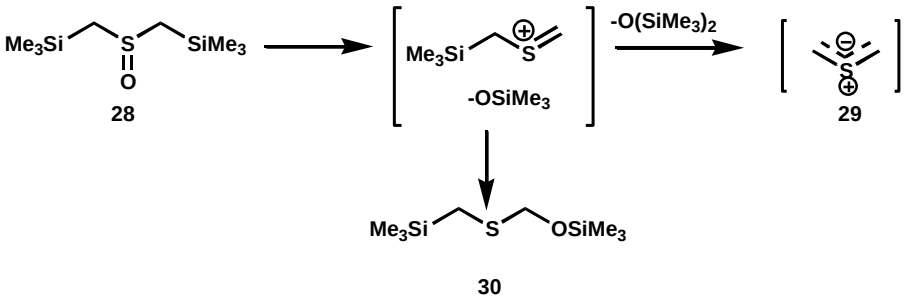
generated a blue compound **25**, and in alcoholic medium (methanol or ethanol), addition of the alcohol to the cycloadduct yielded compound **26**.




**Scheme 7**

### 4.3.3 Thioformaldehyde S-methylide

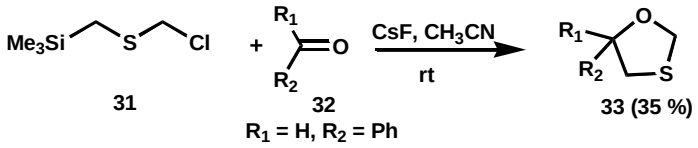
Although ylide generation from thiadiazolines and effective trapping of the ylide has been extensively studied, preparation of the parent thiocarbonyl ylide was reported only in 1986. Achiwa *et al*. were the first to report the generation of the thioformaldehyde S-methylide **29** under neutral and mild conditions. The ylide, generated *in situ* was trapped using conjugated dipolarophiles. The strategy involved is the release of disiloxane from bis(trimethylsilylmethyl) sulfoxide **28** through a pathway related to the sila-Pummerer rearrangement (Scheme 8).[11] The conjugated dipolarophiles used were maleimide, DMAD, maleate and fumarate.




**Scheme 8**

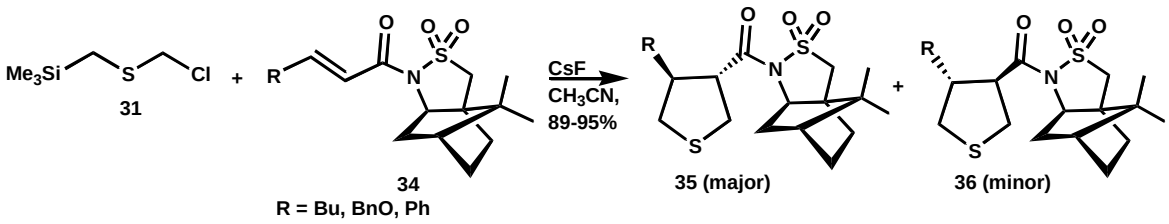
Ohno and co-workers have recently reported the first 1,3-dipolar cycloaddition reaction of [60]fullerene with the thiocarbonyl ylide **29,** the latter being generated *in situ* following the Achiwa protocol.[24]

Hosomi *et al*. reported chloromethyl trimethylsilylmethyl sulfide **31** as a useful precursor for the parent ylide.[25a] They have described the [3+2] cycloaddition of the ylide with dipolarophiles like methyl acrylate, methyl vinyl ketone, benzylidene acetone, DMAD etc. It was later shown that the ylide generated from chloromethyl trimethylsilylmethyl sulfide **31** can also be trapped using carbonyl compounds like aldehydes, ketones, isatins and acenaphthenequinone to give the corresponding 1,3-oxathiolanes **33** (Scheme 9).[25b]




**Scheme 9**

Recently, *trans*-3,4-disubstituted tetrahydrothiophenes **35** and **36** were prepared with high diastereoselectivity by the efficient trapping of the ylide with (E)-*α,β*-unsaturated sultam amides (Scheme 10).[26]



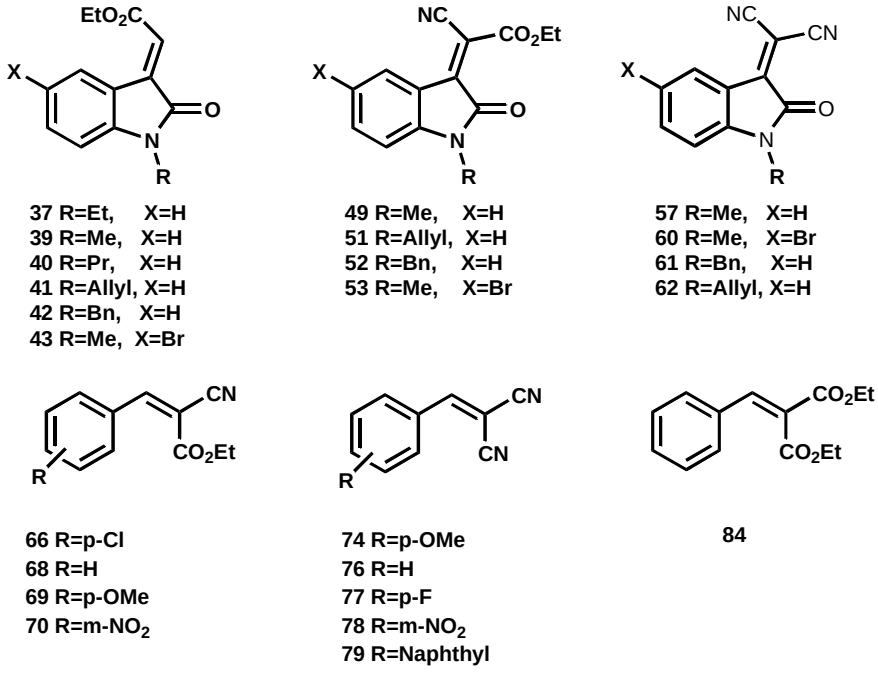

**Scheme 10**

## 4.4 The Present Work

The above discussion reveals that although the chemistry of thiocarbonyl ylides has been the subject of a number of investigations, the reactivity profile of the parent ylide, thioformaldehyde S-methylide **29** has received only scant attention. In view of this obsevation, and in the context of our general interest in the construction of heterocycles using dipolar species, we undertook a detailed study aimed at exploring the reactivity of the ylide towards activated carbon-carbon double bonds. The results are presented in the following sections.

## 4.5 Results and Discussion

The activated carbon-carbon double bonded systems chosen for our studies are listed below (Figure 2).




**37 R=Et, X=H**
**39 R=Me, X=H**
**40 R=Pr, X=H**
**41 R=Allyl, X=H**
**42 R=Bn, X=H**
**43 R=Me, X=Br**

**49 R=Me, X=H**
**51 R=Allyl, X=H**
**52 R=Bn, X=H**
**53 R=Me, X=Br**

**57 R=Me, X=H**
**60 R=Me, X=Br**
**61 R=Bn, X=H**
**62 R=Allyl, X=H**

**66 R=p-Cl**
**68 R=H**
**69 R=p-OMe**
**70 R=m-$NO_2$**

**74 R=p-OMe**
**76 R=H**
**77 R=p-F**
**78 R=m-$NO_2$**
**79 R=Naphthyl**

**84**

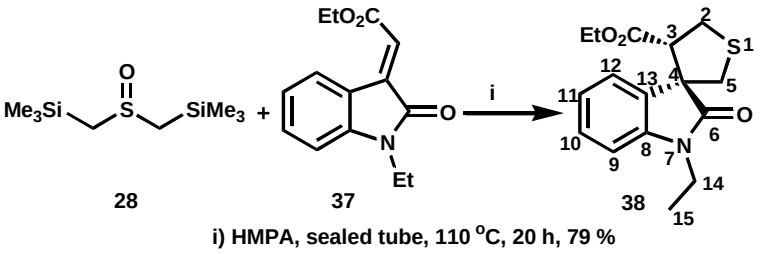
**Figure 2**

The 2-oxoindolin-3-ylidene acetates **37** and **39-43** were prepared from the corresponding isatins by Wittig reaction.[27] The other oxoindolinylidene derivatives and activated styrenes were prepared from the corresponding carbonyl compounds *via* Knoevenagel condensation of the corresponding carbonyl compounds and active methylene compounds in the presence of ammonium acetate and catalytic amount of acetic acid.

### 4.5.1 Reaction with Oxoindolinylidene Acetate

2-Oxoindolin-3-ylidenes are excellent dipolarophiles; they are known to add to various dipolar species like azomethine ylides,[28] carbonyl ylides[29] and diazoalkanes[30] leading to novel spiroindolenin framework. In this context, investigation of the addition of thiocarbonyl ylide to 2-oxoindolin-3-ylidenes was of interest to us. We initiated our studies by heating oxoindolinylidene acetate **37** with bis(trimethylsilylmethyl) sulfoxide

**28** in hexamethylphosphoramide (HMPA) under sealed tube conditions. The reaction proceeded smoothly to afford the adduct **38** in 79 % yield (Scheme 11).




**Scheme 11**

The cycloadduct was separated by column chromatography and characterized using spectroscopic techniques. The IR spectrum of the compound **38** showed a peak at 1717 $cm^{-1}$ corresponding to carbonyls. In the $^{1}H$ NMR (Figure 3), one of the methylene protons on C-2 resonated at $\delta$ 2.9 as a doublet ($J$ = 10.8 Hz ) and the signal due to the other proton was found to overlap with the signals of the methylene protons on C-5 to display a multiplet centered at $\delta$ 3.75. The methyl protons at C-15 and the ester methyl protons were discernible as triplets at $\delta$ 0.97 ($J$ = 7.1 Hz) and $\delta$ 1.48 ($J$ = 7.2 Hz ) respectively. In the $^{13}C$ NMR spectrum, the ester carbonyl resonated at $\delta$ 169.0 and the lactam carbonyl at $\delta$ 175.7. Finally the structure assigned was confirmed unequivocally by single crystal X-ray analysis (Figure 4).

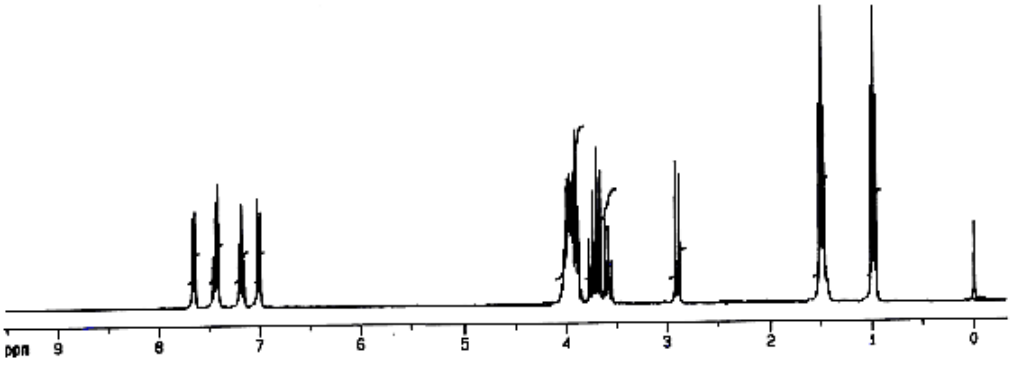
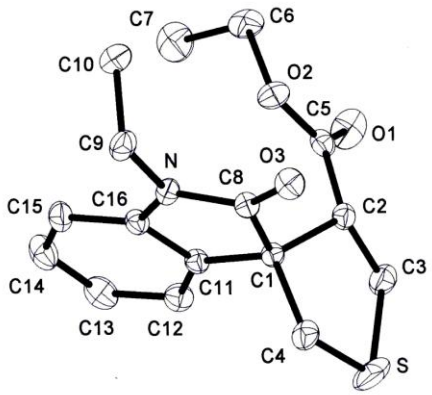
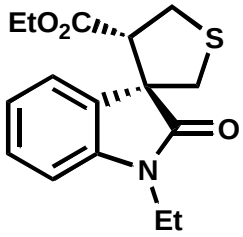



**Figure 3. $^{1}H$ NMR spectrum of 38**




**38**

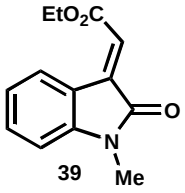
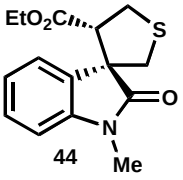
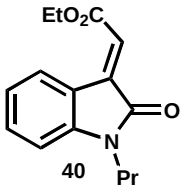
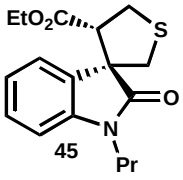
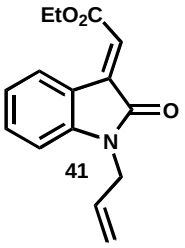
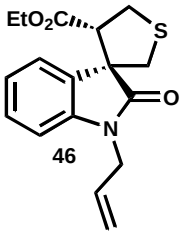
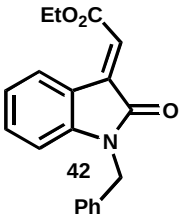
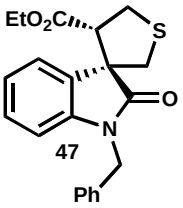
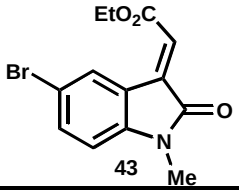
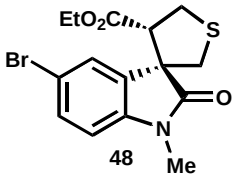
-

- **Single crystal X-ray structure of 38**

**Figure 4**

Similar cycloaddition of the thiocarbonyl ylide occurred with other oxoindolinylidene acetates **39-43** to afford adducts **44-48** in high yields. Only a single isomer was obtained in each case. The reaction occurred chemoselectively and with complete diastereoselectivity. These results are presented in Table 1.

