PUSH-PULL SYSTEMS : SYNTHESIS, REACTIVITY AND STEREOCHEMICAL CONSEQUENCES

A Thesis
Submitted to the

UNIVERSITY OF BOMBAY

For the Degree of
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

By

LAXMIKANT N. PATKAR
Division of Organic Chemistry (Synthesis)
National Chemical Laboratory
Pune 411008

1995

CERTIFICATE

Certified that the work incorporated in the thesis entitled " **Push-Pull Systems : Synthesis, Reactivity and Stereochemical Consequences** " submitted by **L. N. Patkar** was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

S. Rajappa

Date : 1.1.96

(Dr. S. Rajappa)

National Chemical Laboratory

Research Guide

Pune 411008

DECLARATION STATEMENT UNDER 0.771

The work presented in the thesis has been carried by me under the guidance of Dr. S. Rajappa, Organic Chemistry Division (Synthesis), National Chemical Laboratory, Pune 411008.

The experimental work, observations and interpretations of the data in connection with the studies are entirely my own.

The work reported in this thesis is original and has not been submitted in part or full for any degree or diploma to any other University or Institution.

Dr. S. Rajappa
Research Guide

L. N. Patkar
Candidate

Acknowledgements

I would like to express my deep sense of gratitude to my research advisor, Dr. S. Rajappa, F. A. Sc. F. N. A., for his valuable guidance and constant encouragement during the course of this work.

I consider myself lucky for being associated with Dr. A. R. A. S. Deshmukh, Dr. B. M. Bhawal and Dr. A. Sarkar. Their enthusiasm for science ,dynamism and sense of humor provided a lively atmosphere in the lab. This really made daily work in the lab enjoyable. I thank them for their suggestions and help in the lab work. I extend my thanks to the past and present labmates, Dr. D. G. Panse, Dr.(Mrs.) V. S. Joshi, Mrs. V. K. Kale, Mr. V. K. Gumaste, Dr. K. M. Sathe, Dr. S. Ganesh, Dr. M. N. Nandi, Dr. M. Jayaram, Sanjoy, Rasidul Amin, Srirajan, Surojit, Keshavachar, Sunil and Jayprakash for their cooperation. I thank Mr. Vasant Kokate for day-to-day maintenance of lab.

I thank my senior colleagues, Dr. S. G. Manjunatha, Dr. (Mrs.) S. G. Gadre, Dr. (Mrs.) S. P. Maybhate, Dr. T. I. Reddy, Dr. K. V. Reddy, Dr. S. K. Tandel, Dr. P. Chittari, Dr. (Miss) A. Thomas for their helpful suggestions and cooperation during this work. I owe special thanks to my colleague, Mr. A. N. Dixit who has helped me in every possible way during this work as well as in the other matters. I would also like to thank my present colleagues, Mr. M. Anbazahagan, Mr. S. S. Surange and Mr. Uday Joshi for their help during the final stages of this work. I thank Mr. B.V.Bhagwat and Mr.M.G.Malusare for their cheerful company.

The support from the analytical section (NMR, IR, X-ray and Microanalysis) of this laboratory is gratefully acknowledged. In particular , I would like to thank Mr. A. G. Samuel and Mrs. Phalgune of NMR, Microanalytical section and Dr. (Mrs.) V. G. Puranik for their dedicated efforts. Similar support from the library staff is appreciated.

The assistance of administrative staff of the division and the institute is gratefully acknowledged. My special thanks are due to Mrs. S. S. Deshpande who has always willingly extended her help whenever required.

I am greatly indebted to my parents and my sisters. Without their encouragement and support this work would have been impossible.

Finally, I would like thank C.S.I.R. for financial assistance and Director, N.C.L. for providing the necessary facilities and permitting to submit this work for fulfillment of Ph.D. degree.

L. N. Patkar

General Remarks

1. All solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80°C.
2. All the solvents extracts were finally dried over anhydrous sodium sulfate.
3. The compound numbers, scheme numbers and reference numbers etc. given in each chapter refer to that particular chapter only.
4. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
5. TLC was carried out on silica gel plates prepared by spreading slurry (chloroform), drying at room temperature
6. The IR spectra were recorded on a Perkin-Elmer infrared spectrophotometer model 683B.
7. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian FT-80A, Bruker WH-90, Bruker AC-200 spectrometers, using tetramethylsilane as internal standard. The following abbreviations are used : s = singlet, d = doublet, q = quartet, m = multiplet.
8. The mass spectra were recorded on a Finnigan MAT-1020B-70ev mass spectrometer.
9. Elemental analysis were performed by Microanalytical Lab, NCL Pune.
10. All optical rotations were measured using sodium D lines on a JASCO-181-digital polarimeter at room temperature.

Abbreviations

AcOH	acetic acid
DBU	1,8-diazabicyclo [5,4,0] undec-7-ene
DMF	N,N-dimethylformamide
Et	ethyl
eq	equivalent
h	hours
IR	infrared
Me	methyl
mg	milligrams
MS	mass spectrum
nm	nanometer
NMR	nuclear magnetic resonance
Ph	phenyl
pm	pico meter
PTC	phase transfer catalysis
PTSA	p-toluenesulfonic acid
RT	room temperature
TEA	triethyl amine
THF	tetrahydrofuran
TLC	thin layer chromatography

Contents

SYNOPSIS

Push-Pull Systems : Synthesis, Reactivity and Stereochemical Consequences

Introduction to Push-Pull Systems

Push-pull systems are ethylene compounds having an electron donating group viz. amino, alkoxy , alkylthio etc. at one end of the carbon-carbon double bond and an electron withdrawing group viz. nitro, carbonyl, nitrile, sulfonyl etc. at the other end. These systems (nitroenamines, enaminones , enamides etc.) have been reviewed extensively in the literature with emphasis on their synthesis, reactivity and the configuration about the carbon-carbon double bond. As a consequence of the push-pull effect , there is a considerable lowering of the barrier to rotation about the carbon-carbon double bond in these compounds. This particular effect has made it possible to observe a weak non-covalent interaction between sulfur and other heteroatoms in certain specific molecules. Another interesting fact about such systems, evident from the host of experimental data in the literature on thio-Claisen rearrangements, is that the rearrangement of compounds incorporating a push-pull ethylene system in the [3,3] framework takes place under mild conditions. Although, there is no clear proof, it appears that the push-pull effect facilitates the rearrangement. These two aspects of the push-pull effect form the basis of the present work.

Chapter 1: Role of S...N Non-bonded Interaction in Determining Stereoselectivity

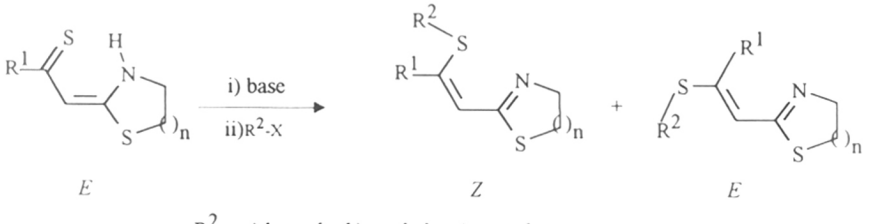
Non-covalent interactions involving sulfur have attracted considerable attention in view of their interest from bonding point of view as well as due to their potential role in determining biomolecular conformations and in crystal engineering applications. The evidence for such interactions comes from experimental data mainly in the solid state by X-ray crystal structure analysis. Recently , for the first time, evidence for S...O non-bonded interaction in the solution state was furnished where change of configuration about

the carbon-carbon double bond occurs as a consequence of this interaction on increasing the solvent polarity.

Enaminothione **1** , a push-pull system, exists exclusively in the intramolecularly hydrogen bonded *E*-configuration in non-polar solvents like benzene and chloroform. As the solvent polarity increases , the population of *Z*-isomer increases perhaps due to S...S non-bonded interaction until the *Z*/*E* ratio reaches a maximum of 1 : 2 in pure DMSO. The *Z*/*E* isomerisation in **1** is possible due to the low barrier to rotation about the carbon-carbon double bond. It would be interesting to find out whether such non-bonded interactions can be observed without change of solvent, preferably by isolation of the two stereoisomers and studying their interconversion..

Alkylation of **1** (*Scheme* 1)with alkyl halides in different solvents at room temperature using various bases (K_2CO_3, DBU, TEA), gives the product **2** as a mixture of two stereoisomers . In all the cases studied, the *Z*-isomer is formed predominantly. However, acid-catalysed equilibration (benzene, PTSA, reflux) , dramatically alters the initial *Z*/*E* ratio to give the *E*-isomer as the major product. It is evident that **2***Z* is formed under kinetic control while **2***E* is the thermodynamically more stable product.

Scheme 1



E *Z* *E*

R^2 = a) benzyl b) methyl c) prenyl

1 : R^1 = Me ; n = 1 **2** : R^1 = Me ; n = 1

3 : R^1 = Ph ; n = 2 **4** : R^1 = Ph ; n = 2

The observed stereoselectivity under kinetic control may be possibly due to the non-bonded attraction arising between exocyclic divalent sulfur and the ring nitrogen in the transition state or at the deprotonated stage of enaminothione **1**. Strong support for

this hypothesis emerges from an X-ray crystallographic analysis of **2***Z* wherein close S...N contact of 284 pm was observed. It was also seen that the 5-membered quasi ring was planar and the three atoms C-S and N were colinear. This is an ideal arrangement for n-σ^* overlap.

Further reinforcement for this view comes from alkylation of **3**, a ring homologue of thiazolidine **1**. Interestingly, in this case the *Z*-isomer is formed under both , kinetic and thermodynamic control. An X-ray crystal structure analysis of the S-benzyl compound **4a** shows short S...N contact of 270 pm. To get a better idea about the nature of S...N non-bonded interaction , alkylation of structural variants of enaminothione **1** was carried out. Unfortunately, no conclusive results could be obtained as these compounds partially decomposed during the acid-catalysed equilibration and hence could not be characterised properly.

In conclusion, these results constitutes a rare example of a weak interaction guiding the stereoselectivity. The only other example of a similar weak interaction influencing the stereochemistry of the product is provided by the acetalisation of menthone with 1,3-alkanediols where van der Waals attraction influences the stereochemical outcome of the reaction.

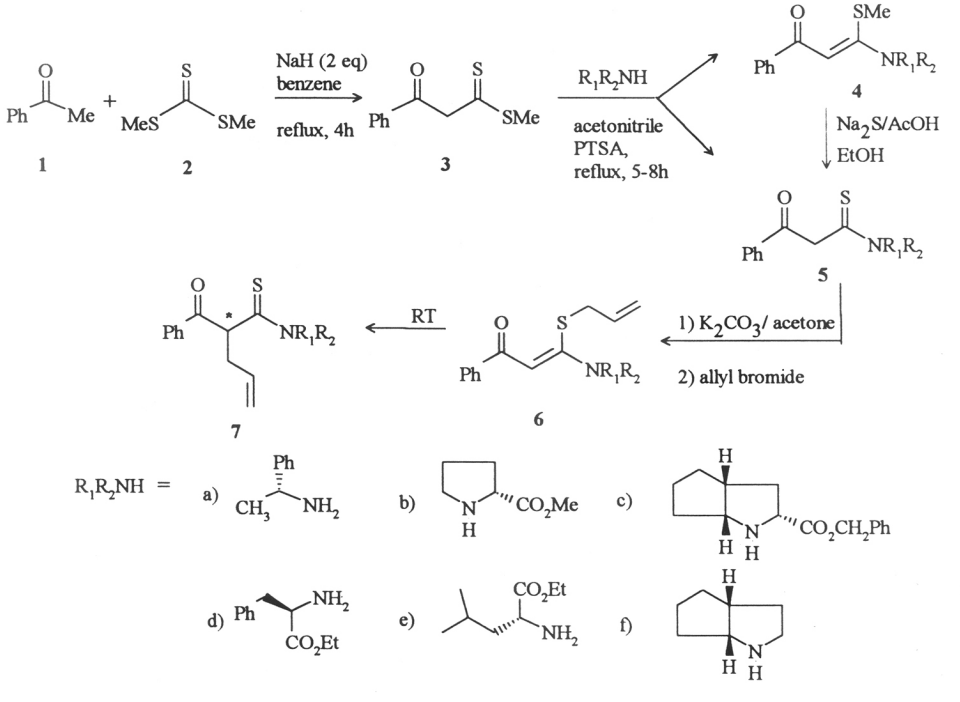
Chapter 2 : Chiral Induction in thio-Claisen Rearrangement Involving Push-Pull Systems

Over the past few decades sigmatropic rearrangement has emerged as a powerful methodology for generating a new chiral center with fairly predictable configuration. One such sigmatropic rearrangement is thio-Claisen rearrangement. However, it is relatively less studied as compared to the Claisen rearrangement. As previously mentioned, the push-pull system accelerates the rearrangement when incorporated as part of the [3,3] system. This effect can be exploited for chiral induction studies with the reasonable assumption that relatively higher induction can be achieved under mild rearrangement

conditions. Since the chiral auxiliary does not constitute part of the rearrangement framework, these studies will provide an example of remote stereocontrol (original chiral center three carbon atoms away from the prochiral center)- an aspect on which virtually no literature exists. Hence thioacetamides having an electron withdrawing group as an α-substituent and readily available chiral amines or aminoacids as a part of thioamide functional group are ideally suited for such remote stereocontrol studies.

The synthesis of thioacetamides **5** possessing a benzoyl group as an electron withdrawing α-substituent and incorporating different chiral amines in the thioamide moiety was carried out as outlined in *Scheme* 2. These were subjected to allylation in acetone with K_2CO_3 as a base at room temperature. The S-allylated product was isolated in almost all the cases and subsequently rearranged in chloroform at room temperature.

Scheme 2



The diastereomeric excess of the thus obtained C-allyl derivative was determined by peak intensities of various signals in the ^{13}C NMR spectrum. Higher diastereoselectivity was observed with α-phenylethylamine and a bicyclic analog of proline ester. No definite trend about the degree of induction with respect to structural variation in the chiral auxiliary could be detected as attempts to synthesize the desired thioacetamides **5** failed in a few cases at one or the other stage of *Scheme* 2. Also, attempts to obtain α-cyano thioacetamides failed, except in the case of α-phenylethylamine derivative where diastereomeric excess was found to be zero.

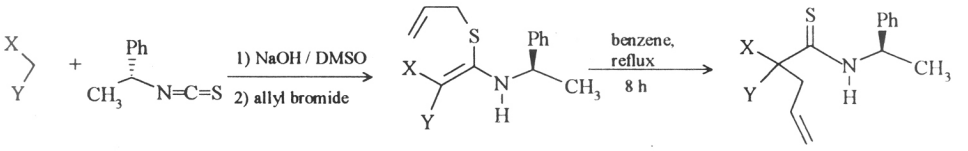
The above study exploits the useful property of push-pull system to effect thio-Claisen rearrangement under mild conditions to get better diastereoselectivity under remote stereocontrol.

Chapter 3 : Chiral Induction in thio-Claisen Rearrangement : Generation of Chiral Quaternary Center

In the previous chapter we have demonstrated the utility of push-pull effect to get fairly high diastereoselectivity under remote stereocontrol in the thio-Claisen rearrangement. As a logical extension to the work described therein, generation of a chiral quaternary center was planned as outlined in *Scheme* 3. Although, such compounds having a quaternary carbon atom have been prepared by thio-Claisen rearrangement, there is no report on chiral induction study in the literature. In the case of compounds **3a-c**, the quaternary asymmetric carbon once formed, has a stable configuration due to lack of acidic hydrogen atom. In contrast, the tertiary asymmetric carbon has an active hydrogen and hence there is a possibility of epimerisation due to thione-enethiol equilibration.

Active methylene compounds having two different electron withdrawing groups were chosen for the reaction with the isothiocyanate derived from a chiral primary amine. The choice of α-phenylethylamine as the chiral auxiliary was due to its easy conversion to the corresponding isothiocyanate and also due to the unexpectedly high chiral induction observed in the case of benzoyl thioacetamides.

Scheme 3



1 2 3

	a	b	c
X	-CN	MeCO-	Ph
Y	-COOEt	-COOMe	-COOEt

Thus active methylene compounds **1a-c** and α-phenylethyl isothiocyanate were added to DMSO containing 1 eq. of finely powdered NaOH; after two hours allyl bromide was added and the reaction mixture stirred at room temperature for two hours. After the usual work up, the S-allylated intermediate **2** was isolated. This on refluxing in benzene for about 8h. rearranges to the C-allylated product **3**.

The diastereomeric excess of the compounds **3a-c** was determined by peak intensities of various signals in the ^{13}C NMR spectrum. The best diastereoselectivity was observed for **3a** (de = 25%). In the remaining two cases it was practically zero. Attempts to incorporate the other moieties like propiophenone or cyclohexanone instead of the active methylene compounds **1a-c** failed to give the desired intermediate **2**.

It may be concluded from the above results that the active methylene compounds are not best suited to achieve higher stereoselectivity as compared to the benzoyl substituent with α-phenylethylamine as the chiral auxiliary in thio-Claisen rearrangement.

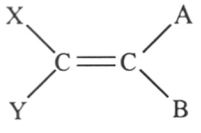
(Dr. S. Rajappa)
Research Guide

(L. N. Patkar)
Candidate

Introduction to Push-Pull System

Push-pull ethylene compounds possess an electron withdrawing group (nitro, carbonyl, nitrile etc.) at one end of the carbon-carbon double bond and an electron donating group (alkoxy, alkylthio, amino etc.) at the other end. In a lesser known variation of this system, where the donor-acceptor groups are attached to the extreme ends of a conjugated diene, it is termed as an extended push-pull system. A push-pull system is schematically presented in *Fig. 1.*

Fig. 1.



A , B = $-NO_2$, -COR, -COOR, $-SO_2R$

X , Y = -OR, -SR, $-NR_1R_2$

Many of these push-pull systems (nitroenamines, enaminones, enaminothiones etc.) have been extensively reviewed with emphasis on their synthesis, reactivity, and configuration about the carbon-carbon double bond.[1-5] Two important aspects, reactivity and configuration about C=C bond, will be discussed briefly in the following paragraphs.

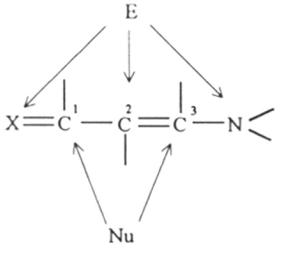
Since these systems have multiple reactive centers, a diverse reactivity pattern is observed with different reagents (hard and soft electrophiles), depending on the extent of push-pull effect i.e. the extent of interaction between the donor groups and the acceptor groups through the intervening π-electron system. Thus some centers are reactive towards soft electrophiles while other centers towards hard electrophiles (*Scheme 1.*).[2-4] However, this reactivity can be altered by choosing suitable reaction conditions or by structural modification by introducing different substituents. This behaviour is summarized in *Scheme 1.* The versatility in the reactivity makes these systems attractive synthons in organic synthesis.

In the thoroughly investigated case of nitroenamines[2], the reactivity pattern was anticipated by comparing the NMR chemical shift values of nitroenamines with those of enaminones and enaminoesters. Subsequently, by making a clever use of different electrophiles, it was established that nitroenamines behave like push-pull ethylenes. This is

in contrast to the behaviour of enaminones and enaminoesters which behave more like an enamine. The push-pull behaviour of nitroenamines was ascribed to the efficient electron withdrawal by the nitro group.

Scheme 1.

ENAMINONES and ENAMINOTHIOKETONES



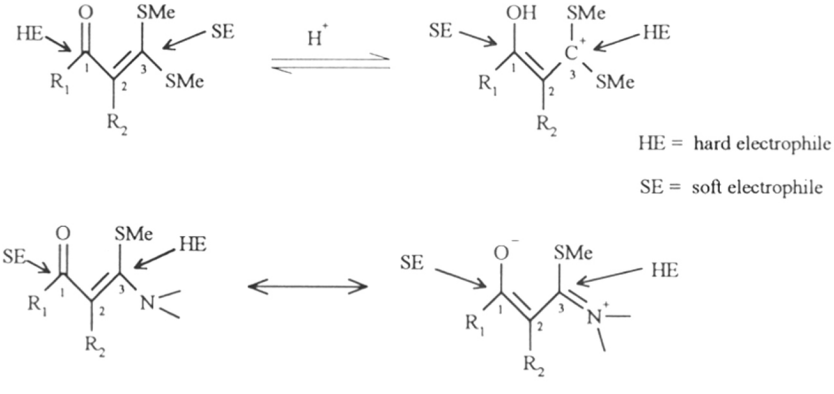
X = O, S

soft electrophiles attack either at S or C^2

hard electrophiles react at the N

E = electrophile , Nu = nucleophile

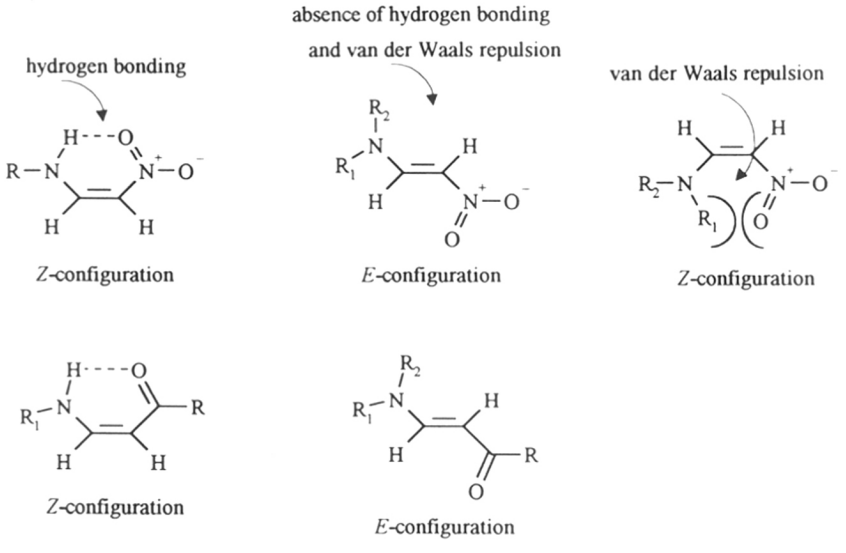
α-OXOKETENE S,S-, N,S-, and O,S- ACETALS



Based on this reactivity pattern and further alteration of reactivity by the structural modification (by the introduction of substituents), many valuable synthetic transformations were carried out in order to construct certain novel compounds and various heterocycles.[2-4] Since nitroenamines have a very high dipole moment in the ground state as well as in the excited state, they are expected to have non-linear optical property and perhaps act as conducting materials.[6] Similarly, α-oxoketene acetals were shown to be versatile synthons in organic synthesis for construction of various heterocycles. Although the synthetic utility of push-pull systems in organic synthesis has been demonstrated, the experts in this field are of opinion that their synthetic potential remains to be explored.

As mentioned earlier, the configuration about the C=C bond is most interesting from the stereochemical point of view. The configuration is influenced by the various forces present within the molecule viz. intramolecular hydrogen bonding, van der Waals attractive and repulsive interactions (*Fig. 2)*, and those outside the molecule viz. intermolecular hydrogen bonding, van der Waals forces and crystal packing. It is interesting to note that, in the solution state, the configuration is greatly influenced by solvent.

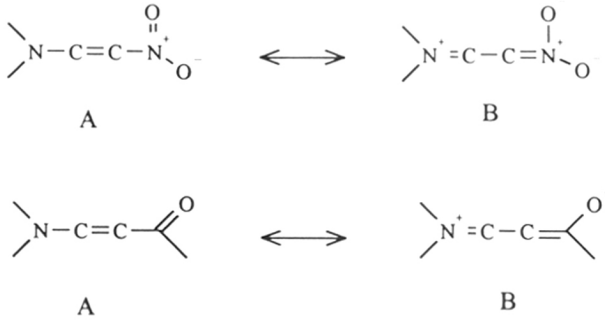
Fig. 2



Any discussion on push-pull systems will be incomplete without reference to the barrier to rotation about the carbon-carbon double bond. In simple ethylenes, cis-trans isomerisation has a free-energy barrier of 62-65 kcal/ mol. This is estimated by the change in NMR band shapes when the isomerisation process is rapid at a particular temperature. As a consequence of the push-pull effect the free-energy barrier is lowered to the order of 25 kcal/ mol or lower; which corresponds to a temperature below 200^{o}C. In a few cases the barrier is below the critical limit of 22 kcal/ mol[1] ; as a consequence, the isomerisation proceeds at appreciable rates, even at room temperature. This is due to the existence of the push-pull ethylenes in the resonance form A and B (*Fig. 3*) where contribution due to form B is greater, imparting considerable single bond character to the formal double bond. This

lowering of the barrier has made it possible to observe weak non-covalent interactions involving sulfur atom and other heteroatoms in certain specific molecules.

Fig. 3



A B

A B

Another interesting fact about push-pull systems, evident from the host of experimental data in the literature on thio-Claisen rearrangement, is that the rearrangement of compounds incorporating a push-pull ethylene system in the [3,3] framework takes place under mild conditions.[7,8] Although there is no clear proof, it appears that the push-pull effect facilitates the rearrangement. The study of these aspects of the push-pull system form the basis of the present work.

References

1. J. Sandstorm, *Topics in Stereochemistry,* **1983**, *vol. 14*, 83.
2. S. Rajappa, *Tetrahedron*, **1981**, *37*, 1480.
3. H. Junjappa, *Tetrahedron*, **1990**, *46*, 5423
4. M. Pulst, D. Greif, E. Kleinpeter, *Z. Chem.*, **1988**, *28*, 345.
5. J. V. Greenhill, *Chem. Soc. Rev.*, **1977**, 277.
6. *Organic Materials for Non-linear Optics*, Ed., R. A. Hann and D. Bloor, Royal Chemical Society, **1989**.
7. a) F. C. V. Larsson, S. O. Lawesson, *Tetrahedron*, **1972**, *28*, 5341. b) F. C. V. Larsson, S. O. Lawesson, *Tetrahedron*, **1974**, *30*, 1283. c) K. Hartke, G. Golz, *Chem. Ber.*, **1974**, *107*, 566. c) J. Z. Mortensen, B. Hedegaard, S. O. Lawesson, *Tetrahedron*, **1971**, *27*, 3831 d) L. Dalgaard, S. O. Lawesson, *Tetrahedron*, **1972**, *27*, 2051
8. K. V. Reddy, S. Rajappa, *Tetrahedron Lett.*, **1992**, 7957.

CHAPTER 1

ROLE OF S...N NON-BONDED INTERACTION IN DETERMINING STEREOSELECTIVITY

Chapter 1: Role of S...N Non-bonded Interaction in Determining Stereoselectivity

Summary

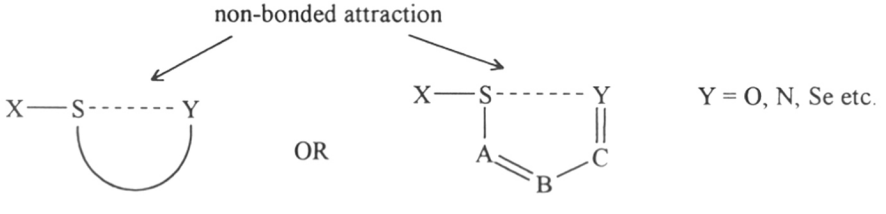
This chapter deals with the role of a weak attractive force, non-bonded S...N interaction, in guiding the stereochemical course of a reaction. Based on the stereochemistry of the products obtained by alkylation of enaminothiones **5** and **16**, and their X-ray crystal structure analysis in the solid state, evidence for S...N non-bonded attraction has been furnished. This is probably the first example of such a weak force influencing the stereoselectivity of a reaction. It has also been shown that non-bonded interaction can be observed in the solution state without resorting to change of solvent.

1. Introduction

Non-covalent weak forces like hydrogen bonds, van der Waals attractive and repulsive interactions have been known for a long time to influence the physical and chemical properties of small organic molecules. Further, they are known to play an important role in many biological systems where the combined operation of a large number of such forces operate to have a significant impact on the structure of large biomolecules and hence, on their function. A very well known example is the structure of the DNA double-helix. In this macromolecular system a large number of hydrogen bonds are responsible for maintaining the three dimensional structure by holding together the two complementary strands.Even a small number of intermolecular hydrogen bonds are important in molecular recognition, a research area of current interest. In organic chemistry, quite often, van der Waals repulsive interaction between substrates and reagents plays an important role in determining the stereochemical course of reactions.[1] Hence, these weak interactions continue to receive a great deal of attention from researchers in all field of chemical sciences.

Another type of such weak force is the non-bonded attraction, usually arising between a sulfur atom and other heteroatoms or between any two heteroatoms when they are situated in a quasi-ring form (*Fig 1*) in certain specific molecules.

Fig 1

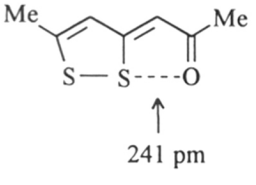


In literature, examples of non-bonded attraction between sulfur and oxygen are known in abundance and have been investigated thoroughly. However, very few examples of non-bonded attraction between two sulfur atoms or that between a sulfur and heteroatoms atoms other than oxygen are known. There has been a report on S...N type

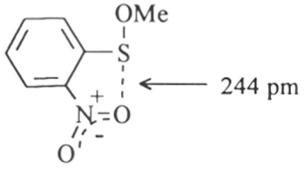
non-bonded interaction, observed in the case of 2-formylthiophene semicarbazone.[14] Recently, non-bonded attraction between a carbon and oxygen, as well as between sulfur and an aromatic ring have also been reported.[3a,b]

Non bonded interaction involving sulfur and oxygen were discovered during the X-ray crystal structure analysis of 2,5-dimethyldithiofurophthene **1** and 2-nitrobenzene sulfenate **2** (*Fig. 2*). These two molecules exhibited in their solid state, short contacts between oxygen and sulfur of 241 and 244 pm respectively. These distances are well below the sum of the van der Waals radii of 325 pm but larger than the S-O covalent bond distance of 156-165 pm.[2] This discovery stimulated further research in this area where X-ray crystal structure analysis of a large number of divalent sulfur compounds having sulfur and oxygen in a quasi-ring form showed S...O short contacts in the range of 200-300 pm. Since then, non-bonded attractive interactions have attracted considerable attention in view of their interest from bonding point of view[6] as well as due to their potential role in determining biomolecular conformation[7] and in crystal engineering applications.[8] The continued interest in this field is evident from several recent publications.[3]

Fig 2



1



2

Non-bonded interaction involving sulfur and other heteroatoms may be classified primarily by taking into consideration the size of the quasi-ring involving the X-S...Y moiety (*Fig 1*) and the valence state of sulfur. The interactions are classified as 1,3; 1,4; 1,5 and 1.6 type, indicating the relative position of sulfur and the other hetero atom ; the corresponding ring size of the quasi-ring varies from three-membered to six-membered. The valence state of sulfur may be II, IV or VI. Among the large number of compounds

having significant S...O close contacts, 1,5 type of interaction involving divalent sulfur was found to be predominant. So far there is no example of 1,6-type interaction, at least in molecules where rotation about the intervening bonds is not completely restricted.

Based on structural features observed by X-ray crystallography of compounds having S...O close contacts, the following generalisations have been derived.

i) S...O non-bonded attraction is controlled primarily by the size of the quasi-ring. While five membered rings are best suited for efficient interaction, six membered rings are unable to promote the interaction.

ii) Effective interaction requires the part structures S-A=B-C=Y (*Fig. 1*) with cis configuration about A=B and s-cis conformation about B-C bond.

iii) A linear X-S...Y array.

iv) The more electronegative or polarisable X(O,N,S) is, the better for S...Y interaction.

v) Unusually short S...Y distance often go with elongated X-S and C=Y bonds.

These observations suggest the highly directional nature of this interaction.

To interpret the above observations in terms of theory and to explain the nature of non-bonded interaction, semi-empirical, MO and *ab initio* studies were carried out on model system. A variety of factors such as electrostatic forces, incipient hypervalency, n-σ^* interaction have been postulated to be responsible for the phenomenon. These factors are summarized below :

1. Electrostatic (dipole-dipole) forces between X-S and C=Y moieties.
2. Extension of the sulfur valence shell with sp^3d hybridization.
3. Delocalisation of lone pair (n_o) on Y to the σ^*_{s-x} antibonding orbital. Thus Y is a donor and S-X is an acceptor.
4. Formation of a six-electron delocalised π system in a quasi-ring.

The evidence for non-bonded attraction discussed above comes only from the X-ray crystal structure analysis of sulfur compounds in the solid state. However, it does not necessarily follow that such weak interactions would still manifest themselves once the solid is dissolved in solution. The first evidence for S...O interaction in the solution state was furnished by NMR studies of compound **3** (*Fig. 3*) where the molecule exhibits solvent

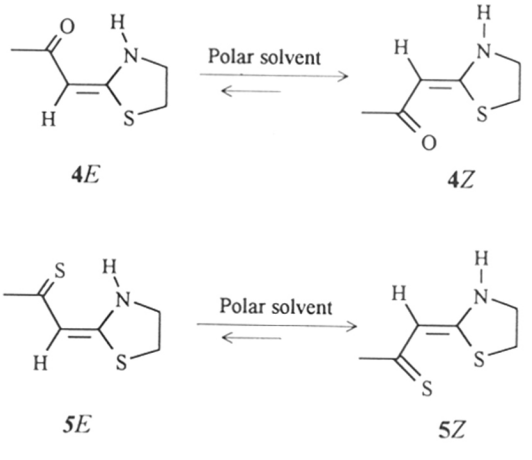
dependent conformational equilibrium.[4] Due to a strong push-pull effect in compound **3**, the barrier to rotation about the formal carbon-carbon double bond is considerably lowered, permitting rapid *E*-*Z* isomerisation at room temperature. At room temperature in non-polar solvents like chloroform, conducive for intramolecular hydrogen bonding, compound **3** exists exclusively in intramolecularly hydrogen bonded *E*-form. However, on addition of polar solvents like DMSO, capable of breaking the hydrogen bonds, the population of the *Z*-form increases as a result of stabilization due to S...O non bonded attraction.

Fig 3

3*E* **3***Z*

This solvent dependent conformational equilibrium study was further extended to carbonyl and thiocarbonyl derivatives **4** and **5**[5] (*Fig. 4*) . In this study attempts were made to estimate the magnitude of S...O and S...S non-bonded attraction relative to well understood O...H-N and S...H-N hydrogen bonds.

Fig 4



4*E* **4***Z*

5*E* **5***Z*

The relative magnitudes of the weak forces involved were shown to be in the following order : N-H...O (hydrogen bond)> N-H...S(hydrogen bond) > S..O non-bonded attraction > S...S non bonded attraction. This was well substantiated by *ab initio* calculation. A comparison of relative strength and bond distances of covalent bonds, hydrogen bonds and non-bonded attraction is given in *Table 1*.

Table 1

Sr.No.	Bond type	Bond length pm	Bond energies kcal. mol^{-1}
1	C-C (covalent)	138 - 154	83-85
2	S-S (covalent)	180 -210	65-70
3	N-H...O (hydrogen bond)	290-305	5
4	S...O (non-bonded)	200 - 320	3

2. Present work

The evidence for S...O and S...S interaction in solution, although convincing, leaves some ambiguity about the role of solvent in stabilizing the *Z*-form of **3**, **4** and **5**. Earlier, indirect evidence for the operation of S...O non-bonded attraction had been provided by demonstrating the crucial role played by the ring sulfur in stabilising the *Z*-form. Analogs in which this sulfur had been replaced by CH_2 or O failed to isomerise from *E* to *Z* in solvents of high polarity. However, it is known that the barrier to rotation around C=C in such push-pull systems decreases in solvents of high dielectric constant. Also the difference in energy between the *E* and Z forms decreases as the solvent polarity increases.[13] Both these factors are conducive for the *E-Z* configurational change and hence may serve to explain the increase in population of the *Z*-form on changing the solvent from chloroform to DMSO. Since the energy of stabilisation by non-bonded attraction and due to solvent effect are of approximately the same magnitude (3 k.cal/mol), the exact contribution of these effects is difficult to estimate. It was therefore essential to find out whether such non-bonded attraction could be observed without resorting to change of solvent.

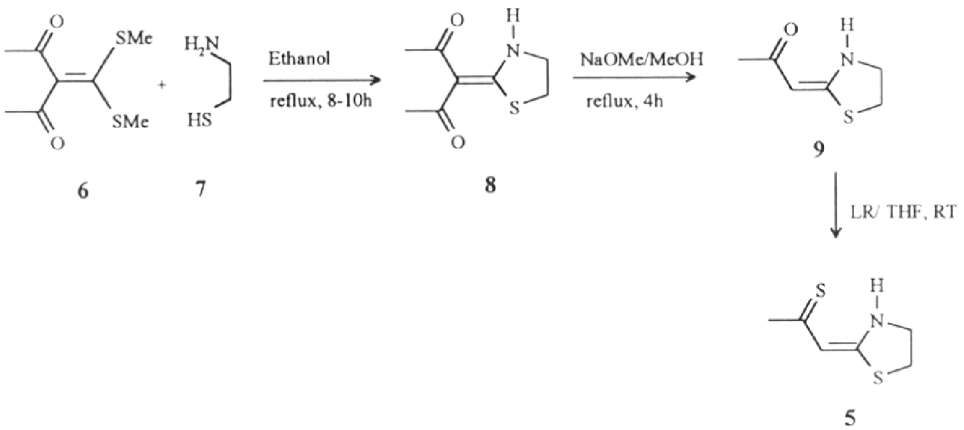
In this chapter it is shown that non-bonded attraction can be observed in the solution state without change of solvent. The presence of this interaction is inferred from the stereochemistry of the products obtained on alkylation of enaminothione **5** (*Scheme 7*, section 3.1). In this case S...N non-bonded attraction plays a critical role in determining stereoselectivity of the products of a reaction. This constitutes a rare example where a weak force such as S...N non-bonded attraction influences the stereochemical course of a reaction.

3. Results and Discussion

3.1 a) Synthesis of Enaminothione 5

The required enaminothione **5** was prepared by thionation of enaminone **9** (*Scheme 1*) which in turn was prepared by literature procedure[9]. The starting compound, ketene dithioacetal **6**, reacts with 2-aminoethanethiol **7** to afford the thiazolidine derivative **8**. This on refluxing in methanol with 4 equivalents of sodium methoxide yields enaminone **9**. Thionation of enaminone **9** with Lawesson reagent (**LR**)(0.6 mole for each mole of **9**) in refluxing benzene or in THF at room temperature (see experimental) gives the required enaminothione **5** in good yields.

Scheme 1



6 7 8 9 5

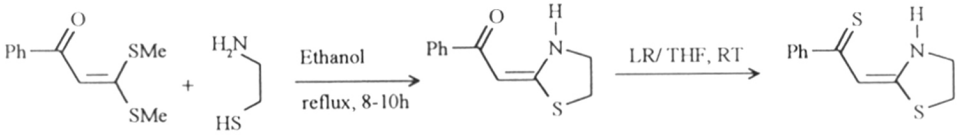
The structure of enaminothione **5** was confirmed by comparing the chemical shift values of ^{1}H NMR spectrum with those reported in the literature.[5]

^{1}H NMR ($CDCl_3$), δ: 2.54 (s, 3H, Me), 3.34 (t, 2H, SCH_2), 4.08 (t, 2H, NCH_2), 6.31 (s, 1H, =CH), 13.50 (bs, 1H, NH)

3.1b Synthesis of 2-thiobenzoylmethylenethiazolidine 12

This compound was prepared by a method similar to that used for **5** and is outlined in *Scheme 2*.

Scheme 2



10 **7** **11** **12**

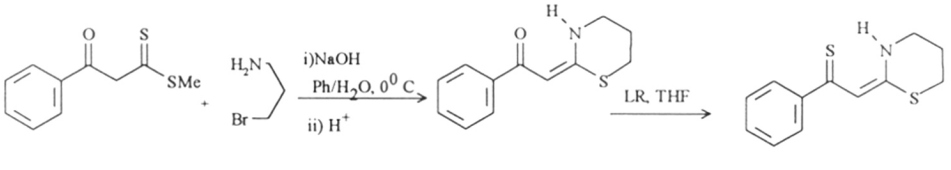
Ketene dithioacetal **10** was reacted with 2-aminoethanethiol to yield the thiazolidine derivative **11**. This on thionation with Lawesson reagent in THF gave the required thio derivative **12**. The structure of **12** was confirmed by comparing the ^{1}H NMR ($CDCl_3$): chemical shift values with those reported in the literature[5].

^{1}H NMR ($CDCl_3$), δ: 3.77 (t, 2H, S-CH_2), 4.12 (t, 2H, N-CH_2), 6.73 (s, 1H, CH=C), 7.33 (m, 3H, Ph), 7.73(m, 2H, Ph) and 13.75 (bs, 1H, NH)

3.1c Synthesis of 2-thiobenzoylmethylenethiazine 16

This six-membered homolog **16** could not be synthesized by a route similar to the one outlined in *Scheme 2*, as the required 3-aminopropanethiol is not readily available and cannot be prepared easily. The thiazine **16** was prepared by the method outlined in *Scheme 3*.

Scheme 3



13 **14** **15** **16**

The benzoyldithioacetic ester **13**, was added to benzene/water followed by 2 equivalents of NaOH and a catalytic quantity of tetrabutylammonium bromide (phase transfer catalyst). The hydrobromide salt of **14** was added to the reaction mixture at ice bath temperature and then heated to 70°C for 2-3 h to afford the thiazine derivative **15**. This on thionation using Lawesson reagent gives the required thio-derivative **16** in good

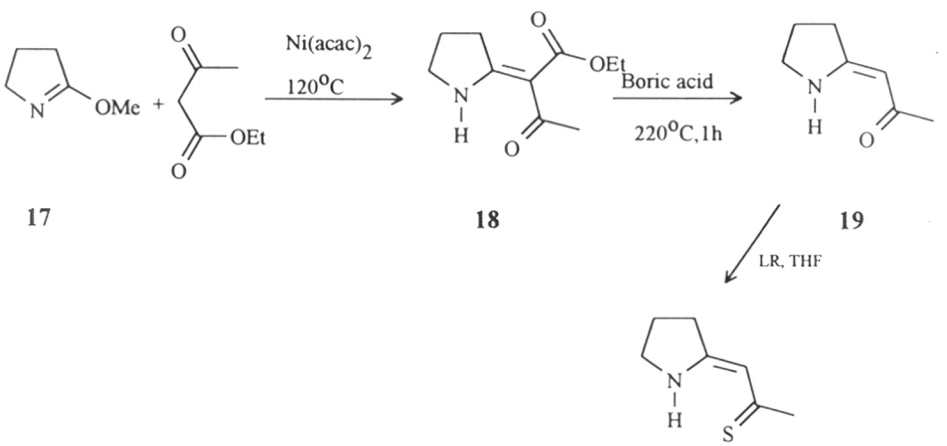
yields. The ^{1}H NMR spectrum showed following peaks. ^{1}H NMR ($CDCl_3$): δ 2.2(m, 2H, CH_2), 3.15(t, 2H, SCH_2), 3.65(t, 2H, NCH_2), 6.5 (s, 1H, HC=C), 7.4-7.8(m, 5H, Ph), 15(bs, 1H, NH)

However, attempts to synthesise the corresponding thioacetyl derivative by the method outlined in *Scheme 3* gave irreproducible results.

3.1d Synthesis of 2-thioacetylmethylenepyrrolidine 20

Enaminothione **20** was prepared by the method outlined in *Scheme 4*. [10] In the first step lactim ether **17** was heated with 1.5 equivalents of ethyl acetoacetate in presence of catalytic amount of nickel acetylacetonate to give compound **18**. This on heating with excess of solid boric acid gave the pyrrolidine derivative **19**. Thionation of compound **19** gave the corresponding thio-derivative in satisfactory yields.

Scheme 4



17 **18** **19**

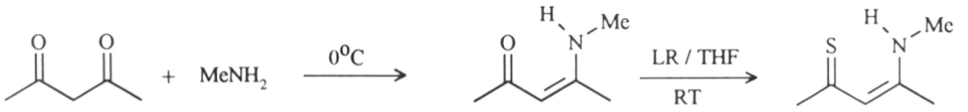
20

The structure of enaminothione **20** was confirmed by comparing the ^{1}H NMR chemical shift values with those reported in the literature.[5] ^{1}H NMR ($CDCl_3$): δ 2.1 (m, 2H, $-CH_2$), 2.5 (s, 3H, CH_3), 2.75 (t, 2H, CH_2-C=), 3.8 (t, 2H, NCH_2), 6.2 (s, 1H, C=CH), 13.2 (b, 1H, NH)

3.1e Synthesis of 4-methylamino-3-pentene-2-thione 22

The required enaminothione **22** was prepared by thionation of enominone **21** which in turn was prepared by condensation of acetyl acetone with methylamine[11] (*Scheme 5*). The structure of enaminothione **22** was confirmed by comparing the ^{1}H NMR chemical sift values reported in the literature.

Scheme 5



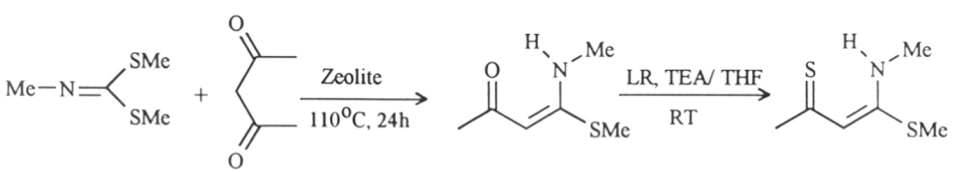
21 **22**

^{1}H NMR ($CDCl_3$): δ 2.30 (s, 3H, C=C-CH_3), 2.5 (s, 3H, $COCH_3$), 3.0 (d, 3H, NCH_3), 6.1 (s, 1H, C=CH), 13.5 (t, 1H, NH).

3.1f Synthesis of 4-methylamino-4-methylthio-3-butene-2-thione 24

The required enaminothione **24** was prepared as shown in *Scheme 6*.[12] N-Methyl carbonimidodithioic acid dimethyl ester was heated in toluene with acetylacetone in presence of zeolite (RE NaY) to afford product **23**. Thionation of **23** with Lawesson reagent in THF in presence of excess of triethylamine gave the thio-derivative **24**.

