PART A : STUDIES ON POLARIZED KETEN-S,S-AND S,N-ACETALS

PART B : STUDIES ON REACTIONS OF TRIMETHYLAMMONIUMCYANOMETHYLID : A NOVEL AMMONIUM YLID

ABSTRACT

By

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A THESIS
SUBMITTED IN FULFILMENT OF THE REQUIREMENT FOR
THE DEGREE OF

DOCTOR OF PHILOSOPHY

To

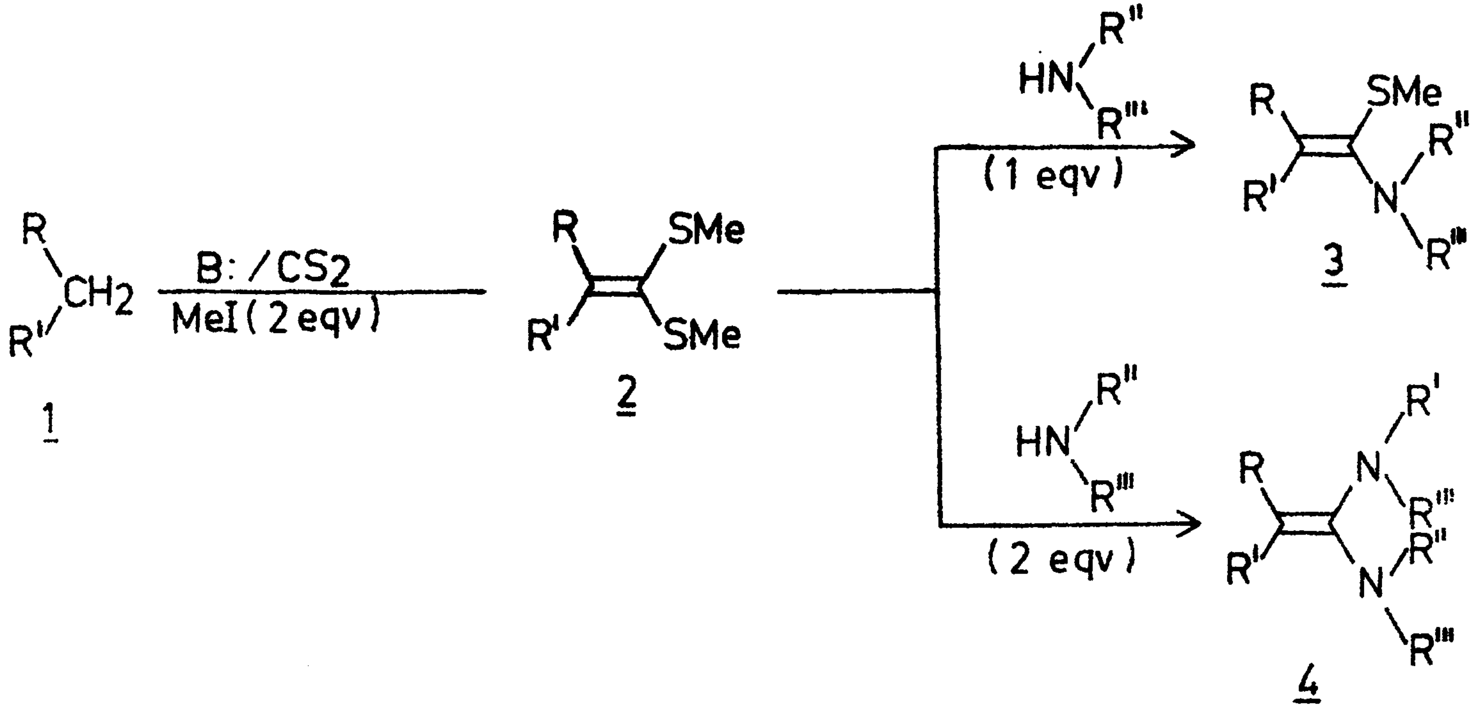
NORTH-EASTERN HILL UNIVERSITY
SHILLONG, MEGHALAYA, INDIA

NOVEMBER, 1983

thesis:

The thesis is divided into two parts, the first part consisting of five chapters, deals with the studies on polarized keten S,S- and S,N-acetals derived from various active methylene compounds, particularly ketones.

Earlier work from this laboratory has successfully demonstrated polarized keten S,S-acetals 2 as useful synthetic intermediates for the construction of a wide variety of heterocyclic and carbocyclic systems.[1] These intermediates are easily derived in relatively simpler reaction conditions from a wide variety of active methylene compounds 1 and carbon disulfide in the presence of two equivalent of a suitable base followed by alkylation in one pot reaction (Scheme 1). Unlike the corresponding O,O-acetals, the S,S-acetals are stable under mild hydrolytic conditions and thus form an interesting class of useful synthetic intermediates. It has been further shown that polarized keten S,S-acetals undergo facile displacement reactions with appropriate nucleophiles to give the corresponding substituted

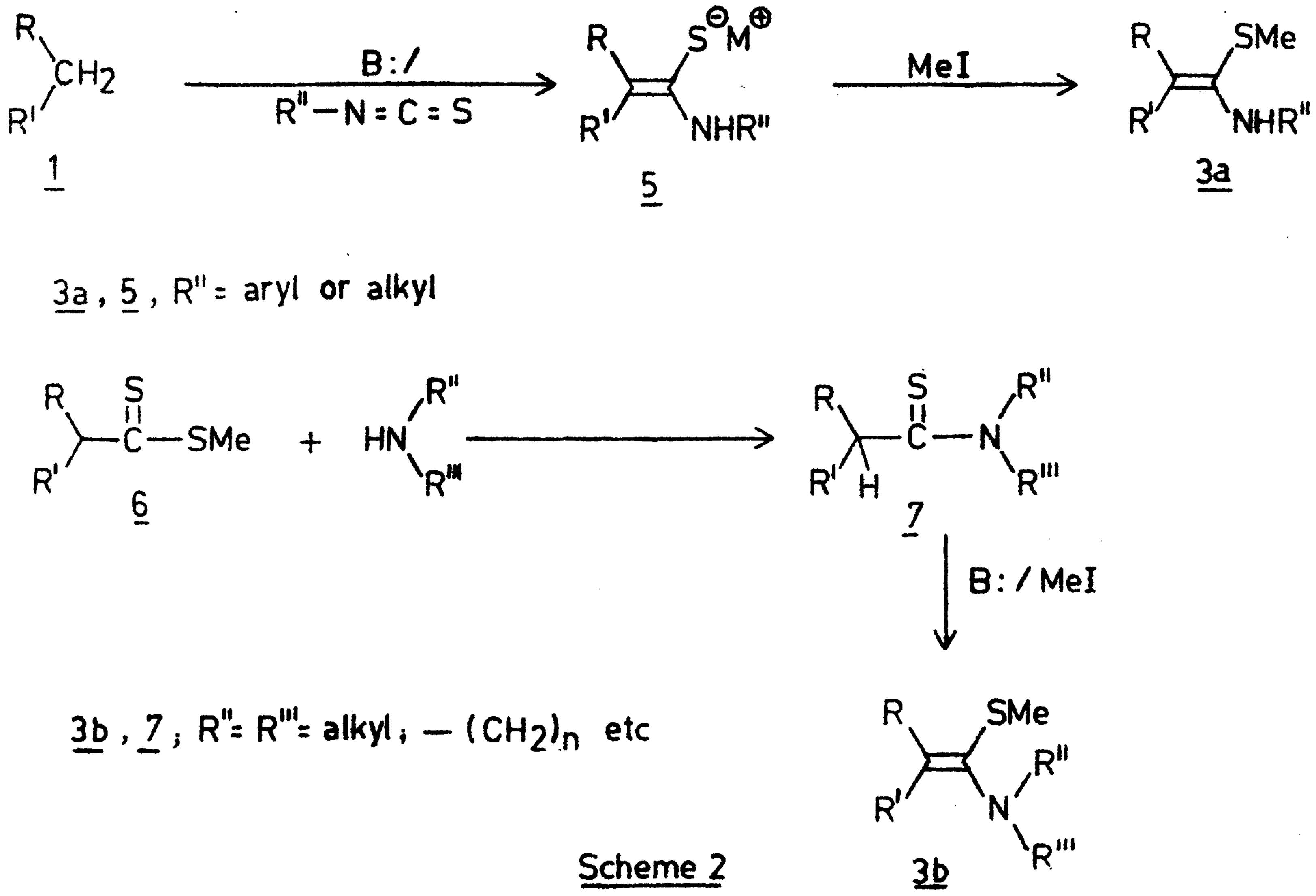


1–4, R = ArCO ; AlkylCO ; CN ; CO_2Et ; $CONH_2$; NO_2 etc
R' = H , alkyl ; aryl ; ArCO ; alkylCO ; CN ; CO_2Et ; NO_2 etc
3–4a , R'' = aryl ; alkyl ; R''' = H (primary amines)
b , R'' = R''' = alkyl , — $(CH_2)n$— etc (secondary amines)

Scheme 1.

acetals in good yields. Particularly when the nucleophile is an amine the displacement can take place either to give the corresponding S,N-acetals 3 or its N,N-acetals 4 depending on the stoichiometry of the amines used or the reaction conditions. Alternatively these S,N-acetals 3a derived from primary amines can also be synthesized in good yields by reactions of corresponding active methylene compounds with alkyl/arylisothiocyanate in the presence of base followed by alkylation (Scheme 2). The keten S,N-acetals 3b derived from secondary amines are obtained by alkylation of the corresponding thioamides 7 (Scheme 2). These polarized keten S,N- and N,N-acetals are also shown to be useful substrates for construction of a variety of heterocycles. Synthetic applications of polarized keten S,S-, S,N- and N,N-acetals are discussed in chapter I.

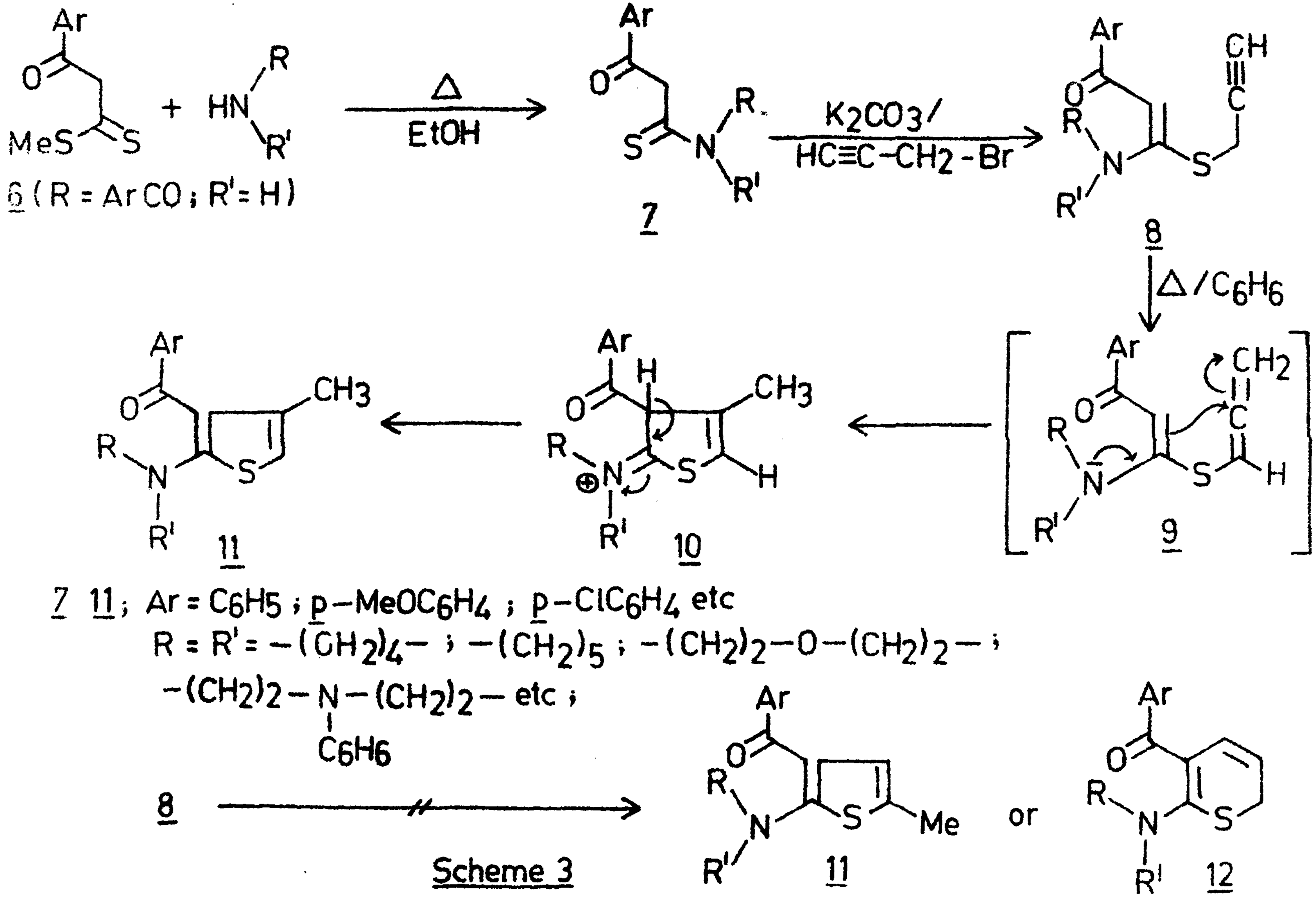
Lawesson and coworkers have extensively studied the thioclaisen rearrangements of unsymmetrical S-allyl and S-propargylacetals. In the present investigation, rearrangement studies on S-propargyl-N-aminoacetals derived from primary and secondary amines have been carried out and these results are described in the chapter III and IV. Thus it has been shown in the chapter III, that S-propargyl-N-aminoacetals 8 prepared by the route shown in the scheme 3 gave 2-amino-3-aroyl-4-methylthiophenes 11 when subjected to thioclaisen rearrangements (Scheme 3).[2]



3a, 5, R'' = aryl or alkyl

3b, 7; R'' = R''' = alkyl; $-(CH_2)_n$ etc

Scheme 2



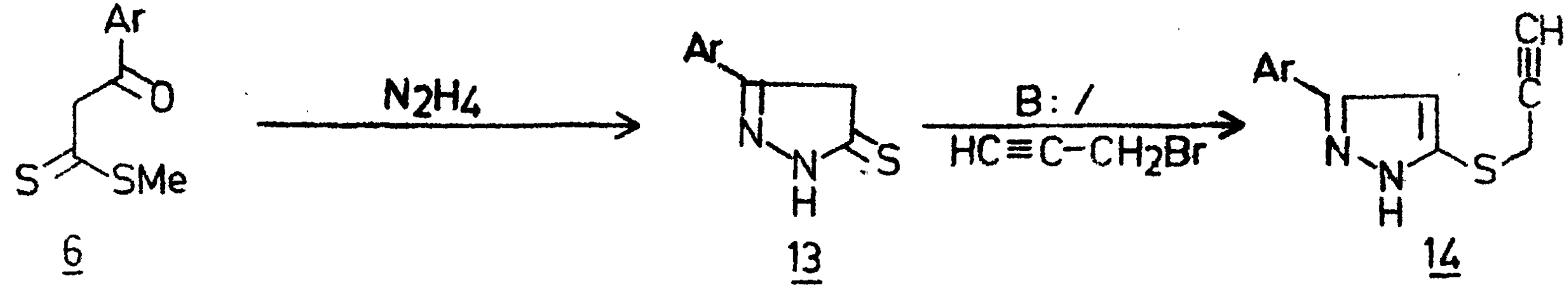
$\underline{7}$ $\underline{11}$; Ar = C_6H_5 ; $\underline{p}$–$MeOC_6H_4$; $\underline{p}$–ClC_6H_4 etc
R = R' = –$(CH_2)_4$– ; –$(CH_2)_5$; –$(CH_2)_2$–O–$(CH_2)_2$– ;
–$(CH_2)_2$–N(C_6H_6)–$(CH_2)_2$– etc ;

Scheme 3

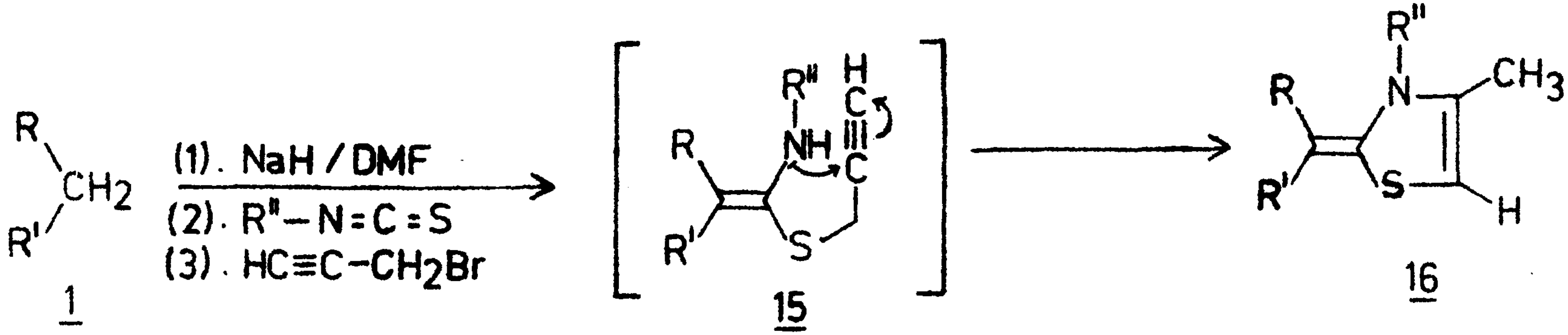
None of the corresponding 5-methylthiophenes 11 or thiopyran 12 could be isolated from the reaction mixture. These products were characterized with the help of spectral and analytical data and a probable mechanism for the formation of 11 has been discussed. Few of the S-propargylthiopyrazoles 14 were prepared according to the route shown in the scheme 4. These pyrazoles 14 however failed to undergo thioclaisen rearrangements under varying conditions.

Attempted preparation of S-propargyl-N-anilino/ethylaminoacetals 15 resulted in *insitu* intramolecular cyclization of 15 to yield the corresponding 3-alkyl/aryl-4-methyl-2-(substituted methylene)thiazolines 16 in excellent yields (Scheme 5). Thus a facile general route for 16 has been developed,[3] which is described in the chapter IV. Attempted preparation of S,N-allylacetal 17 yielded only thioanillide 18, which is formed by thioclaisen rearrangement of 17 (Scheme 6). Alkylation of 18 afforded allyl S,N-acetal 19 (Scheme 6).

In the chapter V, preparation and rearrangement studies of novel α-allylketoketen S,S-acetals 24 have been described (Scheme 9). It has been shown[4] earlier in our laboratory that ketoketen S,S-acetals 20 derived from either propiophenones (20a) or dihydrochalcone (20b) undergo interesting base catalysed 1.3-RS shift to give 3-alkylthio-2-alkylthiomethylacrylophenones (22)



Scheme 4



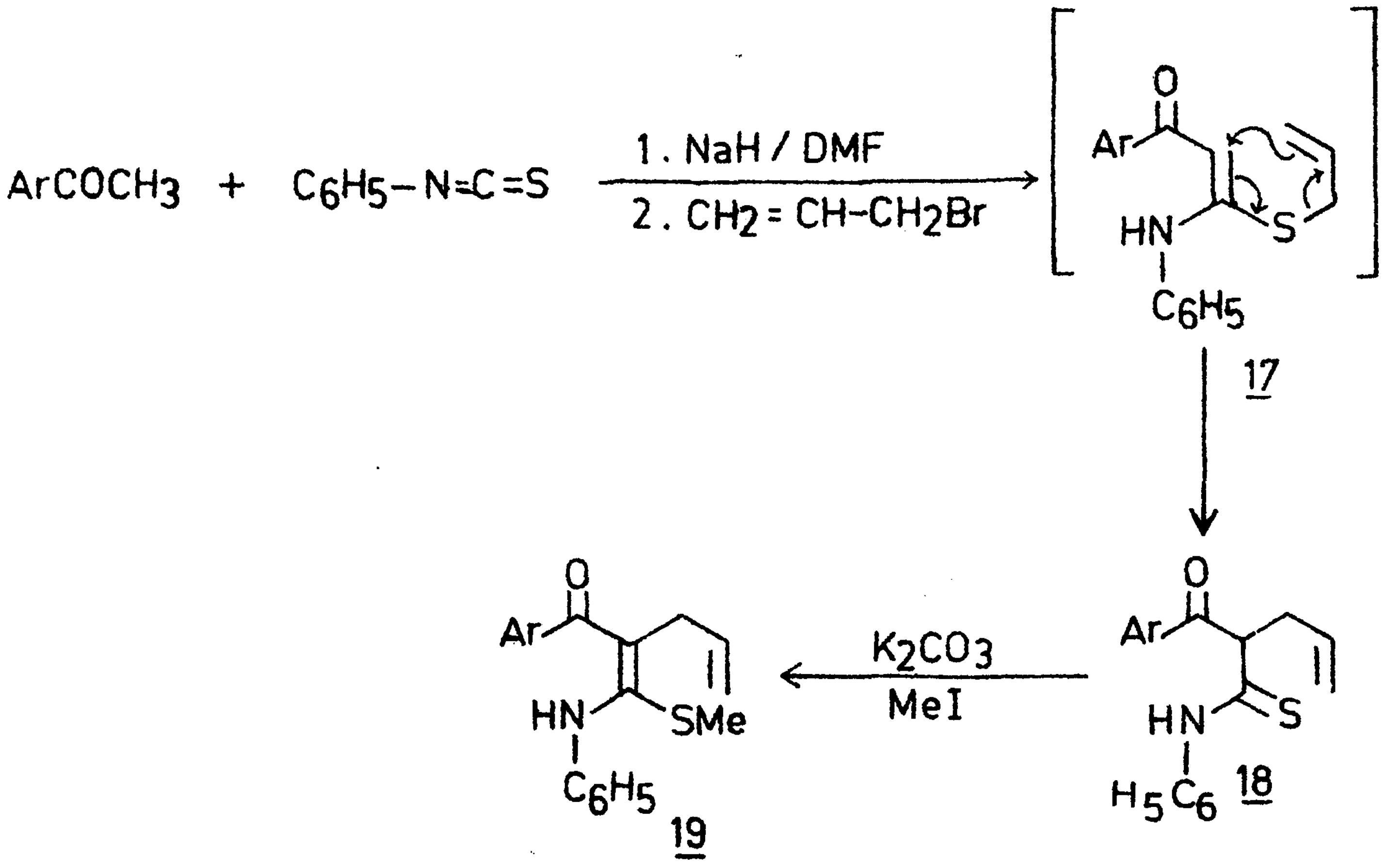
1, 15, 16, R = substituted arylCO; R' = H

R = aryl, R' = CN

R = R' = CH_3CO

15, 16; R'' = C_6H_5 or C_2H_5

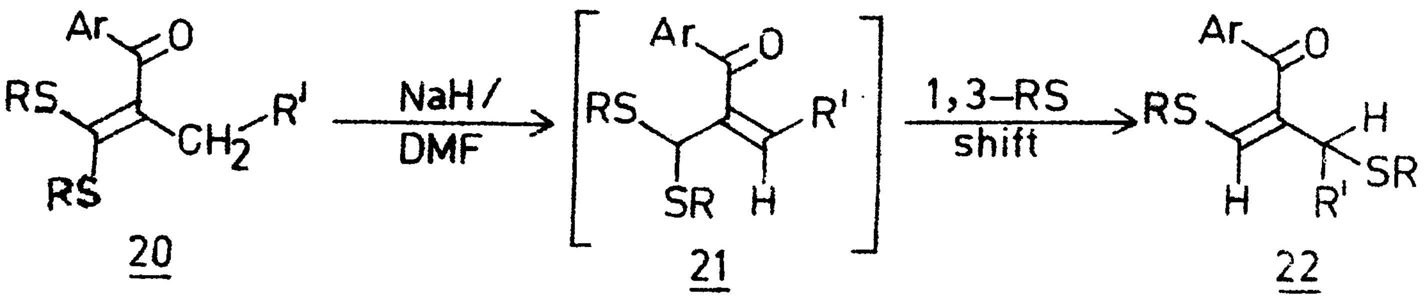
Scheme 5



Scheme 6

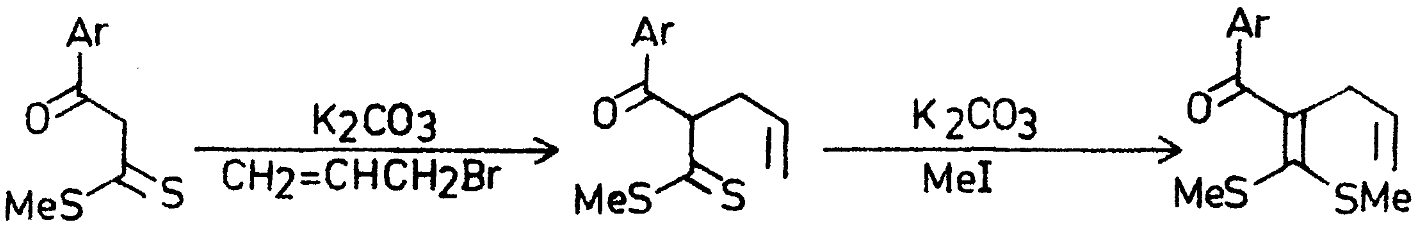
(Scheme 7). A detailed mechanistic studies on this interesting 1,3-RS shift which involves mobile ketoallyl intermediate 21 has already been published.[5] In the present investigation when these base catalysed rearrangement studies were extended to α-allyl-ketoketen S,S-acetals 24, formation of Z, E-1,5-dimethylthio-2-aroyl-1,3-pentadienes 26 was observed (Scheme 9) which involves an interesting 1,5-MeS shift. The desired ketoketen S,S-acetals 24 were prepared by the route shown in the scheme 8. When the dithioacetal 24 were reacted with sodium hydride in dimethylformamide and benzene the dienes 26 were obtained in good yields ((Scheme 9). A mechanism involving mobile ketopentadienyl intermediate 25 has been suggested for this rearrangement (Scheme 9). The intermediate 25 undergoes 1,5-MeS shift to give the rearranged dienes 26. All the present evidences indicate an intramolecular 1,5-MeS shift either via concerted suprafacial 1,5-sigmatropic shift (path a) or through thiopyrilium intermediate 27 via facile 6-endotrig process (path b) (Scheme 9).

For the preparation of keten S,S-acetals 24 (Scheme 8) and thioamides 7 (Scheme 3) β-oxodithioesters 6 were required as initial precursors. Our literature survey revealed that there is no general method available for the preparation of these dithioesters 6. Thus a facile general method for the synthesis of β-oxodithioesters has been developed[6] which is described in the



20–22 a, R = Me ; Et , *i*– Pr ; R′=H ; Ar = substituted aryl
b, R = Me ; R′= C_6H_5 ; Ar = C_6H_5

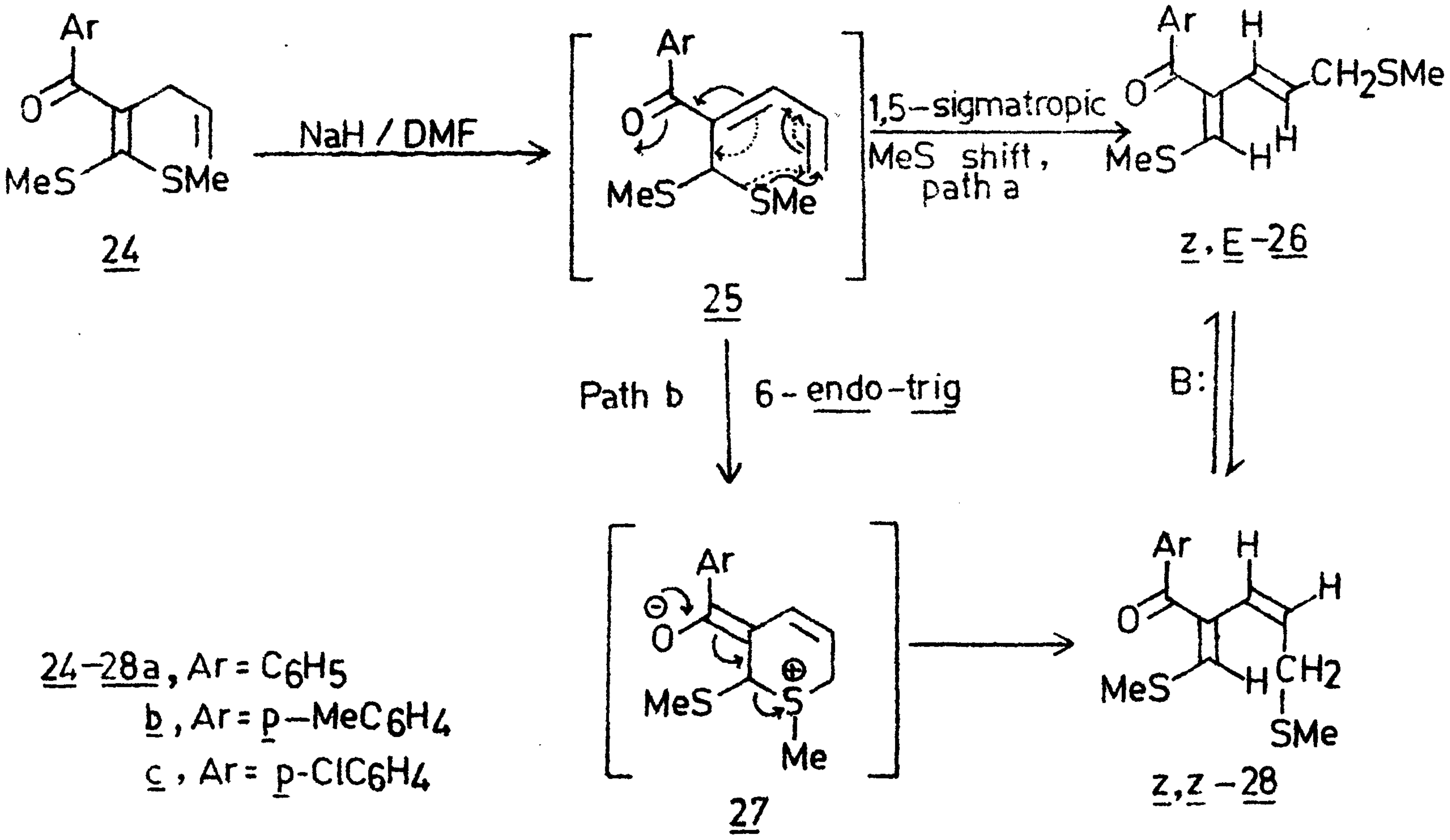
Scheme 7



6 23 24

6, 23, 24, Ar = C_6H_5 ; p-MeC_6H_4 ; p-$MeOC_6H_5$;
p-ClC_6H_4 ; p-$EtOC_6H_4$ etc

Scheme 8

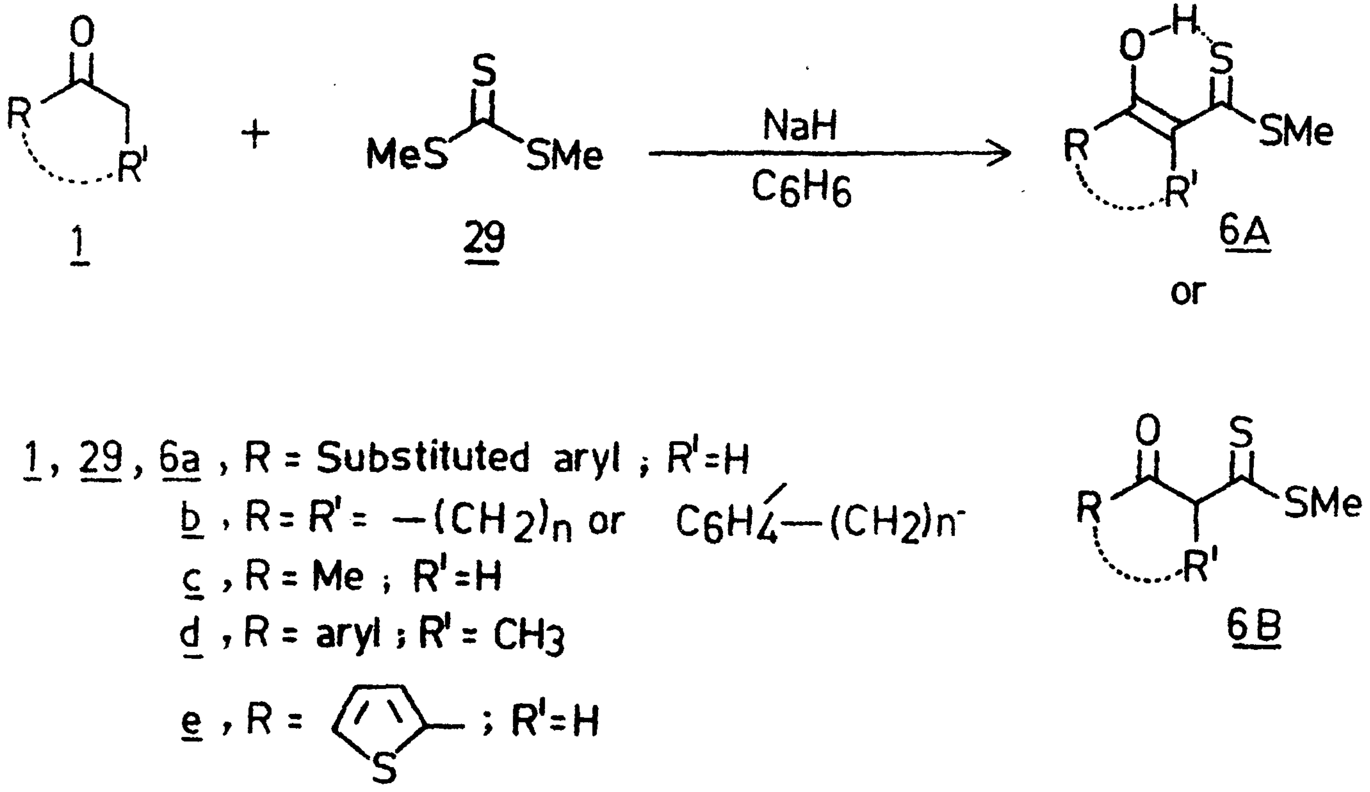


$\underline{24}$–$\underline{28a}$, Ar = C_6H_5
$\underline{b}$, Ar = $\underline{p}$–MeC_6H_4
$\underline{c}$, Ar = $\underline{p}$-ClC_6H_4

Scheme 9

chapter II. The method involves base catalysed methylthiothiocarbonylation of active methylene ketones with dimethyltrithiocarbonate 29 (Scheme 10).

The second part of the thesis deals with the generation and the studies of reactions of trimethylammoniumcyanomethylid 31 (Scheme 11). It is well documented that the nitrogen ylids are different in their thermodyanamic stability and their reactivity towards electrophilic centres from the corresponding phosphorous and sulfur ylids. Although, the formation of stable ammonium ylids have been reported in the literature, their synthetic applications like those of immonium, cycloimmonium, sulfur and phosphorous ylids are not much investigated. The reason for this scant studies appears to be that in most of their reactions, the ammonium ylids behave like classical carbanion, undergoing normal C-C bond formation and not those that appear to be unique to ylidic carbanions. In the chapter VI of the thesis, a systematic investigation on the reactions of trimethylammoniumcyanomethylid 31 (Scheme 11) with carbonyl compound, α,β-unsaturated carbonyl and thiocarbonyl compounds have been carried out. The ylid 31 was generated insitu by treatment of trimethylammoniumcyanomethyliodide with sodium hydride. The reaction of 31 with benzaldehyde gave a product which was characterized as substituted m-dioxin 36 on the basis of spectral and analytical data (Scheme 11). A probable mechanism for the formation of 36 via intermediate expoxide 33 has been suggested (Scheme 11).



$\underline{1}$, $\underline{29}$, $\underline{6a}$, R = Substituted aryl ; R'=H

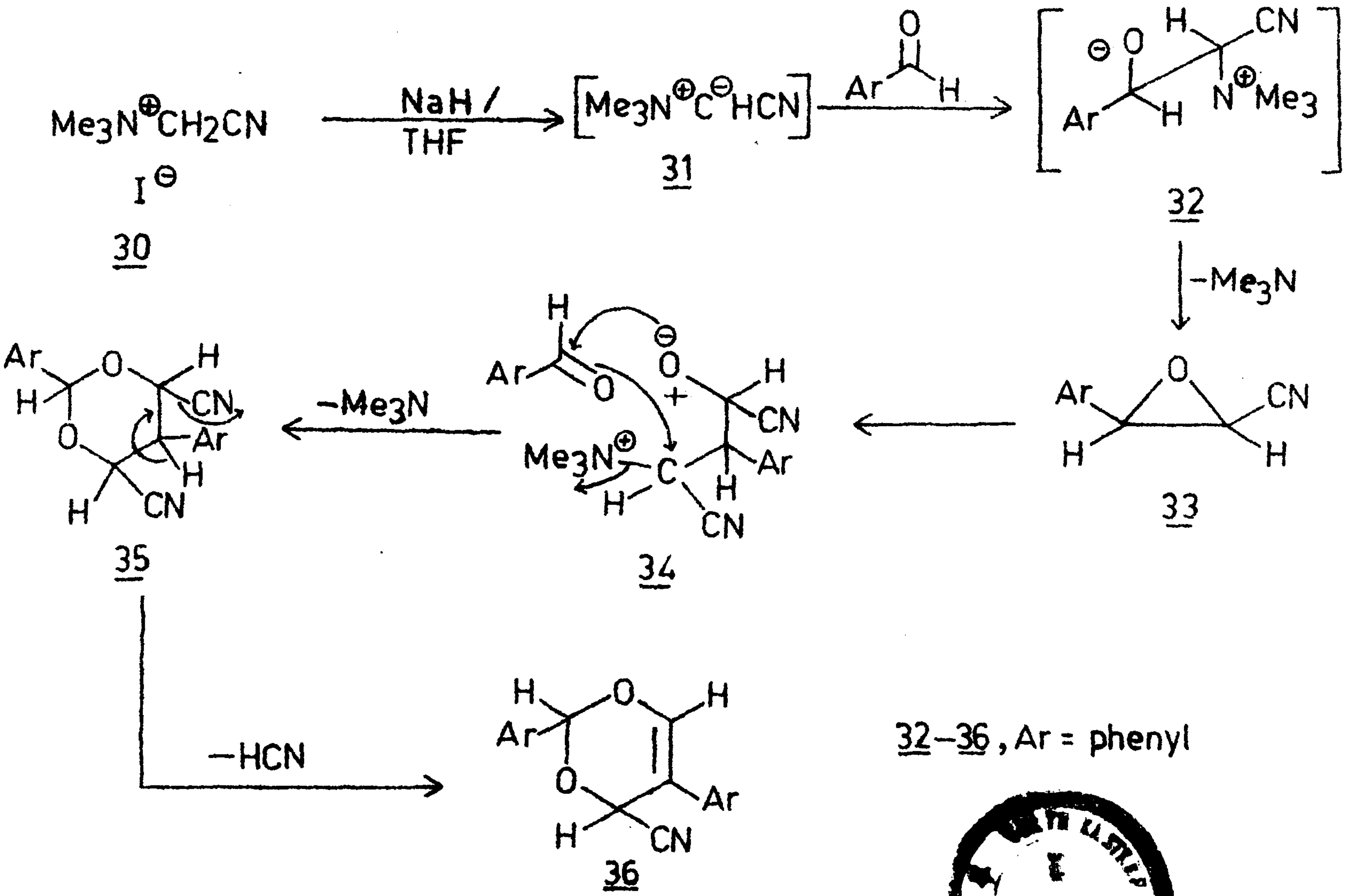
$\underline{b}$, R = R' = $-(CH_2)_n$ or $C_6H_4-(CH_2)_n$

$\underline{c}$, R = Me ; R'=H

$\underline{d}$, R = aryl ; R' = CH_3

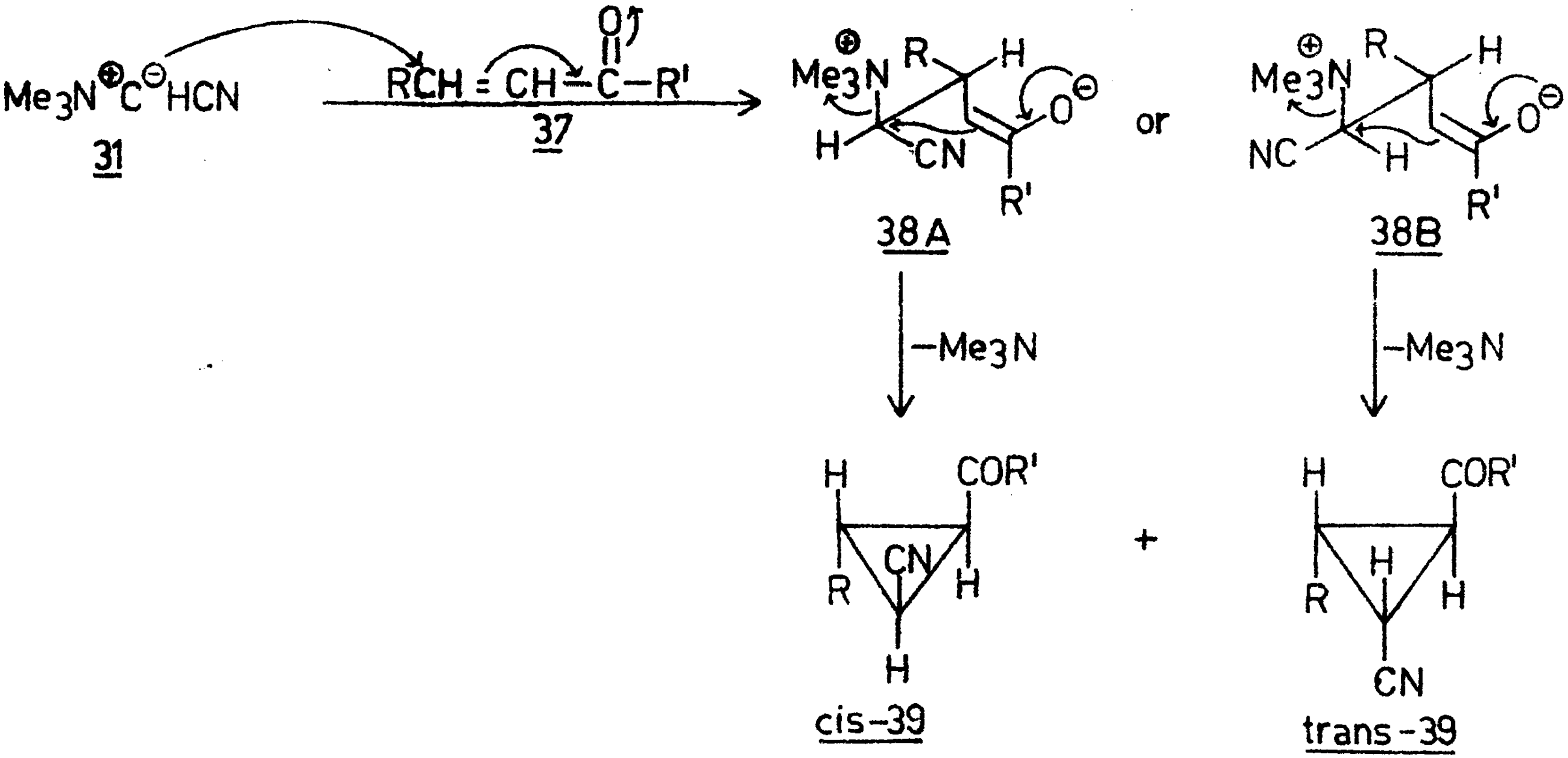
$\underline{e}$, R = ; R'=H

Scheme 10



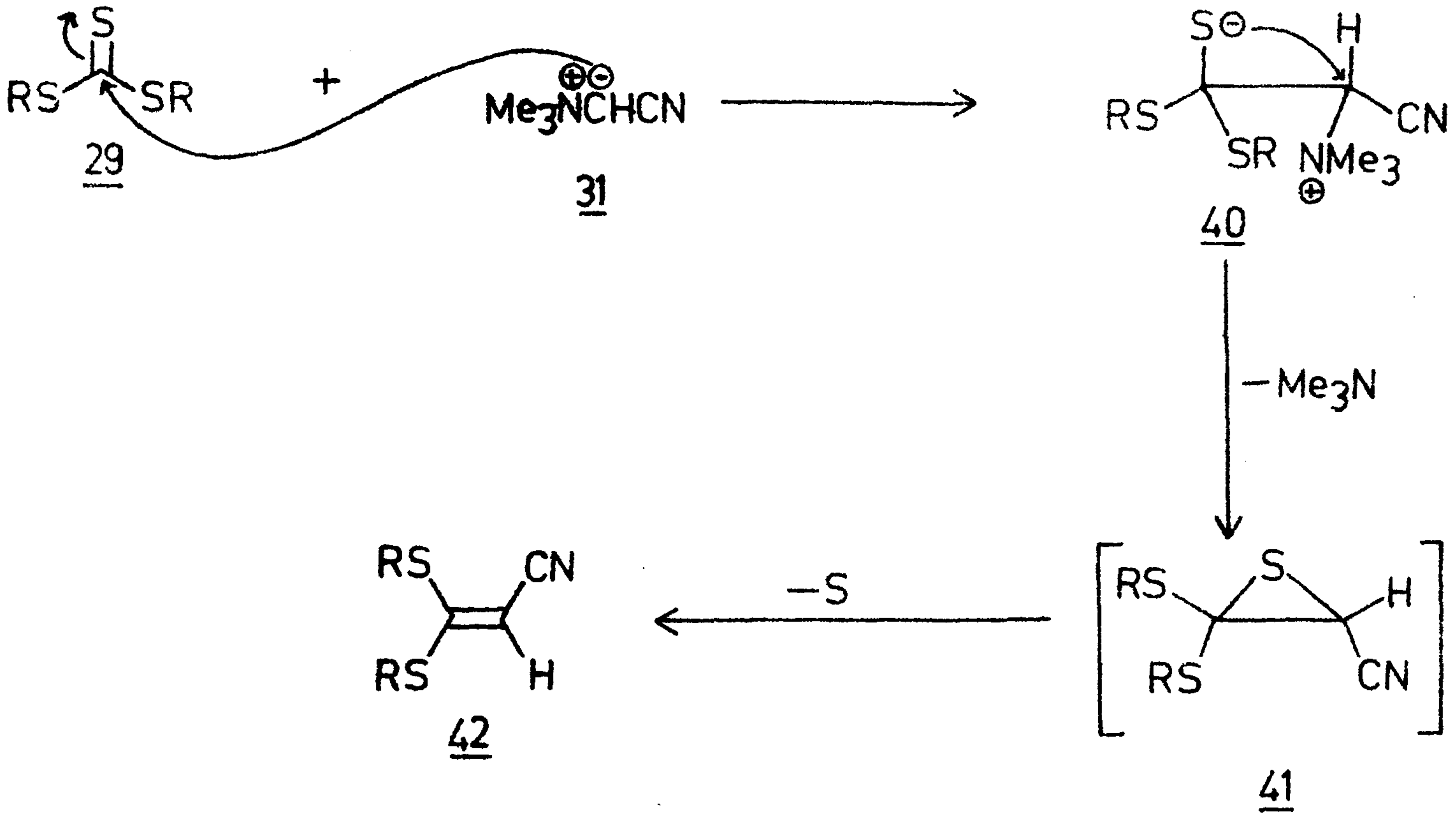
32–36, Ar = phenyl

Scheme 11



37–39 , R = substituted aryl or H ; R' = COAr or CO_2Et

Scheme 12



29, 40, 41, 42 ; R = Me, Et, n−pr, i−pr; $C_6H_5CH_2$, $-(CH_2)_2-$

Scheme 13

The reaction of 31 with α,β-unsaturated carbonyl compounds 37 gave[7] the corresponding *cis*- and *trans*- substituted cyclopropanes 39 in good yields (Scheme 12), which to our knowledge is the first report of cyclopropanation of an activated double bond with an ammonium ylid. A mechanism for the formation of stereoisomeric cyclopropanes has been discussed (Scheme 12).

The reaction of ylid with dialkyltrithiocarbonates 29 resulted in the formation of the corresponding 3,3-bis(alkylthio)-acrylonitriles 42[8] in good yields (Scheme 13). These dithioacetals 42 are apparently formed via episulfide intermediates 41 which undergo facile sulfur extrusion under the reaction conditions to give 42 (Scheme 13). From these studies on the reactions of 31, it was concluded that nitrogen ylids can also behave like their sulfur and phosphorous analogous in their reactions if the ylid possesses proper moderately stabilizing substituents.

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NOVEMBER, 1983

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PROFESSOR OF CHEMISTRY

NORTH-EASTERN HILL UNIVERSITY
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CERTIFICATE

This is to certify that the work described in this thesis has been carried out by Mr. Shakti Sadhan Bhattacharjee under my supervison. He has satisfactorily completed the pre-Ph.D courses prescribed and the period of two years of investigational work for the award of the Ph.D degree in Chemistry.

The work described in this thesis is original and has not been submitted for any other degree or diploma in this or any other University.

Date: November 1983.

(H. Junjappa)

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Department of..................

This is to certify that Mr. Shakti Sadhan Bhattacharjee has completed the following pre-Ph.D courses as prescribed by this university satisfactorily.

1. Application of Molecular Orbital theory.
2. Advance concept in physical chemistry.
3. Advance Inorganic Chemistry.
4. Highlights in Organic Chemistry.

(Professor T.S.B. Narasaraju)
12.x.83.
Head

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(Shakti S. Bhattacharjee)

CONTENTS

PREFACE

Polarized keten dithioacetals, which are prepared in one pot reaction under relatively simple reaction conditions from a wide variety of active methylene compounds have been successfully utilized in this laboratory for the synthesis of a **large number** of heterocyclic compounds. These dithioacetals are known to undergo facile displacement with amines to give the corresponding S,N-acetals or N,N-acetals depending on the stoichiometry of the amines used or the reaction conditions. These S,N- and N,N-acetals have also been shown to be synthetically useful substrates for the construction of a variety of heterocyclic rings. In the first chapter, the synthetic applications of these intermediates for the construction of a wide variety of heterocyclic systems have been discussed. In the second chapter, a facile general method for the synthesis of β -oxodithioesters by methylthiothiocarbonylation of active methylene ketones with dimethyltrithiocarbonate in the presence of sodium hydride is described. These dithioesters were required for the synthesis of unsymmetrical keten S,S-acetals and thioamides in the subsequent studies. A brief review on the reported methods for the preparation of these dithioesters is also described.

The third chapter of the thesis deals with the rearrangement studies on S-propargyl-N-aminoacetals derived from cyclic secondary amines, which afforded 2-amino-3-aroyl-4-methylthiophenes in good yields. A mechanism for the formation of these thiophenes has been discussed.

Attempted preparation of S-propargyl-N-anilino/ethylamino acetals afforded the corresponding 3-alkyl/aryl-4-methyl-2-(substituted methylene)thiazolines in excellent yields. Thus a facile general route for these thiazolines has been developed, which is described in the chapter IV.

In the chapter V of the thesis, synthesis and base catalysed rearrangement studies of α-allyl-α-ketoketen S,S-acetals have been described. These α-allyl α-ketoketen S,S-acetals undergo an interesting stereo-selective 1,5-MeS shift in the presence of sodium hydride to afford 1,5-dimethylthio-2-aroyl-1,5-pentadienes in good yields. A mechanism involving a mobile **ketopentadienyl itermediate** has been suggested for this rearrangement, which undergoes intramolecular 1,5-MeS shift either through concerted suprafacial sigmatropic shift or via 6-endo-trig process.

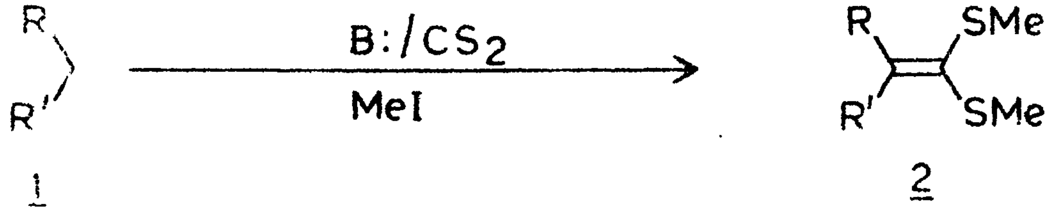
The sixth chapter of the thesis (part B) deals with the generation and reactions of trimethylammonium cyanomethylid, a novel ammonium ylid. The ylid is shown to react with benzaldehyde to give m-dioxin derivative. The reaction of ylid with

α,β -unsaturated carbonyl compounds afford stereoisomeric cyclopropanes by Michael addition and subsequent ring closure. The reaction of ylid with thiocarbonyl compounds like dialkyltrithiocarbonates yields bisalkylthioacrylonitriles, which are formed by sulfur extrusion from the initially formed episulfide intermediates. From these studies it was concluded that nitrogen ylids can also behave like their sulphur and phosphorous analogues in their reactions, if the ylid possesses proper moderately stabilizing substituents..

CHAPTER I

POLARIZED KETOKETEN S,S-, S,N- AND N,N-ACETALS : GENERAL INTRODUCTION

The polarized ketendithioacetals (2) are among the simplest synthetic intermediates, which can be prepared by simple methods[1,2] treating active methylene compounds of general formula (1) with two equivalents of base in the presence of carbon disulphide followed by alkylation. These acetals (2) are either liquids with well defined boiling points or solids with sharp melting points which can be purified by conventional purification methods. They are stable at room temperature, under mild acidic and alkaline conditions and can be stored indefinitely without apparent decomposition. On the other hand, the corresponding O,O-acetals[3] (3) are generally prepared by methods involving more than one step, strictly under moisture free conditions since they undergo rapid hydrolytic cleavage. Besides, active methylene compounds can not be used as starting materials to prepare these compounds employing the same methods used

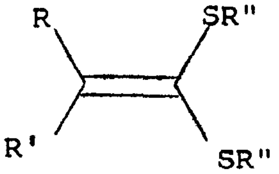


R = ArCO ; Alkyl CO; CN ; CO_2Et ; NO_2 ; etc.

R' = ArCO ; CN ; CO_2Et ; $CONH_2$; H ; alkyl and aryl etc.

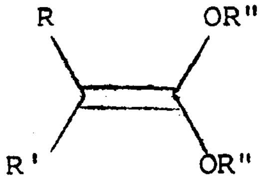
Scheme 1

for the corresponding S,S-acetals. Similarly, ketene dihalogenides (4)[4] are prepared in the laboratory by chlorinating directly the corresponding ketene S,S-acetals (2), thus making the acetals (2) as primary precursors of ketene dihalogenides 4. Similarly the N,N-acetals 5 are useful as potential starting materials, since they



2

Keten S,S-acetals



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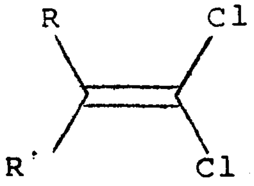
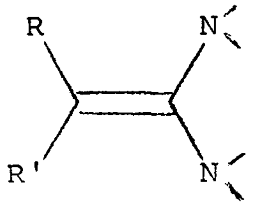
Keten O,O-acetals



4

Keten dihalogenides



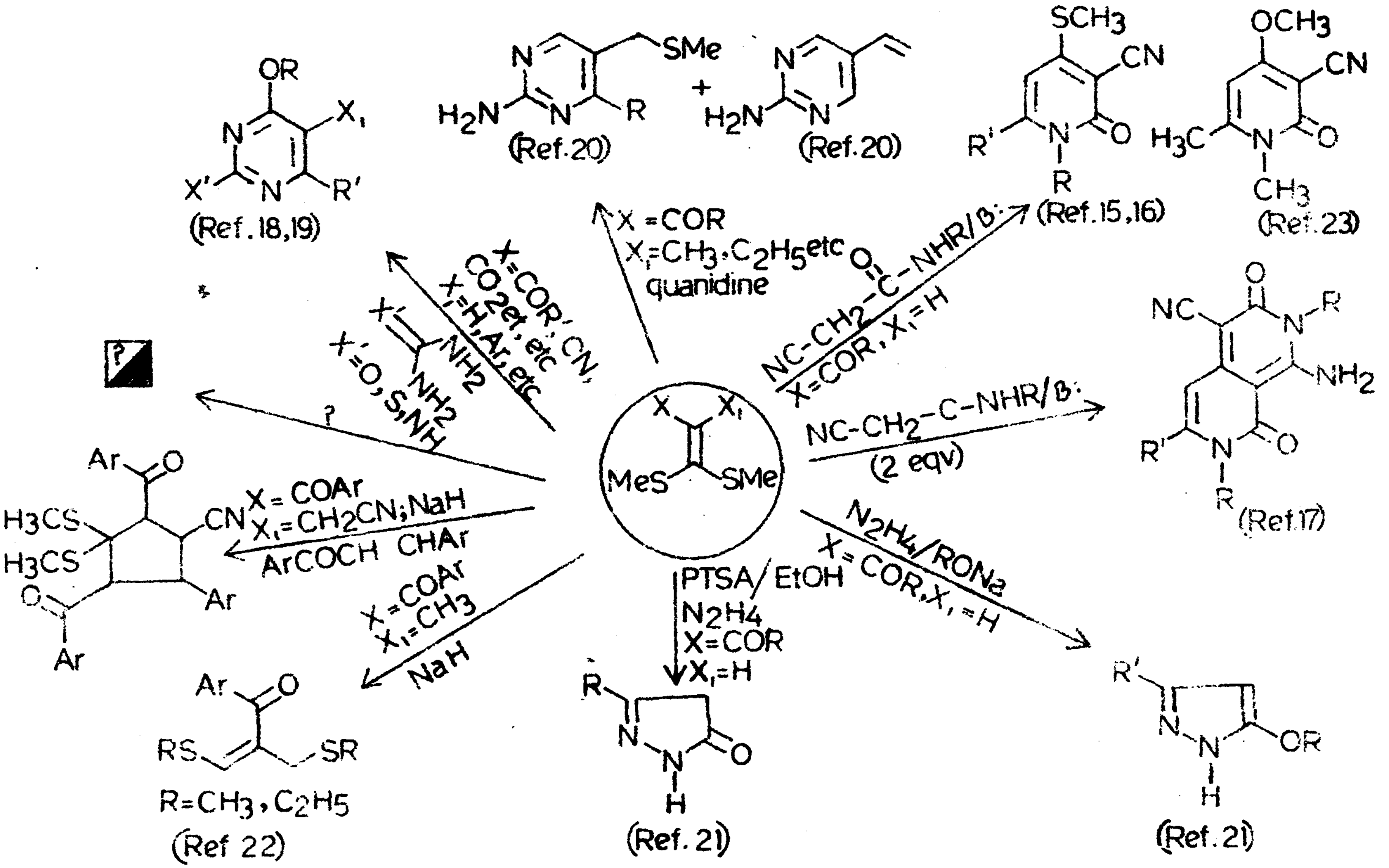
5

Keten N,N-acetals

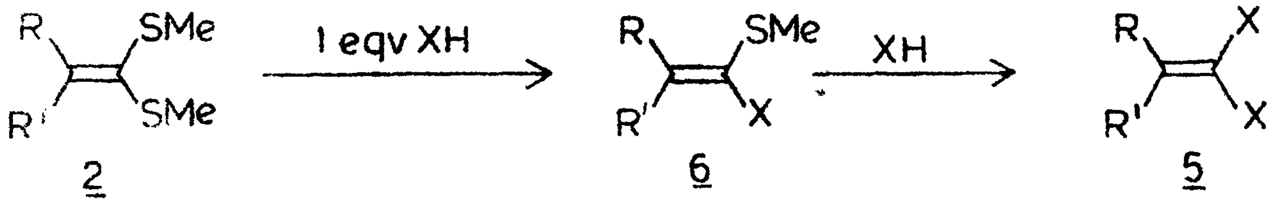
2 - 5 R = H, alkyl, aryl, nitrile, carbonyl, nitro, sulphonyl, etc.
R'= Nitrile, carbonyl, sulphonyl, nitro, etc.
R"= Alkyl groups.

are also derived from either one of the analogues 2, 3 or 4.[5] Apparently, the polarized ketene S,S-acetals 2, form an important class of 1,3 electrophilic three carbon fragments, which are of potential synthetic value. Despite a large number of reports in the literature on their preparation and physical properties,[6-14] a systematic synthetic investigation on their synthetic utility was not much explored until these studies were initiated in our laboratory.

