PART A : STUDIES ON POLARIZED KETEN DITHIOACETALS

PART B : SYNTHESIS OF 1-ARYL-2-CYANOAZIRIDINES AND THEIR REACTION WITH INDOLE

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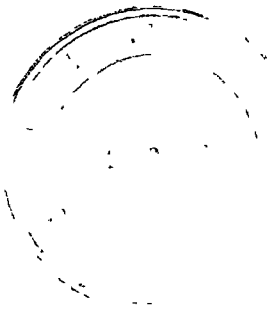

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DOCTOR OF PHILOSOPHY

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CERTIFICATE

This is to certify that the work described in this thesis has been carried out by Mr. Satyam Appa Rao under my supervision. He has satisfactorily completed the pre-Ph.D. courses prescribed and the period of two years of investigational work for the award of 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.

Supervisor

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Pre-Ph.D Course Work evaluation Report

Name : Satyam Appa Rao

No.	Course	Description	Grade	GPA
1.	Chem-401	Inorganic Chemistry I	A	4.63
2.	Chem-421	Organic Chemistry I	A	5.23
3.	Chem-403	Inorganic Chemistry II	B	4.00
4.	Chem-423	Organic Chemistry II	A	4.76
Final Grade Point average :			A	4.65

The following additional Course (s) have been cleared satisfactorily by the candidate:

1. Chem-541 Chemical Bonding
2. Chem-542 Physical Methods
3. Chem-620 Biogenesis & Natural Products

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SATYAM APPARAO

C O N T E N T S

P R E F A C E

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 wide variety of heterocycles like pyrazoles, pyrimidines, pyridones, pyrroles, indoles, etc. It was further shown during these studies, that the polarized ketoketen dithioacetals possessing an alkyl or methylene group in their α-position, undergo base induced 1,3-proton transfer yielding products derived from the rearranged intermediates. The mechanism involving these rearrangements, however, was not well understood and it was therefore considered to study some of the selected transformations in the present investigation.

Thus, the first chapter of the thesis describes the results of investigation of α-methyl/methylene-α-keto-

keten dithioacetals with a view to studying their mechanisms of rearrangements. In the first section of the chapter, a brief introduction has been given regarding the synthetic importance of the polarized keten dithioacetals and similar transformations studied by workers on the analogous area. Subsequently, the results of the present investigation are descussed incorporating the results of three different schools on similar rearrangements with a view to extend evidence in support of the mechanisms proposed for these transformations. The scope and generality of these rearrangements have been studied on selected series of structural variants.

In the second chapter some of these rearranged products have been shown to undergo facile condensation with hydrazine, guanidine and amines to yield the corresponding novel pyrazoles, pyrimidines and enamino-ketones respectively.

In the third chapter a general method for the synthesis of 1-substituted 2-amino-4-aroyl-5-methylthio pyrroles has been described. No attempt has been made to

include the comprehensive review on the methods of preparation of 2-amino-pyrroles, since such reviews on these methods are already described in the literature.

In the last chapter (Part B), synthesis of N-aryl-2-cyanoaziridines from α-chloroacrylonitrile and aromatic amines have been described. These aziridines have been shown to react with indole to give α-arylamino-β-(indolyl)-propanenitrile, which are further shown to undergo hydrolysis to give hitherto unreported dl-N-aryltryptophans.

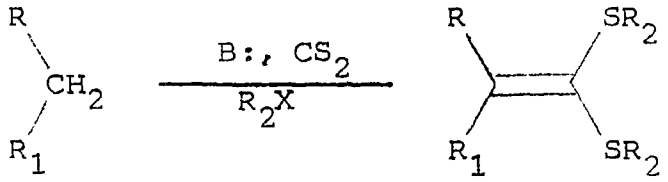
PART A

CHAPTER I

MOBILE KETO ALLYL ANIONS: STUDIES ON BASE CATALYSED REARRANGEMENTS OF α-KETO-α-METHYL/METHYLENE KETENDITHIOACETALS

1.1 Introduction

In an earlier work from our laboratory we have successfully utilized a class of synthetic intermediates generally termed as α-keto and α-cyanoketen S,S-acetals(2), which are derived in relatively simpler reaction conditions from a wide variety of active methylene compounds (1) and



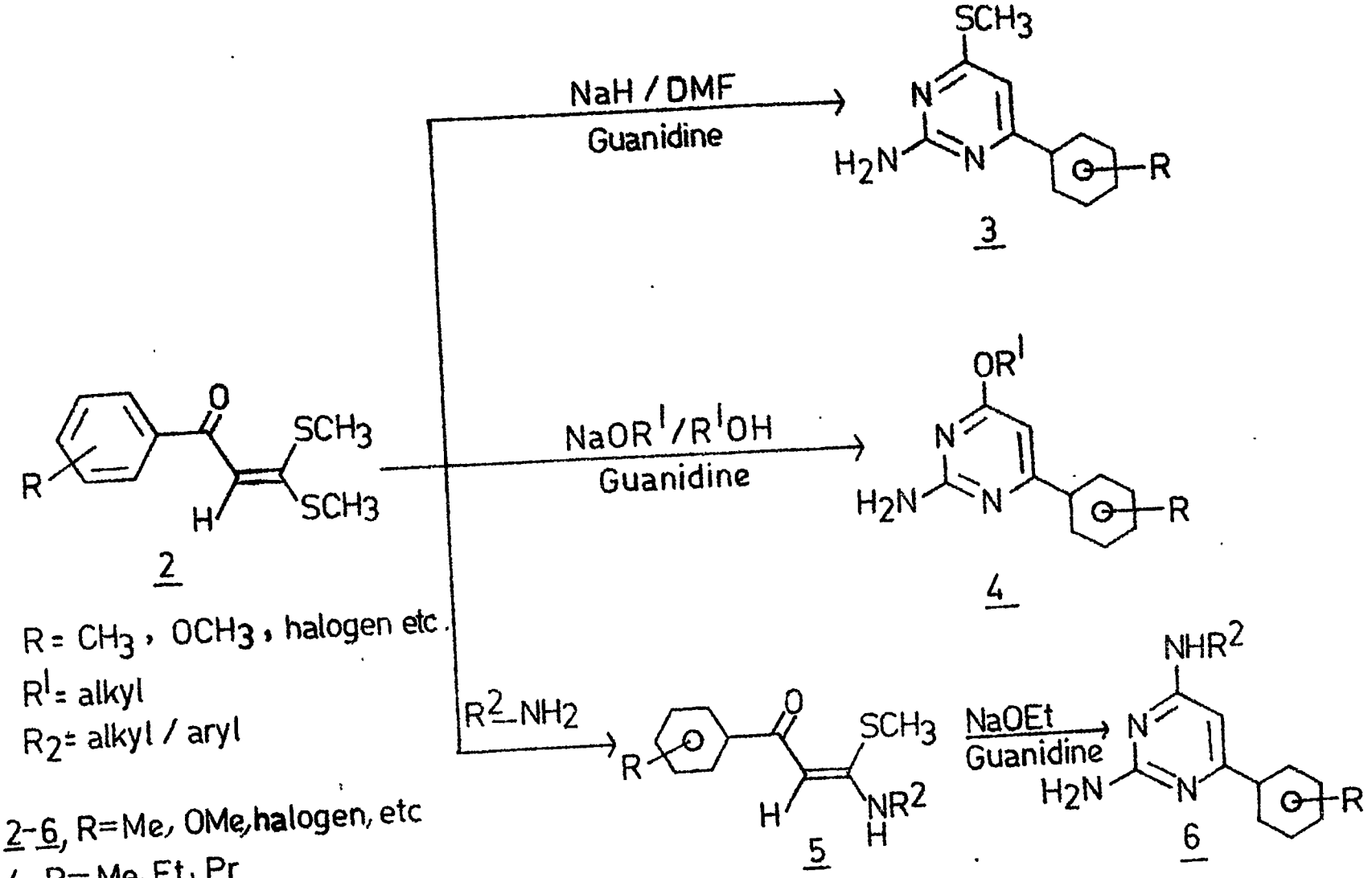
1 2

R = H, alkyl, aryl, nitrile, carbonyl, nitro etc.

R_1= Nitrile, carbonyl, etc.

R_2= Alkyl groups.

carbon disulphide in the presence of two equivalent of a suitable base followed by alkylation in one pot reaction[1-29]. These polarised keten S,S-acetals (2) are among the simplest reactive intermediates with well defined b.ps., if they are liquids and m.ps., if they are solids; which can be purified by conventional methods and preserved indefinitely without apparent decomposition. On the otherhand, the corresponding O,O-acetals greatly differ in their properties undergoing hydrolytic cleavage in the presence of moisture and the methods of their preparation are, therefore, much different from those of keten S,S-acetals[30]. It is further interesting to note that we have successfully demonstrated that the α-keto and α-cyano ketene S,S-acetals could be used in the synthesis of both alkylthiopyrimidines 3 as well as the corresponding alkoxypyrimidine 4 by employing suitable experimental conditions with guanidine or amidines[12-14]. Also, the corresponding aminopyrimidines 6 were prepared by the reaction of the corresponding S,N-acetals 5 with guanidine in excellent yields[24] (Scheme 1).

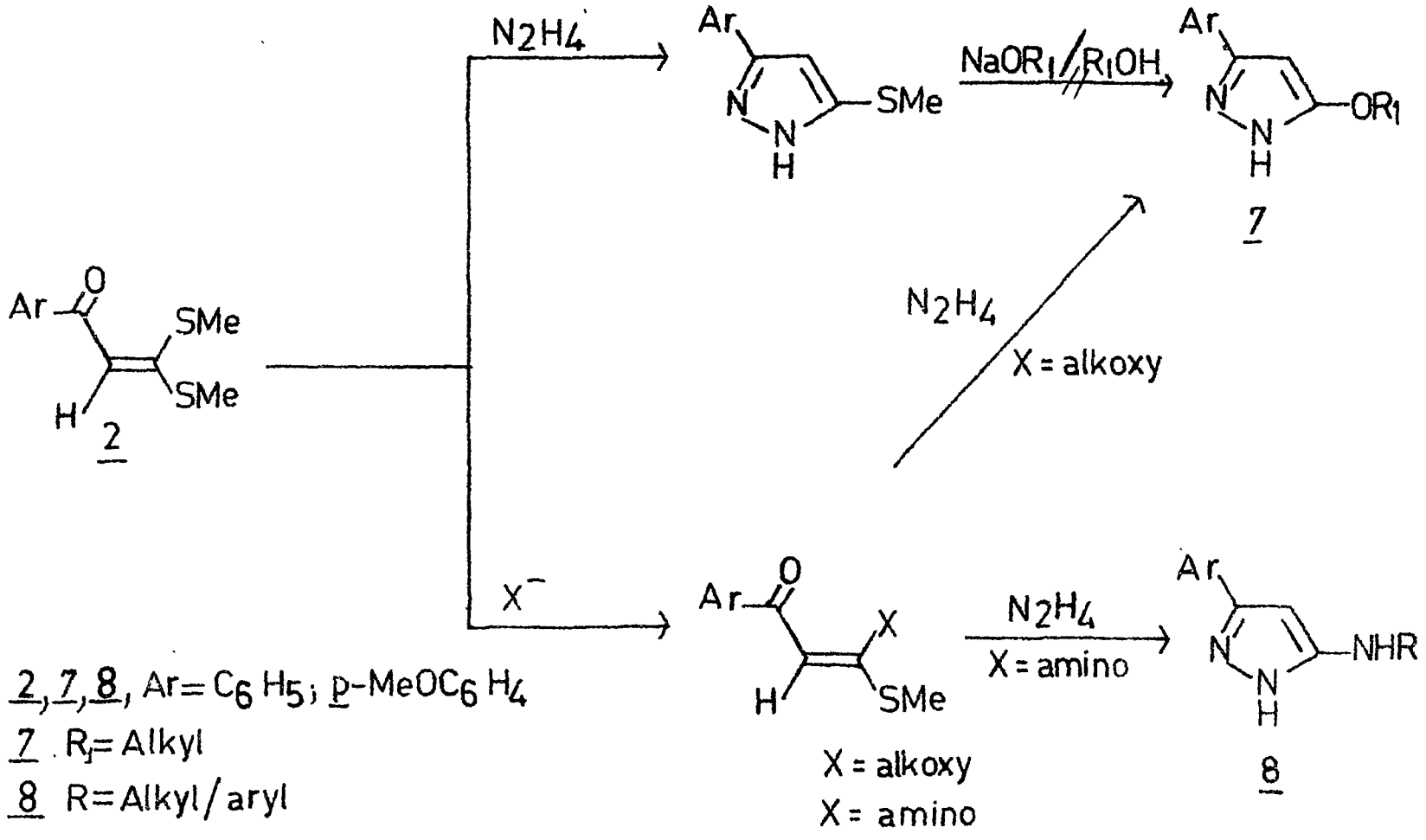


2-6, R=Me, OMe, halogen, etc
4, R=Me, Et, Pr
5, 6, R=aryl, alkyl

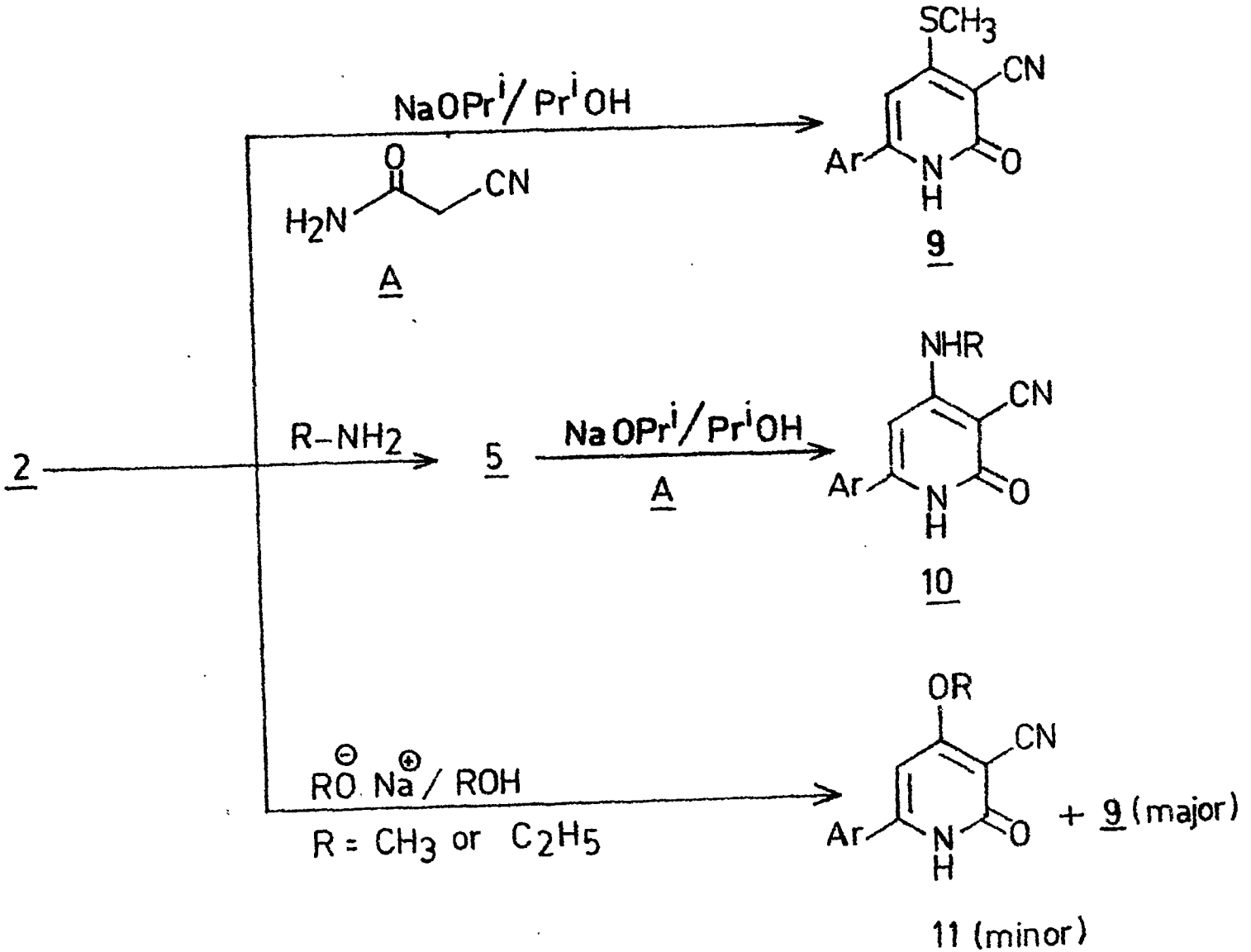
Scheme 1

The advantages of incorporation of alkoxy group in the pyrimidine ring and the synthetic scope of this general method including the mechanism have been discussed in our earliar publications[12-14]. This alkoxy exchange concept has also been extended to pyrazoles to synthesize the 2(5)-alkoxy derivatives (7)[15], which were earliar prepared by classical methods involving alkylation of ambident anion leading to a mixture of N,O and C-alkylation products. Similarly, the corresponding 2(5)-aminopyrazoles (8) were obtained in 60-70% yield by manipulating the reaction conditions incorporating the appropriate amines in place of alkoxides (Scheme 2).

It is also further shown that the 2 underwent a facile condensation with sodio-derivative of cyanoacetamide (A) in the presence of sodium isopropoxide to give 6-substituted-3-cyano-4-alkylthio-2(1H)-pyridones 9 (Scheme 3) in excellent yields[16,20]. The corresponding S,N-acetal 5 derived from 2 and alkyl/aryl amines, also underwent smooth condensation with A to yield the corresponding 6-substituted 3-cyano-4-alkyl/arylamino-2(1H)-pyridones (10) (Scheme 3) in identical yields[27].


N2H4
Ar
SMe
N
N
H
NaOR1 / R1OH
OR1
7
N2H4
X = alkoxy
Ar
O
SMe
SMe
H
2
X⁻
X
SMe
X = alkoxy
X = amino
N2H4
X = amino
NHR
8
2, 7, 8, Ar = C6 H5 ; p-MeOC6 H4
7 R1 = Alkyl
8 R = Alkyl / aryl

Scheme 2


SCH3
CN
NaOPr^i/ Pr^iOH
Ar
N
H
O
9
H2N
CN
A
NHR
CN
2
R–NH2
5
NaOPr^i/Pr^iOH
A
Ar
10
OR
CN
RO⊖ Na⊕/ ROH
R = CH3 or C2H5
Ar
+ 9 (major)
11 (minor)

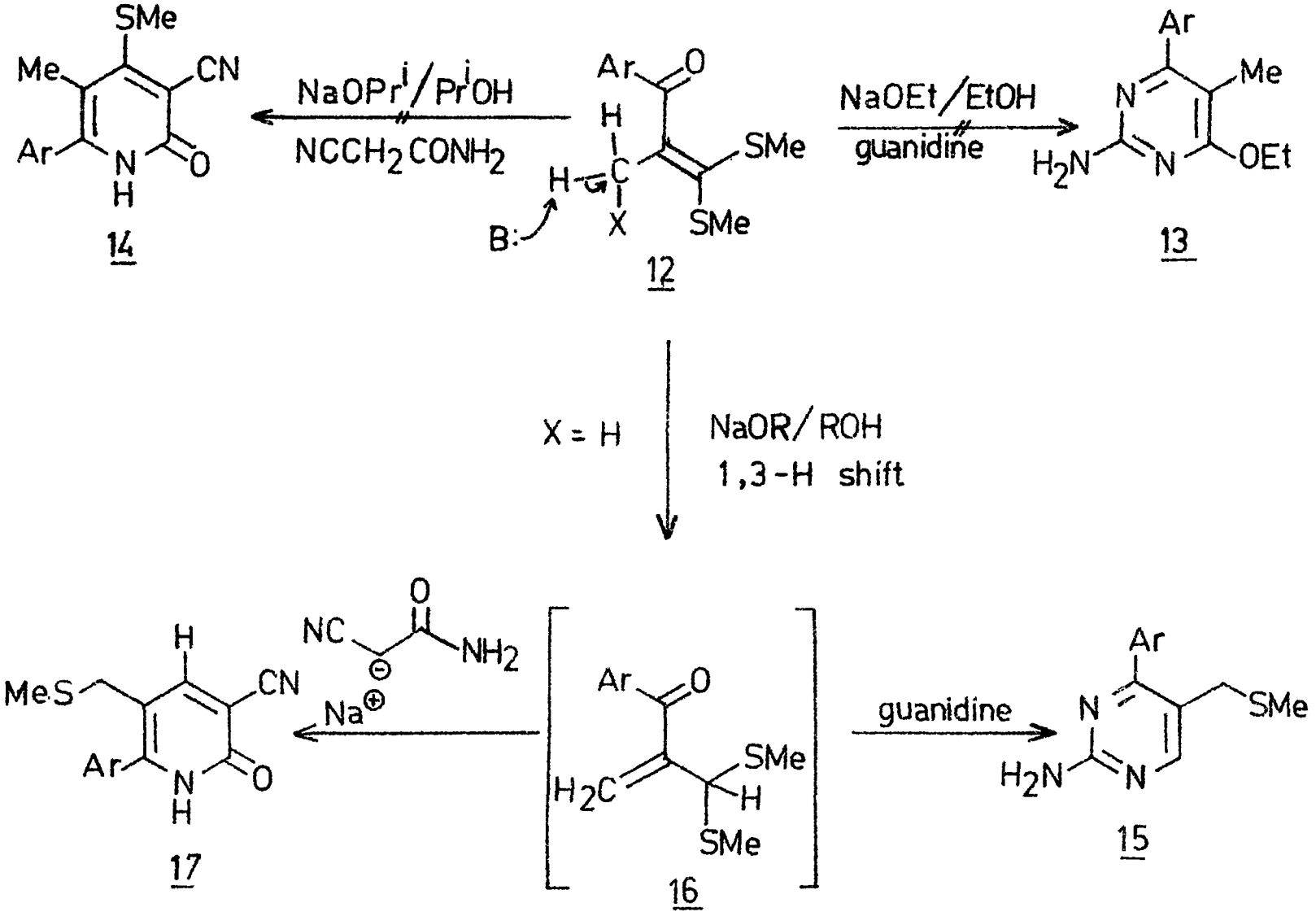
Scheme 3

However, it is interesting to note that in the presence of sodium isopropoxide, only the 4-methylthiopyridone (9) was formed, while the formation of the corresponding 4-isopropoxypyridone was not observed. Even in the presence of sodium methoxide or ethoxide, the formation of the corresponding 4-alkoxypyridone 11 along with 9 was formed only to the extent of 10% yield (NMR), which could not be further improved by attempted variations in the experimental conditions. The separation of 11 from 9 was found to be difficult as they have similar R_f values and they were only detected through their NMR signals[16,20].

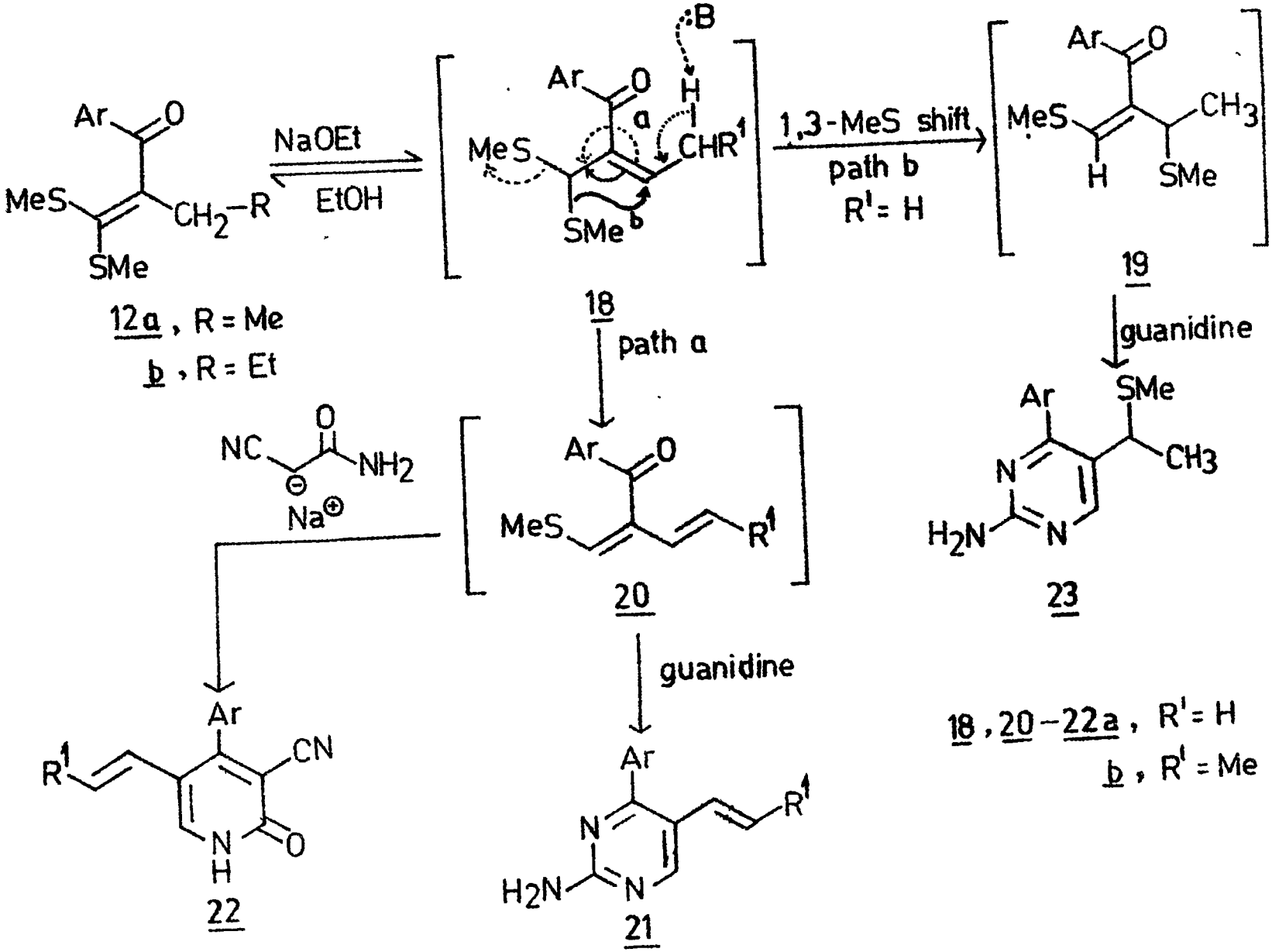
When the pyrimidine synthesis, as shown in scheme 1 and that of pyridone as shown in scheme 3, was extended to α-methyl-α-keto keten S,S-acetals 12, the corresponding pyrimidine (13) and pyridone (14) were not formed; however the products, isolated were characterised as 2-amino-4-aryl-5-methylthiomethyl-pyrimidine (15)[13] and 3-cyano-5-methylthiomethyl-6-aryl-2(1H)-pyridones (17)[20] respectively (Scheme 4). The formation of 15 and 17 was rationalized in terms of

the base induced 1,3-proton transfer to give the intermediate olefin 16 (Scheme 4). The 1,3-proton transfer in these systems is due to the participation of 3d orbitals of adjacent sulphur atoms, which stabilize the negative charge on the carbon atom next to them, permitting the formation of 16, which subsequently undergoes condensation with guanidine and cyanoacetamide to give 15 and 17 respectively. However, when ethyl and n-propyl groups were present in α-position as in 12 (R^1=Me,Et) (Scheme 5), the intermediate 18 was formed after 1,3-proton shift, followed by allylic elimination (path a) to give the dienes 20. The diene 20 (Scheme 5) on condensation with guanidine and cyanoacetamide yielded the corresponding pyrimidines 21[13] (R^1=H,Me) and pyridones 22[20] (R=H,Me) respectively. The formation of 23 (Scheme 5) was explained through 19 involving 1,3-methylthio shift in 18 (path b) (R^1=H)[13].

It is interesting to note that the acrylophenone intermediates 16 and 18 formed by base catalysed 1,3-proton shift represent an interesting class of mobile keto allyl systems, which may undergo rearrangement

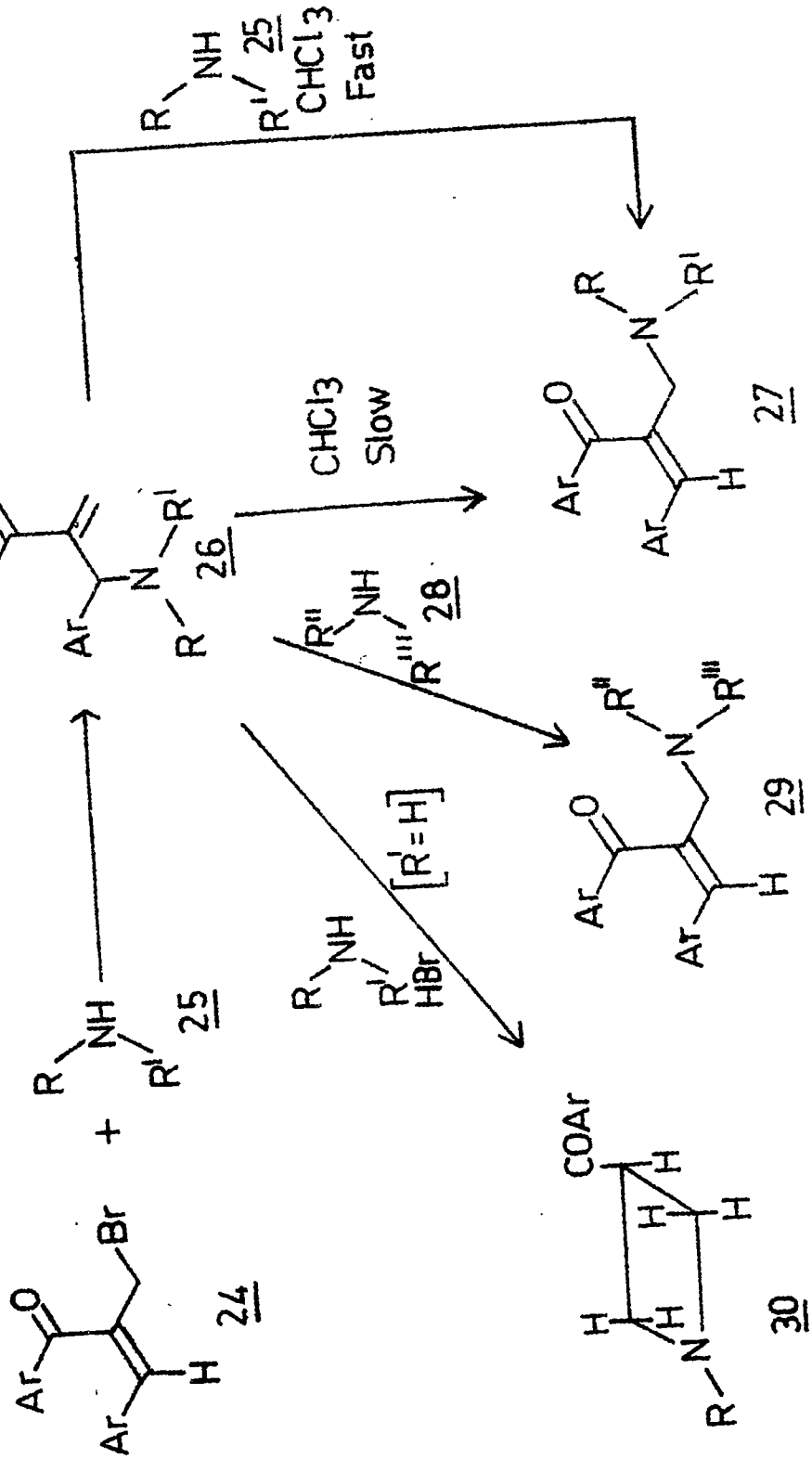

SMe
Me
CN
Ar
N
H
O
14
NaOPr^i/Pr^{i}OH
NCCH$_2$CONH$_2$
Ar
O
H
SMe
H
C
X
SMe
B:
12
NaOEt/EtOH
guanidine
Ar
Me
N
H$_2$N
N
OEt
13
X = H
NaOR/ROH
1,3-H shift
H
CN
MeS
Ar
N
H
O
17
NC
O
NH$_2$
Na$^\oplus$
Ar
O
SMe
H$_2$C
H
SMe
16
guanidine
Ar
N
SMe
H$_2$N
N
15

Scheme 4


Ar
O
MeS
CH2–R
SMe
12a , R = Me
b , R = Et
NaOEt
EtOH
B
H
a
CHR1
MeS
SMe
b
18
path a
1,3-MeS shift
path b
R1 = H
CH3
H
19
guanidine
NC
NH2
Na⊕
20
R1
22
CN
N
21
H2N
23
18 , 20–22a , R1 = H
b , R1 = Me

Scheme 5

similar to those studied by Cromwell and Coworkers. In their series of papers, Cromwell and cowerkers[31] have observed that the α-bromomethyl chalcone (24) reacts with primary and secondary amines 25 in solvent pentane to give rearranged α-aminobenzyl acrylophenones 26 in high yields (Scheme 6). These acrylophenones 26 represent a novel class of mobile keto allyl amines and are found to be reasonably stable, some in crystalline state, and others were found to be stable only in the non-polar solvent like pentane. On the other hand, in polar solvents like chloroform or acetonitrile, they rearranged to thermodynamically more stable allyl amines 27[31] (Scheme 6). The rearrangement of 26 to 27 was found to be facile in the presence of added amine and was observed to proceed even in the solvent pentane. In the presence of different amines 28, 26 was found to undergo the same rearrangement involving amine exchange leading to the formation of 29[31]. They have studied the mechanisms of several mobile keto allyl amines derived from both acyclic[31] and cyclic[32] ketones. They also utilized these intermediates for the synthesis azetidinyl ketones 30[33] (Scheme 6).



25–29 a, R=H, R'= t-Bu, i-Pr
b, R=R'= -(CH2)2O-(CH2)2
c, R=R'= -(CH2)5-

Scheme 6

It was of interest to isolate and study the mobile keto allyl sulfides, 16 and 18 (Schemes 4 and 5) derived from the dithioacetals 12 obtained from propiophenone and its higher homologs. A detailed study of base catalysed rearrangement of 12 has been carried out in the present work. Further studies on similar rearrangements of keten S,S-acetals, 64 derived from dihydrochalcone (Scheme 26), 82 derived from indanone (Scheme 32), 91 derived from tetralone (Scheme 34) and 107 derived from 2,3-dihydro-1-benzothiopyran-4-one (Scheme 39), are investigated and their mechanisms have been proposed.

1.2 Base Catalysed Rearrangement Studies of 3,3-Bisalkylthio-2-methyl-1-aryl-2-propen-1-ones to 3-alkylthio-2-alkylthiomethylacrylophenones via Mobile Ketoallyl Systems*

1.2.1 Results and Discussion

In an attempt to trap the mobile allyl ketones (16) (Scheme 7), which are interesting allyl systems of

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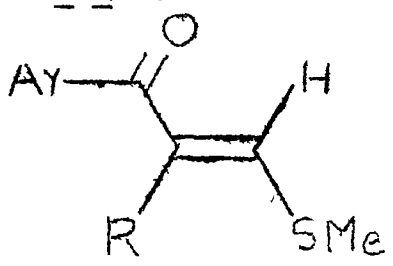
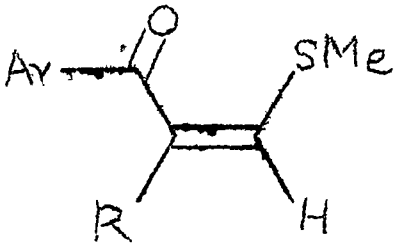
*S. Apparao, A. Rahman, H. Ila and H. Junjappa, Tetrahedron Letters, 23, 971-974 (1982).

potential synthetic utility, isomerization studies on 12 in the presence of different bases and solvents under varying conditions were investigated. Thus, when 12a was stirred with ethanolic sodium ethoxide at room temperature, the unreacted starting material was recovered unchanged. In an another experiment, the same reaction mixture was refluxed and found to yield, after work-up, only intractable polymeric material, from which no starting material was recovered. However, when 12a (0.01 mol) was treated with sodium hydride (0.04 mol, 50% suspension) in the presence of aprotic solvent like dimethylformamide (30 ml) at 50-60° for 3 hours, the formation of a new product along with the starting material was observed (TLC). After chromatographic separation the new product was obtained in 35% yield (55% on the basis of recovered starting material). The new product was found to possess different structural features and the expected olefin 16 was not formed. After the analysis of the spectral data, the structure of the new product was assigned to be 3-methylthio-2-methylthiomethylacrylophenone (31a) (Scheme 7). It was analysed for $C_{12}H_{14}OS_2$(238) and showed the molecular ion

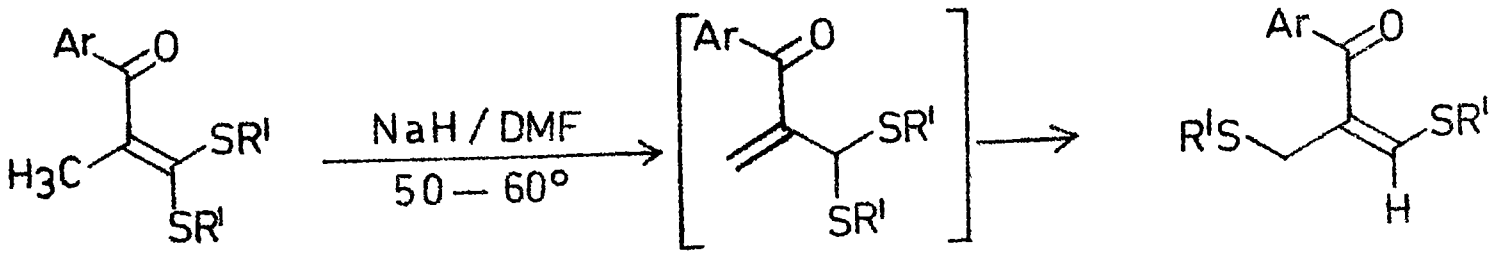
peak at M^+ 238. Its IR (Neat) Spectrum exhibited sharp absorption band at 1635 cm^{-1} due to carbonyl function. Further structural proof for 31a was obtained from its ^{1}H-N.M.R ($CDCl_3$) Spectrum. Thus it exhibited two singlets (3H each) at δ 2.05 and δ 2.25 due to protons on two methylthio groups. A singlet at δ 3.50 (2H) was assigned to two methylene protons, while the vinylic proton appeared as singlet at δ 7.04 (1H). The broad multiplet appeared between δ 7.25-7.53 was assigned to the five aromatic protons. The data was therefore in conformity with the assigned structure, 31a. The rearrangement exhibited high steroselectivety and only E-31a isomer was formed. The configuration was assigned on the basis of chemical shift values of vinyl protons in similar type of compounds, E-A and Z-A, prepared in this laboratory, which showed chemical shifts due to vinylic proton at δ 7.60-7.90 (cis to ArCO) in E-A and at δ 6.00-7.10 (trans to ArCO) in Z-A[28].



E-A



Z-A



12 16 31

12, 31 a , Ar = C_6H_5 ; R^I = CH_3

b , Ar = C_6H_5 ; R^I = C_2H_5

c , Ar = p - $MeOC_6H_4$; R^I = CH_3

d , Ar = p - $MeOC_6H_4$; R^I = C_2H_5

e , Ar = p - MeC_6H_4 ; R^I = CH_3

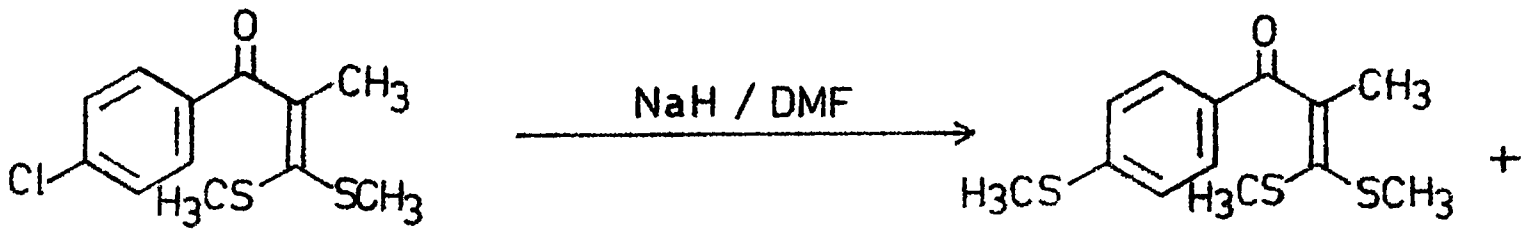
f , Ar = C_6H_5 ; R^I = - $CH(CH_3)_2$

Scheme 7

Attempts to increase the yield of 31a, by carrying out reaction at lower temperature, in the presence of catalytic amount or excess of sodium hydride or under nitrogen atmosphere were not successful. When the reaction was carried out for longer time (12 hr) under similar reaction conditions, although the starting material disappeared completely (TLC), the yield of 31a was reduced to 10%, resulting in an intractable polymer.

