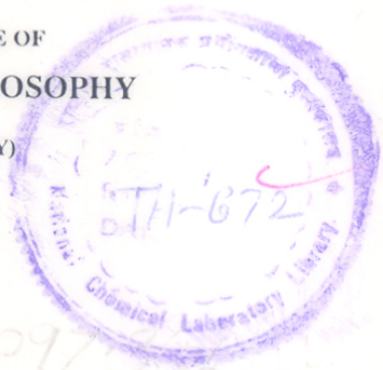
# SYNTHESIS AND REACTIVITY OF PUSH-PULL ETHYLENE SYSTEMS; NEW ZEOLITE CATALYZED CHEMICAL TRANSFORMATIONS



A THESIS
SUBMITTED TO THE
UNIVERSITY OF POONA
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)



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OCTOBER 1992

**To my beloved Parents and Teachers...**

# *CERTIFICATE*

*Certified that the work incorporated in the thesis entitled "**Synthesis and reactivity of push-pull ethylene systems; New zeolite catalyzed chemical transformations**" submitted by **Mr. T. Indrasena Reddy** 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

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*Research Guide.*

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T I Reddy 6.10.92
*(T. Indrasena Reddy)*

# *Contents...*

## Abbreviations

| | | |
|---|---|---|
| aq | : | Aqueous |
| Ar | : | Aryl |
| bp | : | Boiling point |
| cm | : | Centimeter |
| Et | : | Ethyl |
| g | : | Gram/s |
| h | : | Hour/s |
| IR | : | Infrared |
| MS | : | Mass Spectrum |
| mp | : | Melting point |
| Me | : | Methyl |
| mns | : | Minutes |
| $M^+$ | : | Molecular ion |
| nm | : | Nanometer |
| $^nPr$ | : | n-Propyl |
| NMR | : | Nuclear Magnetic Resonance |
| PTSA | : | Para-Toluenesulfonic acid |
| Ph | : | Phenyl |
| $^tBu$ | : | Tertiary Butyl |

# ABSTRACT

Zeolite catalyzed reactions in organic chemistry have been attracting considerable attention in recent years[1]. The unique features of zeolite catalysts are acidity, shape-selectivity and themal stability.

This thesis describes the zeolite catalyzed condensation of carbonimidodithioates with various active methylene compounds resulting in the synthesis of push-pull ethylene systems. This includes a totally new synthesis of 1-methylamino-1-methylthio-2-nitroethylene, a crucial intermediate for the antiulcer drug Ranitidine. This thesis also describes a novel route for the preparation of N-nitroacetyl aminoacid derivatives which are potential intermediates for the synthesis of dipeptides. Finally zeolite catalyzed conversion of carbonimidodithioates of various primary amines and aminoacid derivatives to the corresponding S-methyl thiolcarbamates has also been described.

The thesis has been divided into five chapters as follows:

**Chapter-1: Introduction to zeolites and their importance in organic chemistry:**

Zeolites are aluminosilicates with highly ordered crystalline structure. The use of zeolites as catalysts for industrial purpose began at the beginning of the 1960s and slowly they gained importance in synthetic organic chemistry. The combination of acidity and shape selectivity of the zeolite catalyst is an important factor for this purpose. In recent years the tendency to utilize this potential for highly selective synthesis in the field of intermediates and fine chemicals has increased enormously[1]. Substitution reactions of aromatic as well as aliphatic moieties, addition and elimination reactions, oxidation, reduction, isomerization, etc. have b
een reported with the aid of zeolites.

In this chapter a brief review of some of the important reactions catalyzed by zeolites is presented.

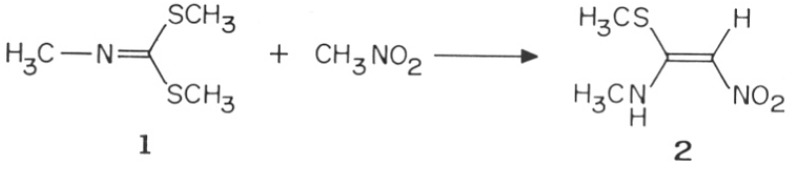
## Chapter-2: Synthesis of l-methylamino-l-methylthio-2-nitroethylene and the kinetics of this reaction:

l-Methylamino-l-methylthio-2-nitroethylene (**2**) is a crucial intermediate for the synthesis of the antiulcer drug Ranitidine. The reported methods for the synthesis of this molecule are the following: a) Reaction of methylamine with l,l-bismethylthio-2-nitroethylene. b) Reaction of nitromethane with methylisothiocyanate followed by methylation. Both these processes suffer from serious drawbacks such as hazardous reaction conditions, formation of unwanted byproducts, use of solvents such as DMSO etc.

A new method has now been developed by us[2] for the synthesis of **2** which offers several advantages. The method involves the condensation of dimethyl N-methyl carbonimidodithioate (**1**) with nitromethane in presence of a zeolite to give the required compound **2**, in good yields (*Scheme I*).

To optimize the yields and the reaction efficiency, various parameters in this reaction have been systematically studied. These include variation in reaction temperature, duration of the reaction, molar ratio of the reactants, catalyst concentration etc. The effect of different zeolites and clays on the product yield has also been studied.

***Scheme I***

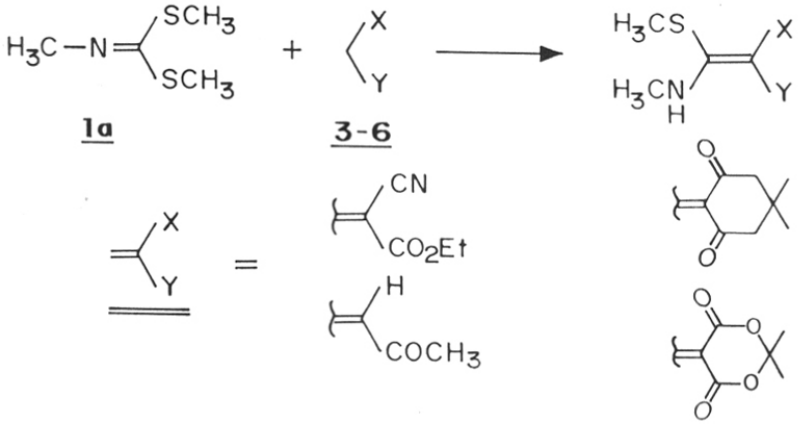



**1** **2**

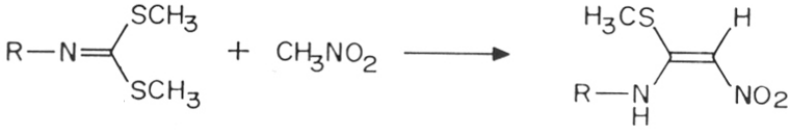
**Chapter-3: Scope of zeolite catalysis: Synthesis of push-pull ethylene systems:**

Push-pull ethylene systems including functionalized ketene S,N-acetals and nitroenamines have been well studied both for their intrinsic properties and also as intermediates for the synthesis of other molecules. In such push-pull compounds one end of the double bond is attached to an electron withdrawing group and the other end to an electron donating group. Consequently there is a delocalization of electrons over the entire push-pull system.

*Scheme II*




*Scheme III*




R = b, Cyclohexyl ; c, Benzyl ; d, Furfuryl

The new method described in chapter **2** for the synthesis of l-methylamino-l-methylthio-2-nitroethylene has been successfully extended for the synthesis of functionalized

ketene S,N-acetals. The method involves the condensation of carbonimidodithioates (**1a-d**) derived from different amines with various active methylene compounds (**3-6**) in presence of zeolite catalysts. The successful products are shown in *scheme II* and *scheme III*.

**Chapter-4: A new approach to N-nitroacetyl derivatives of aminoacid esters:**

The nitroacetyl group is an attractive synthon for peptide synthesis, especially for those involving unnatural α-alkyl and α,α-dialkyl glycine derivatives.

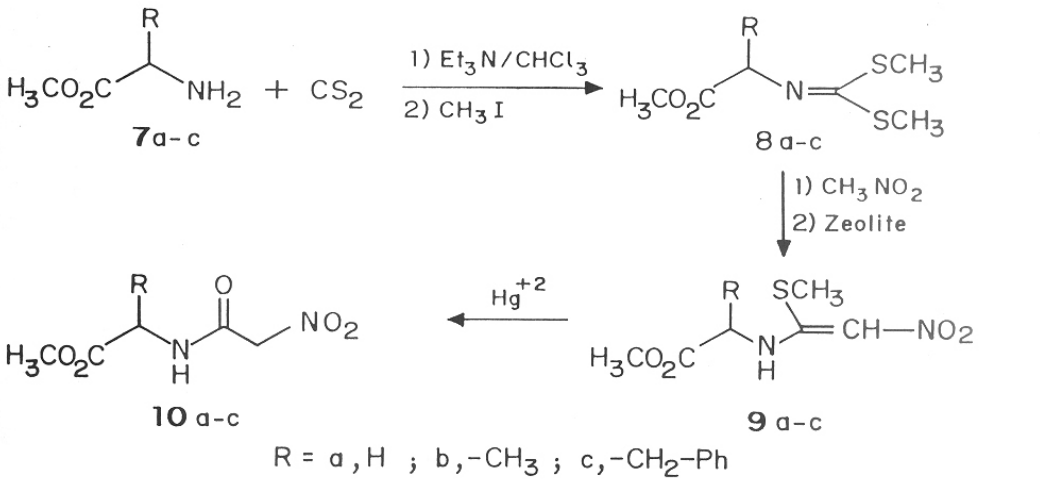
Recently a method for the preparation of N-nitroacetyl derivatives of aminoacid esters has been developed in our group and used for the synthesis of a variety of dipeptides[3]. The method consists in treating 1,1-bismethylthio-2-nitroethylene with aminoacid esters and hydrolysing the enol-thioether under $Hg^{+2}$ catalysis.

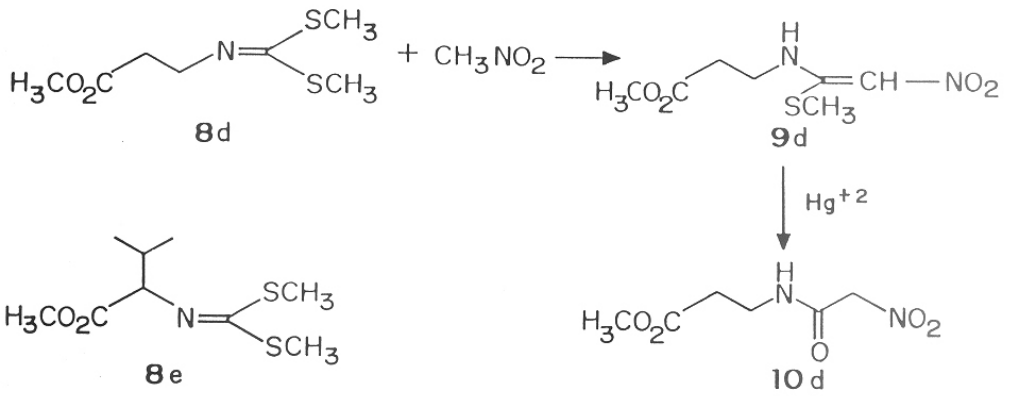
A different method has now been developed for the synthesis of such nitro acetamides under mild conditions using zeolite catalysts. This method is discussed in this chapter. The aminoacid methyl esters (**7a-c**) are treated with carbondisulfide in presence of triethylamine as base followed by methylation to give the corresponding carbonimidodithioates (**8a-c**). These on reaction with nitromethane in presence of a zeolite lead to the 1-methylthio-1-substituted amino-2-nitroethylene **9**. $Hg^{+2}$ mediated hydrolysis of these compounds gives the required nitroacetyl derivatives of amino acid esters **10a-c** (*Scheme IV*).

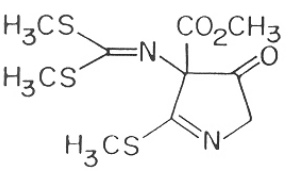
The scheme has been extended to the β -alanine derivative **8d**. The scope of this reaction has been explored. The valine derivative **8e** does not give rise to the required product probably because the pore size of zeolite cannot accommodate the isopropyl group of valine.

During the course of this study we have come across an interesting self condensation of the carbonimidodithioate derived from glycine methyl ester. The product has been shown to have the structure **11**.

*Scheme IV*


R
H3CO2C
NH2
+ CS2
1) Et3N/CHCl3
2) CH3I
SCH3
SCH3
N
7a-c
8a-c
1) CH3NO2
2) Zeolite
Hg+2
O
NO2
H
CH—NO2
10 a-c
9 a-c
R = a, H ; b, -CH3 ; c, -CH2-Ph


SCH3
N
H3CO2C
SCH3
+ CH3NO2
8d
H
CH—NO2
SCH3
9d
Hg+2
8e
NO2
O
10 d


H3CS
CO2CH3
N
O
H3CS
H3CS
N

11

**Chapter-5: A novel synthesis of S-methyl thiolcarbamates using zeolite catalysts.**

There are very few general methods available for the preparation of S-methyl thiolcarbamates. In two recent processes carbon monoxide acts as the source of the carbonyl group of S-alkyl thiolcarbamates. The first is the selenium-catalyzed reaction of amines with carbon monoxide and elemental sulfur, followed by alkylation[4]. Very recently N,N-dialkylcarbamoyl lithium, generated from dialkylamide and carbon monoxide, has been reacted with elemental sulfur and then alkylated to produce the desired S-alkyl thiolcarbamates[5]. Although the yields are good with secondary amines, the only primary amine tried, gave a complex mixture in this reaction.

The method which we have now developed[6] for the synthesis of S-alkyl thiolcarbamates from primary amines has several advantages. It involves the zeolite catalyzed conversion of carbonimidodithioates of various primary amines and aminoacid derivatives to corresponding N-substituted S-methyl thiolcarbamates as shown in *scheme V.*

***Scheme V***

R — N= METHYLAMINE , n — PROPYL AMINE
CYCLOHEXYLAMINE , BENZYL AMINE
GLYCINE METHYL ESTER , ALANINE METHYL ESTER
VALINE METHYL ESTER , PHENYALANINE METHYL ESTER

**References:**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2. Deshmukh, A.R.A.S., Reddy, T.I., Bhawal, B.M., Shiralkar, V.P., Rajappa, P., *J. Chem. Soc., Perkin Trans I,* **1990,** 1218.

3. Manjunatha, S.G., Rajappa, S., *J. Chem. Soc., Chem. Commun.,* **1991,** 372.

4. Sonoda, N., Mizuno, T., Murakami,S., Kondo, K., Ogawa, A., Ryu, I., Kambe, N., *Angew. Chem. Int. Ed. Eng.,* **1989,** 28, 452.

5. Mizuno, T., Nishiguchi, I., Okushi, T., Hirashima, T., *Tetrahedron Lett.,* **1991,** 32, 6867.

6. Reddy, T.I., Bhawal, B.M., Rajappa, S., *Tetrahedron Lett.,* **1992,** 33, 2857.

# CHAPTER - 1

# INTRODUCTION TO ZEOLITES AND THEIR IMPORTANCE IN ORGANIC CHEMISTRY

# 1.1 General:

## 1.1.1 Introduction:

Zeolites form a fascinating class of inorganic solid materials, which are attracting considerable attention in industrial as well as scientific circles. These are crystalline, hydrated, aluminosilicates, having highly ordered rigid three dimensional inifinite frame work. These structures are built by the sharing of $SiO_4$ and $AlO_4^-$, tetrahedra, linked through oxygen bridges. The properties of their aluminosilicate frame work and the presence of well defined channel systems have made zeolites useful for a variety of industrial applications in adsorption such as ion exchange and catalysis.

Zeolites may be represented by the general, empirical unit cell formula[1,2] $Mx/n\,[(AlO_2)\,x\,(SiO_2)y].zH_2O$; where M is a cation with valence of n. The net negetive charge of the frame work generated by alumina is compensated by these cations (M), which are often from group I or II or rare-earth ions, or organic species. Moreover, the cations are mobile and may usually be exchanged.

The use of zeolites as catalysts started in industry at the beginning of the 1960s. The unique properties of zeolite molecular sieves, such as acidity, shape-selectivity and thermal stability also enable them to be used in the field of preparation of intermediates and fine chemicals.

## 1.1.2 Nomenclature:

The International zeolite Association Structure Commission and IUPAC have assigned structural codes for natural and synthetic zeolites[3]. Names consisting of three capital letters have been used to identify the structures, which are generally derived from the names of zeolites and do not include numbers and characters other than Roman Letters. Codes do not depend on composition, or on distribution of various possible atoms such as Si, Al, P, Ga, Ti, etc. Some examples are given in *Table 1-1*.

**Table 1-1: IUPAC Nomenclature of zeolites:**

| Name | Code |
|---|---|
| Mordenite | MOR |
| Faujasite | FAU |
| Sodalite | SOD |
| Laumontite | LAU |
| Heulandite | HEU |
| Erionite | ERI |

Some of the synthetic zeolites are named after their inventors or the institution where they were originally synthesized, eg.,

Zeolite Socony Mobil - **ZSM**

Virginia Polytechnic Institute - **VPI**

### 1.1.3 Classification of zeolites:

Until today, 40 types of natural zeolites and more than 150 synthetic zeolites has been identified. Classification of zeolites have been on the basis of different factors. The zeolite lattice contains cavities of varying diameters, depending on the type of zeolite. Classification based on pore-diameter[4,5] as discussed here in detail, is more relevant to organic chemistry. However, different classifications reported in the literature are based on natural occurrence and morphological characters, crystal structure or chemical composition. Barrer[6] and Sand[4] have classified zeolites into three groups based on their effective pore diameter, viz., small-pore, medium-pore and large-pore zeolites. In the case of small-pore zeolites, the diameter of the cavity is 4.1°A. This is formed by eight $SiO_4$ tetrahedra. All medium-pore zeolites are called pentasil zeolites, having a ten atom ring system with a tubular diameter of

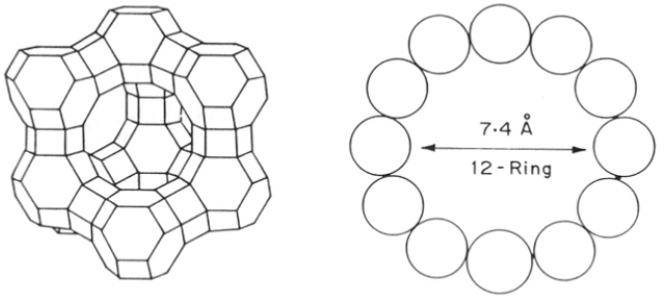
5.6°A. The third category is the larger-pore zeolites having 12 atom rings of cavities with a diameter of 7.4°A. These rings are constructed by the network of $SiO_4$ and $AlO_4^-$ tetrahedra with an oxygen atom bridge separating two metal atoms. Recently, a very large-pore zeolite aluminophosphate molecular sieve (VPI-5), containing an 18-membered ring has been synthesized[7]. An isomorph of VPI-5 called MCM-9 containing Si atoms has also been synthesized[5].

**Table 1-2: Classification of zeolites based on their pore-diameter:**

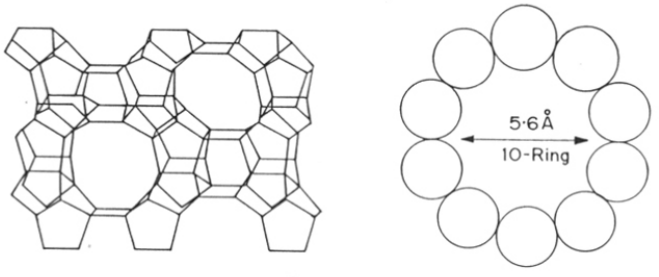
| small-pore | medium-pore | large-pore |
|---|---|---|
| Erionite | ZSM-5 | Faujasite |
| Carbazite | ZSM-12 | X-/Y-Zeolite |
| | TS-1 | Mordenite |
| | Silicalite | |

### 1.1.4 Structure and Properties:

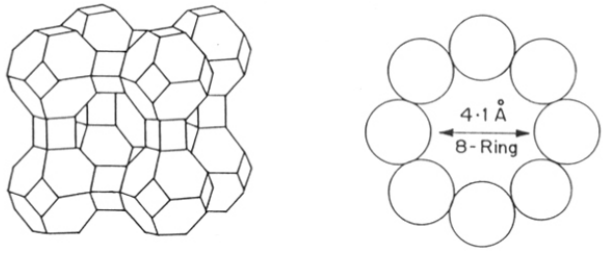
As originally conceived, zeolites are crystalline aluminosilicates with a highly ordered structure. Cavities of a definite size are formed in the rigid, three-dimensional network composed of $SiO_4$ and $AlO^4$- tetrahedra. The central atoms of the zeolite lattice can be replaced in an isomorphous manner by a large number of other tri- and tetravalent atoms. For instance B, Cr, Sb, As, and Ge, Ti, Zr can be incorporated into the zeolite skeleton instead of Al and Si respectively. The isomorphous substitution results in altered lattice constants and therefore it differs in the catalytic properties e.g. the acidity of the zeolite and therefore the activity. The nature and extent of incorporation of the isomorphous replacement can be detected in some cases by means of MAS-NMR Spectroscopy[8,9] and appropriate test reactions[10]. The zeolites are inorganic cation exchangers and their catalytic activity is associated with the presence of acid centers in the intracrystalline surface. In general, zeolite synthesis yields the




Y - zeolite




Pentasil zeolite




A - zeolite

neutral sodium form. By means of ion exchange with ammonium salts and subsequent calcination one can obtain the proton i.e. the acidic form of the zeolites. Ion-exchange from aqueous solution also allows the introduction of many types of cations, e.g. alkali metal ions, transition metal ions and lanthanides in zeolites. One can thus incorporate the desired amount of any specified cation. However, if complete ion-exchange with alkali metal ions such as K, Rb, or Cs is carried out, it is possible not only to neutralize the acidic centers, but also to prepare weakly basic zeolites. It is particularly true if these neutral zeolites are then impregnated with alkali hydroxides[11a].

These variations in structure make zeolites suitable for wide applications in both petrochemical processes and synthesis of organic intermediates and fine chemicals.

**Acidity:** The acid strength and the number of acidic sites can be adjusted in a controlled manner during synthesis and/or by subsequent ion exchange.

**Shape-selectivity:** This implies that only molecules smaller than the pore diameter of the zeolite can react in presence of this catalyst. In addition, only such molecules can be formed whose transition state geometry is smaller than the pore diameter of the zeolite catalyst.

## 1.2 Non-catalytic use of zeolites in organic chemistry:[11b]

Application of zeolites in organic synthesis includes non-catalytic and catalytic uses. The non-catalytic use of zeolites are in brief:

i). Drying and purification of liquids.

ii). Separation of products.

iii). As reactant disperser and slow release carrier.

## 1.3 Catalytic use of zeolites in organic synthesis:

Compared to the successful use of zeolites in hydrocarbon processes, their use in the synthesis of organic intermediates and fine chemicals is at a premature stage of development. The two main reasons for this are:

1. Many of the target organic systems to be synthesized are too bulky: that is, they are bigger in size than the cavities of zeolites.

2. The average synthetic organic chemist is not acquainted with zeolites and their potential, other than their use in industrial processes.

Some of the important reactions which draw attention to the broad potential arising out of the combination of acidity and shape-selectivity offered by zeolites in organic reactions are discussed below[11-13].

### 1.3.1 Substitution reactions:

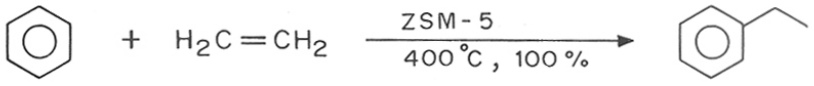
#### 1.3.1.1 Alkylations:

The general liquid phase Friedel-Crafts reactions of arenes with alcohols or olefins using Lewis-acid catalysts such as $AlCl_3$[14] have been carried out on large industrial scale e.g. preparation of ethylbenzene. The use of such catalysts gives rise to several problems, such as corrosivity, toxicity and effluent pollution. This makes it desirable to replace these by heterogeneous catalysts.

### *1.3.1.1a Alkylations on arenes:*

The Mobil-Badger (USA) process is an outstanding and technically proven example of alkylation of aromatic compounds using zeolite catalysis. Ethylbenzene has been produced from ethylene and benzene over ZSM-5 zeolite. Ethylene is completely converted to ethyl benzene, with 99% selectivity[15] at about 400° C (*Scheme 1-1*).

***Scheme 1-1***




Advantages of this reaction over homogeneous catalytic reactions are:

i) The catalyst is non-corrosive and need not be separated by chemical processes but only filtered off.

ii) There are no disposal problems as in the case of $AlCl_3$ process.

iii) Deactivated catalysts can be regenerated and reused without any changes in selectivity and reactivity.

It is a gas phase reaction; in alkylations with longer chain alkenes, reactions are carried out in the liquid phase.

The mechanism of this reaction on H-zeolite has also been studied[16].

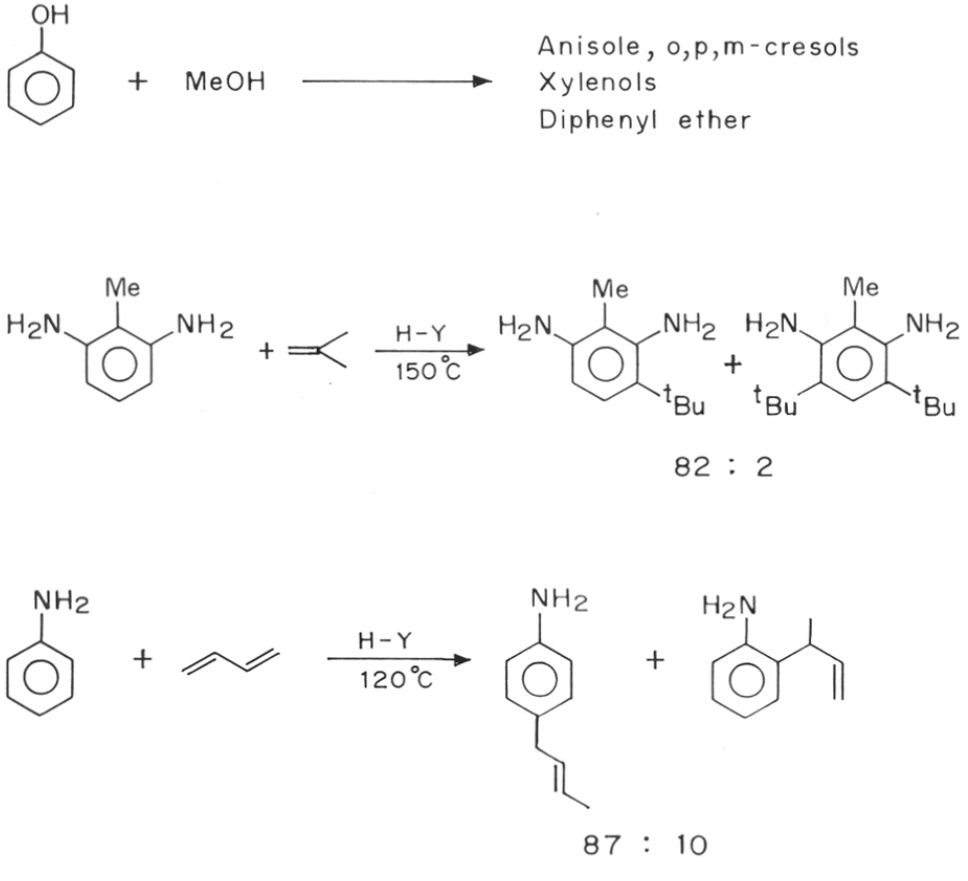
### *1.3.1b Alkylations on substituted arenes:*

Arenes containing functional groups such as hydroxy can also be alkylated on zeolite catalysts. However, these conversions are more complex than the alkylation of benzene and

alkyl benzenes, because the incoming electrophile can attack the aromatic system as well as on the functional group, i.e. in the case of phenol not only ring C-alkylation but also O-alkylation is possible(*Scheme 1-2*). Jacobs et al.[16,17] have discussed the details of the mechanism.

The alkylation process on an arylamine is highly selective. The tert. butylation of 2,6-diamino toluene over H-Y zeolite shows shape-selectivity as it leads essentially to the mono-tert. butyl compound[18,19]. Another interesting reaction is the conversion of aniline and butadiene over H-Y at 120°C. The butenyl group can be attached at the 2-and 4-position in two different ways to give the products 2-isobutenyl aniline and 4-(2-butene)-aniline respectively (*Scheme 1-2*).

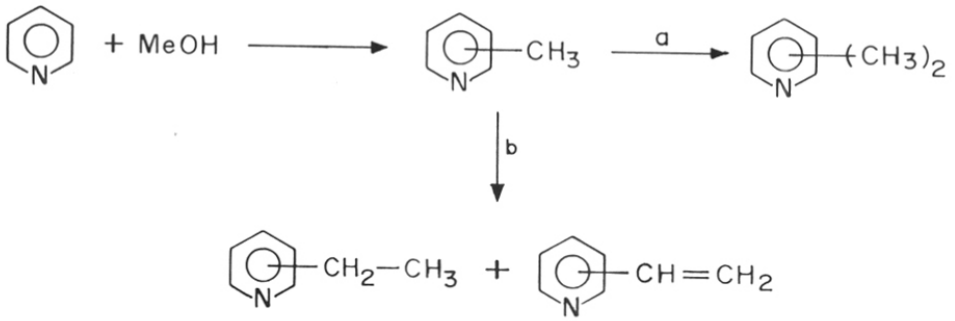
***Scheme 1-2***



### *1.3.1.1c Alkylation on heteroarenes:*

Zeolite catalyzed alkylations of heteroaromatics are relatively less well-known; This may be due to the fact that these are intrinsically more complex systems. The alkylation of pyridine takes place with methanol over faujasite type zeolite[20]. Primarily the substitution takes place at the aromatic nucleus; this may be followed by other secondary reactions, eg. The picoline formed can either undergo further ring alkylations or side chain alkylation. Various possibilities with different catalysts are shown in *Scheme 1-3*. Solinas et al. in 1985 reported alkylations on thiophene[21].

*Scheme 1-3*



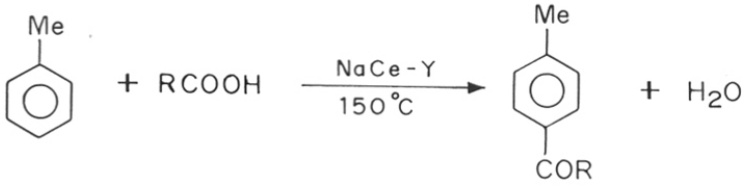

### 1.3.1.2 Acylations:

### *1.3.1.2a Acylation on arenes:*

Friedel-Crafts acylation as practised at present in the industry, generally involves acid chlorides or anhydrides as the acylating agent with stoichiometric amounts of metal chlorides such as $AlCl_3$, $FeCl_3$ as the Lewis acid catalyst.[22] The disadvantages are; substantial amounts of catalyst are required and the work-up of the reaction mixture involves handling corrosive

media. For these reasons Chiche et al.[23] reported for the first time that the use of zeolite as catalyst, with free acids as acylating agents would be very attractive. The direct acylation of toluene and para-xylene by aliphatic acids ($C_2$-$C_{20}$) using zeolite Na(Ce70%)Y as catalyst gave the corresponding acylated products. The acylation of toluene proceeds with increasing yield as the chain length of the acid increases with the maximum yield of 96% being achieved in the case of dodecanoic acid[23]. Shape-selectivity of the zeolite is clearly indicated by the formation of more than 95% of the para-isomer (*Scheme 1-4*). Although other catalysts including $AlCl_3$ also lead to a preponderance of the para-isomer, the zeolite is superior in this selectivity aspect. Gauthier[24] and Chiche[25] have studied the mechanism and reactivity of different zeolites.

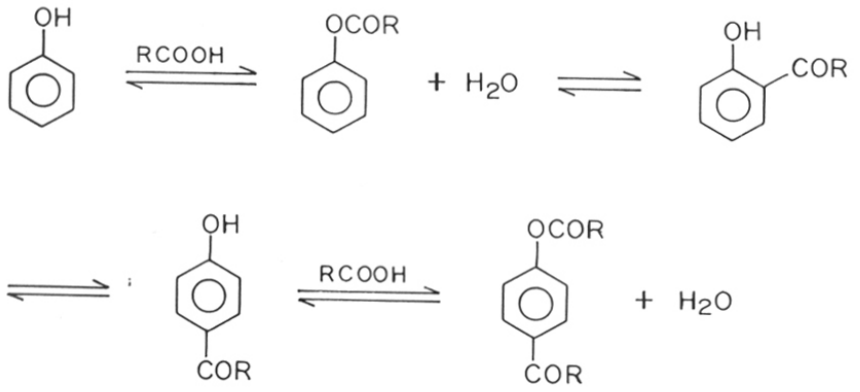
***Scheme 1-4***




### *1.3.1.2b Acylation of phenols and its derivatives:*

As in the case of alkylations of phenols, here too, the formation of a mixture of different products is possible. Phenols react with acids in the presence of zeolite ZSM-5[26,27] at 300°C to give mixtures of O-acylphenols, ortho and para acyl phenols, and para-acyl phenyl acetate. A recent study deals with acylation of anisole with phenylacetic acid[28] (*Scheme 1-5*). In this reaction, Corma et al. studied the acidities of different zeolites and their selectivity factors.

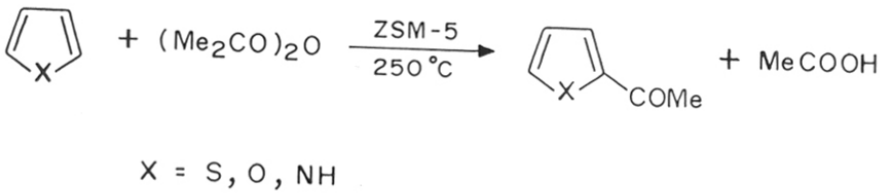
*Scheme 1-5*




### *1.3.1.2c Acylation of heteroarenes:*

Acylation of all heteroaromatics involves homogeneous Lewis acid catalysis. Recently, Holderich et al.[29] have reported a gas phase reaction using zeolite catalysts. The reaction of thiophene with acetic anhydride at 250°C in presence of boron ZSM-5 zeolite leads to 2-acyl thiophene with 25% conversion and 99% selectivity. Similarly pyrrole and furan give the corresponding 2-acyl products (*Scheme 1-6*).

*Scheme 1-6*



The direct C-acylation of imidazoles and pyrazoles by Friedel-Crafts reaction is unknown and it was predicted that this reaction is not possible at all. Recently, Holderich et al.[30] succeeded in the synthesis of 2-methyl-4-acetyl imidazole with the aid of a zeolite catalyst.

### 1.3.1.3 Nitrations:

Arenes and substituted arenes are nitrated with $N_2O_4$ or $NO_2$ in the gas phase using H-ZSM-5 or H-mordenite. Benzene and $N_2O_4$ at 200°C in presence of zeolite H-ZSM-5 produced nitrobenzene with 98% selectivity and 64% conversion[31]. Toluene is nitrated with $NO_2$ at 150°C in presence of H-mordenite to mono-nitrotoluene with 80% selectivity and 30% conversion. The regioselectivity found does not differ much from that obtained in conventional liquid phase nitration.

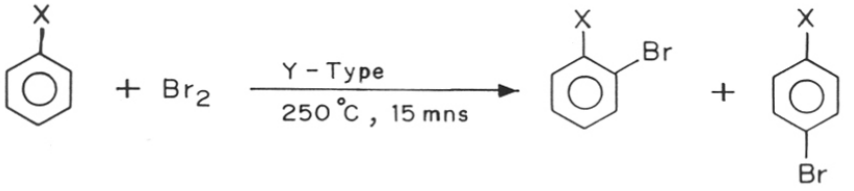
### 1.3.1.4 Halogenation:

Lewis acid catalyzed halogenation of aromatics is known in liquid phase reactions for industrial purposes. The same reaction has been carried out in presence of zeolite either in the gas phase or in liquid phase to reduce corrosion and disposal problems.

First Bekkum et al.[32] later Vega et al.[33,34] studied halogenation using various zeolite catalysts on different halobenzenes (*Scheme 1-7*) and arenes respectively. In particular bromination of toluene in presence of Y-type zeolite proceeded with high selectivity of para-isomer[33].

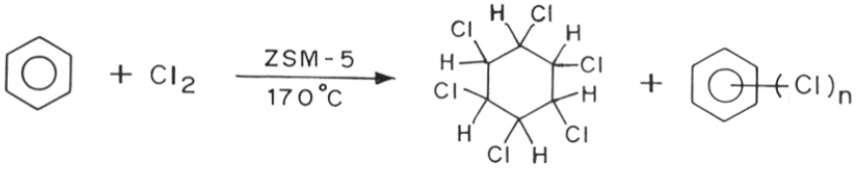
Zeolites of the ZSM-5 type would seem to be well suited for selective para halogenation in view of the geometry of the pore system. However, when ZSM-5 was applied at 170°C, surprisingly, addition reaction was observed but not substitution, leading to a mixture of hexachlorocyclohexanes[35] (*Scheme 1-8*).

*Scheme 1-7*




X = F, Cl, Br

*Scheme 1-8*



### 1.3.1.5 Aminations:

#### *1.3.1.5a Amination of arenes:*

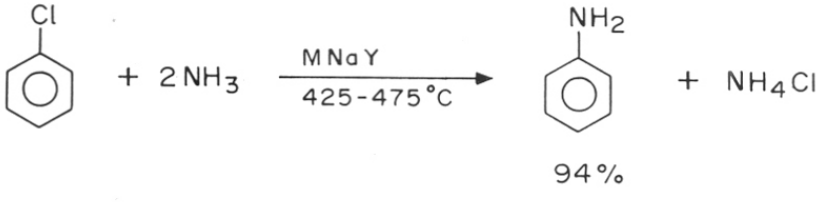
The existing methods for amination are:

1). Nucleophilic substitution of strongly deactivated anisoles (i.e. 2,4,6 trinitro anisole).

2). By benzyne mechanism.

Zeolites have now been used for amination reaction also. Thus,Warawdekar reported for the first time, the synthesis of aniline from chlorobenzene. Synthesis of aniline is of industrial interest.Reaction of chlorobenzene and ammonia (1:2) in presence of Cu-exchanged faujasites yields aniline[36] (*Scheme 1-9*). Phenols and anisole yield aniline in 94% yield over cation exchanged Y type zeolite.[37]

***Scheme 1-9***




#### *1.3.1.5b Reaction of alcohols with ammonia:*

Methylamines are produced by the reaction of methanol with ammonia at 250°C for 1 h on Na-Mordenite. This reaction also gives dimethylamine and trimethylamine as side products[38]. Recently, it was found[39] that when $SiCl_4$-treated Na-Mordenite was employed as the catalyst, the formation of trimethylamine was lowered to 0.5% at 100% conversion of methanol (350°C). The selectivity for dimethylamine is 73%. On the other hand the large pore H-Y zeolite produced 96% trimethylamine under the same conditions. Mochida et al. reported in 1983 the exclusive synthesis of dimethylamine (DMA) with 90% selectivity and 100% conversion of methanol[40].

