# PART A : STUDIES ON POLARIZED KETEN DITHIOACETALS

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

**SATYAM APPARAO**

*DEPARTMENT OF CHEMISTRY*
*SCHOOL OF PHYSICAL SCIENCES*



A THESIS
SUBMITTED IN FULFILMENT OF THE REQUIREMENTS OF THE DEGREE OF

**DOCTOR OF PHILOSOPHY**

To

NORTH-EASTERN HILL UNIVERSITY
SHILLONG, INDIA

**1982**

Professor H. Junjappa
Dean, School of Physical
Sciences

NORTH-EASTERN HILL UNIVERSITY
DEPARTMENT OF CHEMISTRY
SHILLONG -793003 (INDIA)

## 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

H. Junjappa

Date : September 1982

(H. Junjappa)

Phone : 6593
Grams : NEHU

# North-Eastern Hill University

DEPARTMENT OF CHEMISTRY
School of Physical Sciences
Laitumkhrah, SHILLONG-793003.
Meghalaya

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 |

7/9/78
Head
Department of Chemistry
North-Eastern Hill University
Shillong-793 003

ACKNOWLEDGEMENT

The research work described in this thesis was carried out in the Department of Chemistry, North-Eastern Hill University Shillong, under the supervision of Professor H. Junjappa, Dean, School of Physical Sciences It is with great pleasure, I take this opportunity to thank him for suggesting the problem and guiding throughout the course of this investigation. I also wish to express my sincere thanks to Dr. (Mrs) H. Ila, Reader in Chemistry, for her continued guidance, encouragement and help.

I am also greatful to Sri M.S. Krishnamachari, Lecturer in Chemistry, Govt. College, Rajahmudry, for his encouragement from the beginning of my college studies.

The thesis was typed by my wife, Mrs. Vijaya, inspite of her busy schedule and I express my sincere gratitude to her for her understanding, cooperation and patience.

Thanks are also due to my colleague Mr. B. Myrboh for recording NMR spectra, Mrs. Phillipose and my wife Mrs. Vijaya for recording IR spectra. Quite a few spectral and analytical data were obtained from Dr. S.M.S. Chauhan, Department of Chemistry, University of Alberta, Edmonton, Canada and Dr. Arvind Kumar, Institut fur Pharmazeutische Chemie der Phillips Universitat, Marburg/Lahn, West Germany, whom I remain grateful. I further extend my thanks to Directors of Central Drug Research Institute, Lucknow, Regional Research Laboratory, Jorhat and Bose Institute, Calcutta, for providing the analytical service throughout this investigation.

I also wish to express my gratitude to my colleagues, Dr. Arvind Kumar, Miss Veena Aggarwal, Mr. J.N. Vishwakarma, Mr. B. Myrboh, Mr. SS. Bhattacharjee, Mr. A. Rahman, Mr. G. Singh, Mr. L.W. Singh, Mr. C.V. Asokan and Mr. A. Datta, without whose co-operation and help it would not have been possible to complete the work.

Lastly I express my sincere gratitude to my parents, father-in-law and mother-in-law for their continuous encouragement and patience.

SATYAM APPARAO

# C O N T E N T S

# PREFACE

Polarized keten dithioacetals, which are prepared in one pot reaction under relatively simple reaction conditions from a wide variety of active methylene compounds, have been successfully utilized in this laboratory for the synthesis of a 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 $\alpha$-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 $\alpha$-methyl/methylene-$\alpha$-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 $\alpha$-chloroacrylonitrile and aromatic amines have been described. These aziridines have been shown to react with indole to give $\alpha$-arylamino-$\beta$-(indolyl)-propanenitrile, which are further shown to undergo hydrolysis to give hitherto unreported dl-N-aryltryptophans.