Scheme 6



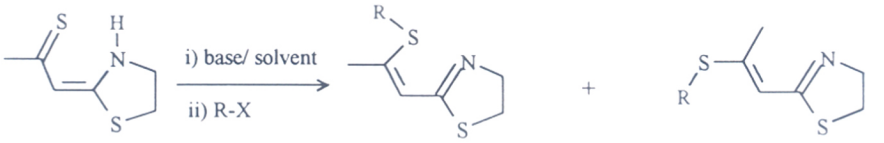
23 **24**

^{1}H NMR ($CDCl_3$): δ 2.4 (s, 3H, CH_3), 2.5 (s, 3H, SCH_3), 3.0 (d, 3H, NCH_3), 6.0 (s, 1H, C=CH), 14.0(b, 1H, NH).

3.2 Alkylation of 2-thioacetylmethylenethiazolidine 5

Enaminothione **5** was subjected to alkylation with a number of alkyl halides like benzyl bromide, prenyl bromide and methyl iodide in solvents of different polarity (benzene, acetone, DMF), in presence of organic and inorganic bases such as (DBU, TEA and K_2CO_3) (*Scheme 7*). The reaction products were properly characterised to establish their structures and stereochemistry. These reactions and the relevant spectral data are discussed in detail in the following section.

Scheme 7



5*E* **25***Z* **25***E*

a : R = $PhCH_2$; X = Br

b : R = $Me_2C{=}CHCH_2$; X = Br

c : R = Me ; X = I

3.2a Alkylation with benzyl bromide

Enaminothione **5** was treated with benzyl bromide (1.2 equivalents) in acetone with K_2CO_3 (1.2 equivalents) as base at room temperature to yield S-benzylated product. The TLC showed two new spots close to each other ; the ^1H NMR spectrum showed the presence of two compounds in unequal amounts. It was obvious from the peak positions that the S-benzylated product was obtained as a mixture of the two possible stereoisomers. The two sets of ^1H NMR ($CDCl_3$), δ: signals were as follows:

Set I ,δ 2.25 (s, 3H, CH_3), 3.25 (t, 2H, -SCH_2), 4.1 (s, 2H, SCH_2Ph), 4.35 (t, 2H, N-CH_2), 6.15 (s, 1H, HC=C), 7.4 (m, SH, Ph)

Set II ,δ 2.4 (s, 3H, CH_3), 3.30 (t, 2H, SCH_2), 4.0 (s, 2H, SCH_2Ph), 4.40 (t, 2H, NCH_2), 5.9 (s, 1H, HC=C), 7.4 (m, 5H, Ph)

The well separated olefinic peaks at 6.15 and 5.9 δ corresponding to the major and minor stereoisomer respectively showed that the ratio of major : minor product was 8 : 1 ; obviously the ratio of two stereoisomers. This olefinic peak integration ratio was used to determine the stereoisomeric product ratio in all the subsequent alkylation reactions discussed in this chapter. This ratio, on acid catalysed equilibration (benzene, reflux, PTSA) drastically changed to 1 : 8, indicating that the major stereoisomer undergoes isomerisation about the carbon-carbon double bond to form the thermodynamically more stable stereoisomer. Such an isomerisation was not observed in the absence of acid. Thus, when the initial reaction mixture was refluxed in benzene without addition of PTSA, no change was observed in the isomer ratio.

In a separate experiment, the S-benzylated product corresponding to olefinic signal at 6.15 δ was isolated in pure form by careful column chromatography followed by crystallization. The stereochemistry about the carbon-carbon double bond was determined by X-ray crystallography and NOE experiments described later.

Further when benzylation of enaminothione **5** was carried out in a highly polar solvent like DMF with K_2CO_3 as base at room temperature, the S-benzylated product was again obtained as a mixture of the two stereoisomers. In this mixture the olefinic peaks at 6.15 and 5.9 δ corresponding to major and minor product of the reaction had the ratio 10 : 1. On acid catalysed equilibration this changed to 1 : 8. The results of this reaction show that the change of solvent from acetone to DMF had very little effect on the stereoisomeric composition on benzylation.

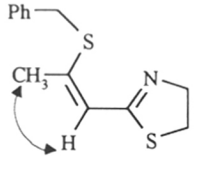
Interestingly, when enaminothione **5** was treated with benzyl bromide (1.2 equivalent) in acetone, without any base, a hydrobromide salt precipitated out. This salt was insoluble in chloroform, but soluble in DMSO. The ^{1}H NMR spectrum of this salt showed the following peaks : δ 2.4 (s, 3H, CH_3), 3.7(t, 2H, SCH_2), 4.2(t, 2H, NCH_2), 4.3 (s, 2H, SCH_2Ph) 6.65 (s, 1H, HC=C), 7.25 - 7.50 (m, 5H, Ph). There was no NH signal in the region 7.0 to 15.0 δ in the product. This NH was seen at 13.5 δ in the starting

enaminothione. Further, on neutralisation of this salt with dilute aqueous sodium hydrogen carbonate solution (5%), the stereoisomer corresponding to olefinic peak position at 5.9δ was obtained, indicating the formation of the thermodynamically more stable isomer.

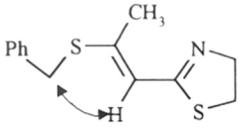
Finally, the stereochemistry of the kinetically controlled and the thermodynamically more stable products was determined by NOE (*Scheme 8*) and subsequently confirmed by X-ray crystal structure analysis. A pure sample of the major stereoisomer of **25a** (corresponding to olefinic peak position at 6.15 δ) was obtained by column chromatography followed by crystallisation. NOE experiment was carried out on this sample as follows: A sample of major stereoisomer of **25a** was prepared in $CDCl_3$ (5mg in 0.4ml) and subjected to freeze-pump-thaw technique to make it oxygen free.

Scheme 8

NOE experiment

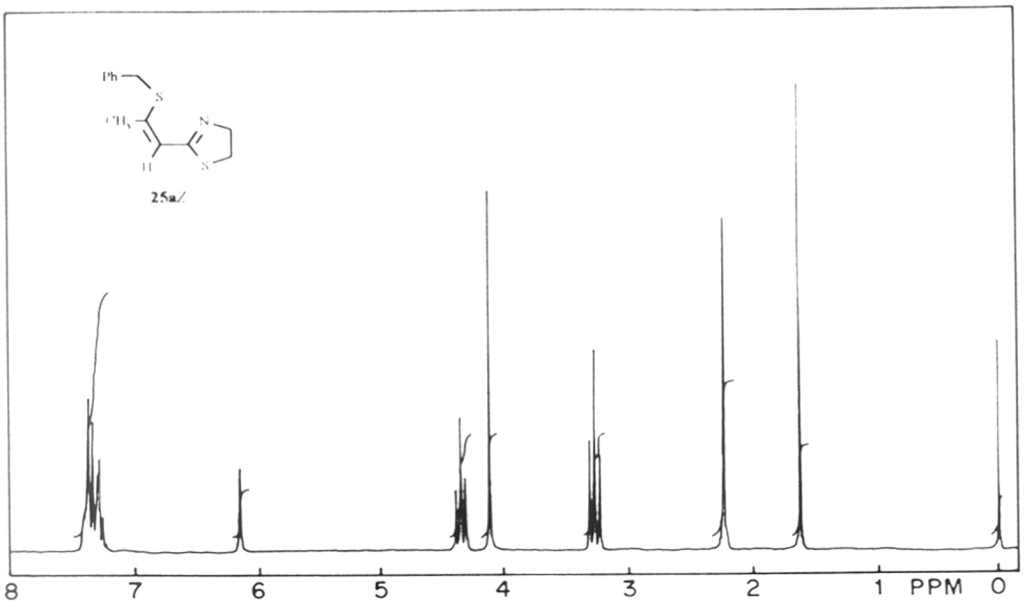


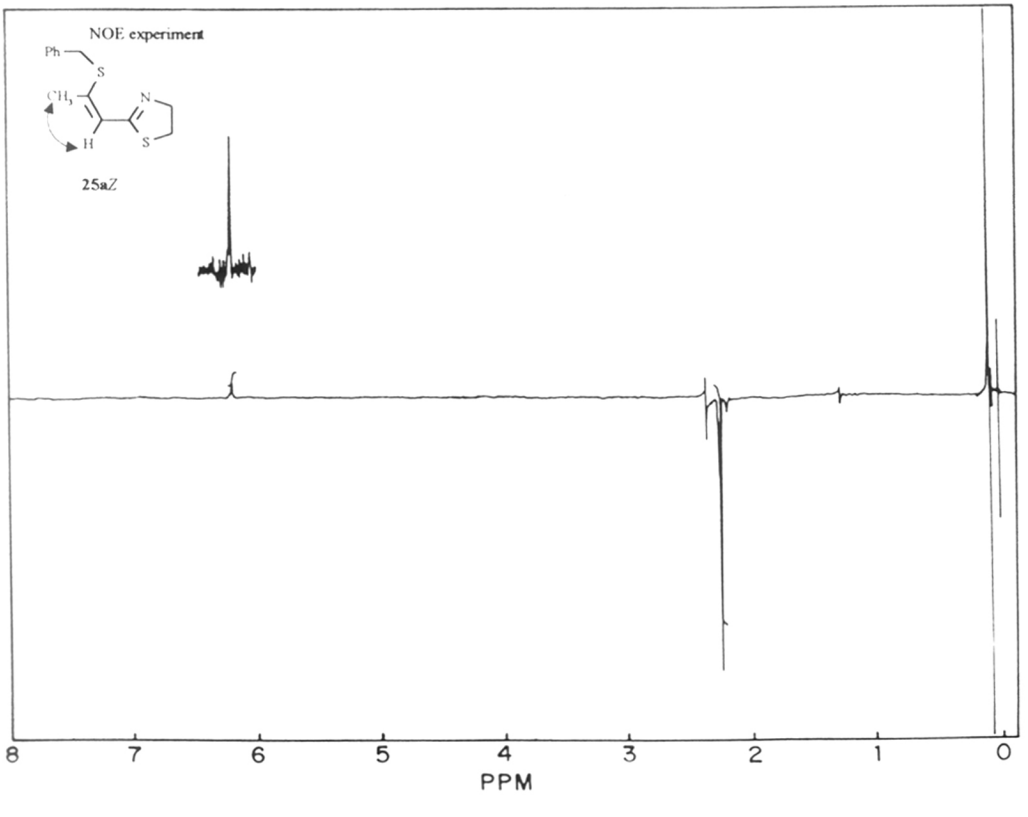
25a*Z*

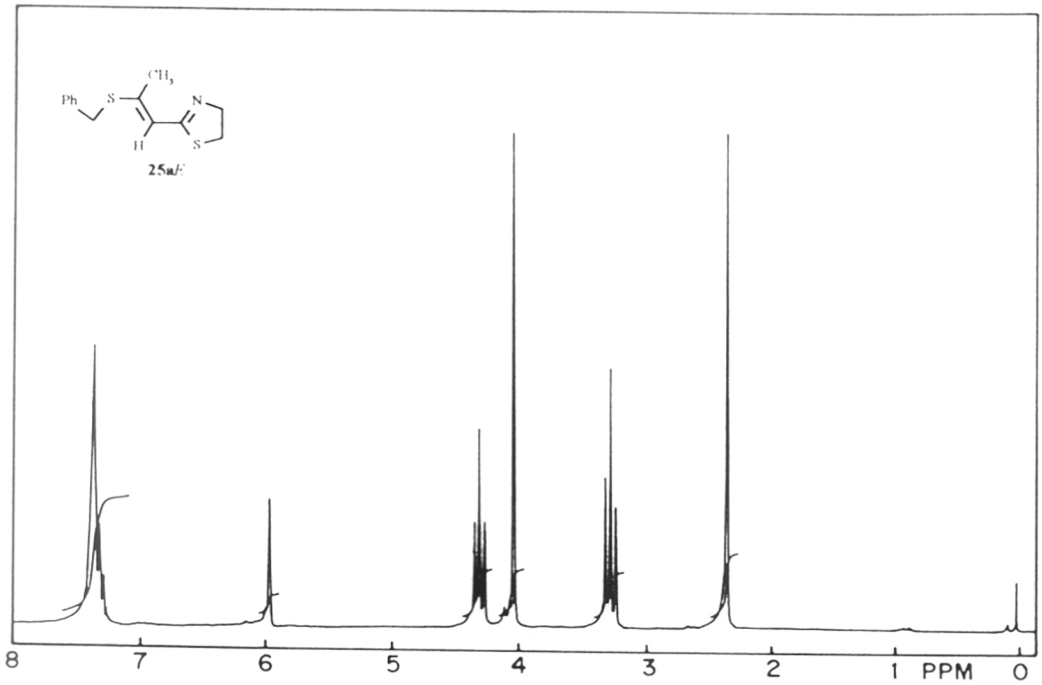


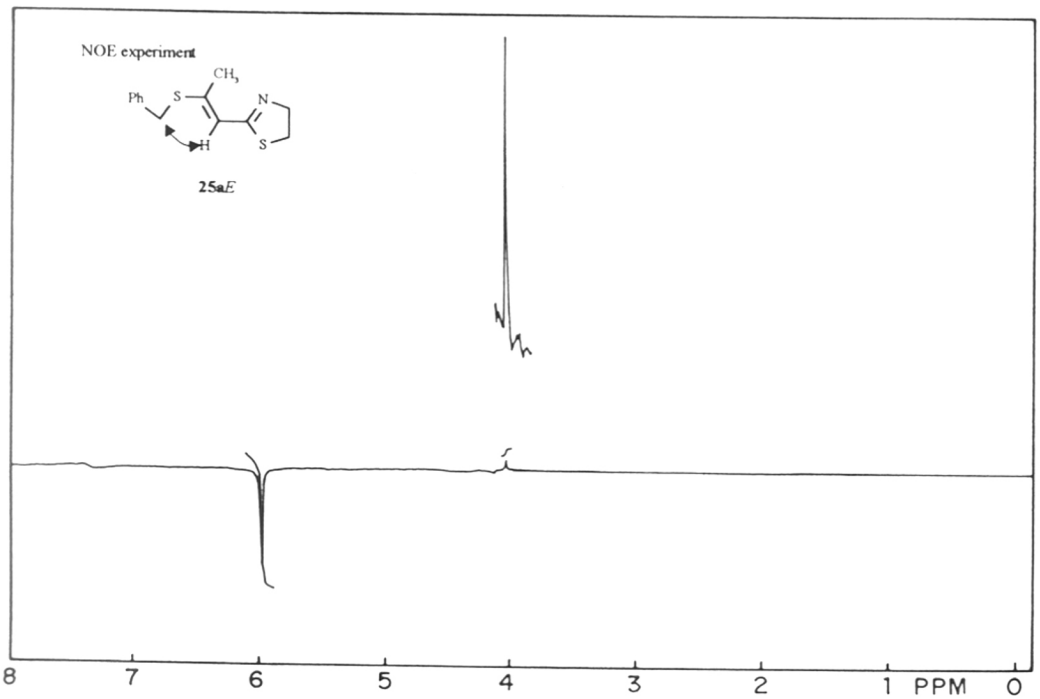
25a*E*

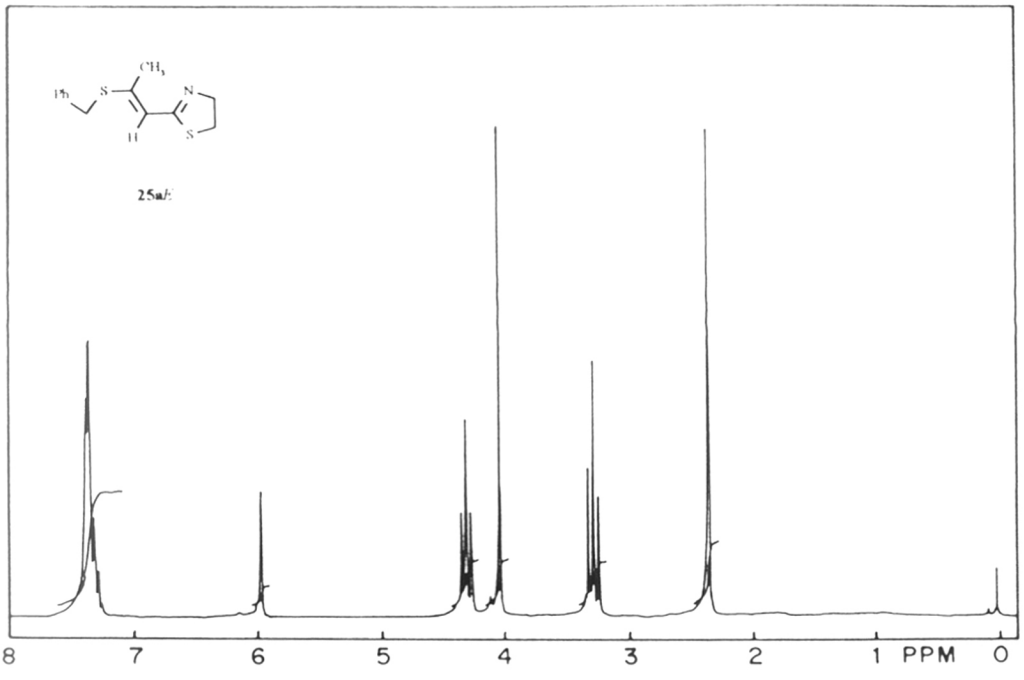
NOE was performed on this sample, first by irradiating the methyl signal at 2.25 δ when NOE was observed at 6.15 δ ; the difference NOE was 6.3%. However, when the olefinic signal at 6.15 δ was irradiated no NOE was observed at 2.25δ. In this case the configurational assignment of the respective stereoisomers was possible after the following convincing result was obtained on performing NOE on the **equilibrated product**. Irradiation at the olefinic signal (5.9 δ) of the major stereoisomer, led to an NOE of 5.5 % on the $PhCH_2$ signal at 4.0 δ. Also a difference NOE of 6% was observed when the reverse experiment was performed. These results are summarized in *Table 3*.


Ph
S
CH3
N
H
S
25aZ
8
7
6
5
4
3
2
1
PPM
0


NOE experiment
Ph
S
CH3
N
H
S
25aZ
8
7
6
5
4
3
2
1
0
PPM


Ph
S
CH3
N
H
S
25aE
8
7
6
5
4
3
2
1 PPM
0


NOE experiment
Ph
S
CH3
N
H
S
25aE
8
7
6
5
4
3
2
1 PPM
0


CH3
Ph
S
N
H
S
8
7
6
5
4
3
2
1
PPM
0

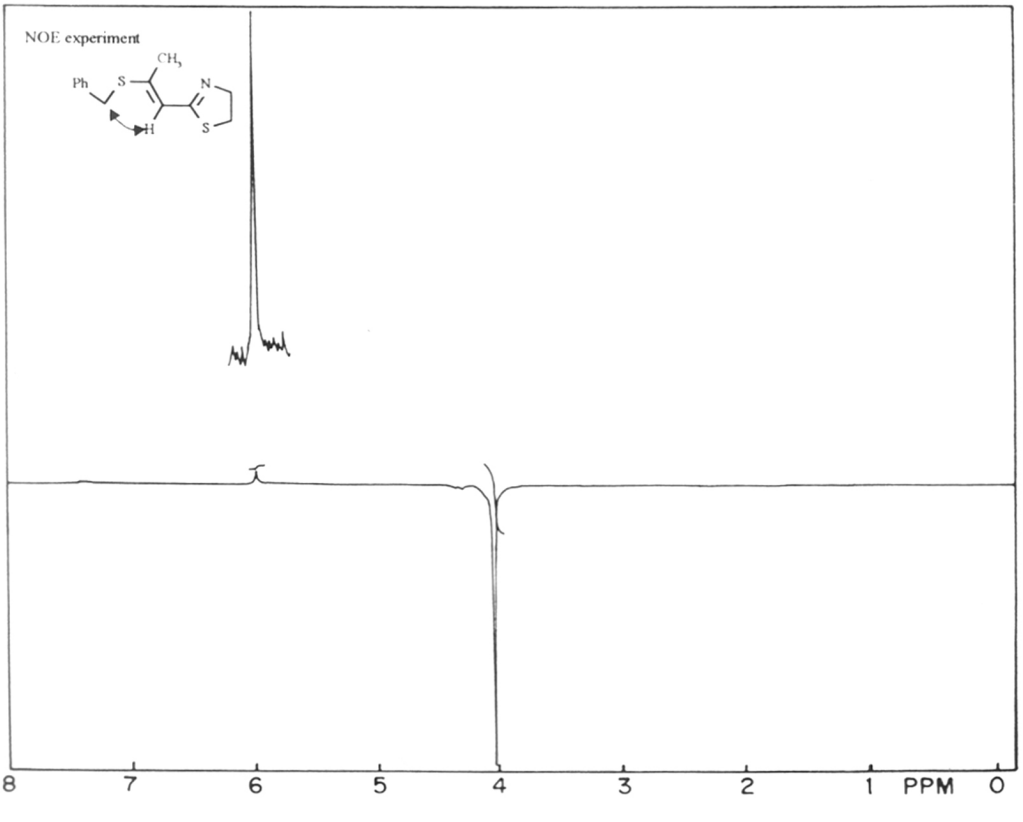

NOE experiment
CH3
Ph
S
N
H
S
8
7
6
5
4
3
2
1
PPM
0

Table 3

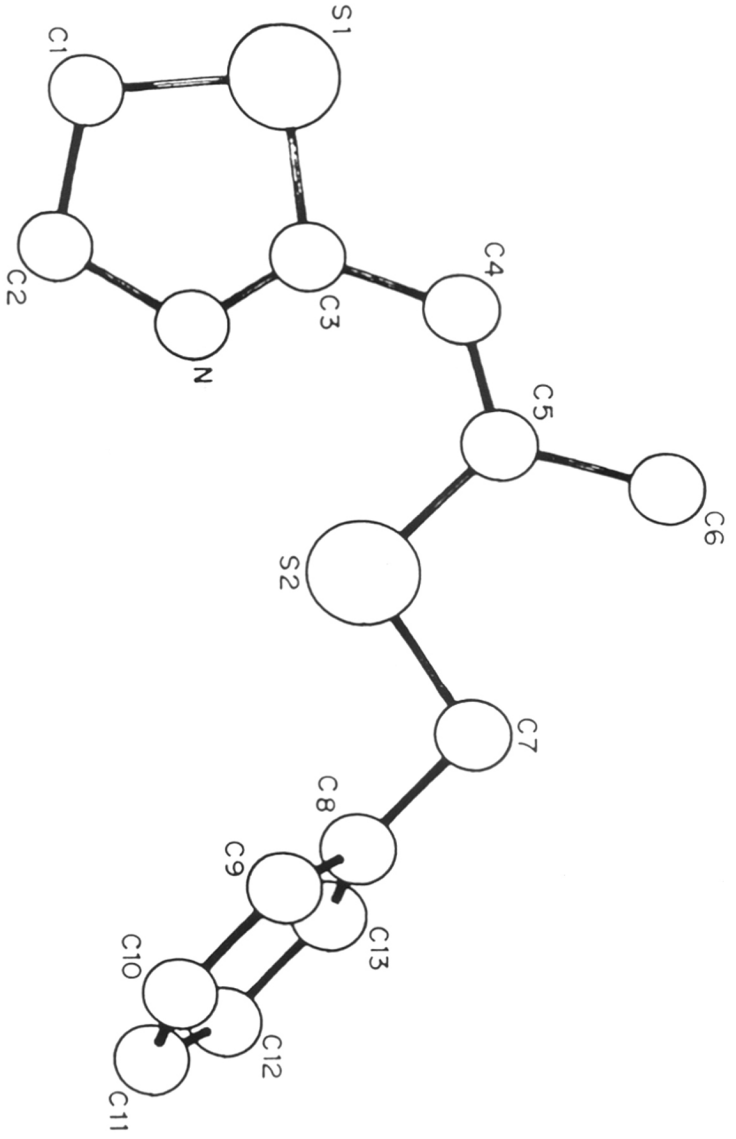
Set No	Irradiation at δ	NOE at δ	Diff. NOE %
I	2..25 (CH_3)	6.15 (=CH)	6.30
I	6.15 (=CH)	2.25 (CH_3)	0
II	5.9 (=CH)	4.0 (CH_2Ph)	5.5
II	4.0 (CH_2Ph)	5.9 (=CH)	6.0

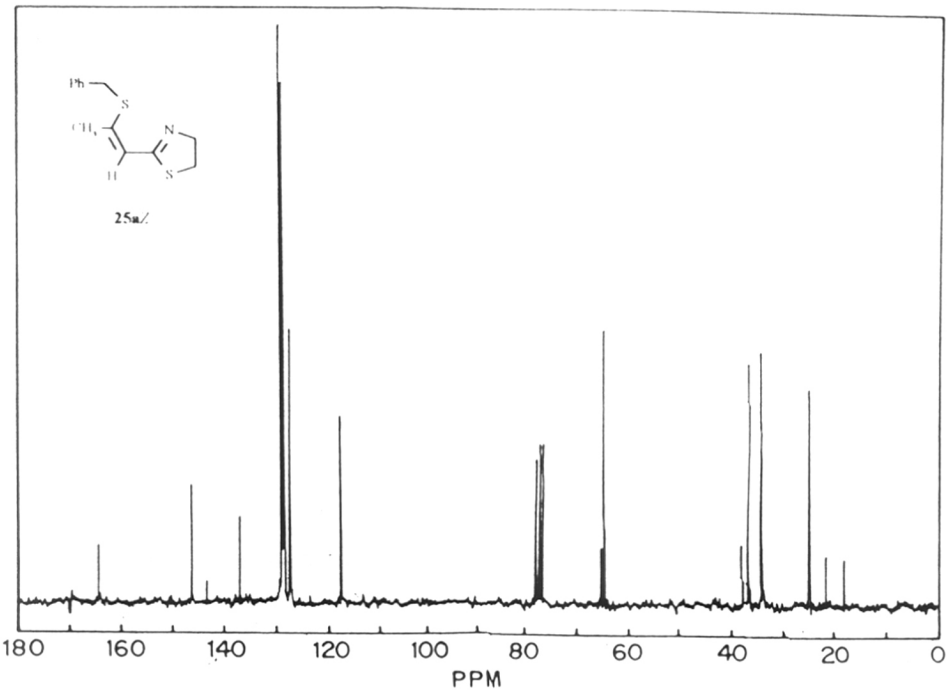
It was obvious from the above NOE results (*Table 3*) that Set I corresponds to the *Z*-stereoisomer while Set II corresponds to the *E*-stereoisomer. Hence the S-benzylated stereoisomer obtained under kinetic control had the *Z*-configuration and that under thermodynamic control had the *E*-configuration. This configurational assignment was later confirmed by the *X-ray crystal structure analysis of the major stereoisomer (corresponding to olefinic signal at 6.15 δ) which was shown to have Z-configuration.*

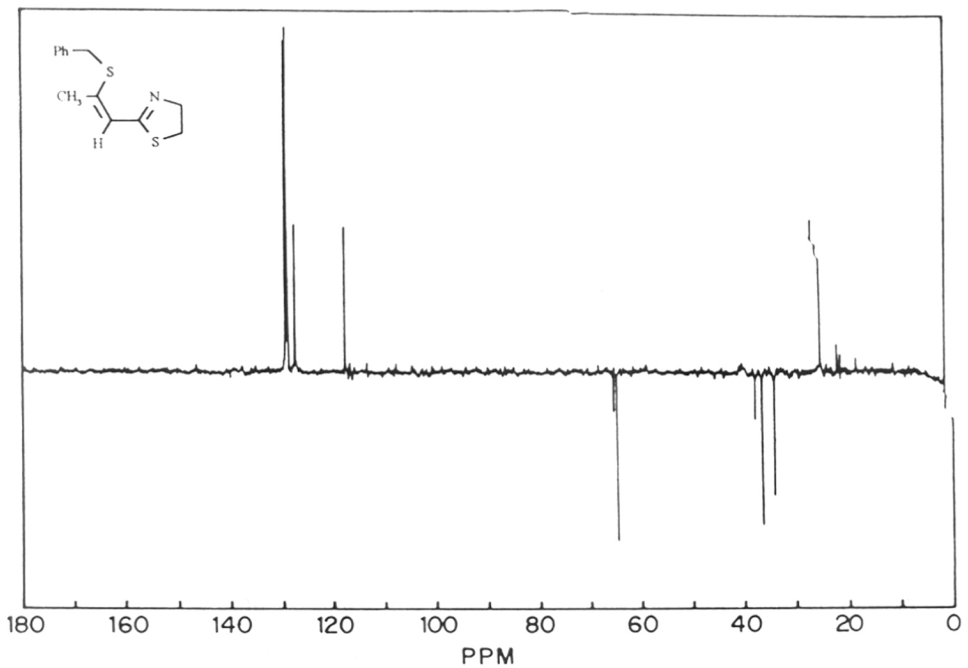
Besides determining the configuration about the carbon-carbon double bond , X-ray crystallographic studies revealed certain interesting facts about the structure of the *Z*-stereoisomer. The distance between the exocyclic sulfur and the nitrogen in the ring was found to be 284 pm, less than the sum of the van der Waals radii of 345 pm. Also, the quasi-ring formed by N=C of the thiazolidine and exocyclic C=C-S was planar with almost linear arrangement of -C-S and N atoms.

3.2b Alkylation with prenyl bromide

Enaminothione **5** was treated with prenyl bromide (1.2 eqv) in acetone with K_2CO_3 (1.2 equivalent) as the base at room temperature to give the alkylated product (*Scheme 7*), as shown by thin layer chromatography (TLC). TLC of the reaction mixture showed the presence of two new very close, but distinct spots; the ^1H NMR spectrum of the crude


S1
C1
C2
C3
N
C4
C5
C6
S2
C7
C8
C9
C13
C10
C12
C11


Ph
S
CH3
N
H
S
25a/
180
160
140
120
100
80
60
40
20
0
PPM


Ph
S
CH3
N
H
S
180
160
140
120
100
80
60
40
20
0
PPM

product showed two sets of peaks, indicating the presence of two compounds in unequal amounts.

^{1}H NMR ($CDCl_3$):

Set I ,δ 1.54 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.07 (s, 3H, CH_3-C-S), 3.07 (t, 2H, S-CH_2), 3.2 (d, 2H, CH_2-C=C), 4.15 (t, 2H, NCH_2), 5.08 (m, 1H, $CH=CMe_2$), 6.05 (s, 1H, HC=C),

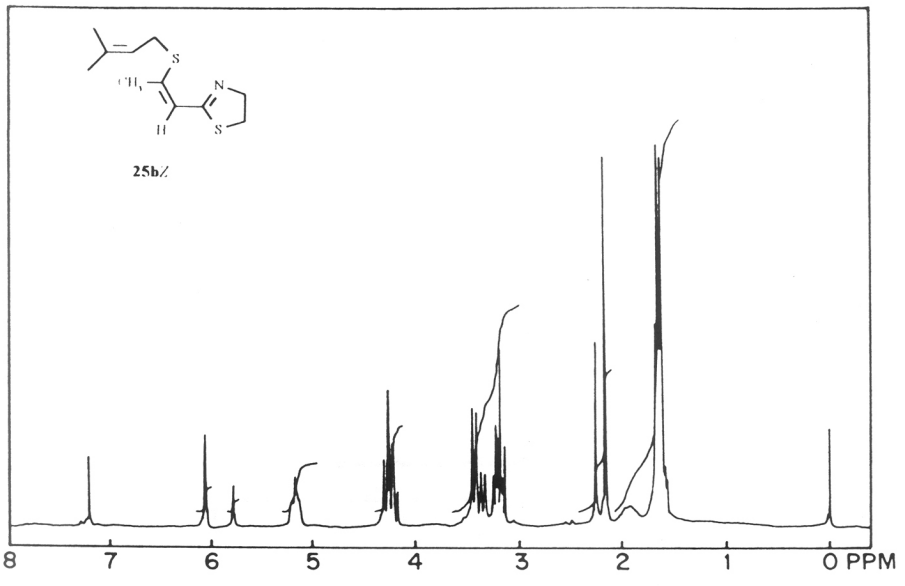
Set II ,δ 1.54 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.13 (s, 3H, CH_3-C-S), 3.10 (t, 2H, SCH_2), 3.176 (d, 2H, CH_2-C=C), 4.10 (t, 2H, NCH_2), 5.08 (m, 1H, $CH=CMe_2$), 5.65 (s, 1H, HC=C),

It was clear from the chemical shift values of the methylene protons of the prenyl moiety that the two sets of peaks belonged to the two possible S-alkylated stereoisomers of the product **25b**, although the configurational assignment was not possible at this stage. The well separated peaks due to the olefinic protons at 6.05 and 5.65 δ had integration ratio 2.3 : 1. This obviously represented the ratio of the two stereoisomers on alkylation.

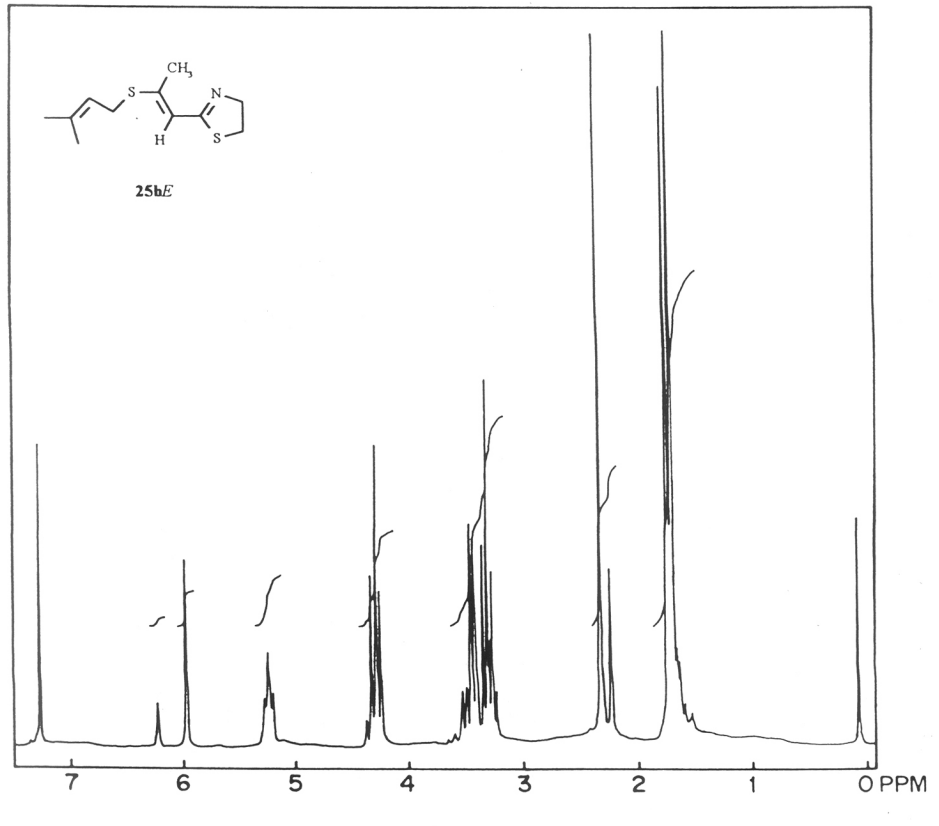
When the initial reaction mixture having the two stereosiomers was subjected to acid-catalysed equilibration in refluxing benzene with a catalytic amount (few crystals) of PTSA, the olefinic peak integration ratio changed dramatically from the initial ratio of 2.3 : 1 to 1 : 5. The ^{1}H NMR spectrum did not show any decomposition product on equilibration, indicating that the major stereoisomer formed initially undergoes isomerisation about the carbon-carbon double bond to form the other stereoisomer, resulting in a drastic change in the stereoisomeric ratio.

In another experiment when enaminothione **5** was treated with prenyl bromide in benzene using an organic base such as DBU, the alkylated product **25b** was obtained as a mixture of two stereoisomers in the ratio 5.4:1. On acid catalysed equilibration this initial ratio changed to 1 : 5. If the alkylation reaction were carried out with TEA instead of DBU as the base, under the same condition, the initial stereoisomeric product ratio was found to be 2 : 1 which on equilibration changed to 1 : 5.

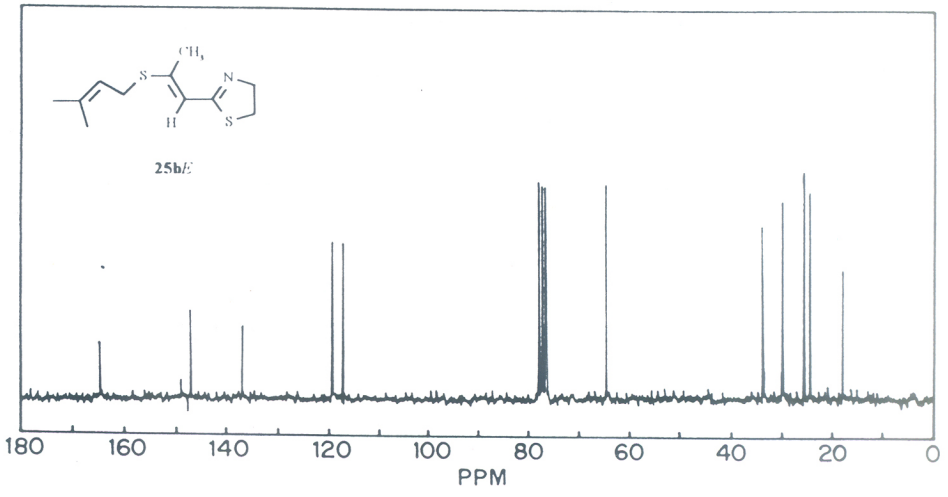
The above experimental facts showed that the alkylation of enaminothione **5** with prenyl bromide was stereoselective where one of the S-alkylated stereoisomers of **25b** is



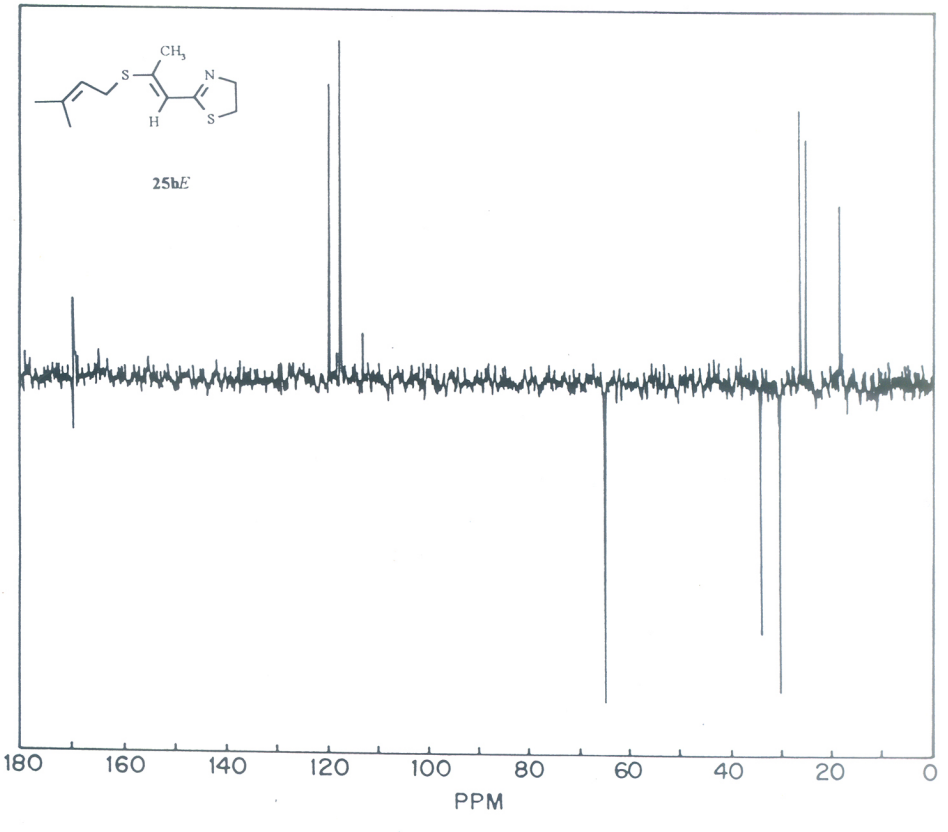
25b*Z*



25b*E*


CH3
S
N
H
S
180
160
140
120
100
80
60
40
20
0
PPM

25b*E*


CH3
S
N
H
S
180
160
140
120
100
80
60
40
20
0
PPM

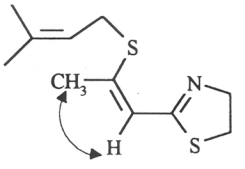
25b*E*

formed preferentially under kinetic control. This major stereoisomer obtained initially, on acid-catalysed equilibration undergoes isomerisation about the carbon-carbon double bond to form the thermodynamically more stable stereoisomer. It is also clear that the type of base or solvent polarity has no remarkable effect on the product ratio of the initial reaction.

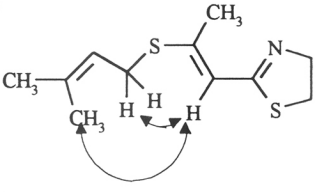
To determine which stereoisomer was formed under kinetic control and which one was thermodynamically more stable, the configurational assignment to the two sets of ^1H NMR peaks had to be done. This was achieved by determining the NOE (Nuclear Overhauser Effect). NOE experiments were performed as outlined in *Scheme 9*.

Scheme 9

NOE experiment



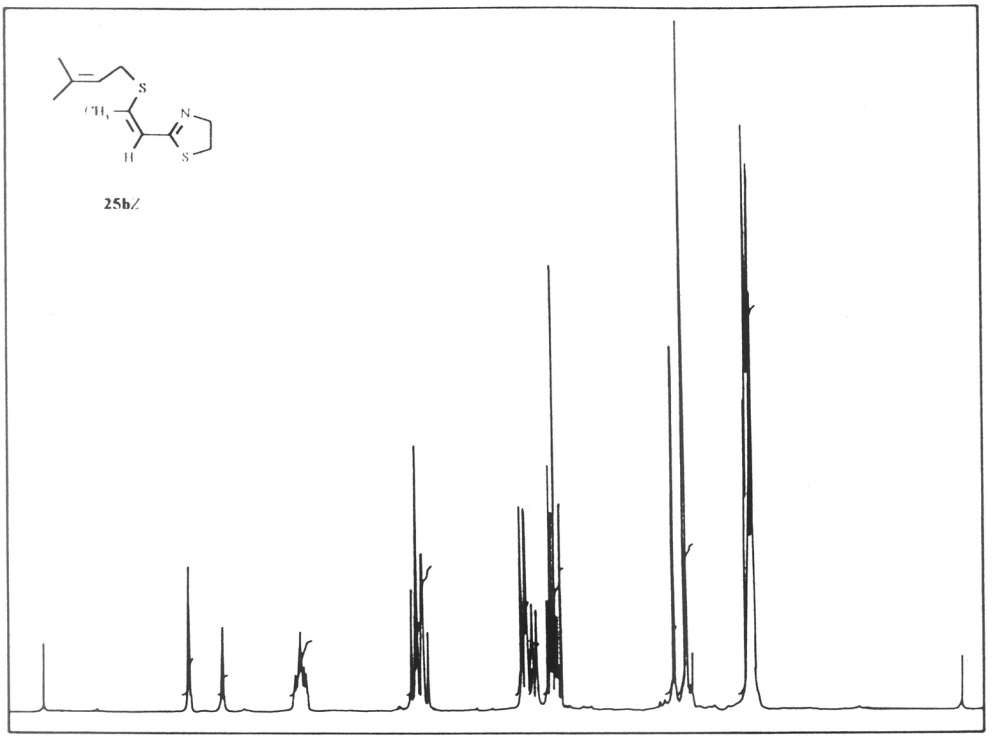
25a*Z*

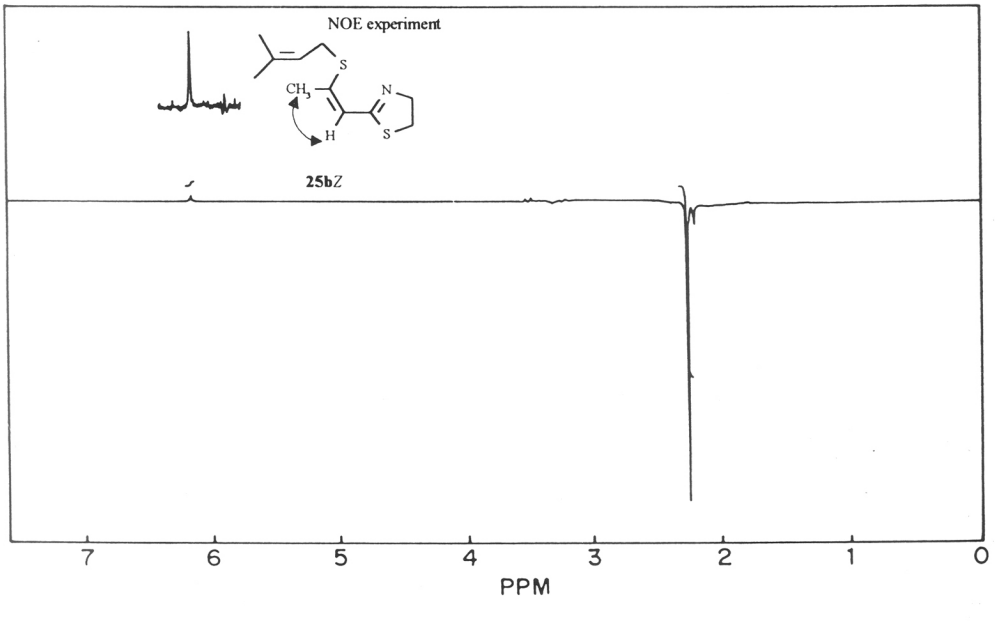


25a*E*

The S-prenylated product **25b** (5mg) consisting of a mixture of the two stereoisomers in the ratio 2 : 1, was dissolved in $CDCl_3$ (0.4 ml) and this solution was subjected to freeze-pump-thaw technique (see experimental) to make it oxygen free. As per *Scheme 9*, when the signal at 2.07 δ corresponding to the methyl protons of the major stereoisomer was irradiated, NOE was observed at the signal at 6.05 δ ; the difference NOE measured was 2.5%. However, when the olefinic signal at 6.05 δ was irradiated , no NOE was observed at the methyl proton signal at 2.07 δ (as one would expect) or at any other signal.