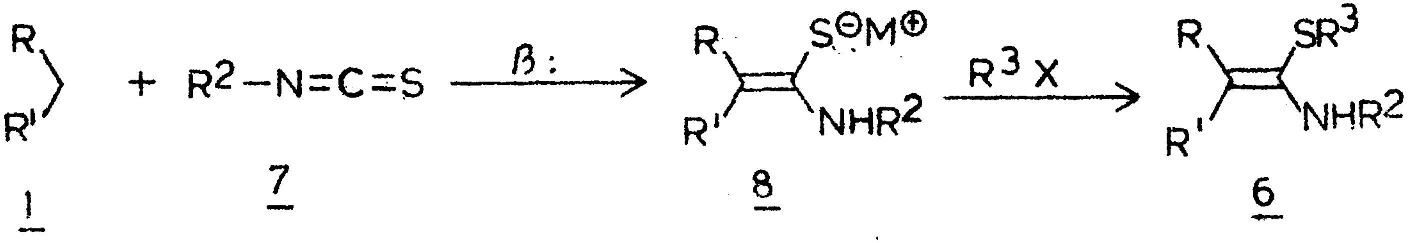
A few of the important synthetic applications[15-23] of 2 for constructing a variety of heterocyclic compounds, and other compounds achieved in this laboratory, are described in scheme 2. The methods thus developed have been shown to be of general synthetic importance, since the choice of structural variants of active methylene compounds is quite large. These dithioacetals 2 have also been shown to undergo facile displacement reactions with primary and secondary amines to give the corresponding S,N,-(6) and N,N-acetals[24-29] (5) depending upon the stoichiometry of amines used (Scheme 3). The S,N-acetals are best prepared by treating active methylene compounds with appropriate isothiocyanates in the presence of a base followed by alkylation (Scheme 3),[24,30] These acetals have been proved to be useful synthetic intermediates. Some of the important synthetic methods developed[21,31-39] in this laboratory, by treating them with a variety of reagents, have been formulated in scheme 4. It is evident from these two schemes


OR
X₁
X′
R′
(Ref.18,19)
SMe
H₂N
R
(Ref.20)
(Ref.20)
SCH₃
CN
R′
R
(Ref.15,16)
OCH₃
CN
H₃C
CH₃
(Ref.23)
X=COR
X₁=CH₃,C₂H₅etc
quanidine
X=COR′,CN,
CO2et,etc
X₁=H,Ar,etc
X′=O,S,NH
NH2
NC-CH2-C(=O)-NHR/B:
X=COR, X₁=H
NC
NH₂
R′
(Ref.17)
NC-CH2-C-NHR/B:
(2 eqv)
?
MeS
SMe
X
X₁
Ar
H3CS
H3CS
CN
Ar
X= COAr
X₁=CH2CN;NaH
ArCOCH CHAr
X=COAr
X₁=CH3
NaH
PTSA/ EtOH
N2H4
X=COR
X₁=H
N2H4/RONa
X=COR,X₁=H
RS
SR
R=CH3,C2H5
(Ref 22)
R
(Ref.21)
R′
OR
(Ref.21)

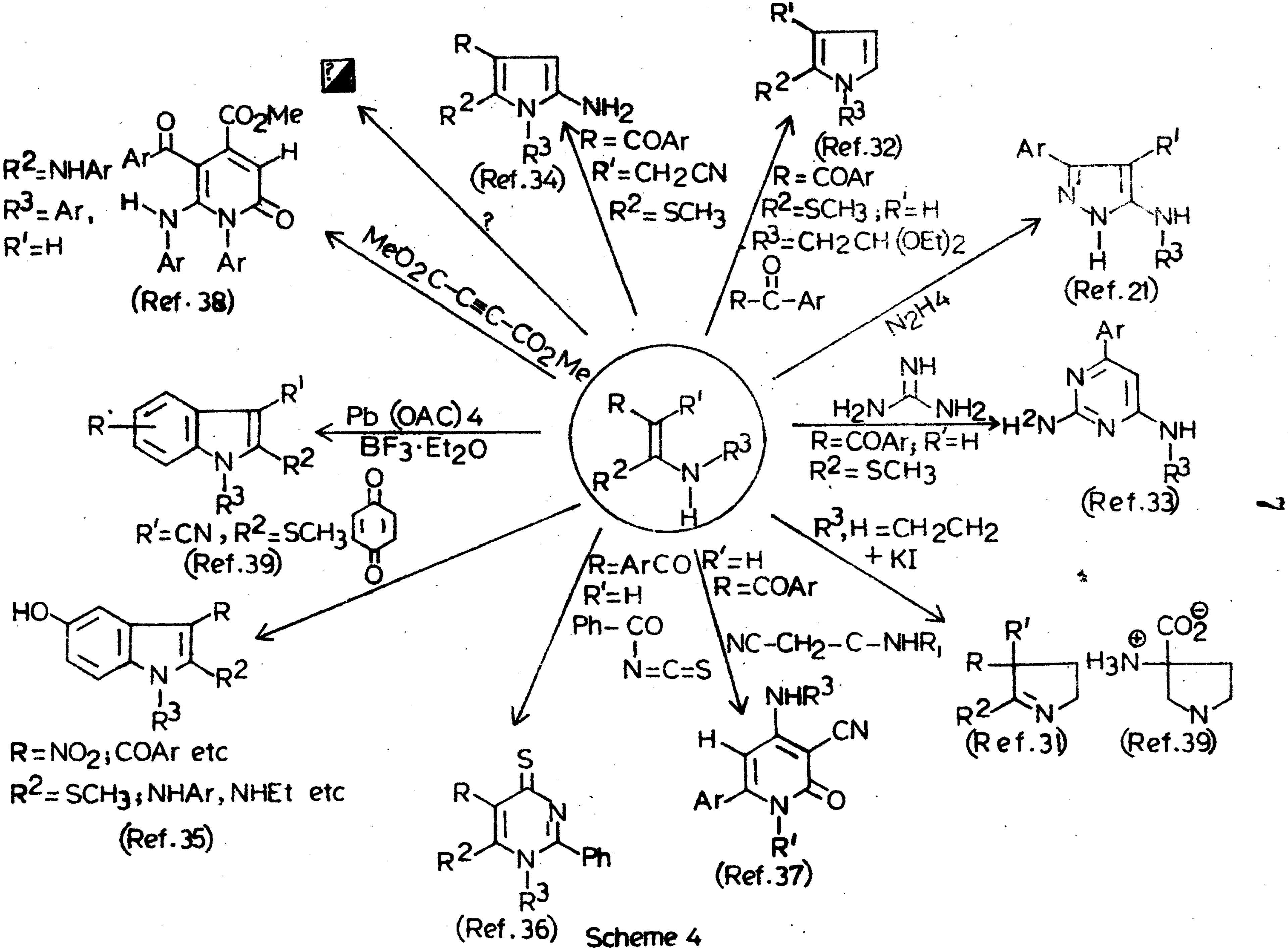
Scheme 2



5,6; R=CN, CO_2Et; NO_2; ArCO; AlkylCO; H
R'=H; CN, CO_2Et; etc.
X=NH_2; ArNH; Alkyl NH; dialkylamino; Cyclic amines



Scheme 3

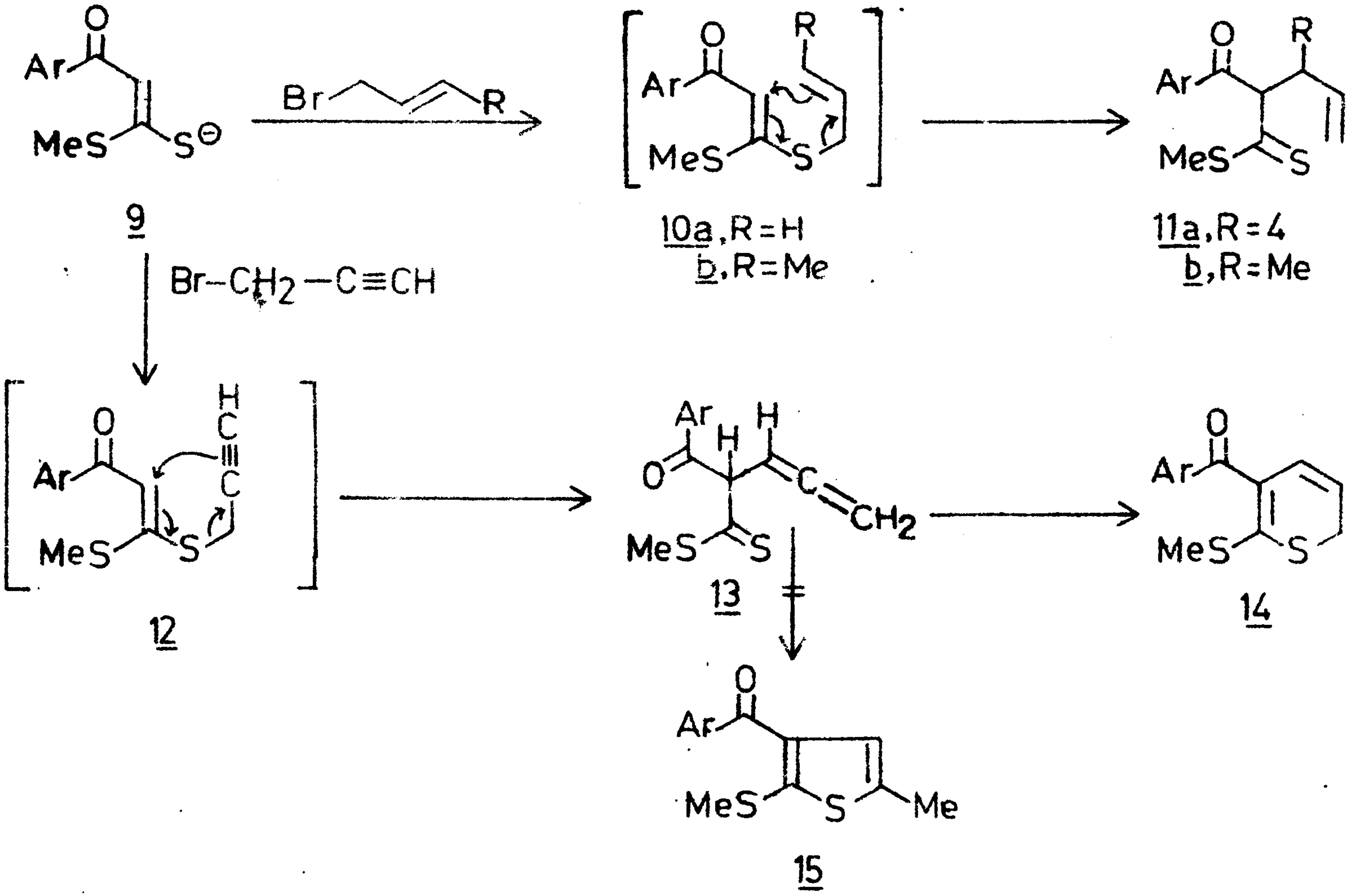

(Ref.38)
R2=NHAr
R3=Ar,
R'=H
CO2Me
?
MeO2C–C≡C–CO2Me
(Ref.34)
R=COAr
R'=CH2CN
R2=SCH3
(Ref.32)
R=COAr
R2=SCH3 ; R'=H
R3=CH2CH (OEt)2
R–C(=O)–Ar
N2H4
(Ref.21)
H2N–C(=NH)–NH2
R=COAr; R'=H
R2=SCH3
(Ref.33)
Pb (OAC)4
BF3·Et2O
R'=CN, R2=SCH3
(Ref.39)
R3,H=CH2CH2
+ KI
(Ref.31)
(Ref.39)
R=NO2; COAr etc
R2=SCH3; NHAr, NHEt etc
(Ref.35)
R=ArCO
R'=H
Ph–CO–N=C=S
(Ref.36)
R'=H
R=COAr
NC–CH2–C–NHR1
(Ref.37)

Scheme 4

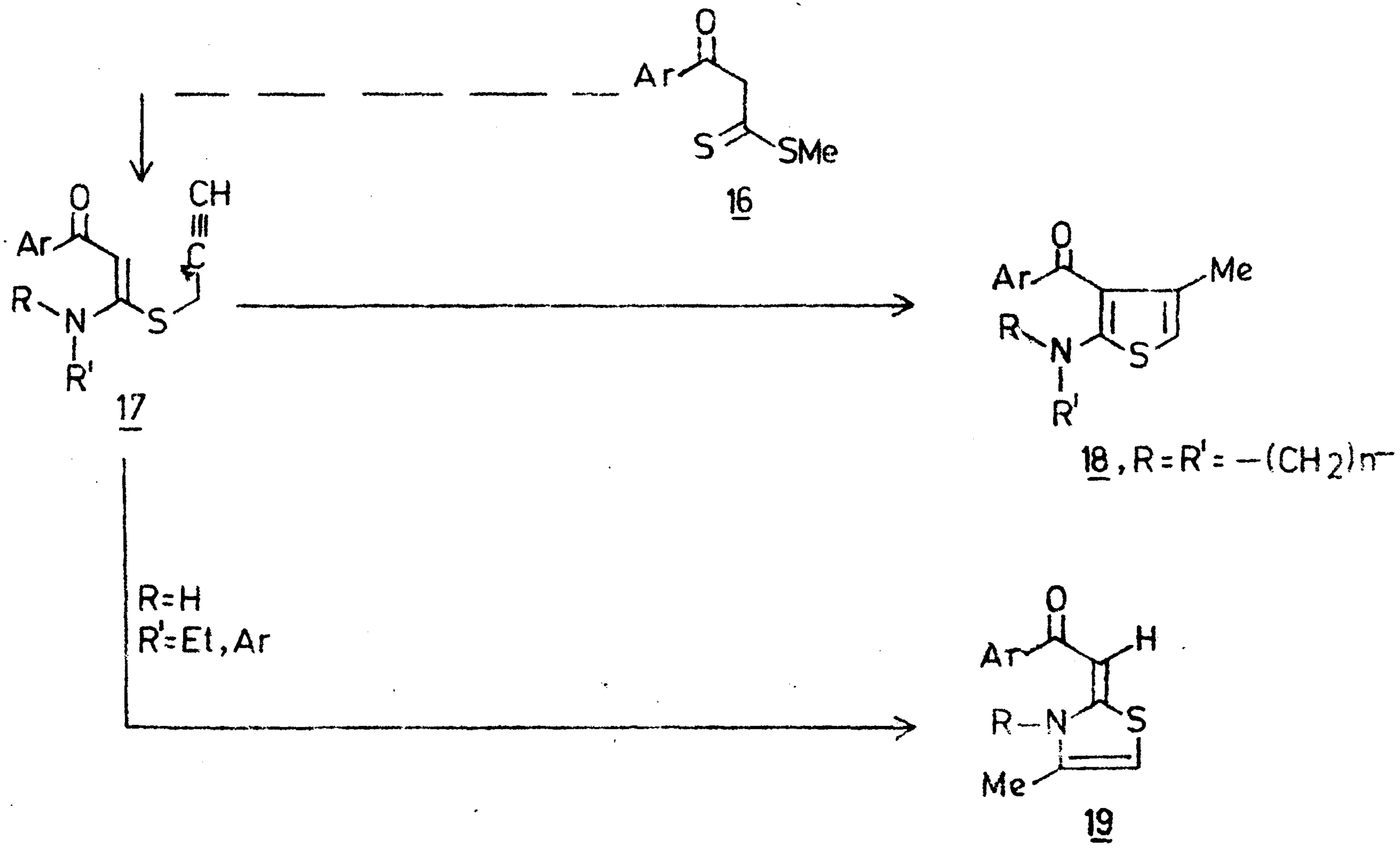
(2 and 4) that the keten S,S-, S,N- and N,N-acetals, which can be prepared in larger quantities from wide structural variants of active methylene compounds can serve as building blocks for the construction of hitherto inaccessible novel heterocyclic systems.

Larsson and Lawesson[40] have extensively studied thio-claisen rearrangements of unsymmetrical S-allyl (10a), S-crotyl (10b) and S-propargylacetals 12 which spontaneously rearrange to products like dithioesters 11a, 11b and thiopyran (14) (Scheme 5) respectively during their preparations. In the present investigations, we have studied thio-claisen rearrangements on the corresponding S,N-propargylacetals 17 which resulted in development of general routes for aminothiophenes[41] 18 and methylthiazolines[42] 19 (Scheme 6). These results have been described in chapter III and IV.

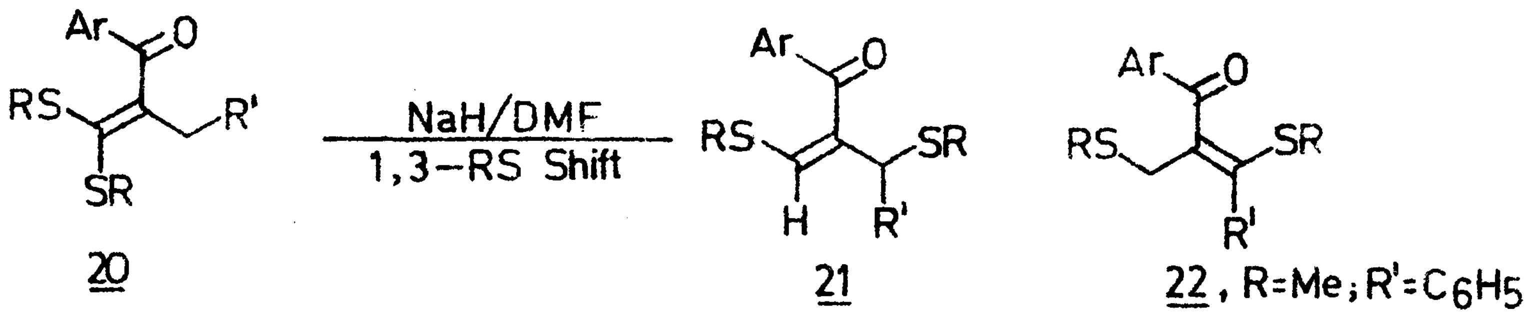
Recent studies from our laboratory have demonstrated[22,43] that ketoketen S,S-acetals derived from propiophenones (20a) and dihydrochalcone (20b) undergo interesting base catalysed 1,3-RS shift to give the corresponding 3-alkylthio-2-alkylthiomethyl acrylophenones 21. The acrylophenone 21b obtained from dihydrochalcone dithio-acetal (20b) undergoes base catalysed 1,3-prototropic shift under reaction conditions to give the thermodynamically more stable chalcone 22 as the major product.


Ar
O
MeS
S⊖
Br
R
9
Br–CH$_2$–C≡CH
10a, R = H
b, R = Me
11a, R = 4
b, R = Me
12
H
C
13
CH$_2$
14
Me
15

Scheme 5



Scheme 6



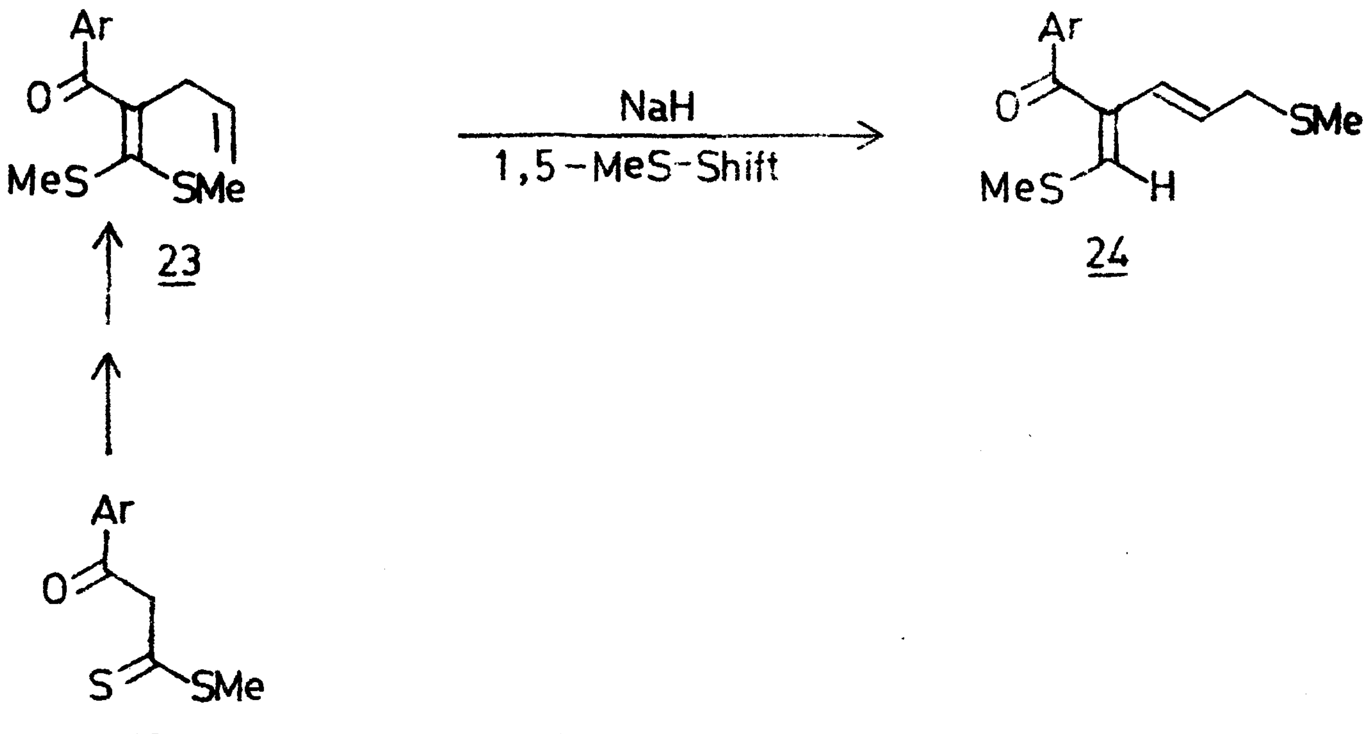
20, 21a, R = Me or Et; R'=H

b, R = Me; R'= C_6H_5

Scheme 7

A detailed mechanistic study on this rearrangement has been published recently.[43] In the present investigation, we have further extended these studies to allyl ketoketen S,S-acetals of general structure 23, which undergo base catalysed 1,5-MeS shift to give diene 24 (Scheme 8). These results have been discussed in chapter V.

For the synthesis of S,N-propargylacetals 17 (Scheme 6), and dithioacetals 23 (Scheme 8), α-oxodithioesters 16 were required as precursors. A survey of the literature revealed that there are no general straightforward synthetic routes available for the preparation of β-oxodithioesters. During the course of these investigations, a facile general method for the preparation of β-oxodithioesters was developed[44] by methylthiothiocarbonylation of active methylene ketones using dimethyltrithiocarbonates. These results and a brief review on the methods of preparations of dithioesters are described in chapter II.



Scheme 8

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CHAPTER II

REACTION OF ACTIVE METHYLENE KETONES WITH DIMETHYL TRITHIOCARBONATE : A FACILE ONE STEP SYNTHESIS OF β-OXODITHIOESTERS*

II. 1. INTRODUCTION

During the course of present investigation, a series of dithioesters were required for further transformations. These dithioesters are important intermediates which can be used to prepare the corresponding symmetrical and unsymmetrical keten S,S-acetals and thioamides. Recently, a series of studies on reactions of Grignard reagents with dithioesters have been published[1-5] and these reactions have been used in the synthesis of natural products. Similarly Michael addition of dithioesters on α,β-unsaturated ketones have been recently published.[6] The literature survey at this stage on dithioesters revealed that the methods described for their preparations were not found to be particularly useful for our studies and a convenient general method for the preparation of β-oxodithioesters was successfully developed in our laboratory, which is described in this chapter. A brief review on the literature methods of preparation of dithioesters is also described.

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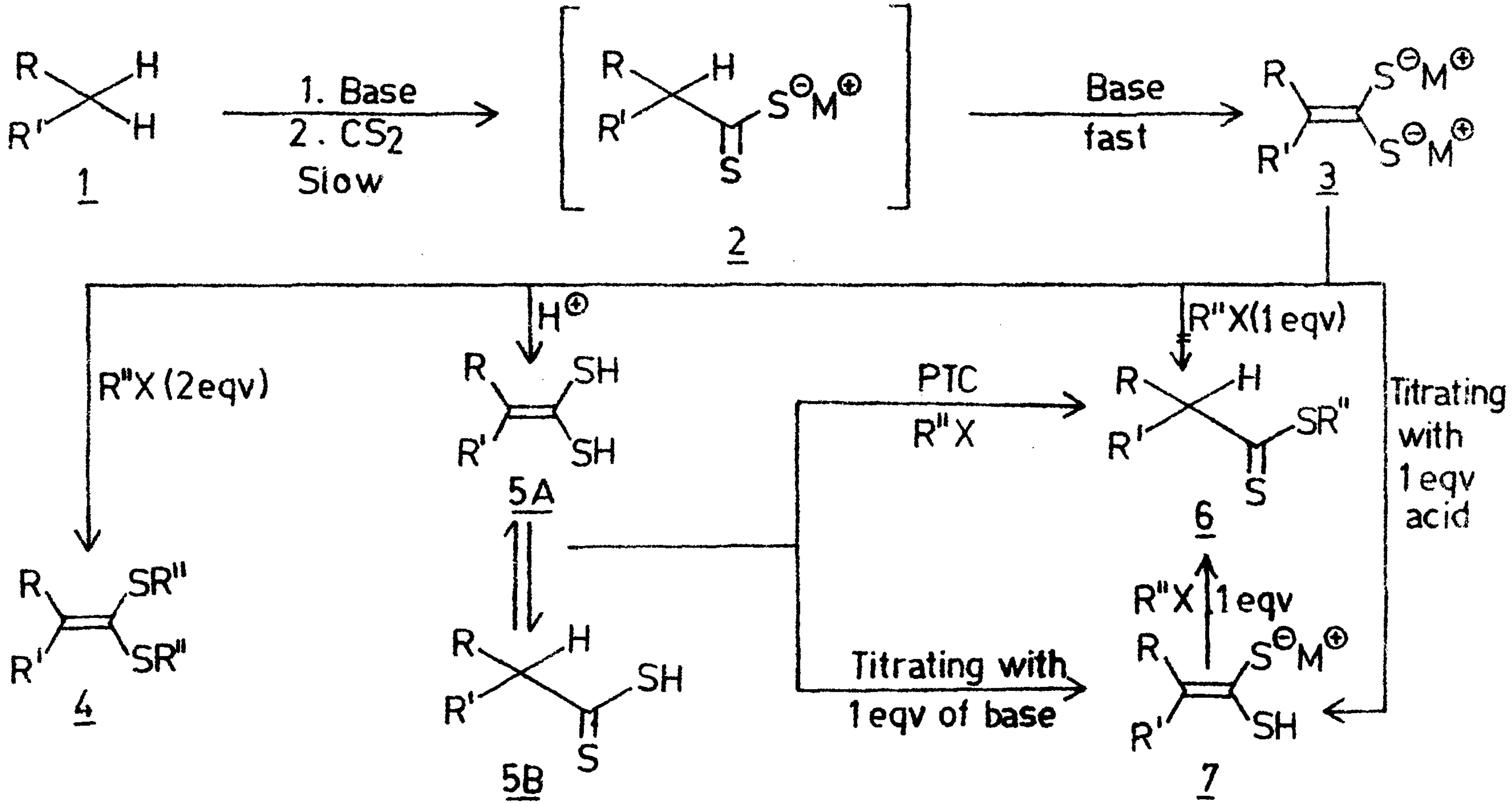
[*] G. Singh, S. S. Bhattacharjee, H. Ila and H. Junjappa, Synthesis 693 (1982).

II. 2. A BRIEF REVIEW ON THE METHODS OF PREPARATIONS OF DITHIOESTERS

II.2.1 Dithioesters via monoalkylation of dimetallic salts of dithioacids

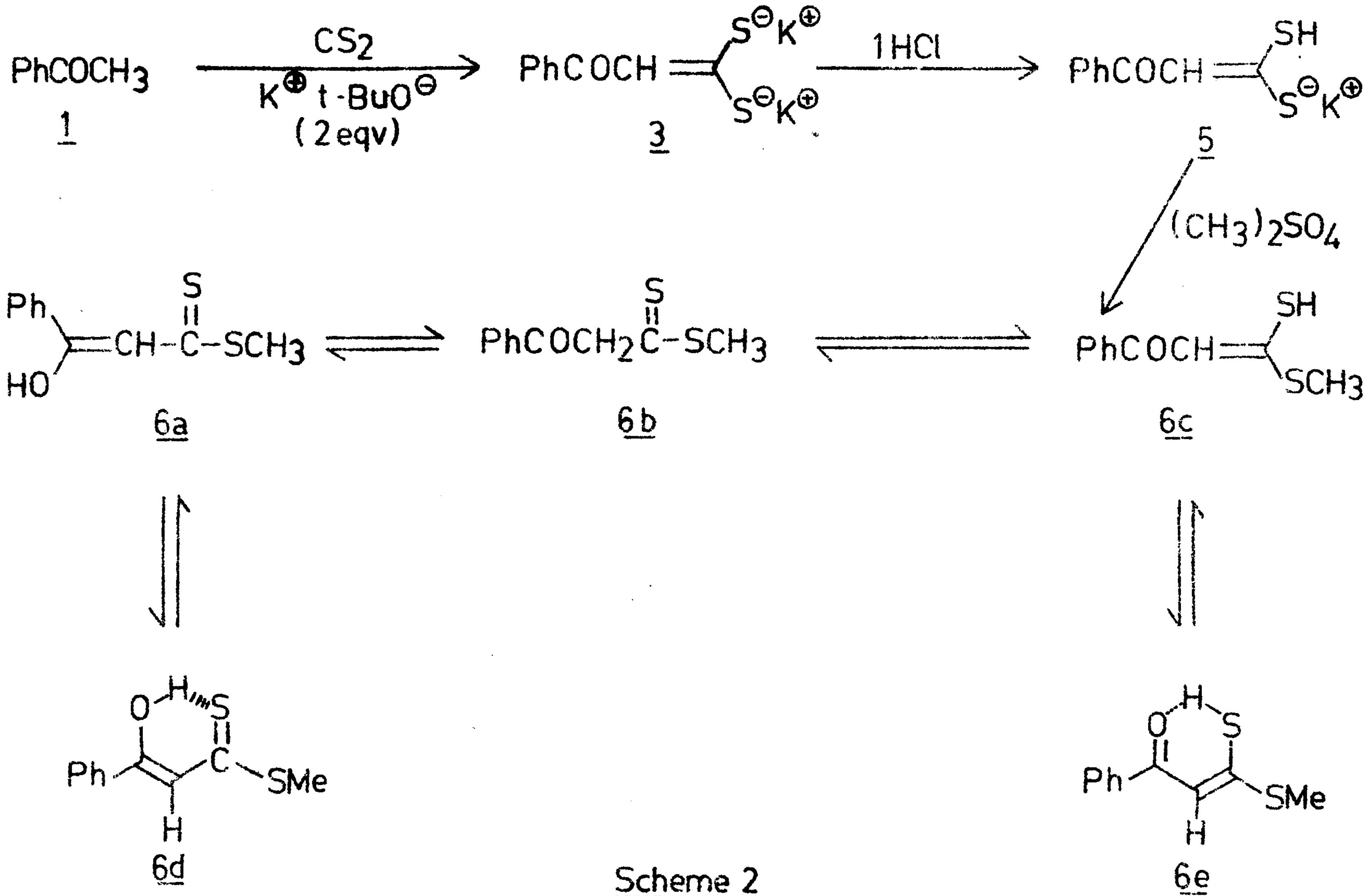
Attempted monoalkylation of dithiolate anion 3 derived from reaction of active methylene compounds with carbon disulfide in the presence of two equivalents of base have posed some experimental difficulties in the past. Direct alkylation of the dianion 3 using one equivalent of alkylating agents yielded only the corresponding S,S-acetals 4 and no trace of dithioesters 6 was detected (Scheme 1).

Gompper and co-workers[7] have attempted the direct monoalkylation of the dianion salt 3 by treating it with one equivalent of dimethylsulfate. They followed a rapid titration of 3 with one equivalent of hydrochloric acid, followed by alkylation with one eqv. of alkyl halide to yield the corresponding dithioester 6 in moderate yields. However subsequent experiments of monoalkylation of 3 (Scheme 1) to give 6 by Lawesson and co-workers[8] have shown that a mixture of 4 and 6 are invariably formed. The same authors have reported[9] the preparation of dithioesters through dianion salt 3 (Scheme 2) derived from acetophenone. The dianion salt 3 was first titrated with one equivalent of hydrochloric acid presumably to get the monosalt 5, which was subsequently alkylated with dimethylsulfate to give the corresponding dithioester 6 in 48% yield. The various tautomeric forms of dithioesters are shown in the scheme 2.



R = Electron with drawing groups such as CN, $-\underset{\underset{O}{\|}}{C}-H$, $-\underset{\underset{O}{\|}}{C}-O$ Alkyl , $-\underset{\underset{O}{\|}}{C}-$Alkyl, $-\underset{\underset{O}{\|}}{C}-$Aryl.
R' = H, alkyl, aryl or any one of R
R" = Alkyl groups

Scheme 1



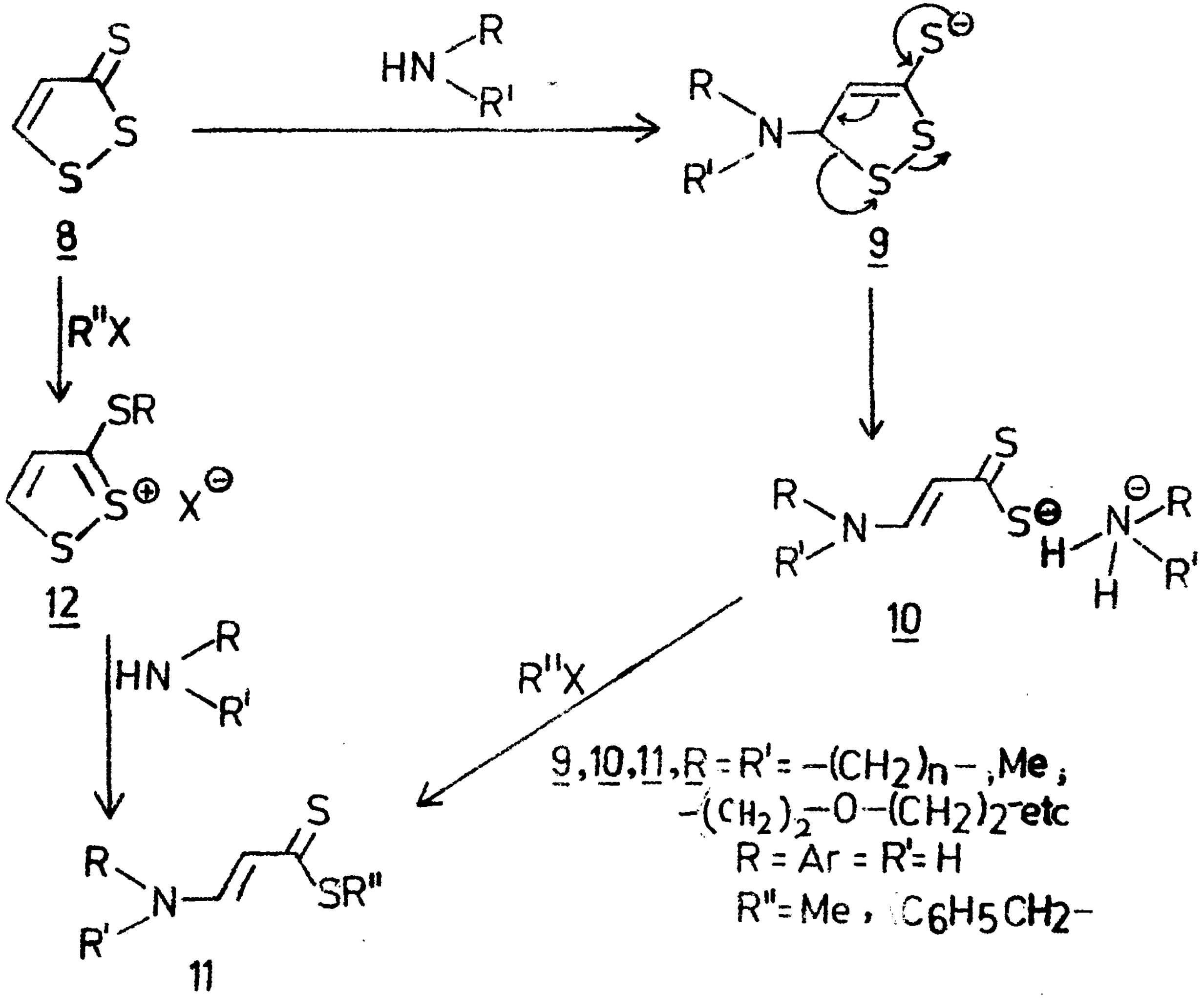
Scheme 2

II. 2.2 Preparation of α,β-unsaturated dithioesters by trithione method

The title compound (3H-1,2-dithiol-3-thione) 8 which is generally called trithione is reported to react with alkylhalides to give the corresponding S-alkyltrithionium salt 12 (Scheme 3) in good yields. Smutny and associates[10] have studied the reactions of trithione 8 with primary and secondary amines, which gave the unsaturated salts 10 and subsequent alkylation of 10 produced 3-aminodithioacrylic esters 11. The S-alkylthionium salt 12 is reported[10] to react with primary and secondary amines to give directly the corresponding α,β-unsaturated dithioesters 11 in a similar way. The method is useful only for β-amino α,β-unsaturated dithioesters. The mechanism for the formation of 3-aminodithioacrylic esters 11 from 8 is shown in the scheme 3. The adduct 9 formed by the Michael addition of amine to trithione 8 suffers cleavage with sulfur extrusion to form the corresponding salt 10, which is subsequently alkylated. No carbon nucleophiles have been used to prepare the α,β-unsaturated dithioesters by this method.

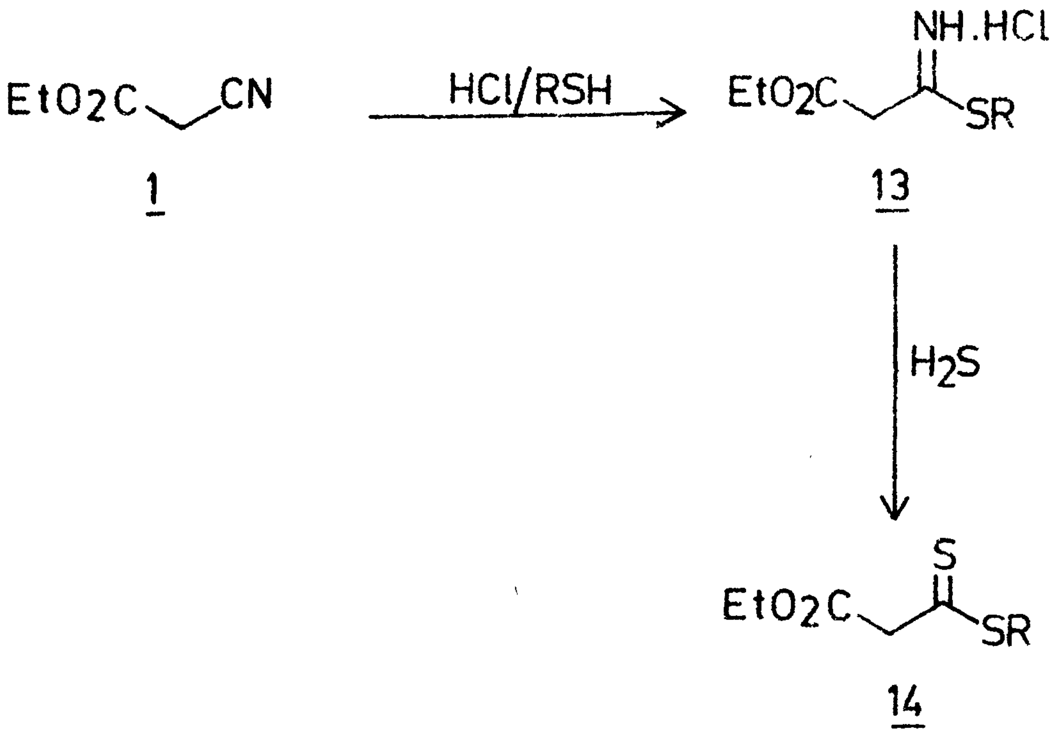
II. 2.3 By addition of mercaptans to nitriles

The dithioesters[11] have also been prepared by reacting nitriles 1 (Scheme 4) with appropriate mercaptans in the presence of acid to give initially the immonium salts 13, which on subsequent treatment with hydrogen sulfide gave dithioesters 14 in good yields. The method requires a cyano group in the active methylene compounds.



$\underline{9}$, $\underline{10}$, $\underline{11}$, $\underline{R}$ = R' = $-(CH_2)_n-$, Me;
$-(CH_2)_2-O-(CH_2)_2-$etc
R = Ar = R' = H
R'' = Me, $C_6H_5CH_2-$

Scheme 3



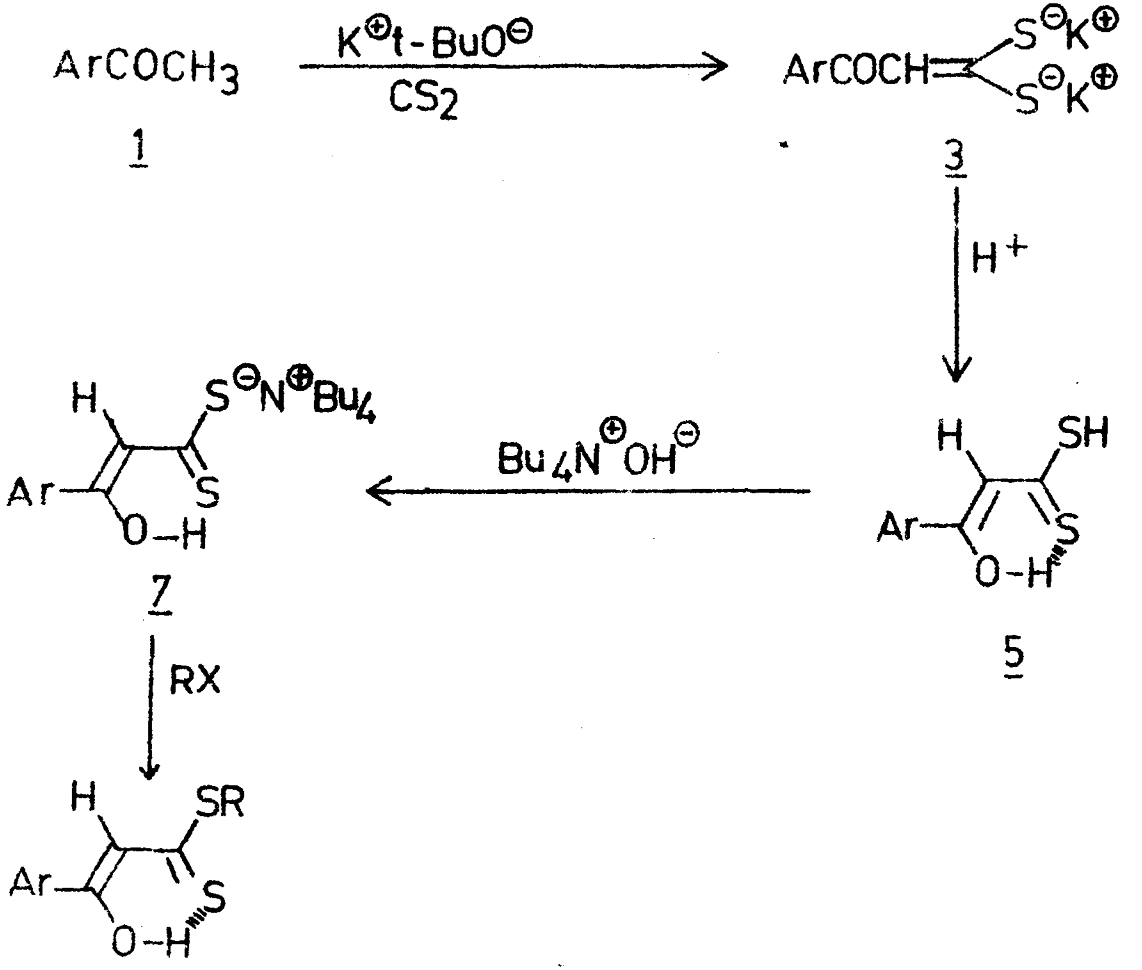
Scheme 4

II.2.4 By use of phase transfer catalyst: Ion pair extraction technique

Larsson and Lawesson,[12] in 1972, have developed an alternative method to prepare β-hydroxydithiocinnamicesters 6 (Scheme 5) from dithiolate salts 3. The dithiolate salts were first acidified to get β-hydroxydithiocinnamic acids 5 which on treatment with tetra-n-butylammoniumhydrogensulfate, a phase transfer catalyst, followed by alkylation with methyliodide afford the desired dithioesters 6 in high yields. However, the method requires prior isolation of dithioacids 5 which are found to be unstable[13] in many cases, thus limiting the scope of the method. They have further demonstrated[12] that the dithioesters 6 are important intermediates for the preparation of unsymmetrical keten S,S-acetals.

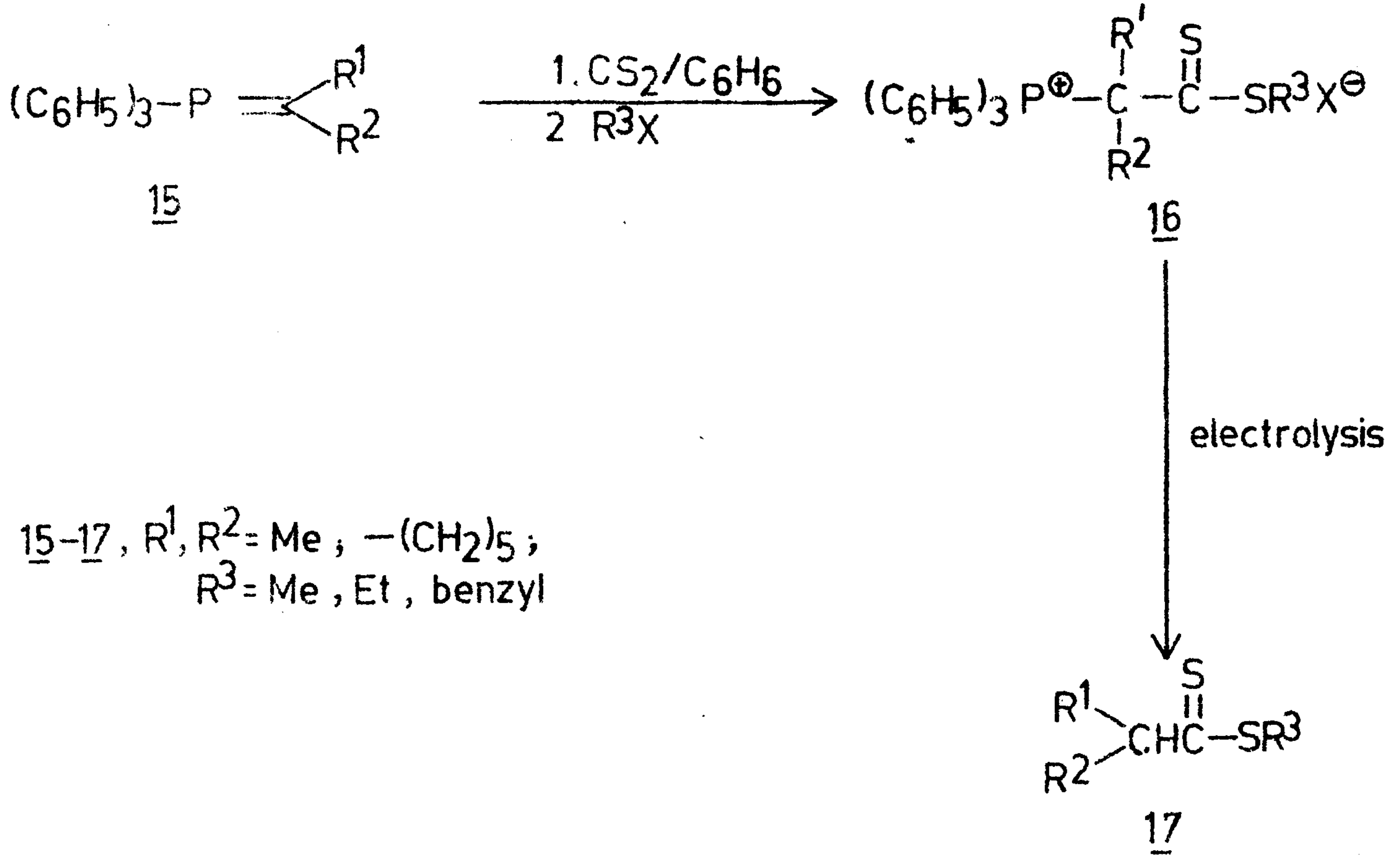
II.2.5 Dithioesters through addition of ylides and Grignard reagents to carbon disulfide

The phosphorane[14] 15 (Scheme 6) derived from the corresponding salt is shown to condense with carbon disulfide to give the dithionate salt which is further alkylated to give the corresponding phosphonium salt 16. The salts 16 on electrolysis gave the dithioesters 17 in 71-75% yield. Kröhnke and Gerlach[15,16] have reported the reactions of pyridinium phenacylid 18 with carbon disulfide to give ethanedithioacid pyridinium betaine 19 which on subsequent alkylation and cleavage gave the pyridinium salts 20.



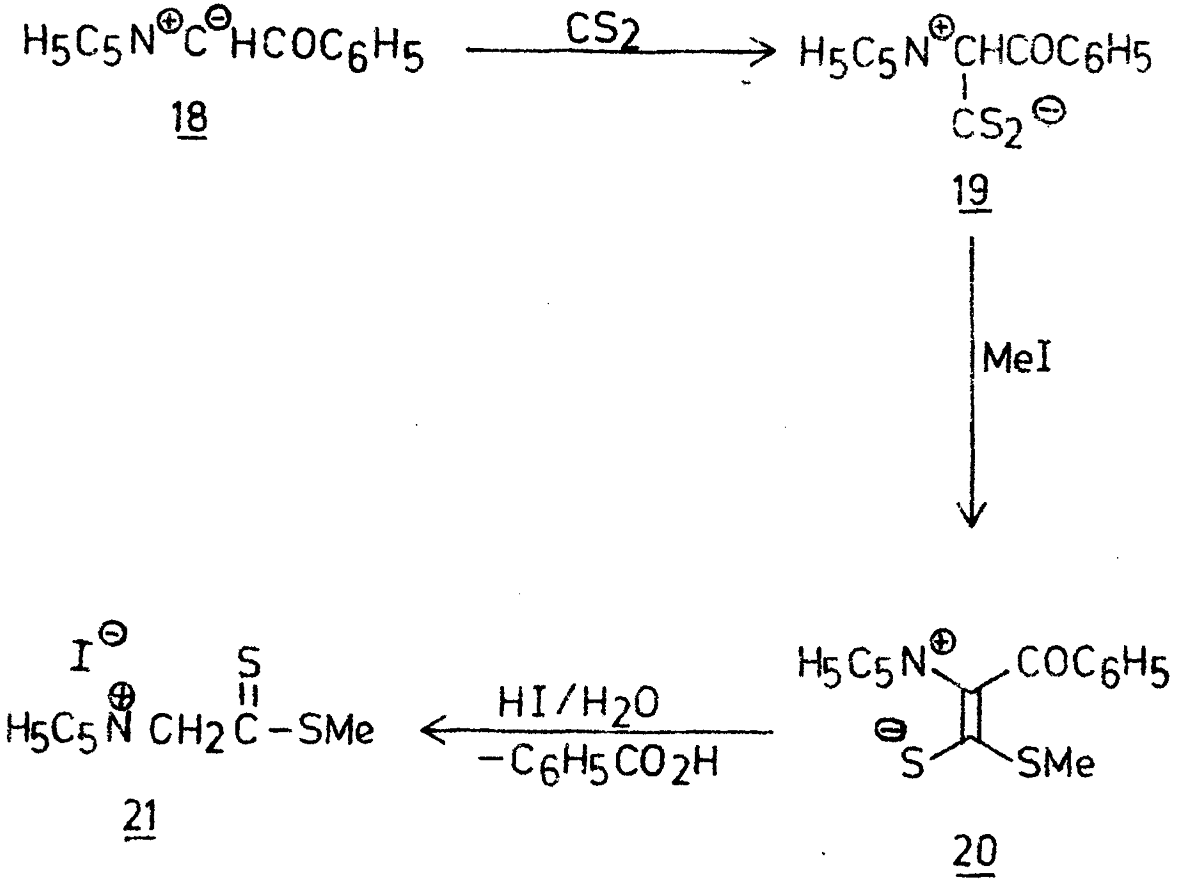
6, Ar = C_6H_5, p MeOC_6H_4; pClC_6H_4; p-BrC_6H_4;
R = Me, Et, n-pr; i-pr; $CH_2-CH=CH_2$; CH_2CO_2Et etc

Scheme 5



$\underline{15}$–$\underline{17}$, $R^1, R^2 = Me$; $-(CH_2)_5$;
$R^3 = Me$, Et , benzyl

Scheme 6


$H_5C_5N^{\oplus}C^{\ominus}HCOC_6H_5$
18
CS2
$H_5C_5N^{\oplus}CH(CS_2^{\ominus})COC_6H_5$
19
MeI
20
HI/H2O
−C6H5CO2H
$I^{\ominus}$ $H_5C_5N^{\oplus}CH_2C(=S)-SMe$
21

Scheme 7

(Scheme 7). Debenzoylation of 20 yielded the corresponding α-pyridinium dithioacetate 21.

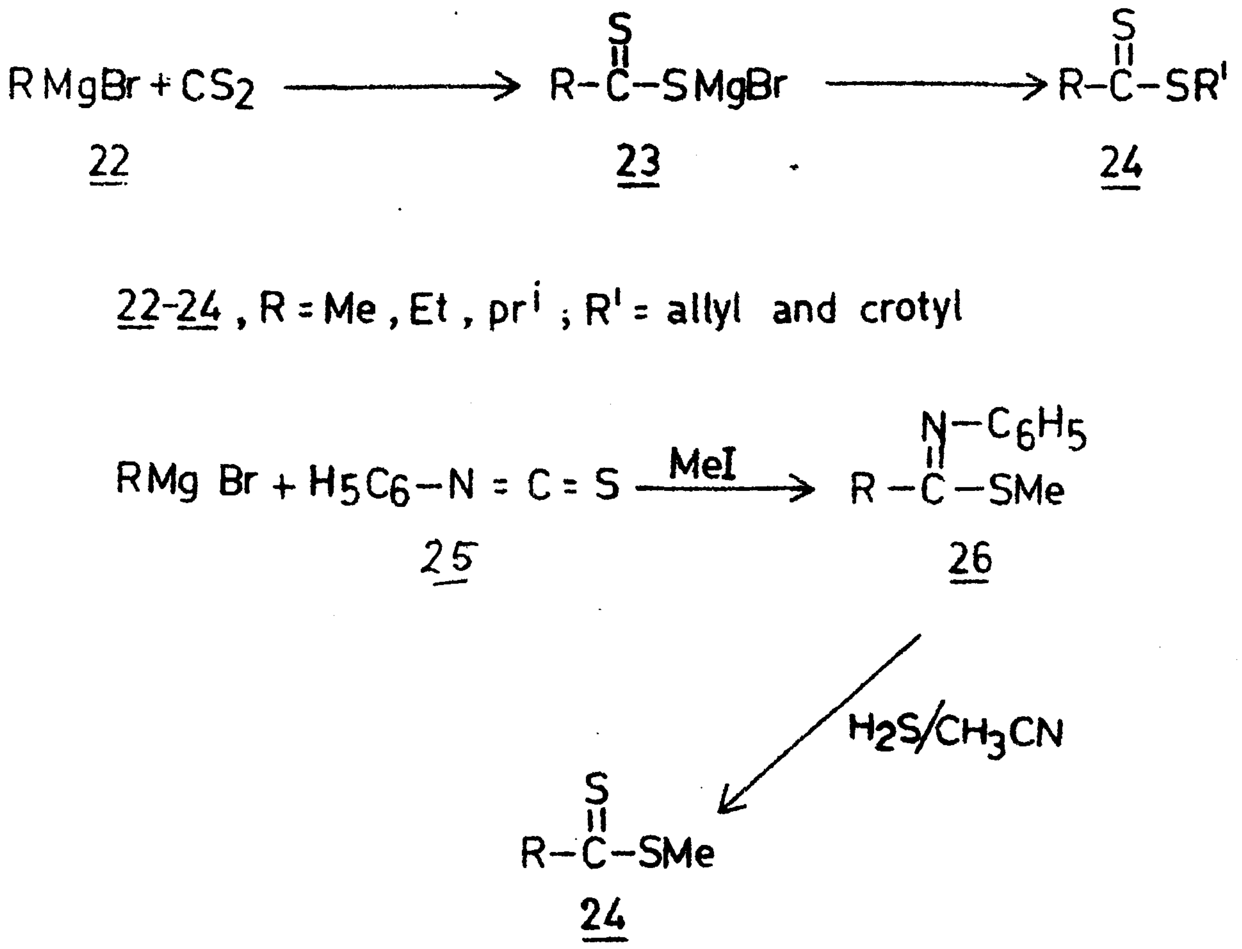
Brandsma and co-workers[17] have reported the synthesis of dithioesters (Scheme 8) by reacting Grignard reagents 22 derived from the corresponding haloalkanes with carbon disulfide followed by alkylation (Scheme 8).

Thullier[18] has reported synthesis of saturated dithioesters by reacting Grignard reagents with phenyl isothiocyanate followed by treatment of resulting thioimidates 26 with hydrogen sulfide (Scheme 8).

In an another report,[19] the Grignard reagents were first reacted with cuprous halide to get the corresponding organocuprates, which were reacted with carbon disulfide and methyl iodide subsequently to give the corresponding dithioesters in good yields.