**Table 1**

| Entry | Oxoindolinylidene | Time (h) | Product | Yield (%)[a] |
|---|---|---|---|---|
| 1 |  39 | 20 |  44 | 80 |
| 2 |  40 | 20 |  45 | 76 |
| 3 |  41 | 20 |  46 | 68 |
| 4 |  42 | 20 |  47 | 75 |
| 5 |  43 | 20 |  48 | 74 |

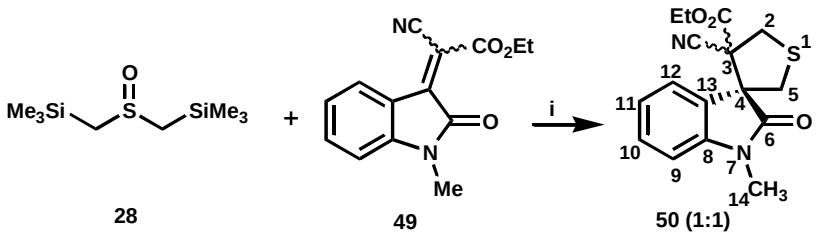
**Reaction Conditions: 28, HMPA, sealed tube, 110 $^{o}$C**

**[a]isolated yield**

## 4.5.2 Reaction with Oxoindolinylidene Cyanoacetate

Encouraged by the successful experiments described above, we extended the reaction to oxoindolinylidene with two electron withdrawing groups.

Thus, when oxoindolinylidene cyanoacetate **49** was treated with bis(trimethylsilylmethyl) sulfoxide **28** in HMPA at 110 $^{o}$C under sealed tube conditions, the cycloadduct **50** was obtained in 70 % yield (Scheme 12).




**28** **49** **50 (1:1)**

**i) HMPA, sealed tube, 110 $^{o}$C, 20 h**

**Scheme 12**

The structure of the product was established by spectroscopic methods. In the vibrational spectrum, the carbonyls of the compound **50** absorbed at 1721 cm$^{-1}$. The $^{1}$H NMR (Figure 5) spectrum was also in agreement with the structure proposed. The C-14 methyl protons resonated as a singlet at $\delta$ 3.28 and one of the methylene protons of C-2 resonated as a doublet ($J$ = 11.2 Hz ) centered at $\delta$ 2.98. The methyl protons of the ester resonated at $\delta$ 0.96 as a triplet ($J$ = 7.1 Hz ). In the $^{13}$C NMR spectrum, the peak at $\delta$ 172.0 was typical of the lactam carbonyl and the one at $\delta$ 163.2 was attributable to the ester carbonyl. The signal for the spiro carbon was visible at $\delta$ 63.3. The resonance signal at $\delta$ 26.8 was assigned to *N*-methyl group; the methyl carbon of the ester resonated at $\delta$ 13.6. Satisfactory elemental analysis was also obtained for the adduct. The oxoindolinylidene cyanoacetate **49** used for the reaction was a 1:1 mixture of the *E:Z* isomers. Apparently the stereochemistry of the starting material was retained in the reaction.

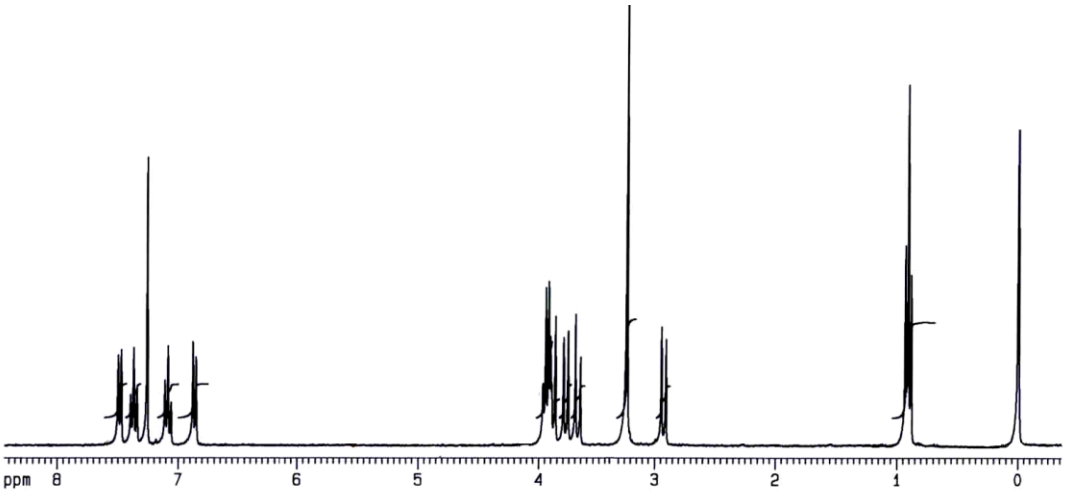
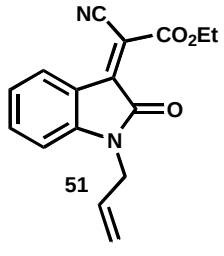
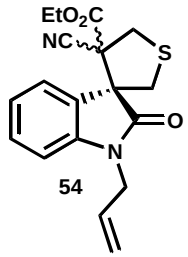
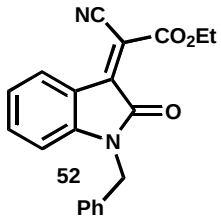
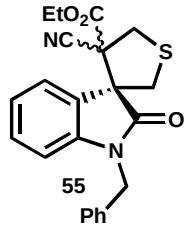
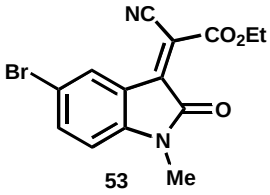
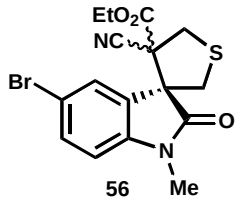



**Figure 5. $^{1}$H NMR spectrum of 50**

Analogous cycloaddition was observed with the oxoindolinylidenes **51-53** also. The results are presented in Table 2.

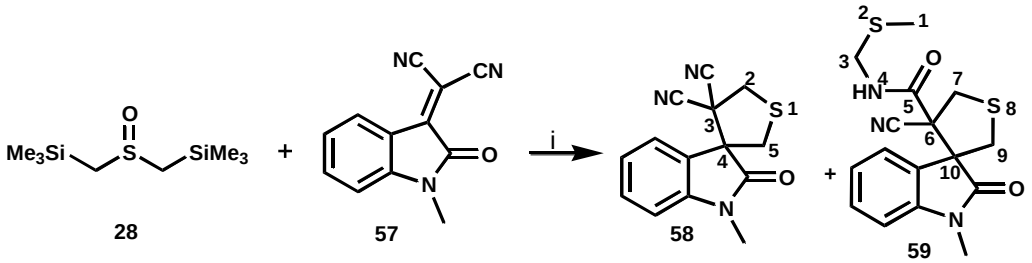
**Table 2**

| Entry | Oxoindolinylidene cyanoacetate | Time (h) | Product | Yield (%)[a] ratio |
|---|---|---|---|---|
| 1 |  51 | 20 |  54 | 56 (1:1) |
| 2 |  52 | 20 |  55 | 68 (1:1) |
| 3 |  53 | 20 |  56 | 67 (1:1) |

**Reaction Conditions : 28, HMPA, sealed tube, 110 $^{o}$C**

**[a]isolated yield**

Subsequent to these investigations, we became interested in the dipolar cycloaddition of the ylide with dicyano oxoindolinylidene derivatives. In a pilot experiment the oxoindolinylidene **57** and bis(trimethylsilylmethyl) sulfoxide **28** were heated in HMPA at 110 $^{o}$C under sealed tube conditions. The reaction afforded the expected spiroindolenin adduct **58** along with another adduct **59** in 30 % and 25 % yields respectively (Scheme 13).




**i) HMPA, sealed tube, 110 $^{o}$C, 20 h**

**Scheme 13**

The products were purified by column chromatography and their structures were ascertained on the basis of spectroscopic data. The IR spectrum of the cycloadduct **58** manifested absorption at 2234 cm$^{-1}$ characteristic of the cyano group. In the $^{1}$H NMR spectrum (Figure 6), a singlet signal appearing at $\delta$ 3.30 was assigned to the *N*-Me protons. The methylene protons at C-5 resonated as doublets at $\delta$ 4.39 ($J$ = 11.3 Hz) and at $\delta$ 3.70 ($J$ = 10.7 Hz). In the $^{13}$C NMR spectrum, the amide carbonyl manifested a signal at $\delta$ 171.9 and the nitrile carbons were discernible at $\delta$ 111.3 and at $\delta$ 112.4. The signals due to C-2 and C-5 were visible at $\delta$ 38.65 and at $\delta$ 35.5 respectively, while the spirocarbon displayed its resonance signal at $\delta$ 60.5. The signal due to C-3 appeared at $\delta$ 46.4. All the other signals were also in agreement with the assigned structure.

The IR spectrum of **59** displayed a strong absorption at 3379 cm$^{-1}$ typical of the –NH functionality, while the absorption bands for the nitrile and carbonyls were discernible at 2270 cm$^{-1}$ and at 1720 cm$^{-1}$ respectively. In the $^{1}$H NMR spectrum (Figure 7) the signal centered at $\delta$ 3.22 corresponded to the *N*-methyl protons. This signal was found to overlap with the signal due to one of the methylene protons, thus giving the appearance of as a multiplet. The singlet at $\delta$ 6.20 was attributed to the N-H proton. In the $^{13}$C NMR spectrum, the carbonyls were discernible at $\delta$ 173.6 and at $\delta$ 162.0. All the other signals were also in agreement with the assigned structure.

Further support for the structure of **59** was obtained from $^{1}$H-$^{1}$H relayed COSY analysis (Figure 8). The COSY spectrum showed the connectivity between the different

sets of protons. The most diagnostic of these is the connectivity shown by the N-H proton ($\delta$ 6.20), with the protons on C-3($\delta$ 4.1 and $\delta$ 4.25).