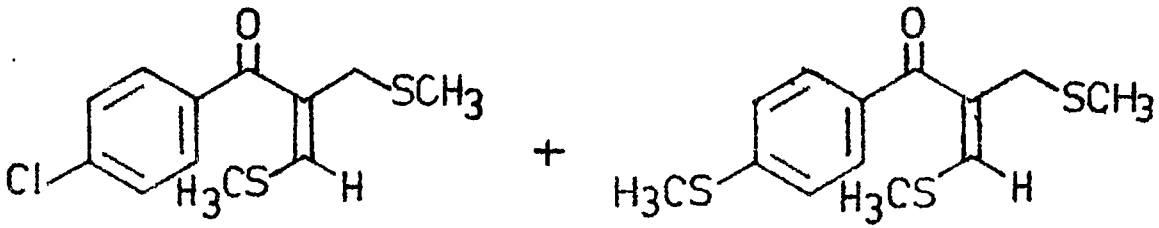
To assess the generality of the rearrangement seven more systems were studied in this series. Thus 12b-e underwent rearrangement to yield the corresponding products E-31b-e in 35-45% over all yield (50-70% on the basis of recovered starting material) (Scheme 7). It may be noted however that the corresponding isopropyl S,S-acetal (12f) under similar reaction conditions gave E-31f in 30% yield indicating that the steric factors do not substantially effect in lowering the yields. Interestingly, the rearrangement of keten S,S-acetal (12g) derived from p-chloropropiophenone, yielded a mixture of three products (TLC) under identical

reaction conditions (Scheme 8). After chromatographic separation, the rearranged product E-31g was obtained in 22% yield, while the other two products were identified as 3,3-bis(methylthio)-2-methyl-1-(p-methylthiophenyl)-2-propen-1-one (32) in 25% yield and 3-methylthio-2-methylthiomethyl-1-(p-methylthiophenyl)-2-propen-1-one (33) in 20% yield. The structure of 31g was confirmed by its analytical and spectral data which are described in experimental section and table 1 respectively. The structure of 32 was assigned by its analytical and spectral data. It was analysed for $C_{13}H_{16}OS_3$ (284) and showed molecular ion peak at M^+ 284. It exhibited in its IR spectrum (neat) a strong band at 1660 cm^{-1}, which was assigned for the carbonyl stretching vibration. Its final structural confirmation was derived from its ^{1}H-N.M.R. (CCl_4) spectral data. Thus a singlet at δ 2.00 (3H) was assigned to the methyl group. The two singlets at δ 2.10 (3H) and δ 2.30 (3H) were assigned to the two SCH_3 protons. A singlet at δ 2.45 (3H) was assigned to the SCH_3 protons in the p-position of the phenyl group. The assignement



12 g

32



31 g

33

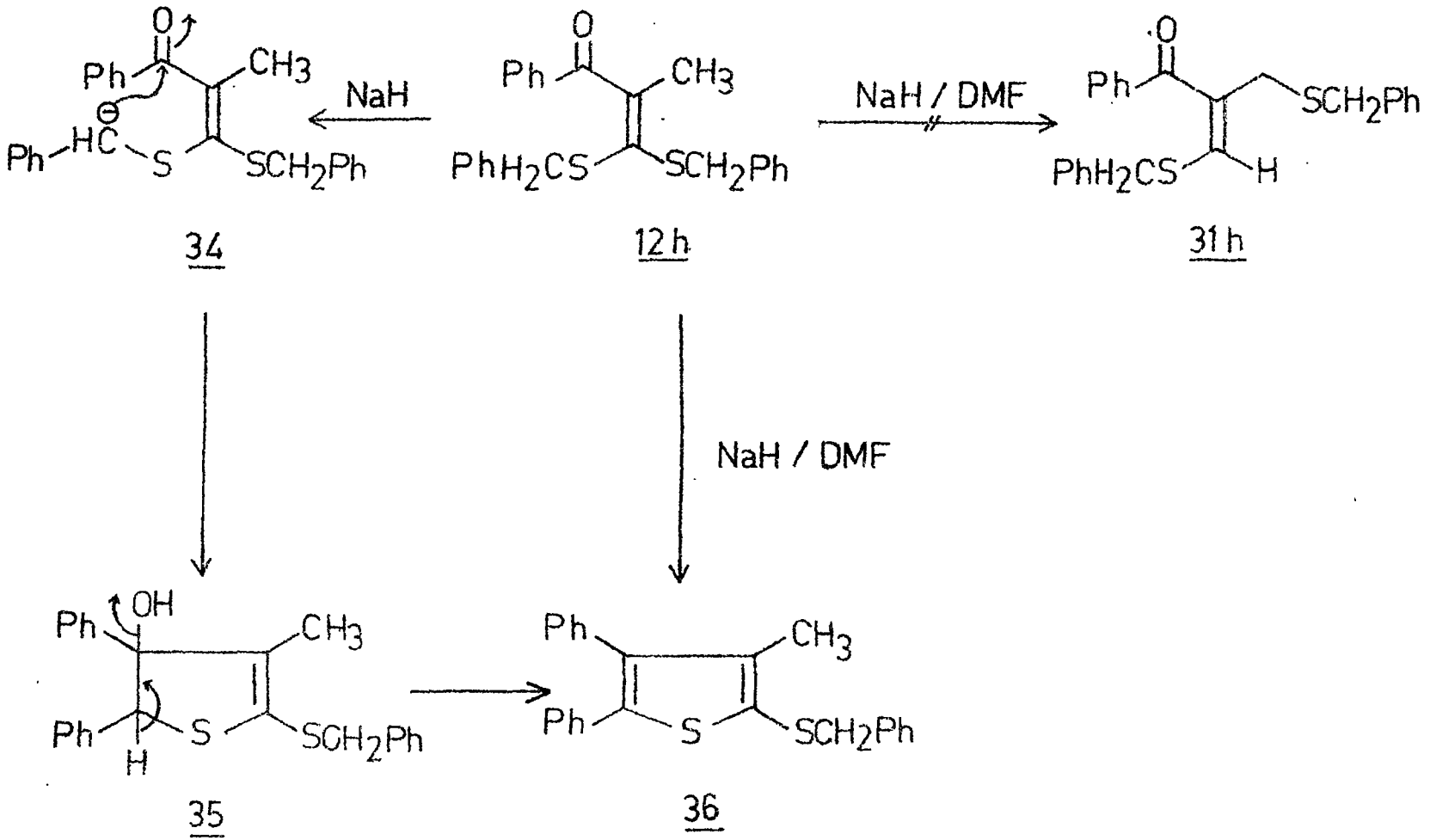
Scheme 8

of $SC\underline{H}_3$ protons on the aryl ring was based on the position of the protons of 2-SMe groups in the p-chloro acetal (12g). The four aromatic protons in 32 appeared at δ 7.10-7.70 (dd, 4H, A_2B_2), which is in conformity with the assigned structure. Similarly, the structure of 33 was confirmed by its analytical and spectral data. It was analysed for $C_{13}H_{16}OS_3$(284) and showed molecular ion peak in its mass spectrum at M^+ 284. Its IR (neat) spectrum exhibited a band at 1632 cm^{-1} which was assigned to the carbonyl stretching frequency. Its final structure was confirmed by its ^{1}H-N.M.R. (CCl_4) spectral data. A singlet at δ 2.00 (3H) was assigned to $CH_2SC\underline{H}_3$ protons. The other singlet at δ 2.35(3H) was due to vinylic $SC\underline{H}_3$ protons and another singlet at δ 2.45 (3H) was assigned to the $SC\underline{H}_3$ protons in the para position of phenyl ring. The assignement of $SC\underline{H}_3$ protons on the phenyl ring was based on the position of the protons of the two $SC\underline{H}_3$ group in the ^{1}H-N.M.R. (CCl_4) spectrum of 31g (Table 1). The singlet at δ 6.85 (1H) was assigned to vinylic proton, indicating its position trans to ArCO group (E-isomer).

The A_2B_2 pattern of aromatic protons appeared as two doublets between δ 7.10-7.60 (4H). The formation of 32 (Scheme 8) can be explained by nucleophilic substitution of chlorine in the p-position of the phenyl ring (12g) by methylthio anion. Similarly, the formation of 33 can be explained through the nucleophilic displacement of chlorine from 31g by methylthio anion. These observations are interesting, since they throw light on the mechanism of the rearrangement of 12 to 31, which is discussed in the section 1.2.2.

When the S,S-dibenzyl acetal (12h) derived from propiophenone was subjected to 1,3-methylthio shift under similar reaction conditions, the expected rearranged product (31h) was not obtained, However, a new product was isolated and identified as 2-benzylthio-3-methyl-4,5-diphenylthiophene (36)[34] (Scheme 9). The structure of 36 was confirmed by its analytical and spectral data. It was analysed for $C_{24}H_{20}S_2$ (372) and its mass spectrum showed molecular ion peak at M^+ 372. It exhibited IR(Nujol) band at

901 cm^{-1}, which was assigned to characteristic 3-mehyl substituted thiophenes[35]. The other band appeared at 695 cm^{-1} was also assigned to characteristic 3-methyl thiophene derivatives[36]. The thiophene ring "breathing" mode ν_3 band[36] was located at 795 cm^{-1}. Further proof of the structure was obtained by its ^1H-N.M.R. ($CDCl_3$) spectral data. A singlet at δ 1.70 (3H) was assigned to the $C\underline{H}_3$ protons, while the singlet at δ 3.85 (2H) was assigned to two benzylic protons. A multiplet between δ 6.90-7.30 amounting to fifteen protons was assigned to protons on three phenyl rings, confirming the formation of 36. The mechanism of the formation of 36 is due to relatively increased acidity of the benzylic protons adjacent to the sulphur atoms than those on the allylic methyl group. These protons are easily obstracted by base generating anion (34), which undergoes intramolecular nucleophilic attack on the carbonyl group to give 36 via 35 after dehydration (Scheme 9).



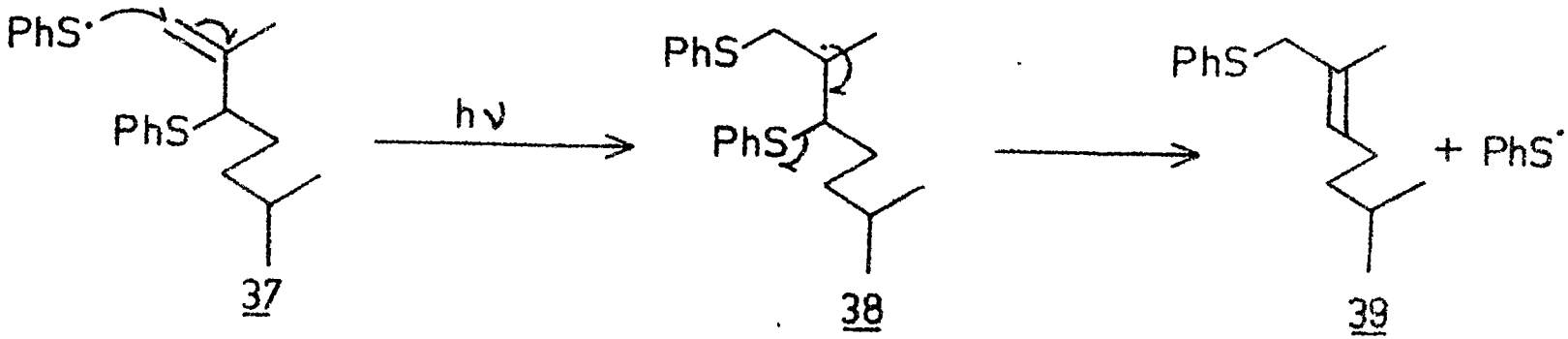
Scheme 9

1.2.2 Mechanistic Studies

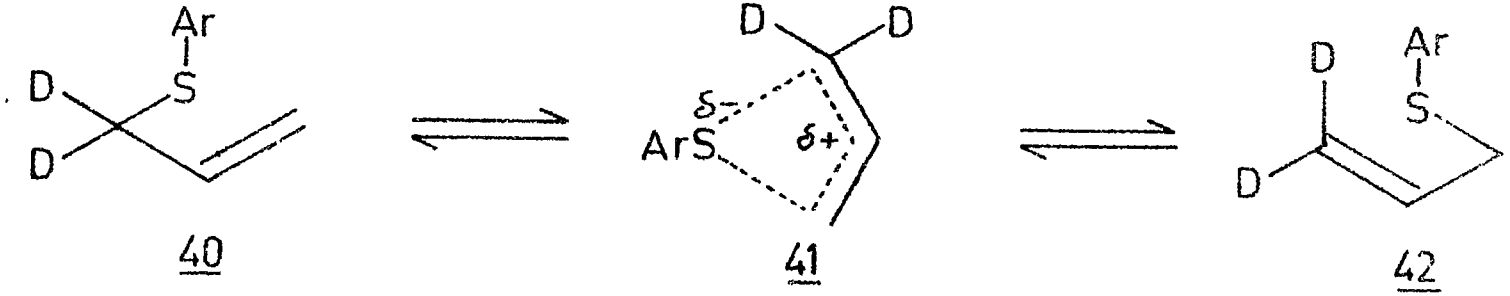
When the transformation of 12 to 31 (Scheme 7) was observed, the mechanism of their rearrangement was considered to involve 1,3-RS shift via mobile keto allyl intermediates 16. Our literature survey on similar systems were of considerable help in arriving at the most plausible mechanism for the rearrangement. A brief discussion of the mechanistic studies on similar systems reported in the literature is presented, so that the mechanism proposed from 12 to 31 will be better appreciated. Thermal and photochemical thioallylic rearrangements observed by both Warren's[37] and Kwart's[38] groups and the mobile keto allylic rearrangement studies by Cromwell[31,32] and coworkers are reviewed here.

Warren's group has used photochemical 1,3-PhS shift for several synthetically useful transformations, which have been reviewed[37] recently and therefore, only one example is cited in the Scheme 10. Thus the allyl phenyl sulfide 37 has been shown to undergo photoinduced rearrangement to give

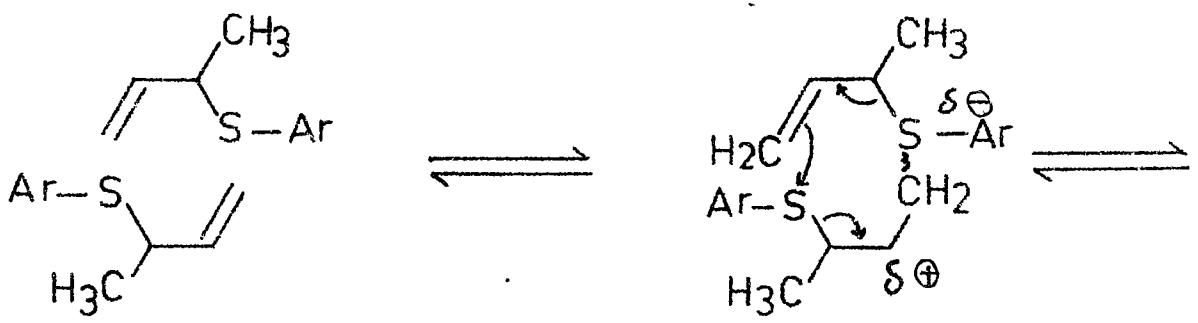
39 and an associative radical chain mechanism for this 1,3-PhS shift has been suggested via intermediate 38. During their studies they have shown that the 1,3-PhS shift can be used only when the final product 39 has more stable C=C bond than that in the starting material 37 (Scheme 10). Also Kwart's group has shown that the appropriately deuterated allyl phenyl sulfide, 40 isomerises to 42 (Scheme 11) under both thermal and photochemical conditions[38]. They have proposed an antipolar concerted mechanism involving the formation of transient complex 41 or 44 by interacting either intra or intermolecularly between olefin and sulfur termini of the thioallylic system (Scheme 11 and 12). Alkyl substituents on the allyl chain appear to hinder formation of unimolecular complex, 41 and favour a bimolecular complex, 44 (Scheme 12). An alternate mechanism involving prior ionisation of the C-S bond, forming ion pairs was ruled out, since thioallylic rearrangements proceeded rapidly in the gas phase without the assistance of solvent[39-40]. They have also ruled out the formation



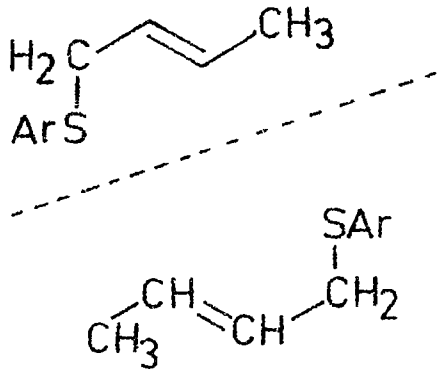
Scheme 10



Scheme 11



43 44

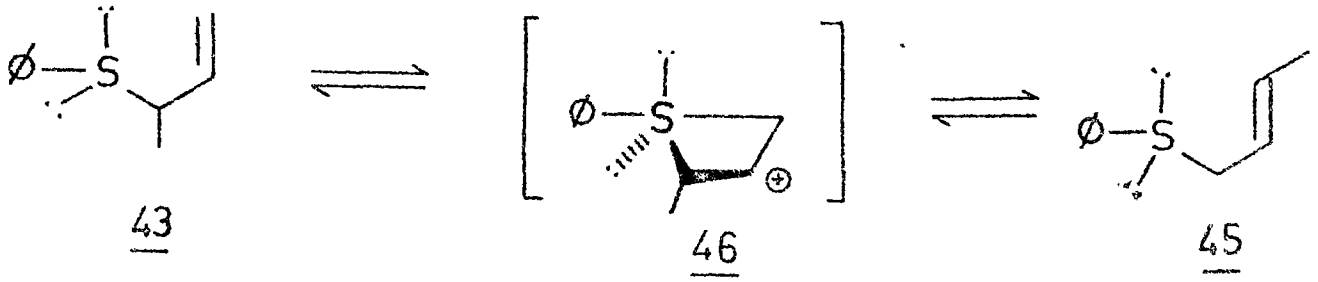


45

Scheme 12

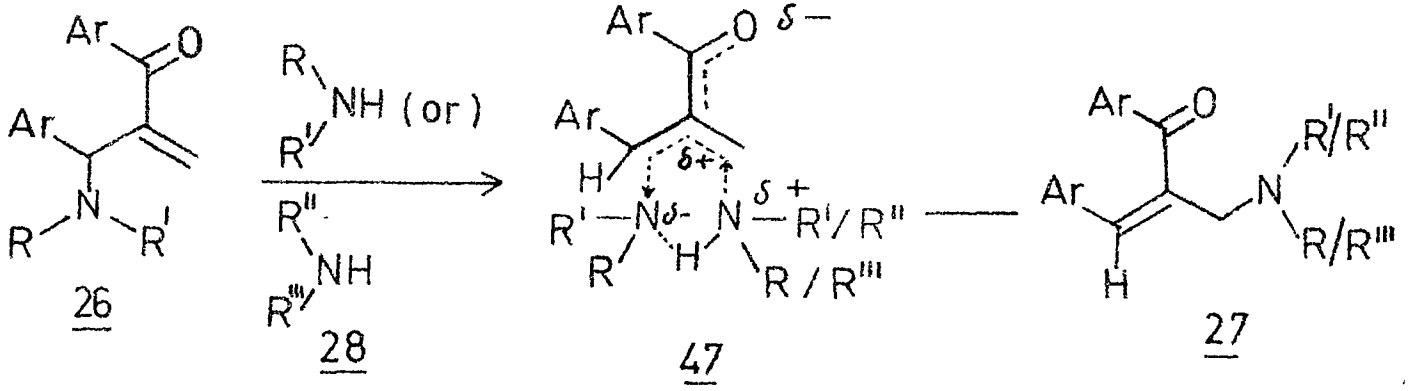
of allyl cation intermediate proposed by Warren and coworkers[41] in their studies on acid catalysed thio-allylic rearrangements. Their findings were based on the fact that on protonation allyl cation is susceptible to the secondary deuterium isotope effect. Consequently, when they treated 40 (Scheme 11) and p-toluenesulphonic acid, the K_H/K_D value was virtually identical with that obtained for the uncatalysed reaction[42]. They, therefore, concluded that these thioallylic rearrangements proceed through an intermediate 46 (Scheme 13) involving octet expansion of sulfur in various states of hypervalency, some created through the agency of catalysis involving some form of coordination of sulfur by the catalytic species[42].

Interestingly the Cromwell's group has studied rearrangements in β-ketoallylamines which are structural analogs of our systems. They have shown[31] that the initially formed β-ketoallylamine 26 rearranges to thermodynamically more stable amine, 27 either in the presence or absence of added amine, 24 (Scheme 6 and 14). In the presence of different amines 28,



43 46 45

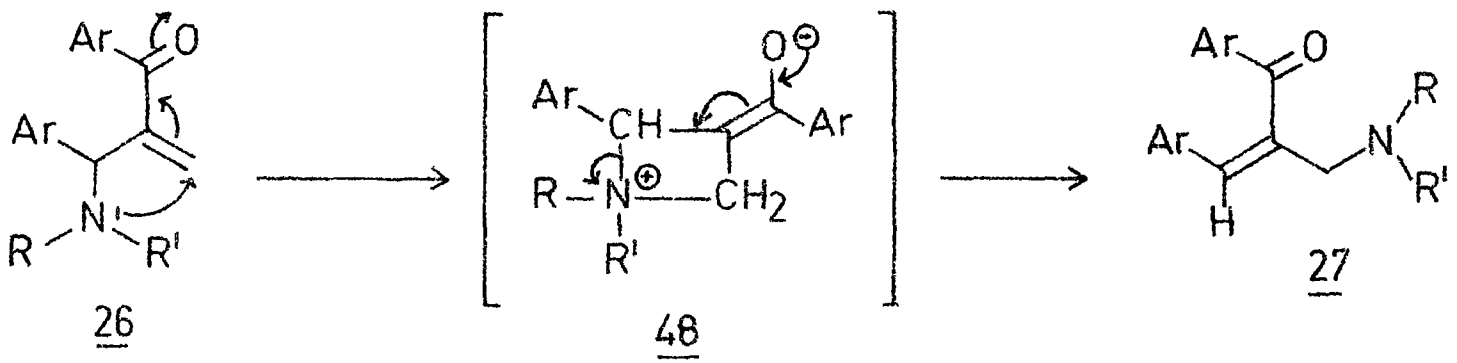
Scheme 13



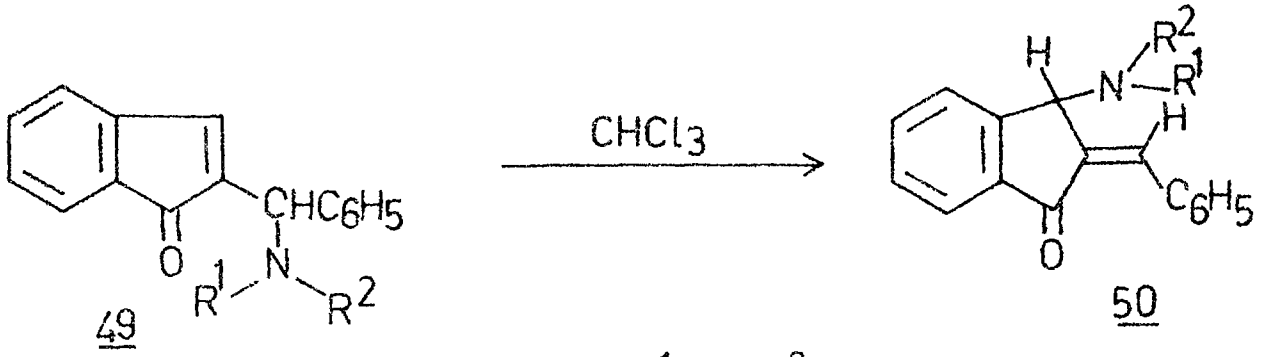
26 28 47 27

Scheme 14

the amine exchange was observed during the rearrangement[31] On the basis of their kinetic studies they have suggested a 'varient' of concerted SN2' mechanism for the amine assisted rearrangement involving a 'cis' dipolar transition state 47[31c] (Scheme 14). Apparently, the β-carbonyl function supports a major portion of the developing negative charge as shown in 47, which is further stabilized by coulombic attraction or by hydrogen bonding between entering and leaving amines. When the kinetic studies were carried out for the rearrangement without the assistance of external amine, the rates followed first order kinetics with low activation energy (Ea ~ 6 K.cal/mole) and low negative entropy ($\Delta S^* \sim -66$ cal./deg./mole) during the transformation from 26 to 27. They therefore suggested that the rearrangement of 26 to 27 in the absence of added amine involves either highly polar transition state or dipolar cyclic intermediate, 48[31a,b] (Scheme 15), where the bond making is far ahead of bond breaking resulting in lowering of the energy "debt". In their subsequent studies on the rearrangement of 2-(α-aminobenzyl)-1-indenone (49) to the isomeric 3-amino-2-benzal-1-indanone (50) (Scheme 16) in the absence of added amine



Scheme 15



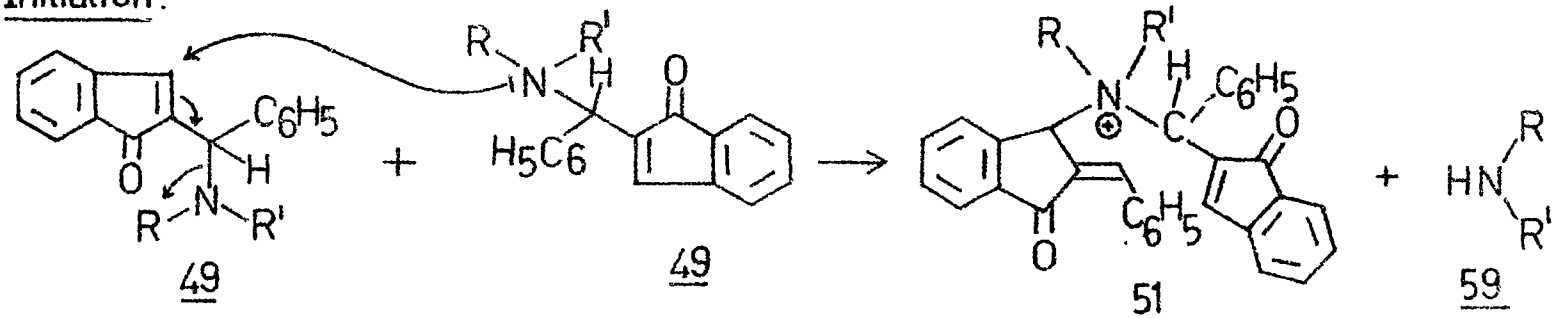
49, 50a, R^1 = H, R^2 = i-pr
b, R^1 = R^2 = i-pr
c, R^1 = H, R^2 = t-Bu

Scheme 16

they have proposed a mechanism involving chain reaction[32c] (Scheme 17). The amino group of aminoindenone 49 will attack initially on the 3-position of the second molecule of 49, followed by allylic elimination of the amine 52 to give the dimeric ammonium salt (51) (Initiation). The free amine (52) can either remove the positive charge on nitrogen by allylic substitution followed by elimination as shown in 51, resulting in the formation of 2 moles of 50 (Termination) or can attack 49 at 3-position with allylic elimination of amine to give 50 and free amine 52 (propagation) (Scheme 17).

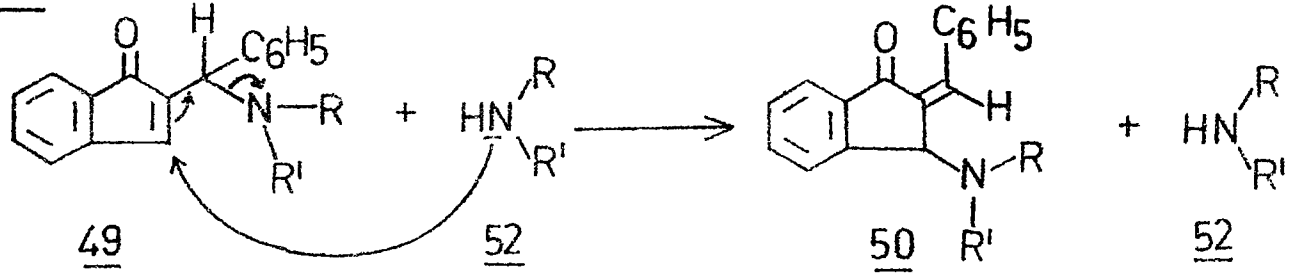
From the preceding discussion on the mechanism of allied systems, it is apparent that the rearrangement from 12 to 31 (Scheme 7) can be envisaged going through one of the possible intermediates proposed. It is imminent that 12 in the presence of a base loses its proton to give the resonating anions 53a and 53b (Scheme 18). The stability of these allyl anions 53 is greatly enhanced by the two sulfur atoms present in the molecule giving rise to increased resonance contribution from 53b. Since the 53 is generated under

Initiation:



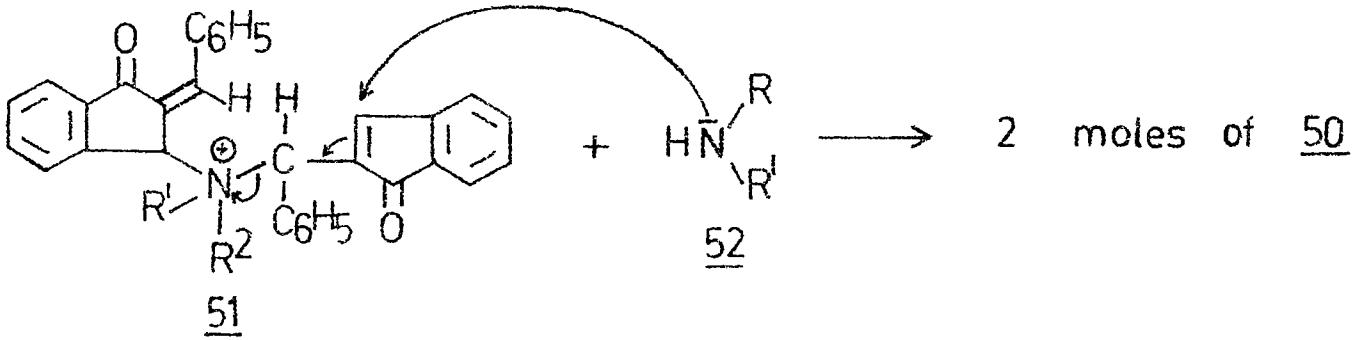
49 + 49 → 51 + 59

Propagation:



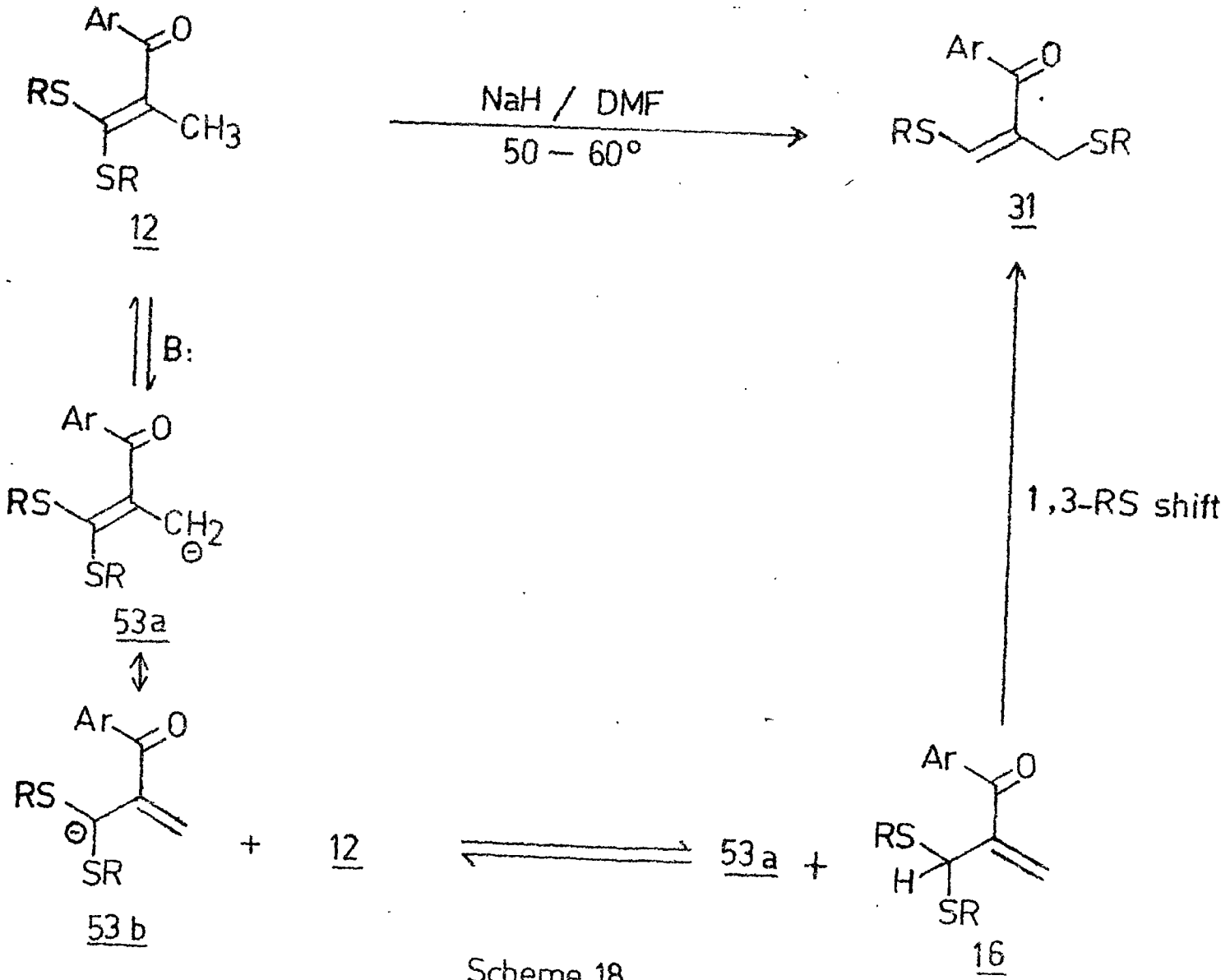
49 + 52 → 50 + 52

Termination:



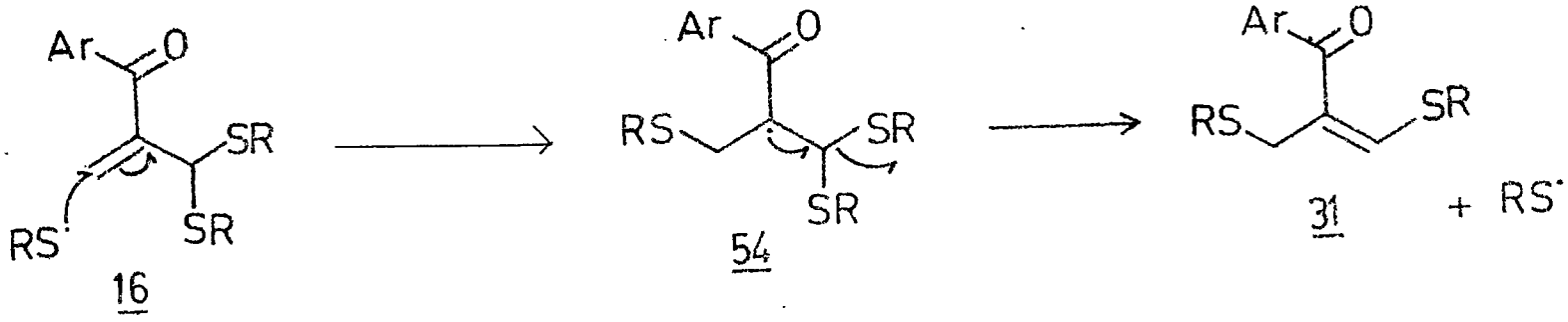
51 + 52 → 2 moles of 50

Scheme 17

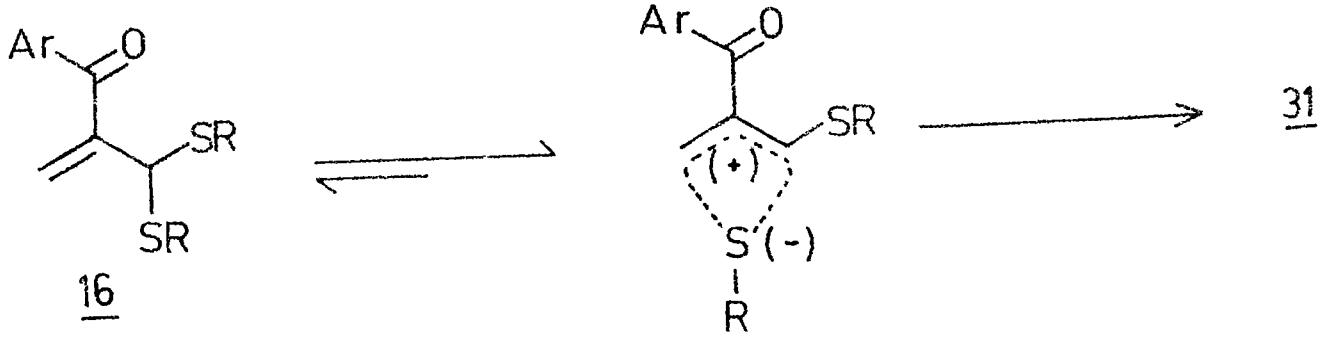

Ar
O
RS
CH3
SR
12
NaH / DMF
50 – 60°
Ar
O
RS
SR
31
B:
Ar
O
RS
CH2
SR
53a
1,3-RS shift
Ar
O
RS
SR
53 b
+
12
53a
+
Ar
O
RS
H
SR
16

Scheme 18

reversible conditions, it competes with sodium hydride in deprotonation of 12 to give 53 and an unstable intermediate 16, which spontaneously rearranges to 31 (Scheme 18). Efforts to isolate 16 were unsuccessful and even the trace of it could not be detected after work-up of the reaction mixture. However, the intermediacy of 16 appears to be a definite step in arriving at the thermodynamically more stable rearranged product 31. It is therefore apparent that 16 undergoes a facile 1,3-RS shift through one of the mechanisms discussed earlier to give 31. Due to geometrical restrictions imposed on 1,3-antarafacial sigmatropic shift, the thermal concerted 1,3-RS shift is ruled out. Similarly, the orbital symmetry considerations do not facilitate 1,3-suprafacial shift. Therefore, the 1,3-RS shift in 16 could involve one of the possibilities of going through an associative radical chain mechanism via intermediate 54 to give 31 and alkylthio radical (Scheme 19). Similar mechanism has been suggested by Warren and coworkers[41] for 1,3-PhS shift observed both thermally and photochemically and they have presented evidence for associative radical chain reaction. However



Scheme 19



Scheme 20

in the present investigation it was observed, that the yield of 31a was uneffected when the reaction was carried out in the presence of radical inhibitor like hydroquinone under nitrogen atmosphere. Similarly, when the reaction was carried out in the presence of dibenzoyl peroxide at 50-60°, there was no change in the yield of 31a. It therefore appears that the radical intermediate in the 1,3-RS shift is unlikely in these transformations.

When the rearrangement of 12a to 31a was attempted in refluxing benzene in the presence of sodium hydride, 12a was recovered unchanged even after prolonged time (12 hr). However, the same reaction in refluxing tetrahydrofuran yielded only 5% of 31a in 3 hr, while it was improved to 30% after 12 hr refluxing. The increase in rate of reaction with the solvent polarity implies the polar nature of the transition state or the reactive intermediate involved in the rearrangement.

Before arriving at the mechanism for the rearrangement of 16 to 31, a series of experiments were

conducted and it was shown that the rearrangement involves intermolecular participation. Thus the keten dithioacetal 12g derived from p-chloropropiophenone yielded two more products, 32 and 33, besides the rearranged product 31g (Scheme 8). The results are interesting, since they clearly demonstrate the existance of free methylthio anion generated in the reaction mixture, which will participate in nucleophilic displacement of active p-chloro group in both 12g and 31g. This clearly rules out the possibility of Kwart's antipolar mechanism[38] via transient complex (55)* (Scheme 20), which will not permit such nucleophilic displacement as it is concerted. Besides, the allyl sulfide intermediate 16 is structurally different from that of Kwart's systems in that 16 carries an electron-withdrawing benzoyl group in conjugation with double bond, thus reverting the nucleophilicity of β-carbon. Consequently, the formation of 55 is highly unfavorable carrying positive charge adjacent to carbonyl function (Scheme 20).