II. 2.6 Synthesis of dithioesters from aliphatic carboxylic acids

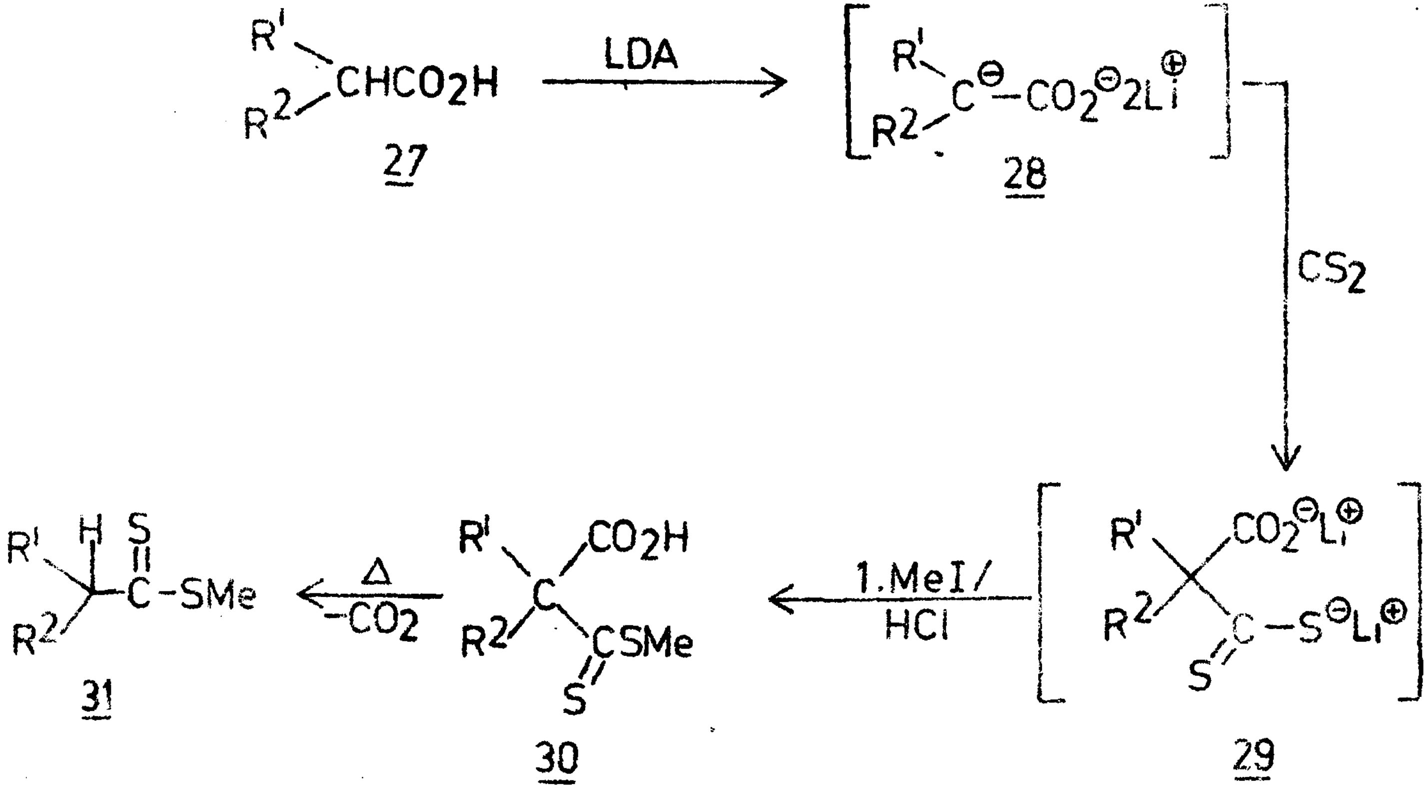
The carboxylic acids 27 (Scheme 9) were converted[20] to the corresponding dilithium salts 28 by treatment with butyl lithium in diisopropylamide and the resulting 28 were condensed with carbon disulfide to yield the corresponding lithium dithiolate salts 29. These salts 29 were then alkylated to give the corresponding dithioesters 30 in 77-78% yield. The carboxylic acids 30 were then subjected to decarboxylation to yield the corresponding dithioesters 31 in good yields (Scheme 9).



22-24, R = Me, Et, pr^i; R' = allyl and crotyl

R = Me, Et, pr^i, Bu^t

Scheme 8



27 – 31, $R^1 = C_7H_{15}$, $C_{14}H_{29}$
$R^2 = H, Me$

Scheme 9

II. 2.7 1,1-Dichloro-2,2-disubstituted ethenes as precursors for dithioesters

The dichloroethenes 32 (Scheme 10) have been shown to undergo facile displacement with tetraethylammonium thioate to give the corresponding salts 33. These salts on rapid addition of methyl iodide at room temperature yielded the corresponding dithioesters[21] 24 in good yields. However when the alkyl halide was added slowly at -15°, a mixture of both dithioesters and dithioacetals was formed.

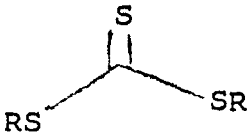
II. 2.8 Dithioesters from dithioacids

Recently,[22] dithioesters have been prepared by Markownikoff's addition of dithioacids to olefins containing electron donating groups. It is pertinent to note that monothioacids add to olefins in anti-Markownikoff's mode (Scheme 11).

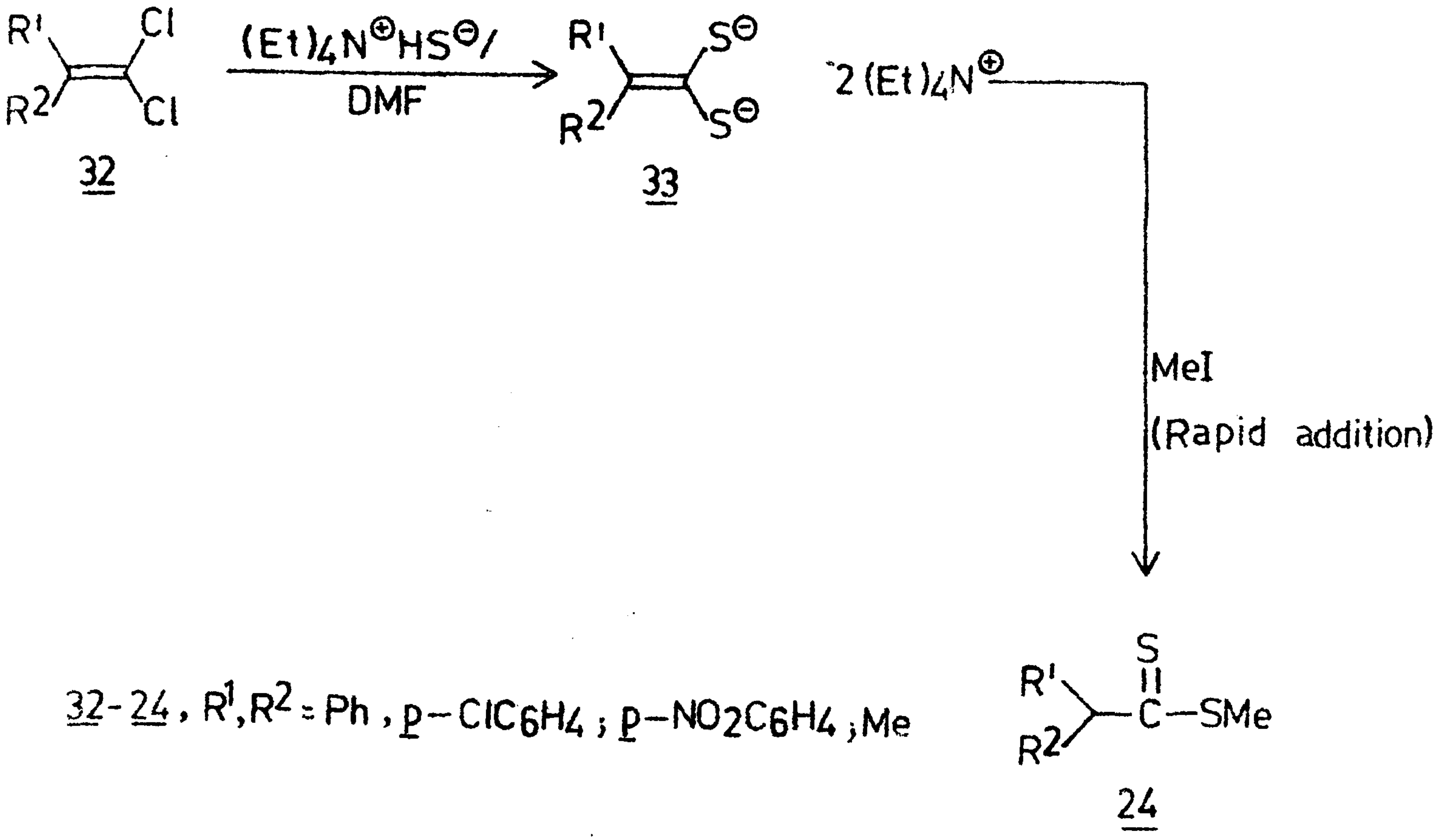
II. 2.9 Trithiocarbonate method

Dialkyl carbonate 36 has been used extensively in organic synthesis to introduce alkoxycarbonyl group in active methylene compounds. Despite a large number of references[23] found in the

36

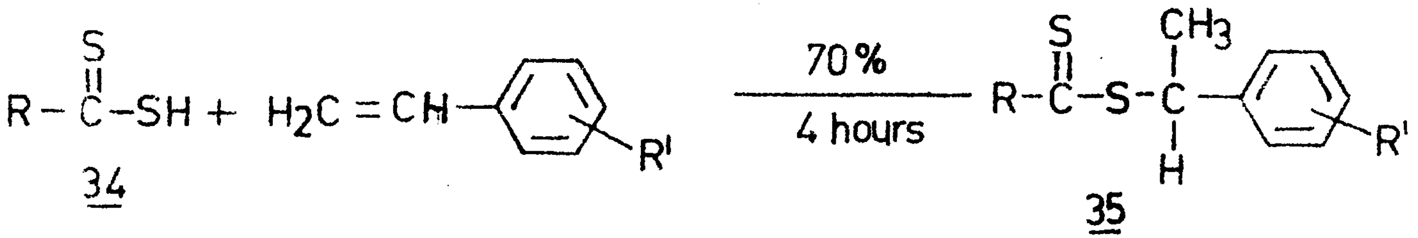


37



32-24, R^1, R^2 = Ph, p-ClC$_6$H$_4$; p-NO$_2$C$_6$H$_4$; Me

Scheme 10



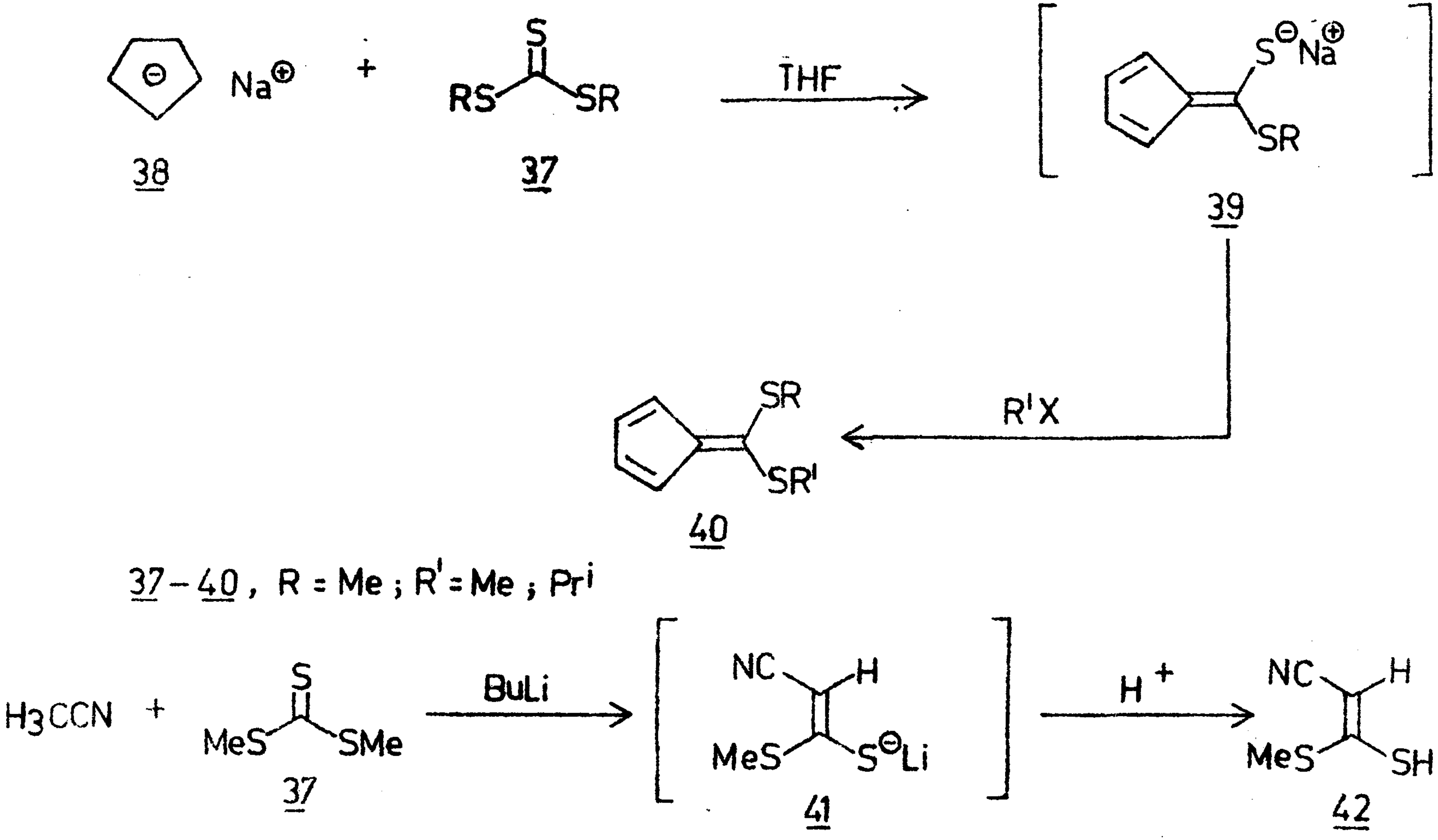
35, R' = electron donating group

Scheme 11

literature on alkoxycarbonylation through dialkylcarbonates, the corresponding dialkyltrithiocarbonates 37 appears to have not been seriously considered for alkylthiothiocarbonylation of active methylene compounds under similar reaction conditions. There are few sporadic[24,25,26] attempts to use this method for the synthesis of dithioesters. Thus Hartke and co-workders[26] have successfully introduced alkylthiothiocarbonyl group by treating sodium salt of cyclopentadiene 38 (Scheme 12) with 37. Similarly, acetonitrle underwent methylthiothiocarbonylation[25] with 37 in the presence of butyllithium to give 41 (Scheme 12). Recently, Japanese group has reported[27] that dimethyl sulfoxide underwent condensation with trithiocarbonate in the presence of n-butyllithium to give the corresponding dithioesters. There is only one method[28] described in the patent literature having extended this trithiocarbonate method to few ketones like acetone, 1-napththylmethyl ketone in the presence of base like sodamide to yield the β-oxodithioesters in unspecified yields.

II. 3 REACTIONS OF ACTIVE METHYLENE KETONS WITH DIMETHYLTRITHIOCARBONATES : A FACILE ONE STEP SYNTHESIS OF METHYL β-OXODITHIOCARBOXYLATES

From the above discussion on the reported methods of preparation of dithioesters from various active methylene compounds, it is apparent, that not a single method described has been shown to be of general synthetic application. In the present investigation



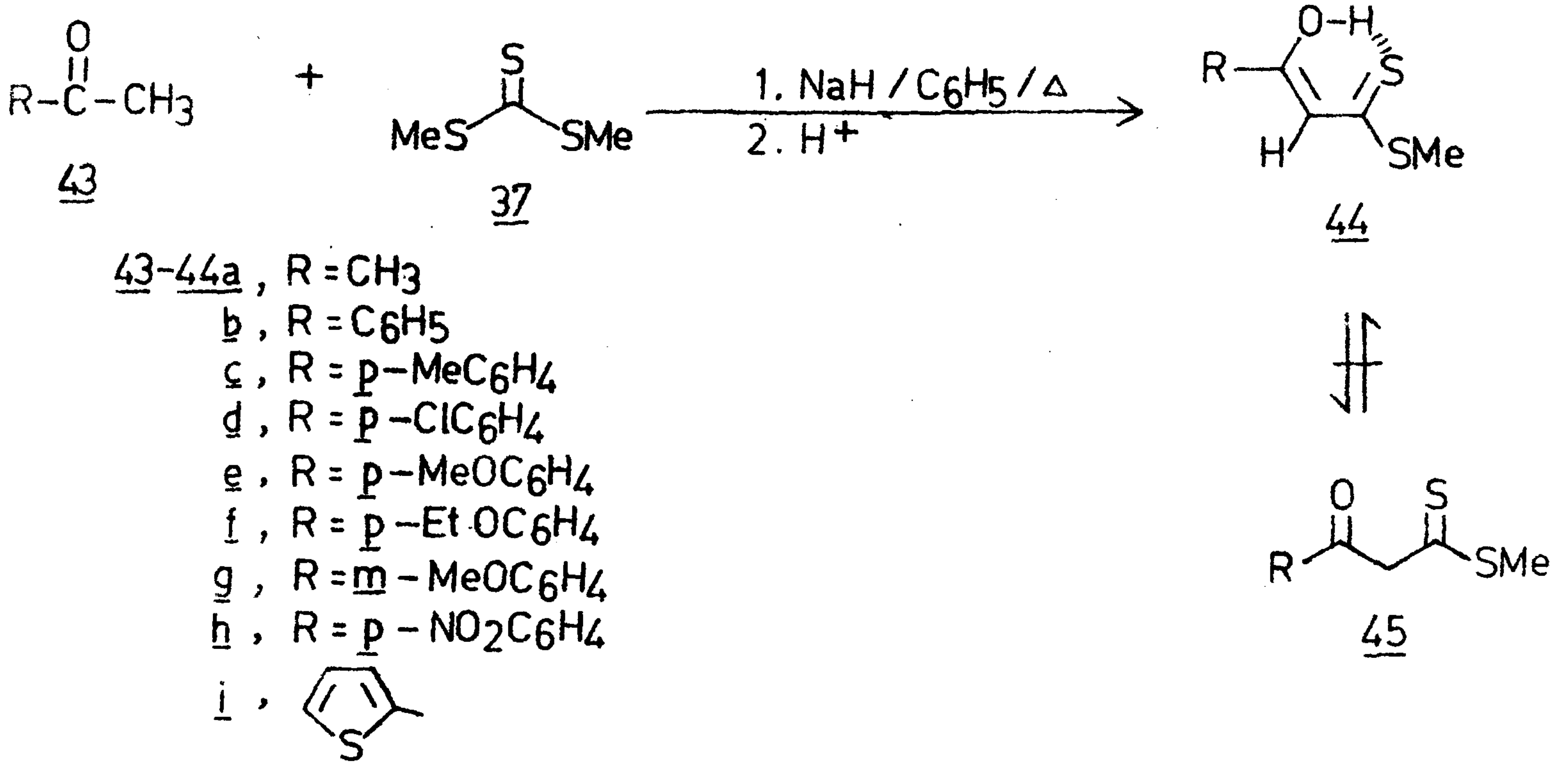
$\underline{37}$ – $\underline{40}$, R = Me ; R' = Me ; Pr^i

Scheme 12

a large number of β-oxodithioesters were required for the preparation of thioamides and unsymmetrical keten S,S-acetals and it was considered appropriate to explore the use of easily available dimethyltrithiocarbonate for introducing methylthiothiocarbonyl group in active methylene ketones.

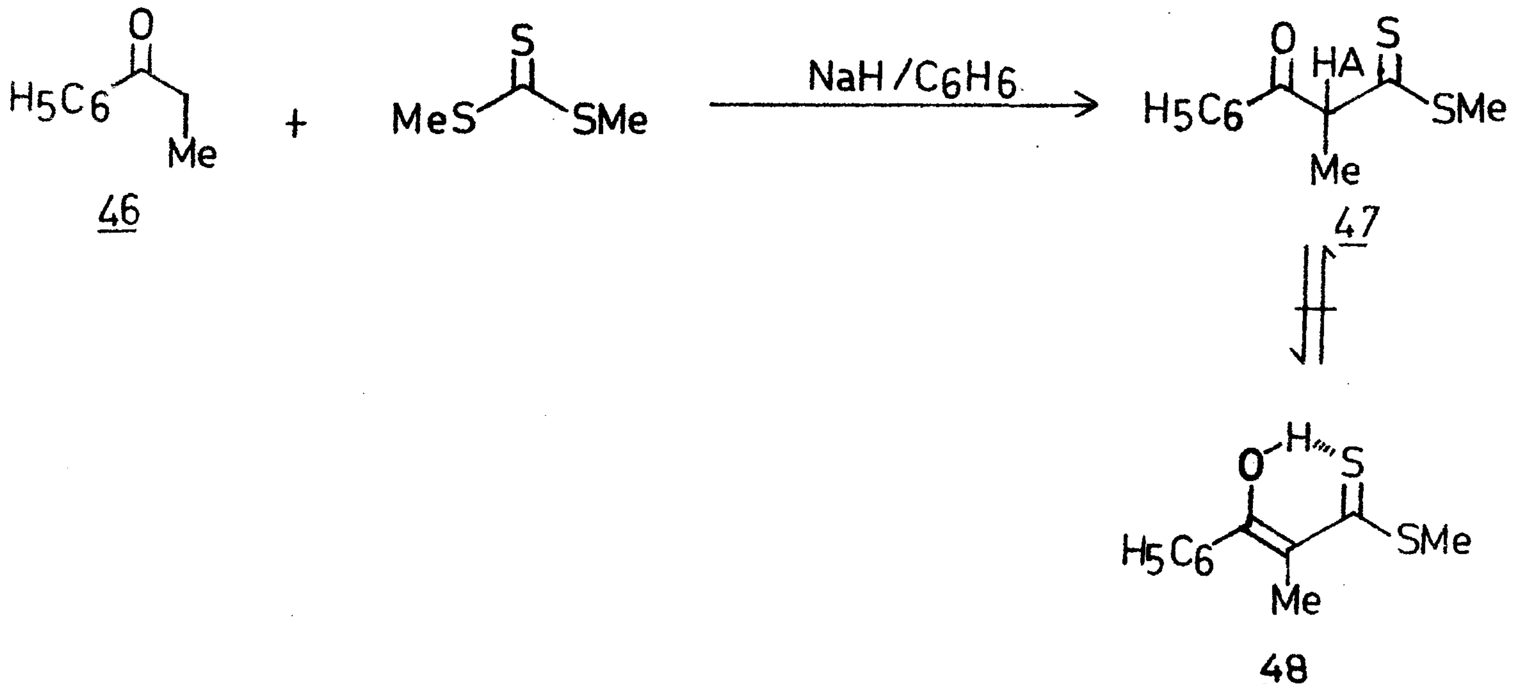
II. 4.1 RESULTS AND DISCUSSIONS

When acetone (43a) was reacted with dimethyltrithiocarbonate in the presence of sodium hydride in refluxing benzene, the corresponding methyl-β-hydroxydithioacrylate (44a) was obtained in 40% yield (Scheme 13). The dithioester 44a was prepared earlier[28] using sodamide in place of sodium hydride to afford 44a in unspecified yields. The spectral and analytical data of 44a were in conformity with the assigned structure. Thus 44a was analysed for $C_5H_8OS_2$ and its i.r. spectrum exhibited absorption bands at 1215, 1560 and 1580 cm^{-1} due to thiocarbonyl group and enol double bond respectively. Its NMR spectrum ($CDCl_3$) showed singlet (3H) at δ 2.0 due to methyl group, while another singlet (3H) at δ 2.52 was assigned to S-Me group. The vinyl proton of 44a appeared as singlet (1H) at δ 6.18, while the proton at δ 15.0, which was exchanged with deuterium oxide, was attributed to the enolic OH proton. Similarly, when acetophenone 43b was reacted with dimethyltrithiocarbonate under identical conditions, the corresponding methyl β-hydroxydithiocinnamate (44b) was obtained in 60% yield. This


43
37
1. NaH / C6H5 / Δ
2. H+
44
45
43-44a , R = CH3
b , R = C6H5
c , R = p-MeC6H4
d , R = p-ClC6H4
e , R = p-MeOC6H4
f , R = p-EtOC6H4
g , R = m-MeOC6H4
h , R = p-NO2C6H4
i ,

Scheme 13

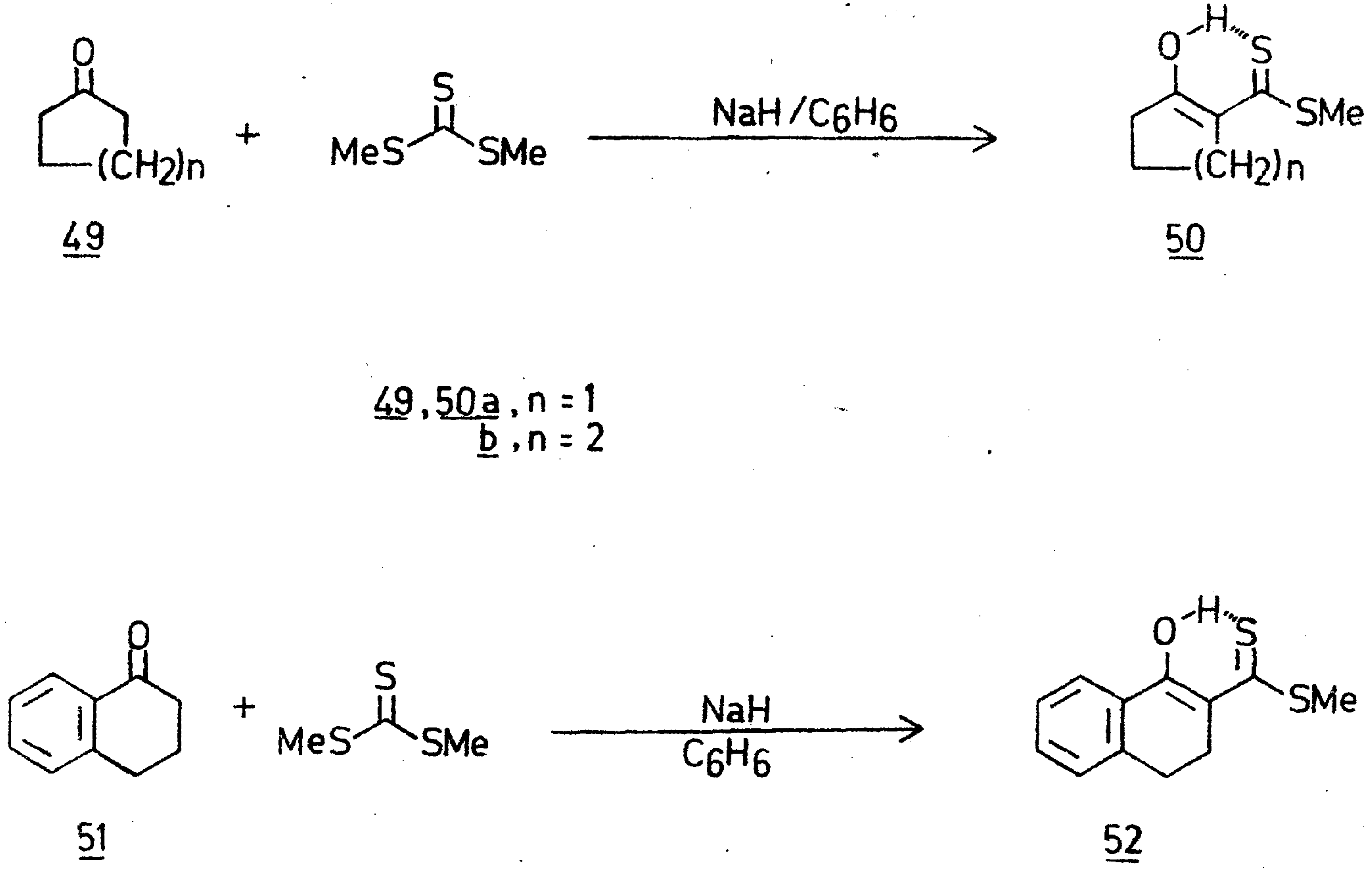
dithioester 44b was also prepared by Larsson and Lawesson in 46% yield using ion pair extraction method.[12] The present method therefore appears to be more efficient than ion pair extraction technique. Similarly the earlier reported[12] dithioesters 44c and 44d were prepared in 62% and 65% yields respectively under identical conditions. The dithioesters 44c and 44d were obtained by ion pair extraction technique in 39% and 72% yields respectively, while the yield of 44d is comparable with that of ion pair technique, but 44c is definitely obtained in much higher yield by the present method. The dithioesters 44e-i, which were hitherto unknown were similarly prepared under identical conditions in 52-57% overall yields (Scheme 13). All the dithioesters were characterized with the help of spectral (Table 1) and analytical data (Table 2). The i.r. spectra of dithioesters 44b-i showed characteristic C=S band at 1225-1260 cm^{-1}, while the absence of absorption band due to aromatic carbonyl group and the presence of enolic double bond (1555-1580 cm^{-1}) shows that dithioesters exist completely in enol tautomeric form 44. The presence of signal due to vinyl protons at δ 6.1-6.88 and enolic OH proton at δ 14-15 further supports the tautomeric structure 44. No trace of the presence of β-oxostructure 45 in the N.M.R. spectra of 44a-i was detected. When the method was extended to propiophenone (46), the corresponding β-oxodithioester 47 was obtained (Scheme 14) in 61% yield under similar reaction conditions. It is interesting to note that the dithioester



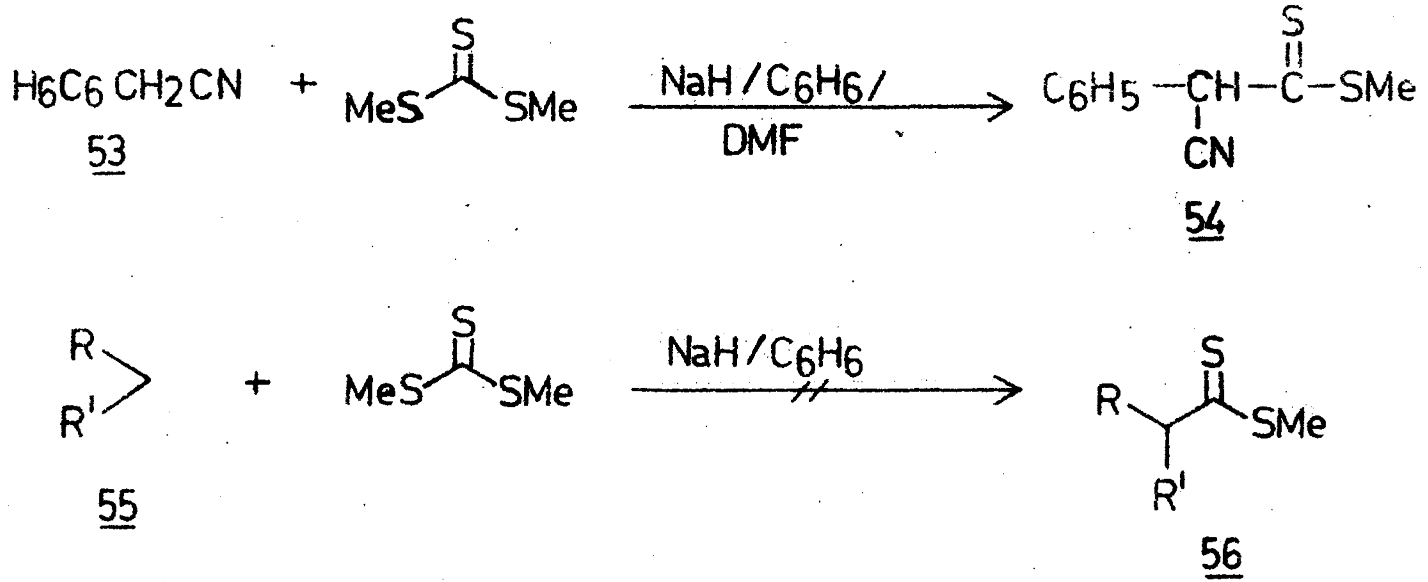
Scheme 14

47 exists purely in ketoform since its IR spectrum showed strong absorption band at 1690 cm^{-1} due to aromatic carbonyl group (Table 1). The presence of a quartet (1H) at δ 5.15 due to methine proton (H_A) and doublet (3H) at δ 1.55 due methyl proton further confirmed the tautomeric structure 47, while no trace of enol tautomer 48 was detected in its NMR spectrum. The cyclic ketones 49a and 49b underwent smooth methylthiothiocarbonylation under similar conditions to yield the corresponding dithioesters 50a and 50b in 57% and 65% yields respectively (Scheme 15). However, under these conditions, 1-tetralone 51 gave the corresponding dithioester 52 in 24% [illegible] only and the yield could not be increased further under varying conditions. The NMR and IR spectra of 50a-b and 52 (Table 1) indicated that they exist in enolic forms.

When phenylacetonitrile was reacted with trithiocarbonate under similar conditions the corresponding methyl α-cyanophenyldithioacetate 54 was obtained in low yields. However, 45% yield of 54 was obtained by carrying out the reaction in benzene and dimethylformamide. The structure of 54 was confirmed with the help of spectral and analytical data (Table 1 and 2). When this methylthiothiocarbonylation method was extended to other active methylene compounds like nitromethane (55a), diethylmalonate (55b), ethylcyanoacetate (55c) and malononitrile (55d), only the polymeric materials were obtained, from which no trace of corresponding dithioesters 56 (Scheme 16) could be obtained.



Scheme 15



55,56a , R = NO_2 ; R = H
b , R = R' = CO_2Et
c , R = CN , R' = CO_2Et
d , R = R' = CN

Scheme 16

TABLE 1

Spectral data for the products 44a-i, 47, 50a-b, 52 and 54.

Product	M.S. m/e(M^+)	I.R. (Nujol) cm^{-1}	^{1}H-N.M.R.(CCl_4/TMS ppm
44a	148	1215, 1560, 1580[a]	2.0 (s, 3H, $C\underline{H}_3$); 2.52 (s, 3H, $SC\underline{H}_3$); 6.18 (s, 1H_{olefin}); 15.0 (s, 1H, O$\underline{H}$).
44b	210	1230, 1555, 1580	2.60 (s, 3H, $SC\underline{H}_3$); 6.90 (s, 1H_{olefin}); 7.40 (m, 3H_{arom}); 7.8 (m, 2H_{arom}).
44c	224	1225, 1560, 1585	2.35 (s, 3H, $C\underline{H}_3$); 2.60 (s, 3H, $SC\underline{H}_3$); 6.90 (s, 1H_{olefin}); 7.0-7.9 (A_2B_2, 4H_{arom}).
44d	244,246	1230, 1560, 1585	2.60 (s, 3H, $SC\underline{H}_3$); 6.85 (s, 1H_{olefin}); 7.25-8.0 (A_2B_2, 4H_{arom}).
44e	240	1220, 1555, 1580	2.60 (s, 3H, $SC\underline{H}_3$); 3.74 (s, 3H, p-$CH_3OC_6H_4$); 6.88 (s, 1H_{olefin}); 6.85-7.8 (A_2B_2, 4H_{arom}); 15.12 (s, 1H, OH).

Thus trithiocarbonate method yields β-oxodithioesters in moderate to good yields. The other method involving phase transfer catalysed (TBAH) monoalkylation of β-oxodithiocarboxylic acids requires prior preparation of these dithioacids, some of which derived from active methylene compounds are unstable.[13] The lack of interest in the chemistry of these dithioesters may primarily be due to nonavailability of efficient methods for their synthesis. The present methods offers a facile one step route for the preparation of β-oxodithioesters.

II.5 EXPERIMENTAL

M.ps. were determined on a "Boetius" (German) apparatus and are uncorrected. The IR spectra were recorded on Perkin-Elmer 297 spectrophotometer. The NMR spectra were recorded on a Varian EM-390 spectrometer using TMS as an internal standard and the chemical shifts are expressed in ppm from TMS taken as 0.00 (δ-units). Mass spectra were recorded on a Hitachi RMU-6E mass spectrometer fitted with a direct inlet system.

The Starting Materials

The commercial samples of acetone, acetophenone, *p*-methylacetophenone, *p*-chloroacetophenone, *p*-methoxy-acetophenone, *m*-methoxyacetophenone, *p*-ethoxyacetophenone, *p*-nitroacetophenone, phenylacetonitrile, propiophenone, cyclopentanone, cyclohexanone, 2-acetylthiophene, tetralone, nitromethane, diethylmalonate ethylcyanoacetate and malononitrile were purified before use.

Dimethyl trithiocarbonate was prepared by the modification of reported procedure.[29] To a solution of sodium sulfide (232g, 1.50 mol, 55%) in 400 ml of water, 152g (2.0 mol) of carbon disulfide was added slowly with stirring at room temperature. The reaction mixture was further stirred for 5 hrs at room temperature and the excess of carbondisulfide was removed by evaporation at reduced pressure to yield a deep red liquid which was cooled at 10-15°C. A solution of dimethylsulfate (94g, 0.75 mol) in 200 ml of benzene was added slowly with stirring to the cooled deep red liquid during 2.5 hr and the stirring was further continued for 1 hr at room temperature and 5 hrs at 60-70°C. The reaction mixture was further diluted with 750 ml of benzene and benzene layer dried (Na_2SO_4) and evaporated to give an orange residue which was distilled under vacuum, yield 120g (87%), bp 82-84°/9 mm (lit. 225/760 mm).[29]

General method for the preparation of β-oxodithioesters 44a-i, 47, 50a-b and 52

To a well stirred suspension of sodium hydride (50% suspension) 2.5g (0.05 mol) in 100 ml dry benzene, dimethyl trithiocarbonate (3.80g, 0.027 mol) was added and the mixture was refluxed with stirring for 10 minutes. A solution of the appropriate ketone (0.025 mol) in 50 ml dry benzene was slowly added dropwise to the refluxing reaction mixture over a period of 3.5-4 hrs, it was further refluxed for 2 hrs, cooled and poured over 250 ml ice-cold water. The aqueous layer was separated, washed with 200 ml benzene. The aqueous layer was cooled and acidified with 3N hydrochloric acid or 20% acetic acid (50a-b, 52) and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to give the β-oxodithioesters (single spot on TLC), which were pure enough ($>$95% purity by NMR) for further reactions. Further purification was achieved by column chromatography on silica gel using hexane as eluent. The preparation of compound 44a was carried out at 40-45°C because of lower boiling point of acetone. The dithioesters, 44a-i, 47, 50a-b, 52, thus prepared by this method have been fully characterised by spectral physical and analytical data given with tables 1 and 2, respectively.

Preparation of methyl phenylcyanodithioacetate (54)

Dimethyl trithiocarbonate, (4.0g, 0.029 mol) was added to a well stirred suspension of sodium hydride (50%) (2.9g, 0.06 mol) in 100 ml dry benzene and the mixture was refluxed with stirring for 15 minutes. A solution of phenylacetonitrile, (2.33g, 0.925 mol) in 50 ml dry dimethylformamide was added dropwise to the mixture at 80-90°C over 2 hrs and stirring at 80-90°C was continued for 8 hrs. The mixture was then poured into ice-cold water and extracted with chloroform. The crude product 54 was purified by column chromatography on silica gel using benzene as eluent. The spectral, physical and analytical data given in the table 1 and 2, respectively.

TABLE 2

Physical and Analytical data of the dithioesters 44a-i, 47, 50a-b, 52 and 54

Product	Yield [%]	M.P. [°C]	Molecular formula	Calc: Found	Analyses C	Analyses H	Analyses N
44a	(47)^{a}40	Viscous liquid	$C_5H_8OS_2$ (148.2)		40.48 40.72	5.39 5.59	-
44b	(71)^{a}60(46)^b	55-56^c	$C_{10}H_{10}OS_2$ (210)		57.14 57.58	4.76 4.52	-
44c	(65)^{a}62(39)^b	54-55	$C_{11}H_{12}OS_2$ (224)		58.92 59.20	5.35 5.66	-
44d	(87)^{a}65(72)^b	70-71	$C_{10}H_9ClOS_2$ (244.5)		49.07 49.29	3.68 3.90	-
44e	(65)^{a}62(55)^b	73^d	$C_{11}H_{12}O_2S_2$ (240.2)		54.95 55.31	4.99 4.75	-

Table 2 (Contd.)

44f	(69)^{a}57	88-89	$C_{12}H_{14}O_2S_2$ (254.3)	56.62 56.89	5.50 5.23	-
44g	(60)^{a}55	58-60	$C_{11}H_{12}O_2S_2$ (240.2)	54.95 54.66	4.99 5.34	-
44h	52	81	$C_{10}H_9NO_3S_2$ (255)	47.05 46.87	3.52 3.70	5.49 5.24
44i	(55)^{a}52	50-51	$C_8H_8OS_3$ (216.2)	44.40 44.09	3.70 3.97	-
47	(67)^{a}61	viscous liquid	$C_{11}H_{12}OS_2$ (224.2)	58.87 58.60	5.35 5.55	-
50a	(62)^{a}57	40-41	$C_7H_{10}OS_2$ (174.2)	48.22 48.54	5.74 5.46	-

Table 2 (Contd.)

50b	(72)[a]65	viscous	$C_8H_{12}OS_2$	51.00	6.37	-
		liquid	(188.2)	51.27	6.13	
52	(38)[a]24	76-77	$C_{12}H_{12}OS_2$	60.96	5.08	-
			(236.2)	61.19	4.32	
54	42	48-49	$C_{10}H_9NS_2$	57.91	4.34	6.75
			(207.2)	58.20	4.63	6.91

---

[a] Improved yield of dithioesters, when 0.04 mol of dimethyltrithiocarbonate and 0.07 mol of sodium hydride were taken instead of 0.29 mol and 0.07 of dimethyltrithiocarbonate and sodium hydride respectively.

[b] Yields of the product isolated by ion-pair extraction technique (Ref. 12).

[c] Lit.,[9] m.p. 57°C; [d] Lit.,[12] m.p. 75°C.

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CHAPTER III

REARRANGEMENT STUDIES ON S-PROPARGYL-N-AMINOACETALS : SYNTHESIS OF NOVEL 3-AROYL-2-(N-AZACYCLOALKYL)-4-METHYLTHIOPHENES.*

III. 1 INTRODUCTION

It has been shown[1-5] that allyl (or crotyl) aryl sulfides and aryl propargyl sulfides undergo thioclaisen rearrangement when heated in basic or acidic solutions. These studies have also been extended to allyl and propargyl thioethers derived from heterocyclic systems like quinoline[4] and thiophene[6] which yield products typical of thioclaisen rearrangement. Thus Lawesson and coworkers[6] have described that allyl and crotyl-2-thienylsulfide 1 undergo typical thioclaisen rearrangements to give products like 3-5 (Scheme 1), when heated in quinoline. In a series of investigations on synthesis and structures of enethiols derived from active methylene compounds, the same workers[7] had alkylated enethiols with allyl, crotyl, and propoargyl bromides to give the corresponding 3-alkylthio-crotonates 7 (E- and Z forms R=Me) and ethyl

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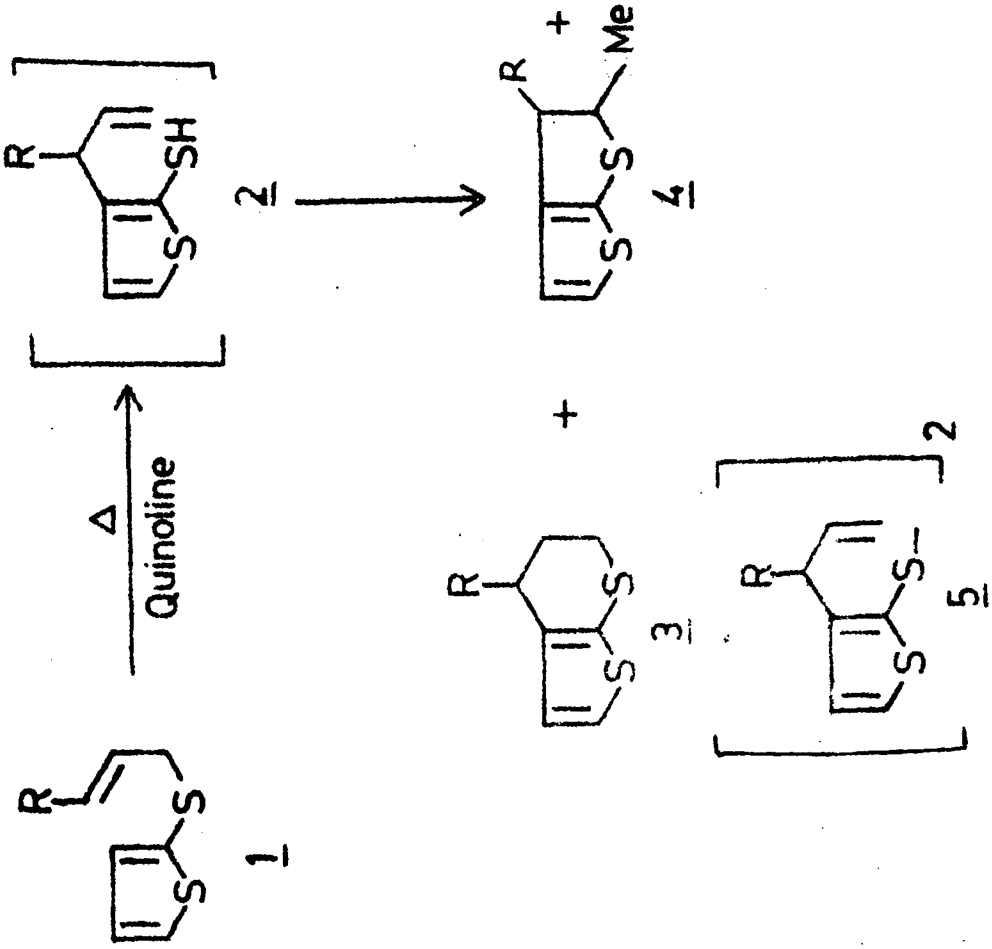
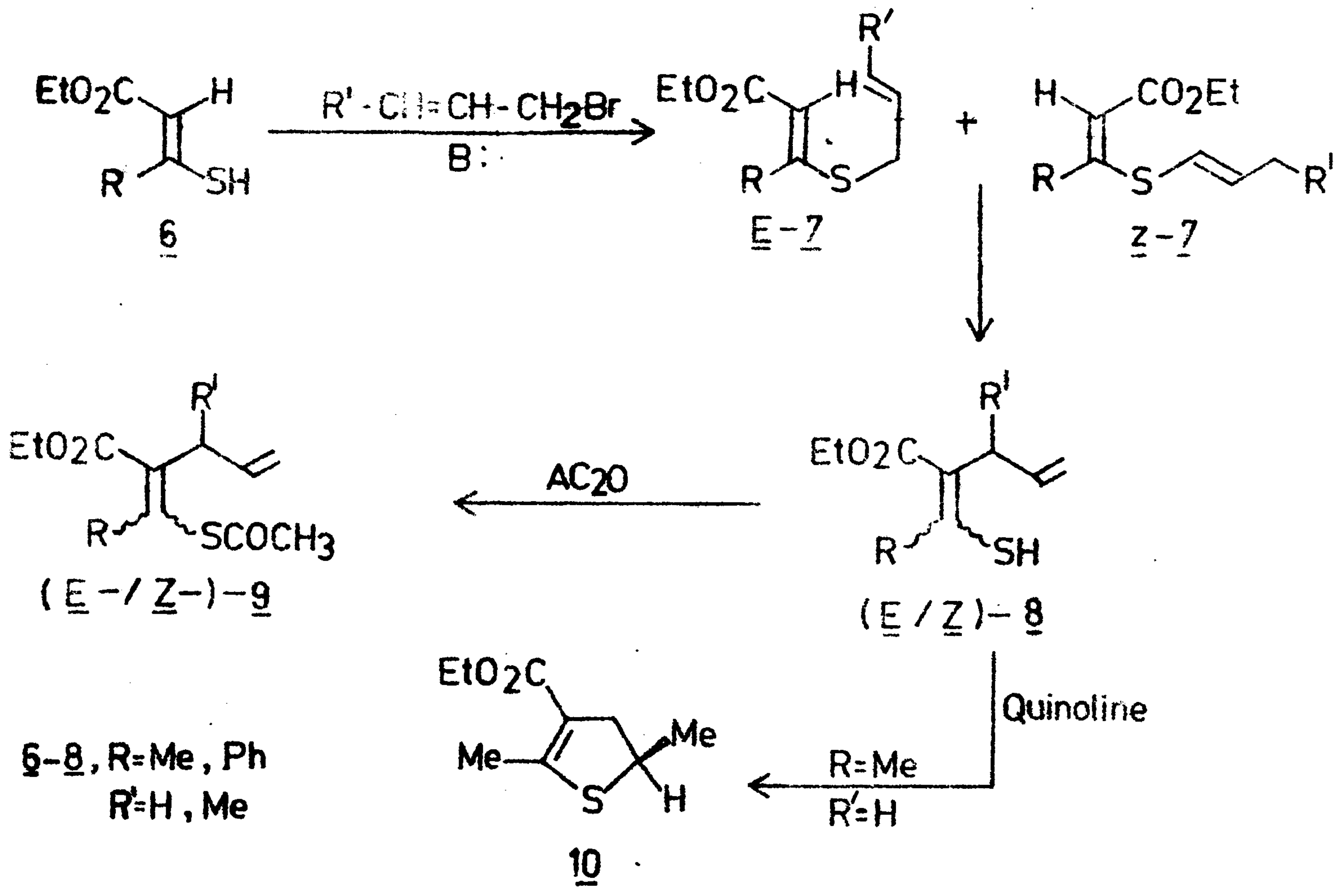
*S.S. Bhattacharjee, H. Ila and H. Junjappa, Synthesis, 410 (1983).



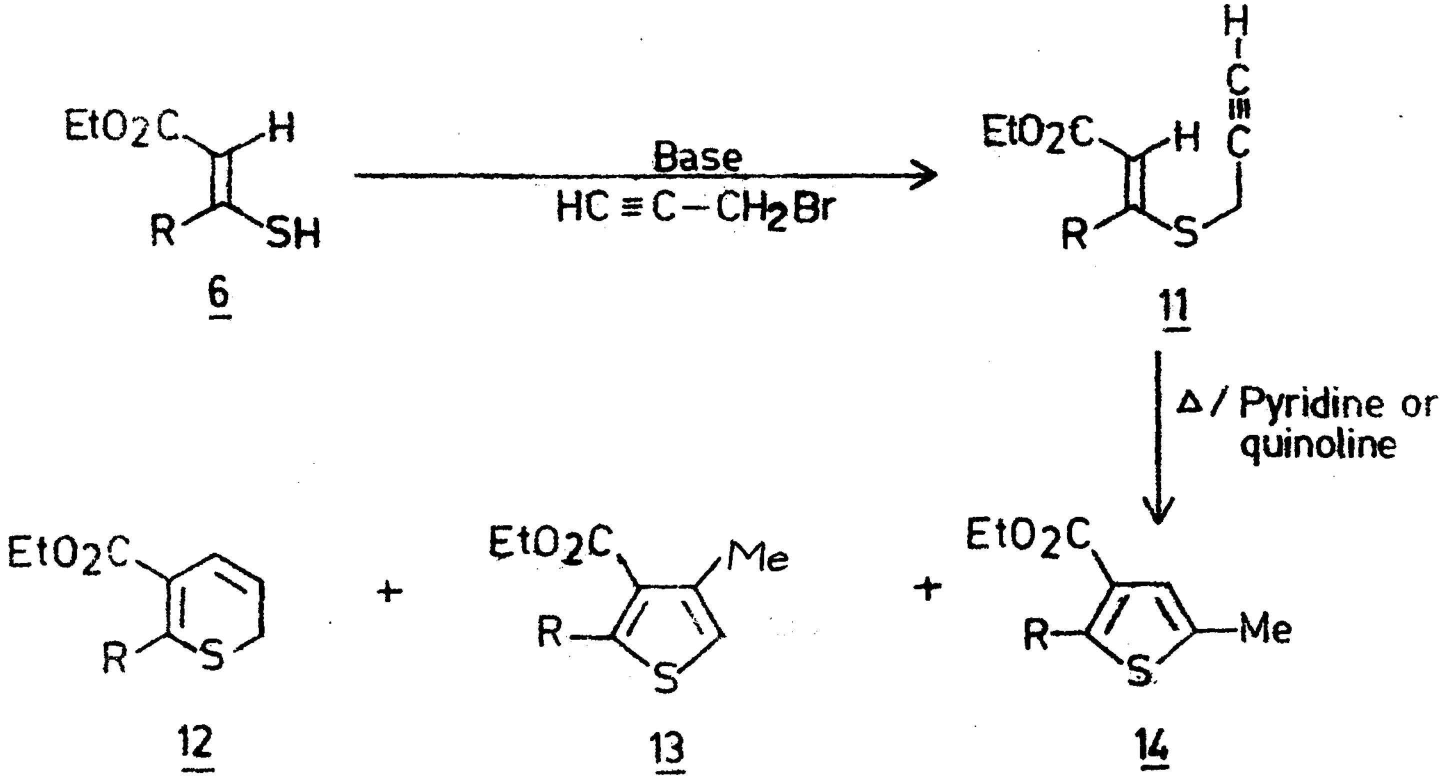
Scheme 1

3-alkylthio cinnammates (Z-form) (7, R=Ph). These S-allyl and crotyl enol-ethers 7 undergo facile thioclaisen rearrangement (Scheme 2) in refluxing acetic anhydride to give S-acylenethiol-ethers (9), while in refluxing quinoline, dihydrothiophene 10 was formed as the only product (Scheme 2). Similar thioclaisen rearrangement studies[7] on S-propargyl ether 11 in refluxing pyridine, quinoline or triethylamine gave thiopyran 12 as the major products together with small amounts of thiophenes 13 and 14 (Scheme 3). Attempts to alkylate dithioacid salts 15 derived from various active methylene compounds with allyl or crotyl bromide gave products of thioclaisen rearrangements exclusively in few cases, while in others, a mixture of dithioacetate 17 and S,S-acetals 16 were obtained. The S,S-acetal 16, on standing at room temperature rearranged to 17 by S → C allyl migration[8] (Scheme 4). The alkylation of the corresponding S-methyldithioesters 18a and 18b with allyl and crotyl bromide[9] similarly gave the corresponding rearranged dithioacetates 20a and 20b,[9] and the corresponding S-methyl-S-allyl (19a) or S-crotyl (19b) acetals could not be isolated from the reactions (Scheme 4). The alkylation of 20a with crotyl bromide on the otherhand gave an equilibrium mixture of keten mercaptal 21 and dithioester 22 which were shown to undergo S → C and C → S rearrangement respectively with inversion of crotyl group (Scheme 5).[8] Contrary to this, the keten dicrotyl



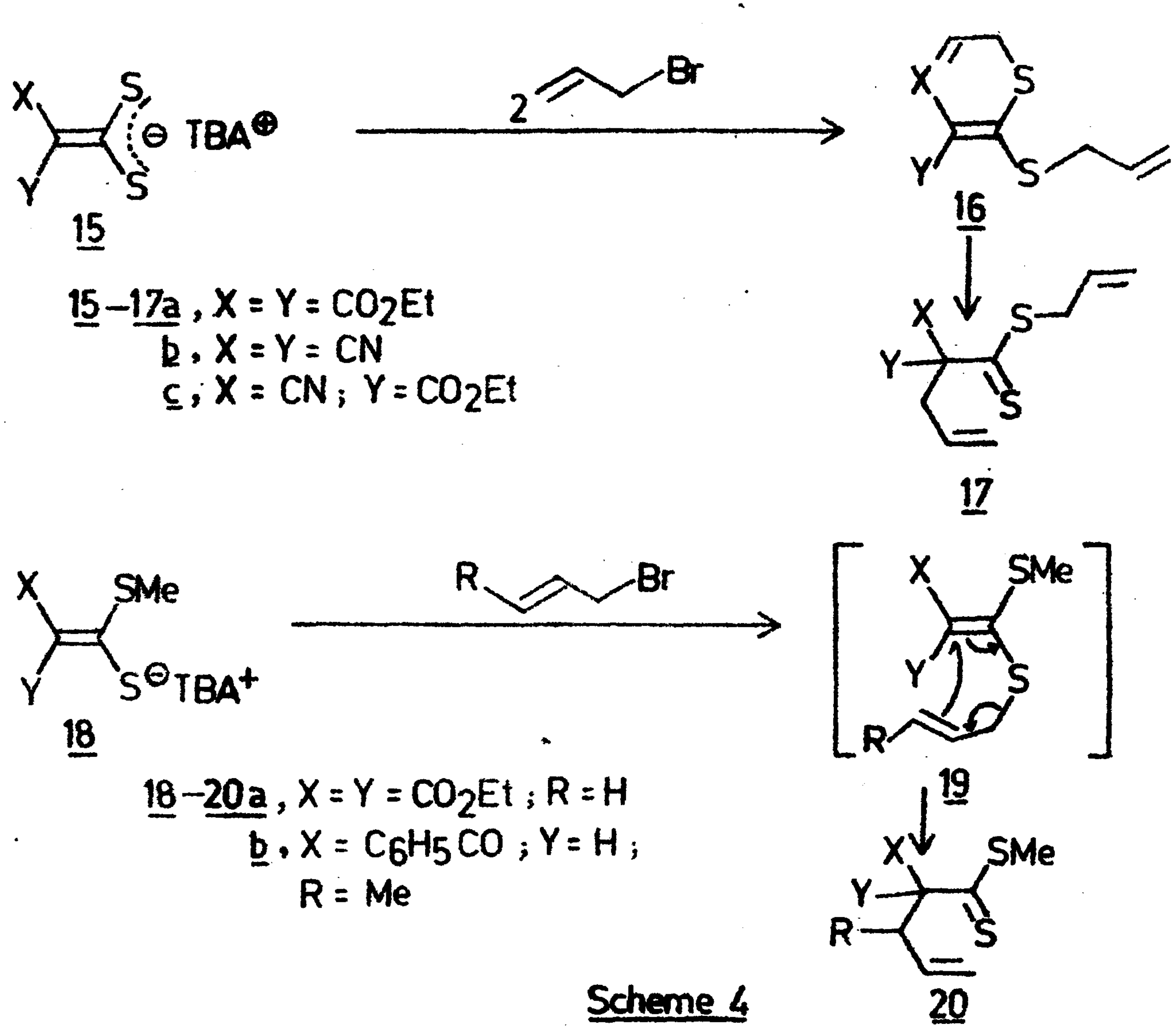
6–8, R=Me, Ph
R'=H, Me

Scheme 2



6, 11–14 ; R = Me , C_6H_5

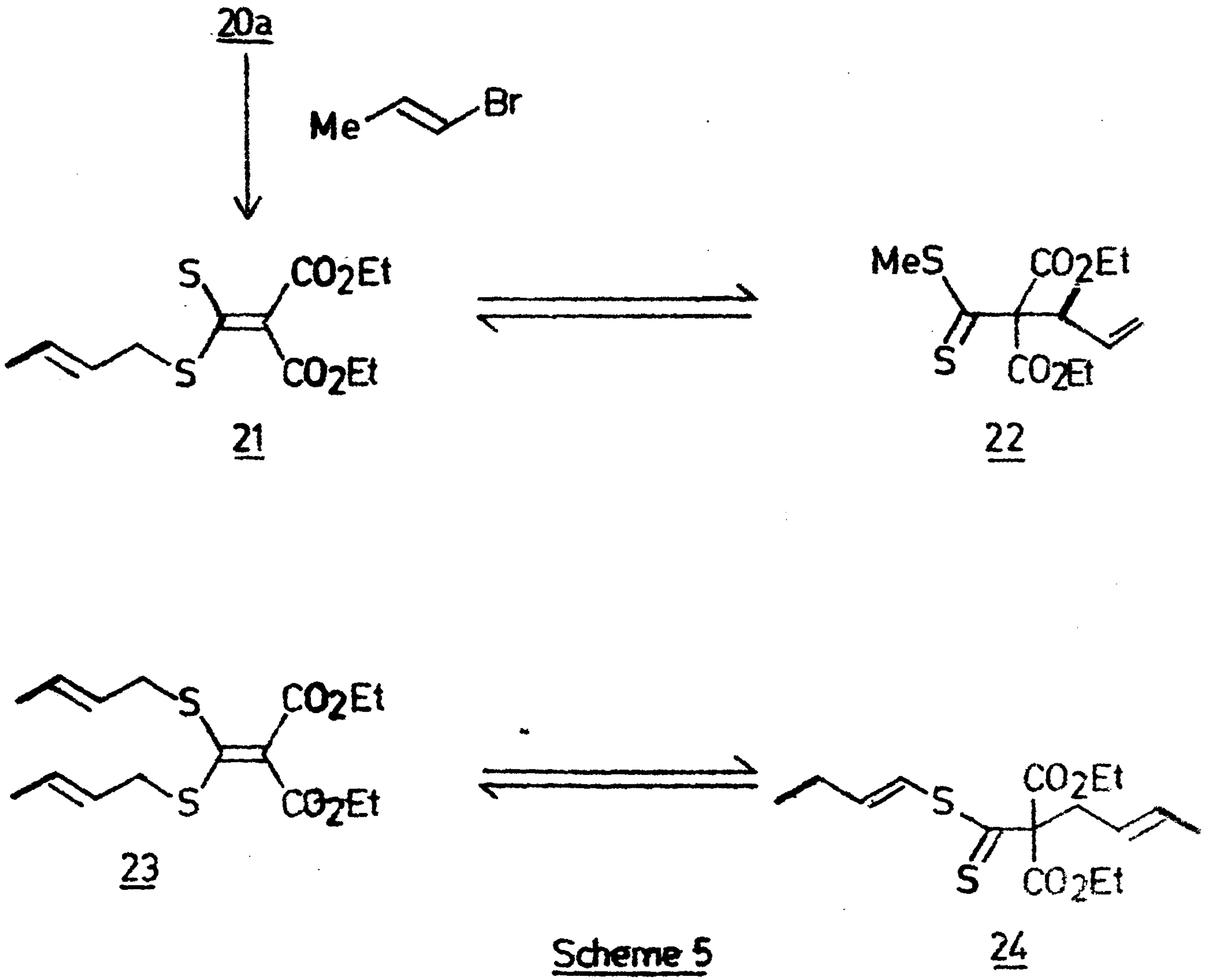
Scheme 3



$\underline{15}$–$\underline{17a}$, X = Y = CO_2Et
$\underline{b}$, X = Y = CN
$\underline{c}$, X = CN ; Y = CO_2Et