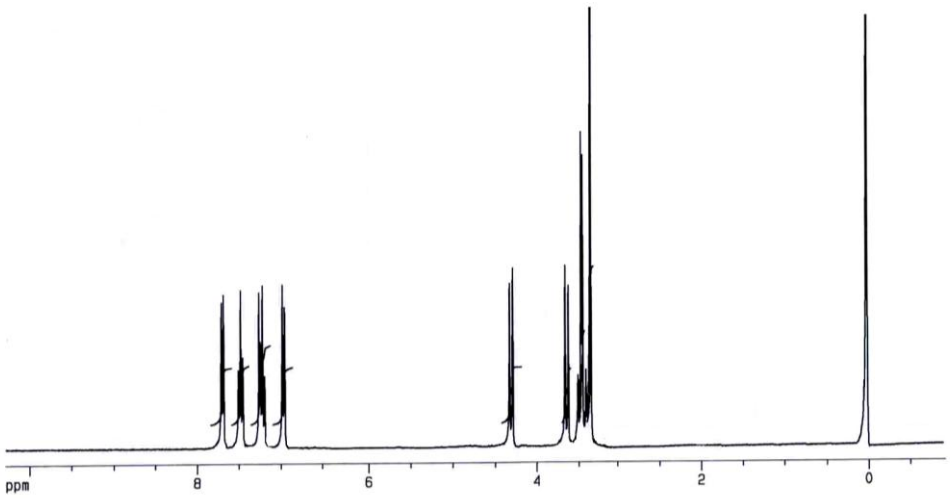



**Figure 6. $^{1}$H NMR spectrum of 58**

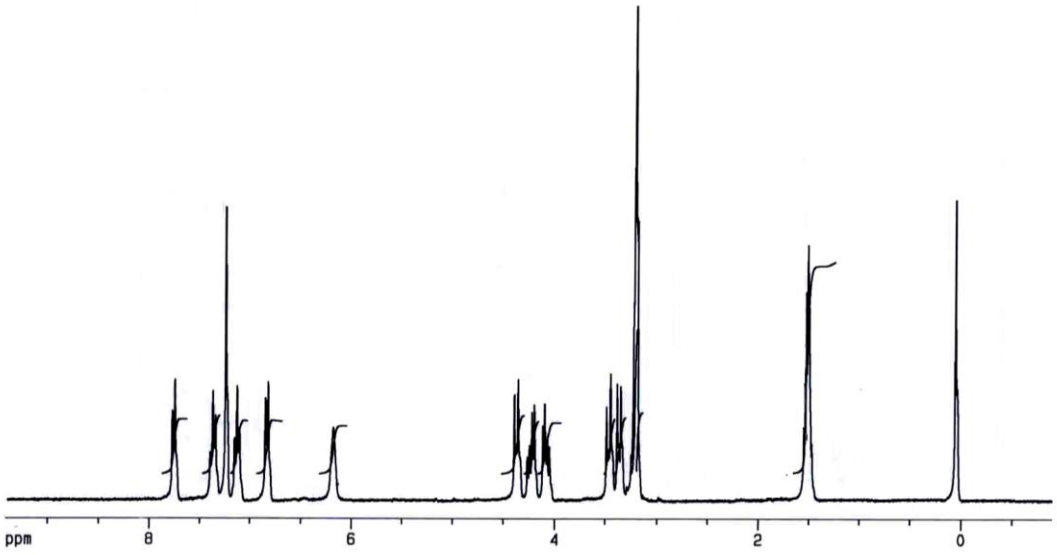



**Figure 7. $^{1}$H NMR spectrum of 59**

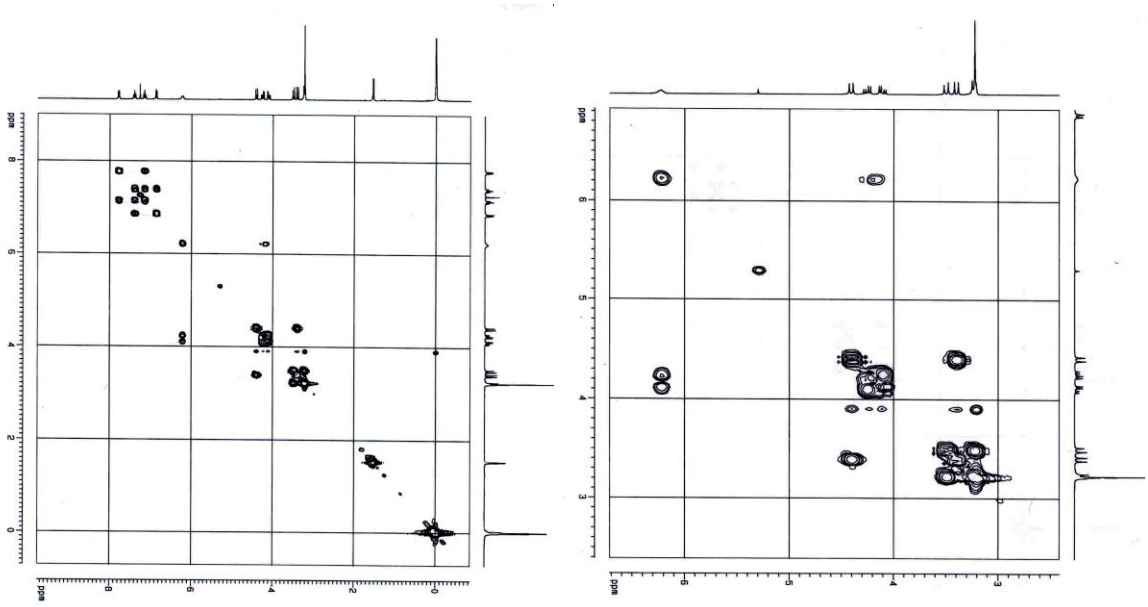
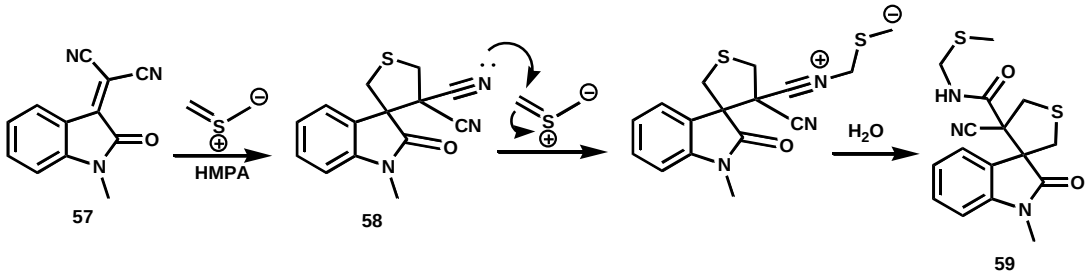


**Figure 8. $^{1}$H-$^{1}$H COSY spectrum of 59**

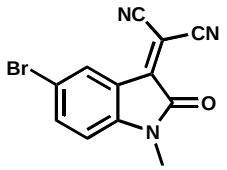
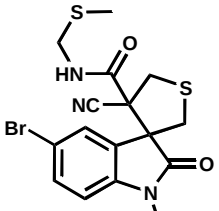
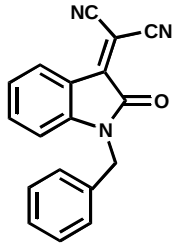
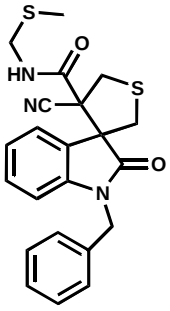
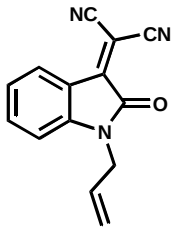
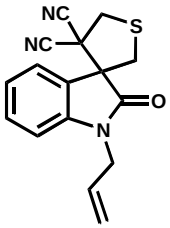
A mechanistic rationale for the formation of the adduct **59** is illustrated in Scheme 14. The initial event essentially involves the 1,3-dipolar cycloaddition reaction of the parent ylide with **57** to afford the cycloadduct **58**. The latter reacts further with a second molecule of the ylide through the nitrile end of the adduct **58** in a manner remotely analogous to the classical Ritter reaction. The resulting dipolar intermediate then gets quenched by water to afford the final product **59**.




**Scheme 14**

The reaction was extended to other dicyano oxoindolinylidenes derivatives. The results are summarized in Table 3.

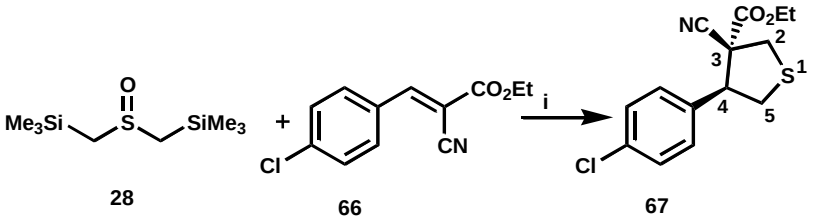
**Table 3**

| Entry | Oxoindolinylidene | Product 1 | Product 2 |
|---|---|---|---|
| 1 |  **60** | 0 |  **63 (32%)** |
| 2 |  **61** | 0 |  **64 (36%)** |
| 3 |  **62** |  **65 (40%)** | 0 |

**Reaction Conditions: 28, HMPA, sealed tube, 110 $^{o}$C, 24 h**
**isolated yields in parentheses**

## 4.5.3 Reactivity Towards Activated Styrenes

Subsequent to the above investigation we extended the reaction to activated styrenes. We initiated our studies by exposing 3-(4-chlorophenyl)-2-cyanoacrylate **66** with bis(trimethylsilylmethyl) sulfoxide **28** in HMPA at 110 $^{o}$C under sealed tube conditions; a facile reaction leading to the formation of the tetrahydrothiophene derivative **67** in 71 % yield occurred (Scheme 15).

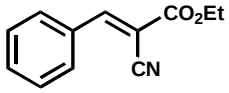
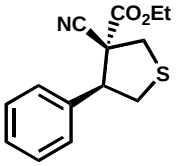
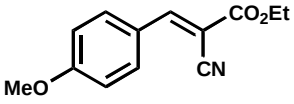
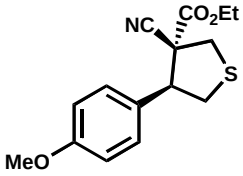
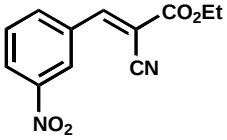
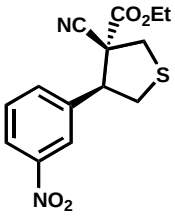



**Scheme 14**

The IR spectrum of **67** showed strong absorption at 2236 $cm^{-1}$ characteristic of the nitrile, and at 1740 $cm^{-1}$ indicating the presence of the ester carbonyl. In the $^{1}H$ NMR spectrum, the benzylic proton on C-4 resonated around $\delta$ 3.86 as multiplet. The methylene protons resonated as a multiplet at $\delta$ 3.46 and 3.29. The ester methylene protons resonated as quartet ($J$ = 7.1 Hz ) at $\delta$ 4.17. In the $^{13}C$ NMR spectrum, the ester carbonyl resonated at $\delta$ 166.3, the C-5, C-2 and C-3 resonated at $\delta$ 34.0, $\delta$ 39.3 and $\delta$ 57.7 respectively. The peak at $\delta$ 116 was attributed to the nitrile carbon.

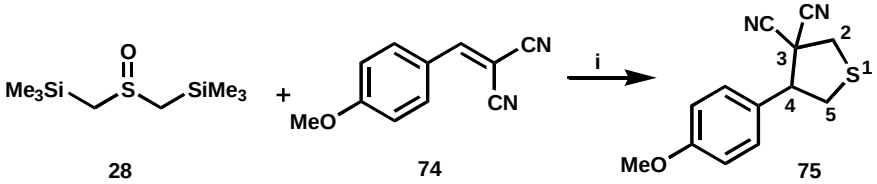
The reaction was extended to other substituted arylcyanoacrylates **68-71** and the tetrahydrothiophene derivatives **72-75** were obtained in good yields; these results are summarized in Table 4.

**Table 4**

| Entry | Aryl cyano acrylate | Time (h) | Product | Yield (%)[a] |
|---|---|---|---|---|
| 1 |  **68** | 16 |  **71** | 60 |
| 2 |  **69** | 16 |  **72** | 59 |
| 3 |  **70** | 16 |  **73** | 63 |

**Reaction Conditions: 28, HMPA, sealed tube, 110 $^{o}$C**
**[a]isolated yield**

Similar cycloaddition leading to tetrahydrothiophene derivatives was observed with dicyanostyrenes also. In a typical experiment, dicyanostyrene **74** and bis(trimethylsilylmethyl) sulfoxide **28**, were taken in HMPA and heated in a sealed tube at 110 $^{o}$C; the reaction afforded the cycloadduct **75** in 59 % yield (Scheme 16).



