SYNTHETIC STUDIES ON HETEROCYCLES

VEENA AGGARWAL
DEPARTMENT OF CHEMISTRY
SCHOOL OF PHYSICAL SCIENCES

SUBMITTED IN FULFILMENT OF THE REQUIREMENT OF THE DEGREE OF
DOCTOR OF PHILOSOPHY

To

THE NORTH-EASTERN HILL UNIVERSITY
SHILLONG-793001
INDIA

JULY, 1982

Chem
(Thesis)

Dr. (Mrs) H. Ila
READER

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 Miss Veena Aggarwal under my supervision. She has satisfactorily completed the pre-Ph.D course 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.

Date : 28th July 1982.

H. Ila
(H. ILA)

Department of Chemistry
School of Physical Sciences
North-Eastern Hill University
Laitumkhrah, Shillong-793003.

phone : 6593
Grams : NEHU

Pre- Ph.D Course Work evaluation Report

Name : Miss Veena Aggarwal

No.	Course	Description	Grade	GPA
1.	Chem-401	Inorganic Chemistry I	A	4.57
2.	Chem-421	Organic Chemistry I	A	4.77
3.	Chem-541	Chemical Bonding	A	5.06
4.	Chem-542	Physical Methods	A	4.53
Final Grade point average :			A	4.73

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

1.	Chem-620	Biogenesis & Natural Products
2.	Chem-423	Organic Chemistry II
3.	Chem-443	Physical Chemistry II

17/7/78

Head
Department of Chemistry
North Eastern Hill University,
Shillong-793003

CONTENTS

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 Dr. (Mrs) H. Ila, Reader in Chemistry. I take this opportunity to thank her for suggesting the problem and guiding throughout the course of this investigation. I also thank Prof. H. Junjappa, Dean, School of Physical Sciences for his guidance and encouragement.

Thanks are also due to my colleague Mr. B. Myrboh for recording NMR spectra, Mrs. Phillipose and Mrs. Apparao 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 für Pharmazeutische Chemie der Phillips Universität, 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.

The thesis was typed by Mr. T.R. Vijayan, whom I express my sincere thanks. I express my gratitude to my fellow co-workers, Dr. Arvind Kumar, Mr. S. Apparao, Mr. B. Myrboh, Mr. S.S. Bhattacharjee, Mr. J.N. Vishwakarma, Mr. A. Rahman, Mr. G. Singh, Mr. L.W. Singh and Miss Mangla Satpute, without whose co-operation and help, it would have not been possible to complete the work.

Lastly I express my sincere gratitude to my parents for their continuous encouragement and patience.

Veena Agg

(VEENA AGGARWAL)

PREFACE

A systematic investigational study was undertaken, to exploit the polarized keten-S,N- and N,N-acetals as useful three and two carbon fragments for the construction of a variety of heterocyclic systems. The study includes development of newer synthetic methods using these S,N- and N,N-acetals for the synthesis of aminopyrimidines, 4-aminopyridones, 4-thioxopyrimidines, 5-hydroxyindoles and 4-carbomethoxypyridones.

In the first chapter, a brief literature survey is given on the methods available in the literature for the synthesis of S,N- and N,N-acetals and their reactions.

In the second chapter, preparation of a few selected keten-S,N- and N,N-acetals is described.

In the third chapter, the reaction of S,N- and N,N-acetals with guanidine has been described, providing one step new general method for the synthesis of aminopyrimidines. The method is original and can be extended further for the synthesis of a large number of aminopyrimidines with wide structural variations.

In the fourth chapter, these S,N- and N,N-acetals have been successfully condensed with cyanoacetamide anion, providing a new general method for the synthesis of 4-amino-2(1H)-pyridones. The generality of the method has been described.

In the next chapter, the concept of these S,N- and N,N-acetals as two carbon fragments has been explored. They are shown to undergo facile condensation with benzoyl isothiocyanate to yield usefully functionalised 4-thioxopyrimidines. The limitations of the method are described.

In the sixth chapter, the S,N- and N,N-acetals have been shown to be a useful class of enamine components through their reaction with 1,4-benzoquinone, yielding 5-hydroxyindoles. The advantage of these S,N- and N,N-acetals as enamine components has been discussed.

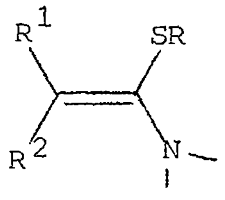
In the last chapter, S,N- and N,N-acetals have been reacted with dimethyl acetylenedicarboxylate, yielding 4-carbomethoxy-2(1H)-pyridones with appropriate substrates in good yields. The scope of this method is discussed.

CHAPTER 1

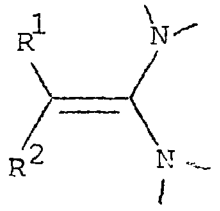
POLARIZED KETEN-S,N- AND N,N-ACETALS : A REVIEW

1.1 Introduction

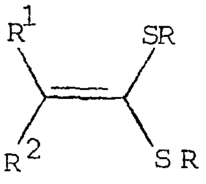
Polarized keten-S,N- A and N,N-acetals B can be prepared either by displacement method, reacting keten-S,S- C/O,O-acetals D[1]/keten-dichlorides E[2] with amines or by direct method starting from active methylene compounds and reacting them with suitable electrophiles. These compounds are either high boiling liquids or well defined crystalline solids, which can be purified by conventional methods. They exhibit good stability and are found resistant to mild hydrolytic conditions. Therefore, they can be prepared from a wide variety of active methylene compounds and stored under ordinary conditions. It may be noted, that S,N- and N,N-acetals derived from these active methylene compounds can be regarded either as vinylogous amides, if they are derived from ketones, or as vinylamines if derived from non-keto active methylene



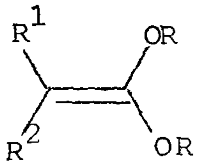
A



B

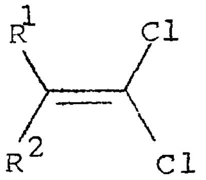


C



D

Keten-O,O-acetals



E

Keten-dichlorides

R^1 = H, alkyl, aryl, nitrile, carbonyl, nitro, sulfonyl etc.

R^2 = Nitrile, carbonyl, sulfonyl, nitro etc.

R = Alkyl

compounds. Although, the chemistry of enamines derived from ketones and primary or secondary amines is well documented, the analogous series of keten-S,N- and N,N-acetals, which should in principle behave like enamines, have scarcely been studied on the lines of enamine chemistry. Apparently, the polarized keten-S,N- and

N,N-acetals form a novel series of compounds, whose studies has so far been confined to their preparation and physical properties. Their synthetic utility as three carbon fragments and as structural analogues of enamines, therefore, demands a systematic study, which forms the major objective of the present investigation.

A brief review of the chemistry of the keten-S,N- and N,N-acetals is discussed in the following two sections:

(1) Methods of synthesis of keten-S,N- and N,N-acetals.

(2) Synthetic applications of keten-S,N- and N,N-acetals.

1.2 Methods of Synthesis of Keten-S,N- and N,N-acetals

There are a number of methods described in the literature for the synthesis of keten-S,N- and N,N-acetals and they can be broadly classified in the following categories:

1.2.1 Direct synthesis of keten-S,N- and N,N-acetals from active methylene compounds.

1.2.2 Synthesis of keten-S,N- and N,N-acetals via displacement by amines from keten-S,S-/O,O-acetals or keten-dichlorides.

1.2.1.1 Using alkyl and aryl isothiocyanates:

One of the efficient methods for the synthesis of keten-S,N-acetals described in the literature,[3-9] involves the reaction of active methylene compounds 1 with alkyl or aryl isothiocyanates in the presence of a base (Scheme 1). The resultant sodium salt 2 of the S,N-acetal can be subsequently alkylated with appropriate alkyl halides to yield the desired keten-S,N-acetals 3 in good to excellent yields. The method has generally been used for the synthesis of a number of keten-S,N-acetals and provides one pot synthesis of these important series of compounds, when alkylation is carried out without isolating the salt. The salts 4 with dibromoethane yield 3-phenylthiazolidin-2-yliden-acetophenone (5)[6,10] in moderate yields. The method is particularly useful for the

Scheme 1

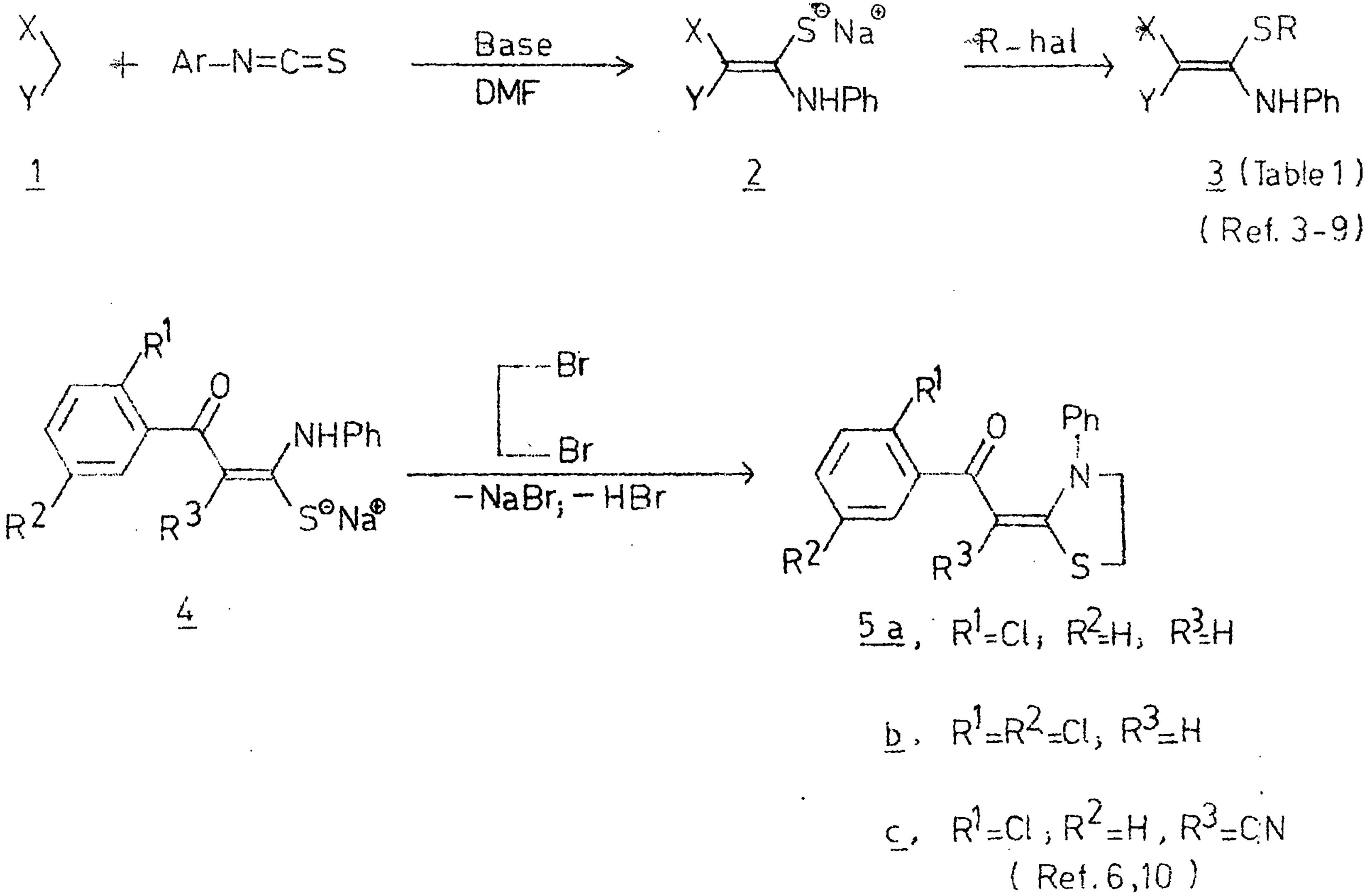
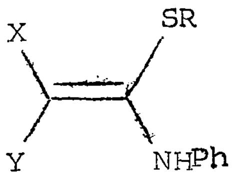

X
Y
+ Ar–N=C=S
Base
DMF
1
X
S⊖Na⊕
Y
NHPh
2
R–hal
X
SR
Y
NHPh
3 (Table 1)
(Ref. 3-9)
R1
O
NHPh
R2
R3
S⊖Na⊕
4
Br
Br
–NaBr; –HBr
R1
O
Ph
N
R2
R3
S
5 a, R1=Cl; R2=H; R3=H
b, R1=R2=Cl; R3=H
c, R1=Cl; R2=H, R3=CN
(Ref. 6,10)

TABLE 1



3

3, X = NO_2; Y = H; R = Me

X = NO_2; Y = PhCO; R = CH_2Ph,

CH_2NO_2, CH_2COMe, CH_2COPh

X = o-ClC_6H_4CO, o-BrC_6H_4CO,

2,5-$Cl_2C_6H_3CO$; Y = H; R = Me

X = CN, COOEt, $CONH_2$, Ph; Y = CN;

R = CH_2CN, CH_2COOR, CH_2CONH_2

X = COOMe; Y = CN, COOMe; R = Me,

allyl, crotyl

X = COOEt; Y = COOEt, COMe; R = Me,

allyl, crotyl

X = COMe; Y = H, COMe; R = Me, allyl

preparation of S,N-acetals exclusively. The S,N-acetals reported by this method are described in Table 1.

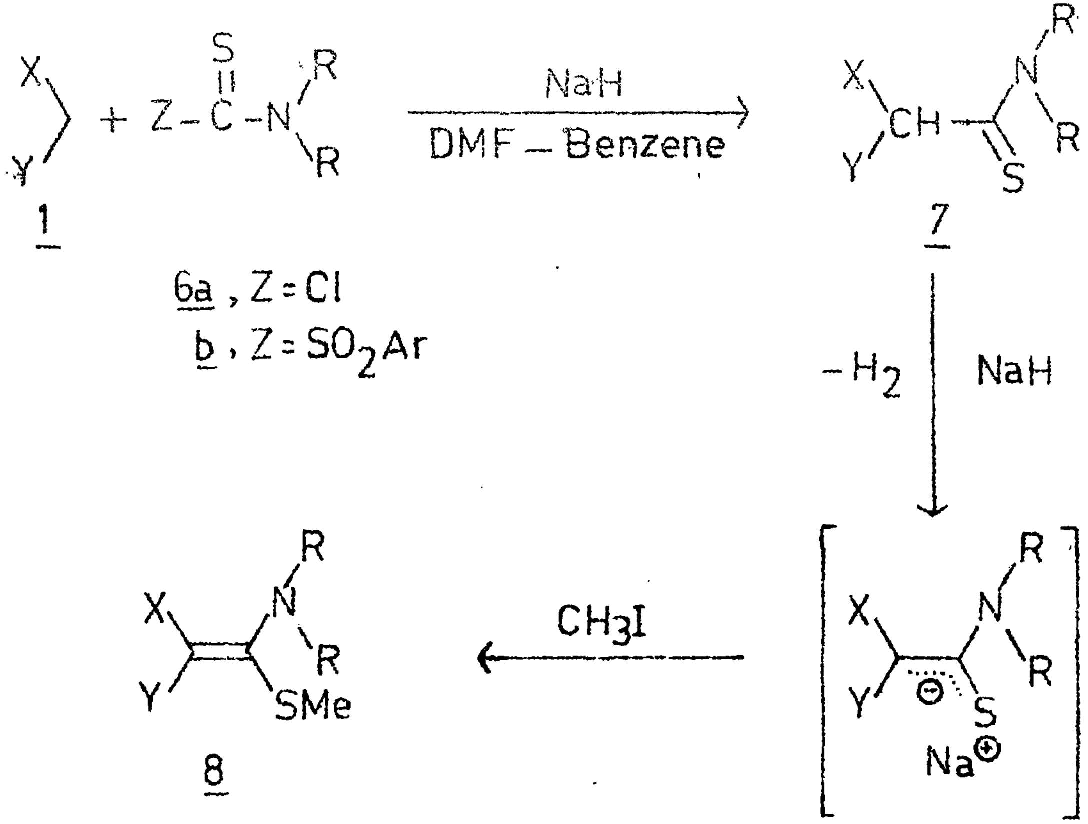
1.2.1.2 Using thiocarbamoyl chlorides and C-arylsulfonylthioformamides:

Active methylene compounds 1 (Scheme 2) have been reacted in the presence of sodium hydride and DMF-benzene mixture with thiocarbamoyl chlorides[11,12] 6a or C-arylsulfonylthioformamides 6b[12,13] to give the corresponding thioamides 7, which on subsequent alkylation gave S,N-acetals 8.

1.2.1.3 Using S-alkyl isothioureas and dithiocarbonic acid diester-imides:

Active methylene compounds are also shown to react with S-methyl isothioureas 9a[3,14,15] (Scheme 3) in neutral medium to give directly the corresponding keten-N,N-acetals 10-12. The method is also extended to prepare S,N-acetals 13 using dithiocarbonic acid-diester-imide 9b[3,14] in place of isothiourea derivatives. Generality of the method is apparent from the structural variants described in the Scheme.

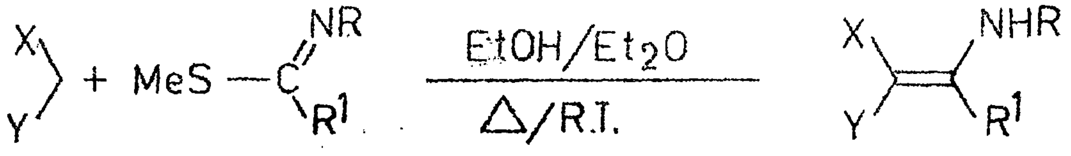
Scheme 2



6a , Z = Cl
b , Z = SO_2Ar

1 , 7 , 8a , X = Y = CN ; R = Me
b , X = Y = CN ; R = Me
c , X = CN ; Y = Ph ; R = Me
d , X = Y = CN ; R = CH_2Ph (Ref. 11–13)

Scheme 3



1 9a, $R^1 = N\Big\langle$ 10 – 13

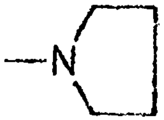
b, $R^1 = SMe$

1, 9, 10, X = C_6H_5CO, p – $CH_3C_6H_4CO$, p-ClC_6H_4CO,

1-thienyl-CO, 5-Cl-1-thienyl-CO;

Y = CN; R, R^1 = –$(CH_2)_3$ – N(Me)–

1, 9, 11, X = NO_2, Y = H; R = Me; $R^1 = -N\begin{smallmatrix}Me\\ Ph\end{smallmatrix}$, —N



1, 9, 12, X = Y = CN; R = Me; $R^1 = NMe_2$

1, 9, 13, X = Y = CN R = Me R^1 = SMe

(Ref. 3, 14, 15)

1.2.1.4 Using carbodiimides:

One of the versatile methods for the synthesis of keten-N,N-acetals 16 (Scheme 4) involves the use of carbodiimides.[3,16,17] Thus, when active methylene compounds are reacted with diaryl carbodiimides 14 in the presence of sodium ethoxide, the corresponding N,N-acetals 16 are formed in good yields (Table 2).

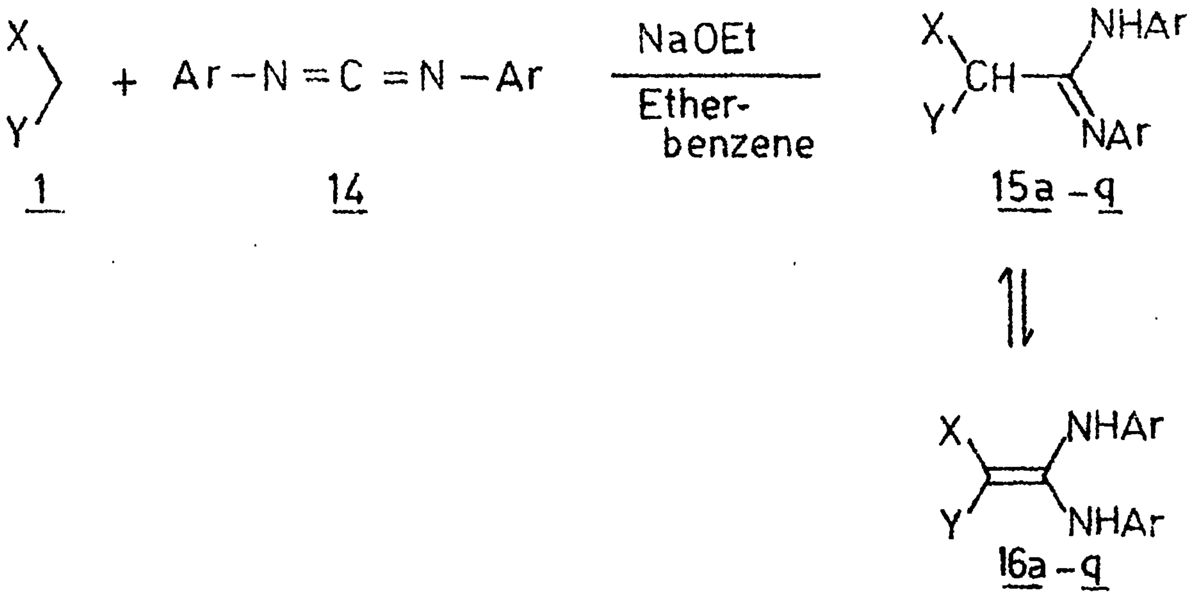
1.2.1.5 Using tris-(dimethylamino)-alkoxymethane:

Active methylene compounds 1 have been shown[18-20] to react with tris-(dimethylamino)-alkoxymethane (17) in dry benzene to give the corresponding keten-N,N-acetals 18 (Scheme 5) in good yields. Various N,N-acetals thus prepared are given in table 3.

1.2.2 Displacement Method

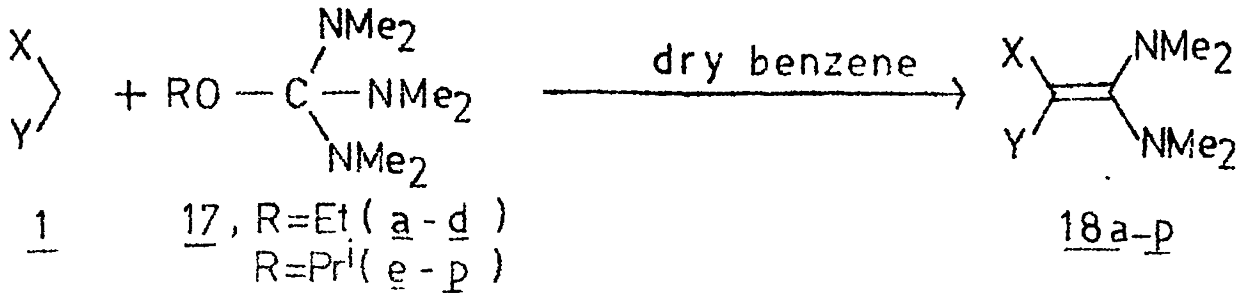
The reaction of keten-S,S-/O,O-acetals and keten-dihalides with amines constitutes one of the general methods for the synthesis of keten-S,N- and N,N-acetals. Easy, one pot preparative method for the synthesis of keten-S,S-acetals and their facile displacement reactions with amines, has made this route, a method of choice for the synthesis of keten-

Scheme 4



(Table 2)
(Ref. 3,16,17)

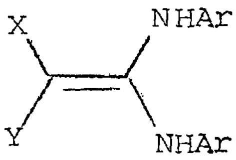
Scheme 5



(Table 3)

(Ref. 18 – 20)

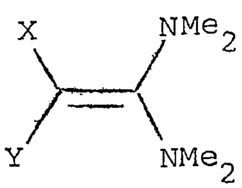
TABLE 2



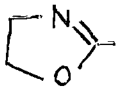
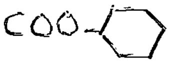
16

Product	X	Y	Ar
16a	COOEt	COOEt	C_6H_5
16b	COOMe	COOMe	C_6H_5
16c	COOEt	CN	C_6H_5
16d	COOMe	CN	C_6H_5
16e	CN	CN	C_6H_5
16f	COPh	COPh	C_6H_5
16g	COOEt	COPh	C_6H_5
16h	COMe	COPh	C_6H_5
16i	COOEt	COOEt	p-MeC_6H_4
16j	COOEt	COOEt	p-$EtOC_6H_4$
16k	COOEt	COOEt	p-$Me_2NC_6H_4$
16l	COOEt	COOEt	p-$NO_2C_6H_4$
16m	COOEt	COOEt	p-FC_6H_4
16n	COOEt	COOEt	3,4-$Cl_2C_6H_3$
16o	COOEt	COOEt	α-$C_{10}H_7$
16p	COOEt	COOEt	β-$C_{10}H_7$
16q	COOEt	CN	α-$C_{10}H_7$

TABLE 3



18

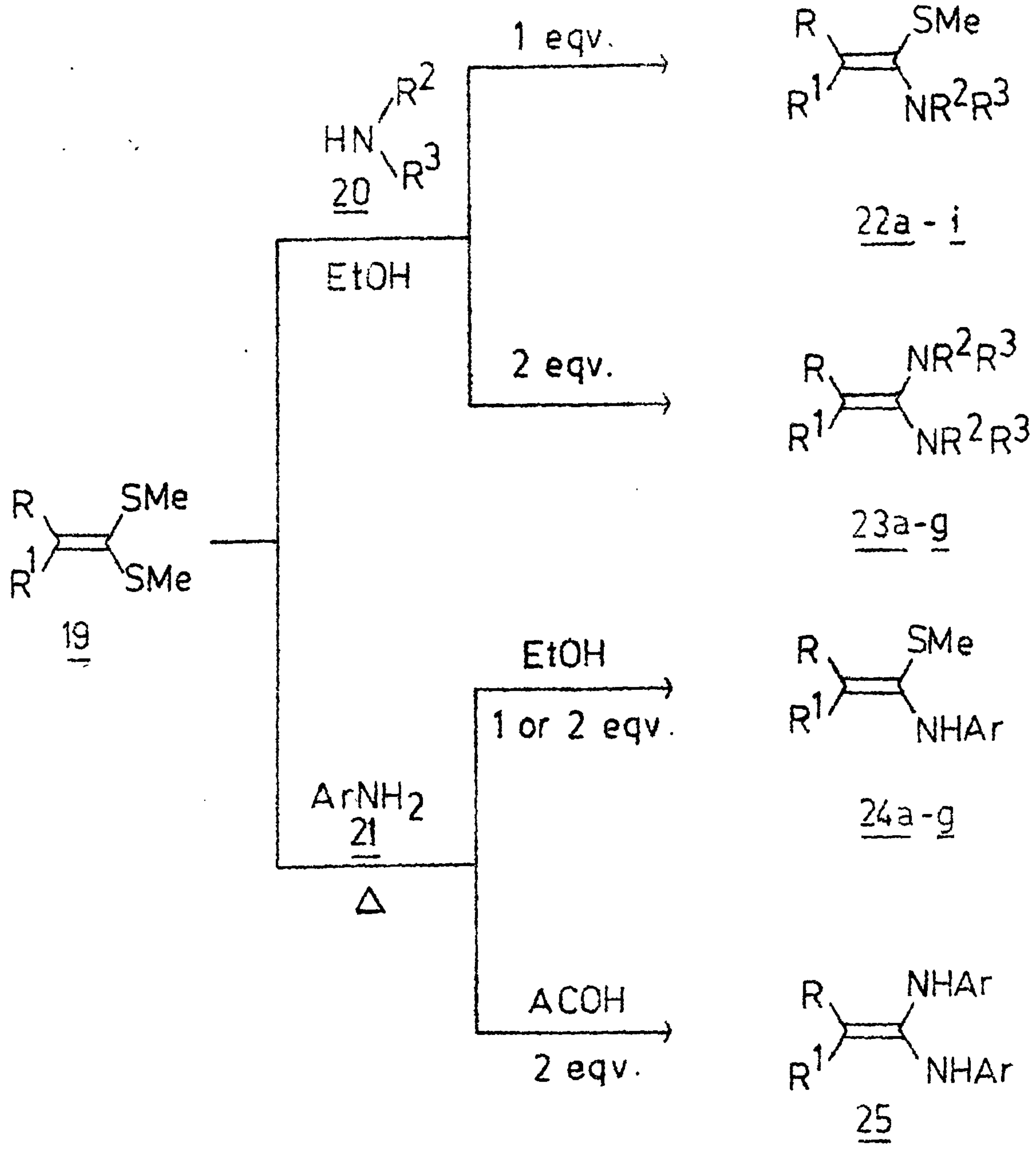
Product	X	Y
18a	PhCO	H
18b	Ph	CN
18c		H
18d	$CONH_2$	$CONH_2$
18e	CN	CN
18f	CN	COOEt
18g	CN	H
18h	CN	Me
18i	CN	n-Pr
18j	CN	NMe_2
18k	CN	OMe
18l	H	COOEt
18m	H	$CON(Pr^i)_2$
18n	H	$CONMe_2$
18o	H	$CON(Pr^n)_2$
18p	H	

S,N- and N,N-acetals. Thus, the keten-S,S-acetals 19 (Scheme 6)[3,4,15,21-25] react with ammonia, primary or secondary aliphatic amines 20 and primary aromatic amines 21 in ethanol to give the corresponding keten-S,N-acetals 22 and 24, N,N-acetals 23, or mixtures of S,N- and N,N-acetals, depending upon the stoichiometry of the amine used and the reaction conditions. However, their reactivity with aromatic amines in boiling acetic acid is more selective. Thus, S,S-acetals 19 when reacted with aniline and substituted anilines[6,26] yielded the corresponding N,N-acetals 25 in good yields. The keten-S,N- and N,N-acetals reported by this method are given in Table 4. The S,N-acetals can be subsequently used to prepare unsymmetrically substituted N,N-acetals.[21]

Dithioesters 30 (Scheme 7) reacted with aziridine in methanol at 20° to give the corresponding cyclic S,N-acetal 33 [3,27] in 57% yield. Similarly, keten-S,S-acetal 19 reacted with sodium-(2-amino-thiophenolate) (34) to give 2-dicyanomethylene-2,3-dihydro-(benzo-1,3-thiazole (35)[3,4] in 77% yield.