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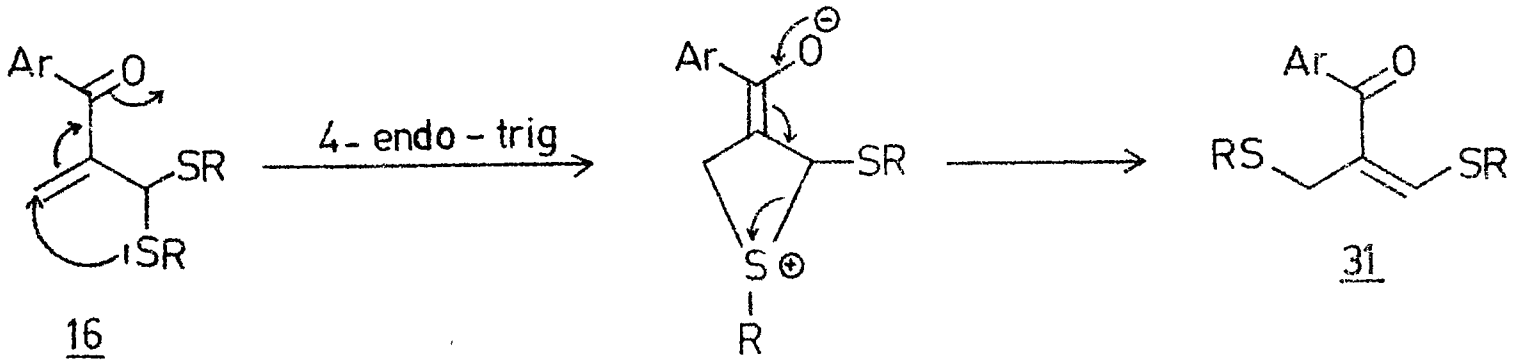
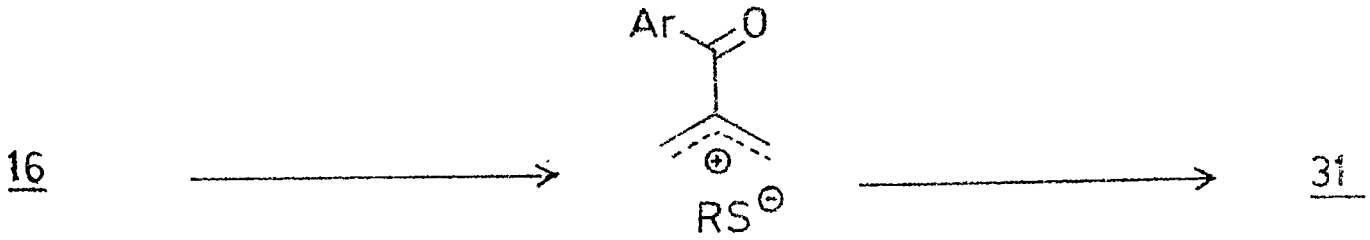
*In our communication, it was proposed that an antipolar transient intermediate (55) as one of the possibilities of this rearrangement.

Alternatively, the β-carbon in 16 (Scheme 21) is electrophilic enough to participate in sulfur lone pair assisted intramolecular polar transition state 56a[42] which can collapse to the desired rearranged product 31. However, such a transition state 56a will not permit the formation of free alkylthio anion proved to be existing in the reaction mixture. Besides, the 4-endo-trig process involving the strained thietonium ion intermediate 56a (Scheme 21) is quite unlikely. An alternative picture involving prior ionisation (S_N1 isomerisation) via β-keto allyl cation or through ion pair 56b appears to be unlikely due to relative unstability of allyl cation cross-conjugated with electron-withdrawing carbonyl group[44] (Scheme 21).

Intermolecularity of the rearrangement was further confirmed from "crossover" experiments carried out with the following systems. Thus, when a 1:1 mixture of 12h and 12c (Scheme 22) was treated with sodium hydride and dimethylformamide under identical conditions, two spots other than the starting materials were observed on TLC plate. After work-up and chromatographic separation



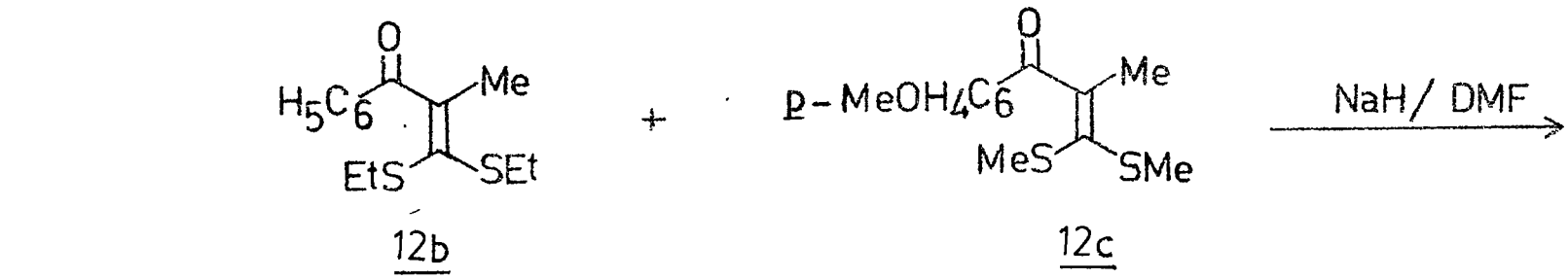
16 56a 31



16 56 b 31

Scheme 21

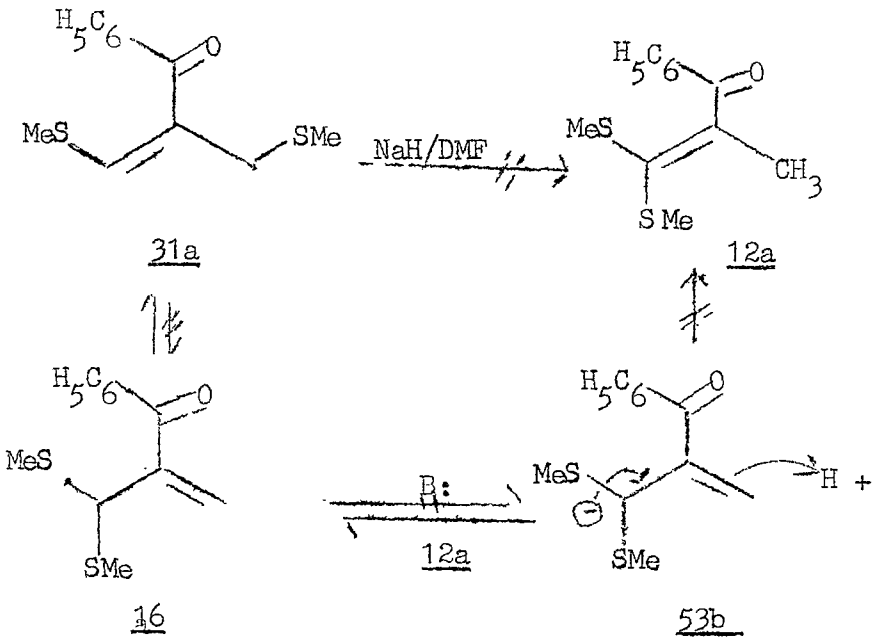
the two products were found to be a mixture of four compounds each (NMR and Mass). Thus, the NMR spectrum of the first product with higher R_f value showed it to be a mixture of four possible rearranged products, 31a, 31b, 57 and 58 respectively. Similarly the NMR spectrum of the second product with lower R_f value showed it to be a mixture of four possible rearranged products, 31c, 31d, 59 and 60 (Scheme 22). The mass spectral studies further confirmed the presence of four compounds in each mixture. Thus the product with higher R_f value showed the molecular ion peaks at M^+ 266, 252 and 238, corresponding to 31a (57 or 58) and 31b respectively. Similarly, the mass spectrum of the second product with lower R_f value showed the molecular ion peaks at M^+ 268, 282 and 296 corresponding to 31c, (59 or 60) and 31d respectively (Scheme 22). In one of the experiments the rearranged product (31c) was treated with sodium hydride in the presence of ethylmercaptan under nitrogen blanket, when the formation of a mixture of four products (31c, 59, 60 and 31d) (Scheme 22) was observed (NMR and Mass). This experiment also demonstrates the existance of free


12b
12c
NaH/ DMF
31b
57
58
31a
Upper Spot
31c
59
60
31d
Lower Spot
NaH/ DMF
EtSH/ N2
31c

Scheme 22

alkylthio anion in the reaction mixture. These experiments therefore strongly suggest that the rearrangement is intermolecular.

The rearrangement of 12a to 31a was found to be irreversible and attempts to equilibriate 31a to 12a under varying conditions were not successful and in no case the keten S,S-acetal 12a could be detected from the reaction mixture. Thus, when 31a was stirred with sodium hydride in dimethylformamide for longer time (12 hr) only polymeric material was formed.



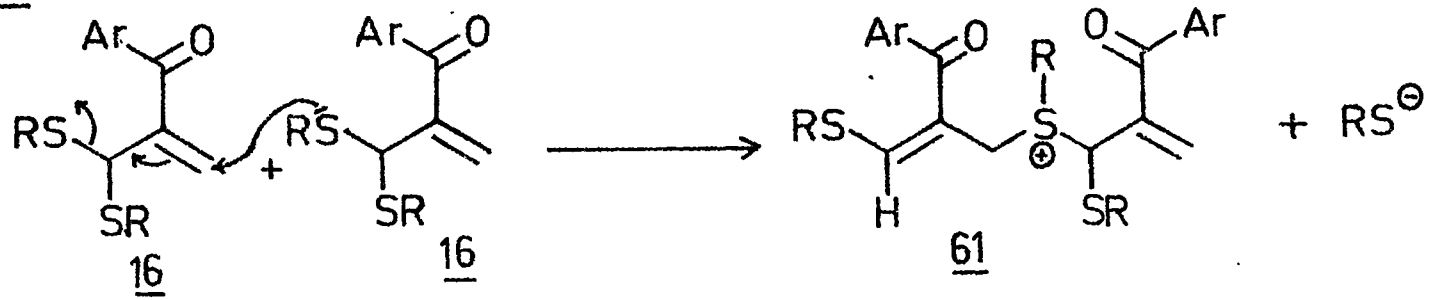
In order to study the progress of the reaction at various time intervals, ten experiments were conducted with 0.005 mole of 12a and 0.02 mole of sodium hydride in 20 ml of dry dimethylformamide under identical reaction conditions and the reactions were worked-up at various time intervals. The results revealed that the yield of 31a was only 7% after 15 minutes, while after 30 minutes, it was increased to 27%. In other experiments, work-up after 0.75 hr, 1.0 hr, 1.5 hr, 2.0 hr, and 3.0 hr yielded 31a between 30-38%, while its yield was decreased to 25% and 20% after 4 hr and 5 hr respectively. However, after 12 hr reaction time, the yield of 31a was reduced to 10% due to its further polymerisation under basic conditions, although the starting material was disappeared completely. So the maximum yield (35-38%) of 31a was obtained between 2-3 hours.

On the basis of these results, the plausible mechanism could be the one similar to that proposed by Cromwell and co-workers for amine unassisted rearrangement of 2-(α-aminobenzyl)-1-indenone (49) to the isomeric 3-amino-2-benzal-1-indanone (50)[32c] (Scheme 16 and 17).

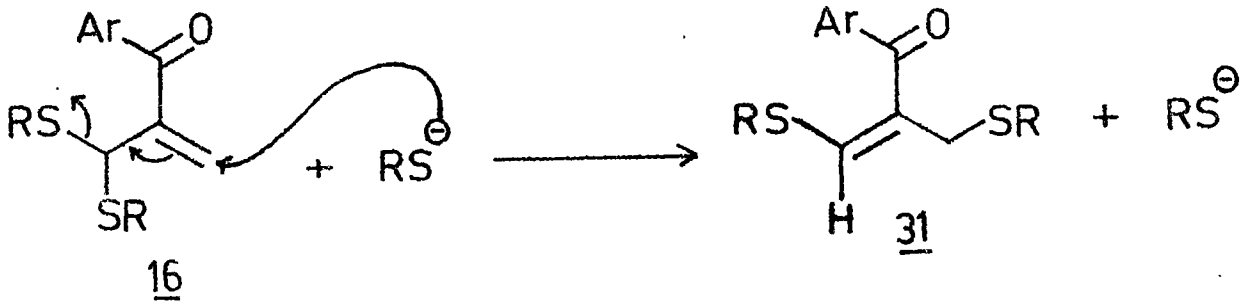
Thus the reaction is initiated by nucleophilic attack at position three of 16 by some nucleophilic species present in the reaction mixture. It appears that the acrylophenone, 16 itself initiates the reaction by nucleophilic attack of its sulfur lone pair on the β-carbon of another molecule of 16 (initiation) (Scheme 23) to give 61 and free alkylthio anion. The alkylthio anion thus released can either attack analogously 16 to give 31 with the release of RS anion (propagation) or can attack 61 to give two molecules of 31 (termination). The rearrangement of 16 to 31 appears therefore similar to chain reaction with an initiation process (release of a alkylthio anion), a propagation process (reaction of alkylthio anion with 16) and a termination process (reaction of alkylthio anion with 61).

It is of interest to note that in one of the experiments, when 12b (Scheme 24) was reacted with sodium hydride in the presence of ethanethiol (added alkylthio anion) the rearranged product 31b was obtained only in comparable yield. It therefore appears that the limiting factor for the yield of 31 is the acrylophenone

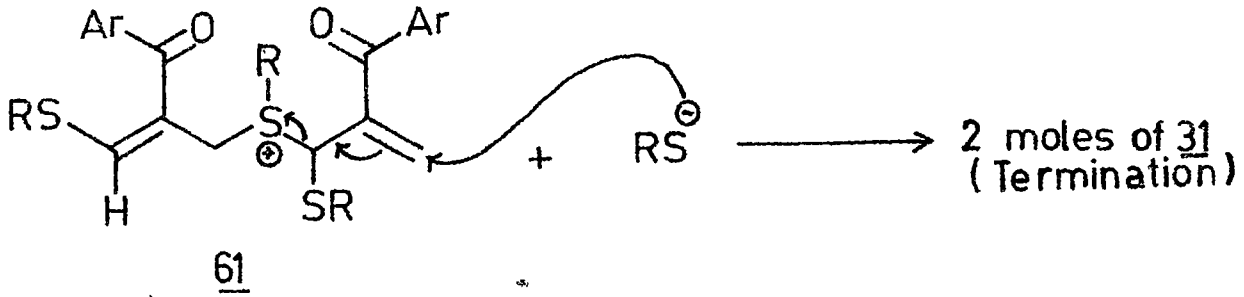
Initiation :



Propogation :



Termination :

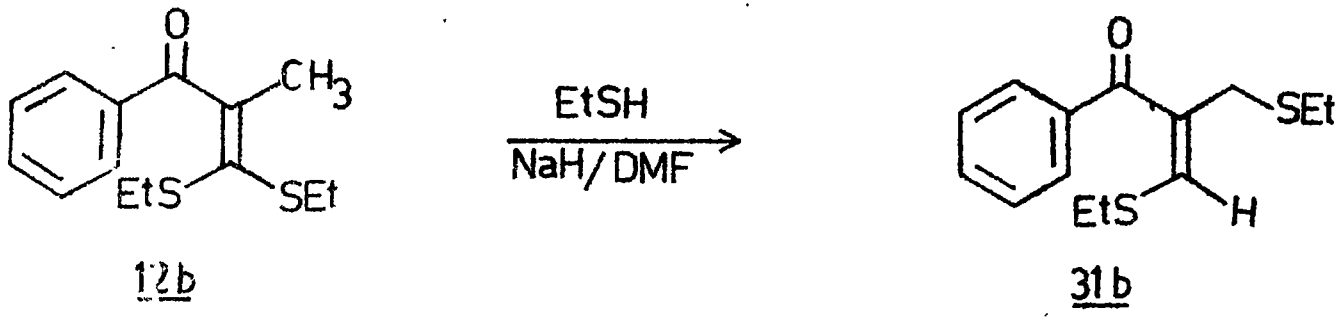


Scheme 23

intermediate 16 present in the reaction mixture which is likely to reach its optimum yield during 0.5 to 3 hr.

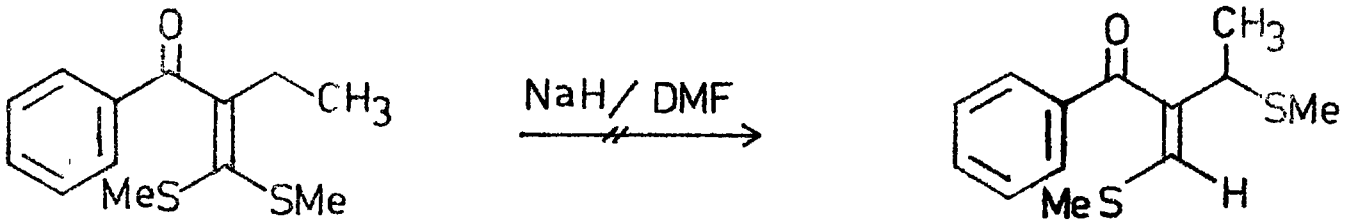
1.3 Base Catalysed Rearrangement Studies on 3,3-Bis (methylthio)-2-benzyl-1-phenyl-2-propen-1-one

When the rearrangement studies were extended to α-ethyl ketoketen S,S-acetal 12i derived from butyrophenone, the expected rearranged product 62 was not formed under varying conditions and the starting material was recovered unchanged in all the cases (Scheme 25). The failure of 12i to give 62 is probably due to the decreased acidity of allylic methylene protons in 12i because of the presence of methyl group and sodium hydride is not strong enough base to abstract proton from 12i. However, its variant 64 (Scheme 26), derived from dihydrochalcone (63), when stirred with sodium hydride and dry dimethylformamide at 35-40° for 2 hr, formation of four products along with the starting material was observed (TLC). After chromatographic separation the expected rearranged product E-66 was isolated in 15% yield and other three compounds were



12b 31b

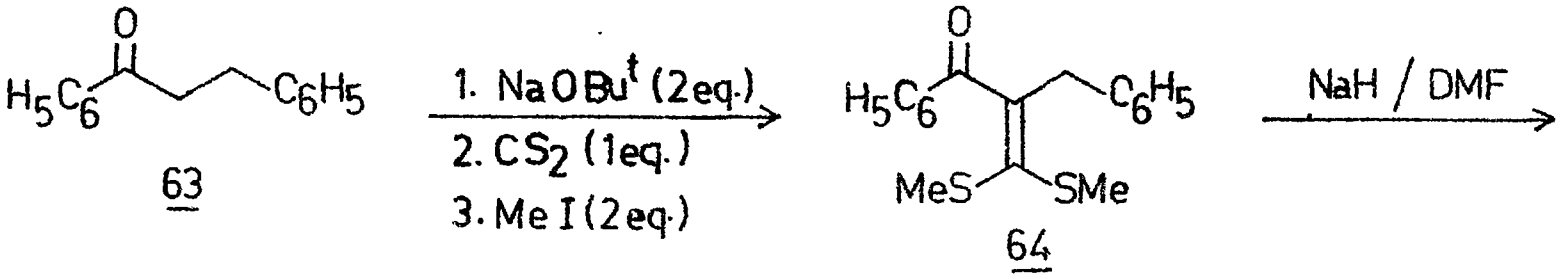
Scheme 24



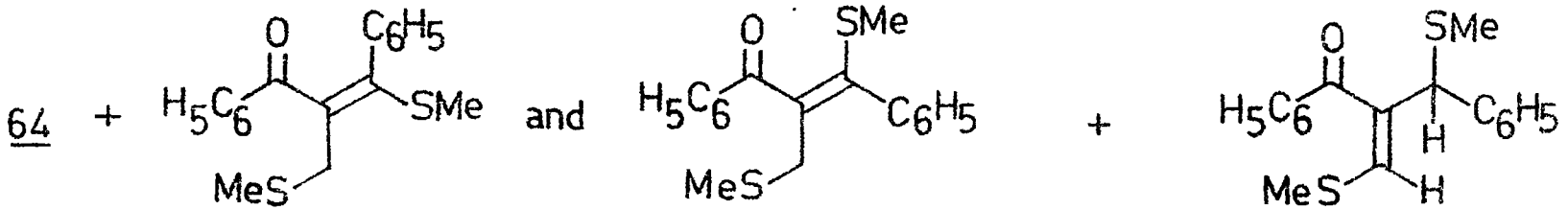
12i 62

Scheme 25

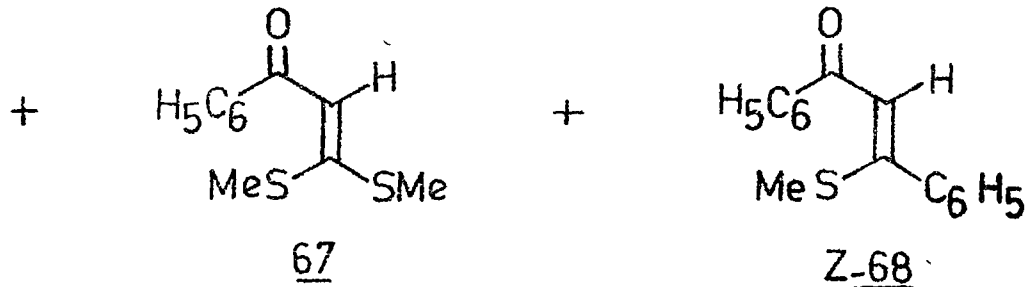
assigned the structures 65 (E and Z-isomers) (35% yield), 67 (20% yield) and Z-68 (5% yield) (Scheme 26). The structure of 65 was confirmed by its spectral and analytical data. Its mass spectrum showed molecular ion peak at M^+ 314 ($C_{18}H_{18}OS_2$). It exhibited IR (neat) band at 1650 cm^{-1} due to νCO of Z-65 isomer, where the carbonyl group is in trans position to the SCH_3 group permitting facile lone pair resonance over the carbonyl group. The other band at 1655 cm^{-1} was assigned to the νCO of E-isomer (E-65). Further structural proof was derived from its ^{1}H-N.M.R. (CCl_4) spectrum, which showed a mixture of E and Z-isomers in the ratio of 3:1 respectively (Figure). Thus a singlet at δ 1.60 (3H) was assigned to the CH_2SCH_3 protons of Z-isomer. The singlet at δ 1.85 (3H) was assigned to vinylic SCH_3 protons of Z-isomer. The methylene protons of Z-isomer appeared as singlet at δ 3.35 (2H). The signal due to CH_2SCH_3 protons of E-65 isomer, appeared at δ 1.80 (s,3H) and the singlet at δ 2.10 (3H) was assigned to the vinylic SCH_3 protons of E-65. The CH_2SCH_3 protons of E-65 appeared as singlet at δ 3.85 (2H). From these signals



63 64



Z-65 E-65 E-66



67 Z-68

Scheme 26

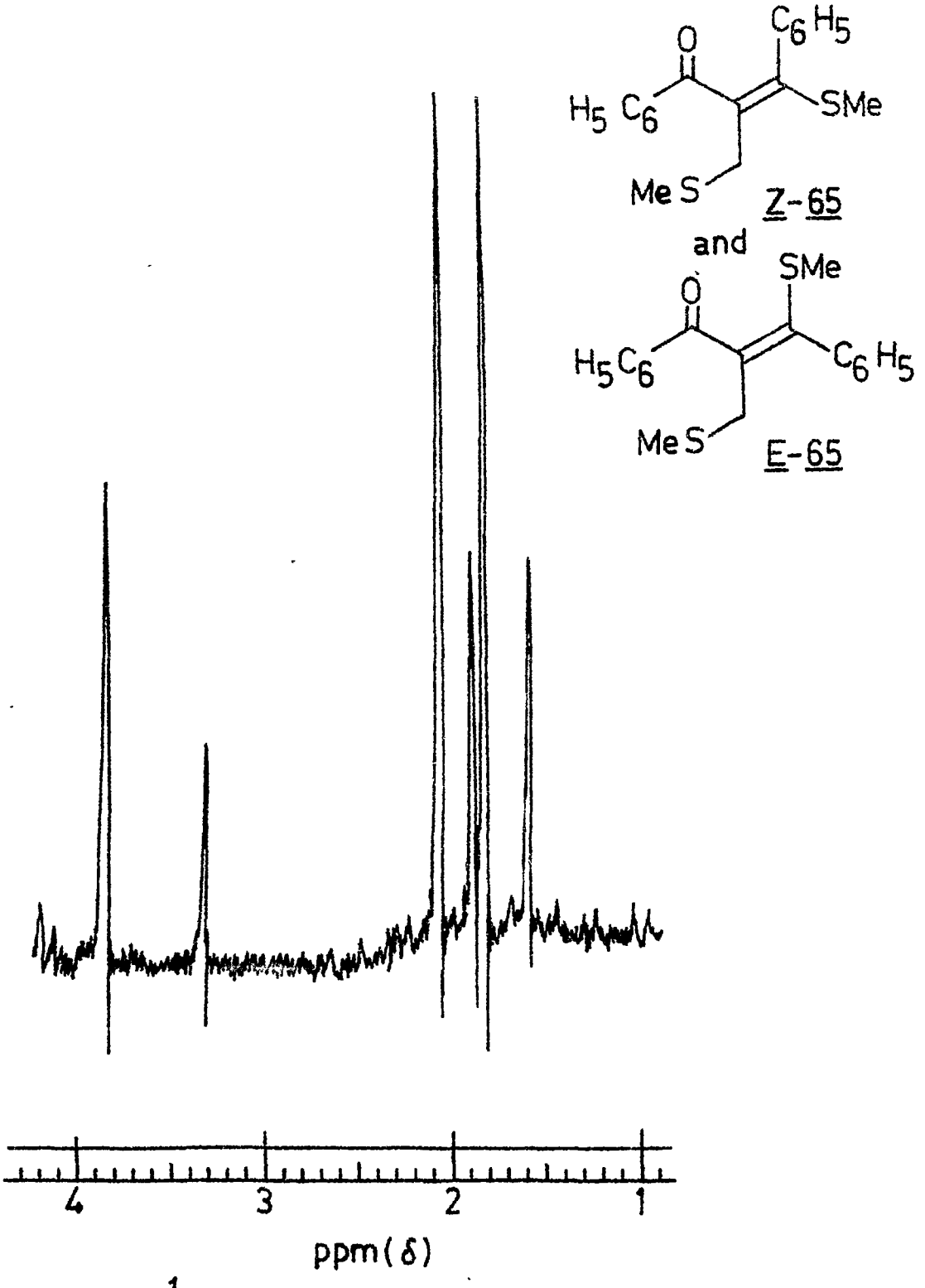
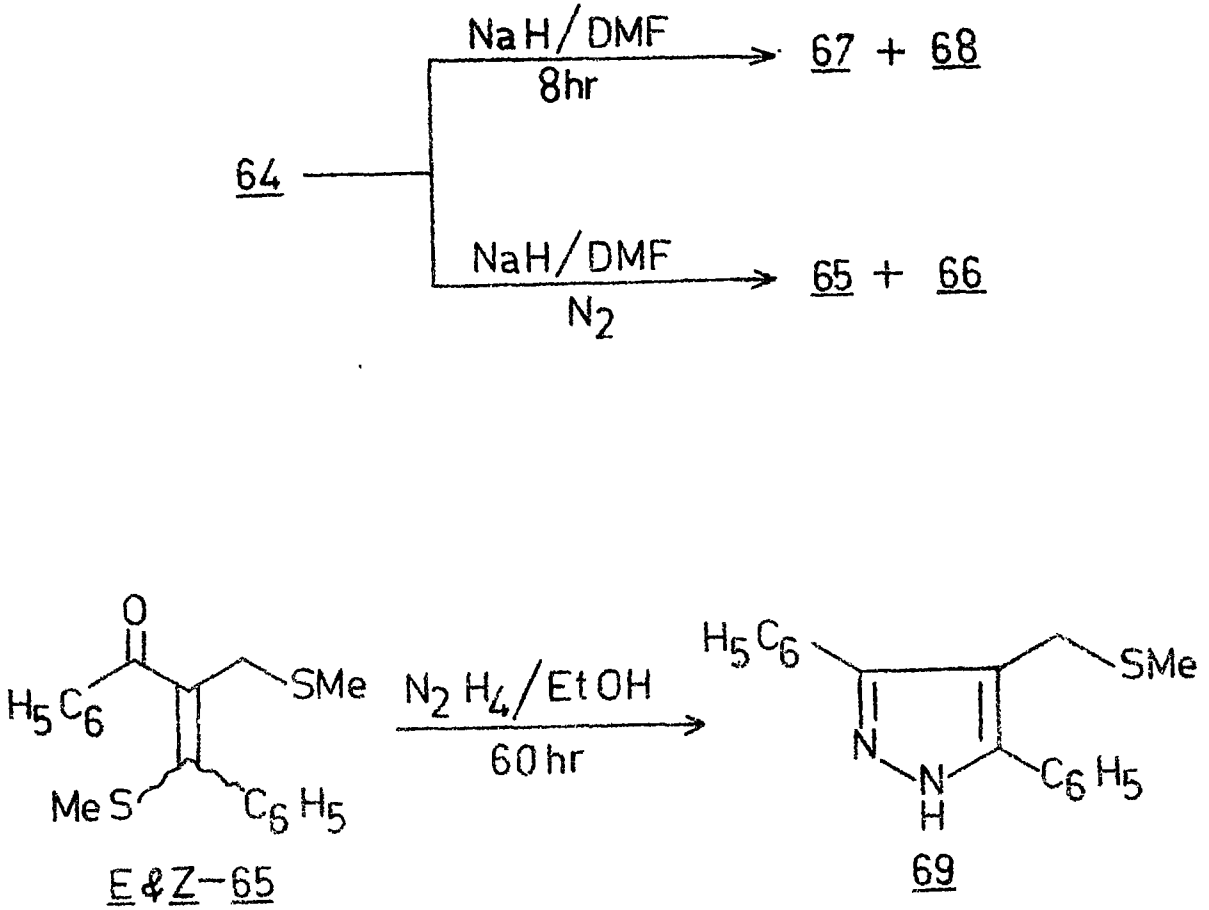


Figure: ^{1}H-NMR spectrum of E-65 and Z-65

the ratio of E-65 and Z-65 isomers (3:1) were calculated. The aromatic protons of both E and Z-isomers were appeared as multiplet between δ 6.90-7.60. Further proof for the structure of E & Z-65 was obtained by its reaction with hydrazine hydrate in refluxing ethanol (60 hr) which gave the expected pyrazole 69 (Scheme 27) in 57% yield. The spectral and analytical data for the 69, which are in agreement with the assigned structure, are described in experimental section. The structure of E-66 was similarly confirmed by its analytical and spectral data. Its mass spectrum showed molecular ion peak at M^+ 314 ($C_{18}H_{18}OS_2$). Its IR (neat) spectrum exhibited $\nu_{C=O}$ band at 1635 cm^{-1} indicating the presence of only one geometrical isomer. The structure of E-66 and its geometry was further confirmed by its ^{1}H-N.M.R (CCl_4) spectrum. Thus the singlet at δ 2.08 (3H) was assigned to the protons of $SC\underline{H}_3$ group on tetrahedral carbon and the singlet at δ 2.20 (3H) was assigned to the protons of vinylic SCH_3 group. The methine proton appeared as a singlet at δ 5.30 (1H), while the singlet at δ 6.92 (1H) was assigned to vinylic proton (trans to ArCO)[28], which

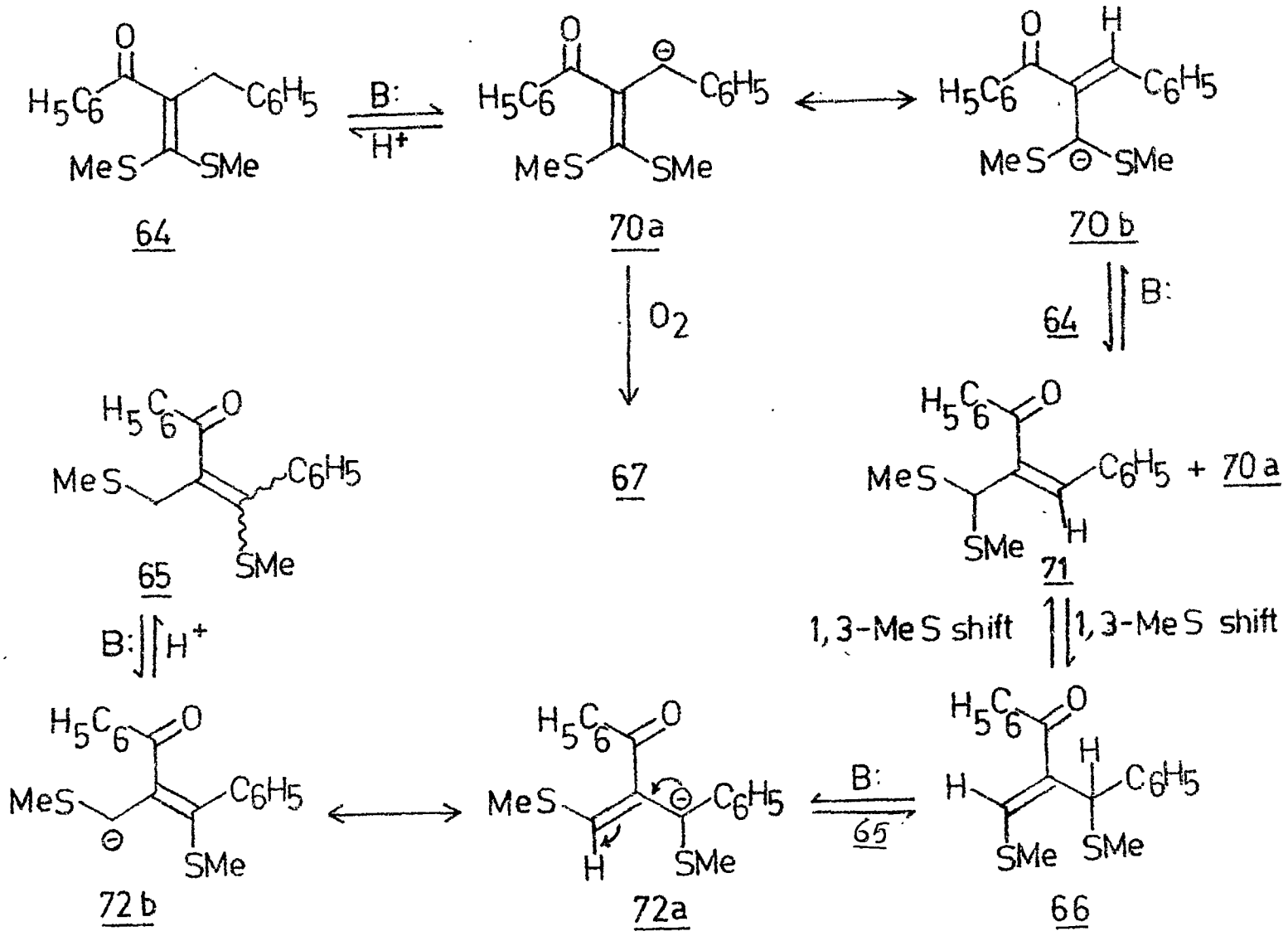

NaH/DMF
8hr
67 + 68
64
NaH/DMF
N2
65 + 66
O
H5C6
SMe
MeS
C6H5
E&Z-65
N2H4/EtOH
60hr
H5C6
SMe
N
N
H
C6H5
69

Scheme 27

indicates the presence of only E-isomer. The aromatic proton appeared as multiplet between δ 7.08-7.60 (10H). From the above data it is evident that only E-65 isomer is formed. The structure of 67 was established by its comparision with the known[45] keten dithioacetal derived from acetophenone (m.m.p. and superimposable I.R &N.M.R). The structure of Z-68 was confirmed by its analytical and spectral data. In its mass spectrum it showed the molecular ion peak at M^+ 254 ($C_{16}H_{14}OS$). It exhibited IR (Nujol) band at 1635 cm^{-1}, which is attributed to the carbonyl group, indicating the formation of only one isomer. Its further structural proof was derived from its ^{1}H-N.M.R (CCl_4) spectrum. It showed a singlet at δ1.82 for three protons of SCH_3 group. The vinylic proton appeared as singlet at δ6.90 (1H). The Z-configuration for 68 was assigned on the basis of chemical shift value of vinylic proton, which was appeared at δ 6.90 (cis to phenyl group), while the vinylic proton in 67 appeared at δ 6.60 (cis to SMe). The multiplet appeared between δ 7.25-7.90, integrated for ten protons, was assigned to the phenyl protons.

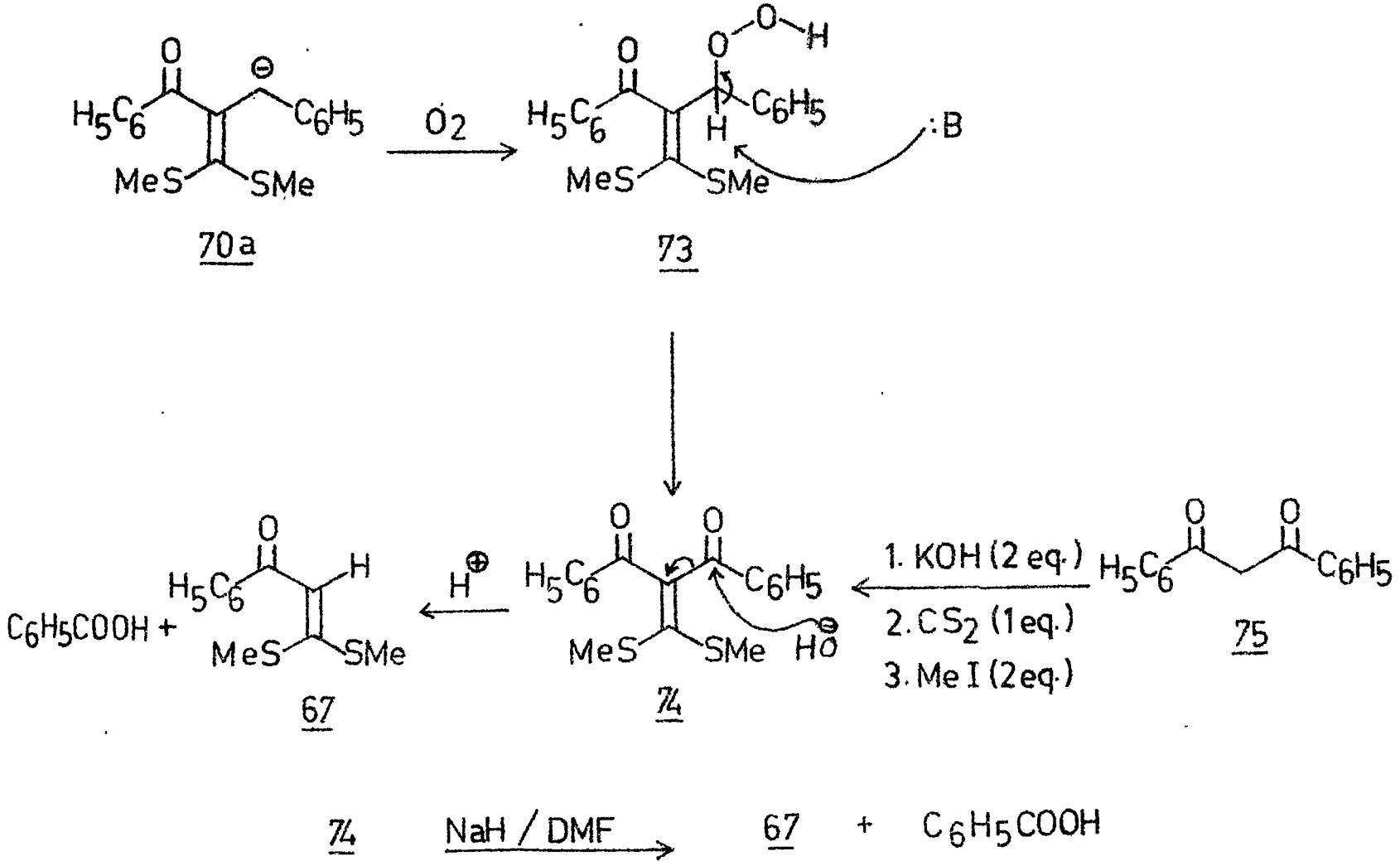
It is interesting to note that when 64 was reacted with sodium hydride in dimethylformamide at 35-40°C for longer time (8 hr), only the keten dithioacetal 67 and β-methylthiochalcone (68) were isolated in 70% and 10% yields respectively and none of the rearranged products 65 or 66 was formed (Scheme 27). Similarly, when 64 was treated with sodium hydride in dimethylformamide under nitrogen blanket for 3 hr, only the rearranged products 65 and 66 were obtained in 50% and 30% yields respectively and none of the products 67 or 68, was formed (Scheme 27). These results indicate that the molecular oxygen is responsible for the formation of 67 and 68.

Based on the above facts, a plausible mechanism for the rearrangement of 64 to 66 and 65 is shown in scheme 28. Thus the resonance forms of anions 70a and 70b, obtained after proton abstraction from 64, will abstract proton inturn from 64 to give unstable intermediate 71. The 71 on 1,3-RS shift (Scheme 23) will yield 66, which on subsequent base induced 1,3-proton shift yield thermodynamically more stable 65 via anion 72 (Scheme 28).