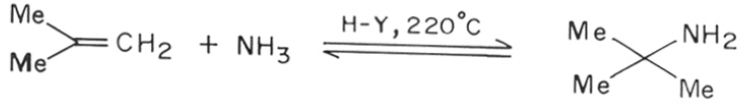
## 1.3.2 Addition reactions:

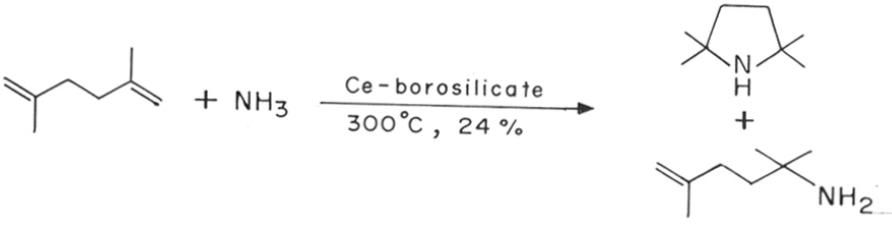
### 1.3.2.1 Addition of ammonia to olefins:

Alkylamines can be prepared from olefins and ammonia at 320° C and above by using zeolite catalysis. It is a temperature dependent reaction. Conversion of olefin increases with temperature. Ethylene with ammonia at 320°C on H-erionite or H-mordenite gave 2% of product, while at a temperature of 380°C 12% product formation is reported[41].

However, in the reaction of isobutene with $NH_3$ over H-Y at 220°C, conversion is 9% with 99% selectivity[42] (*Scheme 1-10*). Although the conversion is low, the simplicity, selectivity and pollution factors provided advantages over the conventional HCN addition based route to tert. butylamine preparation.

*Scheme 1-10*



Deeba et al.[41-43] found that strong acidic sites are necessary for the amination and this occurs via the protonated tert. butyl carbocation intermediate. The reactivity and product formation were studied with different olefins; the following order of reactivity was observed:

**isobutene > propene > ethylene**

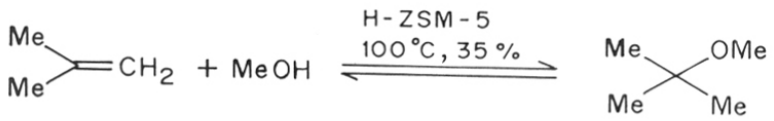
The amination of dienes is also known over zeolite catalysts[44]. 2,5-Dimethyl 1,5-hexadiene reacts with $NH_3$ over Ce-doped borosilicate at 300°C to give 2,2,5,5-tetramethylpyrrole with 25% selectivity and non-cyclic mono-addition product with 31% selectivity at overall 24% conversion of diene (*Scheme 1-10*).

### 1.3.2.2 Addition of alcohols to olefins:

The addition reactions of hydroxy compounds to olefins, over zeolites generally do not offer distinct advantages over conventional Bronsted catalytic method.

Ethers have been obtained by the acid catalysed addition to olefins. Methyl tert. butyl ether (MTBE) has been prepared from isobutene and methanol in presence of H-ZSM-5 zeolite at 100°C with 35% conversion and 95% selectivity (*Scheme 1-11*). The weakly acidic boron zeolite affords MTBE in 86% yield[45].

***Scheme 1-11***



## 1.3.3 Oxidation reactions:

### 1.3.3.1 Oxidation of carbon:

Many straight chain organic molecules with low molecular weight have been oxidized with the aid of zeolite catalysts in presence of either oxygen or hydrogen peroxide. The homogeneous liquid phase oxidation of phenol using perchloric acid to give hydroquinone which is the current method, leads to substantial quantities of side products. However, zeolite catalysis (instead of $HClO_4$) to achieve the same oxidation has been the subject of several recent publications. Hydroquinone predominates over catachol in this reaction, as a result of the shape-selectivity of the zeolite. Apart from the Pd, Cu zeolites reported earlier,[47]., the discovery of titanium containing MF type zeolite TS-1 and MEL type TS-2 has led to remarkable progress in the field of oxidation with $H_2O_2$. Conversion of phenol to hydroquinone with TS-1 and $H_2O_2$ has been studied extensively[48-50] and this method has been employed industrially on a large scale with a selectivity of more than 95% (*Scheme 1-13*).

Another important reaction of titanium zeolite is the liquid phase conversion of cyclohexanone to its oxime in presence of ammonia and hydrogen peroxide[51] (*Scheme 1-13*).

### 1.3.3.2 Oxidation of sulfur:

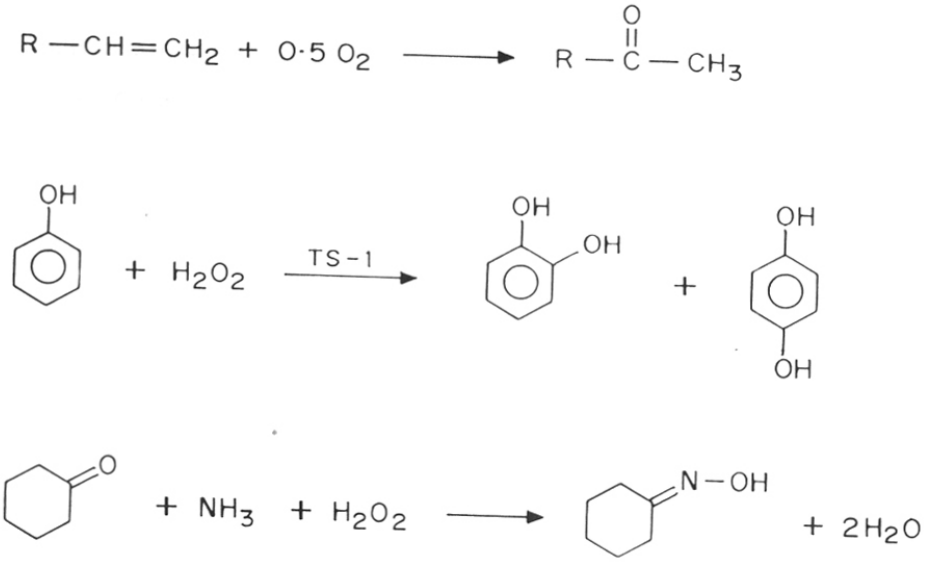
Hydroperoxides[52-54] and peracids[55] are well known to oxidise organic sulfides to sulfoxides and sulfones. Pandey et al.[56] also reported in 1989, the sensitised electron transfer oxidation of 2-substituted 1,3-dithiane to 1,3-dithiolane-1-oxide. Nevertheless, from the pollution point of view and recycling ability of zeolite catalysts, the sulfoxidation process reported using zeolites TS-1 and TS-2[57] is important. The reaction of thioethers with $H_2O_2$ in acetone in the presence of TS-1 or TS-2 at reflux temperature in 3 h, leads to the corresponding

sulfoxides in high yields along with the side product, viz sulfone (*Scheme 1-14*). The conversion rate observed was as follows.

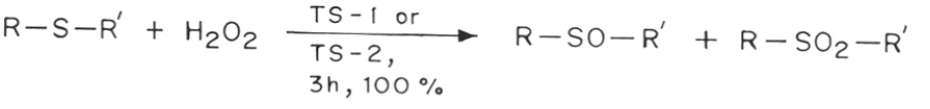
$$Me_2S >> Et_2S > PhSCH_3 > PhSEt$$

The mechanism of this reaction has also been discussed in this article.[57] During the oxidation of thiophenol and ethanethiol with $H_2O_2$ and TS-2 catalyst, the dimeric products PhSSPh and EtSSEt were obtained in almost quantitative yields.

*Scheme 1-13*




*Scheme 1-14*



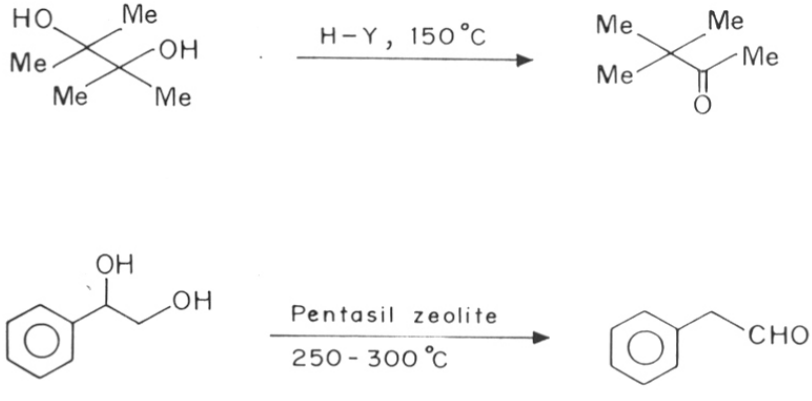
### 1.3.4 Rearrangements:

In some of the industrial rearrangement processes relatively large quantity of non-regenerable catalysts are used. Zeolites have a substantial potential for catalysis of rearrangement reactions and might lead to clean technology. Some of the important rearrangement reactions are discussed here:

#### 1.3.4.1 Pinacol rearrangement:

The classical method for this rearrangement involves acid treatment of glycols with proper substitution, leading to carbonyl compounds[58]. This reaction was also carried out successfully with a zeolite catalyst. 2,3-Dimethyl-2,3-dihydroxybutane in presence of H-Y zeolite at 105°C yields 83% of the rearranged product 3,3-dimethyl-2-butanone[59,60] (*Scheme 1-15*). If the temperature is raised to 300-350°C or higher, dienes are preferably formed.

*Scheme 1-15*

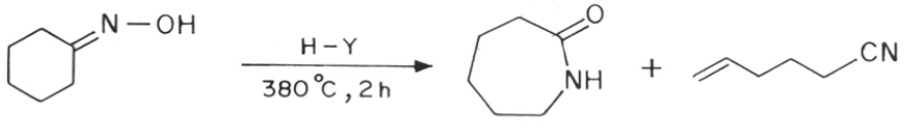


### 1.3.4.2 Beckmann rearrnagement:

Industrially, the most important Beckmann rearrangement is the conversion of cyclohexanoneoxime to caprolactam. Caprolactam is the starting material for Nylon-6. This conversion is conventionally carried out with a variety of acids, mainly, concentrated sulfuric acid[61]. The problems arising in this reaction are the formation of $(NH_4)_2SO_4$ as co-product and handling of large amount of fuming sulfuric acid.

In 1968 Venuto and Landis[13] reported the use of zeolites for achieving this rearrangement. Zeolites -X, -Y and even H-mordenite are employed for this reaction. Cyclohexanone oxime in benzene is converted over H-Y at 380°C to caprolactam with 76% selectivity and 85% yield in 2 h (*Scheme 1-16*). The principal byproduct is 5-cyanopent-1-ene. As the reaction continues, the selectivity and conversion decrease. All the mechanistic studies have been carried out on this reaction[62]. In this zeolite catalyzed rearrangement too, it has been proved that the group which is trans to OH group is the one which migrates.

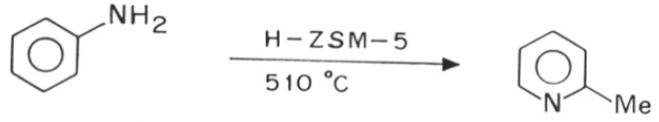
*Scheme 1-16*

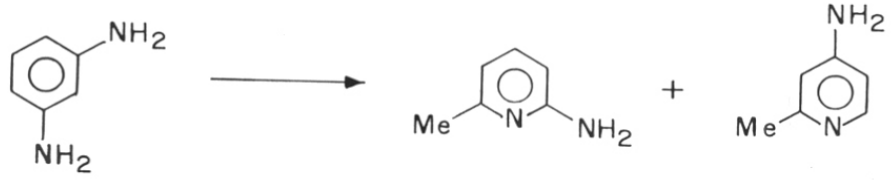


### 1.3.4.3 Benzamine rearrangement:

The conversion of anilines into pyridine derivatives with the aid of zeolite catalysis is chemically very interesting, and has industrial potential as well. Thus aniline has been reacted with ammonia to yield α-picoline at 510° C over H-ZSM-5 with 52% selectivity[63,64]. Similarly the 1,3-diaminobenzene rearranges to a mixture of 4- and 6- amino picolines (*Scheme 1-17*).

*Scheme 1-17*

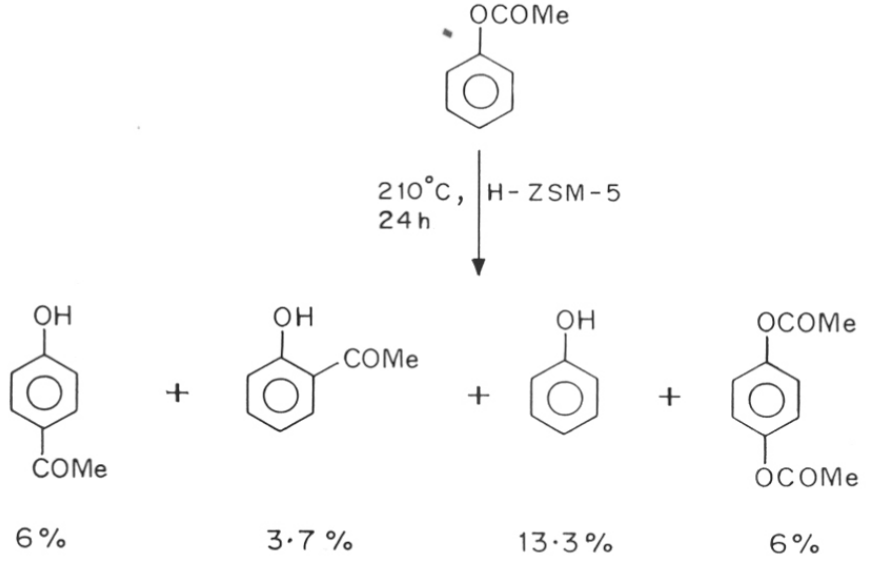


### 1.3.4.4 Fries rearrangement:

The Fries rearrangement of phenylesters to ortho- and para- hydroxy acetophenones is usually performed by $AlCl_3$ as catalyst[65]. In recent studies of zeolite catalysis[66,67] the same Fries rearrangement has been carried out with zeolite H-ZSM-5, but the selectivity is poor (*Scheme 1-18*).

***Scheme 1-18***



### 1.3.6 Summary:

Major applications of zeolites are in the reactions catalyzed by proton acids and Lewis acids, where the change from homogeneous to heterogeneous procedure brings advantages in respect of easy separation, elimination of corrosion and enviromental acceptance. Thermal stability of the zeolites permits them to be used above 150°C.

Numerous economically interesting organic reactions, which are hitherto not feasible, can now be commercially exploited using zeolites[68]. Furthermore, reports are beginning to appear in the literature dealing with stereochemistry of zeolite catalysed reactions[69] and the use of zeolites as carriers for enzymes and microorganisms in biotechnology.

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# CHAPTER - 2

# SYNTHESIS OF 1-METHYLAMINO-1-METHYLTHIO-2-NITROETHYLENE AND THE KINETICS OF THIS REACTION

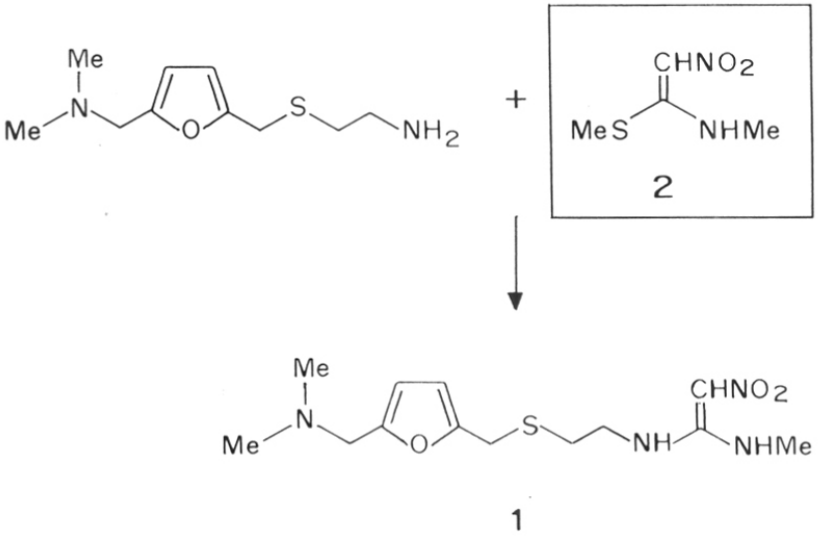
## 2.1 Abstract:

1-Methylamino-1-methylthio-2-nitroethylene is an important intermediate in the synthesis of the antiulcer drug Ranitidine. A new method has been devised for the synthesis of this intermediate under mild and almost neutral conditions. The method involves the condensation of nitromethane with N-methyl carbonimidodithioic acid dimethyl ester in presence of the zeolite catalyst RE(70%)NaY to give 1-methylamino-1-methylthio-2-nitroethylene (**2**) in 50% yield. Prior to the success achieved with the zeolite catalyst, various Lewis acids and bases were tried; but all these efforts were unsuccessful. This chapter of the thesis also describes the systematic study of the above reaction in regard to the amount and composition of the heterogeneous catalyst, duration of the reaction, temperature, and effect of solvent.

## 2.2 Introduction:

### 2.2.1 Background:

Ranitidine (**1**)[1,2] is an $H_2$-receptor antagonist; it is a powerful inhibitor of gastric acid secretion. It is an antiulcer drug being used worldwide. 1-Methylamino-1-methylthio-2-nitroethylene (**2**) is an important intermediate in the synthesis of Ranitidine[3,4]. Both Ranitidine and 1-methylamino-1-methylthio-2-nitroethylene belong to the general class of nitroenamines.



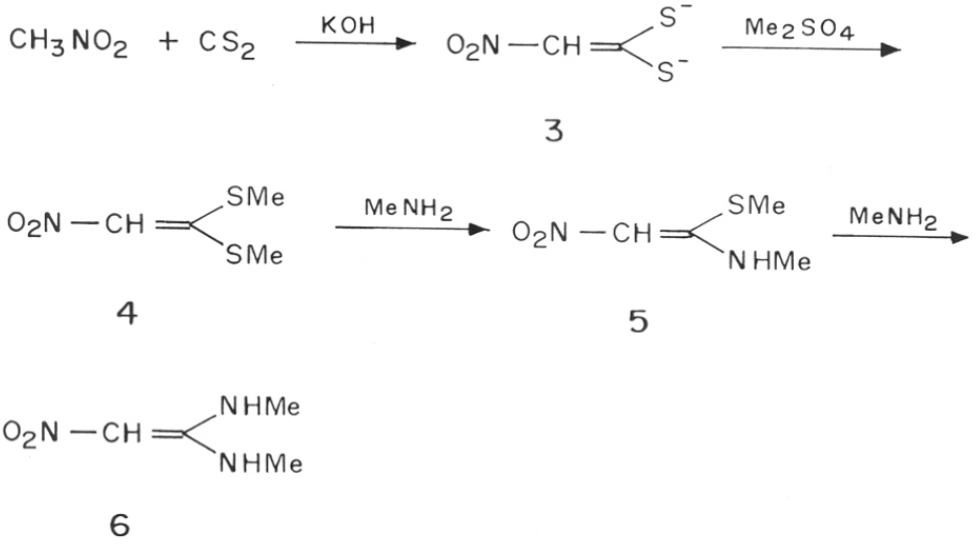

Though, there are a few general methods available for the synthesis of nitroenamines, the three reported routes for the synthesis of 1-methylamino-1-methylthio-2-nitroethylene (**2**) suffer from several serious drawbacks. These are discussed below.

### 2.2.2 Earlier synthetic reports:

#### 2.2.2a *From 1,1-bis(methylthio)-2-nitroethylene:*

The method involves the prior condensation of nitromethane with carbon disulfide in presence of alkali to form the dipotassium salt of the intermediate (**3**); this is then methylated with dimethylsulfate to give 1,1-bismethylthio-2-nitroethylene (**4**).[5] The reaction is innately hazardous, since it involves bringing together nitromethane and potasium hydroxide. In the second step, this bismethylthio compound **4** is reacted with methylamine to produce the required product **5**;[1,6,7] this involves an addition elimination sequence. However, the reaction does not stop cleanly at this stage. The product **5** can react with another molecule of methylamine, to produce the unwanted by-product, 1,1-bismethylamino-2-nitroethylene (**6**) (*Scheme 2-1*). Separation of **5** from the contaminant **6** is difficult; the process is therefore inefficient.

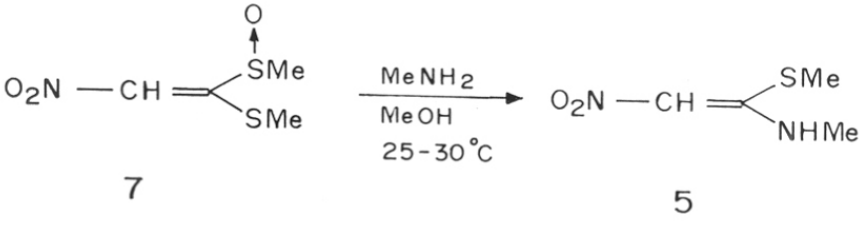
*Scheme 2-1*



### 2.2.2b *From 1-(methylsulfinyl)-1-(methylthio)-2-nitroethylene:*

In the above reaction of methylamine, there does not seem to be a great difference between the rate of displacement of the first SMe group and that of the second. To circumvent this problem, one of the sulfide groups in **4** was initially converted to the sulfoxide (**7**). Subsequent reaction of this reagent **7** with one equivalent of methylamine gave **5**.[8]

*Scheme 2-2*

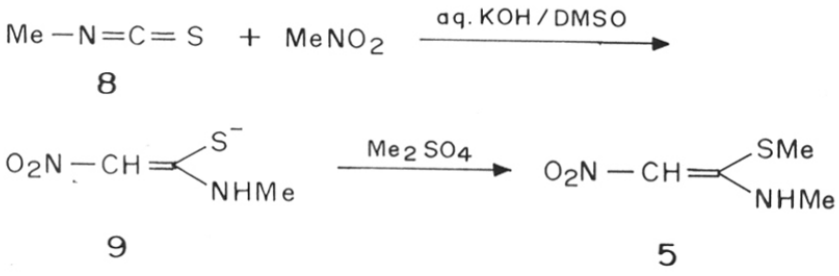



7 5

### 2.2.2c *From methyl isothiocyanate:*

The third approach for the synthesis of 1-methylamino-1-methylthio-2-nitroethylene by Searger et al. was patented in 1985[9,10]. In this method, nitromethane was deprotonated by base (KOH in DMSO, containing 7.5% water) and reacted with methylisothiocyanate (**8**) in DMSO. The resultant potassium salt (**9**) was S-methylated by means of dimethylsulfate to give 1-methylamino-1-methylthio-2-nitroethylene (**5**) in 49.4% yield (*Scheme 2-3*). There are several drawbacks in this method. (i) nitromethane and alkali form a hazardous combination, (ii) the use of DMSO as solvent leads to serious environmental problems, since it is difficult to recover DMSO from the effluent, and (iii) methylisothiocyanate has to be prepared initially for the reaction.

*Scheme 2-3*

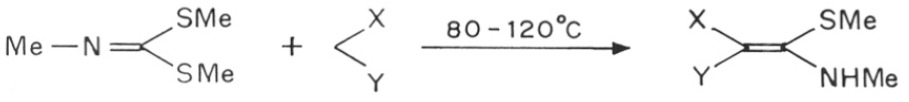



## 2.3 Present Work:

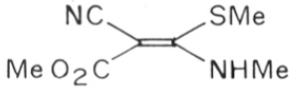
Our objective was to devise a totally new synthesis of 1-methylamino-1-methylthio-2-nitroethylene (**5**) which would avoid the drawbacks of the older methods. In our approach, methylamine is condensed with carbon disulfide in presence of aqueous NaOH. The resultant N-methyl carbonimidodithioic acid disodium salt is methylated with dimethylsulfate to give the corresponding dimethyl ester (**10**). This is then condensed with nitromethane to give the required product. In this strategy, the sequence of putting together the individual components has been reversed from older methods. Additionally it is to be noted that the base-catalysed condensation of carbon disulfide is carried out on methylamine, and not on nitromethane.

Prior to this, Metzger et al[11]. had reported the condensation of **10** with several active methylene compounds such as methyl cyanoacetate and malononitrile to give the corresponding products **11** and **12** in 42% and 95% yields respectively (*Scheme 2-4*). In principle, the reaction of nitromethane with **10** would directly lead to the desired compound 1-methylamino-1-methylthio-2-nitroethylene **5**. However, under similar conditions, the condensation could not be

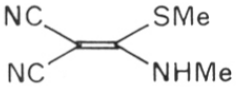
*Scheme 2-4*




10




11

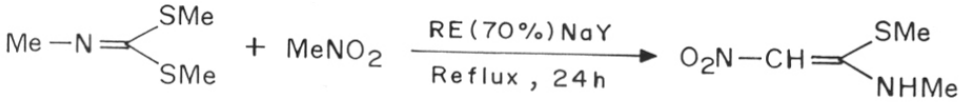



12

induced with the help of conventional catalysts. Finally, success was achieved and the required product obtained when a zeolite was used as the catalyst[12] (*Scheme 2-5*). Of the several zeolites tried, the best results were obtained with RE(70%)NaY, that is a '**Y**' type zeolite in the sodium form, in which 70% of the $Na^+$ ions had been replaced by rare-earth cations.

To optimise the yields and reaction efficiency, we have also studied this reaction with zeolites in which the sodium ion had been exchanged with specific pure rare-earth cations.

*Scheme 2-5*




10

5

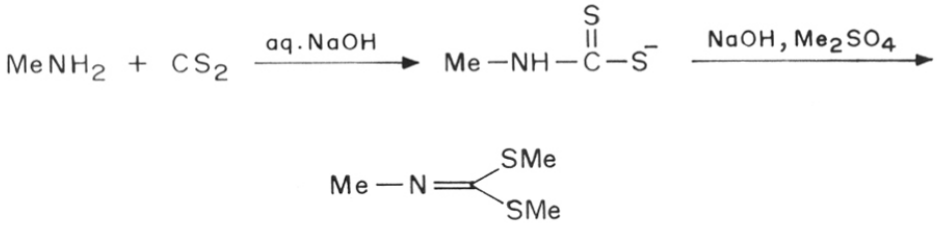
During the study of the kinetics of this reaction, we have also isolated a 5-8% yield of S-methyl N-methyl thiolcarbamate (**13**) (*Scheme 2-7*). All these aspects have been discussed below in detail.

## 2.4 Results and Discussion:

### 2.4.1 Synthesis of N-methyl carbonimidodithioic acid dimethyl ester (10):[13]

N-Methyl carbonimidodithioic acid dimethyl ester is the starting material for the present synthesis of 1-methylamino-1-methylthio-2-nitroethylene (**2**). This has been prepared by the reported procedure with appropriate modifications[13]. The method consists in adding methylamine to carbon disulfide in presence of aq. NaOH to generate the dithiocarbamate sodium salt, which is then methylated on both the sulfur atoms by means of dimethylsulfate to yield the desired product **10** (*Scheme 2-6*). The $^1$H-NMR spectrum of the purified (distillation, b.p. 120-122°C/70mm) sample has shown three singlets at 3.15 δ, 2.55 δ and 2.30 δ corresponding to $NCH_3$, $SCH_3$ and $SCH_3$ respectively. The mass spectrum exhibited the molecular ion peak ($M^+$) at *m/z* 135. This data clearly fits with the structure of the product **10**.

*Scheme 2-6*




**10**

### 2.4.2 Synthesis of 1-methylamino-1-methylthio-2-nitroethylene(5):

The new strategy for the synthesis of 1-methylamino-1-methylthio-2-nitroethylene called for the condensation of nitromethane with N-methyl carbonimidodithioic acid dimethyl ester (**10**). As mentioned in section 2.3, some active methylene compounds had earlier been reported to condense with **10**. The reaction was achieved without the enfluence of any catalyst. Thus malononitrile on being heated with **10** at 80°C in benzene gave the product **12** in 95% yield.[11] With this precedent in mind, N-methyl carbonimidodithioic acid dimethyl ester (**10**) was refluxed with excess nitromethane. However, no trace of the condensation product **5** could be seen in this reaction. In order to facilitate the desired condensation, several catalysts were then tried. These included several Lewis and Bronsted acids [p-toluenesulfonic acid, borontrifluoride etherate, and Zinc chloride], and bases [triethylamine, potassium carbonate, potassium fluoride, sodium hydride, sodium methoxide, and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)]. All these, however, were of no avail; either the unreacted starting materials were recovered, or black tars were generated. Thus, refluxing a mixture of **10** and nitromethane in toluene for 24 h in the presence of p-TsOH, with periodic monitoring of the reaction mixture by tlc showed no trace of the desired product. Similar results were obtained with zinc chloride. When borontrifluoride etherate was used as the catalyst, a black tar was generated, from which no pure compound could be isolated. Bases like potassium carbonate, sodium hydride, sodium methoxide were similarly not effective.

Since the conventional homogenous catalysts failed to bring about the condensation, we decided to investigate the possible use of heterogenous catalysts in this condensation.

The first attempt was made with the acidic zeolite H-ZSM-5. Refluxing a mixture of nitromethane and N-methyl carbonimidodithioic acid dimethyl ester (**10**) in benzene with the above catalyst for 70 h. gave a solid product in 12% yield (*Scheme 2-5*). This was identified as the required product **5** based on the following evidence:

The solid product had m.p. 113°C. The $^1$H-NMR spectrum of the purified solid (*Spectrum No. 2-1*) showed two singlets at 6.65 δ and 2.45 δ in the ratio 1:3 corresponding to the olefinic proton and -$SCH_3$. A doublet at 3.15 δ for three protons ($NHCH_3$) and a broad peak at 10.5 δ (NH) proved that the structure of the product was **5**. The molecular ion peak ($M^+$) in the mass spectrum appeared at *m/z* 148.

The success achieved in condensing nitromethane and **10** with the help of H-ZSM-5, albeit in low yield, prompted us to try out other zeolites in order to find the best catalyst for this reaction.

The following sections are devoted to the efforts made with this in view:

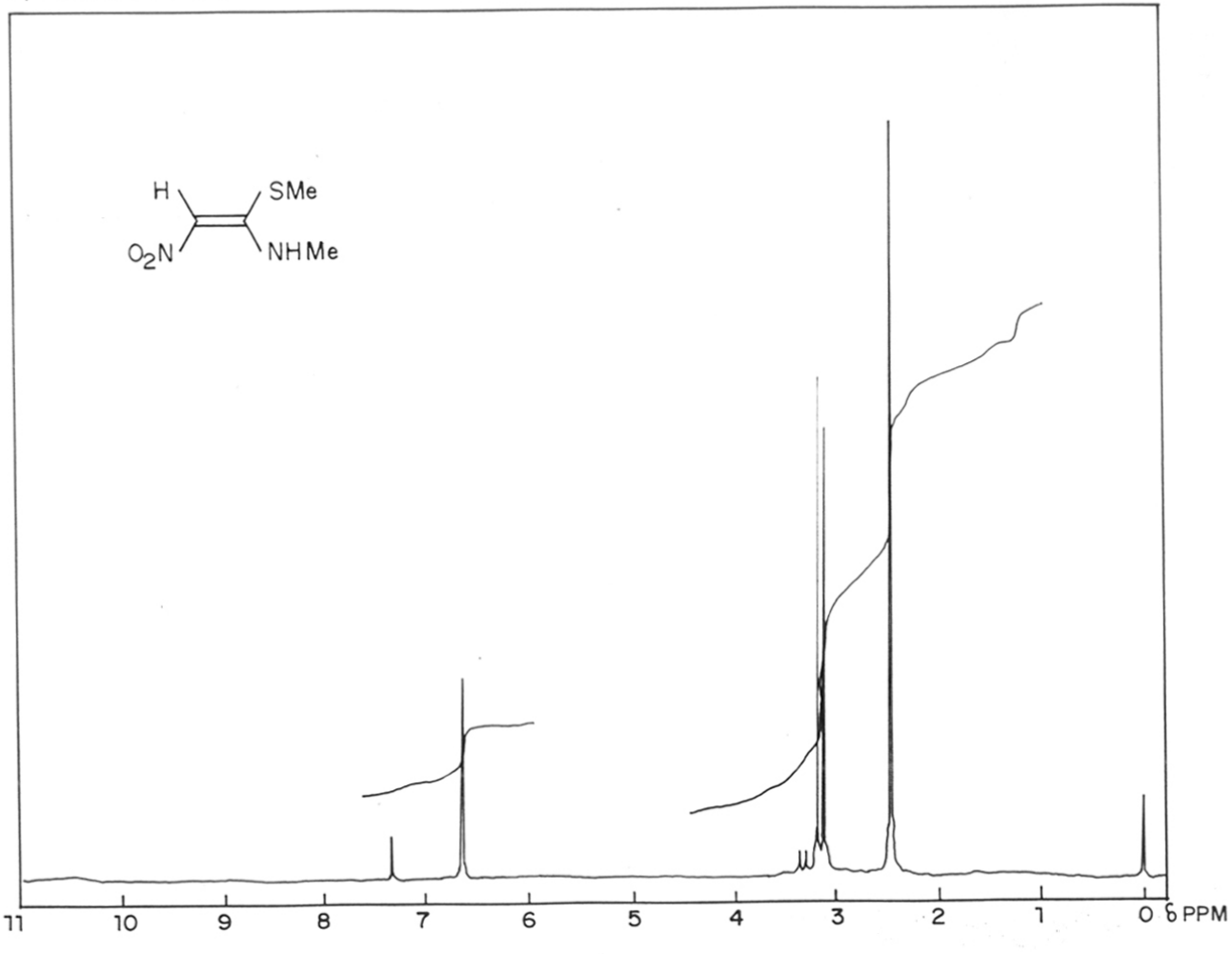
### 2.4.2a *Y-type zeolites and their cation-exchanged forms:*

N-Methyl carbonimidodithioic acid dimethyl ester (**10**) was refluxed with excess nitromethane, with vigorous stirring, in presence of the sodium form of the Y zeolite, NaY. In this catalyst, sodium ions have replaced the protons of the acidic zeolite H-Y. The pore diameter is 0.74 nm. After refluxing the mixture for 48 h, it was found that the desired product was obtained in barely 8% yield; considerable tar formation had also occurred.

As mentioned in Chapter-1, one of the most useful features of the zeolite is the possibility of exchanging the cation ($Na^+$) for others. This exchange can be easily accomplished by stirring NaY with an aqueous solution of the desired metal chloride. In this way, $Cu^{2+}$, $Ni^{2+}$ and $Zn^{2+}$ ions were introduced into the zeolite. However, none of these cation-exchanged zeolites gave rise to the desired product.

The next attempt was the exchange of $Na^+$ ions by a mixture of rare-earth metal ions.[14] A mixture of NaY zeolite (faujasite group with $SiO_2/AlO_3$ = 4.6; pore size 0.74 nm)[15,16] (10g), 5% aqueous solution of Didymium chloride [mixture of rare-earth chlorides supplied by Indian Rare Earth Ltd. as Didymium chloride; the composition of this mixture is as follows : cerium,

Spectrum No. 2-1



traces; Praseodymium, 10-22% Neodymium, 35-40% Samarium, 4-6%; Lanthanum, Yttrium and heavier metals such as Europium, Gadolinium, Terbium, Dysprosium and Holmium are 40-45%] (100 ml) was heated on a water bath at 100°C with mechanical stirring for 6h. The solid was filtered and washed with distilled water (2x20 ml). The same procedure was repeated once more to get the desired amount of rare earth ion insertion into zeolite (about 70%). The exchanged zeolite RE(70%)NaY was thoroughly washed with distilled water, dried at 100°C for 3 h and activated at 400°C for 4 h. The crystallinity of the exchanged zeolite was checked by X-ray powder pattern. The percentage of rare-earth ions exchange was measured by analysis of sodium ion content in the distilled water washings. As before, a mixture of the carbonimidodithioate **10** in excess nitrmethane and the above RE(70%)NaY catalyst was refluxed for 48 h. After filtration of the catalyst and distillation of the excess nitromethane, a 50% yield of the product **5** was obtained as a pure crystalline material.

This significant achievement has resulted in the development of an economically viable process for 1-methylamino-1-methylthio-2-nitromethane.

In order to determine, if possible, which of the rare-earth cations was responsible for this increase in yield, NaY was subjected to cation exchange with several pure rare-earth metals. This included Lanthanum, Cerium, Niodymium, Praseodymium and Samarium. These cation-exchanged zeolites were then utilized for the same reaction, under the same conditions (the duration was reduced to 24 h). The results are tabulated in *Table 2-1*. Surprisingly, while the rare-earth mixture under these conditions (24 h reaction time) gave 42% of the product, none of the other zeolites (exchanged with the individual rare-earth ions) couod match this yield. The yields ranged from 17% to 31%. We are at present unable to explain this curious result.

Of the non-transition metals, surprisingly $Ca^{++}$ exchanged NaY gave a 40% yield of the required product (*See table 2-1*).

**Table 2-1: Condensation over various catalysts and clays:**

| Catalyst | Reaction time (h) | Product distribution, %. Compound 5 | Compound 13 |
|---|---|---|---|
| **zeolite catalysts:** | | | |
| RE(70%)NaY | 40 | 50.0 | 5-10 |
| Ca(70)NaY | 24 | 40.2 | - |
| RE(70%)HY | 24 | - | - |
| NaY | 24 | 08.0 | - |
| CaY | 24 | 05.0 | - |
| NaX | 24 | - | - |
| H-ZSM-5 | 70 | 12.0 | - |
| Si/Al Amorphous | 24 | 06.0 | 02.0 |
| La(70%)NaY | 24 | 22.0 | 05.0 |
| Ce(70%)NaY | 24 | 25.0 | 06.0 |
| Nd(70%)NaY | 24 | 31.0 | 03.0 |
| Pr(70%)NaY | 24 | 30.0 | 08.0 |
| Sm(70%)NaY | 24 | 17.0 | 07.0 |
| **Clays:** | | | |
| Montmorillonite K10 | 34 | 18.0 | 03.0 |
| Al PILC | 24 | 12.0 | 04.0 |
| Ti PILC | 24 | 06.0 | 12.0 |
| Pr-Clay | 24 | 10.0 | 15.0 |

* Imine/nitromethane mole ratio = 1:5; catalyst half the weight of imine.
* Refluxing temperature.
* Zeolites suplied by PQ corporation USA and Hindustan Lever Ltd. Bombay.