$\underline{18}$–$\underline{20a}$, X = Y = CO_2Et ; R = H
$\underline{b}$, X = C_6H_5CO ; Y = H ;
R = Me

Scheme 4

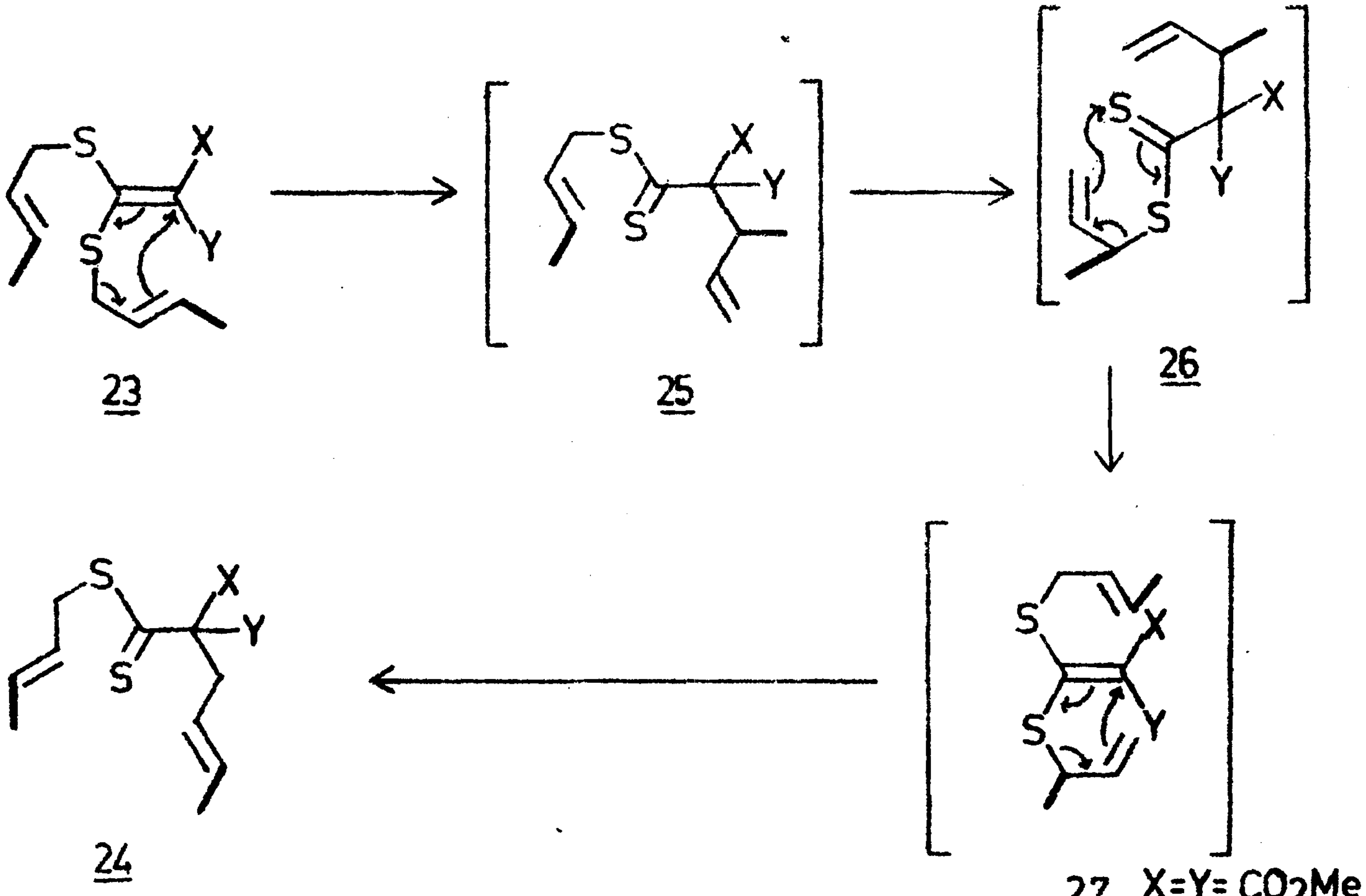

20a
Me
Br
S
S
CO2Et
CO2Et
21
MeS
S
CO2Et
CO2Et
22
S
S
CO2Et
CO2Et
23
S
S
CO2Et
CO2Et
24

Scheme 5

mercaptal 23 rearranged during distillation with retention of crotyl group to give 24 (Scheme 5).[8] The difference in orientation of allyl groups in the rearrangement of symmetrical ketendicrotylmercaptal 23 and the unsymmetrical keten S-methyl crotylmercaptal 21 is explained due to multiple series of concerted and reversible thioclaisen rearrangements in 23 leading to the thermodynamically more stable product 24 (Scheme 6).[8]

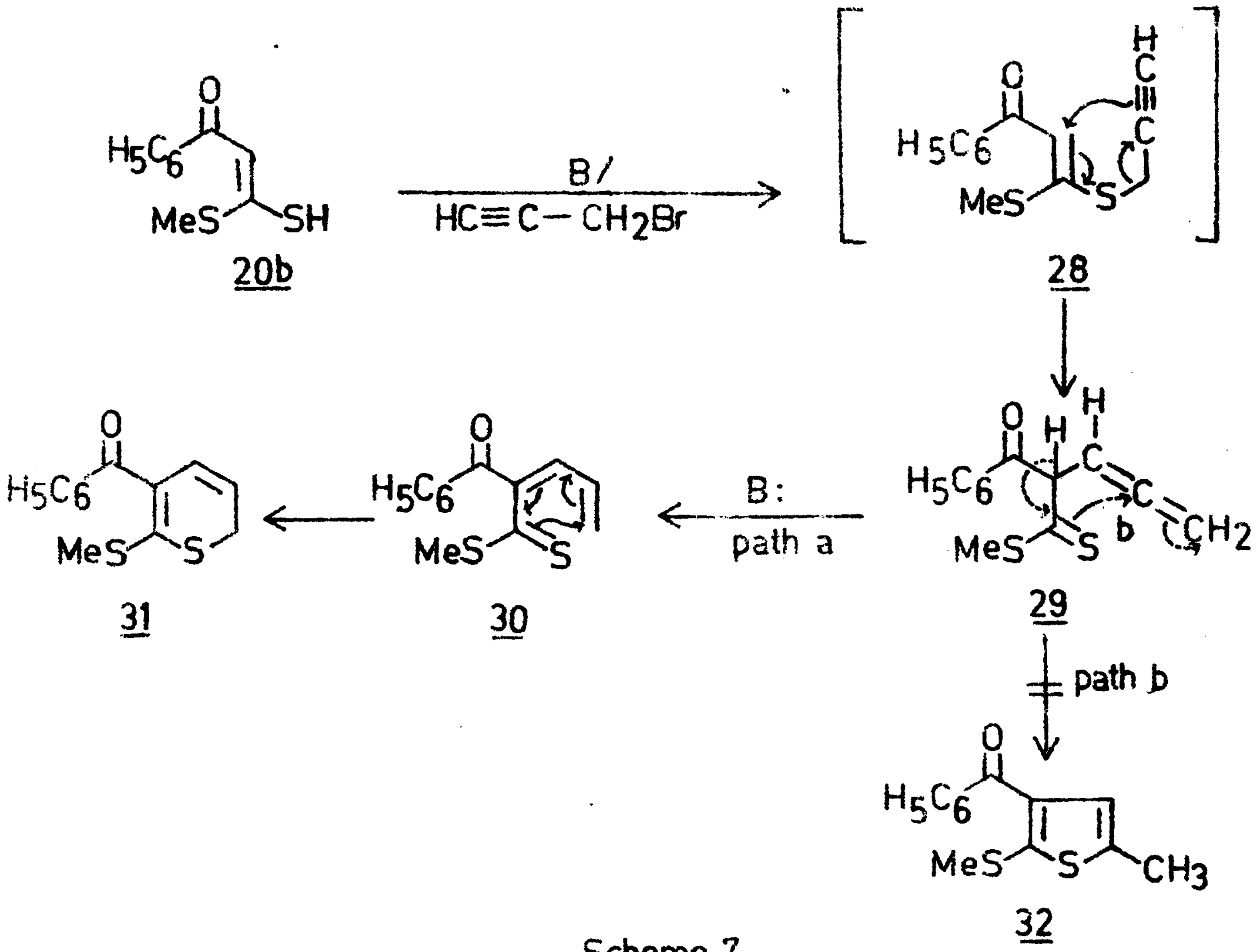
Attempts to prepare S-propargyl S-methylacetal 28 by alkylation of S-methyldithioester 20b gave exclusively the thiopyran 31 and no trace of thiophene 32 could be isolated (Scheme 7). The thiopyran 31 is apparently formed by spontaneous thioclaisen rearrangement of 28 to 29 and its subsequent rearrangement via intermediate 30 (Scheme 7). On the otherhand, alkylation of tetrabutylammonium salt (33) of dithioic acid derived from acetylacetone, with propargyl bromide and subsequent basic extraction gave ring closure to 1,3-dithiolane 35, which was converted to 36 in the presence of acid (Scheme 8).[10]

Inspite of the detailed studies carried out on thioclaisen rearrangements of thioenol ethers and keten S,S-acetals, very few rearrangements on the corresponding S,N-acetals have been described. Rearrangements of S-alkylated thioamides and keten-N,O-acetals are known.[11-13] Lawesson and coworkers have shown[14] that the attempted preparation of 1-allylthio(38a)-and 1-crotylthio(38b)-1-aminoalkenes by alkylation of the Tl salt of corresponding thiomides

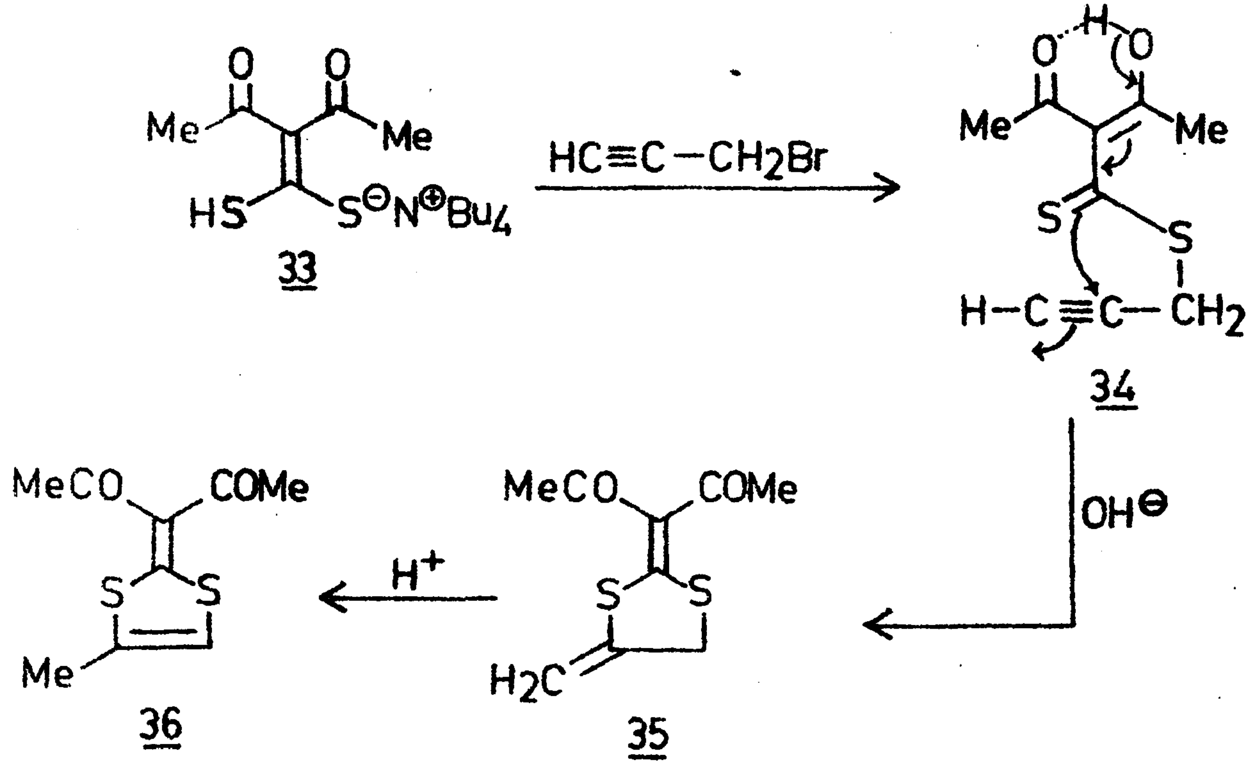


X=Y= CO_2Me

Scheme 6



Scheme 7



Scheme 8

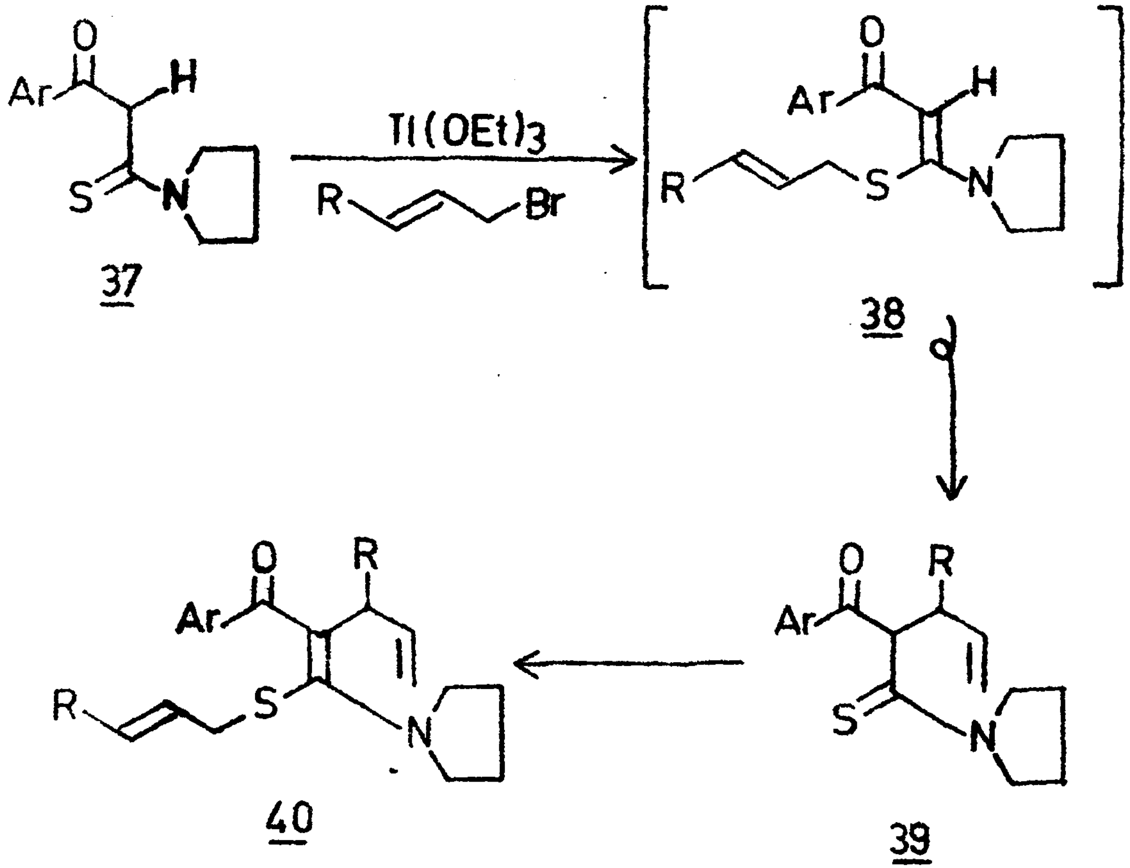
37 afforded only the rearranged thioamides 39 and S-alkyl aminoalkenes 40, which is formed by further alkylation of 39 (Scheme 9). On the otherhand, alkylation of thioanilides derived from various active methylene compounds with either allyl or crotyl bromide yielded a complex mixture of products containing unrearranged 43, dialkylated product 44, rearranged product 45 and the cleavage products 46 and phenylisothiocyanate 47 (Scheme 10).[14a]

In view of sporadic studies carried out on thioclaisen rearrangements of S,N-acetals, we have investigated thioclaisen rearrangement of S-propargyl-N-aminoacetals derived from cyclic secondary amines, which led to synthesis of novel 3-aroyl-2-amino-4-methylthiophenes. These results are presented in this chapter. Results of attempted thioclaisen rearrangements on propargyl thioethers derived from thiopyrazoles are also described.

III. 2 . REARRANGEMENT STUDIES ON S-PROPARGYL-N-AZACYCLOALKYL-ACETALS : SYNTHESIS OF NOVEL 3-AROYL-2-(N-AZACYCLOALKYL)-4-METHYLTHIOPHENES

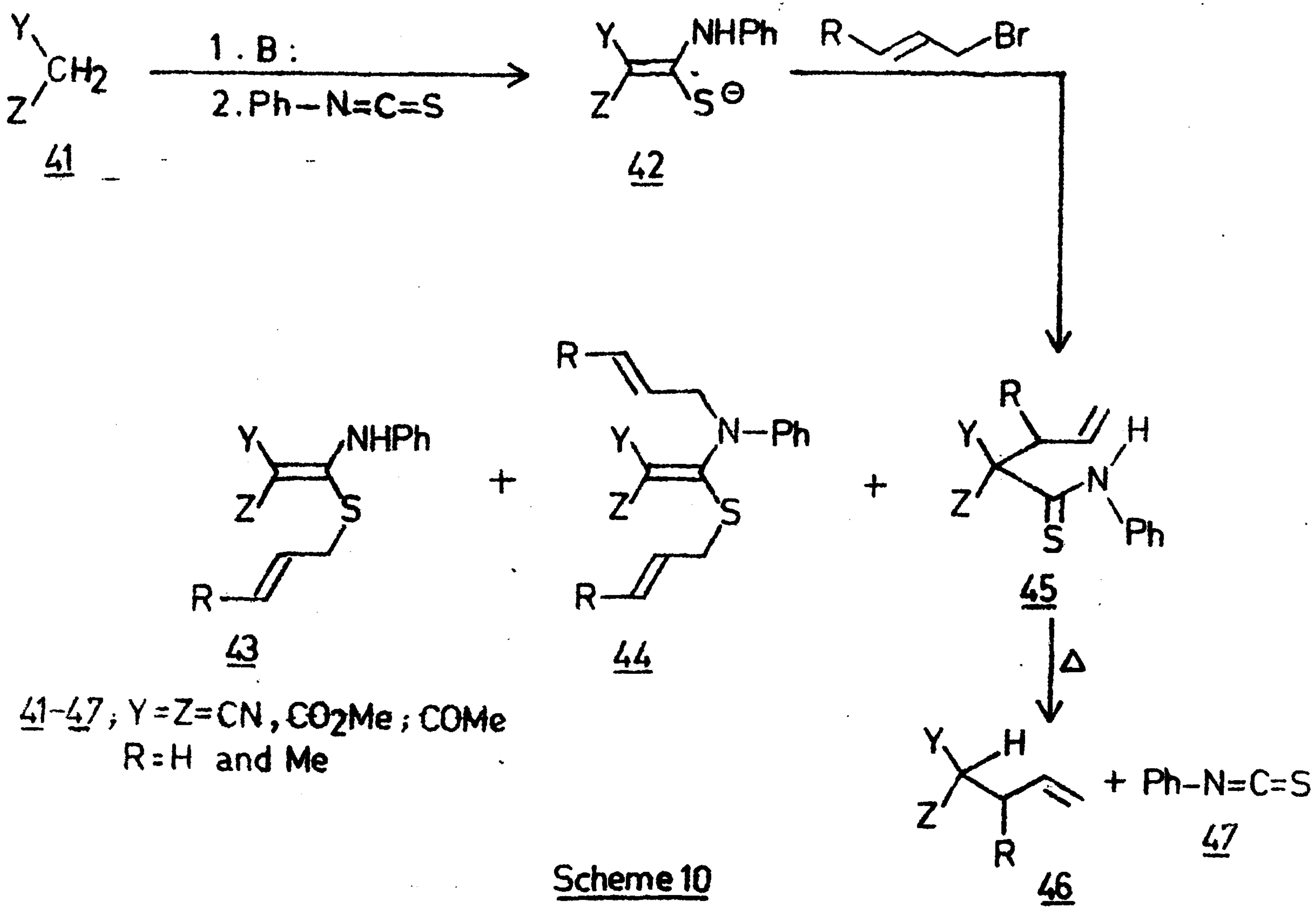
III.2.1 Results and Discussions

The dithioesters 48 prepared according to the method reported in the preceding chapter were reacted with cyclic secondary amines to give the corresponding thioamides 50a-l (Table 1) in 75-90% over yields. Most of these thioamides, which



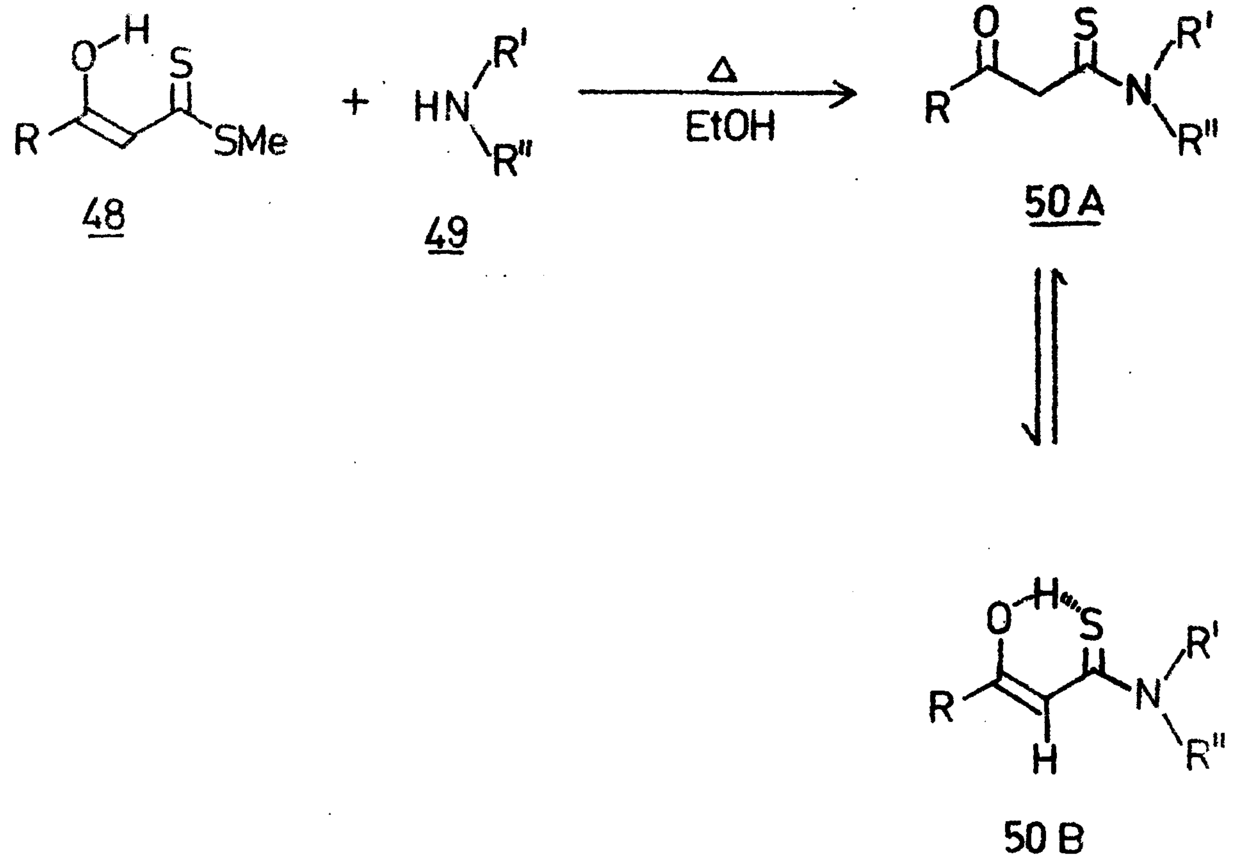
$\underline{37}$–$\underline{40a}$, Ar = $\underline{p}$ MeC_6H_4 ; R = H
$\underline{b}$, Ar = $\underline{p}$ MeC_6H_4 ; R = H

Scheme 9



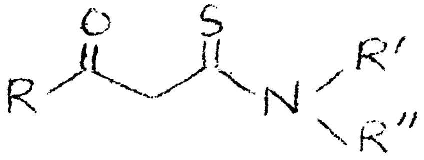
41-47; Y=Z=CN, CO_2Me; COMe
R=H and Me

Scheme 10



Scheme 11

TABLE 1



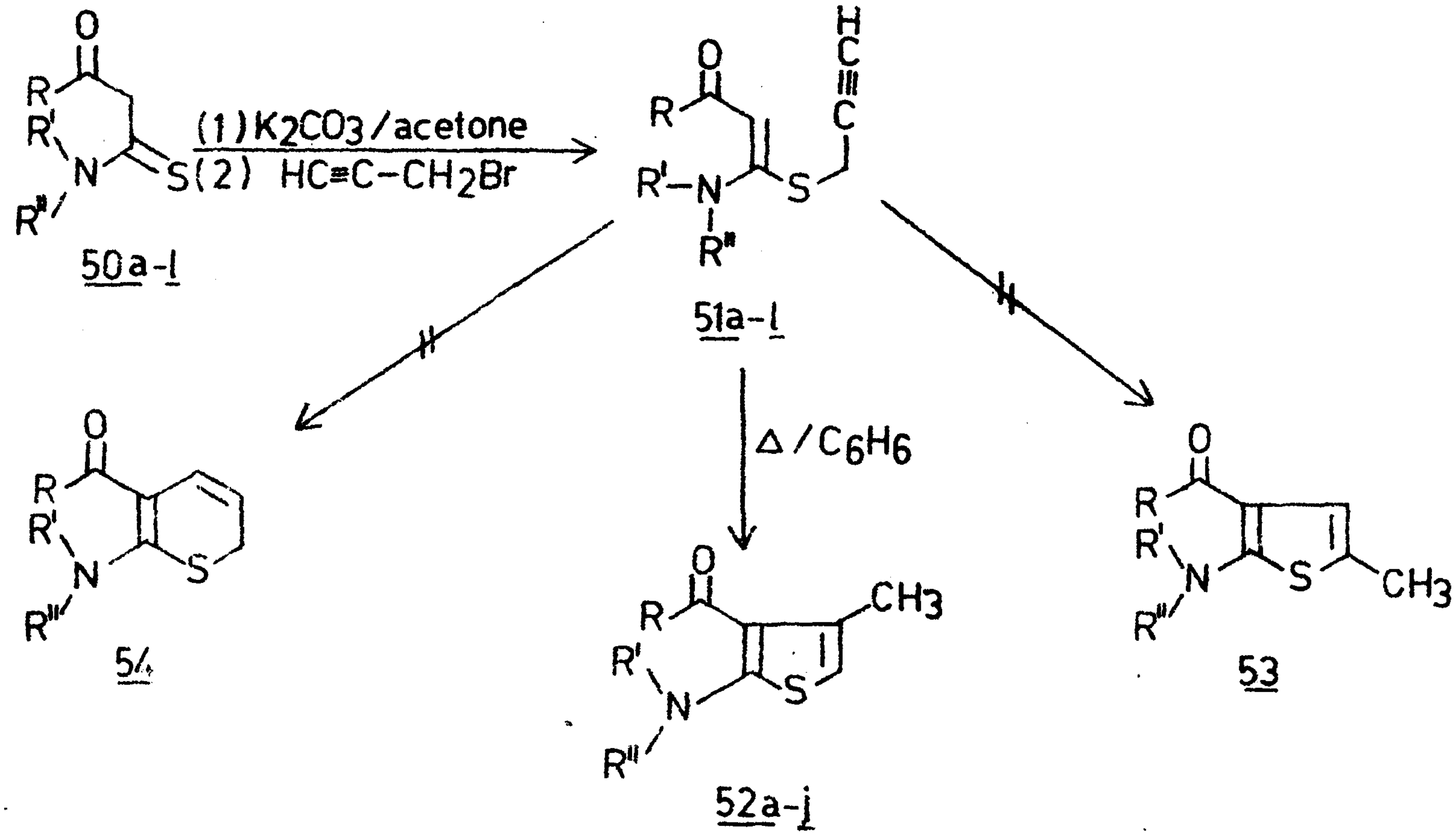
50

No	R	R'	R"
50a	C_6H_5-	$-(CH_2)_4-$	
50b	*p*-$MeOC_6H_4-$	$-(CH_2)_4-$	
50c	*p*-ClC_6H_4-	$-(CH_2)_4-$	
50d	C_6H_5-	$-(CH_2)_5-$	
50e	*p*-$MeOC_6H_4$	$-(CH_2)_5-$	
50f	*p*-$Cl-C_6H_4$	$-(CH_2)_5-$	
50g	C_6H_5	$-(CH_2)_2-O-(CH_2)_2-$	
50h	*p*-$MeOC_6H_4$	$-(CH_2)_2-O-(CH_2)-$	
50i	*p*-ClC_6H_4	$-(CH_2)_2-O-(CH_2)-$	
50j	C_6H_5	$-(CH_2)_2-\underset{C_6H_5}{\underset{\mid}{N}}-(CH_2)_2-$	
50k	C_6H_5	$-(CH_2)_2-\underset{Me}{\underset{\mid}{N}}-(CH_2)_2-$	
50l	CH_3	$-(CH_2)_2-O-(CH_2)_2-$	

are not reported in the literature and were characterized with the help of spectral (Table 3) and anlytical data. The IR and NMR spectra of these thioamides indicated that all of them exist as an equilibrium mixture of keto-(50A) and enol (50B) forms in varying ratio (Table 3). Thus IR spectrum of 50a showed absorption bands at 1685, 1600 and 3430 cm^{-1} due to aromatic CO group of keto form, enolic double bond and enolic OH group respectively. The NMR spectrum of 50a ($CDCl_3$) similarly exhibited singlets at δ 4.5 and 5.95 which were assigned to methylene protons of keto form and vinylic protons of enolic form respectively. Presence of a low field singlet at δ 14.8 due to enolic OH group further confirmed the presence of enol tautomer. In contrast, the NMR spectrum of 50a in CCl_4 reported in the literature[14b], there is no mention of particular peak at δ 4.50. The thioamide 50l on the otherhand exists purely in keto form as supported by its IR and NMR spectra (Table 3).

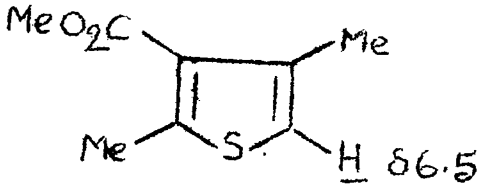
Attempts to prepare N-pyrrolidino-S-propargylacetal 51a by alkylation of 50a with propargyl bromide in the presence of sodium hydride and dimethylformamide were not successful and a complex mixture of products was obtained. However, when 50a was reacted with propargyl bromide in refluxing acetone in the presence of potassium carbonate, the corresponding S,N-acetal 51a was obtained in nearly quantitative yield (TLC single spot). The IR spectrum (neat) of crude 51a showed absorption band at 2200 cm^{-1}

due to acetylenic group. However, the acetal 51a was found to be unstable and further attempts to purify it resulted in a complex mixture of several products. However, when freshly prepared 51a was refluxed in benzene for 6-7 hr, after work-up of the reaction mixture, a yellow crystalline solid was obtained in 59% yield which was characterized as 2-pyrrolidino-3-benzoyl-4-methylthiophene (52a) on the basis of spectral and analytical data. Thus 52a was analysed for $C_{16}H_{17}NOS$ and showed molecular ion peak at m/z 271. Its IR spectrum (KBr) exhibited strong absorption at 1655 cm^{-1} due to aromatic carbonyl group. The final structure of 52a was confirmed by its NMR spectrum ($CDCl_3$). The two broad multiplets at δ 1.8-2.2 (4H) and 3.1-3.4 (4H) were assigned to pyrrolidine protons, while the singlet at δ 2.45 (3H) was assigned to thiophene methyl protons. The thiophene H-5 proton appeared as singlet at δ 5.69, while the aromatic protons were present as multiplets at δ 7.2-7.5 (3H) and δ 7.6-7.9 (2H) respectively. The alternative 5-methylthiophene structure 53 was ruled out on the basis of chemical shift positions of the H-5 proton in 52 and 53. Thus it has been reported[7] in the literature that the H-5 proton in ethyl 2,4-dimethyl-3-thiophene carboxylate(A)appears at δ 6.5 ppm while in the corresponding 2,5-dimethyl-3-thiophene carboxylate (B) the H-4 proton is shifted to lower field at δ 6.95 due to desheilding effect of ethoxycarbonyl group.[15] The significantly high field shift of H-5 proton (δ 5.69) in 52A as compared to A is

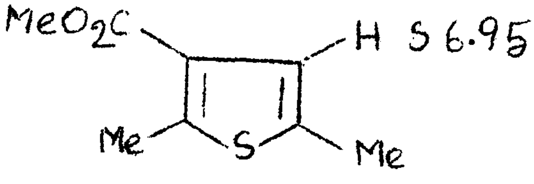

50a-l
(1) K2CO3/acetone
(2) HC≡C-CH2Br
51a-l
Δ/C6H6
52a-j
53
54
CH3
S
N
R
R'
R''

Scheme 12

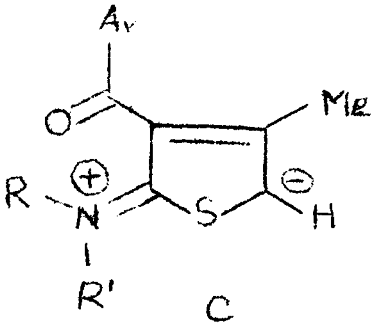
ascribed to +M effect of amino group by relay of charge at 5-position, while a similar effect is not experienced[16] at the 4-position in 5-methylthiophene (53) structure(Structure C)



A



B

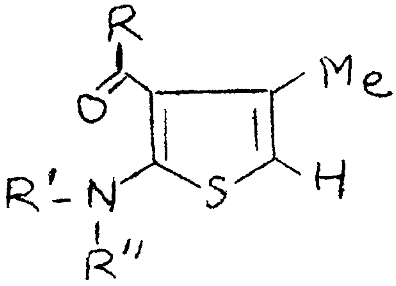


C

The other S-propargyl-N-pyrrolidinoacetals 51b and 51c underwent similar rearrangement to give the corresponding 52b and 52c in 57% and 64% yields respectively. Similarly the unsymmetrical S,N-acetals 51d-f, 51g-i and 51j derived from piperidine, morpholine and N-phenylpiperazine respectively, gave the corresponding thiophenes 52d-i (Table 2) in 42-66% overall yields. The structures of these thiophenes were fully confirmed with the help of spectral (Table 4) and analytical data (Table 5).

TABLE 2

2-amino-3-aroyl-4-methylthiophenes prepared



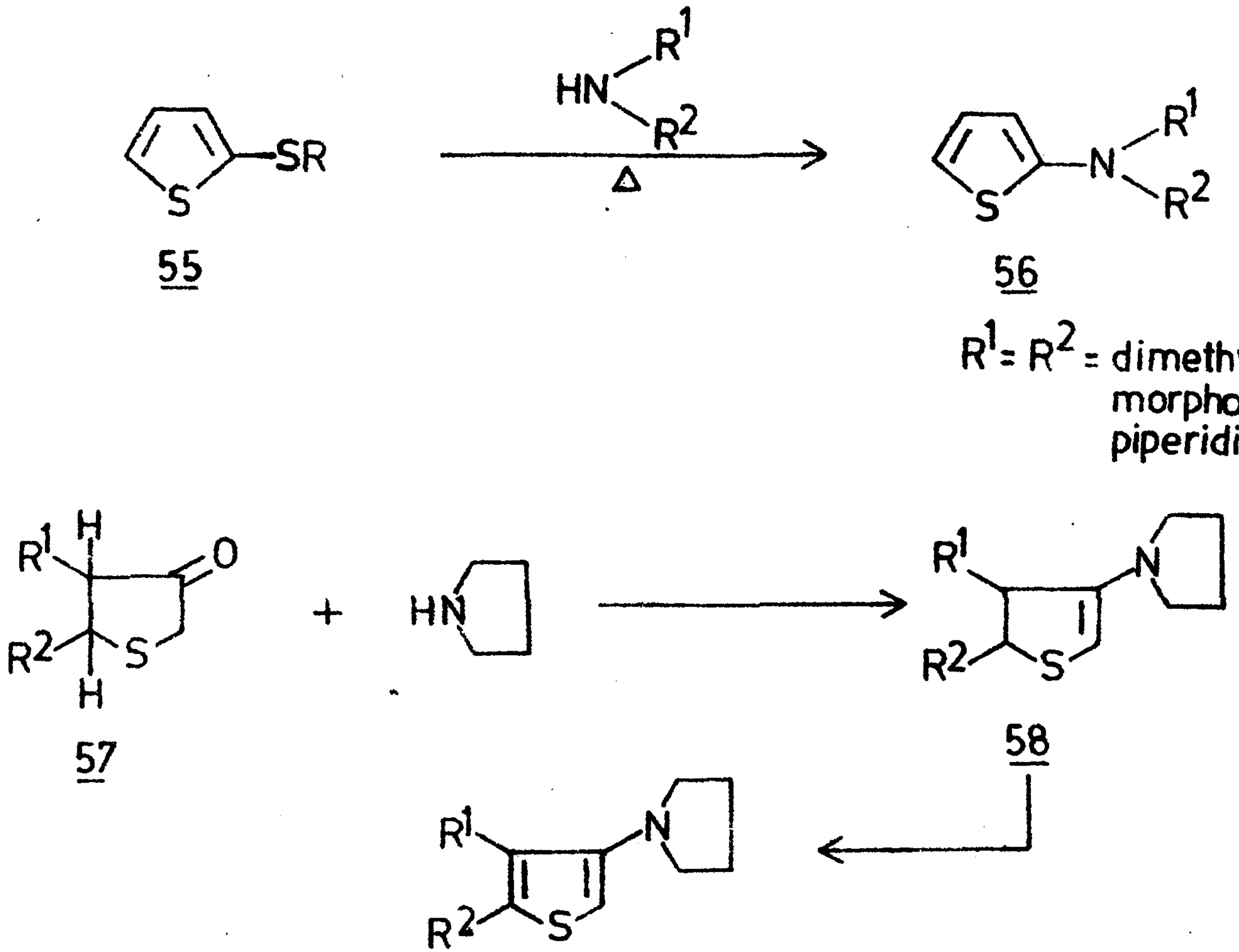
No	R	R'	R"
52a	C_6H_5	$-(CH_2)_4-$	
52b	$\underline{p}\text{-MeOC}_6\text{H}_4$	$-(CH_2)_4-$	
52c	$\underline{p}\text{-ClC}_6\text{H}_4$	$-(CH_2)_4-$	
52d	C_6H_5	$-(CH_2)_5-$	
52e	$\underline{p}\text{-MeOC}_6\text{H}_4$	$-(CH_2)_5-$	
52f	$\underline{p}\text{-ClC}_6\text{H}_4$	$-(CH_2)_5-$	
52g	C_6H_5	$-(CH_2)_2-O-(CH_2)_2-$	
52h	$\underline{p}\text{-MeOC}_6\text{H}_4$	$-(CH_2)_2-O-(CH_2)_2-$	
52i	$\underline{p}\text{-ClC}_6\text{H}_4$	$-(CH_2)_2-O-(CH_2)_2-$	
52j	C_6H_5-	$-(CH_2)_2-\underset{\substack{\vert \\ C_6H_5}}{N}-(CH_2)_2-$	

Attempted isomerization of 51 in either refluxing pyridine, quinoline or triethylamine yielded intractable mixture from which none of these expected products like 4- or 5-methylthiophenes 52, 53 or the dihydropyran 54 could be isolated.

Our survey of the literature revealed that very few N,N-disubstituted aminothiophenes derived from cyclic secondary amines are reported in the literature. They are prepared (1) by reaction of corresponding mercaptothiophenes 55 with secondary amines[17] (2) by condensation of 3-oxotetrahydrothiophenes 57 with pyrrolidine and subsequent aromatization of the enamines 58 (30-50% yield) to 3-aminothiophene 59[18,19] (Scheme 13). The present method therefore provides a convenient route to novel 3-aroyl-2 (N-azacycloalkyl)-4-methylthiophenes (52) in good yields.

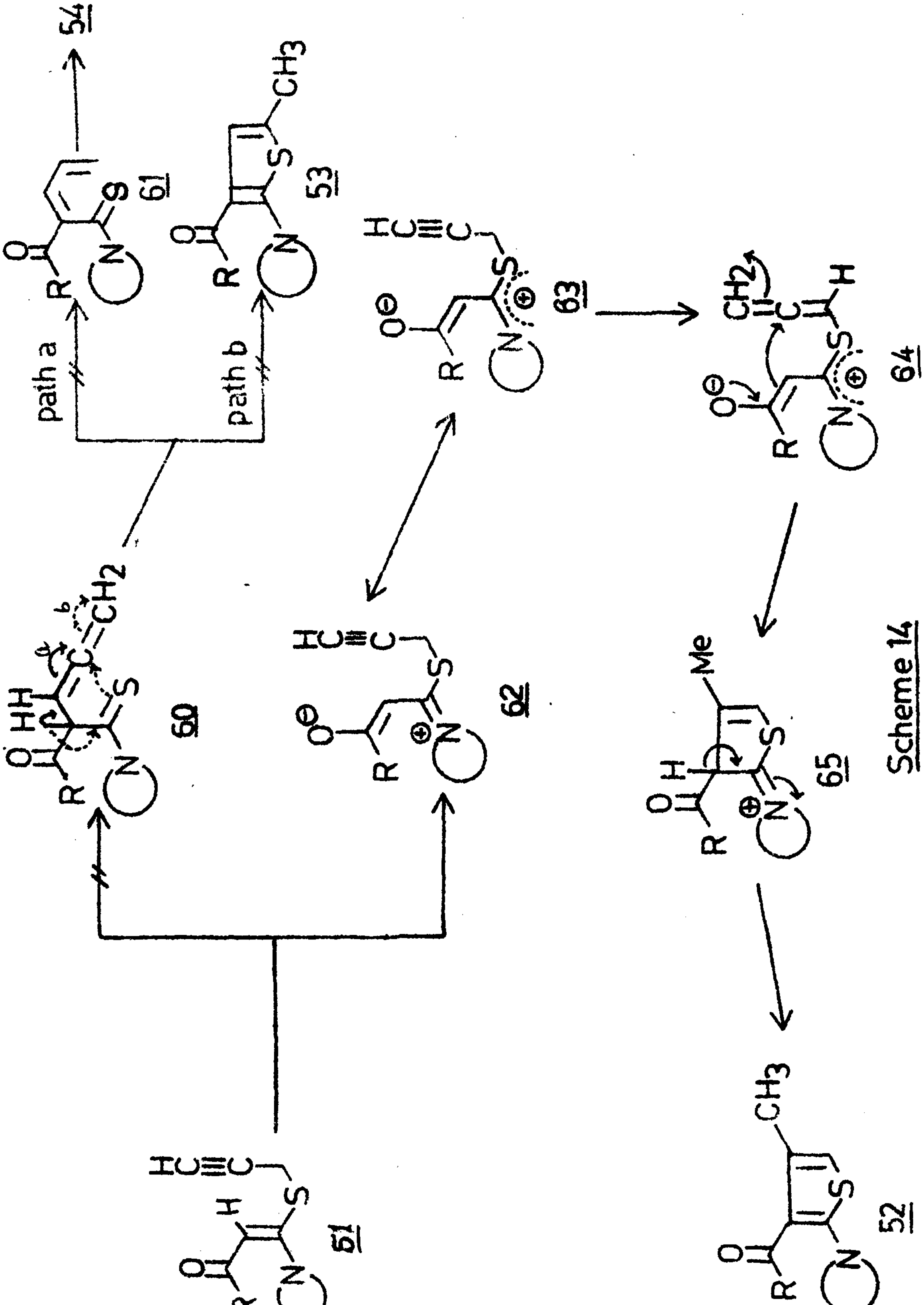
III.2.2 Mechanism of formation of Thiophene (52)

The mechanism governing this rearrangement (51 → 52) appears to be interesting, which shows that S,N-acetal 51 does not favour thioclaisen rearrangement, which could have given rise to either dihydropyran 54 or 5-methylthiophene 53 (path a and b, scheme 14). It is pertinent to note here that the alkylation of thioamide 37 with allyl or crotyl bromide in the presence of thallium ethoxide yields exclusively the thioamide 39 and S,N-acetal 40,[14a] which are products of thioclaisen rearrangement of S,N-acetal 38 (Scheme 9). In the present case of S,N-propargyl acetal 51



$R^1 = R^2 =$ dimethylamino, morpholino and piperidino

Scheme 13



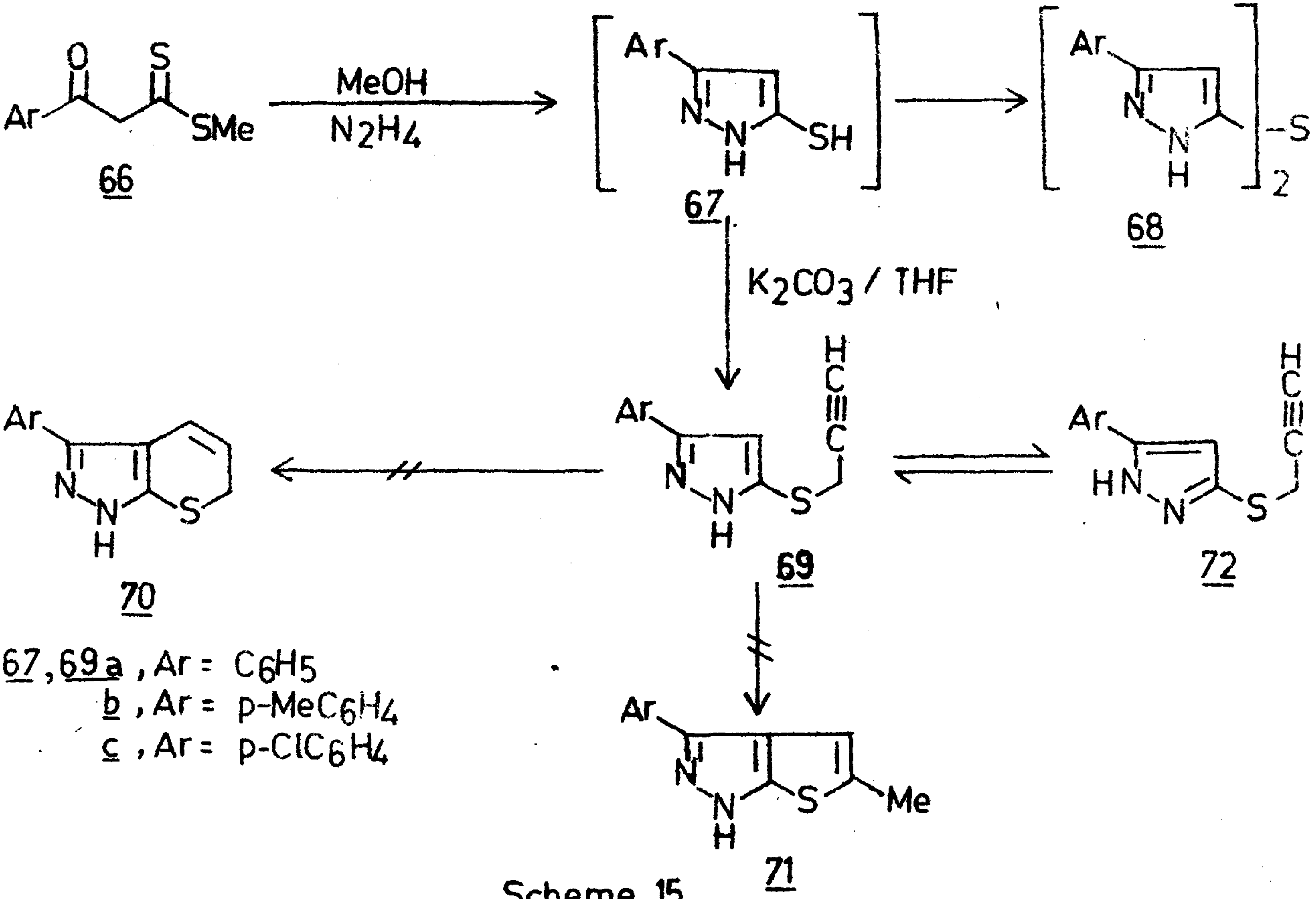
Scheme 14

however, it appears that an intramolecular nucleophilic attack of β-carbon of enaminone 62 to the activated acetylenic bond (63) or to allenic double bond (64) is favoured over 3,3-sigmatopic shift, to give the intermediate 65 which on isomerization yields the thiophene 52.

III.3 SYNTHESIS AND ATTEMPTED THIOCLAISEN REARRANGEMENT STUDIES OF 3-ARYL-5-PROPARGYLTHIOPYRAZOLES

In the preceding chapter we have reported a facile general route for β-oxodithioesters 66, which are potential three carbon fragments for mercaptoheterocycles. It was intended to prepare mercaptopyrazoles 67 by reaction of 66 with hydrazine and study the thioclaisen rearrangement of S-propargyl mercaptopyrazoles 69 obtained by alkylation of 67 with propargyl bromide (Scheme 15).

When the dithioester 66a was refluxed with hydrazine in methanol for 2 hr the product obtained was characterized as dipyrazolyl sulfide (68a) formed by the dimerization of unstable mercaptopyrazole (67a) (Scheme 15). In an alternate experiment, when the crude pyrazoles 67a-c, generated *in situ* by reacting 66a-c with hydrazine in refluxing methanol was alkylated with propargyl bromide, the corresponding S-propargyl pyrazoles 69a-c were obtained in 80-85% overall yields (Scheme 15). The structure of 69a was confirmed with the help of spectral and analytical data, thus 69a showed molecular ion peak at M^+ 214 ($C_{12}H_{10}SN_2$) in its mass



66,67,69 a , Ar = C_6H_5
b , Ar = p-MeC_6H_4
c , Ar = p-ClC_6H_4

Scheme 15

spectrum, while its IR spectrum exhibited weak absorption bands at 3300 and 2215 cm^{-1} due to NH and acetylenic group. It showed in its NMR spectrum a triplet at δ 2.20 (1H, J = 2.5 Hz $-C\equiv C-\underline{H}$) and a doublet at δ 3.52 (2H, J = 2.5 Hz $-SC\underline{H}_2C\equiv CH$) characteristic of propargyl group, while the pyrazole $\underline{H}$-4 proton appeared as sharp singlet (1H) at δ 6.59 along with aromatic proton at δ 7.0-7.51 (m, 5H). However our all attempts to subject 69 to thioclaisen rearrangement failed. Thus when pyrazole 69a was refluxed in solvents like benzene, toluene, quinoline or N,N-dimethylaniline for prolonged time (10-20 hrs) starting material was recovered unchanged in all the cases and in no case products of thioclaisen rearrangements like 70 or 71 could be isolated. Failure of 69 to undergo thioclaisen rearrangement appears to be probably due to its fast tautomerism ($69 \rightleftharpoons 72$) which disturbs the structural framework required for 3,3-sigmatropic shift in 69.

III.4 EXPERIMENTAL

M.ps were determined on a 'Boetius' (German) apparatus and are uncorrected. The IR spectra were recorded on Perkin-Elmer 297 spectrophotometer. The NMR spectra were recorded on a Varian EM-390 spectrometer using T.M.S. as an internal standard and the chemical shifts are expressed in ppm from T.M.S. taken as 0.00 (δ-units).

TABLE 3

Spectral data for the thioamides, 50a-1

Product	I.R. (KBr) ν [cm^{-1}]	^{1}H-NMR ($CDCl_3$) δ [ppm]	Tautomeric ratio (%)[a]	
			Keto	Enol
50a	1600, 1670 (w) 3190 (w)	1.9-2.2 (m, $4H_{pyrrolidine}$, $\underline{H}$-3 and $\underline{H}$-4); 3.5-3.7 (m, $4H_{pyrrolidine}$, $\underline{H}$-2 and $\underline{H}$-5); 4.52 (s, $\underline{H}_{methylene}$, 16 sq); 6.00 (s, $H_{vinylic}$, 22 sq); 7.2-7.8 (m, $5H_{arom}$); 14.8 (br s, H_{enolic}, 18 sq, exchangeable with D_2O).	28.5	71.5
50b	1605, 1680 (w) 3210 (w)	1.95-2.15 (m, $4H_{pyrrolidine}$, $\underline{H}$-3 and $\underline{H}$-4); 3.6-3.85 (m, $4H_{pyrrolidine}$, $\underline{H}$-2 and $\underline{H}$-5 and 3H, p-$OC\underline{H}_3$); 4.48 (s, $H_{methylene}$, 15 sq); 5.9 (s, $H_{vinylic}$, 30 sq); 6.8-7.65 (dd, $4H_{arom}$); 14.9 (br s, H_{enolic}, 15 sq).	25	75

Table 3 (Contd.)

50c	1590, 1675 (w) 3250 (w)	1.9–2.1 (m, 4H$_{\text{pyrrolidine}}$, $\underline{H}$-3 and $\underline{H}$-4); 3.55–3.8 (m, 4H, $\underline{H}$-2 and $\underline{H}$-5); 4.45 (s, H$_{\text{methylene}}$, 12 sq); 5.9 (s, H$_{\text{vinylic}}$, 30 sq); 7.3 (d, 2H$_{\text{arom}}$); 7.65 (d, 2H$_{\text{arom}}$); 14.92 (s, H$_{\text{enolic}}$, 30 sq).	16	84
50d	1560, 1680 2980 (w)	1.4–1.9 (m, 6H$_{\text{piperidine}}$,$\underline{H}$-3, $\underline{H}$-4 and $\underline{H}$-5); 3.0–3.5 (m, 4H$_{\text{piperidine}}$, $\underline{H}$-2 and $\underline{H}$-6); 4.7 (s, H$_{\text{methylene}}$, 10 sq); 6.15 (s, H$_{\text{vinylic}}$, 12 sq); 7.2–7.55 (m, 3H$_{\text{arom}}$); 7.75–7.90 (m, 2H$_{\text{arom}}$); 14.87 (br s, H$_{\text{enolic}}$, 8 sq, exchangeable with D_2O).	33.4	66.6
50e	1540, 1680, 3050 (w)	1.5–1.9 (m, 6H$_{\text{piperidine}}$, $\underline{H}$-3, $\underline{H}$-4 and $\underline{H}$-5); 3.1–3.4 (m, 4H$_{\text{piperidine}}$, $\underline{H}$-2 and $\underline{H}$-6); 3.72 (s, 3H, $\underline{p}$-OC$\underline{H}_3$); 4.62 (s, H$_{\text{methylene}}$, 12 sq); 6.12 (s, H$_{\text{vinylic}}$,16 sq); 6.85 (d, 2H$_{\text{arom}}$); 7.8 (d, 2H$_{\text{arom}}$); 14.82 (br s, H$_{\text{enolic}}$, 14 sq).	28.5	71.5

Table 3 (Contd.)

50f	1585, 1670, 3110 (w)	1.4-1.85 (m, $6H_{piperidine}$, $\underline{H}$-3, $\underline{H}$-4 and $\underline{H}$-5); 3.12-3.42 (m, $4H_{piperidine}$, $\underline{H}$-2 and $\underline{H}$-6); 4.65 (s, $H_{methylene}$, 14 sq); 6.18 (s, $H_{vinylic}$, 30 sq); 7.38 (d, $2H_{arom}$); 7.88 (d, $2H_{arom}$); 14.90 (s, H_{enolic}, 28 sq).	19.8	81.2
50g[b]	1540, 1680, 3250 (w)	3.7 (m, $4H_{morpholino}$); 4.0-4.5 (m, $4H_{morpholino}$); 4.65 (s, $H_{methylene}$, 20 sq); 6.05 (s, $H_{vinylic}$, 5 sq); 7.3-7.9 (m, $5H_{arom}$); 14.9 (br s, H_{enolic}, 5 sq, exchangeable with D_2O).	66.6	34.4
50h	1580, 1690, 3280 (w)	3.62-3.85 (m, $4H_{morpholino}$ and 3H, $\underline{p}$-OC$\underline{H}_3$); 4.18-4.40 (m, $4H_{morpholino}$); 4.7 (s, $H_{methylene}$, 25 sq); 6.10 (s, $H_{vinylic}$, 4 sq); 6.88 (d, $2H_{arom}$); 7.9 (d, $2H_{arom}$); 14.8 (br s, H_{enolic}, 3 sq).	78	22

Table 3 (Contd.)

50i	1600, 1675, 3290 (w)	3.6-3.8 (m, $4H_{\text{morpholino}}$); 4.0-4.4 (m, $4H_{\text{morpholino}}$); 4.65 (s, $H_{\text{methylene}}$, 40 sq); 6.05 (s, H_{vinylic}, 5 sq); 7.4 (d, $2H_{\text{arom}}$); 7.88 (d, $2H_{\text{arom}}$); 14.9 (br s, H_{enolic}, 3 sq).	83.3	16.7
50j	1590, 1680, 2900 (w)	3.55-4.2 (m, $8H_{\text{piperazine}}$); 4.69 (br s, $H_{\text{methylene}}$, 10 sq); 6.22 (s, H_{vinylic}, 15 sq); 7.18-7.62 (m, $10H_{\text{arom}}$); 14.82 (br s, H_{enolic}, 10 sq, exchangeable with D_2O).	28.5	71.5
50k	1580, 1700, 3010(w)	2.18 (s, 3H, N-$C\underline{H}_3$); 2.4 (m, $4H_{\text{piperazino}}$); 3.5-4.0 (m, $4H_{\text{piperazino}}$); 4.67 (s, $H_{\text{methylene}}$, 20 sq); 6.15 (s, H_{vinylic}, 4 sq); 7.3 (m, $3H_{\text{arom}}$); 7.75-7.95 (m, $2H_{\text{arom}}$); 14.78 (s, H_{enolic}, 3 sq, exchangeable with D_2O).	74.	26

Table 3 (contd.)

501	1500, 1710	2.2 (s, $4H_{morpholino}$); 3.55-3.78 (m, $4H_{morpholino}$); 4.12-4.35 (m, $2H_{methylene}$+ 3H,$C\underline{H}_3CO$).	100	-

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[a] The ratio of keto to enol forms was estimated from measurements of signal intensities of methylene, vinylic and hydroxylic protons (Ref. 20).

[b] Ref. 22, keto 61% and enol 39%.

[c] ^1H-NMR in TFA.

