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

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

ABSTRACT

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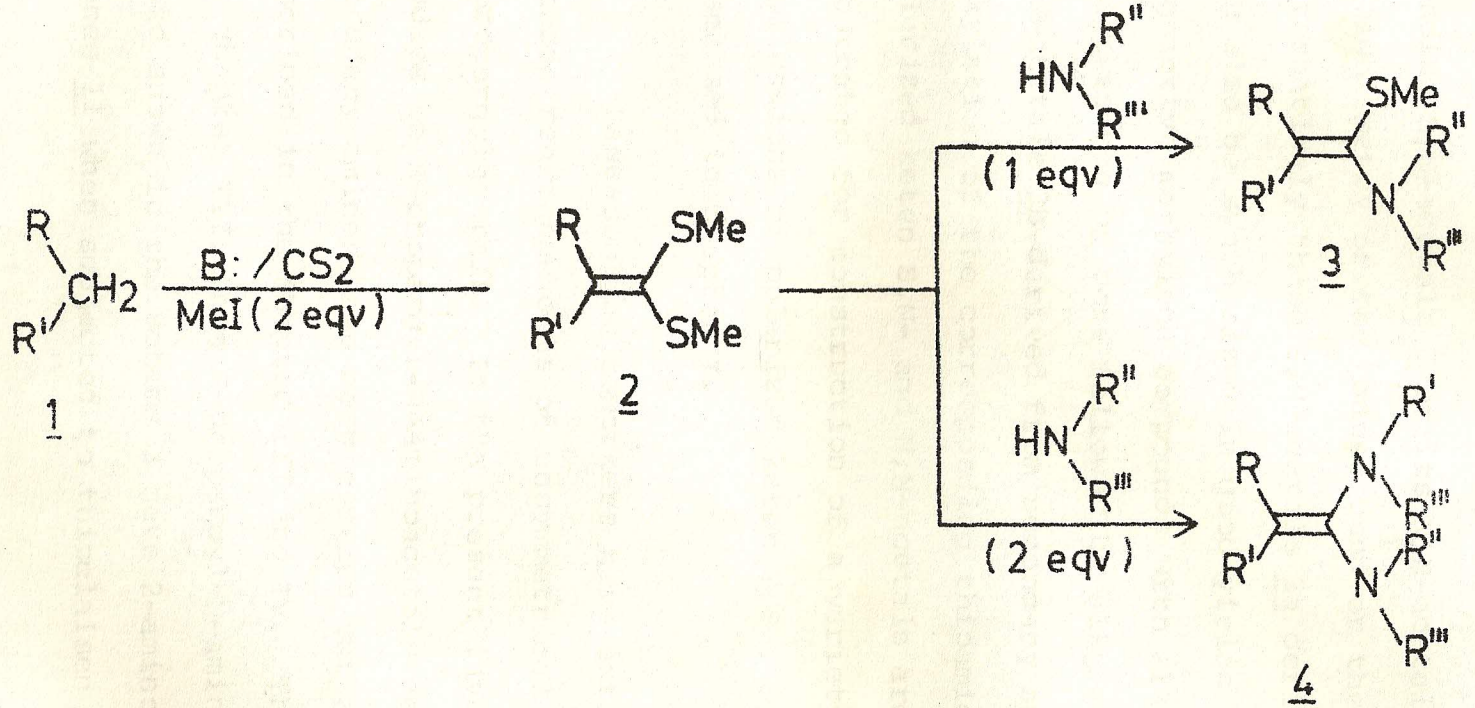
The thesis is divided into two parts, the first part consisting of five chapters, deals with the studies on polarized keten S,S- and S,N-acetals derived from various active methylene compounds, particularly ketones.

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 2 3 4

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

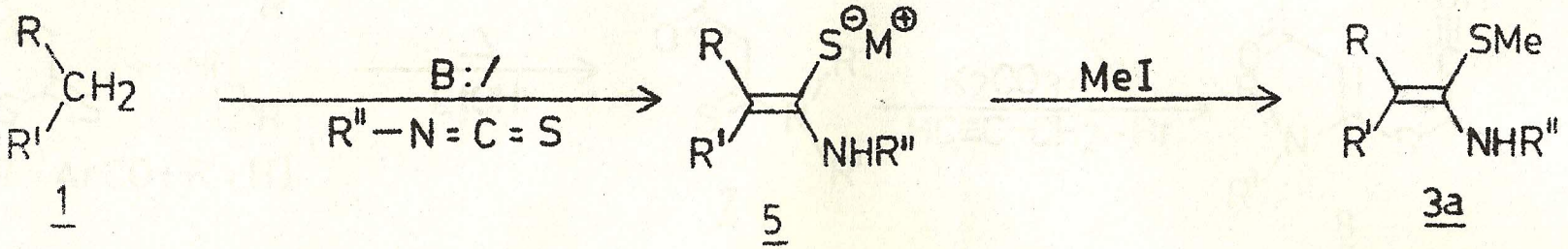
3-4a , R'' = aryl ; alkyl ; R''' = H (primary amines)

b , R'' = R''' = alkyl , $-(CH_2)n-$ etc (secondary amines)

Scheme 1.