### 2.4.2b *Clays and other materials:*

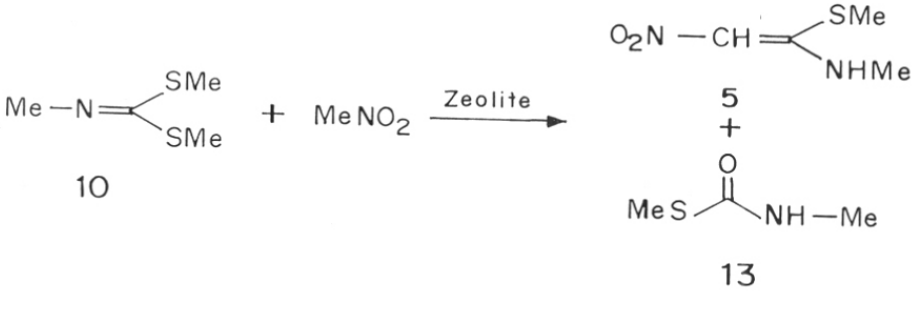
In order to check whether pre-adsorption of the reactants inside the well defined cavity of the crystalline zeolite played any significant role in bringing about the desired condensation, the experiment was repeated using amorphous aluminosilicates, clays and pillared clays (24 h, reflux only). The results are summarized in *table 2-1*. With the amorphous alumina-silica, a 6% yield of the product was realized. While montmorillonite-K10 gave 18% of **5**, the aluminium, titanium and praseodymium pillared clays gave lower yields. (These pillared clays were obtained from RRL Trivandrum).

### 2.4.2c *By-product in the condensation:*

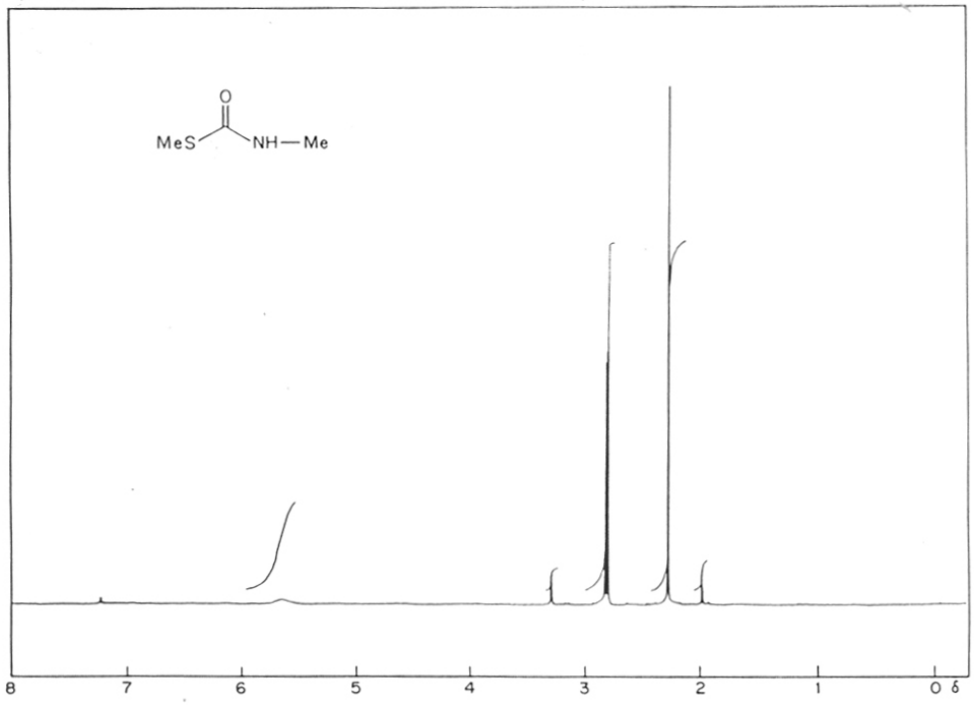
Careful analysis (GC and tlc) of the crude reaction mixture revealed the presence of another product (*Scheme 2-7*) apart from 1-methylamino-1-methylthio-2-nitroethylene (**5**). This was isolated and purified. The product was a liquid having the following characteristics: b.p. 70-74°C/5 mm. $^1$H NMR ($CDCl_3$): (*Spectrum No. 2-2a*) 5.50 (br, NH), 2.75 (d, $NHCH_3$), 2.25 (s, $SCH_3$). The IR spectrum (*Spectrum No. 2-2b*) showed a band at 1670 cm$^{-1}$. The molecular ion ($M^+$) peak in the mass spectrum was observed at *m/z* 105. Based on analytical and spectral data, it was deduced that the compound was S-methyl N-methyl thiolcarbamate (**13**).

The amount of this by-product obtained in the various experiments with different catalysts has been tabulated (*Table 2-1*).

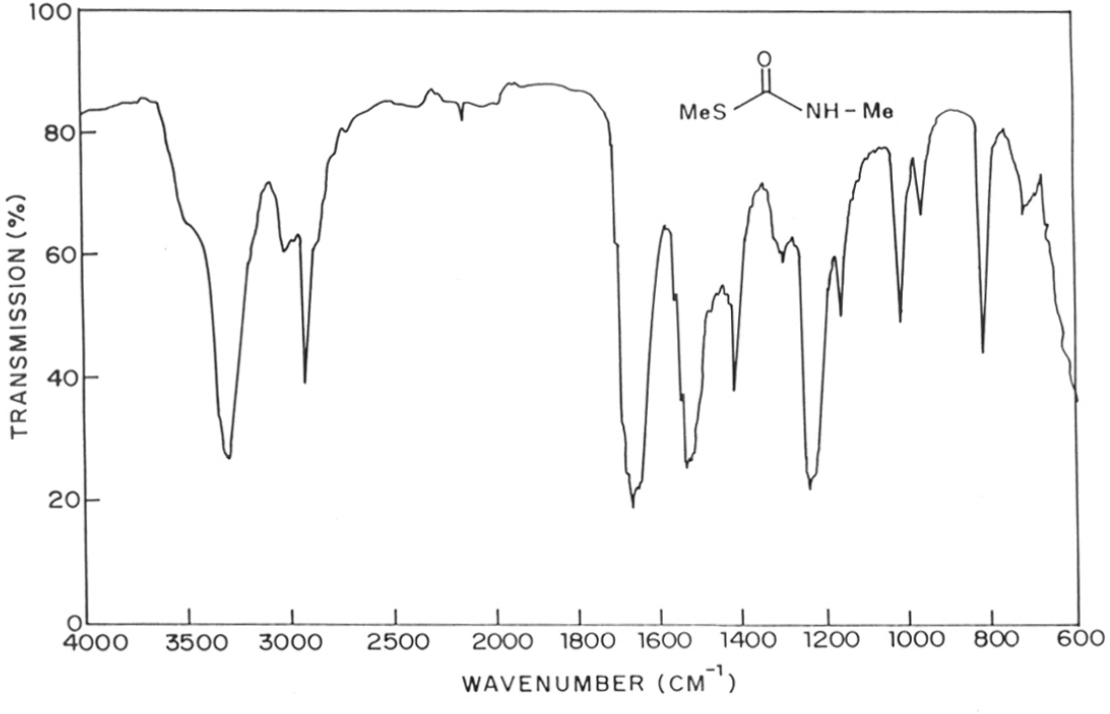
*Scheme 2-7*



Spectrum No. 2-2a




Spectrum No. 2-2b



### 2.4.2d *Variation of other parameters:*

A systematic study has also been carried out on the effect of varying the temperature, duration of the reaction, and proportion of reactants and catalyst on the yield of the required product **5**. The catalyst used in this study is RE(70%)NaY.

**i) Effect of temperature:**

The condensation was carried out at different temperatures, at constant molar ratio of the reactants and catalyst. The duration of the reaction was also kept constant (24 h). There was practically no product formed at room temperature. The yield progressively increased at 60°C, 80°C and 100°C, attaining a maximum of 50% at 100°C (*table 2-2*).

**Table 2-2: Effect of temperature on the yield of the product 5:**

| **Temperature (°C)** | 30 | 60 | 80 | 100 |
|---|---|---|---|---|
| **Weight of the product (in g)** | - | 3.10 | 5.00 | 7.40 |
| **% of the product based on 10** | - | 21 | 34 | 50 |

**ii) Reaction time:**

The reaction was carried out in refluxing nitromethane (~105°C). Different batches were quenched at the end of 14, 20, 24, 30, 36 and 48 h, and the product isolated in each case. The results are tabulated in *table 2-3*. It was observed that the yield increased up to 24-30 h; thereafter the yield decreased and some charring was observed; this was probably due to decomposition of the products formed.

**Table 2-3: Yield of product (5) as a function of duration of the reaction:**

| **Reaction time (h)** | 14 | 20 | 24 | 30 | 36 | 48 |
|---|---|---|---|---|---|---|
| **Weight of 5 (in g)** | 3.29 | 6.05 | 6.25 | 6.40 | 5.95 | 6.75 |
| **% of the product based on 10** | 22.22 | 40.87 | 42.22 | 43.24 | 40.20 | 45.60 |

**iii) Effect of changing the molar proportion of reactants:**

With a fixed quantity of the carbonimidodithioic acid ester, a series of experiments was carried out with varying amounts of nitromethane. All other parameters were kept constant. The results are presented in *table 2-4*. As the molar ratio of the imine to nitromethane was increased from 1:1 to 1:5, there was a progressive increase in the yield of the product **5**. There was a plateau at this point, and any further increase in the amount of nitromethane did not produce a corresponding increase of the product.

**Table 2-4: Influence of nitromethane concentration in the product formation:**

| **Imine/nitromethane mole ratio** | 1:3 | 1:4 | 1:5 | 1:6 | 1:7 |
|---|---|---|---|---|---|
| **Weight of the product (in g)** | 4.44 | 5.47 | 6.25 | 6.36 | 6.03 |
| **% of the product based on 10** | 30.00 | 37.00 | 42.22 | 43.00 | 41.00 |

**iv) Variation in the amount of zeolite catalyst:**

Several condensation reactions were carried out in which only the amount of the zeolite RE(70%)NaY was varied. All other parametors were kept constant. It became obvious that the influence of the relative amount of catalyst on the conversion of the carbonimidodithioate

to the nitroketene N,S-acetals is rather more pronounced than that of other parameters. As expected, the yield increased as the amount of catalyst was increased. However, at around 50% by weight of the zeolite (with respect to the imine), the product yield attained a plateau. It was observed that on further addition of more catalyst, the product quality became inferior, probably as a result of contamination with polymeric, coloured, material (*table 2-5*).

**Table 2-5: Effect of catalyst concentration on product formation:**

| **Catalyst quantity (in g.)** | 4.00 | 5.00 | 6.70 | 8.00 | 9.00 |
|---|---|---|---|---|---|
| **Weight of the product** | 3.33 | 4.50 | 6.25 | 5.65 | 5.40 |
| **% of the product based on 10** | 22.50 | 30.40 | 42.22 | 38.17 | 37.34 |

## 2.5 Summary:

The synthesis of 1-methylamino-1-methylthio-2-nitroethylene described here is a totally new method. The reaction conditions are mild and almost neutral. This reaction was studied systematically and extensively with various clays and zeolite catalysts under different conditions.

## 2.6 Experimental:

**General:**

All the chemicals used in this study were commercial grade purematerials and were used after distillation. All the reactions were monitored by employing standared tlc technique using appropriate solvent system for development and plates were exposed to iodinevapour for developing the spots. All the solvent extracts were washed with brine then dried over anhydrous $Na_2SO_4$ and concentrated at reduced pressure on a Buchi rotary evaporator. Yields reported are isolated yields of material judged homogenous by tlc and NMR spectroscopy.

**Melting points:**

All melting points were recorded on YAMACO instrument model M.P. and are uncorrected.

**Boiling points:**

Distillations were carried out under vacuum using oil bath for all liquid samples and boiling points refer to the condenser temperature.

**Nuclear magnetic resonance spectra:**

$^1H$ NMR spectra recorded on varian FT 80A and BRUKER AC 200 and $^{13}C$ spectra recorded on BRUKER AC 50 MHz, BRUKER MSL 75.5 MHz spectrometors. All the samples were dissolved in chloroform-d solvent and chemical shifts are reported on δ scale using tetramethylsilane ($Me_4Si$) as the internal standard. The abbreviations s, d, t, q and m, refer to singlet, doublet, triplet, quartet and multiplet respectively. Coupling constants (J), wherever mentioned have been given in Hz.

**Infrared spectra:**

Infrared spectra were recorded on Perkin-Elmer 599B spectrophotometer. Solid samples were recorded in Nujol or chloroform, liquids were neat and measured in $cm^{-1}$.

**Mass spectra:**

Mass spectra were recorded on Finnigan MAT-1020 instrument using direct inlet system.

**Elemental analysis:**

Elemental analysis were performed on M/S S.Modern microchemical instruments Holland.

**Chromatography:**

Thin-layer chromatography (tlc) were performed on (6x2 cm) glass plates coated with commercial grade silica gel G and visualisation of the spots on tlc plates was achieved by exposure to iodine vapour or under UV light. Column chromatograpry was performed using SD's commercial grade silica gel (100-200) mesh activated at 130°C for 5 h. and column was usually eluted with ethyl acetate-n-hexane or petroleum ether mixtures.

**Synthesis of N-methyl carbonimidodithioic acid dimethyl ester (10)[13]:**

It has been prepared by reported procedure with appropriate modifications. Aqueous solution (40%) of methylamine (10 mmol) was added to the previously cooled (0°C) mixture of carbon disulfide (10 mmol), water (10 ml), Petroleum ether (20 ml) and phase transfer catalyst Aliquat 336 (tricaprylylmethylammonium chloride) (20 mg), and this mixture was stirred for 10-15 mns. at below 10°C. To this stirring mixture aqueous NaOH solution (20 mmol) and dimethyl sulfate (20 mmol) were then added successively at 10°C. After stirring the reaction mixture

at room temparature over night, the organic layer was separated and washed with water. Aqueous layer was extracted with benzene and combind organic layer was dried with anhyd. sodium sulfate and concentrated to a liquid which was purified by fractional distillation.

| | | |
|---|---|---|
| Yield | : | 72%, yellow colored liquid. |
| b.p. | : | 120-122°C/70 mm (Lit[13]. 188-192°C) |
| $^1$H NMR (80 MHz) | : | δ 3.15 (s, 3H, $NCH_3$), 2.55 (s, 3H, $SCH_3$), 2.30 (s, 3H, $SCH_3$). |
| IR (Nujol) | : | $cm^{-1}$ 1580. |
| MS | : | *m/z* 135 ($M^+$, 60%), 93 (100). |
| Analysis | : | $C_4H_9NS_2$. Calcd. : C, 35.55; H, 6.66; N, 10.37. Found : C, 35.62; H, 6.57; N, 10.42. |

**Synthesis of 1-methylamino-1-methylthio-2-nitroethylene (5):**

**By using conventional catalysts:**

To a mixture of N-methyl carbonimidodithioic acid dimethyl ester (**10**) (10 mmol) and nitromethane (10 mmol), a catalyst for example zinc chloride was added slowly and the mixture was heated at different temperatures. The reaction was monitored by tlc. However, no trace of the condensation product **5** could be seen in this reaction. In order to facilitate the desired condensation, several catalysts were then tried. These included several Lewis Bronsted acids [p-toluenesulfonic acid, borontrifluoride etherate, and Zinc chloride], and bases [Tri-methylamine, potasium carbonate, potasium fluoride, sodium hydride, sodium methoxide, and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)]. All these, however, were failed to give required product **5**, and in all reactions either the unreacted starting materials were recovered, or black tars were generated.

**By using zeolite catalyst RE(70%)NaY:**

Freshly activated zeolite RE(70%)NaY (6.7g) was added to the mixture of N-methyl carbonimidodithioic acid dimethyl ester (13.5g) and nitromethane (28g) at room temperature. The reaction mixture was then refluxed for 24 h, then cooled to room temperature and the catalyst was filtered off and washed with $CH_2Cl_2$ (3x30ml). The solvent and excess nitromethane was removed at reduced pressure. The residue was then taken in n-hexane and stirred for a few min, when the product solidified and unreacted imine remained dissolved in n-hexane. Filtered solid 7.45g (50% crude) crystallized from ethanol to get pure light yellow crystals (7.0) g (48.5%) m.p. 113°C. Filtrate was concentrated and compound **13** was isolated as a liquid by column chromatography.

**By using Clays and other catalysts:**

Freshly activated Titanium pillared clay (Ti PILC) (1g) was added to the mixture of N-methyl carbonimidodithioic acid dimethyl ester (1g) and nitromethane (2 ml) at room temperature. The reaction mixture was then refluxed for 24 h, then cooled to room temperature and the clay was filtered off and washed with $CH_2Cl_2$ (3 x 10ml). The solvent was removed at reduced pressure. The residue was then taken in n-hexane and stirred for a few min, when the product became gum. The n-hexane was decaned and the solid was chromatographed to get pure light yellow coloured crystals of product **5**. The decaned n-hexane washings was concetrated and purified by column chromatography to get S-methyl N-methyl thiolcarbamate **13**. Reaction was repeated with following clays: Montmorillonite K10, Al PILC, Pr Clay and Silica/Alumina amorphous. None of the clay materials gave the encouragiable yield of **5**.

**1-methylamino-1-methylthio-2-nitroethylene (5):**

| | | |
|---|---|---|
| Yield | : | 50% , Light yellow colored crystals. |
| m.p. | : | 113°C (EtOH). |
| $^1$H NMR (80 MHz) | : | δ 10.5 (br, 1H, NH), 6.64 (s, 1H, =CH), 3.15 (d, 3H, $NCH_3$) 2.45 (s, 3H, $SCH_3$). |
| IR (Nujol) | : | $cm^{-1}$ 3350, 1580, 1470, 1390. |
| MS | : | *m/z* 148 ($M^+$, 80%), 101, 55 (100). |
| Analysis | : | $C_4H_8NO_2S$. Calcd. : C, 32.43; H, 5.40; N, 9.45. Found : C, 32.43; H, 5.42; N, 9.46. |

**Methyl N-methyl thiolcarbamate (13):**

| | | |
|---|---|---|
| Yield | : | 08% |
| b.p. | : | 70-74°C/5mm. |
| $^1$H NMR (200 MHz) | : | δ 5.50 (br, 1H, NH), 2.75 (d, 3H, $NCH_3$) 2,25 (s, 3H, $SCH_3$). |
| IR (Nujol) | : | $cm^{-1}$ 3310, 1670, 1540, 1230. |
| MS | : | *m/z* 105 ($M^+$, 95%), 58 (100). |
| Analysis | : | $C_3H_7NOS$. Calcd. : C, 34.28; H, 6.66; N, 13.33. Found : C, 34.32; H, 6.62; N, 13.36. |

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# CHAPTER - 3

# SCOPE OF ZEOLITE CATALYSIS: SYNTHESIS OF PUSH - PULL ETHYLENE SYSTEMS

## 3.1 Abstract:

The scope of the zeolite catalyzed condensation between carbonimidodithioic acid esters and various active methylene compounds has been fully explored. This has led to the synthesis of several functionalized ketene N,S-acetals in more than 70% yields. Our efforts to synthesize push-pull systems with a longer conjugation using this zeolite catalyzed process has however, not succeeded.

## 3.2 Introduction:

### 3.2.1 Background:

Functionalized ketene N,S acetals belong to the general class of push-pull ethylene systems. In such molecules one end of the double bond is attached to an electron donating group (amine) and the other end to an electron withdrawing group (nitro or carbonyl). Consequently, there is delocalization of π-electrons over the entire system. Such compounds have been synthesized in order to study their intrinsic properties.[1] They have also been utilized as versatile intermediates for the synthesis of heterocyclic compounds.[2,3,4] There are only two methods known in the literature for the synthesis of such functionalized ketene N,S-acetals. One is the substitution of one of the S-alkyl groups of ketene S,S-acetals by amines through an addition-elimination mechanism. The other is the addition of active methylene compounds to alkyl or aryl isothiocyanates followed by S-alkylation. The drawbacks in these two routes are the formation of unwanted side products and the necessity of using isothiocyanates as starting materials.

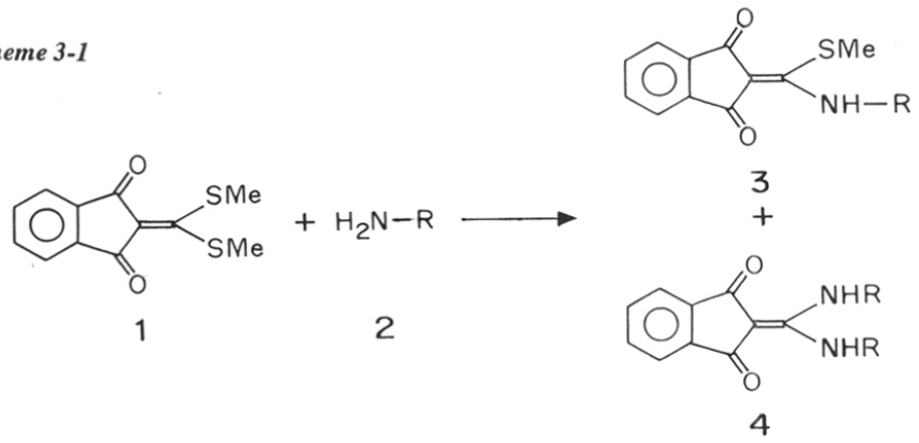
### 3.2.2 Earlier synthetic methods:

#### 3.2.2a *Synthesis of α-oxoketene N,S-acetals:*[5-10]

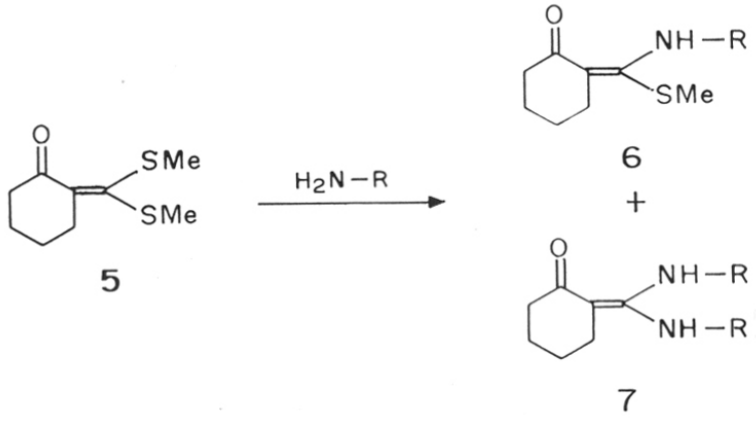
The doubly activated ketene S,S-acetals (**1**) undergo an addition-elimination sequence with amines (**2**) to give the corresponding N,S-acetals (**3**). The reaction however, cannot be stopped cleanly at this stage, it always leads to some amount of the further displacement product, the N,N-acetals (**4**). The formation of the side product can be controlled to some extent by controlling the stoichiometry of the added amines (*Scheme 3-1*). However, the less reactive α-oxoketene S,S-acetals (**5**) required more vigorous conditions for their reaction with amines and generally offered a mixture of N,S and N,N-acetals **6** and **7**.[7-10] (*Scheme 3-2*)

The second method involves the reaction of enolate ions of active methylene compounds (**8**) with isothiocyanates (**9**) followed by S-alkylation to give the required ketene N,S-acetals (**10**)[10-12] (*Scheme 3-3*)

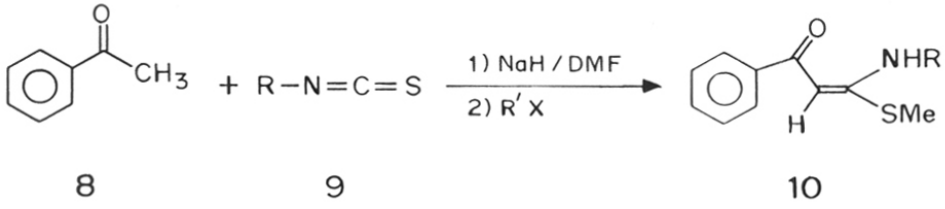
*Scheme 3-1*




*Scheme 3-2*




*Scheme 3-3*

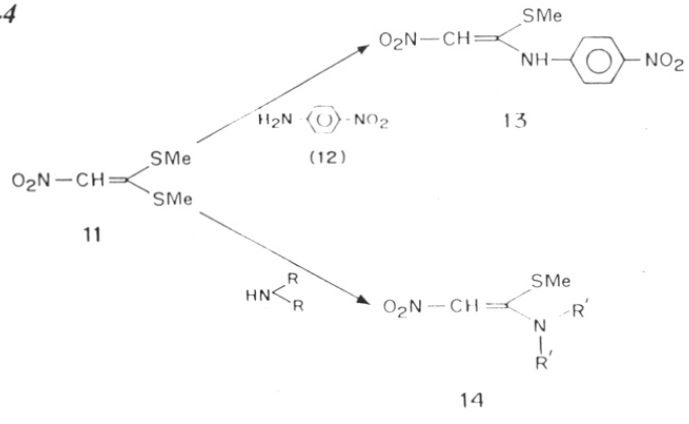


### 3.2.2b *Synthesis of nitroketene N,S-acetals:*[13-16]

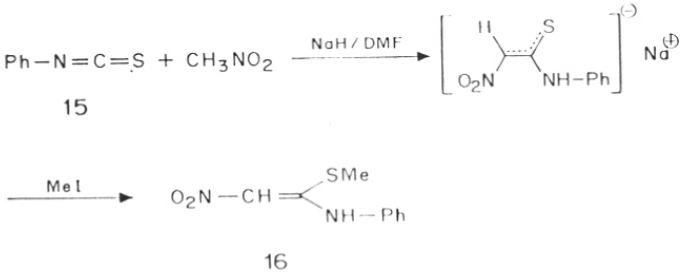
In 1967 Gompper et al.[13] reported for the first time the synthesis of nitroketene N,N-acetals. The method employed was the reaction of secondary amines with nitroketene S,S-acetals (**11**). Later, such compounds were also synthesized by Rajappa et al.[14] in 1977. Their method involved the condensation of S-alkyl isothioureas with nitromethane. Schafer et al.[15] reported the first compound belonging to the group of nitroketene N,S-acetals. This was the synthesis of 1-methylthio-1-para nitro anilino-2-nitroethylene (**13**) in 63% yield. The formation of this reflected the lower nucleophilicity of p-nitroaniline (**12**) compare to the aliphatic secondary amines employed earlier. In 1990 Rajappa et al.[16] reported the synthesis of a series of nitroketene N,S-acetals (**14**) as intermediates for the synthesis of N-nitroacetyl derivatives of various amines and amino acid esters (*Scheme 3-4*).

The second method for the synthesis of such nitroketene N,S-acetals is the addition of nitromethane to arylisothiocyanate (**15**) followed by S-alkylation; this leads to the required compound (**16**) (*Scheme 3-5*).

***Scheme 3-4***




***Scheme 3-5***



## 3.3 Present work:

Chapter-2 had described a new synthesis of 1-methylamino-1-methylthio-2-nitroethylene by the condensation of nitromethane with N-methyl carbonimidodithioic acid dimethyl ester. This condensation was brought about through a specific zeolite catalysis. In the present chapter, we have explored the scope of this condensation by varying the primary amines involved in the carbonimidodithioic acid dimethyl esters as well as the active methylene moieties. In an earlier literature report[17] the condensation of various active methylene compounds such as malononitrile and methyl cyanoacetate with N-methyl carbonimidodithioic acid dimethyl ester had been described. No catalyst was used in this reaction. However, as mentioned in chapter-2 of this thesis, this reaction failed completely when nitromethane was the active methylene component. The reaction was successful when a specific zeolite catalyst RE(70%)NaY was added to the reaction medium. We have therefore, now extended the scope of this particular condensation and used it to synthesize several other functionalized ketene N,S-acetals. Various active methylene compounds such as ethyl cyanoacetate, acetylacetone, dimedone and Meldrum's acid have been condensed with the N-methyl carbonimidodithioate (**17**) to give the corresponding α-oxoketene N,S-acetals **18-21**. In all these condensations the yields of the products have been either higher than or at least equal to those reported in the earlier publication.[17] Thus the uncatalyzed condensation of compound **17** with methyl cyanoacetate has been reported to give the required product in 42% yield. The same reaction with the zeolite catalysis has given the product in 85% yield. However, reaction of **17** with ethyl acetoacetate, diethyl malonate resulted in the formation of polymeric material. In the case of nitroethane, even after prolonged refluxing with **17**, only starting material **17** was recovered. Various other N-alkyl carbonimidodithioic acid dimethyl esters **23a-f** prepared from several primary amines (**22a-f**) have been condensed with nitromethane to give the corresponding nitroketene N,S-acetals (**24a-f**). Finally, an attempt was

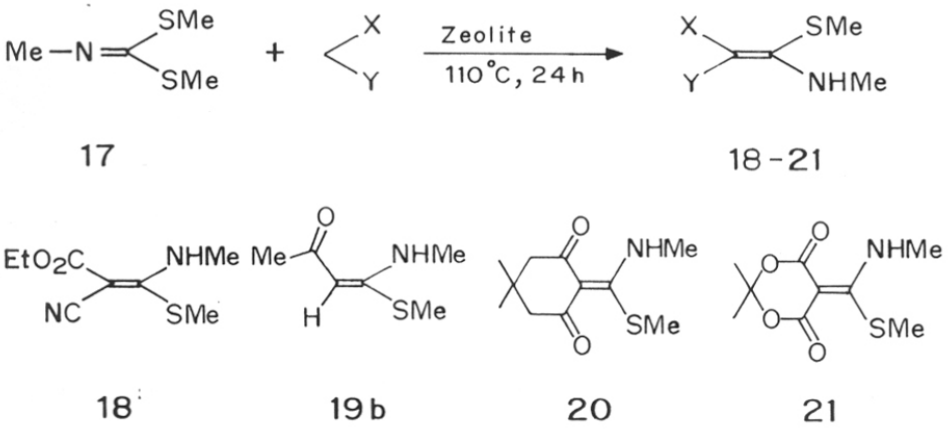
made to synthesize a push-pull butadiene system with the nitro group at one terminus and an amine at the other, by the condensation of 1-nitrocyclohexene; however, this only gave polymeric material. These efforts have been discussed below in greater detail.

## 3.4 Results and discussion:

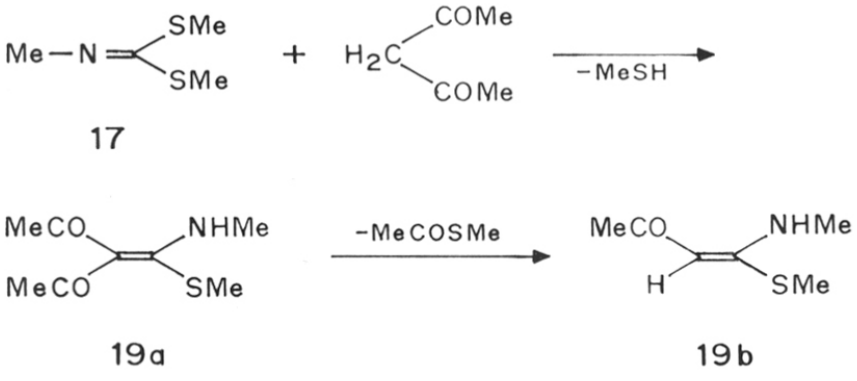
### 3.4.1 Synthesis of α-oxoketene N,S-acetals (18-21):

N-Methyl carbonimidodithioic acid dimethyl ester (**17**) was prepared as described in the earlier chapter. This was heated with active methylene compounds such as ethyl cyanoacetate, acetyl acetone, dimedone and Meldrum's acid in presence of the zeolite RE(70%)NaY to give the corresponding α-oxoketene N,S-acetals (**18-21**) (*Scheme 3-6*). The solid products obtained were characterised by the $^1$H NMR spectra, infrared and mass spectra. Thus ethyl cyanoacetate gave the product **18** in 85% yield. The product exhibited the following bands in the $^1$H NMR spectrum 10.10 (NH), 4.23 (q, 2H, $CH_2$), 3.23 (d, $J$ = 2.7 Hz, 3H, $NCH_3$), 2.70 (s, 3H, $SCH_3$) 1.34 (t, $J$ = 7.14 Hz, 3H, $CH_3$). Similarly dimedone gave the product **20** in 60% yield as a colourless crystalline solid. It exhibited $^1$H NMR signals at 9.80 (NH), 3.00 (d, $J$ = 4.8 Hz, 3H, $NCH_3$), 2.80 (s, 3H, $SCH_3$), 2.35 (s, 4H) and 1.10 (s, 6H). The product from Meldrum's acid (**21**) was obtained as a white crystalline solid in 78% yield. It exhibited $^1$H NMR signals at 11.00 (NH), 3.20 (d, $J$ = 4.5 Hz), 3H $NCH_3$), 2.60 (s, 3H, $SCH_3$) and 1.70 (s, 6H). The product from acetylacetone was however, not the expected compound **19a** but the deacetylated product derived from this. The product is obtained as a crystalline solid in 70% yield. This exhibited $^1$H NMR (*Spectrum No. 3-1*) signals at 11.20 (NH, 4.96 (s, 1H), 2.98 (d, $J$ = 4.89 Hz, 3H, $NCH_3$), 2.36 (s, 3H, $SCH_3$), 2.03 (s, 3H, $COCH_3$). The presence of the olefinic signal at 4.96 and the fact that only one acetylmethyl group was seen in $^1$H NMR spectrum prove the structure of the product to be **19b**. This obviously arises from **19a** by deacetylation, most probably induced by the nucleophilic action of the methyl mercaptan[18] liberated in the first step (*Scheme 3-7*). The structure of **19b** was further confirmed by the $^{13}$C NMR spectrum (*Spectrum No. 3-2*), in which, using the DEPT technique, the =CH carbon was seen at 88.70 ppm. Furthermore in the mass spectrum the molecular ion peak ($M^+$) appeared at *m/z* 145.