A similar NOE experiment was performed in $CDCl_3$ solution on the S-prenylated product mixture after equilibration (stereoisomeric ratio 1:5) as per *Scheme 9*. When the signal at 5.65 δ corresponding to the olefinic proton of the enriched stereoisomer was


25bZ


NOE experiment
25bZ
7
6
5
4
3
2
1
0
PPM

PPM
1
2
3
4
5
6
25bE
NOE experiment

irradiated, NOE was observed at signals due to the methyl groups of prenyl moiety (1.54 and 1.56 δ ; NOE, 17.8% total) and that due to the allylic methylene protons (3.17 δ ; NOE 9%) (*Table 2*). Interestingly, NOE was also observed at 2.13 (NOE, 7%), signal due the protons of the methyl group, supposedly, *trans* to the olefinic proton which was irradiated. In literature examples are known where groups having a *trans* geometry about the C=C do show NOE. However, this experiment suggests that the methylene protons and *gem*-dimethyl protons of the prenyl moiety are closer in space to the olefinic proton.

From the above NOE result it was clear that the major S-alkylated stereoisomer obtained initially under kinetic control had the *Z*-configuration while the thermodynamically preferred stereoisomer had the *E*-configuration about the carbon-carbon double bond.

Table 2

Set No.	Solvent	Irradiated at δ	NOE observed at δ	Diff. NOE %
I	$CDCl_3$	2.07 (CH_3)	6.05 (=CH)	2.5
I	"	6.05 (=CH)	2.07 (CH_3)	0
II	"	5.65 (=CH)	1.54, 1.56 (CMe_2)	17.8
II	"	"	3.17 (CH_2)	9
II	"	"	2.13 (CH_3)	7

3.2c Alkylation with methyl iodide

Similar to the alkylation with prenyl bromide and benzyl bromide, enaminothione **5** was reacted with methyl iodide (1.5 equivalents) in acetone using K_2CO_3 (1.2 equivalents) as the base at ice bath temperature to give the alkylated product **25c**. Formation of two S-methylated stereoisomers was inferred from the presence of two sets of signals in the ^1H NMR spectrum of the reaction product. The two sets of signals were as follows.

Set I ,δ 2.06 (s, 3H, CH_3), 2.15 (s, 3H, SCH_3), 3.1 (t, 2H, SCH_2), 4.1 (t, 2H, NCH_2), 6.02 (s, 1H, HC =C)

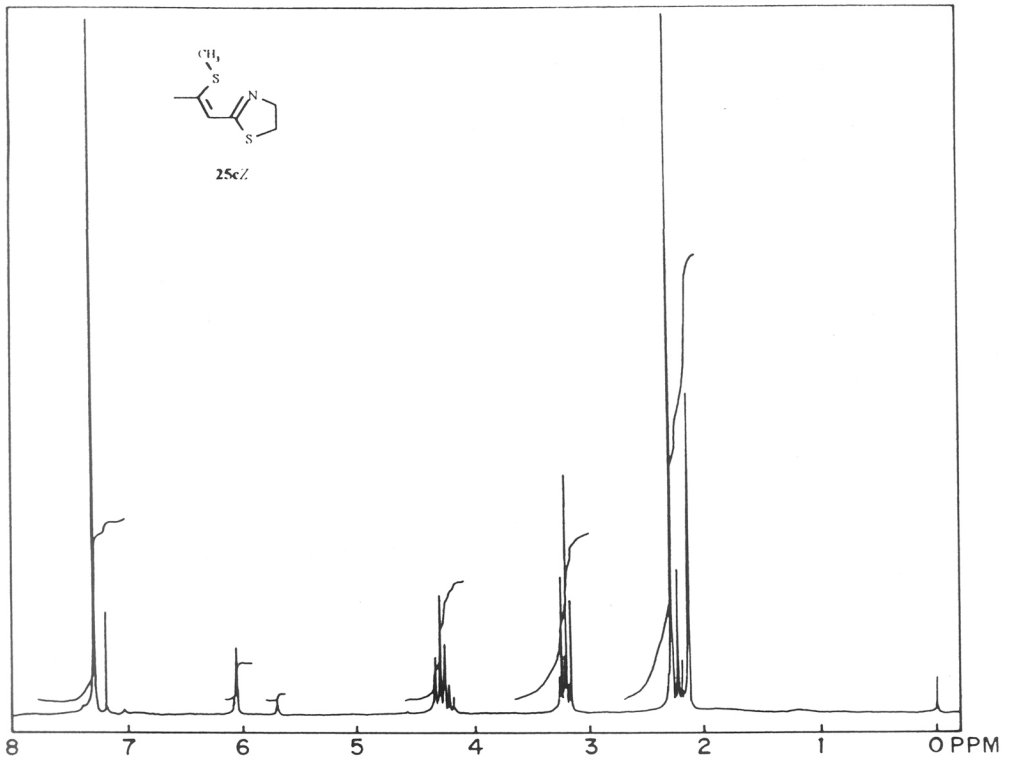
Set II ,δ 2.10 (s, 3H, CH_3), 2.15 (s, 3H, SCH_3), 3.1 (t, 2H, SCH_2), 4.1 (t, 2H, NCH_2), 5.6 (s, 1H, HC=C)

In this case the olefinic signals at 6.02 and 5.6 δ were in the ratio 3.4 : 1. This changed to 1 : 4 on acid-catalysed equilibration (benzene, reflux, PTSA), in conformity with the previous experience. In this case it was impossible to perform the requisite NOE experiment to determine the configuration about the carbon-carbon double bond, since the peak positions of C-methyl protons and the S-methyl protons for both the isomers were close to one another. Assignment of configuration has therefore been made only by analogy with the previous results on prenylation and benzylation. The kinetically controlled product (corresponding to olefinic signal at 6.02 δ) is assumed to have the *Z*-configuration and the thermodynamically preferred product (olefinic signal at 5.6 δ) to have the *E*-configuration.

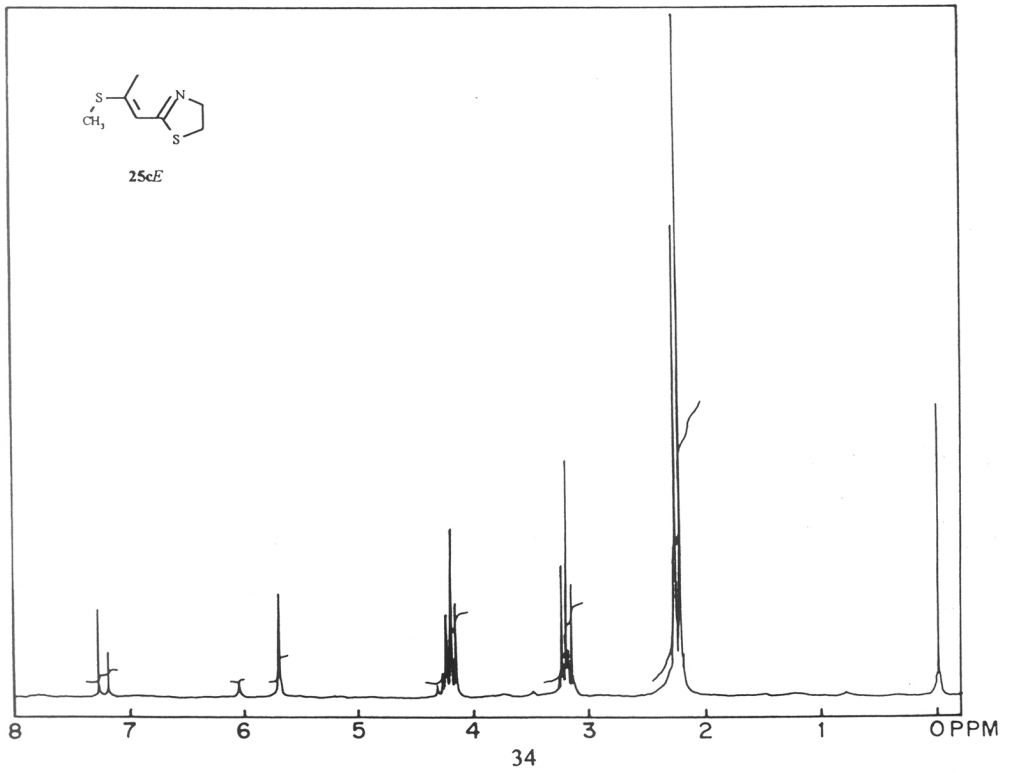
Methylation of enaminothione **5** in benzene with DBU as base at ice-bath temperature yielded the same mixture of S-methylated isomers in the ratio 6.4 : 1. This on acid-catalysed equilibration changed to 1 : 4. This again generalizes the observation that base or solvent polarity has little influence on stereoselectivity of the alkylation reactions of the enaminothione **5**.

From the alkylation reactions of enaminothione **5** it is clear that S-alkylated product is obtained as a mixture of the *Z* and *E* stereoisomers in unequal amounts. The major stereoisomer obtained under kinetic control was shown to have the *Z*-configuration about the carbon-carbon double bond. This kinetic product on acid-catalysed equilibration undergoes *E*-*Z* isomerisation to the thermodynamically more stable *E*-isomer. These results obtained under various conditions are summarized in *Table 4*.

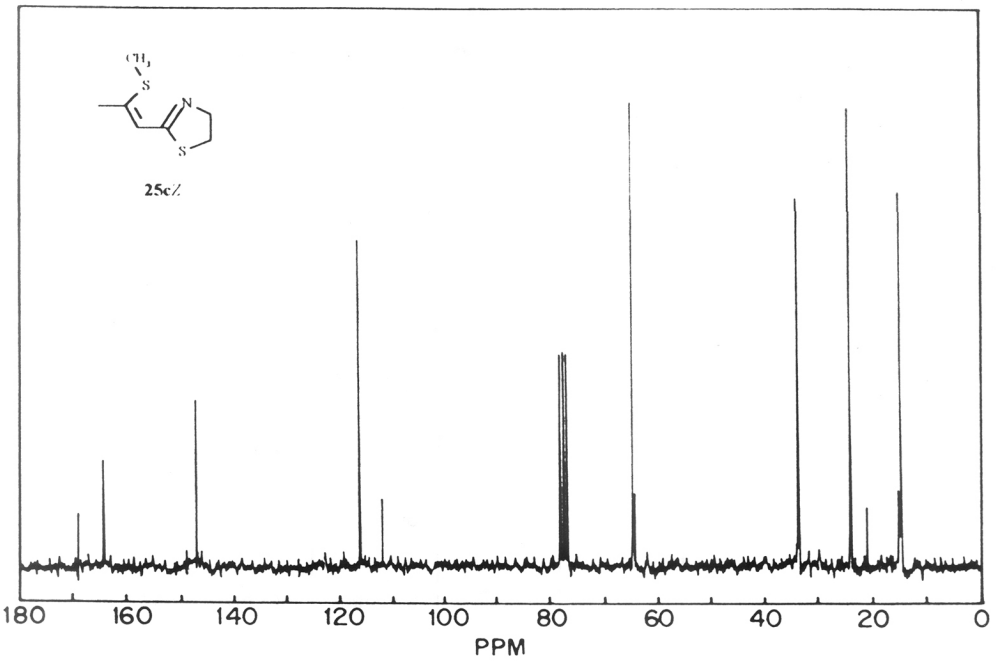
In all the cases studied the well separated olefinic peaks were used to determine the ratio of stereoisomers formed under kinetic and thermodynamic control. It was also observed that the peak position of olefinic protons of *Z*-isomers were downfield compared to those for *E*-isomers.

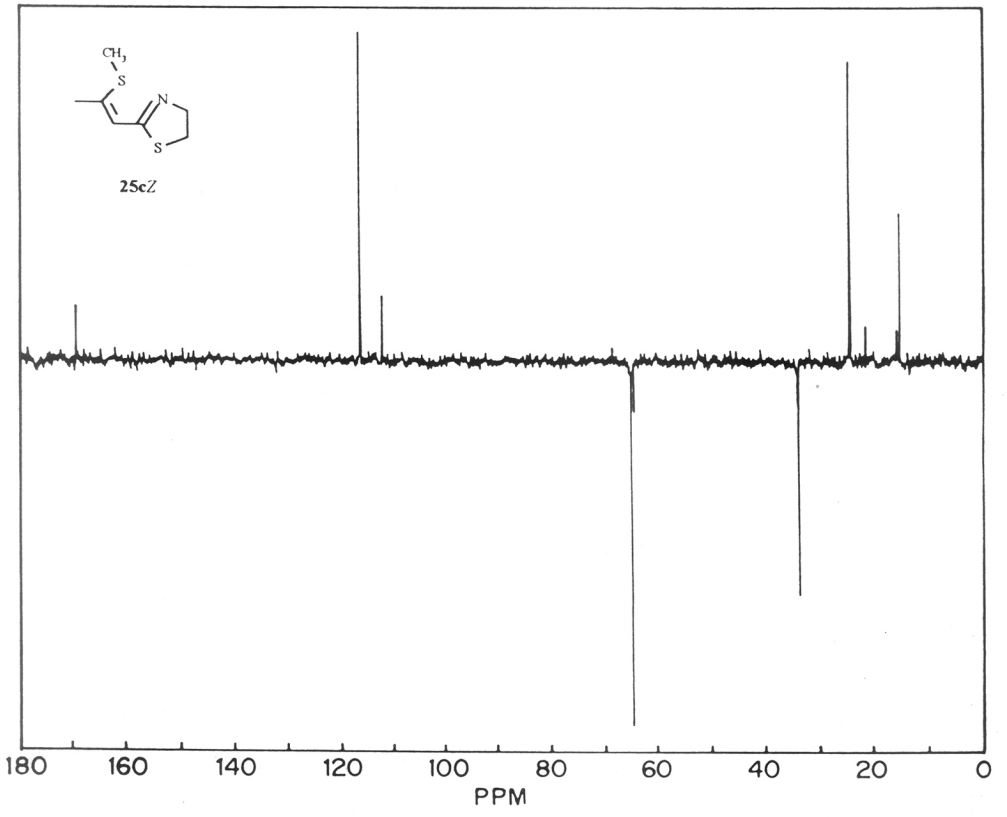


25c*Z*



25c*E*


CH3
S
N
S
25eZ
180
160
140
120
100
80
60
40
20
0
PPM


CH3
S
N
S
25eZ
180
160
140
120
100
80
60
40
20
0
PPM

These results also established the generality of the reaction where different alkyl halides like prenyl bromide, benzyl bromide and methyl iodide were used. Use of variety of bases like K_2CO_3, DBU and TEA and solvents of different polarity (benzene, acetone and DMF) were shown to have little effect on stereoselectivity of the reaction.

Table 4

Sr.No	R-X	Solvent	Base	Product	Z/E ratio before eqbn	*Z/E* ratio after eqbn
1	Prenyl bromide	benzene	DBU	**25b**	5.4 : 1	1:5
		benzene	TEA	**25b**	2 : 1	
		Acetone	K_2CO_3	**25b**	2.3 : 1	
2	Benzyl bromide	Acetone	K_2CO_3	**25a**	8 : 1	1:8
		DMF	K_2CO_3	**25a**	10 : 1	
3	Methyl iodide	Benzene	DBU	**25c**	6.4 : 1	1:4
		Acetone	K_2CO_3	**25c**	3.4 : 1	

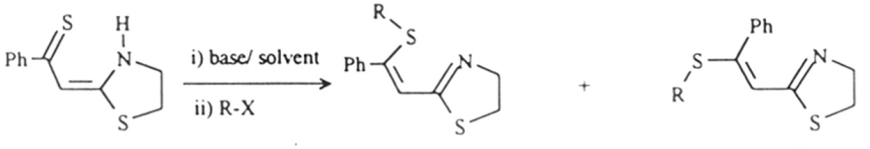
3.2d Alkylation of 2-thiobenzoylmethylenethiazolidine 12

To evaluate the influence of the methyl substituent in the thioacetyl functionality on the stereochemical composition during the alkylation, the thioacetyl group in enaminothione **5** was replaced by the thiobenzoyl group. Alkylation of enaminothione **12** was carried out with benzyl bromide in acetone using K_2CO_3 as the base to afford the product **26a** as a mixture of two isomers as inferred from TLC and ^1H NMR spectrum (*Scheme 10*). The two sets of peaks in the ^1H NMR spectrum are as follows:

Set I ,δ 3.1 (t, 2H, SCH_2), 4.02 (s, 2H, SCH_2Ph), 4.13 (t, 2H, NCH_2), 6.72 (s, 1H, HC=), 7.05 (m, 2H, Ph), 7.25(m, 3H, Ph), 7.45 (m, 5H, Ph).

Set II ,δ 3.3 (t, 2H, SCH_2), 3.72 (s, 2H, SCH_2Ph), 4.3 (t, 2H, NCH_2), 6.62 (s, 1H, HC=), 7.05 (m, 2H, Ph), 7.25(m, 3H, Ph), 7.45 (m, 5H, Ph).

Scheme 10



12*E* **26***Z* **26***E*

a : R = $PhCH_2$; X = Br

b : R = Me ; X = I

It was obvious that the above two sets of ^1H NMR peaks belonged to the S-benzylated stereoisomers similar to **25b.** The well separated olefinic peaks at 6.72 and 6.62 δ had the ratio of 2.2 : 1. On subjecting this product mixture to acid catalysed equilibration, the ratio changed to 1 : 2. Similar results were obtained on methylation of enaminothione **12** under the above mentioned conditions. The two sets of ^1H NMR peaks for **26b** are as follows :

Set I ,δ 2.0 (s, 3H, SMe), 3.32 (t, 2H, SCH_2), 4.37(t, 2H, NCH_2), 6.5 (s, 1H, HC=), 7.3-7.5 (m, 5H, Ph)

Set II ,δ 2.4 (s, 3H, SMe), 3.02 (t, 2H, SCH_2), 4.12(t, 2H, NCH_2), 6.35 (s, 1H, HC=), 7.3-7.5 (m, 5H, Ph)

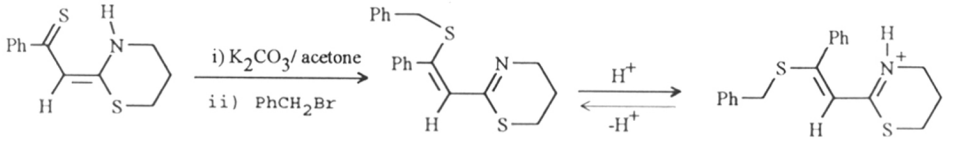
For the S-methyl isomers the olefinic peaks at 6.5 and 6.35 had the initial ratio 2.8 : 1 which changed to 1 : 2.5 on acid catalysed equilibration. The product stereochemistry was assumed to be similar to S-alkylated stereoisomers of **25a-c**. Thus the above alkylation

reaction on enaminothione **12** showed that replacing thioacetyl group with thiobenzoyl group had very little effect on the stereochemical outcome of the above reaction.

3.3 Alkylation of 2-thiobenzoylmethylene-1,3-thiazine 16

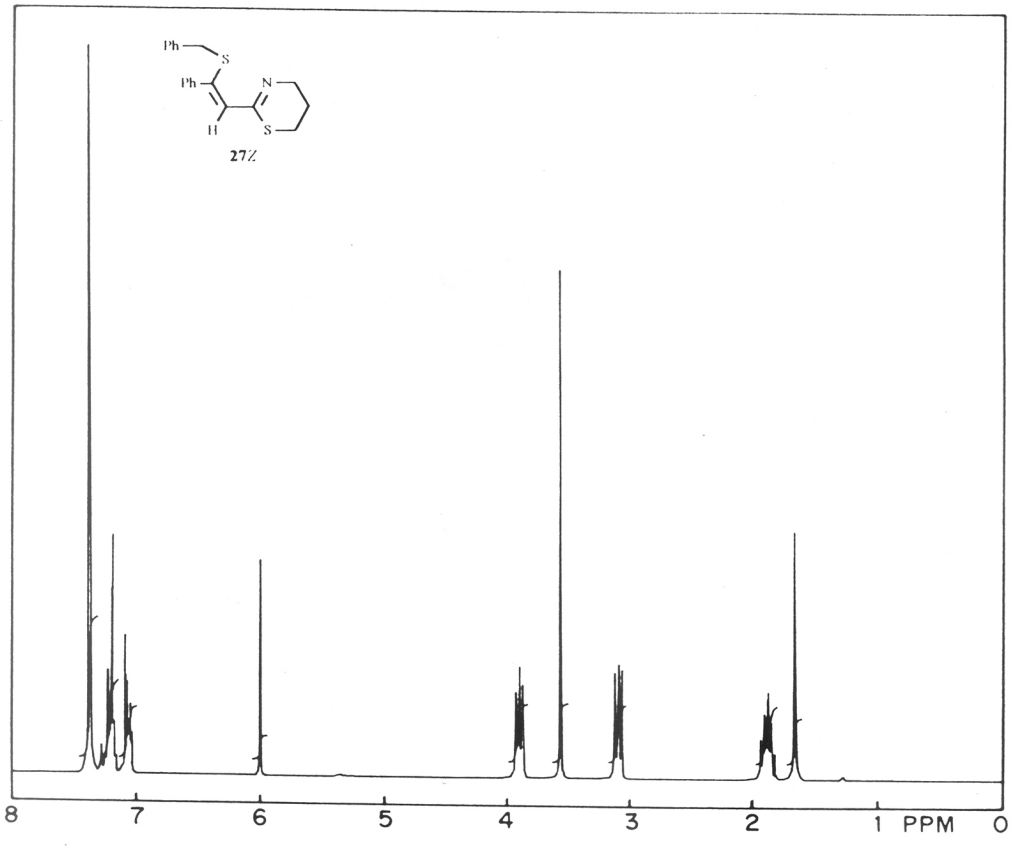
To asses the effect of the heterocyclic ring in enaminothiones of type **5** and **12** described above, alkylation was carried out on the ring homolog, thiazine derivative **16**. When **16** was benzylated under similar conditions (K_2CO_3 / acetone) only one S-benzylated isomer of **27** was obtained (*Scheme 11*). The ^1H NMR ($CDCl_3$), δ spectrum showed the following peaks : 1.8 (m, 2H, CH_2), 3.0 (t, 2H, SCH_2), 3.5 (s, 2H, SCH_2Ph), 3.8(t, 2H, NCH_2), 5.9 (s, 1H, HC=C), 6.95(m, 2H, Ph), 7.1(m, 3H, Ph), 7.25(m, 5H, Ph)

Scheme 11

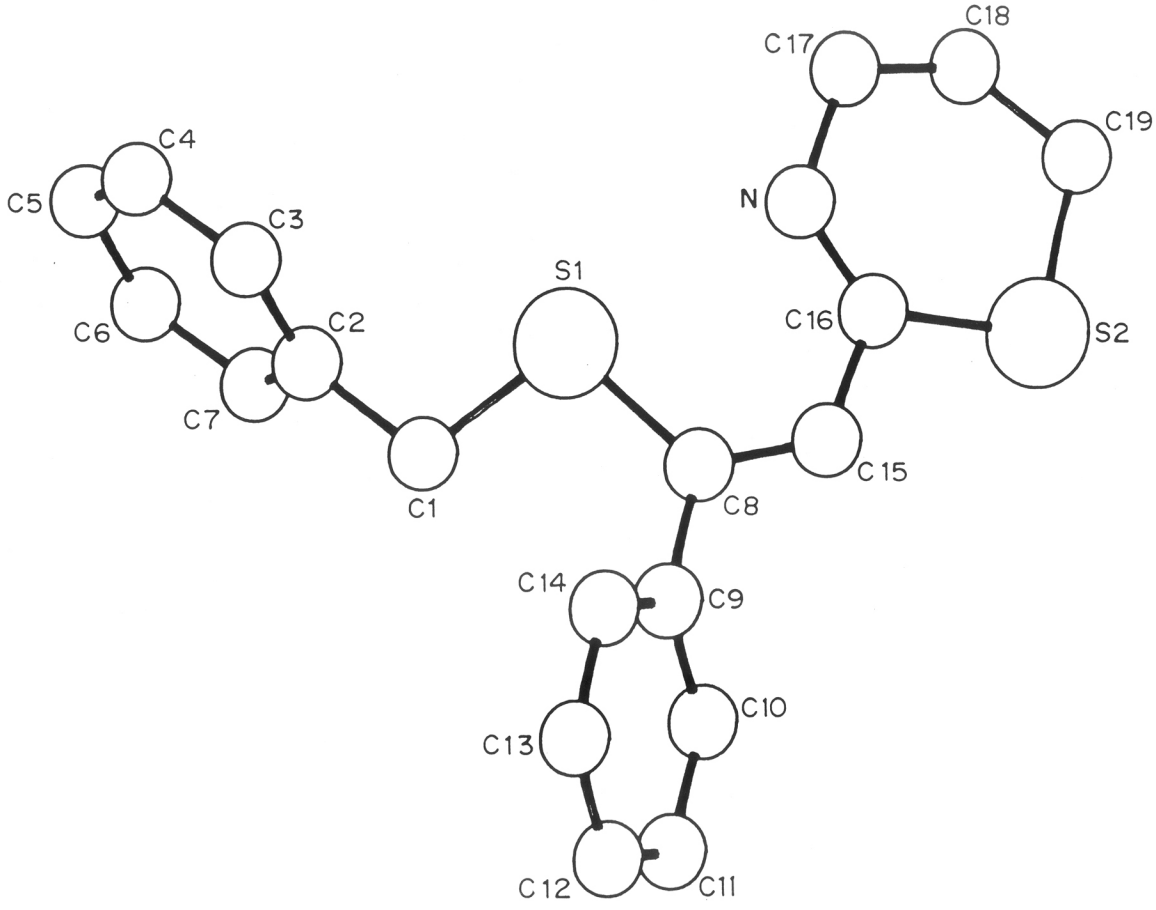


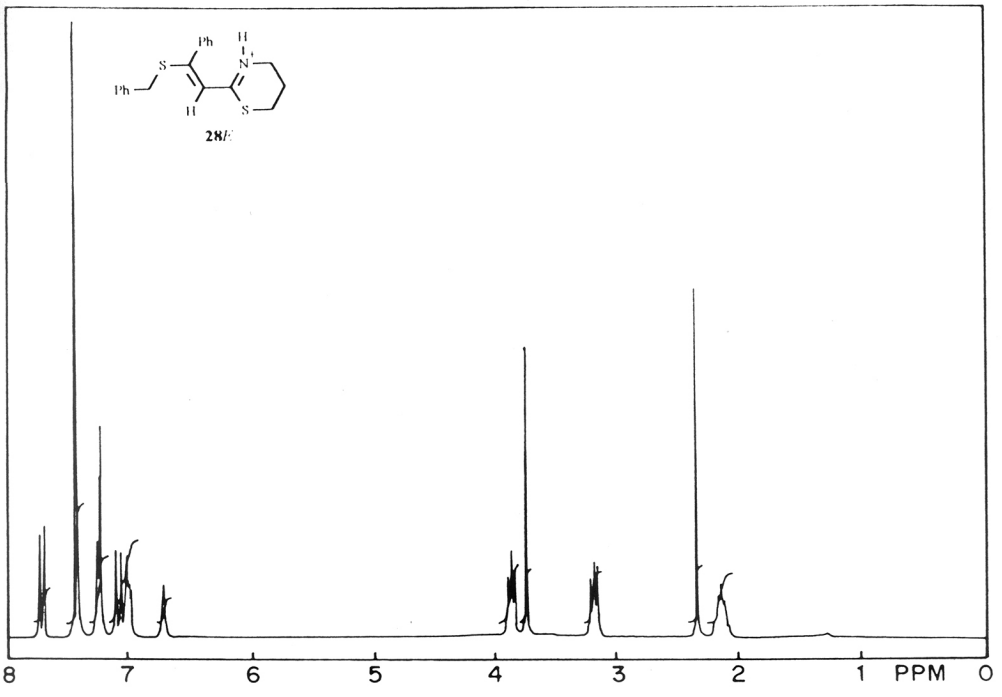
16*E* **27***Z* **28***E*

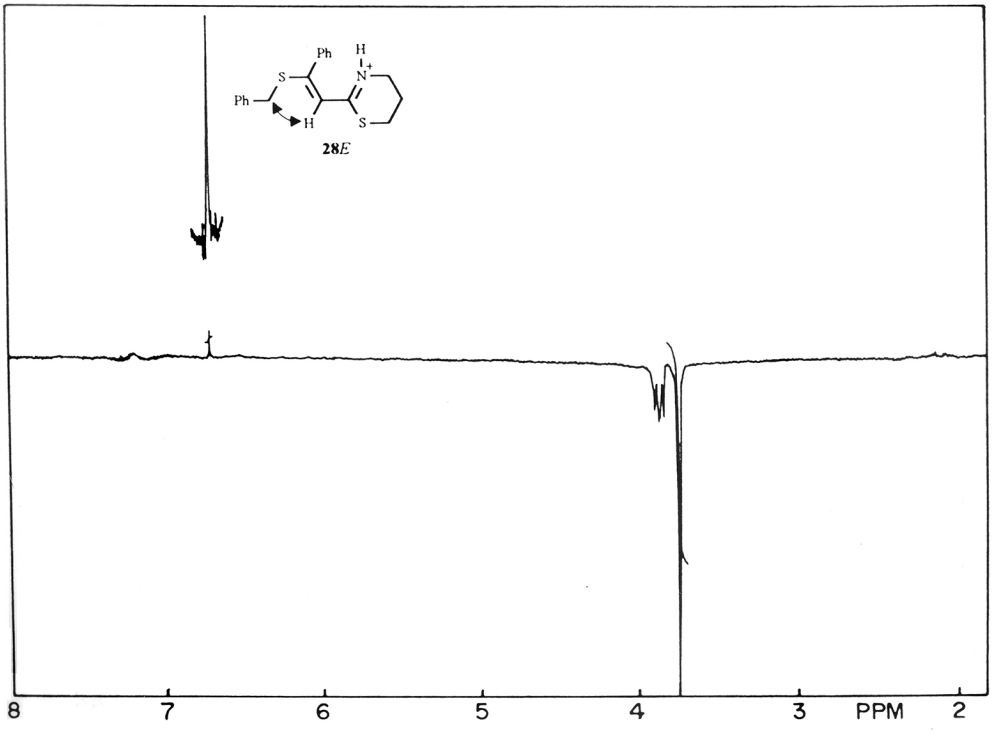
The X-ray crystal structure analysis of this product **27** proved that it was the *Z*-isomer. Most interestingly, the X-ray analysis also revealed a short contact of 270 pm between the exocyclic sulfur and the nitrogen of the ring. In $CDCl_3$ solution, on addition of a few crystals of PTSA, a rapid equilibrium is established between the base **27***Z* and its protonated form as seen by the gradual downfield shift of the olefinic signal, proportional to the amount of PTSA added. As expected, the free base **27***Z* showed no NOE at the benzylic methylene (3.5 δ) when the olefinic signal (5.9 δ) was irradiated. In contrast, irradiation of the methylene signal in the protonated form resulted in 3% NOE on the olefinic proton. This shows that the protonated form of **27** had considerable amount of the *E*-form **28**. The noteworthy point is that on deprotonation of this **28***E*, it goes back to **27***Z*. This clearly indicates a preference for the free base **27** to exist in the Z-form. It is



27Z


C18
C17
C19
C4
C5
N
C3
S1
C16
S2
C6
C2
C7
C15
C1
C8
C14
C9
C10
C13
C12
C11


Ph
H
S
N
Ph
H
S
28E
8
7
6
5
4
3
2
1
PPM
0


Ph
H
S
N
Ph
H
S
28E
8
7
6
5
4
3
PPM
2

interesting to note that the *Z*-isomer of **27**, unlike the thiazolidine derivative **25**, is preferred under both kinetic and thermodynamic control.

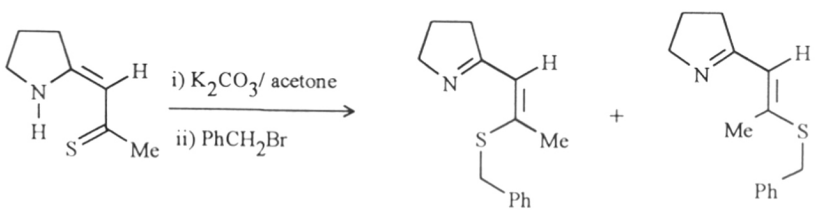
3.4 Alkylation of other structural variants of thiazolidine 5

In order to determine whether this stereoselectivity in alkylation is a general phenomenon, other structural variants of enaminothiones **5** and **16** were tried as substrates. The Cyclic enaminothione having a pyrrolidine ring in place of thiazolidine **20** and acyclic enaminothiones **22** and **24** appeared suitable for this purpose from the synthetic point of view. These compounds were synthesized as outlined in *Scheme 4*, *Scheme 5* and *Scheme 6*. The results of alkylation of these compounds are described in the following paragraphs.

3.4a Alkylation of 2-thioacetylmethylenepyrrolidine 20

Enaminothione **20** was treated with benzyl bromide (1.2 equivalents) in acetone with K_2CO_3 (1.2 equivalents) as base at room temperature (*Scheme 12*). TLC showed the appearance of several new spots . The two major spots appeared close to each other. These were separated from the other minor spots by column chromatography.The ^{1}H NMR spectrum of the mixture of these two major products showed two sets of signals, indicating the presence of two stereoisomers of the S-benzylated product **29**. The following were the peaks observed in the ^{1}H NMR ($CDCl_3$), δ:

Scheme 12



20 **29*Z*** **29*E***

Set I ,δ 1.9 (m, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.65 (t, 2H, N=CCH_2), 3.85(t, 2H,

NCH_2), 4.05 (s, 2H, SCH_2Ph) 6.07 (s, 1H, HC=C), 7.3 (m, 5H, Ph).

Set II ,δ 1.9 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.65 (t, 2H, CH2-C=N), 3.85 (t, 2H, NCH_2), 4.10 (s, 2H, S-CH_2-Ph), 6.17 (s, H, HC=C), 7.3 (m, 5H, Ph).

The well separated olefinic ^{1}H NMR ($CDCl_3$) peaks at 6.17 and 6.07 δ had ratio 1 : 2.5. However, on subjecting to acid catalysed equilibration (benzene, reflux PTSA) the reaction mixture decomposed to give the enaminone **19**. It is well known that the S-benzylated product being an enethiolether is prone to hydrolysis. Also the configuration of the major and minor products obtained initially could not be determined by the NOE technique since the ^{1}H NMR peaks for the two products are not well separated. Therefore, no conclusions regarding the stereochemical outcome could be drawn in this reaction.

3.4b Alkylation of 4-methylamino-3-pentene-2-thione 22

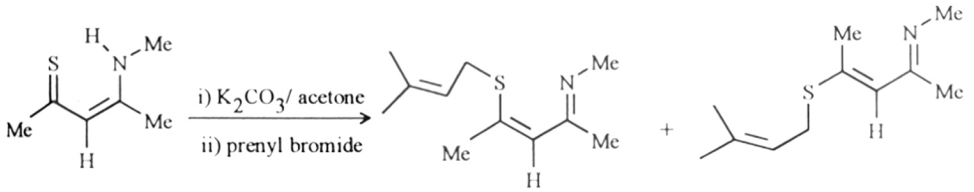
Enaminothione **22**, 4-methylamino-3-pentene-2-thione, was treated with prenyl bromide (1.2 equivalents) in acetone at room temperature with K_2CO_3 (1.2 equivalent) as the base (*Scheme 13*). TLC of reaction mixture showed several new spots. The products corresponding to the two major spots were separated and shown to be stereoisomers of **30** as inferred from the presence of two sets of peaks in the ^{1}H NMR($CDCl_3$) spectrum.

Set I ,δ 1.65 - 1.80 (4s merged, 9H, $(CH_3)_2C$ and CH_3-C=N), 2.15 (s, 3H, CH_3), 2.4 (s, 3H, NCH_3), 3.45 (d, 2H, SCH_2), 5.25 (m, HC=CMe_2), 5.95 (s, 1H, HC=C)

Set II ,δ 1.65-1.8 (4s merged, 9H, $(CH_3)_2C$ and CH_3-C=N), 2.15 (s, 3H, CH_3), 2.25 (s, 3H, NCH_3), 3.5 (d, 2H, SCH_2), 5.25 (m, 1H, HC=CMe_2), 6.25 (s, 1H, HC=C)

The well separated olefinic peaks at 6.25 and 5.95 δ occurred in the ratio 1 : 2.4. On acid-catalysed equilibration this ratio remained unchanged although several new peaks appeared, possibly due to decomposition of **30**. Here again, it was not possible to determine the configuration of the major and minor products of the reaction since the ^{1}H NMR peak positions were not well separated ; this prevented the application of the NOE technique to assign the stereochemistry.

Scheme 13

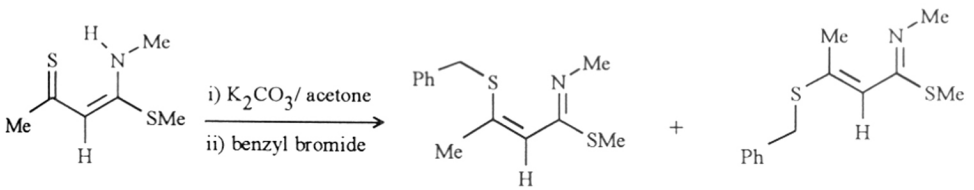


22 **30*Z*** **30*E***

3.4c Alkylation of 4-methylamino-4-thiomethyl-3-butene-2-thione 24

Enaminothione **24** was treated with benzyl bromide (1.2 equivalents) in acetone at room temperature with K_2CO_3 (1.2 equivalent) as the base (*Scheme 14*).

Scheme 14



24 **31*Z*** **31*E***

TLC of the reaction mixture the showed presence of several new spots which could not be separated by column chromatography.However, a mixture of products corresponding to a few of the major spots, bunched together on TLC, was isolated by column chromatography. The ^{1}H NMR ($CDCl_3$) spectrum of this mixture was taken. The spectrum showed a number of signals and no clear-cut identification of the expected reaction product was possible.

3.5 Role of S...N non-bonded interaction in determining stereoselectivity

As mentioned previously, enaminothione **5** is known to remain in an intramolecularly hydrogen bonded *E*-form in non-polar solvents like benzene or chloroform. However, as solvent polarity increases the population of the *Z*-configuration increases until the *Z*/*E* ratio reaches a maximum of 1 : 2 in pure DMSO. S-Alkylation of enaminothione **5** with various alkylating reagents in different solvents and in presence of number of bases yields the product as a mixture of two stereoisomers with the *Z*-stereosiomer being formed predominantly. On acid catalysed equilibration this isomerises to the thermodynamically preferred *E*-stereoisomer.

The product stereochemistry in these alkylations could not have been due to the initial hydrogen-bonded *E*-configuration of enaminothione **5**, since deprotonation, especially with bases such as DBU or triethylamine, would have preceded alkylation. In order to confirm this, the benzylation of enaminothione **5** with benzyl bromide using K_2CO_3 was carried out in the highly polar solvent DMF, in which as mentioned earlier, intramolecular hydrogen bonds would be expected to be largely broken. The result of this would have been removal of the restriction to rotation around C-CS bond. One could then expect the presence of a substantial amount of anion **33** (*Scheme 15*) on deprotonation of enaminothione **5**. This would lead to a significant amount of *E*-stereoisomer on alkylation of enaminothione **5.** However, the product **25b** obtained under these conditions, still had a *Z*/*E* product ratio of 10 : 1.

Finally, when the benzylation of enaminothione **5** was carried out with benzyl bromide in acetone without any added base, the protonated form of **25b** was obtained; careful neutralization of this with sodium hydrogen carbonate yielded predominantly the *E*-isomer, in conformity with the earlier acid catalysed equilibration studies.

From the above experimental evidence, it is clear that the preferred orientation for alkylation is that shown in transition state TS_1 (*Scheme 15*). The kinetic preference for the *Z*-configuration during S-alkylation can be attributed to either of two causes. (i)The anion generated from the enaminothione **5** prefers the U-configuration as in **32**, possibly due to

complexation at the two heteroatom termini with the counter ion as shown in *Fig 5*. This would naturally lead to the preferential formation of the *Z*-stereoisomer product **25***Z*.

Fig. 5

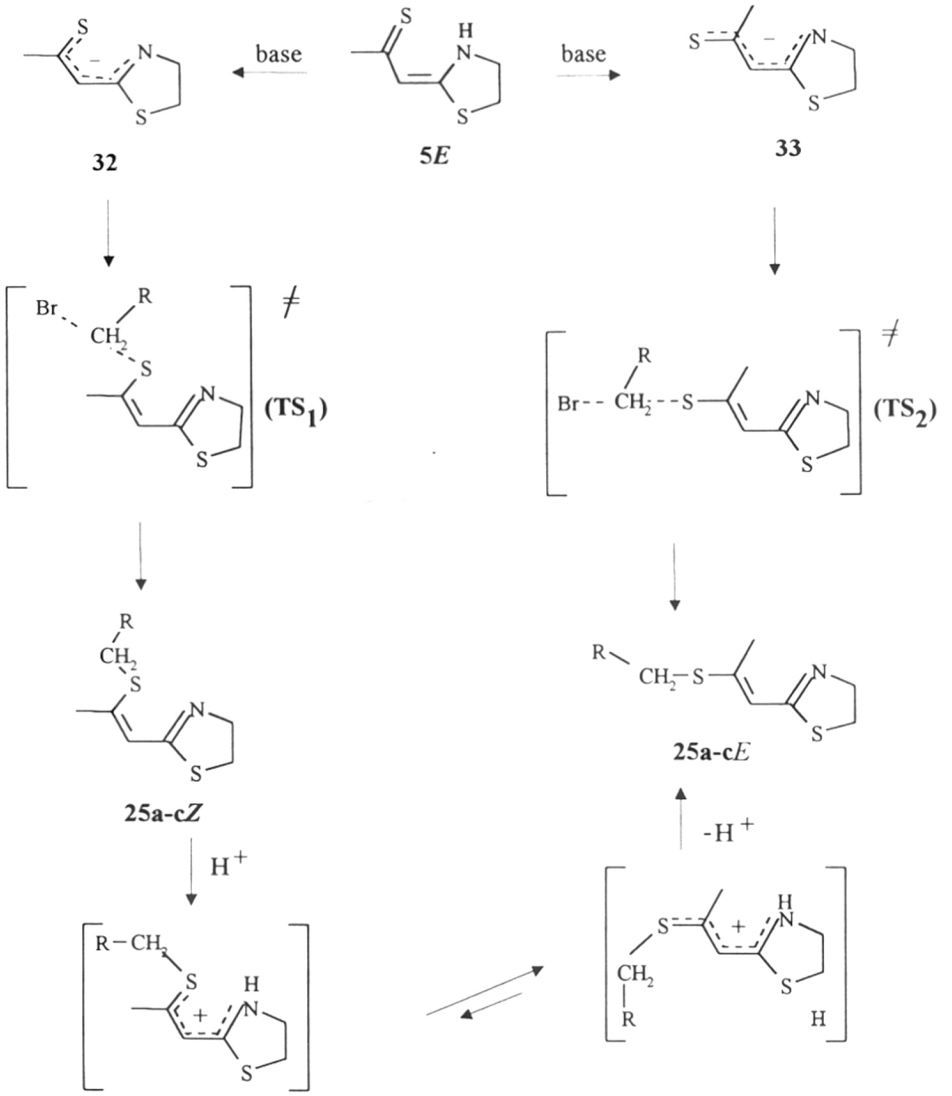
U-configuration of anion due to complexation with counter ion

(ii) The orientation in transition state TS_1 may be the preferred one as a consequence of a weak non-bonded attraction between the exocyclic divalent sulfur and the nuclear nitrogen. It is also possible that this S...N non bonded attraction manifests itself at the deprotonated stage itself as in **32**. This would lead to a preponderance of **25***Z*.

Strong support for the latter hypothesis comes from the X-ray crystallographic study of **25b***Z*. In this case a short S...N contact of 284 pm was observed, much below the sum of the van der Waals radii of 345 pm[14]. Besides, an almost linear arrangement of the three atoms C-S...N was noted ; this is ideal for efficient n-σ* overlap. The planarity of the quasi ring formed by N=C of the thiazolidine and the exocyclic C=C-S lends added support to this hypothesis.

This hypothesis based on S...N non-bonded attraction explains all the experimental facts. In this case S...N non bonded attraction governs the stereoselectivity leading to the preferential formation of *Z*-stereoisomer of product **25**. Although the enaminothione **5** is a push-pull system, the alkylation product **25** is not. Here the barrier to rotation about C=C bond is very high and hence no *E-Z* isomerisation is observed. However, on protonation at the ring nitrogen, S...N non-bonded attraction gets disrupted. Furthermore, the protonated form of product **25** becomes an efficient push-pull system. This leads to considerable lowering of the barrier to rotation about carbon-carbon double bond and hence there is rapid *E-Z* isomerisation to give the thermodynamically more stable *E*-isomer.

Scheme 15



Further strong evidence against the first hypothesis comes from alkylation of ring homologue 2-(thiobenzoylmethylene)1,3-thiazine **16** (*Scheme 11*). When **16** was benzylated under similar conditions (K_2CO_3 / acetone) only one S-benzylated isomer of **27** was obtained.

The X-ray crystal structure analysis of this product **27** proved that it was the *Z*-isomer. Most interestingly, the X-ray analysis also revealed a short contact of 270 pm between the exocyclic sulfur and the nitrogen of the ring. As shown earlier, in $CDCl_3$ solution, on addition of a few crystals of PTSA, a rapid equilibrium is established between the base **27***Z* and its protonated form **28***E*. It was also established that the protonated form of **27** had considerable amount of the *E*-form **28**. The noteworthy point is that on deprotonation of this **28***E*, it goes back to **27***Z*. This clearly indicates a preference for the free base **27** to exist in the *Z*-configuration. Since, in this case there is no question of co-ordination with a counter ion as in *Fig 5*, this preference for the *Z*-isomer might be the result of S...N non-bonded attraction. It is interesting to note that the *Z*-isomer of **27**, unlike the thiazolidine derivative **25**, is preferred under both kinetic and thermodynamic control. This changes to *E*-configuration only on protonation when S...N non-bonded attraction is disrupted and the molecule becomes a push-pull ethylene, thereby lowering the barrier to rotation around carbon-carbon double bond.

Thus in alkylation of enaminothiones **5** and **16**, S...N non-bonded attraction appears to play an important role in determining the product stereochemistry. This constitutes a rare, and probably the first, example of weak non-bonded attraction between two heteroatoms guiding stereoselectivity of a reaction. The role of weak forces in determining the stereochemical outcome of reactions has not received sufficient attention from organic chemists. A recent paper[1] has highlighted the role of one such weak force, viz. van der Waals attraction, in determining the product stereochemistry in acetalization of 1,3-alkanediol with menthone. There is a report which describes the exclusive formation of the *Z*-stereoisomer of α-oxo-ketene O,S-acetals by alkylation of thionoesters.[15] It is likely that in this case S...O non-bonded attraction plays a crucial role in influencing the product stereochemistry.