**28** **74** **75**

**i) HMPA, sealed tube, 110 $^{o}$C, 16 h**

**Scheme 16**

As usual, the product was characterized by spectroscopic analysis. The sharp peak at 2237 $cm^{-1}$ in the vibrational spectrum of **75** was characteristic of the nitrile absorption. In the $^{1}H$ NMR spectrum (Figure 9) of the compound, the methoxy protons resonated as a singlet at $\delta$ 3.83 and the methylene protons at C-2 also resonated at δ 3.54 as a singlet. The C-5 methylene protons resonated as a multiplet at δ 3.35, the benzylic proton also appeared as a multiplet at δ 3.70. The aromatic protons resonated as doublets at $\delta$ 6.94 ($J$ = 8.7 Hz) and $\delta$ 7.52 ($J$ = 7.1 Hz) as doublets. In the $^{13}C$ NMR spectrum, C-5 and C-2 resonated at $\delta$ 32.8 and $\delta$ 39.4 respectively. The signal at $\delta$ 57.2 was assigned to the methoxy carbon and the one at $\delta$ 160.7 to the methoxy-substituted aromatic carbon. All the other signals were also in accordance with the assigned structure.

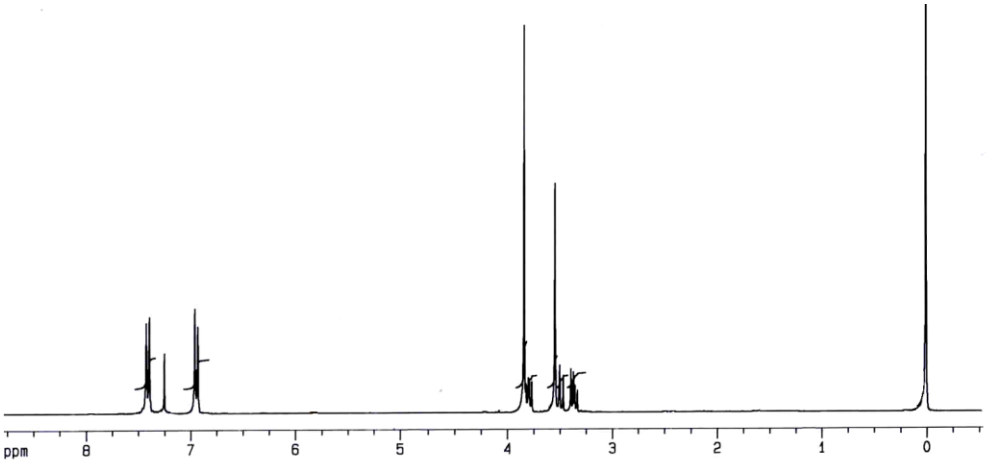
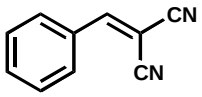
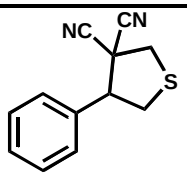
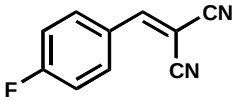
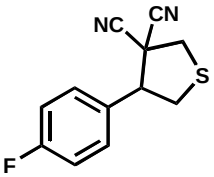
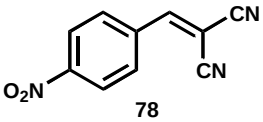
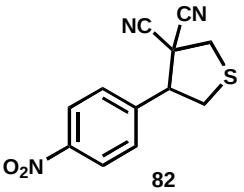
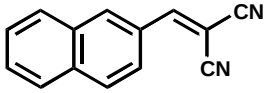
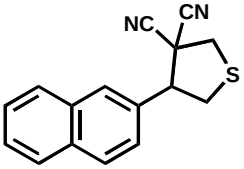



**Figure 9. $^{1}H$ NMR spectrum of 75**

Analogous reactions were observed with dicyanostyrenes **76-79**. The results are presented below in Table 5.

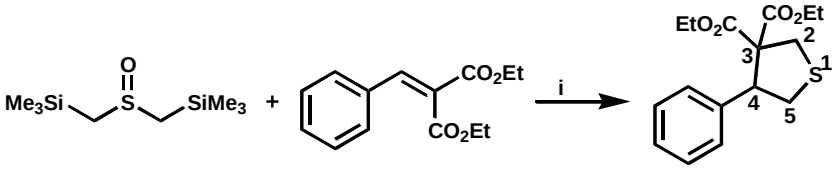
**Table 5**

| Entry | Dicyanostyrene | Time (h) | Product | yield (%)[a] |
|---|---|---|---|---|
| 1 |  **76** | 16 |  **80** | 56 |
| 2 |  **77** | 16 |  **81** | 53 |
| 3 |  **78** | 16 |  **82** | 48 |
| 4 |  **79** | 16 |  **83** | 61 |

**Reaction Conditions : 28, HMPA, sealed tube, 110 $^{o}$C**

**[a]isolate yield**

Benzylidene malonylester **84** under the conditions described in the previous experiments afforded the tetrahydrothiophene derivative **85** in 82 % yield (Scheme 17).



**28** **84** **85**

**i) HMPA, sealed tube, 110 $^{o}$C, 20 h**

**Scheme 17**

As usual, the structure of the product was elucidated on the basis of spectroscopic data. The IR spectrum of the compound **85** exhibited a vibration band at 1734 $cm^{-1}$ diagnostic of the ester carbonyl absorption. In the $^{1}H$ NMR spectrum, the signals due the benzylic proton and the methylene protons of one of the ester groups overlapped to display a multiplet at $\delta$ 4.28. The methylene protons on C-2 and C-5 resonated as multiplets at $\delta$ 3.08, $\delta$ 3.33 and $\delta$ 3.57. The ester methyl protons resonated as triplets at $\delta$ 1.04 ($J$ = 7.1 Hz) and at $\delta$ 1.29 ($J$ = 7.1 Hz). The resonance signal at $\delta$ 169.4 in the $^{13}C$ NMR spectrum was typical of the ester carbonyls. The resonance signal of C-3 was observed at $\delta$ 68.4, and the C-5 and C-2 signals were seen at $\delta$ 34.5 and at $\delta$ 36.2 respectively. All the other signals were also in good agreement with the assigned structure.

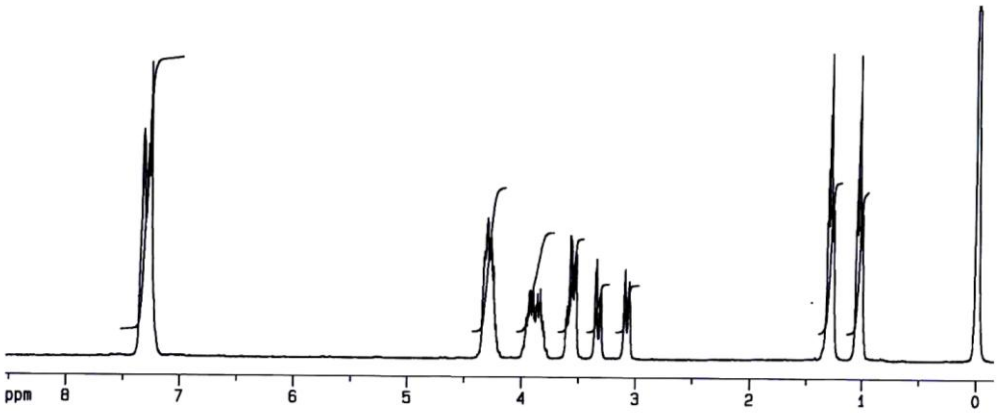



**Figure 10. $^{1}H$ NMR spectrum of 85**

## 4.6 Conclusion

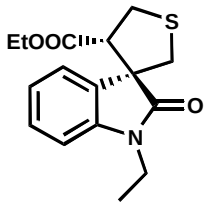
In conclusion, we have found that the parent thiocarbonyl ylide undergoes facile cycloaddition to activated carbon-carbon double bonds leading to the construction of novel tetrahydrothiophene derivatives. Surprisingly it was observed that in certain cases the parent ylide adds to the cyano group also, thus opening up an intersting area for

investigation. It is conceivable that the spirocyclic construction described herein will find practical applications.

## 4.7 Experimental

***Ethyl 1-ethyl-2-oxo-1,2,4',5'-tetrahydrospiro[indole-3,3'-thiophene]-4'-carboxylate 38***

Oxoindolinylidene **37** (60 mg, 0.245 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (162.9 mg, 0.734 mmol) in HMPA (1 mL) was heated at 100 °C in a sealed tube for 24 h. The reaction mixture was diluted with water (200 mL) and extracted with dichloromethane (3 x 10 mL) and the combined extract was dried over anhydrous sodium sulfate. After removal of the solvent using a rotary evaporator, the residue was subjected to chromatography on a silica gel column using 85:15 hexane-ethyl acetate solvent mixture to afford **38** (59 mg, 79%) as a colorless crystalline solid.




**38**

m.p: 100-102$^{o}$C

**IR** (KBr) $\nu_{max}$**:** 2352, 1717, 1614, 1464, 1362, 1207, 1023, 861, 736 cm$^{-1}$.

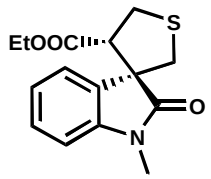
**$^{1}$H NMR:** $\delta$ 0.97 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7.1 Hz), 1.48 (t, 3H, $NCH_2C\underline{H}_3$, $J$ = 7.2 Hz), 2.9 (d, 1H, $C\underline{H}_2CHCO_2Et$, $J$ = 10.8 Hz), 3.55-3.74 (m, 3H, $C\underline{H}_2CHCO_2Et$, $SC\underline{H}_2$ ), 3.91-4 (m, 5H, $NC\underline{H}_2$, $OC\underline{H}_2CH_3$, $C\underline{H}CO_2Et$), 7.03 (d, 1H, Ar$\underline{H}$, $J$ = 7.8 Hz), 7.2 (t, 1H, Ar$\underline{H}$, $J$ = 7.5 Hz), 7.43-7.48 (m, 1H, Ar$\underline{H}$), 7.67 (d, 1H, Ar$\underline{H}$, $J$ = 7.4 Hz)

**$^{13}$C NMR:** $\delta$ 12.6, 13.6, 31.2, 35.1, 41.4, 55.4, 58.3, 60.7, 107.9, 122.6, 124.3, 128.7, 130.0, 142.4, 169.0, 175.7

Anal. Calcd. for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.59; S, 10.50. Found: C, 63.07; H, 6.67; N, 4.79; S, 10.55.

***Ethyl 1-methyl-2-oxo-1,2,4',5'-tetrahydrospiro[indole-3,3'-thiophene]-4'-carboxylate 44***

Oxoindolinylidene **39** (60 mg, 0.259 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (172 mg, 0.778 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **44** (61 mg, 80%) was obtained as a colorless crystalline solid.




**44**

m.p: 106-108 °C

**IR** (KBr) $\nu_{max}$**:** 2357, 1721, 1613, 1465, 1360, 1256, 1120, 720 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 0.83 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7.1 Hz), 2.75 (d, 1H, $C\underline{H}_2CHCO_2Et$, $J$ = 10.8 Hz), 3.38 (s, 3H, NMe), 3.38-3.6 (m, 3H, $C\underline{H}_2CHCO_2Et$, $SC\underline{H}_2$ ), 3.72-3.85 (m, 3H, $OC\underline{H}_2CH_3$, $C\underline{H}CO_2Et$), 6.85 (d, 1H, Ar$\underline{H}$, $J$ = 7 .8 Hz), 7.05 (t, 1H, Ar$\underline{H}$, $J$ = 7.5 Hz), 7.28 (t, 1H, Ar$\underline{H}$, $J$ = 7.8 Hz), 7.5 (d, 1H, Ar$\underline{H}$, $J$ = 7.4 Hz)

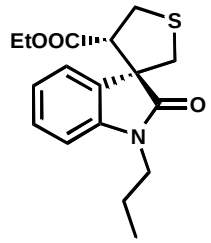
**$^{13}$C NMR:** $\delta$ 13.7, 26.6, 31.2, 41.2, 55.7, 58.4, 60.7, 107.7, 122.8, 124.2, 128.8, 130, 143.5, 169.

Anal. Calcd. for $C_{15}H_{17}NO_3S$ : C, 61.83; H, 5.88; N, 4.81; S, 11.01. Found: C, 61.77; H, 6.18; N, 5.43; S, 11.46.

***Ethyl 1-propyl-2-oxo-1,2,4',5'-tetrahydrospiro[indole-3,3'-thiophene]-4'-carboxylate 45***

Oxoindolinylidene **40** (60 mg, 0.231 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (154 mg, 0.694 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **45** (56 mg, 76%) was obtained as a colorless crystalline solid.