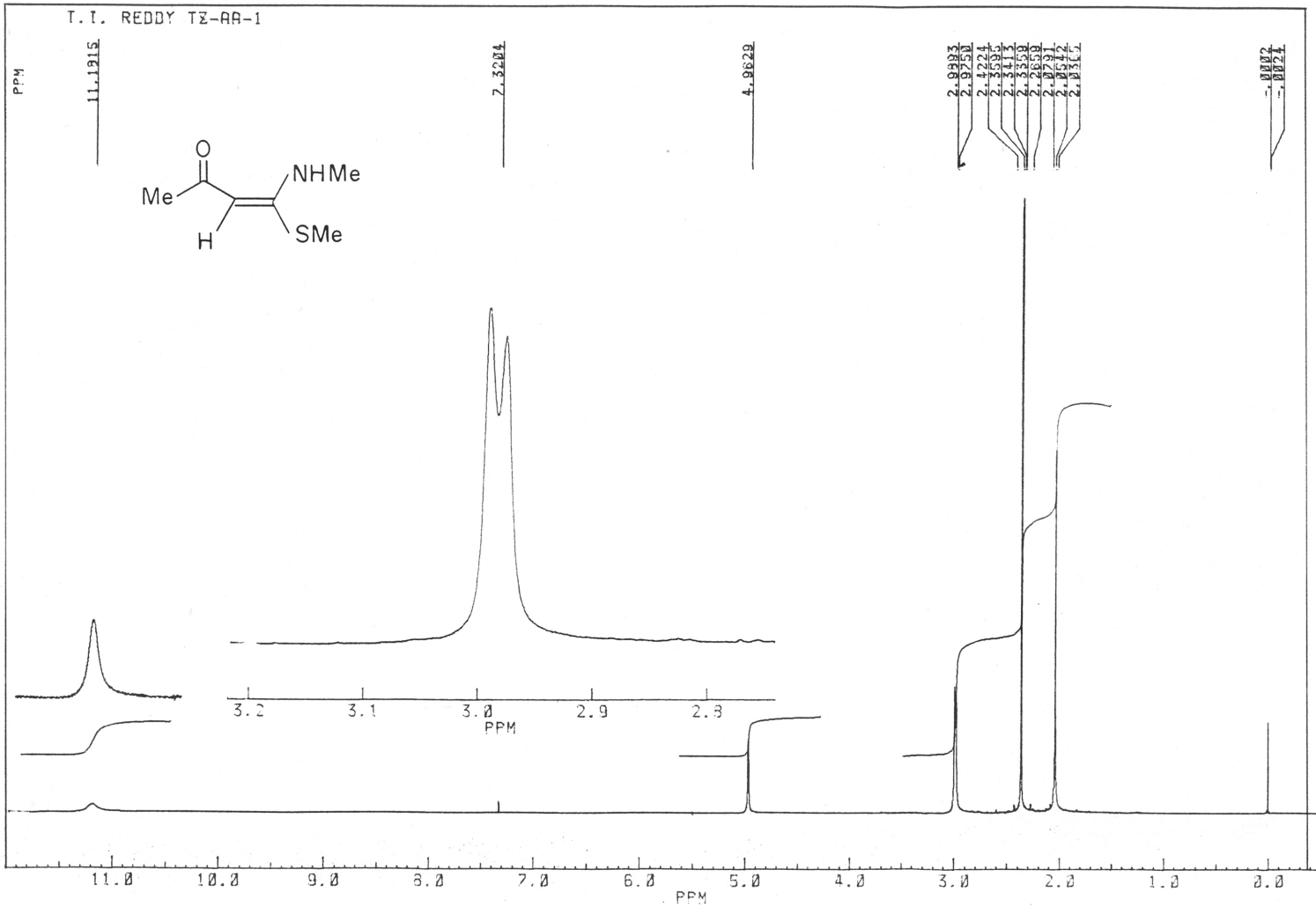
*Scheme 3-6*



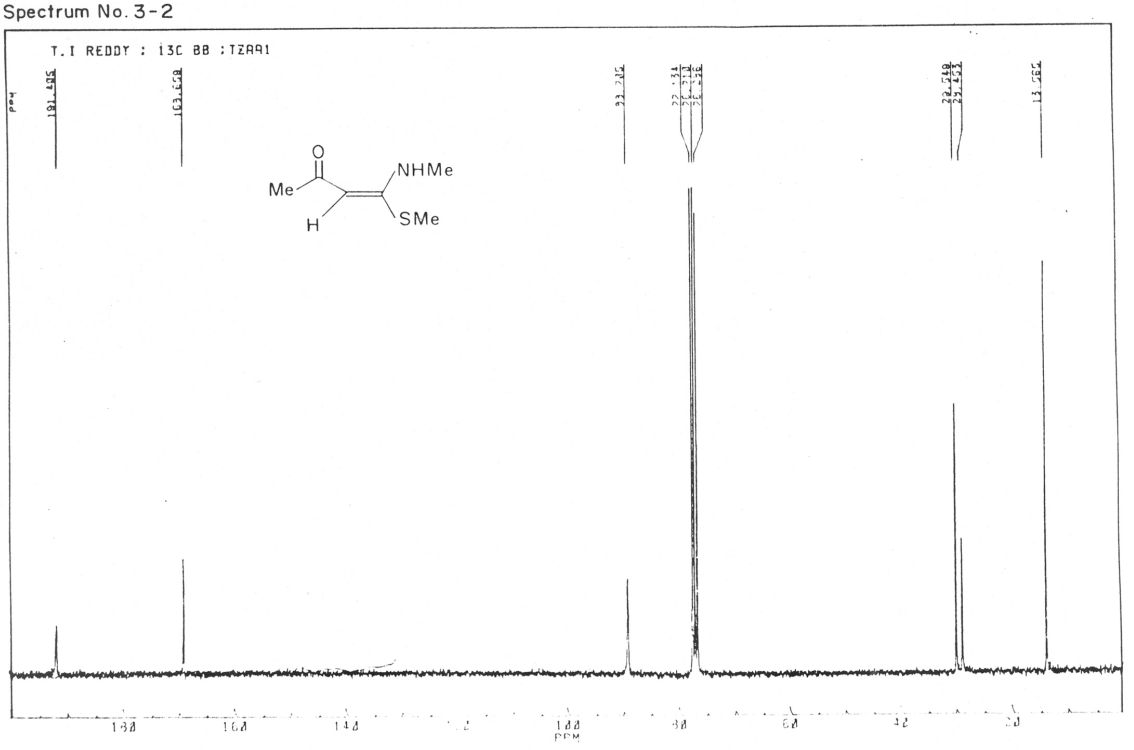

*Scheme 3-7*

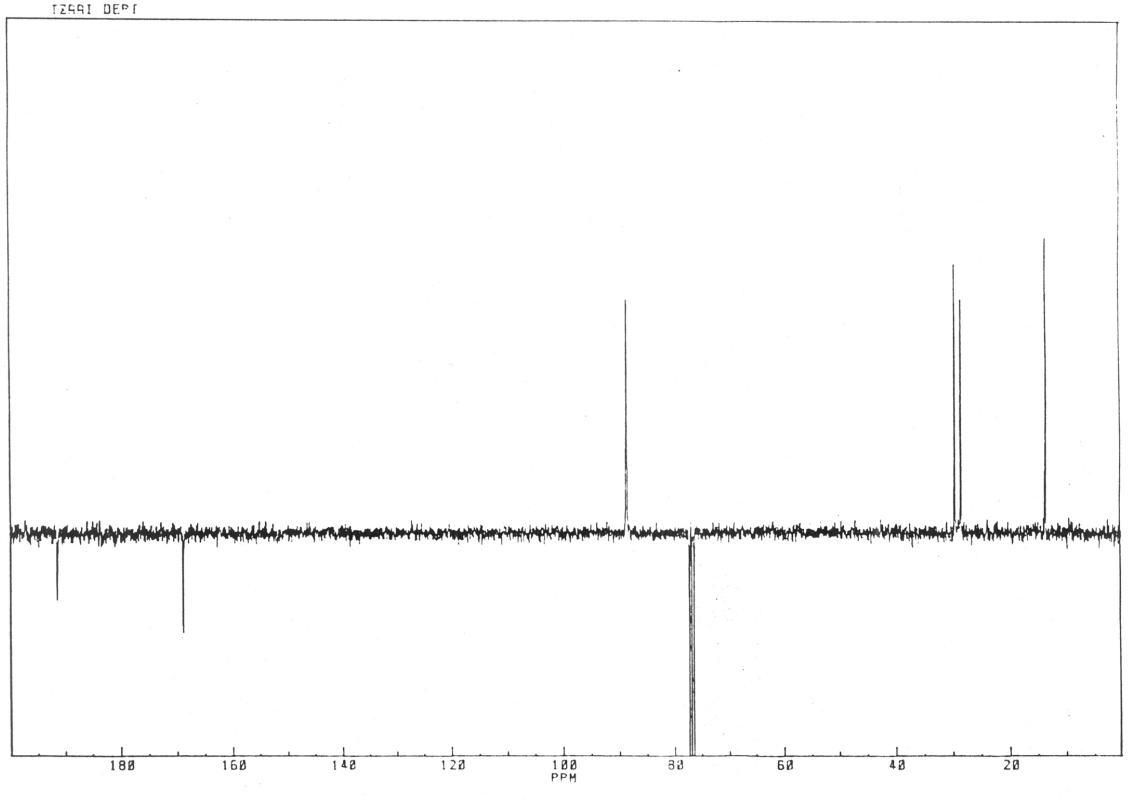


Spectrum No. 3-1



Spectrum No. 3-2



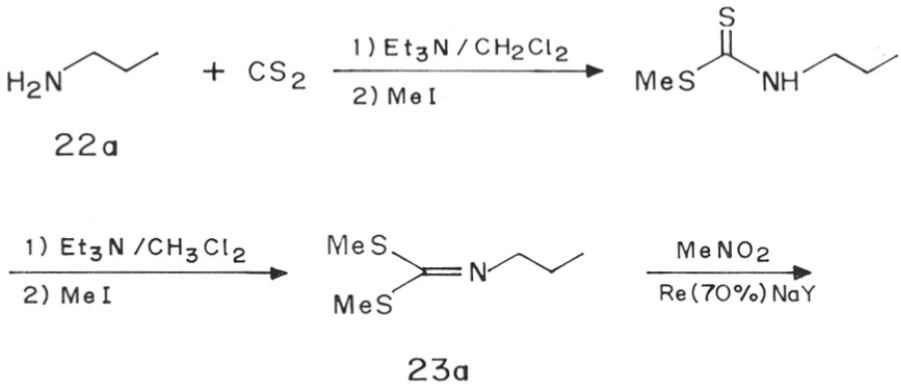
### 3.4.2 Synthesis of 1-substitutedamino-1-methylthio-2-nitroethylenes (24a-f):

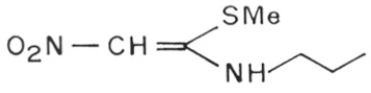
Several primary amines (**22a-f**) were condensed with carbon disulfide by the usual procedure[19] and then methylated to give the N-alkyl carbonimidodithioic acid dimethyl esters (**23a-f**). These compounds condensed with nitromethane in presence of the zeolite RE(70%)NaY to give the products **24a-f**. Thus n-propyl amine (**22a**) was condensed with carbon disulfide in $CH_2Cl_2$ solution in the presence of triethylamine as the basic catalyst. The product was methylated with methyl iodide to give **23a** as a liquid in 72% yield (*Scheme 3-8*). The $^1$H NMR spectrum of the purified sample of **23a** showed the following five signals 3.40 (t, $J$ = 7.2, Hz, 2H, $NCH_2$), 2.55 (s, 3H, $SCH_3$), 2.35 (s, 3H, $SCH_3$), 1.65 (m, 2H, $CH_2$) and 1.00 (t, $J$ = 7.2 Hz, 3H, $CH_3$). The above data confirm the structure assigned. Furthermore, the compound **23a** showed the molecular ion ($M^+$) peak in its mass spectrum at *m/z* 163.

The carbonimidodithioic acid dimethyl esters of the following primary amines (**22b-f**) were synthesized by a similar procedure: Sec.butylamine cyclohexylamine, benzylamine, α-methyl benzylamine and furfurylamine. The yields and spectral data of all these compounds are given in the experimental section.

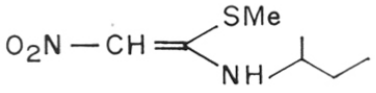
The above carbonimidodithioic acid dimethyl esters (**23a-f**) were then condensed with nitromethane in presence of the zeolite RE(70%)NaY to yield nitroketene N,S-acetals (**24a-f**) (*Scheme 3-8*). Thus the n-propyl derivative (**24a**) was obtained by heating N-n-propyl carbonimidodithioic acid dimethyl ester (**23a**) with excess nitromethane at 100°C in presence of zeolite RE(70%)NaY for 24 h. Separation of the catalyst by filtratoin and removal of excess nitromethane left the product **24a** as a solid in 76% yield. The $^1$H NMR spectrum (*Spectrum No. 3-3*) of the purified sample showed two signals at 6.60 and 2.35 corresponding to =CH and $SCH_3$ protons respectively, and three signals at 3.35 (q, 2H, $NCH_2$), 1.60 (m, 2H, $CH_2$) and 1.00 (t, $J$ = 6.72, Hz, 3H, $CH_3$) corresponding to protons of N-n-propyl group. The NH proton resonated at 10.60 δ. In the mass spectrum, the molecular ion ($M^+$) peak was seen at *m/z* 176. The above spectral data clearly indicate that the structure **24a** assigned to this product is the right one. Similarly, the nitroketene N,S acetals **24b-f** were prepared in 52-85% yield from the starting materials **23b-f**. All the products were characterized by analytical and speeral data.

*Scheme 3-8*

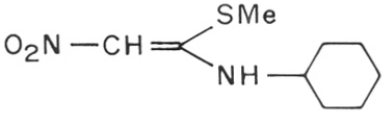


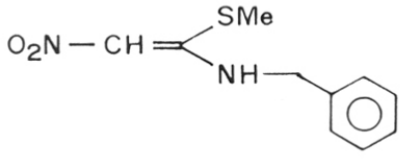

24a



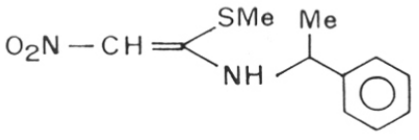

24b



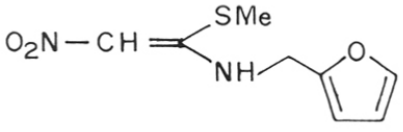

24c




24d

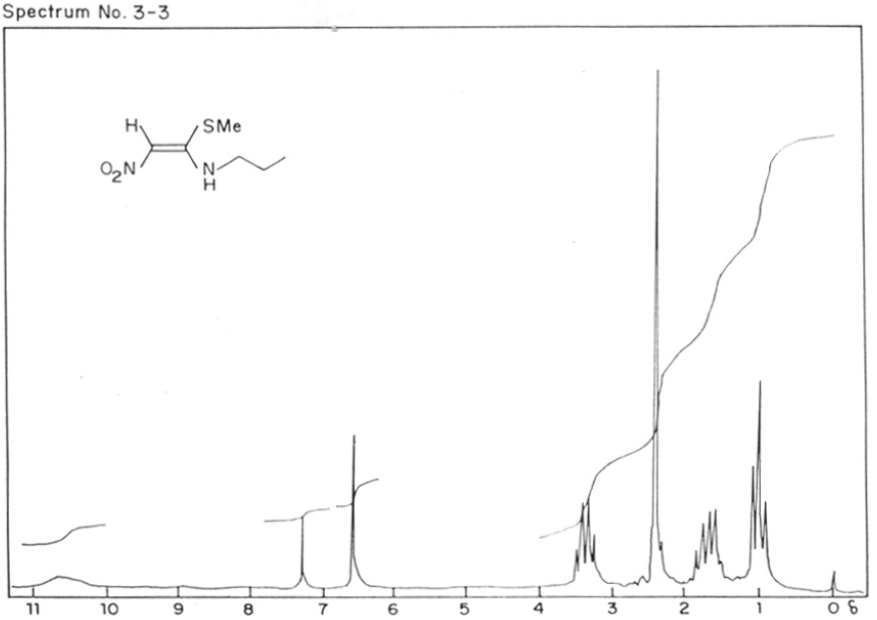


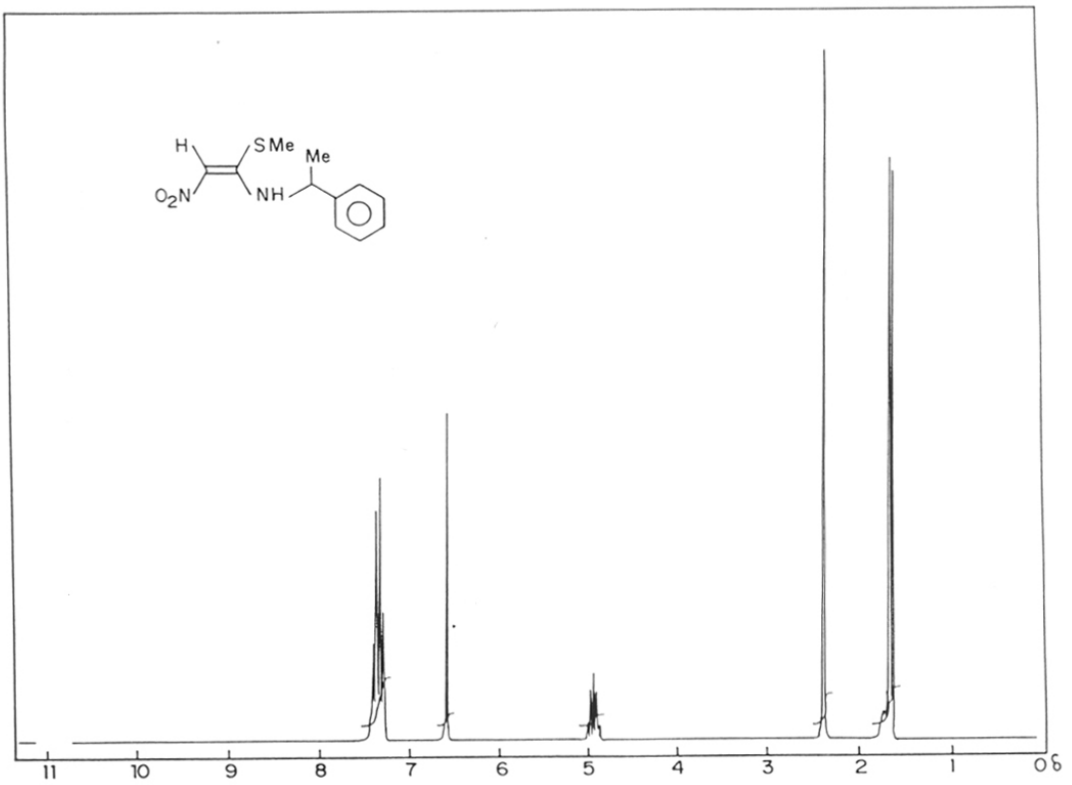

24e




24f

Spectrum No. 3-3

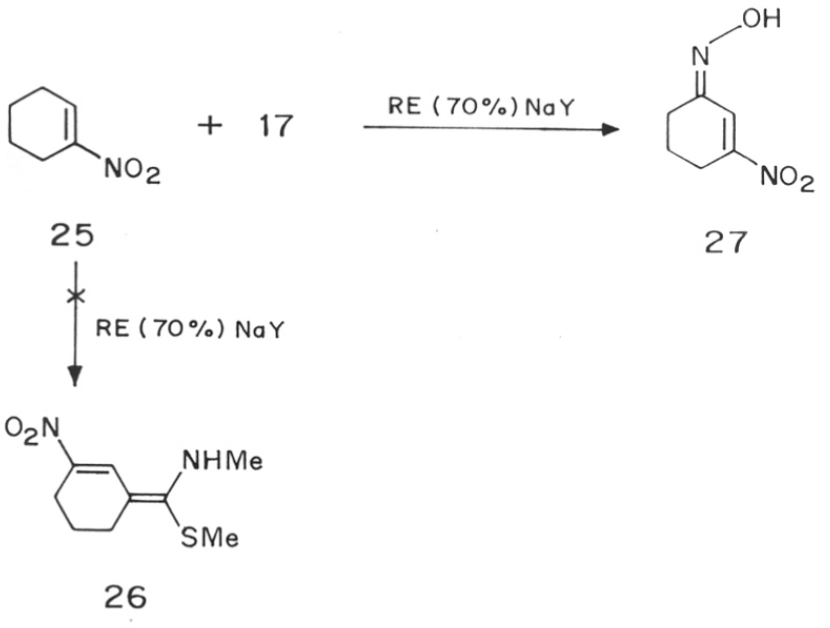


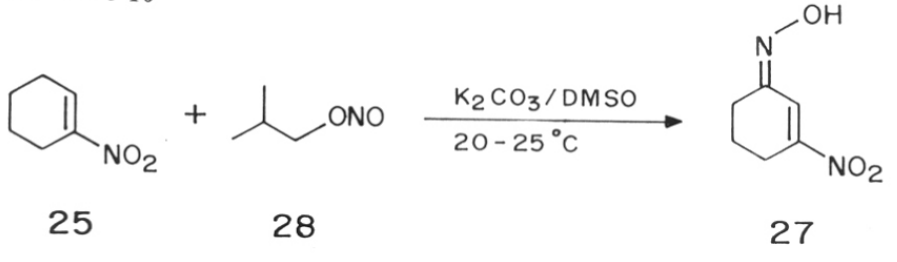
### 3.4.3 An attempt to synthesize a push-pull butadiene system (26):

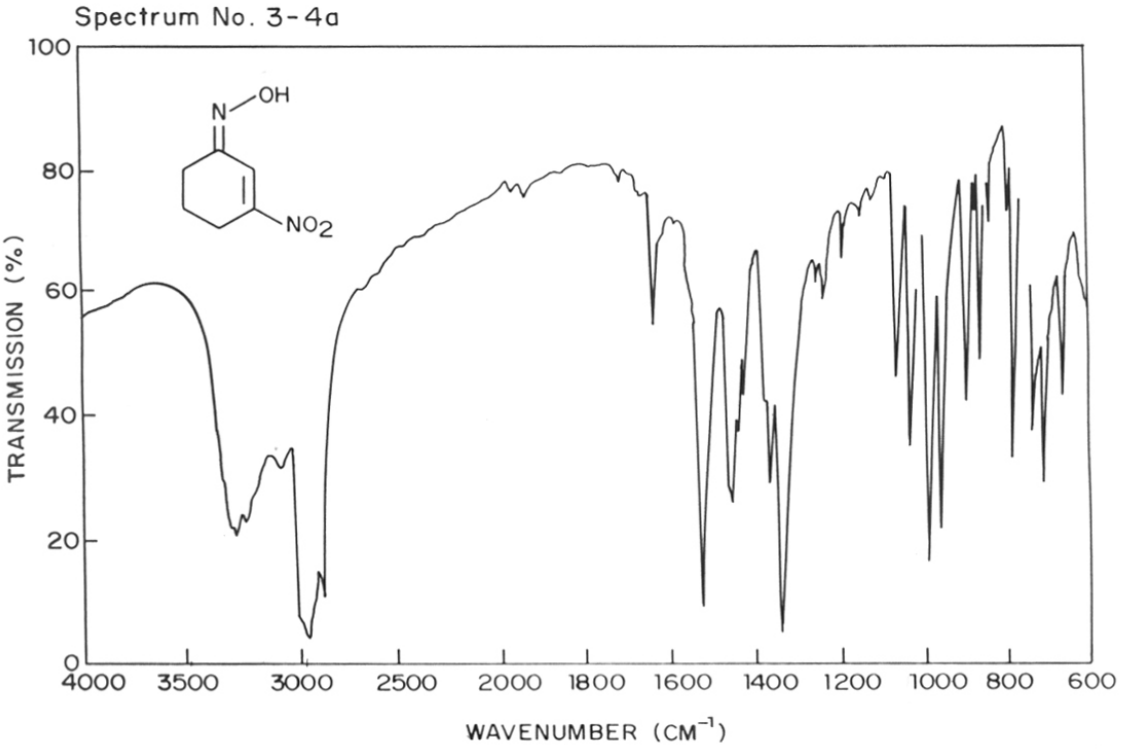
In order to delineate the scope of the zeolite catalyzed condensations, it was decided to see whether a push-pull butadiene system could be generated by a similar reaction. The appropriate starting materials for this projected synthesis are 1-nitrocyclohexene (**25**) and N-methyl carbonimidodithioic acid dimethyl ester (**17**). In a recent review of conjugated aliphatic nitro compounds, it has been explicitly stated that there are very few examples of such nitrovinyl compounds acting as nucleophiles on carbon atom $C_3$[20]. 1-Nitrocyclohexene, prepared by the standard procedure[21] was heated with carbonimidodithioic acid dimethyl ester (**17**) in presence of RE(70%)NaY. There was no evidence for the formation of the required compound **26**. However, in one of the experiments, a small quantity of a solid product was isolated, which from its analytical and spectral data (*Spectrum No.3-4a & 3-4b*) seemed to have the structure **27** corresponding to an oxime (*Scheme 3-9*). The formation of this however, was not reproducible and no mechanistic conclusions can be drawn from this observation. However the authentic sample of this oxime **27** was prepared by the reaction of 1-ntrocy-clohexane (**25**) with isoamylnitrite (**28**)[22] as earlier reported[23] (*Scheme 3-10*) and compared with the $^1$H NMR spectrum of the sample obtained by zeolite catalysis. The two were identical.

*Scheme 3-9*

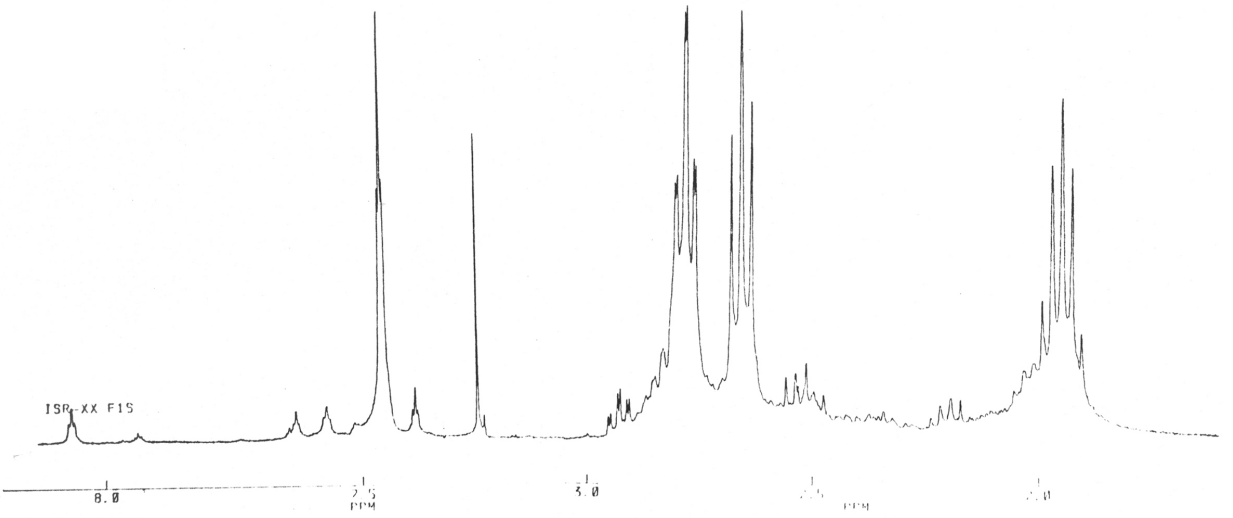



*Scheme 3-10*

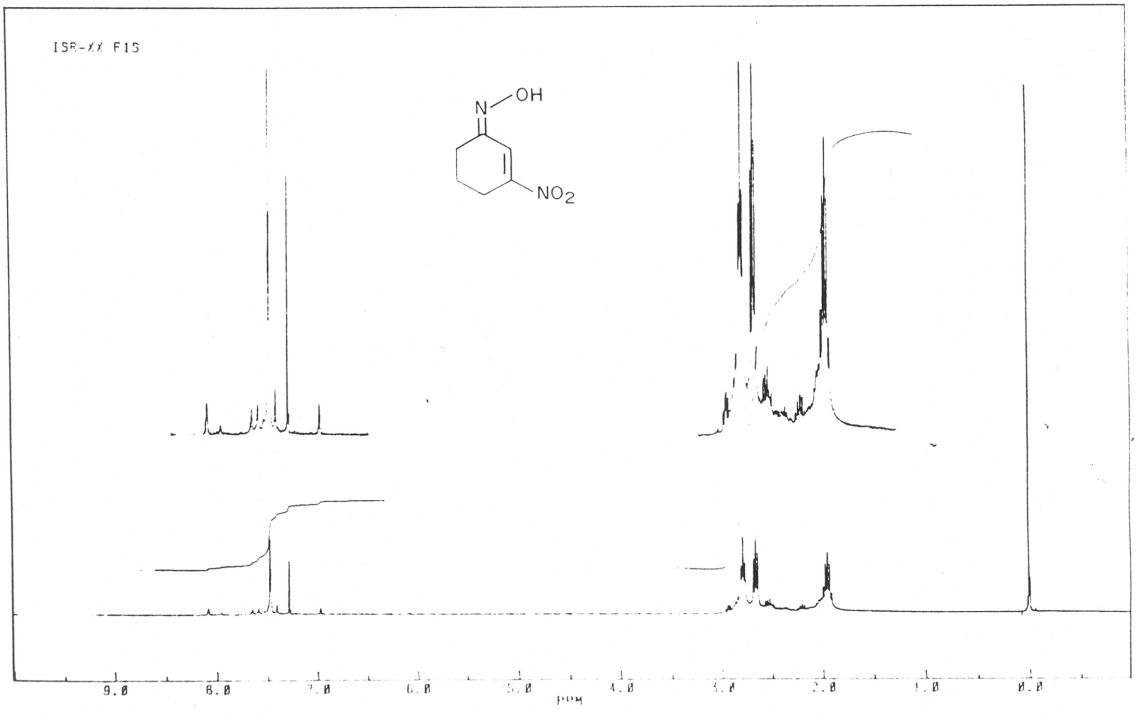



Spectrum No. 3-4a
100
80
60
40
20
0
TRANSMISSION (%)
N
OH
NO2
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER (CM-1)

ISR-XX F1S




Spectrum No. 3-4b



## 3.5 Summary:

The synthesis of functionalized ketene N,S-acetals as described here is a general and mild method proceeding under almost neutral conditions. This method gives exclusively a single product (>90% selectivity). Workup and purification are easy. The catalyst can be reactivated and recycled without affecting its efficacy.

## 3.6 Experimental:

**Synthesis of α-oxoketene N,S-acetals (18-21):**

**General:** A mixture of N-methyl carbonimidodithioic acid dimethyl ester (**17**), (10 mmol), active methylene compound (3 mmol) and zeolite RE(70%)NaY (half the weight of the active methylene compound) was stirred at 100°C for 24-48 h. The reaction mixture was cooled, catalyst filtered off and washed with dichloromethane (2x15 ml). The filtrate was concentrated at reduced pressure. The residue was taken in n-hexane and stirred for a few mns to precipitate the product and most of the unreacted starting material was dissolved. Final purification was carried out by column chromatography to give the pure product (**18-21**) in 60-85% yield.

**3-Methylamino-3-methylthio-2-cyano acrylic acid-ethylester (18):**

| | | |
|---|---|---|
| Yield | : | 85%, colorless crystalline solid. |
| mp | : | 93°C (EtOH-n-hexane). |
| $^1$H NMR (300 MHz) | : | δ 10.10 (br, 1H, NH), 4.23 (q, 2H, $CH_2$), 3.23 (d, $J$ = 2.7 Hz, 3H, $NCH_3$), 2.70 (s, 3H, $SCH_3$), 1.34 (t, $J$ = 7.14 Hz,3H, $CH_3$). |
| IR (Nujol) | : | $cm^{-1}$ 3100, 2120, 1690, 1570, 1360. |
| MS | : | $m/z$ 200 ($M^+$, 90%), 153, 125 (100), 107, 81. |
| Analysis | : | $C_8H_{12}N_2O_2S$. Calcd. : C, 48.00; H, 6.00; N, 14.00. Found : C, 48.08; H, 6.12; N, 14.06. |

**3-Methylthio-3-methylamino butan-3-ene-2-one (19b):**

| | | |
|---|---|---|
| Yield | : | 70%, crystalline solid. |
| mp | : | 65° C (EtOH). |
| $^1$H NMR (300 MHz) | : | δ 11.20 (br, d, 1H, NH), 4.96 (s, 1H), 2.98 (d, $J$ = 4.89 Hz, 3H, $NCH_3$), 2.36 (s, 3H, $SCH_3$), 2.03 (s, 3H, $COCH_3$). |

| | | |
|---|---|---|
| $^{13}C$ NMR (75.5 MHz) | : | ppm 194.40, 168.65, 88.70, ]29.54, 28.45, 13.56. |
| IR ($CHCl_3$) | : | $cm^{-1}$ 3200-3350, 1560, 1470, 1280. |
| MS | : | *m/z* 145 ($M^+$, 100%), 130, 98, 82. |
| Analysis | : | $C_6H_{11}NOS$. Calcd. : C, 49.65; H, 7.58; N, 9.65. |
| | | Found : C, 50.11; H, 7.68; N, 9.79. |

**2-[(Methylamino, methylthio) methylene] dimedone (20):**

| | | |
|---|---|---|
| Yield | : | 60%, colorless crystalline solid. |
| mp | : | 142° C (EtOH). |
| $^1H$ NMR (80 MHz) | : | δ 9.80 (br, 1H, NH), 3.00 (d, *J* = 4.8 Hz, 3H, $NCH_3$), 2.80 (s, 3H, $SCH_3$), 2.35 (s, 4H) 1.10 (s, 6H). |
| IR (Nujol) | : | $cm^{-1}$ 3160, 1670, 1540, 1450, 1200. |
| MS | : | *m/z* 227 ($M^+$, 05%), 210 (100), 180, 153, 138, 123, 83. |
| Analysis | : | $C_{11}H_{17}NO_2S$. Calcd. : C, 58.15; H, 7.48; N, 6.16. |
| | | Found : C, 58.22; H, 7.51; N, 6.21. |

**2,2-Dimethyl-5-[(methylamino)(methylthio)-methylene]-1,3-dioxane-4,6-dione(21):**

| | | |
|---|---|---|
| Yield | : | 78%, white crystalline solid. |
| mp | : | 119°C (MeOH). |
| $^1H$ NMR (90 MHz) | : | δ 11.00 (br, 1H, NH), 3.20 (d, *J* = 4.5 Hz, 3H, $NCH_3$), 2.60 (s, 3H, $SCH_3$), 1.70 (s, 6H). |
| IR (Nujol) | : | $cm^{-1}$ 3200, 1700, 1650, 1550, 1450, 1200. |
| MS | : | *m/z* 231 ($M^+$, 20%), 184, 173, 126 (100), 82. |
| Analysis | : | $C_9H_{13}NO_4S$. Calcd. : C, 46.70; H, 5.60; N, 6.06. |
| | | Found : C, 46.51; H, 6.16; N, 6.11. |

**Synthesis of carbonimidodithioic acid dimethyl esters of various primary amines (23a-f):**

**General:** To a solution of the primary amine (10 mmol) and carbon disulfide (10 mmol) in dichloromethane (50 ml), triethylamine (10 mmol) was added slowly at 20°C. The reaction mixture was stirred for 30 min at room temperature. Methyl iodide (12 mmol) was then added dropwise and the resulting mixture was refluxed for 2-3 h. The reaction mixture was then cooled to room temperature; triethylamine (12 mmol), methyl iodide (12 mmol) were successively added dropwise and it was again refluxed for 2-4 h. After complete conversion of dithiocarbamate to carbonimidodithioate, the reaction mixture was cooled, washed with water (2 X 30 ml) and concentrated under vacuum. The residue was taken in ether (50 ml) and again washed with water (3 X 20 ml) and brine, dried (anhydrous $Na_2SO_4$) and concentrated to give the product (**23a-f**) in 70-90% yield.

**N-n-Propyl carbonimidodithioic acid dimethyl ester (23a):**

| | | |
|---|---|---|
| Yield | : | 72%. Yellow coloured liquid. |
| bp | : | 47°C/0.17 mm. |
| $^1$H NMR (80 MHz) | : | δ 3.40 (t, $J$ = 7.2 Hz, 2H, $NCH_2$), 2.55 (s, 3H, $SCH_3$), 2.35 (s, 3H, $SCH_3$), 1.65 (m, 2H, $CH_2$), 1.00 (t, $J$ = 7.2 Hz, 3H, $CH_3$). |
| IR (Neat) | : | $cm^{-1}$ 1590. |
| MS | : | $m/z$ 163 ($M^+$, 20%), 116 (100), 74. |
| Analysis | : | $C_6H_{13}NS_2$. Calcd. : C, 44.17; H, 7.97; N, 8.58. Found : C, 43.98; H, 8.02; N, 8.27. |

**N-sec-Butyl carbonimidodithioic acid dimethyl ester (23b):**

| | | |
|---|---|---|
| Yield | : | 78%. Yellow coloured liquid. |
| bp | : | 61°C/0.21 mm. |

$^1$H NMR (80 MHz) : δ 3.70 (m, 1H), 2.50 (s, 3H, $SCH_3$), 2.30 (s, 3H, $SCH_3$), 1.45 (m, 2H, $CH_2$), 1.10 (d, $J$ = 6.4 Hz, 3H, $CH_3$), 0.80 (t, $J$ = 7.2 Hz, 3H, $CH_3$).

IR ($CHCl_3$) : $cm^{-1}$ 1600.

MS : *m/z* 177 ($M^+$, 05%), 130 (70), 74 (100).

Analysis : $C_7H_{15}NS_2$. Calcd. : C, 47.45; H, 8.47; N, 7.90.
Found : C, 47.57; H, 8.51; N, 8.02.

**N-Cyclohexyl carbonimidodithioic acid dimethyl ester (23c):**

Yield : 84%. Colourless liquid.

bp : 93°C/4.5 mm.

$^1$H NMR (80 MHz) : δ 3.60 (m, 1H, NCH), 2.55 (s, 3H, $SCH_3$), 2.35 (s, 3H, $SCH_3$), 1.20-1.80 (br, m, 10H).

IR (Neat) : $cm^{-1}$ 1590.

MS : *m/z* 203 ($M^+$, 10%), 156 (100), 83, 74.

Analysis : $C_9H_{17}NS_2$. Calcd. : C, 53.20; H, 8.37; N, 6.89.
Found : C, 52.91; H, 8.26; N, 7.10.

**N-Benzyl carbonimidodithioic acid dimethyl ester (23d):**

Yield : 82%, Yellow coloured liquid.

bp : 124°C/4.5 mm.

$^1$H NMR (80 MHz) : δ 7.30 (m, 5H, aromatic), 4.60 (s, 2H, $NCH_2$), 2.55 (s, 3H, $SCH_3$), 2.40 (s, 3H, $SCH_3$).

IR (Neat) : $cm^{-1}$ 1590.

MS : *m/z* 211 ($M^+$, 05%), 164 (60), 91 (100).

Analysis : $C_{10}H_{13}NS_2$. Calcd. : C, 56.87; H, 6.16; N, 6.63.
Found : C, 56.53; H, 6.71; N, 6.72.

**(S)-N-α-Methylbenzyl carbonimidodithioic acid dimethyl ester (23e):**

| | | |
|---|---|---|
| Yield | : | 86%, Yellow coloured liquid. |
| bp | : | 105°C/4.7 mm. |
| $^1$H NMR (200 MHz) | : | δ 7.40 (m, 5H, aromatic), 4.95 (q, $J$ = 6.3 Hz, 1H), 2.60 (s, 3H, $SCH_3$) 2.50 (s, 3H, $SCH_3$), 1.50 (d, J = 6.3 Hz, 3H, $CH_3$). |
| IR (Neat) | : | $cm^{-1}$ 1585. |
| MS | : | $m/z$ 225 ($M^+$, 00%), 178 (20), 105 (100). |
| Analysis | : | $C_{11}H_{15}NS_2$. Calcd. : C, 58.66; H, 6.66; N, 6.22. Found : C, 59.09; H, 7.06; N, 6.57. |

**(±)-N-α-Methylbenzyl carbonimidodithioic acid dimethyl ester:**

| | | |
|---|---|---|
| Yield | : | 88%, Yellow coloured liquid. |
| bp | : | 121°C/4.4 mm. |
| Analysis | : | $C_{11}H_{15}NS_2$. Calcd. : C, 58.66; H, 6.66; N, 6.22. Found : C, 58.84; H, 6.91; N, 6.55. |

**N-Furylmethyl carbonimidodithioic acid dimethyl ester (23f):**

| | | |
|---|---|---|
| Yield | : | 75%, Light yellow coloured liquid. |
| bp | : | 100° C/4.65 mm. |
| $^1$H NMR (200 MHz) | : | δ 7.30 (m, 1H), 6.30 (m, 2H,), 4.55 (s, 2H, $CH_2$), 2.50 (s, 3H, $SCH_3$), 2.30 (s, 3H, $SCH_3$). |
| IR ($CHCl_3$) | : | $cm^{-1}$ 1595. |
| MS | : | $m/z$ 201 ($M^+$, 05%), 153 (50), 81 (100) |
| Analysis | : | $C_8H_{11}NOS_2$. Calcd. : C, 47.76; H, 5.47; N, 6.96. Found : C, 47.92; H, 5.73; N, 6.84. |

**Preparation of 1-substitutedamino-1-methylthio-2-nitroethylene (24a-f):**

**General procedure:** Freshly activated zeolite RE(70%)NaY (0.5g) was added to the mixture of carbonimidodithioic acid dimethyl ester (10 mmol) and nitromethane (50 mmol) at room temperature and the suspension was refluxed with stirring for 24 h. The reaction mixture was then cooled to room temperature, the catalyst was filtered off and washed with $CH_2Cl_2$ (2 X 30 ml). The filtrate was concentrated at reduced pressure. The residue was taken in n-hexane and stirred for a few mns to precipitate the product. Final purification was carried out by column chromatography to give the pure product (**24a-f**) in 50-82% yield.