TABLE 4

Spectral data of the products 52a-j.

Product	I.R.(KBr) $\nu[cm^{-1}]$	^{1}H-N.M.R.(CCl_4) δ[ppm]	M.S. m/e (M^+)
52a	1655 (CO)	1.81-2.17 (m, 4H, pyrrolidinemethylene); 2.45 (s, 3H, $C\underline{H}_3$); 3.06-3.37 (m, 4H, $-C\underline{H}_2-N-C\underline{H}_2-$); 5.69 (s, 1H, $\underline{H}$-5); 7.2-7.49 (m, $3H_{arom}$); 7.60-7.86 (m, $2H_{arom}$).	271
52b	1640 (CO)	1.85-2.10 (m, 4H, pyrrolidinemethylene); 2.42 (s, 3H, $C\underline{H}_3$); 3.05-3.28 (m, $4H-C\underline{H}_2-N-C\underline{H}_2-$); 3.81 (s, 3H, $\underline{Me}O$); 5.60 (s, 1H, $\underline{H}$-5); 6.68-6.71 (d, $2H_{arom}$) 7.63-7.88 (d, $2H_{arom}$).	301
52c	1652 (CO)	1.88-2.10 (m, 4H, pyrrolidinemethylene); 2.42 (s, 3H, $C\underline{H}_3$); 3.05-3.28 (m, 4H, $-C\underline{H}_2-N-C\underline{H}_2-$); 5.60 (s, 1H, $\underline{H}$-5); 7.22-7.41 (d, $2H_{arom}$); 7.61-7.80 (d, $2H_{arom}$).	305.5

Table 4 (Contd.)

52d	1650[a] (CO)	1.42-1.81 (m, 6H, piperidino methylene); 2.41 (s, 3H, $C\underline{H}_3$); 2.84-3.03 (m, 4H, $-C\underline{H}_2-N-C\underline{H}_2$); 5.91 (s, 1H, $\underline{H}$-5); 7.12-7.50 (m, $3H_{arom}$); 7.61-7.79 (m, $2H_{arom}$).	-
52e	1648[a] (CO)	1.33-2.84 (m, 6H, piperidine methylene); 2.40 (s, 3H, $C\underline{H}_3$); 2.79-3.08 (m, 4H, $-C\underline{H}_2-N-C\underline{H}_2-$) 3.69 (s, 3H, $OC\underline{H}_3$); 5.95 (s, 1H, $\underline{H}$-5); 6.68-6.93 (d, $2H_{arom}$); 7.59-7.78 (d, $2H_{arom}$)[b].	-
52f	1649 (CO)	1.51 (m, 6H, piperidino methylene); 2.50 (s,3H, $C\underline{H}_3$); 2.90-3.11 (m, 4H, $-C\underline{H}_2-N-C\underline{H}_2-$); 5.91 (s, 1H, $\underline{H}$-5); 7.28-7.43 (d, $2H_{arom}$); 7.60-7.78 (d, $2H_{arom}$).	319.5

Table 4 (Contd.)

52g	1651 (CO)	2.43 (s, 3H, $C\underline{H}_3$); 2.90-3.05 (m, 4H, morpholinomethylene); 3.61-3.80 (m, 4H, $-C\underline{H}_2-O-C\underline{H}_2-$); 6.02 (s, 1H, $\underline{H}$-5); 7.30-7.45 (m, $3H_{arom}$); 7.61-7.80 (m, $2H_{arom}$).	287
52h	1630 (CO)	2.42 (s, 3H, $C\underline{H}_3$); 2.83-3.12 (m, 4H, $-C\underline{H}_2-N-C\underline{H}_2-$); 3.65-3.91 (m, 4H, morpholino-methylene); 3.82 (s, 3H, $OC\underline{H}_3$); 6.01 (s, 3H, $\underline{H}$-5); 6.75-6.95 (d, $2H_{arom}$) 7.68-7.85 (d, $2H_{arom}$).	317
52i	1650 (CO)	2.48 (s, 3H, $C\underline{H}_3$); 2.86-3.07 (m, 4H, $-CH_2-N-C\underline{H}_2-$); 3.60-3.80 (m, 4H, $-C\underline{H}_2-O-C\underline{H}_2$); 5.98 (s, 1H, $\underline{H}$-5); 7.25-7.42 (d, $2H_{arom}$); 7.59-7.66 (d, $2H_{arom}$).	321.5
52j	1648 (CO)	2.49 (s, 3H, $C\underline{H}_3$); 3.25 (br s, 8H, piperazinomethylene); 3.82 (s, 3H, $OC\underline{H}_3$); 6.01 (s, $3\underline{H}$, $\underline{H}$-5); 6.75-6.95 (d, $2H_{arom}$); 7.1-7.5 (m, $6H_{arom}$); 7.68-7.85 (d, $2H_{arom}$).	362

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[a] as film. [b] in $CDCl_3$.

The Starting Materials

The commercial samples of acetophenone, p-methoxyacetophenone, p-chloroacetophenone, acetone, morpholine, piperidine, pyrrolidine, N-phenylpiperazine, N-methylpiperazine and propargyl bromide were purified before use.

Dimethyl trithiocarbonate, bp 225° (760 mm)[21] and various dithioesters 48 were prepared according to the procedure described in the chapter II.

General Procedures for Preparation of Thioamides 50 : A solution of methyl β-aroyldithioacetate (48) (0.01 mol) and the appropriate amines 49 (0.012 mol) in ethanol (40 ml) was refluxed for 4-7 hrs. After completion of the reaction (monitored by TLC), ethanol was removed on water bath under reduced pressure and the residue triturated with hexane to remove excess of amine. The crude thioamides 50a-l thus obtained were purified either by crystallization or by column chromatography over silica gel using hexane/benzene (1:1) as eluent. The physical and analytical data of the thioamides prepared are given below, while their spectral data is given in table 3.

Benzoylthioaceticacidpyrrolidide (50a) was purified by crystallization from ethylacetate-hexane to give yellow solid in 88% yield; m.p. 122-124°; (reported 124-126°).[11b]

p-Methoxybenzoylthioaceticacidpyrrolidide (50b) was obtained as light yellow needles (ethylacetate/hexane), in 80% yield, m.p. 135° M$^+$(mass) : 263; (Found : C, 63.49; H, 6.76; N, 5.08; Calc. for $C_{14}H_{17}O_2NS$(263); C, 63.87; H, 6.46; N, 5.32%).

p-Chlorobenzoylthioaceticacidpyrrolidide (50c) was purified by crystallization from chloroform-hexane to give yellowish brown solid in 87% yield, m.p. 163°, M$^+$(mass); 267 (Found: C, 58.69; H, 5.05; N, 4.90; Calc. for $C_{13}H_{14}ClNOS$ (267.5); C, 58.31; H, 5.23; N, 5.23%).

Benzoylthioaceticacidpiperidide (50d) was obtained as brown yellow plates from chloroform/hexane in 84% yield, m.p. 95°; M$^+$(mass) : 247; (Found: C, 67.73; H, 7.18; N, 5.93; Calc. for $C_{14}H_{17}NOS$ (247): C, 68.01; H, 6.88; N, 5.66%).

p-Methoxybenzoylthioaceticacidpiperidide (50e) was purified by crystallization from chloroform-hexane to give pale yellow needless in 77% yield, m.p. 78-79°, M$^+$(mass) : 277; (Found: C, 65.37; H, 7.08; N, 5.32; Calc. for $C_{15}H_{19}NO_2S$ (277); C, 64.98; H, 6.85; N, 5.05%).

p-Chlorobenzoylthioaceticacidpiperidide (50f) was obtained as brown needless (ethylacetate-hexane), in 78% yield, m.p. 108, M$^+$ (mass) 281; (Found: C, 60.04; H, 5.28; N, 5.17; Calc. for $C_{14}H_{16}ClNOS$ (281.5); C, 59.68; H, 5.68; N, 4.97%).

Benzoylthioaceticacid morpholide (50g) was purified by crystallization from chloroform hexane to give shinning rods in 90% yield, m.p. 131° (reported m.p. 127-129°).[14b]

p-Methoxybenzoylthioaceticacid morpholide (50h) was purified by crystallization from chloroform-hexane to give pale yellow plates in 75% yield, m.p. 133-134°, M^+(mass); 297; (Found: C, 60.55; H, 5.81; N, 5.35; Calc. for $C_{14}H_{17}NO_3S$ (279): C, 60.21; H, 6.09; N, 5.01%).

p-Chlorobenzoylthioaceticacid-morpholide (50i) was crystallized as brownish yellow needless from chloroform-hexane in 85% yield, m.p. 155-56°, M^+(mass) 283; (Found: C, 55.39; H, 4.60; N, 5.22; Calc. for $C_{13}H_{14}ClNO_2S$ (283.5): C, 55.02; H, 4.93; N, 4.93%).

Benzoylthioaceticacid-N-phenylpiperazide (50j) was obtained as light yellow plates from hot chloroform in 78% yield, m.p. 95-97°, M^+(mass) : 324; (Found; C, 69.98; H, 6.35; N, 8.21; Calc. for $C_{19}H_{20}N_2OS$ (324): C, 70.37; H, 6.17; N, 8.64%).

Benzoylthioaceticacid-N-methylpiperazide (50k) was purified by crystallization from chloroform-hexane to give dull yellow plates in 82% yield, m.p. 122-123°, M^+(mass); 262; (Found: C, 64.46; H, 6.71; N, 10.53; Calc. for $C_{14}H_{18}N_2OS$ (262): C, 64.12; H, 6.87; N, 10.68%).

Acetylthioaceticacid-morpholide (50l) was purified by column chromatography on silica gel using benzene:hexane (1:3), crystallized from chloroform-hexane (9:1) to give greenish yellow rods in 75% yield, m.p. 98°C, M^+(mass); 187; (Found: C, 51.01; H,7.23; N, 7.66; Calc. for $C_8H_{13}NO_2S$ (187); C, 51.33; H, 6.95; N, 7.48%).

3-Aroyl-2-(N-azacycloalkyl)-4-methylthiophenes (52a-j):

General Procedure

A suspension of thioamide 50 (0.01 mol) and anhydrous potassium carbonate (2g, 0.15 mol) in dry acetone (40 ml) was refluxed for 2.5 hrs with stirring. The reaction mixture was then cooled to room temperature and 1.2g (0.01 mol) of propargyl bromide was added slowly and the mixture was stirred at room temperature for 3 hrs. The crude product 52 thus obtained after filtration and evaporation of acetone under reduced pressure was dissolved in dry benzene (40 ml) or in benzene/chloroform mixture (30+10 ml, for 52b, 52e and 52h) and the solution was heated at 70-80°C with stirring for 6-7 hrs. The solvent was removed under reduced pressure and the pure thiophenes 52a-j were isolated by column chromatography over silica gel using hexane or hexane/benzene (7:3) as eluent and were recrystallized from chloroform/hexane mixtures. The spectral, physical and analytical data of thiophenes 52a-j are given in the table 4 and 5 respectively.

Reaction of Methyl-β-hydroxydithiocinnamate (66) with hydrazine hydrate: Preparation of dipyrazolyl sulfide (68)

A solution of 66a, (0.005 mol) and hydrazine hydrate (2 ml, 50%) in 50 ml methanol was refluxed for 2 hrs. The reaction mixture was poured over crushed ice and neutralized with dilute acetic acid, and the solid thus obtained was filtered and recrystalized from hot chloroform, yield of 68 was 0.7g (50%), m.p. 124°; IR ν_{max} (Nujol) 3140 cm^{-1} (NH); NMR (TFA) : δ 6.90 (s, 2H, H-4); 7.4-7.78 (m, 10H $_{aromatic}$), M^+ (mass); 350, 175, 143; (Found: C, 68.35; H, 4.69; N, 17.28; Calc. for $C_{18}H_{14}N_4S$ (318) : C, 67.92; H, 4.40; N, 17.61%).

General method for preparation of 3-aryl-5-propargylthio-1H-pyrazole 69a-c

A solution of dithioester 66 (0.01 mol) and hydrazine hydrate (95%, 2 ml) was refluxed in 40 ml methanol for 1.5 hrs. The reaction mixture was cooled to room temperature and methanol was removed under reduced pressure. The crude viscous residue thus obtained was dissolved in 40 ml of tetrahydrofuran and to this, 0.015 mol of potassium carbonate was added and the reaction mixture was stirred for two hrs at room temperature. A solution of propargyl bromide (0.01 mol) in 5 ml of THF was added to the reaction mixture and it was further stirred at 60-70°C for 5 hrs. Evaporation of the solvent on water bath gave crude pyrazoles 69 which were purified by crystallization from hot ethanol.

3-phenyl-5-propargylthio-1H-pyrazole (69a) was obtained as pale yellow crystalline solid, 1.7g (80%), m.p. 76-77°C, IR(KBr)ν_{max}: 3290 (NH), 2210 (W,C≡C) cm^{-1}, NMR(CDCl$_3$)δ: 2.20 (t,J=2.5 Hz, 1H, -C≡C-H), 3.52 (d, J=2.5 Hz, 2H, -S-CH$_2$-C≡C-H); 6.59 (s, 1H, H-4), 7.0-7.5 (m, 5H $_{arom}$); M$^+$ 214: (Found : C, 67.65; H, 4.38; H, 13.44; Calc. for $C_{12}H_{10}N_2S$ (214) : C, 67.28; H, 4.67; N, 13.08%).

3-p-methylphenyl-5-propargylthio-1H-pyrazole (69b) was obtained as white plates, 1.8g (82%), m.p. 94°C, IR(KBr): 3280 (NH), 2120 (w, C≡C) cm^{-1}, NMR (CDCl$_3$); 2.20 (t, J=2.5 Hz, 1H, -C≡C-H); 2.35 (s, 3H, CH$_3$); 3.5 (d, J=2.5 Hz, 2H, -S-CH$_2$·C=C-H); 6.65 (s, 1H, H-4) 7-7.7 (A$_2$B$_2$, 4H $_{aromatic}$); M$^+$, 228; (Found: C, 68.70; H, 5.46; N, 12.53; Calc. for $C_{13}H_{12}N_2S$ (228): C, 68.42; H, 5.26; N, 12.28%).

3-p-chlorophenyl-5-propargylthio-1H-pyrazole (69c) was obtained as light yellow needle, 2.1g (85%), m.p. 96°C, IR(KBr) : 3285 (NH), 2210 (w, C≡C) cm^{-1}, NMR (CDCl$_3$);δ2.22 (t, J=2.5 Hz, 1H, -C≡C-H), 3.52 (d, J=2.5 Hz, 2H, -S-CH$_2$-C≡C-H); 6.68 (s, 1H, H-4), 7.2-7.80 (A$_2$B$_2$, 4H$_{arom}$); M$^+$, 248; (Found : C, 58.29; H, 4.03; N, 11.65; Calc. for $C_{12}H_9ClN_2S$ (248·5): C, 57.94; H, 3.62; N, 11.26%).

Attempted Thioclaisen Rearrangement of 69a. The pyrazole 69a (2.14g,01mol) was refluxed in various solvents like benzene, toluene, quinoline and N,N-dimethylaniline for 10-20 hrs. Work-up of the reaction mixture in all the experiments yielded only starting material, 69a, (m.m.p, superimposable IR and NMR spectra).

TABLE 5

Physical and analytical data of 3-aroyl-2-(N-azacycloalkyl)-4-methylthiophenes (52a-j).

Product	Yield [%]	m.p. [°C]	Molecular formula	Calc. Found	Analyses (%) C	H	N
52a[a,c]	59	75	$C_{16}H_{17}NOS$		70.85	6.26	5.16
			(271)		71.09	6.43	5.22
52b[b,d]	57	65-67	$C_{17}H_{19}NO_2S$		67.78	6.30	4.64
			(301)		67.94	6.11	4.86
52c[a,c]	64	106	$C_{16}H_{16}ClNOS$		62.87	5.23	4.58
			(305.5)		62.60	5.54	4.76
52d[a,c]	46	Semi solid	$C_{17}H_{19}NOS$		71.58	6.66	4.90
			(285)		71.89	6.36	4.82
52e[b,d]	56	Semi solid	$C_{18}H_{21}NO_2S$		68.58	6.66	4.44
			(315)		68.31	6.80	4.26

Table 5 (Contd.)

52f[a,c]	64	110	$C_{17}H_{18}ClNOS$	63.88	5.60	4.38
			(319)	63.50	5.86	4.57
52g[a,c]	62	81	$C_{16}H_{17}NO_2S$	66.90	5.91	4.87
			(287)	67.22	5.78	5.06
52h[b,d]	54	123-124	$C_{17}H_{19}NO_3S$	64.36	5.98	4.41
			(317)	64.60	6.27	4.12
52i[a,c]	66	126	$C_{16}H_{16}ClNO_2S$	59.75	4.97	4.35
			(321.5)	59.90	5.18	4.52
52j[b,c]	42	147-148	$C_{22}H_{22}N_2OS$	72.94	6.07	7.73
			(362)	72.61	6.22	8.04

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[a] Reaction was carried out in benzene.

[b] Reaction was carried out in benzene/chloroform.

[c] Purified by column chromatography eluting with hexane.

[d] Purified by column chromatography eluting with hexane/benzene (7:3).

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CHAPTER IV

REARRANGEMENT STUDIES ON S-PROPARGYL-N-ANILINO/ETHYLAMINO ACETALS: A FACILE ONE STEP SYNTHESIS OF 3-PHENYL OR 3-ETHYL-4-METHYL-2-(SUBSTITUTED-METHYLENE)-THIAZOLINES*

IV. 1 INTRODUCTION

In the preceding chapter, thermal rearrangements of S-propargyl-N-aminoacetals derived from cyclic secondary amines were studied which led to the synthesis of novel 2-cycloamino-3-aroyl-4-methylthiophenes. In the present chapter, it was intended to study the sigmatropic rearrangements of S-propargyl-N-aminoacetals derived from primary amines like aniline or ethylamine. However, attempted preparations of S-propargyl-N-anilinoacetals (9) resulted in the formation of novel title thiazolines in excellent yields. These results are described in this chapter.

IV. 2 RESULTS AND DISCUSSIONS

Lawesson and coworkers[2] have reported alkylation of thioanilides 2 derived from active methylene compounds with allyl or crotyl bromide which yielded a complex mixture of unrearranged S,N-acetal 3, dialkylated product 4, rearranged product 5, its

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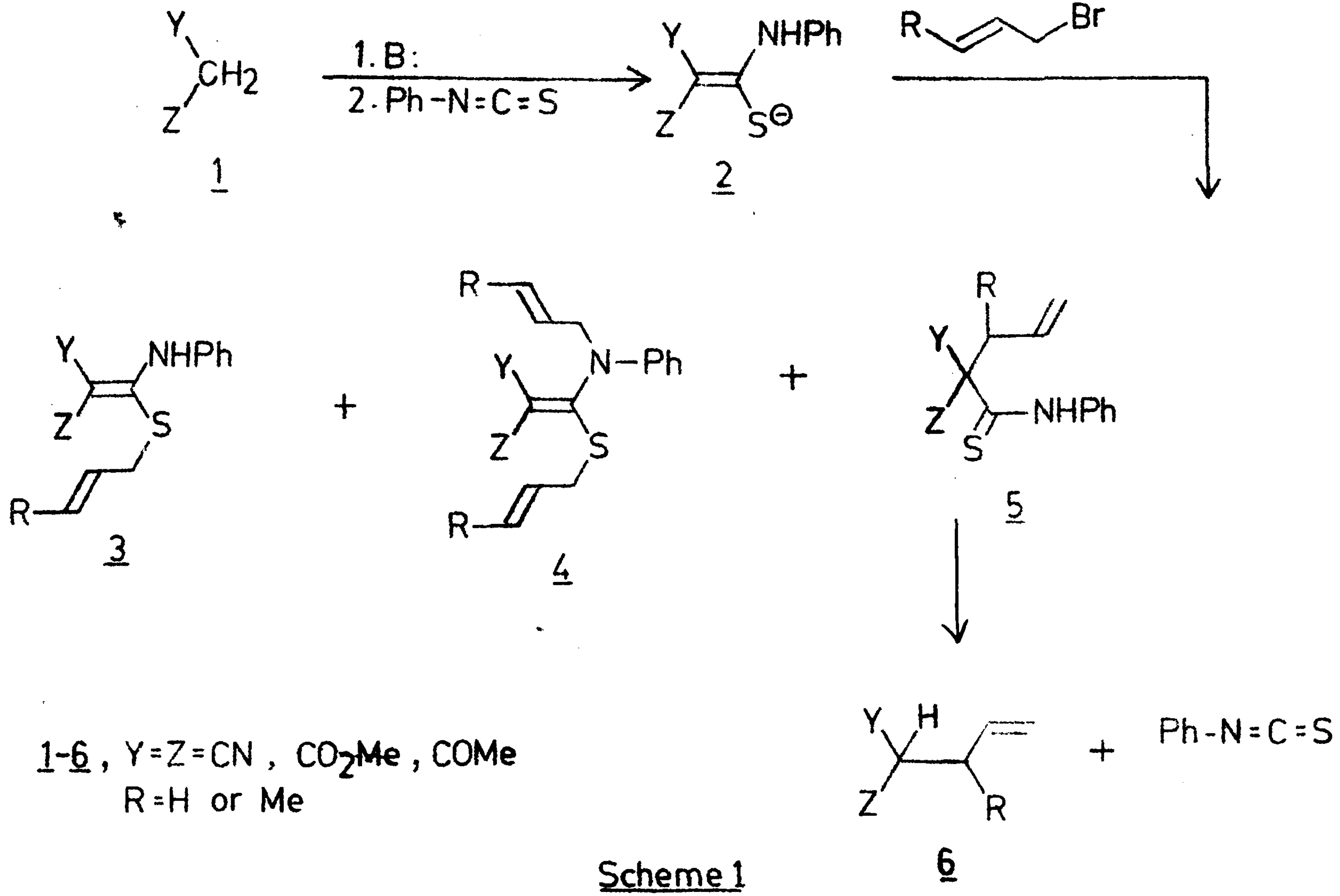
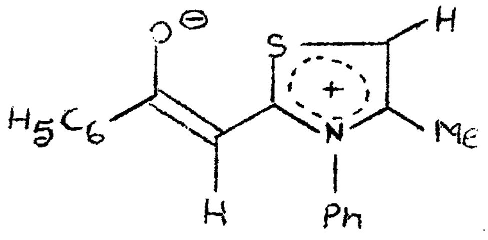
*S.S. Bhattacharjee, C.V. Asokan, H. Ila and H. Junjappa, Synthesis, 1062 (1982).



1-6, Y=Z=CN, CO_2Me, COMe
R=H or Me

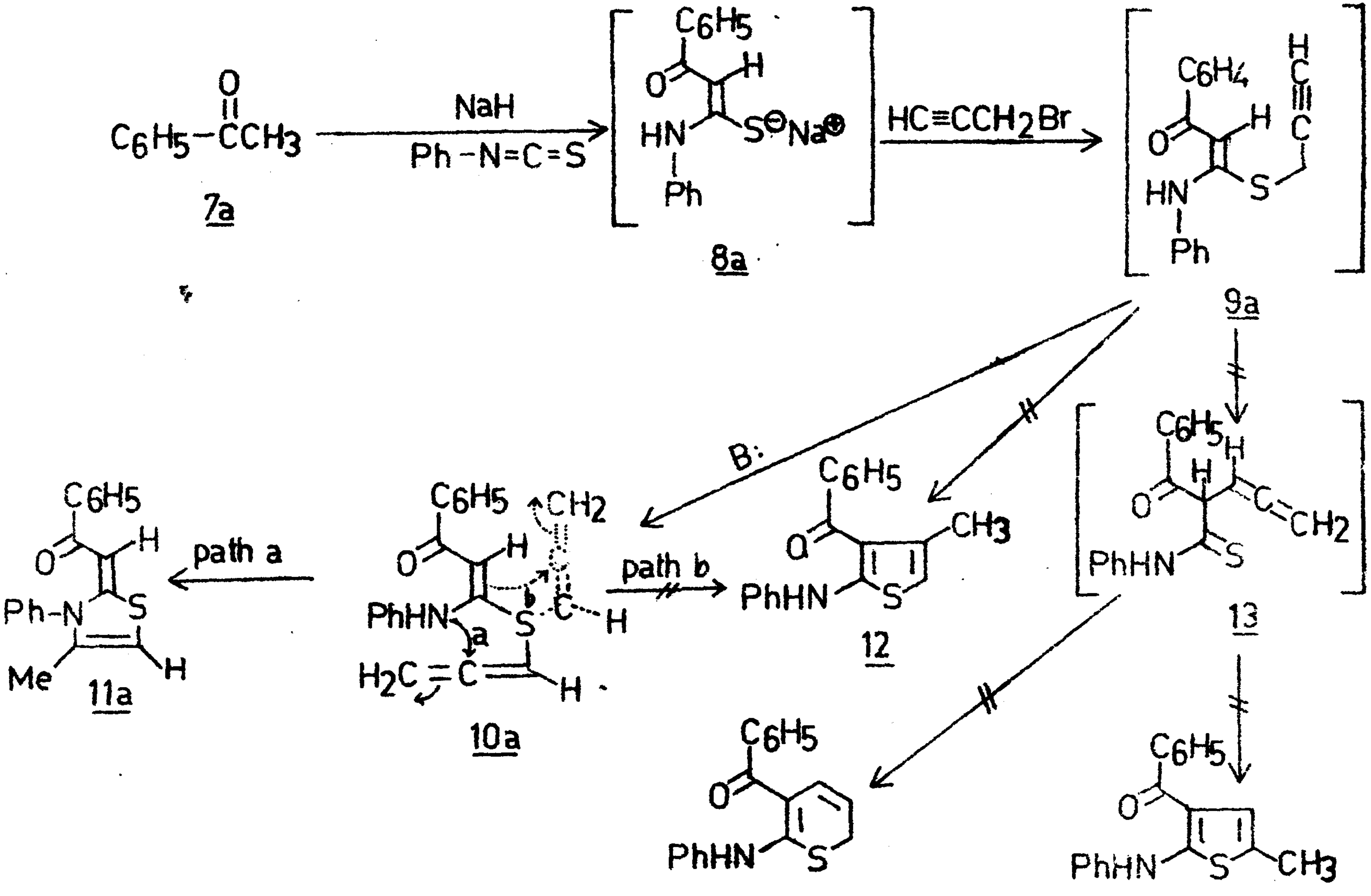
Scheme 1

cleavage products 6 and phenyl isothiocyanate (Scheme 1). No attempts to alkylate these thioanilides (2) with propargyl bromide were made. In an attempt to prepare the corresponding S-propargyl-N-anilinoacetal 9a, when the acetophenone (7a) was reacted with phenylisothiocyanate in the presence of sodium hydride in dimethylformamide, work-up of the reaction mixture did not yield the desired 9a. The product thus obtained in 71% yield was characterized as 3-phenyl-4-methyl-2-(benzoylmethylene)-thiazoline 11a on the basis of spectral and analytical data (Scheme 2). Thus 11a showed molecular ion peak at m/z 293 and was analysed for $C_{18}H_{15}NOS$. Its IR spectrum (Nujol) showed weak and medium intensity bands at 1590 and 1560 cm^{-1}. The absence of carbonyl peak in the IR spectra of 11a is due to the zwittorionic form A which



A

makes major contribution to the resonance hybrid.[3] Further confirmation for the thiazoline structure 11a was obtained from its NMR spectrum ($CDCl_3$) which showed a sharp doublet (3H, J=1.2 Hz) at δ 1.92 assigned to 4-methyl protons which couple with the H-5 allylic protons. The quartet (1H, J=1.2 Hz) at δ 5.92 was assigned to H-5 proton, while the other olefinic proton appeared as broad singlet at δ 6.14 (1H). The ten aromatic protons

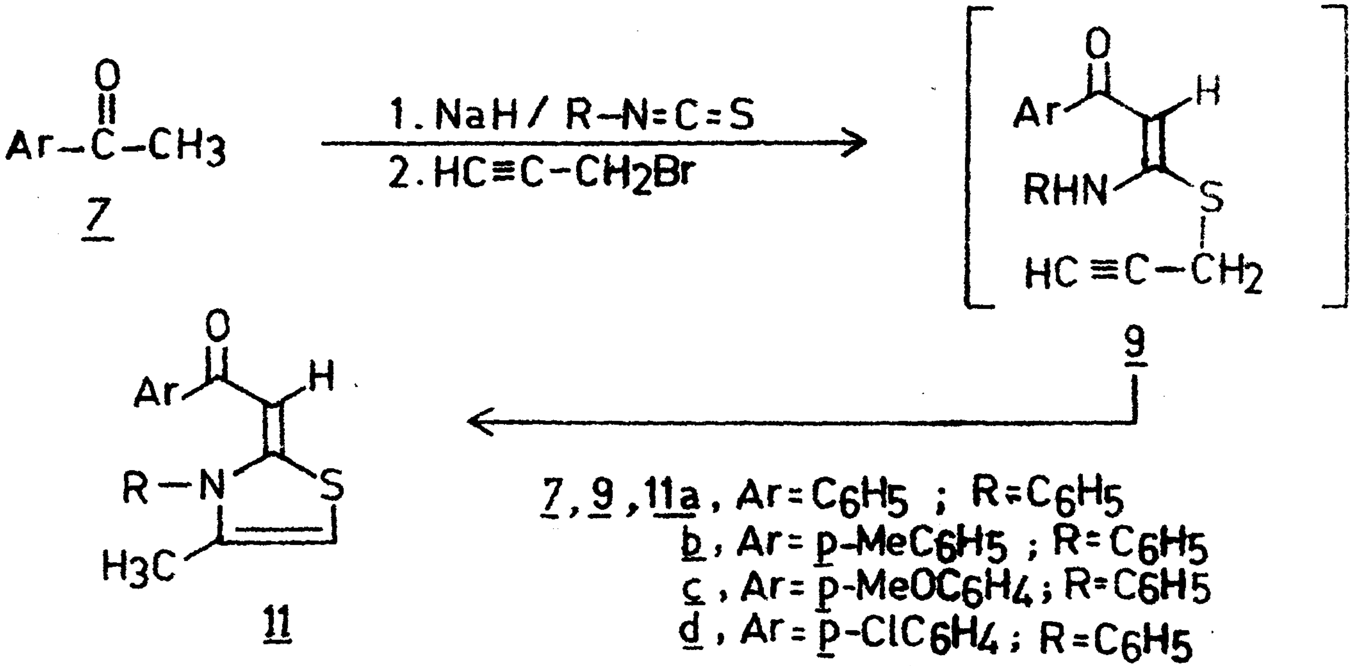

C6H5–CCH3
7a
NaH
Ph–N=C=S
8a
HC≡CCH2Br
9a
B:
10a
path a
path b
11a
12
13
14
15
PhHN
Ph-N
Me

Scheme 2

were present as broad multiplet at δ 7.05-7.85 (m, 10H). The presence of two singlets due to olefinic protons rules out either of the thiophene structures 12 or 15 or dihydropyran 14. The reaction was found to be general and the other substituted thiazolines 11b-g were obtained from various substituted acetophenones and phenyl or ethyl isothiocyanate in 65-72% overall yields (Scheme 3). The structures of 11b-g were confirmed with the help of spectral and analytical data (Table 1 and 2).

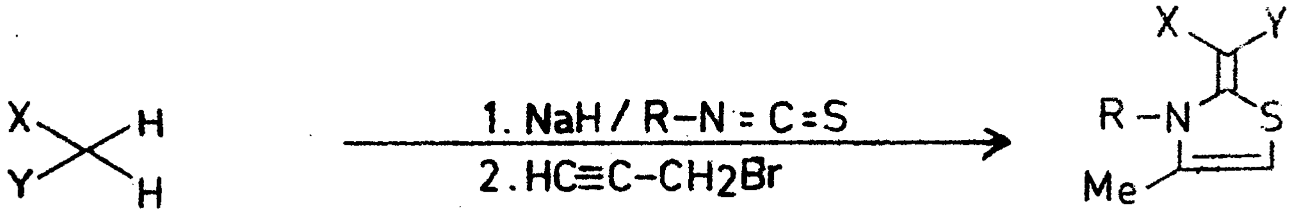
When the reaction was extended to other active methylene compounds like phenylacetonitrile, the corresponding 3-N-phenyl-(17a) and 3-N-ethyl-(17b)-thiazolines were obtained in 83% and 82% yields respectively. Similarly acetylacetone yielded the thiazoline 17c in 75% yield on treatment with phenyl isothiocyanate and propargyl bromide under the identical conditions (Scheme 4). The structures of 17a-c were confirmed with the help of spectral and analytical data (Table 1 and 2). The other active methylene compounds like acetone, nitromethane, ethylacetoacetate and ethylcyanoacetate however, yielded intractable complex reaction mixtures under similar conditions, from which the desired thiazolines could not be isolated.

Our survey of the literature revealed that the three methods for the preparation of thiazolines are reported. In the first



$\underline{7}, \underline{9}, \underline{11a}$, Ar = C_6H_5 ; R = C_6H_5
$\underline{b}$, Ar = $\underline{p}$-MeC_6H_5 ; R = C_6H_5
$\underline{c}$, Ar = $\underline{p}$-MeOC_6H_4 ; R = C_6H_5
$\underline{d}$, Ar = $\underline{p}$-ClC_6H_4 ; R = C_6H_5
$\underline{e}$, Ar = C_6H_5 ; R = Et
$\underline{f}$, Ar = $\underline{p}$-MeOC_6H_4 ; R = Et
$\underline{g}$, Ar = $\underline{p}$-ClC_6H_4 ; R Et

Scheme 3



16

17

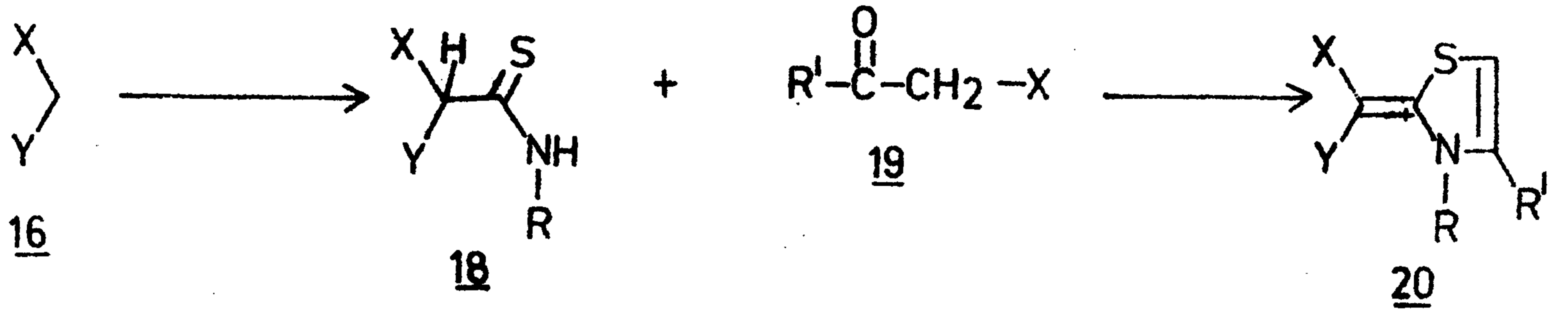
16, 17a, X = C_6H_5 ; Y = CN ; R = C_6H_5
b, X = C_6H_5 ; Y = CN ; R = Et
c, X = Y = MeCO ; R = C_6H_5

Scheme 4

method, the corresponding thioanilides 18 on condensation with α-halocarbonyl compounds 19 afford the corresponding thiazolines 20 (Scheme 5) in varying yields.[3-5] However this method requires prior preparation of thioanillides and yields are low in the case of 4-methylderivatives. In the second method the corresponding 3-alkyl- or 3-aryl-4,5-substituted-2-(benzoylmethylene)-thiazolines 23 are obtained in low yields (20-40%) by base catalysed elimination of sulfur from the corresponding 2-phenacylthiothiazolium salts 22,[6] which are obtained from the respective ketones in three steps via thiazolines 22 (Scheme 6). The third method involves acylation of 2-methylthiazolium salts (24) with 1-oxoalkanephosphonates 25 (Scheme 7), which also requires prior preparation of 24 and 25. The present method therefore provides a convenient route to novel 3-aryl- or 3-alkyl-4-methyl-2 (substituted methylene)-thiazolines directly from active methylene compounds in excellent yields.

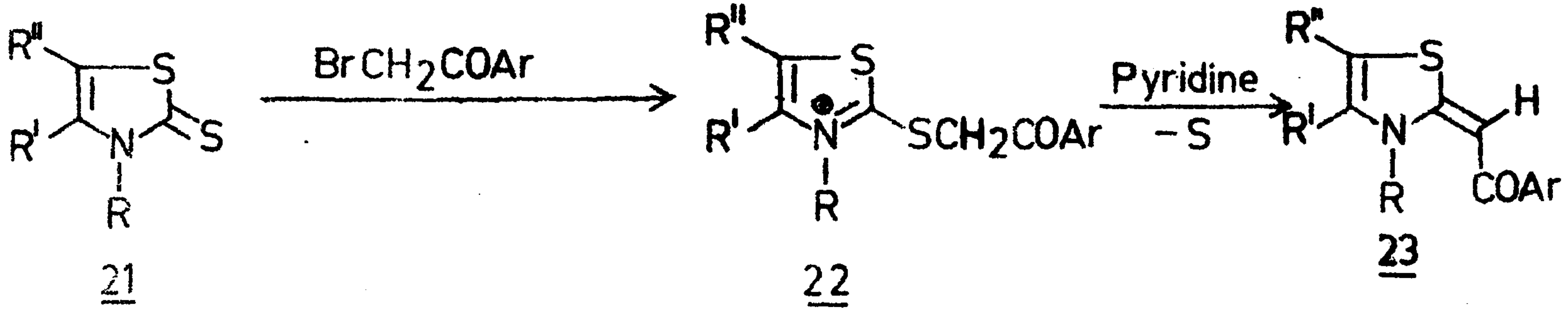
IV. 3 MECHANISM OF THIAZOLINE FORMATION

The mechanism of formation of thiazolines 11 apparently involves intramolecular attack of nitrogen lone pair (or anilino anion) on the activated acetylenic double bond (or allenic double bond in the intermediate 10) in the initially formed S,N-acetals 9 (Scheme 2). Thus the S,N-propargyl acetals 9 do not undergo



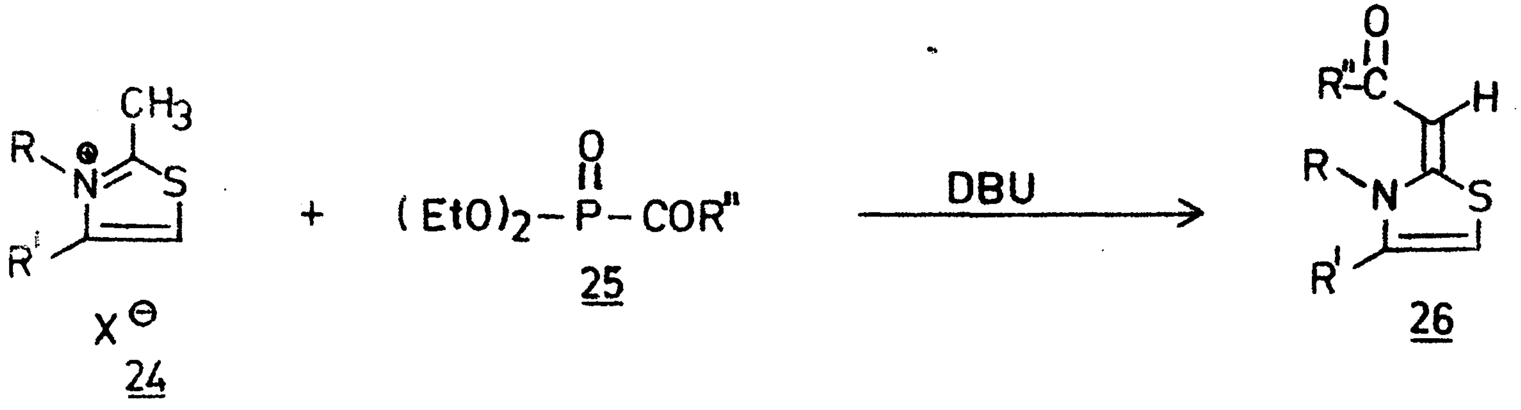
16-20, X = CN or CO_2Et ; R = R' = Substituted aryl
X = CN or CO_2Et ; Y = H ; R = R' = Aryl
X = MeCO ; Y = H ; R = Ph ; R' = Ph or Me

Scheme 5



21–23 R=Me or Ph, R'=Ph; R''=H or Ph; Ar = C_6H_5

Scheme 6

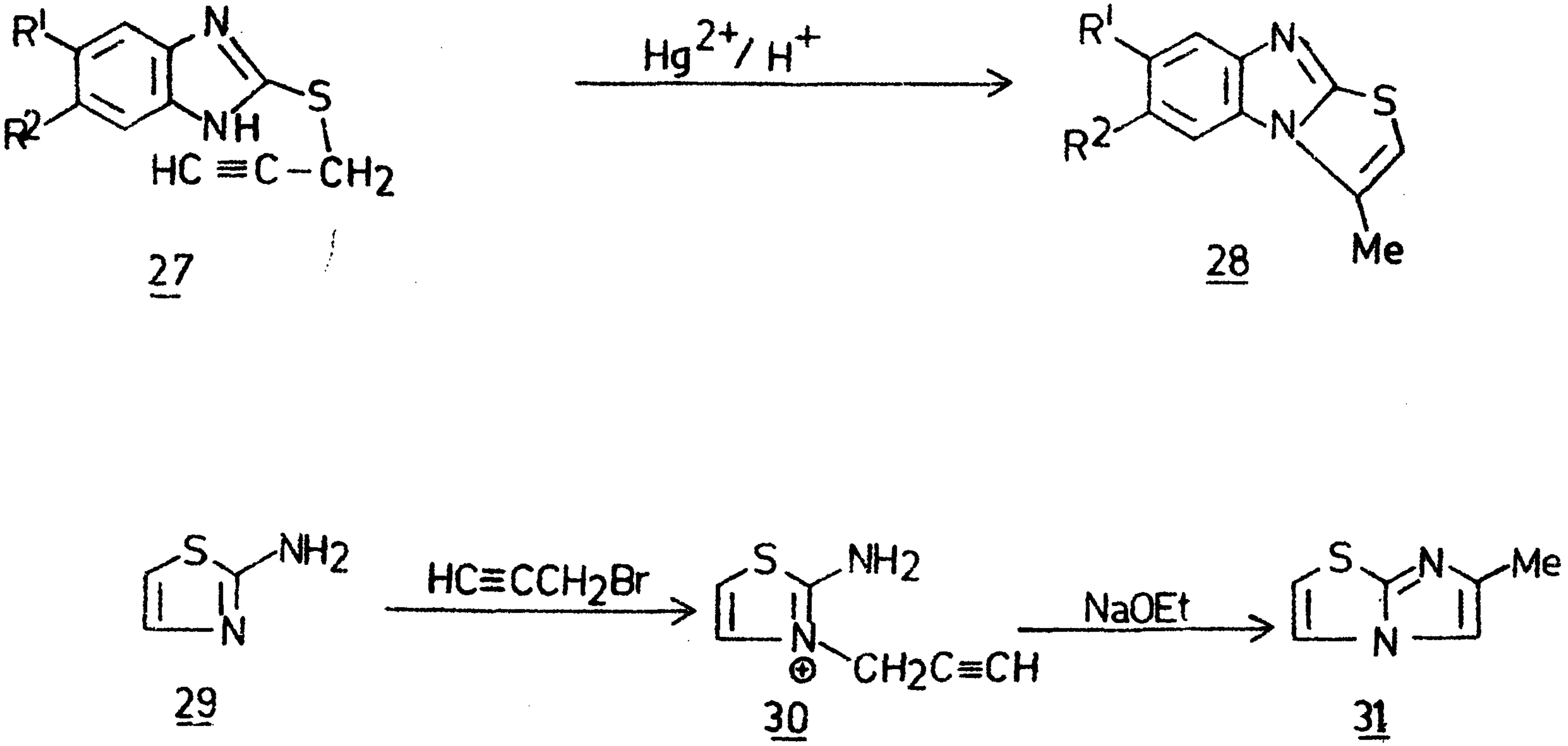


$R = Me$; $R' = Me$; $CH_2=CH-CH_2$; $Me-CH=CH-$ etc
$R'' = C_6H_5$; *p*-$MeOC_6H_4$; *p*-ClC_6H_4 ; *p*-MeC_6H_4
and *m*-BrC_6H_4

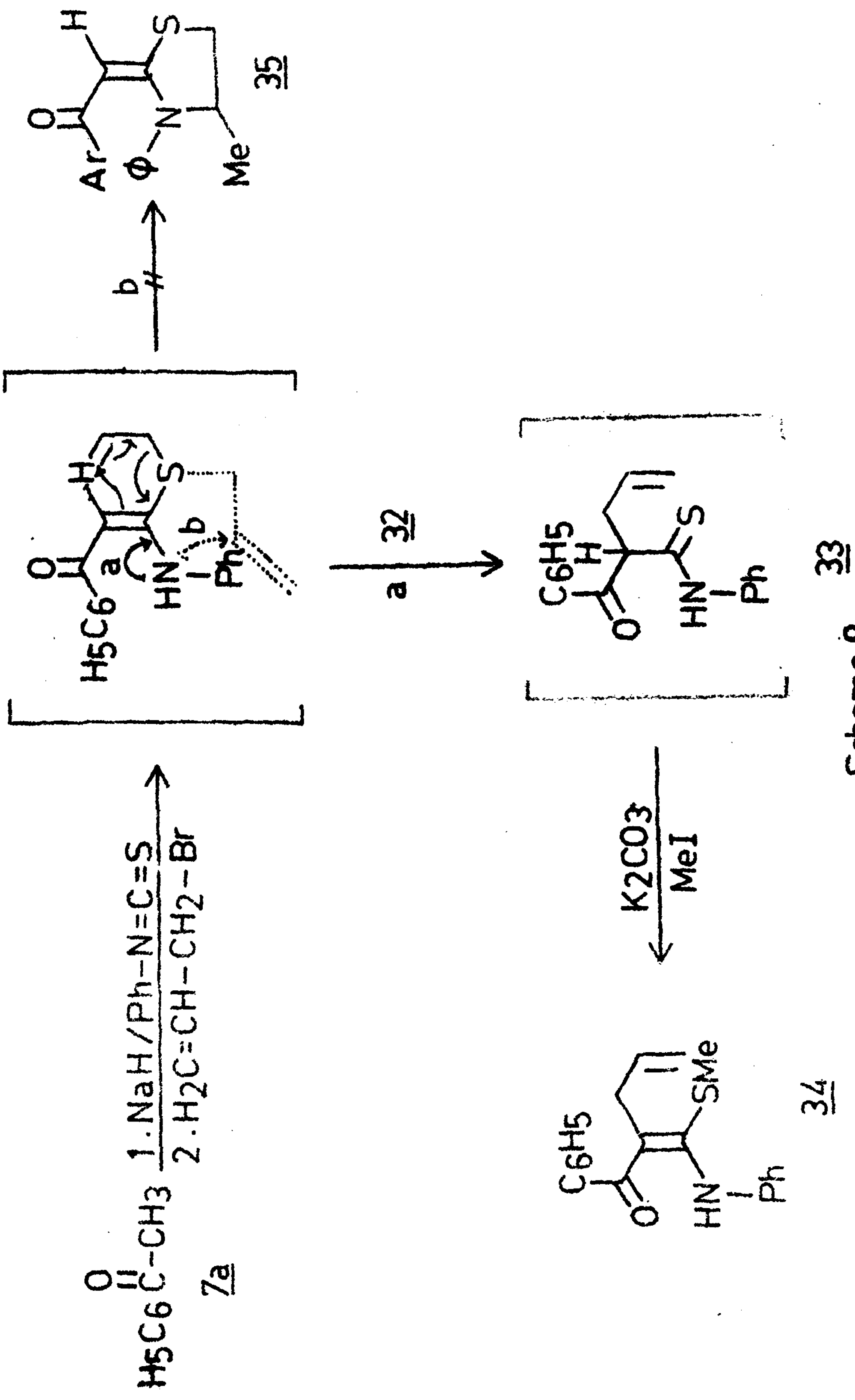
Scheme 7

thioclaisen rearrangements to give either dihydropyrans 14 or 5-methylthiophenes 15. Formation of 4-methylthiophene 12 by nucleophilic attack of β-carbon of enaminone moeity on allenic double bond (in the intermediate 10, path b, scheme 2) is also not observed in the present case. The reason for the facile cyclization of 9 to give 11 appears to be the basic reaction conditions employed, which enhances the nucleophilicity of the amine nitrogen. Similar kind of cyclizations to give fused thiazolines 28 have been observed in mercury (II) catalysed reactions of 2-(2-propargylthio)benzimidazoles 27 (Scheme 8).[9] The corresponding N-propargylthiazolium bromide 30 also undergoes similar base catalysed ring closure to give 6-methylimidazoles [2,1-b] thiazole (31) (Scheme 8).[10]

The thermal rearrangement of 9 under neutral conditions could not be studied since all attempts to isolate S,N-acetal 9 under varying conditions were unsuccessful. Interestingly, when the acetophenone 7a was reacted with phenylisothiocyanate and allyl bromide in the presence of sodium hydride, the corresponding β-benzoyl-α-allylthioacetanilide 33 was obtained in 72% yield. The structure of 33 was confirmed with the help of spectral and analytical data (experimental). The anilide 33 is apparently formed by spontaneous thioclaisen rearrangement of *insitu* generated S-allyl-N-anilinoacetal 32. The alkylation of 33 with methyl


R1
R2
N
NH
S
HC≡C–CH2
27
Hg2+/ H+
R1
R2
N
N
S
Me
28
S
NH2
N
29
HC≡CCH2Br
S
NH2
N
⊕
CH2C≡CH
30
NaOEt
S
N
Me
N
31

Scheme 8


H5C6C(=O)-CH3
7a
1. NaH / Ph-N=C=S
2. H2C=CH-CH2-Br
H5C6
O
H
HN
Ph
S
a
b
a
32
b
Ar
O
H
S
N
Φ
Me
35
C6H5
H
O
S
HN
Ph
33
K2CO3
MeI
C6H5
O
HN
Ph
SMe
34

Scheme 9

iodide in the presence of potassium carbonate in refluxing acetone gave the corresponding S,N-acetal 34. Thus the cyclization pathway to give dihydrothiazoline 35 is not operative (path b) in the case of S,N-acetal 32, which is apparently due to absence of activated acetylenic or allenic double bond in 32. In the absence of such cyclization, thioclaisen rearrangement of 32 to give 33 is favoured.

IV. 4 EXPERIMENTAL

M.ps were determined on a 'Boetius' (German) apparatus and are uncorrected. The IR spectra were recorded on Perkin-Elmer 297 spectrophotometer. The NMR spectra were recorded on a Varian EM-390 spectrometer using TMS as an internal standard and the chemical shifts are expressed in ppm (δ-units).

The Starting Materials

The commercial samples of acetophenone, *p*-methylacetophenone, *p*-methoxyacetophenone, *p*-chloroacetophenone, phenylacetonitrile, acetylacetone, acetone, nitromethane, propargyl bromide, allyl bromide were purified before use.

The ethyl isothiocyanate, bp 130-1°C (760 mm)[11] and phenyl isothiocyanate, bp 120-1°C (35 mm)[12] were prepared by the reported procedures.

TABLE 1

Spectral data of the products, **11a-g** and **17a-c**

Product	IR (Nujol) ν [cm^{-1}]	^{1}H-N.M.R.(CDCl$_3$) δ [ppm]	M.S. m/e (M$^+$)
11a	1590 (w); 1560 (m)	1.92 (s, 3H, C$\underline{H}_3$); 5.92 (br s, 1H, $\underline{H}$-5); 6.14 (s, 1H$_{olefinic}$); 7.05-7.85 (m, 10H$_{arom}$).	293
11b	1595 (w); 1585 (w); 1550 (m)	1.90 (s, 3H, C$\underline{H}_3$); 2.32 (s, 3H, *p*-C$\underline{H}_3$); 5.88 (s, 1H, $\underline{H}$-5); 6.10 (s, 1H$_{olefinic}$); 6.75-7.80 (m, 9H$_{arom}$).	307
11c	1601 (w); 1585 (w); 1550 (m)	1.87 (s, 3H, C$\underline{H}_3$); 3.72 (s, 3H, *p*-OC$\underline{H}_3$); 5.72 (s, 1H, $\underline{H}$-5); 5.98 (s, 1H$_{olefinic}$); 6.5-7.4 (dd, A$_2$B$_2$, 4H$_{arom}$); 7.45-7.70 (m, 5H$_{arom}$).	323

Table 1 (Contd.)

11d	1601 (w); 1584 (w); 1552 (m)	1.90 (s, 3H, $C\underline{H}_3$); 5.82 (s, 1H, $\underline{H}$-5); 6.15 (s, $1H_{olefinic}$); 7.05-7.75 (m, $9H_{arom}$).	$327^{(35\,Cl)}$
11e	1682 (w); 1600 (w); 1560 (s)[a]	1.35 (t, 3H, $-NCH_2C\underline{H}_3$); 2.28 (s, 3H, $C\underline{H}_3$); 3.39 (q, 2H, $-NC\underline{H}_2CH_3$); 5.92 (s, 1H, $\underline{H}$-5); 6.15 (br s, $1H_{olefinic}$); 7.15-7.50 (m, $3H_{arom}$); 7.7-8.0 (m, $2H_{arom}$).	245
11f	1600 (w); 1587 (m); 1550 (s)[a]	1.31 (t, 3H, $-NCH_2C\underline{H}_3$); 2.18 (s, 3H, $C\underline{H}_3$); 3.80 (s, 3H, $\underline{p}$-$OC\underline{H}_3$); 3.85 (q, 2H, $-NC\underline{H}_2CH_3$); 5.95 (s, 1H, $\underline{H}$-5); 6.20 (s, $1H_{olefinic}$); 6.5-7.5 (m, $4H_{arom}$).	275
11g	1600 (m); 1593 (m); 1585 (s)[a]	1.22 (t, 3H, $-NCH_2C\underline{H}_3$); 2.13 (s, 3H, $C\underline{H}_3$); 3.60 (q, 2H, $-C\underline{H}_2CH_3$); 5.95 (s, 1H, $\underline{H}$-5); 6.15 (s, $1H_{olefinic}$); 6.65-6.95 and 7.15-7.9 (two m, $4H_{arom}$).	$279^{(^{35}Cl)}$

Table 1 (Contd.)

17a	2172 (ν_{CN}); 1595 (m) 1547; 1520	1.80 (s, 3H, $C\underline{H}_3$); 5.63 (s, 1H, $\underline{H}$-5); 7.05-7.6 (m, 10H_{arom}).	290
17b	2160 (ν_{CN}); 1610 (w); 1595 (w); 1572 (w)	1.47 (t, 3H, $-NCH_2C\underline{H}_3$); 2.15 (s, 3H, $C\underline{H}_3$); 4.21 (q, 2H, $-NC\underline{H}_2C\underline{H}_3$); 5.53 (s, 1H, $\underline{H}$-5); 7.0-7.5 (m, 5H_{arom}).	242
17c	1695 (m) (ν_{CO}); 1622 (s)	1.90 (s, 3H, $C\underline{H}_3$); 1.98 (s, 3H, $C\underline{H}_3$); 6.45 (s, 1$H_{olefinic}$); 7.09-7.55 (m, 5H_{arom}).	273

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[a] IR spectrum in KBr.

3-N-Aryl/alkyl-4-methyl-2(benzoyl/cyano-phenyl/bisacetylmethylene-thiazolines (11a-g) and (7a-c) : General Procedure :

To an ice cooled and well stirred suspension of sodium hydride (2.0g, 0.041 mol, 50% suspension) in 40 ml of dry dimethylformamide, 0.04 mol of acetophenone or other active methylene compound in 5 ml of dimethylformamide was added followed by subsequent addition of 0.04 mol of aryl/alkyl isothiocyanate in 8 ml of dimethylformamide. The ice cooled reaction mixture was further stirred for 2 hr and 4.8g (0.041 mol) of propargyl bromide in 10 ml of dimethylformamide was slowly added during 30 min. After further stirring with cooling for 1.5 - 2 hr, the reaction mixture was poured over crushed ice and extracted with chloroform(3 x 150 ml). The organic layer was washed with water (3x150 ml), dried (Na_2SO_4) and evaporated to give brown viscous residue, which gave pure thiazolines either by trituration (11a-d, 17a-c) with hexane and methylene chloride or by passing silica gel column (11e-g) and eluting with ethylacetate/hexane(3:7) mixture. All thiazolines 11a-g and 17a-c were crystallyzed from methylene chloride-hexane mixture. The spectral and analytical data of thiazolenes 11a-g and 17a-c is given in table 1 and 2.

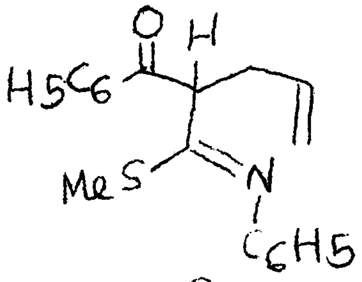
Preparation of α-allyl-β-benzoyl-thioacetanilide (33)

To an ice-cooled and well stirred suspension of sodium hydride(2.0g, 0.04 mol, 50% suspension) in 5 ml dry dimethyl formamide, 4.8g (0.04 mol) of acetophenone was added followed by subsequent addition 5.40g (0.04 mol) of phenyl isothiocyanate. The ice-cooled reaction mixture was further stirred for 2 hrs and allyl bromide (4.84g, 0.04 mol) in 10 ml dimethylformamide was slowly added during 30 minutes. After further stirring with cooling for 2 hr, the reaction mixture was worked up as described above to yield crude 33 which on crystallization from benzene/hexane yielded bright yellow needles of 33, yield 8.5g (72%); mp. 115-116°C; IR(KBr) ν_{max} 3200 (NH), 1690 (CO) cm^{-1}; NMR (CDCl$_3$); 2.88 (t, -C$\underline{H}_2$-CH=CH$_2$); 5.0-5.9 (m, 4H, -C$\underline{H}$=C$\underline{H}_2$ and CO-C$\underline{H}$-); 7.2-8.2 (m, 10H$_{arom}$); M.S; (m/e); M$^+$, 295; (Found: C, 73.54; H, 5.42; N, 4.41; Calc. for $C_{18}H_{17}NOS$ (295.4); C, 73.22; H, 5.76; N, 4.74%).

Preparation of α-allyl S,N-acetal 34 from 33.

A suspension of 2.95g (0.01 mol) of 33 and 2g (0.015 mol) of anhydrous potassium carbonate in 60 ml of dry acetone was refluxed for 3 hr with stirring. The reaction mixture was cooled to room temperature and 1.4g (0.01 mol) of methyl iodide in 10 ml of dry benzene was added slowly with stirring. After further stirring for 4 hr at room temperature, the reaction mixture was poured over ice cooled water, extracted with chloroform, dried (Na$_2$SO$_4$) and evaporated to give crude 34 as viscous liquid which was further purified by column chromatography over silica gel using hexane/benzene (2:1) as eluent. Yield 2.62g (85%), viscous liquid

(TLC single spot); IR(neat) ν_{max} ; 3140 (NH), 1695 (CO) 1600 (C=C) cm^{-1}; NMR ($CDCl_3$): 2.32 (s, 3H, $SC\underline{H}_3$); 2.89-3.30 (m, 2H, $-C\underline{H}_2-CH=CH_2$), 5.2-6.1 (m, 3H, $-C\underline{H}=C\underline{H}_2$); 7.1-7.75 (m, 10$H_{arom}$); M.S. : (m/e): M^+, 309; (Found : C, 73.45; H, 6.51; N, 4.87; Calc. for $C_{19}H_{19}NOS$ (309): C, 73.78; H, 6.14; N, 4.53%). The S,N-acetal 34 exist in imino form B.