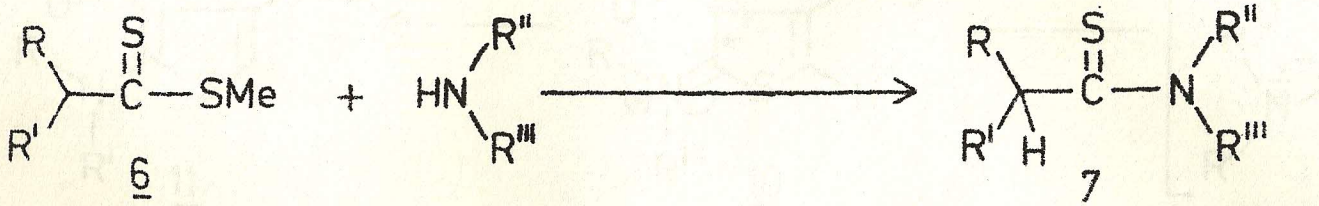
acetals in good yields. Particularly when the nucleophile is an amine the displacement can take place either to give the corresponding S,N-acetals 3 or its N,N-acetals 4 depending on the stoichiometry of the amines used or the reaction conditions. Alternatively these S,N-acetals 3a derived from primary 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]

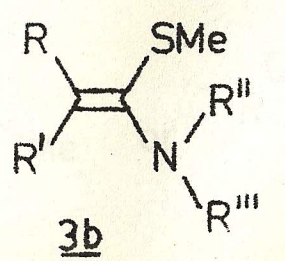


1 5 3a

3a , 5 , R" = aryl or alkyl



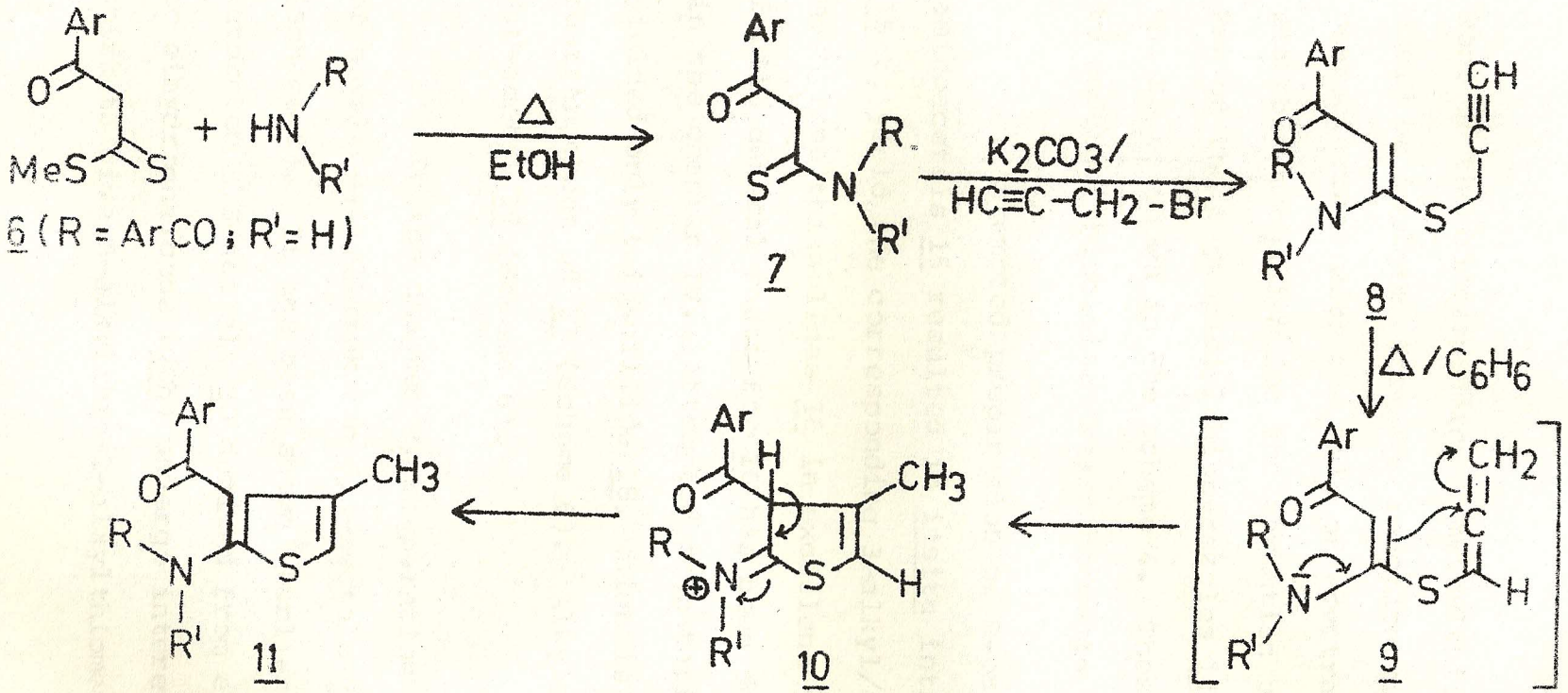
6 7



3b

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

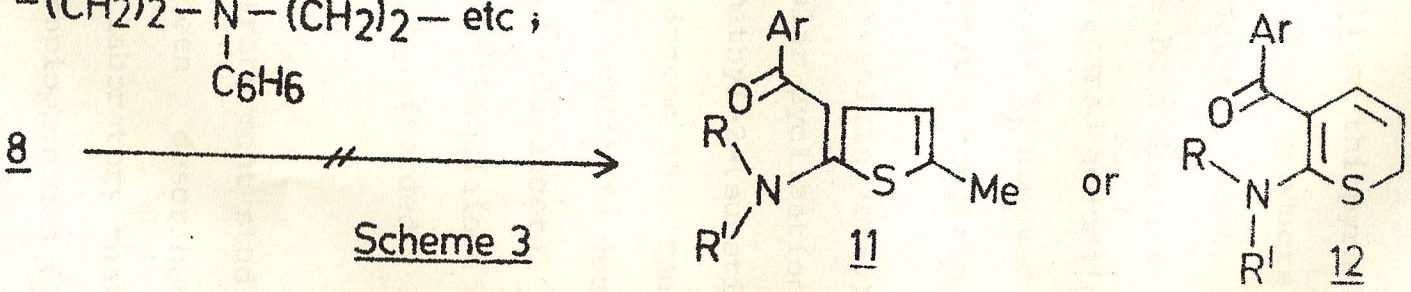