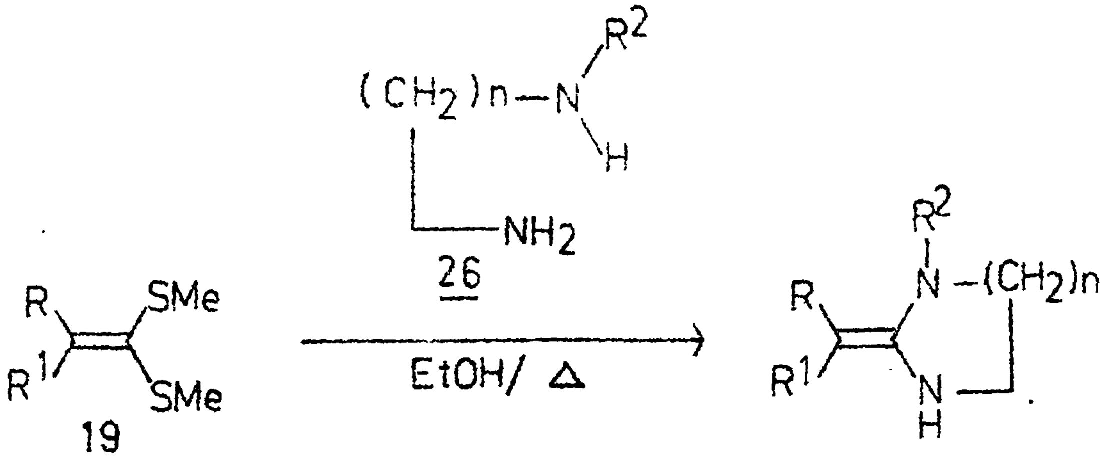
The thioamide 37 (Scheme 8) derived from the corresponding dithioester 36[23,27,28] and amine are

Scheme 6



(Table 4)

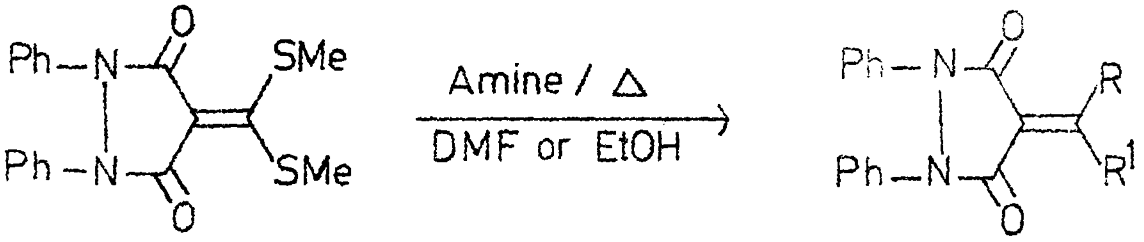
Scheme 6 contd.



19 26 27

$\underline{19}, \underline{26}, \underline{27}$, R = H ; $R^1 = NO_2$; R^2 = H, Me ; n = 1, 2
R = CN ; R^1 = CN ; R^2 = H ; n = 1
R = CN ; R^1 = COOEt ; R^2 = H ; n = 1
R = COOEt ; R^1 = COOEt ; R^2 = H ; n = 1
R = H ; $R^1 = C_6H_5CO$, $\underline{p}$-ClC_6H_4CO,
$\underline{p}$-$NO_2C_6H_4CO$; R^2 = Me ; n = 2

(Ref. 3,15,21,23,54)

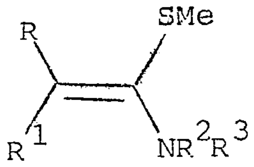


28 29

$\underline{29a}$, R = SMe ; $R^1 = NH_2$
$\underline{b}$, R = SMe ; $R^1 = HNPr^n$
c , R = R^1 = 1-aziridinyl
d , R , $R^1 = HNCH_2CH_2NH$

(Ref. 3 ,53)

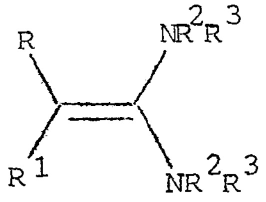
TABLE 4



22

Product	R	R^1	R^2	R^3	Ref.
22a	CN	CN	H	H	21
22b	CN	CN	$-(CH_2)_2-O-(CH_2)_2-$		3
22c	CN	COOMe	Me	Me	21
22d	CN	COOMe	H	H	21
22e	CN	COOEt	$-(CH_2)_2-O-(CH_2)_2-$		22
22f	CN	COOEt	$-(CH_2)_5-$		22
22g	NO_2	H	$-(CH_2)_5-$		25
22h	NO_2	H	H	CH_2Ph	25
22i	NO_2	H	H	$CH_2CH(OEt)_2$	25

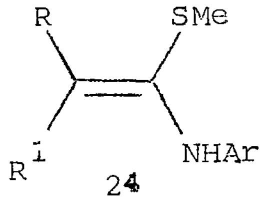
Table 4 (Contd.)



23

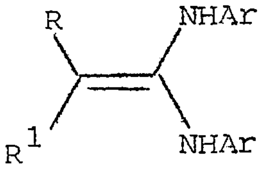
Product	R	R^1	R^2	R^3	Ref.
23a	NO_2	H	Me	Me	15
23b	NO_2	H	H	Me	15
23c	NO_2	H	H	CH_2Ph	15
23d	NO_2	H	$-(CH_2)_2-O-(CH_2)_2-$		15,23
23e	NO_2	H	$-(CH_2)_4-$		15
23f	NO_2	H	$-(CH_2)_5-$		25
23g	CN	COOEt	H	n-Bu	3,4

Table 4 (Contd.)



24

Product	R	R^1	Ar	Ref.
24a	CN	CN	C_6H_5	21
24b	CN	COOMe	C_6H_5	21,24
24c	CN	CN	p-$CH_3OC_6H_4$	21
24d	CN	CN	β-$C_{10}H_7$	21
24e	CN	COOMe	p-$CH_3OC_6H_4$	21
24f	CN	COOMe	β-$C_{10}H_7$	21
24g	NO_2	H	C_6H_5	23



25

25, R =H;

R^1=C_6H_5CO, p-BrC_6H_4CO, p-ClC_6H_4CO,

p-$CH_3OC_6H_4CO$, p-$CH_3C_6H_4CO$,

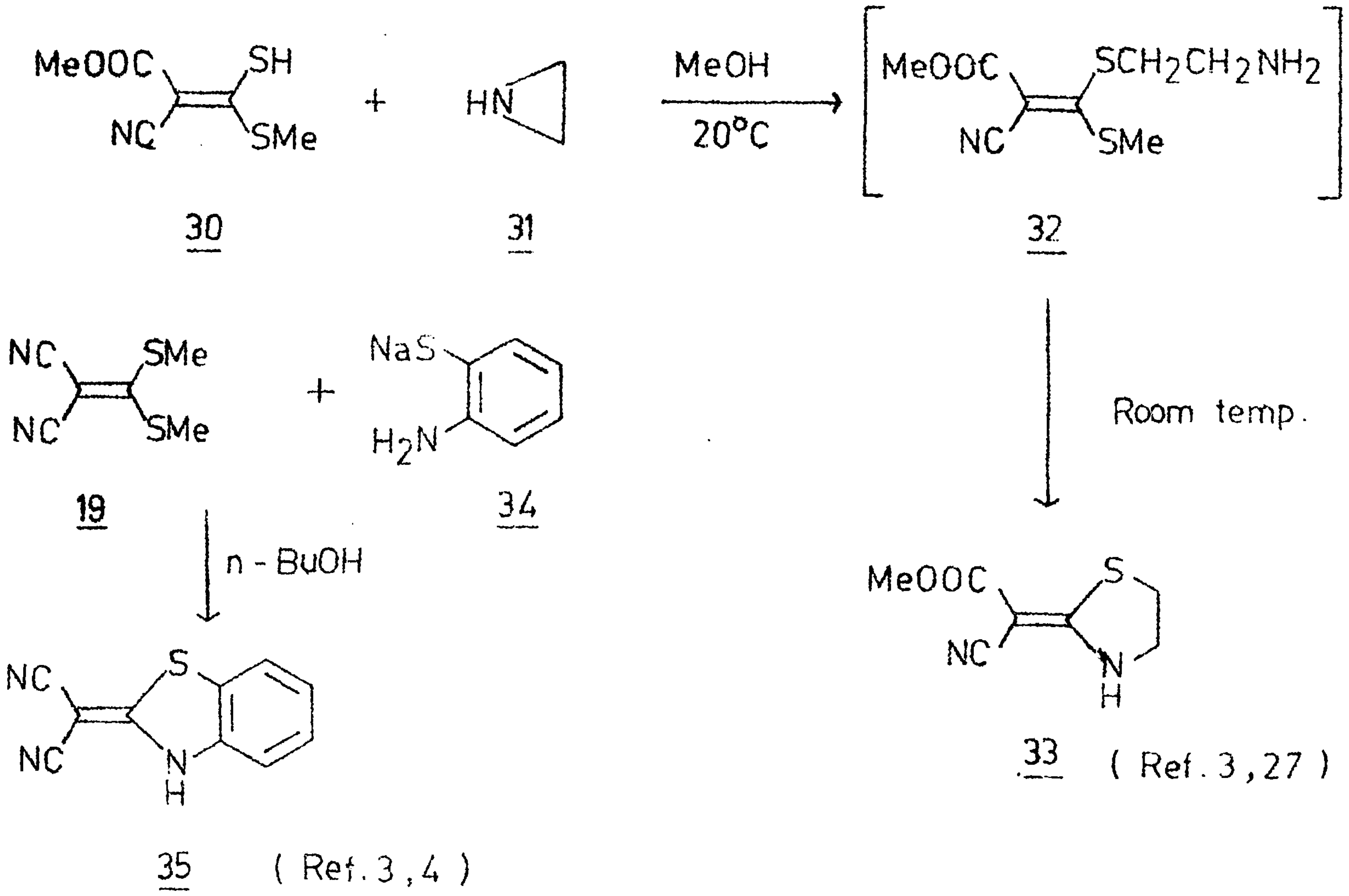
o-ClC_6H_4CO, 2-thienyl-CO;

Ar=C_6H_5, p-$CH_3C_6H_4$, p-$CH_3OC_6H_4$,

o-$CH_3C_6H_4$, m-$CH_3C_6H_4$

(Ref. 6,26)

Scheme 7


MeOOC
SH
NC
SMe
+
HN
MeOH
20°C
SCH2CH2NH2
30
31
32
Room temp.
NC
SMe
NaS
H2N
19
34
n - BuOH
S
N
H
33 (Ref. 3,27)
35 (Ref. 3,4)

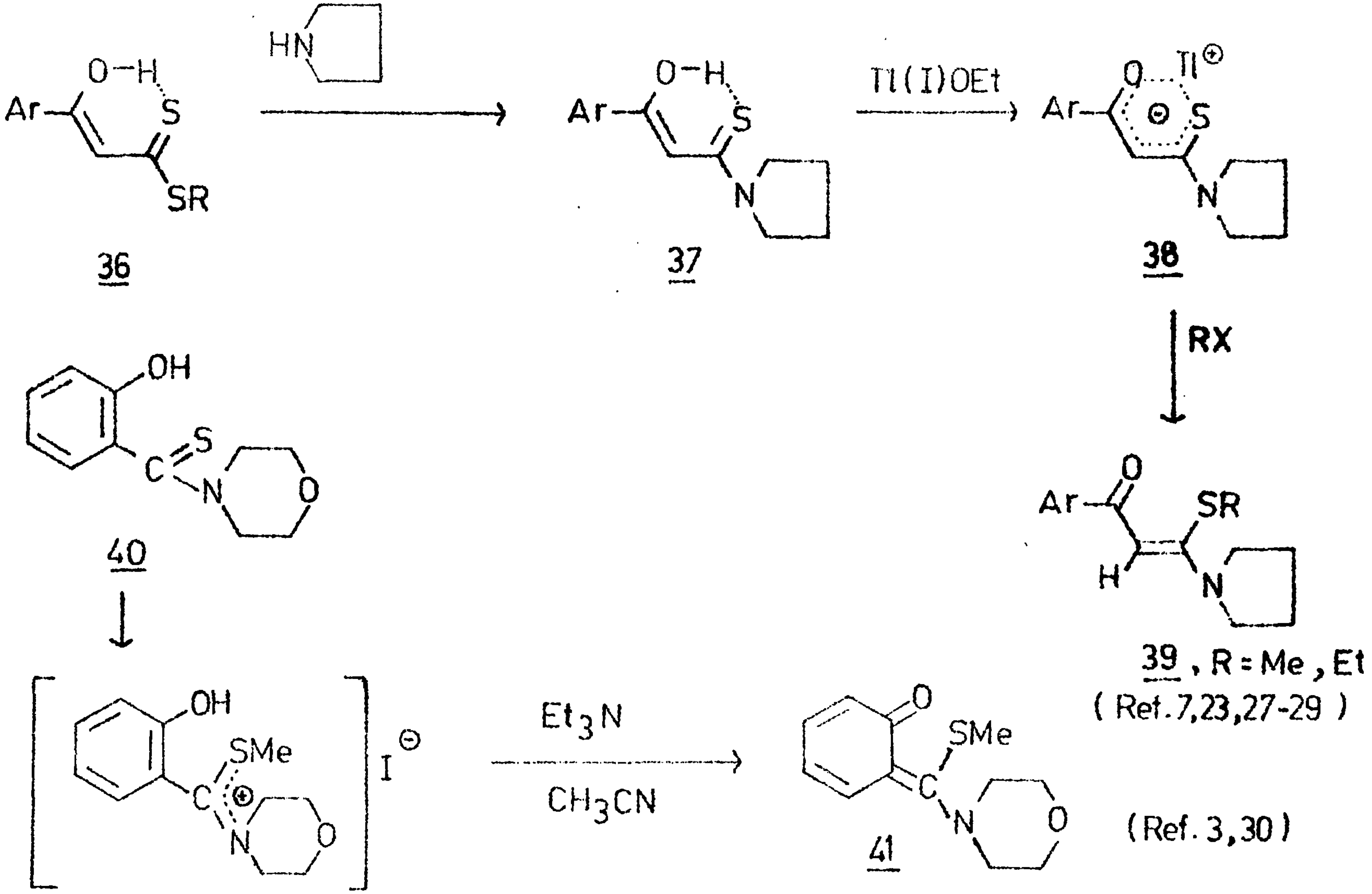
reported[7,29] to be alkylated to the corresponding keten-S,N-acetals 39 in good yields. Similarly, the formation of 41 from 40 is described.[3,30]

The keten-O,O-acetals 42 (Scheme 9) are more reactive towards amines than their sulfur analogues. Thus, 42 are reported[1,3,31-37] to react with one equivalent of amines to give the corresponding O,N-acetals in excellent yields. However, all the O,N-acetals reported in the literature are not discussed here. The formation of keten-N,N-acetals from the reaction of 42 with two equivalents of amines is very facile, and the N,N-acetals thus prepared are shown in the Scheme. The keten-dichlorides 45 (Scheme 9) also undergo facile displacement reaction with amines to give invariably the corresponding keten-N,N-acetals 46[3,38,39] in good yields. The method is not commonly used, since, the keten-dichlorides themselves are prepared from the corresponding keten-S,S-acetals and phosphorous pentachloride.

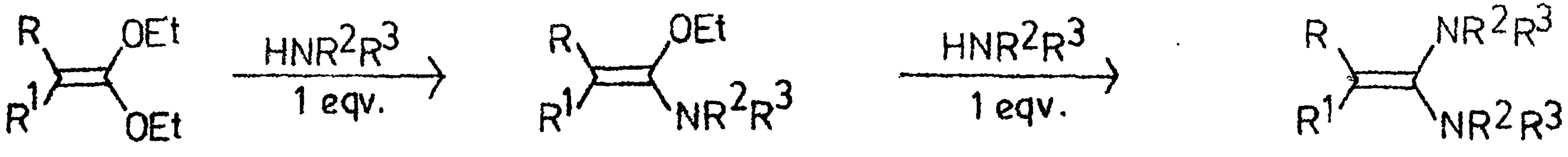
1.3 Reactions of keten-S,N- and N,N-acetals

Despite several methods reported in the literature, for the synthesis of polarized keten-S,N- and N,N-acetals, which are briefly described in the first part

Scheme 8


O–H
Ar
S
SR
36
HN
O–H
Ar
S
N
37
Tl(I)OEt
O
Tl⊕
Ar
⊖
S
N
38
RX
Ar
O
SR
H
N
39, R = Me, Et
(Ref.7,23,27-29)
OH
C
S
N
O
40
OH
SMe
C
⊕
N
O
I⊖
Et3N
CH3CN
O
SMe
C
N
O
41
(Ref. 3,30)

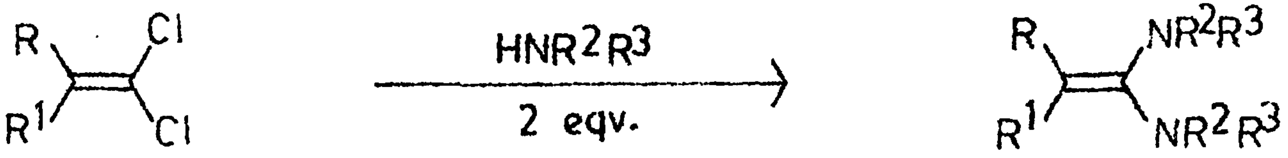
Scheme 9



42 43 44

$\underline{42}$-$\underline{44}$, R = COC_6H_5 ; R^1=H ; R^2=R^3 = $-(CH_2)_5$
R = R^1=H ; R^2=R^3 = $-(CH_2)_{4,5}$
R = R^1 = CN ; R^2 = R^3 = H , Me
R = R^1 = CN ; R^2 = H ; R^3 = Me

(Ref. 1, 3, 31 – 37)



45 46

$\underline{45}$, $\underline{46a}$, R , R^1 = COOMe ; R^2 = H ; R^3 = C_6H_5
$\underline{b}$, R = H ; R^1 = COC_6H_5 ; R^2, R^3 = $-(CH_2)_2-$
$\underline{c}$, R = H ; R^1 = $\underline{p}-ClC_6H_4CO$; R^2, R^3 = $-(CH_2)_2-$

(Ref. 3, 38, 39)

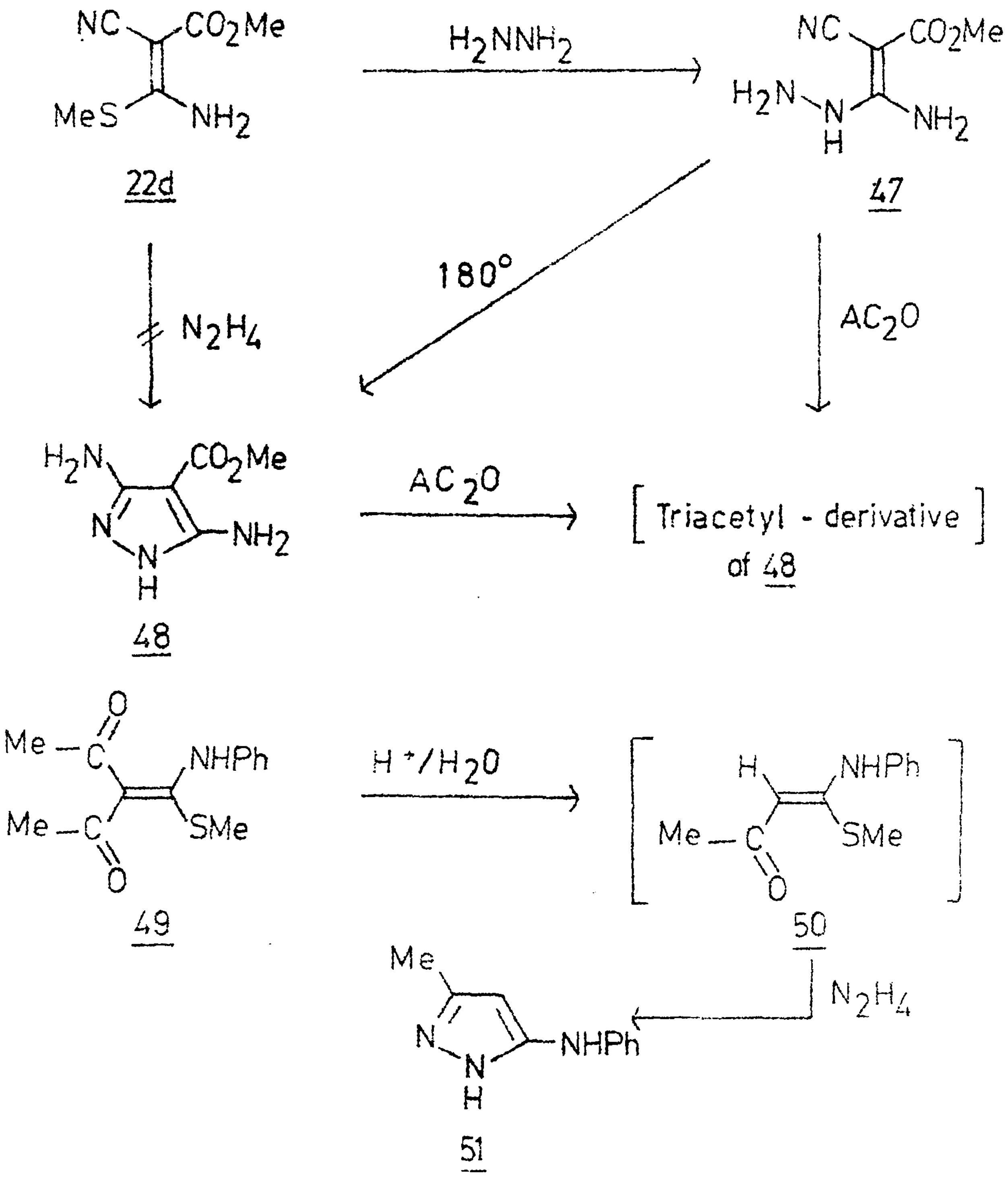
of this chapter, their synthetic utility as three carbon fragments or as a class of vinylamines and vinylogous amides has not been extensively explored. In this section, an attempt has been made to describe various reactions of the keten-S,N- and N,N-acetals, not only exemplifying their reactions as synthetic intermediates but also revealing their further scope in organic synthesis.

1.3.1 Synthesis of Pyrazoles and their derivatives

Although, keten-S,N- and N,N-acetals are less reactive than the corresponding S,S- and O,O-acetals, their reactivity towards nitrogen nucleophiles appears to follow the parallel routes of those of their sulfur analogues.

The keten-S,N-acetal 22d (Scheme 10) when reacted with hydrazine hydrate is reported[40] to undergo only displacement reaction initially, to give an open-chain compound 47 which underwent cyclization at 180° to give 3,5-diamino-4-methoxycarbonyl-pyrazole (48). The S,N-acetal 49, derived from 1,3-diketone, reacted with hydrazine in the presence of an aqueous acid to give 3(5)-anilino-5(3)-methylpyrazole (51) involving deacetylation of 49.

Scheme 10


22d
H2NNH2
47
N2H4
180°
AC2O
48
AC2O
[Triacetyl - derivative of 48]
49
H+/H2O
50
N2H4
51

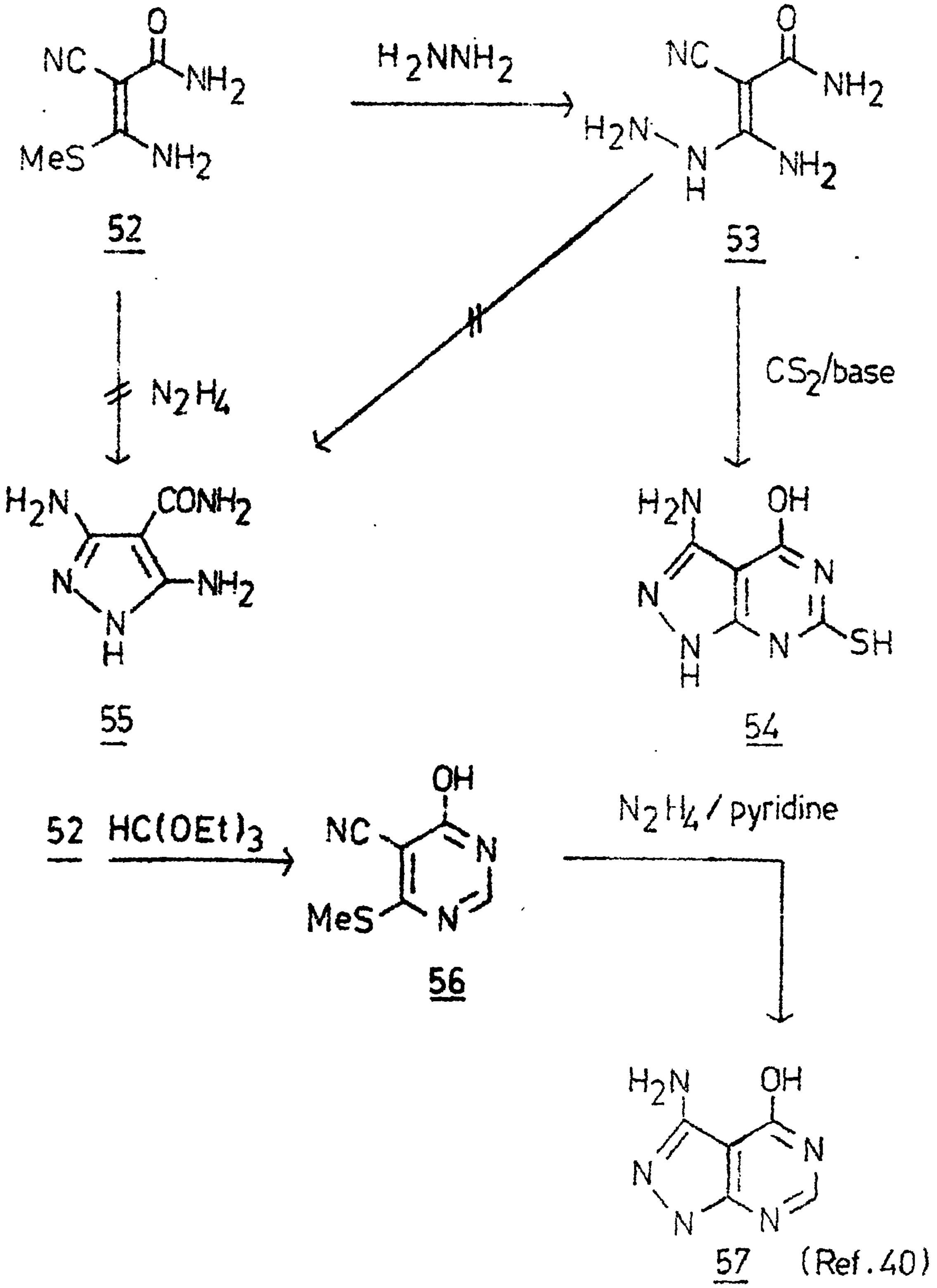
Similar reaction of hydrazine hydrate with keten-S,N-acetal 52 yielded only the open-chain compound 53 which failed to cyclise to 55. However, 53 underwent smooth condensation with carbon disulfide in the presence of a base to give pyrazolopyrimidine 54. Similarly 52 was shown to react with triethylorthoformate to yield functionalised pyrimidine 56 which on reaction with hydrazine hydrate in the presence of pyridine gave the pyrazolopyrimidine 57.