**1-Methylthio-1-n-propylamino-2-nitroethylene (24a):**

| | | |
|---|---|---|
| Yield | : | 76%, Colourless crystalline solid. |
| mp | : | 63-64°C (EtOH). |
| $^1$H NMR (80 MHz) | : | δ 10.60 (br, 1H, NH), 6.60 (s, 1H), 3.35 (q, 2H, $NCH_2$), 2.35 (s, 3H, $SCH_3$), 1.60 (m, 2H, $CH_2$), 1.00 (t, $J$ = 6.72 Hz, 3H, $CH_3$). |
| IR (Nujol) | : | $cm^{-1}$ 3400, 1570, 1470, 1380. |
| MS | : | $m/z$ 176 ($M^+$, 70%), 129, 87, 74 (100). |
| Analysis | : | $C_6H_{12}N_2O_2S$. Calcd. : C, 40.90; H, 6.82; N, 15.90. Found : C, 41.43; H, 6.69; N, 16.22. |

**1-sec-Butylamino-1-methylthio-2-nitroethylene (24b):**

| | | |
|---|---|---|
| Yield | : | 82%, Colourless crystalline solid. |
| mp | : | 116-118°C (EtOH). |
| $^1$H NMR (90 MHz) | : | δ 10.50 (br, 1H, NH), 6.55 (s, 1H), 3.70 (m, 1H), 2.45 (s, 3H, $SCH_3$), 1.60 (m, 2H), 1.30 (d, $J$ = 6.6 Hz, 3H, $CHCH_3$), 1.00 (t, $J$ = 7.2 Hz, 3H, $CH_2CH_3$). |
| IR (Nujol) | : | $cm^{-1}$ 3350-3450, 1560, 1470, 1330, 1230. |
| MS | : | $m/z$ 190 ($M^+$, 30%), 135, 74 (100), 57. |

| | | | |
|---|---|---|---|
| Analysis | : | $C_7H_{14}N_2O_2S$. | Calcd. : C, 44.21; H, 7.36; N, 14.73. |
| | | | Found : C, 44.32; H, 7.21; N, 14.57. |

**1-Cyclohexylamino-1-methylthio-2-nitroethylene (24c):**

| | | |
|---|---|---|
| Yield | : | 75%, Colourless crystalline solid. |
| mp | : | 106°C (EtOH). |
| $^1$H NMR (80 MHz) | : | δ 10.50 (br, 1H, NH), 6.50 (s, 1H), 3.60 (m, 1H, NCH), 2.40 (s, 3H, $SCH_3$), 1.2-2.0 (br, 11H). |
| $^{13}$C NMR (50 MHz) | : | ppm 163.31, 106.13, 53.86, 32.93, 25.21, 24.32, 14.47. |
| IR (Nujol) | : | $cm^{-1}$ 3300, 1570, 1480, 1230. |
| MS | : | *m/z* 216 ($M^+$, 20%), 135 (100), 83, 55. |
| Analysis | : | $C_9H_{16}N_2O_2S$. Calcd. : C, 50.00; H, 7.40; N, 12.96. |
| | | Found : C, 50.21; H, 7.31; N, 13.11. |

**1-Benzylamino-1-methylthio-2-nitroethylene (24d):**

| | | |
|---|---|---|
| Yield | : | 80%, Light yellow coloured solid. |
| mp | : | 104-105°C (EtOH). |
| $^1$H NMR (200 MHz) | : | δ 11.10 (br, 1H, NH), 7.40 (s, 5H, aromatic), 6.65 (s, 1H), 4.70 (d, $J$ = 6.5 Hz, 2H, $NCH_2$), 2.40 (s, 3H, $SCH_3$). |
| IR ($CHCl_3$) | : | $cm^{-1}$ 3400, 1580, 1350. |
| MS | : | *m/z* 224 ($M^+$, 10%), 178, 130, 91 (100). |
| Analysis | : | $C_{10}H_{12}N_2O_2S$. Calcd. : C, 53.57; H, 5.35; N, 12.50. |
| | | Found : C, 53.61; H, 5.42; N, 12.22. |

**(S)-1-α-Methylbenzylamino-1-methylthio-2-nitroethylene (24e):**

| | | |
|---|---|---|
| Yield | : | 52%, Light yellow coloured low melting solid. |
| mp | : | 44-45°C (EtOH). |
| $^1$H NMR (200 MHz) | : | δ 10.95 (br, 1H, NH), 7.35 (m, 5H, aromatic), 6.60 (s, 1H), 4.95 (m, 1H), 2.40 (s, 3H, $SCH_3$), 1.70 (d, $J$ = 7.7 Hz, 3H, $CH_3$). |
| IR ($CHCl_3$) | : | $cm^{-1}$ 3440, 1580, 1360. |
| MS | : | $m/z$ 238 ($M^+$, 05%), 191, 105 (100). |
| Analysis | : | $C_{11}H_{14}N_2O_2S$. Calcd. : C, 55.46; H, 5.88; N, 11.76. Found : C, 55.38; H, 5.92; N, 11.91. |

**(±)-1-α-Methylbenzylamino-1-methylthio-2-nitroethylene:**

| | | |
|---|---|---|
| Yield | : | 50%, Light yellow coloured Crystalline solid. |
| mp | : | 119°C (EtOH). |
| Analysis | : | $C_{11}H_{14}N_2O_2S$. Calcd. : C, 55.46; H, 5.88; N, 11.76. Found : C, 55.32; H, 5.99; N, 11.97. |

**1-Furfurylamino-1-methylthio-2-nitroethylene (24f):**

| | | |
|---|---|---|
| Yield | : | 78%. |
| bp/mp | : | Gum. |
| $^1$H NMR (90 MHz) | : | δ 10.55 (br, 1H, NH), 7.40 (m, 1H), 6.55 (s, 1H), 6.30 (m, 2H), 4.65 (d, J = 5.9 Hz, 2H, $NCH_2$), 2.47 (s, 3H, $SCH_3$). |
| IR ($CHCl_3$) | : | $cm^{-1}$ 3550-3450, 1570, 1360. |
| MS | : | $m/z$ 214 ($M^+$, 10%), 168, 81 (100). |
| Analysis | : | $C_8H_{10}N_2O_3S$. Calcd. : C, 44.85; H, 4.67; N, 13.08. Found : C, 44.74; H, 4.79; N, 12.92. |

**Synthesis of 1-nitrocyclohexene (25):**[21]

This was prepared by the reported method.[21] Mercuric chloride dissolved in the stirring solution of aqueous sodium nitrite. To this pale green solution, cyclohexene was added slowly. This mixture was stirred vigirously at room temperature for 30 h. Nitro mercurial cyclohexane was filterred out. This solid was then dissolved in aqueous NaOH solution in dichloromethane and stirred for 10-15 minutes. The resulting mixture was acidified with 1N HCl and filtered through cintered funnel with celite pad. The filtrate was extracted with $CH_2Cl_2$, dried over $Na_2SO_4$ and concentrated at reduced pressure. Further purified by distillation (b.p. 61-62°C/1mm) to get pure light yellow coloured 1-nitrocyclohexene in 77.68% yield.

**Synthesis of 1-nitrocyclohexene-3-one-oxime (27):**

**A) By using zeolite catalyst:**

Zeolite catalyst RE(70%)NaY was added at room temperature to the mixture of 1-nitrocyclohexene (2 mmol) and N-methyl carbonimidodithioic acid dimethyl ester (1 mmol). This mixture was heated at 100°C for 24 h. The reaction mixture was cooled and the catalyst was filtered out . Filtrate was concentrated and purified by column chromatography to get solid in 15% yield. m.p. 110-112°C (**27**).

**B) By known method:**[23]

Isoamylnitrite (.05 mol) was added dropwise to a solution of the 1-nitrocyclohexene (0.05 moles) and potassium carbonate (.05 mol) in 40 CC of DMSO at 20-25°C. The resulting mixture was stirred at room temperature for 2h. Then the solution was poured into 150 CC of water and extracted with ether. The ether layer was dried over anhydrous sodium sulfate. Evaporation of ether at reduced pressure gave the solid product oxime in 54% yield. Crystallized in $CHCl_3$, $CCl_4$ mixture. m.p. 115°C.

**1-nitrocyclohexene-3-one-oxime (27):**

| | | |
|---|---|---|
| Yield | : | Method-A 15%; Method-B 54%; colorless crystaline solid. |
| m.p. | : | 110-112°C, ($CHCl_3$-$CCl_4$). |
| $^1$H NMR (300 MHz) | : | δ 8.25 (t, 1H, NOH), 7.45 (t, 1H, =CH), 2.85 (tt, 2H, $CH_2$), 2.70 (t, 2H, $CH_2$), 1.95 (m, 2H, $CH_2$). |
| IR (Liq. Film) | : | $cm^{-1}$ 3300, 1700, 1570, 1500, 1300. |
| MS | : | *m/z* 156 ($M^+$, 40%), 80, 65, 53 (100). |
| Analysis | : | $C_6H_8N_2O_3$. Calcd. : C, 46.15; H, 5.12; N, 17.94. Found : C, 46.28; H, 5.22; N, 17.81. |

**Synthesis of isoamylnitrite (28):**[22]

To a cooled solution of sodium nitrite (2.5 mmol) in water (75 ml) at 0°C, a pre-cooled solution of conc. sulfuric acid (1.25 mmol), water and isoamyl alcohol [mixture prepared by the slow addition of sulfuric acid to water then isoamylalcohol (2.5 moles) at 0°C] was added dropwise, for a period of 2 h. The resulting mixture was allowed to stand in the ice-salt bath for 15-20 mns, sodium sulfate was filtered off. The filtrate was washed with $NaHCO_3$ solution and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated at reduced pressure to get light yellow coloured liquid isoamylnitrite (**28**).

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# CHAPTER - 4

# A NEW APPROACH TO N-NITROACETYL DERIVATIVES OF AMINO ACID METHYL ESTERS

## 4.1 Abstract:

The N-nitroacetyl derivatives of amino acid esters are attractive intermediates for dipeptides. A new method has been developed for the synthesis of such N-nitroacetyl derivatives. This depends on the conversion of amino acid esters into carbonimidodithioic acid dimethyl esters by condensation with carbon disulfide followed by methylation. Subsequently these carbonimidodithioic acid dimethyl esters are reacted with nitromethane in presence of a zeolite catalyst to produce the corresponding nitroketene N,S-acetals. Mercuric chloride catalyzed hydrolysis of these leads to the required N-nitroacetyl derivatives of the amino acid esters. The following amino acid esters have been nitroacetylated by this procedure. Glycine, alanine,β-alanine, phenyl alanine and valine methyl esters. The yields are quite good.

## 4.2 Introduction:

### 4.2.1 Background:

The nitroacetyl group is an attractive synthon for peptide synthesis. [1,2,3] The methylene group is quite reactive and can be subjected to mono and bis alkylation reactions; subsequent reduction of the nitro group would lead to dipeptides in which the N-terminal amino acid can have one or more substituents. There are very few general methods available for the synthesis of the starting materials, namely N-nitroacetyl derivatives of amino acid esters. The methods available so far are reviewed below. This is followed by the description of a new method for the synthesis of such N-nitroacetyl derivatives.

### 4.2.2 Earlier synthetic methods:

#### 4.2.2a *From isocyanates:*

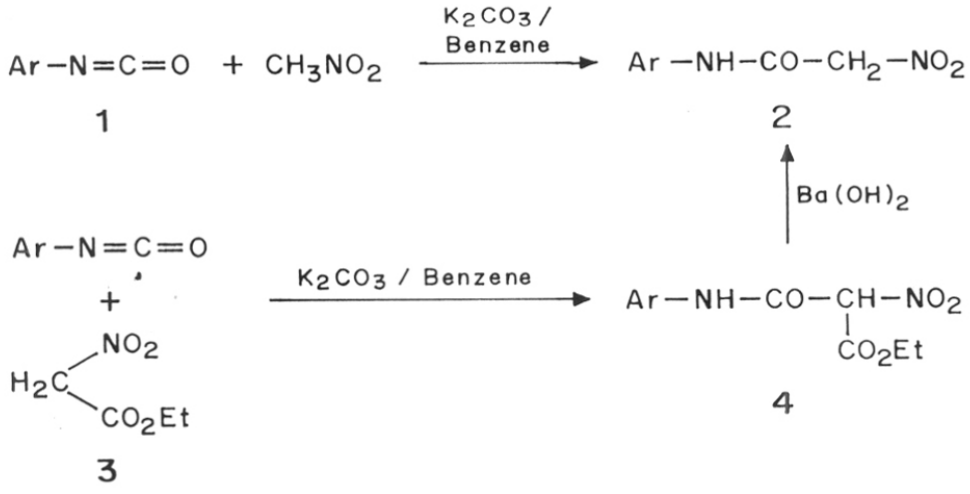
The first report of the synthesis of N-nitroacetyl derivatives of aromatic amines was in 1905 by Michael,[4,5] in which nitromethane was added to phenylisocyanate (**1**) in presence of $K_2CO_3$ to get N-nitroacetyl aniline (**2**). The procedure was subsequently modified by Leshin[6], who reacted ethyl nitroacetate (**3**) with phenylisocyanate in the presence of $K_2CO_3$. The product **4** was hydrolysed and decarboxylated using $Ba(OH)_2$ to give N-nitroacetamides (**2**) (*Scheme 4-1*). Apart from low yields (12-55%) both the methods suffer from the additional drawback of having to use phosgene for the preparation of the isocyanates.

#### 4.2.2b *Direct amide formation:*

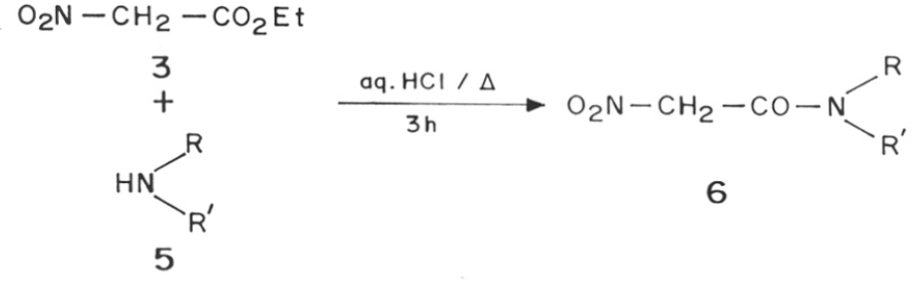
The second approach to the synthesis of N-nitroacetamides was reported in 1981 by Ciommer et al[7]. This was the most obviou one, in which an ester group was directly converted to an amide. Ethyl nitroacetate was refluxed with dimethylamine hydrochloride (**5**) in aqueous solution for 3 h. to get N,N-dimethyl nitroacetamide (**6**) in 42% yield (*Scheme 4-2*). The low yield in this reaction is because of the highly acidic nature (pKa 5.4) of the methylene

protons of ethyl nitroacetate. As a consequence when the amine is added to this it just forms the corresponding salt[8]. Conversion of this salt to the amide naturally leads to very low yields in the direct amidation reaction. This method cannot become a general method for the synthesis of N-nitroacetyl derivatives of amino acids for two reasons: i) drastic conditions necessary for the reaction, which might cause recemisation and ii) the low yields obtained even with such a good nucleophile like dimethylamine.

*Scheme 4-1*




*Scheme 4-2*



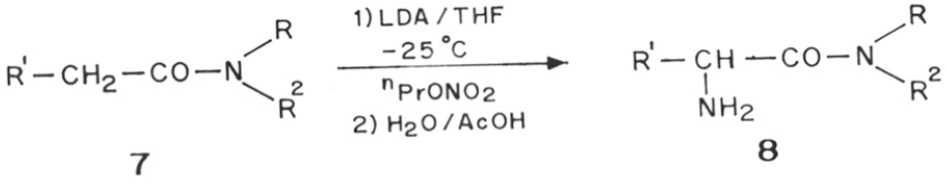
### 4.2.2c *Nitration of acetamides:*

The third approach is due to Feuer; in 1983, he reported the nitration of a pre-formed amide at the α-carbon[9]. The procedure was to take the amide of a secondary amine (**7**), generate the carbanion at the α-methylene by means of LDA and then react this with n-propylnitrate to generate the corresponding nitroacetamide (**8**)[10] (*Scheme 4-3*). This method of course cannot be extended to amino acid esters.

### 4.2.2d *From nitroketene N,S acetals:*

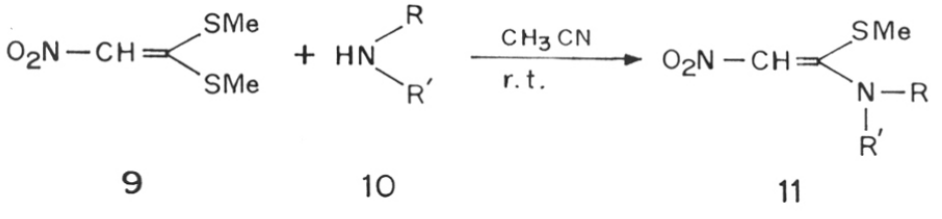
Recently, Rajappa et al.[11] reported a general method for the synthesis of N-nitroacetyl amines and amino acid esters. The method consisted of two steps. The first one is the formation of the nitroketene N,S-acetal by the reaction of 1,1-bismethylthio-2-nitroethylene (**9**) with 1 mole of the amine or the amino acid ester (**10**) to generate the push-pull molecule **11** (*Scheme 4-4*). Hydrolysis of the ene-thiol ether system presenting (**11**) was easily achieved by catalysis with mercuric ion. This led to the require nitroacetamides (**12**).

*Scheme 4-3*

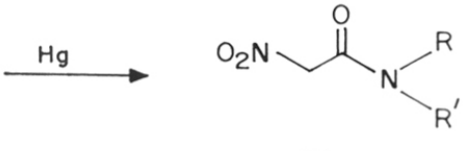



7 8

*Scheme 4-4*




9 10 11




12

## 4.3 Present work:

In Chapters **2** and **3**, we have reported a totally new approach to the synthesis of nitroketene N,S-acetals of the type **11** by condensing carbonimidodithioic acid dimethyl esters with nitromethane under zeolite catalysis. As a further continuation of this work, the present chapter deals with a similar condensation between nitromethane and the carbonimidodithioic acid dimethyl esters (**14a-d**) derived from amino acid derivatives (**13a-d**). This leads to the corresponding nitroketene N,S-acetals in which the amino group is derived from the starting amino acid ester. Subsequently, mercuric chloride catalysed hydrolysis of these compounds results in the formation of the N-nitroacetyl derivatives (**16a-d**) of the amino acid esters. In order to be sure of the structure of the intermediate nitroketene N,S-acetals (**15a-d**), these were also prepared by the alternate earlier route involving the treatment of 1,1-bismethylthio-2-nitroethylene with 1 mole of amino acid ester. The amino acid esters which have been successfully utilized in this reaction are glycine, alanine β-alanine, and phenylalanine.

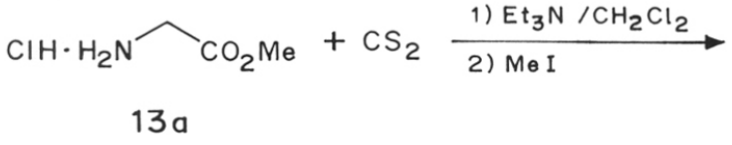
## 4.4 Results and discussion:

### 4.4.1 Synthesis of the carbonimidodithioic acid dimethyl esters from amino acid esters (14a-e):

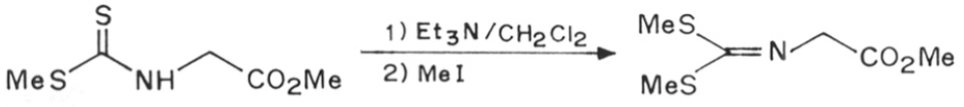
These carbonimidodithioates were prepared by the usual procedure[12] with appropriate modifications. Thus glycine methyl ester hydrochloride (**13a**) was condensed with carbon disulfide in the presence of triethylamine as the base in dichloromethane. Subsequent bis methylation with methyl iodide gave the product **14a** as a liquid in 80% yield (*Scheme 4-5*). The $^1$H NMR spectrum of **14a** showed four singlets at 4.20, 3.76, 2.55 and 2.40 which correspond respectively to $NCH_2$,-$OCH_3$,-$SCH_3$ and -$SCH_3$. Further support to the structure was provided by the mass spectrum which showed the molecular ion ($M^+$) peak at *m/z* 193.

By a similar procedure the bismethylthio methylene derivatives of alanine, β-alanine, phenylalanine and valine methyl esters **14b-d** were prepared in more than 90% yields. All these compounds were characterized by their $^1$H NMR spectra and other analytical data. The reactions are generally clean and fast.

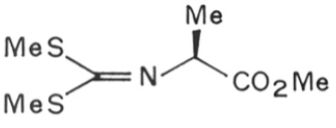
*Scheme 4-5*



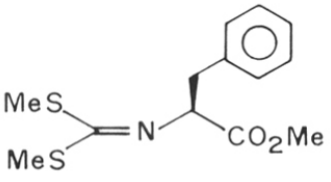

13a



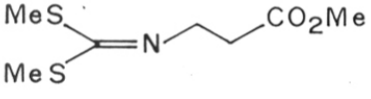

14a



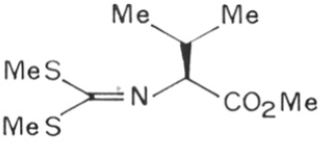

14b




14c




14d



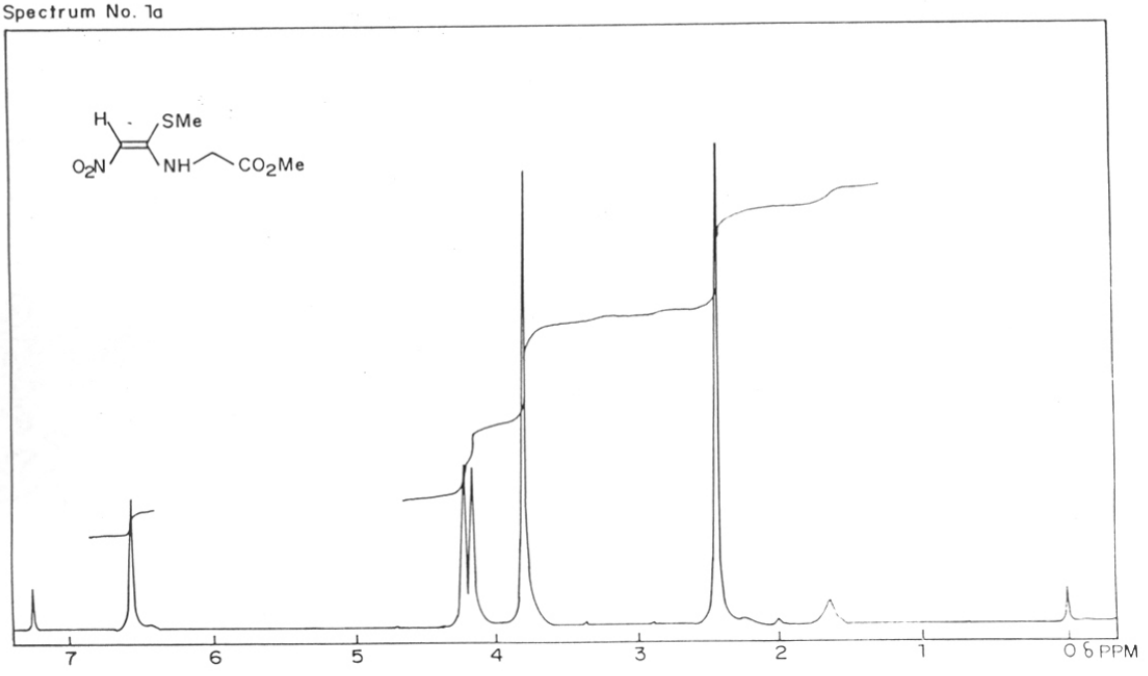

14e

### 4.4.2 Synthesis of N-[(1-methylthio)-2-nitroethenyl] derivatives of amino acid methyl esters (15a-d):

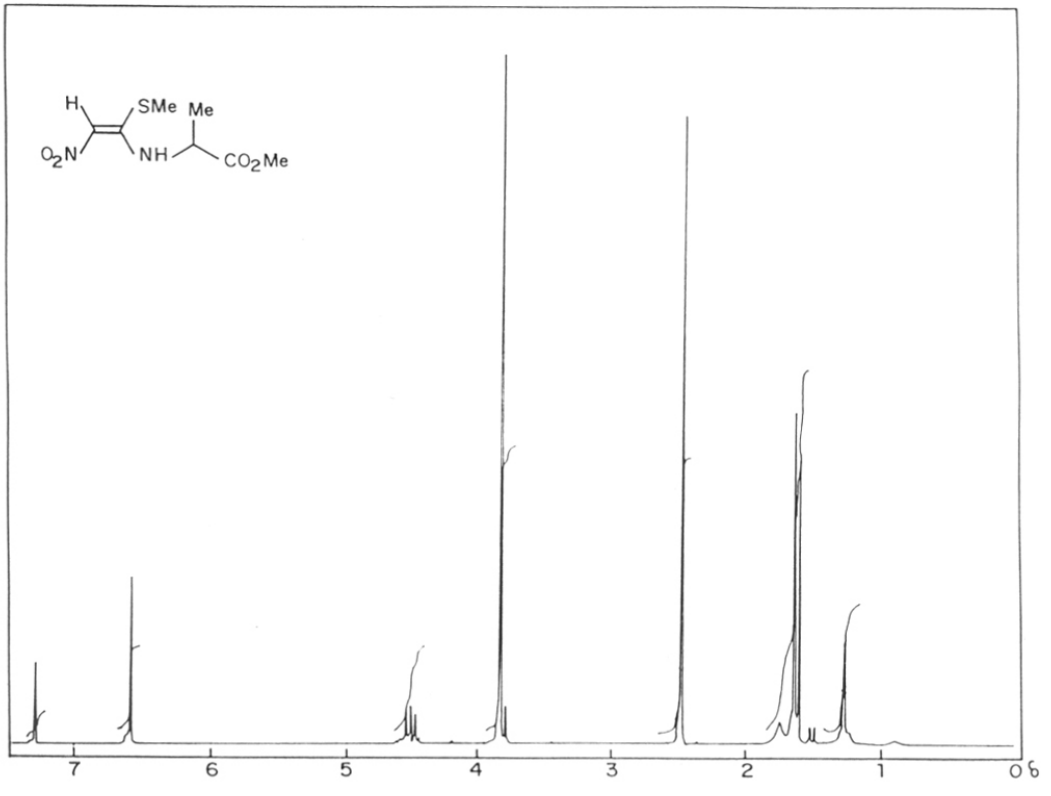
#### 4.4.2a *By the zeolite catalyzed condensation (Method-A):*

As mentioned above, the method consists in the condensation of the N-[bis(methylthio) methylene] derivatives of various amino acid methyl esters (**14a-d**) with nitromethane in the presence of the rare-earth exchanged zeolite RE(70%)NaY. The yield in this reaction depends on the substrate used. Generally the yields obtained are of the order of 25-60%. However, the valine derivative **14e** failed to give any product in this reaction. This is perhaps due to steric reasons, the isopropyl group probably hindering access in to the zeolite cavity. N-[Bis(methylthio) methylene] glycine methyl ester **14a** (10 mmol) and excess nitromethane (50 mmol) were refluxed for 24 h. in the presence of RE(70%)NaY. Filtration of the catalyst and removal of excess nitromethane gave the product **15a** as a thick liquid in 25% yield along with a yellow coloured solid **20** m.p. 113° C in 52% yield. The structure of this solid has been discussed separately under section 4.4.4. The structure of **15a** was confirmed by the spectral data. The $^1$H NMR spectrum (*Spectrum 4-1a*) of a purified sample of **15a** showed three singlets at 6.60 (s, 1H), 3.80 (s, 3H) and 2.45 (s, 3H) corresponding to =CH, -$OCH_3$ and -$SCH_3$ protons respectively in the ratio 1:3:3. A broad peak at 10.50 for NH and a doublet at 4.20 for two protons of $NCH_2$ group were also observed. The mass spectrum of the product showed the molecular ion ($M^+$) peak at *m/z* 206. The above data proved the structure of the product to be **15a**. Similarly, methyl N-[(1-methylthio)-2-nitroethenyl] (L) alaninate, (*Spectrum 4-1b*) methyl N-[(1-methylthio)-2-nitroethenyl] β-alaninate and methyl N-[(1-methylthio)-2-nitroethenyl] (L) phenylalaninate (**15b-d**) were also prepared in 45-65% yield and characterized by their spectral data (*Scheme 4-6*).

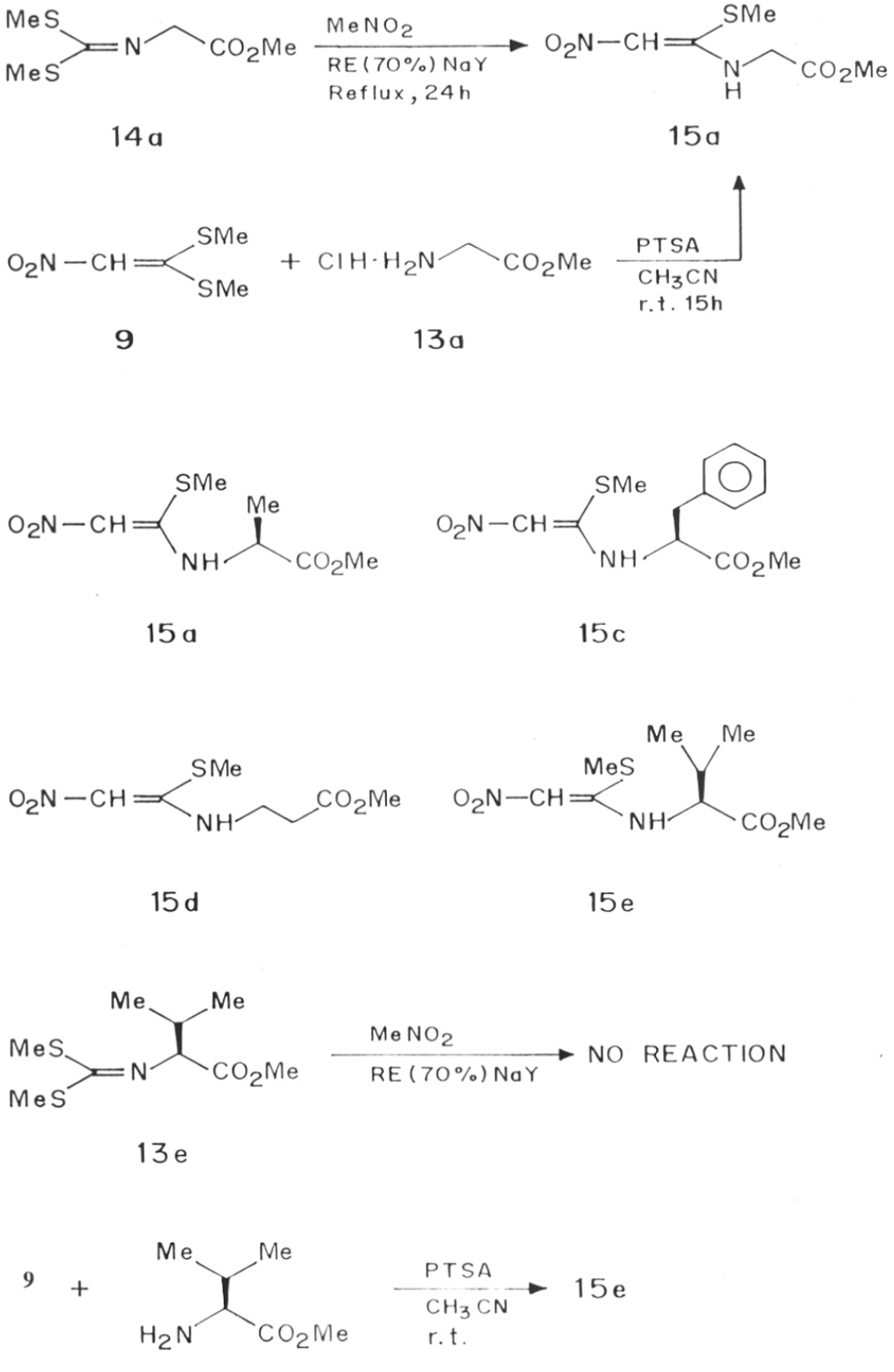
Spectrum No. 1a




Spectrum No. 4-1b



*Scheme 4-6*


MeS
MeS
N
CO2Me
MeNO2
RE (70%) NaY
Reflux, 24h
O2N—CH
SMe
N
H
CO2Me
14a
15a
O2N—CH
SMe
SMe
+ ClH·H2N
CO2Me
PTSA
CH3CN
r.t. 15h
9
13a
O2N—CH
SMe
Me
NH
CO2Me
15a
O2N—CH
SMe
NH
CO2Me
15c
O2N—CH
SMe
NH
CO2Me
15d
Me
Me
MeS
O2N—CH
NH
CO2Me
15e
Me
Me
MeS
MeS
N
CO2Me
MeNO2
RE (70%) NaY
NO REACTION
13e
9
+
Me
Me
H2N
CO2Me
PTSA
CH3CN
r.t.
15e

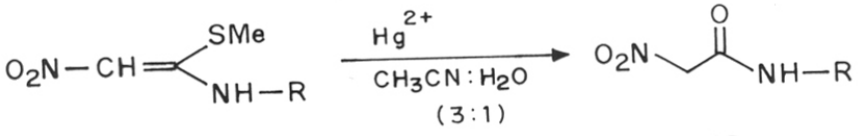
**4.4.2b** ***By condensation of 1,1-bismethylthio-2-nitroethylene with amino acid esters (Method-B):***

Reaction of amino acid methyl ester hydrochlorides **13a-e** with 1,1-bismethylthio-2-nitroethylene (**9**) in the presence of a catalytic amount of para-toluenesulfonic acid at 30-50° C for 12-15 h. gave the nitroenamines **15a-e**. For example, the reaction of glycine methyl ester hydrochloride **13a** (10 mmol) with 1,1-bismethylthio-2-nitroethylene (**9**) (10 mmol) under the above conditions gave the required product methyl N-[(1-methylthio)-2-nitroethenyl] glycinate **15a** in 50% yield (*Scheme 4-6*). The $^1$H NMR spectrum of this sample was exactly identical with that obtained by *Method-A* described earlier. This method was successful with all the amino acid esters including methyl (L)-valinate. The products **15a-e** have been characterized by their spectral and analytical data as described in the experimental section.

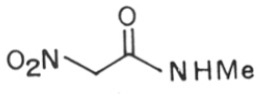
**4.4.3 Hydrolysis of the ene-thiol ethers 15a-e to the nitroacetamides (16a-e):**

The hydrolysis was achieved using mercuric chloride as a catalyst. Mercuric chloride has been widely used for the hydrolysis of dithioacetals and dithioketals to aldehydes and ketones.[13,14] The mechanism of such hydrolysis is known.[15] It has also been used in the hydrolysis of vinyl methyl sulfides to aldehydes or ketones.[16,17] Recently, the hydrolysis of 1-substitutedamino-1-methylthio-2-nitroethylene (**17**) to the nitroacetamides (**18**) has been described[11] (*Scheme 4-7*).

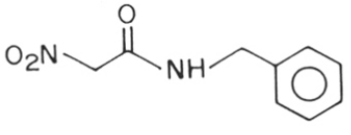
***Scheme 4-7***




17 18



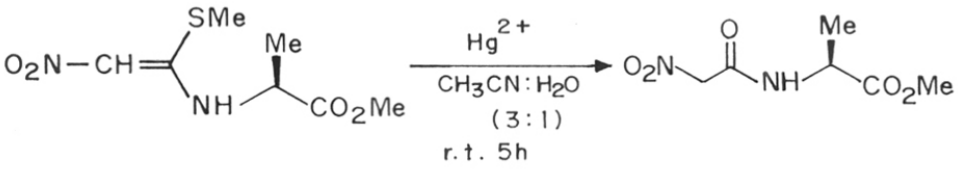

18a



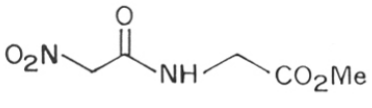

18b

Thus, methyl N-[(1-methylthio)-2-nitroethenyl] (L)-alaninate **15b** (10 mmol) was hydrolysed with mercuric chloride (10 mmol) in $CH_3CN$:$H_2O$ (3:1) for 5 h. at 30° C to give methyl N-nitroacetyl (L) alaninate **16b** in 90% yield (crude) which on purification by chromatography gave the pure product in 72% yield (*Scheme 4-8*). The $^1H$ NMR spectrum of **16b** (*Spectrum No. 4-2a*) showed five singlets at 7.35, 5.20, 4.65, 3.80 and 1.50. The infrared spectrum (*Spectrum No. 4-2b*) showed a band at 1750 $cm^{-1}$ for the ester group along with bands at 1680 and 1570 $cm^{-1}$ for the amide carbonyl and nitro group. The molecular ion ($M^+$) was observed in the mass spectrum at *m/z* 190. These data proved conclusively that the compound had structure **16b**. The N-nitroacetyl derivatives of glycine, β-alanine, (L) phenyl alanine and (L) valine methyl esters (**16a, 16c, 16d** and **16e**) were prepared similarly.