Scheme 2



7 11 ; Ar = C_6H_5 ; p-$MeOC_6H_4$; 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 ;

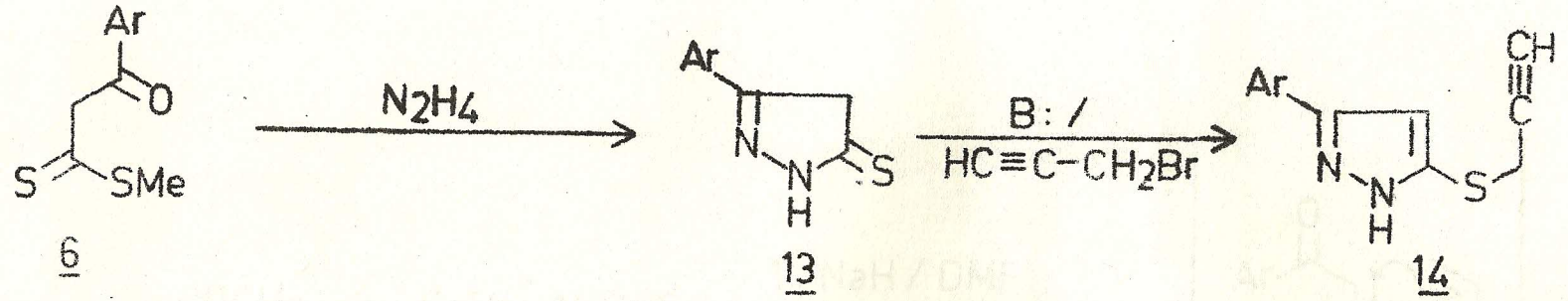


Scheme 3

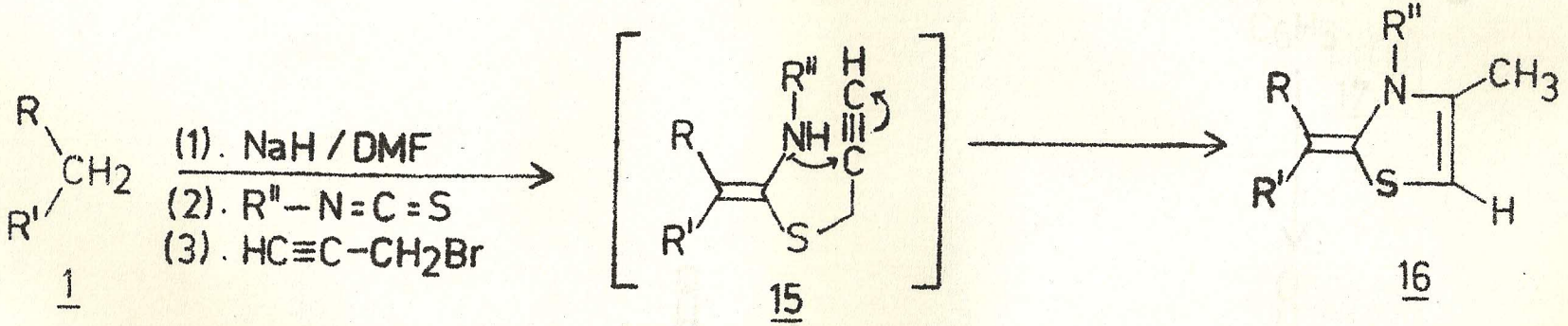
None of the corresponding 5-methylthiophenes 11 or thiopyran 12 could be isolated from the reaction mixture. These products were characterized with the help of spectral and analytical data and a probable mechanism for the formation of 11 has been discussed. Few of the S-propargylthiopyrazoles 14 were 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/ethyl-aminoacetals 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)