An important aspect of the above results is the nature of evidence furnished for weak non-bonded attraction in solution state, different from that for intramolecularly hydrogen bonded nitroenamine **3**, enaminone **4** and enaminothione **5** described in section 1. Enaminothiones **5** and **16**, on alkylation, are converted to ethylene compounds **25** and **27**

which are not push-pull systems and hence are configurationally stable even at elevated temperatures. However, on protonation they are converted into push-pull ethylenes in which rapid *E*-*Z* isomerization is possible. This occurs in refluxing benzene in the case of **25**H$^+$ and at ambient temperature for compound **28**.Under these circumstances for compound **25** S...N non-bonded attraction gets disrupted with concomitant lowering of the barrier (due to push pull effect) to rotation around the formal carbon-carbon double bond, resulting in the formation of the thermodynamically more stable *E* isomer of **25**. Similarly, compound **27***Z* forms thermodynamically more stable protonated *E*-form **28***E*(evident from NOE). These experiments clearly establish the role of S...N non-bonded attraction in stereoselective product formation under kinetic control in the solution. The nature of the above evidence is different from that in the case of **3**,**4** and **5** where non-bonded attraction was suggested to be responsible for *E* - *Z* solvent dependent conformational equilibrium arising out of a balance between intramolecular hydrogen bonds and S..O and S..S non-bonded interaction.

4. Conclusion

From the alkylation studies on various enaminothiones, the following conclusions can be drawn.

1) In the alkylation of enaminothione **5**, the preference for the *Z*-stereoisomer is under kinetic control.
2) In contrast, the preference for *Z*-stereochemistry in case of enaminothione **16** is under kinetic as well as thermodynamic control
3) S...N non-bonded attraction is a weak force, is probably responsible for determining the observed stereoselectivity during alkylation of enaminothiones **5** and **16**.
4) Evidence for such non-bonded attraction in the solution state is furnished by the observed stereoselectivity in the alkylation reaction. This evidence for the occurrence of S...N attraction in the solution state has thus been provided *without resorting to change of solvent.*

5. Experimental

5.1 Synthesis of Enaminones

5.1a Synthesis of 2-acetylmethylenethiazolidine 9

This compound was obtained in three steps starting from acetyl acetone as follows (*Scheme 1*). To a suspension of sodium hydride (0.2 mol) in dry benzene (75 ml), a solution of acetylacetone (0.1 mol) in dry benzene (100 ml) was added slowly over a period of 40 minutes during which time hydrogen evolution was observed. This reaction mixture was cooled down to ice-bath temperature and carbon disulfide (0.1 mol) was added drop by drop in about 10 minutes, followed by DMF(75 ml) in similar manner. A vigorous hydrogen gas evolution was observed with reaction mixture progressively becoming red as room temperature was attained, indicating that sodium hydride is consumed.Reaction mixture was cooled to ice-bath temperature and methyl iodide (0.22 mol) was added slowly over a period of 3h, stirring being continued overnight at room temperature. On the following day, water (50 ml) was added to reaction mixture, benzene layer was separated and washed several times with water to remove DMF. Organic layer was dried over anhydrous Na_2SO_4 and solvent evaporated on rotary evaporator to get crude product. Pure product was obtained by crystallization from methanol is 50% yield. m.p. 60°C.

In second step, a mixture of ketene dithioacetal **6** (20 mmol) 2-amino ethanethiol hydrochloride (22 mmol) and sodium hydroxide (22 mmol) in absolute ethanol (60 ml) was refluxed for 8-10h. During this time methyl mercaptan is evolved, evident from the characteristic smell on cooling the product **8** crystallizes out. This is filtered, dried under suction and used as such for further reaction. Yield = 86%, m.p. ^{1}H NMR ($CDCl_3$): 2.45 (s, 6H, CH_3), 3(t, J=7, 2H, SCH_2), 3.9 (t, J=7, 2H, NCH_2)

In third step, compound **8** (10 mmol) was added to sodium methoxide solution (40 mmol in 40 ml methanol) and refluxed for 4 h. Water was added to the cooled reaction mixture, extracted with chloroform (2 x 30 ml) organic layer dried over anhyd. Na_2SO_4 and solvent was removed on rotary evaporator to get crude product. The crude product was recrystallised from ethanol to get pure product **9** in 78% yield.

^{1}H NMR ($CDCl_3$), δ: 2.0 (s, 3H, CH_3), 3.2 (t, J=7, 2H, SCH_2), 3.9(t, J=7, 2H, NCH_2), 5.3(s, 1H, HC=C), 10.9 (bs, 1H, NH)

5.1b Synthesis of 2-benzoylmethylenethiazolidine 11:

Enaminone **11** was prepared in two steps starting with acetophenone as outlined in *Scheme 2*. In first step ketene dithioacetal is prepared from acetophenone as follows. To a suspension of sodium hydride (20 mmol) in dry benzene (20 ml) a solution of acetophenone (10 mmol) in dry benzene (25 ml) was added dropwise. To the above cooled reaction mixture carbon disulfide (10 mmol) was added followed by addition of dry DMF(20 ml) when the reaction mixture turns dark and remaining sodium hydride is consumed. Reaction mixture was stirred overnight at room temperature and on following day water was added. Organic layer was separated, washed several times with water to remove DMF, dried over anhyd. Na_2SO_4 and solvent evaporated to afford crude product. This was purified by column chromatography (pet.ether : ethylacetate, silica gel 60-120) to get compound **10** in 45% yield.

In the second step, compound **10** was reacted with 2-amino ethanethiol (6 mmol) in absolute ethanol (40 ml) under reflux for 8-10 h. On cooling the product **11** crystallizes out and was used as such for further reaction. Yield = 72%, m.p. 168°C ^{1}H NMR ($CDCl_3$), δ: (t, 2H, SCH_2), 3.9 (t, 2H, NCH_2), 5.9(s, 1H, HC=C), 7.2-7.8 (m, 5H, Ph), 10.,55 (bs 1H, NH), IR cm^{-1} (nujol) : 3200, 1600, 1580

5.1c Synthesis of 2-benzoylmethylene-1,3-thiazine 15

Enaminone **15** was prepared from benzoyl dithioester **13** as outlined in *Scheme 3*. Compound **13** (10 mmol) was dissolved in benzene (25 ml) and water (15 ml) was added to it. To the above stirring solution was cooled to ice-bath temperature and sodium hydroxide (22 mmol) was added along with phase transfer catalyst, tetrabutyl ammonium bromide (100 mg). After 15 minutes, 3-bromo propanamine hydrobromide **14** was added slowly over a period of 30 minutes and stirring was continued for 1h at ice bath temperature and then at 70°C for 2h., benzene layer was separated, aqueous layer (basic) was neutralised with dil HCl and extracted with benzene (30 ml). The two benzene extracts were combined, dried over anhyd. Na_2SO_4 and solvent evaporated to give residue. TLC of this residue

showed three spot which were subsequently separated by column chromatography (pet ether acetone, silica gel 60-120) to yield pure thiazine derivative **15** in 51% yield as one of the products. m.p. 104°C

^{1}H NMR ($CDCl_3$): δ 2.25 (m, 2H, CH_2), 3.20 (t, J=8Hz, 2H, SCH_2), 3.55 (t, J=8Hz, 2H, NCH_2), 5.75 (s, 1H, HC=C), 6.95 - 7.65 (m, 5H, Ph), 12.45 (bs, 1H, NH), IR (nujol) : 3000, 1580, 1470 cm-1

5.1d Synthesis of 2-acetylmethylene pyrollidine 19

Enaminone **19** was prepared in two steps starting with lactim ether **17** (*Scheme 4*)[10] in the first step, lactim ether **19** (20 mmol) was heated with ethyl acetoacetate (30 mmol) 100°C in presence of catalytic amount of nickel (II) acetylacetonate for 12-15h. On cooling, a solid separates out which is filtered and purified by column chromatography (pet ether/acetone, silica gel 60-120) to afford **18** in 74% yield. ^{1}H NMR ($CDCl_3$):

In the second step the ester group in **18** is removed as follows. Compound **18** (10 mmol) is heated with excess of boric acid(2g) at 220°C for 1h. to give a solid on cooling. This solid was dissolved in acidic methonalic solution (MeOH : HCl = 9:1) water was added before neutralising with solid K_2CO_3. The solution so obtained was extracted with chloroform. Organic layer separated and dried over anhydrous Na_2SO_4 and solvent removed under rotary evaporator to afford crude product **19**. This was purified by column chromatography (pet ether/acetone, silica gel 60-120) to get compound 19 as white solid in 64% yield, m.p. ^{1}H NMR ($CDCl_3$): δ 1.98(m, 2H, CH_2), 2.0(s, 3H, CH_3), 2.6(t, J=8Hz, 2H, $C=CCH_2$), 3.55(t, J=7Hz, 2H, NCH_2), 5.05(s, 1H, HC=C)

5.1e Synthesis of 4 methylamino-3-pentene-2-one 21

Enaminone **21** was prepared by method outlined in *Scheme 5* [11]. To an ice cold acetyl acetone (30 mmol) in conical flask a 40% methylamine solution (3.2 ml) was added slowly when a crystalline material was immediately formed. This was filtered and recrystallised from diethylether to yield enaminone **21** in 76% yield. m.,p. 41°C. ^{1}H NMR ($CDCl_3$): δ 1.8(s, 3H, CH_3-C=C), 1.9(s, 3H, CH_3CO), 2.85(d, 3H, NCH_3), 4.9(s, 1H, HC=C).

5.1f Synthesis of 4-methylamino 4-methylthio-3-butene-2-one 23

Enaminone **24** was prepared by reaction between carboimido dithioic dimethyl ester **22** and acetyl acetone in presence of zeolite [12] as follows (*Scheme 6*). Compound **22** (10 mmol) was heard with acetyl acetone (12 mmol) in Toluene (30 ml) in presence of zeolite (RE 30% NaY) to afford crude product **23**. This was recrystallised from pet ether to afford pure enaminone **24** in 70% yield. m.p.65°C ^{1}H NMR ($CDCl_3$): δ 2.03(s, 3H, $COCH_3$), 2.36 (s, 3H, SCH_3), 2.98(d, J = 5H, 3H, NCH_3), 4.96(s, 1H, HC=C), 11.20 (bs, 1H, NH_), IR cm^{-1}($CHCl_3$) : 3200-3350, 1560, 1470, 1280.

5.2 Synthesis of enaminothiones

5.2a General procedure for thionation of enaminones

To a stirring solution of enaminones (5 mmol) in dry THF (40 ml) under argon atmosphere at room temperature, Lawesson reagent (3 mmol) was added slowly over a period of 15 minutes and the progress of reaction was monitored by TLC. Thionation is complete in 15-60 minutes for various enaminones. After completion of reaction solvent was removed on rotary evaporator at temperature not exceeding 50°C and the residue so obtained was column chromatographed (pet ether/acetone, silica gel 60-120) to afford pure enaminothiones. In case of enaminothiones **20** and **24** silica gel was neutralised with TEA before performing column chromatography.

It is important to note that in thionation of enaminone **23** atleast 4 equivalents of TEA was added before addition of Lawesson reagent.

Thionation of enaminones **9** and **21** was also done in dry benzene under argon atmosphere at reflux temperature for 3-5 h. Due to elevated temperature, prolonged reaction time and some what lesser yields than those carried in THF moles this procedure unattractive.

2-thioacetylmethylenethiazolidine 5

Nature	Yellow crystalline solid m.p. 100°C.
Yield	81 %
IR cm^{-1} (nujol)	3400, 1570, 1470, 1390, 1280.
^{1}H NMR δ	2.54 (s , 3H, Me), 3.34(t, 2H, SCH_2), 4.08(t, 2H, NCH_2), 6.31(s, 1H,

($CDCl_3$)	=CH), 13.50 (bs, 1H, NH)

2-Thiobenzoylmethylenethiazolidine 12

Nature	Yellow crystalline solid, m.p. 95°C
Yield	83 %
IR cm^{-1} (nujol)	3000, 2800, 1570, 1550.
^1H NMR δ	3.77 (t, 2H, S-CH_2), 4.12 (t, 2H, N-CH_2), 6.73 (s, 1H, CH=C), 7.33
($CDCl_3$)	(m, 3H, Ph), 7.73(m, 2H, Ph) and 13.75 (bs, 1H, NH)

2-(Thiobenzoylmethylene)-1,3-thiazine 16

Nature	Yellow crystalline solid, m.p. 159°C
Yield	79 %
IR cm^{-1} (nujol)	2940, 2860, 1600, 1510.
^1H NMR δ	2.2(m, 2H, CH_2), 3.15(t, 2H, SCH_2), 3.65(t, 2H, NCH_2), 6.5(s, 1H,
($CDCl_3$)	HC=C), 7.4-7.8(m, 5H, Ph), 15(bs, 1H, NH)

2-Thioacetylmethylene pyrrolidine 20

Nature	Yellow solid, m.p.
Yield	75 %
IR cm^{-1}	3400, 2800-2300 (broad), 1625, 1590, 1510.
^1H NMR δ	2.1(m, 2H, -CH_2), 2.5(s, 3H, CH_3), 2.75(t, 2H, CH_2-C=), 3.8(t, 2H,
($CDCl_3$)	NCH_2), 6.2(s, 1H, C=CH), 13.2 (b, 1H, NH)

4-methylamino-3-pentene-2-thione 22

Nature	Dark red solid,
Yield	53 %
IR cm^{-1} ($CHCl_3$)	3380, 1640, 1570, 1500
^1H NMR δ	2.30(s, 3H, C=C-CH_3), 2.5(s, 3H, $COCH_3$), 3.0 (d, 3H, NCH_3), 6.1(s,
($CDCl_3$)	1H, C=CH), 13.5(t, 1H, NH).

4-methylamino-4-thiomethyl-3-butene-2-thione 24

Nature	Dark red solid, m.p. 64°C
Yield	44 %
IR cm^{-1} ($CHCl_3$)	3370, 1590, 1500, 1360
^1H NMR δ ($CDCl_3$)	2.4(s, 3H, CH_3), 2.5(s, 3H, SCH_3), 3.0(d, 3H, NCH_3), 6.0 (s, 1H, C=CH), 14.0(b,1H, NH).

5.3 Alkylation of enaminothiones

General procedure

To a stirring solution of enaminothione (3 mmol) in 25 ml solvent (benzene, acetone, DMF) base (1.2 equivalent) was added. After 10 minutes alkyl halide (prenyl bromide benzyl bromide and methyl iodide) was added and progress of the reaction was monitored by TLC. After completion of reaction solvent was removed, residue was dissolved in chloroform, dried over anhydrous Na_2SO_4 and the reaction mixture, if necessary, was passed through a short silica gel column of 5 cm. The reaction products so obtained were characterized as described in section **3.2** and **3.4**.

2-benzylthio-2-propenylthiazolidine 25a

Nature	colourless solid, m.p. 120-122°C
Yield	87 %
IR cm^{-1} ($CHCl_3$)	3010, 1590, 1430.
^1H NMR δ ($CDCl_3$)	*Z*-Isomer: 2.25 (s, 3H, CH_3), 3.25(t, 2H, $-SCH_2$), 4.1(s, 2H,SCH_2Ph), 4.35(t, 2H, $N-CH_2$), 6.15 (s, 1H, HC=C), 7.4(m, SH, Ph) *E*-isomer: 2.4(s, 3H, CH_3), 3.30(t, 2H, SCH_2), 4.0(s, 2H, SCH_2Ph), 4.40(t, 2H, NCH_2), 5.9(s, 1H, HC=C), 7.4(m, 5H, Ph)
^{13}C NMR δ ($CDCl_3$)	24.7, 33.81, 36.21, 64.54, 117.6, 127.3, 128.0, 128.9, 136.9, 146.2, 164.2.
Microanalysis	MF : $C_{13}H_{13}NS_2$

Calculated	C, 62.6 ; H, 6.06 ; N, 5.6 ; S, 25.71.
Found	C, 61.53 ; H, 5.08 ; N, 5.52 ; S, 28.2.

2-(2-methyl-2-butenyl)thio-2-propenylthizolidine 25b

Nature	Colourless solid (turns yellow), m.p. 58-60°C
Yield	82 %
IR cm^{-1} ($CHCl_3$)	2900, 1560, 1490, 1390.
^1H NMR δ ($CDCl_3$)	*Z*-Isomer: 1.54(s , 3H, CH_3), 1.56(s, 3H,CH_3), 2.07(s, 3H, CH_3-C-S), 3.07(t, 2H, S-CH_2), 3.2(d, 2H, CH_2-C=C), 4.15(t, 2H, NCH_2), 5.08(m, 1H, CH=CMe_2), 6.05(s, 1H, HC=C), *E*-isomer: 1.54(s, 3H, CH_3), 1.56(s, 3H, CH_3), 2.13(s, 3H, CH_3-C-S), 3.10(t, 2H, SCH_2), 3.17(d, 2H, CH_2-C=C), 4.10(t, 2H, NCH_2), 5.08(m, 1H, CH=CMe_2), 5.65 (s, 1H, HC=C),
^{13}C NMR, δ ($CDCl_3$)	18.0, 24.7, 25.8, 30.0, 33.9, 64.7, 117.4, 119.3, 136.8, 147, 164.5
Microanalysis	MF : $C_{11}H_{17}NS_2$
Calculated	C, 58.10 ; H, 7.53 ; N, 6.15 ; S, 28.2.
Found	C, 58.66 ; H, 6.25 ; N, 5.97 ; S, 25.14

2-methylthio-2-propenylthiazolidine 25c

Nature	Colourless solid, m.p. 51°C
Yield	67 %
IR cm^{-1}	3010, 1590, 1440.
^1H NMR δ ($CDCl_3$)	*Z*-Isomer: 2.06(s, 3H, CH_3), 2.15(s, 3H, SCH_3), 3.1(t, 2H, SCH_2), 4.1(t, 2H, NCH_2), 6.02(s, 1H, HC =C) *E*-isomer: 2.10(s, 3H, CH_3), 2.15(s, 3H, SCH_3), 3.1(t, 2H, SCH_2), 4.1(t, 2H, NCH_2), 5.6 (s, 1H, HC=C)
^{13}C NMR δ ($CDCl_3$)	14.60, 23.90, 33.70, 64.7, 116.0, 147, 164.
Microanalysis	MF : $C_7H_{11}NS_2$
Calculated	C, 48.51 ; H, 6.4 ; N, 8.07 ; S, 37.

Found C, 48.67 ; H, 5.27 ; N, 7.95 ; S, 33.82.

2-benzylthio-2-phenylethenylthiazolidine 26a

Nature colourless solid, m.p. 175 °C

Yield 79 %

IR cm^{-1} 2940, 1600, 1440

^1H NMR δ ($CDCl_3$) *Z*-Isomer: 3.1(t, 2H, SCH_2), 4.02(s, 2H, SCH_2Ph), 4.13(t, 2H, NCH_2), 6.72(s , 1H, HC=), 7.05(m, 2H, Ph), 7.25(m, 3H, Ph), 7.45(m, 5H, Ph).

E-isomer: 3.3(t, 2H, SCH_2), 3.72 (s, 2H, SCH_2Ph), 4.3(t, 2H, NCH_2), 6.62 (s , 1H, HC=), 7.05(m, 2H, Ph), 7.25(m, 3H, Ph), 7.45(m, 5H, Ph).

^{13}C NMR δ ($CDCl_3$) 34, 38.4, 63.4, 125.0, 127.6, 128.3-129.10, 137.1,139.30,148.10, 165.9

2-methylthio-2-phenyethenylthiazolidine 26b

Nature colourless solid , m.p. 127-129 °C

Yield 76 %

IR cm^{-1} 3010, 1580, 1430.

^1H NMR δ ($CDCl_3$) *Z*-Isomer: 2.0(s, 3H, SMe), 3.32(t, 2H, SCH_2), 4.37(t, 2H, NCH_2), 6.5 (s, 1H, HC=), 7.3-7.5 (m, 5H, Ph)

E-isomer: 2.4(s, 3H, SMe), 3.02(t, 2H, SCH_2), 4.12(t, 2H, NCH_2), 6.35(s, 1H, HC=), 7.3-7.5(m, 5H, Ph)

2-benzylthio-2-phenylethenyl-1,3-thiazine 27

Nature colourless solid, m.p. 162 °C

Yield 72 %

IR cm^{-1} 3010, 1590, 1430.

^1H NMR δ ($CDCl_3$) 1.8(m, 2H, CH_2), 3.0(t, 2H, SCH_2), 3.5(s, 2H, SCH_2Ph), 3.8(t, 2H, NCH_2), 5.9(s, 1H, HC=C), 6.95(m, 2H, Ph), 7.1(m, 3H, Ph), 7.25(m, 5H, Ph)

Microanalysis	MF: $C_{19}H_{19}NS_2$
Calculated	C, 70.11 ; H, 5.88 ; N, 4.30 ; S, 19.70
Found	C, 68.39 ; H, 6.15 ; N, 4.32 ; S, 18.59

2-(2-benzylthiopropene)pyrrolidine 29

Nature	dark colour semi-solid
Yield	66 %
IR cm^{-1}	3020, 1610, 1450
^1H NMR δ ($CDCl_3$)	Set I :1.9(m, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.65(t, 2H, N=CCH_2), 3.85(t, 2H, NCH_2), 4.05(s, 2H, SCH_2Ph) 6.07(s, 1H, HC=C), 7.3(m, 5H, Ph). Set II : 1.9(m, 2H, CH_2), 2.25(s, 3H, CH_3), 2.65(t, 2H, CH2-C=N), 3.85 (t, 2H, NCH_2), 4.10(s, 2H, S-CH_2-Ph), 6.17(s, H, HC=C), 7.3 (m, 5H, Ph).

2-(3-methyl-2-butenyl)thio-4-methylimidinepentane-2-ene 30

Nature	dark coloured semi-solid
Yield	56 %
IR cm^{-1}	3010, 1540, 1440.
^1H NMR δ ($CDCl_3$)	Set I :1.65 - 1.80(4s merged, 9H, $(CH_3)_2C$ and CH_3-C=N), 2.15(s, 3H, CH_3), 2.4(s, 3H, NCH_3), 3.45(d, 2H, SCH_2), 5.25(m, HC=CMe_2), 5.95 (s, 1H, HC=C) Set II :1.65-1.8(4s merged, 9H, $(CH_3)_2C$ and CH_3-C=N), 2.15(s, 3H, CH_3), 2.25(s, 3H, NCH_3), 3.5(d, 2H, SCH_2), 5.25(m, 1H, HC=CMe_2), 6.25(s, 1H, HC=C)

5.4 Preparation of NOE sample

To get proper NOE, sample has to be free of paramagnetic impurities; dissolved oxygen in the solvent is a major paramagnetic impurity always present in the sample. A sample for NOE was made oxygen free by a freeze pump than technique as follows. About 5 mg of compound under investigation was dissolved in solvent ($CDCl_3$) in NMR tube

capped with rubber septum. Through the rubber septum hypodermic needle was pierced. The other end of the needle was connected to two way step cook trough which argon or vacuum could be introduced as desired.

Initially the sample is frozen (liq nitrogen/acetone) and vacuum was introduced in NMR tube followed by argon. After this, sample was slowly thawed by allowing it to attain room temperature. During this time, the dissolved oxygen in the sample diffuses into argon atmosphere above the sample. Sample is again subjected to freezing followed by vacuum, argon and thawing. This cycle was repeated five to six times to get almost oxygen free sample.

6. References :

1. T. Harada, A. Inoue, J. Uchimura, S. Tanaka, S. Oku, *J.Am.Chem.Soc.*, **1993**,*115*, 7665.
2. A.Kucsman, I.Kapovits, *Organic Sulfur Chemistry : Theoretical and Experimental Advances*, (Eds. F. Bernardi, I.G.Csizmadia, A.Mangini, Elsevier Science Publishers B.V., **1985**, p. 191.
3. a) T. Kimura, N. Furukawa *Tetrahedron Lett.* **1995**, *36*, 1079. b) F. Dumitrascu, D. D. Rasleanu *Tetrahedron Lett.* **1995**, *36*, 1295. c) F.T. Burling, B.M. Goldstein, *J.Am.Chem.Soc.* **1992**, *114*, 2313. d) D.H.R. Barton, M.B. Hall, Z. Lin, S.I. Parekh, J. Reibenspies, *J.Am.Chem.Soc.* **1993**, *115*, 5056
4. S. Rajappa, B. M. Bhawal, A. R. A. S. Deshmukh, S. G. Manjunatha *J. Chem. Soc. Chem. Commun.*,**1989**, 1729.
5. A.N.Dixit, K.Venodhar Reddy, A.R.A.S.Deshmukh, S.Rajappa, B.Ganguly, J.Chandrasekhar, *Tetrahedron*. **1995**, *51*, 1437.
6. a)R. E. Rosenfield Jr., R. Parthasarathy, *J.Am.Chem.Soc.* **1974**, *96*, 1925. b) R.E. Rosenfield Jr., R. Parthasarathy, *Acta. Crystallog. Sec.B*, **1975**, *31*, 462.
7. a) P. K. Warme, R.S.Morgan, *J.Mol.Biol.* **1978**, *118*, 273. b) R.S.Morgan, J.M. McAdon, *Int.J.Peptide Protein Res.*, **1980**, *15*, 179. c) B.L. Bodner, L.M. Jackman, R.S. Morgan, *Biochem. Biophys. Res.Commun.* **1980**, *94*, 807
8. G. Desiraju, *Prog.Solid State Chem.* **1987**, *17*, 295.
9. Zhi Tang, Xian Shi, *Synthesis*, **1990**, 162.
10. Philippe Delbec, Jean Pierre Celemc, G. Lhommet *Tetrahedron Lett.* **1990**, *31*, 4873.
11. W. Walter, T. Proll, *Synthesis*, **1979**, 941
12. T. Indrasen Reddy, *Ph. D. Thesis*, **1992**, 67 (University of Poona)
13. K. Wiberg, M. W. Wang, M. J. Frisch, *J.Am.Chem.Soc.*, **1991**, *113*, 4776 b)R. R Pappalardo, E. S. Mareas, M. F. Ruiz-Lopez, D.Riveai *J.Am.Chem.Soc.*,**1993**, *115*, 3722.
14. A. E. Koziol,R. C. Palenik, G. J. Palenik *J. Chem. Soc. Chem. Commun.*,**1988**, 226.
15. M. L. Purkayastha, M. Chandrasekharam, J.N. Viswakarma, H. Ila, H.Junjappa, *Synthesis*, **1993**, 245.

CHAPTER 2

CHIRAL INDUCTION IN THIO-CLAISEN REARRANGEMENT INVOLVING PUSH-PULL SYSTEMS

Chapter 2 : Chiral Induction in thio-Claisen Rearrangement Involving Push-Pull System

Summary

In this chapter chiral induction under remote stereocontrol has been studied. Allylation of benzoylthioacetamide **22** having various chiral amines in the thioamide moiety provided the S-allyl compound **23**, a push-pull system for thio-Claisen rearrangement in which the asymmetry-inducing centre is located two atoms away from the [3,3] framework. This S-allyl compound **23** underwent rearrangement under mild conditions to give C-allyl compound **24**. Diastereoselectivity ranging from good to poor was observed depending upon the nature of the chiral amine used.

1. Introduction

Achieving stereocontrol in the construction of acyclic systems is a particularly challenging problem in organic synthesis[1]. Sigmatropic rearrangement is one of the most powerful methodologies developed to address this problem. In sigmatropic rearrangements, the transition state is usually highly ordered, with the result that any specific stereochemical relationship in the starting material can be correlated to that in the product. Moreover, the most favourable transition state geometry can be predicted on the basis of the principles of conformational analysis and therefore the stereochemistry of the product can be anticipated with reasonable certainty.

Claisen rearrangement and its variants[2] belong to the class of [3,3] sigmatropic rearrangements and have been gainfully employed for stereocontrol in acyclic systems with the help of relative or internal asymmetric induction. From the several references in the literature, it has been observed that when the original center of asymmetry is located vicinal to the developing chiral center, modest selectivity is achieved during the rearrangement. But when the original chiral center is farther removed from the rearrangement framework, stereoselectivity is reduced.

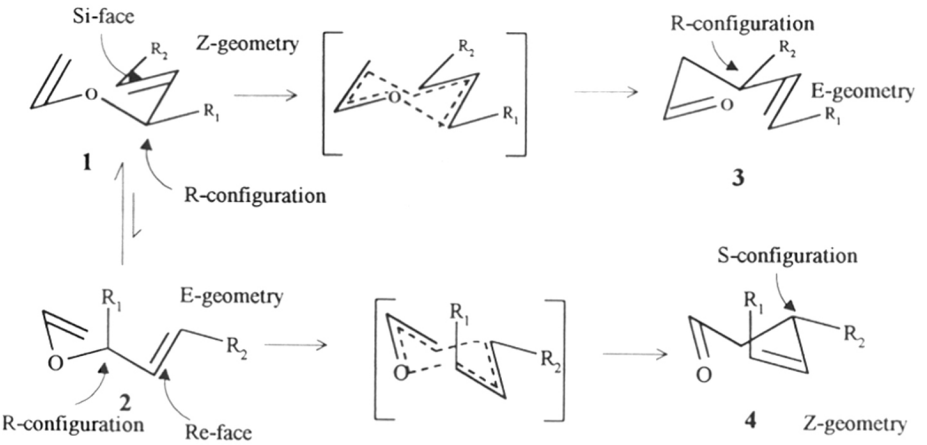
A simple example of asymmetric induction in Claisen rearrangement, more correctly termed as chirality transfer (or internal asymmetric induction), is provided by the enantiomerically pure allyl vinyl ether **1** (*Scheme1*). Here both the original asymmetric center and the newly formed asymmetric center form an integral part of the rearrangement framework. Within this framework, they have a 1,3 relationship. In such cases, the highest chirality transmission achieved was 94-99 %.[3]

If the asymmetry inducing center is outside the rearrangement framework, the level of asymmetric induction drops to 75 %, as observed in the case of allyl vinyl ethers **5** and **7** (*Scheme 2*).[4] In this case the original asymmetric center is vicinal (1,2-relative position in the framework) to the newly created chiral center.

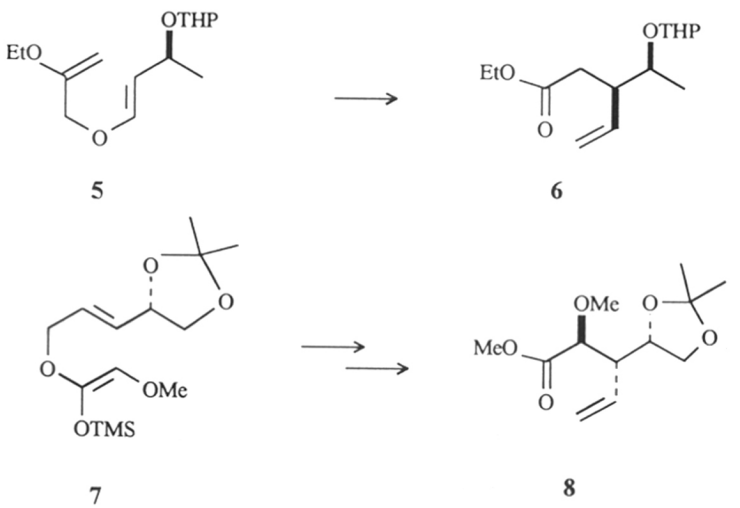
It is therefore interesting to find out what happens when the chirality inducing center is farther removed i.e. separated by one or more atoms away from the rearrangement framework. The first example of chiral induction by remote stereocontrol in such a Claisen

rearrangement was provided by the allyl vinyl ether **9** (*Scheme 3*).[5] In this case the chiral induction drastically dropped down to zero. Thus, the above examples demonstrate that chiral induction diminishes as the chirality inducing center is removed away from the rearrangement framework.

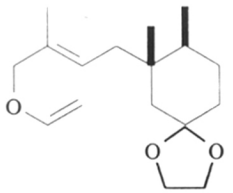
Scheme 1



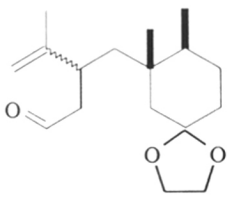
Scheme 2



Scheme 3



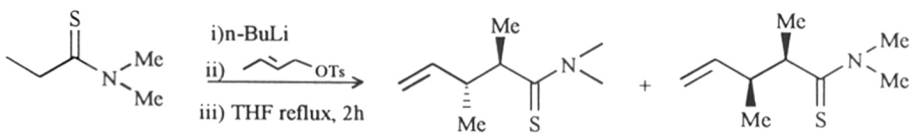
9



10

Thio-Claisen rearrangement has received much less attention as compared to Claisen rearrangement and hence its potential towards achieving stereocontrol has remained largely unexplored.[4] In one of the earliest reports on diastereoselective thio-Claisen rearrangements the S-crotyl derivative of thioamide **11** (*Scheme 4*)[6], was shown to undergo rearrangement with a high level of *syn* selectivity. The high degree of diastereoselectivity in this case was attributed to the selective formation of *Z*-enolate of the anion of **11**.

Scheme 4

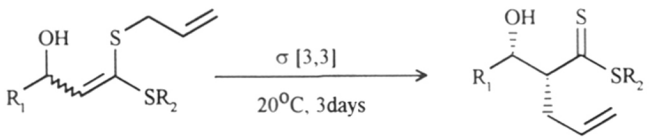


11 erythro threo

Recently, a high *syn* selectivity of 90:10 was observed in the thio-Claisen rearrangement of α-hydroxyketene dithioacetal **12** (*Scheme 5*).[7] It was proposed that the *syn* selectivity in this case arises neither from the ketene geometry nor from the S-allyl or alkylthio part but due to a chair-like transition state and a remarkable stereoelectronic effect of the hydroxyl group of the chiral auxiliary. Based on this proposition, diastereoselectivity as high as 99 : 1 was obtained during the rearrangement of the S-allyl derivatives of α-hydroxyketene dithioacetal **14**[8] (*Scheme 6*) to give the product **15** having three adjacent

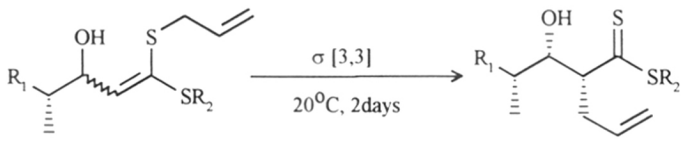
chiral centers. It is important to note that the original chiral center and the newly formed chiral center are vicinal to each other and therefore such high selectivity is not very surprising.

Scheme 5



12 **13**

Scheme 6



14 **15**

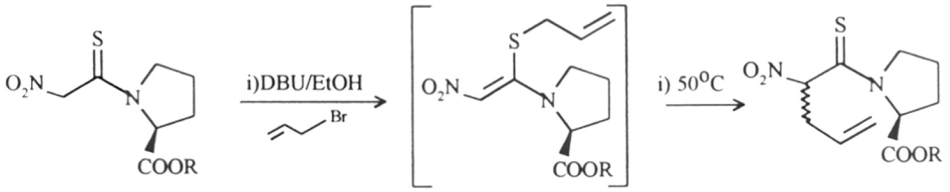
About the same time when the above reports (*Scheme 5* and *Scheme 6*) appeared, a remarkable diastereoselectivity (de = 66%) under remote stereocontrol was observed during a facile thio-Claisen rearrangement of S-allyl N-nitrothioacetyl prolinate **17** (*Scheme 7*) in our group.[9] Here the newly created asymmetric carbon had a 1,4 relationship to the original chirality inducing center. Besides, the original chiral center was located two atoms away from the rearrangement framework.

Two intriguing facts regarding this rearrangement need to be emphasised :

(i) the high chiral induction by an asymmetric center located two atoms away from the [3,3] framework

(ii) the rearrangement takes place at as low a temperature as 50°C (usually these rearrangements proceed only at a temperature of 170°C and above).

Scheme 7



16 **17** **18**

To understand the factors influencing the remote stereocontrol and the ease of this rearrangement, a systematic study was necessary with regard to the nature of the chiral auxiliary and the substituent effect (e.g. replacement of nitro group by other electron withdrawing groups such as -C=O, -CN,). This forms the basis of the present work.

2. Present work

Encouraged by the high stereoselectivity obtained during the thio-Claisen rearrangement of the S-allyl derivative **17** of N-nitrothioacetyl (S)-proline ester **16** (*Scheme 7*) a systematic investigation on chiral induction in thio-Claisen rearrangement on systems similar to the one above was planned.

In the first place, it was evident that the S-allyl derivative **17** involved a push-pull ethylene system in a [3,3] frame work. This led us to suspect the possible role of the push-pull effect in facilitating the rearrangement. Interestingly, other such facile thio-Claisen rearrangements reported in the literature [10] also involve push-pull systems in the vinylic part of the [3,3] framework. It was therefore decided to study the rearrangement of other molecules having a push-pull ethylene system as part of the [3,3] sigmatropic framework. The aim was to study compounds obtained by replacing the nitro group in **16** with other electron withdrawing groups such as nitrile, carbonyl, etc. Secondly, in order to assess the effect of the chiral auxiliary on the degree of diastereoselectivity, easily available chiral aminoacids and amines etc. were planned to be used as donor groups in the push-pull ethylene moiety.

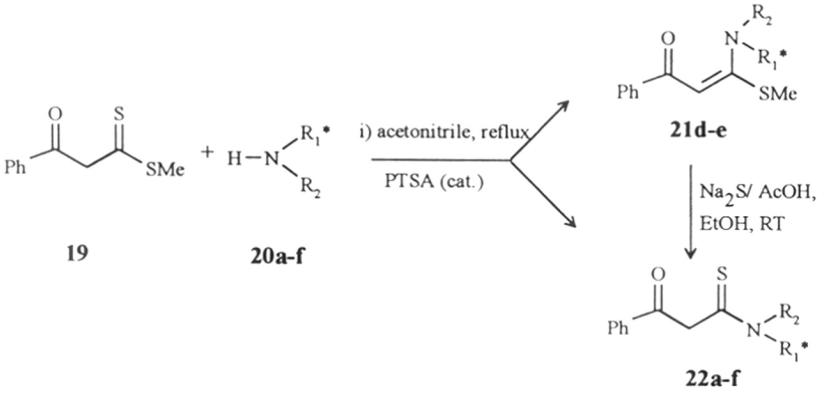
In this chapter, the results of allylation of benzoylthioacetamides **22a-f** (*Scheme 8*) to yield S-allyl intermediates **23a-f** and subsequent thio-Claisen rearrangement of these intermediates to C-allyl products **24a-f** are described. However, the scope of this investigation was restricted due to two factors : Attempts to prepare other β-keto thioamides in which the benzoyl group was replaced by cyclohexanone, cyclopentanone or propiophenone failed. Also, many primary and secondary chiral amines either failed to give the required benzoylthioacetamides such as **22** or the resultant benzoylthioacetamide failed to undergo subsequent reaction.

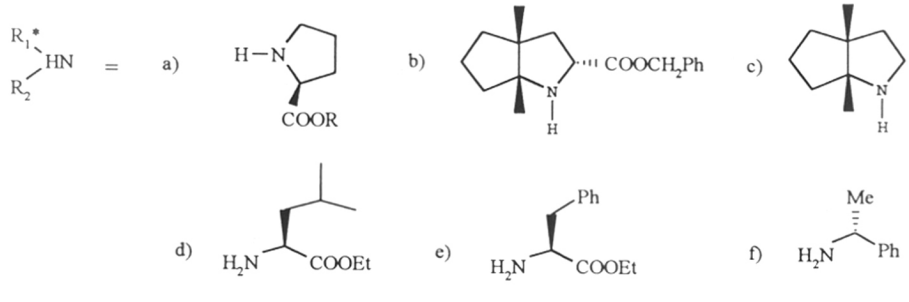
3. Results and Discussion

As mentioned earlier, the objectives of this study were two-fold : i) to find out whether the push-pull effect was responsible for the ease with which the compound **17** underwent the thio-Claisen rearrangement, and ii) to study the effect of various chiral amines in acheiving remote stereocontrol in this process. In order to achieve this, both the acceptor and donor groups in **17** were modified.

The initial target substrate was **23**, a push-pull ethylene similar to **17**, in which the nitro group has been replaced by a carbonyl. This could obviously be prepared from the benzoylthioacetamides **22**. A series of such chiral benzoyl thioacetamides in which the amine part was derived from various chiral amines and aminoacid esters was synthesised as shown in *Scheme 8*.

Scheme 8





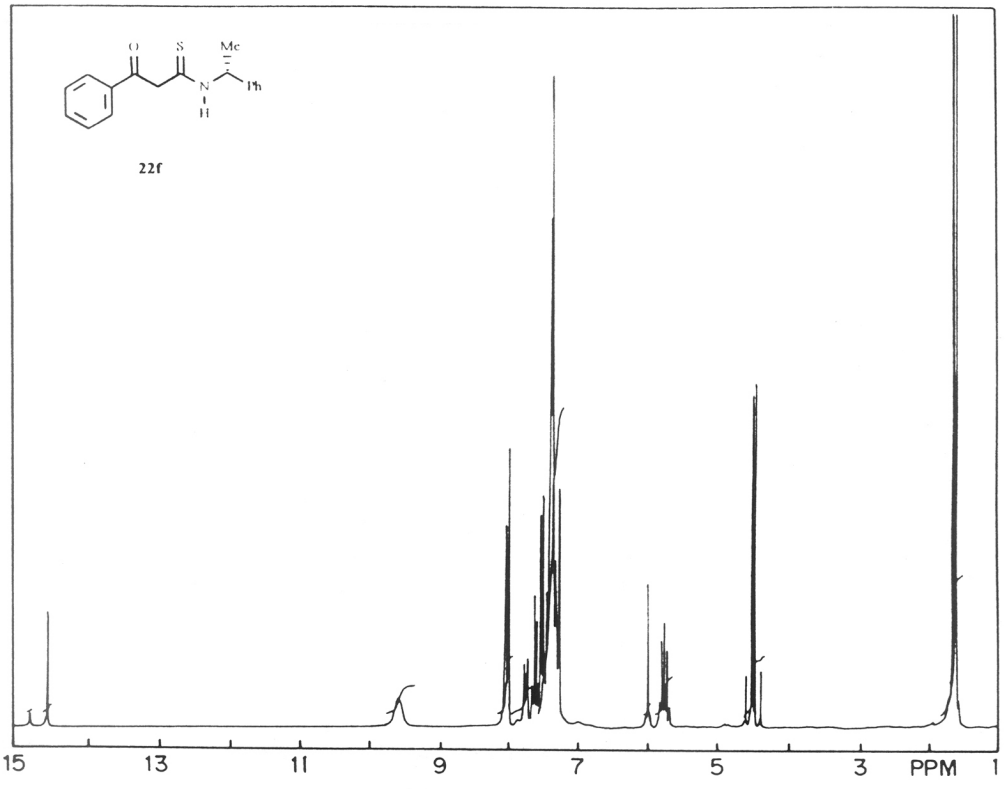
3.1 Synthesis of benzoylthioacetamides

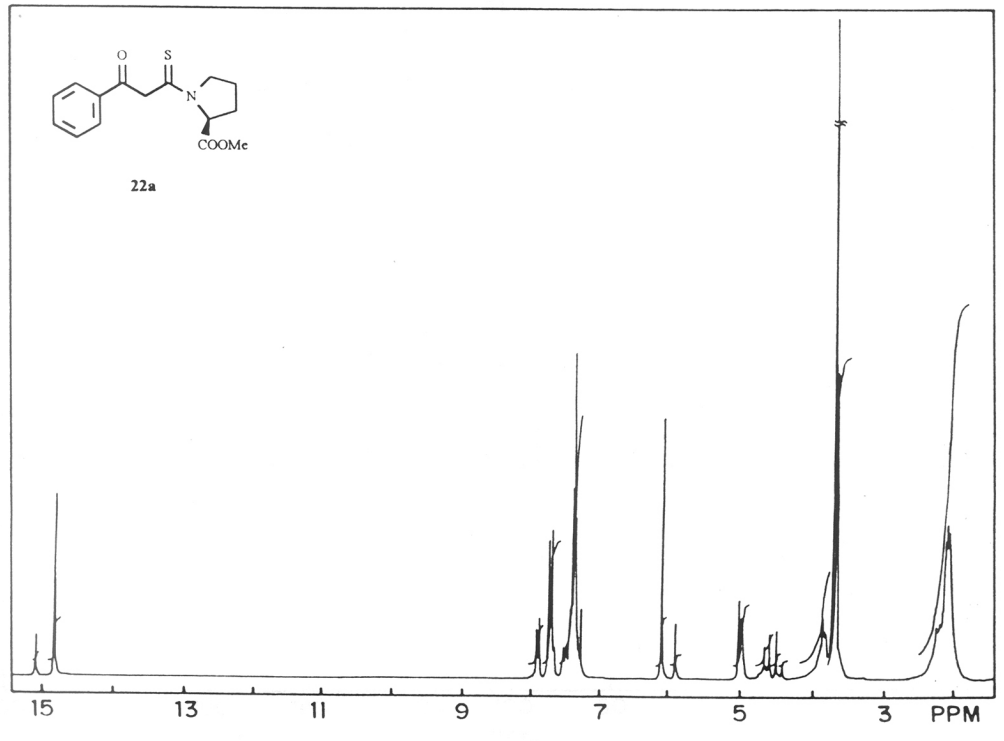
The required benzoylthioacetamides **22a-f** were obtained by refluxing the respective chiral amine **20a-f** with benzoyldithioacetic ester **19** in the presence of a catalytic amount of PTSA in acetonitrile. The starting benzoyldithioacetic ester **19** was obtained by a known procedure.[11] When the secondary chiral amines **20a-c** were used in the above reaction, they directly afforded the required benzoylthioacetamides **22a-c** in good yields. But primary amines, with the exception of α-phenylethylamine **20f**, first afforded the ketene-S,N-acetals **21d** and **21e**, which were converted to benzoylthioacetamides **22d** and **22e** by a procedure developed in our group. This involved replacement of thiomethyl group by SH group.