B

TABLE 2

Physical and analytical data of 3-alkyl or 3-aryl-4-methyl-2-(substituted methylene) 2,3-dihydro-1,3-thiazolines, (11a-g) and (17a-c).

Product	yield[a] (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis (%)		
					C	H	N
11a	71	159-160	$C_{18}H_{15}NOS$		73.73	5.11	4.77
			(293)		73.49	5.23	4.90
11b	68	188-190	$C_{19}H_{17}NOS$		74.28	5.53	4.55
			(307)		74.06	5.38	4.41
11c	73	154-155	$C_{19}H_{17}NO_2S$		70.60	5.25	4.33
			(323)		70.75	5.12	4.57
11d	65	174-175	$C_{18}H_{14}ClNOS$		65.98	4.27	4.27
			(327.5)		66.14	4.40	4.09
11e	67	112	$C_{14}H_{15}NOS$		68.57	6.11	5.70
			(245)		68.28	6.30	5.56

Table 2 (Contd.)

11f	72	149-150	$C_{15}H_{17}NO_2S$	65.46	6.17	5.08
			(275)	65.33	6.05	5.23
11g	69	145	$C_{14}H_{14}ClNOS$	60.13	5.00	5.00
			(279.5)	60.40	5.37	4.86
17a	83	153	$C_{18}H_{14}N_2S$	74.49	4.82	9.64
			(290)	74.71	5.01	9.45
17b	82	118	$C_{14}H_{14}N_2S$	69.39	5.77	11.55
			(242)	69.58	6.03	11.17
17c	75	146-147	$C_{15}H_{15}NO_2S$	65.94	5.49	5.12
			(273)	65.66	5.20	5.36

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[a] Yields were not critically optimized.

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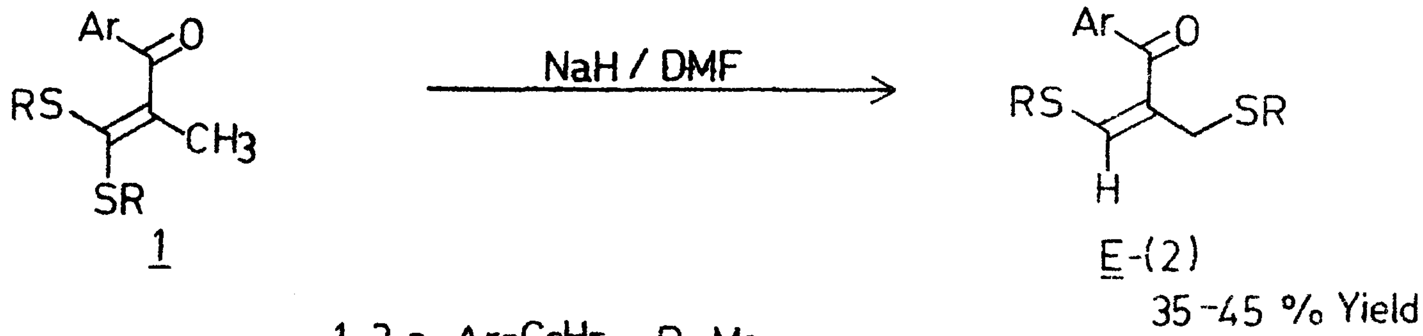
CHAPTER V

BASE CATALYSED REARRANGEMENT STUDIES ON 3,3-BIS-(METHYLTHIO)-2-ALLYL-1-ARYL-2-PROPEN-1-ONES

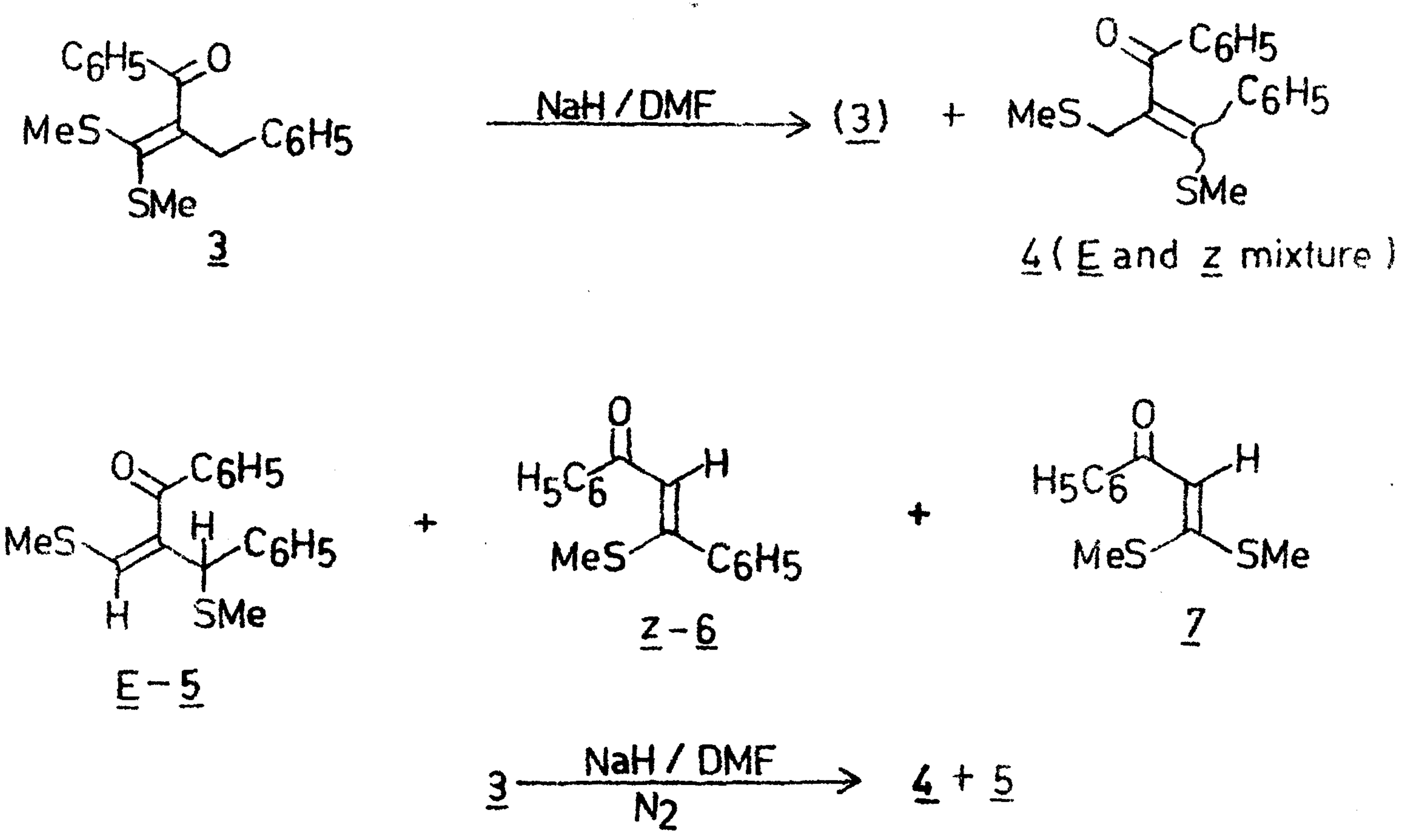
V. 1 INTRODUCTION

It has been shown[1] recently from our laboratory that the keten S,S-acetals (1) derived from various propiophenones undergo facile rearrangement in the presence of sodium hydride in dimethylformamide to give the corresponding 3-alkylthio-2-alkylthiomethylacrylophenones (2)(Scheme 1). It is further shown that the rearrangement involves a 1,3-RS shift and that it is stereoselective and yielded only E-2 isomer. Similarly when the corresponding keten S,S-acetal (3) derived from dihydrochalcone was subjected to this rearrangement a mixture of four products was obtained, which were characterized as 4 (35%), 5 (15%), 6 (5%) and 7 (20%) (Scheme 2).[2] Among these, the products 4 and 5 have been shown to be the rearrangement products of 3, while 6 and 7 are formed via



1,2 a, Ar=C_6H_5 ; R= Me
b, Ar=C_6H_5 ; R=Et
c, Ar = p -$MeOC_6H_4$; R=Me
d, Ar = C_6H_5 ; R=Et
e, Ar= p-$MeOC_6H_4$; R=Et
f, Ar= C_6H_5 ; R = i-Pr
g, Ar = p-ClC_6H_4 ; R=Me

Scheme 1



C6H5
O
MeS
C6H5
SMe
3
NaH / DMF
(3)
+
4 (E and z mixture)
E-5
+
z-6
+
7
3
NaH / DMF
N2
4 + 5

Scheme 2

oxidative cleavage of the intermediate carbonions involved in the overall transformations. This was further proved by reacting 3 with sodium hydride under nitrogen atmosphere, when the formation of 6 and 7 was not observed, while 4 (51%) and 5 (32%) were formed in improved yields. The absence of formation of 6 and 7 under nitrogen blanket confirms the participation of molecular oxygen. A mechanism[*] involving unstable mobile ketoallyl intermediate 9 was suggested for the rearrangement of 1 to 2 (Scheme 3).[1] The allyl anions 8A and 8B generated under reversible conditions compete with sodium hydride in deprotonation of 1 to give either 1 or the rearranged acrylophenone 9. Efforts to isolate 9 were unsuccessful, although the intermediacy of 9 appeared to be a definite step in arriving at the thermodynamically more stable 2. It is therefore apparant that 9 spontaneously undergoes subsequently a facile 1,3-RS shift to give the more stable 2. Among the possible alternative mechanisms for 1,3-RS shift, the thermal concerted 1,3-RS shift was ruled out because of geometrical restrictions imposed on 1,3-antarafacial sigmatropic shift and unfavourable orbital symmetry considerations to facile 1,3-superafacial shift. A sulfur assisted polar concerted mechanism through an antipolar transient complex A was tentatively suggested earlier for the rearrangement of 9 to 2 without ruling out the alternative possibilities.[1] However, our subsequent studies on the rearrangement of p-chloroderivative (1g) revealed that there exists a free alkylthioanion in the reaction mixture, which ruled out the intermediacy

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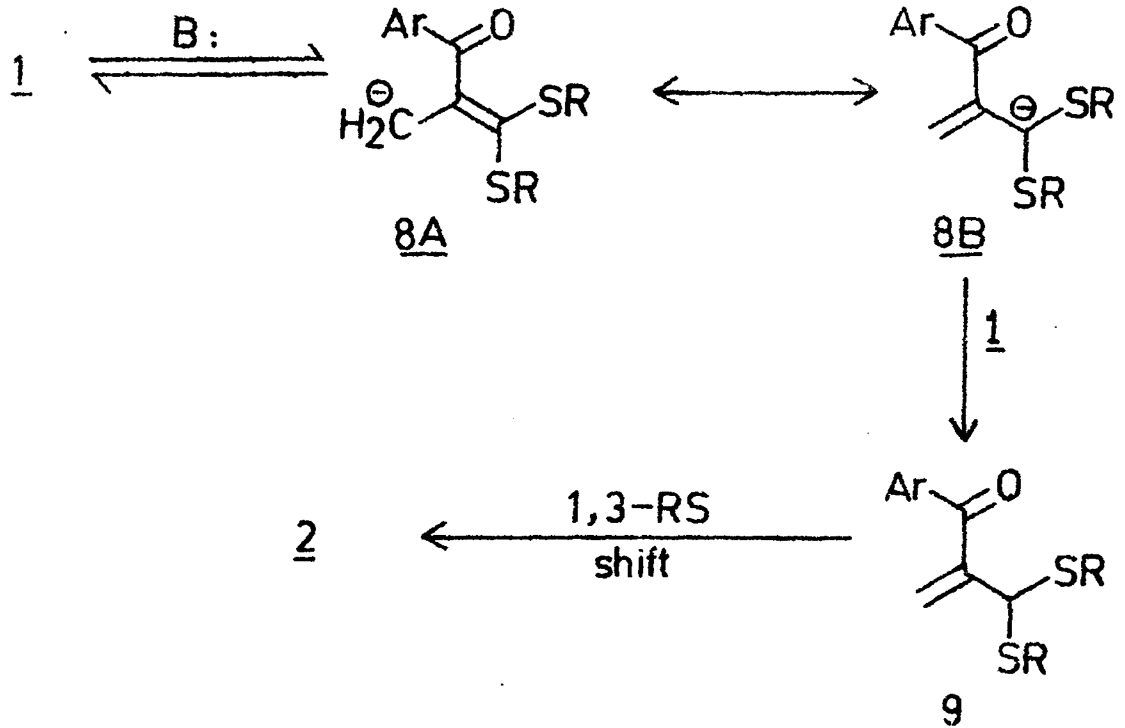
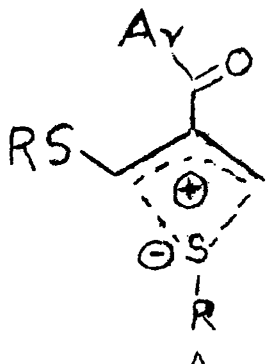
[*] A detailed mechanistic studies on this rearrangements are published in ref. 2

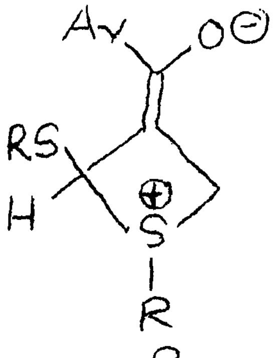


Scheme 3

of A or any other concerted process. Thus when 1g derived from p-chloropropiophenone was subjected to rearrangement under identical conditions the expected product 2g was accompanied by additional two products 10 and 11 (Scheme 4). These results demonstrate that the free methylthio anion is generated in the reaction mixture, which participates in nucleophilic displacement of active p-chloro group in 1g and 2g to give the corresponding 10 and 11 respectively. Similarly, the possibility of sulfur lone pair assisted thiatenium ion intermediate B for the rearrangement of 9 to 2 was also ruled out, since B does not permit the existance of free alkylthio anion. Further the 4-endo-trig process involving a strained intermediate such as B is quite unlikely in view of the facile nature of the rearrangement. The intermolecularity was further confirmed from

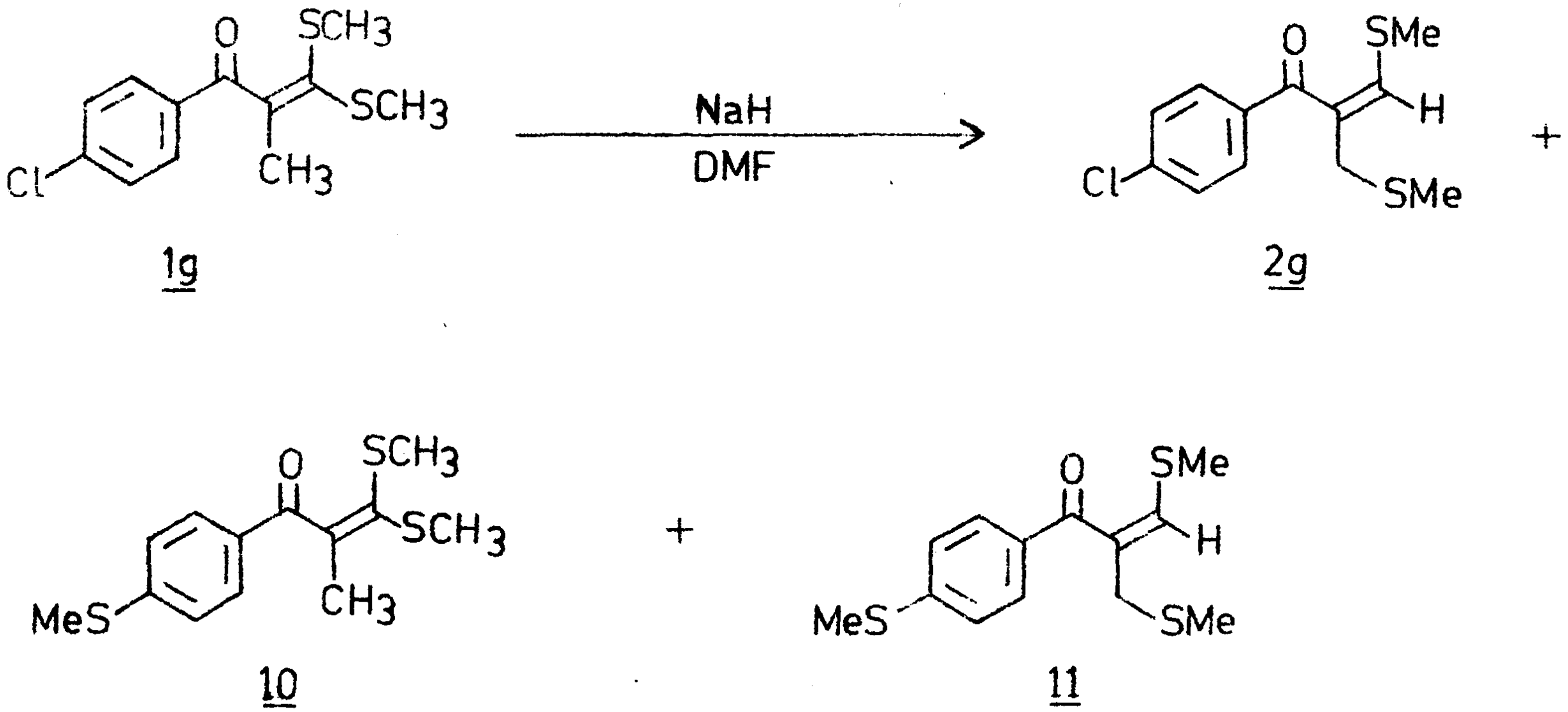


A



B

"crossover" experiments carried out with 1b and 1c. When 1:1 mixture of 1b and 1c was treated with sodium hydride in dimethylformamide

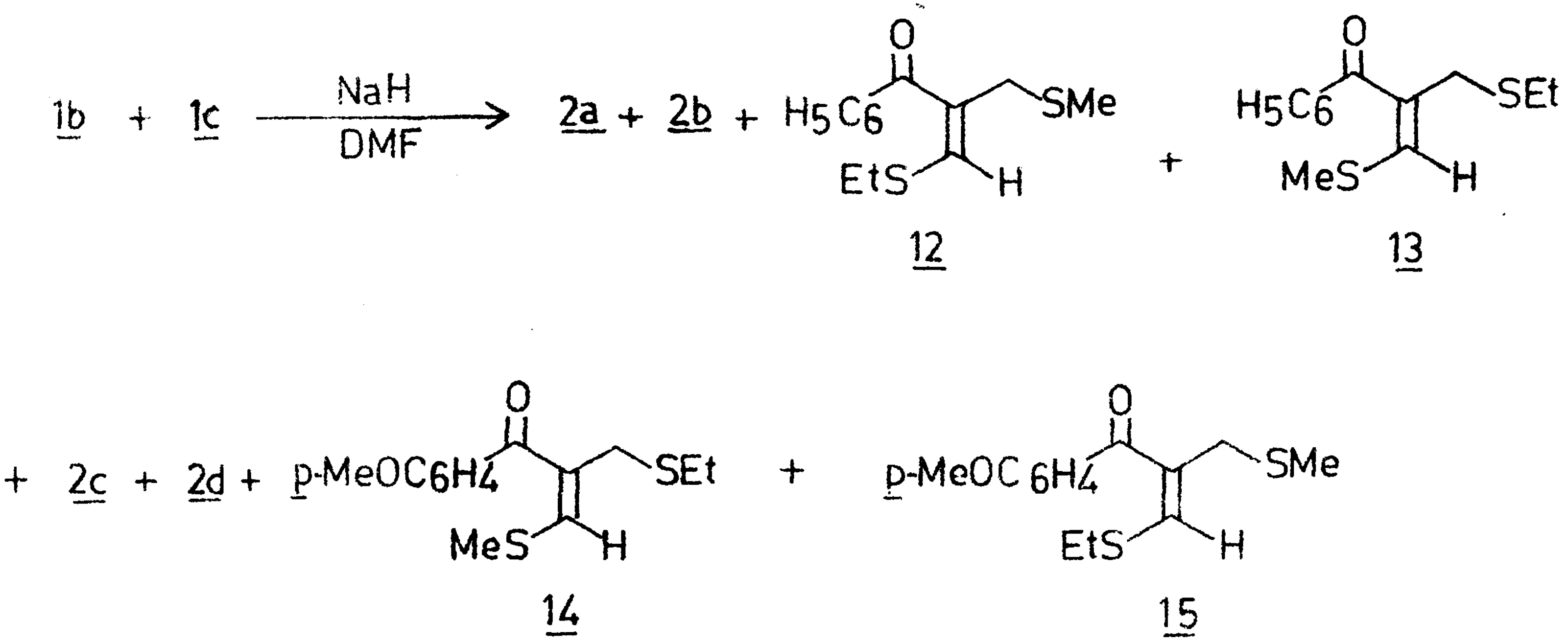

SCH3
SCH3
CH3
Cl
1g
NaH
DMF
SMe
H
SMe
Cl
2g
+
SCH3
SCH3
CH3
MeS
10
+
SMe
H
SMe
MeS
11

Scheme 4

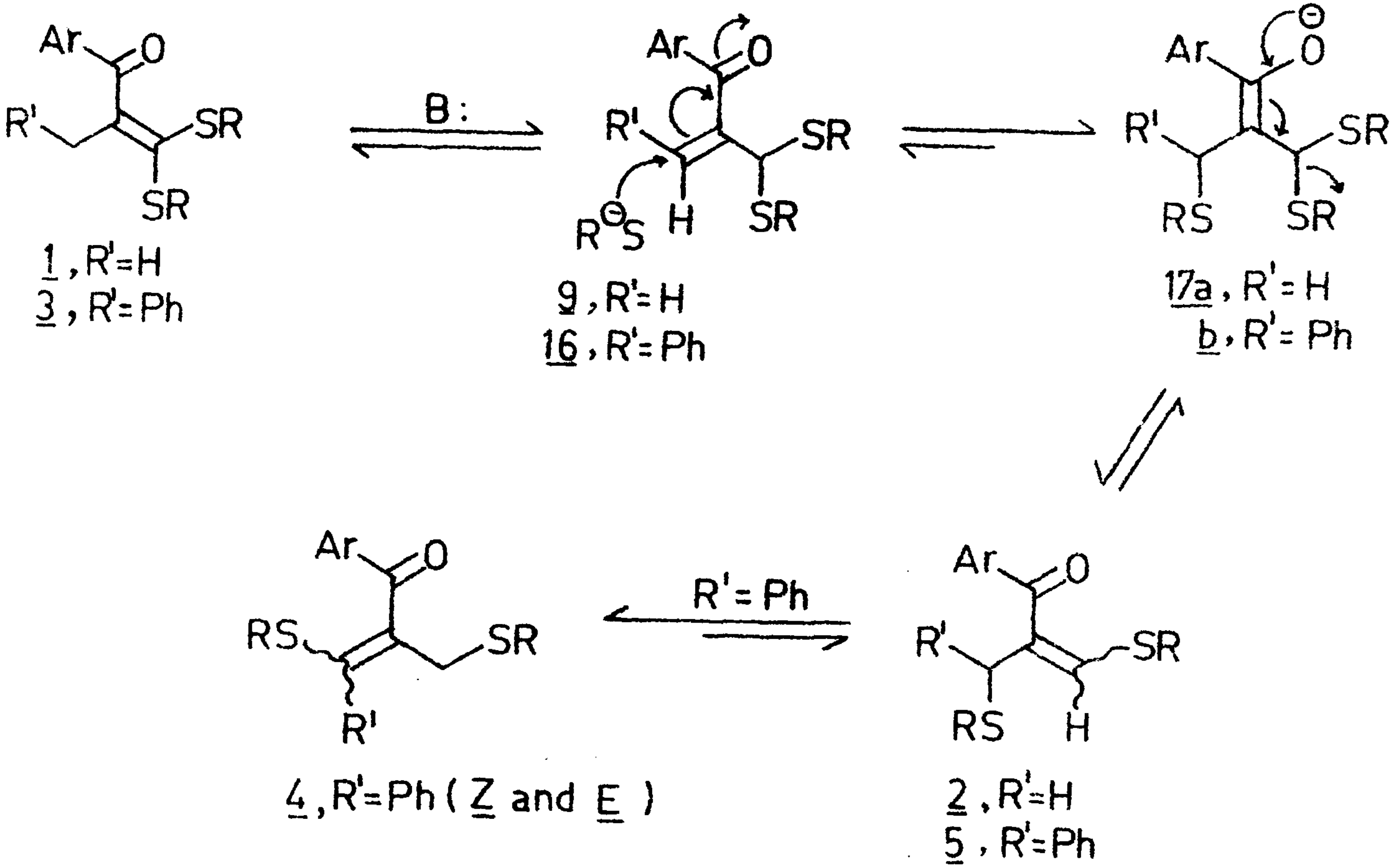
under identical conditions, a mixture of products containing 2a-d, 12, 13, 14 and 15 was obtained, there by proving that the rearrangement is intermolecular.[2] (Scheme 5).

An alternative mechanism involving radical dissociation and combination process for the conversion of 9 to 2 as proposed by Warren and coworkers for thermal and photochemical 1,3-PhS-shift was also ruled out, since the yield of 2a remained unaffected when 1a was rearranged in the presence of radical inhibitors(diphenylpicrylhydrazyl or hydroquinone). Also, the formation of dimeric products like diethylsulfide was not observed when 1b was reacted with sodium hydride either in presence or absence of nitrogen.[2]

On the basis of these results and other studies carried out in different solvents under varying conditions, a probable mechanism for 1,3-RS was suggested[2] which is shown in the scheme 6. It appears that some nucleophilic species present in the reaction mixture initiates the displacement of thiolate anion either in 9 or 16. The thiolate anion thus released in turn attacks 9 or 16. Michaelwise to give the corresponding solvent equilibriated enolate anions 17 which eliminates one of the thiolate anions to give either 2 or 5. The product 5 undergoes base catalysed 1,3-proton shift to yield the thermodynamically more stable chalcone 4. Formation of only E-2 geometrical isomer in the case of propiophenone series (R'=H) was explained due to existance of rapidly


1b
+
1c
NaH
DMF
2a
+
2b
+
H5C6
O
SMe
EtS
H
12
+
H5C6
O
SEt
MeS
H
13
+
2c
+
2d
+
p-MeOC6H4
O
SEt
MeS
H
14
+
p-MeOC6H4
O
SMe
EtS
H
15

Scheme 5


Ar
O
R'
SR
SR
1, R'=H
3, R'=Ph
B:
Ar
O
R'
SR
R⊖S
H
SR
9, R'=H
16, R'=Ph
Ar
⊖
O
R'
SR
RS
SR
17a, R'=H
b, R'=Ph
Ar
O
RS
SR
R'
4, R'=Ph (Z and E)
R'=Ph
Ar
O
R'
SR
RS
H
2, R'=H
5, R'=Ph

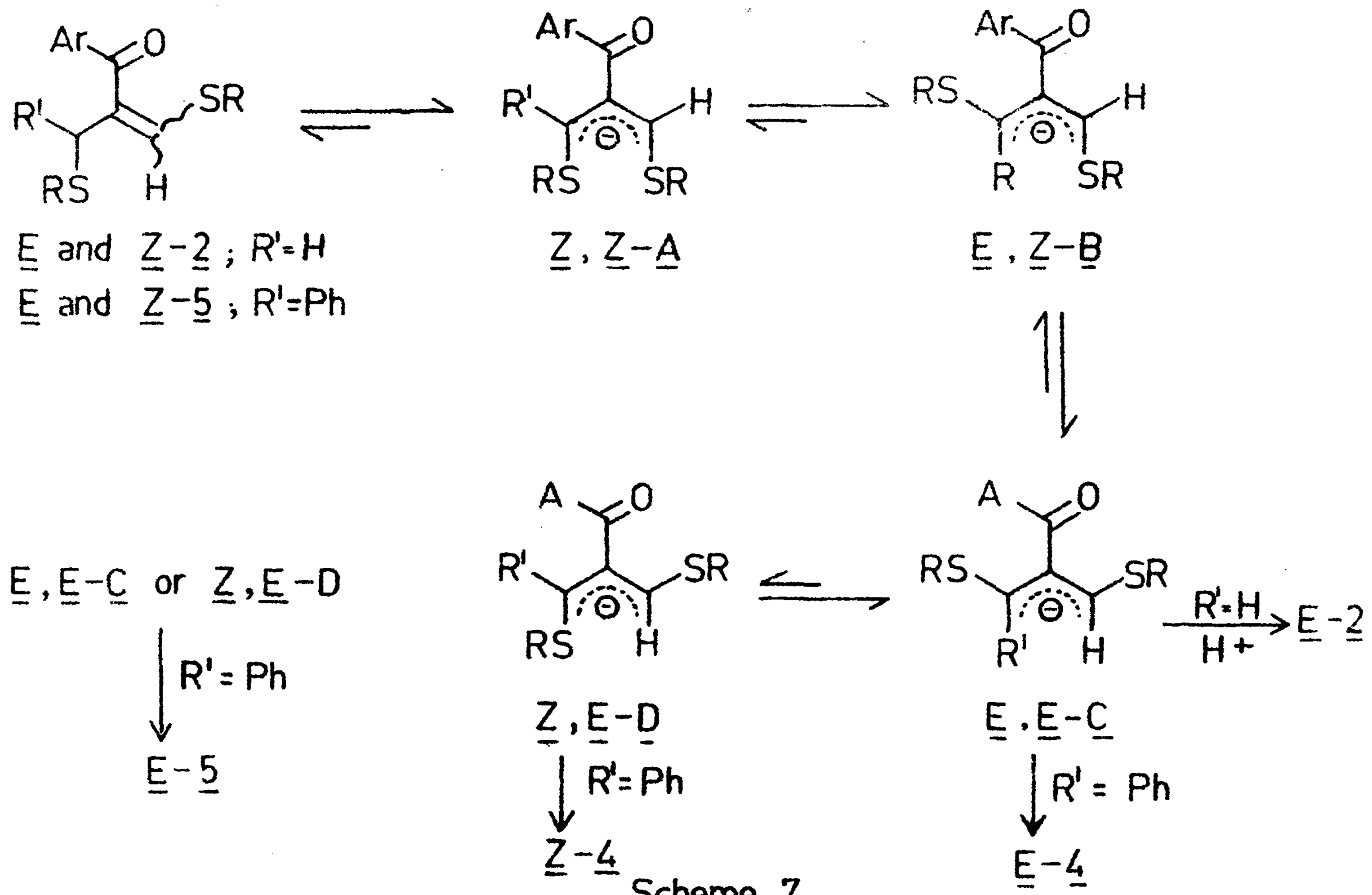
Scheme 6

equilibriating anions like *Z*, *Z*-A and *E*, *Z*-B in the reaction mixture, which rearrange to the thermodynamically more stable *E*,*E*-C form which ultimately picks up the proton during work-up to give exclusively *E*-2 isomers (Scheme 7). However when R'=Ph, the corresponding more stable *E*,*E*-C and *Z*,*E*-D anions appear to exist in equilibrium in 3:1 ratio which on protonation yield either *E*-5 or a mixture of *E* and *Z*-4 in 3:1 ratio (Scheme 7).

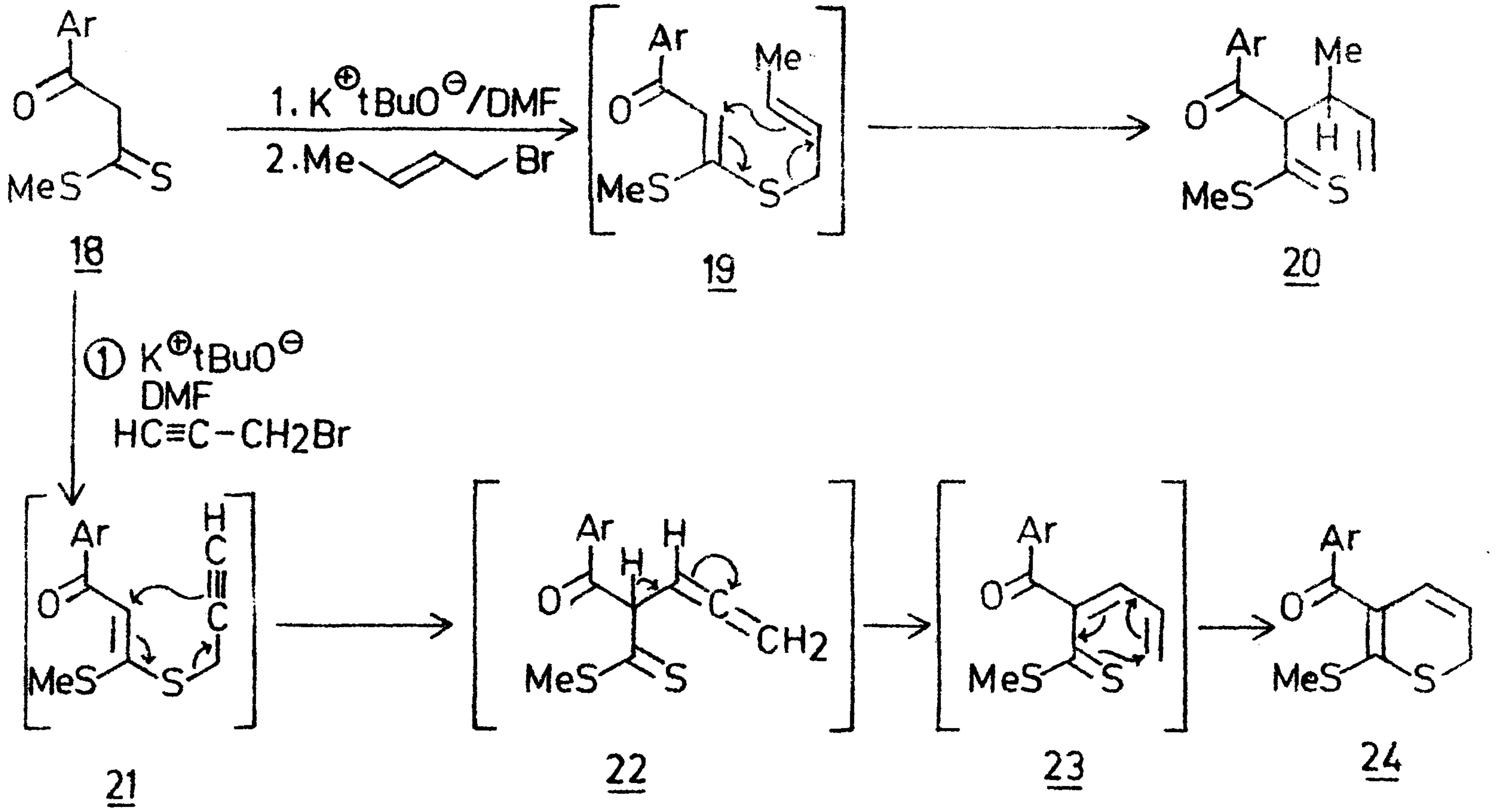
In continuation with foregoing detailed mechanistic studies on base catalysed 1,3-RS shift observed in ketoketen S,S-acetals derived from propiophenones (1) and dihydrochalcone (3), it was intended to extend these rearrangement studies to α-allylketoketen S,S-acetals 27 (Scheme 9), which are expected to undergo 1,5-MeS shift in the presence of base to give product like 31 (Scheme 10) via mobile ketodienyl intermediate 30. The results of our investigation on the synthesis and basecatalysed rearrangements of 27 are described in this chapter.

V. 2 RESULTS AND DISCUSSION

Lawesson[3] has reported that methyl β-benzoyldithioacetate (18) on treatment with potassium *t*-butoxide followed by alkylation with crotyl bromide yields the α-methylallydithioacetate (20) in good yields (Scheme 8). The formation of 20 is rationalized to have been formed by thioclaisen rearrangement of S-crotyl ketoketen S,S-acetals (19) (Scheme 8). Alkylation of 18 with propargyl


E and Z-2 ; R'=H
E and Z-5 ; R'=Ph
Z, Z-A
E, Z-B
E, E-C or Z, E-D
R' = Ph
E-5
Z, E-D
R'= Ph
Z-4
E, E-C
R' = Ph
E-4
R'=H
H+
E-2
Ar
O
R'
RS
SR
H
R
A

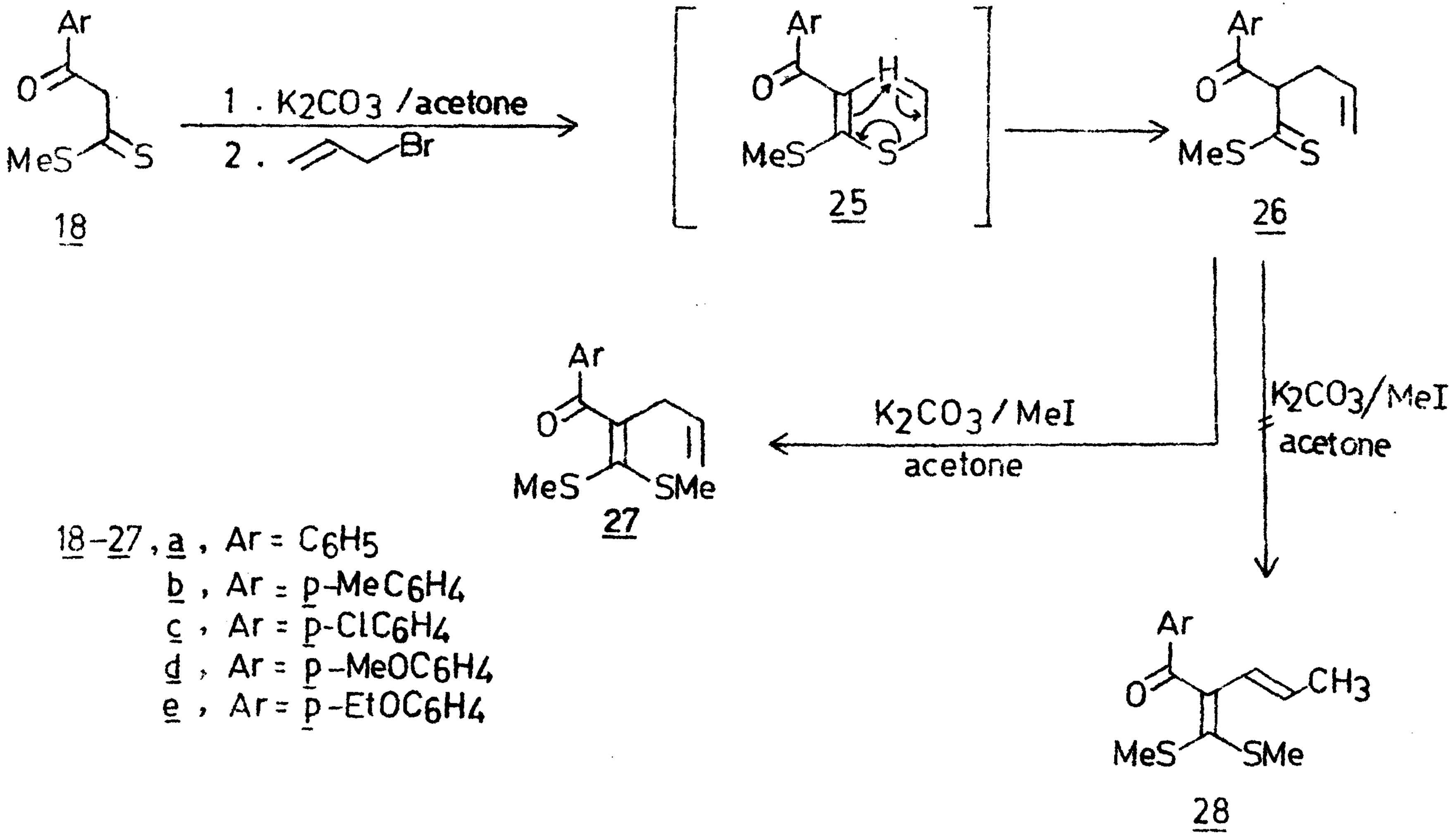
Scheme 7



$\underline{18}$–$\underline{24}$; Ar = C_6H_5

Scheme 8

bromide in the presence of base, is similarly reported[3] to yield the dihydropyran (24) via S-propargyl acetal (21) and its subsequent thioclaisen rearrangement through 22 and 23 (Scheme 8). However, similar alkylation of 18 with allyl bromide to give the rearranged 26 (Scheme 9) is not reported, although few other dithioesters derived from active methylene compounds are known to yield rearranged products on alkylation with allyl bromide.[4] We have used similar synthetic strategy for the preparation of keto-keten S,S-acetals 27 (Scheme 9). Thus when the dithioester (18a) was reacted with allyl bromide in the presence of base like sodium hydride or potassium t-butoxide, a complex reaction mixture was obtained from which 26a could not be isolated. However when the alkylation of 18a with allyl bromide was carried out in presence of weaker base like potassium carbonate in refluxing acetone, the product obtained in 79% yield was characterized as α-allyldithioester (26a) (Scheme 9). The structure of 26a was confirmed by its spectral and analytical data. Thus 26a showed molecular ion peak at m/z 250 and was analysed for $C_{13}H_{14}S_2O$. Its IR spectrum (neat) exhibited strong absorption bands at 1690 and 1220 cm^{-1} due to aromatic carbonyl and C=S bond respectively. The presence of a strong carbonyl frequency at 1690 cm^{-1} proves that 26a exists in keto-form. Further confirmation for the structure 26a was obtained from its NMR spectrum ($CDCl_3$), which

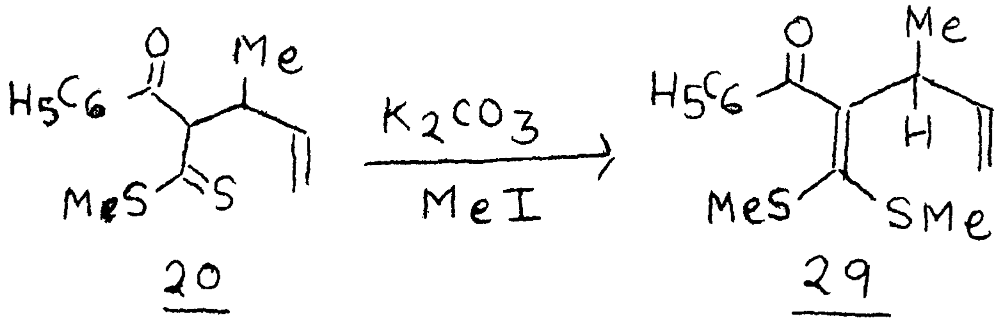


$\underline{18}$–$\underline{27}$, $\underline{a}$, Ar = C_6H_5
$\underline{b}$, Ar = $\underline{p}$-MeC_6H_4
$\underline{c}$, Ar = $\underline{p}$-ClC_6H_4
$\underline{d}$, Ar = $\underline{p}$-$MeOC_6H_4$
$\underline{e}$, Ar = $\underline{p}$-$EtOC_6H_4$

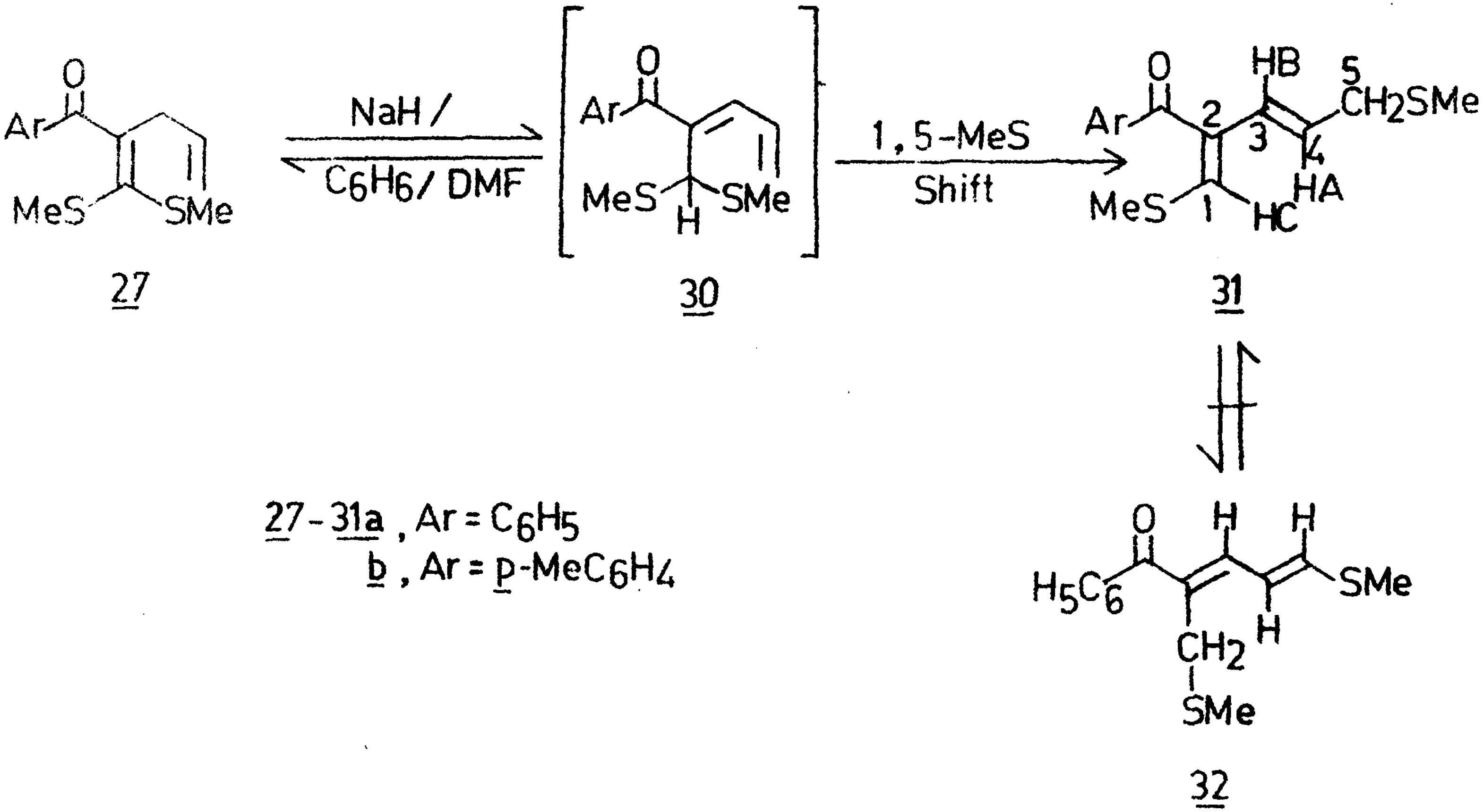
Scheme 9

exhibited a singlet at δ 2.48 (3H) due to SCH_3 protons, while the two methylene protons appeared as broad double doublets at δ 2.62-3.15 (2H). The signal due to methine proton and two olefinic protons of allylic group was present as broad multiplet (3H) at δ 4.85-5.48, while the other olefinic proton appeared at δ 5.51-5.85 (m, 1H). The multiplets at δ 7.21-7.63 and δ 7.82-8.2 (2H) were assigned to five aromatic protons. Alkylation of other dithioesters 18b-e with allyl bromide under identical conditions similarly yielded the corresponding α-allyl-β-benzoyldithioacetates 26b-e in 69-84% overall yields (Scheme 9). The structure of 26b-e were confirmed with the help of spectral and analytical data (Table 1 and 3).

Attempted alkylation of 26a with methyl iodide in the presence of stronger bases like sodium hydride and potassium t-butoxide to give the corresponding dithioacetal 27a yielded complex reaction mixture. However, when methylation of 26a was carried out in the presence of potassium carbonate in refluxing acetone, corresponding α-allylketoketen S,S-acetal 27a was obtained in 71% yield and no trace of isomeric S,S-acetal like 28 was obtained (Scheme 9). The structure of 27a was confirmed with the help of spectral and analytical data. Thus 27a exhibited molecular ion peak at m/z 264 and analysed for $C_{14}H_{16}S_2O$. Its IR spectrum(neat) exhibited strong and the band at 1660 cm^{-1} due to conjugated carbonyl group and the band at 1610 cm^{-1} as assigned to the C=C bond. Final proof for the structure 27a was obtained from its NMR spectrum ($CDCl_3$). The two singlets at δ 2.0(3H) and δ 2.30 (3H) were assigned to two SCH_3 groups, while the signal due to two methylene protons appeared as doublet (2H, J=7Hz) at δ 3.35. The three olefinic protons of allylic group were present as two multiplets at δ 4.81-5.15 (2H) and δ 5.43-5.91 (1H). The signals due to aromatic protons appeared as broad multiplets at δ 7.2-7.51 (3H) and 7.75-7.90. The other α-allyl ketoketen S,S-acetals (27b-e) were similarly obtained by methylation of the corresponding dithioesters 26b-e in 58-75% overall yields. The spectral and analytical data for 27b-e are given in table 2 and 4. The alkylation of α-methylallyldithioester 20 similarly yielded the corresponding S,S-acetal 29. The spectral and analytical data of 20 and 29 were in conformity with the assigned structures (experimental).

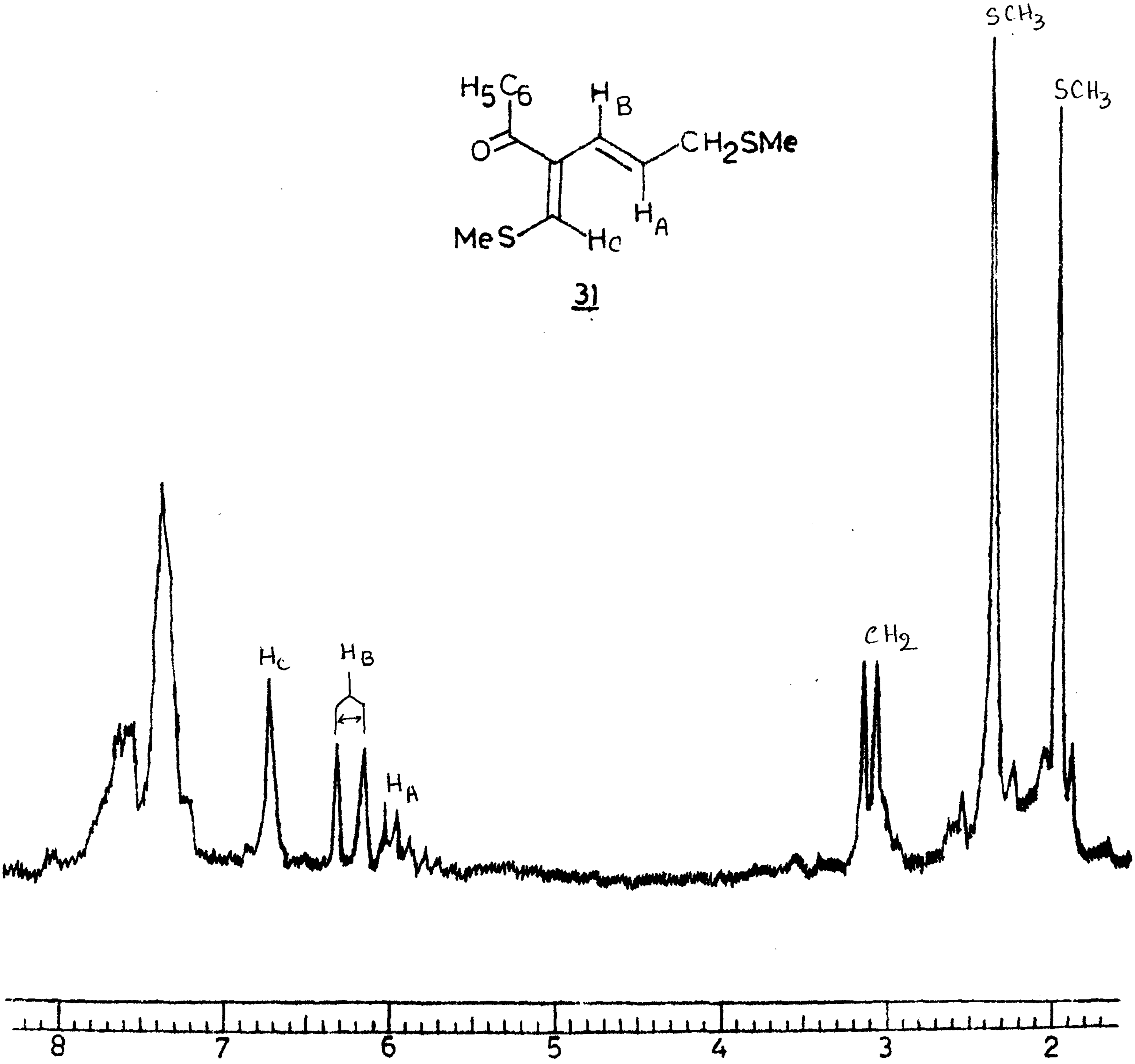


Base catalysed rearrangement of 27a was next studied. Thus when 27a was reacted with sodium hydride in dimethylformamide a polymeric reaction mixture was obtained. However when 27a was stirred with catalytic amount of sodium hydride in benzene and dimethylformamide (10:1 ratio) for 3 hr, work-up and column chromatography of the reaction mixture yielded a viscous liquid (TLC single spot) in 54% yield along with starting material (35%). The compound was characterized as 1-methylthio-2-benzoyl-4-methylthiomethyl-1,3-butadiene (31a) on the basis of spectral and analytical data (Scheme 10). Thus it showed in its mass spectrum, the molecular ion peak at m/z 264 and was analyzed for $C_{14}H_{16}S_2O$. Its IR spectrum exhibited strong band at 1650, 1630 and 1600 cm^{-1} due to conjugated carbonyl group and double bonds respectively. Final confirmation of the structure 31a was obtained from its NMR spectrum ($CDCl_3$) (Figure), which exhibited two sharp singlets at δ 1.98 (3H) and δ 2.35 (3H) due to SCH_3 groups attached to sp^3 and sp^2 carbon atoms respectively. The methylene protons appeared as doublet at δ 3.15 (2H, J=6 Hz) due to coupling with olefinic proton (H_A), which rules out the isomeric diene structure 32 since methylene protons would appear as singlet in 32. The three olefinic protons of allylic group which were present as multiplet at 4.8-5.9 in the NMR spectrum of 27a were absent in 31a. Instead a singlet (1H) present at δ 6.75 was assigned to olefinic H_C proton. The chemical shift position of H_C proton confirms the Z-configuration around 1,2-double pond. This assignment is in



$\underline{27}$-$\underline{31a}$, Ar = C_6H_5
$\underline{b}$, Ar = $\underline{p}$-MeC_6H_4

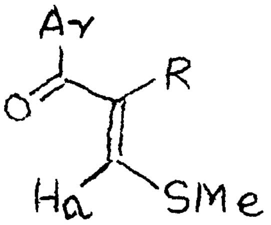
Scheme 10



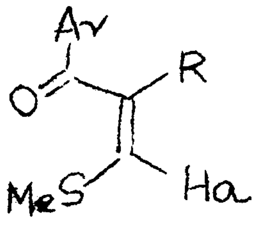
31

Figure

agreement with our earlier observations.[5a] The olefinic proton (Ha) *cis* to aroyl groups in olefin **A** appears down field between δ 7.6-7.9 as compared to **B**, in which olefinic proton (Ha) appears between δ 6.0-7.1.

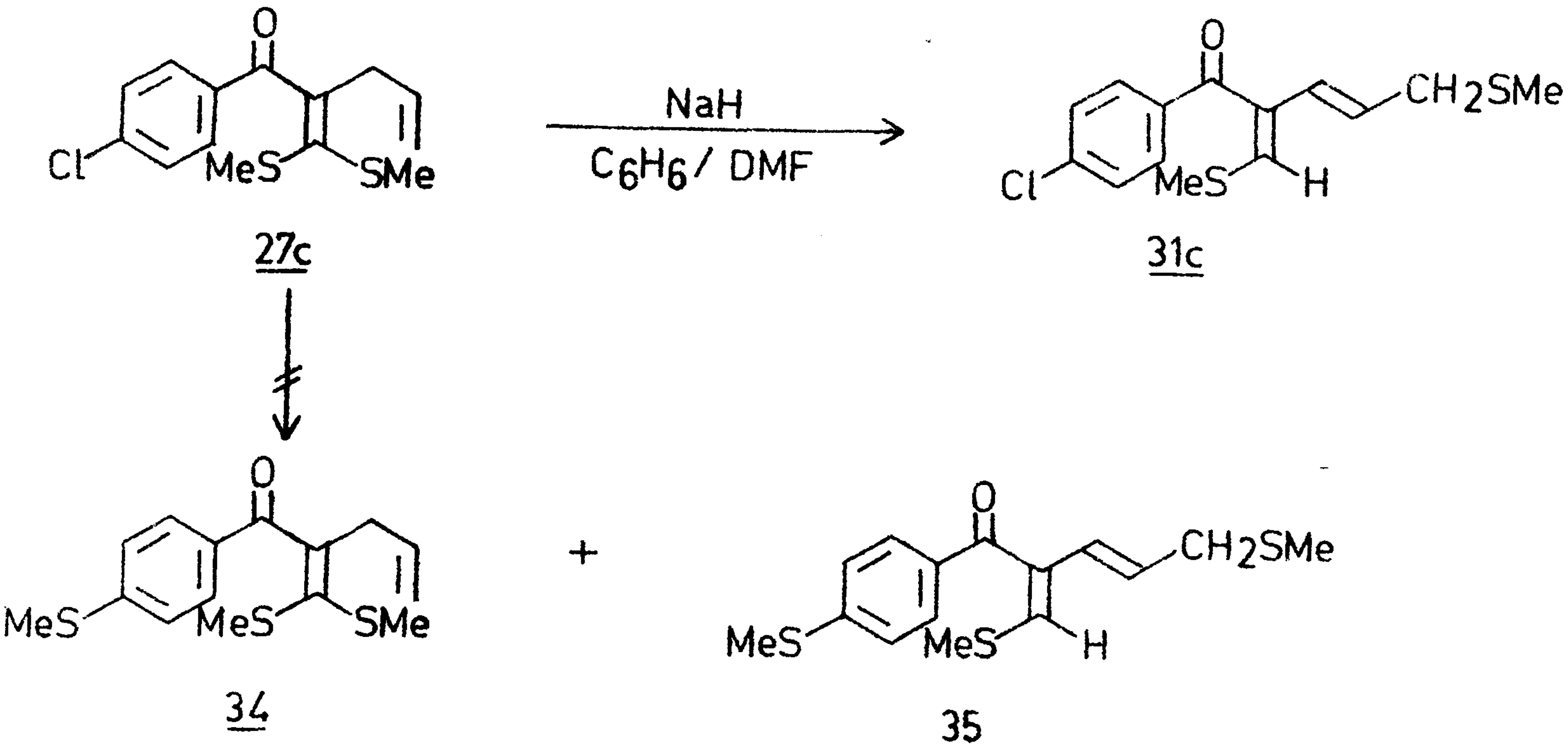


A, $\delta H_a = 7.6-7.9$



B, $\delta H_a = 6.0-7.1$

The olefinic H_A proton in **31** appeared as multiplet (1H) between 5.68-6.10, while the sharp doublet present at δ6.25 (J=15 Hz) was assigned to other olefinic proton H_B which demonstrates the *trans*- configuration around 3,4-double bond. The UV spectrum of **31a** showed the band at λ_{max} 310 (log ϵ 3.15) which shows the presence of diene chromophore in **31a**. When the *p*-methyl keten S,S-acetal **27b** was subjected to similar rearrangement the corresponding rearranged diene **31b** was obtained in 52% yield. The spectral and analytical data of **31b** (experimental) was in agreement with the assigned structure. Interestingly when the corresponding *p*-chlorodithioacetal **27c** was subjected to rearrangement under identical conditions the corresponding **31c** was formed



Scheme 11

exclusively in 58% yield (Scheme 11) along with recovered 27c and no trace of other products like 34 and 35 (formed by nucleophilic displacement of active p-chloro group, by methyl mercaptoanion in 27c and 31c respectively) could be detected (TLC). Earlier it was shown in our laboratory that the displacement products, are indeed formed when the ketene-S,S-acetal 1g derived from p-chloropiophenones (Scheme 4) was treated under similar reaction conditions involving a free alkylthio anion in the reaction mixture.[2] Further variations in the reaction conditions also could not yield 34 and 35, and only 31c could be isolated in varying yields along with considerable polymeric material.