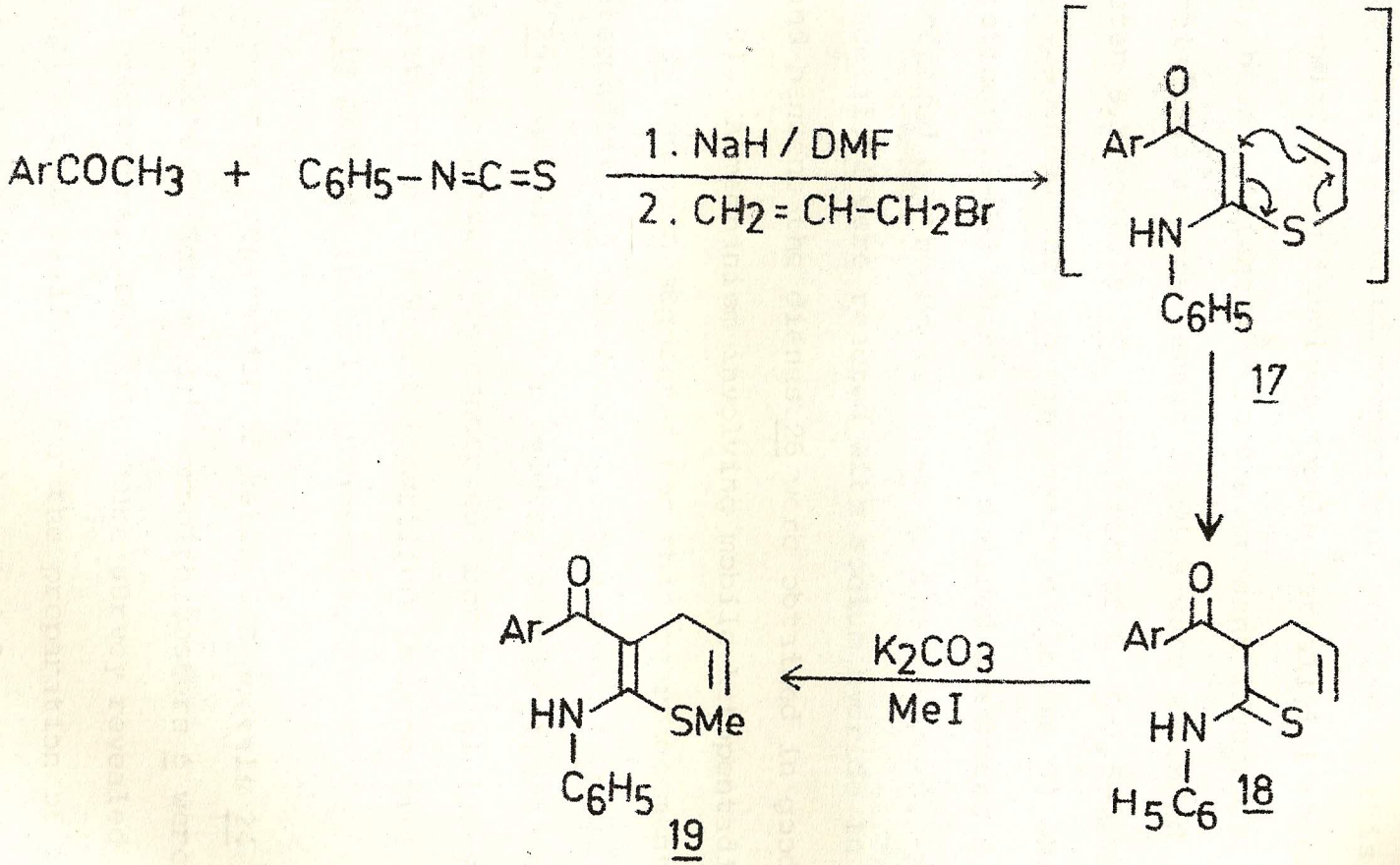


Scheme 4



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

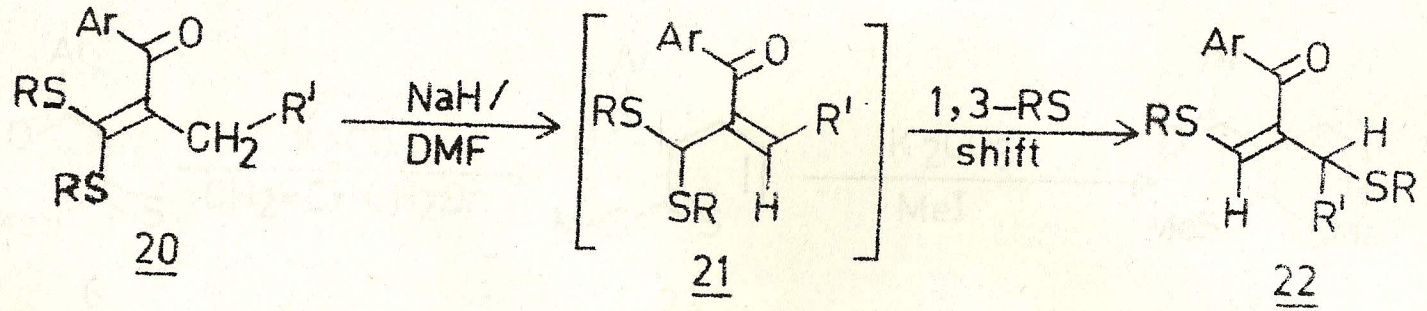
Scheme 5


ArCOCH3 + C6H5–N=C=S
1. NaH / DMF
2. CH2 = CH–CH2Br
Ar
O
HN
S
C6H5
17
18
19
K2CO3
MeI
SMe
H5C6

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).

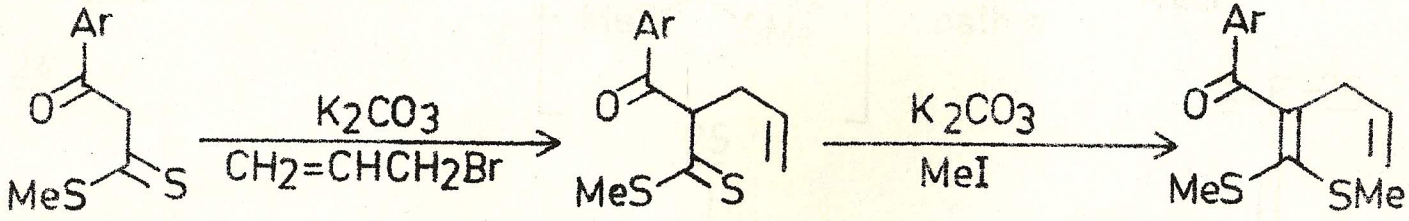
For the preparation of keten S,S-acetals 24 (Scheme 8) and thioamides 7 (Scheme 3) β-oxodithioesters 6 were required as initial precursors. Our literature survey revealed that there is no general method available for the preparation of these dithioesters 6. Thus a facile general method for the synthesis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