In another reaction, the keten-S,N-acetal 58 is reported[10] to react with hydrazine hydrate to give a mixture of 3-aminopyrazole 59 and 3,5-diaminopyrazole 60 (Scheme 11). An interesting variation of the reaction of S,N-acetals, generated *in situ*, by reacting keten-S,S-acetals with amines, is reported[41] from this laboratory. Thus, when 61 was first refluxed with one equivalent of an amine, followed by gradual addition of hydrazine hydrate, the product analysis showed the formation of pyrazole 63 in excellent yield.

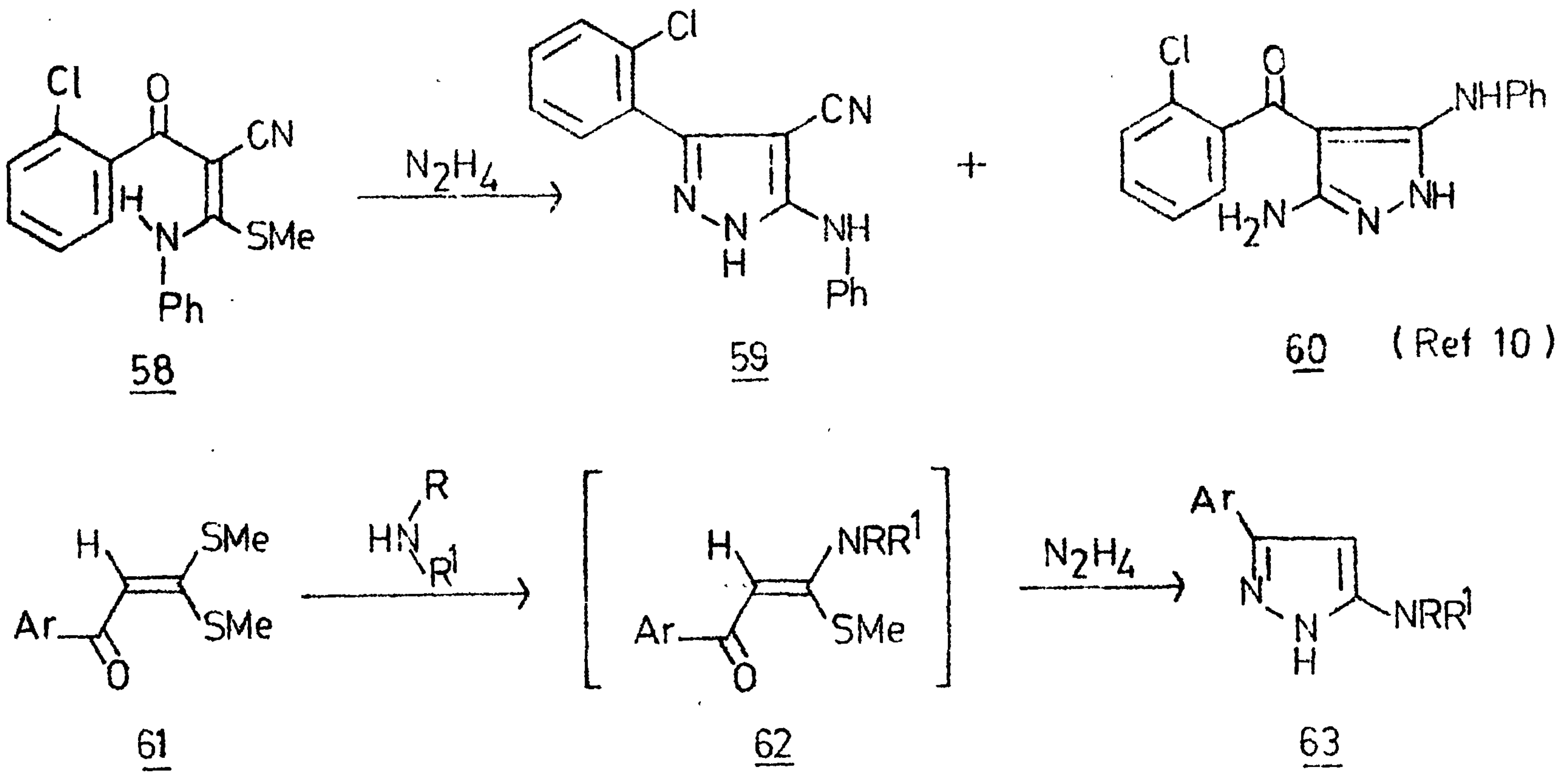
1.3.2 Synthesis of Thiophenes

The nitro-N,N-acetals 64 (Scheme 12) are reported[42,43] to react with alkyl and aryl isothiocyanates in boiling toluene to give thioamide intermediates 65 which are subsequently shown to react

Scheme 10 continued



Scheme 11



61-63, R, R^1 = morpholino;
β-aminoethyl-4-phenyl-piperazino
(Ref. 41)

with α-haloketones to yield the corresponding thiophenes 66.

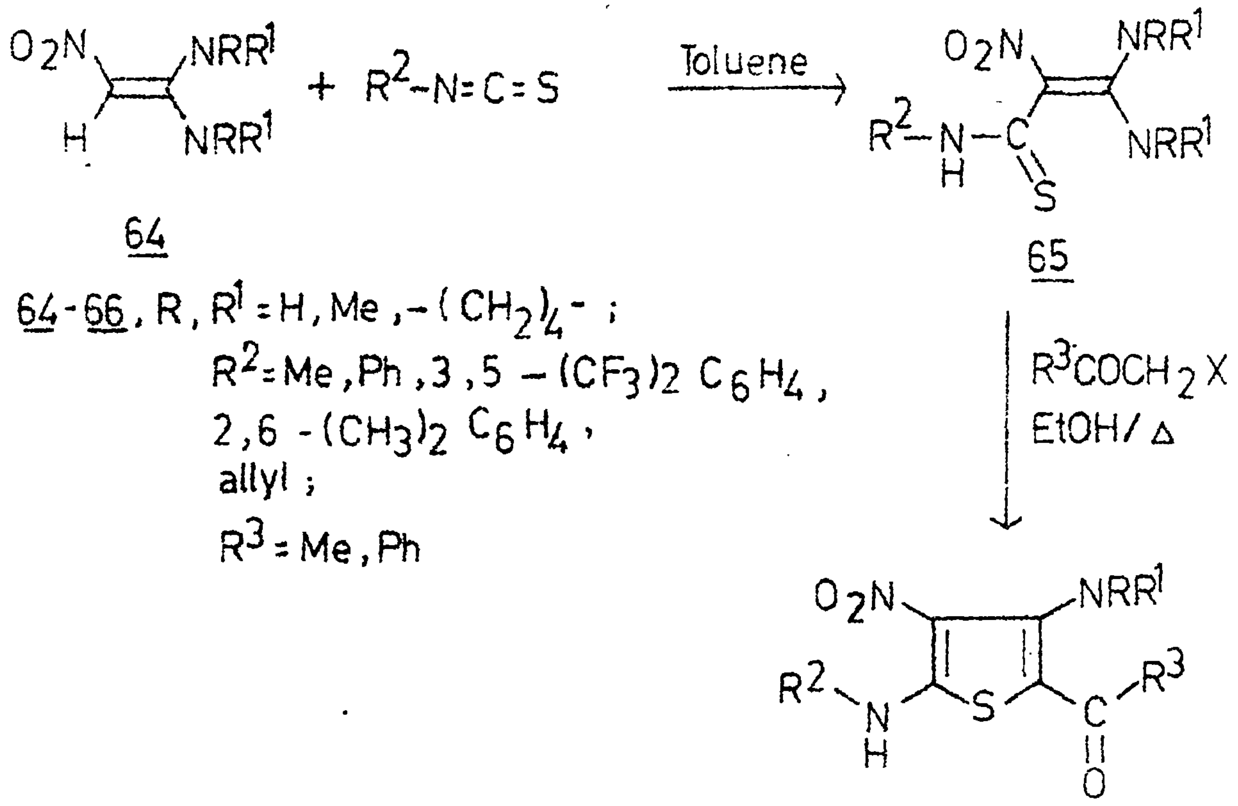
Thiophenes have also been reported[5,8] through base catalysed intramolecular cyclisation of functionalised keten-S,N-acetals. Thus, 67 in the presence of sodium alkoxide, underwent cyclisation to give thiophenes 68. The reaction was shown to be general for substituents described in scheme 12.

1.3.3 Synthesis of Pyrroles and Pyrrolines

We have shown from our laboratory that the keten-S,N-acetals derived from functionalised amines, undergo interesting intramolecular cyclisation to give 2,3-disubstituted-pyrroles (Scheme 13).[44] Thus, when 69 was reacted with aminoacetaldehyde-diethylacetal in refluxing ethanol, the S,N-acetals 70 formed in good yields, underwent cyclisation in ethereal-hydrochloric acid to give 2-thiomethylpyrroles 71.

Another variations of this method is reported[45] again from our laboratory, for the synthesis of 2-aminopyrroles. Keten-S,S-acetals 72 (Scheme 14) derived from 4-aryl-4-oxobutanenitriles, underwent

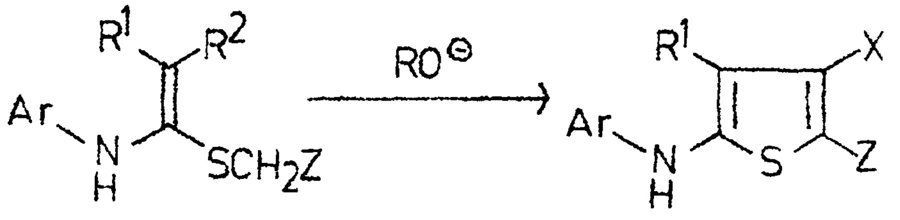
Scheme 12



64 65 66

(Ref. 42,43)

64-66, R, R^1 = H, Me, $-(CH_2)_4-$;
R^2 = Me, Ph, 3,5 $-(CF_3)_2C_6H_4$,
2,6 $-(CH_3)_2C_6H_4$,
allyl ;
R^3 = Me, Ph

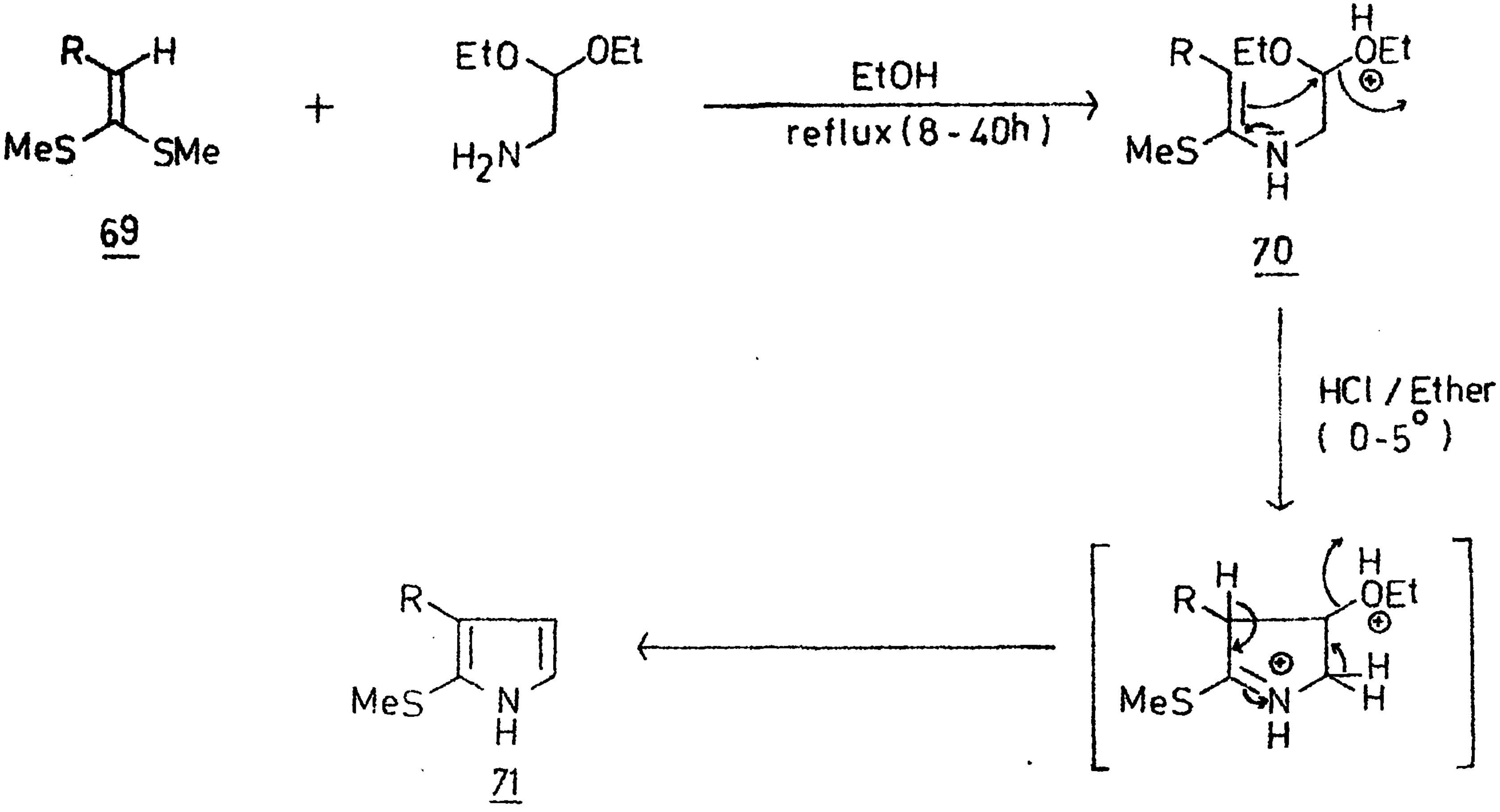


67 68

67, 68, R^1 = CN COOEt $CONH_2$, NO_2 ;
R^2 = CN, PhCO ;
Z = CN, COOEt, $CONH_2$,
MeCO, PhCO, NO_2 ;
X = NH_2, Ph

(Ref. 5,8)

Scheme 13



$\underline{69}$-$\underline{71}$, R = ArCO, NO_2

(Ref. 44)

facile condensation with various amines to give 2-aminopyrroles 74 involving the S,N-acetal , *in situ*. The method is of general application for the synthesis of 2-amino-3-unsubstituted-pyrroles which are useful intermediates for the synthesis of 7-azaindoles.

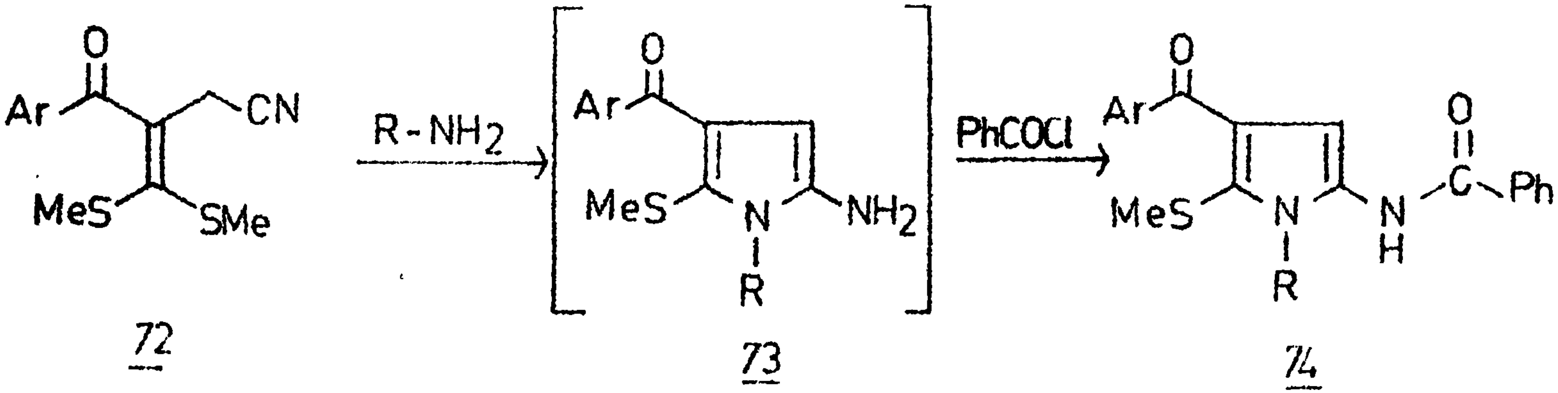
The photochemical transformation of keten-N,N-acetal 75 (Scheme 15) is reported[46] to yield pyrrole 76.

Although polarized keten-S,N-acetals were known to react with primary and secondary amines, their reaction with aziridine was not reported till recently. We have reported in our earlier work,[47] that the doubly polarized keten-S,S-acetals 77 (Scheme 16) reacted with aziridine to yield the corresponding S,N-aziridino acetals 78 in excellent yields. These intermediates were shown to undergo facile potassium iodide induced rearrangement to give the corresponding pyrrolines 79. The method is extended to accomplish identical transformation to give novel spiro-pyrrolines 82, under identical reaction conditions. This is the first report of the pyrroline synthesis via rearrangement of vinylaziridines.

1.3.4 Synthesis of Thiazoles and Isothiazolines

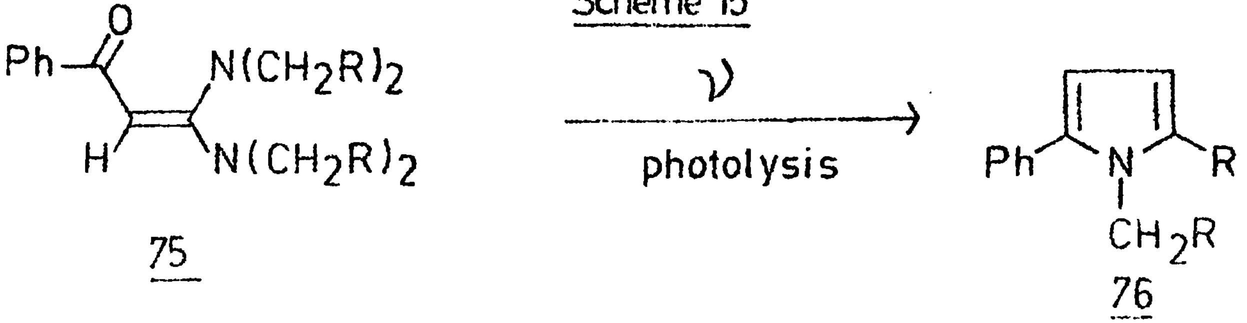
The nitroketen-N,N-acetal 23a[15] (Scheme 17) is

Scheme 14



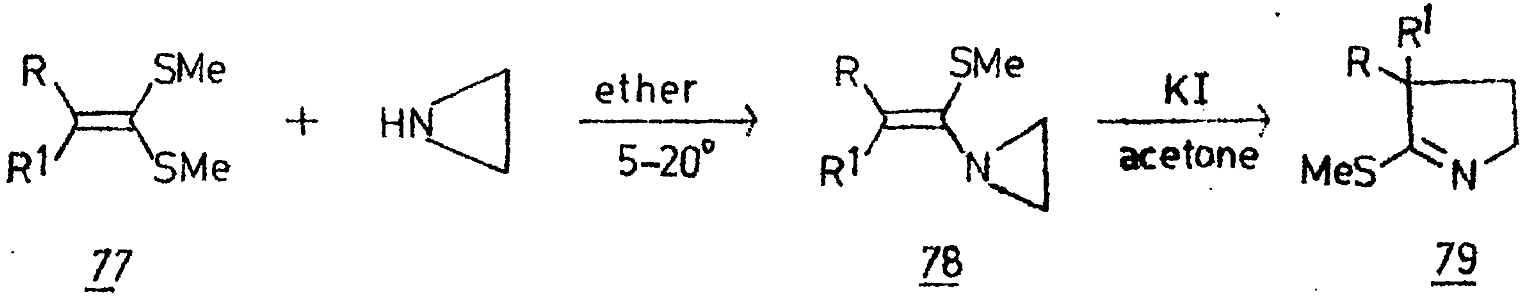
72–74, Ar=C_6H_5, p-ClC_6H_4, p-$MeOC_6H_4$;
R=CH_3, C_2H_5, $CH_2C_6H_5$ (Ref. 45)

Scheme 15

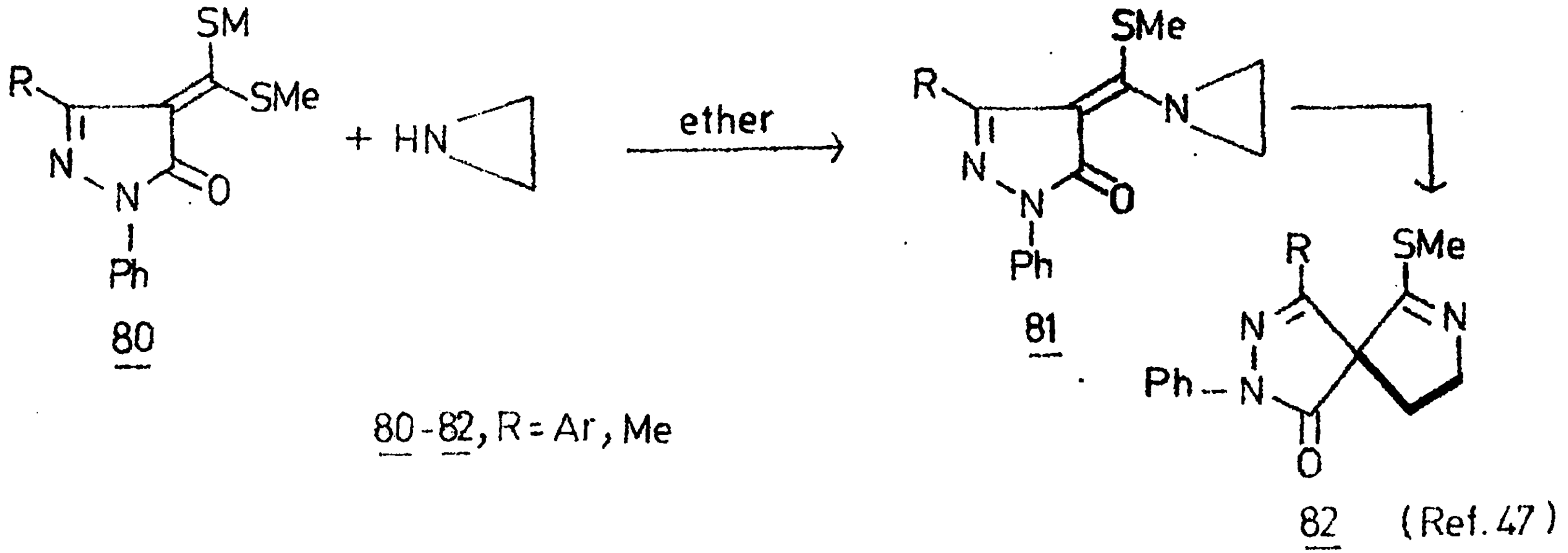


75, 76, R = H, Et, Pr^i (Ref 46)

Scheme 16



77–79, R = CN ; R^1 = $CONH_2$
R = H, CN; R^1 = COOEt



80-82, R = Ar, Me

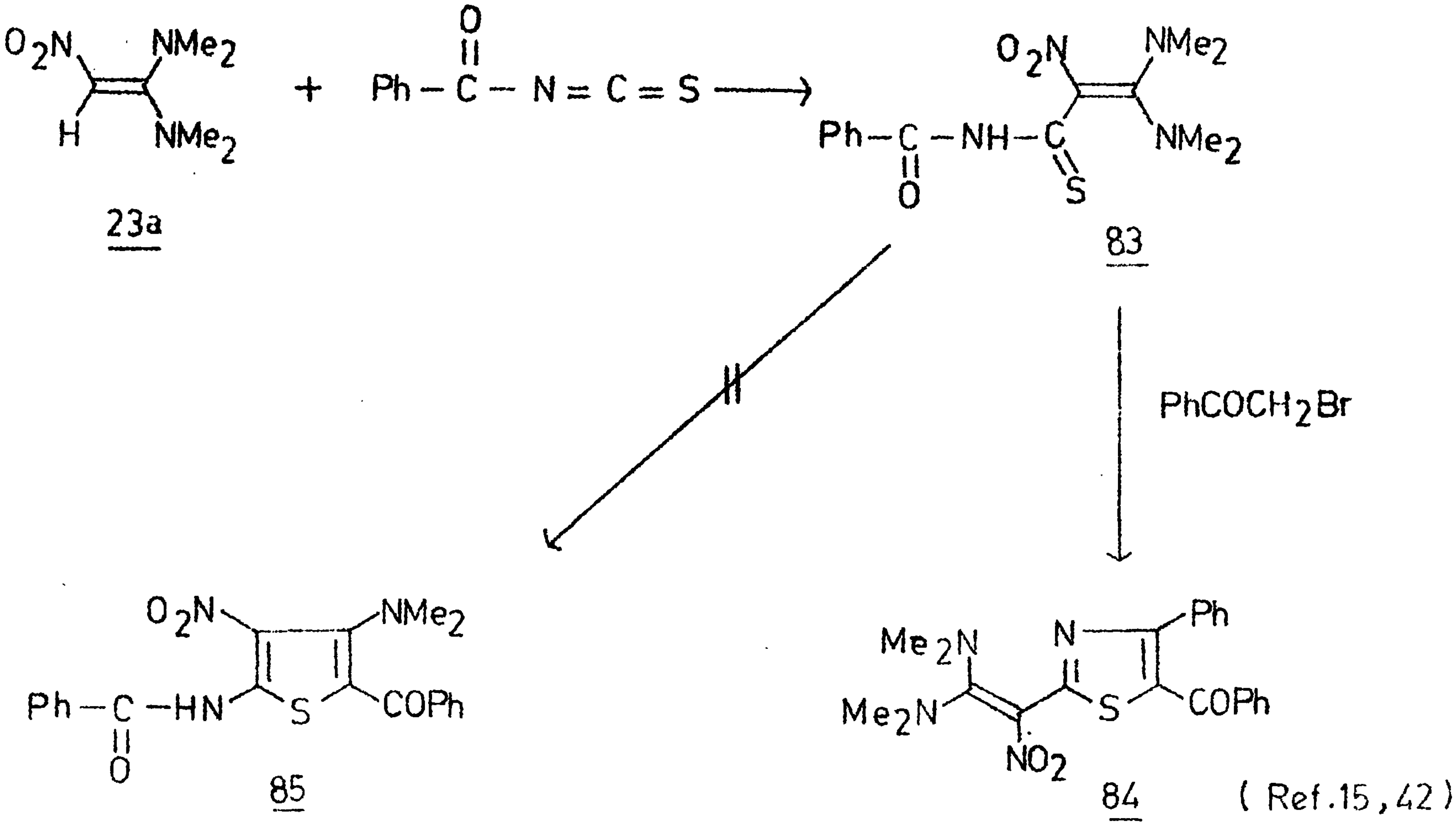
reported[42] to react with aroyl isothiocyanate to yield the adduct 83 which reacted with phenacyl bromide to yield thiazole 84 instead of the expected thiophene 85.

The adduct 86 (Scheme 18)[48,49] derived from nitro-N,N-acetal 23b and aryl isothiocyanates [illegible], underwent oxidative ring closure with bromine in acetic acid to give 4-nitro-isothiazolines 87, while 89 derived from unsymmetrical nitro-N,N-acetal 88 did not yield the isothiazoline 90 *under similar conditions* but gave benzthiazole 91. The condensation products from nitroketen-N,N-acetals 92[15] (Scheme 19) and benzoyl isothiocyanate, on treatment with sulfuryl chloride, are reported[49,50] to yield isothiazolines 93, which were shown to undergo base catalysed fragmentation to give *hitherto* unreported 1,1-diamino-2-nitroacrylonitriles (94) in good yields. Similarly, when the adduct 96 from cyclic ketoketen-N,N-acetals 95 and benzoyl isothiocyanate was treated with sulfuryl chloride, only the chloro product 98 was obtained,[50] although, the formation of 97c was observed in traces when 96c was treated with bromine.