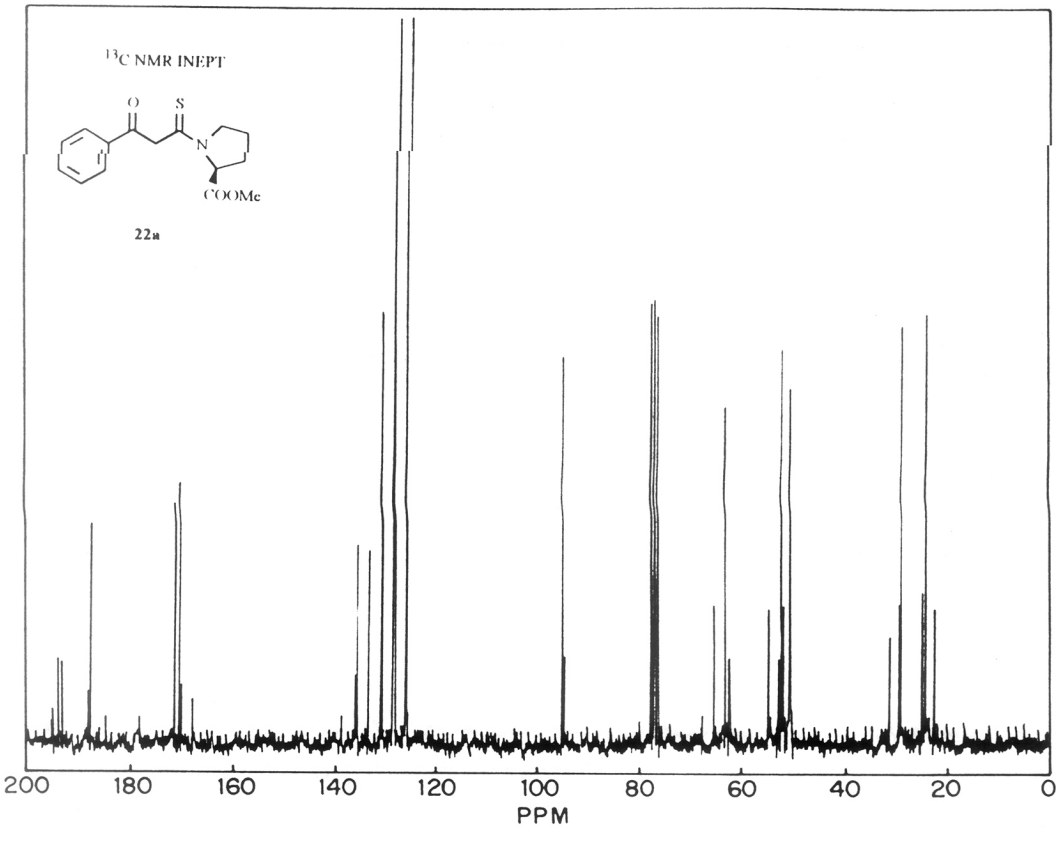
In a typical procedure for converting ketene S,N-acetal **21** to benzoylthioacetamide **22**, a mixture of ketene-S,N-acetal **21**, dry acetic acid (2 moles per mol of **21**) and finely powdered sodium sulfide (1.5 mol per mol of **21**) was stirred in dry ethanol at room temperature; the progress of the reaction was monitored by TLC . On completion of the reaction, ethanol was removed under vacuum. The residue so obtained was shaken with chloroform, the insoluble solid was filtered and the chloroform was evaporated to afford benzoylthioacetamide **22** on purification by column chromatography.

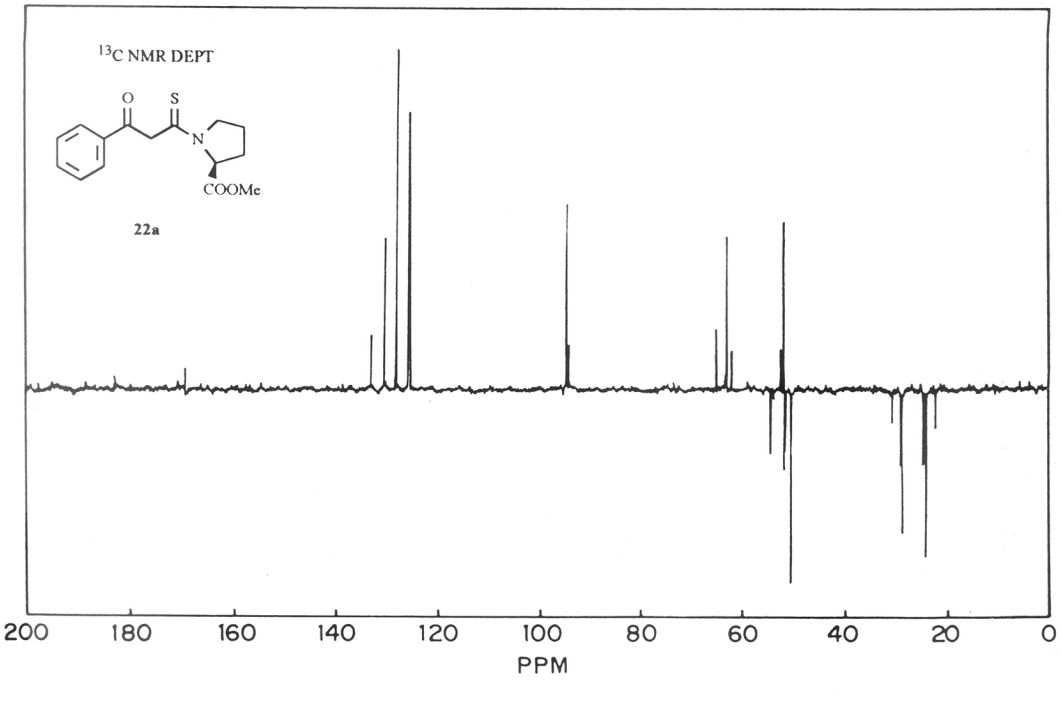
The benzoylthioacetamides **22a-f** were characterized by ^{1}H NMR, ^{13}C NMR and IR spectroscopy. However, satisfactory microanalysis could not be obtained in most of the cases, due to the known propensity of the thiocarbonyl group to undergo rapid decomposition. The relevant spectral data are discussed in the following paragraphs.

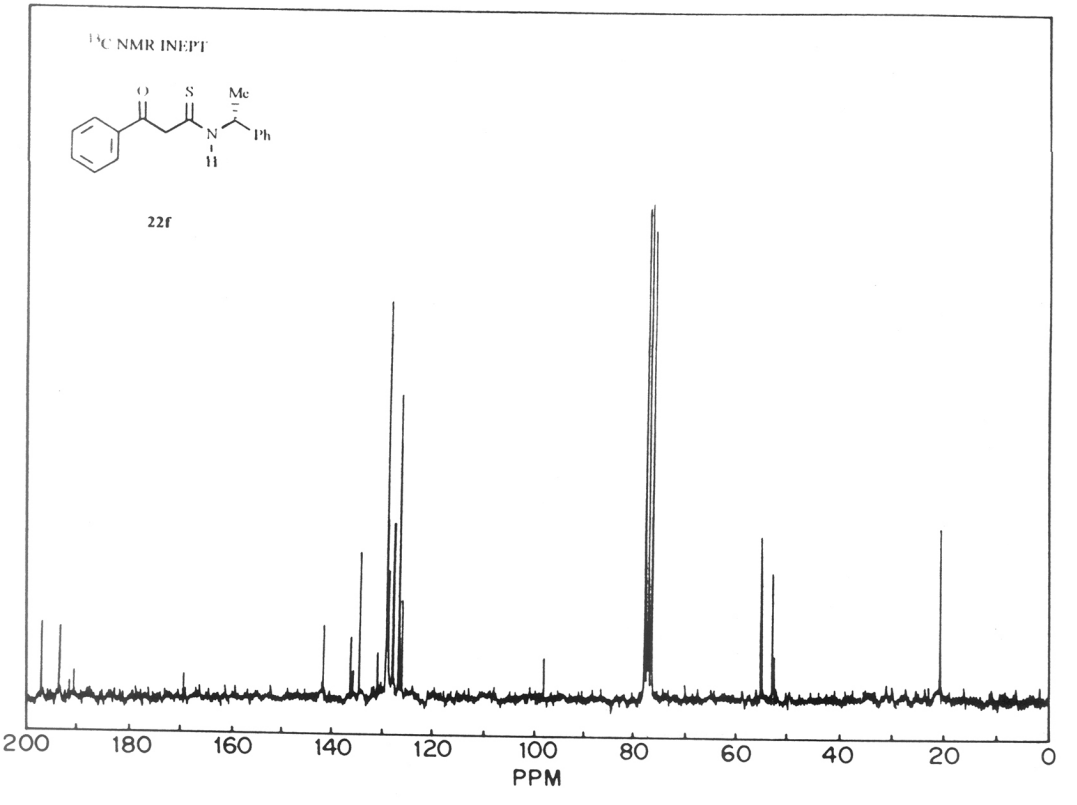
The most striking feature, characteristic of all the benzoylthioacetamides **22a-f** was the presence in the ^{1}H NMR spectra of two peaks in the region of 14-15 δ and two matching peaks in the region around 6 δ. The integration for the above peaks in both the regions was the same, suggesting that they belonged to the same species. This species could be the enethiol **B** or the enol **C** tautomer of the thioacetamide **A** (*Fig.1*). The existence of the thioacetamides **22** in enethiol/enol-form was expected as similar compounds and even the starting dithioester **19** are known to exist in such tautomeric forms. However, the integration for the rest of the peaks in the ^{1}H NMR spectra clearly

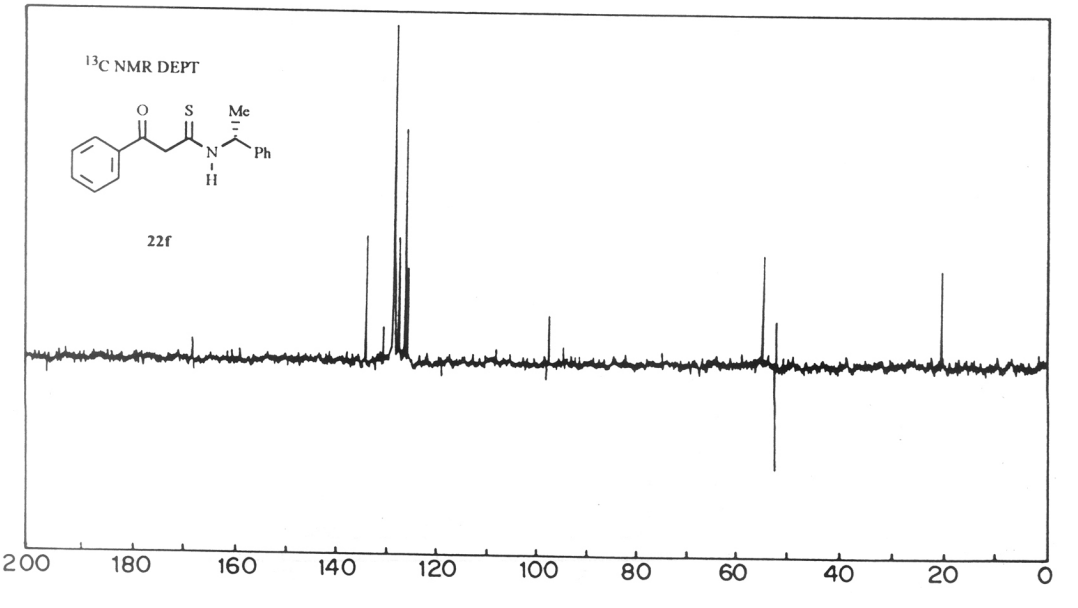

O
S
Me
N
H
Ph
22f
15
13
11
9
7
5
3
PPM

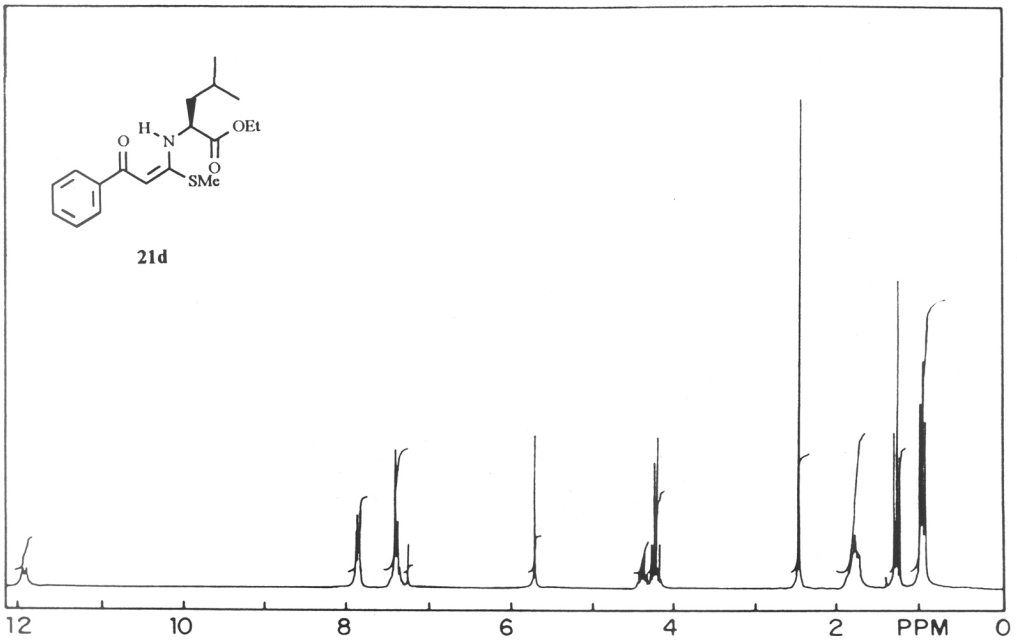

O
S
N
COOMe
22a
15
13
11
9
7
5
3
PPM


^{13}C NMR INEPT
O
S
N
COOMe
22a
200
180
160
140
120
100
80
60
40
20
0
PPM

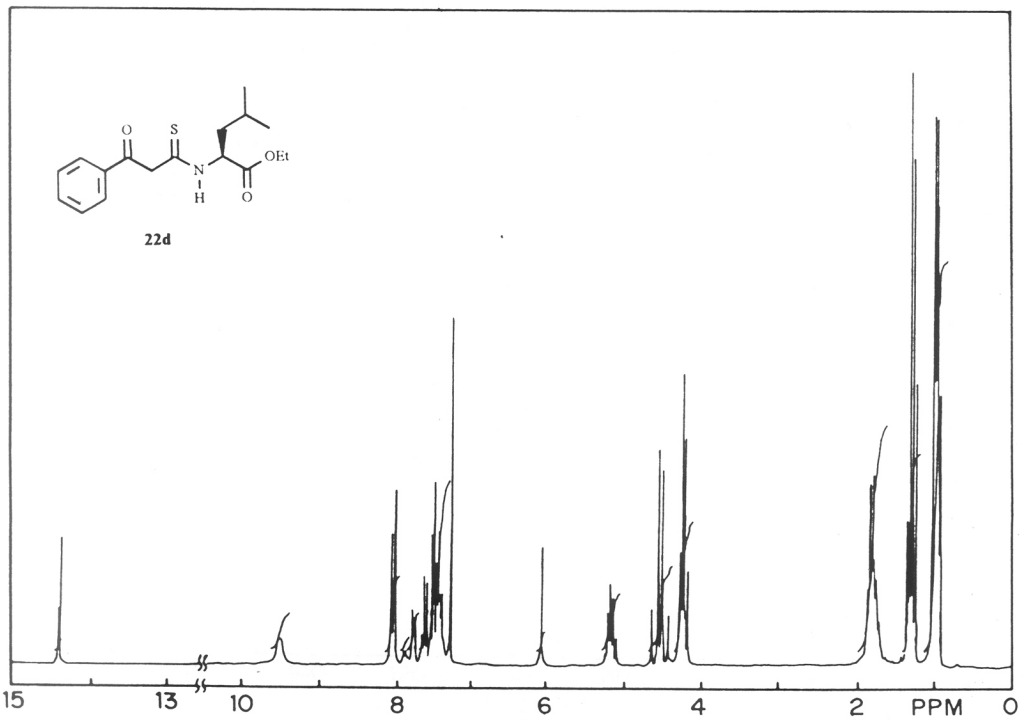

^{13}C NMR DEPT
O
S
N
COOMe
22a
200
180
160
140
120
100
80
60
40
20
0
PPM


13C NMR INEPT
O
S
Me
N
H
Ph
22f
200
180
160
140
120
100
80
60
40
20
0
PPM

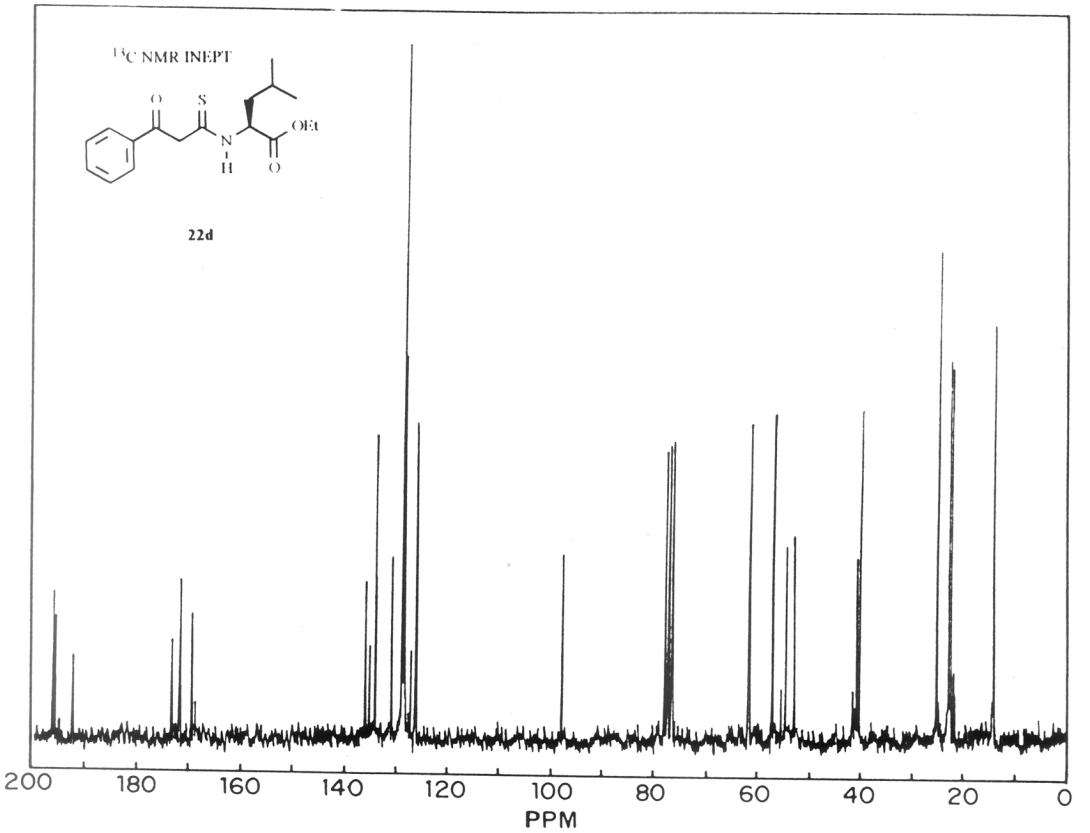

13C NMR DEPT
O
S
Me
N
H
Ph
22f
200
180
160
140
120
100
80
60
40
20
0

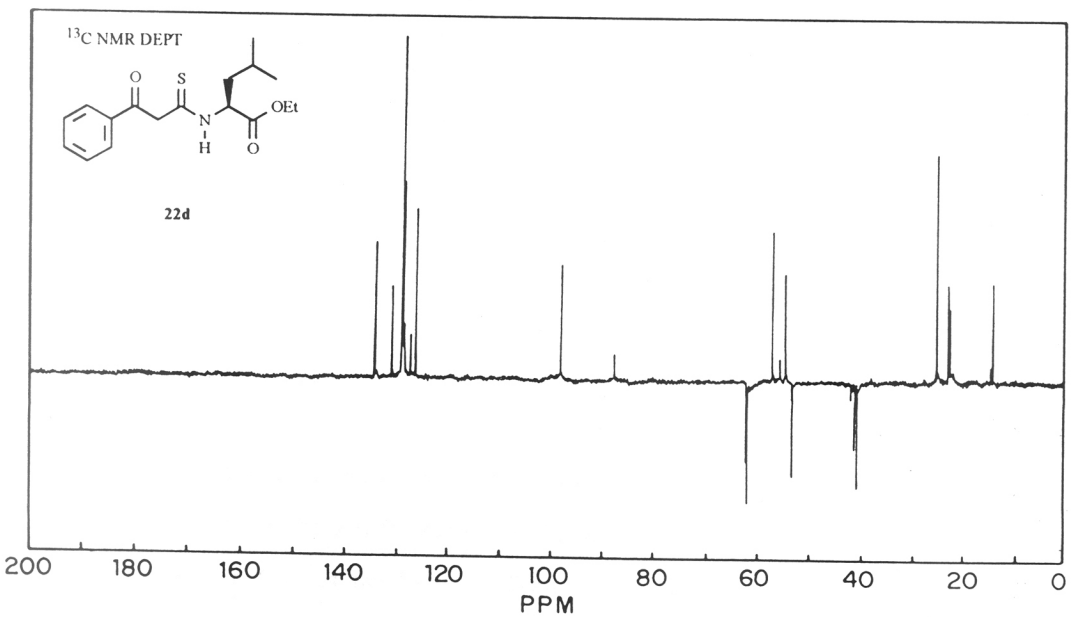


21d



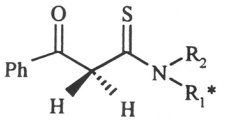
22d


^{13}C NMR INEPT
O
S
OEt
N
H
O
22d
200
180
160
140
120
100
80
60
40
20
0
PPM


^{13}C NMR DEPT
O
S
OEt
N
H
O
22d
200
180
160
140
120
100
80
60
40
20
0
PPM

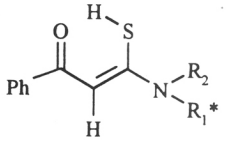
indicated the existence of the β-keto thioamide form (**A**) as well (*Fig 1*). The methylene protons of this tautomer formed an AB quartet pattern. Since the thioacetamides **22a-f** are chiral due to the presence of chiral auxiliaries, the two methylene protons are rendered diastereotopic and hence such an AB quartet pattern is observed

Fig. 1



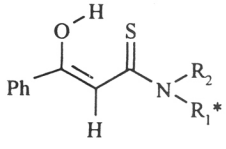
22A

β-keto-thioamide



22B

β-keto-enethiol



22C

enol

The relative amounts of the tautomers **A** and **B** or **C** in the various benzoylthioacetamides **22** are shown in *Table 1*. It was clear that benzoylthioacetamides **22a-c** derived from chiral *sec*-amines existed mainly in the enol form (**B/C**), whereas those derived from primary chiral amines preferred the keto-thione form **A**.

Table 1

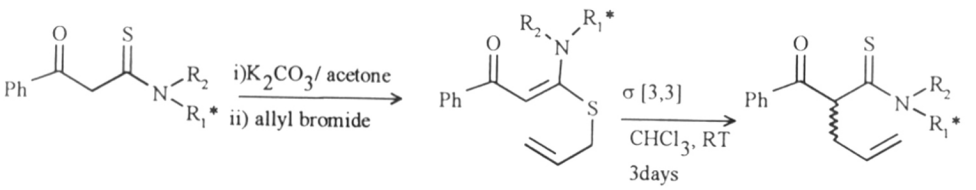
Compound	**B/C : A**
22a	3 : 1
22b	3.5 : 1
22c	1 : 0
22d	1 : 1.5
22e	1 : 1.8
22f	1 : 2.5

3.2 Allylation and rearrangement of benzoylthioacetamides 22

Allylation of benzoylthioacetamides by means of allyl bromide was carried out in acetone with K_2CO_3 as the base to afford initially, the S-allylated product **23**. This rearranged at room temperature in chloroform to the C-allylated product **24** (*Scheme 9*). In

a typical procedure, the benzoylthioacetamide (5 mmol) was dissolved in acetone (30 ml). To this stirring solution, K_2CO_3 (6 m mol) was added followed by allyl bromide (6 m mol) after ten minutes. On addition of K_2CO_3, the colour of the solution changed from yellow to faint orange but was restored to the original colour on addition of allyl bromide. After completion of the reaction (monitored by TLC), the reaction mixture was filtered, solvent evaporated to get the crude product. The crude product was column chromatographed to yield mainly the S-allylated product **23** with some amount of the C-allylated product **24**. This mixture which mainly contained the S-allyl compound, was allowed to stand at room temperature for 3 days in the NMR tube, when the [3,3] sigmatropic rearrangement was found to have gone to completion, yielding the product **24**. The diastereoselectivity of the above rearrangement was determined by measuring the intensities of the peaks in the ^1H NMR and ^{13}C NMR spectra of the product. The diastereoselectivity of the rearrangement and the relevant spectral features of the S-allylated and C-allylated products are discussed for the individual cases in the following paragraphs.

Scheme 9



22a-f **23a-f** **24a-f**

3.2a Allylation and Rearrangement of 22a

Thioacetamide **22a**, methyl N-(benzoylthioacetyl)-(S)-prolinate, was subjected to allylation as described in the general procedure. The progress of the reaction was monitored by TLC which showed the appearance of two new spots close to each other, one much more intense than the other. The two products corresponding to these spots were

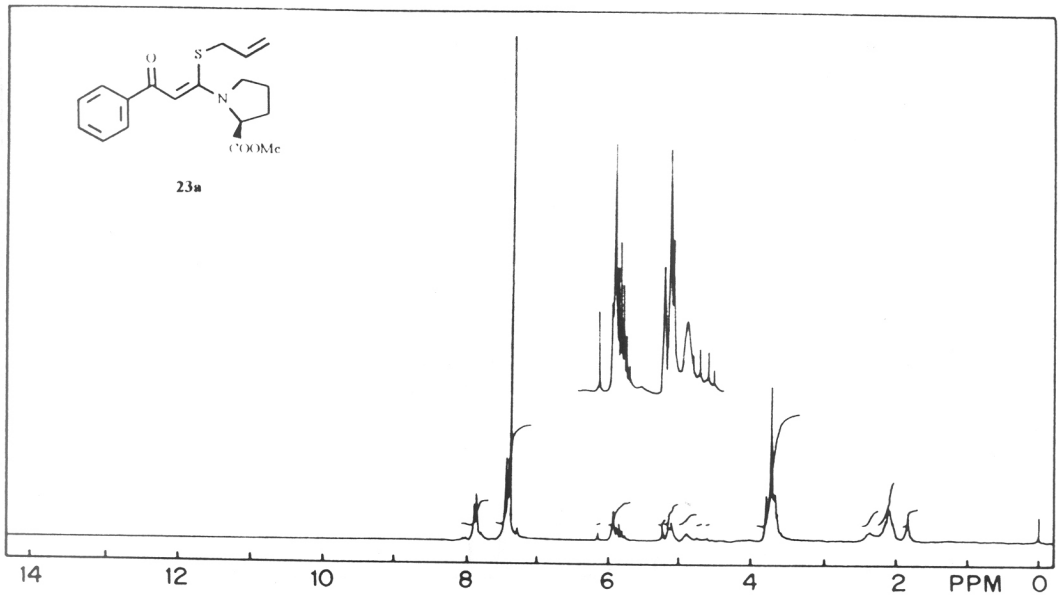
separated by a quick column chromatography. But the product corresponding to the more intense spot once again showed a faint spot on TLC corresponding to the earlier, less intense spot. This clearly indicated that the major product of allylation **23a** was undergoing transformation to **24a**, by a thermal [3,3] sigmatropic rearrangement (*Scheme 9*). This assumption was indeed found to be true when the structures of the two products were determined by ^{1}H NMR spectrum. The column chromatographed product showed two sets of peaks in the ^{1}H NMR spectrum as follows :

Set.I, δ 2.0 - 2.2 (m, 4H, CH_2-CH_2), 3.55 - 3.80 (m, 7H, NCH_2, S-CH_2, OCH_3), 4.90 (m, 1H, N-CH), 5.15 (m, 2H, H_2C=), 5.75 - 5.95 (m, 1H,HC=), 5.95 (s, 1H, H-C=C-S), 7.40 (m, 3H, PhCO), 7.85 (m, 2H, PhCO),

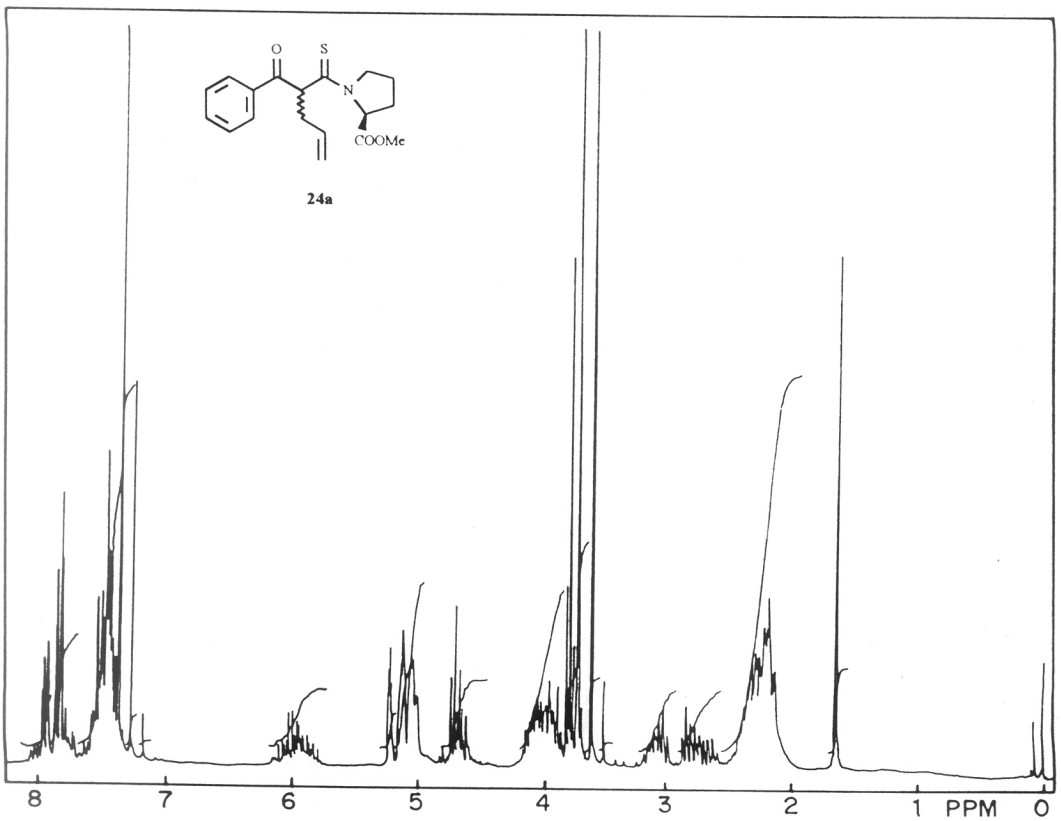
Set II, δ 2.0-2.5 (m, 4H, CH_2=CH_2), 2.6 - 3.2 (m, 2H, CH_2-C=C), 3.70 (s, 3H, OCH_3), 4.0 (m, 2H, NCH_2), 4.7 (dd, 1H, HC=C=S), 4.95-5.25 (m, 3H, H_2C=, HC-N), 5.95 (m, 1H, HC=), 7.4 (m, 3H, PhCO), .78 (m, 2H, PhCO).

Though most of the peaks in the above two sets were overlapping, thus presenting difficulty in identification of the peaks, the olefinic proton at 5.95 δ in Set I was seen as a singlet. This peak could have resulted only from the S-allylated compound **23a** ; the possibility of this peak belonging to the starting thioacetamide **22a** was ruled out by the fact that the olefinic peaks for form **B** and **C** of **22a** (*Fig 1*) were not seen at 6.10 δ and 6.30 δ ; nor were the characteristic peaks at 15 δ observable in the spectrum. This clearly established that the peaks in Set I belonged to the S-allylated product **23a**. Further, when the above sample containing the product mixture was allowed to stand in the NMR tube at room temperature for 3 days and the spectrum recorded once again, peaks belonging to Set I disappeared with concomitant appearance of Set II peaks. This change was also noticed in the TLC .

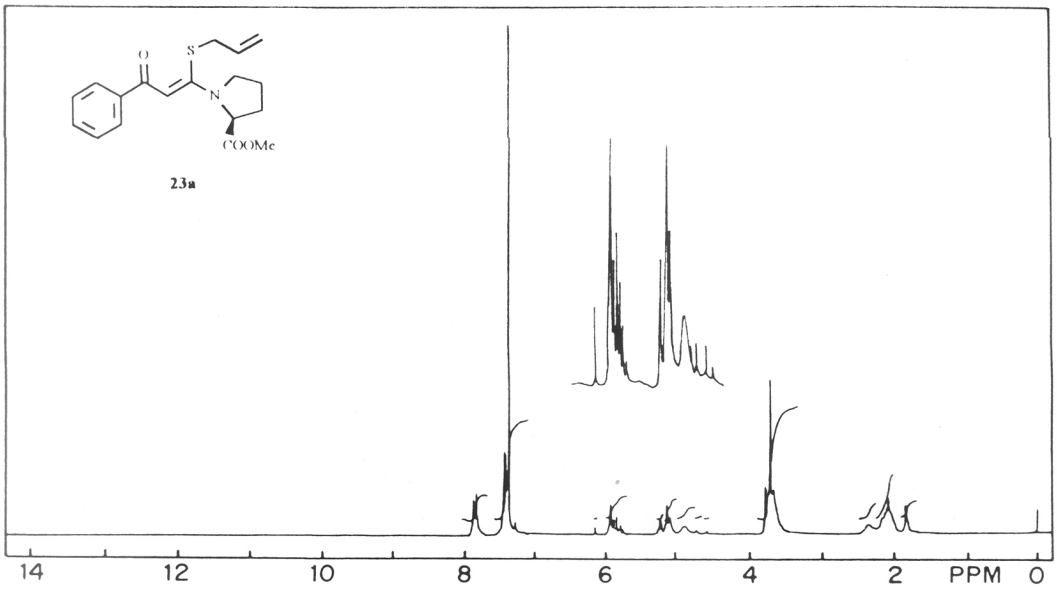
The C-allyl compound **24a** was responsible for the observed ^{1}H NMR peaks in Set-II. Especially noteworthy was the splitting pattern of the two protons of the allylic methylene group at the 2.6 to 3.2 δ. There were 16 lines in all, separated into two sets of 8 lines each in a symmetrical pattern. The 8 line-set for each proton arose out of spin-coupling with the geminal proton as well as with the vicinal protons. Since the two protons



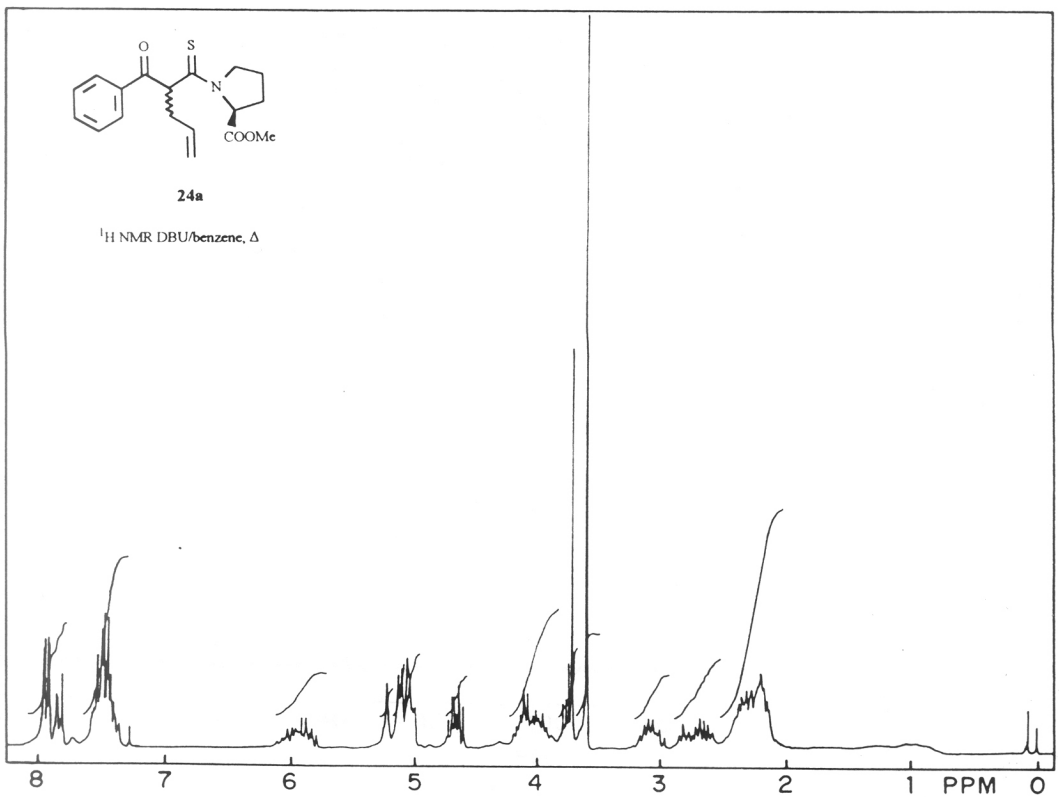
23a



24a

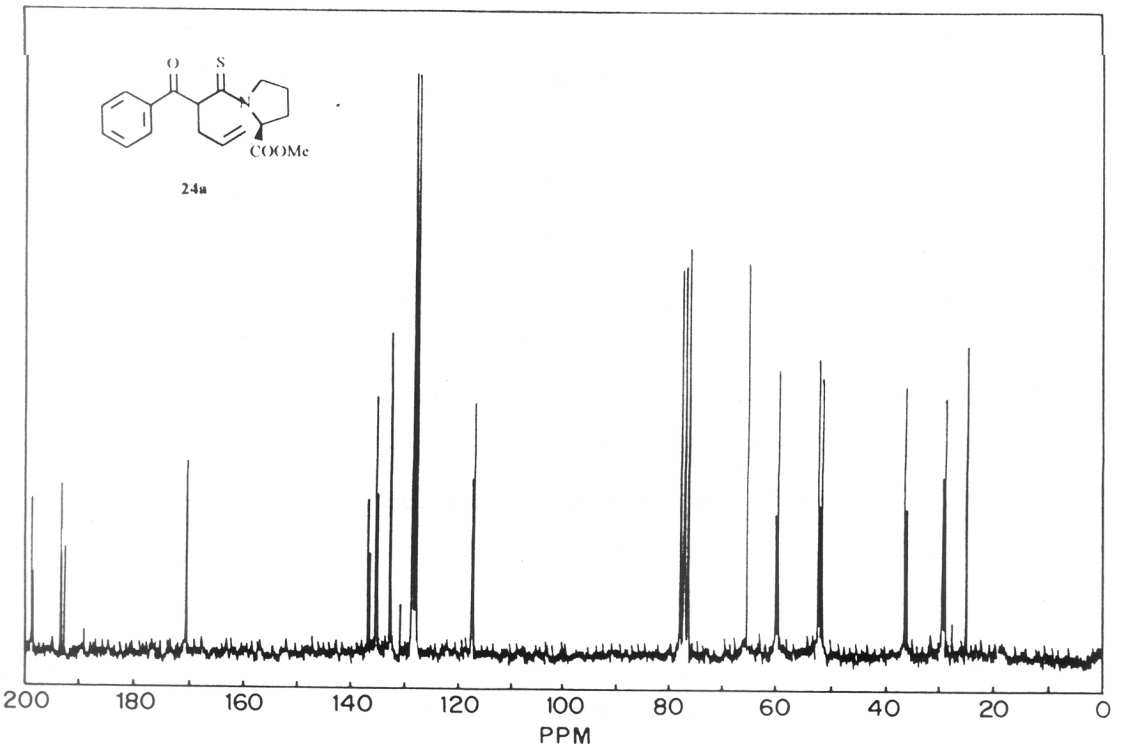


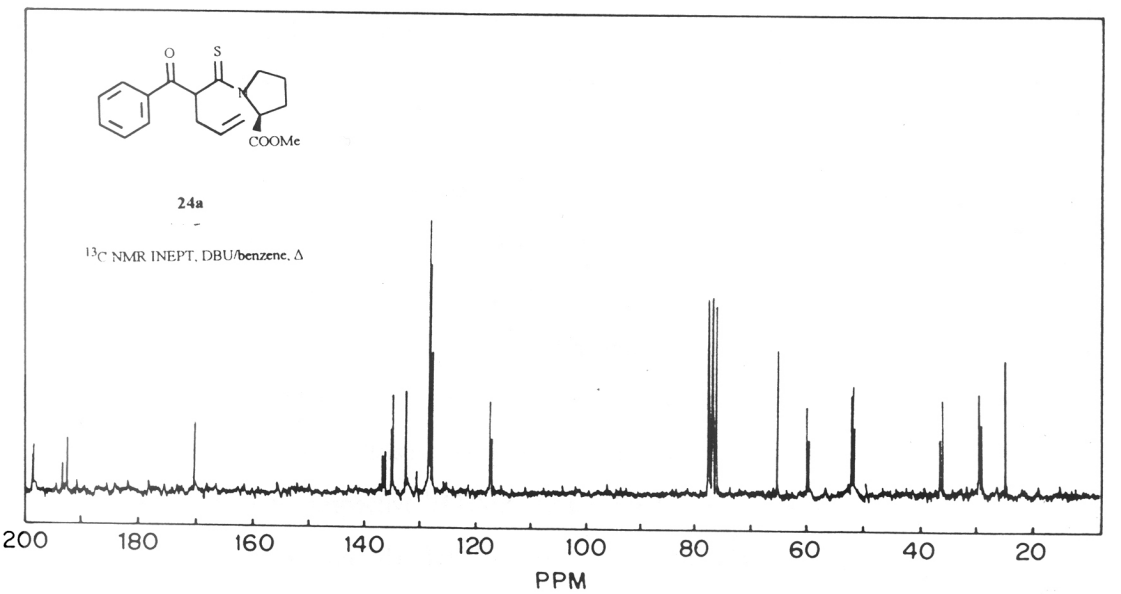
23a



24a

^{1}H NMR DBU/benzene, Δ


O
S
N
COOMe
24a
200
180
160
140
120
100
80
60
40
20
0
PPM


O
S
N
COOMe
24a
^{13}C NMR INEPT, DBU/benzene, Δ
200
180
160
140
120
100
80
60
40
20
PPM

of the allylic CH_2 are diastereotopic, there is a chemical shift difference, giving rise to the observed 16 line pattern.

There were also other peaks in the ^1H NMR spectrum of the product apart from those mentioned above as set-II. These peaks were assigned to the minor second diastereomer of **24a** arising from the creation of the new chiral centre. However, none of these signals could be used for estimating the diastereomeric excess (*de*) since they were not sufficiently well-separated from those of the major diastereomer.

The diastereomeric excess in this case was determined by taking the average of peak heights of the well separated ^{13}C NMR signals of the particular carbon atoms for both the diastereomers. The diastereomeric excess was found to be 33 %. The ^{13}C signals used for determining the diastereomeric excess were those at 36.60 and 36.10 ppm $\mathbf{C}H_2$-C=C; 59.6 and 60 ppm of **C**-C=S and 198.9 and 198.5 ppm of **C**=S.

The diastereoselectivity obtained in the above experiment arose out of kinetic control. Equilibration of this diastereomeric mixture in DBU/benzene reflux resulted in the reversal of the diastereomeric excess to 20% in favor of the other diastereomer as was evident from the change in the relative peak intensities both in ^1H NMR and in ^{13}C NMR spectra. Thus it was shown that thioacetamide **22a** on allylation gave S-allyl product **23a** which undergoes thio-Claisen rearrangement to give C-allylated product **24a** with reasonable diastereoselectivity.

3.2b Allylation and rearrangement of 22b

Thioacetamide **22b** was subjected to allylation under the conditions described previously for **22a**. As in the previous case, TLC of the reaction mixture showed the appearance of two new spots which were separated by column chromatography to yield the S-allyl compound **23b** as the major product along with some C-allylated product **24b** as a consequence of thio-Claisen rearrangement. Structures of product **23b** and **24b** were deduced from the respective ^1H NMR spectra. The two sets of peaks are

Set I, δ 1.5-3.1 (m, 9H, 4=CCH_2, HC), 3.5-3.8 (m, 2H, S-CH_2), 4.4 (m, 2H, N-CH-C=O N-CH), 4.95 -5.25 (m, 4H, SCH_2Ph, H2C=), 5.8 (m, 1H, HC=), 5.97 (s, 1H, HC=C-S), 7.25 -7.75 (m, 8H, Ph, PhCO, 7.8 (m, 2H, PhCO)

Set II, δ 1.4 - 3.25 (m, 11H, 4 CCH_2, H_2C-C=S, H2C=), 4.65 (m, 2H, N-CH-C=O, HC-N), 4.95 - 5.25 (m, 4H, OCH_2Ph, H2C=), 5.8 (m, 1H, HC=), 7.25-7.75 (m, 8H, Ph, PhCO, 7.8 (m, 2H, PhCO).

Here again the assignment of Set I to **23b** and Set II to **24b** was done on the basis of the typical splitting pattern observed for the olefinic peak at 5.97 δ for the S-allyl product and the allylic methylene protons for the C-allylated product. Interestingly, the peak for SCH_2 methylene protons at 3.5 - 3.8 δ in Set I appeared as a symmetrical multiplet with 4 pairs of lines of unequal heights. This pattern is perhaps due to the presence of cisoid and transoid conformers of the S-allyl product **23b** about the C-N bond similar to the situation in N-acyl proline derivatives. The pattern would result from the two merged AB quartets belonging to the two conformers.

Unlike in the previous case, none of the signals due to the major diastereomer of the C-allyl product **24b** was sufficiently separated from the corresponding signal of the other diastereomer in the ^1H NMR spectrum. Therefore the diastereomeric excess in this case was determined by taking the average of ^{13}C NMR peak heights of a particular carbon atom of both the diastereomers (*Table 2*). The diastereomeric excess was found to be 58 %. The peaks in *Table 2* belong either to the asymmetric carbon atom or the carbon adjacent to the asymmetric carbon.