20 21 22

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

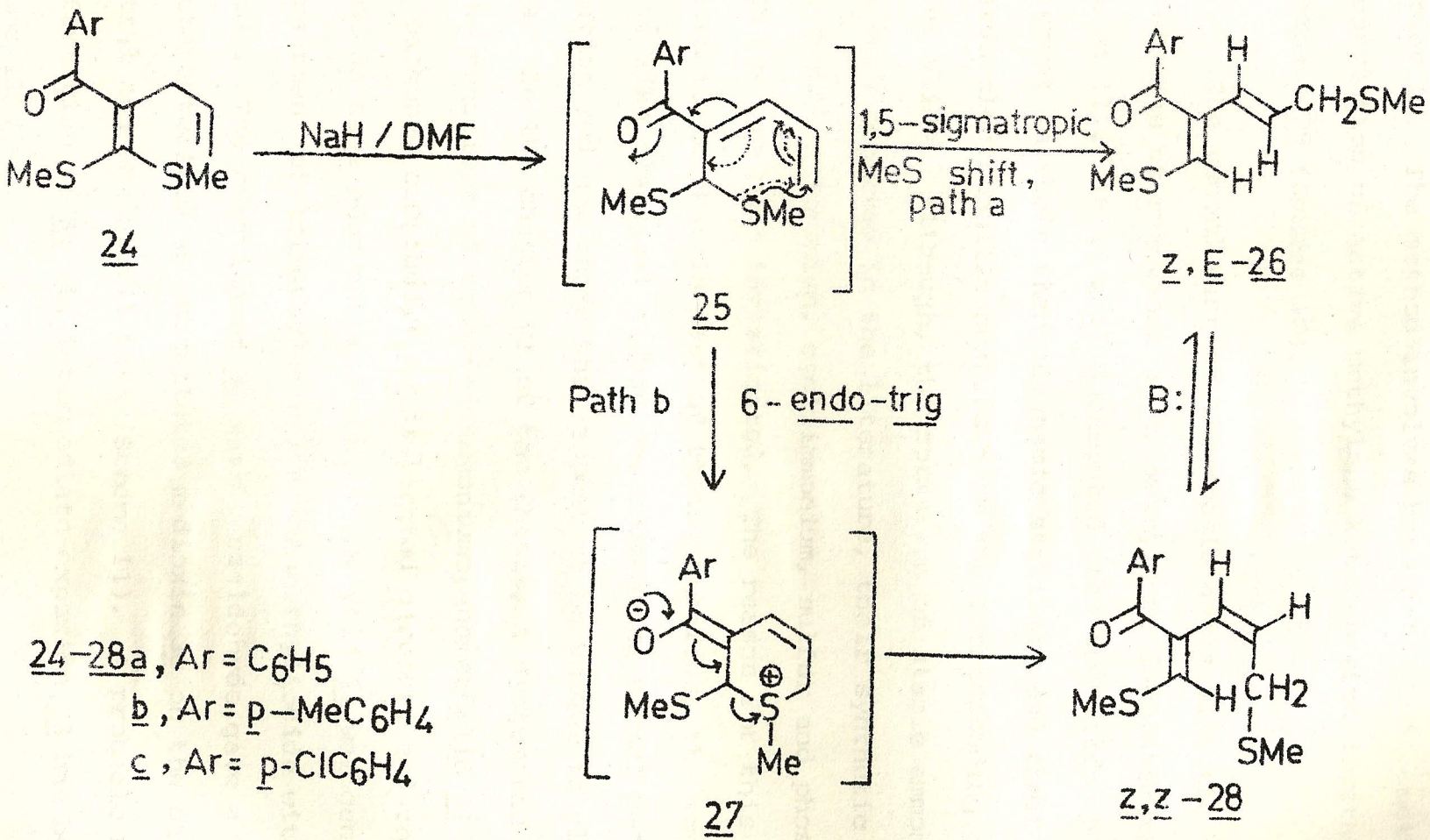
Scheme 7



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

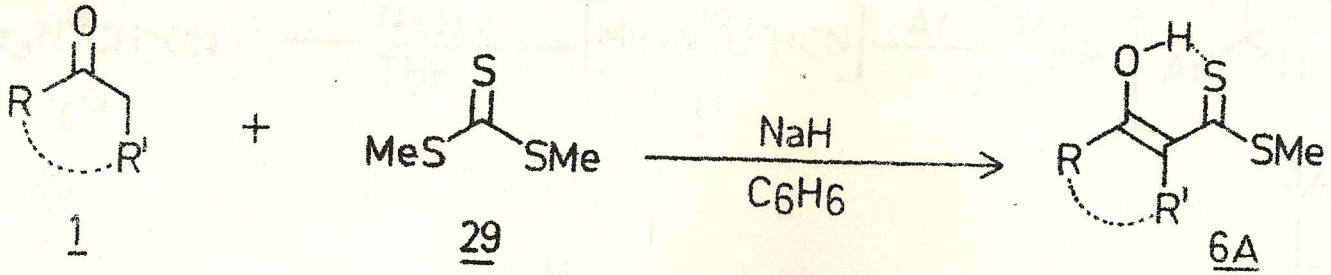
Scheme 8


Ar
O
MeS
SMe
24
NaH / DMF
25
1,5–sigmatropic
MeS shift,
path a
z, E–26
Path b
6 - endo–trig
B:
27
z, z – 28
24–28a, Ar = C6H5
b, Ar = p–MeC6H4
c, Ar = p-ClC6H4

Scheme 9

chapter II. The method involves base catalysed -methylthiothio-carbonylation of active methylene ketones with dimethyltrithio-carbonate 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).