Scheme 28

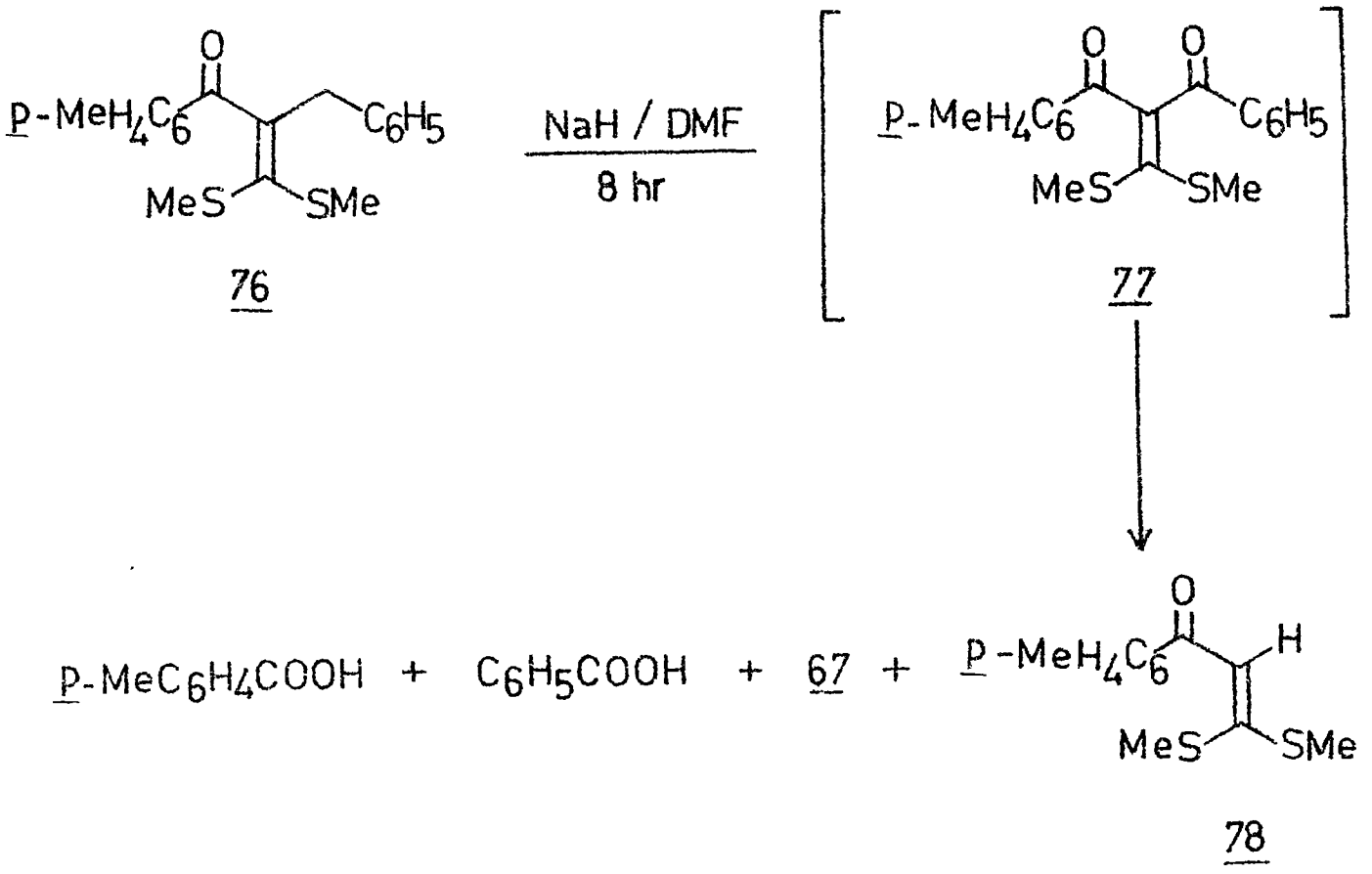
The mechanism of the formation of 67 which is obtained as major product (70%) after 8 hrs in the absence of nitrogen atmosphere is shown in the Scheme 29. The carbanion 70a formed by proton abstraction from 64, reacts with molecular oxygen to give the hydroperoxide intermediate, 73, which in the presence of base, undergoes cleavage to give the keten S,S-acetal 74. The keten S,S-acetal 74 undergoes hydrolytic cleavage in the presence of either hydride or hydroxide ion (during work-up) to give 67 and benzoic acid, which was isolated in 20% yield as described in the experimental section. Similar type of base catalysed autooxidative cleavage has been reported in the case of few hydroxyflavones[46]. However it is not yet clear whether the oxygen incorporation to give hydroperoxide intermidiate 73 involves radical chain mechanism as suggested for oxygenation of carbanion or a direct ionic mechanism. The intermediacy of keten S,S-acetal 74 was established by two experiments. Firstly, when the keten S,S-acetal 74, which was prepared from dibenzoylmethane (75), was reacted with sodium hydride in dry dimethylformamide for


70a
73
74
75
67
1. KOH (2 eq.)
2. CS2 (1eq.)
3. MeI (2eq.)
H⊕
C6H5COOH +
:B
74 NaH / DMF 67 + C6H5COOH

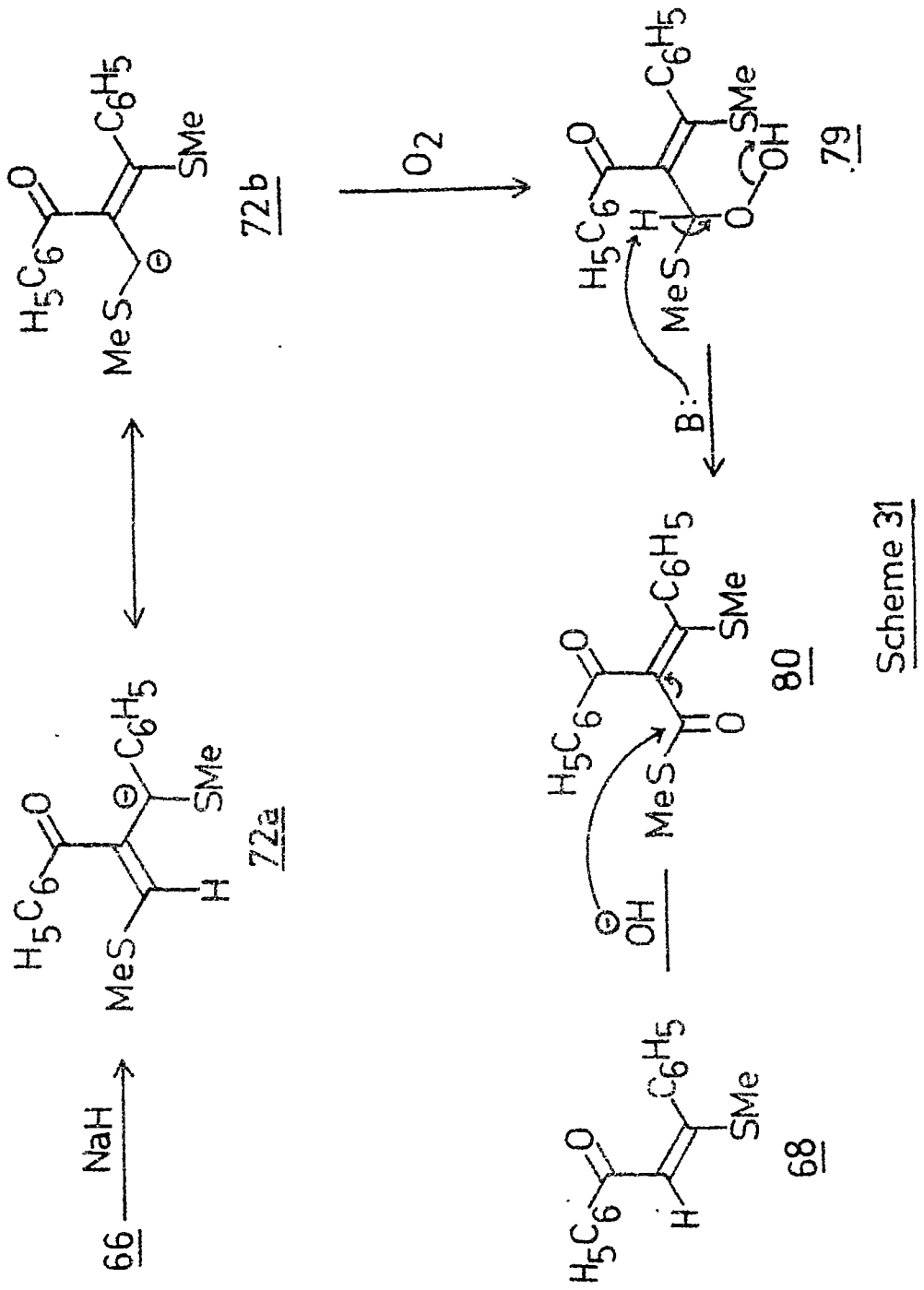
Scheme 29

6 hr under identical reaction conditions, work-up of the reaction mixture yielded 67 as the only product in 90% yield, while the benzoic acid was obtained in 40% yield. (Scheme 29). In the second experiment, when the keten S,S-acetal 76 (Scheme 30), derived from dihydrochalcone having different aryl groups, was reacted with sodium hydride under similar reaction conditions, work-up and column chromatography of the reaction mixture yielded the product which was found to be a mixture of keten S,S-acetals, 67 and 78 along with a mixture of benzoic acid and p-toluic acid. These results clearly demonstrate the intermediacy of dibenzoylmethane S,S-acetals 74 and 77 in the formation 67 and 78 respectively (Schemes 29 & 30)

The probable mechanism for the formation of β-methylthiochalcone (68), which is isolated as the minor product from 64 is shown in the Scheme 31. The rearranged allyl sulfide 66 on proton abstraction by base gives the carbanion 72, which on reaction with molecular oxygen followed by subsequent cleavage of hydroperoxide intermediate 79 yields thioester 80. The thioester 80 undergoes hydrolytic cleavage in the


P-MeH4C6
C6H5
MeS
SMe
76
NaH / DMF
8 hr
77
P-MeC6H4COOH + C6H5COOH + 67 +
78

Scheme 30



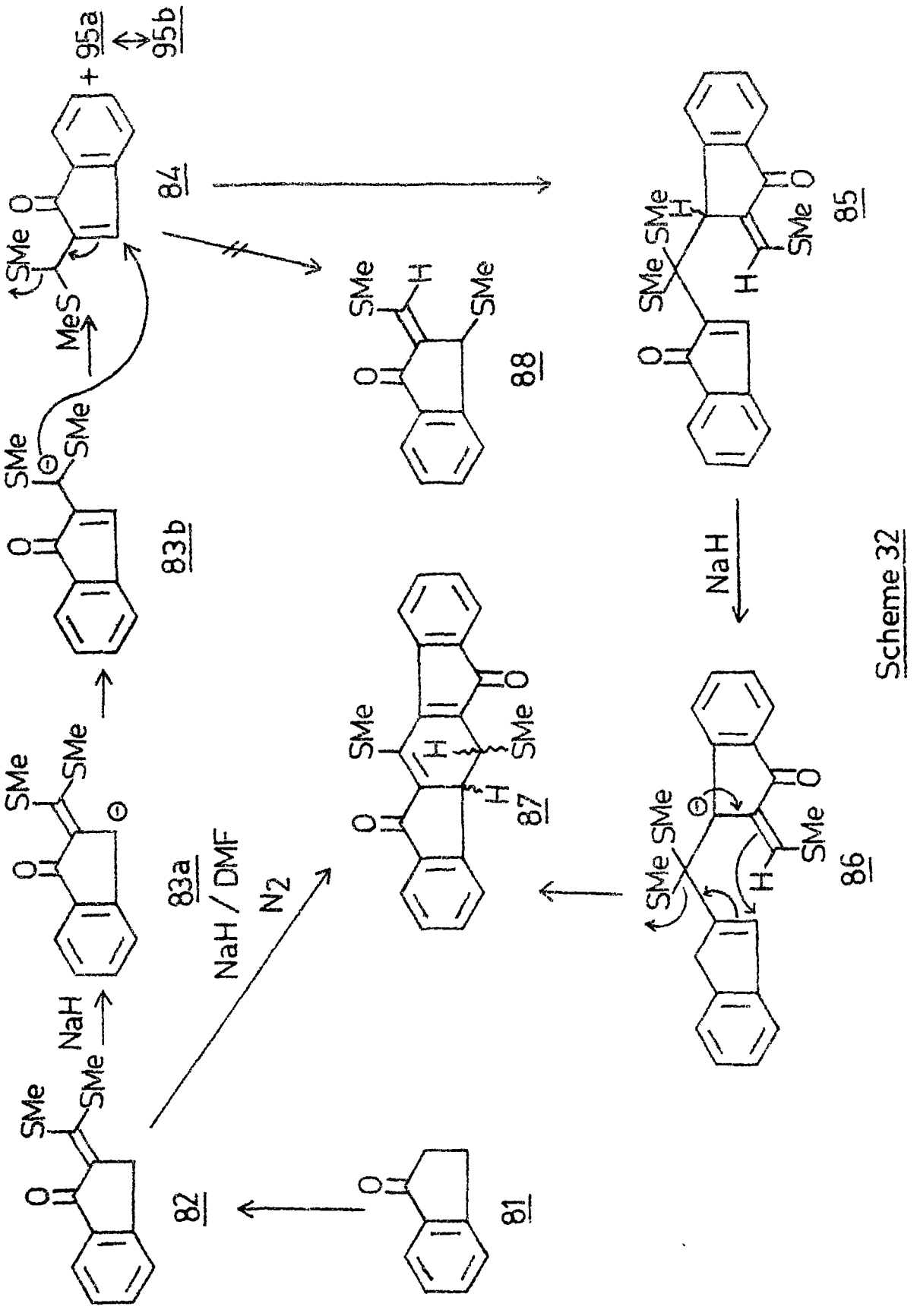
Scheme 31

presence of hydroxide ion during work-up of the reaction mixture to give 68.

It is of interest to note that in one of the experiments, when allyl sulfide 65 was reacted with sodium hydride in dry dimethylformamide at 35-40° in the absence of nitrogen atmosphere for 1 hr, formation of four products corresponding to 64, 66, 67 and 68 were observed along with the starting material 65 (TLC). When the same reaction was allowed to run under similar conditions for 6 hr, only two products, 67 and 68 were isolated in 65% and 15% yields respectively, after work-up and chromatographic separation. These observations indicate that 1,3-methylthio shift in these systems is reversible and the rearranged product 65 undergoes reversible 1,3-proton shift in the presence of sodium hydride to give the intermediate 66, which on subsequent 1,3-methylthio shift gives the intermediate 71 (Scheme 28). The 71 on proton abstraction by base gives the resonating carbanion 70, which on oxidative cleavage yields the keten S,S-acetal 67 (Scheme 29). Similarly, the anion 72b, generated through proton abstraction from 65 by base, also undergoes oxidative cleavage to yield 68 (Scheme 31).

1.4 Studies of Base Catalysed Rearrangement on α-Methylene-α-Ketoketen dithioacetals Derived from Cyclic Ketones

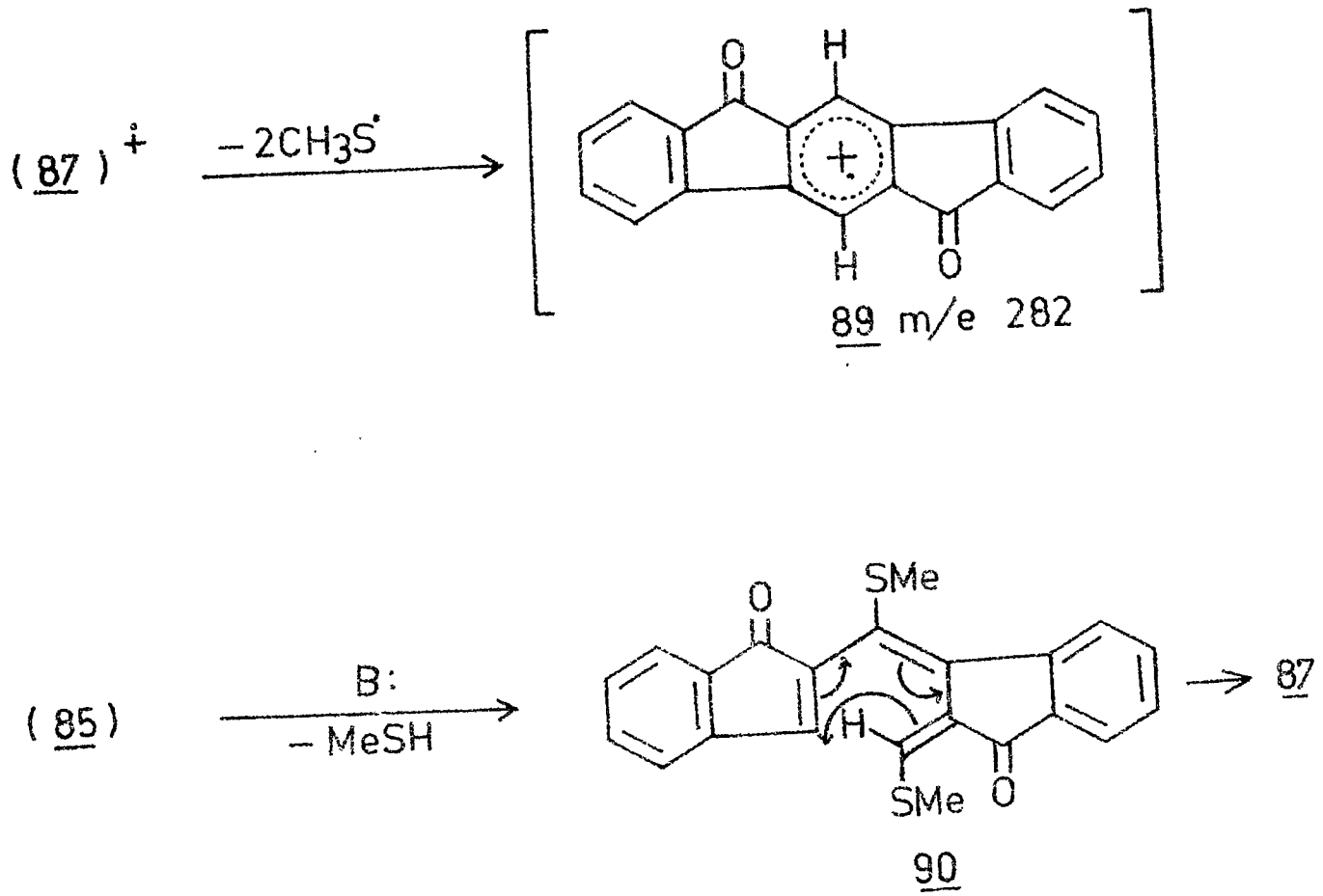
In accordance with the results and mechanism observed during the rearrangements of keten dithioacetals 12 and 64 derived from propiophenones and dihydrochalcone respectively, it was considered of interest to study some of the ketendithioacetals derived from cyclic ketones. Thus when keten dithioacetal 82 (Scheme 32) derived from indanone (81) was reacted with sodium hydride under identical conditions, the expected rearranged product 88 was not formed although starting material was disappeared completely and no well defined crystalline material could be isolated from the reaction mixture. When the same reaction was conducted under nitrogen blanket, a light orange crystalline substance was isolated by preparative TLC in 45% yield. The compound was found to be unstable in solution, while it was stable in crystalline form. The dimeric structure, 87 was assigned on the basis of its analytical and spectral data. Thus, its mass spectrum showed strongest intensity peak at



Scheme 32

m/e 282 (M^+-94), which was possible due to ion 89 (Scheme 33) formed by spontaneous loss of two SCH_3 groups (2 x 47). Consequently, the molecular ion peak at M^+ 376 was not observed while 87 was analysed for $C_{22}H_{16}S_2O_2$. The IR (Nujol) spectrum of 87 showed a strong band at 1672 cm^{-1} due to conjugated carbonyl group. In its NMR ($CDCl_3$) spectrum the singlet at δ 2.20 (3H) was assigned to the protons of $SC\underline{H}_3$ group on sp^3 carbon and the other singlet at δ 2.75 (3H) was due to the protons of $SC\underline{H}_3$ group on sp^2 carbon. The signal due to two methine protons appeared as double doublets at δ 3.50 (1H, J=6 cps) and δ 3.90 (1H, J=6 cps) indicating the presence of a mixture of two stereoisomers. The aromatic protons appeared as multiplet (8H) between δ 7.40-7.70, which are in conformity with the assigned structure, 87.

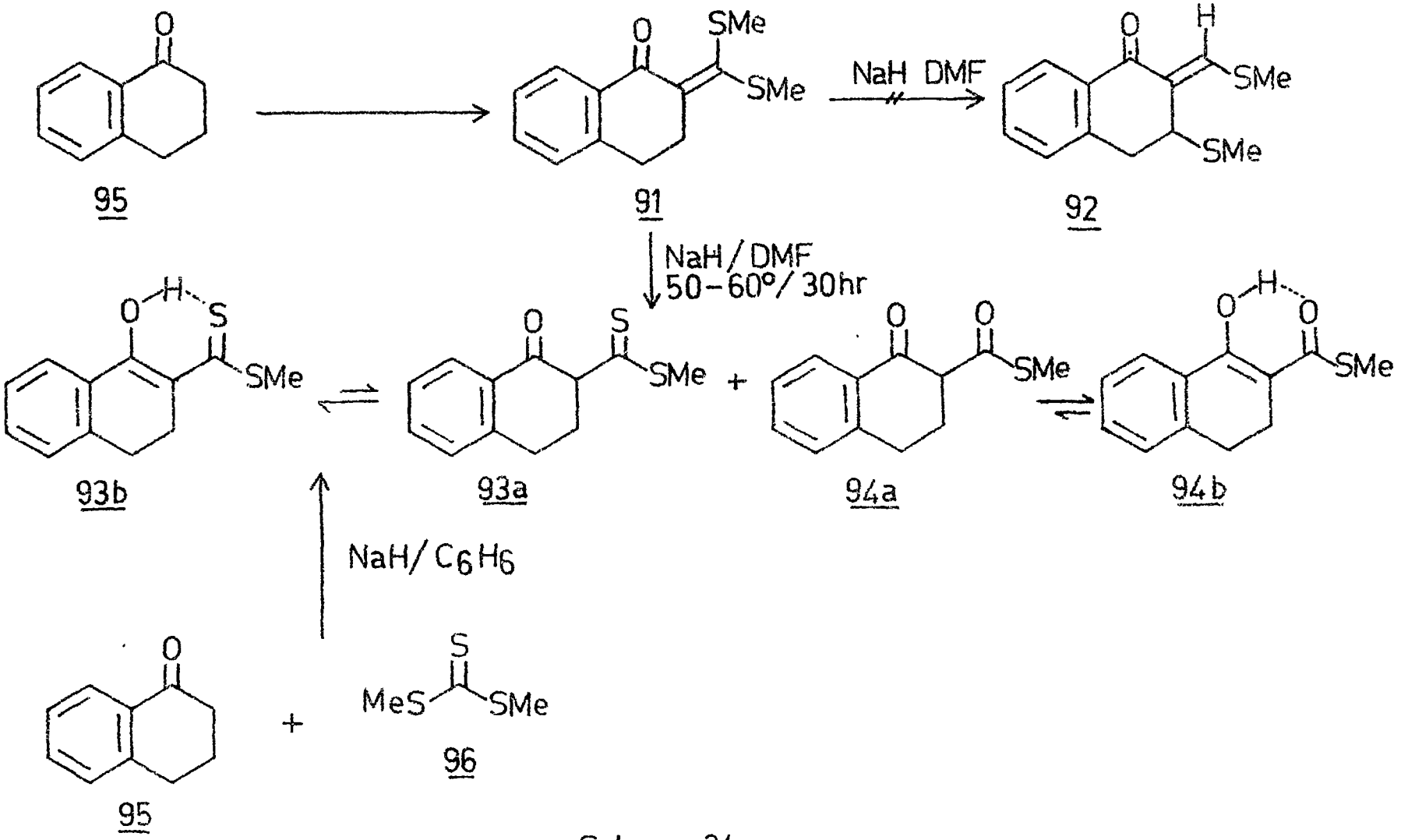
The probable mechanism for the formation of 87 is described in Scheme 32. Thus, the resonance form of anion 83b appears to attack the electrophilic β-carbon of the intermediate 84, which is formed by protonation of 83b, followed by allylic elimination of methyl mercaptan to give 85. The acidic methine proton in 85 is likely to be abstracted by base to give anion



Scheme 33

86, followed by intramolecular cyclization with the elimination of methyl mercaptan to give the dimer, 87 (Scheme 32). Alternatively 85 can also give a triene 90 with the elimination of methyl mercaptan, to yield 87 via electrocyclic ring closure (Scheme 33).

We next extended our studies of base catalysed rearrangement to keten dithioacetal 91 derived from tetralone (Scheme 34). Thus when 91 was reacted with sodium hydride in dimethylformamide under identical conditions for 3 hr, the starting material was recovered unchanged. However when the reaction time was prolonged for 30 hr, two new products were formed which were characterized as dithioester 93 and β-ketomonothioester 94 obtained in 55% and 25% yields respectively. The expected rearranged product 92 was not formed. The structure of 93 was confirmed by its spectral and analytical data. Thus it showed molecular ion peak at M^+ 236 ($C_{12}H_{12}OS_2$). It exhibited absorption bands in its IR spectrum (Nujol) at 1600 (weak, νC=C) and 1190 (νC=S) cm^{-1} which is in conformity with the earlier reported data[29] and shows that 93 exists in tautomeric form 93b. Its NMR spectrum ($CDCl_3$) exhibited a singlet

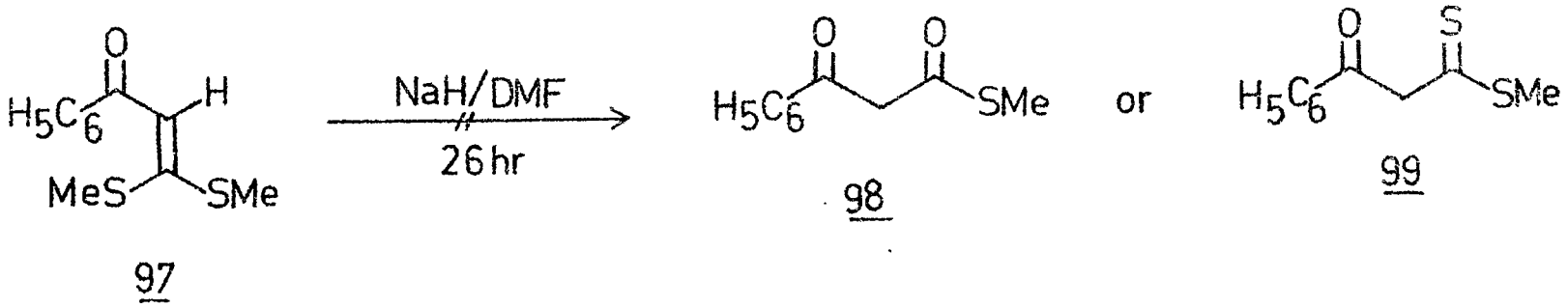


Scheme 34

at δ 2.60 (3H) for SCH_3 protons. The symmetrical A_2B_2 multiplet (4H) at δ 2.80-3.10 was assigned to the four ring methylene protons. The aromatic protons appeared between δ 7.12-7.40 (m, 3H) and the multiplet at δ 7.85-8.00 (1H) was assigned to H-8. The enolic OH proton appeared as broad singlet (1H) at δ 15.6 which is in conformity with the tautomeric structure 93b. The structure of 93 was further confirmed by its alternative preparation. Thus when tetralone (95) was reacted with dimethyltrithiocarbonate (96) (Scheme 34) in the presence of sodium hydride, the corresponding dithioester 93 was formed in 24% yield[29]. The product thus obtained was ~~obtained was~~ found to be identical with 93 (m.m.p. and superimposable IR). The β-ketomonothioester 94 in its mass spectrum exhibited molecular ion peak at M^+ 220 ($C_{12}H_{12}O_2S$). It showed a strong absorption band at 1620 cm^{-1} which is due to H-bonded carbonyl group in 94b. A broad band at 3300 cm^{-1} was due to enolic OH group. Its NMR (CCl_4) spectrum showed a singlet at δ 2.40 (3H) due to SCH_3 protons and a symmetrical A_2B_2 multiplet (4H) was assigned to four methylene protons. The three aromatic protons (H-5, H-6 and H-7) appeared as multiplet

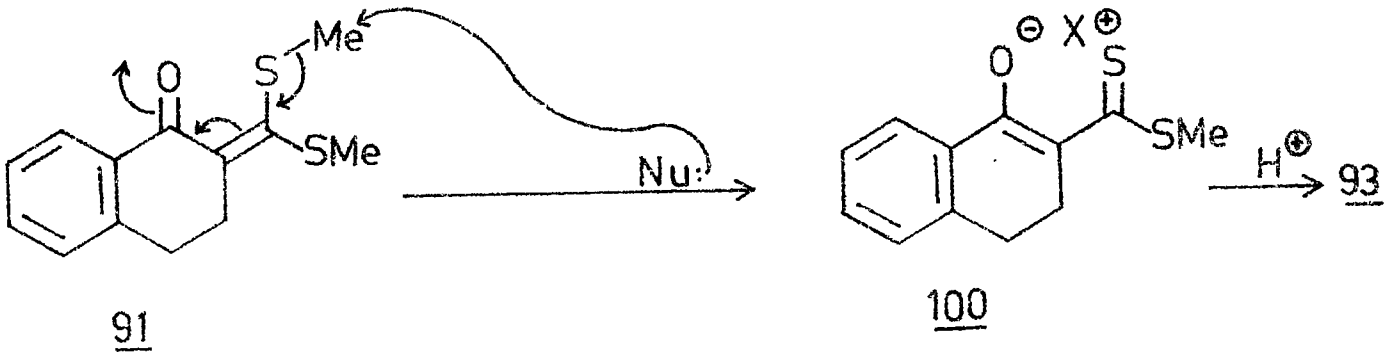
between δ 7.10-7.25 and the multiplet between δ 7.70-7.85 (1H) was attributed to H-8 proton.

Formation of 93 and 94 from 91 is interesting and the same products 93 and 94 were formed in 55% and 30% yields, when 91 was reacted with sodium hydride in the nitrogen blanket under identical conditions. Similarly, when 93 was reacted with sodium hydride for 26 hr under identical conditions, no trace of 94 was obtained. These experiments show that 94 is not formed by oxidation of 93 and both 93 and 94 are formed by independent routes. Formation of 93 and 94 appears to involve demethylation and hydrolytic cleavage of 91 respectively. However other keten S,S-acetals like 97[45] derived from acetophenone did not show the formation of the corresponding β-ketomonothioester 98 or β-ketodithioester 99 on reaction with sodium hydride under identical conditions (Scheme 35). It appears that dithioester 93 is formed by attack of some nucleophilic species like hydride or methylthio anion on 91 present in the reaction mixture (Scheme 36); The probable mechanism for the formation of 94 is shown in the scheme 37. The intermediate 102 formed via anion 101 undergoes base catalysed allylic elimination of the



97 98 99

Scheme 35

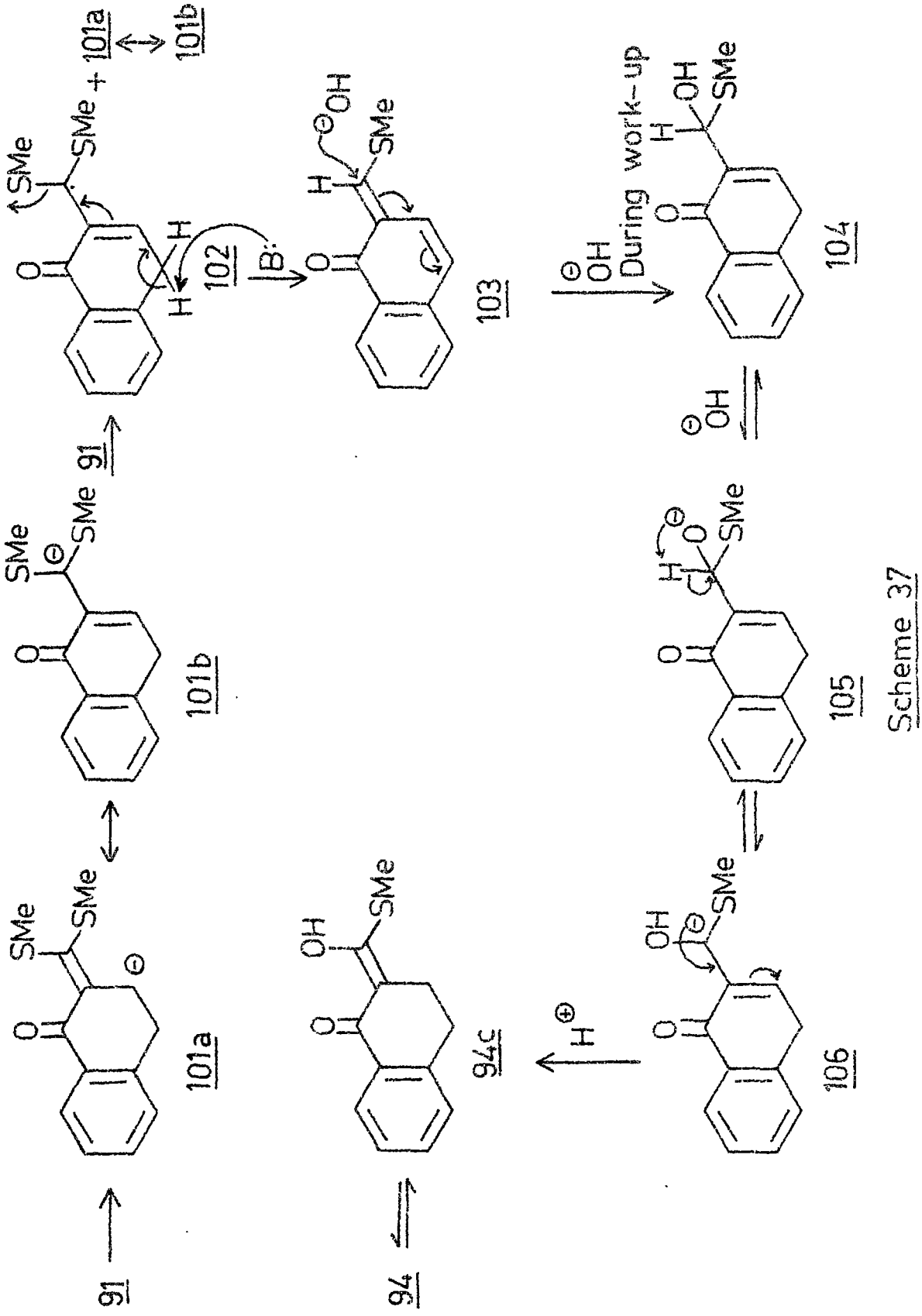


91 100

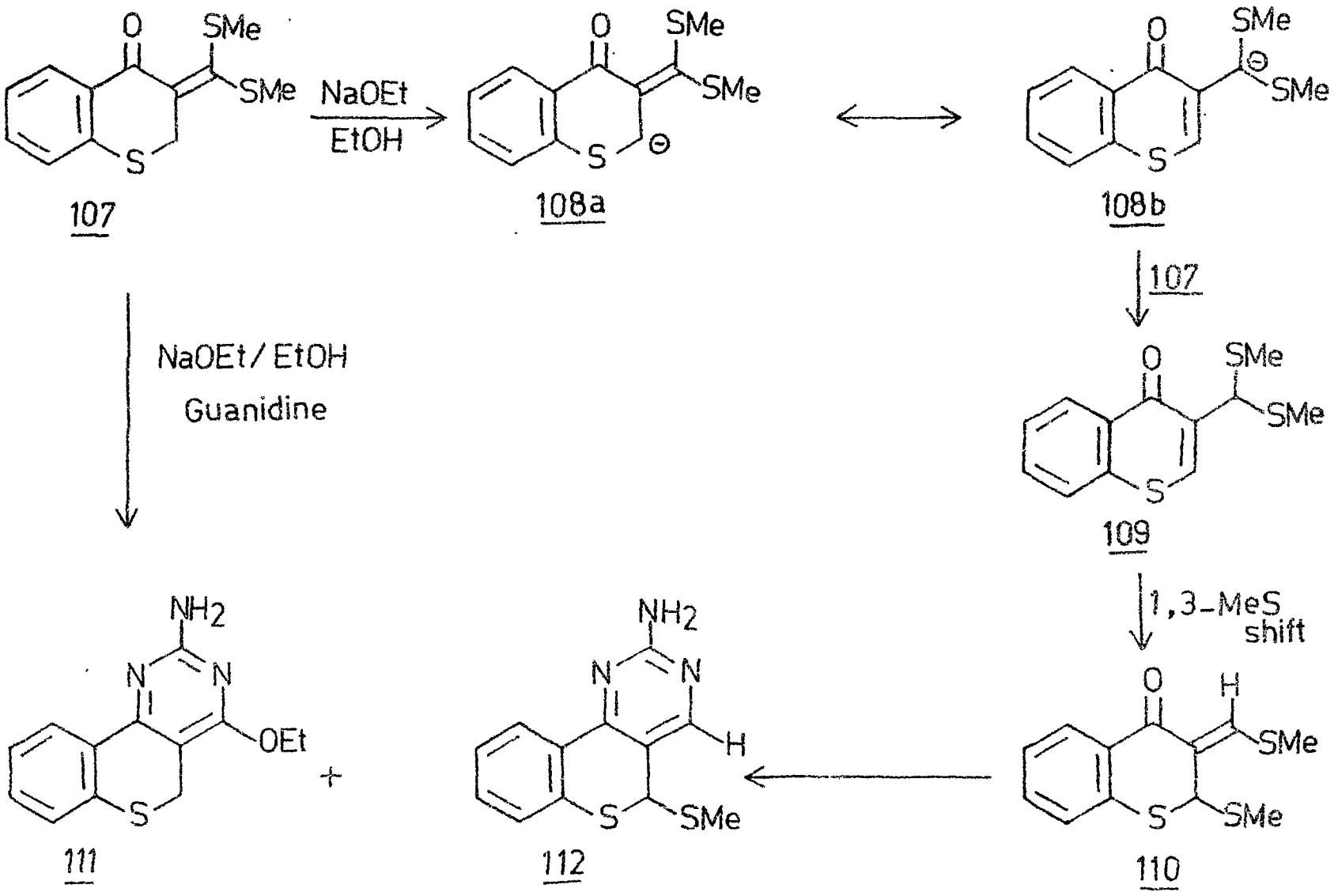
Scheme 36

methyl mercaptan to give intermediate 103. During work-up 103 appears to be susceptible to nucleophilic attack by hydroxide ion and is converted to 94 through intermediate anions 105 and 106 (Scheme 32).