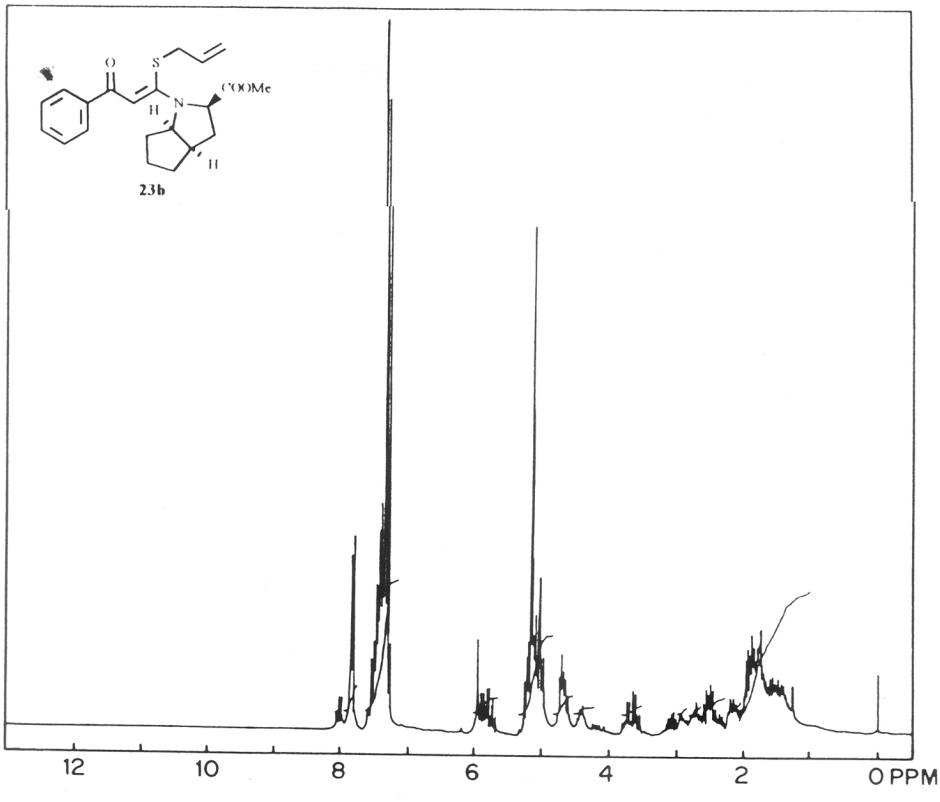
Table 2

diastereomer	H_2C-C*-COO	C*CH_2C*COO	C-C=O	Ph-C=O	C=S
Major	31.1	44.2	59.3	194.0	198.5
Minor	31.5	44.0	60.0	194.4	198.9

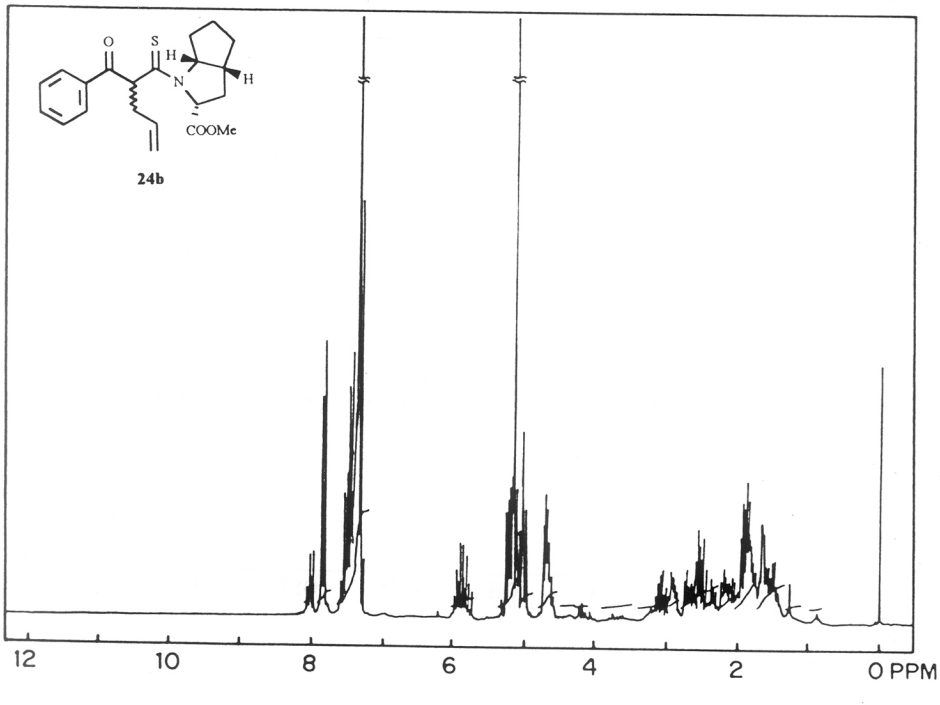
* Asymmetric carbon atoms of the chiral auxiliary.

3.2c Allylation and rearrangement of 22c

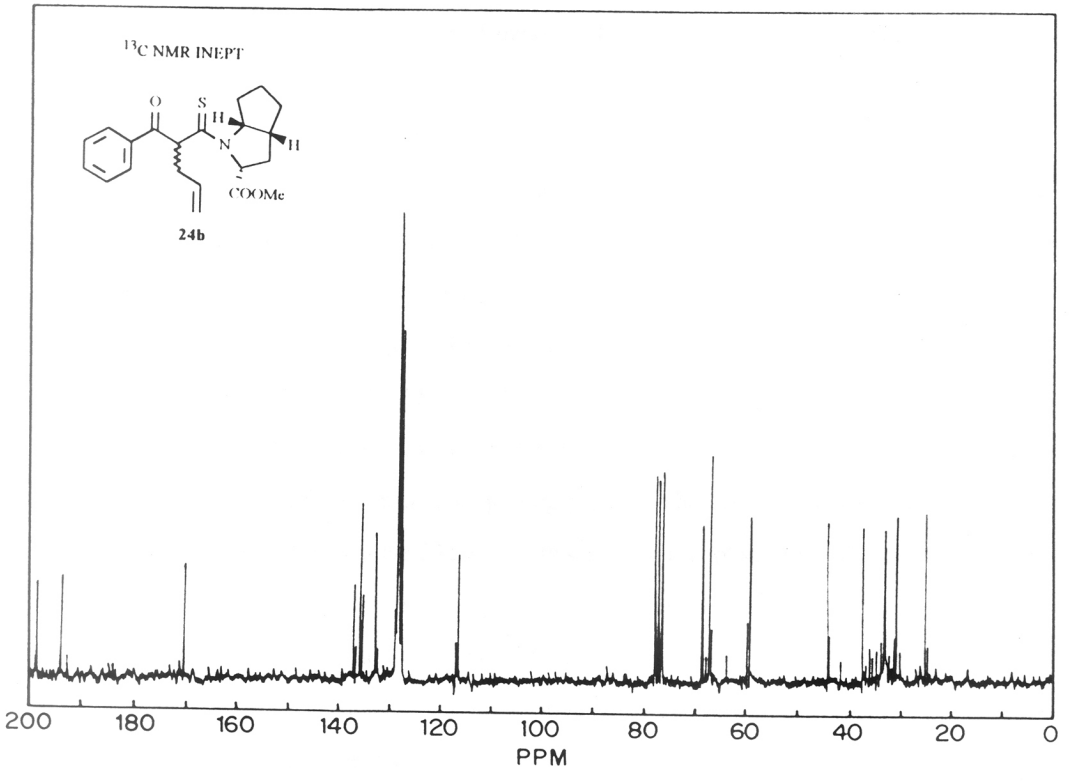
Allylation of thioacetamide **22c**, N-(benzoylthioacetyl)-(1R,SR)-2-azabicyclo-[3.3.0] octane, was carried out under exactly the same conditions as those for **22a** and **22b**. In this case also, two new spots were observed in the TLC. The allylation product was isolated by chromatography. As before, this was found to be a mixture of the S-allyl isomer

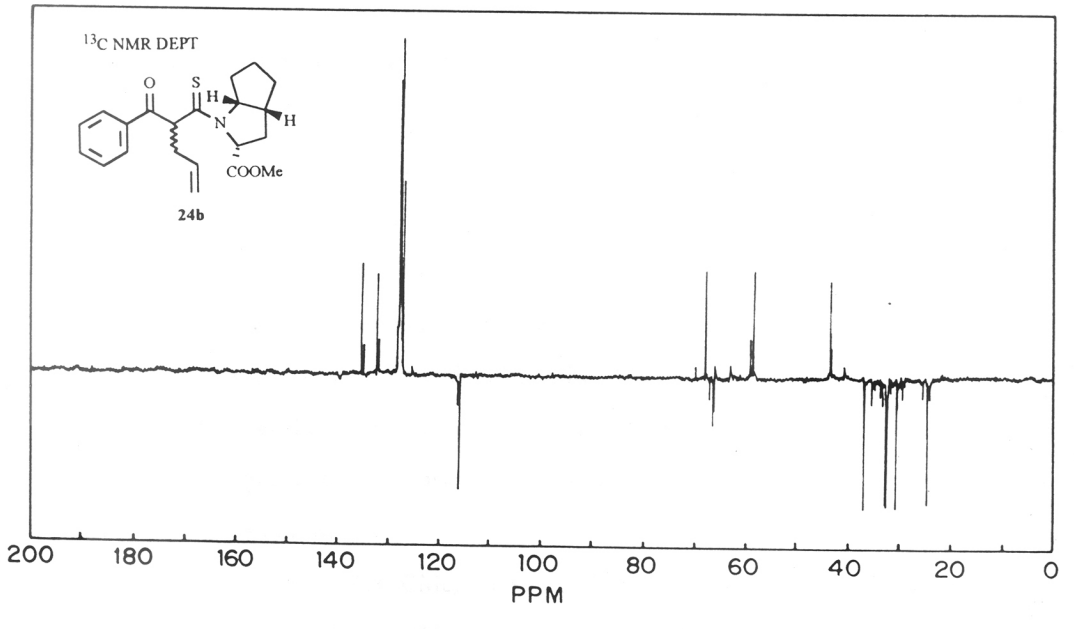


23b



24b


^{13}C NMR INEPT
O
S
H
N
H
COOMe
24b
200
180
160
140
120
100
80
60
40
20
0
PPM


^{13}C NMR DEPT
O
S
H
N
H
COOMe
24b
200
180
160
140
120
100
80
60
40
20
0
PPM

(major ; **23c**) and the C-allyl isomer (minor ; **24c**). The two sets of ^{1}H NMR peaks were as follows

Set I, δ 1.5 - 2.2 (m, 8H, $4CCH_2$), 2.76 (m, 1H, CH), 3.1 - 3.8 (m, 4H, NCH_2, S-CH_2), 4.45 (m, 1H, N-CH), 4.87-5.25 (m, 2H, H_2C=), 5.5-6.07 (m, 1H, HC=), 5.62 (s, 1H, HC=C-S), 7.25 (m, 3H, PhCO), 7.87 (m, 2H, PhCO).

Set II, δ 1.5-2.2 (m, 8H, $4CCH_2$), 2.5-3.7 (m, 3H, CH_2-C=C, CH), 3.5-4.25 (m, 2H, NCH_2), 4.5-4.9 (m, 2H, NCH, HC-C=S), 5.0-5.25 (m, 2H, H_2C=), 5.75-6.0 (m, 1H, HC=), 7.30 -7.55 (m, 3H, PhCO), 7.75-7.90 (m, 2H, PhCO).

The structures were deduced from the typical chemical shift of the protons in the ^{1}H NMR spectra as well as from the splitting pattern. The splitting pattern of the olefinic proton in the S-allyl derivative **23c** was quite similar to that observed in the case of **23a** and **23b**. Similarly, the splitting pattern of the allylic methylene protons in **24c** was similar to that in the case of **24a** and **24b.** The diastereomeric excess in **24c** was estimated from the ^{13}C NMR spectrum by determining the relative heights of the signals (*Table 3*). The *de* in this case was found to be 20 %.

Table 3

diastereomer	H_2**C**-C=C	CH_2-**C***-CH_2	N-**C***-C*	OC-**C**-CS	N-C-CH_2	Ph-C=O
Major	36.5	41.7	51.4	59.9	69.2	193.2
Minor	37.0	41.3	51.8	58.5	69.7	193.9

* Asymmetric carbon atoms of the chiral amine.

3.2d Allylation and Rearrangement of 22d

Allylation of thioacetamide **22d**, ethyl N-(benzoyl thioacetyl)-(S)-leucinate was carried out under the same conditions as those for **22a-c**. Isolation and subsequent product structure determination were also done in a similar manner. The two sets of ^{1}H NMR signals were as follows:

Set I, δ 0.8-1.0 (m, 6H, CMe_2), 1.35 (t, 3H, CH_3), 1.8 (m, 2H, CH_2), 3.65 (d, 2H, SCH_2), 1.8 (m, 1H, $HCCMe_2$), 4.2 (q, 2H, OCH_2), 4.95 -5.15 (m, 3H, H_2C=HC-N), 5.75 (m, 1H, HC=), 5.8 (s, 1H, HC=C-S), 7.35-7.50 (m, 3H,

PhCO), 7.85 (m, 2H, PhCO), 11.90 (bd, 1H, NH)

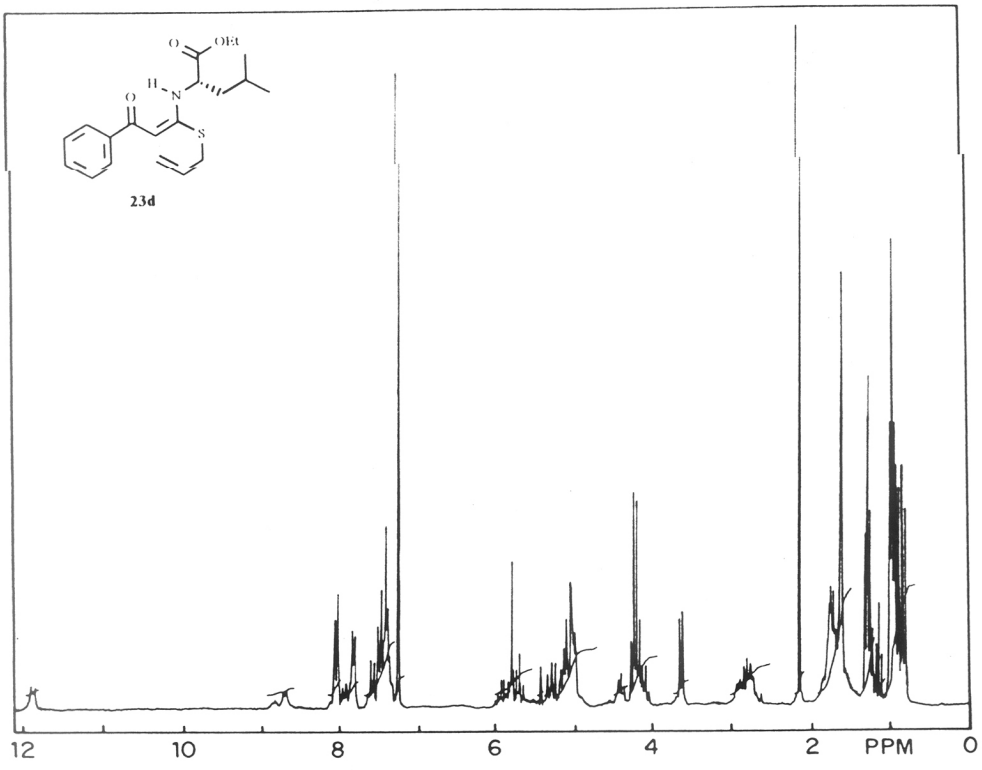
Set II, δ 0.8-1.1 (m, 6H, $CCMe_2$), 1.17 (t, 3H, CH_3), 1.6 (m, 1H, $HCCMe_2$), 1.7 - 1.9 (m, 2H, CH_2), 2.85 (m, 2H, H_2C-C=), 4.25 (q, 2H, OCH_2), 5.0 - 5.25 (m, 4H, H_2C=, HC-N, HC-C=S), 7.35-7.65 (m, 3H, PhCO), 8.10 (m, 2H, PhCO), 8.70 (bd, 1H, NH)

In this case assignment of structure **23d** to Set I and **24d** to Set II was easier than in the previous cases due to the presence of a proton on the nitrogen atom of the chiral auxiliary in the thioamide moiety. In the S-allyl product **23d** this was hydrogen-bonded to the oxygen of the benzoyl group, and hence occurred at lower field of 11.9 δ. As the rearrangement progressed to give the C-allyl product, two broad doublets at 8.7 and 8.9 δ started appearing for the NH which belonged to the two diastereomers of **24d**. It was obvious from the chemical shift position of the NH proton that the S-allyl product had *E*-geometry about the carbon-carbon double bond.

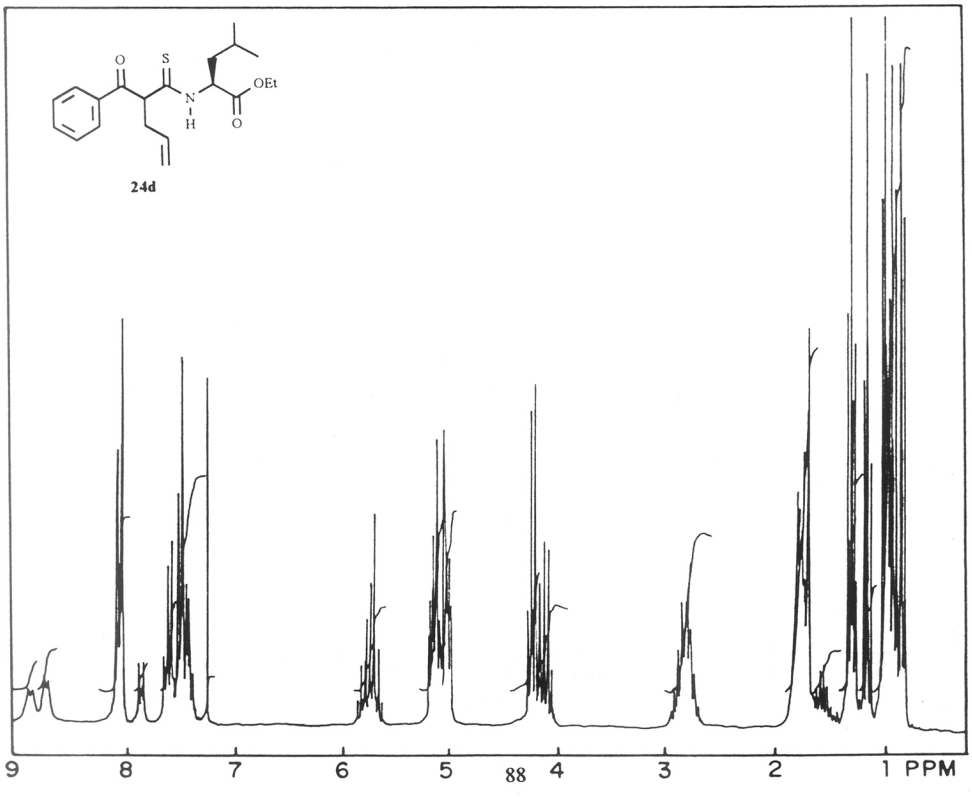
Here, the diastereomeric excess was determined by taking the average of the peak intensities in both ^{1}H NMR and ^{13}C-NMR spectra, both of which gave almost the same results. In the ^{1}H NMR spectrum of the C-allyl product **24d**, the quartet due to the methylene protons of the ester group and the broad doublet of the NH for the two diastereomers were well separated and were used for determination of diastereomeric excess. The *de* was found to be 18%. In the ^{13}C NMR spectrum, the signals at 39.2 and 39.5 ppm for the allylic carbon and those at 40.5 and 40.9 ppm the β-carbon of the leucine moiety, corresponding to the major and minor diastereomers were used for the estimation of *de* . The *de* was found *15* % in this estimation. Thus the results obtained from both the ^{1}H and ^{13}C NMR were in agreement within experimental error.

3.2e Allylation and rearrangement of 22e

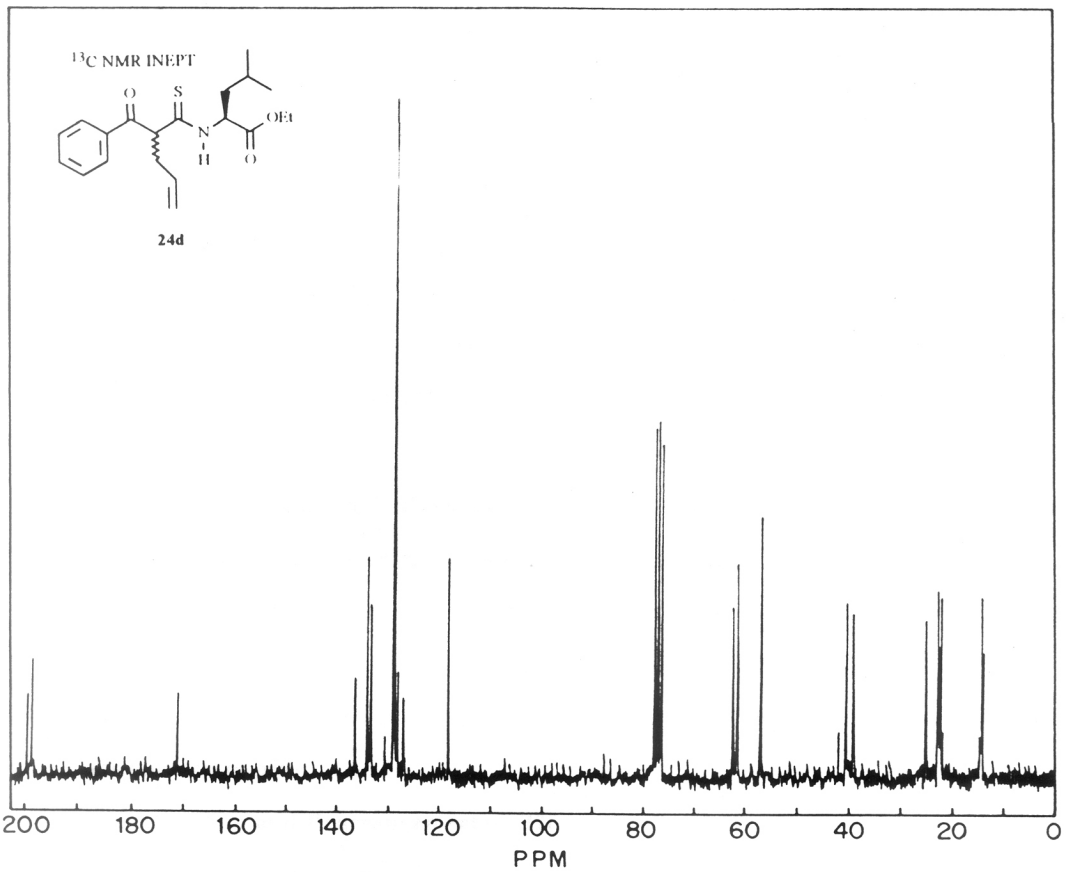
Thioacetamide **22e**, ethyl N-(benzoylthioacetyl)-(S)-phenylalaninate, was subjected to allylation under the standard conditions to give the S-allyl product **23e**. This was rearranged to the C-allyl product **24e** under the same conditions as described in the previous cases. The two sets of ^{1}H NMR peaks were as follows :

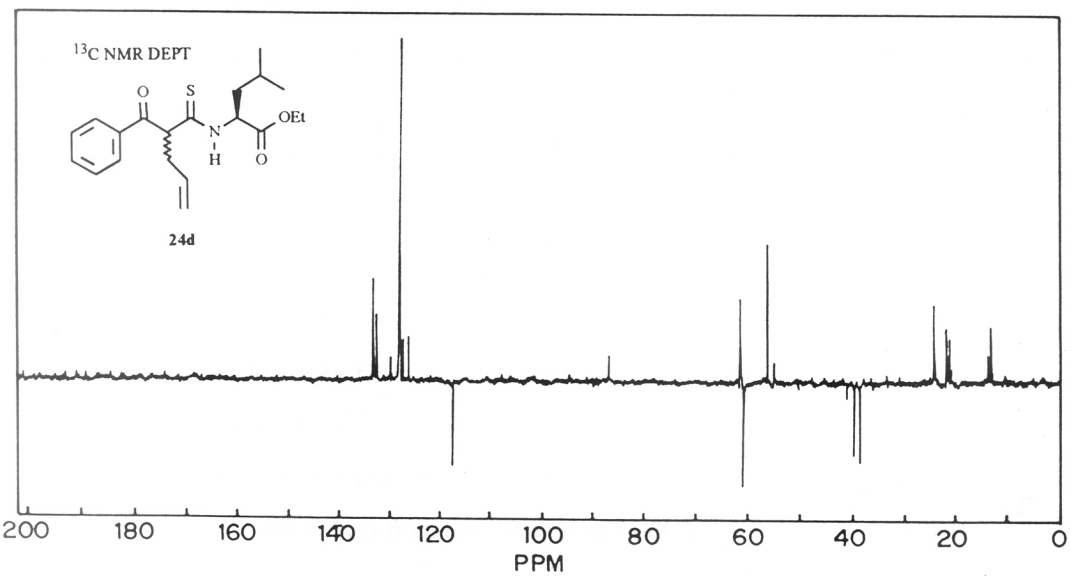


23d



24d


^{13}C NMR INEPT
O
S
OEt
N
H
O
24d
200
180
160
140
120
100
80
60
40
20
0
PPM


^{13}C NMR DEPT
O
S
OEt
N
H
O
24d
200
180
160
140
120
100
80
60
40
20
0
PPM

Set I, δ 1.35 (t, 3H, CH_3), 3.40 (m, 2H, CH_2Ph), 3.72 (d, 2H, S-CH_2), 4.32 (q, 2H, OCH_2), 5.2 (m, 1H, HC-N), 5.3 (m, 2H, H2C=), 5.8 (m, 1H, HC=), 5.95(s, 1H, HC=C-S), 7.4 (m, 5H, Ph), 7.6 (m, 3H, PhCO, 8.0 (m, 2H, PhCO), 12.2 (bd, 1H, NH)

Set II, δ 1.17 (t, 3H, CH_3), 2.55 (m, 2H, H_2C-C=), 3.10-3.45 (m, 2H, CH_2Ph), 4.15 (q, 2H, OCH_2), 4.85-5.15 (m, 2, H_2C=), 5.27 (m, 1H, HCN), 5.7 (m, 1H, HC=), 7.10-7.35 (m, 5H, Ph), 7.55 (m, 3H, PhCO), 8.07 (m, 2H, PhCO), 8.92 (bd, 1H, NH)

For these compounds also structure assignment was quite easy, since an NH group was present which could form a hydrogen bond with the C=O.

The diastereomeric excess was determined from the integration of the signals at 1.17 and 1.30 δ assigned to the methyl protons of the ester group and those at 8.92 and 8.65 δ assigned to the NH protons of the major and minor diastereomers respectively; it was found to be 5%

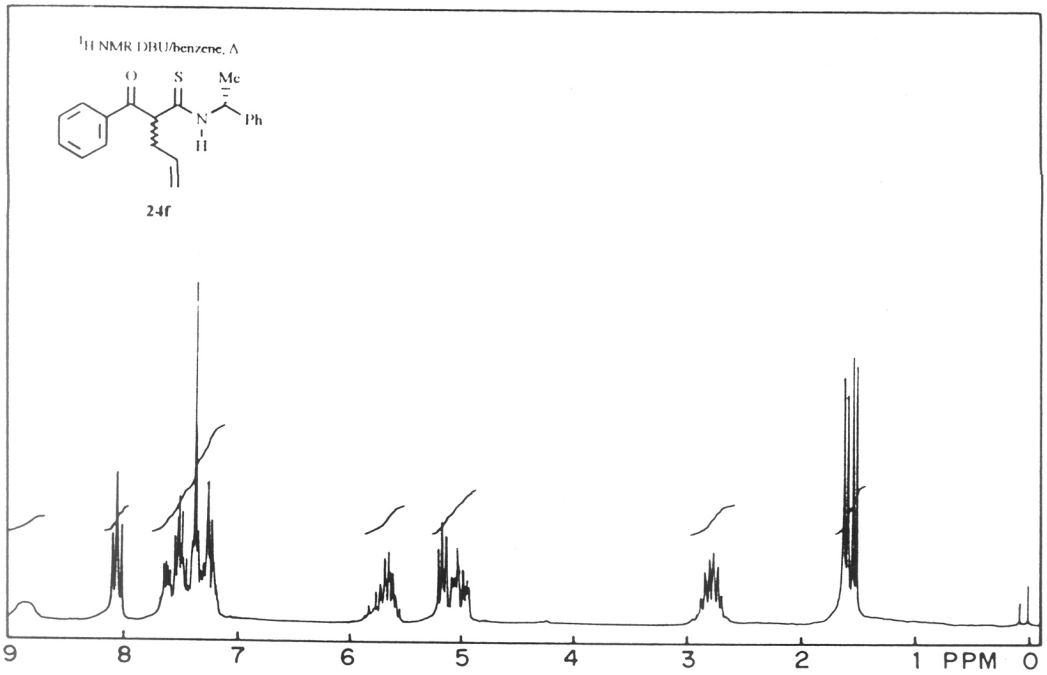
3.2f Allylation and Rearrangement of 22f

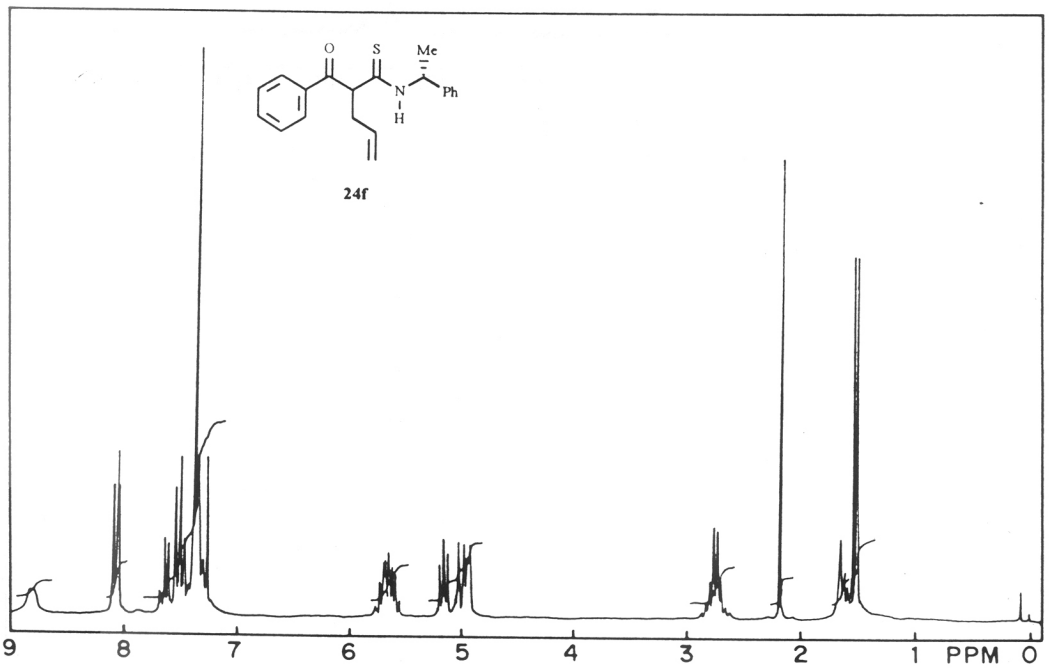
Thioacetamide **22f**, N-(benzoylthioacetyl)-α-phenylethylamine, was subjected to allylation as described for **22a**. The formation of the S-allyl and C-allyl derivatives in the reaction was deduced from the ^{1}H NMR spectrum which showed the following two sets of peaks:

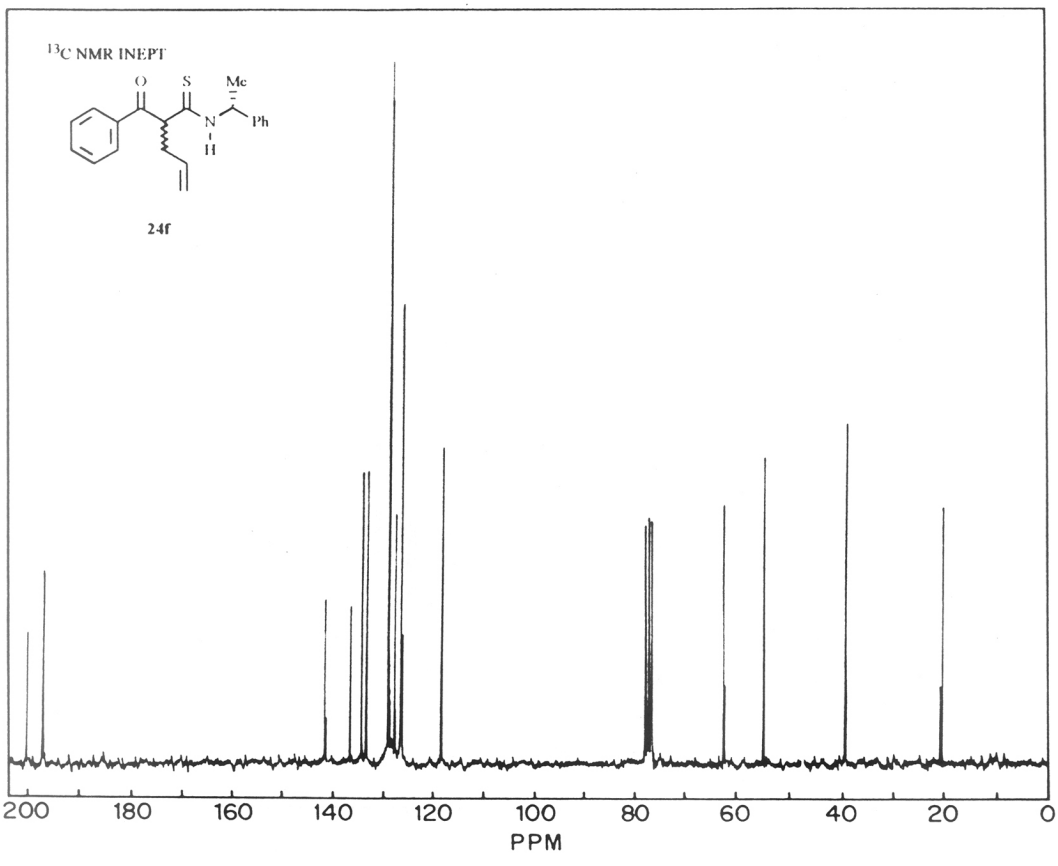
Set I, δ 1.65 (d, 3H, CH_3), 3.60 (d, 2H, SCH_2), 4.85 - 5.45 (m, 3H, N-CH, H_2C=), 5.6-6.0 (m, 2H, HC=, HC=C-S), 7.2-7.6 (m, 8H, Ph, PhCO), 7.8 - 8.15 (m, 2H, PhCO), 12.4 (bs, 1H, NH)

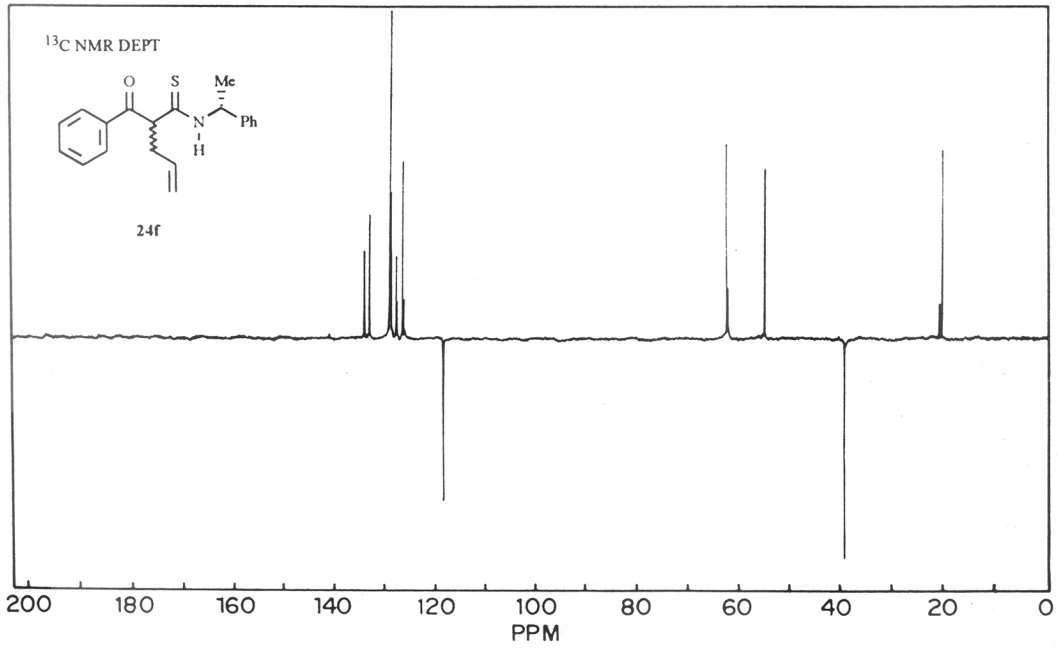
Set II, δ 1.55 (d, 3H, CH_3), 2.75 (q, 2H, CH_2), 5 (m, 2H, H_2C=), 5.15 (dd, 1H, CH), 5.67 (m, 2H, HC=, CH-N), 7.4 (m, 5H, Ph), 7.5 (m, 3H, PhCO), 8.10 (m, 2H, PhCO), 8.8 (bd, 1H, NH)

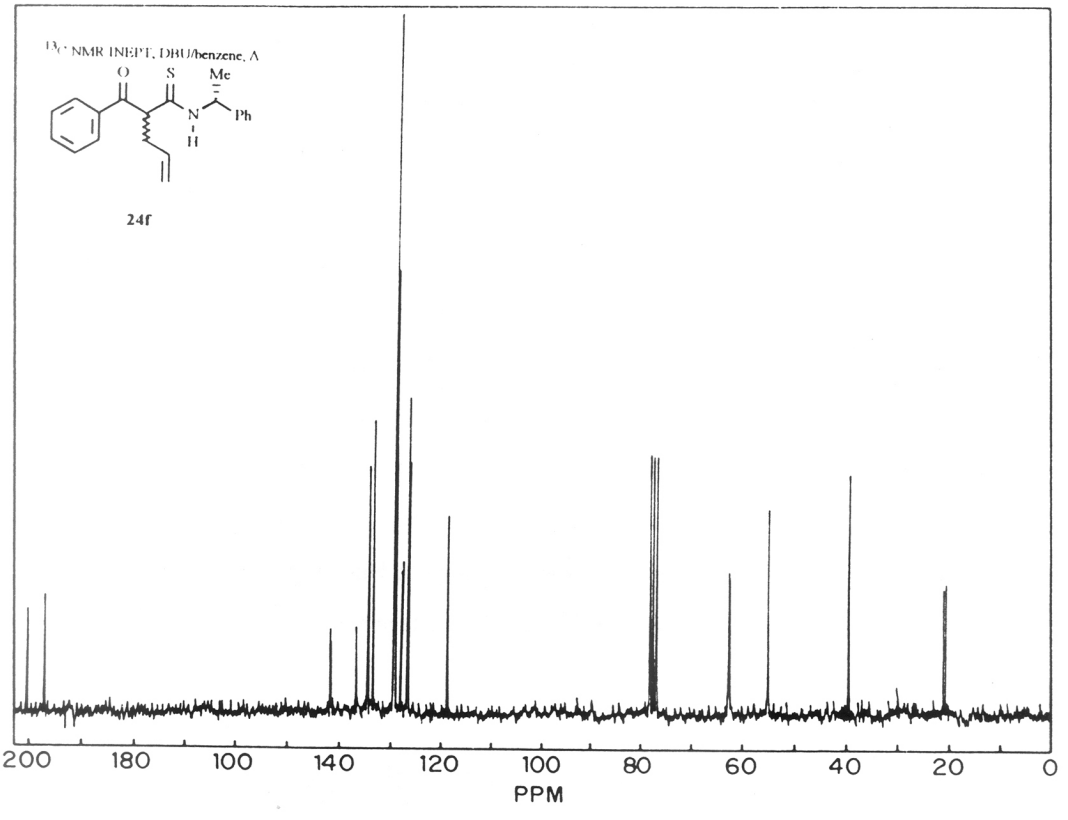
As in the case of products from **22d** and **22e**, here too it was easy to detect the S-allyl and C-allyl derivatives from the chemical shifts of the olefinic and NH proton signals for both the products. In this case the diastereomeric excess could not be determined from

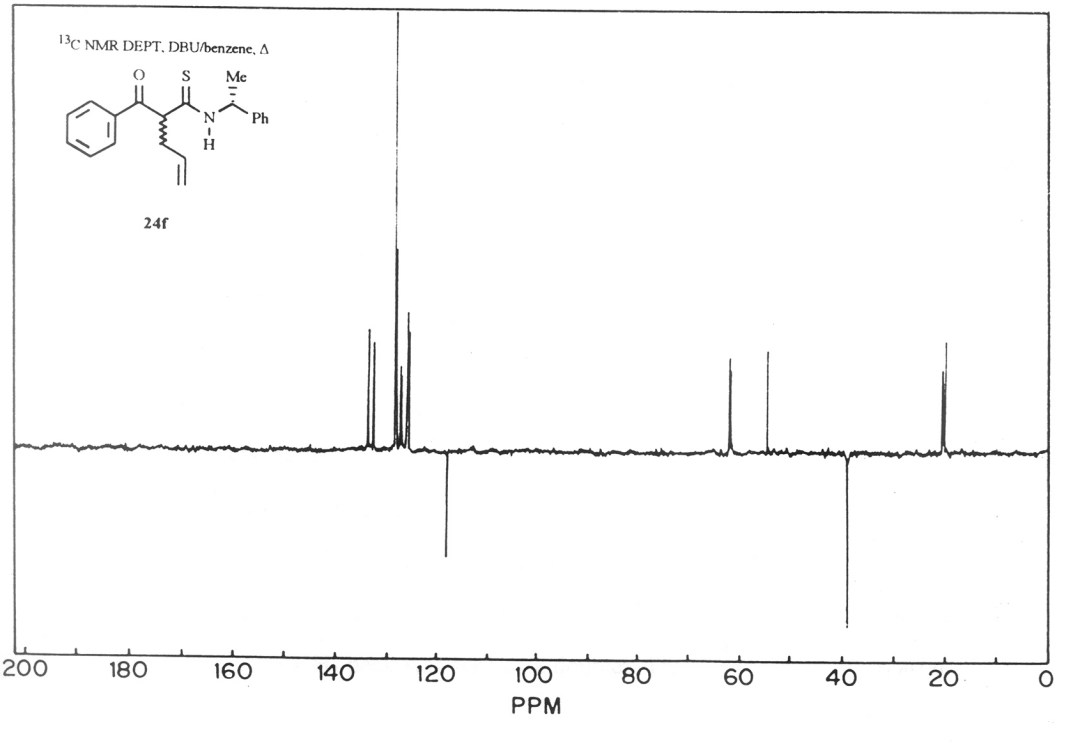

^{1}H NMR DBU/benzene, A
O
S
Me
N
H
Ph
24f
9
8
7
6
5
4
3
2
1 PPM 0


O
S
Me
N
H
Ph
24f
9
8
7
6
5
4
3
2
1 PPM 0


^{13}C NMR INEPT
O
S
Me
N
H
Ph
24f
200
180
160
140
120
100
80
60
40
20
0
PPM


^{13}C NMR DEPT
O
S
Me
N
H
Ph
24f
200
180
160
140
120
100
80
60
40
20
0
PPM


^{13}C NMR INEPT, DBU/benzene, Δ
O
S
Me
N
H
Ph
24f
200
180
100
140
120
100
80
60
40
20
0
PPM


^{13}C NMR DEPT, DBU/benzene, Δ
O
S
Me
N
H
Ph
24f
200
180
160
140
120
100
80
60
40
20
0
PPM

the relative ^{1}H NMR signal intensities. It was determined from the ^{13}C NMR peak heights of specific carbons of the two diastereomers. It was found to be 54 %. The ^{13}C NMR signals taken into account were those due to the methyl carbon of the chiral auxiliary at 20.30 and 20.70 ppm and the methine carbon of the amine moiety at 62.4 and 62.8 ppm for the major and minor isomers. In this case the major diastereomer was formed under kinetic control as shown by an equilibration experiment. The product mixture (*de* , 54%) was left in benzene solution with DBU added on as the base. The final mixture had equal amounts of the two diastereomers as shown by NMR.

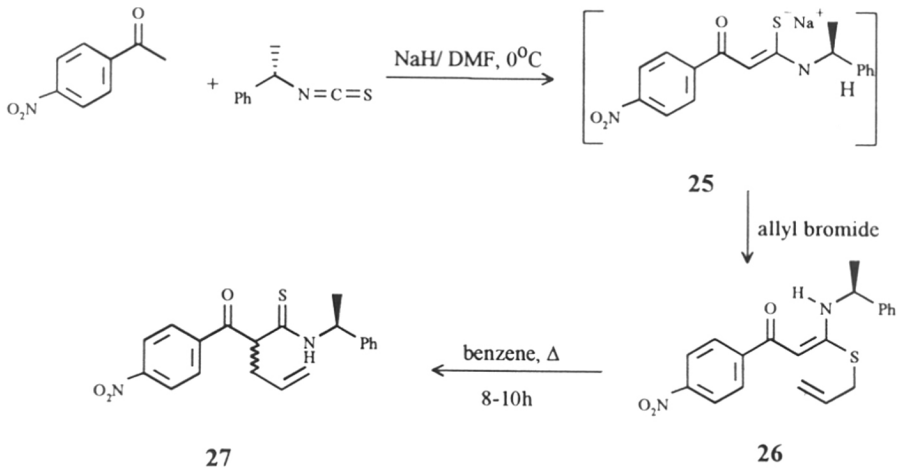
Thus in the allylation of thioacetamides **22a-f** (*Scheme 9*) the initial formation of the S-allyl products **23a-f** was demonstrated in all the cases by isolating them and then rearranging them to the C-allyl compounds **24a-f**. The structures of both the products were deduced from the characteristic chemical shifts and splitting pattern in the ^{1}H NMR spectra. Diastereoselectivity in the thio-Claisen rearrangement was estimated by determining the signal intensities of specific carbons or protons for the two diastereomers. It is important to note that in all the examples, the C-allyl products **24a-f** showed only one spot on TLC , indicating that the diastereomers had almost identical R_f values and therefore were not separable by column chromatography. A varying degree of diastereoselectivity was observed, the *de* ranging from a poor 5% for **24e** to a modest 54-58% in the case of **24b** and **24f**.