When the α-methylallyldithioacetal 29 was subjected to rearrangement under identical conditions, only intractable polymeric reaction mixture was obtained from which no identifiable product could be isolated.

V. 3 MECHANISM OF THE REARRANGEMENT

From the foregoing arguments, it may be inferred that the rearrangement of 27 to 31 involves 1,5-MeS shift, which to our knowledge is unprecedented in the literature.* The dithioacetal (27) undergoes base catalysed proton abstraction to give the resonating pentadienyl anion 36 (Scheme 12). The stability of this anion (36) is greatly enhanced by the two sulfur atoms present

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*A mechnism involving 1,5-sigmatropic shift of sulfide in dithioketal intermediate has been envisaged in 1,2-annelation of cycloheptatrienone with dithiols.[5b]

in the molecule giving rise to increased resonance contribution from 36A. Since the pentadienyl anion (36) is generated under reversible conditions, it competes with sodium hydride in deprotonation of 27 to give either 27, 37 or unstable mobile ketopentadienyl intermediate 30 (Scheme 12). Since no trace of 37 was isolated from the reaction mixture, it appears that 37 undergoes base catalysed equilibriation to give 30 via more stable 36A. Alternatively 37 could undergo 1,5-sigmatropic hydrogen shift to give 30. Similarly the anion 36 does not undergo 1,5-electrocyclization to give cyclopentene derivative (39) via cyclopentenyl anion 38. These 1,5-electrocyclization of pentadienyl anions, despite symmetry allowed, have not been reported to be observed.*[6] However it is still unclear whether this failure is due to thermodyanamic or kinetic reasons.[6]

It is therefore apparent that mobile ketopentadienyl intermediate (30) thus formed, undergoes a facile 1,5-MeS shift to the thermodynamically more stable rearranged product 31. Efforts to isolate 30 were unsuccessful and even trace of it could not be detected after work-up of the reaction mixture. However the intermediacy of 30 appears to be a definite step in arriving at 31. The intermediate 30 can rearrange to 31 by one of the possible mechanisms shown in the scheme 13. Thus 30 can undergo a concerted suprafacial 1,5-sigmatropic MeS shift, which is thermally allowed

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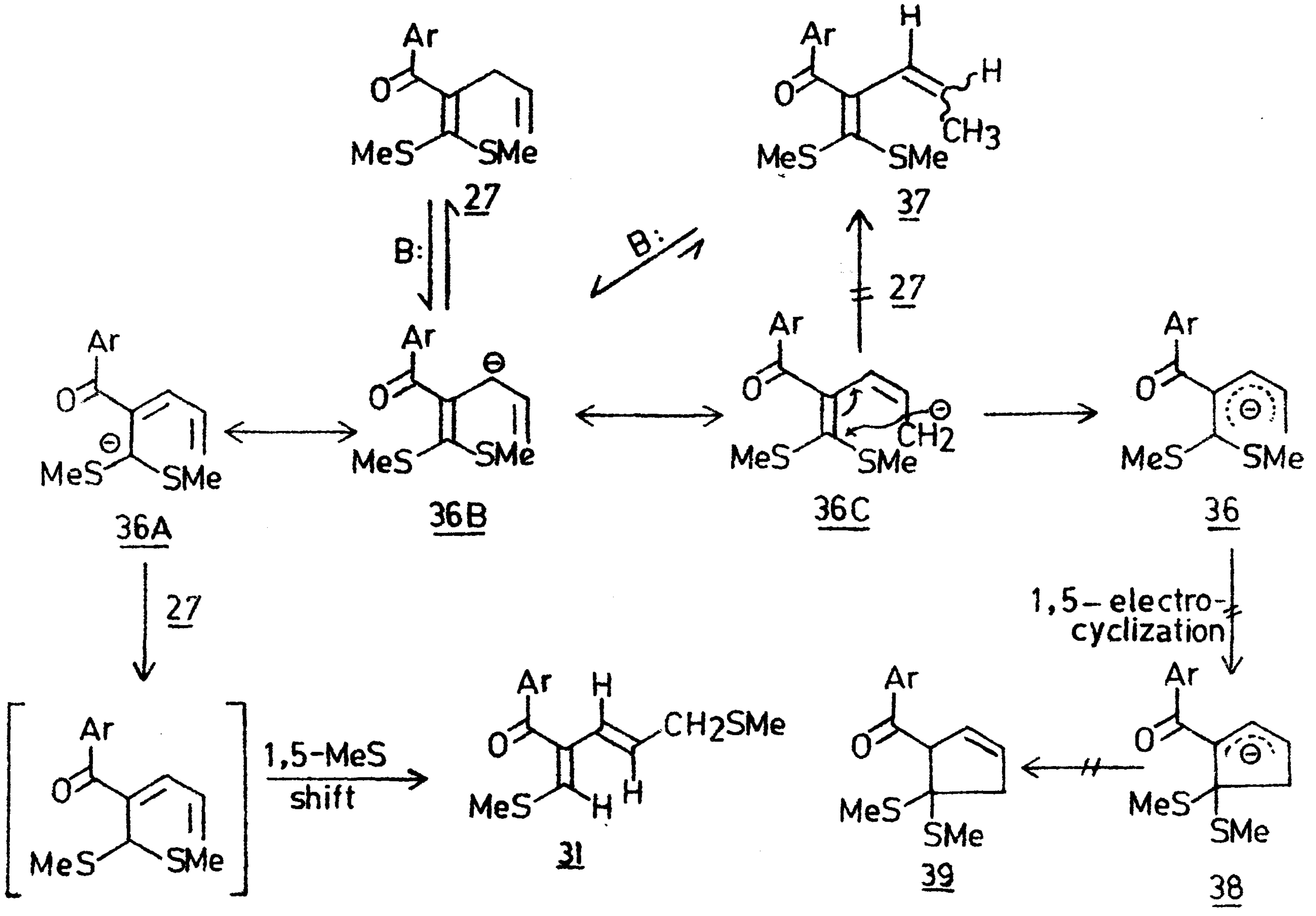
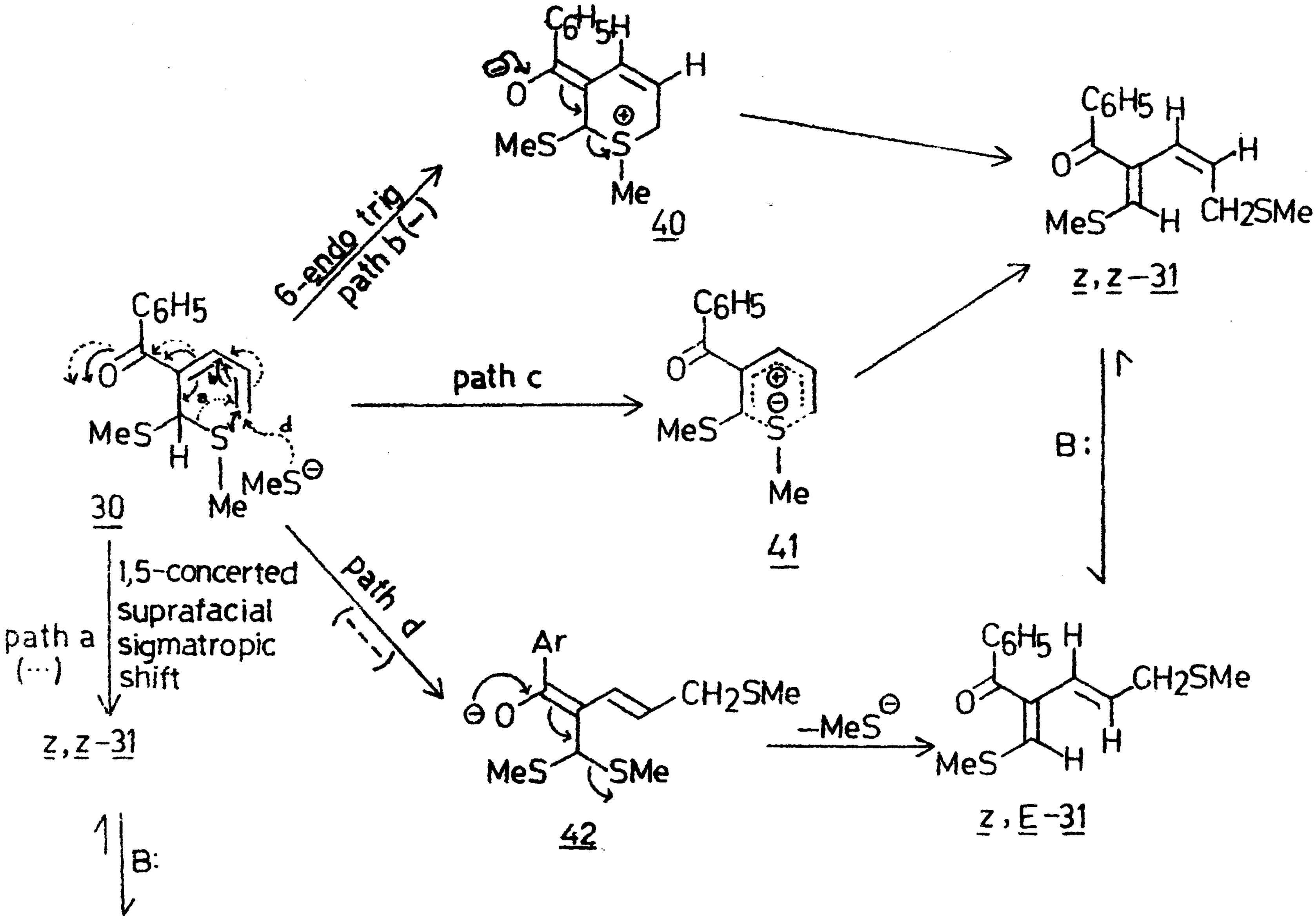
*Few examples of 1,5-electrocyclizations are known, but they are shown to be nonconcerted.[6]


27
B:
B:
37
27
36A
36B
36C
36
27
1,5-electro-cyclization
30
1,5-MeS shift
31
39
38

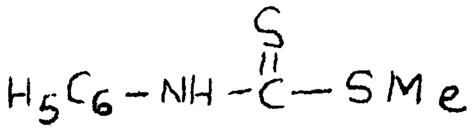
Scheme 12

on the basis of orbital symmetry considerations (path a, doted arrows). Alternatively, the surlfur lone pair of methylmercapto group can attack electrophilic δ-carbon of **30** to give tetrahydrothiopyrilium intermediate **40** via *6-endo-trig* process which is quite facile from steric considerations[7] (path b). The interemediate **40** can subsequently collapse to the rearranged product **31**. A third possibility for concerted 1,5-MeS shift may involve transient complex **41** *via* antipolar mechanism as suggested by Kwart.[8,9] However **41** is structurelly different from that of Kwart's systems in that **41** carries an electron withdrawing benzoyl group in conjugation with double bond, thus reverting the nucleophilicity of δ-carbon. An alternative intermolecular mechanism involving attack of methylmercapto anion at δ-carbon of **30** in Michael fashion to give the solvent equilibriated anion **42** is another likely possibility (path d). The intermediate **42** subsequently eliminates one of the methylthio groups to give **31**. A similar intermolecular mechanism has been suggested by us for 1,3-RS shift in keten S,S-acetals **1**, on the basis of evidences for existance of free alkylthio anion in the reaction mixture.[2] However, as shown in the scheme 11, our attempts to isolate any of the displacement products like **34** and **35** from rearrangement of **27c** were not successful. Similarly, the rearrangement of **27a** in


6-endo trig
path b (—)
path c
path d
(- - -)
path a
(···)
1,5-concerted suprafacial sigmatropic shift
30
40
41
42
z,z-31
z,E-31
B:
−MeS⊖
MeS⊖
C6H5
CH2SMe
Ar

Scheme 13

the presence of phenyl isothiocyanate does not give even traces of methyl-N-phenyl dithiocarbamate 43.* These observations point



$H_5C_6-NH-\overset{\overset{S}{\|}}{C}-SMe$

43

to an intramolecular 1,5-MeS shift either through concerted 1,5-suprafacial sigmatropic rearrangement or through thiopyrilium intermediate 40 formed through 6-*endo* *trig* process, both of which are energetically favourable. From the foregoing observations it is not possible to decide between these two pathways (*a* and *b*) and further work is in progress in this direction. It should be noted that both mechanisms (path a and **b**) would yield *Z,Z*-geometrical isomer of diene 31 (Scheme 13). However only *Z,E*-isomer of 31 was formed in the reaction and no trace of *Z,Z*-isomer could be isolated. It appears that initially formed *Z,Z*-31 undergoes base catalysed configurational equilibriation to yield the thermodynamically more stable *Z,E*-31 (Scheme 14). The pentadienyl anion 36 exists in equilibrium with all U,W and S configurations which rearrange to more stable W-36 and

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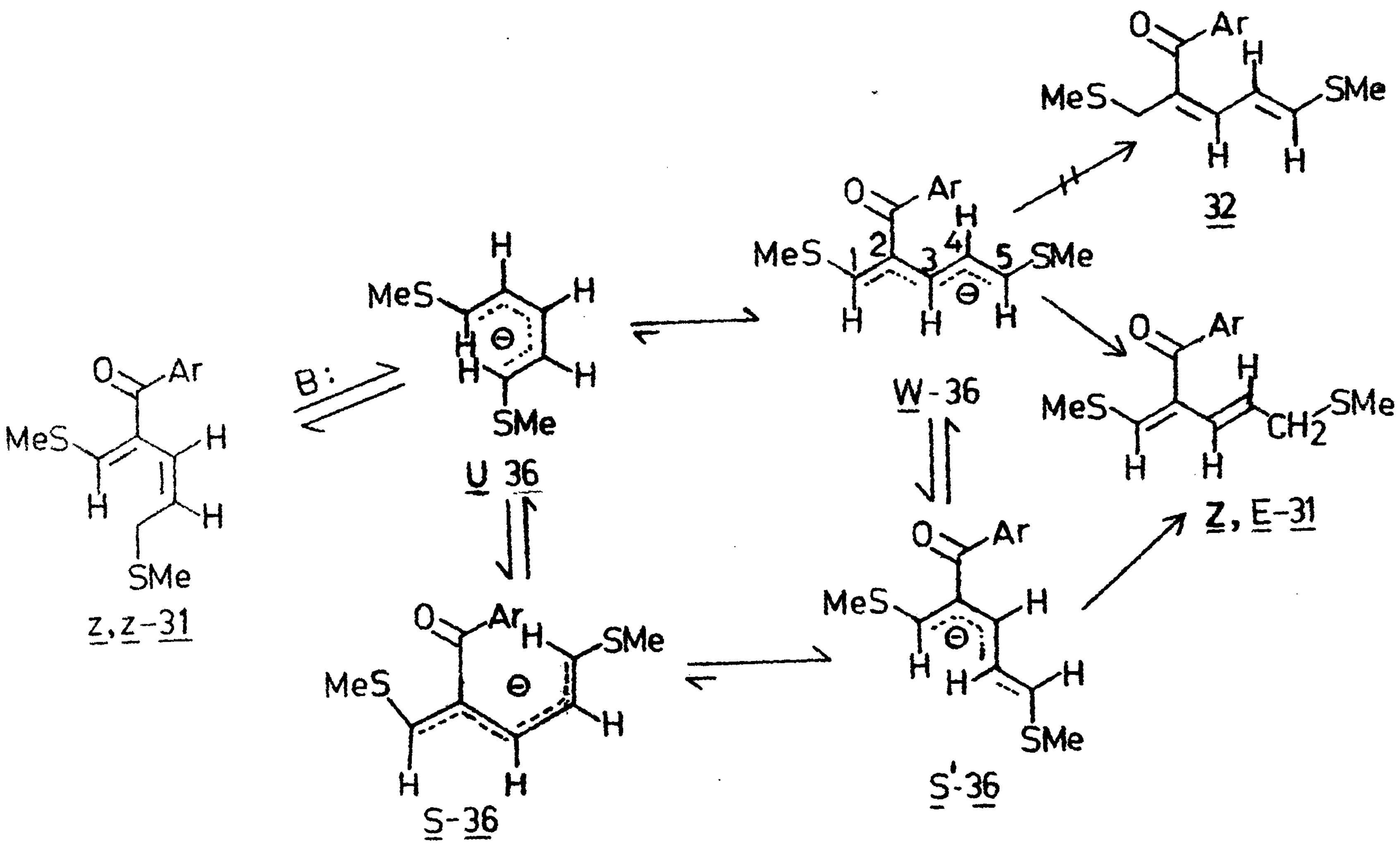
* Rearrangement of 1 in the presence of phenyl isothiocyanate under identical conditions has been shown to yield considerable amount of methyl-N-phenyldithiocarbamate 43.



Scheme 14

S'-36 form,[6] which ultimately picks up proton to give the observed Z,E-31 (Scheme 14). Interestingly, no trace of diene 32, which is expected to be formed by protonation of W-36 at C-1 was detected in the reaction mixture. It is not possible to give a definite explanation for these observations at this stage.

In conclusion, an unprecedented 1,5-MeS shift has been observed in base catalysed rearrangement of keten S,S-acetals 27, which yields the butadiene 31 as exclusive product. All experimental evidences at the present stage point to a concerted intramolecular 1,5-MeS shift, however further experiments are needed to study the detailed mechanism of this rearrangement.

V. 4 EXPERIMENTAL

The IR spectra were recorded on Perkin-Elmer 297 spectrophotometer. The NMR spectra were recorded on a Varian EM-390 spectrometer using TMS as an internal standard and the chemical shifts are expressed in ppm from TMS taken as 0.00 (δ -units). Mass spectra were recorded on a Hitachi RMU-6E mass spectrometer fitted with a direct inlet system.

The Starting Materials

The commercially available samples of acetophenone p-methylacetophenone, p-methoxyacetophenone, p-ethoxyacetophenone, p-chloroacetophenone, allyl bromide and crotyl bromide were purified before use. The dimethyl trithiocarbonate, bp 225° (760 mm) and the dithioesters were prepared according to procedure described in the chapter II.

TABLE 1

Spectral data of the products 26a-e

Product	I.R.(neat) (cm^{-1})	^{1}H-N.M.R.(CDCl$_3$) (ppm)	M.S. m/e(M$^+$)
26a	1690 (C=O) 1595 (C=C) 1220 (C=S)	2.48 (s, 3H, SC$\underline{H}_3$); 2.62-3.15 (dd, 2H, C$\underline{H}_2$-CH=CH$_2$); 4.85-5.48 (br m, 3H, C$\underline{H}$ and CH=C$\underline{H}_2$); 5.51-5.85 (m, 1H, C$\underline{H}$=CH$_2$); 7.21-7.62 (m, 3H$_{arom}$); 7.82-8.20 (m, 2H$_{arom}$).	250
26b	1685 (C=O) 1605 (C=C) 1180 (C=S)	2.42 (s, 3H, SC$\underline{H}_3$); 2.58 (s, 3H, $\underline{p}$-C$\underline{H}_3$); 2.70-3.12 (dd, 2H, C$\underline{H}_2$-CH=CH$_2$); 4.82-5.32 (m, 3H, C$\underline{H}$ and CH=C$\underline{H}_2$); 5.56-5.90 (m, 1H, C$\underline{H}$=CH$_2$); 7.15 (d, 2H$_{arom}$); 7.85 (d, 2H$_{arom}$).	264

Table 1 (contd.)

26c	1680 (C=O) 1590 (C=C) 1210 (C=S)	2.40 (s, 3H, $SC\underline{H}_3$); 2.69-3.20 (dd, 2H, $C\underline{H}_2$-$CH=CH_2$); 4.91-5.22 (m, 3H, $C\underline{H}$ and $CH=C\underline{H}_2$); 5.60-5.90 (m, 1H, $C\underline{H}=CH_2$); 7.40 (d, $2H_{arom}$); 7.75 (d, $2H_{arom}$).	284
26d	1675 (C=O) 1600 (C=C) 1180 (C=S)	2.50 (s, 3H, $SC\underline{H}_3$); 2.70-3.15 (dd, 2H, $C\underline{H}_2$-$CH=CH_2$); 3.80 (s, 3H, p-$C\underline{H}_3O$); 4.85-5.20 (br.m, 3H, $C\underline{H}$ and $CH=C\underline{H}_2$); 5.50-5.88 (m, 1H, $C\underline{H}=CH_2$); 6.80 (d, $2H_{arom}$); 7.90 (d, $2H_{arom}$).	280
26e	1680 (C=O) 1600 (C=C) 1190 (C=S)	1.44 (t, 3H, p-$C\underline{H}_3CH_2O$); 2.55 (s, 3H, $SC\underline{H}_3$); 2.72-3.22 (dd, 2H, $C\underline{H}_2$-$CH=CH_2$); 4.10 (q, 2H, p-$CH_3C\underline{H}_2O$); 4.90-5.28 (br m, 3H, $C\underline{H}$ and $CH=C\underline{H}_2$); 5.60-5.87 (m, 1H, $C\underline{H}=CH_2$); 6.85 (d, $2H_{arom}$); 7.92 (d, $2H_{arom}$).	294

TABLE 2

Spectral data of the products 27a-e

Product	I.R. (neat) (cm^{-1})	^{1}H-N.M.R. ($CDCl_3$) (ppm)	M.S. m/z (M^+)
27a	1660 (C=O) 1610 (C=C)	2.0 (s, 3H, $SC\underline{H}_3$); 2.30 (s, 3H, $SC\underline{H}_3$); 3.35 (d, 2H, $C\underline{H}_2$-CH=CH_2); 4.81-5.15 (m, 2H, CH=$C\underline{H}_2$); 5.43-5.91 (m, 1H, $C\underline{H}$=CH_2); 7.20-7.51 (m, $3H_{arom}$); 7.75-7.90 (m, $2H_{arom}$).	264
27b	1665 (C=O) 1609 (C=C)	2.0 (s, 3H, $SC\underline{H}_3$); 2.33 (d, 6H, $SC\underline{H}_3$ and $\underline{p}$-$C\underline{H}_3$); 3.20 (d, 2H, $C\underline{H}_2$-CH=CH_2); 4.80-5.10 (m, 2H, CH=$C\underline{H}_2$); 5.40-5.80 (m, 1H, $C\underline{H}$=CH_2); 7.15 (d, $2H_{arom}$); 7.62 (d, $2H_{arom}$).	278

Table 2 (contd.)

27c	1655 (C=O) 1595 (C=C)	2.03 (s, 3H, $SC\underline{H}_3$); 2.32 (s, 3H, $SC\underline{H}_3$); 3.56 (d, 2H, $C\underline{H}_2{-}CH{=}CH_2$); 4.90-5.20 (m, 2H, $CH{=}C\underline{H}_2$); 5.50-5.82 (m, 1H, $C\underline{H}{=}CH_2$); 7.40 (d, $2H_{arom}$); 7.80 (d, $2H_{arom}$).	298
27d	1680 (C=O) 1600 (C=C)	2.05 (s, 3H, $SC\underline{H}_3$); 2.35 (s, 3H, $SC\underline{H}_3$); 3.40 (d, 2H, $C\underline{H}_2{-}CH{=}CH_2$); 3.83 (s, 3H, $p{-}C\underline{H}_3O$); 4.90-5.20 (br m, 2H, $CH{=}C\underline{H}_2$); 5.45-5.85 (m, 1H, $C\underline{H}{=}CH_2$); 6.85 (d, $2H_{arom}$); 7.78 (d, $2H_{arom}$).	294
27e	1660 (C=O) 1600 (C=C)	1.45 (t, 3H, $p{-}C\underline{H}_3CH_2O$); 2.10 (s, 3H, $SC\underline{H}_3$); 2.38 (s, 3H, $SC\underline{H}_3$); 3.35 (d, 2H, $C\underline{H}_2CH{=}CH_2$); 4.05 (q, 2H, $p{-}CH_3C\underline{H}_2O$); 4.80-5.18 (br m, 2H, $CH{=}C\underline{H}_2$); 5.45-5.85 (m, 1H, $C\underline{H}{=}CH_2$); 6.80 (d, $2H_{arom}$); 7.69 (d, $2H_{arom}$).	308

General method for the preparation of α-allyl-benzoyldithioacetate (26a-e)

To a solution of dithioester (18) (0.01 mol) in 60 ml of dry acetone, anhydrous potassium carbonate (0.015 mol) was added and the suspension was refluxed with stirring for 3-4 hr. After cooling the reaction mixture to room temperature, allyl bromide (0.01 mol) in 10 ml of acetone was slowly added with stirring and the reaction mixture was further stirred for 4 hr at room temperature. It was then poured into cold water and extracted with ethylacetate (2x100 ml). The organic layer was washed with water dried (Na_2SO_4) and evaporated to give a viscous liquid from which pure 26 were isolated by column chromatography on silica gel using hexane or benzene (1:1) as eluents. All α-allyldithioesters (26a-e) prepared by above method were characterised by spectral physical and analytical data given in the table 1 and 3 respectively.

General method for the preparation of α-allyl ketoketen S,S-acetals (27a-e)

A suspension of α-allyldithioester (26) (0.01 mol) and anhydrous potassium carbonate (0.02 mol) in 50 ml dry acetone was refluxed for 4-5 hr with stirring. The reaction mixture was cooled to 7-10°C and methyl iodide (0.01 mol) in 10 ml benzene was slowly added with stirring. The temperature was then raised to 30-35°C and after further stirring for 3-4 hr at this temperature, the reaction mixture was poured into water, extracted with dichloromethane, dried (Na_2SO_4) and evaporated to give a deep brown viscous liquid. Chromatography of this residue over silica gel using hexane/benzene (1:1) mixture as eluent gave pure 27 as viscous liquids (TLC single spot). Spectral, physical and analytical data of S,S-acetals 27 prepared by this method are given in the table 2 and 4 respectively.

Preparation of α-methylallyl benzoyldithioacetate (20)

The dithioester 18a (2.10g, 0.01 mol) and 2g (0.015 mol) of anhydrous potassium carbonate were taken in 60 ml dry acetone and refluxed for 3 hr with stirring. The reaction mixture was cooled to room temperature and 1.47g (0.01 mol) of crotyl bromide in 10 ml of benzene was added with stirring. After further stirring for 5 hr, the mixture was poured over water, extracted with dichloromethane and dried over sodium sulfate. Evaporation of solvent yielded a residue which on column chromatography over silica gel (hexane as eluent) gave 1.84g (70%) of 20 as yellow viscous liquid; (TLC single spot) IR(neat) : 1685 (CO), 1595 (C=C), 1225 (CS) cm^{-1}; NMR ($CDCl_3$); 1.05 (d, 3H, J=6.5 Hz, C-$\underline{CH}_3$); 2.36 (s, 3H, $S\underline{CH}_3$); 2.82 (d, 1H, J=6 Hz); 3.25-3.52 (m, 1H, $\underline{CH}$-CH_3), 4.78-5.85 (m, 3H, $\underline{CH}$=$\underline{CH}_2$), 7.15-7.85 (m, $5H_{arom}$); M.S. (m/e), M^+ : 264; (Found : C, 63.98; H, 6.35; Calc. for $C_{14}H_{16}OS_2$(264) : C, 63.63; H, 6.06%).

Preparation of α-methylallylketoketen S,S-acetal (29)

A suspension of 2.64g (0.01 mol) of 20 and anhydrous potassium carbonate in 60 ml acetone was refluxed for 6 hr with stirring. After cooling to room termperature 1.54g (0.011 mol) of methyl iodide in 10 ml dry benzene was slowly added during 10 min with stirring and cooling, and the stirring was then continued for 5 hr at room temperature. The reaction mixture was poured over water, extracted with chloroform, dried (Na_2SO_4) and evaporated to give a viscous liquid, from which pure acetal 29 was obtained after chromatography on silica gel using hexane-benzene (65:35) as eluent, 1.98g (75%) of 29 as yellow liquid IR(neat) : 1665 (CO), 1600, 1570 (C=C) cm^{-1}; NMR ($CDCl_3$) :δ1.15 (d, 3H, J= 6.2 Hz, CH-C$\underline{H}_3$); 1.98 (s, 3H, SC$\underline{H}_3$), 2.30 (s, 3H, SC$\underline{H}_3$); 3.8-4.10 (m, 1H, C$\underline{H}$-CH_3), 4.75-5.85 (m, 3H, C$\underline{H}$=C$\underline{H}_2$), 7.32 (br.m, $3H_{arom}$), 7.60-7.90 (m, $2H_{arom}$); M.S. (m/e), M^+: 278 (Found : C, 64.23; H, 6.75; Calc. for $C_{15}H_{18}OS_2$ (278); C,64.74; H, 6.47%).

Rearrangement of 27a-c to 31a-c : General Procedure:

To a suspension of sodium hydride (0.005 mol, 50%) in 40 ml of dry benzene dimethylformamide (10:1), ketoketen S,S-acetal (0.01 mol) in 10 ml same solvent mixture was added and the mixture was heated with stirring at 70-80°C or 40°C (27c) for 2-3 hr. The reaction mixture after cooling was poured over ice cold water, extracted with chloroform. The chloroform layer after washing with water, drying (Na_2SO_4) was evaporated to give a viscous residue which was chromatographed over silica gel. Elution with hexane-benzene (1:1) gave <u>31</u>. The physical and spectral properties of dienes are given below.

<u>1-Methylthio-2-benzoyl-4-methylthiomethyl-1,3-butadiene</u> (<u>31a</u>) was obtained as yellow liquid (TLC single spot) yield 1.43g (54%), spectral data given in text; (Found: C, 63.41, H, 6.29, Calcd. for $C_{14}H_{16}OS_2$(264) : C, 63.64; H, 6.06%).

<u>1-Methylthio-2-p-methylbenzoyl-4-methylthiomethyl-1,3-butadiene</u> <u>(31b)</u> was obtained as yellow viscous liquid (TLC single spot) yield 1.45g (52%); IR(neat: 1660 (CO); 1610, 1590 (C=C) cm^{-1}; NMR ($CDCl_3$): 2.0 (s, 3H, $CH_2-SC\underline{H}_3$), 2.40 (s, 6H, $SC\underline{H}_3$+$\underline{p}$-$C\underline{H}_3C_6H_4$); 3.17 (d, 2H, J=6 Hz, $C\underline{H}_2-SCH_3$), 5.7-6.12 (m, 1H olefinic); 6.28 (d, 1H, J=15 Hz olefinic); 6.80 (s, 1H olefinic); 7.25-7.70 (A_2B_2,dd, $4H_{arom}$); M.S. (m/e) M^+ 278; (Found : C, 64.96; H,6.18; Calc. for $C_{15}H_{17}OS_2$ (278) : C, 64.74; H, 6.47%).

<u>1-Methylthio-2-p-chlorobenzoyl-4-methylthiomethyl-1,3-butadiene</u> (<u>31c</u>) was obtained as deep yellow liquid (TLC single spot), yield 1.72g (58%); IR (neat) : 1650 (CO), 1590, 1570 (C=C) cm^{-1}; NMR ($CDCl_3$) : 2.0 (s, 3H, $CH_2-SC\underline{H}_3$); 2.42 (s, 3H, $SC\underline{H}_3$); 3.20 (d, 2H, J=6 Hz, $C\underline{H}_2-SCH_3$), 6.0-6.25 (m, 1H, olefinic), 6.5 (d,

1H, J=15 Hz olefinic); 6.85 (s, 1H, olefinic), 7.4-7.75 (A_2B_2, dd, $4H_{arom}$); M.S. (m/e). M^+: (298) ; (Found: C, 56.28; H, 5.02%. Calc. for $C_{14}H_{15}ClOS_2$ (298.5): C, 56.28; H, 5.02).

Attempted base catalysed rearrangement of -methyl allyl ketoketen S,S-acetal (29).

A suspension of sodium hydride (0.005 mol, 50%) and S,S-acetal 29 (0.01 mol) in 50 ml dry benzene-dimethyl formamide (10:1) was heated at 70-80°C for 4 hr. After usual work-up a polymeric mixture was obtained, from which no identifiable compound could be isolated.

TABLE 3

Physical and analytical data of α-allyl-benzoyldithioacetals (26a-e)

Product	Yield (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis(%) C	Analysis(%) H
26a[a]	79	viscous	$C_{13}H_{14}OS_2$		62.40	5.60
		liquid	(250)		62.08	5.92
26b[b]	74	viscous	$C_{14}H_{16}OS_2$		63.63	6.06
		liquid	(264)		63.87	6.31
26c[a]	84	viscous	$C_{13}H_{13}ClOS_2$		54.83	4.56
		liquid	(284.5)		55.12	4.20
26d[b]	72	viscous	$C_{14}H_{16}O_2S_2$		60.00	5.71
		liquid	(280)		60.33	6.09
26e[b]	69	viscous	$C_{15}H_{18}O_2S_2$		61.22	6.12
		liquid	(294)		60.95	6.49

[a] Elution with hexane; [b] Elution with benzene-hexane (35:65).

TABLE 4

Physical and analytical data of α-allyl ketoketen S,S-acetals (27a-e)

Product	Yield (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis (%) C	H
27a[a]	71	Viscous	$C_{14}H_{16}OS_2$		63.64	6.06
		liquid	(264)		63.97	6.35
27b[a]	69	Viscous	$C_{15}H_{18}OS_2$		64.74	6.47
		liquid	(278)		65.16	6.88
27c[a]	75	Viscous	$C_{14}H_{15}ClOS_2$		56.28	5.02
		liquid	(298.5)		56.01	5.36
27d[b]	65	Viscous	$C_{15}H_{18}O_2S_2$		61.22	6.12
		liquid	(294)		61.60	5.93
27e[b]	58	Viscous	$C_{16}H_{20}O_2S_2$		62.33	6.49
		liquid	(308)		62.14	6.78

[a] Elution with hexane.

[b] Elution with benzene-hexane (45:55).

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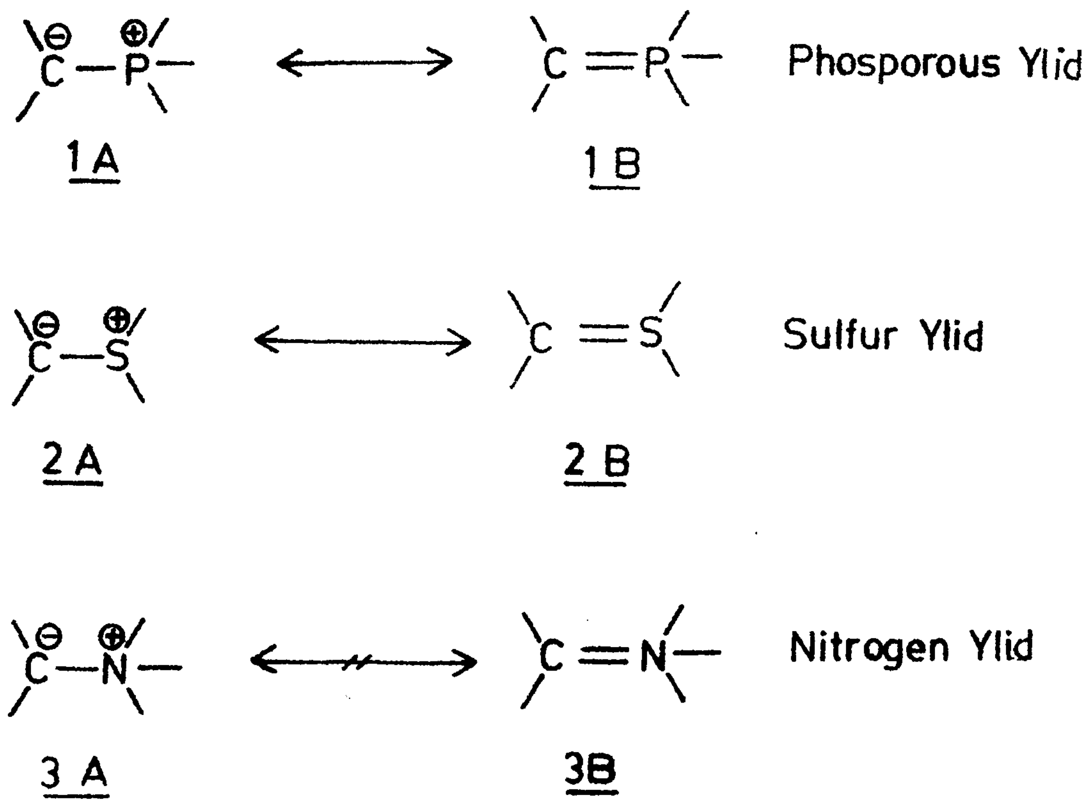
CHAPTER VI

STUDIES ON REACTIONS OF TRIMETHYLAMMONIUM-CYANOMETHYLID: A NOVEL AMMONIUM YLID

VI. 1 INTRODUCTION

It is well documented[1,2] that the nitrogen ylids of the general formulae 3 are different in their thermodynamic stability and their reactivity towards electrophilic centres from the corresponding phosphorous (1) and sulfur (2) ylids. The greater stability of sulfur and phosphorous ylides has been attributed to their ability to form $d\pi - p\pi$ back_bonding through overlap of doubly filled orbital of carbanion and low energy vacant 3d orbitals of sulfur or phosphorous. On the otherhand, stability of nitrogen ylids involve only electrostatic interaction between adjacent charges (Scheme 1). Nitrogen atom being a first row element with filled 2s and 2p orbitals, the next available



Scheme 1

empty 3s orbital is at much higher energy and consequently can not participate in valence shell expansion. The nitrogen ylids are therefore more difficult to prepare, as they are less stable than the phosphorous and sulfur ylids.

Evolution of the chemistry of nitrogen ylides really began with an early attempts to demonstrate the existance of pentavalent nitrogen.[1,2] Thus Schlenk and Holtz had isolated a highly colored tetramethylammonium triphenylmethide 6, by reaction of triphenylmethyl sodium with tetramethylammonium chloride 5, which underwent typical carbanionic reactions with water and carbon dioxide (Scheme 2). However subsequent attempts by Hager and Marvell[4] to prepare expected benzyl tetraethylammonium (9) having all groups equally attached to nitrogen atom were unsuccessful. Thus they concluded that the product isolated by Schlenk and Holtz is not a pentavalent nitrogen derivative but actually tetramethylammonium salt of triphenylcarbanion 7. The existance of such salt is due to relative stability of triphenylmethyl carbanion. Wittig and coworkers[5,6] re-examined the pentavalent nitrogen question and by treating 9-fluorenyltrimethyl ammonium bromide 10 with phenyl lithium, they isolated a red product to which the structure 11, previously assumed by Ingold and Jessop[7] was assigned (Scheme 3). Isolation of the stable trimethylammoniumfluorenylid 11[6] opened the way to the synthesis of various nitrogen, phosphorous, sulfur

Schlenk and Holtz (1917)

$$\underset{\underline{4}}{(C_6H_5)_3C^{\ominus}Na^{\oplus}} + \underset{\underline{5}}{(CH_3)_4N^{\oplus}Cl^{\ominus}} \longrightarrow \underset{\underline{6}\text{ (earlier representation)}}{(C_6H_5)_3\equiv C-N\equiv(CH_3)_4}$$

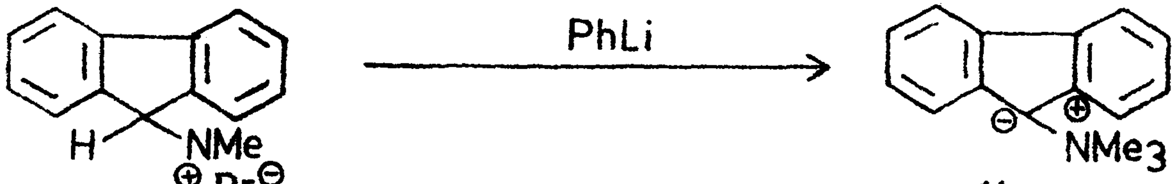
Hager and Marvel (1926)

$$\underset{\underline{7}}{PhCH_2N^{\oplus}Et_3\ Br^{\ominus}} + \underset{\underline{8}}{C_2H_5Li} \not\longrightarrow \underset{\underline{9}}{PhCH_2-NEt_4} + LiBr$$

$$\underset{\underline{7}}{(C_6H_5)_3C^{\ominus}N^{\oplus}(CH_3)_4}$$

Scheme 2

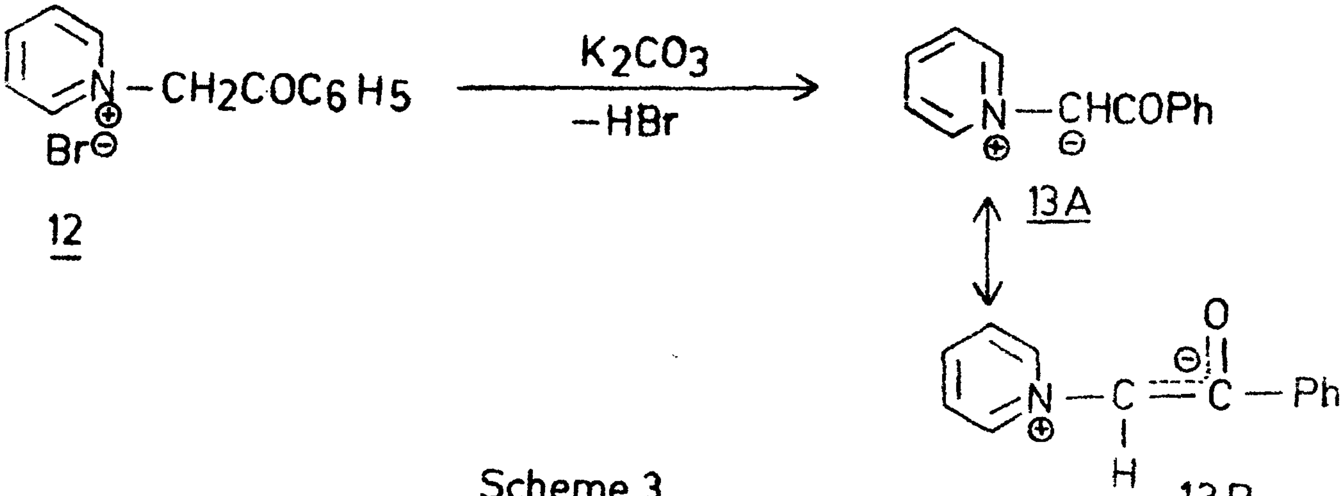
Wittig (1944)



10

11

Kröhnke (1937)



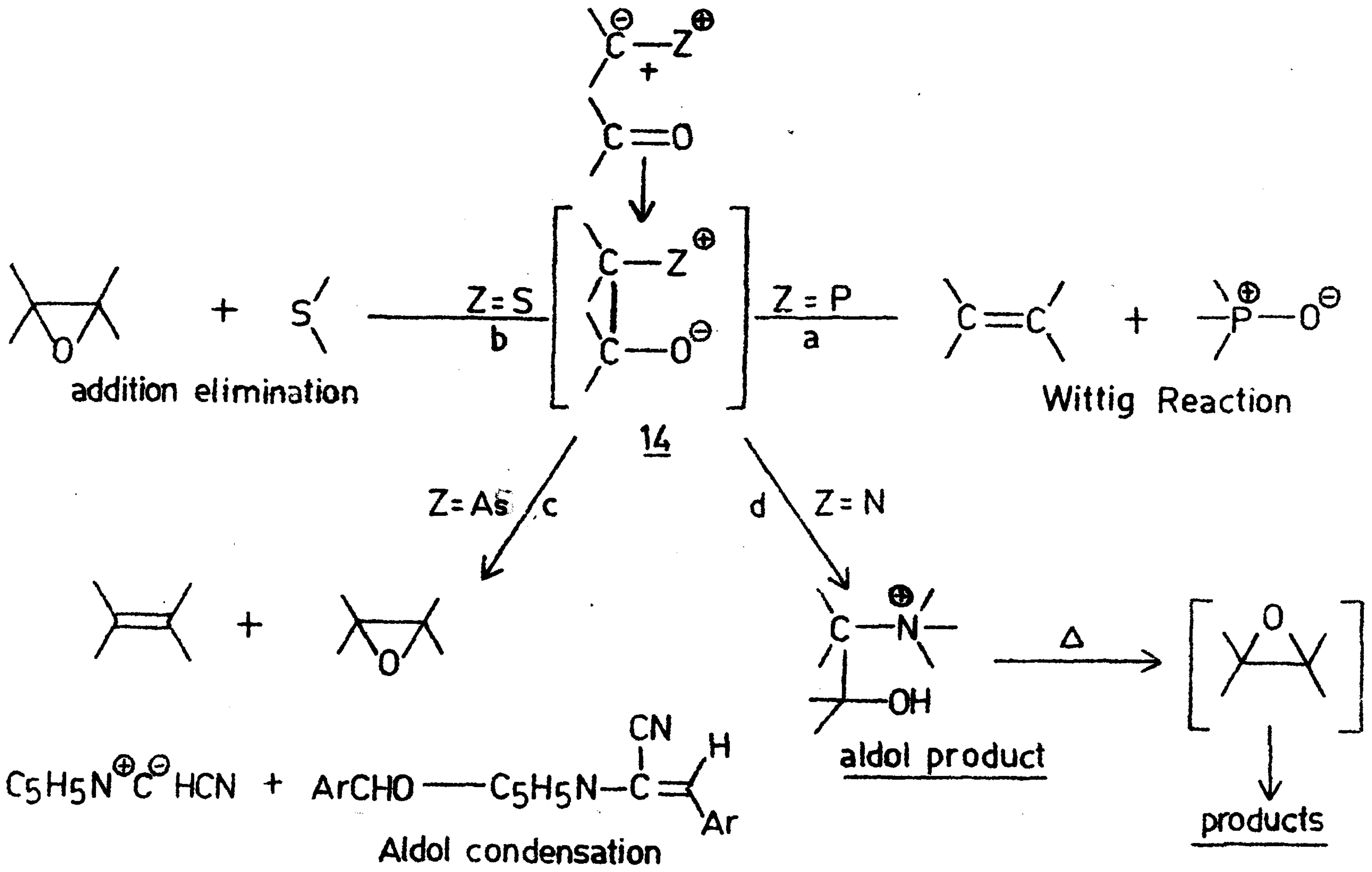
12

13A

13B

Scheme 3

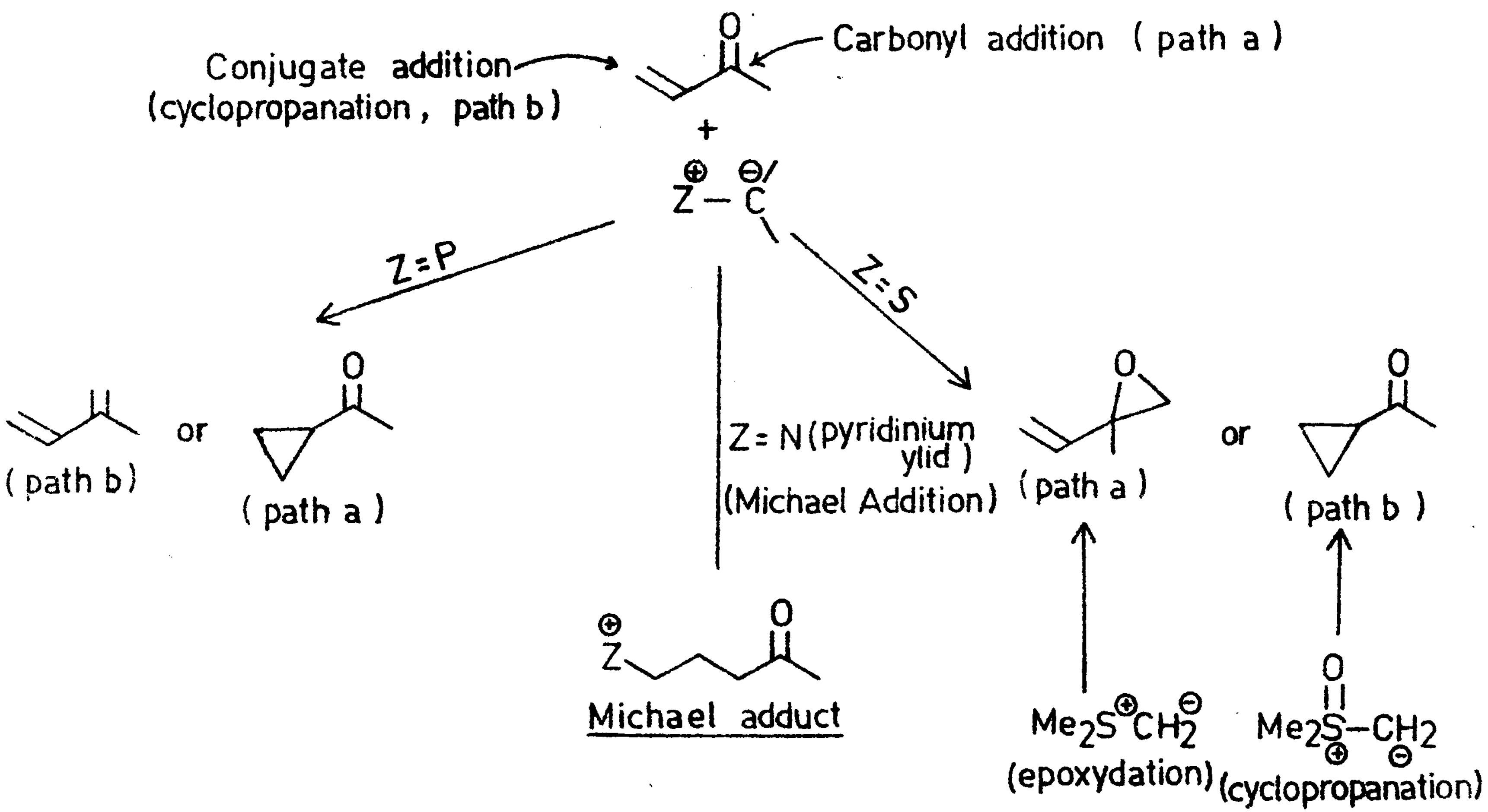
and arsenic ylids. However, the first report of nitrogen ylid appears to be due to Kronhke[8] who isolated a crystalline product by elimination of hydrogen bromide from phenacylpyridinium bromide 12 which was assigned the "enol-betain" structure 13[11] (Scheme 3). He and his coworkers had continued actively to investigate the the chemistry of pyridinium ylides and related substances. Since then the subsequent work on the nitrogen ylid was mainly confined to the study of more stable immonium and cycloimmonium ylids and their synthetic applications.[2] Although, the formation of stable ammonium ylids has been reported in the literature,[9] their synthetic applications like those of immonium, cycloimmonium and sulfur ylids are not much investigated. The reason for this scanty studies appears to be that in most of their reactions, the ammonium ylids behave like classical carbanion undergoing normal c-c bond formation reactions and not those that appear to be unique to ylidic carbanions. Thus in their reactions towards carbonyl compounds, all ylides initially afford the betaine intermediate 14 (Scheme 4) which subsequently yields different products depending on the nature of the heteroatom in the ylid. In the case of phosphorous ylids (Z=P), the betaine intermediate 14 decomposes to afford olefin and phosphine oxide (path a) through transfer of oxyanion to phosphorous (Wittig Reaction),[1] while the corresponding sulfur ylid (Z=S) yields the respective epoxide by intramolecular cyclization of 14 and


Z = S
b
Z = P
a
14
addition elimination
Wittig Reaction
Z = As
c
d
Z = N
OH
Δ
aldol product
products
$C_5H_5N^{\oplus}C^{\ominus}HCN$ + ArCHO
$C_5H_5N-C(CN)=CH-Ar$
Aldol condensation

Scheme 4

subsequent elimination of sulfide (path b).[10] These differences in reactivities of phosphorous and sulfur ylids have been attributed to the combination of differences in phosphorous-oxygen and sulfur-oxygen bond energies coupled with different leaving group abilities of sulfide and phosphine groups. Thus methyl sulfide group is known to be an excellent leaving group, while the formation of highly stable phosphorous-oxygen bond (D.E. P-O bond, 128 Kcal/mole and D.E.S-O bond, 89 Kcal/mole) is the major driving force for Wittig reaction. It should be pointed out that the arsonium ylid exhibits intermediate behaviour affording both epoxides and olefins upon reaction with carbonyl compounds (path c). The nitrogen ylides on the otherhand afford typical aldol condensation products on reaction with carbonyl compounds (path d). Similarly in most oftheir reactions with α,β-unsaturated carbonyl compounds (Scheme 5), the phosphorous ylides react normally yielding the corresponding dienes, while in few stereically croweded α,β-unsaturated ketones, the phosphorous ylid undergoes 1,4-addition yielding cyclopropane derivatives[1] (Scheme 5). The sulfur ylides afford either the epoxy compound or cyclopropane derivatives depending on the structure of ylid as well as the α,β-unsaturated carbonyl compounds.[10] (Scheme 5) The reaction of ammonium ylides with α,β-unsaturated carbonyl compounds, on the otherhand, has not been investigated, while the corresponding phenacylpyridinim ylid <u>13</u> is reported to undergo addition with

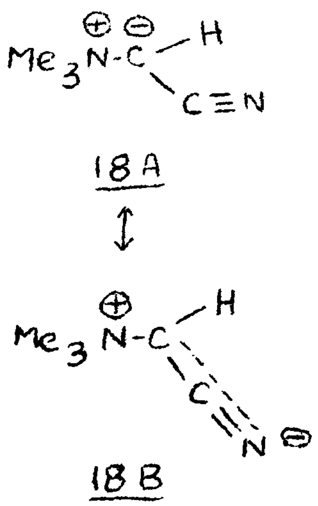
Addition of Ylids to α,β-unsaturated Carbonyl Compounds

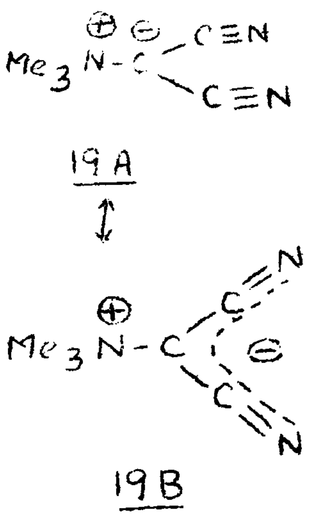


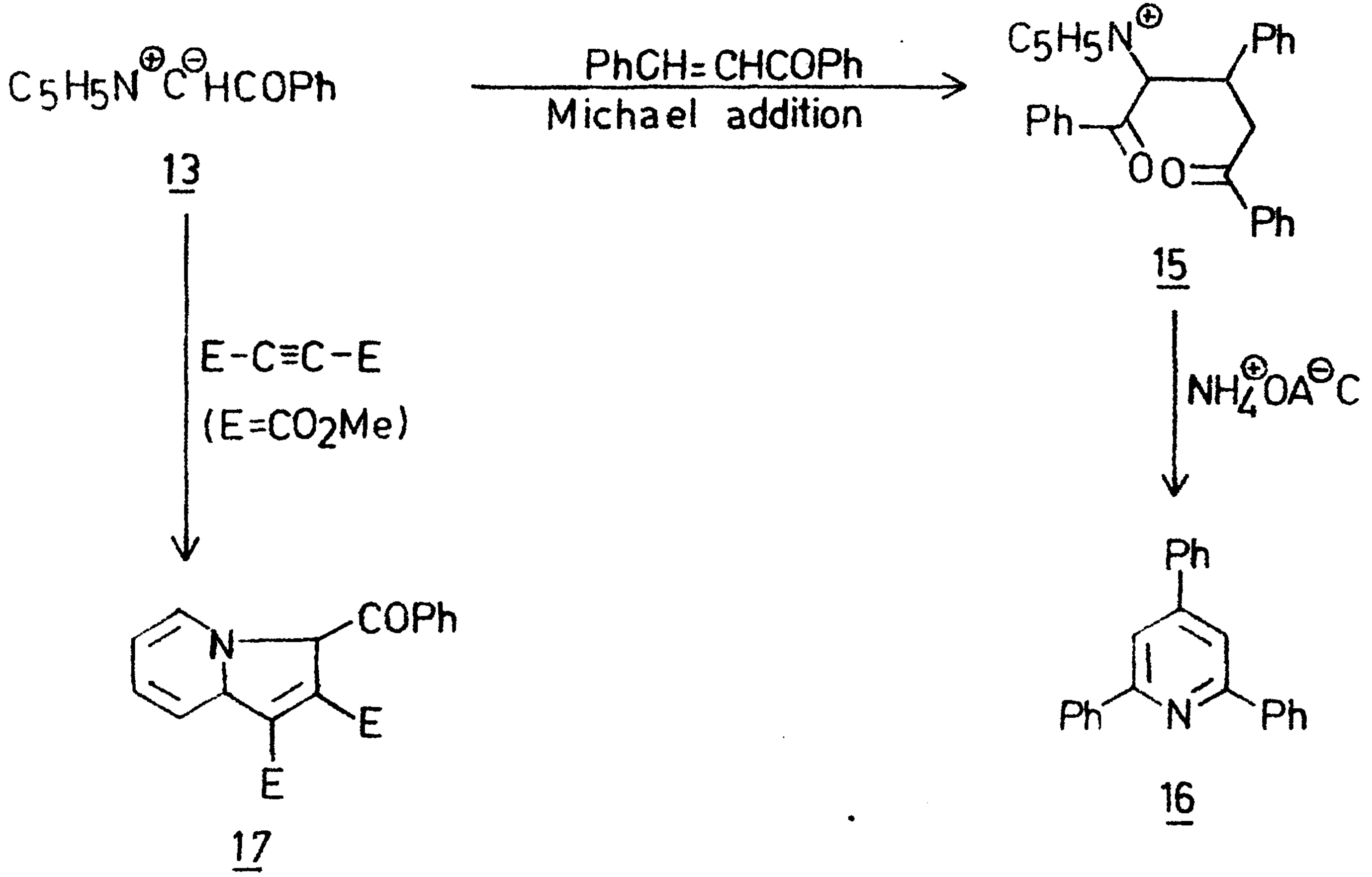
Scheme 5

chalcone to give the Michael adduct 15, which in the presence of ammonium salt affords[11] 2,4,6-triphenylpyridine 16 (Scheme 6). The ylid 13 similarly adds to dimethylacetylene dicarboxylate to afford the cycloadduct 17 (Scheme 6).[12]

In view of the scanty studies available on synthetic applications of ammonium ylides, it was intended to carry out a systematic investigation on the preparation and synthetic applications of novel trimethylammoniumcyanomethylid 18. It should be noted that the most stable ammonium ylid reported to date appears to be trimethylammonium dicyanomethylid (12) obtained from its conjugate acid by treatment with aqueous hydroxides.[13] The ylid 19 has a melting point of 153° and is stable at room temperature in the presence of water and oxygen for indefinite period. However the chemical characteristics of 19 have not been reported. The stability of 19 is apparently due to delocalization of the lone pair of electrons on the carbanion through the two cyano






$C_5H_5N^{\oplus}C^{\ominus}HCOPh$
13
PhCH=CHCOPh
Michael addition
$C_5H_5N^{\oplus}$
Ph
Ph
O
O
Ph
15
$NH_4^{\oplus}OAc^{\ominus}$
Ph
Ph
N
Ph
16
E-C≡C-E
(E=CO2Me)
N
COPh
E
E
17

Scheme 6

groups, in addition to electrostatic stabilization by ammonium group. It was therefore anticipated that α-cyano group attached to the carbanion in ylid 18 will provide extra stabilization to 18, while trimethylamine being a gas, would function as a good leaving group in its reactions with carbonyl compounds. The results of our studies on the reactions of ylid 18 with benzaldehyde, α,β-unsaturated carbonyl compounds and trithiocarbonates ($>$C=S bond) are reported in the following discussion

VI. 2 RESULTS AND DISCUSSIONS

VI.2.1 Reaction of trimethylammoniumcyanomethylid (18) with carbonyl compounds

The ylid 18 was generated insitu by reaction of trimethylammoniumcyanomethyl iodide 20 with sodium hydride in tetrahydrofuran. The required ammonium salt 20 was prepared in 90% yield by known procedure[14] through alkylation of N,N-dimethylaminoacetonitrle with methyl iodide. When the ylid 18 was reacted insitu with benzaldehyde under varying conditions, evolution of trimethylamine was observed. Work-up of the reaction mixture however yielded polymeric products from which only benzoic acid could be isolated. When the reaction of 18 with benzaldehyde was carried out at room temperature for 2 hr under controlled conditions, a viscous liquid was obtained after work-up, in 54% yield.