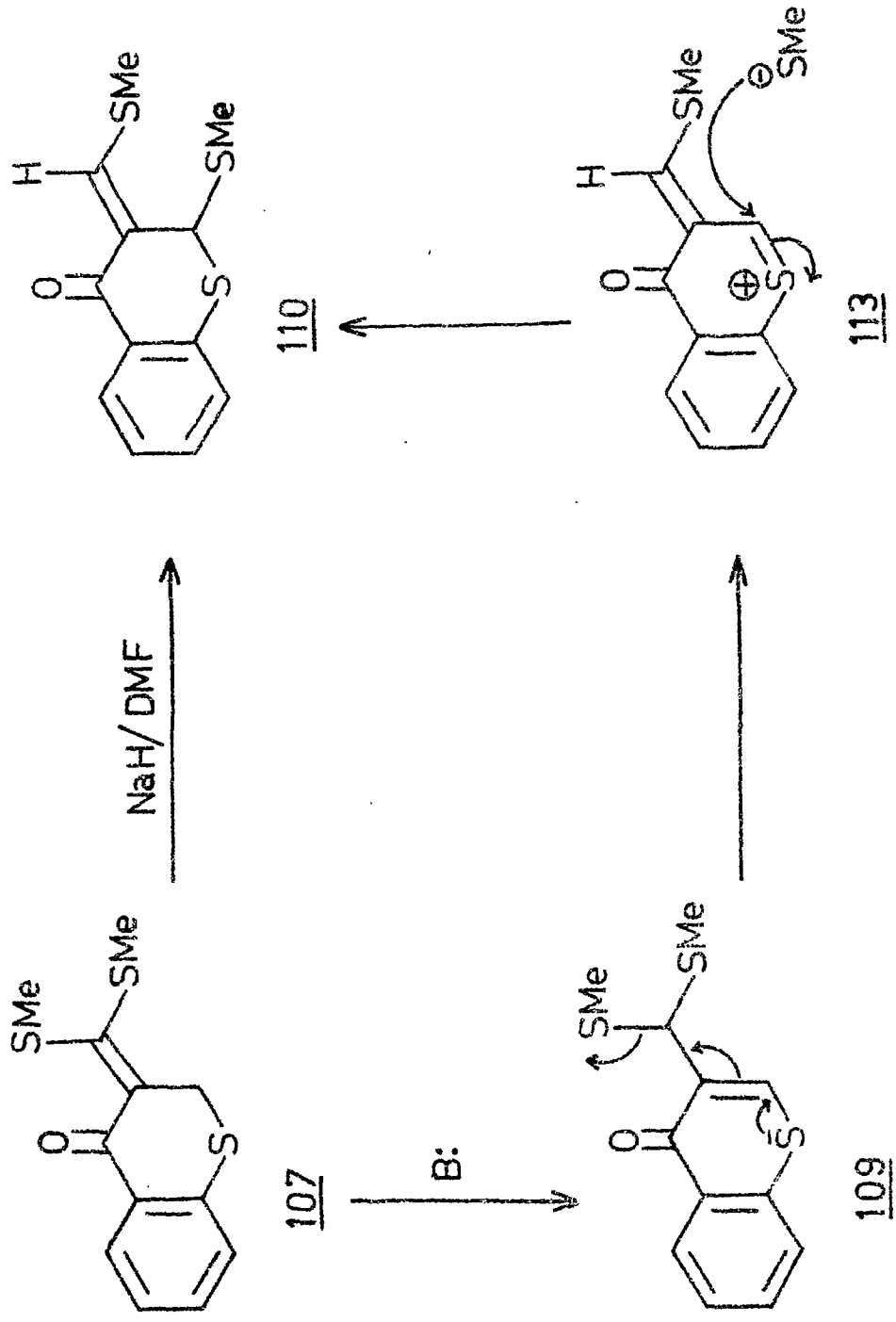
In our earlier studies from our laboratory it was reported that the keten S,S-acetal 107 (Scheme 38) derived from benzothiopyran gives pyrimidines 111 and 112 on treatment with guanidine in refluxing ethanol in the presence of sodium ethoxide[23]. Formation of 112 was postulated through the intermediacy of 110, which is formed by 1,3-methylthio shift in 109 (Scheme 38). So, it appeared of interest to study whether 110 could be isolated from 107 under our standard rearrangement conditions of 1,3-RS shift. Thus when 107 was reacted with sodium hydride in dry dimethylformamide at room temperature, it underwent facile rearrangement to give 110 in 60% yield (Scheme 39). The formation of 110 from 107 was very facile and it was formed even when 107 was reacted with sodium hydride in refluxing benzene while 12a remained unchanged in the presence of sodium hydride in refluxing benzene. The facile nature of this rearrangement is probably due to the formation of


91
101a
101b
91
101a
101b
102
B:
103
During work-up
104
94
94c
H⊕
106
105

Scheme 37


NaOEt
EtOH
NaOEt / EtOH
Guanidine
1,3-MeS
shift
107
108a
108b
109
110
111
112

Scheme 38



Scheme 39

intermediate sulphinium salt 113, which on attack by methylthio anion gives 110 (Scheme 39).

Thus from these studies it appears that the cyclic ketoketen dithioacetals derived from indanone and tetralone behaved differently, while the keten S,S-acetal (107) derived from benzothiopyran gave the expected product of 1,3-RS shift.

Table

Spectral data for 2-Alkylthiomethyl-3-Alkylthioacrylophenones, (31a-g); 3-methylthiomethylene-2-methylthio-2,3-dihydro-1-benzothiopyran-4-one (110):

Product	M.S. m/e (M^+)	IR (neat) ν[cm^{-1}]	^{1}H-NMR (CCl_4) δ[ppm]
31a	238	1635 (C=O)	2.05 (s, 3H, $CH_2SC\underline{H}_3$); 2.25 (s, 3H, vinylic $SC\underline{H}_3$); 3.50 (s, 2H, $C\underline{H}_2SCH_3$); 7.04 (s, $1H_{vinylic}$); 7.25-7.53 (m, $5H_{arom}$)[a].
31b	266	1638 (C=O)	1.25 [two t, 6H, $(SCH_2SC\underline{H}_3)_2$]; 2.50 (q, 2H, $SC\underline{H}_2CH_3$); 2.75 (q, 2H, $SC\underline{H}_2CH_3$); 3.50 (s, 2H, $C\underline{H}_2SCH_2CH_3$); 6.92 (s, $1H_{vinylic}$); 7.25-7.80 (m, $5H_{arom}$).

Table (Contd.)

31c	268	1630 (C=O)[b]	2.00 (s, 3H, $CH_2SC\underline{H}_3$); 2.30 (s, 3H, vinylic $SC\underline{H}_3$); 3.45 (s, 2H, $C\underline{H}_2SCH_3$); 3.75 (s, 3H, $OC\underline{H}_3$); 6.76 (d, 3H, $2H_{arom} + 1H_{vinylic}$); 7.52 (d, $2H_{arom}$).
31d	296	1630 (C=O)	1.30 [two t, 6H, $(SCH_2C\underline{H}_3)_2$]; 2.50 (q, 2H, $SC\underline{H}_2CH_3$); 2.70 (q, 2H, $SC\underline{H}_2CH_3$); 3.50 (s, 2H, $C\underline{H}_2SCH_2CH_3$); 3.80 (s, 3H, $OC\underline{H}_3$); 6.80 (d, 3H, $2H_{arom} + 1H_{vinylic}$); 7.55 (d, $2H_{arom}$).

Table (Contd.)

31c	252	1635 (C=O)	2.05 (s, 3H, p-$C\underline{H}_3$); 2.30 (s, 3H, $CH_2SC\underline{H}_3$); 2.35 (s, 3H, vinylic $SC\underline{H}_3$); 3.45 (s, 2H, $C\underline{H}_2SCH_3$); 6.85 (s, $1H_{vinylic}$); 7.05-7.55 (dd, $4H_{arom}$).
31f	294	1635 (C=O)[b]	1.25 [d, 6H, $(C\underline{H}_3)_2$]; 1.30 [d, 6H, $(C\underline{H}_3)_2$]; 2.80-3.30 (m, $2H_{methine}$); 3.57 (s, 2H, $C\underline{H}_2$); 7.12 (s, $1H_{vinylic}$); 7.40-7.80 (m, $5H_{arom}$).

Table (Contd.)

31g	272.5	1635 (C=O)	2.10 (s, 3H, $CH_2S\underline{CH}_3$); 2.30 (s, 3H, vinylic $SC\underline{H}_3$); 3.45 (s, 2H, $C\underline{H}_2SCH_3$); 6.90 (s, $1H_{vinylic}$); 7.30-7.60 (dd, $4H_{arom}$).
110	268	1615 (C=O)[c]	2.10 [s, 6H, $(SC\underline{H}_3)_2$]; 5.40 (s, $1H_{methine}$); 7.45-7.55 (m, $3H_{arom}$); 8.07 (s, $1H_{vinylic}$); 8.45-8.60 (m, $1H_{arom}$)[a]

[a] in $CDCl_3$; [b] in nujol mull;

[c] in KBr.

EXPERIMENTAL

Melting points were determined on 'Boetius' apparatus (Made in Germany) and are uncorrected. The IR spectra were recorded on "Perkin-Elmer 297" spectrophotometer. The NMR spectra were recorded on varian EM-390 spectrometer using TMS as an internal standard and the chemical shift values are expressed in δ (ppm).

The starting materials

The commercial samples of acetophenone, p-methylacetophenone, benzaldehyde, cinnamic acid, γ-butyrolactone and methyl benzoate were purified before use.

The propiophenone, bp 105-110° (8 mm)[49]; p-methoxypropiophenone, bp 145-150° (15 mm)[50]; p-chloropropiophenone, bp 115-120° (2 mm)[51]; butyrophenone, bp 125-130° (21 mm)[48,52]; α-tetralone (95), bp 140-150° (10 mm)[53]; benzalacetophenone, mp 50-52°[54]; benzal-p-methylacetophenone, mp 58-59°[55]; dihydrocinnamic acid, mp 46-47°[56]; 1-indanone (81), mp 39-40°[57]; 2,3-dihydro-1-benzothiopyran-4-one, bp 150-155° (12 mm)[58] were prepared by the reported methods.

The following previously reported keten S,S-acetals: 3,3-bis(methylthio)-2-methyl-1-phenyl-2-propen-1-one (12a), bp 168-70° (13 mm)[13]; 3,3-bis (ethylthio)-2-methyl-1-phenyl-2-propen-1-one (12b), bp 180-185° (13 mm)[13]; 3,3-bis(methylthio)-2-methyl-1-(p-methoxyphenyl)-2-propen-1-one (12c), bp 180-185° (13 mm)[13]; 3,3-bis(methylthio)-2-methyl-1-(p-methylphenyl)-2-propen-1-one (12e), bp 185-90° (1 mm)[20]; 3,3-bis (methylthio)-2-methyl-1-(p-chlorophenyl)-2-propen-1-one (12g), bp 195-200° (1 mm)[20]; 3,3-bis(benzylthio)-2-methyl-1-phenyl-2-propen-1-one (12h), mp 66°[13]; 3,3-bis (methylthio)-2-ethyl-1-phenyl-2-propen-1-one (12i), bp 190-195° (16 mm)[13]; 2- bis(methylthio)methylene -1-tetralone (91), mp 58°[12]; 3,3-bis(methylthio)-1-phenyl-2-propen-1-one (97), mp 93°[45]; 3-bis(methylthio)methylene -2,3-dihydro-1-benzothiopyran-4-one (107), mp 80-81°[23] and the unknown ones were prepared by the general method described below:

General method for the preparation of keten S,S-acetals using sodium t-butoxide[13]:

A mixture of ketone (0.05 mol) and carbon disulfide (0.05 mol) was added to a well stirred and

cooled suspension of sodium t-butoxide (0.10 mol) in dry benzene (35 ml) and dimethylformamide (10 ml). The reaction mixture was allowed to stand at room temperature for 4 hr and methyl iodide (0.11 mol) was gradually added with cooling and stirring. The reaction mixture was further stirred for 4 hr and left overnight and then it was refluxed on water bath for 1-2 hr. The reaction mixture was then poured over crushed ice and the benzene layer was separated. The aqueous layer was extracted with benzene (2 x 50 ml) and the combined extract was washed with water (1 x 100 ml), dried (Na_2SO_4) and concentrated to give crude keten dithioacetals, which were further purified either by column chromatography or by distillation under reduced pressure. The physical and spectral properties of some of the unknown keten S,S-acetals are given below:

3,3-Bis(ethylthio)-2-methyl-1-(p-methoxyphenyl)-2-propen-1-one (12d) was obtained as orange coloured viscous liquid after purification by distillation, bp 180-185°(1 mm); Yield 9.0 g (60%); IR (neat): 1630 cm^{-1} ($\nu_{C=O}$); NMR (CCl_4): 1.05 (t, 3H, $SCH_2\underline{CH_3}$); 1.30 (t, 3H, $SCH_2\underline{CH_3}$); 2.10 (s, 3H, $\underline{CH_3}$); 2.60 (q, 2H, $SCH_2\underline{CH_3}$);

2.80 (q, 2H, $SC\underline{H}_2CH_3$); 3.80 (s, 3H, $OC\underline{H}_3$); 6.80 (d, $2H_{arom}$); 7.70 (d, $2H_{arom}$); M^+ 296; (Found: C, 60.37; H, 6.43; Calc. for $C_{15}H_{20}O_2S_2$ (296): C, 60.81; H, 6.76%).

3,3-Bis(isopropylthio)-2-methyl-1-phenyl-2-propen-1-one (12f) was yellow viscous liquid after purification by distillation, bp 155-160° (1 mm), yield 7.5 g (50%); IR (neat): 1668 cm^{-1} ($\nu_{C=O}$); NMR (CCl_4): 1.05 [d, 6H, $(C\underline{H}_3)_2$]; 1.30 [d, 6H, $(C\underline{H}_3)_2$]; 2.15 (s, 3H, $C\underline{H}_3$); 2.80-3.40 (m, $2H_{methine}$); 7.30-7.85 (m, $5H_{arom}$); M^+ 294; (Found: C, 65.78; H, 7.83; Calc. for $C_{16}H_{22}OS_2$ (294): C, 65.31; H, 7.48%).

3,3-Bis(methylthio)-2-benzyl-1-phenyl-2-propen-1-one (64) was obtained as light yellow prisms after purification by column chromatography over silicagel using hexane: benzene (9:1) mixture as eluent; Yield 9.2 g (57%); mp 66° (chloroform:hexane); IR (Nujol): 1660 cm^{-1} ($\nu_{C=O}$); NMR (CCl_4): 2.35 (s, 3H, $SC\underline{H}_3$); 2.70 (s, 3H, $SC\underline{H}_3$); 4.35 (s, 2H, $C\underline{H}_2$); 7.10-7.75 (m, $10H_{arom}$); M^+ 314; (Found: C, 68.34; H, 5.37; Calc. for $C_{18}H_{18}OS_2$ (314): C, 68.79; H, 5.73

3,3-Bis(methylthio)-2-benzyl-1-(p-methylphenyl)-2-propen-1-one (76) was obtained as yellow needles after purification by column chromatography over silica gel using hexane; ethylacetate (9:1) as eluent. Yield 6.56 g (40%); mp 74-75°; IR (Nujol): 1640 cm^{-1} ($\nu_{C=O}$); NMR (CCl_4) 2.00 (s, 3H, p-CH_3); 2.35 (s, 3H, SCH_3); 2.45 (s, 3H, SCH_3); 4.00 (s, 2H, CH_2); 6.95-7.50 (m, $9H_{arom}$); M^+ 328; (Found: C, 69.87; H, 6.46; Calc. for $C_{19}H_{20}OS_2$ (328): C, 69.51; H, 6.10%)

2-[Bis(methylthio)methylene] -1-indanone (82) was obtained as yellow shining needles after purification by column chromatography over silica gel using hexane: ethylacetate (1:9) as eluent; Yield 8.25 g (70%); mp 70-71°; IR (Nujol): 1663 cm^{-1} ($\nu_{C=O}$); NMR (CCl_4): 2.52 (s, 3H, SCH_3); 2.55 (s, 3H, SCH_3); 3.78 (s, 2H, CH_2); 7.30-7.90 (m, $4H_{arom}$); M^+ 236; (Found: C, 61.48; H, 5.37; Calc. for $C_{12}H_{12}OS_2$ (236): C, 61.02; H, 5.08%).

Dibenzoyl methane (75) was prepared by a modified procedure as follows:

To a well stirred suspension of sodium hydride (6g, 50% suspension, 0.12 mol) in dry benzene (250 ml),

methyl benzoate (27 g, 0.2 mol) was added dropwise with refluxing. A solution of acetophenone (12 g, 0.1 mol) in 150 ml of benzene was added dropwise with stirring and refluxing over a period of 4 hr and the reaction mixture was further refluxed with stirring for 3 hr. The reaction mixture was left overnight, poured over cushed ice and acidified with concentrated sulfuric acid (10 ml). The organic layer was separated and the aqueous layer was extracted with benzene (3 x 250 ml) and the combined extract was washed with 5% sodium bicarbonate solution (1 x 50 ml) and then with water, dried ($CaCl_2$) and concentrated over water bath. The unreacted methyl benzoate was removed by distillation under reduced pressure and the crude dibenzoyl methane was transferred into a 250 ml beaker while hot. The crude dibenzoyl methane was solidified on cooling and was purified by recrystallization from methanol, yield 13.0 g (60%), mp 72-73°C (reported mp 73°)[59]; IR (Nujol): 1600 cm^{-1} ($\nu_{C=O}$); NMR (CCl_4): 6.70 (s, $1H_{vinylic, enol\ from}$); 7.30-7.45 (m, $6H_{arom}$); 7.80-7.95 (m, $4H_{arom}$).

Preparation of 3,3-bis(methylthio)-2-benzoyl-1-phenyl-2-propen-1-one (74)[60]:

To a solution of dibenzoyl methane (75) (2.24 g, 0.01 mol) in dimethyl sulfoxide (10 ml), a solution of KOH (1.2 g, 0.02 mol) in water (2 ml) and carbon disulfide (2.4 g, 0.03 mol) was added dropwise over a period of 2 hr with stirring and cooling. After further stirring for 4 hr, dimethyl sulfate (2.6 g, 0.02 mol) was added dropwise with ice cooling and it was further stirred at room temperature for 2hr. The reaction mixture was then poured over 200 ml of ice cold water, extracted with chloroform, dried (Na_2SO_4) and concentrated to give crude 74, which was purified by column chromatography over silica gel using ethyl acetate:hexane (1:4) as eluent. The product obtained as a yellow crystals, mp 67-68° (reported 68-69°C)[61]; yield 0.6 g (25%), IR (Nujol): 1650, 1660 cm^{-1} ($\nu_{C=O}$); NMR (CCl_4): 2.10 s, 6H, $(SCH_3)_2$; 7.20-7.50 (m, $6H_{arom}$); 7.80-7.95 (m, $4H_{arom}$); M^+ 328; (Found: C, 65.47; H, 4.43; Calc. for $C_{18}H_{16}O_2S_2$ (328): C, 65.85; H, 4.88%).

α-Benzylacetophenone (63) was prepared by slight modification of the reported procedure[62] by hydrogenation

of benzalacetophenone over Raney Ni instead of Platinum catalyst. Thus 20.8 g (0.1 mol) of benzalacetophenone was dissolved in 150 ml of hot ethanol and was hydrogenated in parr hydrogenation apparatus over Raney Ni (~15 g) at 50 psi for 0.5 hr. The catalyst was filtered and the solvent was evaporated to yield 19.0 g (90%) of 63 as white shining plates, mp 68-69° (reported mp 70-71°C)[62].

α-Benzyl-p-methylacetophenone was similarly prepared by hydrogenation of 22.2 g of benzal-p-methylacetophenone. The product was obtained as white shinning plates; yield 18.0 g (80%), mp 50-52°C (reported mp 50-51°C)[63].

Attempted isomerisation of 3,3-bismethylthio-2-methyl-1-aryl-2-propen-1-one (12a) with ethanolic sodium ethoxide:

To a solution of sodium ehoxide (prepared by dissolving sodium, 0.02 atom, in 30 ml of absolute alcohol), the keten S,S-acetal 12a (2.38 g, 0.01 mol) was added and the solution was stirred at room temperature for 10 hr. The solvent was distilled off and the residue was quenched with crushed ice. It was extracted with chloroform, washed with water and dried. Evaporation of

the solvent gave the unreacted starting material.

In an alternate experiment when the same reaction mixture was refluxed with stirring for 10 hr, work-up of the reaction mixture yielded only intractable polymeric material and no identifiable compound could be isolated.

Base catalysed rearrangement of 3,3-bis(alkylthio)-2-methyl-1-aryl-2-propen-1-ones (12a-f) to 2-alkylthiomethyl-3-alkylthioacrylophenones (31a-f); General Procedure:

A solution of 12 (0.01 mol) in dry dimethyl formamide (20 ml) was added dropwise over a period of 15 minutes to a well stirred suspension of sodium hydride (2g, 50% suspension, 0.04 mol) in 20 ml of dimethylformamide at 50-60°. The reaction mixture was further stirred at 50-60° for 2.5 to 3.5 hr. It was then poured over crushed ice (100 g), neutralised with dilute acetic acid, extracted with chloroform (3 x 30 ml) and the combined extract was washed with water (4 x 100 ml), dried (Na_2SO_4) and evaporated to give a residue, which was chromatographed over silica gel.

Elution with hexane:ethylacetate (9:1) mixture gave first the unreacted starting materials 12a-f and further elution with hexane:ethylacetate (4:1) mixture yielded pure rearranged products 31a-f. The physical and spectral data of 31a-f are given below, while their spectral data are described in table.

3-Methylthio-2-methylthiomethyl-1-phenyl-2-propen-1-one (31a) was obtained as yellow viscous oil, (TLC single spot), yield 0.83 g (35%) (55% on the basis for recovered starting material); M^+ 238; (Found: C, 60.15; H, 5.39; Calc. for $C_{12}H_{14}OS_2$ (238): C, 60.50; H, 5.88%).

3-Ethylthio-2-ethylthiomethyl-1-phenyl-2-propen-1-one (31b) was obtained as orange viscous oil, (TLC single spot), yield 1.15 g (43%) (50% on the basis of recovered starting material); M^+ 266; (Found: C, 63.57; H, 6.34; Calc. for $C_{14}H_{18}OS_2$ (266): C, 63.16; H, 6.77%).

3-Methylthio-2-methylthiomethyl-1-(p-methoxyphenyl)-2-propen-1-one (31c) was obtained as orange solid, mp 57-58° (hexane), yield 1.3 g (45%) (70% on the basis of recovered starting material);

M^+ 268; (Found: C, 58.63; H, 5.56; Calc. for $C_{13}H_{16}O_2S_2$ (268): C, 58.21; H, 5.97%).

3-Ethylthio-2-ethylthiomethyl-1-(p-methoxyphenyl)-2-propen-1-one (31d) was obtained as orange viscous oil, (TLC single spot); yield 1.2 g (40%) (61% on the basis of recovered starting material); M^+ 296; (Found: C, 60.48; H, 6.37; Calc. for $C_{15}H_{20}O_2S_2$ (296): C, 60.81; H, 6.76%).

3-Methylthio-2-methylthiomethyl-1-(p-methylphenyl)-2-propen-1-one (31e) was obtained as red viscous oil, (TLC single spot); yield 1.0 g (36%) (60% on the basis of recovered starting material); M^+ 252 (Found: C, 61.53; H, 6.71: Calc. for $C_{13}H_{16}OS_2$ (252): C, 61.90; H, 6.35%).

3-Isopropylthio-2-isopropylthiomethyl-1-phenyl-2-propen-1-one (31f) was obtained as light yellow prisms, mp 46-47° (hexane); yield 0.9 g (30%) (45% on the basis of recovered starting material); M^+ 294 (Found: C, 65.67; H, 7.86; Calc. for $C_{16}H_{22}OS_2$ (294): C, 65.31; H, 7.48).

In an another experiment when 12a (1.2 g, 0.005 mol) was treated with sodium hydride (0.02 mol)

in dimethylformamide (20 ml) under identical reaction conditions for longer time (12 hr), the reaction mixture after work-up and purification as described above yielded only 120 mg (10%)of 31a (superimposable IR and NMR) along with intractable polymeric material while starting material 12a was consumed completely.

In an alternate experiment, when a solution of 12a (1.2 g, 0.005 mol) in dimethylformamide (20 ml) was treated with sodium hydride (0.02 mol) at lower temperature (0-5^{o}) for 6 hr, the reaction mixture, after work-up and purification as described in the above general procedure yielded unreacted starting material 12a (superimposable IR and NMR).

Similarly, when 12a (1.2 g, 0.005 mol) was treated with catalytic amount of sodium hydride (0.1 g, 50% suspension) under identical reaction conditions for 6 hr, the reaction mixture after work-up and purification as described above yielded 0.25 g (10%) of 31a (superimposable IR and NMR). In an another experiment, when the same reaction under identical conditions was continued for 15 hr with catalytic amount of sodium hydride,

work-up and purification of the reaction mixture as above yielded 0.6 g (25%) of 31a (superimposable IR & NMR).

The reaction of 12a (1.2 g, 0.005 mol) with excess of NaH (0.04 mol) under identical reaction conditions yielded after the usual work-up and purification 0.35 g (30%) of 31a (superimposable IR and NMR).

Similarly in an attempt to increase the yield of 31a, when 12a (2.38 g, 0.01 mol) was treated under identical conditions with sodium hydride (0.04 mol) in dimethylformamide (30 ml) under nitrogen atmosphere, the reaction mixture after usual work-up and purification yielded 0.4 g (35%) of 31a (superimposable IR and NMR) and there was no increase in the yield of 31a.

Attempted rearrangement of 12a to 31a in benzene:

A solution of 12a (1.2 g, 0.005 mol) in 5 ml of benzene was added to a stirred suspension of sodium hydride in 20 ml of dry benzene at 80-90° and the reaction mixture was refluxed with stirring for 10 hr. The reaction mixture after usual work-up and purification

yielded the unreacted starting material 12a (superimposable IR and NMR) and no trace of 31a was formed (TLC).

Rearrangement of 12a to 31a in tetrahedrofuran:

To a stirred suspension of sodium hydride (0.02 mol) in 25 ml of dry tetrahydrofuran at 50-60°, a solution of 12a (1.2 g, 0.005 mol) in 5 ml of dry tetrahedrofuran was added and the reaction mixture was refluxed with stirring for 3 hr. The reaction mixture after the usual work-up and purification yielded only 60 mg (5%) of 31a (superimposable IR and NMR) along with 0.9 g of unreacted starting material, 12a (superimposable IR and NMR).

In an another experiment when the same reaction mixture in tetrahydrofuran was refluxed at 65-70° for 12 hr, the reaction mixture after usual work-up and purification yielded 0.35 g (30%) of 31a (superimposable IR and NMR) along with 0.4 g of unreacted starting material 12a (superimposable IR and NMR).

Reaction of 12a with sodium hydride in the presence of hydroquinone:

A mixture of hydroquinone (0.1 g, 0.001 mol) and 12a (1.2 g, 0.005 mol) in 10 ml dry dimethylformamide was slowly added to a suspension of sodium hydride (1.5 g, 50% suspension, 0.03 mol) in 15 ml of dry dimethylformamide at 50-60° and under nitrogen atmosphere, with stirring. The reaction mixture was stirred for further 3 hr. The reaction mixture after work-up and purification described in the general procedure yielded 0.4 g (33%) of 31a (superimposable IR and NMR).

Reaction of 12a with sodium hydride in the presence of dibenzoyl peroxide:

A mixture of 12a (1.2 g, 0.005 mol) and dibenzoyl peroxide (100 mg) in 5 ml of dry dimethylformamide was added slowly (15 min) to a well stirred suspension of sodium hydride (1 g, 50% suspension, 0.02 mol) in 15 ml of dry dimethylformamide at 50-60° and the stirring continued for further 3 hr. The

reaction mixture after work-up and purification as described in the earlier experiments, yielded 0.43 g (36%) of 31a (superimposable IR and NMR).

Attempted equilibriation of 31a to 12a:

A solution of 31a (0.6 g, 0.0025 mol) in 5 ml dry dimethylformamide was added to a suspension of sodium hydride (0.01 mol, 50% suspension) in 5 ml of dry dimethylformamide and the reaction mixture was stirred at 50-60° for 4 hr. The reaction mixture after the usual work-up gave a crude residue, from which no identifeable compound could be isolated and no trace of 12a was detected (TLC).

Reaction of 3,3-bis(methylthio)-2-methyl-1-(p-chloro-phenyl)-2-propen-1-one (12g) with sodium hydride:

To a well stirred suspension of sodium hydride (0.04 mol, 50% suspension) in 20 ml dry dimethylformamide at 50-60°, a solution of 12g (2.73 g, 0.01 mol) in 15 ml of dry dimethylformamide was added slowly with stirring and the reaction mixture was stirred at 50-60°

for 5 hr. The reaction mixture after work-up as described above gave red viscous liquid, which was purified by column chromatography over silica gel. Elution with hexane:ethylacetate (95:5) yielded 0.7 g (25%) of 3,3-bis(methylthio)-2-methyl-1-(p-methylthiophenyl)-2-propen-1-one (32) as red viscous liquid; (TLC single spot); M^+ 284 (Found: C, 55.15; H, 5.67; Calc. for $C_{13}H_{16}OS_3$ (284): C, 54.93; H, 5.63%). The spectral data for 32 is described in text.

Further elution with ethylacetate:hexane (1:9) yielded 0.6 g (22%) of 3-methylthio-2-methylthiomethyl-1-(p-chlorophenyl)-2-propen-1-one (31g) as red viscous oil; (TLC single spot); M^+ 272.5 (Found: C, 52.48; H, 4.93; Calc. for $C_{12}H_{13}ClOS_2$ (272.5): C, 52.84; H, 4.77%). The spectral data for 31g is described in table 1.

Subsequent elution with ethylacetate:hexane (1:4) yielded 0.55 g (20%) of 3-methylthio-2-methylthiomethyl-1-(p-methylthiophenyl)-2-propen-1-one (33) as red viscous liquid (TLC single spot); M^+ 284 (Found: C, 54.67; H, 5.38; Calc. for $C_{13}H_{16}OS_3$ (284): C, 54.93; H, 5.63%). The spectral data for 33 is described in the text.

Reaction of 3,3-bis(benzylthio)-2-methyl-1-phenyl-2-propen-1-one (12h) with sodium hydride; Formation of 2-benzylthio-3-methyl-4,5-diphenylthiophene (36):

A solution of 12h (1.95 g, 0.005 mol) in 10 ml of dry dimethylformamide was added dropwise to a well stirred suspension of sodium hydride (0.02 mol, 50% suspension) in 15 ml of dry dimethylformamide at 50-60° and the reaction mixture was stirred at 50-60° for 6 hr. The reaction mixture after usual work-up, followed by chromatographic purification over ailica gel column using hexane as eluent yielded 0.95 g (50%) of 36 as white needles, mp 91-92° (hexane); M^+ 372 (Found: C, 77.83; H, 5.71; Calc. for $C_{24}H_{20}S_2$ (372): C, 77.42; H, 5.38%). The spectral data of 36 is described in the text.

Reaction of 12b and 12c with sodium hydride; A 'crossover' experiment:

A mixture of 12b (2.66 g, 0.01 mol) and 12c (2.68 g, 0.01 mol) in 25 ml of dry dimethylformamide was added dropwise to a well stirred suspension of sodium hydride (0.08 mol, 50% suspension) in 40 ml of dry

dimethylformamide at 50-55° and the reaction mixture was stirred at 50-55° for 3 hr. The reaction mixture after usual work-up gave red viscous liquid, which was purified by column chromatography over silica gel. Elution with hexane:ethylacetate (95:5) gave a mixture of unreacted starting materials 12b and 12c (IR and NMR). Further elution with the same solvent mixture yielded a mixture (TLC single spot) of four possible products, 31a, 31b, 57 and 58 (NMR and Mass). Thus its NMR (CCl_4) spectrum displayed signals due to above mentioned four products. The mass spectrum of this mixture gave the following significant peaks: m/e 266 (95%), 252 (100%), 238 (100%) 223 (85%), 205 (90%), 191 (95%), 175 (90%), 105 (100%) etc. The peaks at m/e 266, 252 and 238 are the molecular ion peaks of 31b, (57 or 58), and 31a, thus proving the presence of the corssover products (particularly 57 and/or 58) in the mixture.

Further elution with ethylacetate:hexane (1:4) mixture, gave an orange oil, (TLC single spot), which also in its NMR spectrum displayed signals due to four possible products, 31c, 31d, 59 and 60. Its mass spectrum displayed the following significant peaks: m/e 296 (10.3%), 282 (40.5%), 268 (70%), 253 (20%), 235 (50%), 221 (80%), 135 (100%) etc. The peaks at m/e 296, 282 and 268 are

the molecular ion peaks of 31d, (59 and/or 60) and 31c, thus proving the presence of the crossover products (particularly 59 and/or 60) in the mixture.

Reaction of 31c with sodium hydride in the presence of ethylmercaptan:

A solution of ethyl mercaptan (0.6 g, 0.01 mol) in 2 ml of dimethylformamide was added slowly to a well stirred suspension of sodium hydride (1g, 50% suspension, 0.02 mol) in dry dimethylformamide (10 ml) under nitrogen blanket at room temperature. A solution of 31c (0.8 g, 0.003 mol) in dry dimethylformamide (3 ml) was added slowly to the reaction mixture with stirring and the reaction temperature was raised upto 50° and the stirring continued at this temperature and under nitrogen blanket for further 30 minutes. After the usual work up, the crude product showed single spot (major) on TLC and it was purified by passing through silica gel column using ethylacetate; hexane (1:4) mixture as eluent. The pure orange oil (TLC single spot) thus obtained was also a mixture of four possible products, 31c, 31d, 59 and 60 (NMR and Mass).

Reaction of 12b with sodium hydride in the presence of ethylmercaptan (added alkylthio anion):

A mixture of ethylmercaptan (1.2 g, 0.02 mol) and 12b (2.66 g, 0.01 mol) in 15 ml of dry dimethylformamide was reacted with sodium hydride identical conditions as described in the preceding experiment for 2 hr. The reaction mixture after usual work-up followed by column chromatographic purification over silica gel gave 1.2 g (45%) of 31b (superimposable IR and NMR) along with 0.8 g (30%) of 12b (superimposable IR and NMR).

Attempted rearrangement of 12i to 62:

When 12i (2.52 g, 0.01 mol) was treated with sodium hydride (0.04 mol, 50% suspension) in dry dimethylformamide (30 ml) under identical reaction conditions for 10 hr, the reaction mixture after usual work-up followed by column chromatographic purification yielded 2.30 g (90%) of unreacted starting material, 12i (superimposable IR and NMR).

Rearrangement studies on 3,3-bis(methylthio)-2-benzyl-1-phenyl-2-propen-1-one (64); Reaction of 64 with sodium hydride:

A solution of 64 (3.14 g, 0.01 mol) in dry dimethylformamide (10 ml) was added to a stirred suspension of sodium hydride (0.03 mol) in 20 ml of dry dimethylformamide at 35-40° and the reaction mixture was stirred at this temperature for 2 hr. The reaction mixture after usual work-up as described in the earlier experiments yielded 2.7 g (85%) of red viscous liquid. The crude reaction mixture thus obtained showed 5 spots on TLC, which were separated by column chromatography over silica gel. Elution with hexane:ethylacetate (99:1) gave first 160 mg (5%) of 64 (superimposable IR, NMR and mmp)

Further elution with hexane:ethylacetate (95:5) gave 1.1 g (35%) of 3-methylthio-2-methylthiomethylchalcone (65) as red viscous oil; (TLC single spot); M^+ 314 (Found: C, 68.43; H, 5.47; Calc. for $C_{18}H_{18}OS_2$ (314): C, 68.79; H, 5.73%). The spectral data for 65 is described in the text.

Further elution with ethylacetate:hexane (5:95) gave 0.5 g (15%) of 2-(α-methylthiobenzyl)-3-methylthio-acrylophenone (66) as red viscous oil, (TLC single spot); M^+ 314 (Found: C, 68.53; H, 5.47, Calc. for $C_{18}H_{18}OS_2$ (314): C, 68.79; H, 5.73%). The spectral data for 66 is described in the text.

Subsequent elution with ethylacetate:hexane (1:9) gave 130 mg (5%) of 3-methylthiochalcone (68) as light yellow solid, mp 94-95° (hexane): M^+ 254 (Found: C, 75.93; H, 5.87; Calc for $C_{16}H_{14}OS$ (254): C, 75.59; H, 5.51%). The spectral data for 68 is described in the text.

Further elution with ethylacetate:hexane (1:4) gave 0.45 g (20%) of 3,3-bis(methylthio)-1-phenyl-2-propen-1-one (67) as light yellow solid, (mp, mmp, superimposable IR, NMR and Mass).

In an alternate experiment, 6 (1.6 g, 0.05 mol) was reacted with sodium hydride (0.015 mol) in dry dimethylformamide (20 ml) under identical reaction conditions for 8 hr. The reaction mixture was then poured over crushed ice, acidified with 20% acetic acid,

extracted with chloroform (2 x 50 ml) and washed the combined extract with water (4 x 50 ml). The organic layer thus obtained was washed with saturated sodium bicarbonate solution (2 x 50 ml) and then with water (2 x 50 ml). The chloroform layer was then dried (Na_2SO_4), concentrated and purified by column chromatography over silica gel using ethylacetate:hexane (1:4) as eluent to give first 130 mg (10%) of 68 (superimposable IR, NMR and mmp) and 0.8 g (70%) of 67 (superimposable IR, NMR and mmp).

Acidification of the sodium bicarbonate extract with dilute hydrochloric acid gave a solid suspension, which was extracted with ether. Evaporation of the ether gave 0.12 g (20%) of benzoic acid (mmp, superimposable IR and NMR)

Similarly, when 64 (1.6g, 0.05 mol) was treated with sodium hydride (0.015 mol) in dry dimethylformamide under identical reaction conditions and under nitrogen atmosphere for 3 hr, the reaction mixture after usual work-up followed by chromatographic purification yielded 0.8 g (51%) of 65 (superimposable IR and NMR) and 0.5 g

(32%) of 66 (superimposable IR and NMR) on elution with hexane.

3,5-Diphenyl-4-methylthiomethylpyrazole (69); Procedure:

A solution of 65 (1.6 g, 0.005 mol) and hydrazine hydrate (0.5 ml) in ethanol (15 ml) was refluxed for 60 hr. cooling of the reaction mixture yielded white solid, which was recrystallized from ethanol. Yield of the pyrazole 69 was 0.8 g (57%); mp 171-173°; IR (Nujol): 3200 cm^{-1} (ν_{NH}); NMR ($CDCl_3$): 1.65 (s, 3H, $CH_2SC\underline{H}_3$); 3.35 (s, 2H, $C\underline{H}_2SCH_3$); 6.70-7.50 (m, $10H_{arom}$); M^+ 280; (Found: C, 72.47; H, 5.34; N, 10.23; Calc. for $C_{17}H_{16}N_2S$ (280): C, 72.86; H, 5.71; N, 10.00%).

Reaction of 3,3-bis(methylthio)-2-benzoyl-1-phenyl-2-propen-1-one (74) with sodium hydride:

A solution of 74 (1.64g, 0.005 mol) in dry dimethylformamide (5 ml) was added slowly (10 min) to a well stirred suspension of sodium hydride (1 g, 50% suspension, 0.02 mol) in 15 ml of dry dimethylformamide at 35-40° with stirring and stirring continued for

further 6 hr, when TLC showed complete disappearance of starting material with only one major product. The reaction mixture was poured over crushed ice, acidified with 20% acetic acid, extracted with chloroform (3 x 30 ml) and washed the combined extract with water (4x 50 ml). The organic layer thusobtained was washed with saturated sodium bicarbonate solution (2 x 50 ml) and then with water (2 x 50 ml). The chloroform layer was then dried (Na_2SO_4), concentrated and purified by column chromatography over silica gel using ethylacetate:hexane (1:4) mixture as eluent to give 0.9 g (80%) of 67 (mp, mmp; superimposable IR, NMR and Mass).

Acidification of the sodium bicarbonate extract with dil. hydrochloric acid, gave a solid suspension, which was extracted with ether. Evaporation of the ether gave 0.25 g (40%) of white solid, mp 120-121°, which was identified as benzoic acid. (mmp, superimposable IR, NMR and Mass).

Reaction of 3,3-bis(methylthio)-2-benzyl-1-(p-methylphenyl)-2-propen-1-one (76) with sodium hydride:

A solution of 76 (1.64 g, 0.005 mol) in dry dimethylformamide was treated with sodium hydride (0.15 mol)

for 9 hr under identical conditions as described for 64. The organic extract obtained, after usual work-up as described in the preceding experiments, was washed with saturated sodium bicarbonate solution (2 x 50 ml). The bicarbonate extract, after acidification with dilute hydrochloric acid, gave a white solid suspension, which was extracted with ether (3 x 25 ml). Evaporation of the ether gave 0.3 g of white solid, which was confirmed as a mixture of benzoic acid and p-toluic acid by NMR, IR and melting points. Thus a part of the solid melted at 119-120° (reported mp of pure benzoic acid is 122.4°C) and the remaining part of it melted at 176-178° (pure p-toluic acid melts at 179-180°).

The organic layer, after bicarbonate washing, was washed with water (1 x 50 ml), dried (Na_2SO_4) and concentrated to give crude product, which, after purification by column chromatography over silica gel using ethylacetate:hexane (1:4) mixture as eluent, gave 0.8 g of yellow solid, The solid thus obtained was identified as a mixture of 3,3-bis(methylthio)-1-phenyl-2-propen-1-one (67) and 3,3-bis(methylthio)-1-(p-methylphenyl)-2-propen-1-one (78) (NMR and Mass). Thus, a part of it melted at 89-90°

(reported mp of pure 67 is 93°)[45] and the remaining part of it melted at 99-101° (reported mp of pure 78 is 104-5°)[45] (The R_f values of 67 and 78 are almost same).

Rearrangement studies on 2- bis(methylthio)methylene - 1-indanone (82): Reaction of 82 with sodium hydride:

When 82 (1.2 g, 0.005 mol) was treated with sodium hydride (0.02 mol, 50% suspension) in dry dimethylformamide under nitrogen atmosphere and under standard rearrangement conditions for 1.5 hr, the reaction mixture after the usual work-up yielded red viscous liquid, which was purified by preparative TLC over silica gel plate using ethylacetate as mobile phase to give 0.4 g (45%) of 87 as orange solid, mp 194-195°. Its analytical and spectral data are described in the text.