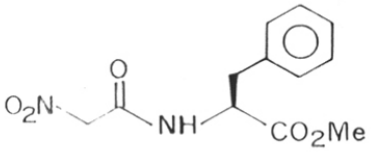
*Scheme 4-8*



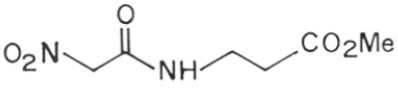

15b 16b



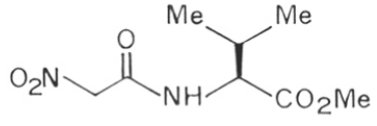

16a




16c

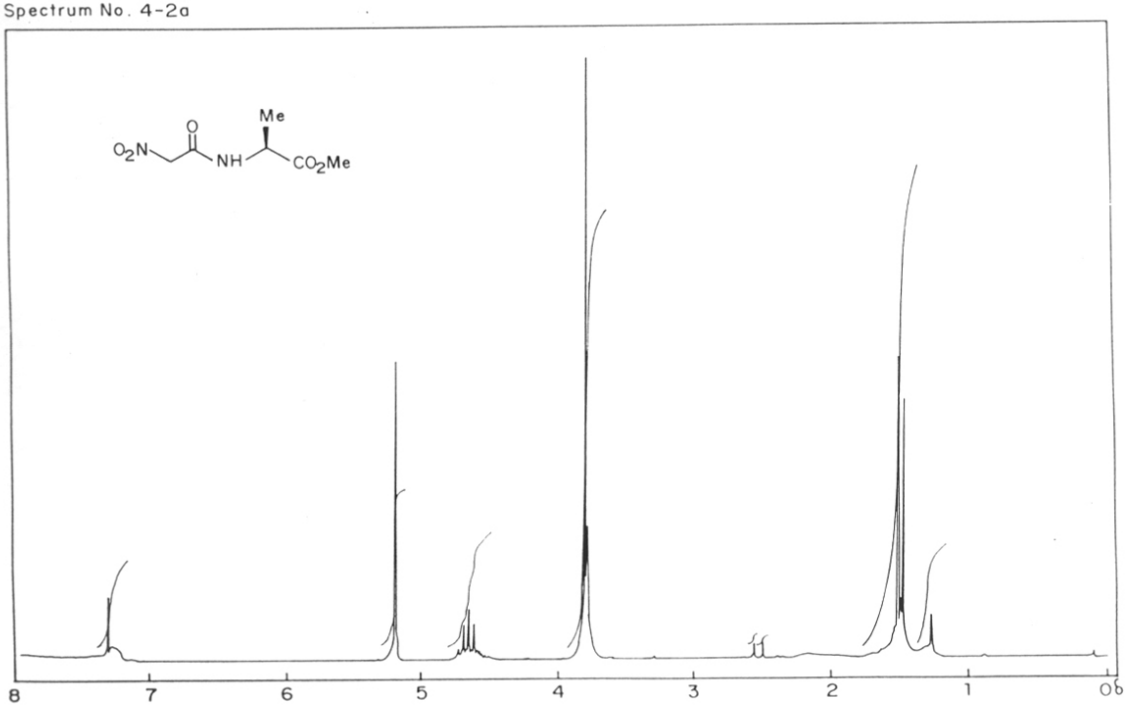



16d

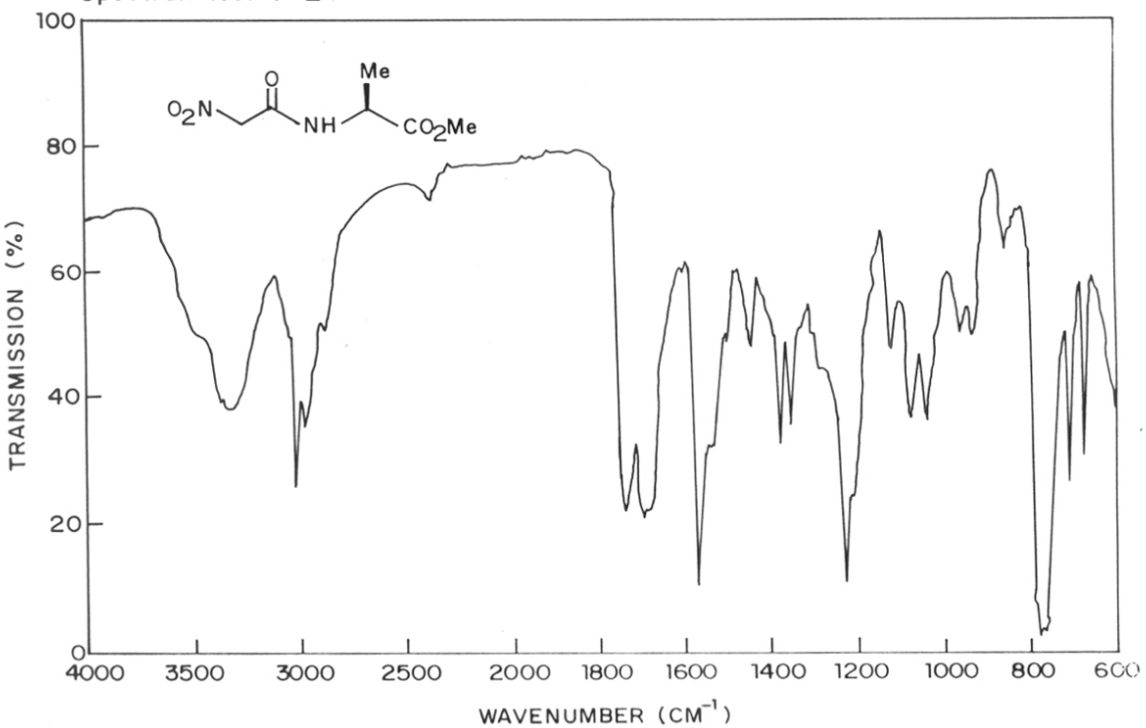



16e

Spectrum No. 4-2a




Spectrum No. 4-2b



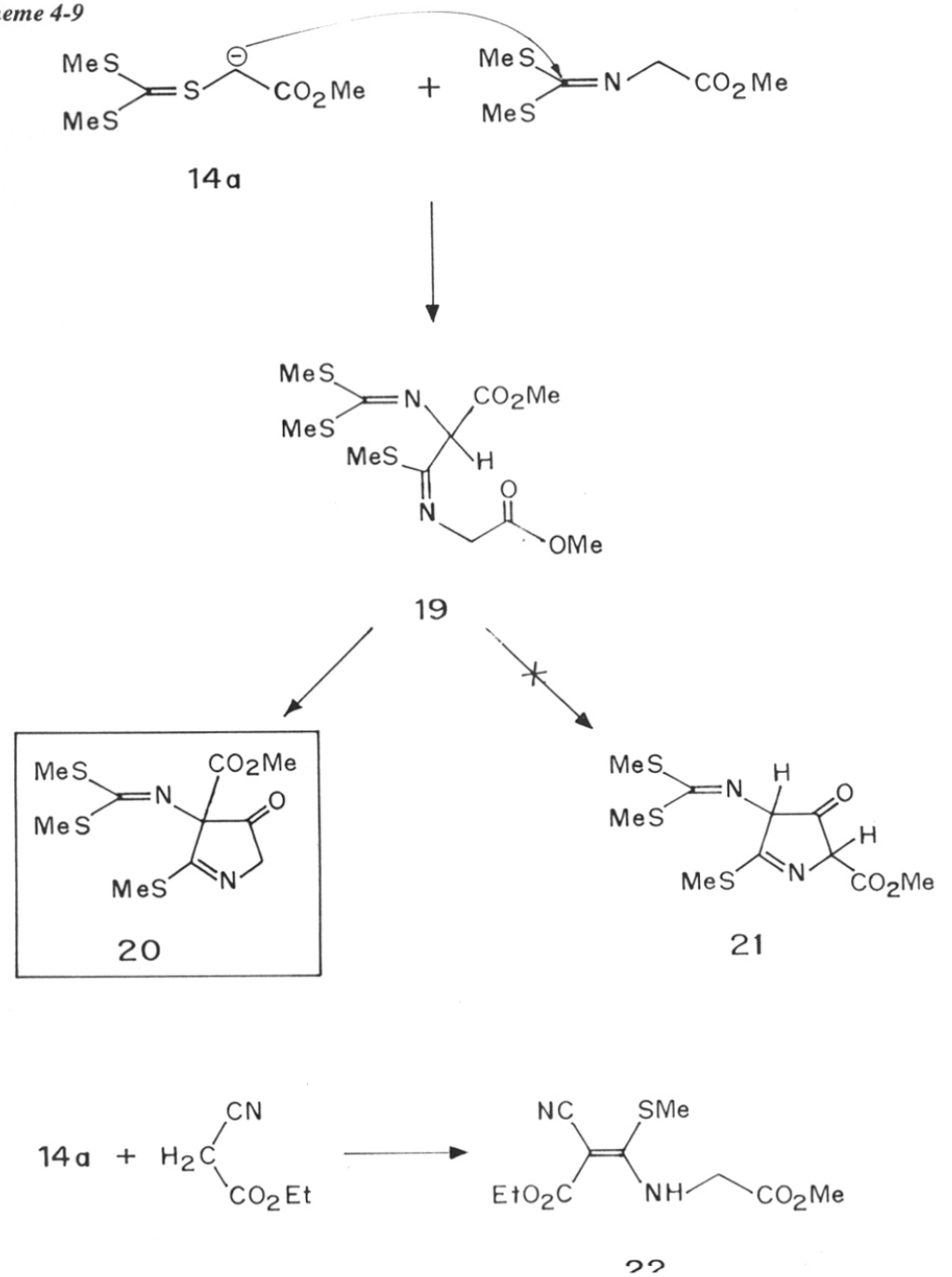
### 4.4.4 Synthesis of dimethyl N-[3-(3-carbomethoxy-2-methylthio-4-keto-4,5 -dihydro)-3(H)-pyrrolyl] carbonimidodithioate (20):

Structure of the by-product obtained in the zeolite catalyzed condensation of nitromethane with the carbonimidodithioic acid dimethyl ester derived from glycine methyl ester: The reaction of N-[bis(methylthio)methylene] glycine methyl ester (**14a**) with excess nitromethane in presence of zeolite RE(70%)NaY gave the expected product **15a** in 25% yield as discussed in section 4.4.2a. Apart from this an unexpected crystalline by-product was also obtained in 52% yield. The same product was obtained in 72% yield when nitromethane was omitted and the sole reactant **14a** refluxed in toluene solution in presence of the same zeolite. The analytical data and mass spectrum (molecular ion at *m/z* 306) led to the formula $C_{10}H_{14}N_2O_3S_3$ for the product, thus indicating that it was obtained from 2 moles of the starting material. It is known that the methylene group of the compounds such as **14a** can be deprotonated and could act as a nucleophilic site,[18] the carbon atom of the imine group is, of course, an electrophile especially when it is protonated. Initial bond-formation between these two carbon atoms could give the intermediate **19**. There are two ways in which **19** can cyclize to form a five membered ring giving either **20** or **21**. (*Scheme 4-9*). The $^1$H NMR spectrum of the product (*Spectrum No. 4-3*) consisted of only the following five singlets. 4.34 (2H), 3.76 (3H), 2.76 (3H), and 2.64 (3H), 2.58 (3H). The last three singlets are obviously assignable to $-SCH_3$ groups. The singlet at 3.76 is obviously due to the $-OCH_3$ of the ester function. The two proton singlet at 4.34 must be due to a methylene which does not couple with any adjacent protons. In the $^{13}$C NMR spectrum employing the DEPT technique (*Spectrum No. 4-4*) this methylene group resonated at 41.26 ppm. The above NMR data clearly prove structure **20** for the product and ruled out structure **21**. This unique dimerisation of the glycine derivative **14a** has not been observed before with conventional basic catalysts. The zeolite seems to be a specific catalyst for this process.

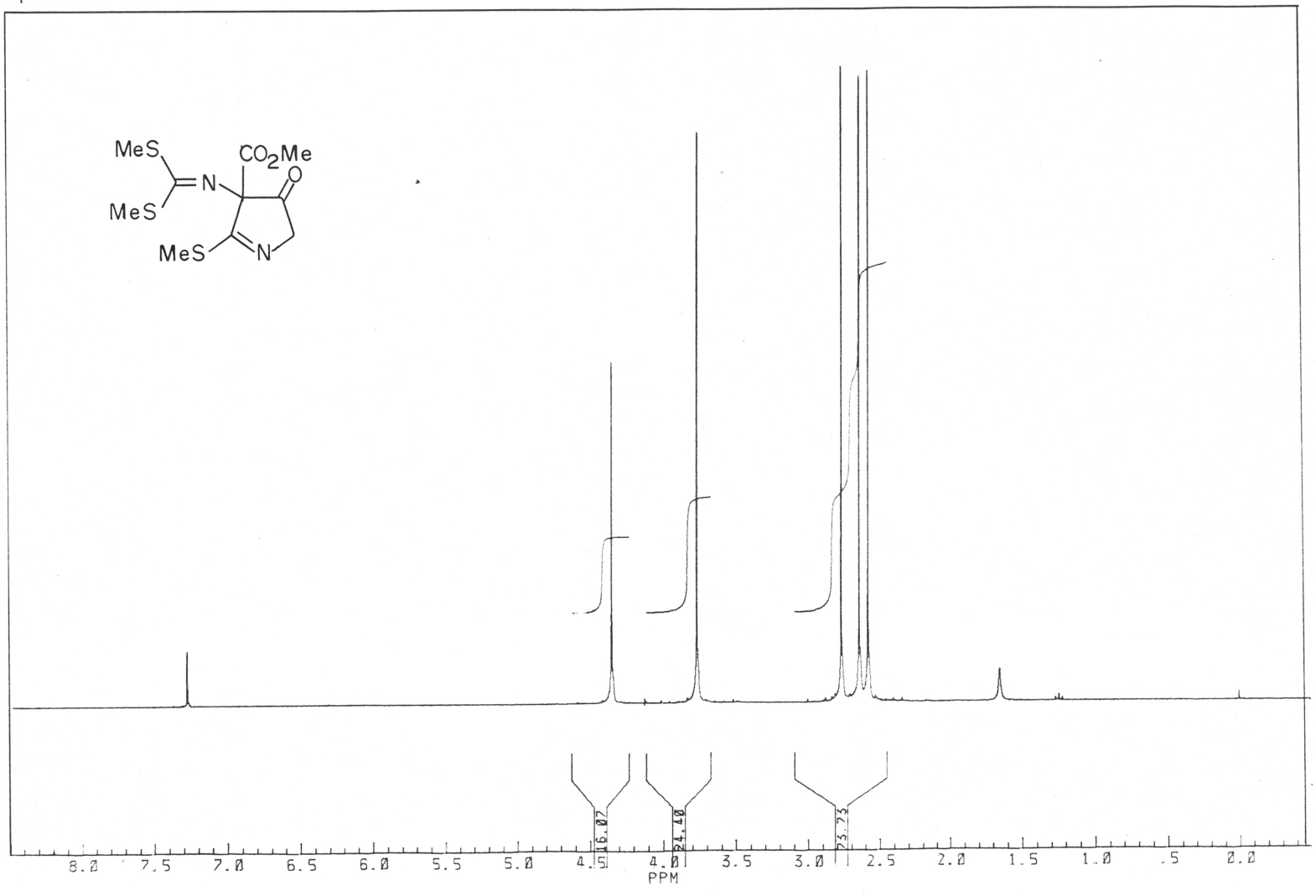
Our attempts to carry out a similar reaction of **14a** with other electrophiles such as methyl vinyl ketone, crotonaldehyde, acrylonitrile, ethyl acrylate and epichlorohydrin,

however, met with failure. In each case, the only isolable product was **20**. The glycine derivative **14a** did not react with methyl nitroacetate, only the self-condensed product **20** was formed in this reaction. However, ethyl cyanoacetate reacted with **14a** to give **22** in 80% yield.

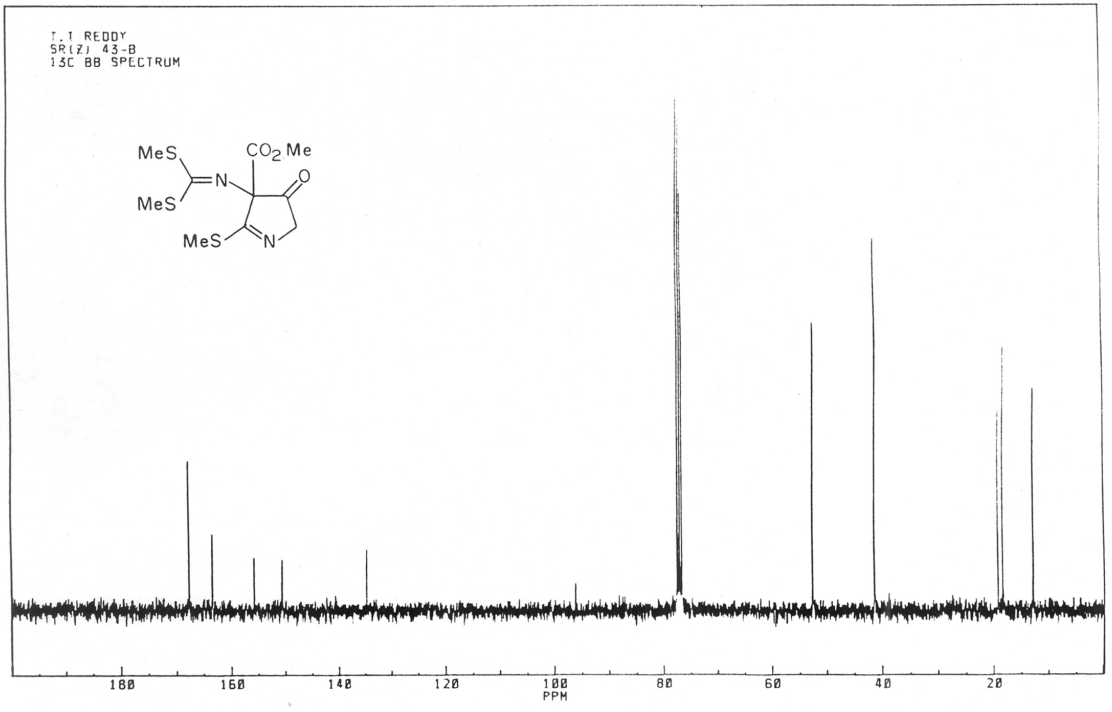
*Scheme 4-9*

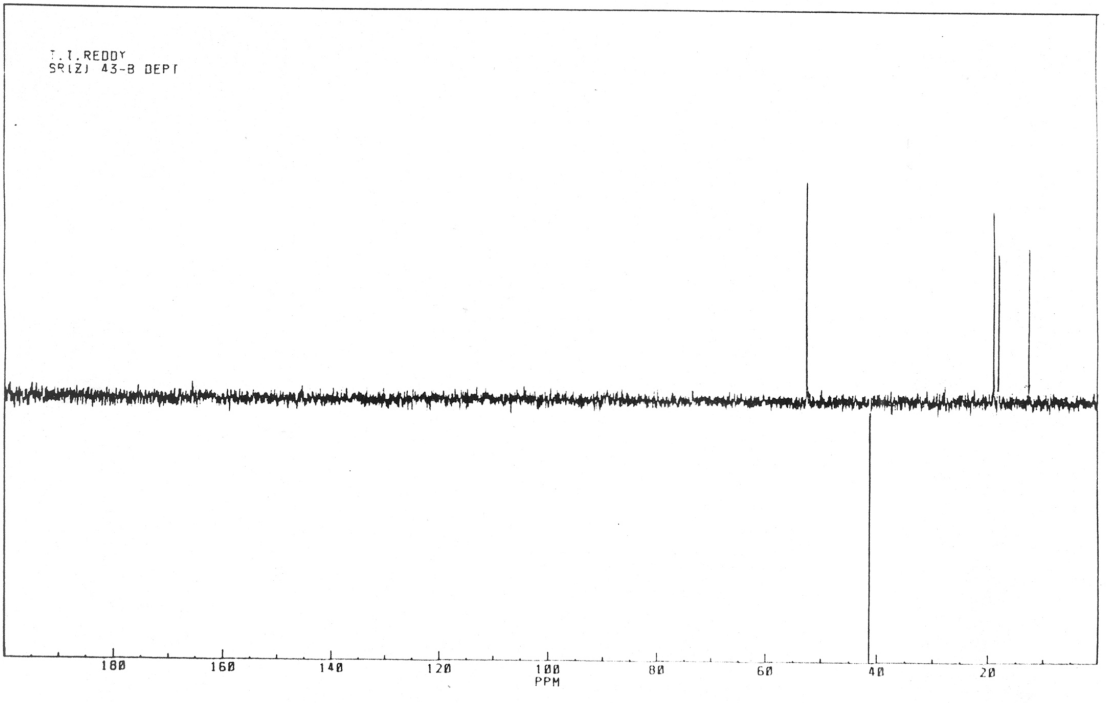


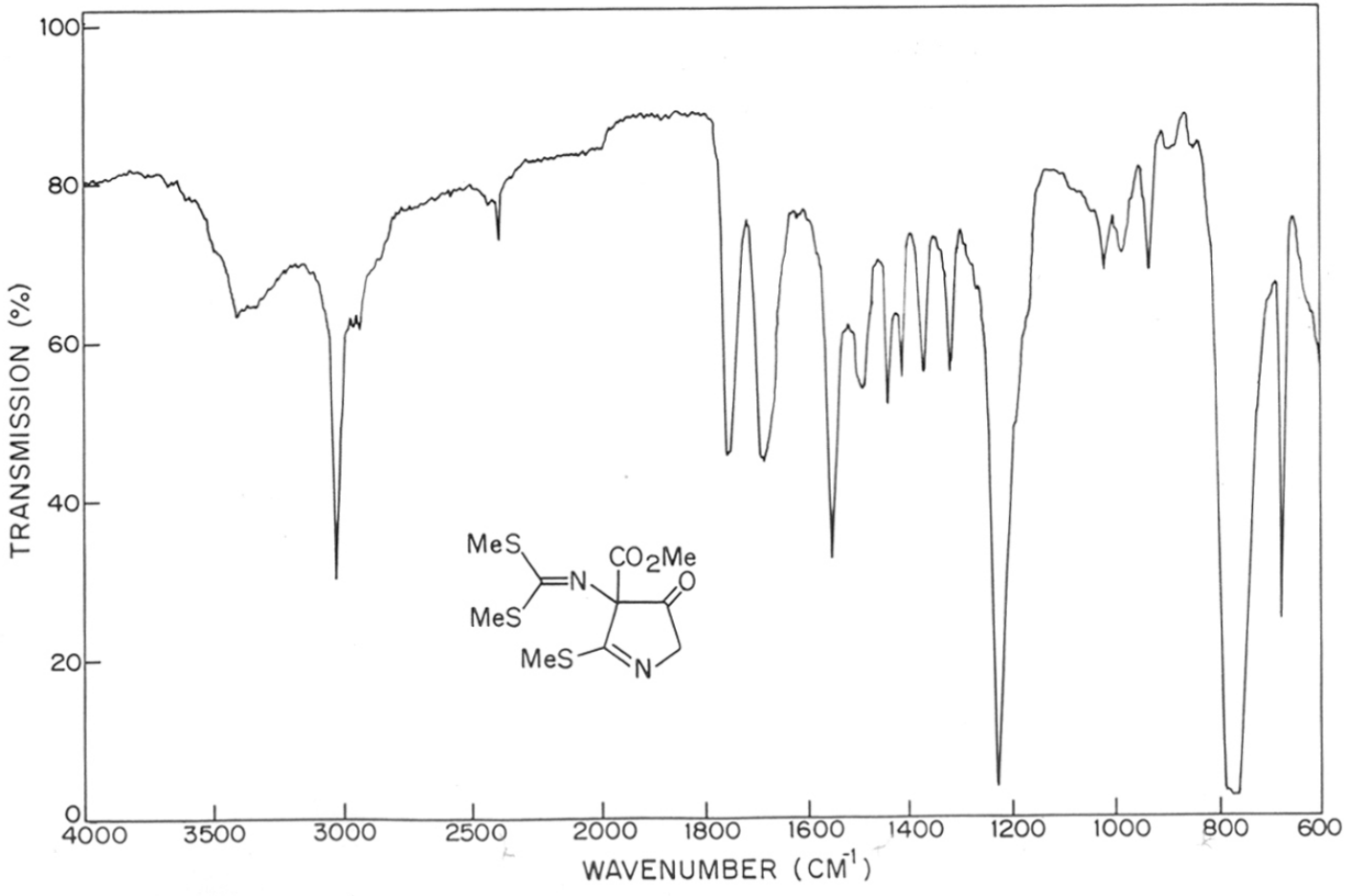
Spectrum No. 4-3



Spectrum No. 4-4




100
80
60
40
20
0
TRANSMISSION (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER (CM-1)
MeS
MeS
N
CO2Me
O
MeS
N

## 4.5 Summary:

1. Carbonimidodithioates are useful substrates to prepare nitroenamines.This process avoids the combination of nitromethane and base to synthesize 1,1-bis(methylthio)-2-nitroethylene

2. Zeolites are efficient in condensing the carbonimidodithioates withnitromethane, whereas all other bases such as $K_2CO_3$, DBU and NaH have failed.

3. Reaction conditions to prepare intermediates **15a-d** are almost neutral and mild when zeolite is employed.

## 4.6 Experimental:

**Synthesis of amino acid methyl esters (13a-e):**

**General procedure:** Thionylchloride (80 mmol) was added slowly with a dropping funnel to a suspension of amino acid (40 mmol) in dry methanol (60 mmol) at 0-5°C. A clear solution was obtained and the reaction mixture was stirred for 12 h. at room temperature. Excess methanol was removed at reduced pressure. The residue containing some amount of methanol was stirred at ice salt temperature to get a solid. This was filtered through a Buchner funnel to yield the amino acid methyl ester hydrochloride in quantitative yield. The salt was used as such for further reaction.

**Synthesis of carbonimidodithioic acid dimethyl esters of amino acid methyl esters (14a-e):**

**General procedure:** To a solution of the amino acid ester hydrochloride (10 mmol) and carbon disulfide (10 mmol) in dichloromethane (50 ml), triethylamine (20 mmol) was added slowly at 20°C. The reaction mixture was stirred for 30 min at room temperature. Methyl iodide (12 mmol) was then added dropwise and the resulting mixture was refluxed for 2-3 h. The reaction mixture was then cooled to room temperature; triethylamine (12 mmol), methyl iodide (12 mmol) were successively added dropwise and it was again refluxed for 2-4 h. After complete conversion of dithiocarbamate to carbonimidodithioate, the reaction mixture was cooled, washed with water (2 X 30 ml) and concentrated under vacuum. The residue was taken in ether (50 ml) and again washed with water (3 X 20 ml) and brine, dried (anhyd. $Na_2SO_4$) and concentrated to give the product (**14a-e**) in 70-90% yield.

**N-[Bis (methylthio) methylene] glycine methyl ester (14a):**

| | | |
|---|---|---|
| Yield | : | 70%, Yellow coloured liquid. |
| bp | : | 110°C/1.5 mm. |
| $^1$H NMR (90 MHz) | : | δ 4.20 (s, 2H, $NCH_2$), 3.75 (s, 3H, $OCH_3$), 2.55 (s, 3H, $SCH_3$), |

2.45 (s, 3H, $SCH_3$).

IR (Liq.film) : $cm^{-1}$ 1755, 1585.

MS : *m/z* 193 ($M^+$, 20%), 146 (100).

Analysis : $C_6H_{11}NO_2S_2$. Calcd. : C, 37.30; H, 5.69; N, 7.25.

Found : C, 37.58; H, 5.83; N, 7.44.

**N-[Bis (methylthio) methylene] (L)-alanine methyl ester (14b):**

Yield : 82%; Colourless liquid.

bp : 94°C/4.5 mm.

$^1H$ NMR (90 MHz) : δ 4.55 (q, *J* = 7.2 Hz, 1H), 3.75 (s, 3H, $OCH_3$), 2.40 (s, 3H, $SCH_3$), 2.20 (s, 3H, $SCH_3$), 1.45 (d, *J* = 7.2 Hz, 3H, $CH_3$).

IR (Neat) : $cm^{-1}$ 1750, 1580.

MS : *m/z* 207 ($M^+$, 10%), 160 (100), 132.

Analysis : $C_7H_{13}NO_2S_2$. Calcd. : C, 40.57; H, 6.28; N, 6.76.

Found : C, 39.95; H, 6.90; N, 6.76.

**N-[Bis (methylthio) methylene] (L)-phenylalanine methyl ester (14c):**

Yield : 90%; Colourless crystalline solid.

mp : 49-51°C.

$^1H$ NMR (90 MHz) : δ 7.30 (s, 5H, aromatic), 4.70 (m, 1H), 3.70 (s, 3H, $OCH_3$), 3.15 (m, 2H), 2.40 (s, 3H, $SCH_3$), 2.35 (s, 3H, $SCH_3$).

IR (Nujol) : $cm^{-1}$ 1735, 1575.

MS : *m/z* 283 ($M^+$, 05%), 236 (100).

Analysis : $C_{13}H_{17}NO_2S_2$. Calcd. : C, 55.12; H, 6.00; N, 4.94.

Found : C, 55.27; H, 6.24; N, 4.94.

**N-[Bis (methylthio) methylene] β-alanine methyl ester (14d):**

| | | |
|---|---|---|
| Yield | : | 87%; Colourless liquid. |
| bp | : | 101°C/4.5 mm. |
| $^1$H NMR (90 MHz) | : | δ 3.70 (s, 3H, $OCH_3$), 3.65 (t, $J$ = 6.9 Hz, 2H, $NCH_2$), 2.65 (t, $J$ = 6.9 Hz, 2H, $COCH_2$), 2.50 (s, 3H, $SCH_3$) 2.35 (s, 3H, $SCH_3$). |
| IR ($CHCl_3$) | : | $cm^{-1}$ 1745, 1590. |
| MS | : | $m/z$ 207 ($M^+$, 05%), 160 (90), 87 (100). |
| Analysis | : | $C_7H_{13}NO_2S_2$. Calcd. : C, 40.57; H, 6.28; N, 6.76. Found : C, 40.31; H, 6.44; N, 6.78. |

**N-[Bis (methylthio) methylene] (L)-valine methyl ester (14e):**

| | | |
|---|---|---|
| Yield | : | 84%; Colourless liquid. |
| bp | : | 90°C/5.2 mm. |
| $^1$H NMR (80 MHz) | : | δ 4.20 (d, $J$ = 6.4 Hz, 1H), 3.70 (s, 3H, $OCH_3$), 2.50 (s, 3H, $SCH_3$) 2.40 (s, 3H, $SCH_3$), 2.30 (m, 1H), 1.00 (d, $J$ = 6.8 Hz, 6H). |
| IR (Neat) | : | $cm^{-1}$ 1750, 1590. |
| MS | : | $m/z$ 235 ($M^+$, 00), 188 (100). |
| Analysis | : | $C_9H_{17}NO_2S_2$. Calcd. : C, 45.95; H, 7.23; N, 5.95. Found : C, 45.79; H, 7.84; N, 6.08. |

**General procedure for the preparation of nitroethylene compounds (15a-d) from carbonimidodithioic acid dimethyl esters (14a-d):**

**By zeolite catalyzed condensation (*Method-A*):**

**General procedure:** Freshly activated zeolite RE(70%)NaY (0.5g) was added to the mixture of **14a-d** (10 mmol) and nitromethane (50 mmol) at room temperature and the suspension was refluxed with stirring for 24 h. The reaction mixture was then cooled to room temperature, the catalyst was filtered off and washed with $CH_2Cl_2$ (2 x 30 ml). The filtrate was concentrated

at reduced pressure. The residue was taken in n-hexane and stirred for a few min to solidify the product. Final purification was carried out by column chromatography to give the pure product (**15a-d**) in 50-60% yield.

**By condensation of 1,1-bis methylthio-2-nitroethylene with amino acid esters (*Method-B*):**

**General procedure:** A solution of amino acid methyl ester hydrochloride (**13a-e**) (10 mmol) in dry acetonitrile (15 ml) was added slowly to a suspension of 1,1-bis methylthio-2-nitroethylene (**9**) (10 mmol) and catalytic amount of PTSA in acetonitrile (15 ml) at room temperature. Clear solution was obtained. Then the reaction mixture was heated at 60° C for 12-15 h. The evolution of methanethiol was observed by its characteristic smell. The reaction was followed by tlc. Reaction mixture was cooled and solvent was removed under vacuum to get a gum. The unreacted starting material **9** was precipitated by treating the gum with ice cold EtOH. It was filtered and the filtrate was concentrated and the resulting gum was again washed with n-hexane. Final purification was done by column chromatography to get the product (**15a-e**).

**Methyl N-[1-(Methylthio)-2-nitroethenyl] glycinate (15a):**

| | | |
|---|---|---|
| Yield | : | Method-A, 25%,(compound **20** was isolated in 52% yield); Method-B, 53%. |
| bp/mp | : | Thick liquid. |
| $^1$H NMR (90 MHz) | : | δ 10.55 (br, 1H, NH) 6.60 (s, 1H), 4.20 (d, $J$ = 5.7 Hz, 2H, $NCH_2$), 3.80 (s, 3H, $OCH_3$), 2.45 (s, 3H, $SCH_3$). |
| IR ($CHCl_3$) | : | $cm^{-1}$ 3300-3500, 1760, 1580. |
| MS | : | $m/z$ 206 ($M^+$, 30%), 159, 147, 131, 74 (100). |
| Analysis | : | $C_6H_{10}N_2O_4S$. Calcd. : C, 34.95; H, 4.85; N, 13.59. Found : C, 35.12; H, 4.73; N, 13.67. |

**Methyl N-[(1-methylthio)-2-nitroethenyl] (L)-alaninate (15b):**

| | | |
|---|---|---|
| Yield | : | Method-A, 65%; Method-B, 54%, Light yellow coloured crystalline solid. |
| mp | : | 113-114°C (EtOH). |
| $^1$H NMR (80 MHz) | : | δ 10.70 (br, 1H, NH), 6.60 (s, 1H), 4.58 (m, 1H), 3.85 (s, 3H, $OCH_3$), 2.50 (s, $SCH_3$), 1.65 (d, $J$ = 7.6 Hz, 3H, $CH_3$). |
| IR ($CHCl_3$) | : | $cm^{-1}$ 3280-3450, 1770, 1580. |
| MS | : | $m/z$ 220 ($M^+$, 25%), 174, 161, 141, 74 (100). |
| Analysis | : | $C_7H_{12}N_2O_4S$. Calcd. : C, 38.18; H, 5.45; N, 12.72. Found : C, 38.06; H, 5.57; N, 12.79. |

**Methyl N-[(1-methylthio)-2-nitroethenyl] (L)-phenylalaninate (15c):**

| | | |
|---|---|---|
| Yield | : | Method-A, 45%; Method-B, 58%. |
| bp/mp | : | Gum. |
| $^1$H NMR (200 MHz) | : | δ 10.50 (br, 1H, NH), 7.10-7.30 (m, 5H, aromatic) 6.60 (s, 1H), 4.65 (m, 1H), 3.70 (s, 3H, $OCH_3$), 3.15 (m, 2H), 2.30 (s, 3H, $SCH_3$). |
| IR ($CHCl_3$) | : | $cm^{-1}$ 3500-3280, 1745, 1570. |
| MS | : | $m/z$ 296 ($M^+$, 15%), 237, 219, 176, 91 (100), 74. |
| Analysis | : | $C_{13}H_{16}N_2O_4S$. Calcd. : C, 52.70; H, 5.40; N, 9.45. Found : C, 52.82; H, 5.52; N, 9.59. |

**Methyl N-[(1-methylthio)-2-nitroethenyl] β-alaninate (15d):**

| | | |
|---|---|---|
| Yield | : | Method-A, 62%; Method-B, 50%. |
| bp/mp | : | an oil. |
| $^1$H NMR (80 MHz) | : | δ 10.70 (br, 1H, NH), 6.60 (s, 1H), 3.75, (s, 3H, $OCH_3$), 3.70 (m, |

2H, $NCH_2$), 2.70 (t, $J$ = 6.4 Hz, 2H, $COCH_2$), 2.45 (s, 3H, $SCH_3$).

IR ($CHCl_3$) : $cm^{-1}$ 3300-3500, 1740, 1570.

MS : *m/z* 220 ($M^+$, 15%), 173, 87 (100).

Analysis : $C_7H_{12}N_2O_4S$. Calcd. : C, 38.18; H, 5.45; N, 12.72.

Found : C, 38.13; H, 5.55; N, 12.81.

**Methyl N-[(1-methylthio)-2-nitroethenyl] (L)-valinate (15e):**

Yield : Method-A, 00%; Method-B, 57%.

bp/mp : Gum.

$^1H$ NMR (80 MHz) : δ 10.80 (br, 1H, NH), 6.60 (s, 1H, =CH), 4.35 (dd, 1H), 3.80 (s, 3H, $OCH_3$), 2.30 (s, 3H, $SCH_3$), 2.20 (m, 1H), O.90 (dd, 6H, $2CH_3$).

IR (Liq.Film) : $cm^{-1}$ 3400-3250, 1750, 1570.

MS : *m/z* 248 ($M^+$, 30%), 189, 91 (100).

Analysis : $C_9H_{16}N_2O_4S$. Calad. : C, 43.55; H, 6.45; N, 11.29.

Found : C, 43.62; H, 6.43; N, 11.39.

**General procedure for the preparation of nitroacetamides (16a-e):**

To the solution of $HgCl_2$ (10 mmol) in $CH_3CN/H_2O$ (3:1) (20 ml), a solution of **15a-e** (10 mmol) in the same solvent (20 ml) was added drop wise and the mixture was stirred for 4-6 h at 40-50°C. The reaction mixture was cooled, and then filtered through celite pad and concentrated under vacuum. The residue was taken in $CHCl_3$ (40 ml) washed with water, dried (anhyd $Na_2SO_4$), concentrated and purified by column chromatography to get pure product (**16a-e**) in 85-90% yield.