3.3 S-Allylation of N-(4'nitro)-benzoylthioacetyl-(S)-α-phenylethylamine 25, followed by thio-Claisen rearrangement

The title compound **25**, N-[(4'-nitro) benzoylthioacetyl]-(S)-α-phenylethylamine was generated as the sodium salt by reaction between p-nitroacetophenone and (S)-α-phenylethyl isothiocyanate in DMF at 0°C (*Scheme 10*). To this reaction mixture at 0°C, allyl bromide was added. The reaction was worked up as usual by adding water and extracting with chloroform to afford the crude product. This crude product was column chromatographed to yield the almost pure S-allyl product **26**, as was evident from the singlet olefinic proton signal at 5.8 δ and a broad NH doublet at 12.5 δ in the ^{1}H NMR spectrum. Also, the SCH_2 peak was seen as a doublet. This product had not rearranged to

any appreciable extent to the C-allyl derivative **27** at room temperature in chloroform for 7 days.

Scheme 10



25

27 **26**

Rearrangement was achieved by refluxing **26** in benzene for 8 hrs. The rearranged product **27** exhibited a multiplet at 2.8 δ for the allylic methylene protons.The characteristic ^{1}H NMR signals of **26**, the olefinic singlet at 5.8 δ, broad NH doublet at 12.5 δ and SCH_2 doublet at 3.6 δ were absent in the product, indicating that **26** had completely rearranged to **27**. For product **27**, the diastereomeric excess could be determined from the two signals for methyl protons at 1.55 δ and 1.65 δ for the major and minor diastereomer respectively. The *de* was found to be 15%. Identical results were obtained from the ^{13}C NMR spectrum by measuring the peak heights of methyl carbon atom of the amine moiety at 19.5 and 18.7 ppm, as well as the thiocarbonyl carbon at 197.1 and 197.5 ppm for the major and minor diastereomer respectively.

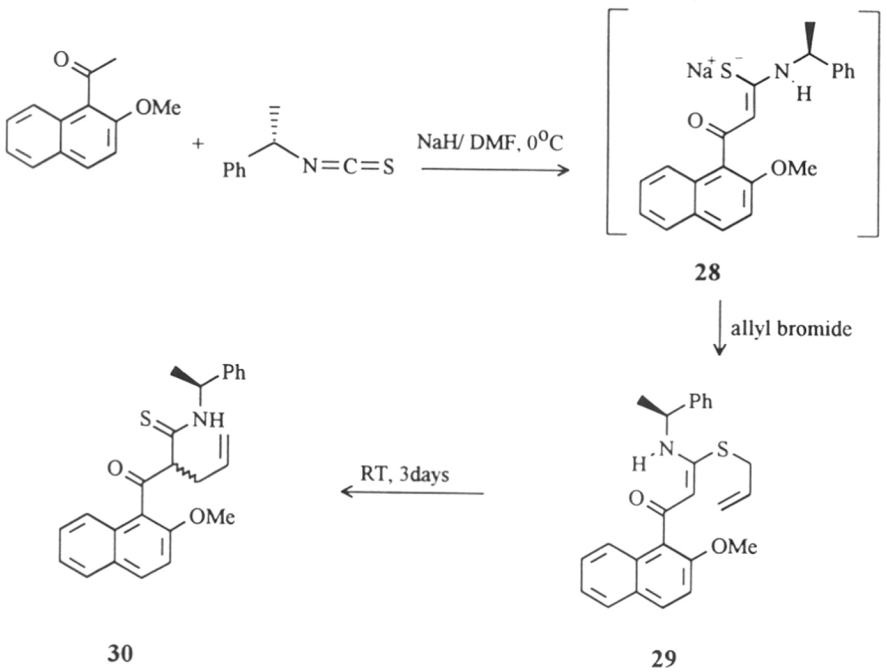
3.4 Thio-Claisen rearrangement of 29

Compound **28**, N-[(2'-methoxynaphthoyl)thioacetyl]-(S)-α-phenylethylamine, was generated as a sodium salt by reaction of 2-methoxyacetonaphthone anion with (S)-α–phenylethyl isothiocyanate in DMF at 0°C. Allyl bromide was then added to this salt to generate S-allyl compound **29** (*Scheme 11*). After usual work up, the TLC showed two

spots indicating the existence in the reaction mixture of **29**, and the rearranged product **30**. This neat mixture on standing for three days at room temperature gave almost pure **30**, evident from the characteristic NMR peaks of the C-allyl product described previously.

The diastereomeric excess in this case was determined from the OMe proton signals at 4.0 and 3.9δ for the major and minor diastereomer respectively in the ^{1}H NMR spectrum. The *de* was found to be 33 %. This was in agreement with that measured from the ^{13}C NMR peak heights of the methyl carbon of the amine moiety at 20.4 and 20.9 ppm and the thiocarbonyl carbon atom 205.9 and 206.4 ppm for the major and minor diastereomer.

Scheme 11



In all the above examples of thio-Claisen rearrangement, the initially formed S-allyl product was isolated and then rearranged to the C-allyl derivative under mild conditions (RT, $CHCl_3$, 3 days), with the exception of **26** (under benzene reflux 8-10 hrs). This observation supports the view that the push-pull effect accelerates the thio-Claisen rearrangement. The diastereoselectivity observed in these examples varied from good to

poor (see *Table 4*) although no clear trend with respect to steric bulk or any other structural features of the chiral auxiliary or the rearrangement framework was evident., When (S)-proline methyl ester was the chiral auxiliary, diastereomeric excess in this reaction was 33 %. This dramatically increased to 58 % when the proline ring was fused to another five-membered ring as in the **23b**. But, when the ester moiety in **23b** was removed, in **23c**, the *de* drastically got reduced to 20 %. These three examples indicate that the presence of an ester group, preferably benzyl ester, helps in achieving higher diastereoselectivity. Further, the presence of a cyclic secondary amine also seems to help in increasing the diastereoselectivity since in analogous compounds having an acyclic amino acid ester (eg.,leucine or phenylalanine) the *de* fell down drastically. Here the steric bulk seems to have hardly any influence. Surprisingly, **23f** having an α-phenylethylamine as the chiral auxiliary gave ahigher diastereomeric excess of 54 % in the rearrangement. Here the phenyl group of the amine moiety seems to have some role in enhancing the diastereoselectivity.

Table 4

No.	Compd. No.	*de* %
1	**24a**	33
2	**24b**	58
3	**24c**	20
4	**24d**	15
5	**24e**	5
6	**24f**	54
7	**27**	15
8	**30**	33

Attempts to prepare starting materials with N-methyl-α-phenylethylamine or N-benzyl-α-phenylethylamine failed, possibly for steric reasons. The projected synthesis of several other precursors also failed at one or the other of the steps involved (*Scheme 8*). Thus, the S-allyl derivatives **23** incorporating the following chiral amines could not be

obtained : ethyl esters of valine and alanine, O,N-acetals of acetone derived from (S)-valinol, (S)-phenyalaninol and 3-phenyl-2-aminopropan-1,3-diol, and (S)-prolinol. This severely hampered any attempts at deriving rational conclusions regarding remote stereocontrol in thio-Claisen rearrangements.

It was then decided to check whether the benzoyl group has any role in influencing diastereoselectivity. This was done by replacing the phenyl ring with p-nitrophenyl group or by a naphthyl ring. In both these cases, the diastereoselectivity was not encouraging as seen from entries 6,7 and 8 in *Table 4*. Attempts to replace the benzoyl group by cyclohexanone or cyclopentanone failed since the starting dithioester of these compounds could not be prepared.

Thus from the above study on chiral induction in thio-Claisen rearrangement, it has been demonstrated that high diastereoselectivity could be achieved through remote stereocontrol by the use of cyclic as well as acyclic chiral amines. Cyclic chiral amines with α-carboxylic ester appeared to be attractive, since the required thioacetamides could be obtained in one step (*Scheme 8*) besides inducing high diastereoselectivity. Considering that the highest diastereomeric excess so far obtained by remote stereocontrol in a [3,3] sigmatropic rearrangement has been 66 % [9], the above results can be termed as fairly good.

4. Conclusion

From the thio-Claisen rearrangement of S-allyl derivatives of β-ketothioacetamides, the following conclusions can be drawn.

i) Thio-Claisen rearrangement involving a push-pull system in the [3,3] framework proceeds smoothly under mild conditions, possibly due to the push-pull effect.

ii) Cyclic chiral amines having a carboxylic ester group at the α-position to the amino group are helpful in achieving reasonably good asymmetric induction in thio-Claisen rearrangement.

5. Experimental

5.1 Synthesis of benzoylthioacetamides 22

Benzoylthioacetamides **22** were obtained by reacting chiral amines **20a-f** with benzoyldithioacetic ester **19**. In cases where primary amines were used, S,N-acetal derivatives **21** were obtained and had to be converted to the respective thioacetamides by a procedure developed in our laboratory. This involved replacing the thiomethyl group by -SH.

Thus a mixture of benzoyldithioester **19** (5 mmol), chiral amine **20a-f** (5 mmol) and catalytic amount of PTSA in dry acetonitrile (40 ml) was refluxed and the progress of the reaction was monitored by TLC. On completion of reaction, solvent was removed under vaccum to get the crude product. This crude product was purified by column chromatography on silica gel (60-120 grade) with petroleum ether-acetone (97:3) as eluant to afford benzoylthioacetamides **22**.

For conversion of S,N-acetals **21** to the respective thioacetamides **22**, the following procedure was adopted. To a stirring solution of S,N-acetal **21**(3 mmol) in dry ethanol at room temperature, dry acetic acid (6 mmol) was added, followed by addition of finely powdered sodium sulfide (5 mmol) in small portions over a peroid of one hour. The progress of the reaction was monitored by TLC. After the completion of the reaction solvent was removed on rotavapor at lower temperature, the residue so obtained was stirred with chloroform and the solid residue was filtered. Solvent of the filtrate was evaporated to get crude product. This crude product was subjected to column chromatography on silica (60-120 grade) with petroleum ether-acetone as an eluant to afford benzoylthioacetamide **22**.

Methyl N-(benzoylthioacetyl)-(S)-prolinate 22a

Nature	Yellow gum.
Yield	86 %
$[\alpha]_D$, (c = 1, CH_2Cl_2)	-16.3
IR, cm^{-1}, ($CHCl_3$)	3040, 1750, 1620, 1590, 1460,1370
^1H NMR, ($CDCL_3$), δ	2.0-2.4(m, 4H, $2CH_2$), 3.7(s, 3H, OMe), 3.9(m, 2H, NCH_2),

	4.55(q, J=16Hz, 2H, CH_2C=S), 4.7(m, 1H, NCH-C=O), 7.35 (m, 5H, Ph).
	enethiol-enol: 4.95 (m,1H, NCH-C=O), 6.1(s, 1H, HC=CS), 7.45(m, 3H, Ph), 7.7(m, 2H, Ph)
^{13}C NMR, ppm	25, 29.5, 51.0, 53.0, 63.8, 95.5, 126.5, 129.0, 131.5, 134.0, 136.0, 170.8, 187.8.

Benzyl N-(benzoylthioacetyl)-(1R,3R,5R)-2-azabicyclo [3.3.0] octane-3-carboxylate 22b

Nature	yellow gum
Yield	74 %
$[\alpha]_D$, (c = 1, CH_2Cl_2)	-74.4
IR, cm^{-1}, ($CHCl_3$)	3000, 1690, 1600, 1450
^{1}H NMR, ($CDCL_3$), δ	1.5-2.2(m,8H, $4CH_2$), 2.9(m, 1H, CCH), 4.6(m, 1H, NCH), 5.2(d, J=10Hz, OCH_2Ph), 5.2(m, 1H, NCH-C=O), 6.2(s, 1H, =CH), 7.4(m, 8H, Ph), 7.8(dd, J = 10, 3 Hz, 2H, PhCO).
^{13}C NMR, ppm	25.6, 31.9, 33.3, 33.6, 44.0, 67.1, 68.0, 95.8, 128.2, 128.4, 128.6, 131.0, 135.7, 136.2, 170.2, 171.3, 187.6
Microanalysis	MF : $C_{24}H_{25}NO_3S$
Calculated	C, 70.8 ; H, 6.18 ; N, 3.16 ; S, 7.86
Found	C, 70.54 ; H, 6.53 ; N, 3.05 ; S, 7.49

N-(benzoylthioacetyl)-(1R,5R)-2-azabicyclo [3.3.0] octane 22c

Nature	yellow gum
Yield	76 %
$[\alpha]_D$, (c = 1, CH_2Cl_2)	-84.6
IR, cm^{-1}, ($CHCl_3$)	2980, 1690, 1610, 1440, 1370.
^{1}H NMR, ($CDCL_3$), δ	1.5 - 2.2(m, 8H, $4CH_2$), 2.85(m, 1H, CH), 3.6 - 4.2(m, 2H, NCH_2), 4.4 - 4.8(m, 1H, NCH), 6.1(s, 1H, HC=), 7.45(m, 3H, PhCO), 7.75(m, 2H, PhCO).
^{13}C NMR, ppm	25.0, 29.0, 31.5, 34.5, 44.8, 51.5, 67.0, 95.5, 126.0, 128.4, 130.9,

	136.9, 169.8, 185.7.
Microanalysis	MF :$C_{16}H_{19}NOS$
Calculated	C, 70.32 ; H, 6.95 ; N, 5.12 ; S, 11.72.
Found	C, 70.20 ; H, 7.10 ; N, 5.0 ; S, 11.40.

Ethyl N-(benzoylthioacetyl)-(S)-leucinate 22d

Nature	yellow gum
Yield	72 %
$[\alpha]_D$, (c = 1, CH_2Cl_2	+8.52
IR, cm^{-1}, ($CHCl_3$)	3020, 1750, 1620, 1550.
^1H NMR, ($CDCl_3$), δ	1.0(d, 6H, Me_2C), 1.35(t, 3H, CH_3), 1.8(m, 3H, CH_2-CH), 4.2(q, 2H, OCH_2), 4.55(q, 2H, CH_2-C=S), 5.17(t, 1H, NCH), 7.4 - 7.55(m, 3H, PhCO), 8.05(m, 2H, PhCO), 9.5(bs, 1H, NH).
^{13}C NMR, ppm	14.0, 22.0, 22.5, 25.0, 41.0, 53.2, 54.8, 57.8, 62.0, 126.5, 128.5, 129.0, 131.0, 134.5, 172.0, 195.8, 196.2.
Microanalysis	MF :$C_{17}H_{23}NO_3S$
Calculated	C, 63.52 ; H, 7.20 ; N, 4.35 ; S, 9.97.
Found	C, 61.29 ; H, 7.16 ; N, 4.32 ; S, 10.6.

Ethyl N-(benzoylthioacetyl)-(S)-phenylalaninate 22e

Nature	yellow gum
Yield	62 %
$[\alpha]_D$, (c = 1, CH_2Cl_2)	+105.5
IR, cm^{-1}, ($CHCl_3$)	3300, 3060, 1700, 1530.
^1H NMR, ($CDCl_3$), δ	1.2(t, 3H, CH3), 3.15(m, 2H, CH2-Ph), 4.0(q, 2H, OCH2), 4.4(s, 2H, CH2-C=S), 5.3(m, 1H, NCH), 7.0(m, 5H, Ph), 7.4(m, 3H, PhCO), 7.85(m, 2H, PhCO),
^{13}C NMR, ppm	14.0, 37.0, 54.0, 59.8, 61.8, 127.2, 128.5, 129.0, 129.8, 134.5, 135.8, 171.0, 191.5, 195.0.
Microanalysis	MF : $C_{20}H_{21}NO_3S$
Calculated	C, 67.58 ; H, 5.95 ; N, 3.93 ; S, 9.03.

Found C, 66.82 ; H, 6.17 ; N, 4.05 ; S, 10.05.

N-(benzoylthioacetyl)-(R)-2-phenylethyl amine 22f

Nature yellow gum

Yield 61 %

IR, cm^{-1}, ($CHCl_3$) 3300, 3050, 1690, 1620, 1520.

^1H NMR, ($CDCl_3$), δ 1.7(d, 3H, J = 6 Hz, CH_3), 4.5(d, 2H, J = 6 Hz, CH_2), 5.78(q, 1H, J = 6 Hz, NCH), 7.4(s, 5H, Ph), 7.4 - 7.6(m, 3H, PhCO), 8.05(m, 2H, PhCO), 9.6(bs, 1H, NH).

^{13}C NMR, ppm 21.0, 53.0, 55.1, 127.0, 128.0, 128.8, 129.0, 135.0, 136.5, 142.0, 193.8, 197.2.

Ethyl N-(2-benzoyl-1-thiomethylethene)-(S)-leucinate 21d

Nature yellow gum

Yield 86 %

IR, cm^{-1}, ($CHCl_3$) 3150, 1790, 1620, 1550.

^1H NMR, ($CDCl_3$), δ 1.0(t, 6H, Me_2), 1.3(t, 3H, CH_3), 1.85(m, 3H, CH_2CH), 2.5(s, 3H, SMe), 4.25(q, 2H, OCH_2), 4.4(t, 1H, NCH), 5.75(s, 1H, SC=), 7.42(m, 3H, PhCO), 7.9(m, 2H, PhCO), 11.95(bd, 1H, NH)

Ethyl N-(2-benzoyl-1-thiomethylethene)-(S)-phenylalaninate 21e

Nature yellow gum

Yield 89 %

IR, cm^{-1}, ($CHCl_3$) 3020, 1750, 1550.

^1H NMR, ($CDCl_3$), δ 1.25(t, 3H, CH_3), 2.45(s, 3H, SCH_3), 3.2(m, 3H, CH_2CH), 4.2(q, 2H, OCH_2), 4.62(m, 1H, NCH), 5.72(s, 1H, HC=), 7.3(m, 5H, Ph), 7.42(m, 3H, PhCO), 7.85(m, 2H, PhCO), 12.10(bd, 1H, NH).

5.2 Allylation and Rearrangement of benzoylthioacetamides 22

Benzoylthioacetamides **22a-f** were allylated at room temperature with allyl bromide to get S-allyl product **23a-f** which on standing at room temperature for three days rearranged to C-allyl product **24a-f** (*Scheme 9*). This was carried out as follows. To a stirring solution of benzoylthioacetamide **22a-f** (5 mmol) in acetone at room temperature,

K_2CO_3 (6 mmol) was added when the colour of the reaction mixture changed from yellow to faint orange. After ten minutes allyl bromide (6 mmol) was added in one shot when the original colour was restored. The progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was filtered and solvent evaporated from the filtrate to get the crude product. This crude product was column chromatographed to yield a product which showed an intense spot and a faint spot. On allowing to stand this product at room temperature in $CDCl_3$ for three days the original faint spot became intense with concomitant fainting of the original intense spot, indicating that the S-allyl product **23** was undergoing thio-Claisen rearrangement to yield C-allyl product **24**.

Methyl N-(allylbenzoylthioacetyl)-(S)-Prolinate 24a

Nature	yellow gum
Yield	82 %
IR cm^{-1} ($CHCl_3$)	3000, 1700, 1640, 1440
^1H NMR, ($CDCl_3$), δ	S-allyl : 2.0 - 2.2 (m, 4H, CH_2-CH_2), 3.55 - 3.80 (m, 7H, NCH_2, S-CH_2, OCH_3), 4.90 (m, 1H, N-CH), 5.15 (m, 2H, H_2C=), 5.75 - 5.95 (m, 1H,HC=), 5.95 (s, 1H, H-C=C-S), 7.40 (m, 3H, PhCO), 7.85 (m, 2H, PhCO), C-allyl : 2.0-2.5 (m, 4H, CH_2=CH_2), 2.6 - 3.2 (m, 2H, CH_2-C=C), 3.70 (s, 3H, OCH_3), 4.0 (m, 2H, NCH_2), 4.7 (dd, 1H, HC-=C=S), 4.95-5.25 (m, 3H, H_2C=, HC-N), 5.95 (m, 1H, HC=), 7.4 (m, 3H, PhCO), .78 (m, 2H, PhCO).
^{13}C NMR, ppm	19.20, 25.1, 36.6, 51.7, 52.3, 59.6, 65.4, 117.3, 128.2, 128.6, 128.7, 132.9, 135.4, 137.0, 170.6, 193.4, 198.9
de %	33
Microanalysis	M.F. : $C_{18}H_{21}NO_3S$
Calculated	C, 65.30 ; H, 6.38 ; N, 4.22 ; S, 9.67.
Found	C, 64.35 ; H, 6.19 ; N, 3.83 ; S, 8.29.

Benzyl N-(allylbenzoylthioacetyl)-(1R,3R,5R)-2-azabicyclo [3.3.0] octane-3-carboxylate 24b

Nature	yellow viscous liquid
Yield	80 %
IR cm^{-1} ($CHCl_3$)	2990, 1690, 1440, 1330.
^1H NMR, ($CDCl_3$), δ	S-allyl : 1.5-3.1 (m, 9H, 4=CCH_2, HC), 3.5-3.8 (m, 2H, S-CH_2), 4.4 (m, 2H, N-CH-C=O N-CH), 4.95 -5.25 (m, 4H, SCH_2Ph, H2C=), 5.8 (m, 1H, HC=), 5.97 (s, 1H, HC=C-S), 7.25 -7.75 (m, 8H, Ph, PhCO, 7.8 (m, 2H, PhCO) C-allyl : 1.4 - 3.25 (m, 11H, 4 CCH_2, H_2C-C=S, H2C=), 4.65 (m, 2H, N-CH-C=O, HC-N), 4.95 - 5.25 (m, 4H, OCH_2Ph, H2C=), 5.8 (m, 1H, HC=), 7.25-7.75 (m, 8H, Ph, PhCO, 7.8 (m, 2H, PhCO).
^{13}C NMR, ppm	25.2, 31.1, 33.3, 37.5, 44.2, 59.3, 67.2, 68.8, 116.7, 128.4, 128.5, 128.8, 132.9, 135.9, 137.2, 170.3, 194.0, 198.7.
de %	58
Microanalysis	M.F. :$C_{27}H_{29}NO_3S$
Calculated	C, 72.52 ; H, 6.54 ; N, 3.17 ; S, 7.20.
Found	C, 72.32 ; H, 6.75 ; N, 3.05 ; S, 6.80.

N-(allylbenzoylthioacetyl)-(1R,5R)-2-azabicyclo [3.3.0] octane 24c

Nature	yellow gum
Yield	82 %
IR cm^{-1} ($CHCl_3$)	2980, 1740, 1600, 1580, 1440, 1360.
^1H NMR, ($CDCl_3$), δ	S-allyl : 0.8-1.0 (m, 6H, CMe_2), 1.35 (t, 3H, CH_3), 1.8 (m, 2H, CH_2), 3.65 (d, 2H, SCH_2), 1.8 (m, 1H, $HCCMe_2$), 4.2 (q, 2H, OCH_2), 4.95 -5.15 (m, 3H, H_2C=HC-N), 5.75 (m, 1H, HC=), 5.8 (S, 1H, HC=C-S), 7.35-7.50 (m, 3H, PhCO), 7.85 (m, 2H, PhCO), 11.90 (bd, 1H, NH) C-allyl : 0.8-1.1 (m, 6H, $CCMe_2$), 1.17 (t, 3H, CH_3), 1.6 (m, 1H,

	$HCCMe_2$), 1.7 - 1.9 (m, 2H, CH_2), 2.85 (m, 2H, H_2C-C=), 4.25 (q, 2H, OCH_2), 5.0 - 5.25 (m, 4H, H_2C=, HC-N, HC-C=S), 7.35-7.65 (m, 3H, PhCO), 8.10 (m, 2H, PhCO), 8.70 (bd, 1H, NH)
^{13}C NMR, ppm	25.0, 30.7, 32.6, 36.5, 41.7, 51.4, 59.9, 69.2, 117.4, 127.9, 128.4, 128.5, 132.66, 135.2, 136.9, 193.2, 195.6.
de %	18
Microanalysis	M.F. : $C_{19}H_{23}NOS$
Calculated	C, 72.84 ; H, 7.34 ; N, 4.47 ; S, 10.32.
Found	C, 72.52 ; H, 7.65 ; N, 4.27 ; S, 9.78.

Ethyl N-(allylbenzoylthioacetyl)-(S)-leucinate 24d

Nature	yellow gum
Yield	67 %
IR cm^{-1} ($CHCl_3$)	3300, 3020, 2980, 1740, 1680, 1540.
^1H NMR, ($CDCl_3$), δ	S-allyl : 0.8-1.0 (m, 6H, CMe_2), 1.35 (t, 3H, CH_3), 1.8 (m, 2H, CH_2), 3.65 (d, 2H, SCH_2), 1.8 (m, 1H, $HCCMe_2$), 4.2 (q, 2H, OCH_2), 4.95 -5.15 (m, 3H, H_2C=HC-N), 5.75 (m, 1H, HC=), 5.8 (S, 1H, HC=C-S), 7.35-7.50 (m, 3H, PhCO), 7.85 (m, 2H, PhCO), 11.90 (bd, 1H, NH)
	C-allyl : 0.8-1.1 (m, 6H, $CCMe_2$), 1.17 (t, 3H, CH_3), 1.6 (m, 1H, $HCCMe_2$), 1.7 - 1.9 (m, 2H, CH_2), 2.85 (m, 2H, H_2C-C=), 4.25 (q, 2H, OCH_2), 5.0 - 5.25 (m, 4H, H_2C=, HC-N, HC-C=S), 7.35-7.65 (m, 3H, PhCO), 8.10 (m, 2H, PhCO), 8.70 (bd, 1H, NH)
^{13}C NMR, ppm	14.7, 22.1, 23.0, 25.5, 39.0, 40.9, 57.0, 61.5, 62.5, 119.2, 129.0, 133.8, 134.4, 136.9, 171.0, 198.8, 199.5.
de %	15
Microanalysis	M.F. : $C_{20}H_{27}NO_3S$
Calculated	C, 66.44 ; H, 7.53 ; N, 3.87 ; S, 8.86.
Found	C, 66.63 ; H, 7.0 ; N, 4.00 ; S, 9.16.

Ethyl N-(allylbenzoylthioacetyl)-(S)-phenyalaninate 24e

Nature	yellow gum
Yield	72 %
IR cm^{-1} ($CHCl_3$)	3300, 3020, 1740, 1680.
^1H NMR, ($CDCl_3$), δ	S-allyl : 1.35 (t, 3H, CH_3), 3.40 (m, 2H, CH_2Ph), 3.72 (d, 2H, S-CH_2), 4.32 (q, 2H, OCH_2), 5.2 (m, 1H, HC-N), 5.3 (m, 2H, H2C=), 5.8 (m, 1H, HC=), 5.95(s, 1H, HC=C-S), 7.4 (m, 5H, Ph), 7.6 (m, 3H, PhCO, 8.0 (m, 2H, PhCO), 12.2 (bd, 1H, NH) C-allyl : 1.17 (t, 3H, CH_3), 2.55 (m, 2H, H_2C-C=), 3.10-3.45 (m, 2H, CH_2Ph), 4.15 (q, 2H, OCH_2), 4.85-5.15 (m, 2, H_2C=), 5.27 (m, 1H, HCN), 5.7 (m, 1H, HC=), 7.10-7.35 (m, 5H, Ph), 7.55 (m, 3H, PhCO), 8.07 (m, 2H, PhCO), 8.92 (bd, 1H, NH)
^{13}C NMR, ppm	14.1, 36.7, 38.8, 59.2, 61.8, 62.4, 62.8, 118.3, 127.4, 128.6, 128.8, 129.0, 129.1, 129.4, 133.5, 133.6, 134.2, 135.8, 136.6, 170.3, 198.2, 199.2.
de %	5
Microanalysis	M.F. : $C_{23}H_{25}NO_3S$
Calculated	C, 69.84 ; H, 6.37 ; N, 3.54 ; S, 8.10.
Found	C, 69.88 ; H, 6.36 ; N, 3.79 ; S, 8.22.

N-(allylbenzoylthioacetyl)-(R)--2phenylethylamine 24f

Nature	yellow gum
Yield	79 %
IR cm^{-1} ($CHCl_3$)	2980, 1680, 1550, 1450.
^1H NMR, ($CDCl_3$), δ	S-allyl : 1.65 (d, 3H, CH_3), 3.60 (d, 2H, SCH_2), 4.85 - 5.45 (m, 3H, N-CH, H_2C=), 5.6-6.0 (m, 2H, HC=, HC=C-S), 7.2-7.6 (m, 8H, Ph, PhCO), 7.8 - 8.15 (m, 2H, PhCO), 12.4 (bs, 1H, NH) C-allyl : 1.55 (d, 3H, CH_3), 2.75 (q, 2H, CH_2), 5 (m, 2H, H_2C=), 5.15 (dd, 1H, CH), 5.67 (m, 2H, HC=, CH-N), 7.4 (m, 5H, Ph), 7.5

	(m, 3H, PhCO), 8.10 (m, 2H, PhCO), 8.8 (bd, 1H, NH)
^{13}C NMR, ppm	20.35, 39.2, 54.9, 62.4, 118.4, 126.6, 127.8, 128.9, 129.0, 133.3, 134.3, 136.5, 141.5, 196.9, 200.1.
de %	54
Microanalysis	M.F. : $C_{20}H_{21}NOS$
Calculated	C, 74.26 ; H, 6.54 ; N, 4.32 ; S, 9.91.
Found	C, 74.22 ; H, 6.80 ; N, 4.63 ; S, 9.69.

Synthesis of 27 and 30

The title compounds were prepared by reaction between anion of ketones, *p*-nitroacetophenone and 2-methoxyacetonaphthone, with (S)-α-phenylethylisothiocyanate to generate S-allyl product on allylation of the anion **25** and **28**. The S-allyl product so obtained underwent thio-Claisen rearrangement in refluxing benzene to afford C-allyl products **27** and **30**.

This synthesis was carried as follows. To a stirring solution of the above mentioned ketone (5 mmol) and (S)-α-phenylethylisothiocyanate (5 mmol) in dry DMF (40 ml) at ice-bath temperature solid sodium hydride (6 mmol) was added slowly over a peroid of thirty minutes when the solution turns progressively brown. After two hours allyl bromide (6 mmol) was added and stirring continued for another two hours. Finally the reaction mixture was poured in ice-cold water (100 ml) and extracted in chlorofom (50 ml). The organic layer was separated, washed several times with water to remove DMF, dried over anhydrous sodium sulfate and evaporated to get crude product. The crude product was column chromatographed on silica (60-120 grade) with petroleum ether-ethylacetate as eluant to afford pure product. This product on heating in refluxing benzene transformed into another product as obseved by the disappearance of the original spot on TLC and appearance of a new spot.

N-(allyl(4'nitro)benzoylthioacetyl)-(S)-α-Phenylethylamine 27

Nature	yellow solid
Yield	76 %

IR cm^{-1} ($CHCl_3$)	3400, 3200, 3000, 1710, 1540, 1440, 1360.
^1H NMR, ($CDCl_3$), δ	S-allyl : 1.7(d, 3H, CH_3), 3.65(d, 2H, SCH_2), 5.0(m, 1H, NCH), 5.3(m, 2H, H_2C=), 5.75(s, 1H, HC=C-S), 5.9(m, 1H, HC=), 7.37(m, 5H, Ph), 7.97(d, 3H, PhCO), 8.25(d, 2H, PhCO), 12.5(bd, 1H, NH) C-allyl : !.55(d, 3H, CH_3), 2.80(m, 2H, CH_2), 5.0-5.2(m, 3H, H_2C=, NCH), 5.5-5.8(m, 2H, HC=, HC-C=S), =), 7.37(m, 5H, Ph), 7.97(d, 3H, PhCO),
^{13}C NMR, ppm	19.5, 35.7, 53.7, 61.8, 117.1, 123.0, 126.4, 127.2, 128.0, 128.9, 134.3, 141.0, 141.5, 149.5, 193.5, 197.1.
de %	15

N-[allyl(2'-methoxy-naphthoyl)thioacetyl]-(S)-α-phenylethylamine 30

Nature	colourless viscous liquid
Yield	79 %
IR cm^{-1} ($CHCl_3$)	
^1H NMR, ($CDCl_3$), δ	S-allyl : 1.65(d, 3H, CH_3), 2.87(m, 2H, CH_2), 4.0(s, 3H, OCH_3), 4.9(m, 1H, NCH), 4.95-5.25(m, 2H, H_2C=), 5.6-5.95(m, 2H, HC-C=S, HC=), 7.25-7.6(m, 3H, Ph, Naph), 8.9(bd, 1H, NH).
^{13}C NMR, ppm	17.0, 39.3, 54.8, 56.8, 68.3, 92.6, 112.6, 118.0, 124.0, 124.5, 126.6, 127.8, 128.4, 128.9, 131.0, 133.7, 141.6, 156.4, 197.6, 205.9.
de %	35

6. References

1. a) P. A. Bartlett, *Tetrahedron*, **1980**, *36*, 2. b) J. W. ApSimon, T. L. Collier, *Tetraheron*, **1986**, *42*, 5157. c) D. A. Oare, C. H. Heathcock, *Topics in Stereochemistry*, **1991**, *20*, 87.
2. a) F. E. Ziegler, *Acc.Chem.Res.*, **1977**, *10*, 227. b)G. B. Bennett, *Synthesis*, **1977**, 589. c) R.P.Lutz, *Chem.Rev.*, **1984**, 205.
3. a) R. K. Hill, A. G. Edwards, *Tetrahedron Lett.*, **1964**, 3239. b) K. K. Chan, N. Cohen, J. P. DeNoble, G. Sancy, *J.Org.chem.*, **1976**, *41*, 3497
4. a) M. J. Kurth, C. M. Yu, *Tetrahedron Lett.*, **1984**, *25*, 5003. b) M. J. Kurth, G. M. Yu, *J.Org.chem.*, **1985**, *50*, 1840.
5. F. E. Ziegler, G. R. Reid, W. L. Studt, P. A. Wender, *J.Org.Chem.*, **1977**, *42*, 1991.
6. Y. Tamura, Y. Furukawa, M. Mizutani, O. Kitao, Z. Yoshida, *J.Org.chem.*, **1983**, *48*, 3631.
7. P. Beslin, S. Perrio, *Tetrahedron*, **1991**, *47*, 6275.
8. P. Beslin, S. Perrio, *Tetrahedron*, **1992**, *48*, 4135.
9. K. V. Reddy, S. Rajappa, *Tetrahedron Lett.*, **1992**, 7957.
10. a) J. Z. Mortensen, B. Hedegaard, S. O. Lawesson, *Tetrahedron*, **1971**, *27*, 3831
    b) L. Dalgaard, S. O. Lawesson, *Tetrahedron*, **1972**, *27*, 2051
11. A. J. Bridges, G. H. Whitham, *J.Chem.Soc., Perkin Trans I*, **1975**, 1603.

CHAPTER 3

CHIRAL INDUCTION IN THIO-CLAISEN REARRANGEMENT : GENERATION OF CHIRAL QUATERNARY CENTER

Chapter 3 : Chiral Induction in thio-Claisen Rearrangement : Generation of Quaternary Center

Summary

This chapter is a logical extension of Chapter 2. The study of chiral induction under remote stereocontrol has been extended to the generation of a quaternary asymmetric center. Active methylene compounds were reacted with a chiral isothiocyanate to generate the required thioacetamide as an anion **3**. This anion on allylation gave the S-allyl compound **4** which on subsequent rearrangement gave the C-allyl compound **5**. Moderate diastereoselctivity was obtained.

1. Introduction

Several biologically active natural products contain quaternary carbon atom(s) in their molecular structures. Hence during the course of synthesis of such complex natural products, the task of creating a quaternary carbon atom is commonly encountered. Although there exists a vast armamentarium of synthetic reactions for generation of a new carbon-carbon bond, creation of quaternary centers is among the most difficult tasks in organic synthesis. This is partially a consequence of limited accessibility of commercially or otherwise readily available starting materials which have the requisite tertiary carbon atoms, and also, due to the fact that the reactions used in these transformations have inherent limitations arising out of poor yields and occurrence of side reactions. Therefore, several synthetic operations may be required before a fully substituted carbon can be generated.

Reactions used for generating quaternary carbon atoms are classified into four main types as follows :

1. ionic reactions involving nucleophiles and electrophiles
2. oxidative or reductive coupling
3. rearrangement reactions
4. cyclo addition reactions

Each of the above class of reactions has been widely used for the generation of quaternary carbons, albeit with the limitations that generally accompany them. In a concluding section of a review article written in 1980 on the creation of quaternary carbon atom[1], the author had pointed out the virtual lack of asymmetric routes to this class of compounds. But, in the following decade numerous methodologies have been developed for this purpose.[2]

Many efficient enantioselective and diastereoselective methods have been reported for the creation of quaternary chiral centers. Among them, Michael additions and alkylations were found to be widely used. In such reactions, chiral induction as high as 99% could be attained, as expected, since the chirality transmission in most of the cases is vicinal to the chirality inducing center and in any case, did not exceed beyond the 1,3-relative position between the original and the newly created asymmetric center. Somewhat lower

chiral induction (highest *ee* = 74%) was observed in aminoacid catalysed aldol reactions. A complete chirality transmission was reported for intramolecular chiral transfer reactions like Claisen rearrangement and oxy-Cope rearrangement. For such stereospecific reactions involving chirality transfer to adjacent or 1,3-relative positions, high chiral induction is not very surprising.

Surprisingly, there are no reports on the generation of asymmetric quaternary carbon atoms via thio-Claisen rearrangement, although there are a few reports on such rearrangements leading to the formation of quaternary carbon atoms.[3] It was therefore felt necessary to extend the remote stereocontrol studies on thio-Claisen rearrangement, described in the previous chapter, to the creation of asymmetric quaternary carbon atoms. This particular aspect is dealt with in this chapter.

2. Present work

After observing a reasonably good diastereoselectivity in the thio-Claisen rearrangement of S-allyl compounds derived from thioacetamides, which resulted in the formation of a tertiary chiral center, it was decided to extend this methodology for creating a quaternary chiral center. It was obvious from the literature reports that the method which allowed generation of a quaternary carbon atom via thio-Claisen rearrangement of S-allyl thioacetamides had certain drawbacks such as harsh reaction conditions. This resulted in the formation of a mixture of products, and consequently very poor yields of pure product were obtained. The harshness of the reaction condition also resulted in the decomposition of the rearranged product. The methodology was also restricted to the use of secondary amines only.

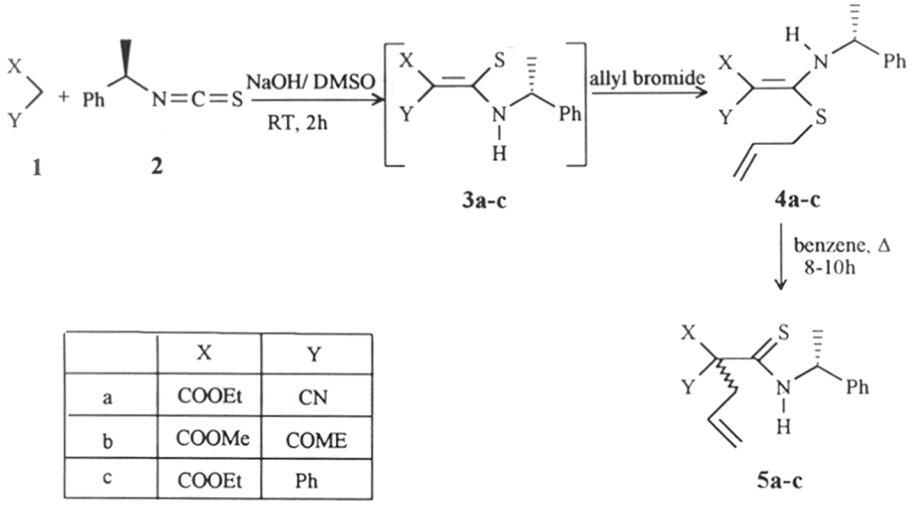
In order to overcome the above mentioned drawbacks, a different route involving reaction between the anion of an active methylene compound and a chiral isothiocyanate was used to generate an α,α–disubstituted thioacetamide anion **3** (*Scheme 1*). Allylation of this anion and subsequent rearrangement allowed the generation of a quaternary asymmetric carbon atom. Readily accessible (S)-α-phenylethyl isothiocyanate was used to prepare the required thioacetamides (*Scheme 1*). The results of this investigation are presented in the following section.

3. Results and Discussion

3.1 Generation of Chiral Quaternary Center : Synthesis of α-allyl-thioacetamides 5

The title compounds were prepared by reaction between the anion of active methylene compounds **1** and chiral isothiocyanate **2** to yield the thioacetamide anion **3** (*Scheme 1*). These on S-allylation and subsequent thio-Claisen rearrangement of the S-allyl products **4** gave the desired compounds **5** having a quaternary chiral carbon atom.

Scheme 1



1 **2** **3a-c** **4a-c** **5a-c**

	X	Y
a	COOEt	CN
b	COOMe	COME
c	COOEt	Ph

A typical procedure involved addition of the active methylene compound **1a-c** (5 m.mol) and (S)-α-phenylethyl isothiocyanate **2** (5 m.mol) to a stirring solution of finely powdered sodium hydroxide (6 m.mol) in dry DMSO (25 ml). After 2h allyl bromide (5 m.mol) was added to the reaction mixture and stirred for further 2h, by which time allylation of **3** was complete. Work-up of the reaction mixture usually gave a product which showed the presence of both the S-allyl **4** (more intense spot on TLC) and C-allyl **5** (less intense spot on TLC) derivatives. The structures of **4** and **5** were established by ^{1}H and ^{13}C NMR spectroscopy as well as by UV spectral determination.