**IR** (KBr) $\nu_{max}$**:** 2350, 1715, 1615, 1465, 1364, 1209, 1027, 862, 730 $cm^{-1}$.



**45**

m.p: 98-100 °C

**$^1$H NMR:** $\delta$ 1.1 (t, 3H, $OCH_2C\underline{H}_3$, *J* = 7.1 Hz), 1.3 (t, 3H, $NCH_2CH_2C\underline{H}_3$, *J* = 7.2 Hz), 2.00-2.07 (m, 2H, $NCH_2C\underline{H}_2CH_3$) 3.03 (d, 1H, $C\underline{H}_2CHCO_2Et$, *J* = 10.7 Hz), 3.72-3.87 (m, 3H, $C\underline{H}_2CHCO_2Et$, $SC\underline{H}_2$ ), 3.99-4.1 (m, 5H, $NC\underline{H}_2$, $OC\underline{H}_2CH_3$, $C\underline{H}CO_2Et$), 7.15 (d, 1H, Ar<u>H</u>, *J* = 7.8 Hz), 7.32 (t, 1H, Ar<u>H</u>, *J* = 7.5 Hz), 7.58 (t, 1H, Ar<u>H</u>, *J* = 7.6 Hz), 7.8 (d, 1H, Ar<u>H</u>, *J* = 7.4 Hz)

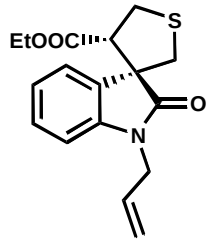
**$^{13}$C NMR:** $\delta$ 11.4, 13.6, 20.7, 31.3, 41.6, 42.1, 55.4, 58.3, 60.6, 108.0, 122.5, 124.2, 128.6, 130.1, 142.9, 169, 176

Anal. Calcd. for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39; S, 10.04. Found: C, 64.06; H, 6.58; N, 4.44; S, 10.53.

***Ethyl 1-allyl-2-oxo-1,2,4',5'-tetrahydrospiro[indole-3,3'-thiophene]-4'-carboxylate <u>46</u>***

Oxoindolinylidene **41** (60 mg, 0.233 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (155 mg, 0.699 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **46** (50 mg, 68%) was obtained as a colorless crystalline solid.

**IR** (KBr) $\nu_{max}$**:** 2339, 1719, 1618, 1470, 1357, 1250, 1173, 973, 720 $cm^{-1}$.



**46**

m.p: 100-102 °C

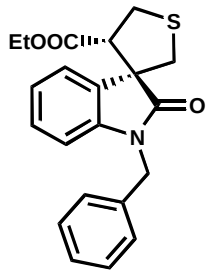
**$^1$H NMR:** $\delta$ 1.11 (t, 3H, $OCH_2C\underline{H}_3$, *J* = 7.1 Hz), 3.05 (d, 1H, $C\underline{H}_2CHCO_2Et$, *J* = 10.8 Hz), 3.69-3.91 (m, 3H, $C\underline{H}_2CHCO_2Et$, $SC\underline{H}_2$), 4.03-4.13 (m, 3H, $CH_2C\underline{H}CO_2C\underline{H}_2CH_3$), 4.68 (t, 2H, $NC\underline{H}_2$), 5.53-5.67 (m, 2H, $CH=C\underline{H}_2$), 6.1-6.23 (m, 1H, $C\underline{H}=CH_2$), 7.15 ( d, 1H, Ar<u>H</u>, *J* = 7.8 Hz), 7.34 (t, 1H, Ar<u>H</u>, *J* = 7.6 Hz), 7.54-7.59 (m, 1H, Ar<u>H</u>), 7.81 (d, 1H, Ar<u>H</u>, *J* = 7.3 Hz)

**$^{13}$C NMR:** $\delta$ 13.6, 31.3, 41.5, 41.6, 42.9, 55.6, 58.3, 60.7, 108.7, 117.9, 122.7, 124.2, 128.6, 130.0, 131.5, 142.6, 168.9, 175.9.

Anal. Calcd. for $C_{17}H_{19}NO_3S$ : C, 64.33; H, 6.03; N, 4.41; S, 10.10. Found: C, 64.07; H, 6.18; N, 4.63; S, 10.40.

***Ethyl 1-benzyl-2-oxo-1,2,4',5'-tetrahydrospiro[indole-3,3'-thiophene]-4'-carboxylate 47***

Oxoindolinylidene **42** (60 mg, 0.195 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (130 mg, 0.586 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **47** (54 mg, 75%) was obtained as a colorless crystalline solid.




**47**

m.p: 104-106 °C

**IR** (KBr) $\nu_{max}$**:** 2360, 1720, 1617, 1460, 1362, 1257, 1123, 726 cm$^{-1}$.

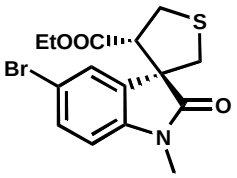
**$^{1}$H NMR:** $\delta$ 0.64 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7.1 Hz), 2.79 (d, 1H, $C\underline{H}_2CHCO_2Et$, $J$ = 10.8 Hz), 3.41-3.48 (m, 1H, $CH_2$), 3.6-3.65 (m, 3H, $CH_2C\underline{H}CO_2Et$, SC<u>H</u>2), 3.75-3.82 (m, 2H, $COOC\underline{H}_2CH_3$), 4.93 (s, 2H, $NC\underline{H}_2$), 6.76 (d, 1H, Ar<u>H</u>, $J$ = 7.8 Hz), 6.98-7.03 (m, 1H, Ar<u>H</u>), 7.16-7.37 (m, 6H, Ar<u>H</u>), 7.5 (d, 1H, Ar<u>H</u>, $J$ = 7.1 Hz).

**$^{13}$C NMR:** $\delta$ 13.5, 26.9, 31.4, 41.9, 44.2, 55.4, 58.4, 60.8, 108.9, 122.8, 124.2, 127.7, 127.8, 128.6, 128.7, 129.9, 135.8, 142.5, 169.1, 176.4.

Anal. Calcd. for $C_{21}H_{21}NO_3S$ : C, 68.64; H, 5.76; N, 3.81; S, 8.73. Found: C, 68.46; H, 6.06; N, 3.57; S, 8.73.

***5-Bromo ethyl 1-methyl-2-oxo-1,2,4',5'-tetrahydrospiro[indole-3,3'-thiophene]-4'-carboxylate 48***

Oxoindolinylidene **43** (60 mg, 0.193 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (129 mg, 0.530 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **48** (53 mg, 74%) was obtained as a colorless crystalline solid.




**48**

m.p: 138-140 °C

**IR** (KBr) $\nu_{max}$**:** 2357, 1721, 1613, 1465, 1360, 1256, 1120, 720 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 0.9 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7.1 Hz), 2.73 (d, 1H, $C\underline{H}_2CHCO_2Et$, $J$ = 10.9 Hz), 3.25 (s, 3H, NMe), 3.44-3.54 (m, 3H, $C\underline{H}_2CHCO_2Et$, $SC\underline{H}_2$ ), 3.72-3.93 (m, 3H, $OC\underline{H}_2CH_3$, $C\underline{H}CO_2Et$), 6.73 (d, 1H, Ar<u>H</u>, $J$ =8.3 Hz), 7.45 (d, 1H, Ar<u>H</u>, $J$ =8.3 Hz), 7.63 (s, 1H, Ar<u>H</u>)

**$^{13}$C NMR:** $\delta$ 13.8, 26.7, 30.8, 41.2, 55.6, 58.2, 60.9, 107.8, 109.2, 115.5, 127.2, 131.7, 142.5, 168.7, 175.5.

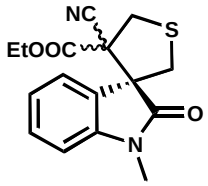
Anal. Calcd. for $C_{15}H_{16}BrNO_3S$ : C, 48.66; H, 4.36; N, 3.78; S, 8.66. Found: C, 48.90; H, 4.60; N, 3.90; S, 9.30.

***Ethyl 4'-cyano-1-methyl-2-oxo-1,2,4',5'-tetrahydrospiro[indole-3,3'-thiophene]-4'-carboxylate 50***

Oxoindolinylidene **49** (60 mg, 0.234 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (156 mg, 0.702 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **50** (52 g, 70%) was obtained as a colorless crystalline solid in the ratio 1:1.

**IR** (KBr) $\nu_{max}$**:** 2245, 1721, 1613, 1465, 1360, 1256, 1120, 720 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 0.96 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7.1 Hz), 2.98



**50**

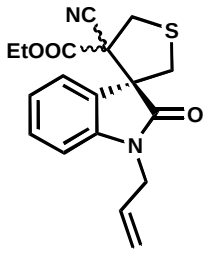
(d, 1H, C<u>H</u>$_2$CHCO$_2$Et, *J* = 11.2 Hz), 3.28 (s, 3H, NMe), 3.69 (d, 1H, C<u>H</u>$_2$CHCO$_2$Et, *J* = 12.3 Hz), 3.8 (d, 1H, SC<u>H</u>$_2$, *J* = 11.2 Hz), 3.88-3.98 (m, 3H, OC<u>H</u>$_2$CH$_3$, C<u>H</u>$_2$S), 6.86 (d, 1H, Ar<u>H</u>, *J* = 7.8 Hz), 7.09 (t, 1H, Ar<u>H</u>, *J* = 7.6 Hz), 7.37 (t, 1H, Ar<u>H</u>, *J* = 7.8 Hz), 7.49 (d, 1H, Ar<u>H</u>, *J* = 7.5 Hz)

**$^{13}$C NMR:** $\delta$ 13.6, 26.8, 37.5, 38.6, 58.3, 59.6, 63.3, 108.3, 115.2, 125.0, 126.0, 136.1, 143.4, 163.2, 172.0.

HRMS (EI) Cacd for $C_{16}H_{14}N_2O_3S$: 316.0881. Found: 315.0823.

***Ethyl 4'-cyano-1-allyl-2-oxo-1,2,4',5'-tetrahydrospiro[indole-3,3'-thiophene]-4'-carboxylate <u>54</u>***

Oxoindolinylidene **51** (60 mg, 0.213 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (141 mg, 0.638 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **54** (41 mg, 56%) was obtained as a colorless crystalline solid in the ratio 1:1.



**54**

**IR** (KBr) $\nu_{max}$**:** 2240, 1721, 1613, 1465, 1360, 1256, 1120, 720 cm$^{-1}$.

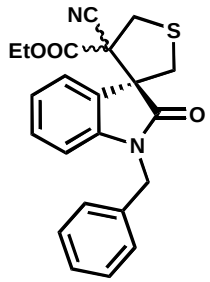
**$^{1}$H NMR:** $\delta$ 0.96 (t, 3H, OCH$_2$C<u>H</u>$_3$, *J* = 7.1 Hz), 3 (d, 1H, C<u>H</u>$_2$C(CN)CO2Et, *J* = 11.2 Hz), 3.69-3.91 (m, 3H, C<u>H</u>$_2$C(CN)CO$_2$Et, C<u>H</u>$_2$S), 3.97 (quartet, 2H, CO$_2$C<u>H</u>$_2$CH$_3$, *J* = 7.1 Hz), 4.4 (uneven t, 2H, NCH$_2$), 5.26-5.36 (m, 2H, CH=C<u>H</u>$_2$), 5.81-5.9 (m, 1H, C<u>H</u>=CH$_2$), 6.89 (d, 1H, Ar<u>H</u>, *J* = 7.8 Hz), 7.07 (t, 1H, Ar<u>H</u>, *J* =7.6 Hz), 7.33 (t, 1H, Ar<u>H</u>, *J* = 7.7 Hz), 7.47 (d, 1H, Ar<u>H</u>, *J*= 7.6 Hz)

**$^{13}$C NMR:** $\delta$ 13.4, 29.6, 37.5, 38.7, 43.0, 58.1, 59.4,

63.2, 109.2, 118.5, 122.9, 124.8, 130.0, 130.9, 142.5, 163.1, 171.6.

***Ethyl 4'-cyano- 1-benzyl-2-oxo-1,2,4',5'-tetrahydrospiro[indole-3,3'-thiophene]-4'-carboxylate 55***

Oxoindolinylidene **52** (60 mg, 0.181 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (120 mg, 0.542 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **55** (48 mg, 68%) was obtained as a colorless crystalline solid in the ratio 1:1.