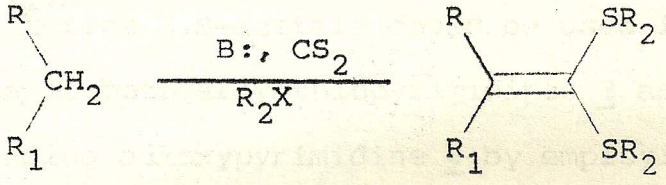
PART A

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



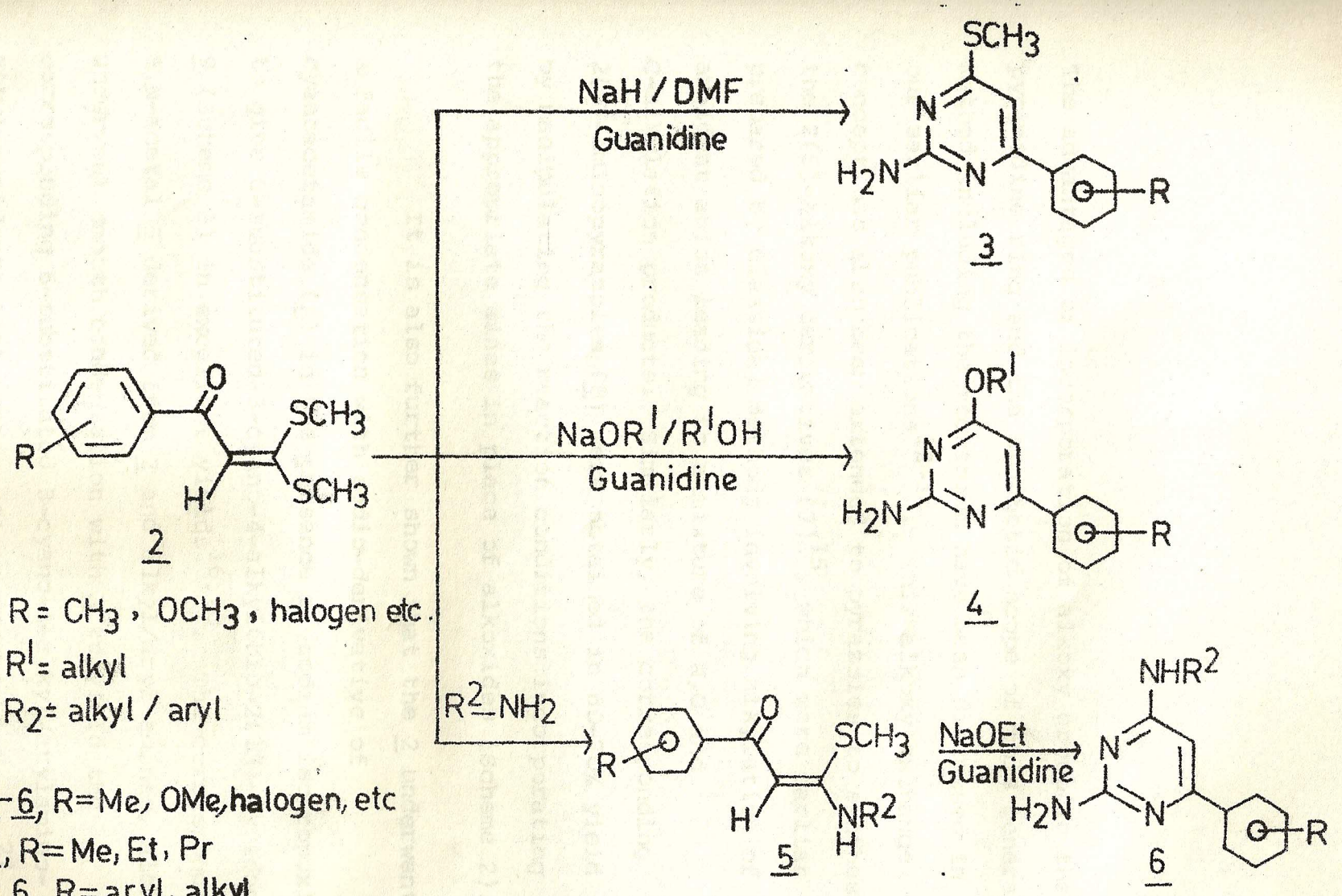

1 2

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

$R_1$= Nitrile, carbonyl, etc.

$R_2$= Alkyl groups.