1.3.5 Synthesis of Isoxazoles

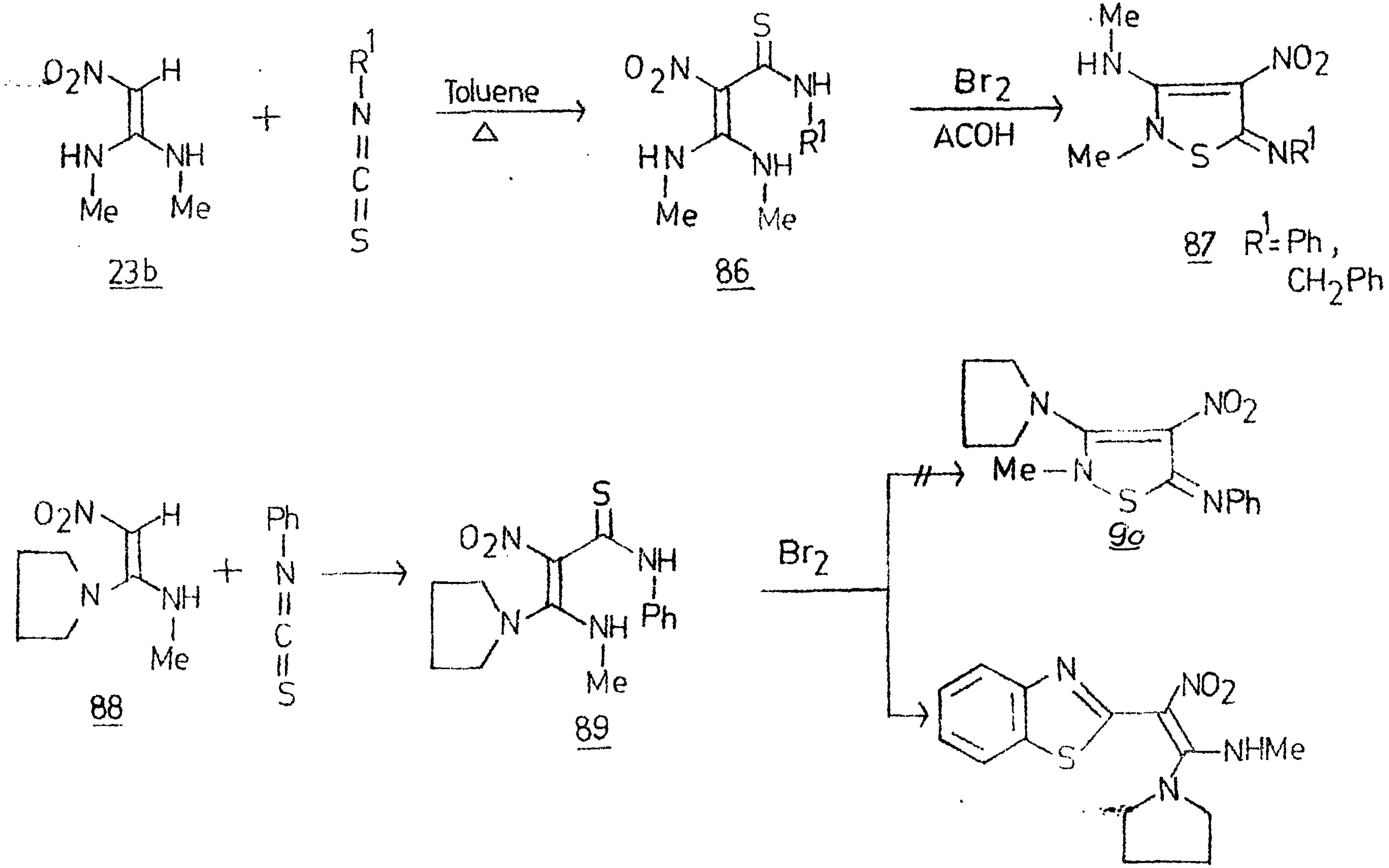
The keten-S,N-acetal 49 (Scheme 20) is reported[40] to react with hydroxylamine hydrochloride to give

Scheme 17



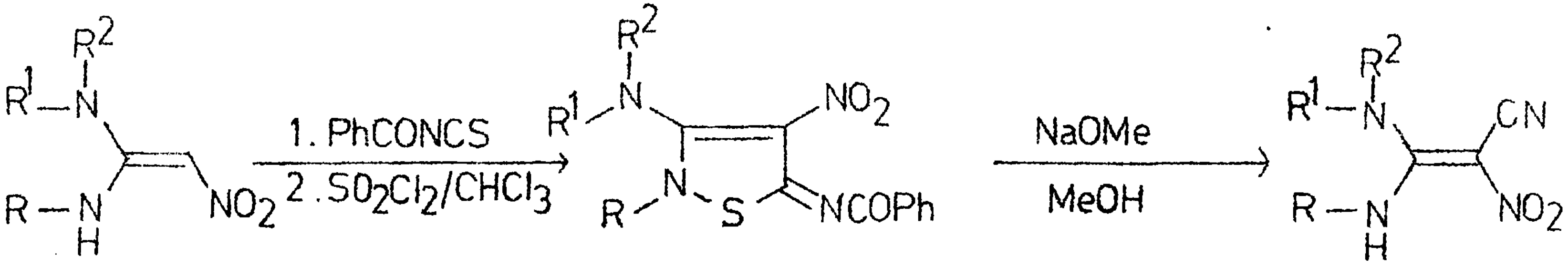
(Ref.15, 42)

Scheme 18



(Ref.48,49)

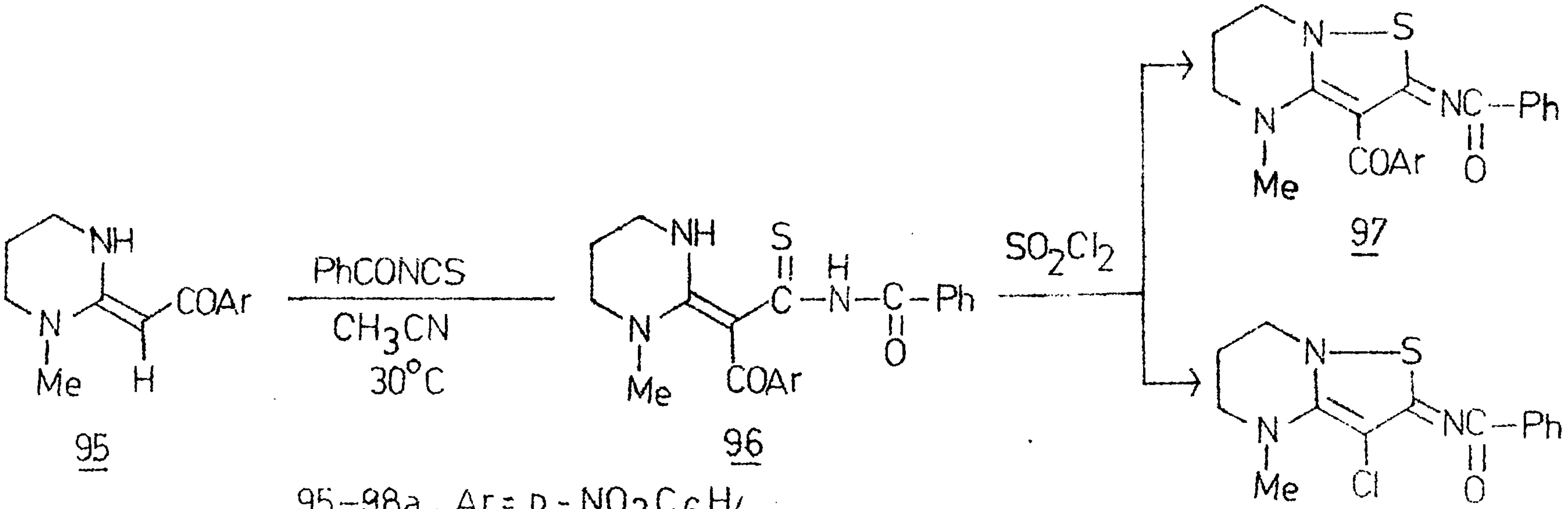
<ins>Scheme 19</ins>



92 93 94

92–94, R, R^1, R^2 = alkyl

(Ref.49)



95 96 97 98

95–98a, Ar = p - $NO_2C_6H_4$
b, Ar = C_6H_5
c, Ar = p - ClC_6H_4

(Ref. 50, 54)

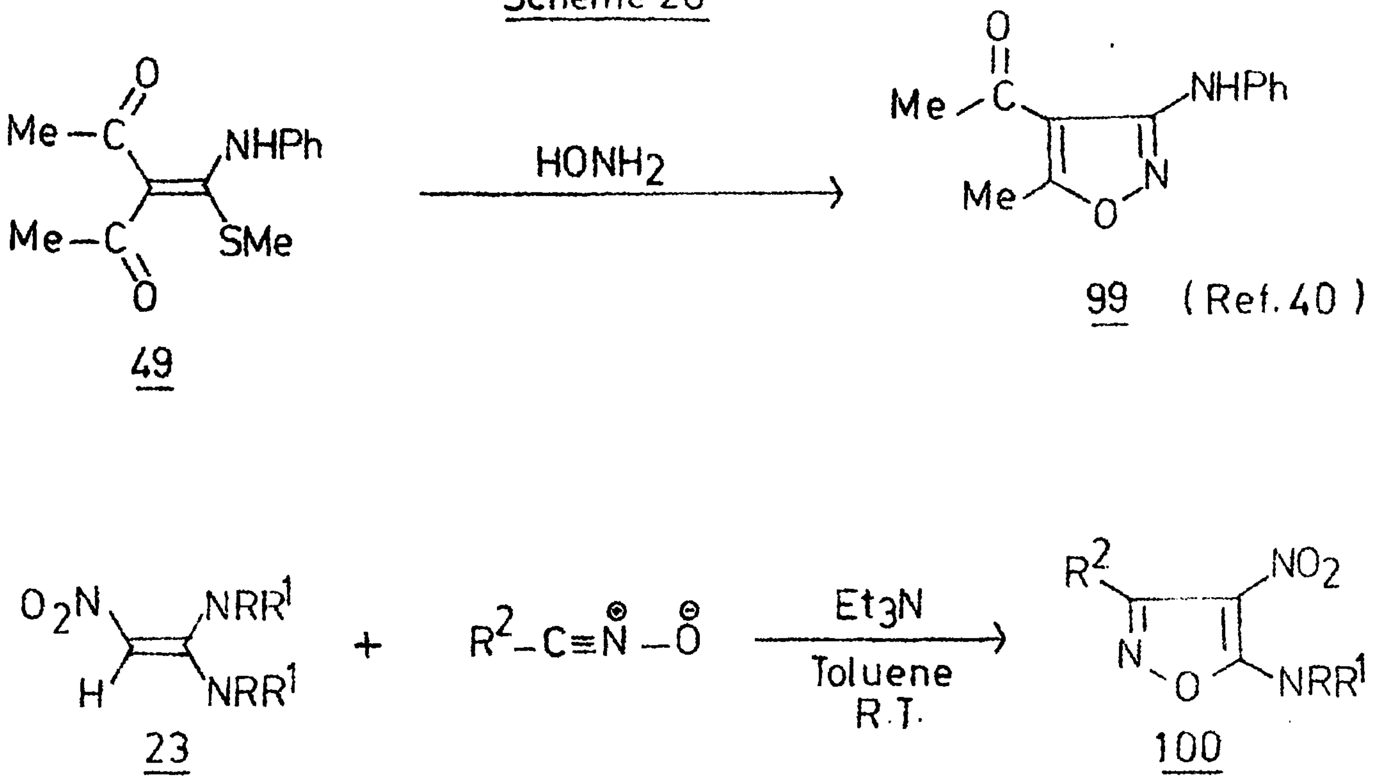
isoxazole 99. The nitroketen-N,N-acetals 23 and nitrile oxides were reacted[43] in the presence of triethylamine to give 4-nitroisoxazoles 100.

1.3.6 Synthesis of Quinolines and Pyrimidines

The keten-N,N-acetal 101a (Scheme 21) underwent thermal cyclisation in the presence of diphenylether to give quinolin-4-one 102, while 101b under similar conditions yielded tetrahydro-dibenzo-[b.g]-1,8-naphthyridin-dione-(11,12) (103).[16] The keten-N,N-acetal 101b and S,N-acetal 101c (Scheme 21) underwent intramolecular cyclisation in the presence of phosphorous oxychloride to give 4-chloroquinolines 104b and 104c[16,21,24] respectively. The S,N-acetal 105 however, in the presence of sodium hydride gave quinolin-4-one 106.[6,10]

Keten-N,N-acetal 18g reacted with formamidinium acetate (Scheme 22)[51] to yield pyrimidine-carbonitrile 107. Its reaction with acetyl chloride gave 108, which on alkylation yielded the N,N-acetal 109a. 109a subsequently reacted with guanidine or formamidine to give pyrimidines 110.

Scheme 20



49

99 (Ref. 40)

23

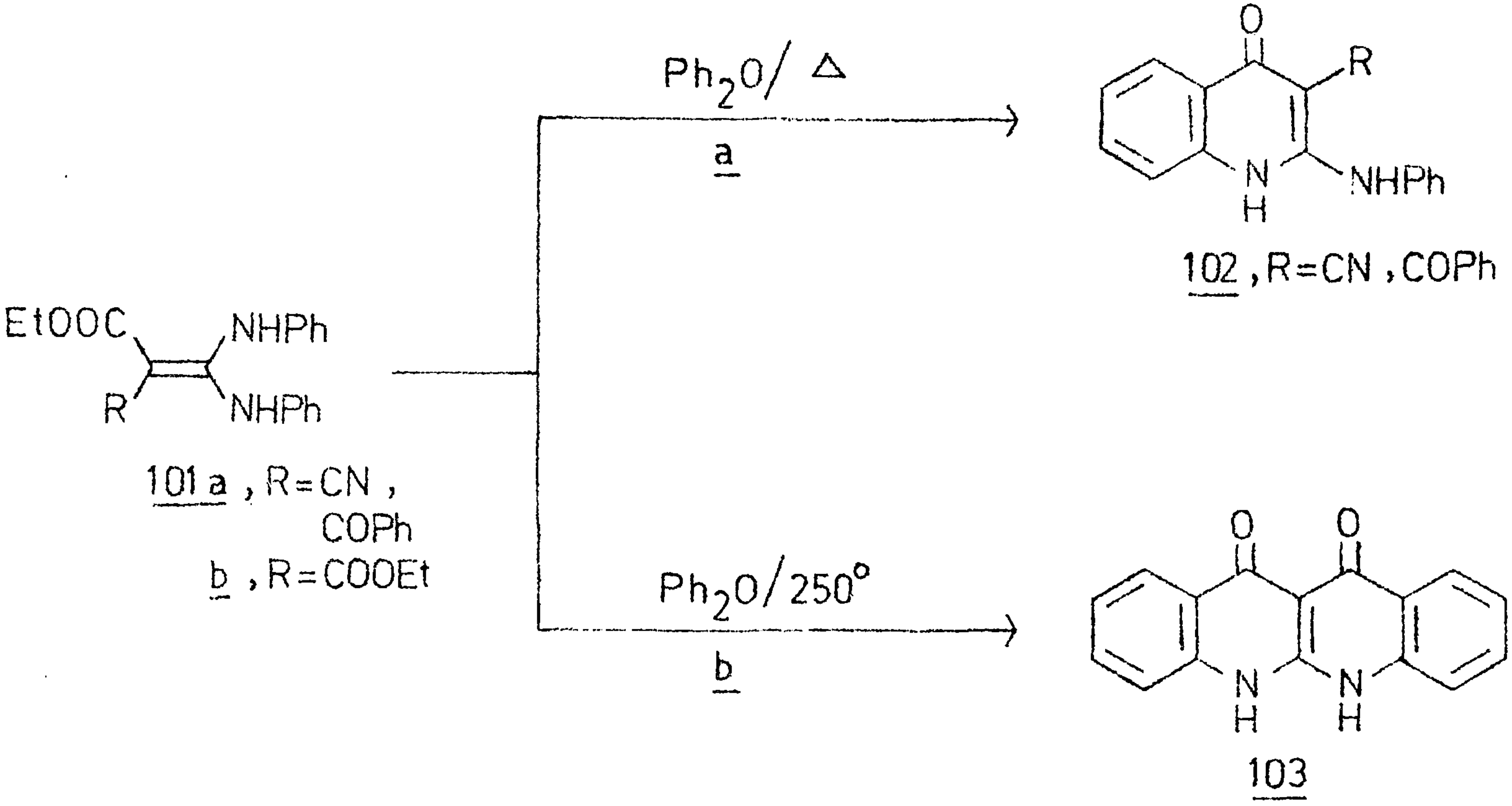
100

23, 100, $R, R^1 = -(CH_2)_4-$; $R^2 = $ p $- ClC_6H_4$, C_6H_5, Bu^t

$R = H$; $R^1 = Me$; $R^2 = $ p $- ClC_6H_4$

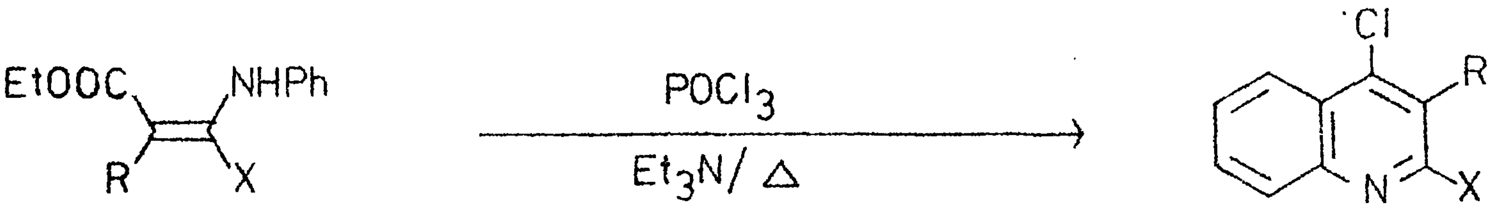
(Ref. 43)

Scheme 21



(Ref.16)

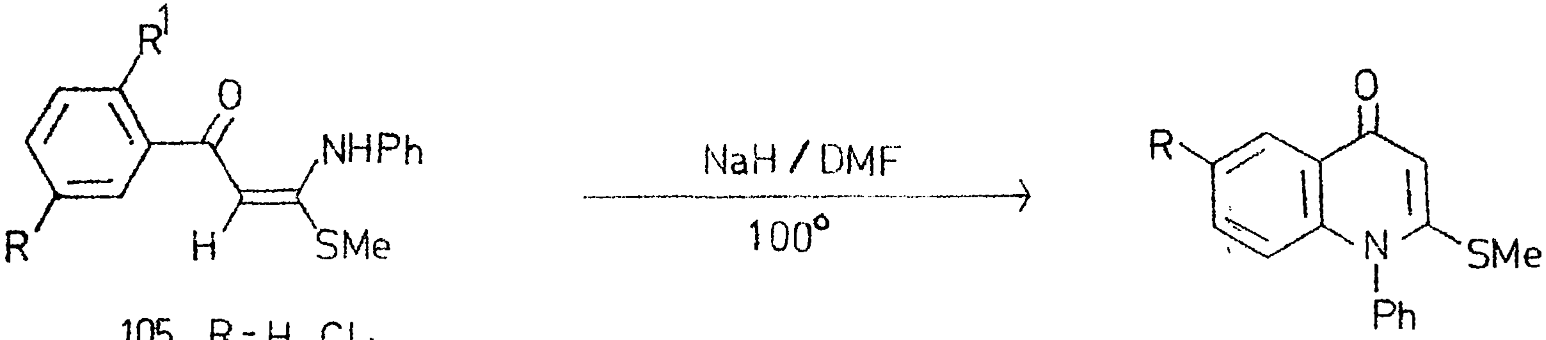
Scheme 21 contd.



101

104 (Ref.16,21,24)

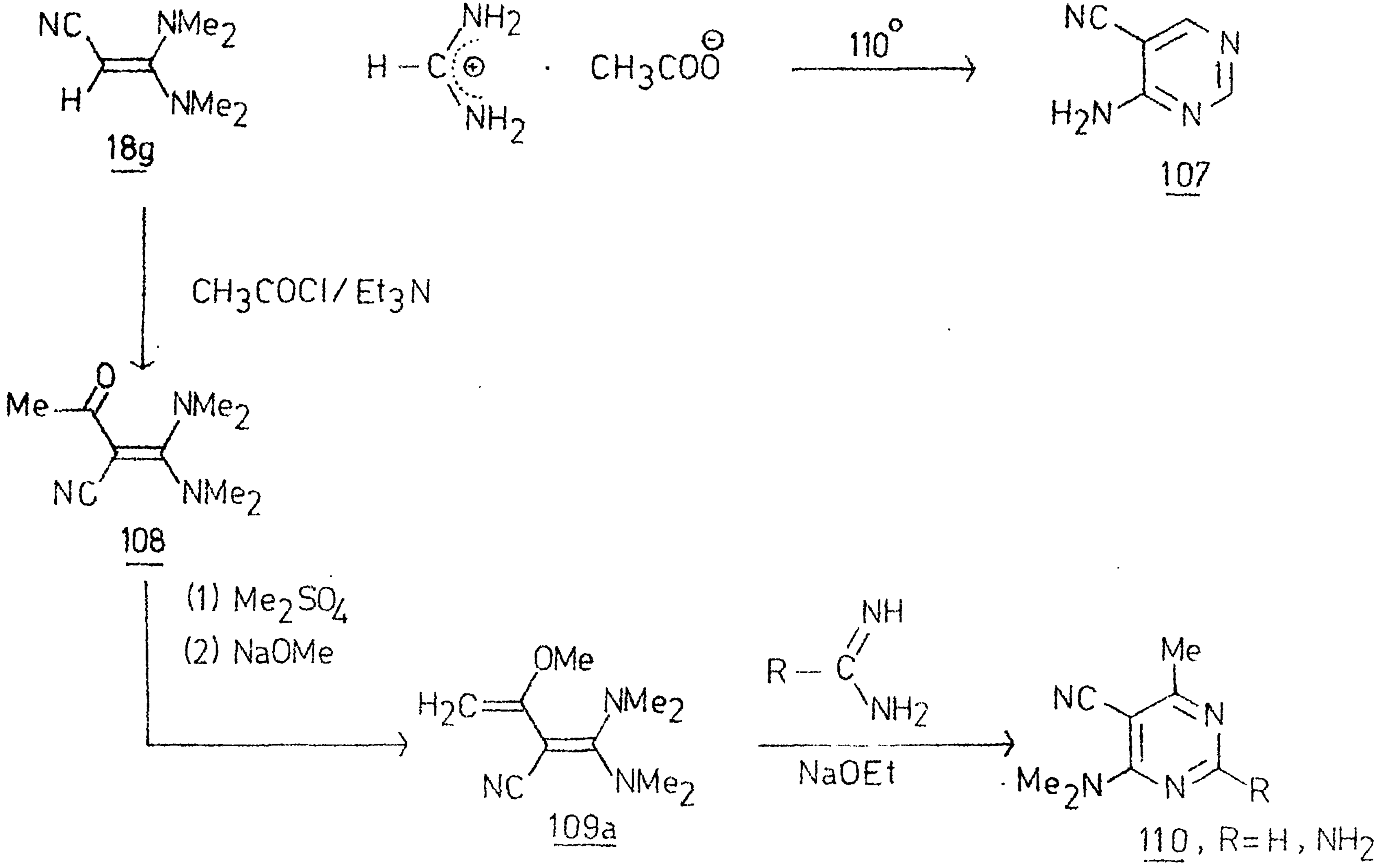
101, 104b, R = COOEt ; X = NHPh
c, R = CN ; X = SMe



105, R = H, Cl ;
R^1 = Cl, Br

106, R = H, Cl
(Ref. 6,10)

Scheme 22



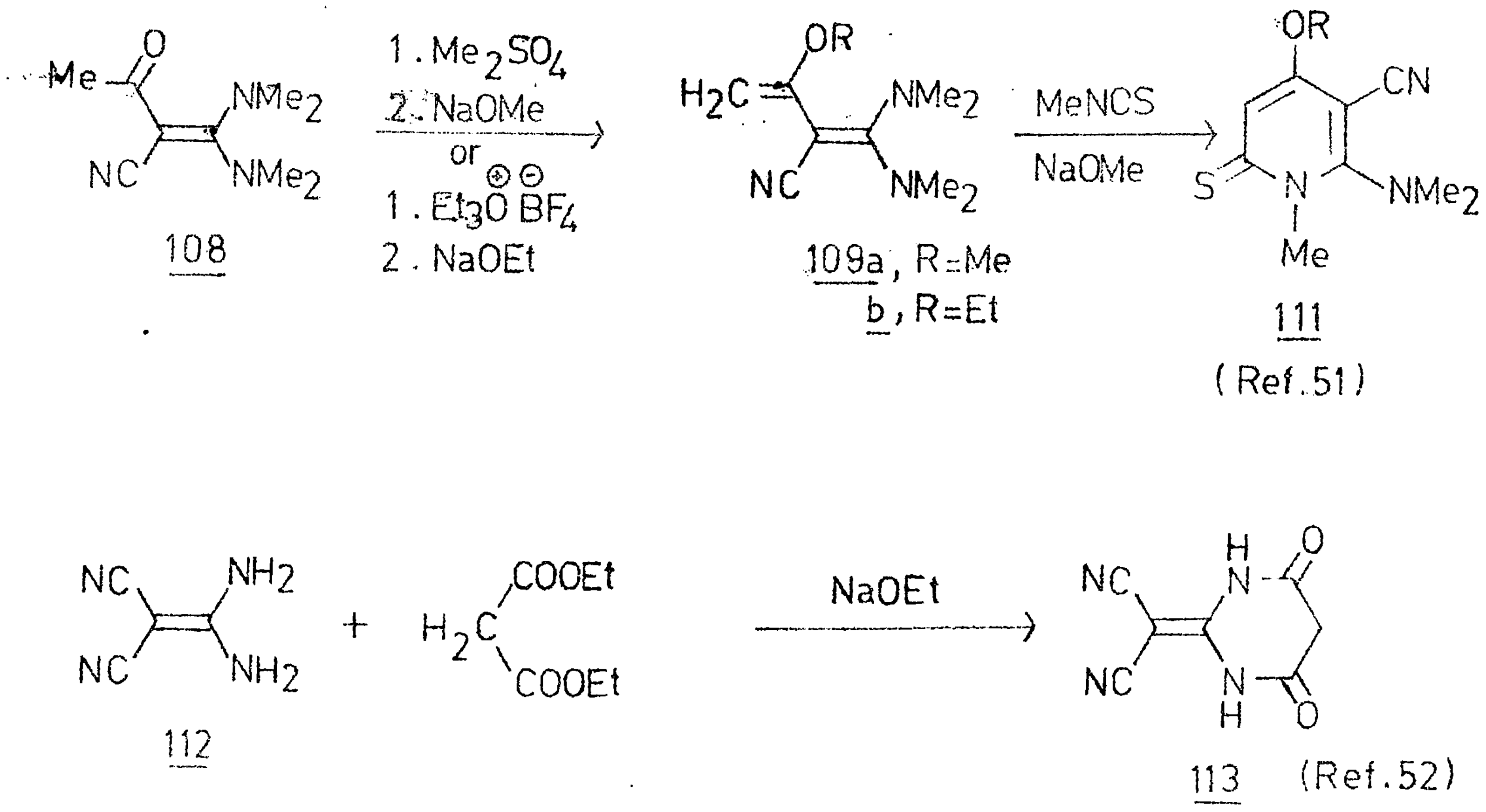
(Ref.51)

1.3.7 Miscellaneous Reactions

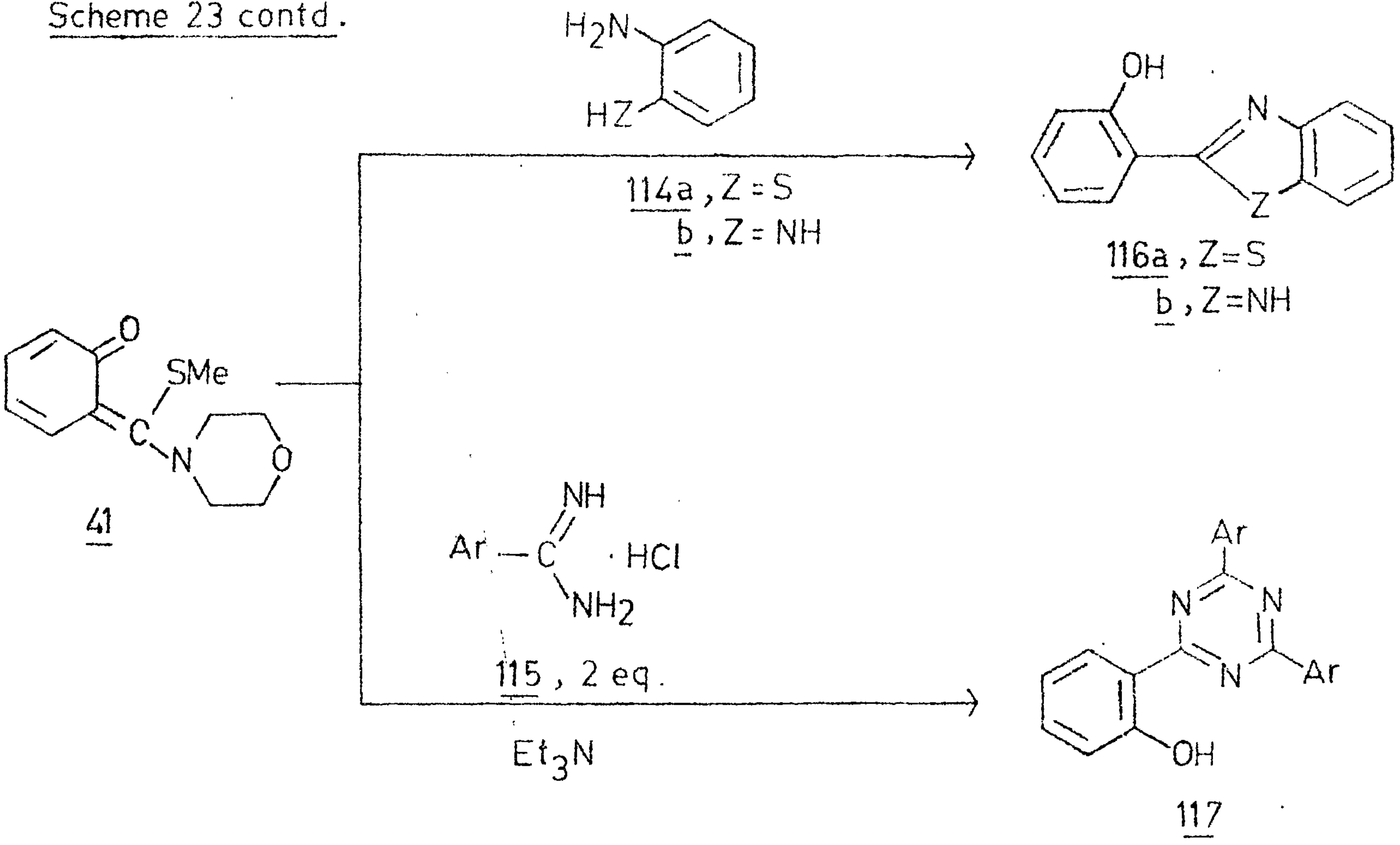
The enol ethers 109 derived from ketoketen-N,N-acetal 108 reacted with methyl isothiocyanate to give pyridin-2-thione 111[51] (Scheme 23). The N,N-acetal 112 condensed[52] with diethylmalonate in the presence of sodium ethoxide to give 113.