In an alternate experiment, when 82 (1.2 g, 0.005 mol) was reacted with sodium hydride (0.02 mol) under identical reaction conditions but without nitrogen atmosphere for 1.5 hr, the reaction mixture after work-up as described above yielded a black tar, from which no identifiable sample could be isolated.

Rearrangement studies on 2- bis(methylthio)methylene - 1-tetralone (91); Reaction of 91 with sodium hydride:

To a stirred suspension of sodium hydride (0.04 mol) in 20 ml dry dimethylformamide at 50-60°, a solution of 91 (2.5g, 0.01 mol) in 10 ml dry dimethylformamide was added and the reaction mixture was stirred at 50-60° for 30 hr. Work-up of the reaction mixture as described in the above experiments gave bright yellow viscous liquid which was purified by column chromatography over silicagel. Elution with hexane gave 1.2 g (51%) of β-ketodithioester 93 as bright yellow solid, mp 77-78°. (reported melting point of 93 is 78-79°)[29]. The analytical and spectral data of 93 are described in the text.

Further elution with hexane yielded 0.45 g (20%) of S-methyl-2-tetralone carboxylthioate (94) as light yellow prisms, mp 63-64°C; M^+ 220 (Found: C, 65.73; H, 5.78- Calc. for $C_{12}H_{12}O_2S$ (220): C, 65.45; H, 5.45%). The spectral data of 94 is described in the text.

In an alternate experiment, when 91 (1.25 g, 0.005 mol) was treated with sodium hydride (0.02 mol) in 15 ml dry dimethylformamide under nitrogen atmosphere and

under identical reaction conditions for 30 hr, the reaction mixture after usual work-up, followed by purification as above, yielded 0.85 g (54%) of 93 (superimposable IR and NMR) and 0.65 g (30%) of 94 (superimposable IR and NMR).

Reaction of β-ketodithioester 93 with sodium hydride:

A solution of 93 (0.47 g, 0.002 mol) in 5 ml dry dimethylformamide was added to asuspension of sodium hydride (0.01 mol) in 10 ml of dry dimethylformamide at 50-60° and the reaction mixture was stirred at 50-60° for 25 hr. The reaction mixture after usual work-up followed by purification yielded the unchanged 93 (mmp superimposable IR and NMR) and the formation of 94 was not observed.

Reaction of 3,3-(bismethylthio)-1-phenyl-2-propen-1-one(97) with sodium hydride:

When 97 (1.12 g, 0.005 mol) was treated with sodium hydride (0.02 mol) under identical reaction conditionsfor 26 hr, the work-up of the reaction as usual followed by purification by column chromatography

gave 1.0 g (90%) of unchanged 97 (superimposable IR and NMR) and the formation of 98 or 99 was not observed.

Rearrangement studies on 3- bis(methylthio)methylene - 2,3-dihydro-1-benzothiopyran-4-one (107) with sodium hydride:

(a) In dimethylformamide:

A solution of 107 (2.68 g, 0.01 mol) in 10 ml dry dimethylformamide was added to a suspension of sodium hydride (0.02 mol) in 20 ml of dry dimethylformamide at room temperature and the reaction mixture was stirred at room temperature for 5 hr. The reaction mixture after usual work-up followed by purification by recrystallization from ethylacetate:hexane (1:9) yielded 1.6 g (60%) of 110 as light yellow needles; mp 109°; M^+ 268 (Found: C, 53.57; H, 4.27; Calc. for $C_{12}H_{12}S_3O$ (268): C, 53.73; H, 4.48%). The spectral data of 110, which is in conformity with the assigned structure is described in table.

(b) In benzene:

When 107 (1.34 g, 0.005 mol) was stirred similarly with sodium hydride (0.01 mol) in solvent benzene

at room temperature for 5 hr, the reaction mixture after usual work-up followed by purification gave the unchanged starting material 107 (superimposable IR and NMR) and the formation of 110 was not observed.

However, when the same reaction was carried out in refluxing benzene for 5 hr, the reaction mixture after usual work-up followed by purification by recrystallization yielded 0.7 g (50%) of expected rearranged product 110 (superimposable IR and NMR).

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CHAPTER II

STUDIES ON THE REACTIONS OF 3-ALKYLTHIO-2-ALKYLTHIOMETHYLACRYLOPHENONES WITH HYDRAZINE, GUANIDINE AND AMINES : SYNTHESIS OF NOVEL PYRAZOLES, PYRIMIDINES AND ENAMINOKETONES*

In the preceding chapter, optimum conditions for the preparation of 3-alkylthio-2-alkylthiomethyl-acrylophenones of the general formula (1) (Scheme 1) have been described[1]. The mechanism governing the formation of 1 has also been discussed. It was considered to utilize these intermediates for the synthesis of some heterocyclic compounds by reacting them with appropriate binucleophiles. Thus when 1a was reacted with hydrazine in refluxing ethanol the corresponding pyrazole 2a was obtained in 85% yield. The structure of 2a was confirmed by its analytical and spectral data. Thus 2a exhibited in its mass spectrum molecular ion peak at M^+ 204 ($C_{11}H_{12}N_2S$). Its IR(neat) spectrum showed absorption band at 3165 cm^{-1} due to NH stretching frequency. The final structural proof

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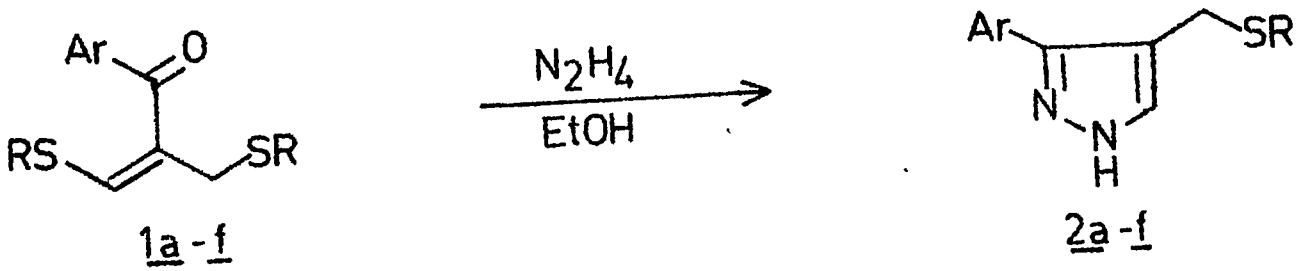
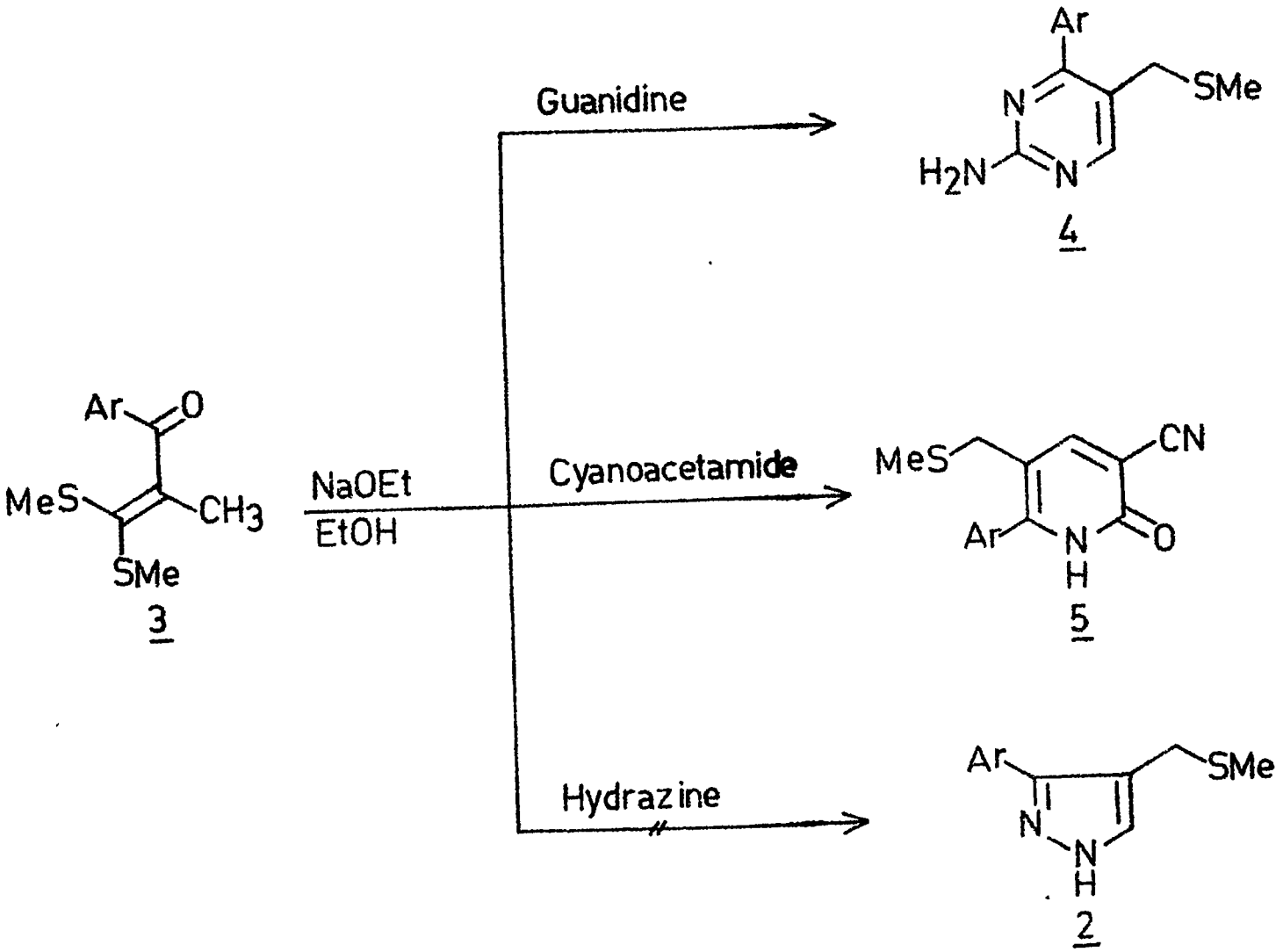
for 2a was derived from its ^{1}H-N.M.R ($CDCl_3$) spectrum. It showed signal at δ 1.94 (s, 3H) for SCH_3 protons, while the signal at δ 3.53 (s, 2H) was assigned to the methylene protons. The multiplet at δ 7.20-7.60 (6H) was accounting for five aromatic protons and H-5 of pyrazole ring. A broad signal appeared at δ 11.80 was assigned to the NH proton, which disappeared on D_2O exchange. The pyrazoles 2b-f (Scheme 1) were similarly obtained in 70-90% over all yields. The physical and spectral data for 2b-f are described in tables 4 and 1, respectively. It is interesting to note that the formation of pyrazole 2 was not observed when the keten dithioacetal 3 (Scheme 2) was reacted with hydrazine in refluxing ethanolic sodium ethoxide, while the similar reactions with guanidine and cyanoacetamide yielded the corresponding pyrimidines (4)[2] and pyridones (5)[3] respectively. (Scheme 2). Similarly, when 1 reacted with guanidine in the presence of sodium ethoxide in refluxing ethanol, pyrimidine 4a was obtained in 70% yield. The 4a thus obtained was identical (m.m.p, IR, ^{1}H-NMR) with the compound obtained directly from 3 and guanidine. The pyrimidines 4b and 4c were similarly



1a-f 2a-f

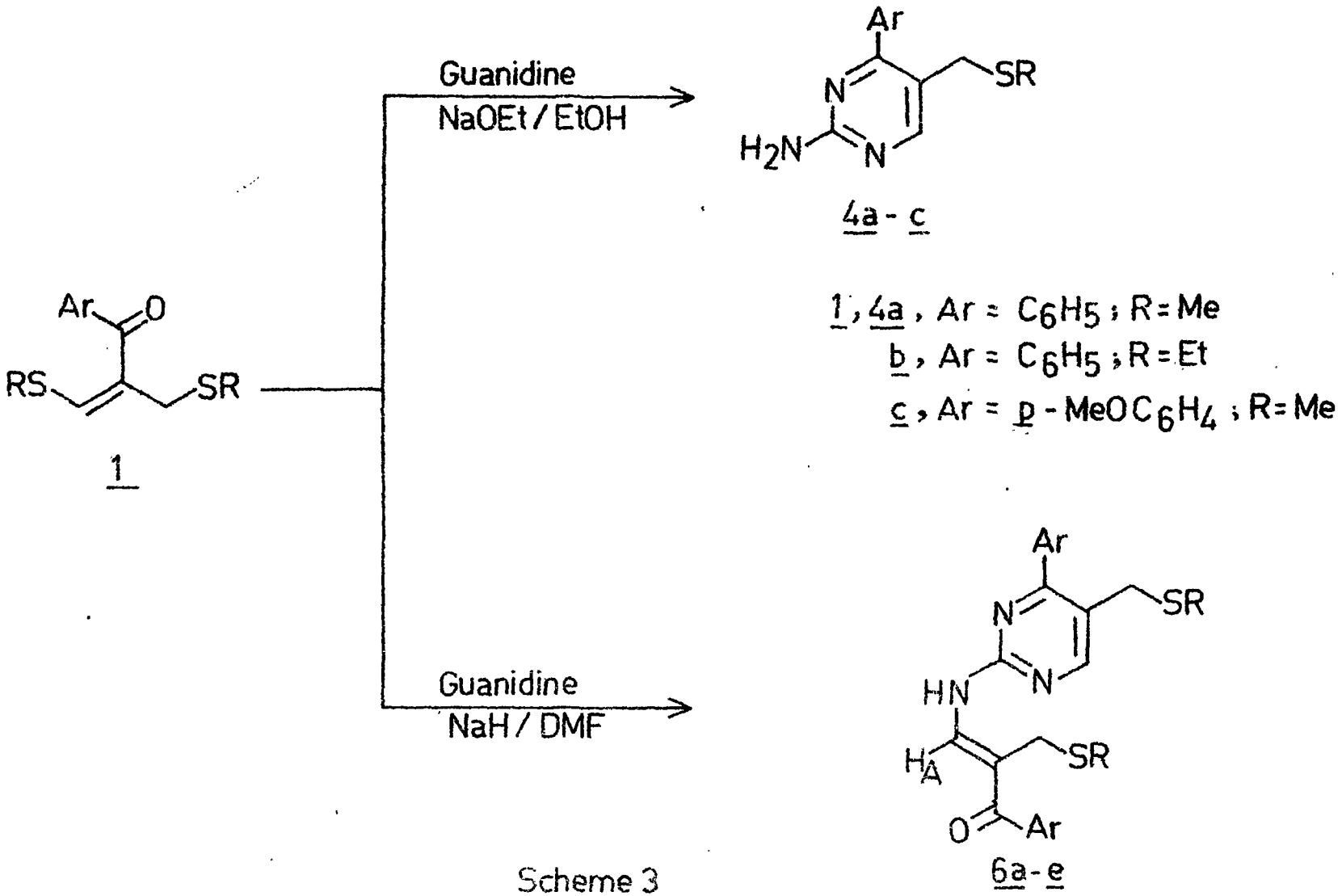
1, 2a, Ar = C_6H_5, R=Me
b, Ar = C_6H_5; R=Et
c, Ar = p-$MeOC_6H_4$; R=Me
d, Ar = p-$MeOC_6H_4$; R=Et
e, Ar = p-MeC_6H_4; R=Me
f, Ar = p-Cl C_6H_4; R=Me

Scheme 1


Ar
O
MeS
CH3
SMe
3
NaOEt
EtOH
Guanidine
Cyanoacetamide
Hydrazine
Ar
N
SMe
H2N
N
4
MeS
CN
Ar
N
H
O
5
Ar
SMe
N
N
H
2

Scheme **2**

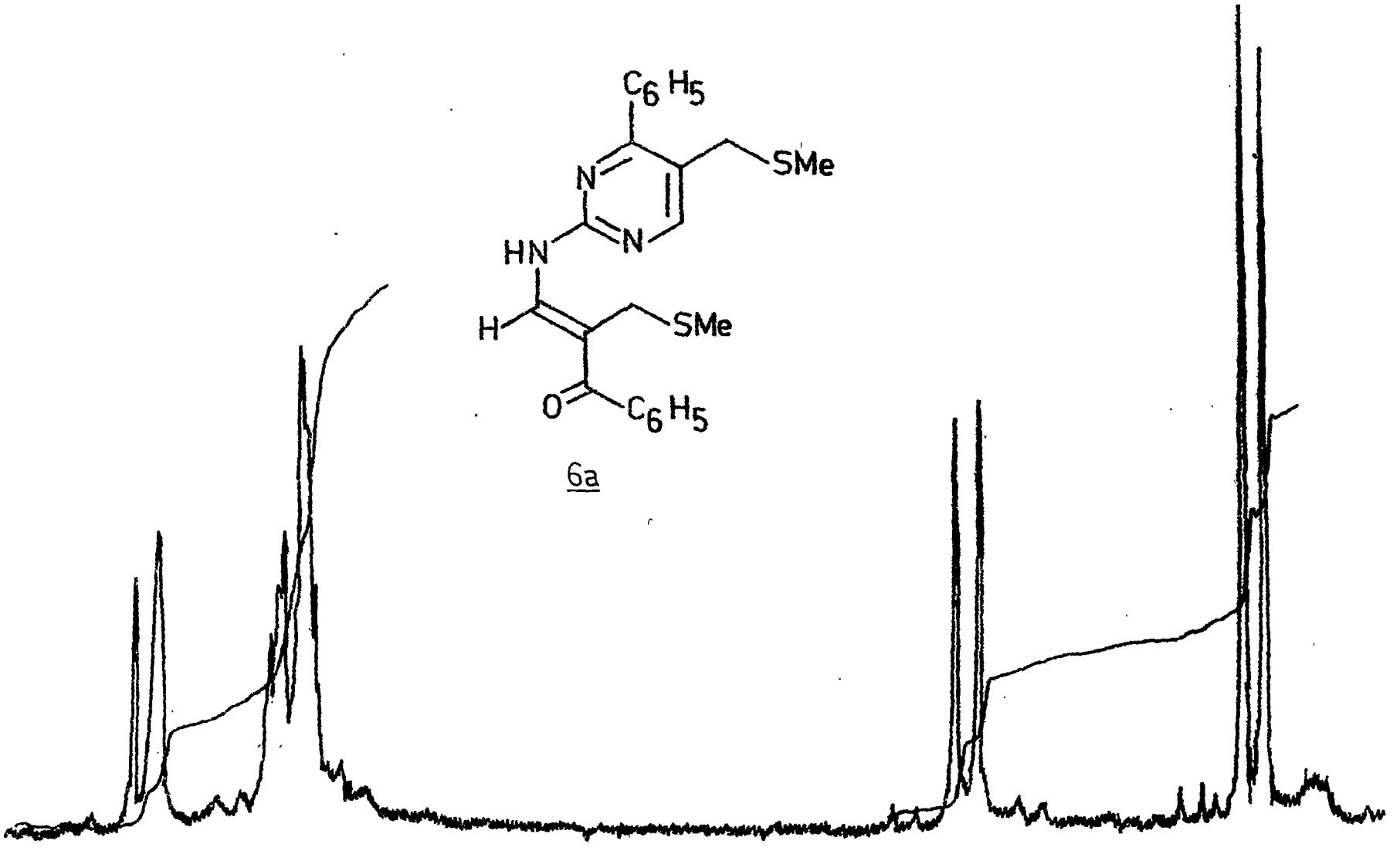
obtained from the corresponding 1b and 1c in 70% and 75% yield respectively. Apparently, the yields of 4 from 1 are higher than that of 4 from 3. However, when the reaction of 1a with guanidine was carried out in the presence of sodium hydride in dimethylformamide, the product obtained after chromatographic separation was identified as 6a (Scheme 3). The structural evidence for 6a was derived from its analytical and spectral data. Thus, its mass spectrum exhibited molecular ion peak at M^+421 ($C_{23}H_{23}N_3OS_2$). Its IR (Nujol) spectrum displayed a band at 1640 cm^{-1}, which is also the region for NH_2 deformation. Short and Thompson[4] and Brown et al[5] have assigned this band to H-N-H internal deformation on the basis of their deuteration experiments. However, this band is known to shift in chloroform to a lower value of 1600 cm^{-1}. In the present case, when the spectra was recorded in chloroform, it was observed in the same position i.e. at 1640 cm^{-1}. Therefore the 1640 cm^{-1} band is assigned to the carbonyl function. This observation proves that side chain is attached to the 2-amino group of the pyrimidine (6). Further proof for the structure 6a was confirmed by its NMR spectrum (Figure).


Guanidine
NaOEt / EtOH
Ar
SR
N
H_2N
N
4a - c
Ar
O
RS
SR
1
1, 4a, Ar = C_6H_5 ; R = Me
b, Ar = C_6H_5 ; R = Et
c, Ar = p - $MeOC_6H_4$; R = Me
Guanidine
NaH / DMF
Ar
N
SR
HN
N
H_A
SR
O
Ar
6a - e

Scheme 3

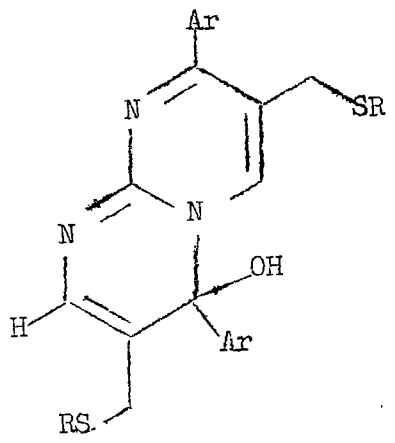
It showed two singlets at δ 2.00 (3H) and δ 2.15 (3H) due to two SCH_3 groups. The two singlets at δ 3.60 (2H) and δ 3.73 (2H) were assigned to protons on two methylene groups. The aromatic protons appeared as broad multiplet between δ 7.30-7.65 accounting for ten protons. The vinyl proton on the exocyclic chain and NH proton appeared together as broad singlet at δ 8.30 and after D_2O shaking the sharp singlet was integrated for only one proton. The low field singlet at δ 8.43 was assigned to H-6 on pyrimidine ring.

The possibility of bicyclic alcohol structure (A) or the dipolar structure (B) for 6a were ruled out on the basis of spectral data. Its ^{1}H-N.M.R spectrum showed no signal due to OH proton, which rules out the structure A. The dipolar structure B was ruled out on the basis of its IR band at 1640 cm^{-1}, which is assigned to the carbonyl function. The further structural proof of 6a was derived from its independent preparation from 1 and 4. Thus when 1 and 4 were treated in the presence of sodium hydride and dimethylformamide, 6a was obtained in 70% yield. Attempts to isolate the intermediate pyrimidine, (4), when 1 and guanidine were reacted in the

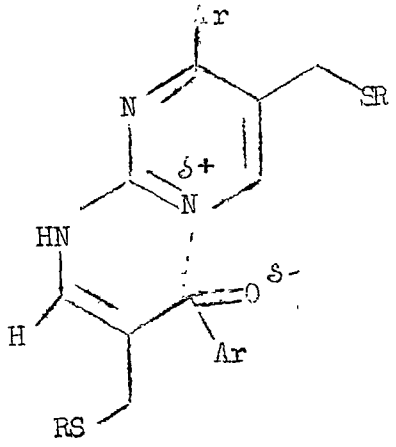


6a

Figure



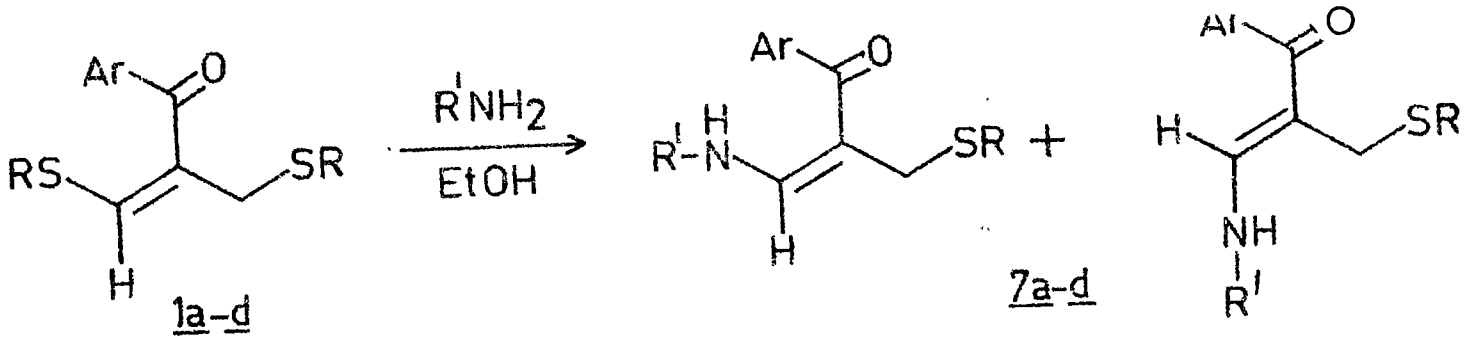
A



B

presence of NaH and dimethylformammide, were not successful. The other pyrimidines, 6b-e were similarly obtained in 56-65% over all yields (Scheme 3). The physical and spectral data of 6b-e are described in tables 5 and 2 respectively.

Incidentally, when 1 was reacted with aliphatic amines, the corresponding enaminoketones (7) were obtained in excellent yields. Thus 1a and methylamine in refluxing ethanol yielded the corresponding enaminoketone 7a in 80% yield. The enaminoketones 7b-d were



1, 7a, Ar = p-MeC_6H_4; R = Me; R' = Me

b, Ar = p-MeC_6H_4; R = Me; R' = C_6H_{11}

c, Ar = p-$MeOC_6H_4$; R = Me; R' = Me

d, Ar = p-$MeOC_6H_4$; R = Me; R' = C_6H_{11}

Scheme 4

similarly obtained from the respective amines in 75-80% overall yields (Scheme 4). The spectral and analytical data for 7a-d, which are in agreement with the assigned structures, are described in tables 3 and 6 respectively. However, 1 failed to react with aromatic amines under similar reaction conditions or at higher temperature.

Table 1

Spectral data for products 2a-f

Product	M.S. m/e (M^+)	IR (neat) ν [cm^{-1}]	^{1}H-NMR (CCl_4) δ [ppm]
2a	204	3165 (NH)	1.94 (s, 3H, CH_2SCH_3); 3.53 (s, 2H, CH_2SCH_3); 7.20-7.60 (m, $5H_{arom}$+ H-5); 11.80 (brs, 1H, NH)
2b	218	3160 (NH)	1.20 (t, 3H, SCH_2CH_3); 2.45 (q, 2H, SCH_2CH_3); 3.65 (s, 2H, $CH_2SCH_2CH_3$); 7.30-7.75 (m, $5H_{arom}$+ H-5); 11.70 brs, 1H, NH)
2c	238.5	3150 (NH)[a]	1.98 (s, 3H, SCH_3); 3.50 (s, 2H, CH_2SCH_3); 7.20-7.50 (m, 5H, $4H_{arom}$+ H-5); 12.30 (brs, 1H, NH)

Table 1 (Contd.)

2d	218	3150 (NH)	1.95 (s, 3H, $SC\underline{H}_3$); 2.34 (s, 3H, $C\underline{H}_3$); 3.55 (s, 2H, $C\underline{H}_2SCH_3$); 7.03-7.50 (dd, $4H_{arom}$+ H-5); 11.60 (brs, 1H, NH)
2e	234	3150 (NH)[a]	1.95 (s, 3H, $CH_2SC\underline{H}_3$); 3.52 (s, 2H, $C\underline{H}_2SCH_3$); 3.70 (s, 3H, $OC\underline{H}_3$); 6.75 (d, $2H_{arom}$); 7.20 (s, 1H, H-5); 7.42 (d, $2H_{arom}$); 11.20 (brs, 1H, NH)
2f	248	3150 (NH)[a]	1.20 (t, 3H, $SCH_2C\underline{H}_3$); 2.45 (q, 2H, $SC\underline{H}_2CH_3$); 3.60 (s, 2H, $C\underline{H}_2SCH_2CH_3$); 3.80 (s, 3H, $OC\underline{H}_3$); 6.70 (d, $2H_{arom}$); 7.40 (s, 1H, H-5); 7.50 (d, $2H_{arom}$); 11.70 (brs, 1H, N$\underline{H}$)

[a] Nujol mull

Table 2

Spectral data for products 6a-f

Product	M.S. m/e (M^+)	IR (Nujol) ν [cm^{-1}]	^{1}H-NMR ($CDCl_3$) δ [ppm]
6a	421	1640; 1610; 1575 1550; 1460[a]	2.00 (s, 3H, $SC\underline{H}_3$); 2.15 (s, 3H, $SC\underline{H}_3$); 3.60 (s, 2H, $C\underline{H}_2SCH_3$) 3.73 (s, 2H, $C\underline{H}_2SCH_3$); 7.30-7.65 (m, $10H_{arom}$); 8.30 (brs, 2H, $\underline{H}_A$+N$\underline{H}$, exchangeable with D_2O); 8.43 (s, 1H, H-6)

Table 2 (Contd.)

6b	449	1638; 1605; 1580 1550; 1458[a]	1.17 (t, 3H, $SCH_2\underline{CH}_3$); 1.30 (t, 3H, $SCH_2\underline{CH}_3$); 2.43 (q, 2H, $S\underline{CH}_2CH_3$); 2.57 (q, 2H, $S\underline{CH}_2CH_3$); 3.63 (s, 2H, $\underline{CH}_2SCH_2CH_3$); 3.77 (s, 2H, $\underline{CH}_2SCH_2CH_3$); 7.30-7.70 (m, $10H_{arom}$); 8.30 (brs, 2H, $\underline{H}_A$ + $N\underline{H}$, exchangeable with D_2O); 8.42 (s, 1H, H-6).
6c	449	1638; 1605; 1580; 1550; 1460[a]	2.00 (s, 3H, $S\underline{CH}_3$); 2.10 (s, 3H, $S\underline{CH}_3$); 2.40 [s, 6H, $(\underline{CH}_3)_2$]; 3.60 (s, 2H, $\underline{CH}_2SCH_3$); 3.72 (s, 2H, $\underline{CH}_2SCH_3$); 7.10-7.60 (dd, $8H_{arom}$); 8.25 (brs, 2H, $\underline{H}_A$+$N\underline{H}$, exchangeable with D_2O); 8.38 (s, 1H, H-6)

Table 2 (Contd.)

6d	431	1635; 1610; 1570; 1545; 1460[a]	2.00 (s, 3H, $SC\underline{H}_3$); 2.08 (s, 3H, $SC\underline{H}_3$); 3.60 (s, 2H, $C\underline{H}_2SCH_3$); 3.70 (s, 2H, $C\underline{H}_2SCH_3$); 3.83 [s, 6H, $(OC\underline{H}_3)_2$]; 6.86 (dd, $4H_{arom}$); 7.60 (d, $4H_{arom}$); 8.25 (brs, 2H, $\underline{H}_A+N\underline{H}$, exchangeable with D_2O); 8.33 (s, 1H, H-6).
6e	509	1640; 1605; 1583; 1548; 1460[a]	1.30 [q, 6H, $(SCH_2C\underline{H}_3)_2$]; 2.53 [t, 4H, $(SC\underline{H}_2CH_3)_2$]; 3.68 (s, 2H, $C\underline{H}_2SCH_2CH_3$); 3.78 (s, 2H, $CH_2SCH_2CH_3$); 3.87 [s, 6H, $(OCH_3)_2$]; 6.90 (dd, $4H_{arom}$); 7.65 (dd, $4H_{arom}$); 8.25 (br s, 2H, $\underline{H}_A+N\underline{H}$, exchangeable with D_2O); 8.38 (s, 1H, H-6)

[a] In $CHCl_3$ broad peak between 3220-3400 cm^{-1} was observed and there was no change in the positions of other peaks.

Table 3

Spectral data for Products 7a-d

Product	M.S m/e (M^+)	I.R. (neat) ν [cm^{-1}]	^{1}H-NMR (CCl_4) δ [ppm]
7a	235	3300; 3275; 1638; 1575; 1540	1.90, 2.05 (2s, 3H, SCH_3); 2.38 (s, 3H, CH_3); 2.88, 3.10 (2d, 3H, NCH_3); 3.25, 3.55 (2s, 2H, CH_2SCH_3); 5.75 (m, 1H, NH); 6.80-7.40 (m, $4H_{arom}$+ $1H_{vinyl}$)[a]
7b	303	3265; 3220; 1625; 1540[b]	1.20-1.85 (m, $10H_{cyclohexyl}$); 2.00 (s, 3H, SCH_3); 2.33 (s, 3H, CH_3); 2.93 (m, $1H_{cyclohexyl}$); 3.60 (s, 2H, CH_2); 5.55 (m, 1H, NH); 7.00-7.35 (m, $4H_{arom}$+ $1H_{vinyl}$)[c]

Table 3 (Contd.)

7c	251	3310; 3250; 1640; 1605; 1580	1.92, 2.00 (2s, 3H, $SC\underline{H}_3$); 2.90, 3.10 (2d, 3H, $NC\underline{H}_3$); 3.30, 3.55 (2s, 2H, $C\underline{H}_2SCH_3$); 3.80 (s, 3H, $OC\underline{H}_3$); 5.65 (m, 1H, $N\underline{H}$); 6.85-7.60 (m, $4H_{arom}$+ $1H_{vinyl}$)[a]
7d	319	3270; 3225; 1630; 1540[b]	1.15-1.90 (m, $10H_{cyclohexyl}$); 1.94 (s, 3H, $SC\underline{H}_3$); 2.95 (m, $1H_{cyclohexyl}$); 3.50 (s, 2H, $C\underline{H}_2$); 3.75 (s, 3H, $OC\underline{H}_3$); 5.45 (m, 1H, $N\underline{H}$); 6.65-7.40 (m, $4H_{arom}$+ $1H_{vinyl}$)[c]

[a] Both geometrical isomers are present (1:1); [b] Nujol mull

[c] After D_2O shake, NMR spectrum displayed signals due to the presence of both geometrical isomers (4:1).

EXPERIMENTAL

Melting points were determined on 'Boetius' apparatusand are uncorrected. The IR spectra were recorded on "Perkin-Elmer 297" spectrophotometer. The NMR spectra were recorded on varian EM-390 spectrometer using TMS as an internal standard and the chemical shift values are expressed in δ(ppm).

The starting materials

The 3-alkylthio-2-alkylthiomethylacrylophenones (1a-f) were prepared by the general methods as described in the preceding chapter (I) by the reaction of appropriate keten S,S-acetals with sodium hydride in dry dimethylformamide.

3-Aryl-4-alkylthiomethylpyrazoles 2a-f; General Procedure:

A solution of 1 (0.005 mol) and hydrazine hydrate (0.5 ml) in ethanol (15 ml) was refluxed for

1-2 hr. Removal of solvent under reduced pressure gave the crude pyrazoles 2a-f, which were further purified by column chromatography over neutral alumina using benzene as eluent. The physical, analytical and spectral data are described in Table 4 and 1 respectively.

Reaction of 1 with Guanidine:

Method A, in sodium ethoxide/ethanol; General Procedure:

To a solution of sodium ethoxide [prepared by dissolving sodium, (0.01 atom) in 20 ml of absolute alcohol] guinidine nitrate (0.6 g, 0.005 mol) was added and the reaction mixture was stirred for 10-15 min. The compounds 1 (0.005 mol) was then added and the reaction mixture was refluxed for 5-6 hr. The solvent was removed under reduced pressure and the residue was quenched over crushed ice (20 g). It was extracted with chloroform (3 x 20 ml), thecombined extract was washed with water(1 x 50 ml), dried, and evaporated to give the crude pyrimidines, 4a-c which were further purified by passing through a silica gel column using benzene:ethylacetate (7:3) as eluent. The spectral and analytical data of 4a-c are reported in Ref.2(mp, mmp, IR, ^{1}H-N.M.R.).

Method B, in sodium hydride/dimethylformamide/benzene; General Procedure:

To a stirred suspension of guanidine nitrate (0.6 g, 0.005 mol) and sodium hydride (1.5 g, 0.03 mol), 50% suspension) in dimethylformamide (15 ml) and benzene (10 ml), compound 1 (0.005 mol) dissolved in benzene (5 ml) was added and the temperature was raised with stirring to 80-85°C. The reaction mixture was further stirred at 80-85°C for 5-8 hr and poured over crushed ice (200 g). The reaction mixture was neutralised with acetic acid (20%) and the benzene layer was separated. The aqueous layer was further extracted with chloroform (2 x 50 ml) and the combined organic layer was washed with water (5 x 50 ml), dried with sodium sulphate, and evaporated to give crude 6a-e, which were further purified by column chromatography over silica gel using hexane:ethyl acetate (7:3) as eluent. The physical, analytical and spectral data are described in tables 5 and 2, respectively.

Reaction of 4a with 1a:

To a well stirred suspension of sodium hydride (0.01 mol, 50% suspension) in 10 ml dry dimethylformamide,

a mixture of 1a (0.48 g, 0.002 mol) and 4a (0.46 g, 0.002 mol) in 10 ml dry dimethylformamide was added dropwise with stirring at 80-85° and the reaction mixture was stirred at 80-85° for 3 hr. Work-up of the reaction mixture followed by column chromatographic purification as described in the above experiment gave 0.6 g (71%) of 6a (mp, mmp, superimposable IR and NMR).

3-Alkylamino-2-alkylthiomethyl-1-aryl-2-propen-1-ones 7a-d; General Procedure:

A solution of 1 (0.005 mol) and the respective amine (0.01 mol) in ethanol (15 ml) was refluxed for 6-7 hr (2 hr in case of methylamine). Removal of solvent under reduced pressure gave the crude enaminoketones 7a-d, which were further purified by column chromatography over neutral alumina using benzene:ethyl acetate (9:1) as eluent. The physical, analytical and spectral data of 7a-d are described in tables 6 and 3 respectively.

Table 4

3-Aryl-4-alkylthiopyrazoles 2a-f

Product	Ar	R	Yield[a] (%)	m.p. (°C) (solvent)	Molecular formula	Calc. Found:	Analysis(%) C	H	N
2a	C_6H_5	CH_3	85	Viscous liquid	$C_{11}H_{12}N_2S$ (204)		64.71	5.88	13.73
							64.32	5.43	13.28
2b	C_6H_5	C_2H_5	70	Viscous liquid	$C_{12}H_{14}N_2S$ (218)		66.06	6.42	12.84
							66.47	6.79	12.43
2c	p-ClC_6H_4	CH_3	76	82-83 (hexane)	$C_{11}H_{11}ClN_2S$ (238.5)		55.35	4.61	11.74
							55.83	4.97	11.32

Table 4 (Contd.)

2d	p-$H_3CC_6H_4$	CH_3	80	Viscous liquid	$C_{12}H_{14}N_2S$ (218)	66.06 66.48	6.42 6.81	12.84 12.46
2e	p-$H_3COC_6H_4$	CH_3	93	67-68 (hexane)	$C_{12}H_{14}N_2OS$ (234)	61.54 61.13	5.98 5.53	11.97 12.33
2f	p-$H_3COC_6H_4$	C_2H_5	90	52-53 (hexane)	$C_{13}H_{16}N_2OS$ (248)	62.90 62.52	6.45 6.89	11.29 10.92

[a] Yield of pure, isolated product.

Table 5

Physical and analytical data of pyrimidines 6a-e

Product	Ar	R	Yield[a] (%)	m.p. (°C) (solvent)	Molecular formula	Calc. Found:	Analysis(%) C	H	N
6a	C_6H_5	CH_3	65	143-144 (C_2H_5OH)	$C_{23}H_{23}N_3OS_2$ (421)		65.56 65.18	5.46 5.85	9.98 9.47
6b	C_6H_5	C_2H_5	60	106-107 (C_2H_5OH)	$C_{25}H_{27}N_3OS_2$ (449)		66.82 66.36	6.01 5.69	9.35 9.88
6c	p-$H_3CC_6H_4$	CH_3	56	111-112 (C_2H_5OH)	$C_{25}H_{27}N_3OS_2$ (449)		66.82 66.34	6.01 6.44	9.35 9.93

Table 5 (Contd.)

6d	$p\text{-}H_3COC_6H_4$	CH_3	64	134-135 (C_2H_5OH)	$C_{25}H_{27}N_3O_3S_2$ (481)	62.37 62.03	5.61 5.14	8.73 9.04
6e	$p\text{-}H_3COC_6H_4$	C_2H_5	59	121 (C_2H_5OH)	$C_{27}H_{31}N_3O_3S_2$ (509)	63.65 63.98	6.09 6.51	8.25 8.73

[a] Yield of pure, isolated product.