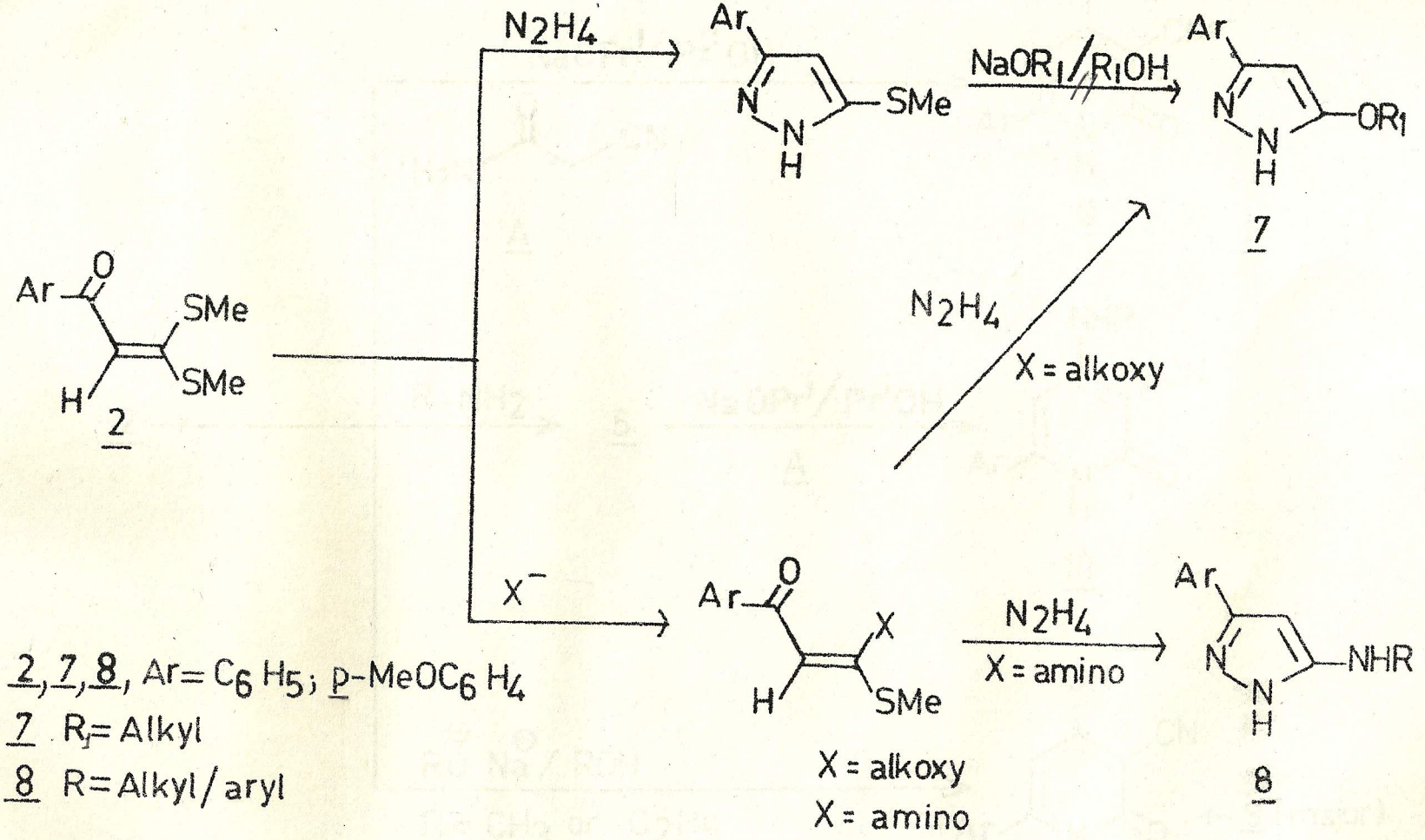
carbon disulphide in the presence of two equivalent of a suitable base followed by alkylation in one pot reaction[1-29]. These polarised keten S,S-acetals (2) are among the simplest reactive intermediates with well defined b.ps., if they are liquids and m.ps., if they are solids; which can be purified 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).


NaH / DMF
Guanidine
NaOR¹ / R¹OH
Guanidine
R² NH₂
NaOEt
Guanidine
2
3
4
5
6
R = CH₃ , OCH₃ , halogen etc.
R¹ = alkyl
R₂ = alkyl / aryl
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].