The S,N-acetal 41 reacted with 1,2-bifunctional aromatic compounds such as *o*-aminothiophenol (114a) and *o*-phenylenediamine (114b) to give benzothiazole 116a[30] and benzimidazole 116b[30] respectively, while 41 condensed with amidine hydrochloride (115) to give s-triazine 117.[30]

Scheme 23


Me
O
NC
NMe2
NMe2
108
1. Me2SO4
2. NaOMe
or
1. Et3O BF4
2. NaOEt
OR
H2C
NC
NMe2
NMe2
109a, R=Me
b, R=Et
MeNCS
NaOMe
OR
CN
S
N
Me
NMe2
111
(Ref.51)
NC
NC
NH2
NH2
112
+
H2C
COOEt
COOEt
NaOEt
NC
NC
H
N
N
H
O
O
113
(Ref.52)

Scheme 23 contd.



115, 117, Ar = C_6H_5, p- ClC_6H_4,
p-$CH_3C_6H_4$, p-$NO_2C_6H_4$

REFERENCES

1. S.M. McElvain, Chem. Reviews, 45, 453 (1949).
2. A.E. Pohland and W.R. Benson, Chem. Reviews, 66, 161 (1966).
3. D. Borrman, in Houben-Weyl, Methodern Der Organischen Chemie, B. VII/4, pp. 391-441, Georg Thieme Verlag, Stuttgart (1968).
4. R. Kunz, Dissertation, Universität Stuttgart, 1964.
5. R. Gompper and E. Kutter, Angwandte Chem. Int. Ed. 1, 216 (1962).
6. W.-D. Rudorf, A. Schierhorn and M. Augustin, Tetrahedron, 35, 551 (1979).
7. F.C.V. Larsson and S.-O. Lawesson, Tetrahedron, 30, 1283 (1974).
8. W.-D. Rudorf, Z. Chem. 19, 100 (1979); Chem. Abstr. 91, 5058^{p} (1979).
9. R. Gompper and R. Kunz, Chem. Ber. 99, 2900 (1966).
10. W.-D. Rudorf, Tetrahedron, 34, 725 (1978).
11. N.H. Nilsson, Tetrahedron, 30, 3181 (1974).
12. N.H. Nilsson and J. Sandström, Synthesis, 433 (1974).

13. N.H. Nilsson, C. Jacobsen, O.N. Sørensen, N.K. Haunsøe, A. Senning, Chem. Ber. 105, 2854 (1972).

14. K. Hartke, Angwandte Chem. Int. Ed. 3, 640 (1964).

15. S. Rajappa, R. Sreenivasan and B.G. Advani, Ind. J. Chem. 15B, 297 (1977).

16. R. Gompper and R. Kunz, Chem. Ber. 98, 1391 (1965).

17. A. Stephan, M. 97, 695 (1966).

18. W. Kantlehner, W.W. Mergen, Synthesis, 343 (1979).

19. W. Kantlehner, H. Jaus, L. Kienitz and H. Bredereck, Liebigs Ann. Chem. 2096 (1979).

20. W. Kantlehner, B. Funke, E. Haug, P. Speh, L. Kienitz and T. Maier, Synthesis, 73 (1977).

21. R. Gompper and W. Töpel, Chem. Ber. 95, 2871, 2881 (1962).

22. Y. Kuwayama and S. Katoaka, J. Pharm. Soc. Japan, 85, 387 (1965); Chem. Abstr. 63, 8342^h(1965).

23. R. Gompper and H. Schaefer, Chem. Ber. 100, 591 (1967).

24. R. Gompper and W. Töpel, DBP. 1170955 (1961); Chem. Abstr. 61, 5617^h (1964).

25. M. Sone, Y. Tominaga, Y. Matsuda, G. Kobayashi, Yakugaku Zasshi, 97, 262 (1977); Chem. Abstr., 87, 53195^v(1977).

26. F. Clesse, H. Quinion, Bull. Soc. Chim. France, (2), 581 (1973); Chem. Abstr. 78, 147877^{k} (1973).

27. R. Gompper and W. Töpel, Chem. Ber. 95, 2861 (1962).

28. (a) A. Thuillier and J. Vialle, Bull. Soc. Chim. France, 1398 (1958); (b) A. Thuillier and J. Vialle, ibid, 2182, 2187 (1962).

29. F.C.V. Larsson and S.-O. Lawesson. Tetrahedron, 28, 5341 (1972).

30. R. Gompper and R.R. Schmidt, Chem. Ber. 98, 1385 (1965).

31. H.M. Barnes, D. Kundiger and S.M. McElvain, J. Amer. Chem. Soc. 62, 1281 (1940).

32. H. Böhme and F. Soldan, Chem. Ber. 94, 3109 (1961).

33. H.D. Stachel, Arch. Pharm. 296, 89 (1963).

34. W.J. Middleton, V.A. Engelhardt and B.S. Fischer, J. Amer. Chem. Soc. 80, 2822 (1958).

35. W.J. Middleton and V.A. Engelhardt, J. Amer. Chem. Soc. 80, 2829 (1958).

36. W.J. Middleton, A.P. 2883368 (1954); Chem. Abstr. 53, 18872^{a} (1959).

37. T.L. Cairns and B.C. McKusick, Angwandte Chem. 73, 520 (1961).

38. W. Schroth, G. Dill, Ger. (East) 106642; Chem. Abstr. 82, P170649^{d} (1975).

39. R. Gompper and Mitarbb, Angwandte Chem. 76, 583 (1964).

40. A. Dornow and K. Dehmer, Chem. Ber. 100, 2577 (1967).

41. S.M.S. Chauhan and H. Junjappa, Synthesis, 798 (1975).

42. S. Rajappa and R. Sreenivasan, Ind. J. Chem. 15B, 301 (1977).

43. S. Rajappa, B.G. Advani and R. Sreenivasan, Synthesis, 656 (1974).

44. A. Kumar, H. Ila and H. Junjappa, J. Chem. Soc. Chem. Comm. 593 (1976).

45. S. Apparao, H. Ila and H. Junjappa, Synthesis, 65 (1981).

46. H. Aoyama, T. Hasegawa, T. Nishio, Y. Omote, Bull. Chem. Soc. Japan, 48, 1671 (1975); Chem. Abstr. 83, 50663^{c} (1975).

47. A. Kumar, H. Ila and H. Junjappa, J. Chem. Soc. Chem. Comm. 592 (1976).

48. S. Rajappa, B.G. Advani and R. Sreenivasan, Ind. J. Chem. 15B, 886 (1977).

49. S. Rajappa, B.G. Advani, and R. Sreenivasan, Tetrahedron, 33, 1057 (1977).

50. S. Rajappa, M.D. Nair, B.G. Advani and R. Sreenivasan, J. Chem. Soc. Perkin Trans. I, 3161 (1981).

51. W. Kantlehner, I.C. Ivanov, W.W. Mergen, H. Bredereck, Liebigs Ann. Chem. 3, 372 (1980).

52. H.J. Middleton and V.A. Engelhardt, J. Amer. Chem. Soc. 80, 2788 (1958).

53. K. Swincicki, R. Gompper and W. Töpel, Belg. P617873 (1961); Chem. Abstr. 59, 636^c (1963).

54. M.D. Nair, S. Rajappa and J.A. Desai, Ind. J. Chem. Sec.B (in press).

55. K. Hartke, Tetrahedron Letters, 2737 (1964).

CHAPTER 2

PREPARATION OF POLARIZED KETEN-S,N- AND N,N-ACETALS

2.1 Introduction

The reported methods of preparation and synthetic applications of keten-S,N- and N,N-acetals are described in the preceding chapter. Apparently, any active methylene compound carrying two replaceable hydrogen atoms on the α-position of the electron withdrawing group can, in principle, be converted to its corresponding S,N- and N,N-acetals. However, in the present investigation, only a few active methylene compounds carrying suitable electron withdrawing functional groups, useful for subsequent synthetic applications were chosen, and converted into the corresponding S,N- and N,N-acetals. The various methods used for the preparation of these S,N- and N,N-acetals and their spectral characteristics are described in this chapter.

2.2 Preparation of Polarized keten-S,N- and N,N-acetals

The preparation of keten-S,N- and N,N-acetals have been accomplished through one of the following methods:

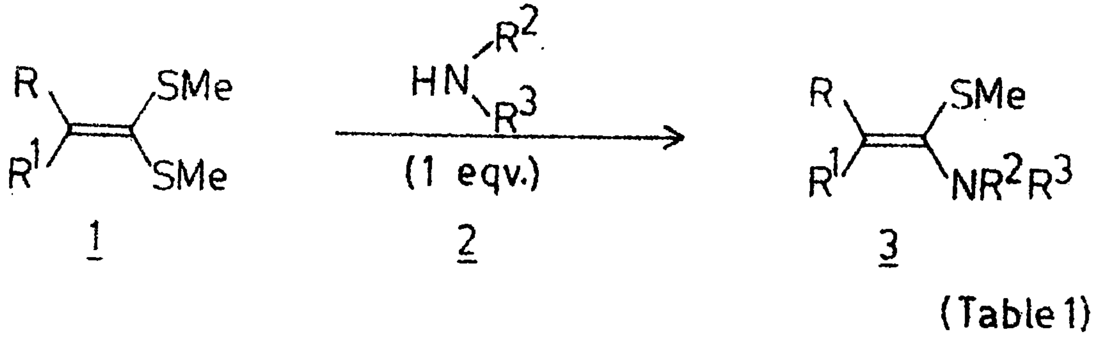
2.2.1 Displacement method.
2.2.2 Direct method using isothiocyanates.
2.2.3 Thioamide method.

2.2.1 Displacement method

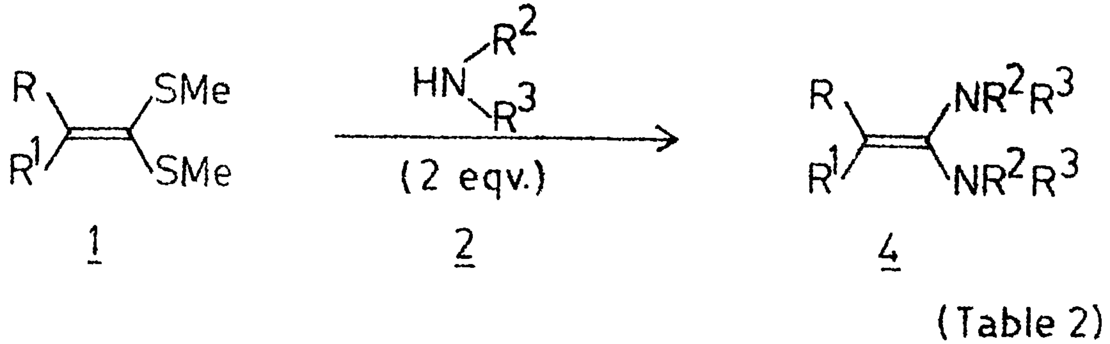
The keten-S,S-acetals are known[1,2,3] to undergo facile displacement reaction with primary or secondary amines to give the corresponding S,N- and N,N-acetals depending upon the reaction conditions and the stoichiometry of the amine used.

Thus, when 1a (R=CN; R^1=COOEt) (Scheme 1) (Table 1) reacted with one equivalent of amine 2, the corresponding S,N-acetal 3a was formed in 77% yield. The displacement reaction with one equivalent of amine gave exclusively the S,N-acetals, when R and R^1 were

Scheme 1



Scheme 2

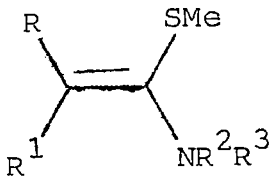


both electron withdrawing groups. Similarly, 3b-f (Table 1) were obtained in 71-76% overall yields. The structural assignment of these keten-S,N- and N,N-acetals were fully in conformity with their analytical (Table 6) and spectral data (Table 3). Similar reaction of 1b ($R=C_6H_5CO$; $R^1=H$) with one equivalent of aniline, initially yielded[4] a mixture of S,N- 3g (Table 1) and N,N-acetal 4a (Table 2). However, it was possible to prepare the S,N-acetal 3g in greater proportion by carefully manipulating the reaction conditions and separating the undesired N,N-acetals by column chromatography. The S,N-acetals 3h-i, 3k and 3l (Table 1) were similarly prepared from the respective keten-S,S-acetals (Table 1) and were characterised by their analytical (Table 6) and spectral data (Table 3). On the other hand, the S,N-alkylacetals 3q-u (Table 1) were obtained exclusively in 64-95% overall yields, when the respective S,S-acetals were reacted with one equivalent of amine 2. Their analytical and spectral data are described in table 6 and table 3 respectively.

The displacement method also proved to be useful for the preparation of keten-N,N-acetals

TABLE 1

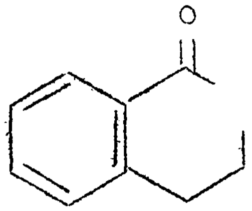
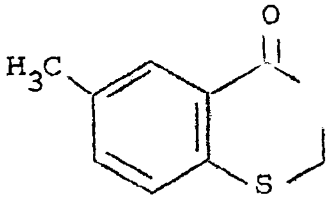
Preparation of keten-S,N-acetals



3

Starting Compd	Product	R	R^1	R^2	R^3
1a	3a[a]	CN	COOEt	H	C_6H_5
1a	3b[a]	CN	COOEt	H	p-$CH_3OC_6H_4$
1a	3c[a]	CN	COOEt	H	p-ClC_6H_4
1a	3d[a]	CN	COOEt	H	p-FC_6H_4
1a	3e[a]	CN	COOEt	H	p-$CH_3C_6H_4$
1a	3f[a]	CN	COOEt	$-(CH_2)_2-O-(CH_2)_2-$	
1b,5a	3g[a,b]	C_6H_5CO	H	H	C_6H_5
1c,5b	3h[a,b]	p-$CH_3OC_6H_4CO$	H	H	C_6H_5
1d,5c	3i[a,b]	p-BrC_6H_4CO	H	H	C_6H_5
5d	3j[b]	p-ClC_6H_4CO	H	H	C_6H_5

Table 1 (Contd.)

1b,5e	3k[a,b]	C_6H_5CO	H	H	*p*-ClC_6H_4
1b,5f	3l[a,b]	C_6H_5CO	H	H	C_2H_5
5g	3m[b]	*p*-$CH_3C_6H_4CO$	H	H	C_2H_5
5h	3n[b]	*p*-$CH_3OC_6H_4CO$	H	H	C_2H_5
5i	3o[b]	*p*-BrC_6H_4CO	H	H	C_2H_5
5j	3p[b]	*p*-ClC_6H_4CO	H	H	C_2H_5
1e	3q[a]	CH_3CO	H	H	C_2H_5
1f	3r[a]	NO_2	H	H	C_2H_5
1b	3s[a]	C_6H_5CO	H	H	$CH_2CH_2CH_3$
1g	3t[a]	*p*-$CH_3C_6H_4CO$	H	H	$CH_2CH_2CH_3$
1b	3u[a]	C_6H_5CO	H	H	$CH_2C_6H_5$
5k	3v[b]	C_6H_5	CN	H	C_6H_5
5l	3w[b,c]	NO_2	H	H	C_6H_5
5m	3x[b]			H	C_6H_5
5n	3y[b]			H	C_6H_5

---

[a] prepared by displacement method.

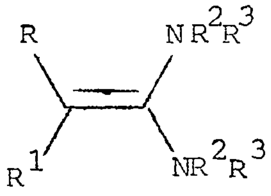
[b] prepared by isothiocyanate method.

[c] Reported in the literature.[3]

(Scheme 2) (Table 2). Although, the initial experiments with 1b and aniline (2) in boiling ethanol,[4] gave a mixture of S,N- and N,N-acetals, the reaction yielded exclusively the N,N-acetal 4a in 64% yield, when acetic acid was used as the reaction medium. Similarly, various keten-N,N-acetals 4b-i (Table 2) were prepared in 50-74% overall yields. Their analytical and spectral data are found in table 7 and table 4 respectively and are in conformity with their assigned structures. Further, the N,N-acetals 4j-l were prepared in high yields, when ethylamine (2) and the corresponding S,S-acetals 1 were heated in sealed tube at 150-160°C. Their analytical (Table 7) and spectral data (Table 4) are described. Acetophenone S,S-acetal 1b and morpholine (2) yielded in boiling ethanol, the corresponding N,N-acetal 4m in 82% yield. Similarly, 1f and ethylamine (50% aqueous solution) gave the corresponding N,N-acetal 4n in 75% yield, under controlled experimental conditions. The S,S-acetal 1b underwent uniformly facile displacement with ethylenediamine to give the corresponding cyclic keten-N,N-acetal 4o in 80% yield. The N,N-acetal 4p was similarly

TABLE 2

Preparation of keten-N,N-acetals



Starting Compd	Product	R	R^1	R^2	R^3
1b	4a	C_6H_5CO	H	H	C_6H_5
1c	4b	p-$CH_3OC_6H_4CO$	H	H	C_6H_5
1d	4c	p-BrC_6H_4CO	H	H	C_6H_5
1h	4d	p-ClC_6H_4CO	H	H	C_6H_5
1b	4e	C_6H_5CO	H	H	p-ClC_6H_4
1c	4f	p-$CH_3OC_6H_4CO$	H	H	p-ClC_6H_4
1c	4g	p-$CH_3OC_6H_4CO$	H	H	p-$CH_3C_6H_4$
1g	4h	p-$CH_3C_6H_4CO$	H	H	p-$CH_3OC_6H_4$
1f	4i	NO_2	H	H	C_6H_5
1b	4j	C_6H_5CO	H	H	C_2H_5

Table 2 (Contd.)

1c	4k	p-$CH_3OC_6H_4CO$	H	H	C_2H_5
1h	4l	p-ClC_6H_4CO	H	H	C_2H_5
1b	4m	C_6H_5CO	H	$-(CH_2)_2-O-(CH_2)_2-$	
1f	4n	NO_2	H	H	C_2H_5
1b	4o	C_6H_5CO	H	H	$-CH_2-$
1f	4p*	NO_2	H	H	$-CH_2-$

---

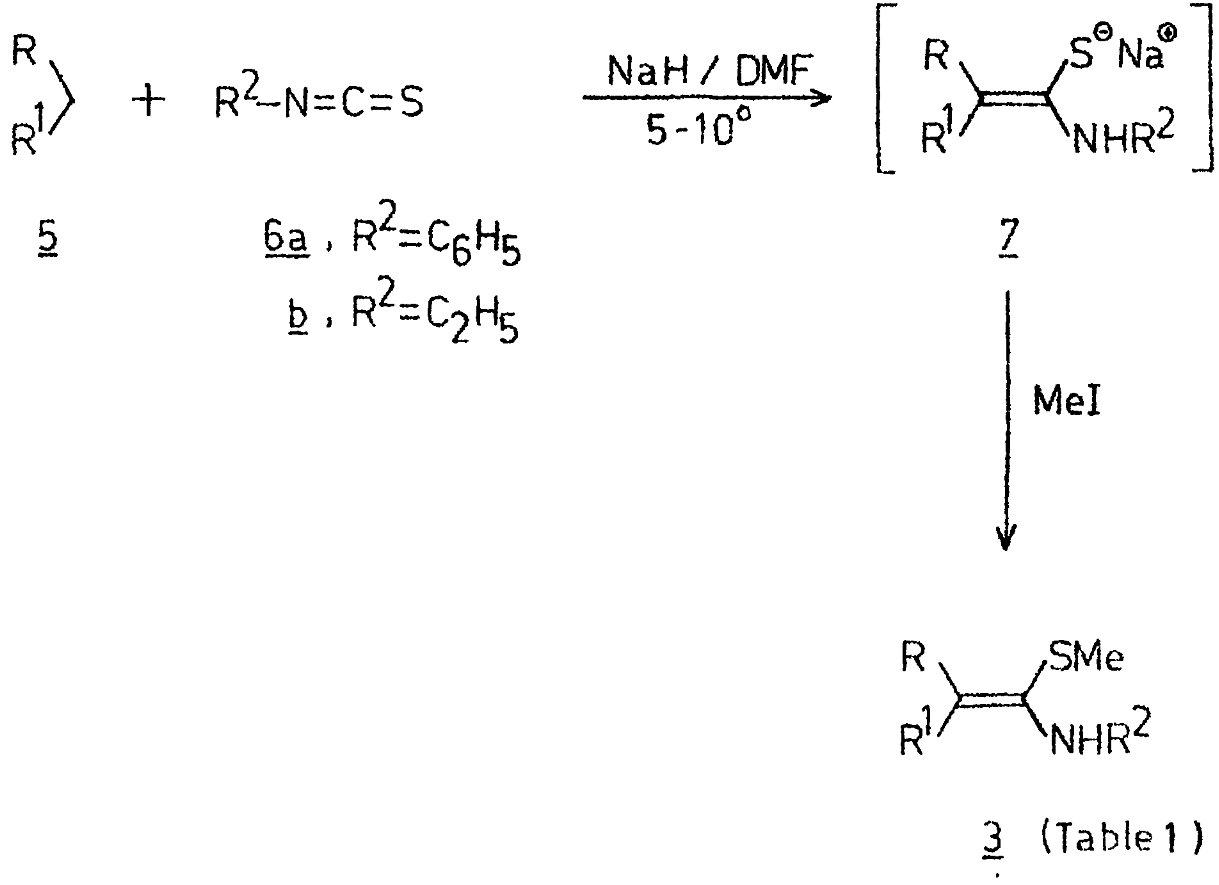
* Reported in the literature.[3,5]

prepared, in yield comparable to that reported in the literature.[5] The N,N-acetals 4m-p were characterised by their analytical (Table 7) and spectral data (Table 4).

2.2.2 Direct method

The direct method for the synthesis of S,N-acetals by reacting active methylene compounds with alkyl and aryl isothiocyanates in the presence of sodium hydride and dimethylformamide followed by subsequent alkylation with methyl iodide, constitutes an alternative practical method.[1,5-8,9a] Some of the keten-S,N-acetals which were not satisfactorily obtained by the displacement method, were successfully prepared by this method. Thus, when 5a and 6a (Scheme 3) were reacted in the presence of sodium hydride and dimethylformamide, the salt 7 separated, *in situ*, was alkylated with methyl iodide to give the corresponding S,N-acetal 3g (Table 3) in 82% yield. Similarly, the S,N-acetals 3h-p, 3v and 3w were prepared in 70-84% overall yields from the respective 5, using either 6a or 6b as the case may be, under identical reaction conditions. The cyclic ketones 5m and 5n were similarly reacted with 6a to

Scheme 3

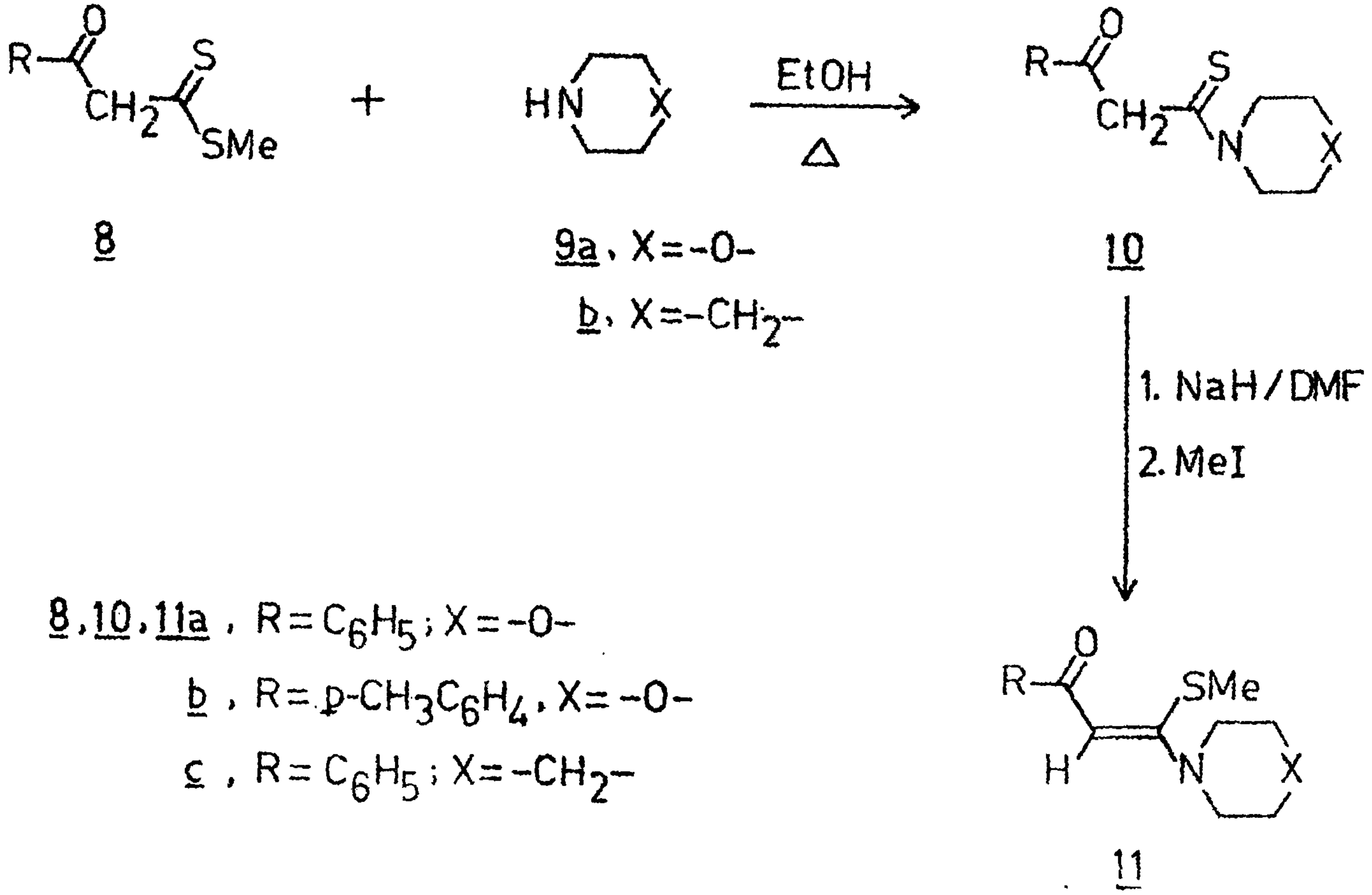


give the corresponding S,N-acetals 3x and 3y in 78% and 90% yields respectively. Compounds, thus prepared, have been confirmed by their analytical (Table 6) and spectral data (Table 3).