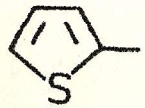
1 + 29 → 6A or

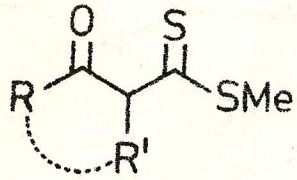
1, 29, 6a , R = Substituted aryl ; R'=H

b , R = R' = $-(CH_2)_n$ or $C_6H_4-(CH_2)_n$

c , R = Me ; R'=H

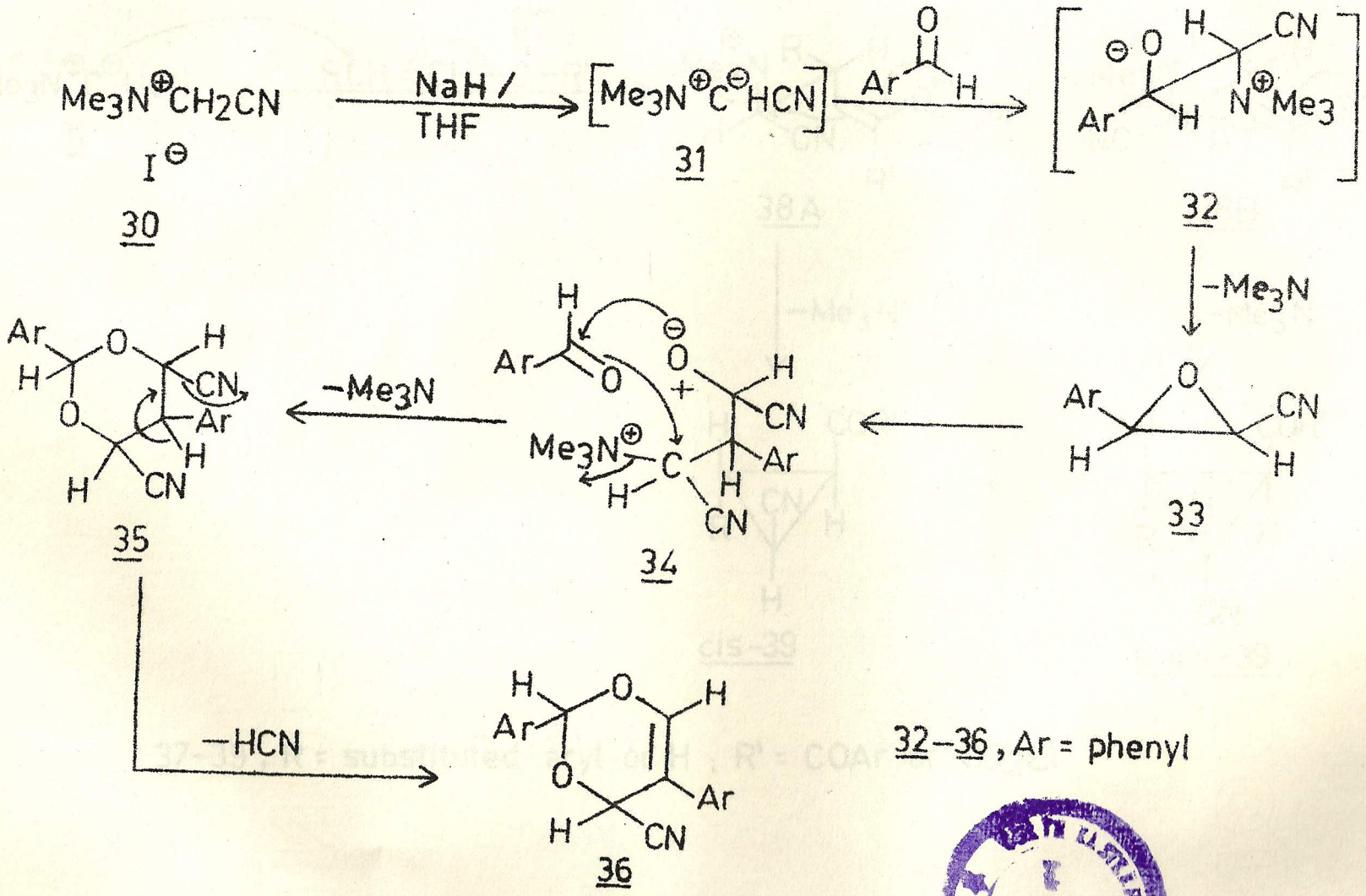
d , R = aryl ; R' = CH_3

e , R =  ; R'=H



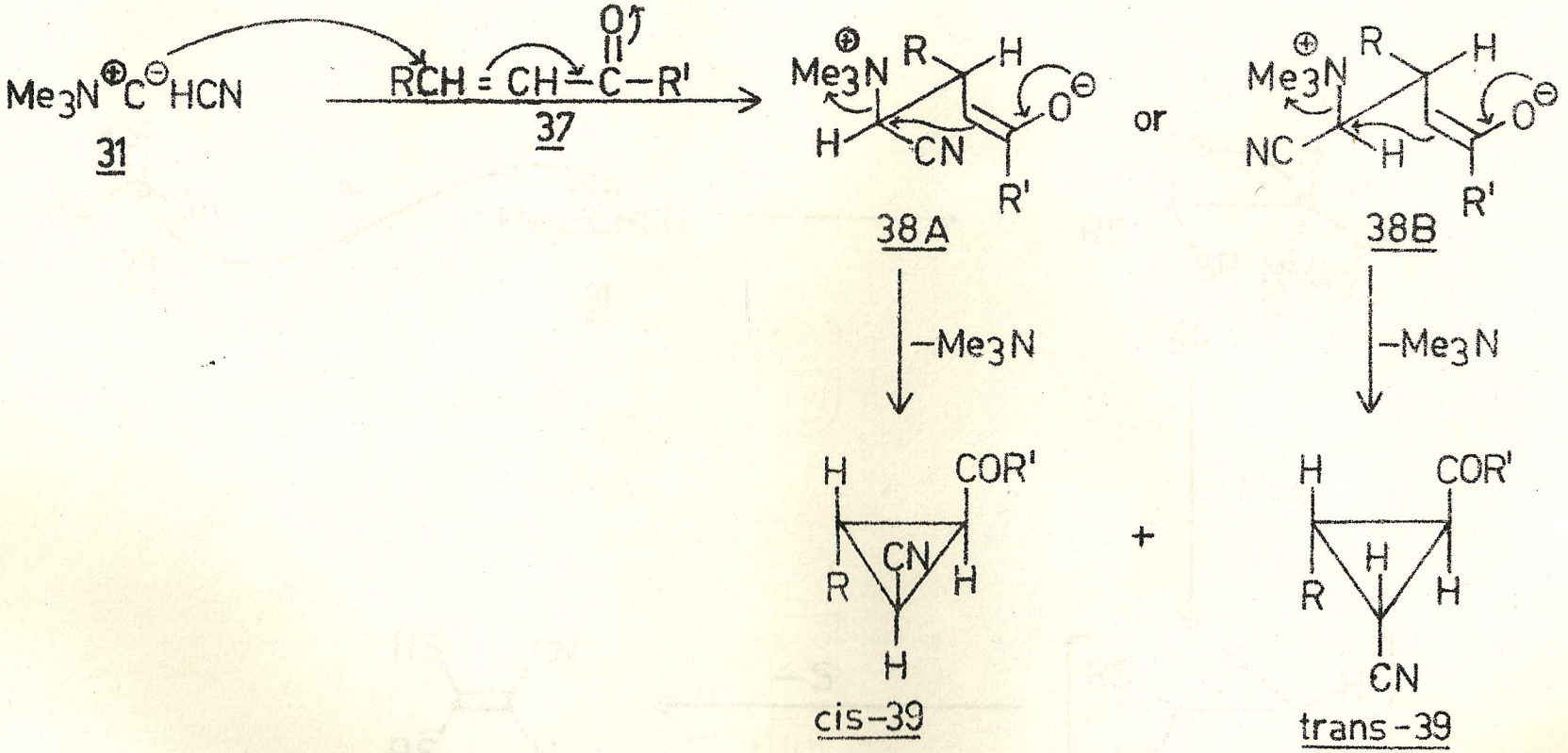
6B

Scheme 10