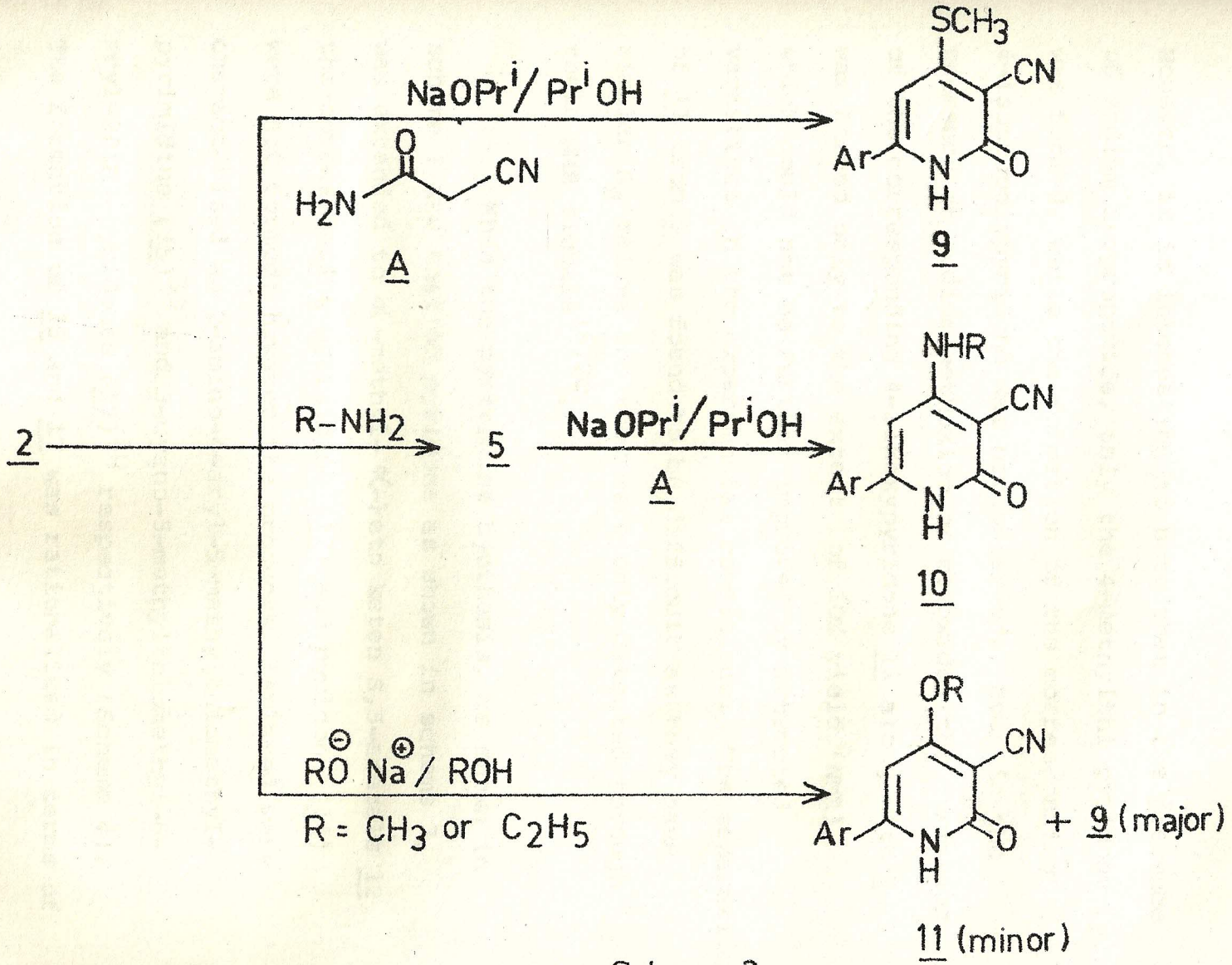



2, 7, 8, Ar= $C_6H_5$; p-$MeOC_6H_4$

7 $R_1$= Alkyl

8 R= Alkyl/aryl

Scheme 2