2.2.3 Thioamide method[5,9]

The displacement method failed to yield S,N-morpholino acetal 11a (Scheme 4), which could also not be prepared by the direct method. It was therefore, attempted successfully via its thioamide intermediate. We have recently reported[10] a facile preparation of dithioesters 8 (Scheme 4) by reacting ketones with trithiocarbonate in excellent yields. The dithioester 8a thus prepared, underwent smooth condensation with morpholine (9a) in boiling ethanol to give the corresponding thioamide 10a which was subsequently alkylated with methyl iodide in the presence of sodium hydride to give 11a in 92% yield. Similarly, 11b and 11c were prepared, by reacting 8b and 8c with 9a and 9b respectively. Their analytical (Table 8) and spectral data (Table 5) are described.

Scheme 4



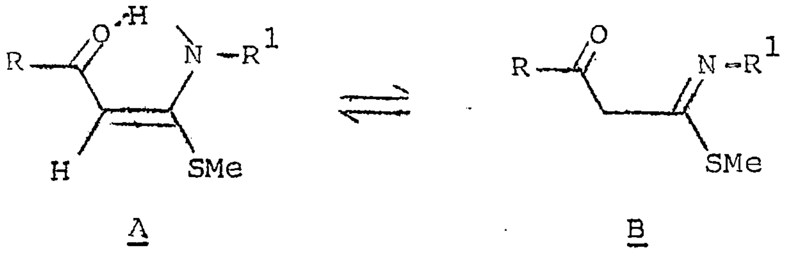
8, 10, 11a, $R = C_6H_5$; $X = -O-$

b, $R = p\text{-}CH_3C_6H_4$, $X = -O-$

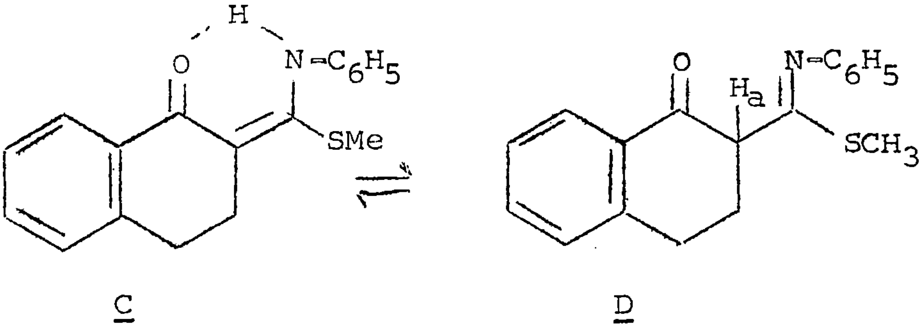
c, $R = C_6H_5$; $X = -CH_2-$

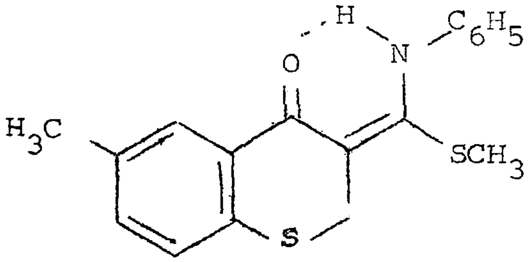
2.3 Spectral studies

Polarized keten-S,N-acetals are known[11] to exist in tautomeric equilibrium between enamino A and imino form B which can be easily distinguished with the help of IR and NMR spectroscopy. The spectral studies on polarized keten-S,N-acetals (Scheme 1) prepared for the present investigation, indicated that all of them exist in the enamino form A. Thus, IR spectra of the keten-S,N-arylacetals 3g-k (Table 3) derived from acetophenones, exhibit absorption band due to carbonyl group between 1608-1590 cm^{-1}, whereas in S,N-alkylacetals 3l-q and 3s-u (Table 3), the carbonyl frequency appears between 1575-1550 cm^{-1}. The lower value of carbonyl frequency in S,N-aryl and S,N-alkylacetals is due to delocalization of lone pair of electrons on nitrogen over the carbonyl group and also due to the presence of



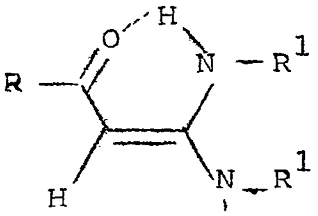
intramolecular hydrogen bonding. In the imino form B, the carbonyl frequency would appear at a higher value (~1700-1680 cm^{-1} comparable to acetophenones) since, the carbonyl group in B is no longer conjugated with the double bond and the lone pair on nitrogen atom. In the NMR spectra of S,N-arylacetals 3g-k (Table 3), the signal due to the olefinic proton appears between δ5.70-6.18 whereas, in S,N-alkylacetals 3l-q and 3s-u (Table 3), it is shifted to slightly higher field between δ4.75-5.66 due to greater delocalization of the lone pair on nitrogen atom, resulting in higher electron density on the ~~β~~α-carbon. The signal due to -NH proton appears as a broad singlet between δ13.20-13.66 in 3g-k and between δ11.30-12.10 in 3l-q and 3s-u. Thus the chemical shift values for the olefinic and -NH proton in the NMR spectra of S,N-aryl and S,N-alkylacetals support the enamine structure A. In the case of nitroketen-S,N-acetals 3r and 3w, the olefinic proton signals appear downfield at δ6.44 and δ6.73 respectively, due to greater electron withdrawing effect of nitro group. The signal due to -NH proton in keten-S,N-acetal 3v derived from phenylacetonitrile, appears at higher field (δ6.47), thus indicating the absence of intramolecular hydrogen bonding in 3v. The S,N-acetal 3x derived from tetralone, showed the presence of both enamino (C) and imino form (D) in 7:3 ratio respectively. Thus, in the NMR spectrum of 3x, a triplet present at δ 4.21 was assigned to methine proton (H_a). The methylene ring protons in D were shifted to higher field (δ 1.5–1.85) as compared to C (δ 1.9–2–7). In the IR spectrum of 3x, the carbonyl frequency due to imino and enamino form were found at 1722 cm^{-1} and 1680 cm^{-1} respectively. The signal due to -NH proton appeared at δ 12.10, thus showing the existance of intramolecularly hydrogen bonded structure C. The carbonyl frequency in the S,N-acetal 3y derived from benzothiopyrone, appeared at 1580 cm^{-1} and the signal due to -NH proton in its NMR spectrum was found at δ 11.70, thus showing the existance of hydrogen bonded enamine structure (E).





E

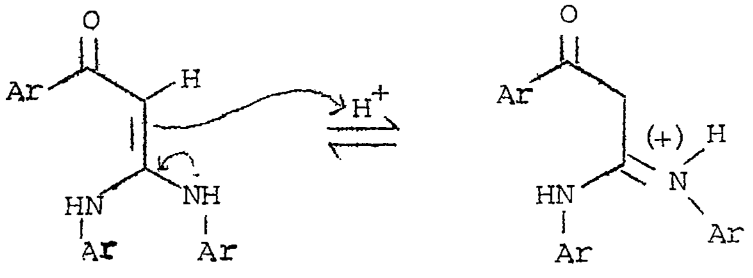
The N,N-acetals 4a-h and 4j-l (Scheme 2), derived from various acetophenones, were also found to exist in the enamino form (F). The olefinic protons in the NMR



F

spectra ($CDCl_3$) of N,N-phenylacetals 4a-c and 4e (Table 4) appeared between δ 5.56-5.66, while in N,N-ethylacetals 4j-l (Table 4), they are present between δ5.10-5.18. The signal due to hydrogen bonded -NH proton in S,N-arylacetals 4a-c and 4e, appeared at lower field between δ 13.50-13.66, while the other -NH proton was present between δ 6.43-6.50. Similarly, in

N,N-ethylacetals 4j-l, the two -NH protons appeared between δ11.40-12.40 and δ4.74-6.40 respectively. The band due to carbonyl group appeared at lower frequency, between 1600-1550 cm^{-1} in the IR spectrum of N,N-acetals 4a-c, 4e and 4j-l, due to delocalisation of the lone pair of electrons present on the two amino groups. It was interesting to note, that when the NMR spectrum of 4a was taken in trifluoroacetic acid, the signal due to olefinic proton at δ5.65 in its NMR spectrum in $CDCl_3$ was absent, while a new signal due to two protons was present at δ 4.40. Thus, in trifluoroacetic acid the N,N-acetal exists in the imino form G, due to protonation at β-carbon and the signal due to two methylene protons appears at δ4.40. The NMR spectra of keten-N,N-acetals 4d and 4f-4h in trifluoroacetic acid, similarly showed signals due to methylene protons at δ4.42, 4.21, 4.30 and 4.55 respectively.



F

G

TABLE 3

Spectral data of keten-S,N-acetals 3a-y

Product	IR (cm^{-1})	^{1}H-NMR (δ/ppm)
3a	3130 (ν_{NH}); 2190 (ν_{CN}); 1675 (ν_{CO})[a]	1.30 (t, 3H, $CH_2C\underline{H}_3$); 2.23 (s, 3H, $SC\underline{H}_3$); 4.43 (q, 2H, $C\underline{H}_2CH_3$); 7.28 (br.s, $5H_{arom}$); 11.40 (br, 1H, $N\underline{H}$).[d]
3b	3125 (ν_{NH}); 2190 (ν_{CN}); 1650 (ν_{CO})[a]	1.36 (t, 3H, $CH_2C\underline{H}_3$); 2.30 (s, 3H, $SC\underline{H}_3$); 3.88 (s, 3H, $OC\underline{H}_3$); 4.33 (q, 2H, $C\underline{H}_2CH_3$); 7.16 (dd, $4H_{arom}$); 11.71 (br, 1H, $N\underline{H}$).[d]
3c	3120 (ν_{NH}); 2180 (ν_{CN}); 1648 (ν_{CO})[a]	1.38 (t, 3H, $CH_2C\underline{H}_3$); 2.33 (s, 3H, $SC\underline{H}_3$); 4.31 (q, 2H, $C\underline{H}_2CH_3$); 7.33 (dd, $4H_{arom}$); 11.35 (br, 1H, $N\underline{H}$).[d]

Table 3 Contd.

3d	3110 (ν_{NH}); 2200 (ν_{CN}); 1660 (ν_{CO})[a]	1.35 (t, 3H, $CH_2C\underline{H}_3$); 2.28 (s, 3H, $SC\underline{H}_3$); 4.26 (q, 2H, $C\underline{H}_2CH_3$); 6.96-7.33 (m, $4H_{arom}$); 11.33 (br, 1H, $N\underline{H}$).[d]
3e	3135 (ν_{NH}); 2208 (ν_{CN}); 1662 (ν_{CO})[a]	1.33 (t, 3H, $CH_2C\underline{H}_3$); 2.23 (s, 3H, $SC\underline{H}_3$); 2.33 (s, 3H, $C\underline{H}_3$); 4.28 (q, 2H, $C\underline{H}_2CH_3$); 7.05-7.30 (m, $4H_{arom}$); 11.38 (br, 1H, $N\underline{H}$).[d]
3f	2175 (ν_{CN}); 1670 (ν_{CO})[a]	1.33 (t, 3H, $CH_2C\underline{H}_3$); 2.60 (s, 3H, $SC\underline{H}_3$); 3.83 (s, 8H, $-(C\underline{H}_2)_2-O\cdot(C\underline{H}_2)_2-$); 4.25 (q, 2H, $C\underline{H}_2CH_3$).[d]
3g	3330 (br, ν_{NH}); 1590 (ν_{CO})[a]	2.50 (s, 3H, $SC\underline{H}_3$); 6.11 (s, 1H, $\underline{H}$-2); 7.38-7.81 (m, $8H_{arom}$); 8.03-8.33 (m, $2H_{arom}$); 13.66 (br, 1H, $N\underline{H}$).[d]

Table 3 contd.

3h	3340 (br, ν_{NH}); 1595 (ν_{CO})[a]	2.31 (s, 3H, SC$\underline{H}_3$); 3.75 (s, 3H, OC$\underline{H}_3$); 5.70 (s, 1H, $\underline{H}$-2); 6.70-6.95 (m, 3H$_{arom}$); 7.28 (m, 4H$_{arom}$); 7.80 (dd, 2H$_{arom}$); 13.20 (br, 1H, N$\underline{H}$).[e]
3i	3300 (br, ν_{NH}); 1595 (ν_{CO})[a]	2.48 (s, 3H, SC$\underline{H}_3$); 6.01 (s, 1H, $\underline{H}$-2); 7.30-7.70 (m, 7H$_{arom}$); 7.73-8.16 (m, 2H$_{arom}$); 13.52 (br, 1H, N$\underline{H}$).[d]
3j	3380 (br, ν_{NH}); 1590 (ν_{CO})[b]	2.38 (s, 3H, SC$\underline{H}_3$); 5.95 (s, 1H, $\underline{H}$-2); 7.30 (br s, 5H$_{arom}$); 7.60 (A_2B_2 dd, 4H$_{arom}$); 13.45 (br, 1H, N$\underline{H}$).[e]
3k	3300 (br, ν_{NH}); 1608 (ν_{CO})[a]	2.51 (s, 3H, SC$\underline{H}_3$); 6.18 (s, 1H, $\underline{H}$-2); 7.55-7.90 (m, 7H$_{arom}$); 8.16-8.40 (m, 2H$_{arom}$); 13.58 (br, 1H, N$\underline{H}$).[d]

Table 3 Contd.

3l	3350 (br, ν_{NH}); 1550 (ν_{CO})[c]	1.33 (t, 3H, $CH_2C\underline{H}_3$); 2.48 (s, 3H, $SC\underline{H}_3$); 3.48 (br,q, 2H, $C\underline{H}_2CH_3$); 5.66 (s, 1H, $\underline{H}$-2); 7.30-7.65 (m, $3H_{arom}$); 7.70-8.05 (m, $2H_{arom}$); 11.70-12.10 (br, 1H, $N\underline{H}$).[d]
3m	3330 (br, ν_{NH}); 1560 (ν_{CO})[c]	1.22 (t, 3H, $CH_2C\underline{H}_3$); 2.37 (s, 6H, $C\underline{H}_3$, $SC\underline{H}_3$); 3.34 (br.q, 2H, $C\underline{H}_2CH_3$); 5.46 (s, 1H, $\underline{H}$-2); 7.38 (A_2B_2.dd, $4H_{arom}$); 11.75 (br, 1H, $N\underline{H}$).[d]

Table 3 Contd.

3n	3390 (br, ν_{NH}); 1558 (ν_{CO})[b]	1.32 (t, 3H, $CH_2C\underline{H}_3$); 2.42 (s, 3H, $SC\underline{H}_3$); 3.38 (br q, 2H, $C\underline{H}_2CH_3$); 3.79 (s, 3H, $OC\underline{H}_3$); 5.44 (s, 1H, $\underline{H}$-2); 7.25 (A_2B_2 dd, $4H_{arom}$); 11.50 (br, 1H, $N\underline{H}$).[e]
3o	3400 (br, ν_{NH}); 1575 (ν_{CO})[c]	1.32 (t, 3H, $CH_2C\underline{H}_3$); 2.34 (s, 3H, $SC\underline{H}_3$); 3.32 (br q, 2H, $C\underline{H}_2CH_3$); 5.40 (s, 1H, $\underline{H}$-2); 7.48 (A_2B_2 dd, $4H_{arom}$); 11.60 (br, 1H, $N\underline{H}$).[e]
3p	3460 (br, ν_{NH}); 1560 (ν_{CO})[c]	1.25 (t, 3H, $CH_2C\underline{H}_3$); 2.35 (s, 3H, $SC\underline{H}_3$); 3.30 (br.q, 2H, $C\underline{H}_2CH_3$); 5.40 (s, 1H, $\underline{H}$-2); 7.42 (A_2B_2.dd, $4H_{arom}$); 11.71 (br, 1H, $N\underline{H}$).[d]

Table 3 Contd.

3q	3435 (br, ν_{NH}); 1575 (ν_{CO})^{c}	1.22 (t, 3H, $CH_2C\underline{H}_3$); 1.98 (s, 3H, $C\underline{H}_3CO$); 2.37 (s, 3H, $SC\underline{H}_3$); 3.32 (br,q, 2H, $C\underline{H}_2CH_3$); 4.75 (s, 1H, $\underline{H}$-2); 11.30 (br, 1H, $N\underline{H}$).^{e}
3r	3170 (br, ν_{NH}); 1560, 1375 (ν_{NO_2})^{b}	1.40 (t, 3H, $CH_2C\underline{H}_3$); 2.52 (s, 3H, $SC\underline{H}_3$); 3.52 (q, 2H, $C\underline{H}_2CH_3$); 6.44 (s, 1H, $\underline{H}$-2); 10.73 (br, 1H, $N\underline{H}$).^{e}
3s	3360 (br, ν_{NH}); 1565 (ν_{CO})^{b}	1.00 (t, 3H, $CH_2C\underline{H}_3$); 1.61 (m, 2H, $CH_2C\underline{H}_2CH_3$); 2.32 (s, 3H, $SC\underline{H}_3$); 3.05-3.44 (br,q, 2H, $NHC\underline{H}_2$); 5.46 (s, 1H, $\underline{H}$-2); 7.24 (br s, $3H_{arom}$); 7.70 (s, $2H_{arom}$); 11.42 (br, 1H, $N\underline{H}$).^{e}

Table 3 Contd.

3t	3360 (br, ν_{NH}); 1565 (ν_{CO})[b]	1.05 (t, 3H, $CH_2C\underline{H}_3$); 1.63 (m, 2H, $CH_2C\underline{H}_2CH_3$); 2.32, 2.40 (two s, 6H, $SC\underline{H}_3$+ $C\underline{H}_3$); 3.28 (q, 2H, $NHC\underline{H}_2$); 5.48 (s, 1H, $\underline{H}$-2); 7.33 (A_2B_2.dd, 4H_{arom}); 11.50 (br, 1H, $N\underline{H}$).[e]
3u	3300 (br, ν_{NH}); 1575 (ν_{CO})[b]	2.40 (s, 3H, $SC\underline{H}_3$); 4.50 (d, 2H, $NHC\underline{H}_2$); 5.58 (s, 1H, $\underline{H}$-2); 7.00-7.42 (m, 8H_{arom}); 7.70 (m, 2H_{arom}); 11.64 (br, 1H, $N\underline{H}$).[e]
3v	3240 (ν_{NH}); 2180 (ν_{CN})[a]	2.18 (s, 3H, $SC\underline{H}_3$); 6.47 (br, 1H, $N\underline{H}$); 6.85-7.50 (m, 10H_{arom}).[d]

Table 3 contd.

3w	1525 (ν_{NO_2})[a]	2.35 (s, 3H, SC$\underline{H}_3$); 6.73 (s, 1H, $\underline{H}$-2); 7.38 (br, 5H$_{arom}$); 11.80 (br s, 1H, N$\underline{H}$).[d]
3x	3350 (br, ν_{NH}); 1722[f], 1680 (ν_{CO})[b]	1.50-1.85 (br.m)[f]; 1.90-2.70 (two br q, 4H, -C$\underline{H}_2$C$\underline{H}_2$-); 2.90 (s, 3H, SC$\underline{H}_3$); 4.21 (t, H$_a$)[f]; 6.81-7.50 (m, 8H$_{arom}$); 7.90 (d, 1H$_{arom}$); 12.10 (br, 1H, N$\underline{H}$).[e]
3y	3380 (br, ν_{NH}); 1580 (ν_{CO})[b]	2.08 (s, 3H, C$\underline{H}_3$); 2.35 (s, 3H, SC$\underline{H}_3$); 4.05 (s, 2H, -C$\underline{H}_2$S-); 7.04 (br s, 3H$_{arom}$); 7.20-7.35 (m, 4H$_{arom}$); 7.76 (s, 1H$_{arom}$); 11.70 (br, 1H, N$\underline{H}$).[e]

---

[a] in KBr; [b] in Nujol; [c] neat; [d] in CDCl$_3$; [e] in CCl$_4$; [f] due to imino form D.

TABLE 4

Spectral data of N,N-acetals 4a-q

Product	IR (cm^{-1})	^{1}H-NMR (δ/ppm)
4a	3258, 3200 (ν_{NH}); 1550 (ν_{CO})[a]	5.65 (s, 1H, $\underline{H}$-2); 6.50 (br, 1H, N$\underline{H}$); 7.03-7.56 (m, 13H$_{arom}$); 7.76 (m, 2H$_{arom}$); 13.60 (br, 1H, N$\underline{H}$).[c] 4.40 (s, 2H, C$\underline{H}_2$CO); 6.80-7.45 (br.m, 13H$_{arom}$); 7.60 (m, 2H$_{arom}$).[d]
4b	3385, 3190 (ν_{NH}); 1550 (ν_{CO})[a]	3.83 (s, 3H, OC$\underline{H}_3$); 5.66 (s, 1H, $\underline{H}$-2); 6.43 (br, 1H, N$\underline{H}$); 6.93 (d, 2H$_{arom}$); 7.10-7.55 (m, 10H$_{arom}$); 7.80 (d, 2H$_{arom}$); 13.60 (br, 1H, N$\underline{H}$).[c]

Table 4 (Contd.)

4c	3270, 3210 (ν_{NH}); 1570 (ν_{CO})[a]	5.56 (s, 1H, $\underline{H}$-2); 6.50 (br, 1H, N$\underline{H}$); 7.04-7.50 (m, 10H_{arom}); 7.50-8.10 (m, 4H_{arom}); 13.50 (br, (1H, N$\underline{H}$).[c]
4d	3410, 3260 (ν_{NH}); 1560 (ν_{CO})[b]	4.42 (s, 2H, C$\underline{H}_2$CO); 6.60-7.80 (m, 14H_{arom}).[d]
4e	3300, 3250 (ν_{NH}); 1600 (ν_{CO})[a]	5.66 (s, 1H, $\underline{H}$-2); 6.45 (br, 1H, N$\underline{H}$); 7.16-7.65 (m, 11H_{arom}); 7.75-7.98 (m, 2H_{arom}); 13.66 (br, 1H, N$\underline{H}$).[c]
4f	3390, 3370 (ν_{NH}); 1600 (ν_{CO})[b]	3.65 (s, 3H, OC$\underline{H}_3$); 4.21 (s, 2H, C$\underline{H}_2$CO); 6.50-7.65 (br m, 12H_{arom}).[e]

Table 4 (contd.)

4g	3400, 3340 (ν_{NH}); 1600 (ν_{CO})[b]	2.15 (s, 3H, $C\underline{H}_3$); 2.24 (s, 3H, $C\underline{H}_3$); 3.67 (s, 3H, $OC\underline{H}_3$); 4.30 (s, 2H, $C\underline{H}_2CO$); 6.42–7.30 (br m, 10H$_{arom}$); 7.32–7.70 (m, 2H$_{arom}$).[e]
4h	3340, 3310 (ν_{NH}); 1595 (ν_{CO})[b]	2.50 (s, 3H, $C\underline{H}_3$); 3.78 (s, 3H, $OC\underline{H}_3$); 4.00 (s, 3H, $OC\underline{H}_3$); 4.55 (s, 2H, $C\underline{H}_2CO$); 6.82–7.90 (br m, 12H$_{arom}$).[e]
4i	3410, 3160 (ν_{NH});	4.98 (s, 1H, $\underline{H}$-2); 7.00–7.95 (m, 10H$_{arom}$).[f]
4j	3400, 3260 (ν_{NH}); 1590 (ν_{CO})[b]	1.23 (t, 6H, two $CH_2C\underline{H}_3$); 3.16 (q, 4H, two $C\underline{H}_2CH_3$); 5.10 (s, 1H, $\underline{H}$-2); 6.40 (br, 1H, $N\underline{H}$); 7.16–7.43 (m, 3H$_{arom}$); 7.56–7.83 (m, 2H$_{arom}$); 11.55 (br, 1H, $N\underline{H}$).[c]

Table 4 (Contd.)

4k	3420, 3270 (ν_{NH}); 1588 (ν_{CO})[b]	1.20 (t, 6H, two $CH_2C\underline{H}_3$); 3.13 (br.q, 4H, two $C\underline{H}_2CH_3$); 3.72 (s, 3H, $OC\underline{H}_3$); 5.00 (br, 1H, $N\underline{H}$); 5.18 (s, 1H, $\underline{H}$-2); 6.82 (d, $2H_{arom}$); 7.78 (d, $2H_{arom}$); 11.40 (br, 1H, $N\underline{H}$).[c]
4l	3450, 3380 (ν_{NH}); 1585 (ν_{CO})[b]	1.30 (t, 6H, two $CH_2C\underline{H}_3$); 2.90-3.51 (br.q, 4H, two $C\underline{H}_2CH_3$); 4.74 (br, 1H, $N\underline{H}$); 5.14 (s, 1H, $\underline{H}$-2); 7.51 (A_2B_2 dd, $4H_{arom}$); 12.40 (br, 1H, $N\underline{H}$).[c]
4m	1675 (ν_{CO})[b]	3.30 (br.s, 8H, morpholino); 3.72 (br s, 8H, morpholino); 5.08 (s, 1H, $\underline{H}$-2); 7.34 (br s, $3H_{arom}$); 7.76 (dd, $2H_{arom}$).[c]

Table 4 (Contd.)

4n	3250, 3170 (ν_{NH}); 1595, 1375 (ν_{NO_2})[b]	0.96 (t, 6H, two $CH_2C\underline{H}_3$); 3.10 (q, 4H, two $C\underline{H}_2CH_3$); 5.20 (s, 1H, $\underline{H}$-2); 7.12 (br, 1H, N$\underline{H}$); 7.80 (br, 1H, N$\underline{H}$).[f]
4o	3310, 3170 (ν_{NH}); 1580, 1605 (ν_{CO})[a]	3.63 (s, 4H, $-C\underline{H}_2C\underline{H}_2-$); 4.02 (s, 1H, $\underline{H}$-2); 6.80-7.20 (m, $3H_{arom}$); 7.30-7.60 (dd, $2H_{arom}$); 8.00 (br, 2H, N$\underline{H}$).[f]
4p	3260, 3200 (ν_{NH}); 1550, 1375 (ν_{NO_2})[a]	3.81 (s, 4H, $-C\underline{H}_2C\underline{H}_2-$); 5.30 (s, 1H, $\underline{H}$-2).[f]

---

[a] in KBr; [b] in Nujol; [c] in $CDCl_3$; [d] in TFA, exists in imino form G;

[e] in TFA, exists in imino form G, insoluble in $CDCl_3$; [f] in TFA.

TABLE 5

Spectral data of products 11(a-c)

Product	IR (cm^{-1})^{a}	^{1}H-NMR (δ /ppm)^{b}
11a	1685 (w), 1630 (ν_{CO})	2.38 (s, 3H, SC$\underline{H}_3$); 3.50, 3.56 (two s, 8H, morpholino); 5.63 (s, 1H, $\underline{H}$-2); 6.95-8.00 (m, 5H_{arom}).
11b	1685 (w), 1620 (ν_{CO})	2.20 (br s, 6H, SC$\underline{H}_3$+ C$\underline{H}_3$); 3.40 (s, 4H, morpholino); 3.64 (s, 4H, morpholino); 5.68 (s, 1H, $\underline{H}$-2); 7.32 (A_2B_2 dd, 4H_{arom}).
11c	1690 (w), 1620 (ν_{CO})	1.67 (br.s, 6H, -(C$\underline{H}_2$)$_3$-; 2.33 (s, 3H, SC$\underline{H}_3$); 3.12-3.68 (m, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-); 5.70 (s, 1H, $\underline{H}$-2); 7.15-7.54 (m, 3H_{arom}) 7.55-7.94 (m, 2H_{arom}).