**Methyl N-nitroacetyl glycinate (16a):**

Yield : 85%.

mp : Gum.

| | | |
|---|---|---|
| $^1$H NMR (80 MHz) | : | δ 7.50 (br, 1H, NH), 5.25 (s, 2H), 4.15 (d, $J$ = 5.7 Hz, 2H, $NCH_2$), 3.80 (s, 3H, OCH3). |
| IR (Nujol) | : | $cm^{-1}$ 3340, 1740, 1680, 1575. |
| MS | : | $m/z$ 176 ($M^+$, 10%), 117 (100). |
| Analysis | : | $C_5H_8N_2O_5$. Calcd. : C, 34.09; H, 4.54; N, 15.90. Found : C, 34.12; H, 4.68; N, 16.12. |

**Methyl N-nitroacetyl (L)-alaninate (16b):**

| | | |
|---|---|---|
| Yield | : | 88%. |
| bp | : | an oil. |
| $^1$H NMR (80 MHz) | : | δ 7.35 (br, 1H, NH), 5.20 (s, 2H), 4.65 (m, 1H), 3.85 (s, 3H, $OCH_3$), 1.50 (d, $J$ = 6.1 Hz, 3H, $CHCH_3$). |
| IR (Nujol) | : | $cm^{-1}$ 3300, 1750, 1680, 1570. |
| MS | : | $m/z$ 190 ($M^+$, 05%), 131 (100). |
| Analysis | : | $C_6H_{10}N_2O_5$. Calcd. : C, 37.89; H, 5.26; N, 14.73. Found : C, 37.78; H, 5.38; N, 14.79. |

**Methyl N-ntroacetyl (L)-phenylalaninate (16c):**

| | | |
|---|---|---|
| Yield | : | 90%; Crystalline solid. |
| mp | : | 79° C. |
| $^1$H NMR (80 MHz) | : | δ 7.30 (m, 5H, aromatic), 5.15 (s, 2H), 4.90 ( m, 1H), 3.15 (m, 2H). |
| IR (Nujol) | : | $cm^{-1}$ 3320, 1740, 1670, 1570. |
| MS | : | $m/z$ 266 ($M^+$, 10%), 207, 176, 131, 91 (100). |
| Analysis | : | $C_{12}H_{14}N_2O_5$. Calcd. : C, 54.13; H, 5.26; N, 10.52. Found : C, 54.31; H, 5.28; N, 10.54. |

**Methyl N-nitroacetyl β-alaninate (16d):**

| | | |
|---|---|---|
| Yield | : | 90%. |
| bp/mp | : | Gum. |
| $^1$H NMR (80 MHz) | : | δ 7.10 (br, 1H, NH), 5.15 (s, 2H, $CH_2$), 3.70 (s, 3H, $SCH_3$), 3.60 (q, 2H, $CH_2$) 2.60 (t, 2H, $CH_2$). |
| IR (Liq.Film) | : | $cm^{-1}$ 3320, 1740, 1685, 1570. |
| MS | : | *m/z* 190 ($M^+$, 40%), 159, 144, 55 (100). |
| Analysis | : | $C_6H_{10}N_2O_5$. Calcd. : C, 37.89; H, 5.26; N, 14.73. Found : C, 37.94; H, 5.31; N, 14.85. |

**Methyl N-nitroacetyl (L)-valinate (16e):**

| | | |
|---|---|---|
| Yield | : | 70 %. |
| bp/mp | : | Semisolid. |
| $^1$H NMR (80 MHz) | : | δ 7.2 (br, d, NH), 5.2 (s, 2H, $CH_2$), 4.6 (dd, 1H, CH), 2.2-2.3 (m, 1H, 1H), O.9 (dd, 6H, $2CH_3$). |
| IR (Liq.Film) | : | $cm^{-1}$ 3340, 1750, 1685, 1570. |
| MS | : | *m/z* 218 ($M^+$, 50%), 159, 98, 88 (100). |
| Analysis | : | $C_8H_{14}N_2O_5$. Calcd. : C, 44.03; H, 6.42; N, 12.84. Found : C, 44.18; H, 6.29; N, 12.98. |

**Dimethyl N-[3-(3-carbomethoxy-2-methylthio-4-keto-4,5-dihydro)-3(H)-pyrrolyl] carbonimidodithioate (20):**

A mixture of **14a** (1g) and zeolite RE(70%)NaY (0.5g) was refluxed in 10 ml of toluene for 24 h. The reaction mixture was cooled, the catalyst filtered and washed with dichloromethane (3 x 20 ml). The filtrate was concentrated and the residue was taken in n-hexane. The solid product was isolated and purified by column chromatography to get a yellow coloured solid **20** in 72% yield.

| | | |
|---|---|---|
| Yield | : | 72%, Yellow coloured solid. |
| mp | : | 119 °C (EtOH). |
| $^1$H NMR (300 MHz) | : | δ 4.34 (s, 2H, $NCH_2$), 3.76 (s, 3H, $OCH_3$), 2.76 (s, 3H, $SCH_3$), 2.64 (s, 3H, $SCH_3$), 2.58 (s, 3H, $SCH_3$). |
| $^{13}$C NMR (75.5 MHz) | : | ppm 167.40, 163.18, 155.39, 134.47, 52.48, 41.25, 19.10, 18.24, 12.76. |
| IR ($CHCl_3$) | : | $cm^{-1}$ 1760, 1690, 1560. |
| MS | : | *m/z* 306 ($M^+$, 100%), 245, 72, 61. |
| Analsis | : | $C_{10}H_{14}N_2O_3S_3$. Calcd. : C, 39.21; H, 4.57; N, 9.15. Found : C, 39.19; H, 4.62; N, 9.27. |

**Methyl N-[(1-methylthio-2-carbethoxy-2-cyano) ethenyl] glycinate (22):**

A mixture of **14a** (1 g, 5 mmol), ethylcyanoacetate (5 mmol) and zeolite RE(70%)NaY (0.5 g) was refluxed in toluene (15 ml) for 16 h. The reaction mixture was worked up according to the procedure described above for **20** to give light yellow coloured solid (**22**) in 80% yield.

| | | |
|---|---|---|
| Yield | : | 80%, Light yellow coloured solid. |
| mp | : | 127 °C (EtOH). |
| $^1$H NMR (90 MHz) | : | δ 10.40 (br, 1H, NH), 4.30 (m, 4H, $OCH_2$ and $NCH_2$), 3.80 (s, 3H, $OCH_3$), 2.65 (s, 3H, $SCH_3$), 1.30 (t, $J$ = 6.9 Hz, 3H, $CH_3$). |
| IR ($CHCl_3$) | : | $cm^{-1}$ 3000, 2210, 1750, 1660, 1580. |
| MS | : | *m/z* 258 ($M^+$, 90%), 153 (100), 137 (95). |
| Analysis | : | $C_{10}H_{14}N_2O_4S$. Calcd. : C, 46.51; H, 5.42; N, 10.85. Found : C, 46.78; H, 5.71; N, 10.86. |

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# CHAPTER - 5

# A NOVEL SYNTHESIS OF S-METHYL THIOLCARBAMATES

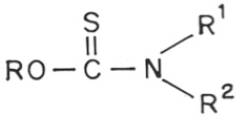
## 5.1 Abstract:

This chapter deals with the discovery of a very simple and mild synthesis of S-methyl thiolcarbamates, for which very few general methods are available. The method involves the zeolite catalyzed hydrolysis of N-substituted carbonimidodithioic acid dimethyl esters. The reaction proceeds in moderate to good yields. The reaction can also be brought about by the $ZnCl_2$ mediated hydrolysis in $CH_3CN$ : $H_2O$ (3:1). Attempts at similar hydrolysis of carbonimidodithioates derived from sulfonamides however failed. The concept of the zeolite catalyzed hydrolysis has been applied to ketene S,S-acetals in which a carbon-carbon double bond is present, instead of a carbon-nitrogen double bond. This has succeeded only when a strong electron attracting group is present at the other end.

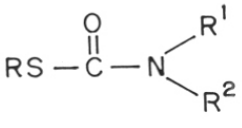
## 5.2 Introduction:

### 5.2.1 Background:

Two isomeric structures **1** and **2** are possible for monothio carbamates. The former is referred to as O-alkyl thionocarbamate and the later S-alkyl/aryl thiolcarbamate. The S-alkyl thiolcarbamates (**2**) would be useful intermediates since the thiolate anion can be easily displaced by other nucleophiles.



1



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### 5.2.2 Earlier synthetic studies:

#### 5.2.2a *From thiocyanates:*

The first report of the synthesis of S-aryl thiolcarbamates from arylthiocyanates (**3**) appeared in 1951 by Riemschneider et al[1]; this was extended to the synthesis of S-alkyl derivatives (**4**) by the reaction of secondary and tertiary alcohols or olefins with alkyl thiocyanates[2] (*Scheme 5-1*). The reaction failed with primary alcohols. Use of fuming sulfuric acid was the major drawback of this method.

### 5.2.2b *Using phosgene:*

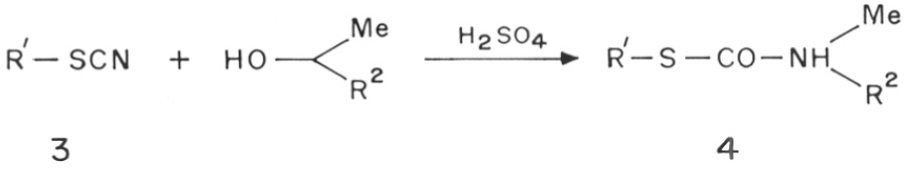
In another method reported by the same auther[3] in 1953, the secondary amine (**5**) was treated with an alkyl chlorothiolformate (**6**) (obtained from alkylthiol and phosgene) in ether to give the thiolcarbamate (**7**). The compound **7** was also synthesized[4] by treating sodium alkylmecaptide with the appropriate dialkylcarbamoyl chloride (**8**) in refluxing xylene.

In 1965 Elingsfeld and Mobius[5] synthesized thiolcarbamates of various secondary amines. Their method involved the reaction of dithiocarbamate with phosgene, to generate the mercapto formamidochloride salt (**9**), which on hydrolysis gave the required thiolcarbamate (**10**). These appear to be general methods, but the starting materials **6, 8** and **9** were prepared by using phosgene which is highly toxic.

### 5.2.2c *From thionocarbamates:*

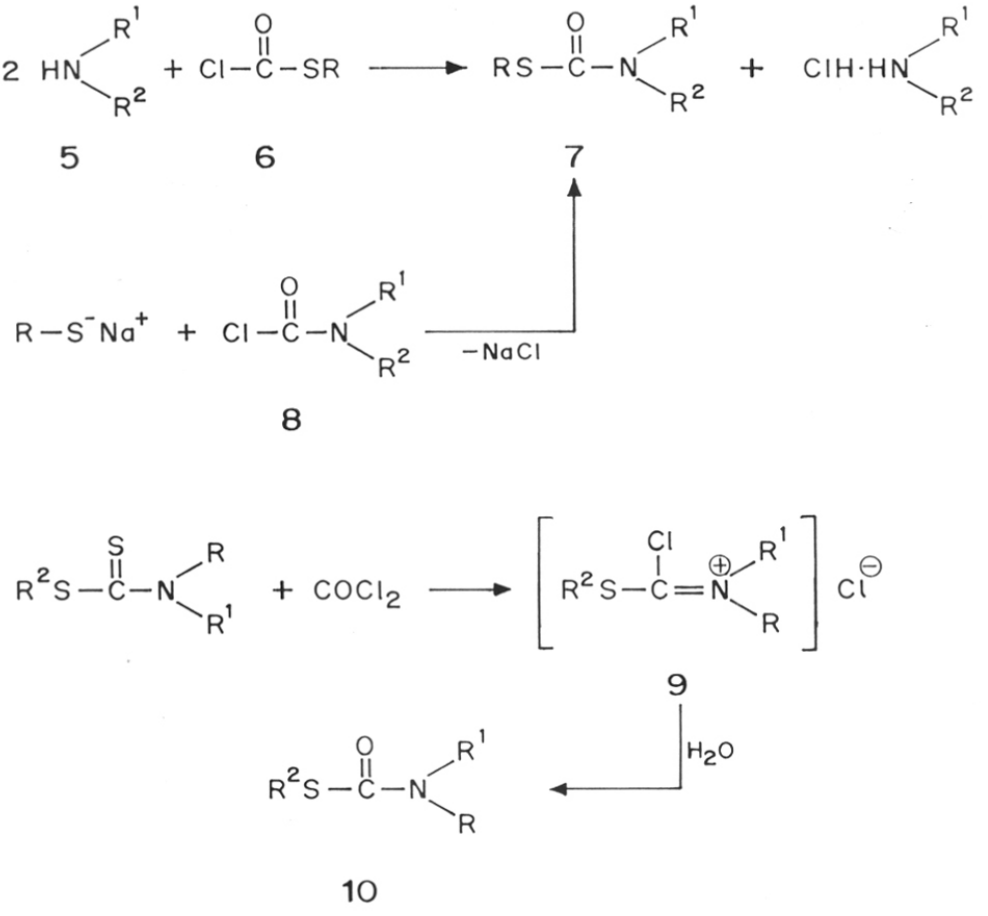
Thiolcarbamates have also been prepared by acid catalyzed rearrangement of thionocarbamates derived from primary and secondary amines by Kinoshita et al.[6,7,8]. N,N-Disubstituted thionocarbamates **11** in presence of boron trifluoride etherate or p-toluenesulfonic acid in ether/$CH_2Cl_2$ at reflux temperature gave thiolcarbamates **12** (*Scheme 5-3*). This method, however, suffers from the formation of side products and low yields.

*Scheme 5-1*

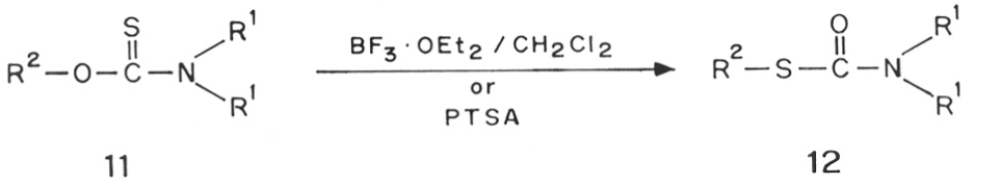



3 4

*Scheme 5-2*



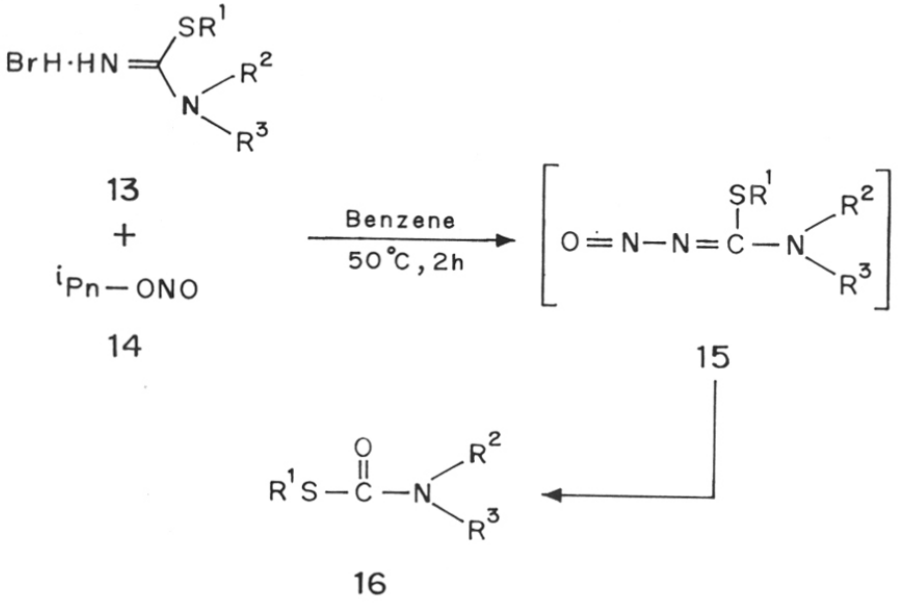

*Scheme 5-3*



### 5.2.2d *From S-alkyl isothiourea:*

This method was reported in 1973 by Inamoto et al[9]. A mixture of S-alkyl isothiourea **13** and isopentyl nitrite **14** in benzene at 50°C in 2 h gives an unstable N-nitroso intermediate **15** which collapses to give the S-alkyl thiolcarbamate **16** (*Scheme 5-4*). By this method S-alkyl thiolcarbamates of various amines have been reported in moderate to good yields.

*Scheme 5-4*




### 5.2.2e *Using carbonyl sulfide:*

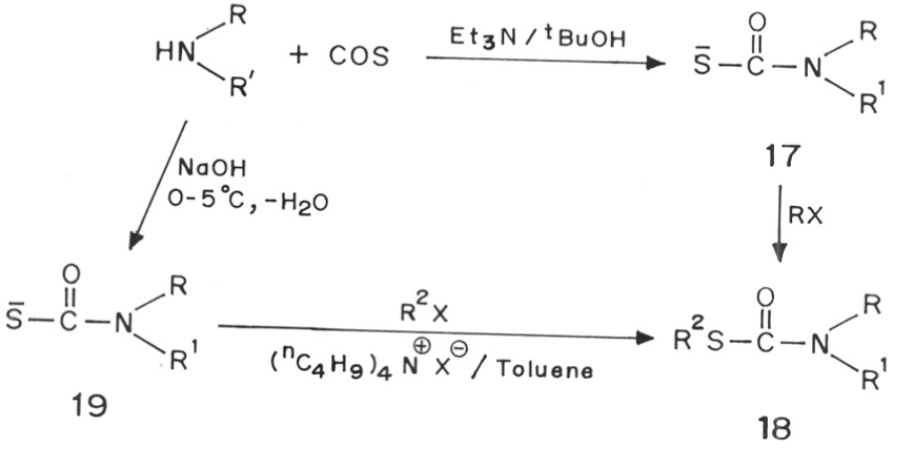
The first method using carbonyl sulfide was reported in 1959 by Tilles[4]. This method involves the passing of carbonyl sulfide into the solution of a mixture of the secondary amine and triethylamine in tert-butanol to give the thiolcarbamate salt **17**, which on alkylation with an alkyl halide under refluxing condition provided the S-alkyl thiolcarbamate **18** in 13-84%.

This method was modified by Chin-Hsien[11]. Carbonylsulfide was bubbled through a solution of the secondery amine in aqueous NaOH (8.4 g in 34 ml) at 0-5°C for 30 mns.

The product formed was the sodium salt of the thiolcarbamate (**19**). It was then alkylated with an alkyl halide in presence of tetrabutyl ammonium halide in toluene to get the S-alkyl thiolcarbamate (**18**) in 60-90% yield (*Scheme 5-5*).

Although the yields are good, only sec. amines can be used in these methods. In both the methods the major drawback is the use of carbonyl sulfide.

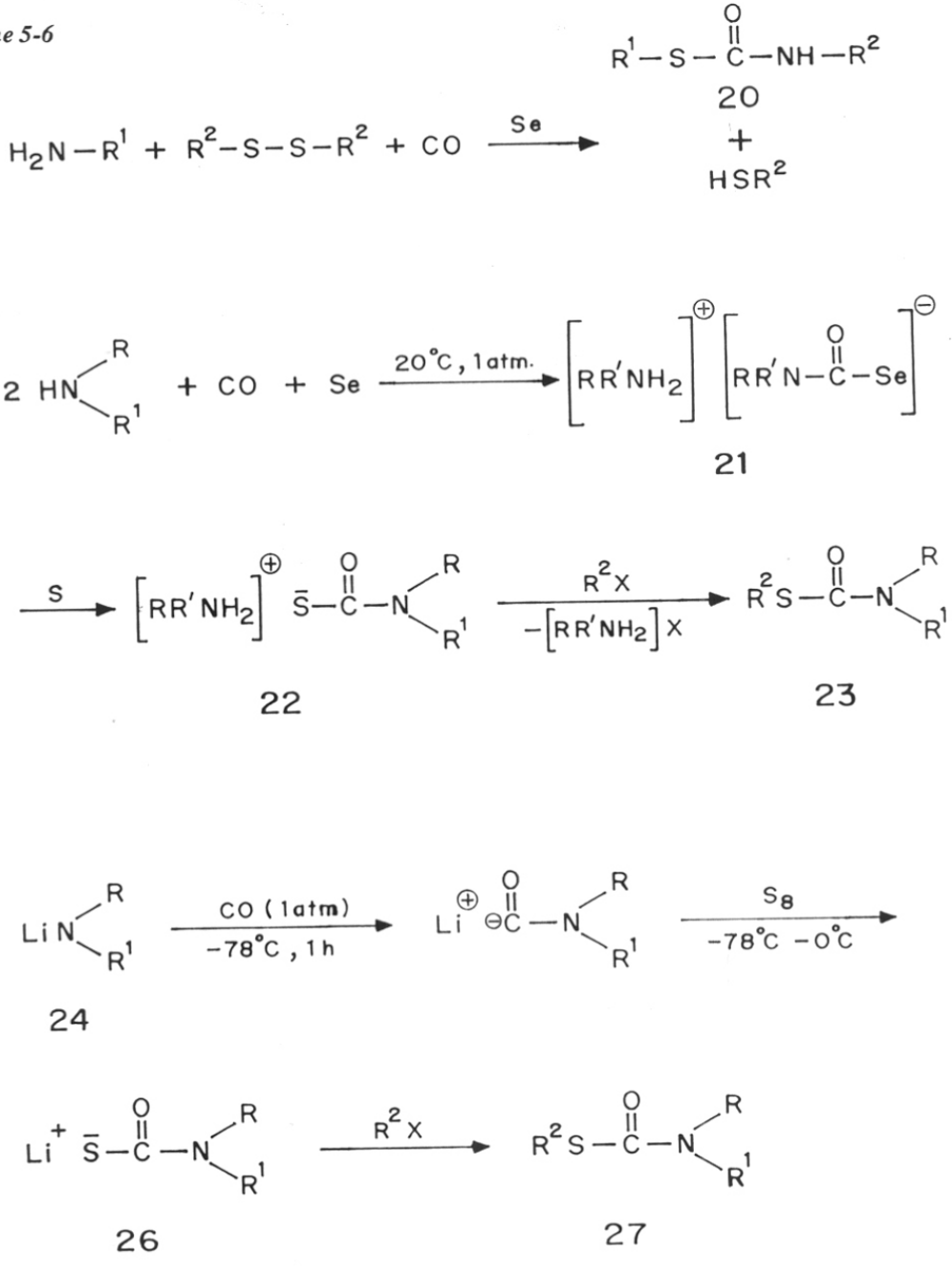
***Scheme 5-5***




### 5.2.2f *Using carbonmonoxide and sulfur:*

The first reaction of this type was reported in 1975 by Koch[12]. Carbonmonoxide gas was passed through a mixture of the primary amine, dialkyl or diphenyl disulfide and selenium metal in $CH_3CN$ at 20-60°C for 0.5-3.5 h to give S-alkyl or aryl thiolcarbamates (**20**) in good yield. In 1989, Sonoda et al.[13] reported a modification of this method. The amine salts of selenocarbamates (**21**) (derived from amine, CO and metallic selenium) were treated with elemental sulfur to give the amine salts of thiolcarbamates **22**, which on alkylation with an alkyl halide at 0°C-30°C yielded S-alkyl thiolcarbamates **23**. In a recent report[14], lithium salts of secondary amines in presence of CO gas gave N,N-dialkyl carbomoyl lithium **25**; this on treatment with sulfur gave the lithium salt of thiolcarbamate **26**. This salt was alkylated to give S-alkyl thiolcarbamate **27** (*Scheme 5-6*).

*Scheme 5-6*


R1–S–C(=O)–NH–R2
20
H2N–R1 + R2–S–S–R2 + CO
Se
+
HSR2
2 HN(R)(R1)
+ CO + Se
20°C, 1atm.
[RR'NH2]⊕ [RR'N–C(=O)–Se]⊖
21
S
[RR'NH2]⊕ S̄–C(=O)–N(R)(R1)
22
R2X
–[RR'NH2]X
R2S–C(=O)–N(R)(R1)
23
LiN(R)(R1)
24
CO (1atm)
–78°C, 1h
Li⊕ ⊖C(=O)–N(R)(R1)
S8
–78°C –0°C
Li+ S̄–C(=O)–N(R)(R1)
26
R2X
R2S–C(=O)–N(R)(R1)
27

## 5.3 Present work:

The synthesis of 1-methylamino-1-methylthio-2-nitroethylene has been discussed in Chapter 2. During scale up of this reaction, we have observed the formation of a side product in 5% yield. The structure of this was determined to be S-methyl N-methyl thiolcarbamate (**29a**). The $^1$H NMR spectrum of this compound showed a singlet at 2.25 δ, and a doublet at 2.75 δ in the ratio of 1:1, corresponding to -$SCH_3$ and -$NHCH_3$ respectively. A broad singlet also appeared at 5.5 δ showing the presence of a proton attached to nitrogen atom; the deuterium exchanged spectrum showed only the two singlets corresponding to -$SCH_3$ and -$NCH_3$. The IR spectrum showed a band at 1680 $cm^{-1}$ corresponding to amide carbonyl. Mass spectrum showed the molecular ion ($M^+$) at *m/z* 105. The formation of S-methyl N-methyl thiolcarbamate could be due to the hydrolysis of N-methyl carbonimidodithioic acid dimethyl ester (**28a**), catalysed by the zeolite employed in the reaction.

This observation encouraged us to find the best method for the hydrolysis of N-substituted carbonimidodithioic acid dimethyl esters (**28a-m**) to S-methyl N-substituted thiolcarbamates (**29a-m**). Initial attempts were made by using heterogeneous catalysts like clays and zeolites. H-mordenite and H-Y zeolite were found to be the best catalysts for this conversion. We next turned our attention to Lewis acid catalysed hydrolysis of the same substrates. We found that either $ZnCl_2$ or $ZnBr_2$ in $CH_3CN$:$H_2O$ (3:1) proved to be extremely effective in bringing about this conversion (*Scheme 5-7*). Our attempts to hydrolyse carbonimidodithioic acid dimethyl esters derived from various aromatic and aliphatic sulfonamides however, resulted in failure. This may be due to the non-availability of the nitrogen lone pair for protonation owing to the strong electron withdrawing ability of the sulfonyl group attached to nitrogen.

We have extended the concept of hydrolysis using zeolite catalysts for functionalised ketene S,S-acetals in which a carbon-carbon double bond is present instead of a carbon-nitrogen double bond. In our very first attempt, hydrolysis of the nitroketene S,S-acetal (**31**)

in the presence of H-Mordenite gave nitro thiolacetic acid methyl ester (**32**) in 90% yield. However, diacetyl ketene S,S-acetal (**33**) derived from acetylacetone gave the deacetylated product **34** in 80% yield instead of the hydrolysis compound **35**.

Finally, the S-methyl thiolcarbamate (**29f**) derived from α-methylbenzylamine has been converted to the carbamate (**30**) by sodium methoxide, thereby demonstrating the feasibility of displacing the -SMe group by nucleophiles.

## 5.4 Results and discussion:

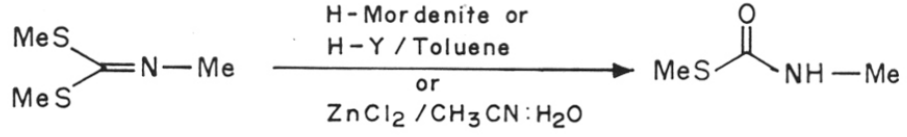
### 5.4.1 Hydrolysis of N-substituted carbonimidodithioic acid dimethyl esters (28a-m) to S-methyl N-substituted thiolcarbamates (29a-m):

In chapter 2, we had described a new zeolite catalyzed condensation of N-methyl carbonimidodithioic acid dimethyl ester with nitromethane to give 1-methylamino-1-methylthio-2-nitroethylene. During scale-up studies of this reaction, a by-product was isolated in 5% yield. This was a liquid, whose analytical and spectral data proved that it was the thiolcarbamate (**29a**) (*Scheme 5-7*). When the reaction was carried out without nitromethane, and using toluene as the solvent, yield of this thiolcarbamate increased to 35%. A systematic study was therefore undertaken to optimise the yield in this hydrolysis and to determine the scope of the reaction.

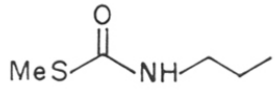
Our initial attempts were focussed towards determining the efficacy of different heterogeneous catalysts. Apart from various zeolites (differing in their pore size and acidity), some clays and pillared clays have also been tried. The best results were obtained with H-Mordenite and H-Y zeolite.

Subsequently, we could demonstrate that $ZnCl_2$ or $ZnBr_2$ was a better catalyst for these hydrolyses.

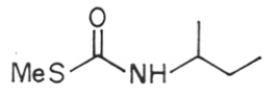
*Scheme 5-7*



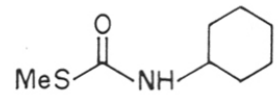

28a 29a



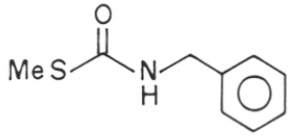

29b



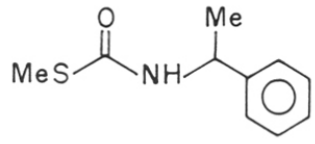

29c



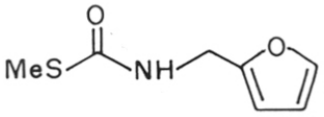

29d



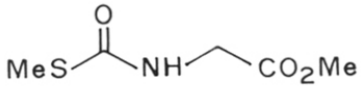

29e



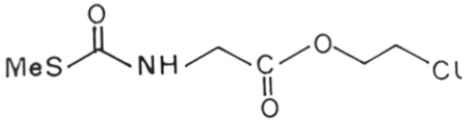

29f



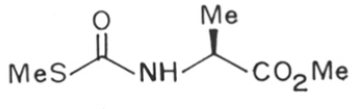

29g



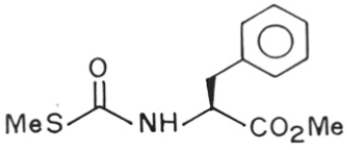

29h



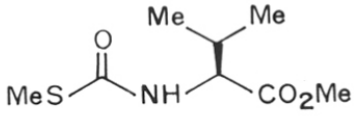

29i



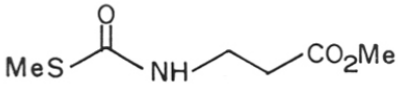

29j




29k




29m




29l

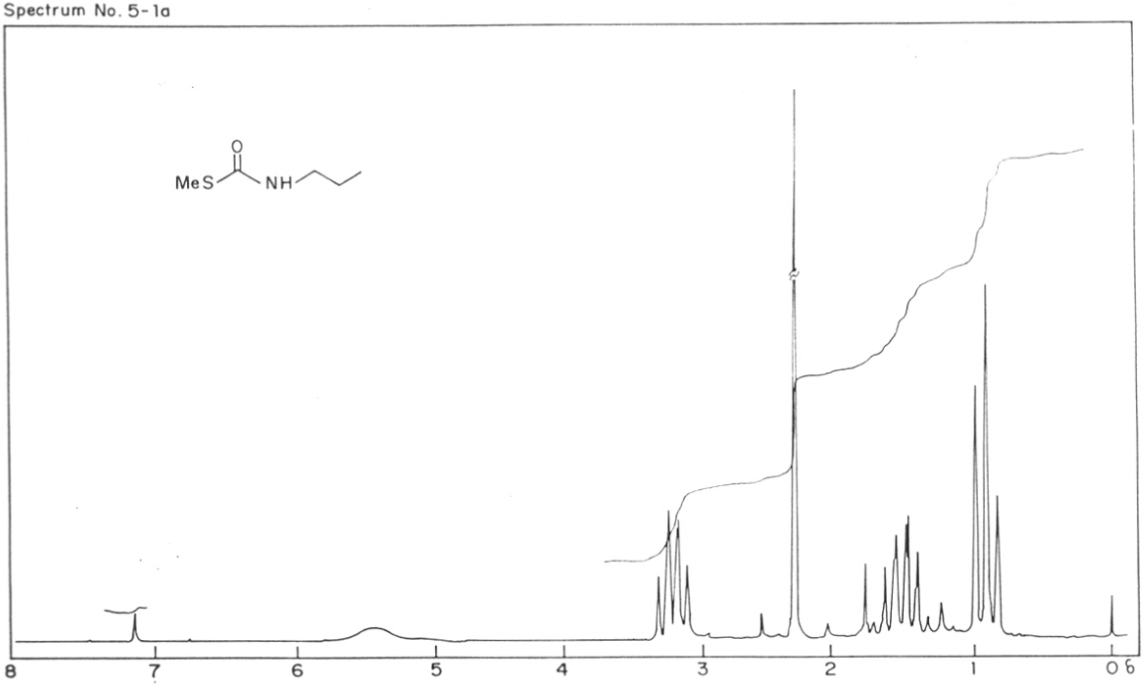
### 5.4.1a *Hydrolysis catalyzed by pillared clay:*

The pillared clays used in these experiments were kindly supplied by RRL Trivandrum. N-Methyl carbonimidodithioic acid dimethyl ester was refluxed in toluene with alumina pillared clay (Al PILC) for 24 h. The reaction was monitored by tlc; the reaction mixture was then cooled to room temperature, and filtered through a sintered funnel. Work-up of the filtrate and purification by chromatography gave S-methyl N-methyl thiolcarbamate in 20% yield (*Scheme 5-7*). The $^1$H NMR spectrum of the purified sample exhibited a doublet at 2.75 δ and a singlet at 2.25 δ corresponding to -$NHCH_3$ and -$SCH_3$ respectively; a broad peak at 5.50 δ which corresponds to NH confirmed the formation of product **29a**. The yield was not increased either by prolonging the reaction time or by increasing the amount of the catalyst. Similarly the same reaction was performed with titanium pillared clay (TiPILC), Preseodymium pillared clay, montmorillonite K10 and amorphous silica/alumina under the same conditions. The results are tabulated in *table 5-1*. The best yield (32%) was obtained with the Titanium-pillared clay.

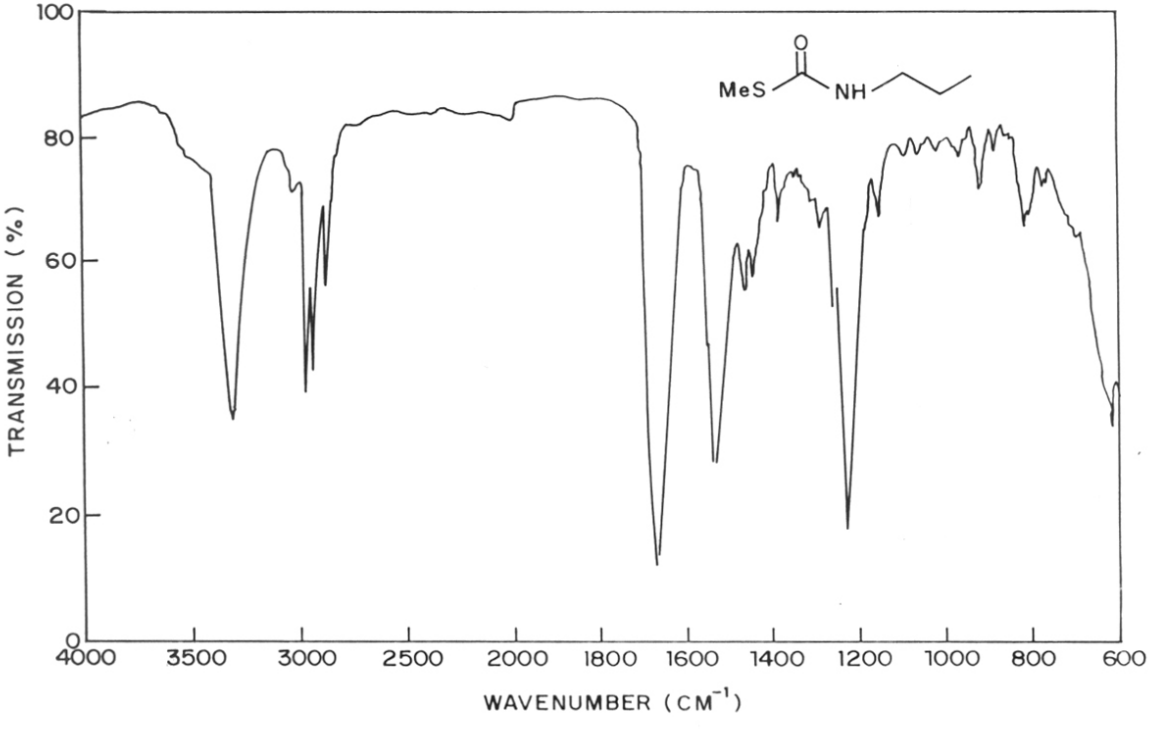
**Table 5-1: Conversion of 28a to 29a with different clays:**

| Clay | Yield |
|---|---|
| Al PILC | 20% |
| Ti PILC | 32% |
| Pr Clay | 30% |
| Montmorillonite K10 | 17% |
| Si/Al amorphous | 12% |

Spectrum No. 5-1a




Spectrum No. 5-1b



### 5.4.1b *Hydrolysis catalyzed by zeolite catalysts:*

Several zeolites were tried; among these H-mordenite and H-Y zeolite were found to be the most suitable for the conversion of N-methyl carbonimidodithioic acid dimethyl ester (**28a**) to S-methyl N-methyl thiolcarbamate (**29a**). The $^1$H NMR spectrum of the purified sample was compared with that of the sample prepared using pillared clay. The success of these zeolites may be due to their large pore size and the presence of more active acidic sites in their cavities (*Table 5-2*).

**Table 5-2: Composition of zeolite catalysts:**[17]

| zeolite | Si/Al ratio | pore size, nm |
|---|---|---|
| H-Y | 02.45 | 0.74 |
| H-Mordenite | 10.06 | 0.70 |
| H-ZSM-5 | 45.00 | 0.56 |
| Na-Y | 04.62 | 0.74 |

Similarly, the cyclohexylamine derivative (**28d**) was refluxed in toluene with H-Mordenite for 24 h. The usual work up gave S-methyl N-cyclohexyl thiolcarbamate (**29d**) in 72% yield, as a solid, m.p. 103-104°C. The $^1$H NMR spectrum of a column purified sample showed a singlet at 2.35 δ and a broad multiplet from 1.1-1.9 δ corresponding to -$SCH_3$ and cyclohexyl group respectively. One proton signals at 5.2 δ (broad) and at 3.75 δ (multiplet) could be assigned to NH and NCH respectively. This structure was further confirmed by the occurrence of the molecular ion ($M^+$) peak in the mass spectrum at *m/z* 173. Several other S-methyl N-substituted thiolcarbamates (**29a-c & e-m**) have been prepared by this method using H-Mordenite or H-Y[18]. The results are tabulated in *table 5-3*.

### 5.4.1c *Zinc chloride catalyzed hydrolysis:*

Mercuric chloride is widely used in the hydrolysis of dithioacetals and dithioketals to aldehydes and ketones[19,20] respectively and of vinyl methyl sulfides to aldehydes or ketones[21,22]. The mechanism of such hydrolysis has been reviewed recently[23]. The conversion of 1-substituted amino 1-methylthio-2-nitroethylenes to N-nitroacetyl amides has also been reported from our group, using $HgCl_2$ mediated hydrolysis[24]. In order to avoid the environmental pollution and toxicity associated with the use of mercuric salts, we decided to investigate whether zinc salts could be used as catalysts for the hydrolysis of carbonimidodithioates to S-alkyl thiolcarbamates. In the event, we found that this reaction proceeded in very good yields in the presence of $ZnCl_2$. Thus N-benzyl carbonimidodithioic acid dimethyl ester (**28e**) in $CH_3CN$:$H_2O$ (3:1) was stirred with $ZnCl_2$ at 60°C for 8 h. to give S-methyl N-benzyl thiolcarbamate (**29e**) in 90% yield, m.p. 79-80°C. $^1$H NMR δ 7.40 (s, 5H, aromatic), 5.75 (br, 1H, NH), 4.50 (d, 2H), 2.45 (s, 3H, $SCH_3$). IR 3300-3400, 1680, 1220 $cm^{-1}$. The above spectral data proved the structure to be **29e**. Similarly we prepared several S-methyl N-substituted thiolcarbamates (**29a-d & f-m**) (*Scheme 5-7*) by the same procedure and the results are given in ***Table 5-3***. It was also observed that $ZnBr_2$ gave equally good results.