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

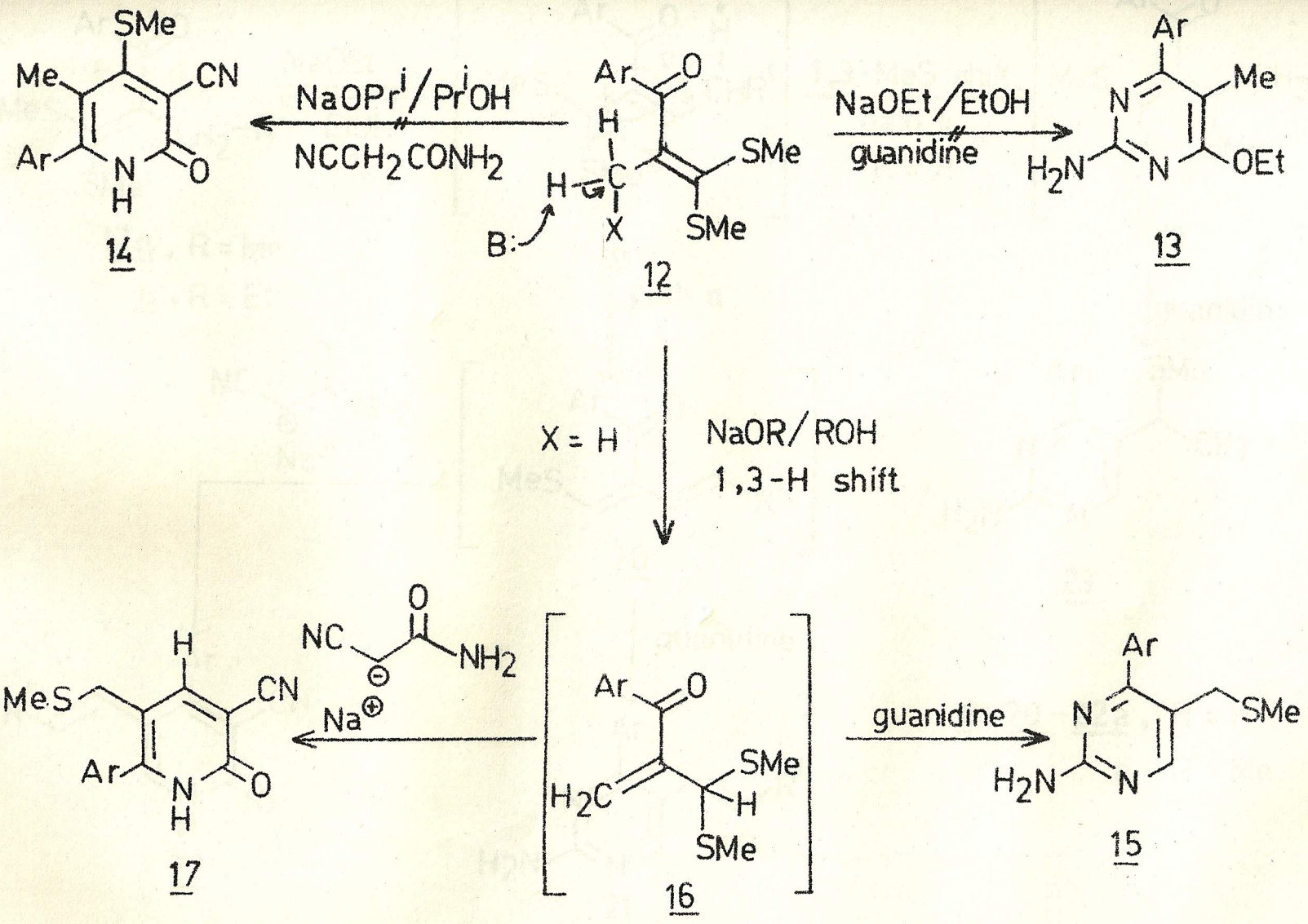
Scheme 3

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].