The product however was not the expected epoxide <u>22</u>,[15] and it was assigned the probable <u>m</u>-dioxin structure <u>25</u> on the basis of spectral and analytical data. Thus <u>25</u> was analysed for $C_{17}H_{13}NO_2$, while its infra-red spectrum (neat) showed strong absorption bands at 1620 and 1230 cm^{-1} due to vinyl ether group, while a band at 2210 cm^{-1} was assigned to nitrile stretching frequency. The strong bands at 1025, 1080 and 1130 cm^{-1} indicated the presence of acetal moiety in the product <u>25</u>. The NMR spectrum of <u>25</u> ($CDCl_3$) showed a broad singlet* (1H) at δ 4.80 which was assigned to H_A proton, while the other singlet at δ 5.45 (1H) was designated to H_B proton. The assignments were based on the chemical shift position of methine proton in <u>m</u>-dioxin <u>A</u>, which is reported to appear at δ 5.32.[16] The down field shift of H_B proton observed in <u>25</u> is probably due to conjugation of lone pair on one of the oxygen atoms with double bond (Structure D). The other broad singlet at δ 5.15 was assigned to olefinic H_C proton. It should be noted that the signal due to olefinic proton in 1-phenylcyclohexene (<u>C</u>) appears at δ 5.38,[17] while in pyran <u>B</u>, the olefinic H_A proton appears at δ 4.3,[18] The higher field shift of olefinic H_C proton in <u>25</u> as compared to 1-phenylcyclohexene (<u>C</u>) is probably due to

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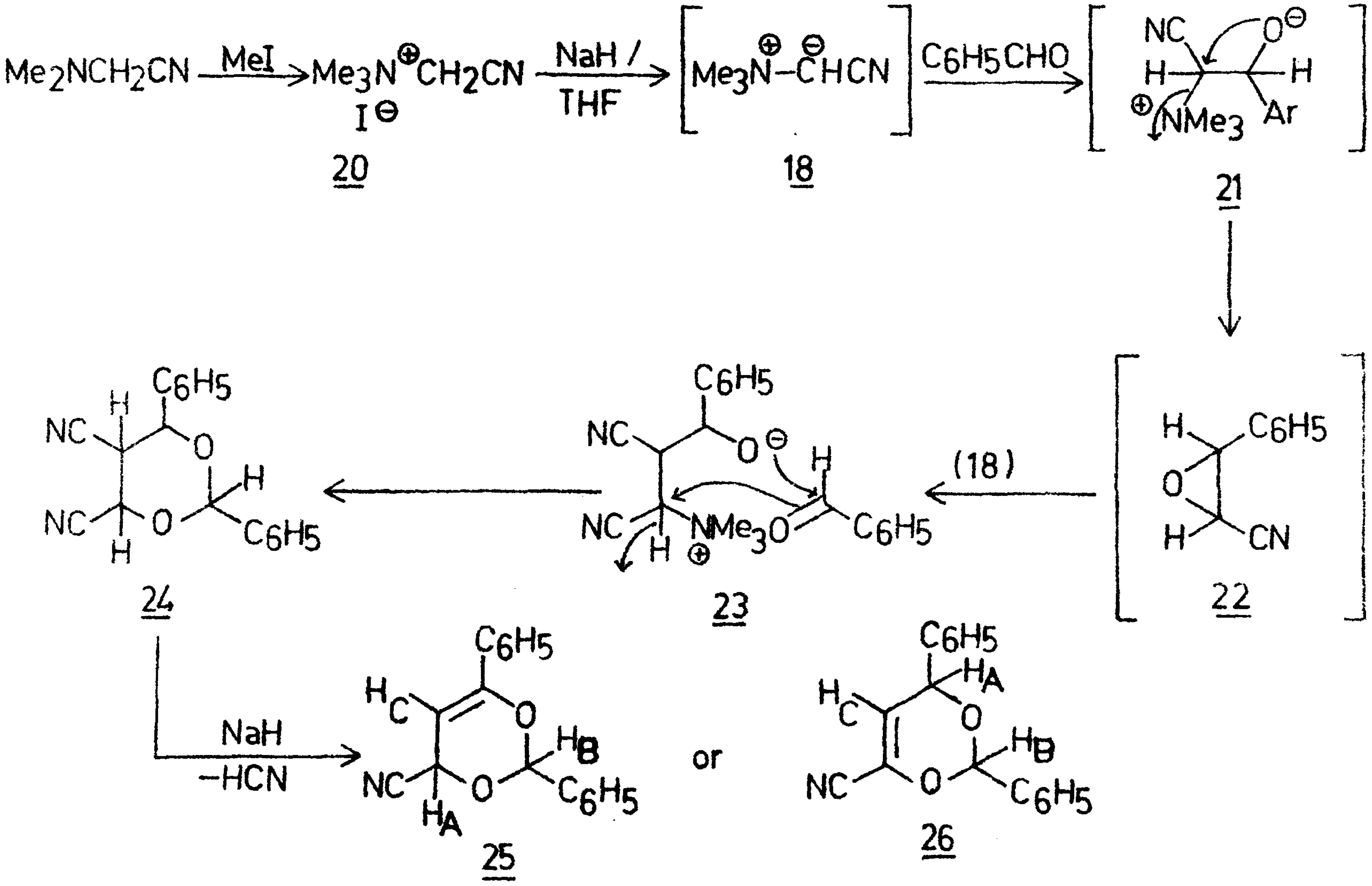
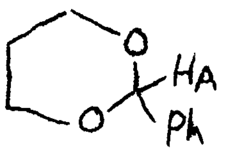
*The broadening of signals due to H_A and H_C protons were probably due to coupling between H_A and H_C (J_{AB} = 3 cps) which was not resolved in the spectrum.

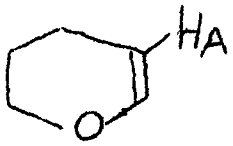

Me2NCH2CN
MeI
Me3N⊕CH2CN I⊖
20
NaH / THF
Me3N⊕–C⊖HCN
18
C6H5CHO
21
22
(18)
23
24
NaH
–HCN
25
or
26

Scheme 7

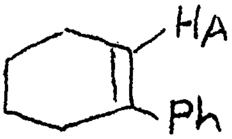
delocalization of lone pair of oxygen as shown (D), which increases the electron density at C-5. Further proof for the structure 25 will be obtained from its C^{13} NMR. spectrum.



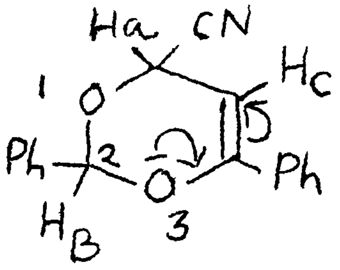
A, $\delta H_A = 5.32$



B, $\delta H_A =$ 4.3



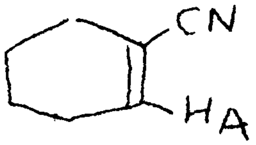
C, $\delta H_A =$ 5.38



D

The probable mechism for the formation of 25 is shown in the scheme 7. It appears that the epoxide 22 formed through betaine intermediate 21 undergoes further ring opening by the ylid 18 to give the betaine intermediate 23, which on subsequent reaction with another molecule of benzaldehyde and further cyclization and elimination of trimethylamine affords 24. The intermediate 24 after elimination of HCN yields either 25 or 26. However the structure 25 was preferred over 26 due to chemical shift position of olefinic proton (H_C) (δ 5.15), which will appear further down field in the structure 26 due to stronger desheilding effect of nitrle group. The olefinic proton in 1-cyanocyclohexene

(E) is reported to appear at δ6.58.[19] Similar kind of cyclization to yield m-dioxin derivatives have been observed in the reactions of dimethyl-2-butynylsulfonium ylids with bezaldehyde in the sodium hydride.[20]



$\delta H_A = 6.58$

E

VI.2.2 Reactions of Trimethylammonium Cyanomethylid (18) with α,β-unsaturated carbonyl compounds: Novel cyclopropanation with an Ammonium Ylid*

When the ylid 18 was reacted insitu with chalcone 27a, work-up and column chromatography of the reaction mixture yielded two white solids in 10% and 51% yields, which were characterized as cis- 1-benzoyl-2-cyano-trans-3-phenylcyclopropane and trans-1-benzoyl-2-cyano-3-phenylcyclopropane respectively by comparison of their physical and spectral data with that of the authentic samples.+ (Scheme 8) The reaction was found to be general and the stereoisomeric cyclopropanes 28b and 28c were similarly obtained by the reactions of 18 with the respective chalcones 27b and 27c. The reaction of chalcone 27d with 18 gave only the trans-cyclopropane 28d in 34% yield, while the cis- 28d could not be

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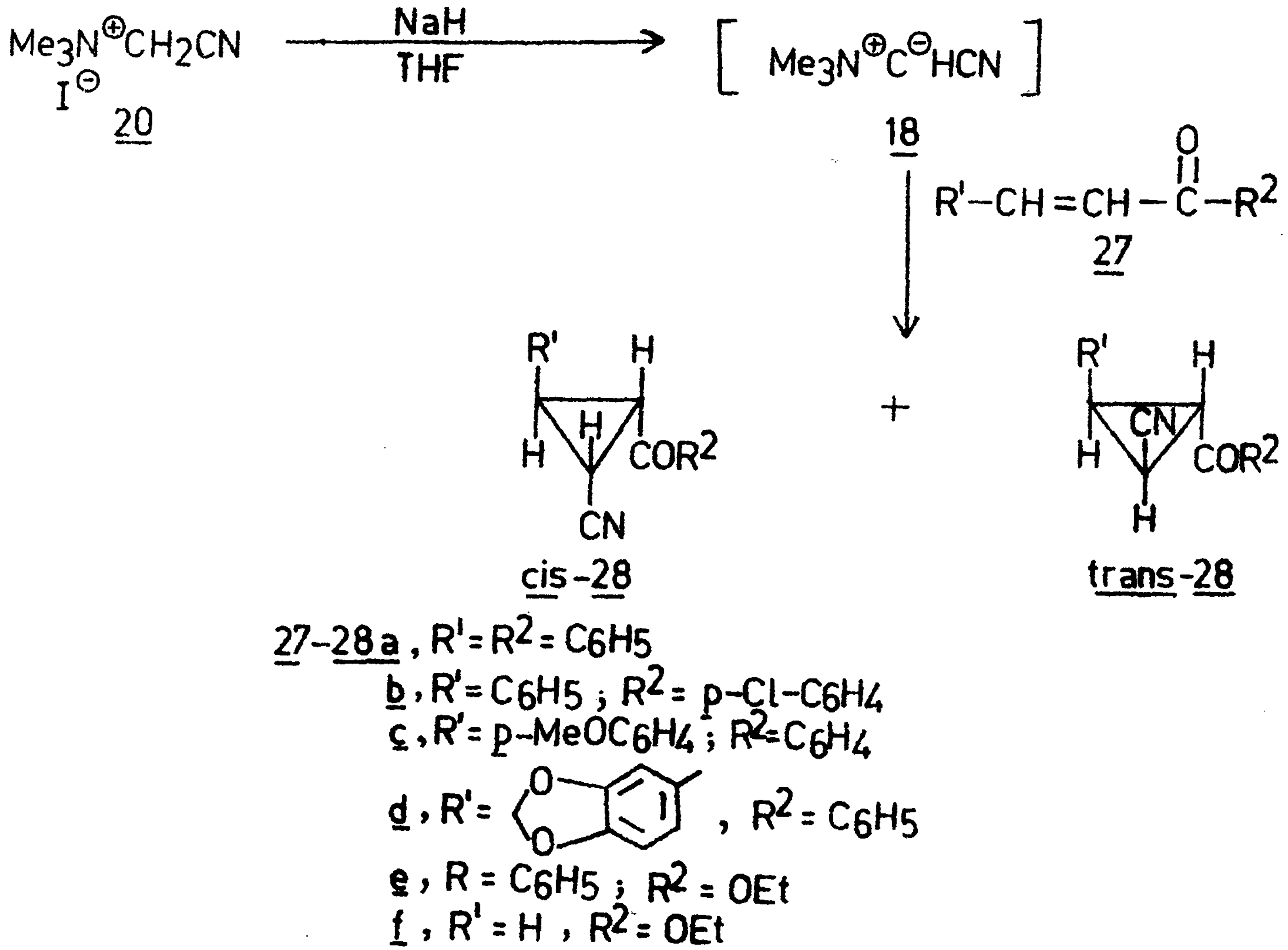
*S.S. Bhattacharjee, H. Ila and H. Junjappa, Synthesis, 301 (1982).



27–28 a, $R' = R^2 = C_6H_5$
b, $R' = C_6H_5$; $R^2 = p\text{-}Cl\text{-}C_6H_4$
c, $R' = p\text{-}MeOC_6H_4$; $R^2 = C_6H_4$
d, R' = , $R^2 = C_6H_5$
e, $R = C_6H_5$; $R^2 = OEt$
f, $R' = H$, $R^2 = OEt$

Scheme 8

isolated from the reaction mixture. The reaction of ylid 18 with ethyl cinnamate 27e gave only the *trans*- 28e in 65% yield(Scheme 8) while ethylacrylate (27f) yielded the inseparable mixture of *cis* and *trans*- 28f in 21% yield. The structures of all 28b-f were confirmed with the help of spectral and analytical data (Table 1 and 2). The stereochemistry of 28b-e was assigned by comparison of N.M.R. chemical shifts and viccinal coupling constants with those of known *cis*- and *trans*- 28a.* The reaction of ylid 18 with 2-cyclohexen-1-one did not give any identifiable product. Similarly the reactions of 18 with acrylamide, cinnamaldehyde and nitrostyrene yielded only polymeric mixtures.

The mechanism of the formation of *cis*- and *trans*- cyclopropanes 28 is shown in the scheme 9. Nucleophilic addition of the anionic center of the ylid 18 to chalcone 27 in Michael fashion yields the zwitterionic intermediate 29, which on 1,3-elimination, affords the stereioisomeric mixtures of cyclopropanes 28. An alternate mechanism through decomposition of 18 through a cyanocarbene intermediate followed by its addition to the double bond is ruled out since 18 does not add to unactivated double bonds such as those of cyclohexene or stilbene and no trace of 1,2,3-tricyanopropane was obtained in any of the reactions. The predominant formation of *trans*- 1-benzoyl-2-cyanocyclopropanes in these reactions can be reationalized in terms of relative thermodyanamic stabilities of diastereomeric zwitterionic intermediates[21a] for the formation of *cis* and *trans*- cyclopropanes. The conformations

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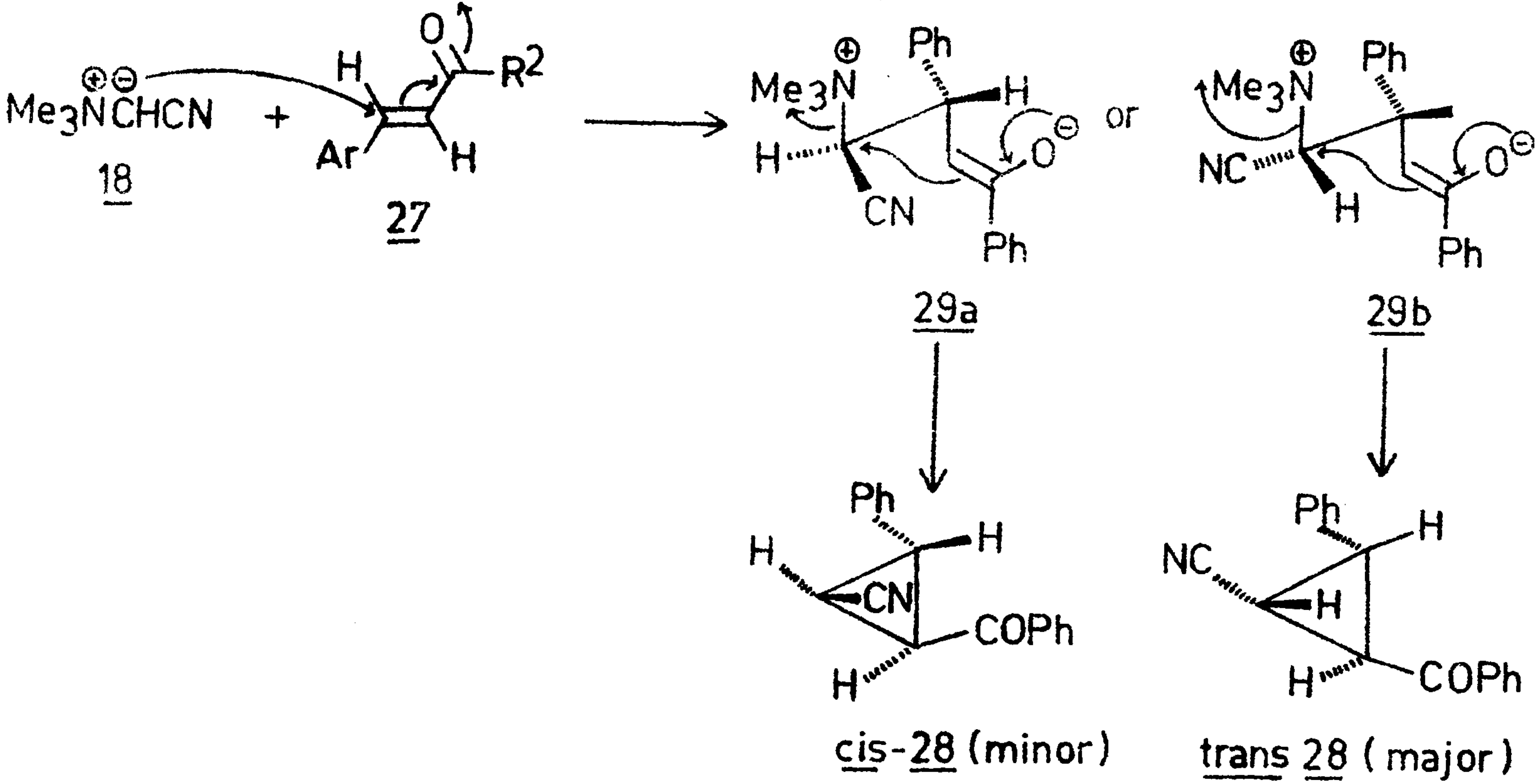
* We are thankful to Professor Barry M. Trost for sending us the physical and spectral data for *cis*- and *trans*- 28a.


Me$_3$N$^{\oplus}$C$^{\ominus}$HCN
18
+
H
O
R^2
Ar
H
27
Me$_3$N$^{\oplus}$
Ph
H
O$^{\ominus}$
H
CN
Ph
29a
or
Me$_3$N$^{\oplus}$
Ph
O$^{\ominus}$
NC
H
Ph
29b
Ph
H
H
CN
COPh
H
cis-28 (minor)
Ph
H
NC
H
H
COPh
trans 28 (major)

Scheme 9

29c and 29d require eclipsing of the enolate and the bulky phenyl group for attainment of the desired conformation for 1,3-elimination and need not be considered further. Of the remaining conformations 29a and 29b for 1,3-elimination, conformation 29a minimizes unfavourable eclipsing interactions which would be expected to collapse to cis cyclopropane at a faster rate than the diastereoisomer 29b resulting in the predominant formation of cis-1-benzoyl-2-cyano-3-phenyl cyclopropane 28 as a major product. However, the cis-28 is formed as a minor product in the present reaction conditions. It should be noted however that although the depicted conformations 29a and 29b for the two diastereomers are best for 1,3-elimination, the most stable conformations for these diastereoisomers 29a' and 29b' place the enolate groups close to ammonium centers to minimize charge separation, of which the diastereoisomer 29b' involves least unfavourable eclipsing interaction. Thus the relative thermodynamic stability of two diastereoisomers 29a and 29b is reversed, which determines the product stereochemistry (thermodynamic control). Interestingly, the reaction of dimethylcyanosulfonium methylid with chalcone also yields the corresponding trans- 1-benzoyl-2-cyano-3-phenyl cyclopropane 28a as the major product [21b*] (Scheme 11).

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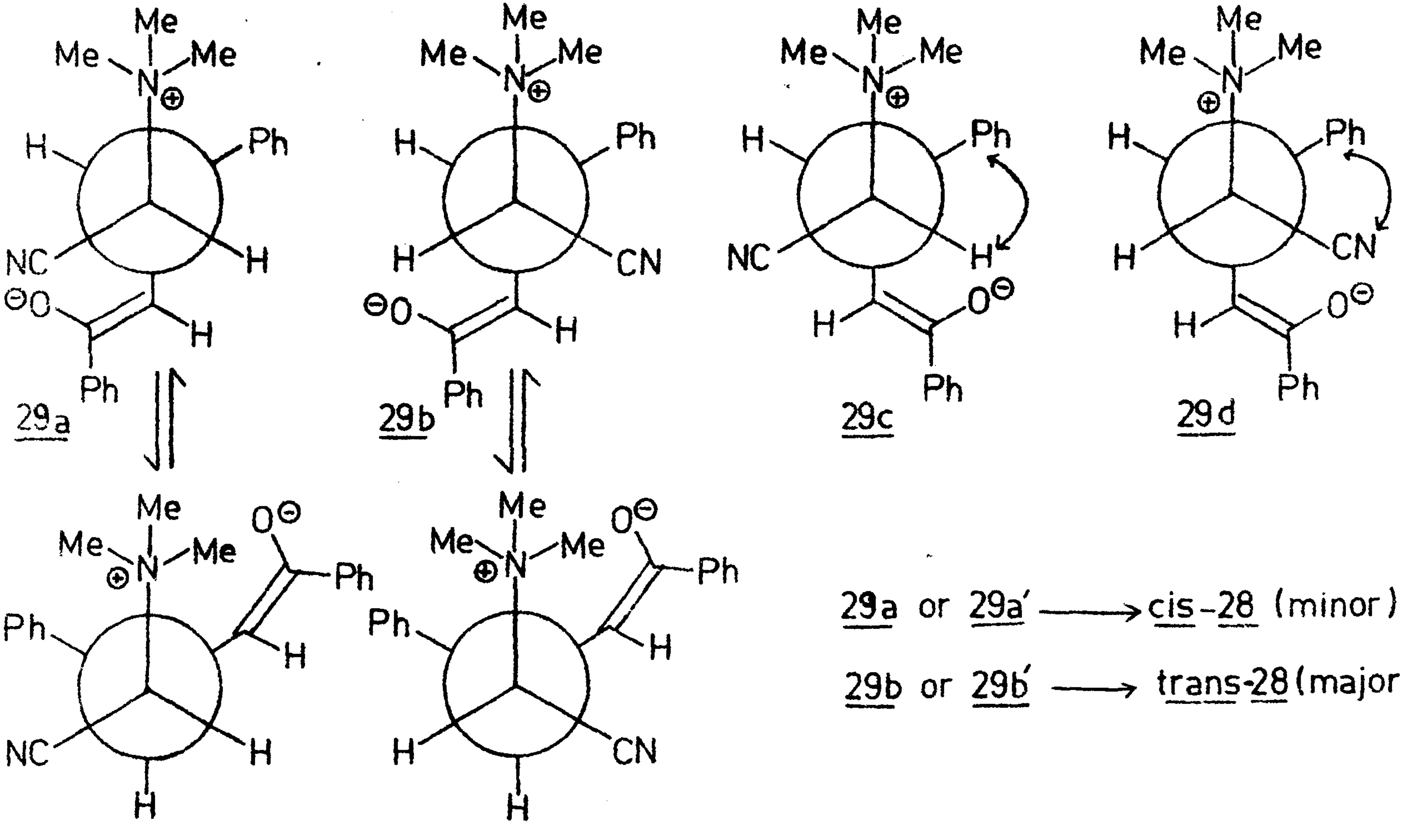
[*] Full experimental details of this reaction were obtained by personal communication with Prof. Barry M. Trost.



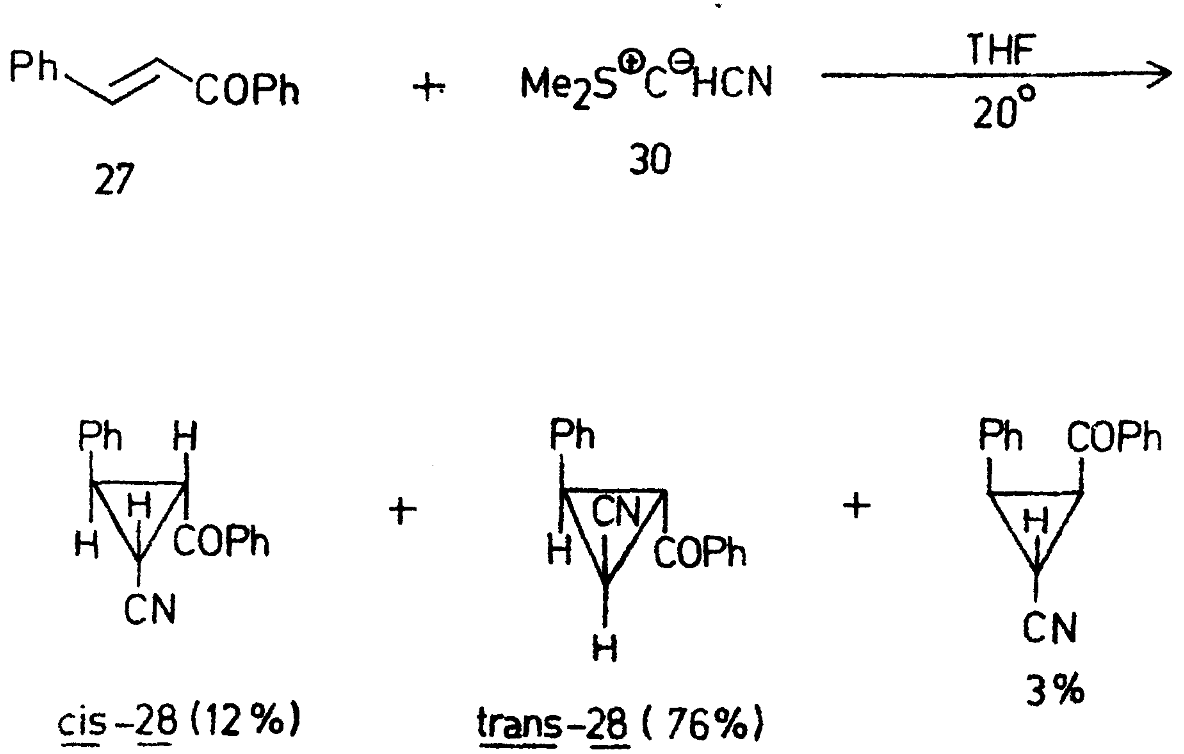
29a 29b 29c 29d

29a′ 29b′

29a or 29a′ $\longrightarrow$ cis-28 (minor)

29b or 29b′ $\longrightarrow$ trans-28 (major)

Scheme 10


Ph
COPh
27
Me2S⊕C⊖HCN
30
THF
20°
Ph
H
H
COPh
CN
cis-28 (12 %)
Ph
CN
H
COPh
H
trans-28 (76%)
Ph
COPh
H
CN
3%

Scheme 11

VI.2.3 Reaction of trimethylammoniumcyanomethylid (18) with dialkyltrithiocarbonate: A Facile Synthesis of 3,3-Bis(alkylthio)acrylonitriles through sulfur extrusion*

Although the reactions of a few heterocyclic and nitrile ylides with thiocarbonyl compounds have been reported to yield the corresponding cycloadducts,[2] the reaction of ammonium ylides with thiocarbonyl compounds have not been investigated. In continuation with our studies on the reactions of trimethylammonium cyanomethylid (18) we have studied the reaction of 18 with dialkyltrithiocarbonate (31) and the results are reported here.

When the ylid (18) generated insitu was reacted with dimethyl trithiocarbonate (31a) at 35°, work-up of the reaction mixture yielded a low melting solid in 55% yield, which was characterized as 3,3-bis(methylthio)acrylonitrle 33a (Scheme 12) by comparison of its physical and spectral data with that of authentic sample.[22] The dithioacetal (33a) is apparently formed by nucleophilic addition of ylid (18) on C=S bond of 31a followed by subsequent elimination of trimethylamine to give episulfide intermediate (32a), which on sulfur extrusion under reaction conditions yields 33a (Scheme 12). Similar sulfur extrusion reactions via episulfide intermediates to give olefinic compounds have also been reported in the reaction of diphenyldiazomethane (34) with

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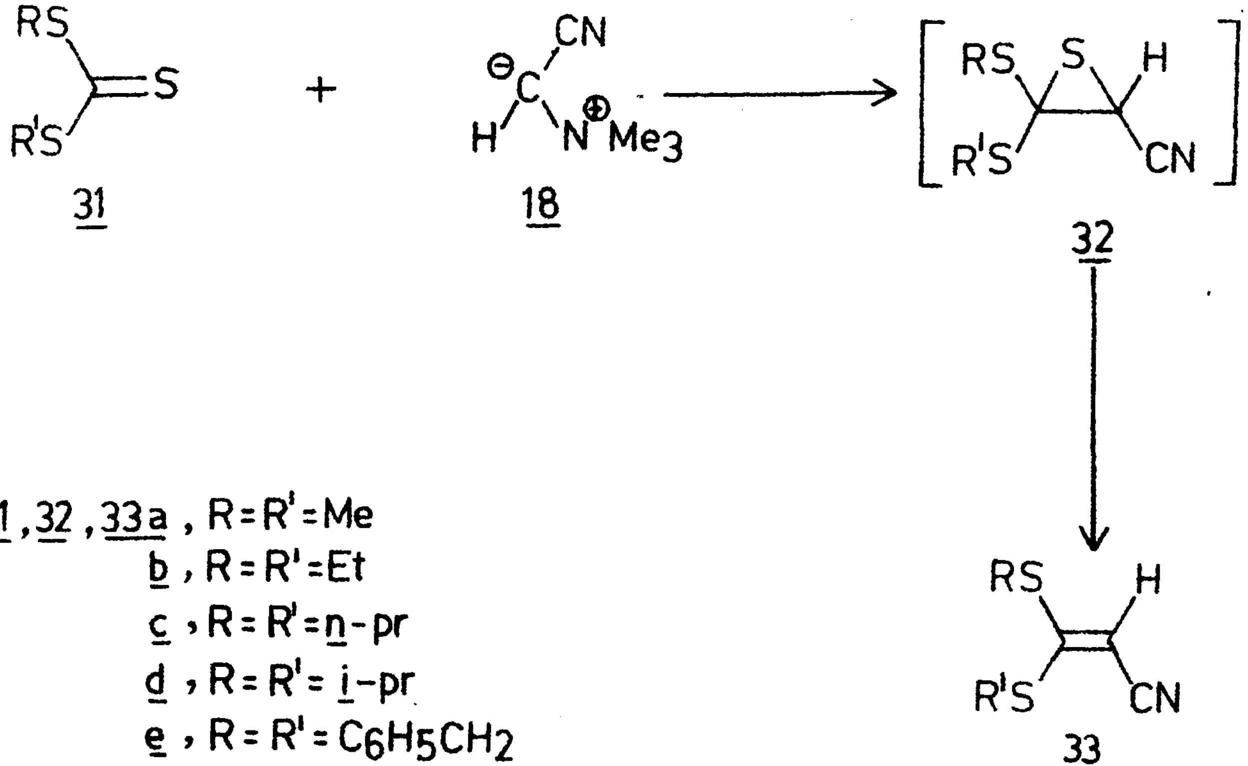
* S.S. Bhattacharjee, H. Ila and H. Junjappa, Synthesis, (accepted for publication).

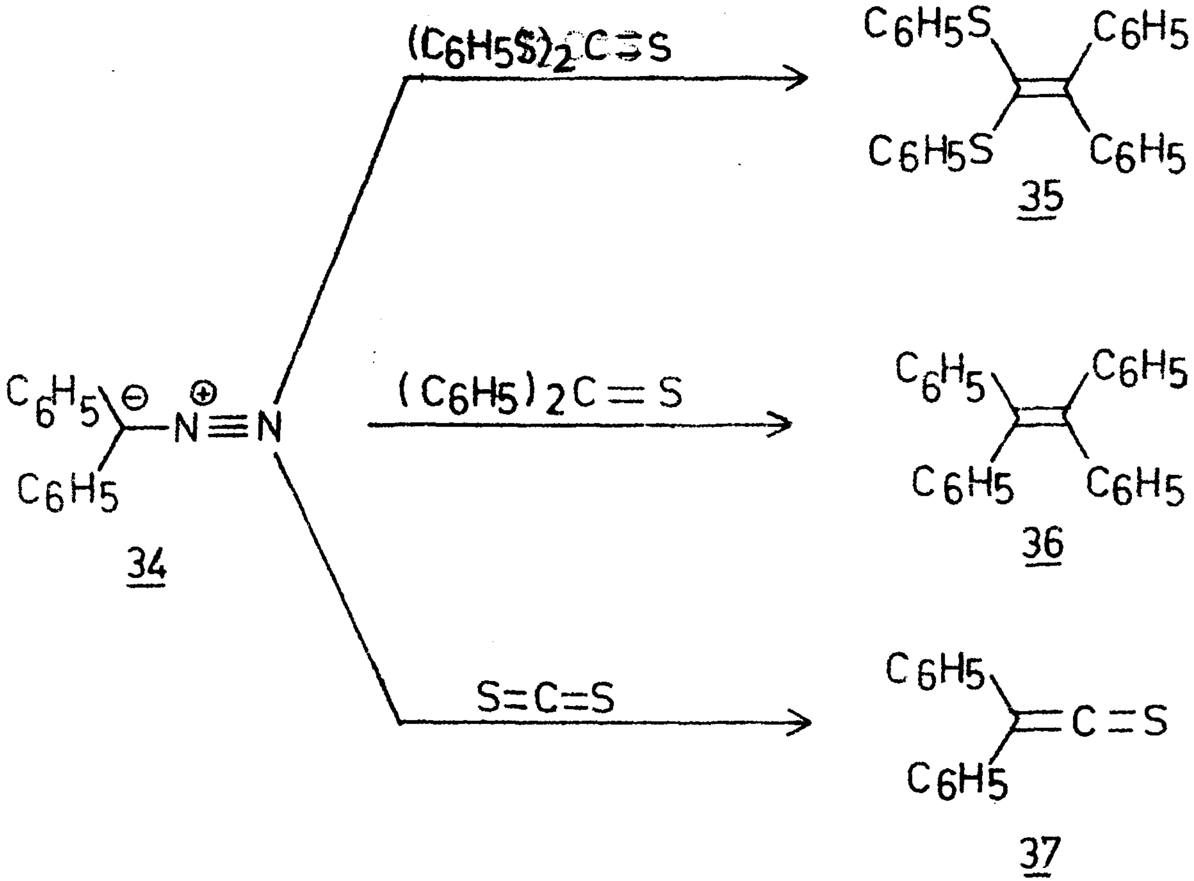


31, 32, 33 a, R = R' = Me
b, R = R' = Et
c, R = R' = *n*-pr
d, R = R' = *i*-pr
e, R = R' = $C_6H_5CH_2$
f, R = R' = $-CH_2-CH_2-$

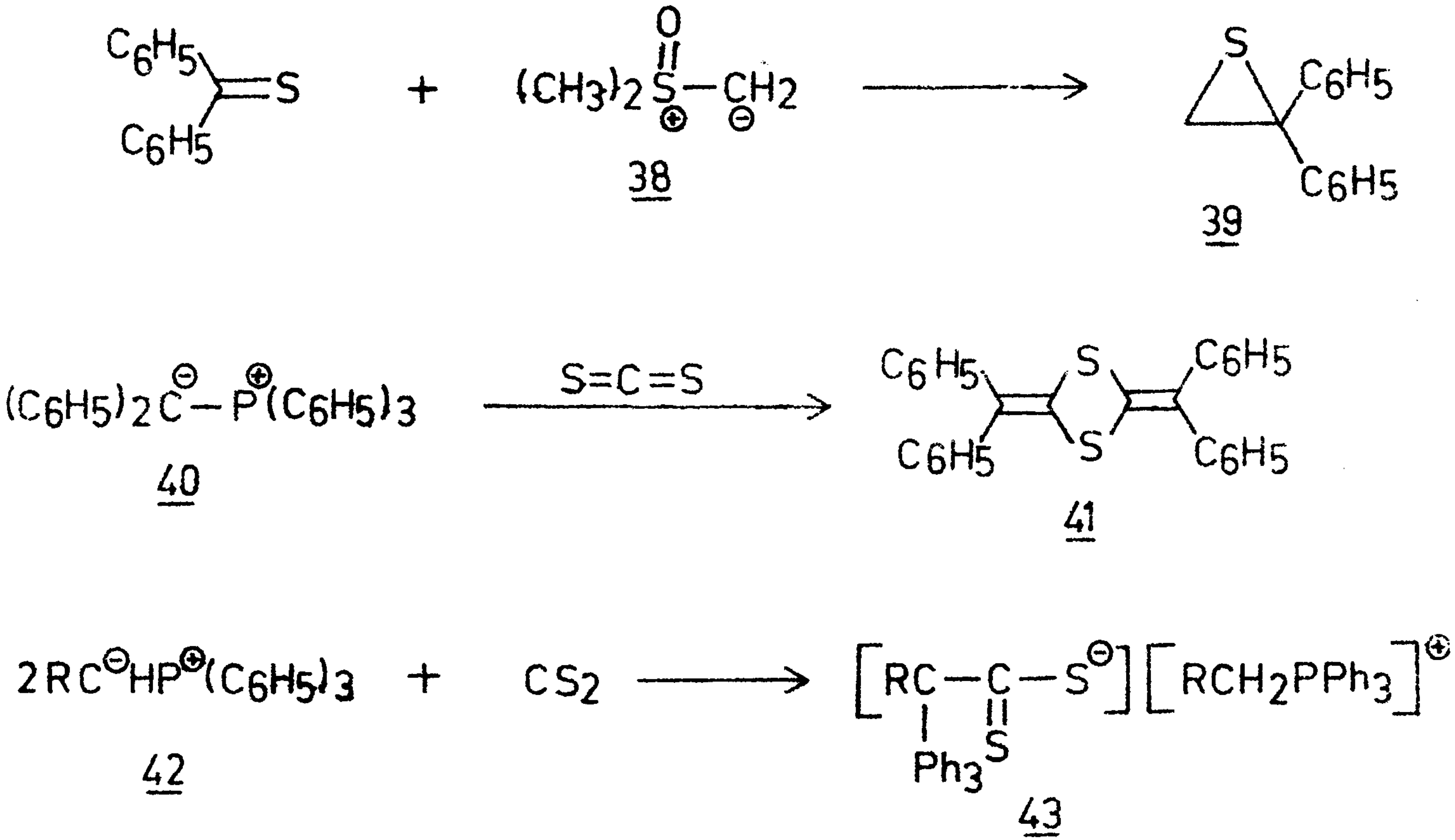
Scheme 12

thiobenzophenone,[23] diphenyltrithiocarbonate[24] and carbon disulfide (Scheme 13). It is pertinent to note that the reaction of dimethyl oxosulfonium ylid 38 with thiobenzophenone yields[25] the corresponding 1,1-diphenylthiirane 39 in good yields (Scheme 14). The reaction of a few stable phosphorous ylides like diphenylmethylenes and fluorenylidenetriphenylphosphorane with carbon disulfide on the other hand affords polymeric or dimeric thioketenes 41,[26] while a few of the basic phosphinealkylenes 42 interact with carbon disulfide giving phosphonium salts of α-(triphenylphosphoranylidene)-dithiocarboxylic acids 43 (Scheme 14).[26]

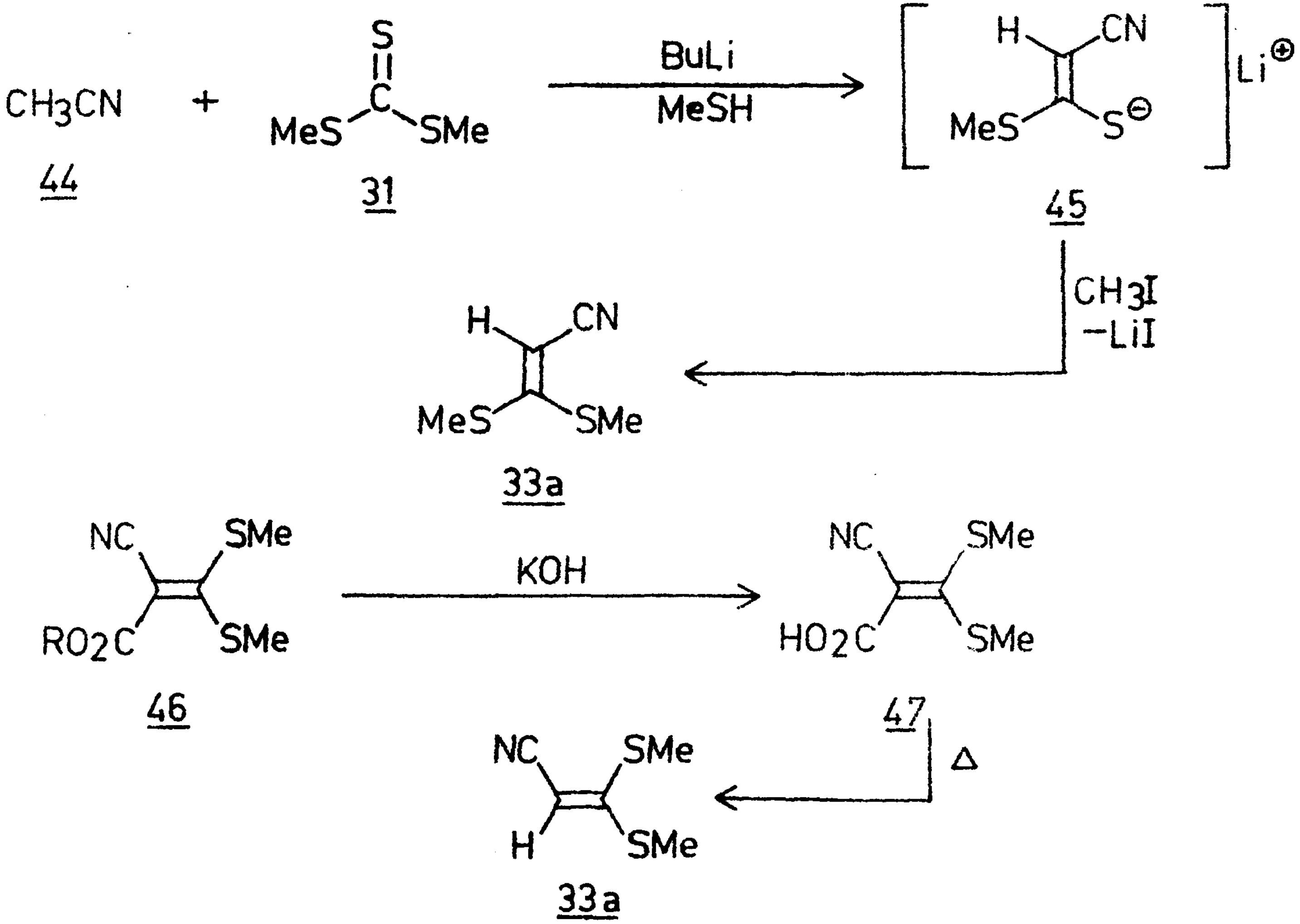
The reaction of 18 with 31 was found to be general and other trithiocarbonates 31b-f similarly gave the corresponding dithioacetals 33b-f in 56-58% overall yields. The reaction provides a facile route for 3,3-bis(alkylthio)acrylonitriles in moderate to good yields. The dithioacetal 33a has been earlier prepared[22] in 40% yield by condensation of lithium salt of acetonitrile with dimethyltrithiocarbonate followed by alkylation of resulting lithium salt of (thioacyl)acetonitrile 45 (Scheme 15). The acetal 33 has also been prepared in unspecified yields by soponification of 2-(bismethylthio)-2-ethoxycarbonylacrylonitrile (46) and subsequent decarboxylation of the resulting acid 47 (Scheme 15).[27]



Scheme 13



Scheme 14



Scheme 15

In the light of current activities in carbon-carbon bond forming reaction via sulfur extrusion, the reaction of 18 with trithiocarbonate is of particular interest. Further work on the reaction of 18 with other thionocompounds like thiobenzophenone and carbon disulfide is in progress in our laboratory.

VI. 3 CONCLUSION

From the foregoing studies it is apparent that the reaction of trimethylammoniumcyanomethylid (18) with benzaldehyde gives a product formed by further reaction of 18 with the intermediate epoxide 22. The reaction definitely requires further investigation. The ylid 18 undergoes conjugate addition to α,β-unsaturated carbonyl compounds to yield stereoisomeric cyclopropanes in moderate to good yields. To our knowledge this is the first report of cyclopropanation of an activated double bond with an ammonium ylid (or nitrogen ylid). Only one reference[28] has reported the formation of tribenzoylcyclopropane as one of the minor products, when phenacylpyridinium methylid was reacted with phenacyl bromide. Thus the ylid 18 in its reaction with α,β-unsaturated carbonyl compounds behaves like stabilized sulfonium ylides, which are known to undergo generally cyclopropanation. The reaction of 18 with dialkyltrithiocarbonate 31 to give dithioacetals 33 via sulfur extrustion in the resulting thiiranes 32 is similar to the reaction of diphenyldiazoalkanes with thiocarbonyl compounds.

These results confirm that the stabilized nitrogen ylides can also behave like their sulphur and phosphorous analogoues in their reactions if the ylid possesses proper moderatly stabilising substituents.

VI. 4 EXPERIMENTAL

M.ps were determined on a "Boetius"(German) apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer. The NMR spectra were recorded on a Varian EM-390 spectrometer using TMS as an internal standard and the chemical shifts are expressed in ppm from TMS taken as 0.00 (δ units). Mass spectra were recorded on a Hitachi RMU-6E mass spectrometer fitted with a direct inlet system.

The Starting Materials

The commercial samples of acetopheone, *p*-chloroacetophenone, *p*-methoxyacetophenone, benzaldehyde, *p*-methoxybenzaldehyde, piperonal, ethylcinnamates, acrylamide, 2-cyclohexene-1-one, cinnamaldehyde and ethyl acrylate were purified before use.

The N,N-dimethylaminoacetonitrile, bp 138° (760 mm)[14] and trimethylammoniumcyanomethyliodide,[14] m.p. 210°(d), were prepared by the reported procedure.

TABLE 1

Spectral data of the products, 28a-f

Products	I.R.(nujol) (cm^{-1})	^{1}H-N.M.R.(CDCl$_3$) (ppm)	M.S. m/e(M$^+$)
cis-28a	2240 (CN) 1675 (CO)	2.30 (t, 1H, J=7 Hz); 3.45 (d, 2H, J=7 Hz); 7.0-7.8 (m, 8H$_{arom}$); 8.05 (m, 2H$_{arom}$).	247
trans-28a	2240 (CN) 1672 (CO)	2.62 (dd, 1H, J=8.5 Hz and 4.5 Hz); 3.01 (dd, 1H, J=8.5 Hz and 6.0 Hz); 3.61 (dd, 1H, J=6.0 Hz and 4.5 Hz); 7.0-7.8 (m, 8H$_{arom}$); 8.05 (m, 2H$_{arom}$).	247
cis-28b	2240 (CN) 1670 (CO)	2.36 (t, 1H, J=7 Hz); 3.36 (d, 2H, J=7 Hz); 6.8-7.7 (m, 8H$_{arom}$); 8.0 (m, 2H$_{arom}$).	281.5

Table 1 (Contd.)

trans-28b	2236 (CN) 1670 (CO)	2.75 (dd, 1H, J = 9 Hz and 4.5 Hz); 3.02 (dd, 1H, J = 9 Hz and 6 Hz); 3.58 (dd, 1H, J = 6 Hz and 4.5 Hz); 6.9-7.7 (m, $7H_{arom}$); 8.1 (m, $2H_{arom}$).	281.5
cis-28c	2238 (CN) 1668 (CO)	2.26 (t, 1H, J = 7 Hz); 3.32 (d, 2H, J=7 Hz); 3.76 (s, 3H, *p*-C$\underline{H}_3$O); 7.01 (dd, $4H_{arom}$); 7.6 (m, $3H_{arom}$); 8.0 (m, $2H_{arom}$).	277

Table 1(Contd.)

trans-28c	2240 (CN) 1670 (CO)	2.60 (dd, 1H, J=8.5 Hz and 4.5 Hz); 2.92 (dd, 1H, J=8.5 Hz and 6 Hz); 3.50 (dd, 1H, J=6 Hz and 4.5 Hz); 3.72 (s, 3H, $\underline{p}$-C$\underline{H}_3$O); 7.04 (dd, 4H_{arom}); 7.5 (m, 3H_{arom}); 8.0 (m, 2H_{arom}).	277
trans-28d	2240 (CN) 1665 (CO)	2.60 (dd, 1H, J=9 Hz and 4.5 Hz); 2.95 (dd, 1H, J=9 Hz and 6Hz); 3.52 (dd, J=6 Hz and 4.5 Hz); 5.93 (s, 2H, -O-C$\underline{H}_2$-O-); 6.80 (s, 3H_{arom}); 7.2-7.65 (m, 3H_{arom}); 8.02 (dd, 2H_{arom}).	291
Trans-28e	2240 (CN) 1730 (CO)^a	1.30 (t, 3H, OCH$_2$C$\underline{H}_3$); 2.40 (dd, 1H, J=8.5 Hz and 6 Hz); 2.73 (t, 1H, J=6 Hz); 2.98 (dd, J=8.5 Hz and 6 Hz); 4.25 (q, 2H, OC$\underline{H}_2$CH$_3$); 7.40 (brs, 5H_{arom})	215

Table 1 (Contd.)

cis/trans-**28f**	2240 (CN) 1738 (CO)[a]	1.1–1.8 (m, 5H, $OCH_2C\underline{H}_3$ and $2H_{cyclopropyl}$); 1.8–2.55 (m, $2H_{cyclopropyl}$); 4.18 (q, 2H, $OC\underline{H}_2CH_3$).	139

[a] I.R. as film.

Dimethyl trithiocarbonate, bp 225°(760 mm);[29] diethyltrithiocarbonate, bp 102-104° (7mm); diisopropyl trithiocarbonate,[30] mp 32°; di-n-propyltrithiocarbonate;[30] bp 98° (7.5 mm); dibenzyltrithiocarbonate,[30] mp 28° and ethylene trithiocarbonate[31] mp 37° were prepared by the procedure described in the chapter 2.

Benzalacetophenone (27a),[32] mp 55-57°; 4'-chlorobenzalacetophenone, mp 101°;[33] 4-methoxybenzalacetophenone, mp 79°[34] and 3,4-methylenedioxybenzalacetophenone, mp 122°[34] were prepared by the reported methods.[32]

<u>Generation of trimethylammoniumcyanomethylid and its reaction with benzaldehyde: Formation of 2,4-diphenyl-6-cyano-1,3-m-dioxin</u>

A suspension of sodium hydride (0.022 mol, 50% suspension) and cyanomethyltrimethylammonium iodide (4.5g, .02 mol) in dry tetrahydrofuran (30 ml) was stirred at room temperature for 2 hr till evolution of hydrogen was complete. A solution of benzaldehyde (2.4g, 0.02 mol) in dry THF (20 ml) was added dropwise to the reaction mixture with stirring and stirring was continued further for 5 hr at room temperature and then at 40°C for 2 hr. The reaction mixture was poured into 200 ml of cold water after cooling and extracted with dichloromethane (2x50 ml). The combined extracts were washed once with 50 ml of water, dried (Na_2SO_4), and evaporated to give a viscous residue, which was chromatographed on silica gel column. Elution with benzene-hexane (3:1) gave 2.8g (54%) of 25; NMR and IR data are described in the text, M.S.(m/s).M^+ : 263 (Found: C, 77.92; H, 5.20; N, 5.49; Calc. for $C_{17}H_{13}NO_2$ (263): C, 77.56; H, 4.94; N, 5.32%).

Reactions of trimethylammoniumcyanomethylid (18) with α,β-unsaturated carbonyl compounds : Formation of cis- and trans-1,2,3-trisubstituted cyclopropanes (28) : General Procedure

A suspension of sodium hydride (0.025 mol, 50% suspension) and cyanomethyltrimethylammonium iodide (20; 0.02 mol) in dry tetrahydrofuran (25 ml) was stirred at room temperature for 1.5 hr till the evolution of hydrogen was complete. A solution of 27a-f (0.02 mol) in dry tetrahydrofuran (25 ml) was slowly added to the reaction mixture during 15 minutes with stirring and then temperature was slowly raised to 40-50°C, till the evolution of trimethylamine started. The reaction mixture was stirred at 40-50°C for 12-16 hr and the reaction was monitored frequently by checking the evolution of trimethylamine. When the evolution of trimethylamine was completed, the mixture was worked by removing the solvent under reduced pressure, diluting with water, neutralizing with dilute acetic acid (3N), and extracting with ether (3x100 ml). The ether extracts were washed twice with water, dried (Na_2SO_4) and evaporated to give a thick viscous residue which was chromatographed on silica gel column. Elution with benzene / hexane (1:1) gave first the trans-isomers of 28a-c, while further elution with benzene:hexane (4:1) yielded the cis-isomers of 28a-c. In the case of 27d, only trans-28d was obtained on elution with benzene/hexane mixture (3:1) and no trace of cis-28d could be isolated. Column chromatography of the reaction mixture obtained from 27e and 18, first yielded unreacted ethyl cinnamate (5%) on elution with benzene/hexane (:1); while further elution with benzene/hexane (4:1) yielded trans-28e.

Column chromatography of the reaction mixture obtained from the reaction of 27f and 18 gave a crude mixture of cis-28f and trans-28f, which on distillation (Vigreus column, 3 inch) under reduced pressure gave a mixture of pure cis and trans-28f. The spectral, physical and analytical data of cis and trans-28a-f prepared by this procedure are given in the table 1 and 2 respectively.

Attempted cyclopropanation of 2-cyclohexene-1-one, acrylamide, cinnamaldehyde and nitrostyrene with ylid 18

A solution of the ylid was prepared as previously described from sodium hydride (0.025 mol) and cyanomethyltrimethylammonium iodide (0.02 mol) in tetrahydrofuran (25 ml). A solution of freshly distilled 2-cyclohexane-1-one (0.02 mol) was added slowly with stirring. The stirring was continued for 10 hr at 40-45°C. After usual work-up, neither cyclopropane nor any identifiable product could be isolated and only polymeric mixture was obtained. Similarly, acrylamide, cinnamanilide, cinnamaldehyde and nitrostyrene when reacted with ylid 18 under identical conditions, yielded only polymeric mixtures, while starting materials were completely consumed.

Reactions of trimethylammoniumcyanomethylid (18) with dialkyltrithiocarbonate: Preparation of 3,3-bis(alkylthio)acrylonitriles (33a-f) : General Procedure

A suspension of sodium hydride (0.024 mol, 50% suspension) and cyanomethyltrimethylammonium iodide (20; 0.021 mol) in dry tetrahydrofuran (40 mol) was stirred at room temperature for 1.5 hr. A solution of 31 (0.02 mol) in dry dimethyl formamide (10 ml) was added to the reaction mixture with stirring and the temperature was slowly raised to 30-35°C. The stirring was continued for 6-10 hr at room temperature and the reaction was monitored by frequently checking the evolution of trimethylamine. When the evolution of trimethylamine was stopped, the mixture was poured into ice cold water and the product extracted with ethylacetate (3x60 ml). The combined extracts were washed once with water, dried (Na_2SO_4), and evaporated to give 33 as thick viscous liquids which were further purified by passing through a silica gel column; using hexane/benzene (1:1) as eluent. The physical, spectral and analytical data of the compounds 33a-f prepared by this method are given below:-

3,3-Bis(methylthio)acrylonitrile (33a) was obtained as light yellow crystals (benzene-hexane), 1.6g (55%); mp 35° (reported[22] 37°); IR(KBr): 2205 (CN) cm^{-1}; NMR ($CDCl_3$): 2.50 (s, 3H, $SC\underline{H}_3$), 2.55 (s, 3H, $SC\underline{H}_3$), 5.10 (s, 1H, olefinic); M.S.(m/e)M^+: 145;(Found: C, 41.52; H, 5.09; N, 9.48; Calc. for $C_5H_7NS_2$ (145.2): C, 41.35; H, 4.82; N, 9.64%).

3,3-Bis(ethylthio)acrylonitrile (33b) was obtained as deep yellow liquid (TLC single spot) yield 1.9g (58%); IR(neat): 2205 (CN) cm^{-1}; NMR ($CDCl_3$) : 1.35 (t, 6H, $SCH_2C\underline{H}_3$), 2.88 (q, 2H, $SC\underline{H}_2CH_3$), 3.08 (q, 2H, $CH_3C\underline{H}_2S$); 5.23 (s, 1H, olefinic); M.S.(m/e).M^+: 173; (Found:C, 48.31 H, 6.52, N, 7.91 Calc. for $C_7H_{11}NS_2$(173.3); C, 48.53; H, 6.35, N; 8.08%).

3,3-Bis(n-propylthio)acrylonitrile (33c) was obtained after column chromatography on silica gel using benzene/hexane (1:4) as yellow viscous liquid, yield 2.2g (55%); IR(neat): 2205 (CN), cm^{-1} NMR δ ($CDCl_3$): 1.02 (t, 6H, $SCH_2CH_2C\underline{H}_3$); 1.65 (q, 4H, $SCH_2C\underline{H}_2CH_3$); 2.80 (m, 4H, $SC\underline{H}_2CH_2CH_3$); 5.20 (s, 1H, olefinic); M.S.(m/e) M^+; 201; (Found: C, 53.94; H, 7.33; N, 6.72; Calc. for $C_9H_{15}NS_2$ (201.2): C, 53.72 H, 7.45, N, 6.95%).

3,3-Bis(isopropylthio)acrylonitrile (33d) was obtained after column chromatography on silica gel using benzene/hexane (1:3) as deep yellow viscous liquid, yield 2.5g, (58%); IR(neat) : 2203 (CN) cm^{-1}; (C=C) ; NMR (CDCl$_3$) : 1.35 (d, 12H, SCH(C$\underline{H}_3$)$_2$); 3.35 (hept, 1H, SC$\underline{H}$(CH$_3$)$_2$; 3.65 (hept, 1H,(CH$_3$)$_2$C$\underline{H}$S); 2.28 (s, 1H, olefinic); M.S. (m/e) M$^+$: 201; (Found: C, 53.50; H, 7.61; N, 7.24; Calc. for $C_9H_{15}NS_2$ (201.2) : C, 53.72; H, 7.45; H, 6.95%).

3,3-Bis(benzylthio)acrylonitrile (33e) was obtained after column chromatography on silica gel using benzene/hexane (1:1) as brown semi solid, yield 2.5g (42%); IR(nujol): 2203 (CN), cm^{-1}; NMR (CDCl$_3$): 4.10 (br·S, 4H, C$\underline{H}_2$-C$_6$H$_5$), 5.18 (S, 1H, olefinic), 7.25 (br.S, 10H, arom); M.S.(m/e).M$^+$; 297 (Found: C, 69.02 H, 5.18; N, 4.46; Calc. for $C_{17}H_{15}NS_2$ (297.3): C, 68.67; H, 5.04; N, 4.70%).

3,3-Bis(ethylenethio)acrylonitrile (33f) was obtained after column chromatrography on silica gel using benzene/hexane (1:2) as brown liquid, yield 1.4g,(50%); IR(nujol): 2200 (CN) cm^{-1}; NMR(CDCl$_3$): 3.53 (s, 4H, -(CH$_2$)$_2$-S), 5.27 (s, 1H, olefinic); M.S.(m/e) M$^+$: 143; (Found: C, 42.21; H, 3.70; N, 9.54; Calc. for $C_5H_5NS_2$ (143.2) : C, 41.93; H, 3.49; N, 9.77%).