**55**

**IR** (KBr) $\nu_{max}$**:** 2241, 1721, 1613, 1465, 1360, 1256, 1120, 720 $cm^{-1}$.

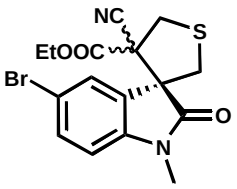
**$^1$H NMR:** $\delta$ 0.75(t, 3H, $OCH_2C\underline{H}_3$, *J* = 7.1 Hz), 3.03 (d, 1H, $C\underline{H}_2C(CN)CO_2Et$, *J* = 11.2 Hz), 3.72-3.94 (m, 5H, $C\underline{H}_2C(CN)CO_2C\underline{H}_2CH_3$, $SC\underline{H}_2$), 4.94 (pseudo dd, 2H, $NCH_2$, *J* = 15.3 Hz, *J* = 17.6 Hz), 6.83 (d, 1H, Ar<u>H</u>, *J* = 7.8 Hz), 7.04-7.07 (m, 1H, Ar<u>H</u>), 7.24-7.47 (m, 7H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 13.3, 37.8, 39.3, 44.6, 58.1, 59.6, 63.4, 109.3, 115.4, 123.1, 125.0, 126.0, 128.0, 128.8, 130.1, 135.3, 142.6, 163.3, 172.2.

HRMS (EI) Cacd for $C_{22}H_{20}N_2O_2S$: 392.1194. Found: 392.1093.

***5-Bromo ethyl 4'-cyano-1-methyl-2-oxo-1,2,4',5'-tetrahydrospiro[indole-3,3'-thiophene]-4'-carboxylate 56***

Oxoindolinylidene **53** (60 mg, 0.179 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (119 mg, 0.537 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **56** (47 mg, 67%) was obtained as a colorless crystalline solid in the ratio 1:1.




**56**

**IR** (KBr) $\nu_{max}$**:** 2234, 1721, 1613, 1465, 1360, 1256, 1120, 720 $cm^{-1}$.

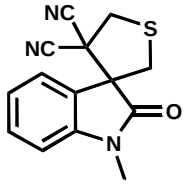
**$^1$H NMR:** $\delta$ 1.03 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7.1 Hz), 2.99 (d, 1H, $C\underline{H}_2C(CN)CO_2Et$, $J$ = 11.2 Hz), 3.27 (s, 3H, NMe), 3.71-3.88 (m, 3H, $C\underline{H}_2C(CN)CO_2Et$, $SC\underline{H}_2$), 4.02 (quartet, 2H, $OC\underline{H}_2CH_3$, $J$ = 7.1 Hz), 6.76 (d, 1H, Ar$\underline{H}$, $J$ = 8.3 Hz), 7.5 (t, 1H, Ar$\underline{H}$, $J$ = 7.7 Hz), 7.6 (s, 1H, Ar$\underline{H}$).

**$^{13}$C NMR:** $\delta$ 13.7, 26.9, 38.4, 39.8, 58.4, 59.8, 63.5, 109.7, 115.8, 128.2, 133.1, 144.5, 163.7, 172.0.

HRMS (EI) Cacd for $C_{16}H_{15}BrN_2O_3S$: 393.9986. Found: 393.9998.

***4'-Dicyano-1-methyl-2-oxo-1,2,4',5'-tetrahydrospiro[indole-3,3'-thiophene] <u>58</u> and 4'-cyano-1-methyl-N-[(methylthio)methyl]-2-oxo-1,2,4', 5'-tetrahydrospiro[indole-3,3'-thiophene]-4'-carboxamide <u>59</u>***

Oxoindolinylidene **57** (60 mg, 0.287 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (191 mg, 0.86 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The products **58** (23 mg, 30%) and **59** (25 mg, 25%) were obtained as a colorless crystalline solids.




**58**

m.p: 48-50 °C

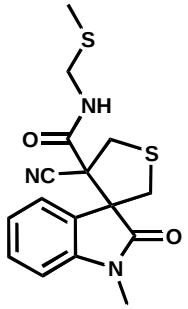
**IR** (KBr) $\nu_{max}$**:** 2234, 1721, 1613, 1418, 1370, 1253, 1134, 746 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 3.30 (s, 3H, NMe), 3.36-3.45 (m, 2H, $C\underline{H}_2$), 3.70 (d, 1H, $C\underline{H}_2$, $J$ = 10.7 Hz), 4.39 (d, 1H, $C\underline{H}_2$, $J$ = 11.3 Hz), 6.97 (d, 1H, Ar$\underline{H}$, $J$ = 7.9 Hz), 6.98-7.19 (m, 1H, Ar$\underline{H}$), 7.48 (t, 1H, Ar$\underline{H}$, $J$ = 7.7 Hz), 7.77 (d, 1H, Ar$\underline{H}$, $J$ = 7.6 Hz).

**$^{13}$C NMR:** $\delta$ 26.8, 35.5, 38.7, 46.4, 60.5, 109.2, 111.3, 112.4, 123.9, 124.7, 131.4, 143.7, 171.9.

Anal. Calcd. for $C_{14}H_{11}N_3OS$: C, 62.43; H, 4.12; N, 15.60; S, 11.91. Found: C, 62.12; H, 4.37; N, 15.48; S, 11.87.

**IR** (KBr) $\nu_{max}$**:** 3379, 2270, 1720, 1589, 1413, 1377, 1134, 1093, 850, 746 cm$^{-1}$.




**59**

m.p: 63-65 °C

**$^{1}$H NMR:** $\delta$ 1.57 (s, 3H, SC<u>H</u>$_3$), 3.2-3.23 (m, 4H, NMe, C<u>H</u>$_2$), 3.38 (d, 1H, C<u>H</u>$_2$, $J$ = 11 Hz), 3.49 (d, 1H, C<u>H</u>$_2$, $J$ = 11 Hz), 4.07-4.13 (m, 1H, C<u>H</u>$_2$), 4.22-4.28 (m, 1H, CH$_2$), 4.39 (d, 1H, CH$_2$, $J$ = 11Hz), 6.20 (s, 1H, NH), 6.85 (d, 1H, Ar<u>H</u>, $J$ = 7.6 Hz), 7.15 (t, 1H, Ar<u>H</u>, $J$ = 7.6 Hz), 7.39 (t, 1H, Ar<u>H</u>, $J$ = 7.7 Hz), 7.78 (d, 1H, Ar<u>H</u>, J = 7.5 Hz).

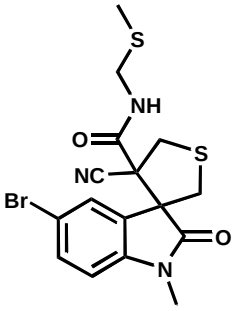
**$^{13}$C NMR:** $\delta$ 17.1, 26.6, 37.1, 37.5, 45.5, 58.5, 60.5, 108.7, 118.1, 123.1, 124.0, 124.8, 130.4, 144.2, 162.0, 173.6.

***5-Bromo-4'-cyano-1-methyl-N-[(methylthio)methyl]-2-oxo-1,2,4',5'-tetrahydrospiro[indole-3,3'-thiophene]-4'-carboxamide <u>63</u>***

Oxoindolinylidene **60** (60 mg, 0.208 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (138 mg, 0.624 mmol) were taken in HMPA (1 mL) and subjected to the usual experimental conditions. The reaction mixture was processed as described for **38**. The product **63** (28 mg, 32%) was obtained as a colorless crystalline solid.

**IR** (KBr) $\nu_{max}$**:** 3390, 2272, 1662, 1589, 1416, 1387, 1134, 1096, 845, 734 cm$^{-1}$.

**$^{1}$H NMR:** $\delta$ 1.60 (s, 3H, SC<u>H</u>$_3$), 3.18-3.22 (m, 4H,



**63**

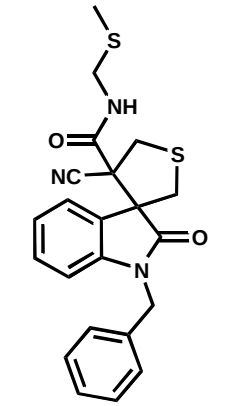
m.p: 67-69 °C

NMe, C<u>H</u>$_2$), 3.36-3.50 (m, 2H, C<u>H</u>$_2$), 4.18 (d, 1H, C<u>H</u>$_2$, *J* = 5.7 Hz), 4.24 (d, 1H, C<u>H</u>$_2$, *J* = 6.2 Hz), 4.35 (d, 1H, CH$_2$, *J* = 10.9 Hz), 6.28 (s, 1H, NH), 6.73 (d, 1H, Ar<u>H</u>, *J* = 8.3 Hz), 7.50 (d, 1H, Ar<u>H</u>, *J* = 8.3 Hz), 7.87 (s, 1H, Ar<u>H</u>,).

**$^{13}$C NMR:** $\delta$ 13.4, 29.6, 37.5, 38.6, 42.9, 58.1, 63.2, 118.5, 122.9, 124.8, 129.8, 130.9, 142.5, 163.1, 171.6.

***4'-cyano-1-benzyl-N-[(methylthio)methyl]-2-oxo-1,2,4',5'-tetrahydrospiro[indole-3,3'-thiophene]-4'-carboxamide <u>64</u>***

Oxoindolinylidene **61** (60 mg, 0.210 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (140 mg, 0.630 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **64** (32 mg, 36%) was obtained as a colorless crystalline solid.



**64**

m.p: 66-68 °C

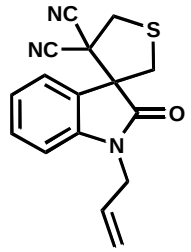
**IR** (KBr) $\nu_{max}$**:** 3384, 2267, 1667, 1589, 1414, 1388, 1134, 1096, 856, 745 cm$^{-1}$.

**$^{1}$H NMR:** $\delta$ 1.56 (s, 3H, SC<u>H</u>$_3$), 3.16 (d, 1H, C<u>H</u>$_2$, *J* = 11 Hz), 3.69-3.86 (m, 3H, C<u>H</u>$_2$), 3.93 (d, 1H, C<u>H</u>$_2$, *J* = 11 Hz), 4.15-4.22 (m, 1H, C<u>H</u>$_2$), 4.95(s, 1H, NCH$_2$), 6.53 (s, 1H, NH), 6.83 (d, 1H, Ar<u>H</u>, *J* = 7.9 Hz), 7.08 (t, 1H, Ar<u>H</u>, *J* = 7.7 Hz), 7.23-7.35 (m, 6H, Ar<u>H</u>), 7.78 (d, 1H, Ar<u>H</u>, J = 7.5 Hz).

**$^{13}$C NMR:** $\delta$ 13.5, 26.6, 37.1, 37.5, 45.5, 49.0, 58.5, 60.5, 108.6, 118.1, 123.1, 124.0, 124.8, 126.7, 127.1, 128.1, 131.4, 144.2, 162.0, 171.6.

***4'-Dicyano-1-allyl-2-oxo-1,2,4',5'-tetrahydrospiro[indole-3,3'-thiophene] 65***

Oxoindolinylidene **62** (60 mg, 0.255 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (169 mg, 0.765 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **65** (30 mg, 40%) was obtained as a colorless crystalline solid




**65**

m.p: 53-55 °C

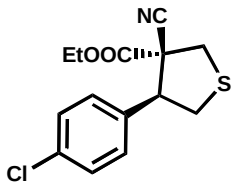
**IR** (KBr) $\nu_{max}$**:** 2228, 1724, 1618, 1420, 1367, 1250, 1139, 745 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 3.41-3.46 (m, 2H, $CH_2$), 3.60 (d, 1H, C$\underline{H}_2$, J = 11.3 Hz), 4.20-4.30 (m, 2H, NC$\underline{H}_2$), 4.57 (d, 1H, C$\underline{H}_2$, *J* = 11.3 Hz), 5.24-5.36 (m, 2H, CH=C$\underline{H}_2$), 5.78-5.89 (m, 1H, C$\underline{H}$=$CH_2$), 6.95 (d, 1H, Ar$\underline{H}$, *J* = 7.9 Hz), 7.21 (t, 1H, Ar$\underline{H}$, J = 7.6 Hz), 7.44 (t, 1H, Ar$\underline{H}$, *J* = 7.7 Hz), 7.71 (d, 1H, Ar$\underline{H}$, J = 7.6 Hz).

**$^{13}$C NMR:** $\delta$ 35.5, 36.7, 38.4, 53.3, 60.6, 109.2, 111.3, 112.4, 121.9, 124.7, 131.4, 143.7, 172.0.

***Ethyl 4-(4-chlorophenyl)-3-cyanotetrahydrothiophene-3-carboxylate 67***

Aryl cyanoacrylate **66** (60 mg, 0.255 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (169 mg, 0.764 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **67** (54 mg, 71%) was obtained as a viscous liquid.