Table 6

3-Alkylamino-2-alkylthiomethyl-1-aryl-2-propen-1-ones, 7a-d

Product	Ar	R	R^1	Yield[a] (%)	m.p. (°C) (solvent)	Molecular formula	Calc. Found:	Analysis(%) C	H	N
7a	p-$H_3CC_6H_4$	CH_3	CH_3	80	Viscous yellow liquid	$C_{13}H_{17}NOS$ (235)		66.38 65.93	7.23 7.64	5.96 6.31
7b	p-$H_3CC_6H_4$	CH_3	C_6H_{11}	83	107-108 (hexane)	$C_{18}H_{25}NOS$ (303)		71.29 70.85	8.25 8.67	4.62 4.17

Table 6 (Contd.)

7c	p-$H_3COC_6H_4$	CH_3	CH_3	75	viscous yellow liquid	$C_{13}H_{17}NO_2S$ (251)	62.15 62.71	6.77 6.23	5.58 5.07
7d	p-$H_3COC_6H_4$	CH_3	C_6H_{11}	82	89-90 (hexane)	$C_{18}H_{25}NO_2S$ (319)	67.71 67.25	7.84 7.43	4.39 4.84

[a] Yield of pure, isolated products.

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CHAPTER III

A NEW GENERAL SYNTHESIS OF 1-SUBSTITUTED 2-AMINO-4-AROYL-5-METHYLTHIOPYRROLES USING-α-KETOKETEN S,S-ACETALS*

The importance of 2-and 3-aminopyrroles without any substituents in their respective adjacent positions has been recently demonstrated by the conversion of 1-substituted 2-amino-4-cyanopyrroles to 7-azaindole derivatives[1]. This method proved to be superior to the conventional approach of construction of the pyrrole moiety on a suitably substituted pyridine ring. The required 2-amino-4-cyanopyrrole was prepared by reacting the succinonitrile (1) with ethylformate in the presence of base followed by its conversion to enamine 2 via its enol ether. The enamine 2 was found to undergo facile intramolecular nucleophilic attack on the nitrile carbon to yield the corresponding 2-aminopyrrole 3[1,2], which was treated with 1,3-diketones to give 7-azaindoles 4[2], (Scheme 1). The method suffers from the limitations imposed on the choice of structural variation in the

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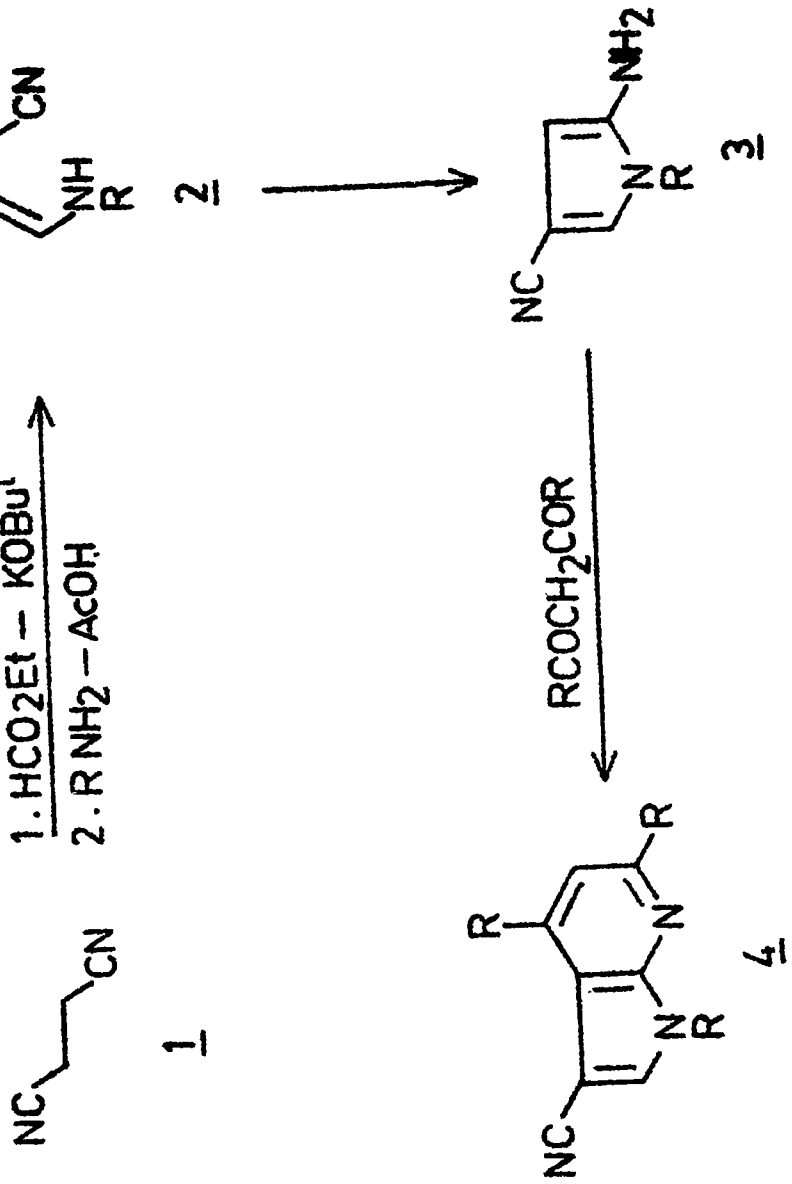
*S. Apparao, H. Ila and H. Junjappa, Synthesis, 65 (1981)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RCOCH2COR
NC
CN
1
NC
CN
NH
R
2
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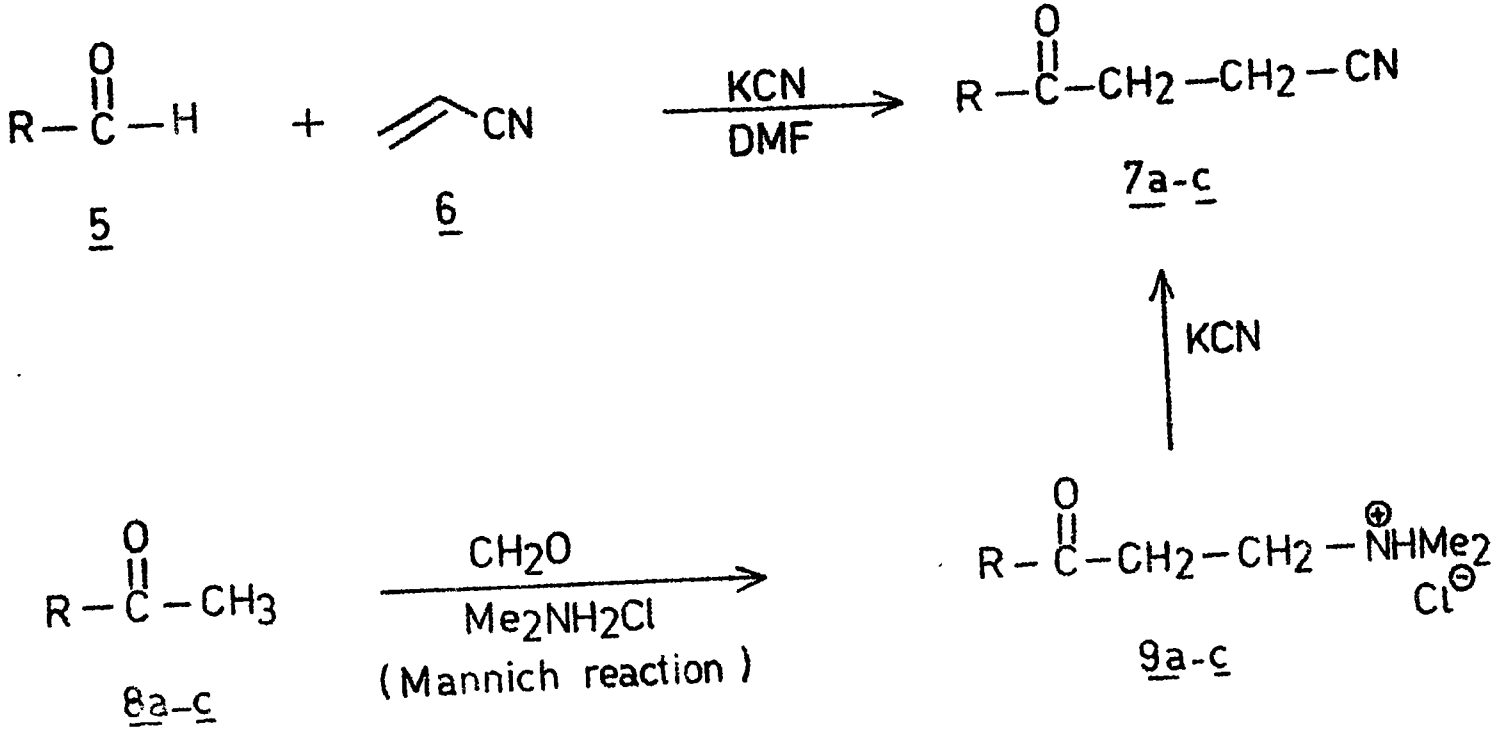
NH2
N
R
3
R
R
N
N
R
NC
4

Scheme 1

preparation of the enamines 2. The other methods[3] for the preparation of 2 and 3-aminopyrroles involve either functional group transformations on pyrrole ring or the total ring synthesis from 2-carbon units. However, the aminopyrroles obtained by these methodsare not suitable for further synthetic elaboration, as they possess substituents on all other three positions. Therefore the only method suitable for such synthetic elaboration appears to be the one described in Scheme 1. Apparently, a general method for the synthesis of 2-aminopyrroles carrying no substitution at 3-position with possible liberal structural variations in the 4 and 5 positions is desirable. In continuation of the synthetic programme on α-ketoketen dithioacetals[4], it was considered to prepare suitably functionalised α-ketoketen S,S-acetals, which can serve as useful intermediates for the synthesis of 2-aminopyrroles. Thus the keten S,S-acetal 10a was considered suitable for such synthetic approach. The keten dithioacetals 10 were not reported earlier and their preparation was accomplished by suitably modifying one of the methods reported[5] from this laboratory. The required β-benzoyl propionitriles. 7a-c were prepared

by two alternative methods, employing reported procedures[6,7]. In one of the methods, benzaldehyde (5) was treated with potassium cyanide in the presence of dimethylformamide, followed by gradual addition of acrylonitrile (6)[6]. After work-up of the reaction mixture, the β-benzoyl-propionitrile (7a) was obtained in 50% yield[6] (Scheme 2). Alternatively 7a was also prepared[7] by subjecting acetophenone (8) to Mannich reaction to give the β-dimethylamino propiophenone hydrochloride (9a) in 85% yield. The hydrochloride 9a was treated with potassium cyanide to give the β-benzoyl-propionitrile (7a) in 80% yield[7]. Similarly the p-substituted nitriles, 7b and 7c were also prepared, following the latter method, in 75% and 85% yields respectively (Scheme 2). When a mixture of 7a and carbon disulfide were stirred with cooling in the presence of sodium ter-butoxide followed by alkylation with two equivalents of methyl iodide, after work-up and chromatographic separation, the corresponding α-ketoketen dithioacetal, 10a was obtained in 45% yield (Scheme 3). The structure of 10a was confirmed by its analytical and spectral data. Its mass spectrum showed molecular ion peak at 263 ($C_{13}H_{13}NOS_2$). It showed the

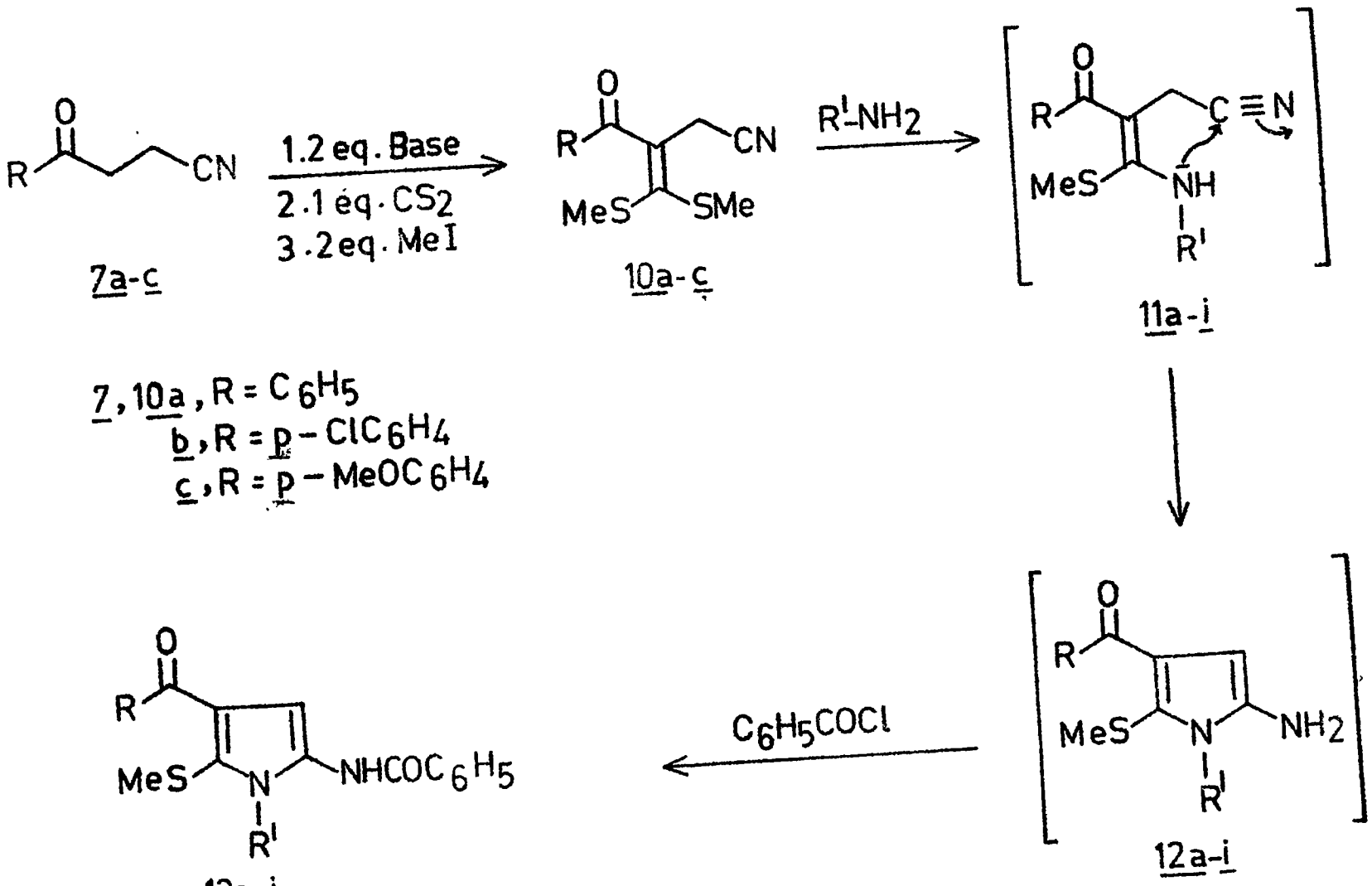


5, R = C_6H_5
7, 8, 9a, R = C_6H_5
b, R = p - Cl C_6H_4
c, R = p - MeO C_6H_4

Scheme 2

characteristic nitrile band in its IR (Nujol) spectrum at 2240 cm^{-1}. The carbonyl band appeared at 1648 cm^{-1}. Its ^{1}H-N.M.R. ($CDCl_3$) spectrum displayed two singlets at δ 2.05 (3H) and δ 2.40 (3H) for two $SC\underline{H}_3$ group protons. The methylene protons appeared as singlet at δ 3.78 (2H). The broad multiplet at δ 7.40-7.90 was assigned to the five aromatic protons. The ketoketen dithioacetals, 10b and 10c were also similarly prepared and their physical, analytical and spectral data, which are in conformity with the assigned structures, are described in experimental section.

The ketoketen dithioacetal 10a, when reacted with methylamine in refluxing ethanol, after work-up and chromatographic separation the corresponding 1-methyl-2-amino-4-benzoyl-5-methylthiopyrrole (12a) was obtained. However, it was found, that aminopyrrole, 12a was unstable resulting in tarry mass. It was therefore isolated and characterized as its monobenzoyl derivative 13a (Scheme 3). The structureof 13a was confirmed by its analytical and spectral data. Its mass spectrum exhibited molecular ion peak at M^+ 350 and was analysed for $C_{20}H_{18}N_2O_2S$. It exhibited in its IR (Nujol) spectrum, a band at 3330 cm^{-1}



7a-c

10a-c

11a-i

12a-i

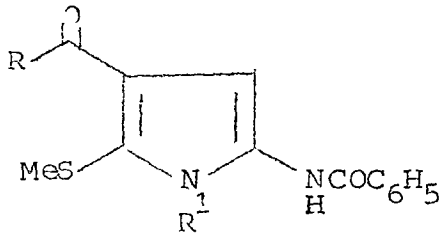
13a-i

7, 10a, R = C_6H_5
b, R = p-ClC_6H_4
c, R = p-$MeOC_6H_4$

Scheme 3

Table

1-Alkyl-2-benzoylamino-3-aroyl-4-methylthiopyrroles (13a-i)



Compound	R	R^1
13a	C_6H_5	CH_3
13b	C_6H_5	C_2H_5
13c	C_6H_5	$C_6H_5CH_2$
13d	p-ClC_6H_4	CH_3
13e	p-ClC_6H_4	C_2H_5
13f	p-ClC_6H_4	$C_6H_5CH_2$
13g	p-$MeOC_6H_4$	CH_3
13h	p-$MeOC_6H_4$	C_2H_5
13i	p-$MeOC_6H_4$	$C_6H_5CH_2$

for NH stretching vibration and the carbonyl stretching band appeared at 1673 cm^{-1}. The band appeared at 1632 cm^{-1} was assigned to the amide carbonyl function. The clear absence of a band around 1660 cm^{-1}, characteristic H-N-H out of plane deformation mode, is indicative of the N-benzoylation of the amino group. Its structure was further confirmed by its ^{1}H-N.M.R (TFA) spectrum. Thus the singlet at δ 2.05 (3H) was assigned to the SCH_3 protons. The singlet at δ 3.40 (3H) was assigned to the $N-CH_3$ protons. The H-3 proton of the pyrrole ring appeared as singlet at δ 7.12 (1H). The aromatic protons appeared as multiplet between δ 7.20-7.70, accounting for ten protons. The pyrroles 12b-i were similarly prepared and characterised as their mono-benzoyl derivatives (13b-i). The analytical and spectral data of 13b-i, which are in agreement with the assigned structures are described in tables 2 and 1 respectively.

Table 1

Spectral data for the products 13a-i

Product	M.S. m/e (M^+)	IR (nujol) ν [cm^{-1}]	^{1}H-NMR ($CDCl_3$) δ[ppm]
13a	350	3330 (NH); 1673 (CO); 1632 (CO)	2.05 (s, 3H, SCH_3); 3.40 (s, 3H, SCH_3); 3.40 (s, 3H, NCH_3); 7.12 (s, 1H, H-3); 7.20-7.70 (m, $10H_{arom}$)[a]
13b	364	3300 (NH); 1663 (CO); 1620 (CO)	1.23 (t, 3H, CH_2CH_3); 2.20 (s, 3H, SCH_3); 3.82 (q, 2H, CH_2CH_3); 6.90 (s, 1H, H-3); 7.40 (m, $6H_{arom}$); 7.80 (m, $4H_{arom}$); 8.42 (s, 1H, NH)

Table 1 (Contd.)

13c	426	3295 (NH); 1672 (CO); 1620 (CO)	2.34 (s, 3H, SCH_3); 5.06 (s, 2H, CH_2); 7.00 (s, 1H, H-3); 7.10-9.90 (m, $15H_{arom}$); 7.90 (s, 1H, NH)
13d	384	3305 (NH); 1688 (CO); 1620 (CO)	2.23 (s, 3H, SCH_3); 3.50 (s, 3H, NCH_3); 6.93 (s, 1H, H-3); 7.30-8.10 (m, $9H_{arom}$); 8.44 (s, 1H, NH)
13e	398	3210 (NH); 1685 (CO); 1615 (CO)	1.36 (t, 3H, CH_2CH_3); 2.23 (s, 3H, SCH_3); 3.84 (q, 2H, CH_2); 6.97 (s, 1H, H-3); 7.20-8.00 (m, $9H_{arom}$); 8.30 (s, 1H, NH)
13f	460	3300 (NH); 1678 (CO); 1618 (CO)	2.04 (s, 3H, SCH_3); 4.95 (s, 2H, CH_2); 6.60-7.70 (m, $15H_{arom}$ and H-3)[a]

Table 1 (Contd.)

13g	380	3307 (NH); 1678 (CO); 1620 (CO)	1.98 (s, 3H, SCH_3); 3.22 (s, 3H, NCH_3); 3.56 (s, 3H, OCH_3); 6.70-7.90 (m, $9H_{arom}$); 8.67 (s, 1H, NH)
13h	394	3305 (NH); 1667 (CO); 1612 (CO)	1.10 (t, 3H, CH_2CH_3); 2.03 (s, 3H, SCH_3); 3.65 (s, 3H, OCH_3); 3.82 (q, 2H, CH_2); 6.85 (s, 1H, H-3); 7.00-8.00 (m, $9H_{arom}$)[a]
13i	456	3260 (NH); 1670 (CO); 1615 (CO)	2.38 (s, 3H, SCH_3); 3.90 (s, 3H, OCH_3); 5.12 (s, 2H, CH_2); 6.90-7.90 (m, $16H_{arom}$ and NH)

[a] in trifluoroacetic acid solution

EXPERIMENTAL

M.P's were determined on 'Boetius' apparatus and are uncorrected. The IR spectra were recorded on 'Perkin-Elmer 297' spectrophotometer. The spectra were recorded on 'Varian EM-390' spectrometer using TMS as an internal standard and the chemical shift values are expressed in δ(ppm).

The starting materials:

The commercial samples of acetophenone, p-chloroacetophenone, p-methoxyacetophenone, carbon disulfide, benzylamine, benzoyl chloride were purified before use.

The 4-aryl-4-oxobutanenitriles, 7a-c were prepared by the following two reported methods[6,7].

Method A[6]: A solution of acrylonitrile (7.0 g, 0.13 mol) in 25 ml of dry dimethylformamide was added with stirring into a solution of the benzaldehyde (10.6 g, 0.1 mol)

and sodium cyanide (4.9 g, 0.1 mol) in dry dimethyl-formamide (50 ml) at 30-35°C. The reaction mixture was stirred for 3 hr at 35°C, it was then poured in to water, extracted with chloroform (2 x 50 ml), and the combined extract was washed with water (1 x 50 ml), dried (Na_2SO_4) and concentrated to give red viscous liquid, which was purified by vacuum distillation. The 4-phenyl-4-oxobutanenitrile (7a), was obtained (8.0 g, 50%) as colour less blades, mp 75-76° (Reported mp 76°)[6,7] from benzene-petroleum ether.

Method B[7]; From Mannich base: β-dimethylaminopropiophenone hydrochloride (9a)[8] (21.4 g, 0.1 mol) and potassium cyanide (13.0 g, 0.2 mol) were dissolved in 250 ml of hot water and the mixture was refluxed for 30 minutes. On cooling in ice, the 4-phenyl-4-oxobutanenitrile (7a) was obtained as colour less plates, yield 12.7 g (80%), mp 75-76° (reported mp 76°)[6,7], from benzene-light petroleum.

The other two nitriles: 4-p-chlorophenyl-4-oxobutanenitrile (7b), mp 71-72° (reported mp 72.5°)[7] and 4-p-methoxyphenyl-4-oxobutanenitrile (7c), mp 94-95° (reported mp 95°)[7] were prepared following the method B in 75% and 85% yields respectively.

The unknown keten S,S-acetals (10a-c) were prepared according to the general method given below[5].

General method for the preparation of keten S,S-acetals (10a-c):

A mixture of 4-aryl-4-oxobutanenitrile 7 (0.1 mol) and carbon disulfide (6 ml, 0.1 mol) is added to a well stirred and cooled suspension of sodium t-butoxide (19.2 g, 0.2 mol) in dry benzene (150 ml) and dry dimethylformamide (10 ml). After stirring of the reaction mixture at 5-10°C for 5 hr, methyl iodide (14.5 ml, 0.22 mol) is gradually added with external cooling. The reaction mixture is stirred at room temperature for 5 hr, left overnight, and again stirred at 30-35°C for 3 hr. The reaction mixture was poured on crushed ice and the benzene layer was separated. The aqueous portion was extracted with benzene and the combined extract was washed with water, dried (Na_2SO_4) and concentrated to give the crude 10a-c, which were purified by column chromatography over silica gel using benzene:hexane (25:75) as eluent. The physical, analytical and spectral properties of these unknown

keten S,S-acetals are described below:

4-phenyl-3-[bis(methylthio)methylene]-4-oxobutanenitrile (10a) was obtained as colourless plates from chloroform-hexane, 18 g (69%); mp 68°; M^+ 263; (Found: C, 58.92; H, 4.71; N, 5.02; Calc. for $C_{13}H_{13}NOS_2$ (263.4): C, 59.27; H, 4.97; N, 5.32%) The spectral data for 10a is described in the text.

4-p-chlorophenyl-3-[bis(methylthio)methylene]-4-oxobutanenitrile (10b) was obtained as light yellow plates from chloroform, 12.5 g (41%), mp 111-112°, IR (Nujol): 2250 (ν_{CN}); 1650 (ν_{CO}) cm^{-1}; ^{1}H-N.M.R. ($CDCl_3$): 2.02 (s, 3H, SCH_3); 2.32 (s, 3H, SCH_3); 3.69 (s, 2H, CH_2); 7.36 (d, $2H_{arom}$); 7.75 (d, $2H_{arom}$); M^+ 297; (Found: C, 52.11; H, 3.88; N, 4.92; Calc. for $C_{13}H_{12}ClNOS_2$ (297.8): C, 52.43; H, 4.06; N, 4.70%).

4-p-methyoxyphenyl-3-[bis(methylthio)methylene]-4-oxobutanenitrile (10c) was obtained as light yellow plates from ethanol, 14 g (48%), mp 98-99°; IR (Nujol): 2243 (ν_{CN}); 1645 (ν_{CO}) cm^{-1}; ^{1}H-N.M.R. ($CDCl_3$): 2.20 (s, 3H, SCH_3); 2.48 (s, 3H, SCH_3); 3.84 (s, 2H, CH_2);

3.96 (s, 3H, $OC\underline{H}_3$); 7.10 (d, $2H_{arom}$); 8.00 (d, $2H_{arom}$); M^+ 293; (Found: C, 57.93; H, 5.53; N, 4.98; Calc. for $C_{14}H_{15}NO_2S_2$ (293.3): C, 57.31; H, 5.15; N, 4.77%).

General Procedure for the preparation of 1-substituted 2-Amino-4-aroyl-5-methylthiopyrroles (12a-i) and 1-substituted 4-aroyl-2-benzoylamino-5-methylthiopyrroles (13a-i) :

A solution of 10 (0.01 mol) and amine (0.011 mol) in ethanol (15 ml) was refluxed for 1-1.5 hr. Removal of solvent under reduced pressure gave the crude amino-pyrroles 12a-i which were dissolved in dry benzene (50 ml) and treated with anhydrous potassium carbonate (0.01 mol) and benzoyl chloride (0.015 mol) with vigorous stirring and cooling. After stirring for 2 hr at room temperature the mixture was poured over crushed ice (200 g). The benzene layer was separated, the aqueous layer further extracted with benzene (2 x 100 ml), and the combined organic layer was dried with sodium sulphate. Evaporation of the benzene gave the crude 13a-i which were further purified by crystallisation (13b, c & f) or by column

chromatography (13a, d-e) over silica gel using benzene:ethylacetate (95:5) as eluent. The compounds 13a-i were prepared by this procedure and their physical, analytical and spectral data are given in tables 2 and 1 respectively.

Table 2

N-Substituted 4-Aroyl-2-benzoylamino-5-methylthiopyrroles 13a-i

Product	R	R^1	Yield[a] (%)	m.p. (°C) (solvent)	Molecular formula	Calc. Found:	Analysis(%) C	H	N
13a	C_6H_5	CH_3	46	108-109°	$C_{20}H_{18}N_2O_2S$		68.55	5.17	7.99
				($CHCl_3$/hexane)	(350.4)		68.07	5.65	8.34
13b	C_6H_5	C_2H_5	55	146-147°	$C_{21}H_{20}N_2O_2S$		69.20	5.53	7.68
				(C_2H_5OH)	(364.5)		68.93	5.17	7.32
13c	C_6H_5	$C_6H_5CH_2$	59	175°	$C_{26}H_{22}N_2O_2S$		73.22	5.20	6.57
				(C_2H_5OH)	(426.5)		73.63	5.53	6.87

Table 2 (Contd.)

13d	p-ClC_6H_4	CH_3	46	154° ($CHCl_3$/hexane)	$C_{20}H_{17}ClN_2O_2S$ (384.5)	62.40 62.83	4.45 4.07	7.28 7.59
13e	p-ClC_6H_4	C_2H_5	41	170° ($CHCl_3$/hexane)	$C_{21}H_{19}ClN_2O_2S$ (398.5)	63.23 63.71	4.80 4.35	7.02 7.47
13f	p-ClC_6H_4	$C_6H_5CH_2$	54	209° (C_2H_5OH)	$C_{26}H_{21}ClN_2O_2S$ (460.5)	67.74 67.97	4.59 4.23	6.08 6.49.
13g	p-$MeOC_6H_4$	CH_3	61	154° ($CHCl_3$/hexane)	$C_{21}H_{20}N_2O_3S$ (380.5)	66.29 66.67	5.30 5.63	7.36 7.76

Table 2 (Contd.)

13h	p-$MeCC_6H_4$	C_2H_5	45	185°	$C_{22}H_{22}N_2O_3S$	66.98	5.61	7.10
				($CHCl_3$/hexane)	(394.5)	66.51	5.27	7.53
13i	p-$MeOC_6H_4$	$C_6H_5CH_2$	57	173°	$C_{27}H_{24}N_2O_3S$	71.03	5.30	6.14
				($CHCl_3$/hexane)	(456.5)	71.43	5.68	6.49

[a] Yield of pure, isolated product

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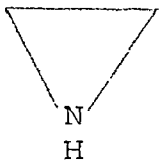
PART B

CHAPTER IV

a: REACTION OF AROMATIC AMINES WITH α-CHLOROACRYLONITRILE: A CONVENIENT TWO-STEP SYNTHESIS OF N-ARYL-2-CYANOAZIRIDINES USING A PHASE-TRANSFER CATALYST*

b: REACTION OF 1-ARYL-2-CYANOAZIRIDINES WITH INDOLE: A GENERAL APPROACH FOR THE SYNTHESIS OF N-ARYLTRYPTOPHANS

Aziridines are a class of compounds having three membered ring containing two carbon atoms and one nitrogen atom. The unsubstituted aziridine (1) is generally refered to, in chemical Abstracts, as ethylenimine, where as its all derivatives are indexed as aziridines as described in ring index system[1].



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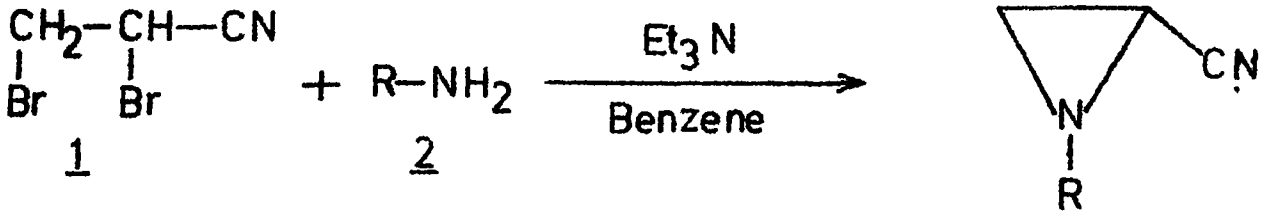
* S. Apparao, A. Kumar, H. Ila and H. Junjappa, Synthesis, 623 (1981).

Aziridines have drawn considerable attention because of fundamental academic interest due to their highly strained reactive rings. The ethylenimine and its derivatives have found use in many branches of applied chemistry such as textiles, plastics, coatings and Pharmacologically active substances[1b]. As a result of this interest, there have been many reviews on various aspects of these derivatives[2].

There have been several methods for the synthesis of ethylenimine and its derivatives described in the literature[2f], of which one of the widely used methods involves the intramolecular nucleophilic displacement by amino group to give aziridine ring systems via trans ring closure[3]. Therefore, the α-halo-β-amino substituted alkanes form useful starting compounds for the synthesis of aziridines by following this method.

A number of N-aryl-2-cyanoaziridines were required by us for further synthetic use. Literature survey for a suitable procedure for the synthesis of these compounds revealed that only four methods are described.

In the first method, the reaction of amines with either 2,3-dibromopropanenitrile (1)[4] (Scheme 1) or with 2-bromo-2-propenenitrile (4)[5] (Scheme 2) in the presence of a suitable base to yield the corresponding aziridines, has been described. However the reaction of amines with 2,3-dibromo-propanenitrile (1) is less satisfactory then with 2-bromo-2-propenenitrile (4)[5]. On the otherhand, the 2-bromo-2-propenenitrile (4) is reported to be unstable, undergoing polymerisation on standing[6], requiring its preparation in small quantities for each experiment. The other method used for the synthesis of only N-phenyl-2-cyano-aziridine (8) (Scheme 3) was due to Szeimies and Huisgen[7], who reacted phenyl azide (5) with acrylonitrile (6) to give the corresponding triazoline (7) involving 1,3-dipolar cycloaddition. The triazoline (7) on subsequent pyrolysis in toluene gave the desired aziridine 8 in 84% yield. Although this method is reported to give excellent yields, the preparation of substituted azides will remain as the limiting factor due to the difficulties involved during their preparation. The method developed by Rodanti and Brulants[8] involves the reaction of diazoacetonitrile (10)

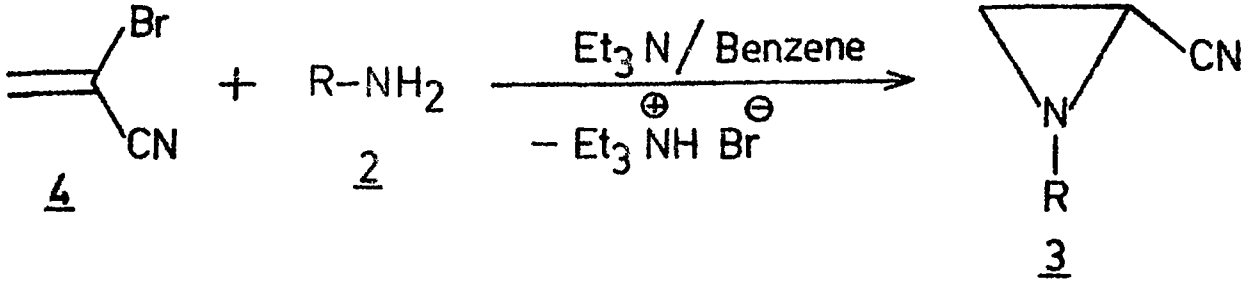


2, 3a, R = H;

b, R = Me, C_6H_{11}, CH_2Ph;

c, R = n-C_4H_9, CH_2CMe_3, $CH_2C_6H_4$-Cl(p)

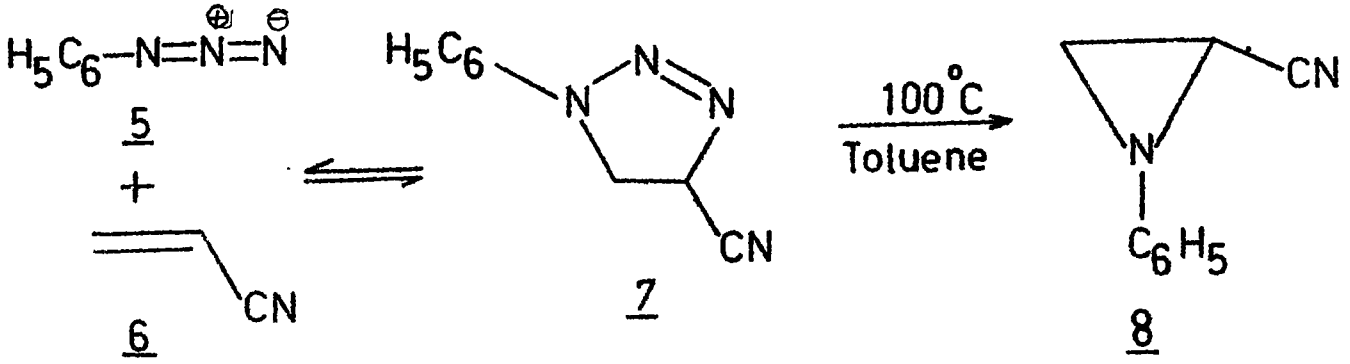
Scheme 1



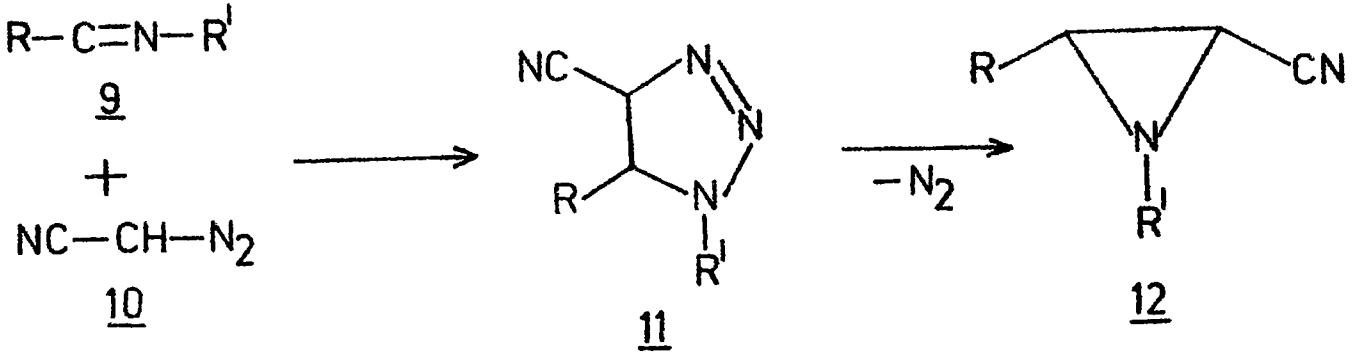
2, 3, R = Me, C_3H_7, $CHMe_2$, CMe_3, C_5H_{11}, C_6H_{13}, $CH_2C_6H_4$·Cl(p)

$CH_2C_6H_4$·OMe, $CHPh_2$, CH(Ph)C_6H_4·OMe(p); C_6H_5

Scheme 2



Scheme 3

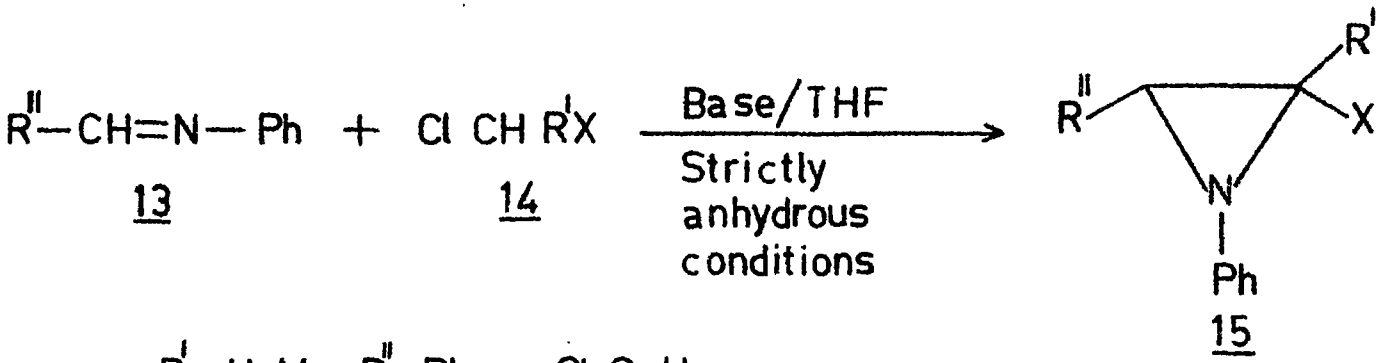


9,11,12, R= C_6H_5; p-$Me_2NC_6H_4$; p-$O_2NC_6H_4$

R'= p-MeO C_6H_4; p-$Me_2NC_6H_4$; p-$O_2NC_6H_4$

Scheme 4

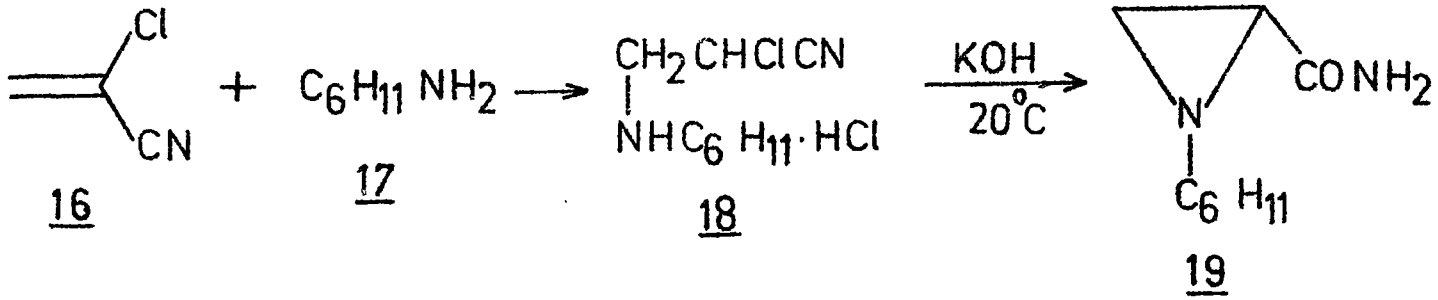
(Scheme 4) as dipolar species with benzalanilines 9 to yield the corresponding triazolines 11, which on subsequent pyrolysis loses nitrogen to give the 2-cyano-3-substituted-1-aryl aziridines 12. The method has been used to prepare only 2-cyano-1,3-disubstituted aziridines and found to be not suitable for the synthesis of the corresponding 2-cyano-3-unsubstituted aziridines. Similarly, the other method[9] involves the reaction of haloacetonitriles 14 (Scheme 5) with benzalanilines 13 in the presence of a base in anhydrous conditions is known to give 1-aryl-2-cyano-3-substituted aziridines in good yields. However, the method suffers due to the lack of flexibility to synthesise the corresponding 3-unsubstituted 2-cyanoaziridines. As a result there is a lack of general method for the synthesis of 2-cyano-3-unsubstituted aziridines. These aziridines were of particular interest as they are excellent substrates for the synthesis of α-aminonitrile compounds by reacting them with various organic nucleophiles. It was therefore contemplated to undertake preliminary studies to develop the synthesis of 2-cyano-3-unsubstituted aziridine derivatives. The results of present investigation on the



$R' = H, Me$; $R'' = Ph$, m-$Cl\ C_6H_4$;

$X = CN, CO_2Bu^t$

Scheme 5



Scheme 6

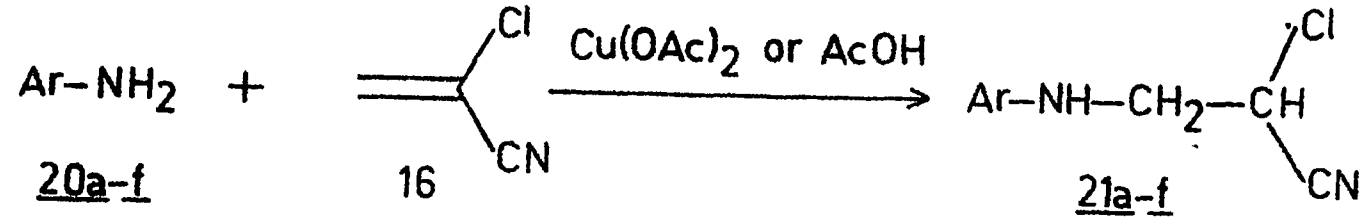
synthesis of these compounds and their reaction with indole are described in this chapter.