[a] in nujol; [b] in CCl_4.

EXPERIMENTAL

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

The starting materials

The commercial samples of acetophenone, p-methylacetophenone, p-methoxyacetophenone, p-chloroacetophenone, p-bromoacetophenone, tetralone, phenylacetonitrite, ethyl acetoacetate, aniline, p-chloroaniline, p-fluoroaniline, p-toluidine, p-anisidine, benzylamine, ethylenediamine, morpholine and piperidine were purified before use.

The 6-methyl-2,3-dihydro-1-benzothiopyran-4-one, bp 154° (12 mm);[12] dimethyl trithiocarbonate, bp 225° (760 mm);[13] ethyl isothiocyanate, bp 130-1° (760 mm)[14a] and phenyl isothiocyanate, bp 120-1° (35 mm)[14b] were prepared by the reported methods.

The keten-S,S-acetals: 1,1-bis(methylthio)-2-cyano-2-carboethoxyethylene (1a), mp 53°;[15] 3,3-bis(methylthio)-1-phenyl-2-propen-1-one (1b), mp 93°;[16] 3,3-bis(methylthio)-1-(*p*-methoxyphenyl)-2-propen-1-one (1c), mp 100-1°;[16] 3,3-bis(methylthio)-1-(*p*-bromophenyl)-2-propen-1-one (1d), mp 106-7°;[16] 3,3-bis(methylthio)-1-methyl-2-propen-1-one (1e), mp 66-7°;[17] 1,1-bis(methylthio)-2-nitroethylene (1f), mp 125°;[5] 3,3-bis(methylthio-1-(*p*-methylphenyl)-2-propen-1-one (1g), mp 104-5°;[16] 3,3-bis(methylthio)-1-(*p*-chlorophenyl)-2-propen-1-one (1h), mp 109-10°;[16] were prepared by the reported methods. The S,S-acetals derived from ketones were prepared by reacting one eqv. of the respective ketone with one eqv. of CS_2 and two eqv. of *t*-BuONa in dry benzene followed by alkylation with methyl iodide. The nitroketene-S,S-acetal 1f was prepared by methylation of the corresponding dipotassium salt with dimethylsulfate.[5]

The reported methyl benzoyldithioacetate (8a), mp 55°[10] and methyl *p*-methyl-benzoyldithioacetate (8b), mp 54-5°[10] were also prepared by reacting acetophenones with dimethyl trithiocarbonate in the presence of two eqv. of sodium hydide in refluxing benzene.

Preparation of keten-S,N- and N,N-acetals

Method A. By displacement method :

A-1. In refluxing ethanol: A solution of keten-S,S-acetal 1 (0.02 mol) and the appropriate amine 2 (0.025-0.05 mol) in ethanol (50 ml) was refluxed for 3.5-9 hr. After completion of the reaction (TLC), the solvent was removed and the crude S,N- or N,N- acetals thus obtained were either purified by crystallization (3a-f and 4m-p) or by column chromatography over silica gel (3l and 3q-u) using hexane/benzene (1:1) as eluent (Table 6 & 7).

A-2. By direct heating: A mixture of keten-S,S-acetal 1 (0.02 mol) and the appropriate amine 2 (0.022 mol) was heated at 160-165°C for 15 hr in an oil bath (monitored by TLC). The mixture of S,N-acetal and N,N-acetal thus obtained was separated by column chromatography over silica gel using benzene/hexane (1:1) as eluent. The S,N-acetals 3g-i and 3k (Table 6) and N,N-acetals 4a-c and 4e (Table 7) thus obtained were further purified by crystallization from hexane and chloroform/hexane mixture respectively.

The N,N-acetals 4j-l derived from ethylamine were prepared by direct heating of the respective S,S-acetals

1 (0.05 mol) and ethylamine (100%, 0.15 mol) in a sealed tube at 150-160°C for 3-6 hr (Table 7). After complete disappearance of keten-S,S-acetal (TLC), the reaction mixture was diluted with water to remove excess of amine, extracted with ethyl acetate, dried (Na_2SO_4) and evaporated to give crude N,N-acetals 4j-1 (Table 7) which were purified by crystallization from hexane.

A-3.In refluxing acetic acid: A solution of keten-S,S-acetal 1 (0.01 mol) and the appropriate amine 2 (0.025 mol) in gl. AcOH (20 ml) was refluxed for 1-10 hr (Table 7). The solvent was removed under reduced pressure, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated to give crude N,N-acetals 4a-i (Table 7), which were purified by crystallization from chloroform/hexane mixture.

Method B. By the reaction of active methylene compounds with aryl/alkyl isothiocyanates: To an ice cooled and well stirred suspension of sodium hydride (2.4g, 0.15 mol) (washed 2-3 times with dry benzene) in dry DMF (50 ml), a solution of active methylene compound 5 (0.05 mol) in dry DMF (25 ml) was added dropwise during 0.5 hr. A solution of alkyl/aryl isothiocyanate (0.05 mol) in dry DMF (25 ml) was then added and the reaction mixture was further stirred for 1.5–2 hr, followed by subsequent addition of methyl iodide (0.05 mol) in DMF (20 ml). After further stirring for 2 hr, the reaction mixture was poured over crushed ice, neutralized with gl. AcOH and extracted with chloroform. The chloroform layer was washed with water (3x100 ml), dried (Na_2SO_4) and concentrated to give crude S,N-acetals 3g-p and 3v-y (Table 6), which were either purified by crystallization (3v and 3w) or by passing through silica gel column using benzene/hexane (1:1) as eluent.

Method C. Thioamide method:

Preparation of thioamides: A mixture of methyl benzoyldithioacetate (8) (0.01 mol) and the appropriate amine 9 (0.01 mol) in ethanol (25 ml) was refluxed for 4-7 hr. After completion of the reaction (monitored by TLC), ethanol was removed on water bath and the residue triturated with hexane to remove excess of amine. The crude thioamides 10a-c thus obtained, were purified by crystallization from ether/hexane mixture as yellow crystalline solids. Benzoylthioaceticacid-morpholide (10a), mp 126-7° (reported mp 127-9°),[5] was obtained in 90% yield. (IR and NMR same as reported).[5]

p-methylbenzoylthioaceticacid-morpholide (10b), mp 128° was obtained in 92% yield; IR ν_{max} (nujol): 1680 (C=O) cm^{-1}; NMR(TFA) : δ 2.42 (s, 3H, $C\underline{H}_3$); 3.67-4.40 (br.s, 8H, $-(C\underline{H}_2)_2-O-(C\underline{H}_2)_2-$); 5.02 (s, 2H, $C\underline{H}_2CO$); 7.55 (A_2B_2.dd, $4\underline{H}_{arom}$); Found : C, 63.49%; H, 6.25%; N, 5.14%; Calc. for $C_{14}H_{17}NO_2S$ (263) : C, 63.87%; H, 6.46%; N, 5.32%.

Benzoylthioaceticacid-piperidide (10c), mp 130-1°, was obtained in 88% yield; IR ν_{max} (nujol) : 1730 (C=O) cm^{-1}; NMR(TFA) : δ 1.40 (s, 6H, $-(C\underline{H}_2)_3-$); 3.18-3.65 (m, 4H, $-C\underline{H}_2-N-C\underline{H}_2-$); 4.50 (s, 2H, CH_2CS); 6.75-7.50 (br, $5H_{arom}$); Found : C, 67,88%; H, 7.02%; N, 5.45%; Calc. for $C_{14}H_{17}NOS$ (247): C, 68.01%; H, 6.88%; N, 5.66%.

Preparation of keten-S,N-acetals: To an ice cooled and well stirred suspension of sodium hydride (o.24g, 0.012 mol) washed 2-3 times with dry benzene) in dry DMF (10 ml), a solution of thioamide 10 (0.01 mol) in dry DMF (15 ml) was added and after stirring for 5-10 min., 0.01 mol of methyl iodide was added. The reaction mixture was further stirred overnight, diluted with water and extracted with chloroform. The chloroform layer was washed with water (3x100 ml), dried (Na_2SO_4) and concentrated to give crude S,N-acetals <u>11a-c</u> (Table 8), which were purified by passing through silica gel column and using benzene/hexane (2:1) as eluent.

TABLE 6

1-(N-Arylamino)/morpholino-2-carboethoxy-2-cyano-1-methylthioethylenes (3a-f); 1-aryl/methyl-3-N-aryl/alkylamino-3-methylthio-1-oxo-2-propenes (3g-q and 3s-u); β-anilino-β-methylthio-2-phenylacrylonitrile (3v); 2-anilino/N-ethylamino-2-methylthio-1-nitroethylenes (3r and 3w); 2-(anilino-methylthio) methylene-1-tetralone (3x); 3-(anilino-methylthio)methylene-6-methyl-2,3-dihydro-1-benzothiopyran-4-one (3y).

Product[a,b]	Reaction time (hr)	Yield[c] (%)	m.p. (°C)	Molecular formula	Analysis (%) Calc. Found	C	H	N
3a[d]	7	77	74	$C_{13}H_{14}N_2O_2S$		59.54	5.34	10.68
				(262)		59.06	5.27	10.41

Table 6 (Contd.)

3b[d]	4	75	79	$C_{14}H_{16}N_2O_3S$	57.53	5.47	9.58
				(292)	57.30	5.32	9.40
3c[d]	3.5	76	104-	$C_{13}H_{13}ClN_2O_2S$	52.61	4.38	9.44
			105	(296)	52.44	4.42	9.25
3d[d]	5	75	98-	$C_{13}H_{13}FN_2O_2S$	55.71	4.64	10.00
			99	(280)	55.31	4.73	9.88
3e[d]	6	72	79-	$C_{14}H_{16}N_2OS$	60.86	5.79	10.14
			80	(276)	61.14	5.90	10.40
3f[d]	8	71	90-	$C_{11}H_{17}N_2O_3S$	51.36	6.61	10.89
			91	(257)	50.98	6.59	10.77

Table 6 (Contd.)

3g[e]	8	82(40)	56-	$C_{16}H_{15}NOS$	71.37	5.57	5.20
			57	(269)	70.98	5.60	5.33
3h[e]	10	74(32)	66-	$C_{17}H_{17}NO_2S$	68.22	5.68	4.68
			67	(299)	68.70	5.61	4.45
3i[e]	8	84(41)	85-	$C_{16}H_{14}BrNOS$	55.17	4.02	4.02
			86	(348)	54.89	3.91	3.89
3j[g]	–	77	77	$C_{16}H_{14}ClNOS$	63.26	4.61	4.61
				(303.5)	63.64	4.55	4.86
3k[e]	11	76(31)	116-	$C_{16}H_{14}ClNOS$	63.26	4.61	4.61
			117	(303.5)	63.60	4.88	4.92
3l[f]	9	70(75)	oil	$C_{12}H_{15}NOS$	65.15	6.78	6.33
				(221)	65.32	6.66	6.08

Table 6 (Contd.)

3m[g]	-	76	oil	$C_{13}H_{17}NOS$	66.38	7.23	5.95
				(235)	66.07	7.11	6.23
3n[g]	-	76	oil	$C_{13}H_{17}NO_2S$	62.15	6.77	5.57
				(251)	61.79	6.95	5.92
3o[g]	-	78	oil	$C_{12}H_{14}BrNOS$	48.00	4.66	4.66
				(300)	47.73	4.51	4.82
3p[g]	-	75	oil	$C_{12}H_{14}ClNOS$	56.36	5.47	5.47
				(255)	56.71	5.60	5.75
3q[d]	25	88	oil	$C_7H_{13}NOS$	52.83	8.17	8.80
				(159)	53.12	8.00	8.53

Table 6 (Contd.)

3r^{d}	2	64	61–	$C_5H_{10}N_2O_2S$	37.03	6.17	17.28
			62	(162)	36.71	6.32	17.09
3s^{d}	17	92	oil	$C_{13}H_{17}NOS$	66.38	7.23	5.95
				(235)	66.61	6.99	6.17
3t^{d}	15	90	oil	$C_{14}H_{19}NOS$	67.46	7.63	5.62
				(249)	67.31	7.71	5.80
3u^{d}	12	95	oil	$C_{17}H_{17}NOS$	72.08	6.00	4.94
				(283)	71.72	6.18	5.32
3v^{g}	–	77	112–	$C_{16}H_{14}N_2S$	72.18	5.26	10.52
			114	(266)	71.90	5.18	10.71

Table 6 (Contd.)

3w[g]	–	92	147– 148	$C_9H_{10}N_2O_2S$ (210)	Known		
3x[g]	–	78	oil	$C_{18}H_{17}NOS$ (295)	73.22 73.71	5.76 5.49	4.74 4.66
3y[g]	–	90	oil	$C_{18}H_{17}NOS_2$ (327)	66.05 65.68	5.19 5.47	4.28 4.04

---

[a] Crystallized from chloroform:hexane (3a–f, 3v and 3w).

[b] Purified by column chromatography (3g–u, 3x and 3y).

[c] The yields were not critically optimised.

[d] Prepared by method A-1.

[e] Prepared by method A-2 and method B, yields in parentheses are by method A-2.

[f] Prepared by method A-1 and method B, yield in parentheses is by method A-1.

[g] Prepared by method B only.

TABLE 7

1-Aryl-3,3-bis (N-aryl/ethylamino)/morpholino -1-oxo-2-propenes (4a-h) and 4j-m); 2,2-bis(anilino/N-ethylamino)-1-nitroethylenes (4i and 4n); 2-(benzoyl/nitro)-methylene-imidazolidine (4o and 4p)

Product	Reaction time(hr)	Cryst. solvent	Yield[a] (%)	m.p. (°C)	Molecular formula	Calc. found	Analysis (%) C	H	N
4a[b]	1[c]	$CHCl_3$:	64(10)	132-	$C_{21}H_{18}N_2O$		80.25	5.73	8.91
		hexane		133	(314)		79.92	5.90	8.81
4b[b]	1[c]	$CHCl_3$:	74(12)	161-	$C_{22}H_{20}N_2O_2$		76.74	5.81	8.13
		hexane		162	(344)		76.47	5.99	7.86
4c[b]	1.5[c]	$CHCl_3$:	68(12)	137-	$C_{21}H_{17}BrN_2O$		64.12	4.32	7.12
		hexane		138	(393)		63.85	4.15	6.89

Table 7 (Contd.)

4d[d]	1.5	$CHCl_3$: hexane	71	188–189	$C_{21}H_{17}ClN_2O$ (348.5)	72.30 71.88	4.87 4.95	8.03 7.89
4e[b]	8[c]	$CHCl_3$: hexane	50(11)	193–195	$C_{21}H_{16}Cl_2N_2O$ (383)	65.79 66.17	4.17 3.98	7.31 7.58
4f[d]	10	$CHCl_3$: hexane	51	198	$C_{22}H_{18}Cl_2N_2O_2$ (413)	63.92 64.27	4.35 4.17	6.77 6.85
4g[d]	2	$CHCl_3$: hexane	69	113–114	$C_{24}H_{24}N_2O_2$ (372)	77.14 76.86	6.45 6.68	7.52 7.77
4h[d]	2	$CHCl_3$: hexane	72	140–141	$C_{24}H_{24}N_2O_3$ (388)	74.22 73.90	6.18 6.00	7.21 7.53

Table 7 (Contd.)

4i[d]	2.5	$CHCl_3$:	70	157-	$C_{14}H_{13}N_3O_2$	65.88	5.09	16.47
		hexane		158	(255)	66.12	4.89	16.67
4j[e]	6	hexane	77	76-	$C_{13}H_{18}N_2O$	71.55	8.25	12.84
				77	(218)	71.73	7.99	12.58
4k[e]	5	hexane	75	70-	$C_{14}H_{20}N_2O_2$	67.74	8.06	11.29
				71	(248)	67.62	7.86	11.57
4l[e]	3	hexane	72	93-	$C_{13}H_{17}ClN_2O$	61.78	6.73	11.08
				95	(252.5)	61.93	6.80	10.75
4m[f]	9	$CHCl_3$:	82	138-	$C_{17}H_{22}N_2O_3$	67.54	7.28	9.27
		hexane		140	(302)	67.82	7.57	9.46
4n[f]	6	EtOAC	75	127-	$C_6H_{13}N_3O_2$	45.28	8.17	26.41
				128	(159)	45.45	8.01	26.21

Table 7 (Contd.)

4o[f]	8	EtOAC:	80	186–	$C_{11}H_{12}N_2O$	70.21	6.33	14.89
		EtOH		188	(188)	69.86	6.02	15.17
4p[f]	8	EtOAC	82	155–	$C_4H_7N_3O_2$	Known		
				157	(129)			

---

[a] The yields were not critically optimised.

[b] Prepared by method A-2 and A-3, yields in parentheses correspond to method A-2.

[c] Reaction time for method A-3.

[d] Prepared by method A-3.

[e] Prepared by method A-2 in sealed tube.

[f] Prepared by method A-1.

TABLE 8

1-Aryl-3-methylthio-3-morpholino/piperidino-1-oxo-2-propenes (11a-c)[a]

Product	Yield (%)	m.p. (°C)	Molecular formula		Analysis (%)		
				Calc. Found	C	H	N
11a	92	oil	$C_{14}H_{17}NO_2S$		63.87	6.46	5.32
			(263)		64.11	6.70	5.24
11b	90	oil	$C_{15}H_{19}NO_2S$		64.98	6.85	5.05
			(277)		65.33	6.72	4.82
11c	93	oil	$C_{15}H_{19}NOS$		68.96	7.27	5.36
			(261)		69.20	7.05	5.14

[a] Prepared by method C.

REFERENCES

1. D. Borrman, in Houben-Weyl, Methodern Der Organischen Chemie, B. VII/4, pp. 391-441, Georg Thieme Verlag, Stuttgart (1968).
2. R. Gompper and W. Töpel, Chem. Ber. 95, 2861, 2871, 2881 (1962).
3. M. Sone, Y. Tominaga, Y. Matsuda, G. Kobayashi, Yakugaku Zasshi, 97, 262 (1977); Chem. Abstr. 87, 53195^{v} (1977).
4. A. Kumar, V. Aggarwal, H. Ila and H. Junjappa, Synthesis, 748 (1980).
5. R. Gompper and H. Schaefer, Chem. Ber. 100, 591 (1967).
6. W.-D. Rudorf, A. Schierhorn, M. Augustin, Tetrahedron 35, 551 (1979).
7. W.-D. Rudorf, Z. Chem. 19 (3), 100 (1979); Chem. Abstr. 91, 5058^{p} (1979).
8. R. Gompper and E. Kutter, Ang. Chem. Inter. Ed. 1, 216 (1962).
9. (a) F.C.V. Larsson and S.-O. Lawesson, Tetrahedron, 30, 1283 (1974); (b) F.C.V. Larsson and S.-O. Lawesson, ibid, 28, 5341 (1972).

10. G. Singh, S.S. Bhattacharjee, H. Ila and H. Junjappa, Synthesis (1982) (in press)

11. W. Walter and H.-W. Meyer, Liebigs Ann. Chem. 19 (1975).

12. F. Krollpfeiffer and H. Schultze, Ber. 56B, 1919 (1923); Chem. Abstr. 18, 230 (1924).

13. D.J. Martin, C.C. Greco, J. Org. Chem. 33, 1275 (1968).

14. (a) M. Deliphe, Compt. Rend., 144, 1125-27; Chem. Abstr. 1, 2236 (1907); (b) A text book of practical Organic Chemistry by A.I. Vogel, pp. 643, ELBS and Longman (1968).

15. J. Sandstrom and I. Wennerbeck, Acta Chem. Scand. 24, 1191 (1970).

16. A. Thuillier and J. Vialle, Bull. Soc. Chim. France, 1398 (1959).

17. A. Thuillier and J. Vialle, Bull. Soc. Chim. France, 2182 (1962).

CHAPTER 3

REACTION OF POLARIZED KETEN-S,N- AND N,N-ACETALS WITH GUANIDINE: A NOVEL AND CONVENIENT SYNTHESIS OF 2-AMINO-4-(N-ALKYL-N-ARYLAMINO) PYRIMIDINES*

3.1 Aminopyrimidines : A brief Literature Survey

A large number of biologically important aminopyrimidines have been described in the literature.[1,2] Their synthesis have been achieved either directly using appropriately functionalized carbon fragments or by multistep process starting mainly from the corresponding oxopyrimidines. A brief survey of the literature covering the various synthetic methods for aminopyrimidines, is described in this chapter.

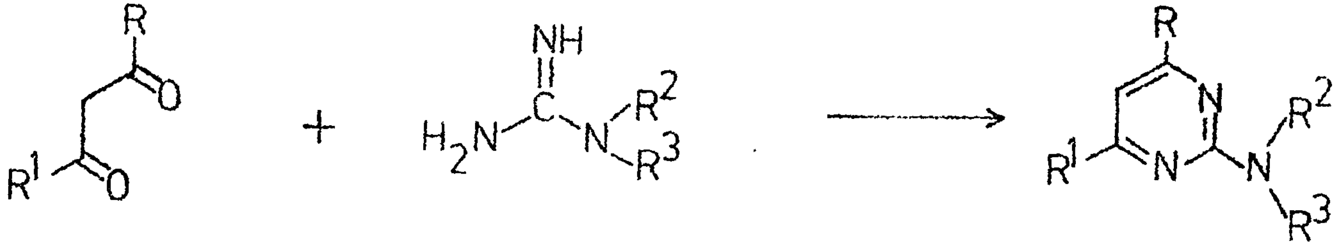
3.1.1 Synthesis of Aminopyrimidines : Principal Synthetic Method

When guanidine (2a) (Scheme 1)[3] is reacted with three carbon fragments 1a or 1b, the corresponding 2-aminopyrimidines 3a are obtained in good to excellent yields. This method is further extended to prepare

---

* A. Kumar, V. Aggarwal, H. Ila and H. Junjappa, Synthesis 748 (1980).

Scheme 1



1a , R, R^1 = alkyl, aryl

b , R = alkoxy; R^1 = alkyl, aryl

2a , $R^2 = R^3 = H$

b , R^2 = alkyl; $R^3 = H$

c , $R^2 = R^3$ = alkyl

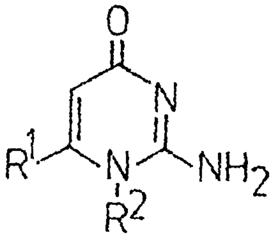
3a , R = alkyl, aryl, OH; R^1 = alkyl, aryl; $R^2 = R^3 = H$

b , R, R^1 = alkyl, aryl; R^2 = alkyl , $R^3 = H$

c , R = OH , R^1 = alkyl, aryl; R^2 = alkyl , $R^3 = H$

d , R, R^1 = alkyl, aryl; $R^2 = R^3$ = alkyl

e , R = OH , R^1 = alkyl, aryl; $R^2 = R^3$ = alkyl



4 , R^1 = alkyl, aryl; R^2 = alkyl

N-alkyl- and N,N-dialkylaminopyrimidines. The reaction of N,N-dialkylguanidine (2c) with β-diketones 1a and β-ketoesters 1b gave unequivocally the corresponding 2-(N,N-dialkyl)aminopyrimidines 3d and 3e respectively. Similarly, N-alkylguanidine (2b) reacted with β-diketones 1a to yield only 2-N-alkylaminopyrimidines 3b, while with β-ketoesters 1b, a mixture of 2-N-alkylaminopyrimidines 3c and the pyrimidine 4 carrying an alkyl group on one of the ring nitrogen atoms is formed.

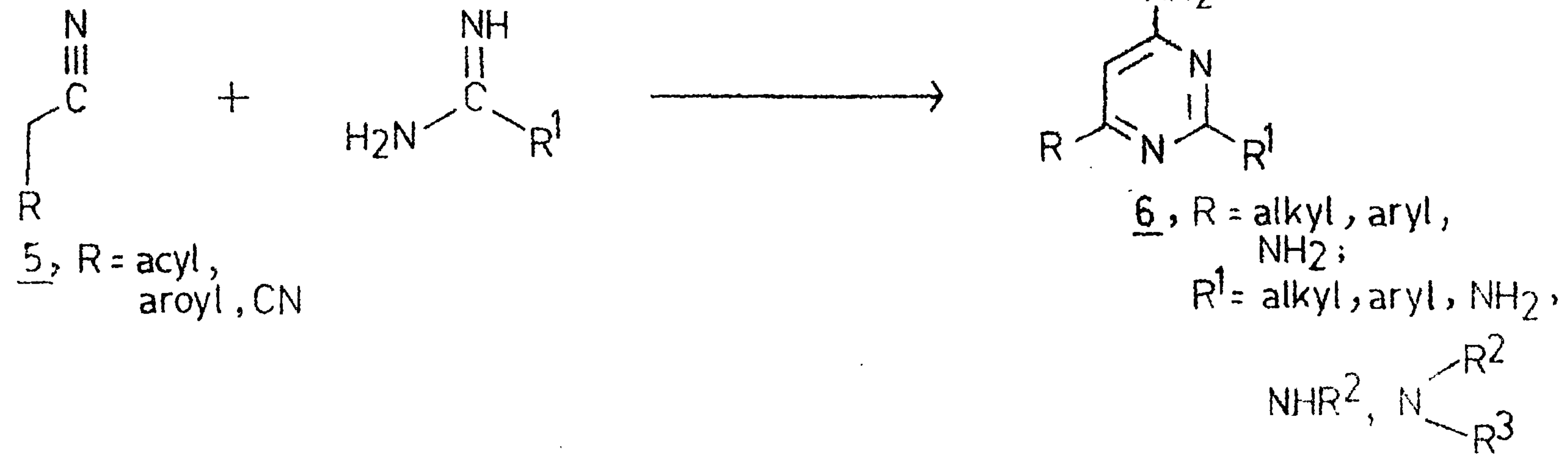
The synthesis of 4-or (and) 6-aminopyrimidines 6 (Scheme 2)[3] is achieved by reacting guanidine/amidines with three carbon fragments 5 having terminal nitrile groups. However, the method cannot be used for the synthesis of the corresponding pyrimidines having secondary and tertiary amino groups in the 4 and 6-positions.

There are other methods of Primary Synthesis reported in the literature,[3] which are of less practical importance.