**67**

**IR** (Neat) $\nu_{max}$**:** 2236, 1740, 1540, 1360, 1258, 1110, 814, 730 $cm^{-1}$.

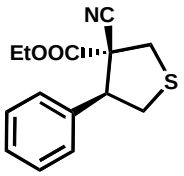
**$^1$H NMR:** $\delta$ 1.17 (t, 3H, $OCH_2C\underline{H}_3$, *J* = 7.1 Hz), 3.25-3.29 (m, 1H, S$C\underline{H}_2$), 3.39-3.53 (m, 3H, S$C\underline{H}_2$, C$C\underline{H}_2$), 3.83-3.89 (m, 1H, ArC$\underline{H}$), 4.19 (quartet, 2H, $OC\underline{H}_2CH_3$, *J* = 7.1 Hz), 7.31-7.35 (m, 4H, Ar$\underline{H}$).

**$^{13}$C NMR:** $\delta$ 13.9, 34.0, 39.3, 55.9, 57.7, 63.4, 116.1, 129.0, 129.3, 129.6, 133.1, 134.9, 166.3.

HRMS (EI) Cacd for $C_{14}H_{14}ClNO_2S$: 295.0434. Found: 295.0367.

***Ethyl 3-cyano-4-phenyltetrahydrothiophene-3-carboxylate 71***

Aryl cyanoacrylate **68** (60 mg, 0.298 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (198 mg, 0.895 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **71** (47 mg, 60%) was obtained as a viscous liquid.




**71**

**IR** (Neat) $\nu_{max}$**:** 2236, 1740, 1540, 1360, 1258, 1110, 814, 730 cm$^{-1}$.

**$^{1}$H NMR:** $\delta$ 1.12 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7.1 Hz), 3.25-3.29 (m, 1H, $SC\underline{H}_2$), 3.39-3.53 (m, 3H, $SC\underline{H}_2$, $CC\underline{H}_2$), 3.83-3.89 (m, 1H, ArC<u>H</u>), 4.15 (quartet, 2H, $OC\underline{H}_2CH_3$, $J$ = 7.1 Hz), 7.31-7.38 (m, 5H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 13.9, 34.0, 39.2, 55.9, 57.6, 63.5, 116.1, 129.2, 129.3, 129.5, 133.1, 134.9, 166.4.

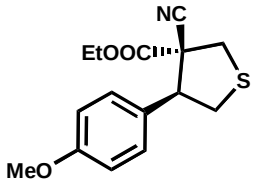
HRMS (EI) Cacd for $C_{14}H_{15}NO_2S$: 261.0823. Found: 261.0820.

***Ethyl 3-cyano-4-(4-methoxyphenyl)tetrahydrothiophene-3-carboxylate 72***

Aryl cyanoacrylate **69** (60 mg, 0.259 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (173 mg, 0.778 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product 7**2** (45 mg, 59%) was obtained as a pale yellow viscous liquid.

**IR** (Neat) $\nu_{max}$**:** 2237, 1743, 1545, 1362, 1260, 1107, 820, 736 cm$^{-1}$.

**$^{1}$H NMR:** $\delta$ 1.15 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7 Hz), 3.21-3.27 (m, 1H, $SC\underline{H}_2$), 3.4 (t, 1H, $CC\underline{H}_2$, $J$ = 11.7 Hz),




**72**

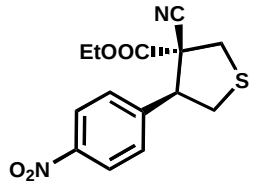
3.52 (uneven triplet, 2H, SC$\underline{H}_2$), 3.8 (s, 3H, OC$\underline{H}_3$), 3.84-3.9 (m, 1H, ArC$\underline{H}$), 4.36 (uneven quartet, 2H, OC$\underline{H}_2$CH$_3$), 6.87 (d, 2H, Ar$\underline{H}$, *J* = 8.2 HZ), 7.32 (d, 2H, Ar$\underline{H}$, *J* = 8.6 Hz ).

**$^{13}$C NMR:** $\delta$ 13.9, 34.1, 39.2, 55.5, 56.3, 58.0, 63.2, 114.8, 129.2, 133.6, 159.9, 166.6.

HRMS (EI) Cacd for $C_{13}H_{12}NO_2S$: 244.0670. Found: 244.0624.

***Ethyl 3-cyano-4-(4-nitrophenyl)tetrahydrothiophene-3-carboxylate <u>73</u>***

Aryl cyanoacrylate **70** (60 mg, 0.243 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (162 mg, 0.728 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **73** (47 mg, 63%) was obtained as a pale yellow crystalline solid.




**73**

m.p: 78-80 °C

**IR** (KBr) $\nu_{max}$**:** 2235, 1741, 1531, 1460, 1325, 1256, 1103, 811, 720 cm$^{-1}$.

**$^{1}$H NMR:** $\delta$ 1.2 (t, 3H, OCH$_2$C$\underline{H}_3$, *J* = 7.1 Hz), 3.32-3.38 (m, 1H, SC$\underline{H}_2$), 3.44-3.61 (m, 3H, SC$\underline{H}_2$, CC$\underline{H}_2$), 4.01-4.07 (m, 1H, ArC$\underline{H}$), 4.22 (quartet, 2H, OC$\underline{H}_2$CH$_3$, *J* = 7.1 Hz), 7.6 (t, 1H, Ar$\underline{H}$, *J* = 7.9 Hz ), 7.84 (d, 1H, Ar$\underline{H}$, *J* = 7.6 Hz), 8.24 (d, 2H, Ar$\underline{H}$, *J* = 11.4 Hz).

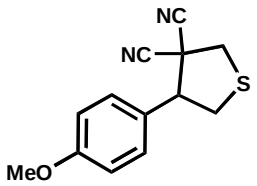
**$^{13}$C NMR:** $\delta$ 13.9, 34.4, 39.7, 56.9, 57.6, 61.5, 119.1, 129.2, 133.1, 138.9, 144.9, 167.4.

HRMS (EI) Cacd for $C_{14}H_{14}N_2O_4S$: 306.3440. Found: 306.3686.

***4-(4-Methoxyphenyl)-3,3-dicyanotetrahydrothiophene <u>75</u>***

Dicyanostyrene **74** (60 mg, 0.246 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (164 mg, 0.737 mmol) were reacted in HMPA (1 mL) and the reaction mixture was

processed as described for **38**. The product **75** (44 mg, 59%) was obtained as a colorless crystalline solid.




**75**

m.p: 136-138 °C

**IR** (KBr) $\nu_{max}$**:** 2237, 1721, 1613, 1465, 1360, 1256, 1120, 720 $cm^{-1}$.

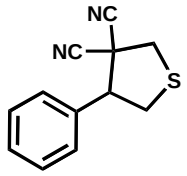
**$^1$H NMR:** $\delta$ 3.32-3.38 (m, 1H, SC<u>H</u>$_2$), 3.46-3.49 (m, 1H, SC<u>H</u>$_2$), 3.54 (s, 2H, CC<u>H</u>$_2$), 3.59-3.81 (m, 1H, ArC<u>H</u>), 3.83 (s, 3H, $OCH_3$), 6.94 (d, 2H, Ar<u>H</u>, *J* = 8.7 Hz), 7.52 (d, 2H, Ar<u>H</u>, J = 7.1 Hz).

**$^{13}$C NMR:** $\delta$ 32.8, 39.4, 44.9, 55.3, 57.2, 112.7, 113.9, 114.7, 124.3, 129.3, 160.7.

HRMS (EI) Calcd for $C_{13}H_{12}N_2OS$: 244.0670. Found 244.0624.

***3,3-Dicyano-4-phenyltetrahydrothiophene <u>80</u>***

Dicyanostyrene **76** (60 mg, 0.389 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (259 mg, 0.117 mmol)were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **80** (47 mg, 56%) was obtained as a colorless crystalline solid.




**80**

m.p: 84-86 °C

**IR** (KBr) $\nu_{max}$**:** 2226, 1613, 1465, 1360, 1256, 1120, 720 $cm^{-1}$.

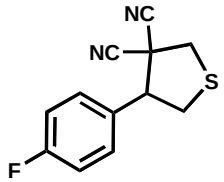
**$^1$H NMR:** $\delta$ 3.36-3.42 (m, 1H, SC<u>H</u>$_2$), 3.5-3.53 (m, 1H, $CH_2$), 3.56 (s, 2H, $CCH_2$), 3.81 (m, 1H, ArC<u>H</u>), 7.43-7.5 (m, 5H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 32.7, 39.5, 44.7, 57.6, 113.7, 112.5, 128.1, 129.2, 129.7, 130.7, 132.54.

HRMS (EI) Cacd for $C_{12}H_{10}N_2S$: 214.0565. Found: 214.0535.

***4-(4-Fluorophenyl)-3,3-dicyanotetrahydrothiophene 81***

Dicyanostyrene **77** (60 mg, 0.258 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (172 mg, 0.775 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **81** (40 mg, 53%) was obtained as a colorless crystalline solid.




**81**

m.p: 130-132 °C

**IR** (KBr) $\nu_{max}$**:** 2227, 1613, 1465, 1360, 1256, 1120, 720 $cm^{-1}$.

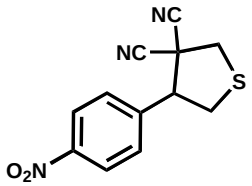
**$^1$H NMR:** $\delta$ 3.35-3.41 (m, 1H, SC<u>H</u>$_2$), 3.46-3.53 (m, 1H, SC$H_2$), 3.56 (s, 2H, C$CH_2$), 3.81 (m, 1H, ArC<u>H</u>), 7.15 (t, 2H, Ar<u>H</u>, J = 8.4 Hz), 7.47-7.52 (m, 2H, Ar<u>H</u>).

**$^{13}$C NMR:** $\delta$ 32.7, 39.6, 44.7, 57.0, 112.4, 113.6, 116.6, 128.3, 130.1, 161.8, 165.1.

HRMS (EI) Cacd. for $C_{12}H_9FN_2S$: 232.0470. Found: 232.0449.

***4-(4-Nitrophenyl)-3,3-dicyanotetrahydrothiophene 82***

Dicyanostyrene **78** (60 mg, 0.301 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (200 mg, 0.901 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **82** (38 mg, 48%) was obtained as a colorless crystalline solid.




**82**

m.p: 143-145 °C

**IR** (KBr) $\nu_{max}$**:** 2232, 1613, 1462, 1361, 1252, 1124, 728 $cm^{-1}$.

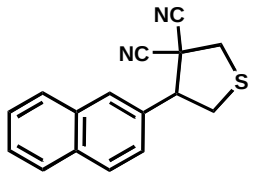
**$^1$H NMR:** $\delta$ 3.36-3.42 (m, 1H, SC<u>H</u>$_2$), 3.48-3.55 (m, 1H, SC$H_2$), 3.55 (s, 2H, C$CH_2$), 3.83 (m, 1H, ArC<u>H</u>), 7.6 (t, 1H, Ar<u>H</u>, *J* = 7.9 Hz ), 7.84 (d, 1H, Ar<u>H</u>, *J* = 7.6 Hz), 8.24 (d, 2H, Ar<u>H</u>, *J* = 11.4 Hz).

**$^{13}$C NMR:** $\delta$ 32.8, 39.4, 44.8, 56.9, 112.4, 113.6, 124.3,

130.1, 137.1, 148.6.

***4-(2-Naphthyl)-3,3-dicyanoetrahydrothiophene 83***

Dicyanostyrene **79** (60 mg, 0.226 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (151 mg, 0.681 mmol)were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **83** (45 mg, 61%) was obtained as a colorless crystalline solid.




**83**

m.p: 70-72 °C

**IR** (KBr) $\nu_{max}$**:** 2243, 1613, 1465, 1360, 1256, 1120, 720 $cm^{-1}$.

**$^1$H NMR:** $\delta$ 3.54-3.57 (m, 2H, C$\underline{H}_2$), 3.67-3.69 (m, 2H, SC$\underline{H}_2$), 4.87 (uneven t, 1H, NpC$\underline{H}$, $J$ = 7.8 Hz, $J$ = 8.1 Hz), 7.52- 7.65 (m, 3H, Ar$\underline{H}$), 7.88-7.94 (m, 3H, ArH), 8.13 (d, 1H, ArH, $J$ = 8.4 Hz).