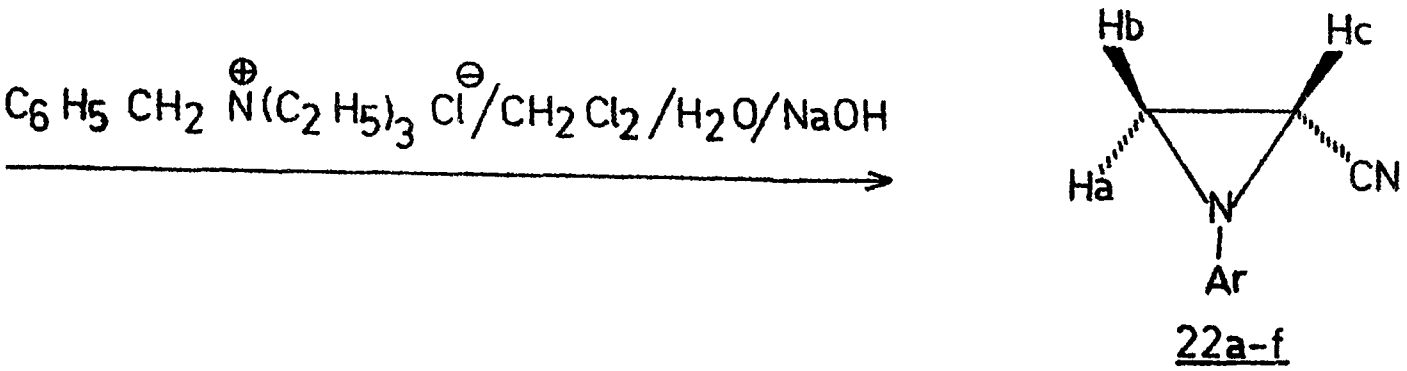
Although the preparation of these compounds were initially attempted by reacting aromatic amines with labile α-bromoacrylonitrile (4) (Scheme 2) the yields of 2-cyano-N-aryl aziridines were not satisfactory primarily due to rapid polymerisation of 4 during its preparation and subsequent reactions. Thus, the α-chloroacrylonitrile (16), which is commercially available in quantities at low-price, was considered for its reaction with amines, with a view to developing general method for the synthesis of 2-cyano-3-unsubstituted aziridines.

The reaction of α-chloroacrylonitrile (16) with aromatic amines have not been reported in the literature. The only reference[10] involving the reaction of 16 with cyclohexylamine (17) (Scheme 6) is reported to have yielded the aziridine 19 in poor yield along with several mixtures.

Thus, when aniline 20a was reacted with 16 in ethanol, or benzene, the Michael adduct 21a was obtained only in poor yield (40%). The yield was not altered,

even in the presence of triethylamine in the reaction mixture. In an alternate experiment, when aniline 20a and 16 (Scheme 7) were refluxed in acetic acid for 6 hr, the adduct 21a was obtained in slightly improved yields (55%). The best yield of 21a (80%) was accomplished by reacting 20a (Scheme 7) with 16 in the presence of copper (II)acetate at 100-110°C. These reaction conditions were found to be optimum and they were employed further to prepare the adducts 21b-f by reacting the corresponding 20b-f with 16 in 65-85% overall yields. The structures of these compounds were confirmed by their analytical and spectral data, which are described in tables 4 and 1 respectively. The adduct 21a was then subjected to cyclization under varying conditions to give the corresponding 1-phenyl-2-cyanoaziridine (22a). Thus, when 21a was treated with triethylamine in refluxing benzene, the corresponding aziridine 22a was not formed and the unreacted 21a was recovered. Similarly, when 21a was treated with sodium hydride in refluxing benzene, the 22a was obtained in poor yield (30%). The compound after chromatographic separation gave pure 22a as red oil


Ar–NH2
20a–f
16
Cl
CN
Cu(OAc)2 or AcOH
Ar–NH–CH2–CH
Cl
CN
21a–f


C6 H5 CH2 N(C2 H5)3 Cl / CH2 Cl2 / H2 O / NaOH
Hb
Hc
Ha
CN
N
Ar
22a–f

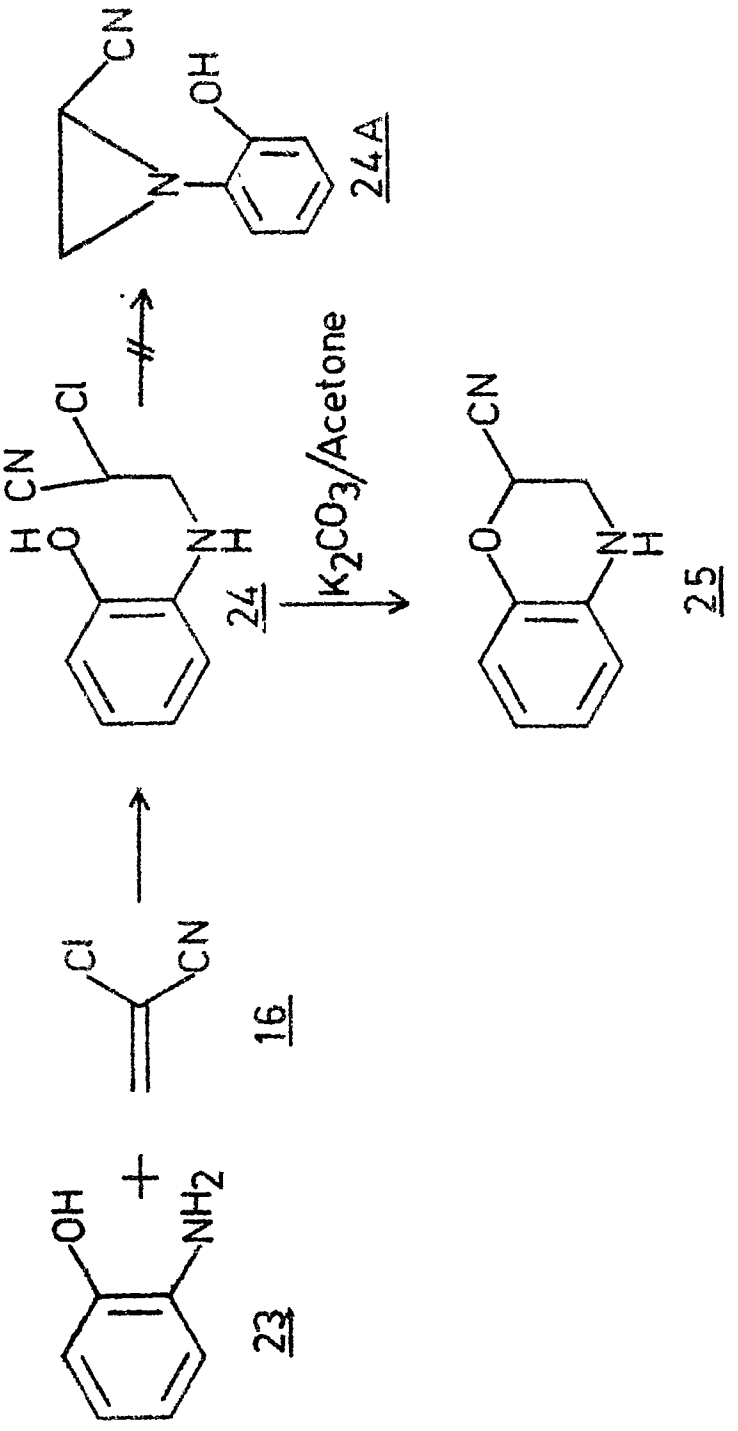
Scheme 7

identical with that reported[5,7] (superimposable IR and NMR). However, when 21a (Scheme 7) was subjected to cyclization in the presence of phase transfer catalyst, benzyl-triethylammonium chloride and 50% aqueous sodium hydroxide solution with dichloromethane as the organic phase, the reaction mixture after work-up, gave the corresponding aziridine 22a in 83% yield. Similarly the 21b-f were cyclized using phase transfer catalyst to yield the corresponding N-aryl-2-cyano-aziridines 22b-f in 73-93% overall yields. The structures of unknown compounds 22b-e were confirmed on the basis of their analytical and spectral data, which are described in tables 5 and 2 respectively.

Under similar reaction conditions, when this method was extended to prepare N-alkyl-2-cyanoaziridines by reacting 16 with aliphatic amines like cyclohexyl-, benzyl-, and isopropylamine a mixture of compounds not isolable by column chromatography were obtained.

When the 2-aminophenol (23) similarly reacted with 16 in refluxing ethanol, the open chain adduct 24 was obtained in 70% yield (Scheme 8). The structure of

the open chain compound 24 was confirmed by its spectral and analytical data, which are described in the experimental section. When the compound 24 was subjected to cyclization in acetone in the presence of anhydrous potassium carbonate, the desired aziridine 24A was not formed. However, the product thus isolated in 80% yield was identified as 2-cyano-1,4-benzoxazine (25) (Scheme 8) by its analytical and spectral data. Thus, it exhibited molecular ion peak at M^+ 160 and was analysed for $C_9H_8N_2O$. Its IR (Nujol) spectrum showed a band at 3400 cm^{-1} was assigned to NH stretching frequency. The characteristic 2240 cm^{-1} band was assigned to $\nu_{C\equiv N}$ group. Its final structure was confirmed by its ^{1}H-NMR($CDCl_3$) spectrum. Thus, the signal at δ 3.40 (d, 2H) was assigned to methylene protons adjacent to nitrogen. A signal at δ 3.80 (br s) accounting for one proton, exchanged with deuterium oxide was assigned to the NH proton. The triplet at δ 4.88 accounting for one proton was assigned to the methine proton. The signal at δ 6.75 (4H) was due to four aromatic protons, thus providing evidence for the formation of the compound 25.



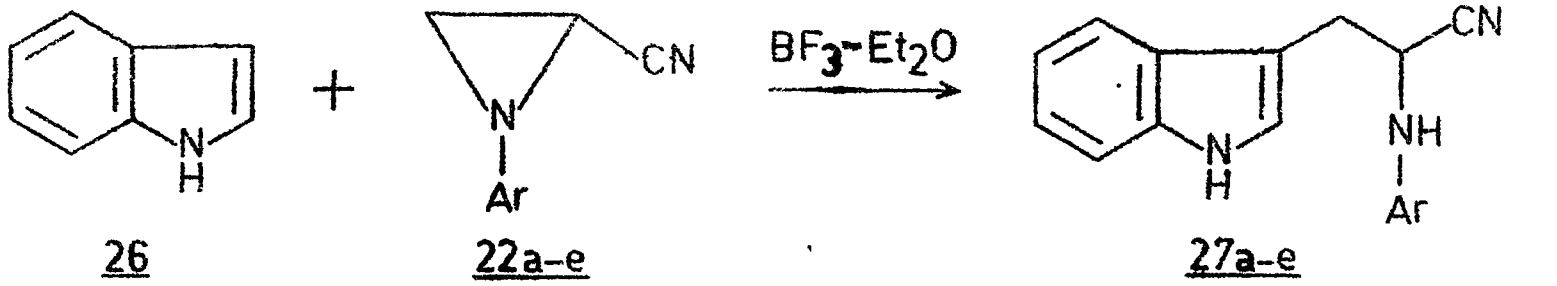
Scheme 8

b: REACTION OF 1-ARYL-2-CYANOAZIRIDINES WITH INDOLE: A GENERAL APPROACH FOR THE SYNTHESIS OF N-ARYL TRYPTOPHANS

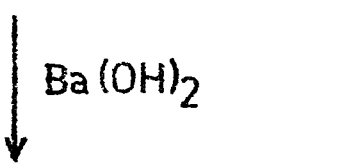
The most general methods described for the synthesis of tryptophan and its derivatives involve the gramine derivative[11, 12] or the Fisher type cyclization[13] of a ketone or aldehyde carrying the desired amino and carbonyl functions in the chain. There are several miscellaneous approaches described in the literature[14] for the syntheses of tryptophan and all these methods have been investigated for the synthesis of aminoacids carrying no substitution on the α-amino group. Although aziridinium fluoroborate is reported[15] to react with indole to give one step synthesis of tryptamine in good yield, no efforts have been made to utilize this simple approach for the synthesis of tryptophan and N-substituted tryptophans. Therefore it is interesting that the 2-cyanoaziridine and 2-cyano-N-substituted aziridines should react with indole under similar reaction conditions to yield the corresponding tryptophans. It was therefore considered to react the indole with N-aryl-2-cyanoaziridines with a view to

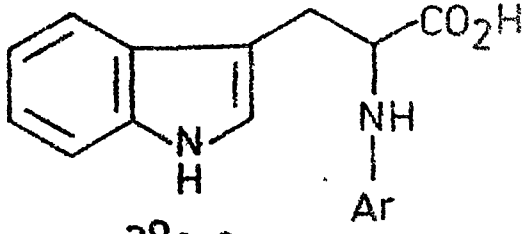
developing a new general method for the synthesis of α-aminonitrile compounds (27), which are precursors for the synthesis of hitherto unreported N-aryltryptophans.

Thus when indole (26) was reacted with 1-phenyl-2-cyanoaziridine (22a), in presence of borontrifluoride-etherate, after work-up and chromatographic purification, corresponding α-anilino-β-indolyl propanenitrile 27a (Scheme 9) was obtained in 60% yield. The structure of 27a was confirmed by its analytical and spectral data. It showed molecular ion peak at M^+ 261 and was analysed for $C_{17}H_{15}N_3$ (261). In its IR (Nujol) spectrum, it exhibited a broad band at 3410 cm^{-1}, which was assigned to the stretching frequencies of indole NH and aryl NH. The characteristic nitrile band appeared at 2240 cm^{-1}. The final structure of 27a was confirmed by its NMR ($CDCl_3$) spectrum. A signal at δ 3.54 (d, 2H) was assigned to the methylene protons. The signal at δ 3.85 (m, 1H) which was assigned to anilino NH exchanged with deuterium oxide. The triplet at δ 4.20 (1H) was assigned to the methine proton. The broad multiplet between δ 6.40-7.60 (m, 10H) was assigned to nine aromatic protons and one 2-H indole



26 22a-e 27a-e





28a-c

22, 27a, Ar = C_6H_5;
b, Ar = p-FC_6H_4;
c, Ar = p-ClC_6H_4;
d, Ar = p-MeC_6H_4;
e, Ar = p-MeOC_6H_4
28a, Ar = C_6H_5;
b, Ar = p-FC_6H_4;
c, Ar = p-MeOC_6H_4

Scheme 9

proton. The low field broad singlet at δ 8.28 (1H) was assigned to the indole NH, which was exchanged with deuterium oxide, thus confirming the structure of 27a. Similarly 26 was reacted with 22b-e under similar reaction conditions to give the corresponding α-arylamino-β-indolyl propanenitriles 27b-e in 50-60% overall yields. The analytical and spectral data for 27b-e, which are in conformity with the assigned structures, are described in tables 6 and 3 respectively.

The above arylaminonitriles 27 were subjected to hydrolysis to yield the corresponding dl-(α-N-aryl) tryptophans. Several hydrolytic conditions were studied since the hydrolysis of these aminonitriles did not give consistantly the desired tryptophans. However, when 27a was subjected to hydrolysis using aqueous/ethanolic barium hydroxide the corresponding tryptophan 28a (Scheme 9) was obtained in 50% yield. The structure of tryptophan 28a thus obtained was confirmed by its analytical and spectral data. It was analysed for $C_{17}H_{16}N_2O_2$ (280) and showed IR (KBr) peaks at 3400 cm^{-1} (νOH) and 1700 cm^{-1} (νCO) indicating that it does not exist in zwitterionic form[17]. Its further

structural proof is obtained from its NMR ($CDCl_3$) spectrum. Thus, the doublet at δ 3.40 (2H) was assigned to two methylene protons. The signal at δ 3.65 (m, 1H, exchangeable with D_2O) was due to aryl NH while the triplet appeared at δ 4.05 (1H) assigned to methine proton. Nine aromatic protons and H-2 of indole appeared together as multiplet between δ 6.40-7.60 . The broad singlet appeared at δ 8.30 (1H) was assigned to indole NH, Similarly, two more α-aminonitriles, 27b and 27e were hydrolysed under similar conditions to give dl-N-aryltryptophans, 28b and 28c in 45% and 48% yields respectively. The physical, analytical and spectral data for 28b-c are described in the experimental section.

Table 1

Spectral data for Products 21a-f

Product	M.S. m/e(M^+)	I.R. (neat) ν [cm^{-1}]	^{1}H-NMR ($CDCl_3$) δ [ppm]
21a	180.5	3330 (NH); 2215 (CN)	3.96 (br d, 2H, CH_2); 4.26 (br s, 1H, NH); 4.66 (t, 1H, CH); 6.80-730 (m, $5H_{arom}$)
21b	198.5	3325 (NH); 2200 (CN)	2.44 (br d, 2H, CH_2); 3.63 (br s, 1H, NH); 4.46 (t, 1H, CH); 6.30-7.00 (m, $4H_{arom}$).
21c	215	3445 (NH); 2250 (CN)[a]	3.36 (br d, 2H, CH_2); 4.02 (br s, 1H, NH); 4.18 (t, 1H, CH); 6.40 (d, $2H_{arom}$); 7.00 (d, $2H_{arom}$).

Table 1 (Contd.)

21d	215	3400 (NH); 2240, 2220 (CN)	3.58 (br d, 2H, $C\underline{H}_2$); 4.05 (br s, 1H, N$\underline{H}$); 4.43 (t, 1H, C$\underline{H}$); 6.40-7.10 (m, $4H_{arom}$)
21e	194.5	3378 (NH); 2208 (CN)[a]	2.43 (s, 3H, $C\underline{H}_3$); 3.86 (br d, 2H, $C\underline{H}_2$); 4.20 (br s, 1H, N$\underline{H}$); 4.63 (t, 1H, C$\underline{H}$); 6.63 (d, $2H_{arom}$); 7.13 (d, $2H_{arom}$)
21f	210.5	3400 (NH); 2245 (CN)	3.33 (br d, 2H, $C\underline{H}_2$); 3.66 (s, 3H, $OC\underline{H}_3$); 4.10 (br s, 1H, NH); 4.33 (t, 1H, C$\underline{H}$); 7.00-7.50 (m, $4H_{arom}$).

[a] Nujol Mull

Table 2

Spectral data for products 22a-f

Product	M.S. m/e (M^+)	I.R (neat) ν [cm^{-1}]	^{1}H-NMR ($CDCl_3$) δ [ppm]
22a	144	2245 (CN); 1599 1493, 765, 693	2.35 (dd, 1H, H_b, J_{cis} = 6Hz); 2.55 (d, 1H, H_a, J_{trans} = 3Hz); 2.75 (t, 1H, H_c J_{cis} = 6Hz, J_{trans} = 3Hz); 6.80-7.46 (m, $5H_{arom}$)[b]
22b	162	2250 (CN); 1550, 1220, 838, 695	2.45 (dd, 1H, H_b, J_{cis} = 6Hz); 2.62 (q, 1H, H_a, J_{trans} = 3Hz); 2.75 (t, 1H, H_c J_{cis} = 6Hz, J_{trans} = 3Hz); 6.90 (dd, $4H_{arom}$)

Table 2 (Contd.)

22c	178.5	2238 (CN); 1595, 1490, 1375, 825, 760, 650[a]	2.46 (dd, 1H, $\underline{H}_b$, J_{cis} = 5Hz); 2.65 (q, 1H, $\underline{H}_a$, J_{trans} = 2.5 Hz); 2.78 (t, 1H, $\underline{H}_c$, J_{cis} = 5Hz, J_{trans} = 2.5 Hz); 6.85-7.20 (m, $4H_{arom}$)
22d	178.5	2238 (CN); 1595, 1460, 1375, 849 765, 660[a]	2.43 (d, 1H, $\underline{H}_b$, J_{cis} = 6Hz); 2.65 (q, 1H, $\underline{H}_a$, J_{trans} = 3Hz); 2.74 (t, 1H, $\underline{H}_c$, J_{cis} = 6Hz, J_{trans} = 3Hz); 6.80-7.20 (m, $4H_{arom}$).
22c	158	2248 (CN); 1610, 1510, 1275, 820, 695	2.25 (s, 3H, $C\underline{H}_3$); 2.30 (d, 1H, $\underline{H}_b$, J_{cis} = 5Hz); 2.48 (q, 1H, $\underline{H}_a$, J_{trans}= 2.5 Hz); 2.57 (t, 1H, $\underline{H}_c$, J_{cis}= 5Hz); J_{trans} = 2.5 Hz); 6.75-7.12 (q, $4H_{arom}$)

Table 2 (Contd.)

22f[b]	174	2243 (CN); 1595, 1508, 1275, 820, 695	2.35 (d, 1H, $\underline{H}_b$, J_{cis} = 6Hz); 2.55 (q, 1H, $\underline{H}_a$, J_{trans} = 3Hz); 2.70 (t, 1H, $\underline{H}_c$, J_{cis} = 6Hz, J_{trans} = 3Hz); 3.70 (s, 3H, $OC\underline{H}_3$); 6.80-7.35 (m, $4H_{arom}$)[b]

[a] Nujol mull

[b] Known aziridines, see references 7 and 4c

Table 3

Spectral data for products 27b-e

Product	M.S. m/e (M^+)	IR (Nujol) ν[cm^{-1}]	^{1}H-NMR ($CDCl_3$) δ[ppm]
27b	279	3412 (NH); 3365 (NH) 2260 (CN)	3.65 (d, 2H, $C\underline{H}_2$); 3.80 (m, 1H, $N\underline{H}$, exchangeable with D_2O); 4.28 (t, 1H, $C\underline{H}CH_2$); 6.40-7.60 (m, 9H, $8H_{arom}$ + $H\text{-}2_{indole}$); 8.25 (br s, 1H, $N\underline{H}_{indole}$, exchangeable with D_2O)
27c	295	3420 (NH); 3350 (NH); 2245 (CN)	3.75 (d, 2H, $C\underline{H}_2$); 4.00 (m, 1H, NH, exchangeable with D_2O); 4.33 (t, 1H, $C\underline{H}CH_2$); 6.35-7.75 (m, 9H, $8H_{arom}$+ $H\text{-}2_{indole}$); 8.25 (br s, 1H, $N\underline{H}_{indole}$ exchangeable D_2O)

Table 3 (Contd.)

27d	275	3430 (NH); 3360 (NH); 2250 (CN)	2.25 (s, 3H, p-$C\underline{H}_3$); 3.60 (d, 2H, $C\underline{H}_2$); 3.75 (m, 1H, NH, exchangeable with D_2O); 4.35 (t, 1H, $C\underline{H}CH_2$); 6.35-7.70 (m, 9H, $8H_{arom}$ + $H\text{-}2_{indole}$); 8.30 (br s, 1H, NH_{indole}, exchangeable with D_2O)
27e	291	3400 (br, NH) 2240	3.45-3.65 (m, 5H, $C\underline{H}_2$ + $OC\underline{H}_3$); 3.70 (m, 1H, NH, exchangeable with D_2O); 3.90 (t, 1H, $C\underline{H}CH_2$); 6.30-7.40 (m, 9H, $8H_{arom}$ + $H\text{-}2_{indole}$); 8.30 (br s, 1H, $N\underline{H}_{indole}$, exchangeable with D_2O).

EXPERIMENTAL

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

The starting materials:

The commercial samples of aniline, p-fluoroaniline, p-chloroaniline, m-chloroaniline, p-methoxyaniline and α-chloroacrylonitrile were purified before use.

The phase transfer catalyst, triethylbenzylammonium chloride (TEBA) was prepared by the following reported procedure[16].

A solution of triethylamine (33.7 g, 0.33 mol) and benzyl chloride (50.0 g, 0.40 mol) in 60 ml of

absolute ethanol was refluxed for 64 hr. The solution was cooled to room temperature and 300 ml of ether was added. The precipitated ammonium salt was removed by filtration, redissolved in the minimum amount of hot dry acetone and reprecipitated with ether; yield 43.7 g (58%).

Preparation of 3-arylamino-2-chloropropanenitriles 21:

(a) in refluxing ethanol: A mixture of aniline (20a) (9.3 g, 0.1 mol) and 2-chloro-2-propenenitrile (16) (9.5 g, 0.11 mol) in 25 ml ethanol was refluxed at 80-90° for 30-40 hr. The solvent was removed under reduced pressure and the residue was chromatographed over silica gel column using benzene/hexane (1:2) as eluent to give 7.2 g (40%) of pure 21a as yellow oil (TLC single spot). The spectral and analytical data for 21a are described in tables 1 and 4 respectively.

(b) in refluxing benzene: When the reaction of aniline (20a) (9.3 g, 0.1 mol) and α-chloroacrylonitrile (16) (10.5 g, 0.12 mol) was carried out in refluxing benzene for 20 hr, the work-up of the reaction mixture followed by purification as above yielded 6.3 g (35%) of 21a (superimposable IR and NMR).

(c) in refluxing benzene/triethylamine: When the reaction of 20a (9.3 g, 0.1 mol) and 16 (10.5 g, 0.12 mol) was carried out in refluxing benzene in the presence of triethylamine (10.1 g, 0.1 mol) for 24 hr, the work-up of the reaction mixture followed by chromatographic purification gave 6.9 g (38%) of 21a (superimposable IR and NMR)

(d) in refluxing acetic acid: A mixture of 20a (9.3 g, 0.1 mol) and 2-chloro-2-propenenitrile (16) (10.5 g, 0.12 mol) in glacial acetic acid (30 ml) was refluxed at 120-130°C for 2-6 hr. The solvent was then removed under reduced pressure and the residue thus obtained was passed through a silica gel column using benzene:hexane as the eluent to give 1.0 g (55%) of 21a (superimposable IR and NMR)

(e) in the presence of copper (II) acetate: A mixture of 20a (9.3 g, 0.1 mol) and 16 (10.5 g, 0.12 mol) and copper (II) acetate (5% by weight of aniline) in 10 ml of 95% alcohol was refluxed with stirring at 90-100° for 15 hr. The solvent was removed under reduced pressure, the residue was then dissolved in chloroform/ethylacetate (200 ml), washed with water (2 x 100 ml), dried (Na_2SO_4),

the solvent was removed under reduced pressure and the crude product thus obtained was purified by column chromatography over silica gel using hexane:benzene (4:1) as eluent to give 14.5 g (80%) of 21a (superimposable IR and NMR). Similarly the compounds 21b-f were also prepared following this method in 65-85% over all yield (Table 4). The spectral and analytical data for 21a-f are described in tables 1 and 4 respectively.

Attempted cyclization of 21a to 22a with triethylamine in benzene:

A mixture of 21a (1.8 g, 0.01 mol) and triethylamine (2.02 g) in 10 ml dry benzene was stirred at room temperature for 48 hr. The solvent was removed and the reaction mixture was purified by passing through column on silica gel to give 1.6 g (90%) of unreacted starting materia 21a (superimposable IR and NMR).

Cyclization of 21a to 22a:

(a) with sodium hydride in refluxing benzene: A solution of 21a (1.8 g, 0.01 mol) in 5 ml of dry benzene was added to a suspension of sodium hydride (0.5 g, 50% suspension)

in 5 ml dry benzene and refluxed the reaction mixture with stirring at 80-90° for 15 hr. The reaction mixture was poured over crushed ice, extracted with chloroform (3 x 15 ml), washed with water (2 x 20 ml), dried (Na_2SO_4) and concentrated to give crude reaction mixture, which was purified by passing through silica gel column using benzene:hexane (1:2) as eluent to give 0.43 g (30%) of 22a red oil identical with that reported[5,7] (superimposable IR and NMR).

(b) with benzyltriethylammonium chloride: To a solution of the adduct 21a (1.8 g, 0.01 mol) in dichloromethane (20 ml), 50% aqueous sodium hydroxide solution (10 ml) and benzyltriethylammonium chloride (50 mg) were added and the mixture was vigorously stirred at room temperature for 3 hr [monitored by TLC on silica gel using ethylacetate: benzene (1:9)]. The mixture was then diluted with water (50 ml) and dichloromethane (20 ml). The organic layer was separated, washed with water (2 x 50 ml), dried (Na_2SO_4) and evaporated on water bath to give the crude aziridine 22a, which was purified as described above to give 1.2 g (83%) of pure 21a (superimposable IR and NMR). Similarly,

the adducts 21b-f were also cyclized following this method to give the corresponding 22b-f in 73-93% over all yields (Table 5). The spectral and analytical data for 22a-f are described in tables 2 and 5 respectively.

Reaction of ∝ -chloroacrylonitrile (16) with 2-aminophenol (23): Formation of 3-(o-hydroxyphenylamino)-2-chloro-propanenitrile (24)

A mixture of 2-aminophenol (23) (10.9 g, 0.1 mol) and 2-chloropropionitrile (16) (10.5 g, 0.12 mol) in ethanol (60 ml) was refluxed at 100-110° for 22 hr, when the TLC showed the complete disappearance of starting material. The solvent was removed from the reaction mixture under reduced pressure and the residue thus obtained was purified by column chromatography over silica gel using benzene as eluent, to give 14 g (70%) of 24 as red viscous oil, (TLC single spot); IR (Neat): 3400 cm^{-1} (br, ν_{OH}+ ν_{NH}); 2250 cm^{-1} (ν_{CN}); ^{1}H-NMR ($CDCl_3$): 3.62 (d, 2H, $NC\underline{H}_2$); 4.45 (t, 1H, $C\underline{H}CH_2$); 4.60-5.00 (m, 2H, N$\underline{H}$ + O$\underline{H}$, exchangeable with D_2O); 6.65 (s, $4H_{arom}$); M^+ 196.5; (Found, C, 54.53; H, 4.32; N, 14.67; Calc. for $C_9H_9ClN_2O$ (196.5): C, 54.96; H, 4.58; N, 14.25%).

Cyclisation of 3-(O-hydroxyphenylamino)-2-chloropropio-nitrile (24) to 2-cyano-1,4-benzoxazine (25):

The michael adduct (24) (1.97 g, 0.01 mol) dissolved in dry acetone (10 ml) was added to anhydrous potassium carbonate in dry acetone (30 ml) with stirring and the reaction mixture was stirred further for 3.5 hr at 55-60°. (The reaction was monitored by TLC). Removed the solvent, the residue diluted with water (20 ml) extracted with chloroform (2 x 30 ml), dried (Na_2SO_4) and concentrated to give the crude product, which on column chromatography on silica gel using benzene as eluent followed by recrystallisation from ethylacetate:hexane (1:9) gave 2-cyano-1,4-benzoxazine (25) as light brown prisms; yield 1.3 g (80%); mp 69-70°; M^+ 160; (Found: C, 67.17; H, 5.28; N, 17.86; Calc. for $C_9H_8N_2O$ (160); C, 67.50; H, 5.00; N, 17.50%). The spectral data for 25 is described in the text.

Reaction of 1-aryl-2-cyanoaziridines (22) with indole (26); Synthesis of 3-(3'-indolyl)-2-arylaminopropanenitrile (27); General Procedure:

A mixture of 1.17 (0.01 mol) of indole (26) and 1-aryl-2-cyanoaziridine (22) (0.01 mol) in 20 ml of

dry ether was placed in a 100 ml round bottomed flask fitted with reflux condensor. Boron trifluoride etherate (10 ml) was added slowly from the top of the condenser with stirring (exothermic). The reaction mixture was refluxed at 60-70° for 2.5 hr. The solid separated initially in the reaction mixture slowly dissolves on heating. The reaction mixture was then poured into a 400 ml beaker containing 50 ml of cold water and neutralised with sodium bicarbonate, extracted with ethylacetate (3 x 50 ml) and the combined extract was washed with water (2 x 50 ml), dried (Na_2SO_4) and concentrated. The crude product thus obtained was purified by column chromatography on silica gel using ethyl acetate:hexane (1:4) as eluent. The compounds 27a-e were prepared by this method and their analytical and spectral data are described in tables 6 and 3 respectively.

Hydrolysis of 3-(3'-indolyl)-2-arylaminopropanenitriles (27); Synthesis of dl-N-aryltryptophans (28): General Procedure:

A mixture of 27 (0.005 mol) and Barium hydroxide (0.025 mol) in 10 ml of water and 10 ml of ethanol was

refluxed at 120-130° for 70-80 hr. The ethanol was distilled off as much as possible. The reaction mixture was then acidified with 20% acetic acid, extracted with chloroform and the combined extract was washed with water and concentrated. The residue was then dissolved in 20% sodium hydroxide solution, treated with charcoal and filtered hot through fluted filter paper and the charcoal was washed with hot ethanol. The dl-N-aryltryptophans (28) were precipitated after acidification of the filtrate with 20% acetic acid as white solids. The dl-N-aryl-tryptophans 28a-c are prepared by this method and their physical, analytical and spectral data are given below:

dl-N-Phenyltryptophan (28a) was obtained as white solid, yield 0.7 g (50%) mp 133-140° (Found: C, 73.24; H, 6.17; N, 10.43; Calc. for $C_{17}H_{16}N_2O_2$ (280): C, 72.86; H, 5.71; N, 10.00%). The spectral data is described in the text.

dl-N-(p-Fluorophenyl)-tryptophane (28b) was obtained as white solid, yield 0.67 g (45%) mp. 146-152°; IR (KBr): 3400 cm^{-1} (ν_{OH}); 1710 cm^{-1} (ν_{CO}); ^{1}H-NMR: insoluble; (Found: C, 68.95; H, 5.51; N, 9.89; Calc. for

$C_{17}H_{15}FN_2O_2$ (298): C, 68.46; H, 5.03; N, 9.40%).

dl-N-(p-Methoxyphenyl)-tryptophan (28c) was obtained as white solid, yield 0.75 g (48%), mp. 50-55° IR (KBr): 3520 cm^{-1} (ν_{OH}); 1710 cm^{-1} (ν_{CO}); ^{1}H-NMR: insoluble; (Found: C, 70.07; H, 5.98; N, 9.47; Calc. for $C_{18}H_{18}N_2O_3$ (310): C, 69.68; H, 5.81; N, 9.03%).

Table 4

3-Arylamino-2-chloropropanenitrile 21a-f

Product	Ar	Yield (%)[a]	m.p. (°C) (solvent)	Molecular formula	Calc. Found:	Analysis(%) C	H	N
21a	C_6H_5	80	Yellow oil	$C_9H_9ClN_2$		59.83	15.51	4.99
				(180.5)		59.41	15.15	4.65
21b	p-FC_6H_4	70	Orange oil	$C_9H_8ClFN_2$		54.41	14.11	4.03
				(198.5)		54.73	14.52	4.44
21c	p-ClC_6H_4	79	175° (C_2H_5OAc/ hexane)	$C_9H_8Cl_2N_2$		50.23	13.02	3.72
				(215)		50.14	13.41	4.02

Table 4 (Contd.)

21d	m-ClC_6H_4	65	orange oil	$C_9H_8Cl_2N_2$	50.23	13.02	3.72
				(215)	50.55	13.45	3.99
21e	p-$CH_3C_6H_4$	82	72°	$C_{10}H_{11}ClN_2$	60.70	14.40	5.66
			(C_2H_5OAc/	(194.5)	60.44	14.88	5.35
			hexane)				
21f	p-$MeOC_6H_4$	85	red oil	$C_{10}H_{11}ClN_2O$	57.00	13.30	5.23
				(210.5)	57.43	13.71	5.61

[a] for copper (II) acetate method

[b] Dioxan was used as solvent

Table 5

1-Aryl-2-cyanoaziridines, 22a-f

Product	Ar	Yield (%)	m.p. (°C) (solvent)	Molecular formula	Calc. Found:	Analysis(%) C	H	N
22a[a]	C_6H_5	83	Red Oil	$C_9H_8N_2$		75.00	19.44	5.56
				(144)		75.40	19.63	5.14
22b	p-FC_6H_4	93	Yellow oil	$C_9H_7N_2F$		66.67	17.28	4.32
				(162)		66.31	17.68	4.72
22c	p-ClC_6H_4	90	55-56°	$C_9H_7N_2Cl$		60.50	15.69	3.92
			(Hexane/	(178.5)		60.88	15.24	3.58
			acetone)					

Table 5 (Contd.)

22d	m-ClC_6H_4	82	68-69° (EtOAc/ hexane)	$C_9H_7N_2Cl$ (178.5)	60.50	15.69	3.92
					60.79	15.51	3.62
22e	p-MeC_6H_4	80	Red Oil	$C_{10}H_{10}N_2$ (158)	75.95	17.72	6.33
					75.61	17.43	6.73
22f[a]	p-$MeOC_6H_4$	73	Orange oil	$C_{10}H_{10}N_2O$ (174)	68.97	16.09	5.75
					68.56	16.48	5.39

[a] known aziridines, see references 7 and 4c.

Table 6

3-(3'-indolyl)-2-arylamino propanenitriles 27a-e

Product	Ar	Yield (%)	m.p. (°C) (solvent)	Molecular formula	Calc. Found:	Analysis (%) C	H	N
27a	C_6H_5	60	106-107° (no solvent)	$C_{17}H_{15}N_3$ (261)		78.16	5.75	16.09
						78.53	5.47	16.47
27b	p-F-C_6H_4	55	98-99° (EtOAc + hexane)	$C_{17}H_{14}FN_3$ (279)		73.12	5.02	15.05
						73.61	5.51	15.43
27c	p-Cl-C_6H_4	60	119-120 (EtOAc + hexane)	$C_{17}H_{14}ClN_3$ (295.5)		69.04	4.74	14.21
						69.37	4.34	14.63

Table 6 (Contd.)

27d	$p\text{-}CH_3\text{-}C_6H_4$	50	102-103 ($CHCl_3$ + hexane)	$C_{18}H_{17}N_3$ (275)	78.55 78.80	6.18 6.56	15.27 15.63
27e	$p\text{-}CH_3O\text{-}C_6H_4$	50	Semi solid	$C_{18}H_{17}N_3O$ (291)	74.23 74.52	5.84 5.57	14.43 14.74

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V I T A E

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