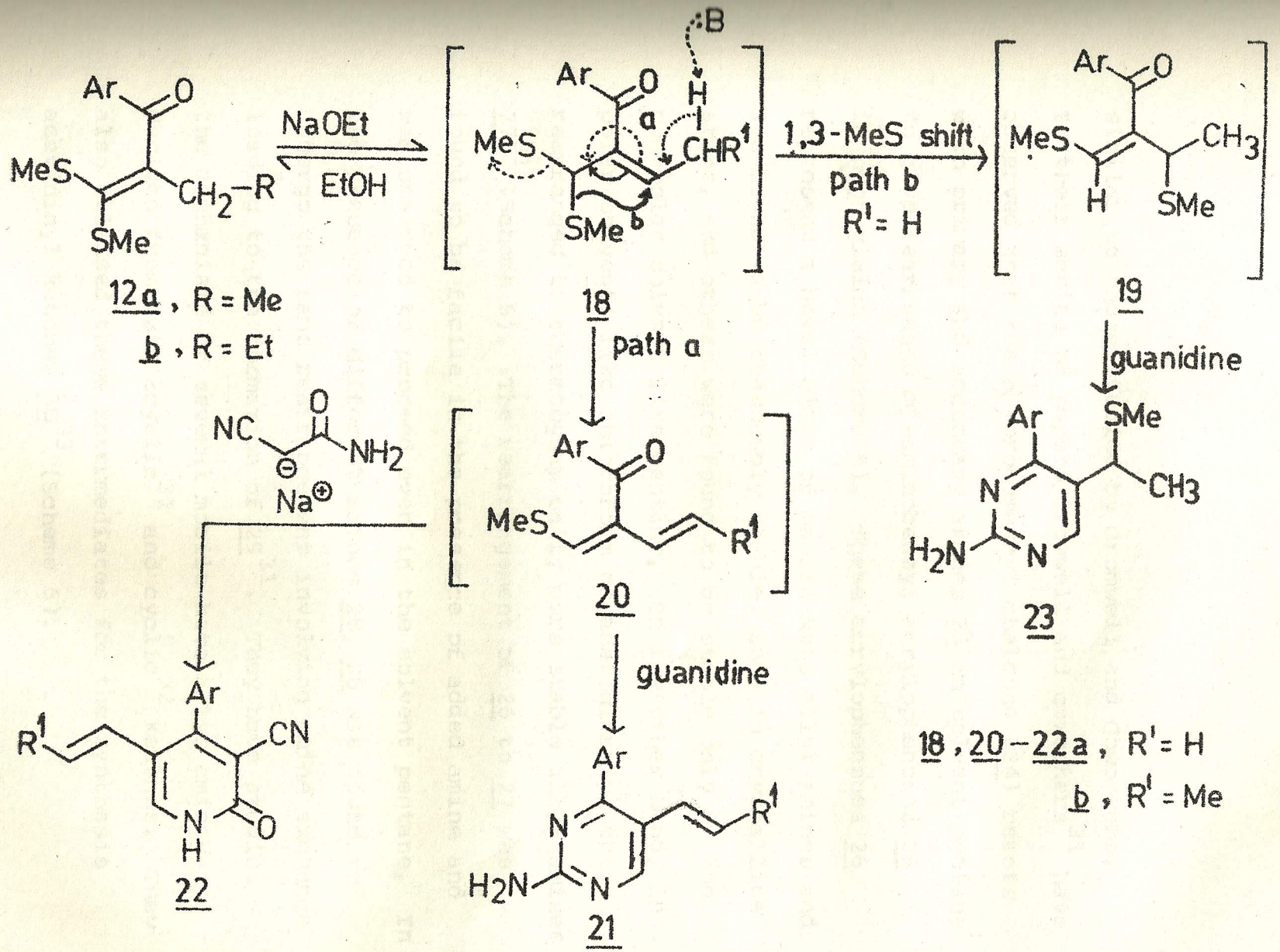
When the pyrimidine synthesis, as shown in scheme 1 and that of pyridone as shown in scheme 3, was extended to α-methyl-α-keto keten S,S-acetals 12, the corresponding pyrimidine (13) and pyridone (14) were not formed; however the products, isolated were characterised as 2-amino-4-aryl-5-methylthiomethyl-pyrimidine (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 $\alpha$-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