**Table 5-3: % of conversion of 28 to 29 by zeolites and zinc chloride catalysts:**

| Compound | m.p (° C) | $ZnCl_2$ | H-Mordenite | H-Y[a] |
|---|---|---|---|---|
| **29a** | liquid | 52.7 | 35 | 35 |
| **29b** | an oil | 68.3 | 42 | 36 |
| **29c** | semisolid | 67.6 | 40 | 42 |
| **29d** | 103-104 | 86.8 | 72 | 70 |
| **29e** | 79-80 | 88.3 | 78 | 72 |
| **29f** | 85 | 82.2 | 70 | 76 |
| **29g** | semisolid | 78.8 | 68 | - |
| **29h** | semisolid | 69.3 | 40 | - |
| **29i** | 73 | 76.7 | 43 | - |
| **29j** | 46 | 86.0 | 50 | - |
| **29k** | 85-87 | 85.5 | 48 | - |
| **29l** | semisolid | 86.3 | 47 | - |
| **29m** | thick liquid | 89.1 | 45 | - |

**a** *Yields are based on GC analysis.*

### 5.4.2 Synthesis of (S)-methyl N-α-methylbenzyl carbamate (30):

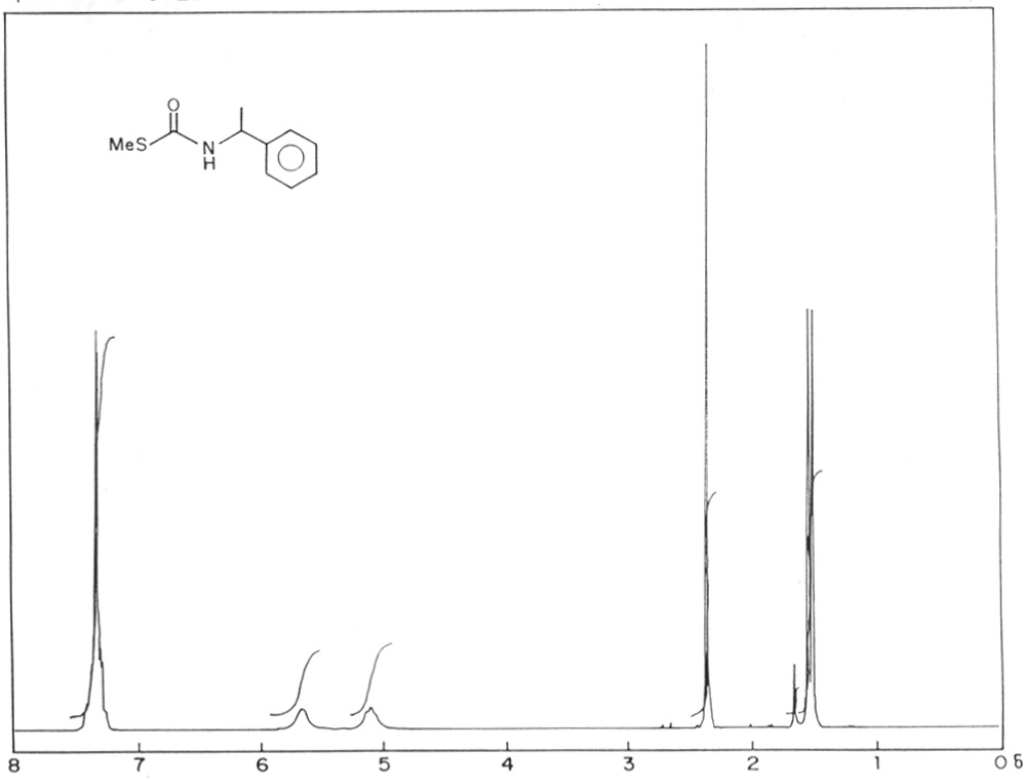
#### 5.4.2a *From (S)-S-methyl N-α-methylbenzyl thiolcarbamate (29f):*

S-methyl N-α-methylbenzyl thiolcarbamate (**29f**) prepared by the above method, using $ZnCl_2$, was refluxed in dry methanol (excess) with catalytic amount of freshly cut metallic sodium. The reaction was monitored by tlc; after 12 h the starting material had disappeared. The reaction mixture was cooled, filtered and the excess methanol was removed at reduced pressure. The residue was purified by column chromatography to give **30** in 90% yield, m.p. 50-51°C. The $^1$H NMR spectrum of solid exhibited (*Spectrum No. 5-2b*), the characteristic singlet for -$OCH_3$ at 3.70 δ, whereas the -$SCH_3$ of the starting material (**29f**) (*Spectrum No. 5-2a*) was at 2.35 δ. The structure was further confirmed by combustion data and the occurrence of the molecular ion ($M^+$) at *m/z* 179 in the mass spectrum (*Scheme 5-8*).

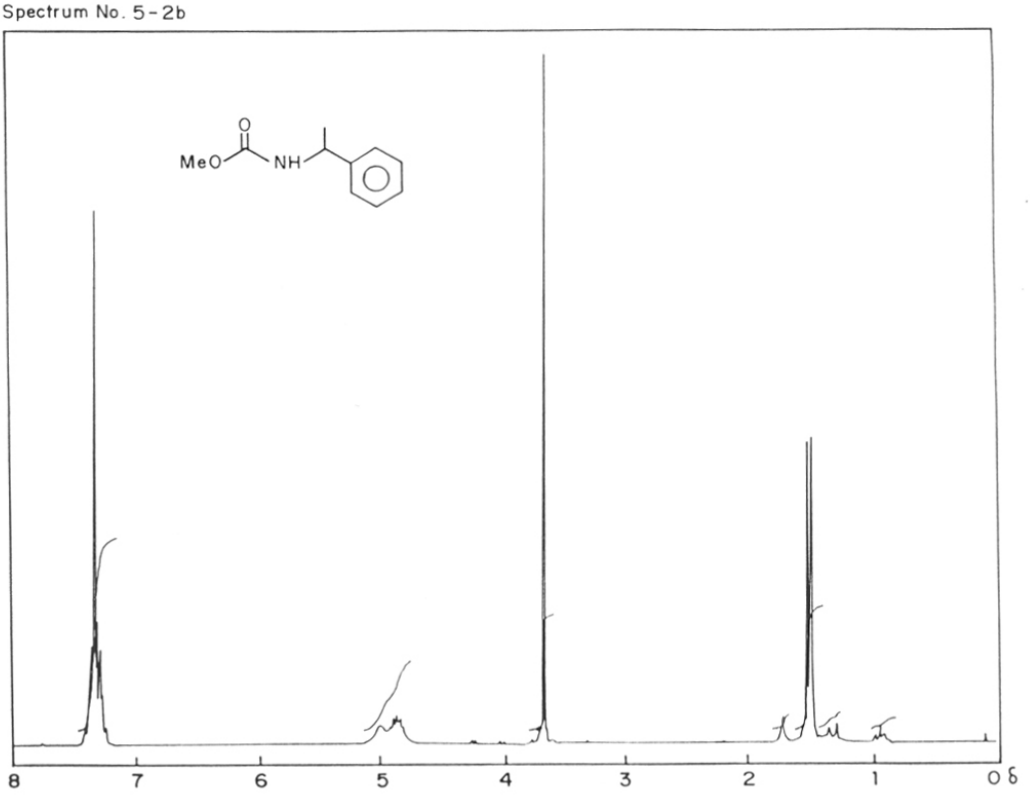
#### 5.4.2b *From (S)-N-α-methylbenzyl carbonimidodithioic acid dimethyl ester (28f):*

N-α-Methylbenzyl carbonimidodithioic acid dimethyl ester was refluxed in methanol:water mixture (3:1) in presence of zinc chloride for 12 h. The reaction was monitored by tlc. It was observed that the starting material was getting converted first to S-methyl thiolcarbamate (**29f**) and then to carbamate (**30**). The reaction mixture was filtered, concentrated and extracted with dichloromethane. The product was obtained in 82% yield and was purified and characterized as methyl (S)-N-α-methylbenzyl carbamate (**30**) by comparing the spectra with those of an authentic sample obtained from thiolcarbamate (**29f**).

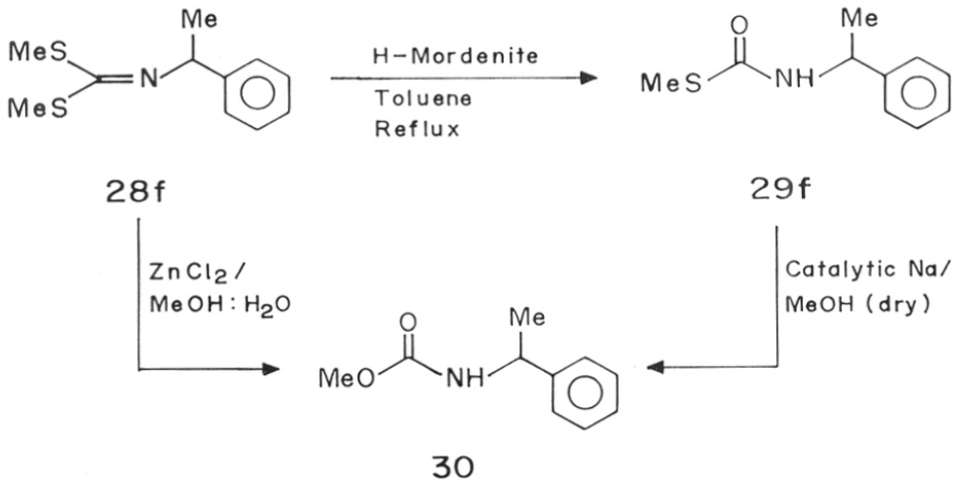
Spectrum No. 5-2a




Spectrum No. 5-2b



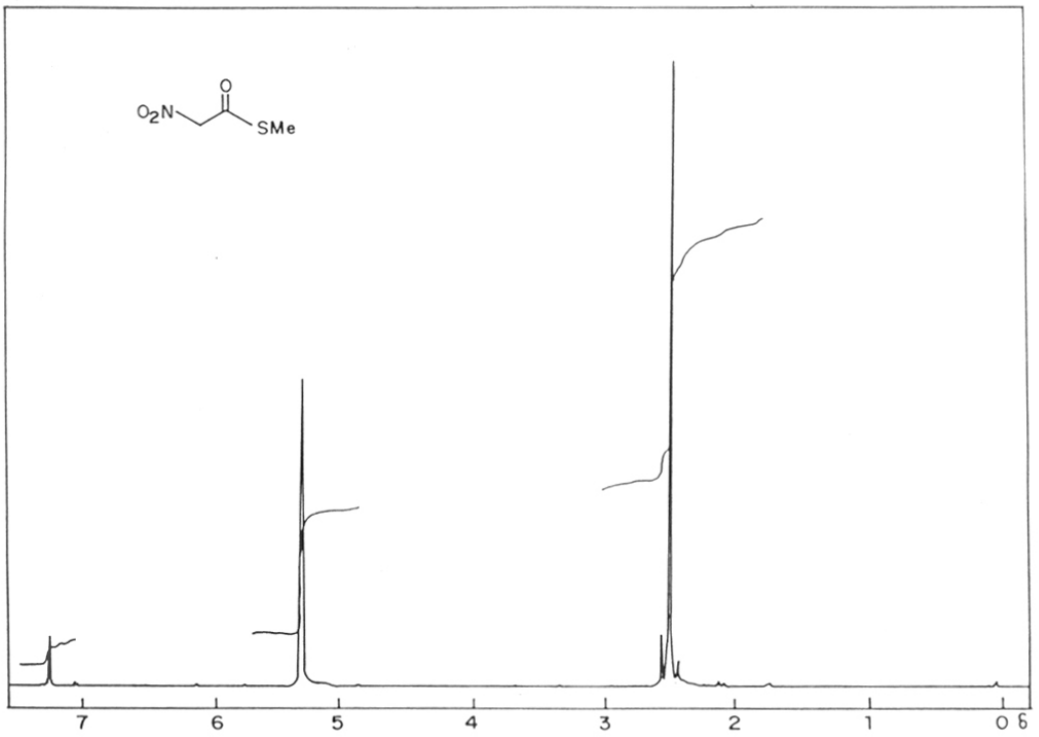
*Scheme 5-8*



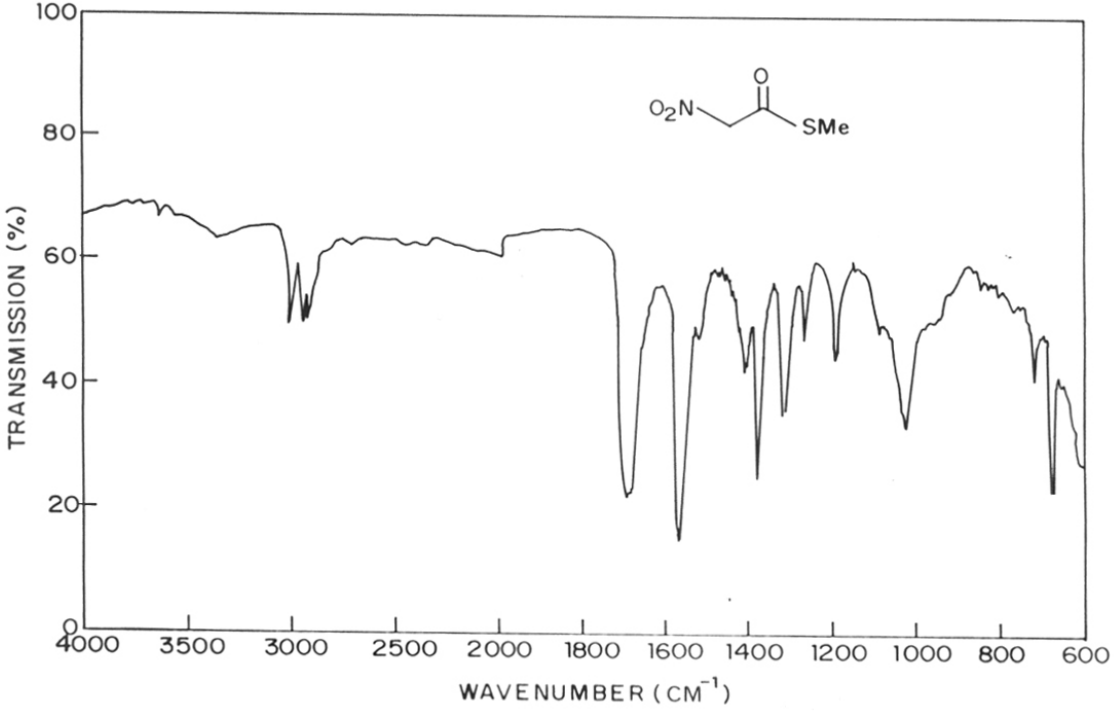

### 5.4.3 Hydrolysis of functionalised ketene S,S-acetals:

1,1-Bis methylthio-2-nitroethylene was prepared from nitromethane, by condensation with carbon disulfide, followed by methylation.[25] This nitroketene S,S-acetal (**31**) was refluxed in toluene with H-Mordenite. The reaction was monitored by tlc; after 20 h all the starting material had been consumed. Filtration and usual workup gave a liquid in 90% yield. The $^1$H NMR spectrum (*Spectrum No. 5-3b*) of this liquid showed two singlets at 5.30 and 2.45 δ in the ratio of 2:3, corresponding to $COCH_2$ and $SCH_3$. The IR spectrum (*Spectrum No. 5-3a*) showed a carbonyl band at 1700 $cm^{-1}$, and nitro at 1570 $cm^{-1}$. In the mass spectrum, the molecular ion ($M^+$) was seen at *m/z* 135. The spectral data clearly show that the liquid compound is the methyl ester of nitro thiolacetic acid (**32**) (*Scheme 5-9*). To our knowledge, this is the first time this compound has been reported. In order to check whether such a facile hydrolysis would occur with other substituted ketene S,S-acetals, the compound (**33**)[26] (derived from acetylacetone by condensation with carbon disulfide followed by methylation)

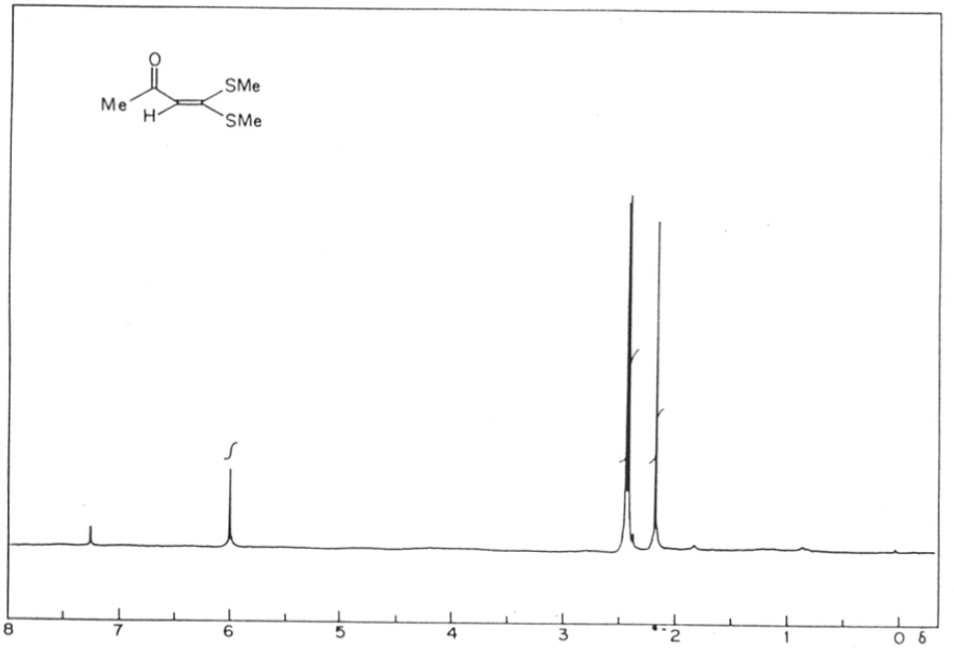
Spectrum No. 5-3b



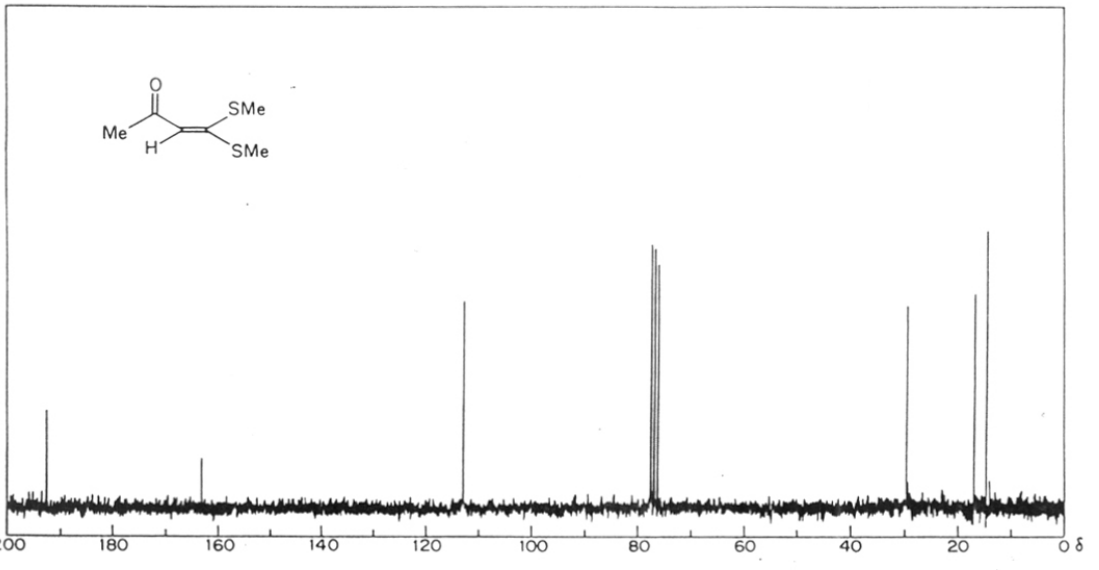

Spectrum No. 5-3a



Spectrum. No. 5-4a

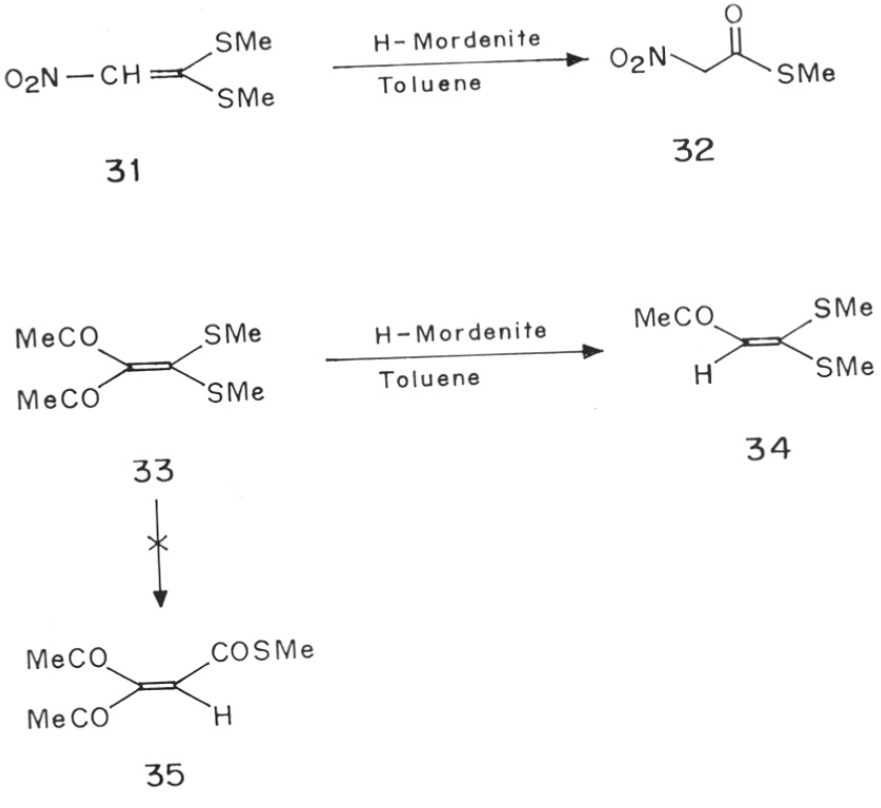



Spectrum No. 5-4b



was subjected to the same reaction conditions. In this case, however, the product isolated in 80% yield, proved to be the deacetylated product **34** and not the expected hydrolysis product **35**. The structure of **34** rests on the following spectral data: Mass spectrum showed the molecular ion at *m/z* 162. IR spectrum showed only one band for carbonyl group at 1640 $cm^{-1}$. $^1H$ NMR spectrum (*Spectrum No. 5-4a*) of the sample exhibited only four singlets; the characteristic olefinic proton absorbed at 6.00 δ and three singlets were observed at 2.47 (s, 3H), 2.45 (s, 3H) and 2.30 (s, 3H) corresponding to $-SCH_3$, $-SCH_3$ and $COCH_3$ respectively. The $^{13}C$ NMR spectrum (*Spectrum No. 5-4b*) also showed presence of only one carbonyl signal at 192.45 ppm.

*Scheme 5-9*



## 5.5 Summary:

The synthesis of S-methyl N-substituted thiolcarbamates described here is a general and mild method. No recemization has been observed in the synthesis of (S)-(-)-S-methyl N-α-methylbenzyl thiolcarbamate (**29f**).

## 5.6 Experimental:

**General:**

A general write-up is given in the experimental section of chapter-2.

**Synthesis of amino acid methyl esters:**

A general procedure has been given in Chapter-4.

**Synthesis of N-substituted carbonimidodithioic acid dimethyl ester (28a-m):**

A general procedure for these compounds has been given in Chapter-3 for **28a-h** and in chapter-4 for **28i-m**.

**Hydrolysis of 28a-m to 29a-m:**

A) *Zeolite catalyzed hydrolysis:*

**General procedure:** Zeolite H-mordenite or H-Y (0.5g) added at room temperature to a solution of N-substituted carbonimidodithioic acid dimethyl esters (**28a-m**) (1g) in toluene. The reaction mixture was refluxed for 24 h. Cooled, filtered through sintered funnel and washed with $CH_2Cl_2$ (3 x 15 ml). Filtrate was concentrated and purified by column chromatography using 2-4% EtOAc in petrolium ether to give S-methyl N-substituted thiolcarbamates (**29a-m**) in 37-78% yield.

B) *Pillared clay catalyzed hydrolysis:*

N-Methyl carbonimidodithioic acid dimethyl ester to S-methyl N-methyl thiolcarbamate: To a solution of N-methyl carbonimidodithioic acid dimethyl ester (2g) in toluene pillared clay (1g) was added portion wise at room temparature and refluxed for 24 h. Reaction mixture was cooled to room temperature, filtered and washed with $CH_2Cl_2$ (3 x 20 ml). Filtrate was concentrated and purified by column chromatography, elution with 4% EtOAc in petrolium ether offered pure S-methyl N-methyl thiolcarbamate in 20% yield.

C) *Zinc chloride catalyzed hydrolysis:*

$ZnCl_2$ (10 mmol) was dissolved in a mixture of $CH_3CN$:$H_2O$ (3:1, 10 ml) and a solution of N-substituted carbonimidodithioic acid dimethyl esters (**28a-m**) in the same mixture of solvents was added dropwise. The mixture was stirred at 60°C for 8 h, when a clear solution was obtained in the beginning and turned to white precipitate. The reaction was followed by tlc. After the completion of the reaction it was filtered through sintered funnel. Filtrate was reduced to half the quantity and passed through column of anhydrous sodium sulfate to remove inorganic material. Fractions collected from column were concentrated and the residue was taken into $CH_2Cl_2$, washed with $H_2O$ (twice), brine, dried with anhydrous sodium sulfate and concentrated to give product (crude) which was further purified either by column chromatography or by crystalisation.

**S-Methyl N-methyl thiolcarbamate (29a):**

| | | |
|---|---|---|
| Yield | : | 37%. |
| bp | : | 70-74°C/5.0 mm |
| $^1$H NMR (80 MHz) | : | δ 5.50 (br, 1H, NH) 2.75 (d, 3H, $NCH_3$), 2.25 (s, 3H, $SCH_3$). |
| IR (Nujol) | : | $cm^{-1}$ 3310, 1670, 1540, 1230. |
| MS | : | *m/z* 105 ($M^+$, 95%), 75, 58 (100). |
| Analysis | : | $C_3H_7NOS$ Calcd. : C, 34.28; H, 6.66; N, 13.33. |
| | | Found : C, 34.28; H, 6.67; N, 13.29. |

**S-Methyl N-n-Propyl thiolcarbamate (29b):**

| | | |
|---|---|---|
| Yield | : | 42%. |
| mp/bp | : | an oil. |
| $^1$H NMR (90 MHz) | : | δ 5.50 (br, 1H, NH), 3.20 (q, 2H, $NCH_2$), 2.30 (s, $SCH_3$), 1.50 (m, 2H, $CH_2$), 0.90 (t, 3H). |
| IR (Liq.film) | : | $cm^{-1}$ 3310, 1670, 1540, 1230. |
| MS | : | *m/z* 133 ($M^+$, 95%), 86, 75, 48, 43 (100). |

Analysis : $C_5H_{11}NOS$ Calcd. : C, 45.11; H, 8.27; N, 19.52.

Found : C, 45.22; H, 8.29; N, 19.76.

**S-Methyl N-sec.butyl thiolcarbamate (29c):**

Yield : 40%.

mp/bp : semisolid.

$^1$H NMR (200 MHz) : δ 5.30 (br, 1H, NH), 3.55 (m, 1H, CH), 2.35 (s,$SCH_3$), 1.60 (m, 2H, $CH_2$), 1.15 (d, 3H, $CH_3$), 0.90 (t, 3H, $CH_3$).

IR (Liq.film) : $cm^{-1}$ 3320, 1730, 1670, 1530, 1220.

MS : *m/z* 147 ($M^+$, 75%), 118 (100), 100, 75.

nalysis : $C_6H_{13}NOS$ Calcd. : C, 48.97; H, 8.84; N, 9.52.

Found : C, 49.09; H, 8.92; N, 9.45.

**S-Methyl N-Cyclohexyl thiolcarbamate (29d):**

Yield : 72%.

mp : 103-104°C.

$^1$H NMR (80 MHz) : δ 5.30 (br, 1H, NH), 2.35 (s, 3H, $SCH_3$), 1.1-2.0 (m, 11H).

$^{13}$C NMR (50 MHz) : ppm 166.96, 50.89, 33.48, 25.69, 24.99, 12.49.

IR (Nujol) : $cm^{-1}$ 3320, 1660, 1470, 1220.

MS : *m/z* 173 ($M^+$, 75%), 126, 83 (100).

Analysis : $C_8H_{15}NOS$ Calcd. : C, 55.49; H, 8.67; N, 8.09.

Found : C, 55.55; H, 8.72; N, 7.89.

**S-Methyl N-benzyl thiolcarbamate (29e):**

Yield : 78%.

mp : 79-80°C.

$^1$H NMR (80 MHz) : δ 7.40 (s, 5H, aromatic), 5.70 (br, 1H, NH), 4.50 (d, 2H,), 2.40 (s, $SCH_3$).

IR ($CHCl_3$) : $cm^{-1}$ 3320-3420, 1680, 1510, 1230.

MS : *m/z* 181 ($M^+$, 45%), 133, 91 (100).

| | | | |
|---|---|---|---|
| Analysis | : | $C_9H_{11}NOS$ | Calcd. : C, 59.66; H, 6.07; N, 7.73. |
| | | | Found : C, 59.77; H, 6.05; N, 7.73. |

**(S)-(-)-S-Methyl N-α-methylbenzyl thiolcarbamate (29f):**

| | | |
|---|---|---|
| Yield | : | 70%. |
| mp | : | 85°C. |
| $^1$H NMR (200 MHz) | : | δ 7.35 (m, 5H, aromatic), 5.65 (br, 1H, NH) 5.10 (m, 1H), 2.35 (s, $SCH_3$), 1.55 (d, 3H, $CH_3$). |
| $^{13}$C NMR (75.5 MHz) | : | ppm 166.93, 143.09, 128.65, 127.39, 126.09, 51.09, 22.12, 12.32. |
| IR ($CHCl_3$) | : | $cm^{-1}$ 3350, 1640, 1510, 1230. |
| MS | : | *m/z* 195 ($M^+$, 48%), 147, 105 (100). |
| Analysis | : | $C_{10}H_{13}NOS$ Calcd. : C, 61.53; H, 6.66; N, 7.17. |
| | | Found : C, 61.75; H, 6.67; N, 7.22. |

**S-Methyl N-furfuryl thiolcarbamate (29g):**

| | | |
|---|---|---|
| Yield | : | 68 %. |
| mp/bp | : | Low melting solid. |
| $^1$H NMR (200 MHz) | : | δ 7.35 (d, 1H), 6.30 (t, 1H), 6.20 (d, 1H), 5.60 (br, 1H, NH), 4.40 (d. 2H), 2.30 (s, $SCH_3$). |
| IR ($CHCl_3$) | : | $cm^{-1}$ 3300-3400, 1680, 1570, 1500, 1220. |
| MS | : | *m/z* 171 ($M^+$, 25%), 123, 81 (100), 83. |
| Analysis | : | $C_7H_9NO_2S$ Calcd. : C, 54.19; H, 5.80; N, 9.03. |
| | | Found : C, 54.27; H, 5.85; N, 8.92. |

**Methyl N-(thiomethyl carbonyl) glycinate (29h):**

| | | |
|---|---|---|
| Yield | : | 40%. |
| mp/bp | : | semisolid. |
| $^1$H NMR (200 MHz) | : | δ 6.25 (br, 1H, NH), 4.10 (d, 2H), 3.60 (s, $OCH_3$), 2.15 (s, $SCH_3$). |
| IR (Liq.film) | : | $cm^{-1}$ 3350, 1780, 1680, 1530, 1200. |
| MS | : | *m/z* 163 ($M^+$, 20%), 144 (100), 116, 88. |
| Analysis | : | $C_5H_9NO_3S$ Calcd. : C, 36.80; H, 5.52; N, 8.58. |
| | | Found : C, 36.87; H, 5.52; N, 8.56. |

**Chloroethyl N-(thiomethyl carbonyl) glycinate (29i):**

| | | |
|---|---|---|
| Yield | : | 43%. |
| mp | : | 73°C. |
| $^1$H NMR (80 MHz) | : | δ 5.80 (br, 1H, NH), 4.30 (t, 2H), 4.00 (d, 2H), 3.50 (t, 2H), 2.20 (d, $SCH_3$). |
| IR ($CHCl_3$) | : | $cm^{-1}$ 3410, 1760, 1690, 1500, 1230. |
| MS | : | *m/z* 211 ($M^+$, 10%), 164, 136 (100). |
| Analysis | : | $C_6H_{10}NO_3SCl$ Calcd. : C, 34.12; H, 4.73; N, 6.63. |
| | | Found : C, 34.13; H, 4.82; N, 6.57. |

**Methyl N-(thiomethyl carbonyl) (L)-alaninate (29j):**

| | | |
|---|---|---|
| Yield | : | 50%. |
| mp/bp | : | an oil. |
| $^1$H NMR (200 MHz) | : | δ 5.95 (br, 1H, NH), 4.50 (m, 1H), 3.85 (s, $OCH_3$), 2.55 (s, $SCH_3$), 1.55 (d, 3H). |
| IR (Liq.film) | : | $cm^{-1}$ 3320, 1770, 1680, 1520, 1200. |
| MS | : | *m/z* 177 ($M^+$, 05%), 130 (100). |

Analysis : $C_6H_{11}NO_3S$ Calcd. : C, 40.67; H, 6.21; N, 7.90.
Found : C, 40.75; H, 6.24; N, 7.82.

**Methyl N-(thiomethyl carbonyl) (L)-phenylalaninate (29k):**

Yield : 48%.
mp : 85-87°C.
$^1$H NMR (80 MHz) : δ 7.10-7.45 (m, 5H), 5.95 (br, d, 1H, NH), 4.90 (q, 1H), 3.70 (s, $OCH_3$), 3.10 (d, 2H), 2.35 (s, $SCH_3$).
IR ($CHCl_3$) : $cm^{-1}$ 3400, 1740, 1670, 1500, 1220.
MS : *m/z* 253 ($M^+$, 02%), 206, 194, 162 (100), 146, 134, 91.
Analysis : $C_{12}H_{15}NO_3S$ Calcd. : C, 56.91; H, 5.92; N, 5.53.
Found : C, 57.22; H, 5.98; N, 5.42.

**Methyl N-(thiomethyl carbonyl) β-alaninate (29l):**

Yield : 47%.
mp/bp : Semisolid.
$^1$H NMR (80 MHz) : δ 5.90 (br, 1H, NH), 3.55 (s, $OCH_3$), 3.40 (q, 2H) 2.45 (t, 2H) 2.10 (s, $SCH_3$).
$^{13}$C NMR (75.5 MHz) : ppm 172.52, 167.86, 51.65, 36.52, 33.78, 12.08.
IR ($CHCl_3$) : $cm^{-1}$ 3320, 1760, 1670, 1510, 1450.
MS : *m/z* 177 ($M^+$, 07%), 130, 98 (100), 75, 70, 59.
Analysis : $C_6H_{11}NO_3S$ Calcd. : C, 40.67; H, 6.21; N, 7.90.
Found : C, 40.52; H, 6.25; N, 7.98.

**Methyl N-(thiomethyl carbonyl) (L)-valinate (29m):**

Yield : 45%.
bp : Thick liquid.
$^1$H NMR (80 MHz) : δ 5.80 (br, d, 1H, NH), 4.40 (dd, 1H), 3.55 (s, $OCH_3$), 2.10 (s,

| | | |
|---|---|---|
| | | $SCH_3$), 2.05 (m, 1H) O.89 (2d, 6H). |
| $^{13}C$ NMR (75.5 MHz) | : | ppm 171.76, 167.91, 58. ]58, 51.86, 31.18, 18.60, 17.46, 12.01. |
| IR ($CHCl_3$) | : | $cm^{-1}$ 3360, 1750, 1680, 1540. |
| MS | : | *m/z* 205 ($M^+$, 94%), 158, 146, 130 (100). |
| Analysis | : | $C_8H_{15}NO_3S$ Calcd. : C, 46.82; H, 7.31; N, 6.82. |
| | | Found : C, 46.79; H, 7.37; N, 6.71. |

**Synthesis of (S)-methyl N-α-methylbenzyl carbamate (30):**

**From (S)-S-methyl N-α-methylbenzyl thiolcarbamate (29f):**

Catalytic amount of freshly cut metallic sodium was added to the mixture of (S)-S-methyl N-α-methylbenzyl thiolcarbamate (**29f**) (10 mmol) in methanol (15 ml) and refluxed for 12 h. The reaction was monitored by tlc. After completion of the reaction it was filtered to remove sodium methoxide and filtrate was concentrated to get solid (crude). It was further purified by column chromatography to offer (S)-methyl N-α-methylbenzyl carbamate in 90% yield (**30**).

**From (S)-N-α-methylbenzyl carbonimidodithioic acid dimethyl ester (28f):**

$ZnCl_2$ (10 mmol) was dissolved in the mixture of MeOH:$H_2O$ (3:1, 10 ml) and a solution of **28f** in the same mixture of solvent was added dropwise. The mixture was stirred at 60°C for 12 h, the reaction was followed by tlc and it was found that the **28f** was first converting to **29f** and then to **30.** After the completion of the reaction it was filtered through sintered funnel. Filtrate was reduced to half the quantity and passed through column of anhydrous sodium sulfate to remove inorganic material. Fraction collected from column was concentrated and the residue was taken into $CH_2Cl_2$, washed with $H_2O$ (twice), brine and dried with sodium sulfate and concentrated to give product (crude) which was further purified over silicagel column to furnish the carbamate **30** in 82% yield.

| | | |
|---|---|---|
| Yield | : | 90%. |
| bp | : | 50-51°C. |
| $^1$H NMR (200 MHz) | : | δ 7.35 (m, 5H, aromatic), 5.00 (br, 1H, NH), 4.90 (m, 1H,CH), 3.70 (s, 3H, $OCH_3$), 1.50 (d, 3H, $CH_3$). |
| IR ($CHCl_3$) | : | $cm^{-1}$ 1720, 1520, 1230, 1770. |
| MS | : | *m/z* 179 ($M^+$, 25%), 164 (100), 125, 105, 77, 42. |
| Analysis | : | $C_{10}H_{13}NO_2$ Calcd. : C, 61.53; H, 6.66; N, 7.17. |
| | | Found : C, 61.54; $H_2$ 6.71; N, 7.12. |

**Hydrolysis of functionalyzed ketene S,S-acetals:**

**General procedure:** Zeolite H-mordenite (1g) added at room temperature to a solution of ketene S,S-acetals (**31, 33**) (1g) in toluene. The reaction mixture was refluxed for 20 h. The reaction cooled, filtered through sintered funnel and washed with $CH_2Cl_2$ (3 x 15 ml). Filtrate was concentrated and purified by column chromatography using 2-4% EtOAc in petrolium ether to give hydrolyzed products **32, 34** in 90%, 96% respectively.

**Synthesis of S-methyl Nitrothiolacetic acid (32):**

| | | |
|---|---|---|
| Yield | : | 94%. |
| mp/bp | : | Liquid. |
| $^1$H NMR (90 MHz) | : | δ 5.30 (s, 2H), 2.45 (s, $SCH_3$). |
| IR ($CHCl_3$) | : | $cm^{-1}$ 1700, 1570, 1390. |
| MS | : | *m/z* 135 ($M^+$, 15%), 93 (100), 88, 75, 47. |
| Analysis | : | $C_3H_5NO_3S$ Calcd. : C, 26.66; H, 3.70; N, 10.37. |
| | | Found : C, 26.66; H, 3.72; N, 10.28. |

**1,1-Bismethylthio-2-acetylethylene (34):**

| | | |
|---|---|---|
| Yield | : | 96%. |
| mp | : | 69-70°C. |
| $^{1}$H NMR (200 MHz) | : | δ 6.00 (s, 1H), 2.47 (s, 3H), 2.45 (s, 3H), 2.30 (s, 3H). |
| $^{13}$C NMR (50 MHz) | : | ppm 192.45, 163.01, 112.83, 30.11, 16.89, 14.56. |
| IR (Neat) | : | $cm^{-1}$ 1640, 1500, 1200. |
| MS | : | *m/z* 162 ($M^+$, 50%), 147 (100), 43. |
| Analysis | : | $C_6H_{10}OS_2$ Calcd. : C, 44.44; H, 6.17. |
| | | Found : C, 44.48; H, 6.25. |

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