**$^{13}$C NMR:** $\delta$ 33.2, 34.1, 39.4, 46.7, 115.8, 118.2, 121.9, 124.2, 125.9, 126.7, 127.1, 129.0, 131.8, 134.0.

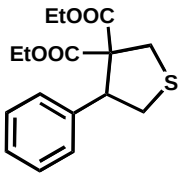
Anal. Calcd. for $C_{16}H_{12}N_2S$: C, 72.70; H, 4.58; N, 10.6; S, 12.13. Found: C, 72.59; H, 4.29; N, 10.71; S, 12.16.

***Diethyl 4-phenyltetrahydrothiophene-3,3-dicarboxylate 85***

Benzylidene malonylester **84** (60 mg, 0.242 mmol) and bis(trimethylsilylmethyl) sulfoxide **28** (160 mg, 0.725 mmol) were reacted in HMPA (1 mL) and the reaction mixture was processed as described for **38**. The product **85** (61 mg, 82%) was obtained as a colorless crystalline solid.

**IR** (KBr) $\nu_{max}$**:** 2347, 1734, 1613, 1465, 1360, 1256, 1120, 720 $cm^{-1}$..

**$^1$H NMR:** $\delta$ 1.04 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7.1 Hz), 1.29 (t, 3H, $OCH_2C\underline{H}_3$, $J$ = 7.1 Hz), 3.06-3.1 (m, 1H, SC$\underline{H}_2$), 3.31-3.35 (m, 1H, C$\underline{H}_2$C$(CO_2Et)_2$), 3.53-3.6 (m, 2H,




**85**

m.p: 44-46 °C

SC$\underline{H}_2$, C$\underline{H}_2$C$(CO_2Et)_2$), 3.82-3.96 (m, 3H, OC$\underline{H}_2CH_3$), 4.2-4.33 (m, 2H, OC$\underline{H}_2CH_3$, ArC$\underline{H}$), 7.26-7.32 (m, 5H, Ar$\underline{H}$).

**$^{13}$C NMR:** $\delta$ 13.9, 14.1, 34.5, 36.2, 51.9, 61.3, 61.9, 68.4, 127.5, 127.9, 128.3, 128.7, 139.8, 169.3, 169.4.

HRMS (EI) Cacd. for $C_{14}H_{20}O_4S$: 308.3920. Found: 308.3909.

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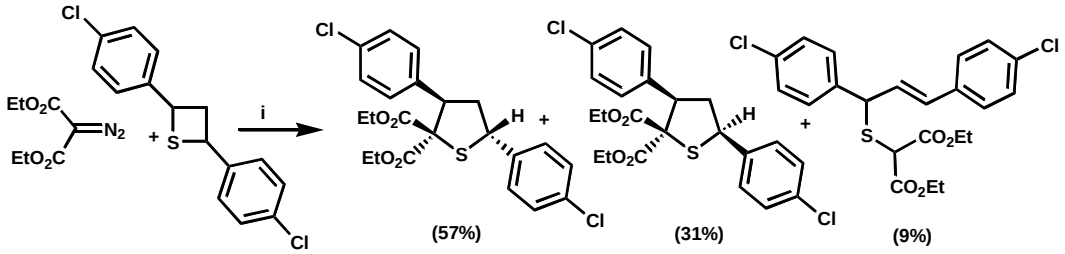
# SUMMARY

The thesis entitled "**Exploration of the Reactivity of Sulfur Ylides: Novel Synthesis of Tetrahydrothiophenes and Thiazolidines**" embodies the results of our studies aimed at exploring the reactivity of sulfur ylides. The reactions of sulfonium ylides, sulfimides and thiocarbonyl ylide leading to the construction of heterocycles are presented in this thesis.

A general introduction to organosulfur chemistry and a brief survey on sulfur ylides, intended to provide a qualitative understanding of the topic is given in chapter 1.

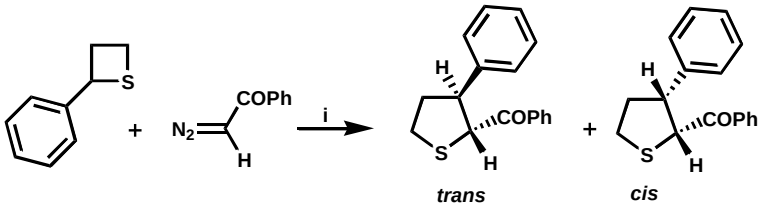
The second chapter of the thesis deals with the Stevens rearrangement of sulfonium ylides towards the diastereoselective synthesis of tetrahydrothiophenes; allylthioethers are obtained as the minor products in these reactions. Transition metal [Cu(II) and Rh(II)] catalyzed reaction of diethyl diazomalonate with thietanes generated sulfonium ylides; and the latter on rearrangement afforded the products. A typical example is given in Scheme 1.




i) $Rh_2(OAc)_4$, benzene, Argon, 80 $^oC$, 16 h,

**Scheme 1**

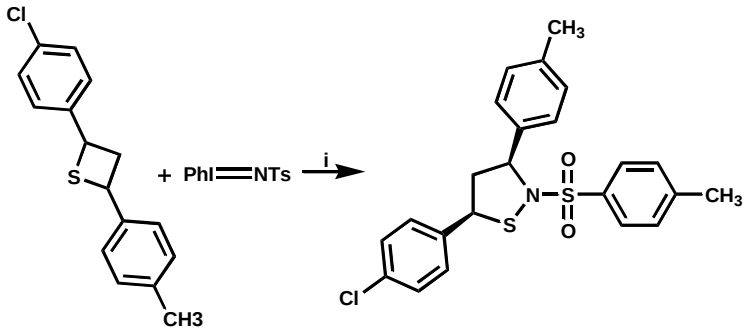
The reaction described above could be easily extended to engage a number of other diazo compounds, to afford the products in moderate yields (Scheme 2).




i) Benzoyl diazomethane, $Cu_2(acac)_2$, benzene, argon, 80 $^oC$,16 h, 63%, 3.2:1

**Scheme 2**

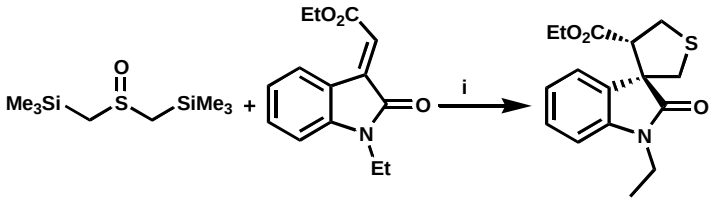
The third chapter deals with the reactivity of thietanes towards nitrene. The Cu(II) catalyzed reaction of [*N*-(p-tolylsulfonyl)imino]phenyliodinane with diastereomeric mixture of thietanes afforded thiazolidines. An illustrative example representing the completely diastereoselective synthesis of thiazolidine is given in Scheme 3.




i) Cu(acac)$_2$, benzene, 80 $^{o}$C, argon, 10min, 76 %

**Scheme 3**

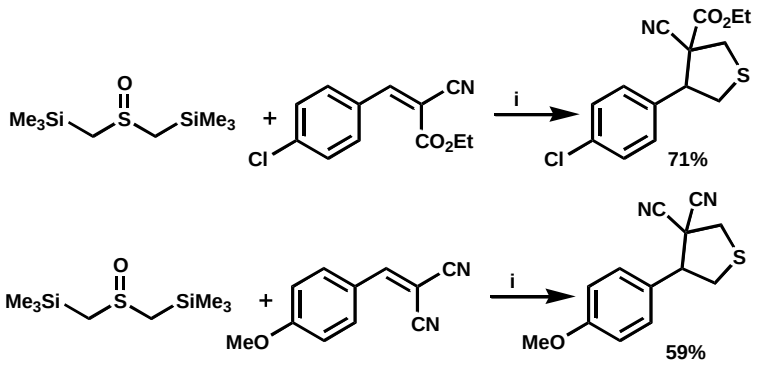
The Huisgen dipolar cycloaddition reaction of thioformaldehyde *S*-methylide with activated carbon-carbon double bonds forms the subject matter of the fourth and final chapter. The reaction of oxoindolinylidene acetate with bis(trimethylsilylmethyl) sulfoxide afforded spiroindolenins in good yields (Scheme 4).




i) HMPA, sealed tube, 110 $^{o}$C, 20 h, 79%

**Scheme 4**

The reaction of bis(trimethylsilylmethyl) sulfoxide with activated styrenes furnished tetrahydrothiophene derivative in good yields. The following examples are illustrative (Scheme 5).




**i) HMPA, sealed tube, 110 $^{o}$C, 16 h**

**Scheme 5**

In conclusion, we have exploited the reactivity of sulfur ylides for the synthesis of substituted sulfur heterocycles. The reactivity of sulfonium ylide generated from thietanes and a variety of electrophilic carbenes furnished tetrahydrothiophenes in good yields. It was found that nitrene, also reacted, *à la* carbene with thietanes to afford thiazolidines in a completely diastereoselective manner. A simple and efficient method for the synthesis of spirocyclic systems by the Huisgen 1,3-dipolar cycloaddition reaction of the parent thiocarbonyl ylide has also been developed. It is worthy of mention that tetrahydrothiophene and thiazolidine moieties are structural fragments of biologically active compounds such as biotin, biocytin, thiophthalene Lu 5003 and many penicillin derivatives.

## List of Publications

1. The Rh (II) Catalyzed Reaction of Diethyl Diazomalonate with Thietanes: A Facile Synthesis of Tetrahydrothiophene Derivatives *via* Sulfonium Ylides. Nair, V.; **Nair, S. M**.; Mathai, S.; Liebscher, J.; Ziemer, B.; Narsimulu, K. *Tetrahedron Lett*. **2004**, *45*, 5759.
2. A Facile Three Component Reaction of Dicarbomethoxy Carbene, Aldehydes and *o*- Quinones: Synthesis of Novel Spiro-Dioxolanes. Nair, V.; Mathai, S.; **Nair, S. M**.; Rath N. P. *Tetrahedron Lett*. **2003**, *44*, 8407
3. $SnCl_4$- Catalyzed reaction of *o*-Benzoquinones and Aryl Acetylenes: An Unprecedented One-Pot Synthesis of Tropone Derivatives. Nair, V.; Sethumadhavan, D.; **Nair, S. M**.; Rath, N. P.; Eigendorf, G. K. *J. Org. Chem.* **2002**, *67*, 7533.
4. Reaction of Nitrile Ylides with Isatins and o-Benzoquinones: Formation of Novel Spirooxazoline Derivatives. Nair, V.; Sethumadhavan, D.; **Nair, S. M**.; Viji, S.; Rath, N. P. *Tetrahedron* **2002**, *58*, 3003.
5. Dipolar Cycloaddition of Carbonyl Ylide with [60]Fullerene: Formation of Novel Heterocycle Fused Fullerene Derivatives. Nair, V.; Sethumadhavan, D.; Sheela, K. C.; **Nair, S. M**.; Eigendorf, G. K. *Tetrahedron* **2002**, *58*, 3009.
6. Reaction of Allenamides with [60]Fullerene: Formation of Novel Cyclobutane Annulated Fullerene Derivatives. Nair, V.; Sethumadhavan, D.; **Nair, S. M**.; Tressa, P. M.; Eigendorf, G. K. Synthesis **2002**, 1655.
7. A Diastereoselective Synthesis of Thiazolidines *via* Sulfonium Ylides Formed by The Reaction of Thietanes and Nitrene. Nair, V.; **Nair, S. M**.; Devipriya, S.; Sethumadhavan, D. (to be communicated to *Tetrahedron Lett.*).

8. Parent Thiocarbonyl Ylide Cycloaddition: A Facile Approach to Functionalized Spiroindolenins. Nair, V.; **Nair, S. M**.; Devipriya, S.; Sethumadhavan, D.(to be communicated).

## Posters Presented at Symposia

**1**. The Rh(II) Catalyzed Reaction of Diethyl Diazomalonate with Thietanes: A Facile Synthesis of Tetrahydrothiophene Derivatives *via* Sulfonium Ylides.
**Smitha M. Nair**, Vijay Nair, 6$^{th}$ National Symposium in Chemistry, Kanpur, India, February 06-08, 2004.

**2**. $SnCl_4$ Catalyzed Reaction of *o*-Benzoquinones and Aryl acetylenes: An Unprecedented One-Pot Synthesis of Tropone Derivatives.
**Smitha M. Nair**, Vijay Nair, 5$^{th}$ National Symposium in Chemistry, Chennai, India, February 2003.