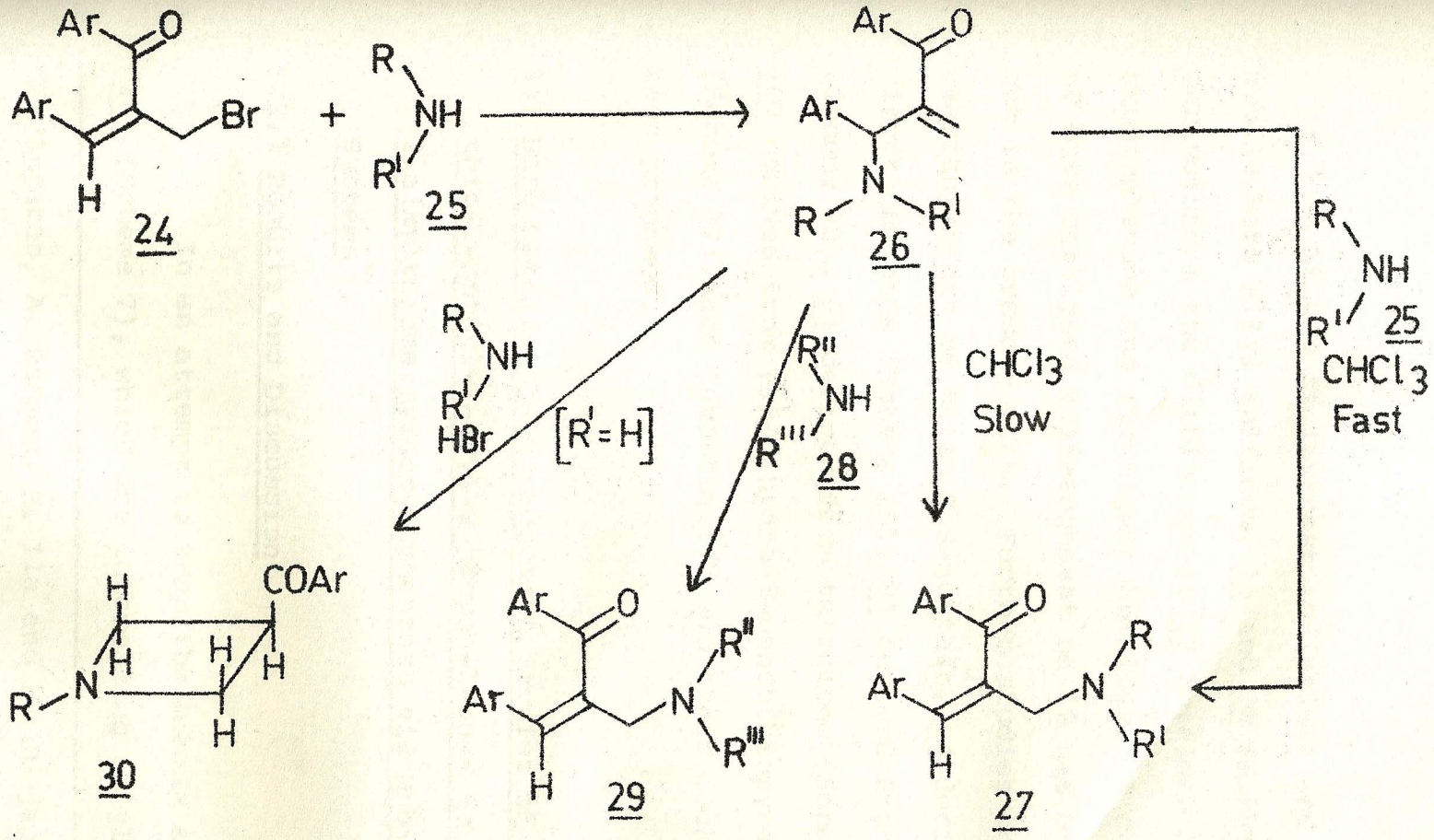

SMe
Me
CN
Ar
N
H
O
14
NaOPr$^i$/Pr$^i$OH
NCCH$_2$CONH$_2$
Ar
O
H
SMe
H
C
X
SMe
B:
12
NaOEt/EtOH
guanidine
Ar
Me
N
H$_2$N
N
OEt
13
X = H
NaOR/ROH
1,3-H shift
H
MeS
CN
Ar
N
H
O
17
NC
O
NH$_2$
Na$^\oplus$
Ar
O
SMe
H$_2$C
H
SMe
16
guanidine
Ar
N
SMe
H$_2$N
N
15

Scheme 4


Ar
O
MeS
CH2–R
SMe
12a , R = Me
b , R = Et
NaOEt
EtOH
:B
H
a
CHR1
b
18
1,3-MeS shift
path b
R1 = H
CH3
H
19
path a
guanidine
NC
NH2
Na⊕
20
R1
CN
N
H
22
guanidine
H2N
21
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'= $-(CH_2)_2-O-(CH_2)_2-$

c, R=R'= $-(CH_2)_5-$

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

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