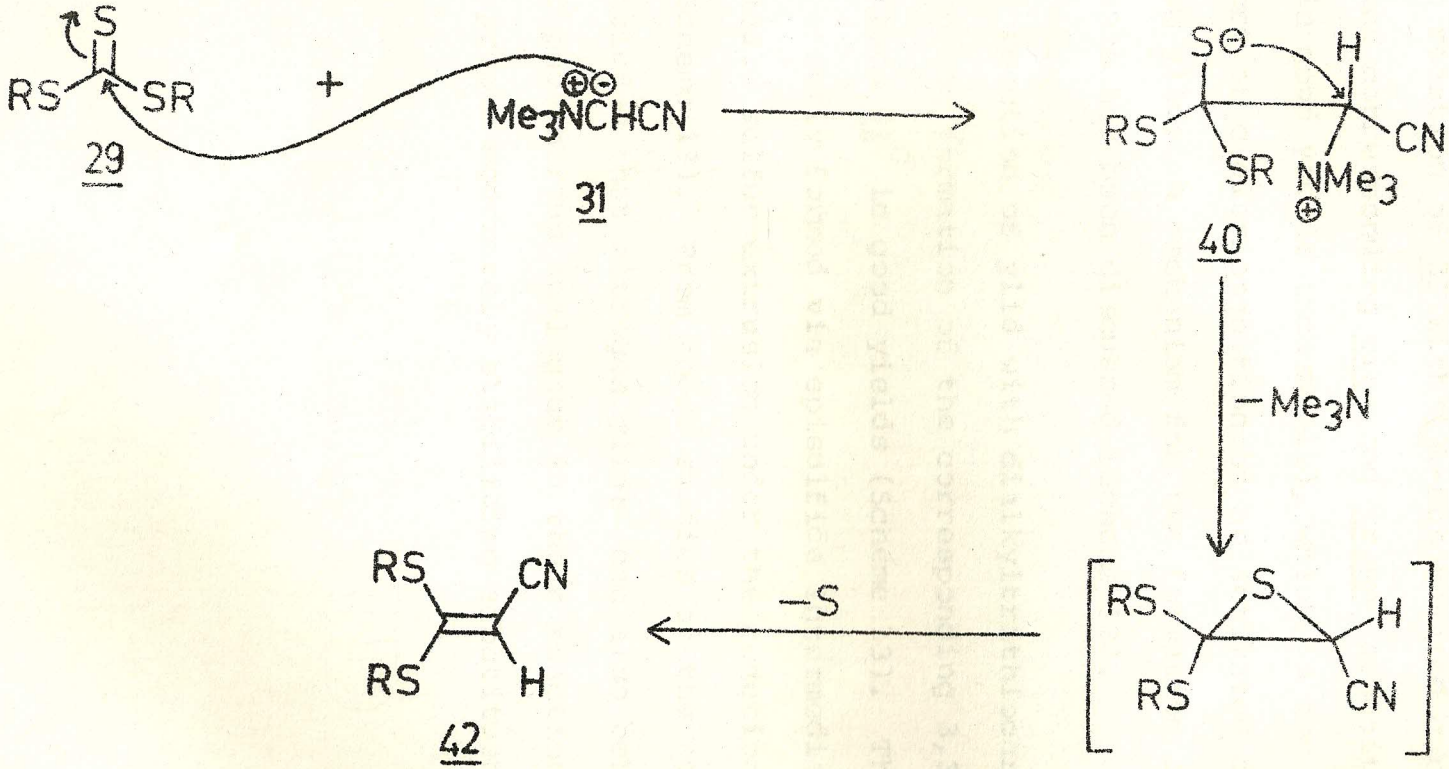
32–36, Ar = phenyl

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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