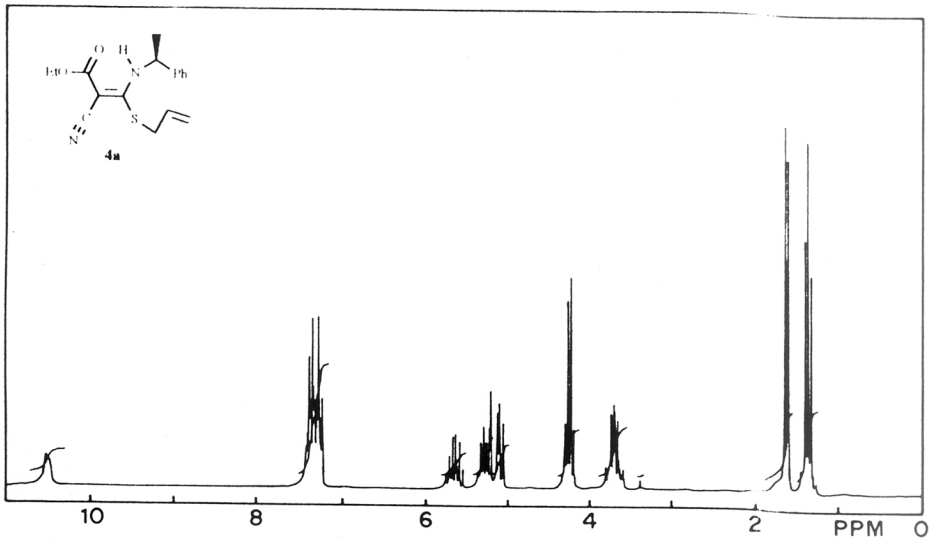
3.1a Allylation of N-(2-carboethoxy-2-cyanothioacetyl)-(S)-α-phenylethylamine 3a

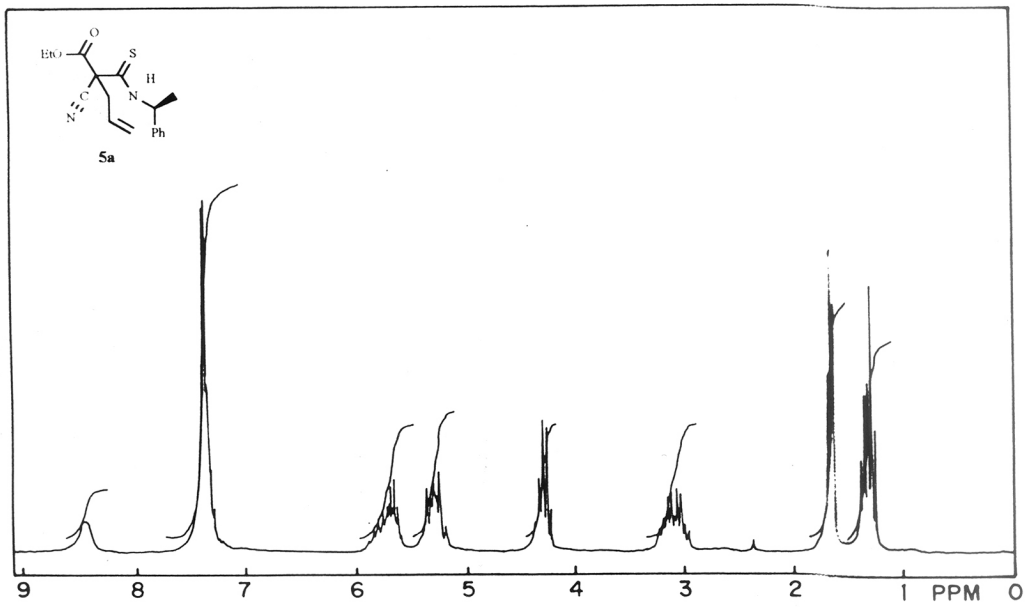
Ethyl cyanoacetate was reacted with (S)-α-phenylethyl isothiocyanate in presence of NaOH in dry DMSO to give the sodium salt of N-(2-carboethoxy-2-cyanothioacetyl)-(S)-α-phenylethylamine **3a**. This was subjected to allylation at room temperature with allyl bromide. After the usual work-up, the crude product which exhibited several spots on TLC, was purified to yield a material which showed only two spots, one more intense than the other. The ^{1}H NMR spectrum of this product showed the following signals for the major component:

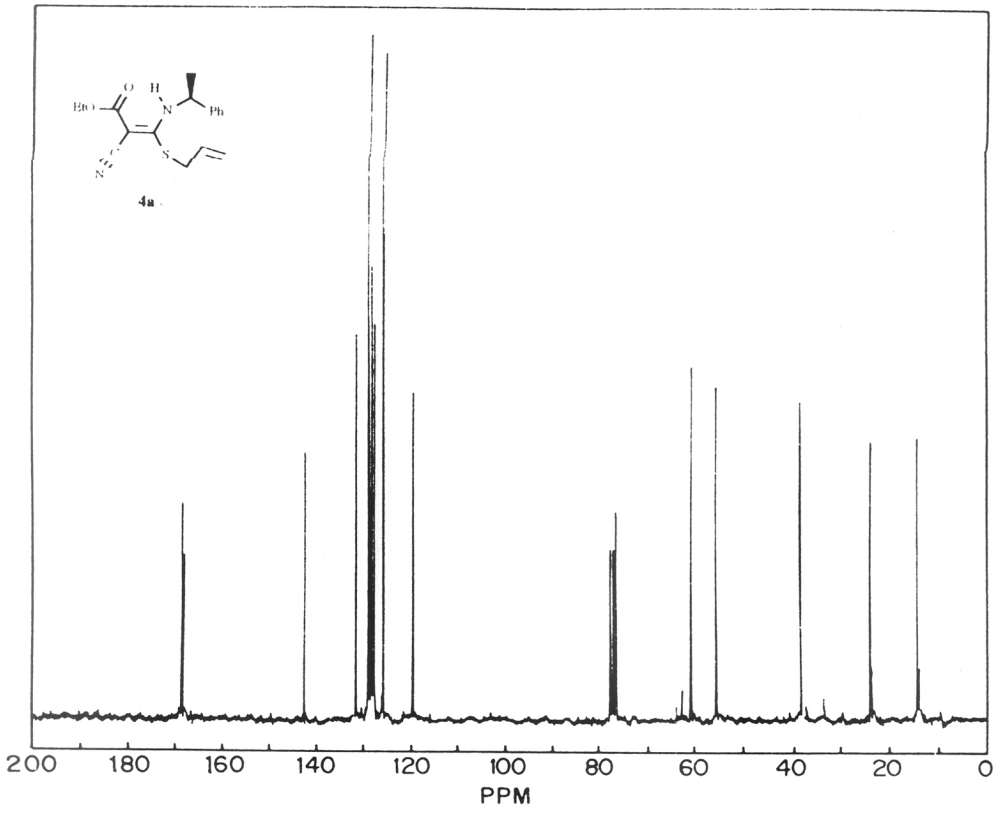
Set I, ($CDCl_3$), δ : 1.35 (t,3H, CH_3), 1.6 (d, 3H, CH_3, C-N), 3.55-3.80(m, 2H, SCH2), 4.25 (q, 2H, OCH_2), 5.0-5.35 (m, 3H, N-CH, H_2C=), 5.50-5.75(m, 1, HC=), 7.2 - 7.45 (m, 5H, Ph), 10.5 (bd, 1H, NH)

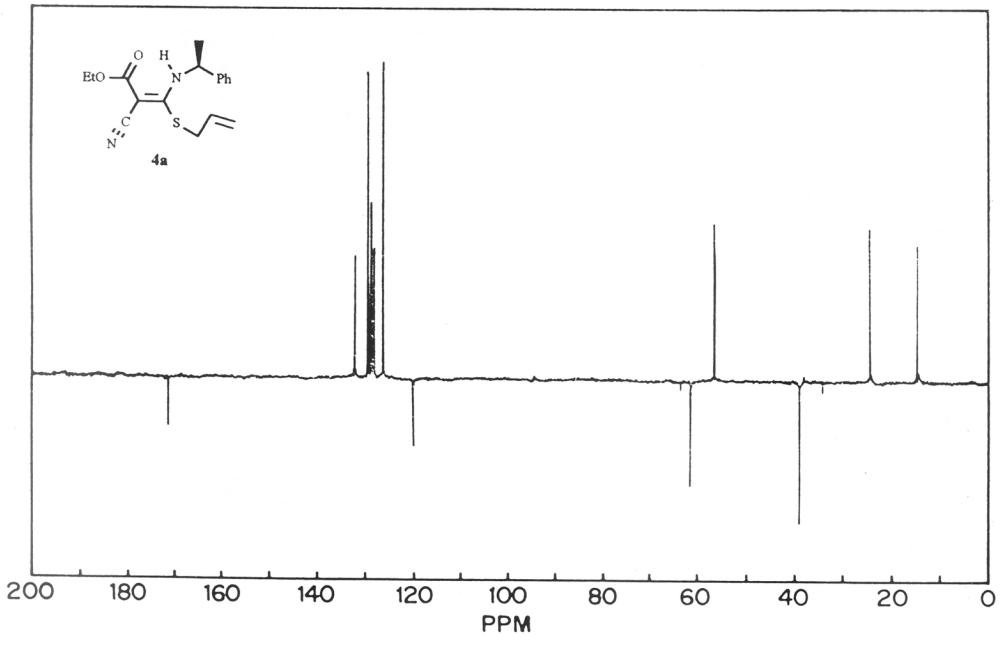
The identification of this major component as the S-allyl derivative **4a** was tentatively based on the chemical shift values and splitting pattern for the S-CH_2 and the NH protons. The NH proton signal was seen as a broad doublet at 10.5 δ indicating intramolecular hydrogen bonding between NH proton and the carbonyl oxygen of the ester function. However, the allylic methylene signal was seen as a multiplet of eight lines of unequal heights in the region 3.55 -3.80 δ. This was different from the doublet pattern observed for the S-CH_2 methylene protons of the S-allyl derivatives of benzoylthioacetamide (Chapter 2). In principle, such an eight line pattern can arise from an AA'B spin-coupled or A_2B spin-coupled system of protons. This suggested that the allylic methylene protons in **4a** are diastereotopic with each proton giving rise to 4 lines due to spin-coupling with the vicinal olefinic proton and the other geminal methylene proton. Since, the allylic methylene protons are diastereotopic, they are expected to have different chemical shifts. Hence the observed pattern.

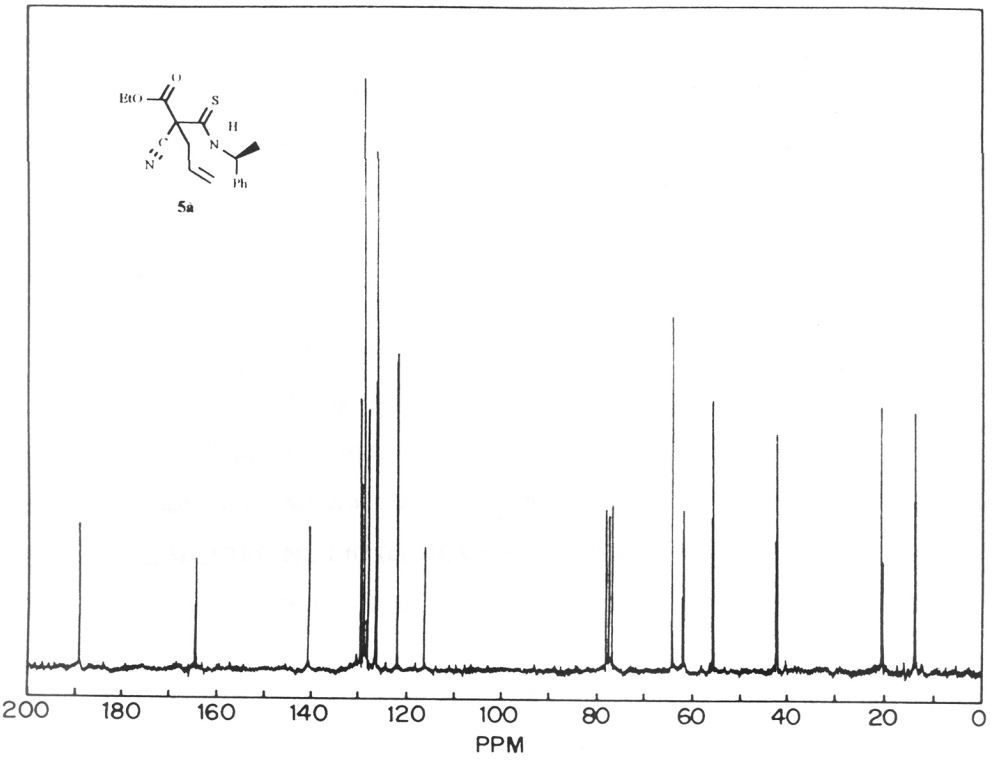
However, in the S-allyl derivative **4a**, the above CH_2 is far removed from the chiral carbon ; diastereotopicity is therefore rather unexpected. It was therefore necessary to provide further confirmation that this product was indeed the S-allyl derivative **4a** and not the rearranged C-allyl compound **5a**.

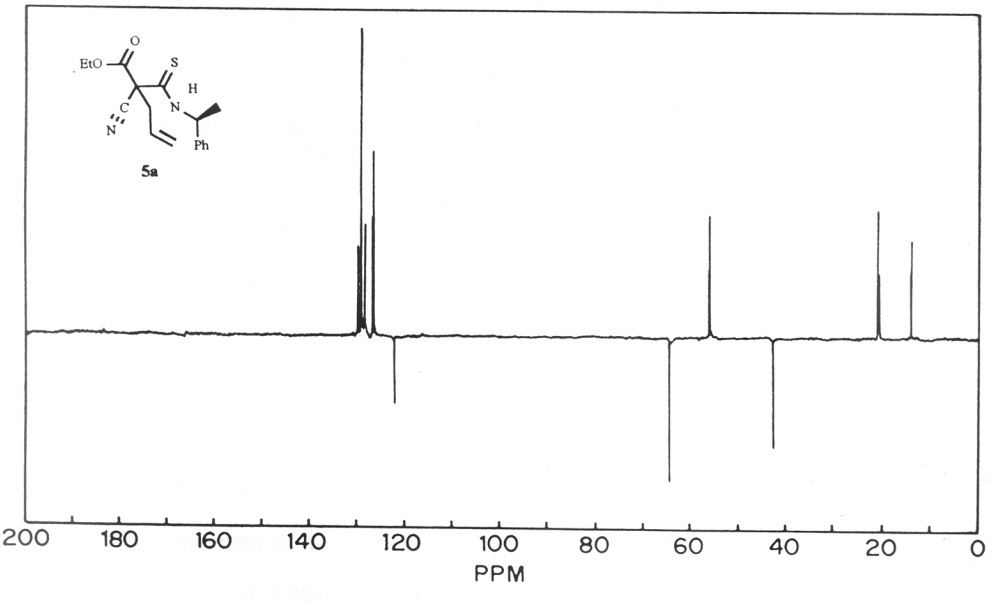

EtO
O
H
N
Ph
S
N
4a
10
8
6
4
2
PPM
0


EtO
O
S
H
N
Ph
N
5a
9
8
7
6
5
4
3
2
1
PPM
0


EtO
O
H
N
Ph
S
4a
200
180
160
140
120
100
80
60
40
20
0
PPM


EtO
O
H
N
Ph
S
4a
200
180
160
140
120
100
80
60
40
20
0
PPM

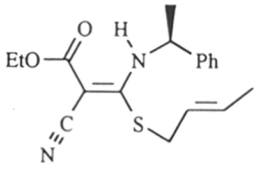

EtO
O
S
H
N
Ph
5a
200
180
160
140
120
100
80
60
40
20
0
PPM


EtO
O
S
H
N
Ph
5a
200
180
160
140
120
100
80
60
40
20
0
PPM

The UV spectrum of this material showed a long wave-length absorption maximum at 314 nm as expected for a conjugated enamine. In contrast, the C-allyl derivative **5a** showed only benzene absorption at 276 nm.

In the ^{13}C NMR spectrum of **4a**, there was no signal in the region beyond 170 ppm. If the compound had been the C-allyl isomer **5a**, one would have expected the thiocarbonyl carbon peak at about 190 ppm, as observed for the C-allyl derivatives of benzoylthioacetamides reported in Chapter 2.

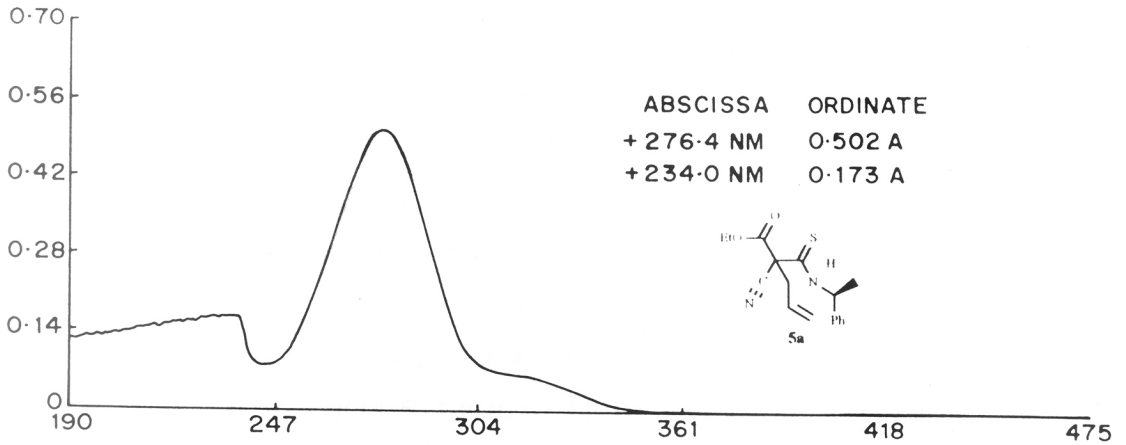
Finally, reaction of **3a** with crotyl bromide gave the S-crotyl derivative **6**. The observed ^1H NMR signals correspond well with this structure. The rearranged product would have had the methyl group on an sp^3 carbon. ^1H NMR ($CDCl_3$), δ : 1.35(t, 3H, CH_3), 1.6 (d, 3H,,CH_3C-N), 1.62 (d, 3H, CH_3C=), 3.60-3.85 (m, 2H, SCH_2), 4.25 (q, 2H, OCH_2), 5.15-5.40 (m, 2H, HC-N, HC=), 5.55-5.75 (m, 1H, HC=C-Me), 7.2-7.4 (m, 5h, Ph), 10.5 (bd, 1H, NH).

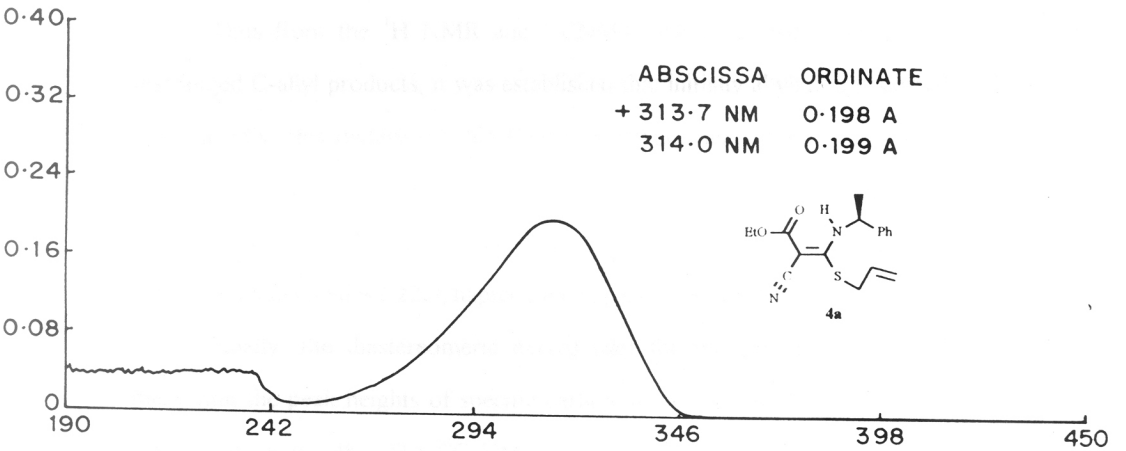


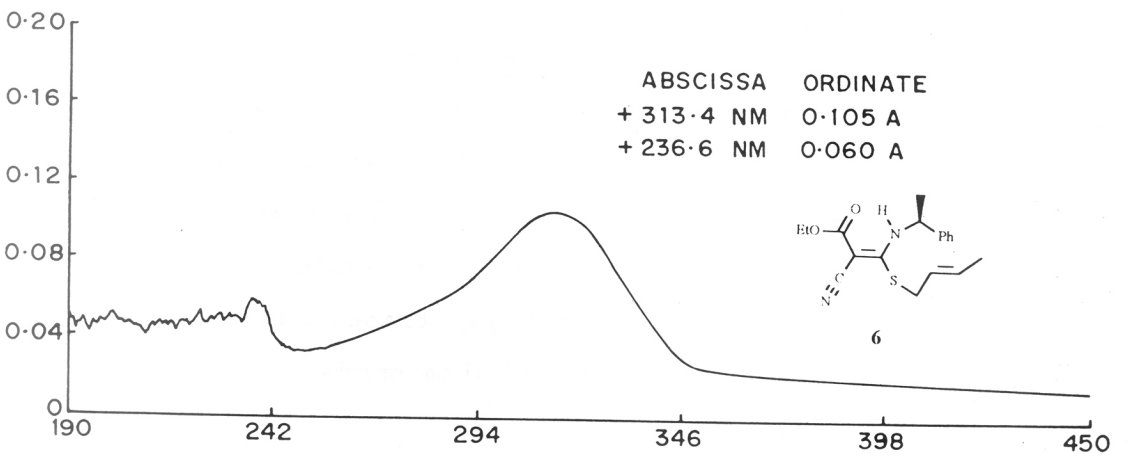
6

The typical NH signal and allylic methylene proton signal were seen at 10.5 δ and 3.60-3.85 δ respectively, similar to those for **4a**. In addition, the methyl proton signal of crotyl moiety was seen at 1.62 δ, indicating that it was vinylic methyl proton signal. In the rearranged product this signal would belong to an allylic methyl and is expected in the region 1.0 - 1.2 δ for the allylic methyl group. The ^{13}C NMR spectrum of this compound did not show any peak beyond 170 ppm. From the ^1H NMR and ^{13}C NMR spectra it can be concluded that this is the S-crotyl product. Unfortunately, subjecting this product to benzene reflux for rearrangement resulted in decomposition of the material.

Rearrangement of **4a** to **5a** would provide the final proof for the above structure assignment. When the allylation product (two spots on TLC ; major presumed to be **4a**) was allowed to stand in chloroform at room temperature for 4-5 days, it was expected by


0·70
0·56
0·42
0·28
0·14
0
190
247
304
361
418
475
ABSCISSA ORDINATE
+276·4 NM 0·502 A
+234·0 NM 0·173 A
5a


0·40
0·32
0·24
0·16
0·08
0
190
242
294
346
398
450
ABSCISSA ORDINATE
+313·7 NM 0·198 A
314·0 NM 0·199 A
4a


0·20
0·16
0·12
0·08
0·04
0
190
242
294
346
398
450
ABSCISSA ORDINATE
+313·4 NM 0·105 A
+236·6 NM 0·060 A
6

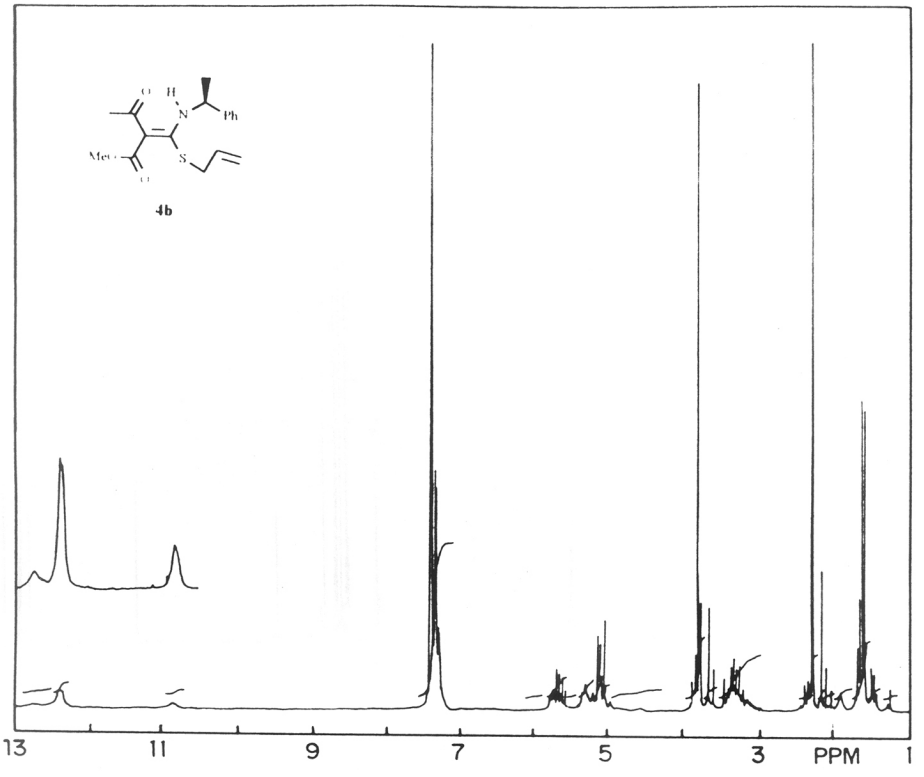
analogy with the examples presented in the previous chapter, that rearrangement would be complete. Unexpectedly however, there was no observable change either in the TLC or in the ^{1}H NMR spectrum. Rearrangement could be accomplished by refluxing the above in benzene for 8-10 h. The TLC of the reaction mixture showed progressive intensification of the initial faint spot with concomitant decrease in the intensity of the other (initially more intense) spot. The ^{1}H NMR spectrum of this rearranged product **5a** showed the following signals : Set II, ($CDCl_3$), δ : 1.30 (t, 3H, CH_3), 1.65 (d, 3H, CH_3, C-N), 2.95-3.25(m, 2H, SCH2), 4.30 (q, 2H, OCH_2), 5.17-5.40 (m, 3H, N-CH, H_2C=), 5.57-5.90(m, 1, HC=), 7.3-7.50 (m, 5H, Ph), 8.45 (bd, 1H, NH)

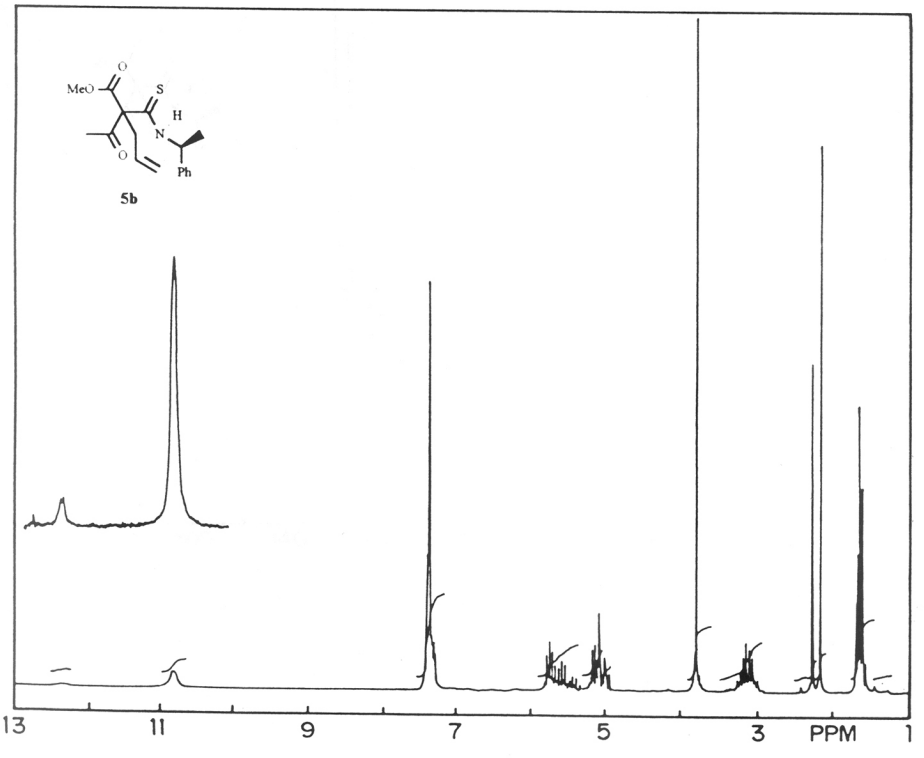
Thus from the ^{1}H NMR and ^{13}CNMR spectra of the S-allyl, S-crotyl, and the rearranged C-allyl products, it was established that initially allylation occurred at the sulfur. Subsequently, this underwent thio-Claisen rearrangement to give the C-allyl product. In case of compound **4a** the S-CH_2 protons are diastereotopic due to the presence of a chiral center in the molecule. Similar diastereotopicity for methylene protons was observed in benzoyl thioacetamides (**22,** Chapter 2) which exhibited an AB quartet.

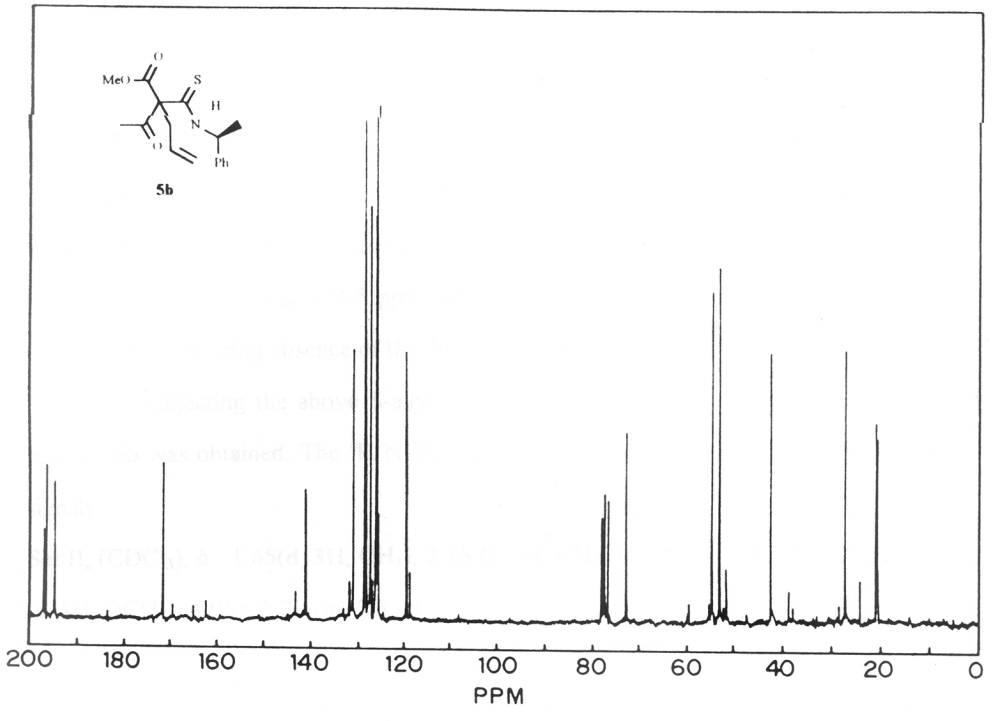
Finally, the diastereomeric excess (*de*) for the product **5a** was determined by measuring the peak heights of specific carbon atom(s) for both the diastereomers. The *de* was found to be 34%. The ^{13}C NMR signals taken into account for measuring *de* were those at 42.5 and 43.0 ppm (allylic carbon) ; 62.0 and 62.3 ppm (newly created quaternary carbon) and at 164.3 and 164.7 ppm (thiocarbonyl carbon atom) for the major and minor diastereomers.

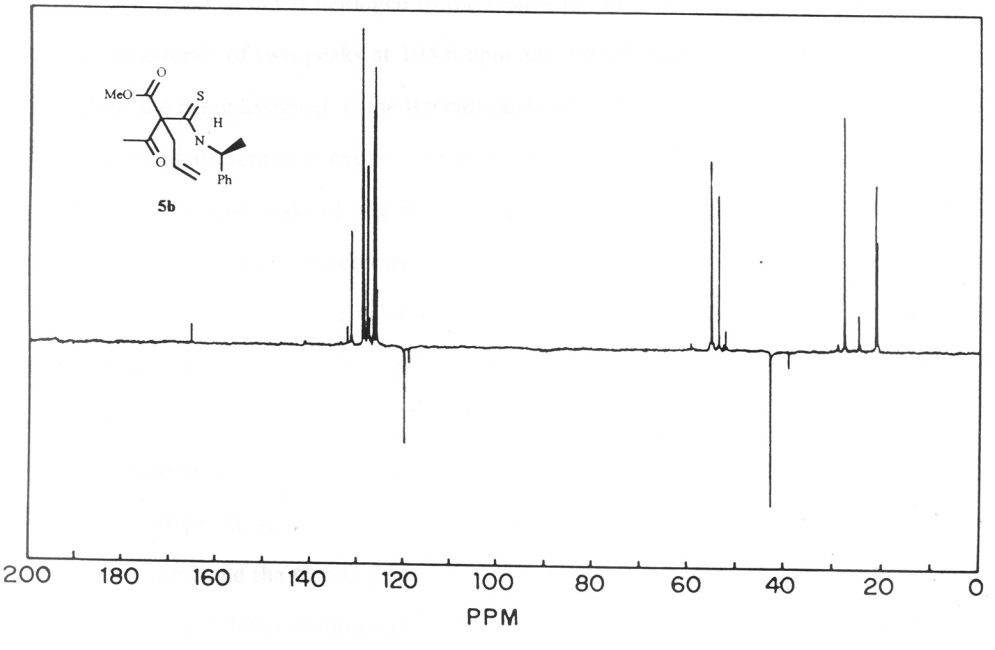
3.1b Allylation of N-(2-carbomethoxy-2-acetylthioacetyl)-(S)-α–phenylethylamine 3b

As done in the previous case, anion **3b** was generated by reaction between methyl acetoacetate and (S)-α–phenylethyl isothiocyanate in presence of NaOH in dry DMSO. This anion **3b** was treated with allyl bromide at room temperature and after the usual work up the crude product was isolated. This showed the presence of several spots on TLC. The major product was isolated in a pure form and characterised by ^{1}H NMR and ^{13}C NMR spectra. The following are the ^{1}H NMR peaks.


4b
13
11
9
7
5
3
PPM


MeO
S
H
N
Ph
5b
13
11
9
7
5
3
PPM


MeO
O
S
H
N
O
Ph
5b
200
180
160
140
120
100
80
60
40
20
0
PPM


MeO
O
S
H
N
O
Ph
5b
200
180
160
140
120
100
80
60
40
20
0
PPM

Set I, ($CDCl_3$), δ : 1.6 (d, 3H, CH_3), 2.25 (s, 3H, CH_3CO), 3.2 - 3.5 (m, 2H, SCH_2), 3.8 (s, 3H, OCH_3), 5.0 - 5.15 (m, 3H, H_2C=, N-CH), 5.55 - 5.80 (m, 1H, HC=), 7.25 - 7.45 (m, 5H, PH), 12.40 (bs, 1H, NH)

On the basis of the chemical shift values for the allylic methylene protons and the NH proton, Set I was assigned to the S-allyl product **4b**. In the ^{13}C NMR spectrum, only one peak was observed at 194.5 ppm which was assigned to the carbonyl carbon of the acetyl group, indicating absence of the thiocarbonyl group.

On subjecting the above S-allyl product **4b** to benzene reflux for 8h, the C-allyl product **5b** was obtained. The ^1H NMR spectrum of this compound showed the following signals.

Set II, ($CDCl_3$), δ : 1.65(d, 3H, CH_3), 2.15 (s, 3H, CH_3CO), 3.0-3.3 (m, 2H, CH_2-C=), 3.8 (s,,3H, OCH_3), 4.95 - 5.20 (m, 2H, H_2C=), 5.4-5.9 (m, 2H, HC=, N-CH), 7.25 - 7.45 (m, 5H, Ph), 10.85 (bs, 1H, NH)

It was evident from the peak positions of the allylic methylene protons and the NH proton that peaks in Set II belonged to the C-allyl product **5b**. This was further supported by the occurrence of two peaks at 194.6 ppm and 196.30 ppm in the ^{13}C NMR spectrum, the latter one being assigned to the thiocarbonyl carbon atom of the C-allyl product **5b**. In this case the diastereomeric excess was determined by measuring the integrated intensities of the well separated peaks of the methyl protons of the acetyl group at 2.17 δ and 2.27 δ for the major and minor diastereomer respectively in the ^1H NMR spectrum. It was found to be 25%. Exactly the same value of *de* was obtained by measuring the peak heights of the well separated thiocarbonyl carbon peaks at 196.5 and 197.0 ppm in the ^{13}C NMR spectrum respectively for the major and minor diasteromers.

3.1c Allylation of N-(2-carboethoxy-2-phenylthioacetyl)-(S)-α–phenylethylamine 3c

By using the same procedure as before, ethyl phenylacetate was reacted with the isothiocyanate **2** and the resulting adduct **3c** was allylated with allyl bromide. Purification of the product by column chromatography gave the S-allyl derivative **4c**. This showed the following signals in the ^1H NMR spectrum.

Set I, ($CDCl_3$), δ : 1.25 (t, 3H, CH_3), 1.65 (d, 3H, CH_3-C-N), 2.70 - 2.95 (m, 2H, SCH_2), 4.20 (q, 2H, OCH_2), 4.90 - 5.50 (m, 4H, H_2C =, HC-N), 7.25 - 7.50 (m, 10H, 2Ph), 9.9 (bd, 1H, NH).

The allylic methylene signal was seen as a multiplet consisting of 8 lines of unequal height, similar to that observed for the S-allyl compound **4a**. However, the NH proton signal was seen at 9.9 δ at higher field as compared to that of compound **4a**, in which it was seen at 10.5 δ. Thus the peaks in Set I were assigned to the S-allyl product **4c**. Also the ^{13}C NMR spectrum did not show any peaks beyond 170 ppm, indicating the absence of thiocarbonyl carbon, proving thereby that it was not the rearranged product **5c**.

On refluxing the S-allyl compound **4c** in benzene, the rearranged C-allyl product **5c** was obtained as confirmed by ^1H NMR and ^{13}CNMR spectra. The ^1H NMR spectrum showed the following peaks :

Set II, ($CDCl_3$), δ : 1.2 (t, 3H, CH_3), 1.60 (d, 3H, CH_3C-N), 3.10 - 3.25 and 3.75 -3.90 (m, 2H, CH_2-C=), 4.25 (q, 2H, OCH_2), 4.95 - 5.30 (m, 2H, H_2C=), 5.55 - 5.90 (m, 2H, HC=, HC-N), 7.25 - 7.45 (m, 10H, 2Ph), 10.15 - 10.40 (bd, 1H, NH)

Two distinct signals, each of 4 lines of almost equal heights were seen for the allylic methylene protons at 3.10 - 3.25 δ and 3.75 - 3.90 δ. This is due to the fact that the two allylic methylene protons are rendered diastereotopic because of the presence of a vicinal chiral center, coupled with a significant difference in the chemical shift value of these diastereotopic protons. In contrast, for the previous C-allyl compounds **5a** and **5b** the chemical shift values for these protons were fairly close to each other. This resulted in an 8-line multiplet from the two sets of doublet-of-doublet signals. Surprisingly, the NH protons for the rearranged product **5c** were seen at lower field at 10.40 δ as compared to the S-allyl product **4c** in which it was seen at 9.9 δ. This is again in contrast to the previously observed trend where such the intramolecularly hydrogen bonded NH signal in the S-allyl compounds **4a** and **4b** were seen at lower field in the ^1H NMR as compared to NH protons in the respective C-allyl products **5a** and **5b**. This deviation from the previous trend cast some doubt about the structure of the C-allyl product **5c**. However, the ^{13}C NMR spectrum showed the presence of thiocarbonyl peaks at 200.8 ppm and 200.40 ppm, assigned to the

two diastereomers of **5c**, confirming that the peaks in Set II belonged to the C-allyl product **5c**.

Finally the *de* was determined by measuring the peak heights of the following pairs of ^{13}C NMR signals corresponding to the major and minor diastereomers : the quaternary carbon at 66.0 and 65.8, the carbonyl carbon at 174.5 and 175 ppm , and the thio carbonyl atom a 200.5 and 200 ppm. It was found to be 26%.

Thus in the allylation reaction of **3a-c**, S-allyl products **4a-c** were isolated in pure form and then subjected to rearrangement in refluxing benzene to give the C-allyl products **5a-c**. Both the S-allyl and C-allyl isomers were characterised by ^{1}H NMR and ^{13}C NMR spectroscopy to establish their structure. The diastereomeric excess in all the cases were determined by measuring the peak heights of the newly created quaternary carbon atom and the thiocarbonyl carbon in ^{13}C NMR spectrum. Moderate diastereoselectivity (de = 25 to 34%) was observed in the thio-Claisen rearrangement leading to the formation of a new chiral quaternary center.

4. Conclusion

From the above study on thio-Claisen rearrangement the following conclusions can be drawn :

1. Thio-Claisen rearrangement can be used to create a quaternary chiral center with moderate diastereoselectivity under the influence of a remote chiral center.
2. The rearrangement requires higher temperatures as compared to that for S-allyl derivatives of benzoylthioacetamides (Chapter 2).

5. Experimental

5.1 Generation of Chiral Quaternary Center : Synthesis of α-allyl-thioacetamides 5

To a stirring solution of finely powdered sodium hydroxide (6 mmol) in dry DMSO (25 ml), active methylene compound **1a-c** (5 mmol) and (S)-α-phenylethylisothiocyanate **2** (5 mmol) were added. After 2h allyl bromide (5 mmol) was added and stirred further for 2h during which time the reaction is completed. Reaction mixture was poured in ice-cold water (100 ml) and extracted with chloroform. The organic layer was separated, washed several times with water to remove DMSO, dried over anhydrous sodium sulfate and solvent evaporated to give the crude product. This crude product was purified by column chromatography on silica (60-120 grade) with petether-ethylacetate as eluant to afford S-allyl product **4a-c**. This was subjected to rearrangement in refluxing benzene for 8-10h to C-allyl product **5a-c**. This was purified by column chromatograpy as done before.

Ethyl 3-allylthio-3-(1-phenylethyl)amino-2-cyano acrylate 4a

Nature	colourless viscous liquid
Yield	76 %
IR cm^{-1} ($CHCl_3$)	3000, 2200, 1720, 1650, 1540, 1420.
^1H NMR , ($CDCl_3$), δ	1.35 (t,3H, CH_3), 1.6 (d, 3H, CH_3, C-N), 3.55-3.80(m, 2H, SCH2), 4.25 (q, 2H, OCH_2), 5.0-5.35 (m, 3H, N-CH, H_2C=), 5.50-5.75(m, 1, HC=), 7.2 - 7.45 (m, 5H, Ph), 10.5 (bd, 1H, NH)
^{13}C NMR ppm	14.2, 23.7, 38.3, 55.6, 60.7, 76.6, 119.5, 125.7, 127.6, 128.2, 128.9, 131.6, 142.6, 168.2, 168.5.

Ethyl 3-allylthio-3-(1-phenylethyl)amino-2-cyano acrylate 6

Nature	colourless viscous liquid
Yield	71 %
IR cm^{-1} ($CHCl_3$)	2980, 2200, 1730, 1650, 1540, 1420
^1H NMR , ($CDCl_3$), δ	1.35(t, 3H, CH_3), 1.6 (d, 3H, CH_3C-N), 1.62 (d, 3H, CH_3C=), 3.60-3.85 (m, 2H, SCH_2), 4.25 (q, 2H, OCH_2), 5.15-5.40 (m, 2H, HC-N,

	HC=), 5.55-5.75 (m, 1H, HC=C-Me), 7.2-7.4 (m, 5h, Ph), 10.5 (bd, 1H, NH)
^{13}C NMR ppm	14.0, 17.3, 23.4, 37.7, 55.3, 60.3, 76.3, 118.0, 124.2, 125.5, 127.3, 128.5, 130.8, 142.3, 167.9, 168.5.

N-(2-carboethoxy-2-cyano- thiopentan-4-ene-1-oyl)-(S)-α-phenylethylamine 5a

Nature	colourless viscous liquid
Yield	89 %
IR cm $^{-1}$ ($CHCl_3$)	3300, 2990, 2200, 1740, 1520, 1400
^1H NMR , ($CDCl_3$), δ	1.30 (t,3H, CH_3), 1.65 (d, 3H, CH_3, C-N), 2.95-3.25(m, 2H, SCH2), 4.30 (q, 2H, OCH_2), 5.17-5.40 (m, 3H, N-CH, H_2C=), 5.57-5.90(m, 1, HC=), 7.3- 7.50 (m, 5H, Ph), 8.45 (bd, 1H, NH)
^{13}C NMR ppm	13.7, 20.3, 42.2, 55.6, 61.7, 64.0, 121.9, 126.3, 126.5, 128.0, 128.3, 128.9, 129.6, 140.5, 164.3, 188.9
Microanalysis	M.F.: $C_{17}H_{20}N_2O_2S$
Calculated	C, 64.52 ; H, 6.37 ; N, 8.85 ; S, 10.13.
Found	C, 64.87 ; H, 5.82 ; N, 9.19 ; S, 8.60.

Methyl 2-acetyl-3-allylthio-3-(1-phenylethyl)amino acrylate 4b

Nature	colourless viscous liquid
Yield	68 %
IR cm $^{-1}$ ($CHCl_3$)	3280, 3010, 2980, 1720, 1540, 1480.
^1H NMR , ($CDCl_3$), δ	1.6 (d, 3H, CH_3), 2.25 (S, 3H, CH_3CO), 3.2 - 3.5 (m, 2H, SCH_2), 3.8 (S, 3H, OCH_3), 5.0 - 5.15 (m, 3H, H_2C=, N-CH), 5.55 - 5.80 (m, 1H, HC=), 7.25 - 7.45 (m, 5H, PH), 12.40 (bs, 1H, NH)
^{13}C NMR ppm	24.5, 28.8, 38.9, 51.8, 55.4, 119.0, 125.9, 127.4, 128.3, 128.6, 128.9, 132.1, 143.4, 162.6, 169.7, 194.0.

N(2-acetyl-2-carbomethoxy thiopentan-4-ene-1-oyl)-(S)-α-phenyethylamine 5b

Nature	colourless viscous liquid
Yield	91 %
IR cm^{-1} ($CHCl_3$)	3280, 2980,1720, 1520, 1420.
^1H NMR , ($CDCl_3$), δ	1.65(d, 3H, CH_3), 2.15 (s, 3H, CH_3CO), 3.0-3.3 (m, 2H, CH_2-C=), 3.8 (s,,3H, OCH_3), 4.95 - 5.20 (m, 2H, H_2C=), 5.4-5.9 (m, 2H, HC=, N-CH), 7.25 - 7.45 (m, 5H, Ph), 10.85 (bs, 1H, NH)
^{13}C NMR ppm	20.7, 27.0, 42.2, 53.0, 54.5, 72.7, 119.0, 126.0, 127.2, 128.6, 131.0, 141.2, 171.3, 194.6, 196.3.
de %	25
Microanalysis	M.F. : $C_{17}H_{18}NO_3S$
Calculated	C, 63.92 ; H, 6.62 ; N, 4.38 ; S, 10.03.
Found	C, 63.34 ; H, 6.82 ; N, 4.84 ; S, 12.34.

Ethyl 3-allylthio-2-phenyl-3-(1-phenylethyl)amino acrylate 4c

Nature	Colourless viscous liquid
Yield	56 %
IR cm^{-1} ($CHCl_3$)	3280, 2990, 1740, 1510.
^1H NMR , ($CDCl_3$), δ	1.25 (t, 3H, CH_3), 1.65 (d, 3H, CH_3-C-N), 2.70 - 2.95 (m, 2H, SCH_2), 4.20 (q, 2H, OCH_2), 4.90 - 5.50 (m, 4H, H_2C =, HC-N), 7.25 - 7.50 (m, 10H, 2Ph), 9.9 (bd, 1H, NH).
^{13}C NMR ppm	14.5, 24.7, 37.4, 55.3, 59.6, 117.8, 126.0, 126.7, 127.4, 127.7, 128.4, 128.7, 129.3, 133.0, 138.3, 145.2, 159.7, 169.7.

N-(2-carboethoxy-2-phenyl thiopentan-4-ene-1-oyl)-(S)-α-phenylethylamine 5c

Nature	colurless viscous liquid
Yield	82 %
IR cm^{-1} ($CHCl_3$)	3250, 2990, 1720, 1500,1380.
^1H NMR , ($CDCl_3$),	1.2 (t, 3H, CH_3), 1.60 (d, 3H, CH_3C-N), 3.10 - 3.25 and 3.75 -3.90

δ	(m, 2H, CH_2-C=), 4.25 (q, 2H, OCH_2), 4.95 - 5.30 (m, 2H, H_2C=), 5.55 - 5.90 (m, 2H, HC=, HC-N), 7.25 - 7.45 (m, 10H, 2Ph), 10.15 - 10.40 (bd, 1H, NH)
^{13}C NMR ppm	13.8, 20.5, 41.4, 43.1, 55.0, 62.0, 65.8, 119.0, 126.4, 127.0, 127.7, 128.5, 133.2, 140.4, 141.7, 174.0, 200.8.
de %	26
Microanalysis	M.F. : $C_{22}H_{25}NO_2S$
Calculated	C, 71.90 ; H, 6.85 ; N, 3.80 ; S, 8.72.
Found	C, 70.50 ; H, 7.37 ; N, 3.38 ; S, 8.01.

6. References

1. S. F. Martin, *Tetrahedron*, **1980**, *36*, 419.
2. K. Fuji, *Chem. Rev.*, **1993**, *93*, 2037.
3. a) F. C. V. Larsson, S. O. Lawesson, *Tetrahedron*, **1972**, *28*, 5341. b) F. C. V. Larsson, S. O. Lawesson, *Tetrahedron*, **1974**, *30*, 1283. c) K. Hartke, G. Golz, *Chem. Ber.*, **1974**, *107*, 566.
4. R. Gompper, H. Schaefer, *Chem. Ber.*, **1967**, *100*, 591.

Publications

1. *Alkylation of Enaminothiones : What causes the observed Stereoselectivity?* **L.N. Patkar**, A. R. A. S. Deshmukh and S. Rajappa, Tetrahedron Lett., 1995, (in press).
2. *Utilisation of the Bicyclic Proline-analogue(all-R)-2-Azabicyclo[3.3.0]octane-3-carboxylic acid*, **L. N. Patkar**, A. N. Dixit, P. Chittari, S. Rajappa, C. Thorey, J. Muzart, S. Wallbaumac, J. Wilkenc and J. Martens,First Electronic Conference on Trends in Organic Chemistry (ETOC),June 12-23, 1995. (communicated to *Liebig's Annalen* in Oct.,95)
3. *Chiral Induction in thio-Claisen Rearrangemen.*, **L. N. Patkar**, A.R. A. S. Deshmukh, A. N. Dixit and S. Rajappa, (manuscript under preparation)