3.1.2 From Chloropyrimidines

The reaction of ammonia or its alkyl/aryl derivatives with chloropyrimidines 8 (Scheme 3) to give

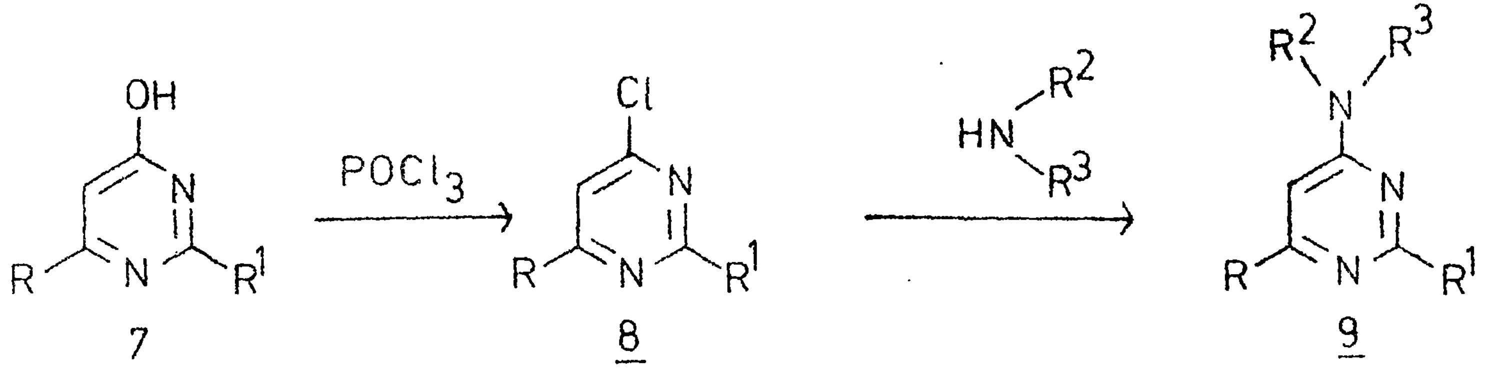
Scheme 2



5, R = acyl, aroyl, CN

6, R = alkyl, aryl, NH_2; R^1 = alkyl, aryl, NH_2, NHR^2, $N(R^2)R^3$

Scheme 3



7, 8, 9, R, R^1 = alkyl, aryl, NH_2

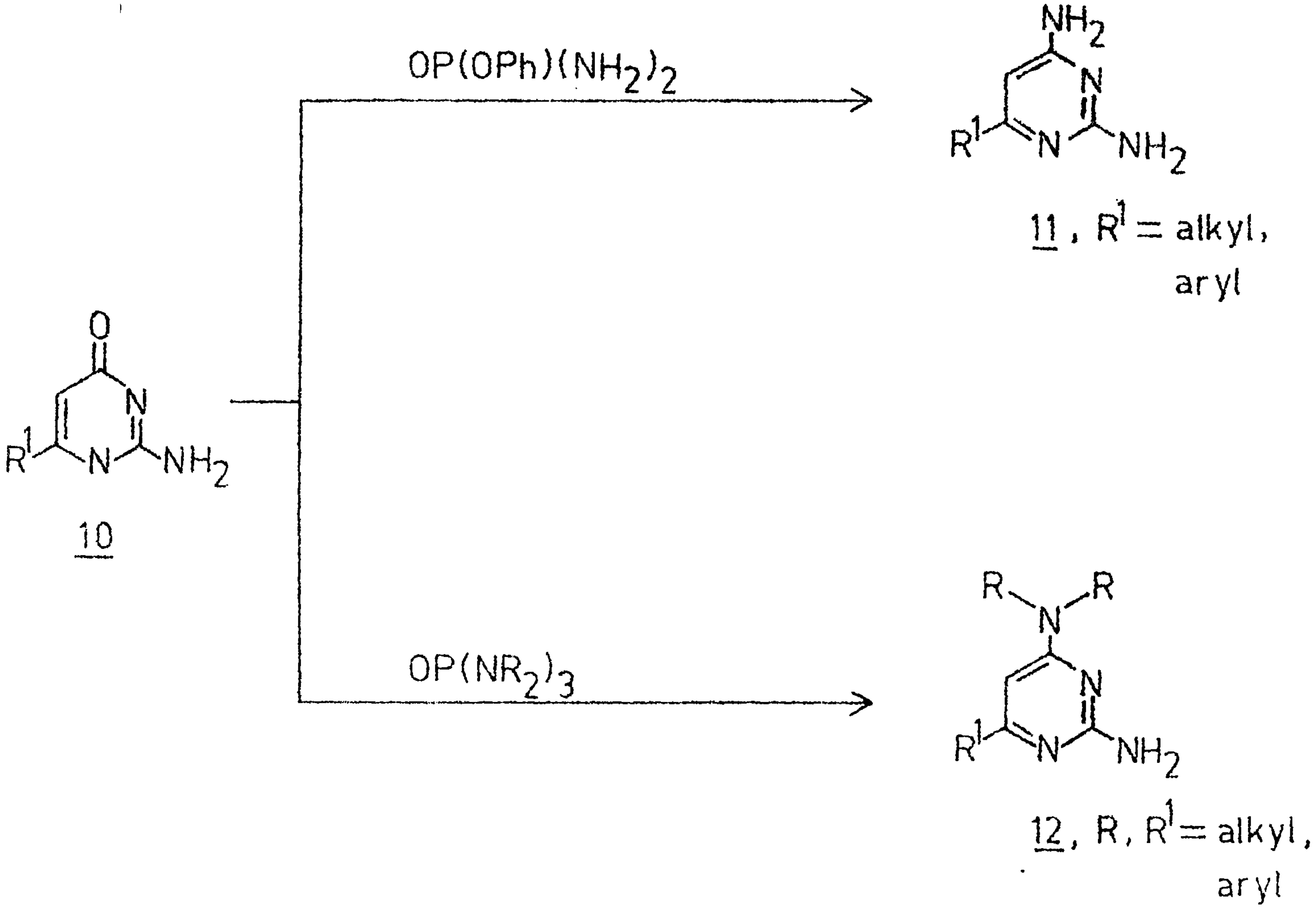
9, R^2, R^3 = H, alkyl, aryl

the corresponding aminopyrimidines 9, constitutes one of the important methods described in the literature.[3] However, there is no direct method for the synthesis of chloropyrimidines, which are derived from the corresponding oxopyrimidines 7 by reacting with phosphorous oxychloride. This conversion of oxopyrimidines to chloropyrimidines, suffers from multi-step operations resulting in overall poor yields. The practical difficulties of separation have been reported when the pK_b's of the chloropyrimidines are close to that of N,N-diethylaniline,[3a] which is generally used as a solvent in these reactions. Nevertheless, the method has been used since it provides the most practical procedure for the synthesis of aminopyrimidines.

3.1.3 Direct Synthesis of Aminopyrimidines from Oxopyrimidines

The synthesis of 2,4-diaminopyrimidines 11 (Scheme 4)[4] is described through the reaction of the corresponding 2-amino-4-oxopyrimidines 10 with appropriate phenyl phosphorodiamidates. Phosphoric triamides are similarly used to prepare 4-(N,N-dialkyl)

Scheme 4



10

11, R^1 = alkyl, aryl

12, R, R^1 = alkyl, aryl

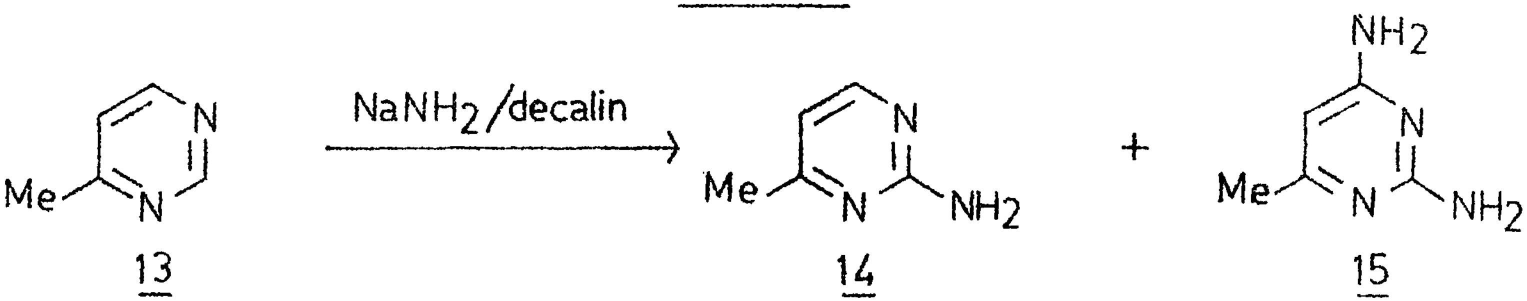
aminopyrimidines 12 from the corresponding oxopyrimidines. However, phosphoric triamides, other than their hexamethyl derivative (HMPT), which is commercially available, have to be prepared, which further increases the number of steps involved in the aminopyrimidine synthesis. This difficulty has been overcome by treating the oxopyrimidines with a mixture of phosphorous pentaoxide and appropriate dialkylamines to yield the corresponding N,N-dialkylaminopyrimidines.[5]

The overall yields of the pyrimidines derived from these methods are not satisfactory.

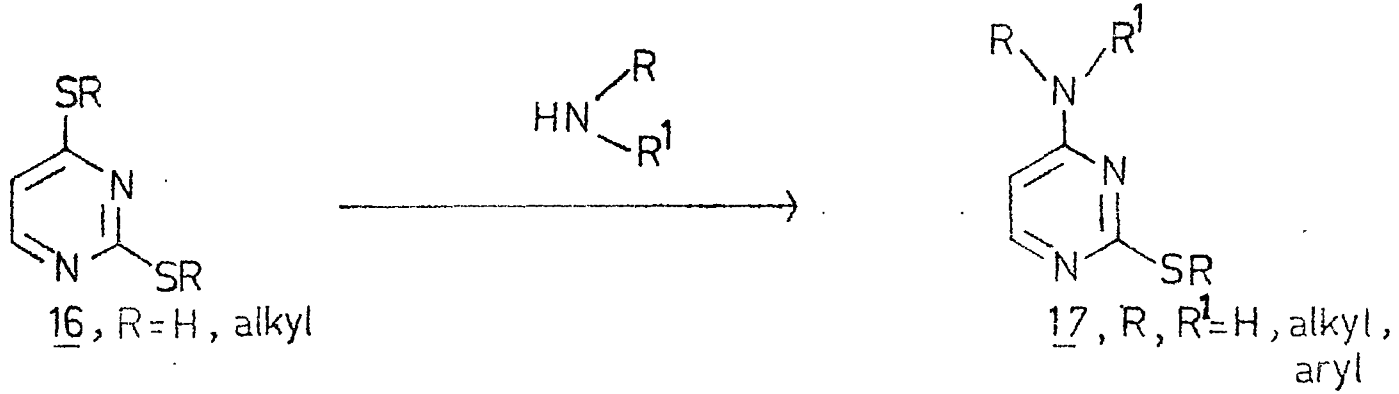
3.1.4 Aminopyrimidines by Direct Amination

Direct amination of pyrimidines using sodamide in decalin have been reported[3] to yield either mono or diaminopyrimidines as exemplified in Scheme 5. Thus 4-methylpyrimidine 13, on treatment with sodamide gave a mixture of the corresponding 2-amino-6-methylpyrimidine (14) and 2,4-diamino-6-methylpyrimidine (15) along with other unidentified products. The method seems to be of little practical importance and there is not much literature on the studies of this reaction.

Scheme 5



Scheme 6



3.1.5 From Mercapto or Alkythiopyrimidines

Mercapto pyrimidines 16, by reacting with ammonia or amines, are converted into the corresponding aminopyrimidines 17 (Scheme 6),[3] in moderate to good yields. The displacement of 2-mercapto group with an amine requires activating substituents in the pyrimidine ring. It may be noted here, that although the synthesis of 2-mercaptopyrimidines can be easily achieved by using thiourea as one carbon fragment, the methods described for the synthesis of 4 and 6-mercaptopyrimidines are not satisfactory.

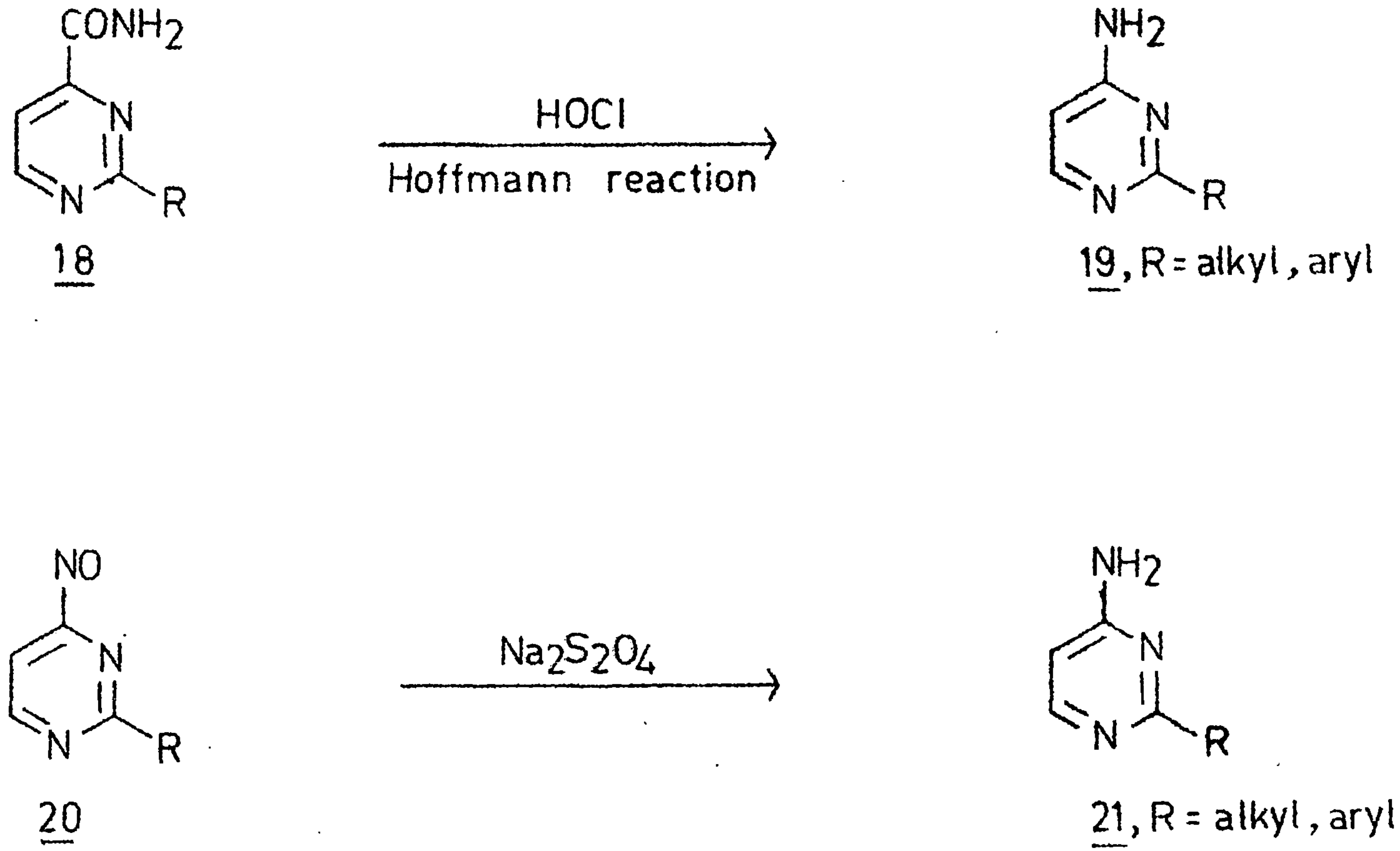
3.1.6 Aminopyrimidines by other Methods

A variety of miscellaneous reactions have been reported for the synthesis of aminopyrimidines, which are not of general synthetic applications and the details of their synthesis are reported elsewhere (Scheme 7 & 8).[3]

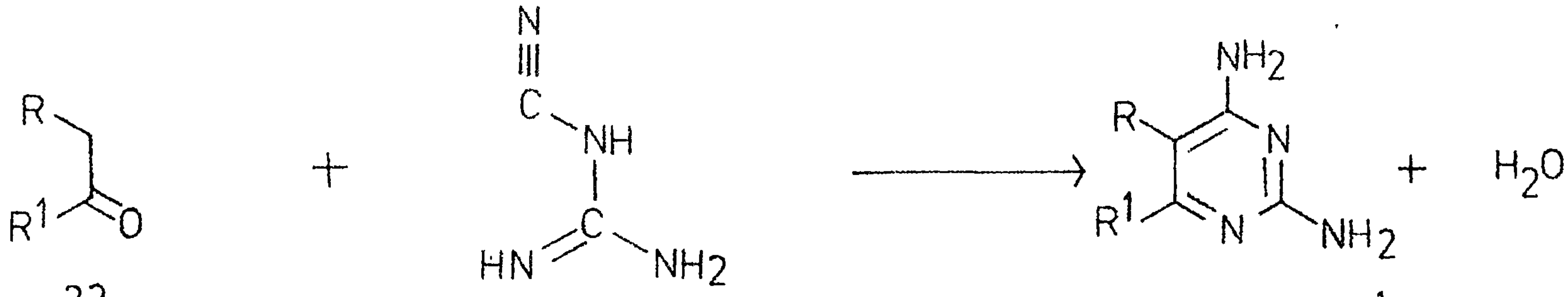
3.1.7 From Alkoxypyrimidines

Although alkoxypyrimidines 28 (Scheme 9) were known to undergo facile displacement reactions with amines to give the corresponding aminopyrimidines 30, the method was not popular, since the alkoxypyrimidines themselves,

Scheme 7


CONH2
N
N
R
18
HOCl
Hoffmann reaction
NH2
N
N
R
19, R = alkyl, aryl
NO
N
N
R
20
Na2S2O4
NH2
N
N
R
21, R = alkyl, aryl

Scheme 8

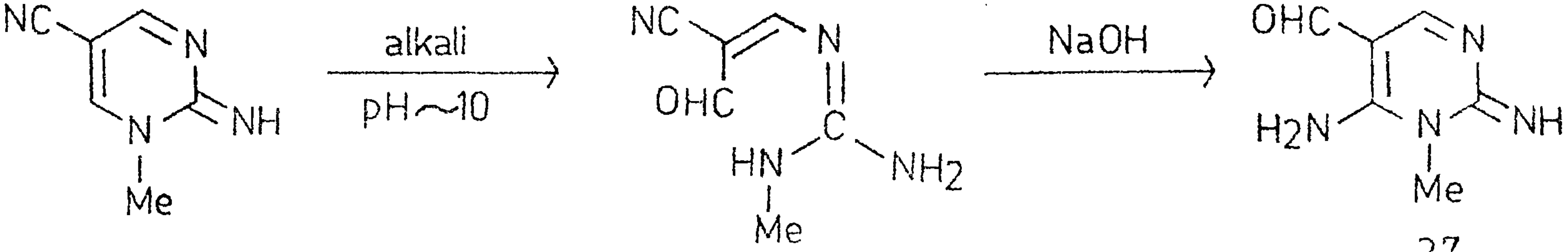


22

23

24, R, R^1= alkyl aryl

Dimroth rearrangement

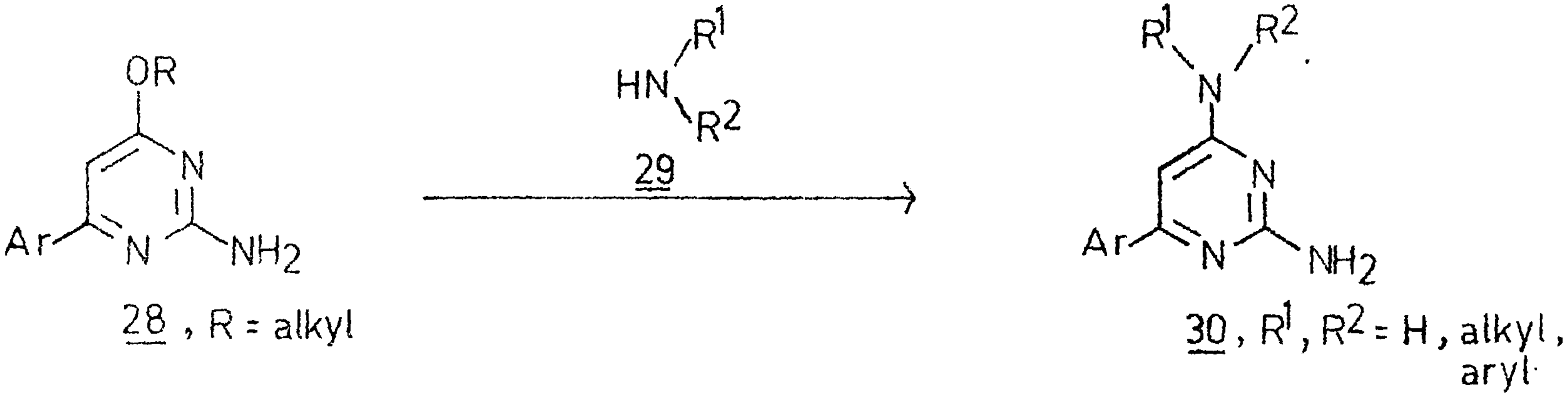


25

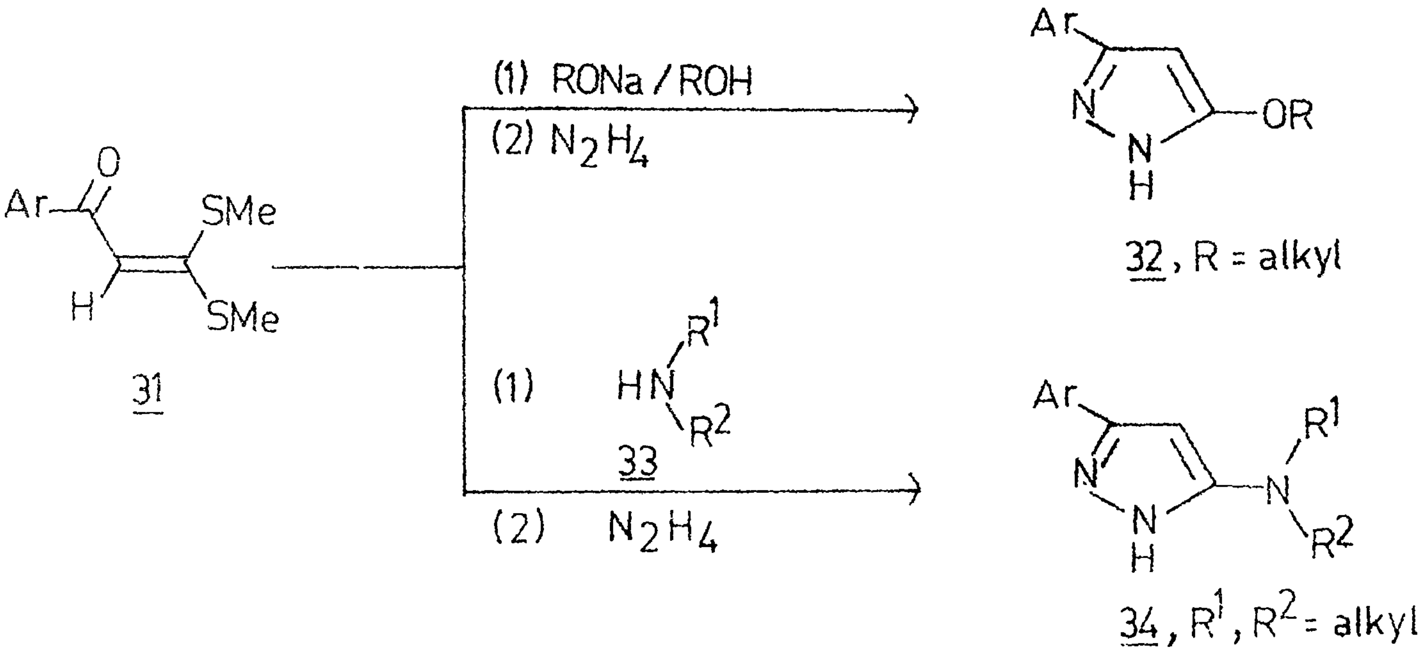
26

27

Scheme 9



Scheme 10



in turn, were obtained by the displacement reaction of the corresponding chloropyrimidines with appropriate alkali metal alkoxides.[3]

Recently, a general method for the synthesis of alkoxypyrimidines, by reaction guanidine and its derivatives with polarized keten dithioacetals 31, in the presence of appropriate sodium alkoxides, has been formulated from our laboratory.[6,7] The incorporation of the appropriate alkoxy group in the keten dithioacetal has been proved experimentally by using different alcohols. This has been further proved by designing an experiment, manipulating the reaction conditions, through incorporating appropriate nucleophiles such as alkoxides and amines, for the synthesis of the corresponding alkoxy 32 and aminopyrazoles 34 respectively (Scheme 10).[8]

Therefore, it is possible to contemplate similar synthetic strategy for the construction of various heterocycles, derivable from the keten dithioacetals and various binucleophiles, by incorporating *in situ*, appropriate nucleophiles.

3.2 Results and discussion

From the literature survey, it is evident that the various methods described for the synthesis of aminopyrimidines suffer from multi step operations and lack of generality for structural variation. The objective in the present investigation is therefore, aimed at exploring the synthetic utility of keten-S,N- and N,N-acetals as three carbon fragments for the synthesis of aminopyrimidines. The keten-S,N- and N,N-acetals can be prepared with liberal structural variations from a variety of active methylene compounds. The method constitutes the first general approach to one step synthesis of aminopyrimidines. A few ketoketen-S,N- and N,N-acetals have been chosen for the present studies which are described in chapter 2. Thus, the keten-S,N-acetal 35a (Scheme 11) underwent smooth reaction with guanidine nitrate in the presence of sodium ethoxide in refluxing ethanol to yield the corresponding 2,4-diaminopyrimidine 37a in 57% yield. Similarly, aminopyrimidines 37b-f (Table 1) were prepared in 47-57% overall yields by reacting the keten-S,N-acetals 35b-f with guanidine nitrate under identical conditions. Alternatively, the pyrimidines 37a-f were also prepared in one pot reaction, by refluxing the keten-S,S-acetal 38 with appropriate amines 39a-f, generating the corresponding S,N-acetals *in situ*, followed by subsequent reaction with guanidine. The structures

Scheme 11

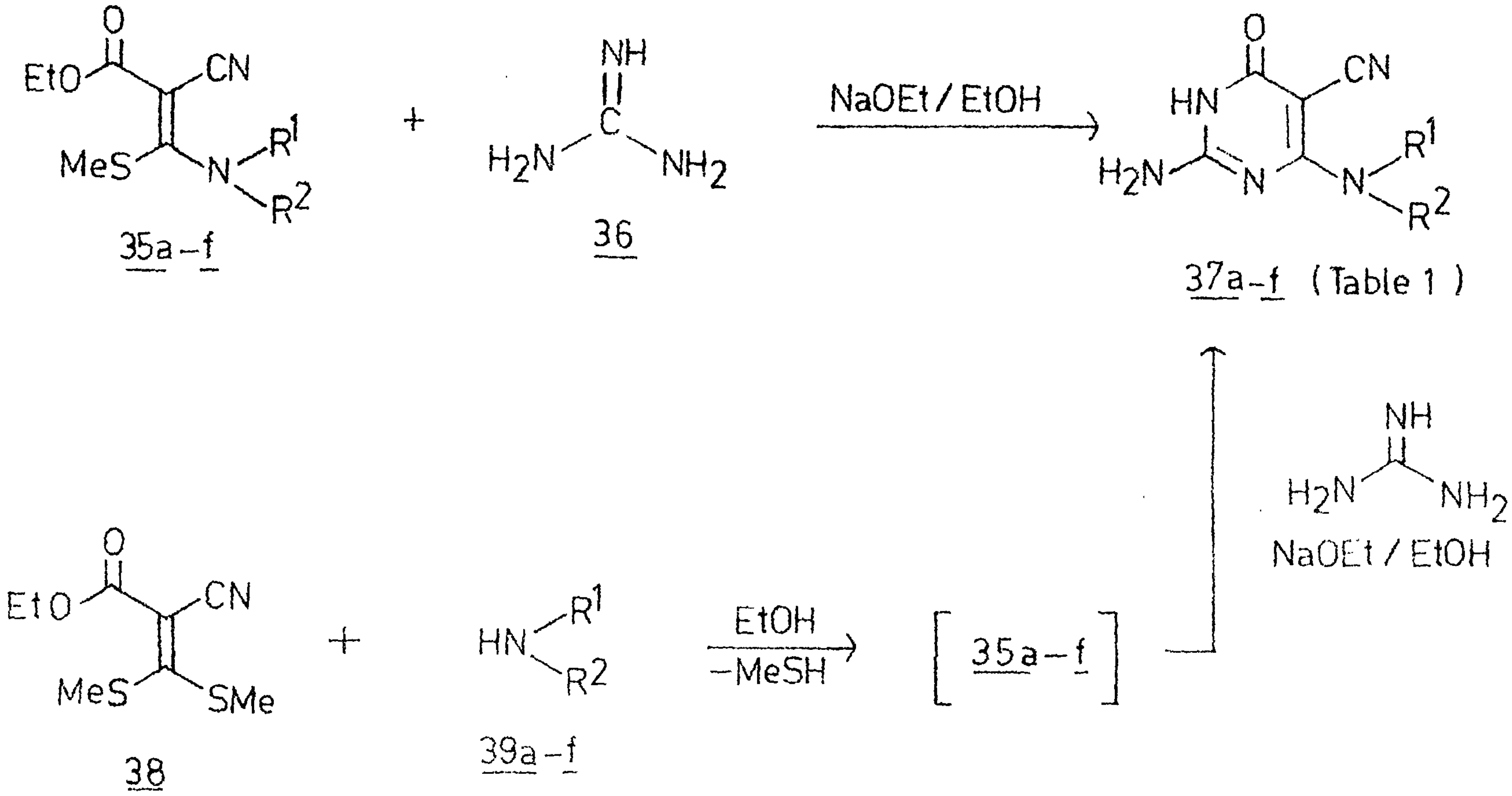
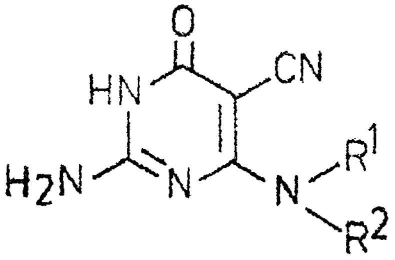

EtO
O
CN
MeS
N
R^1
R^2
35a–f
+
NH
C
H_2N
NH_2
36
NaOEt / EtOH
O
CN
HN
H_2N
N
N
R^1
R^2
37a–f (Table 1)
NH
H_2N
NH_2
NaOEt / EtOH
EtO
O
CN
MeS
SMe
38
+
HN
R^1
R^2
39a–f
EtOH
–MeSH
35a–f

Table 1

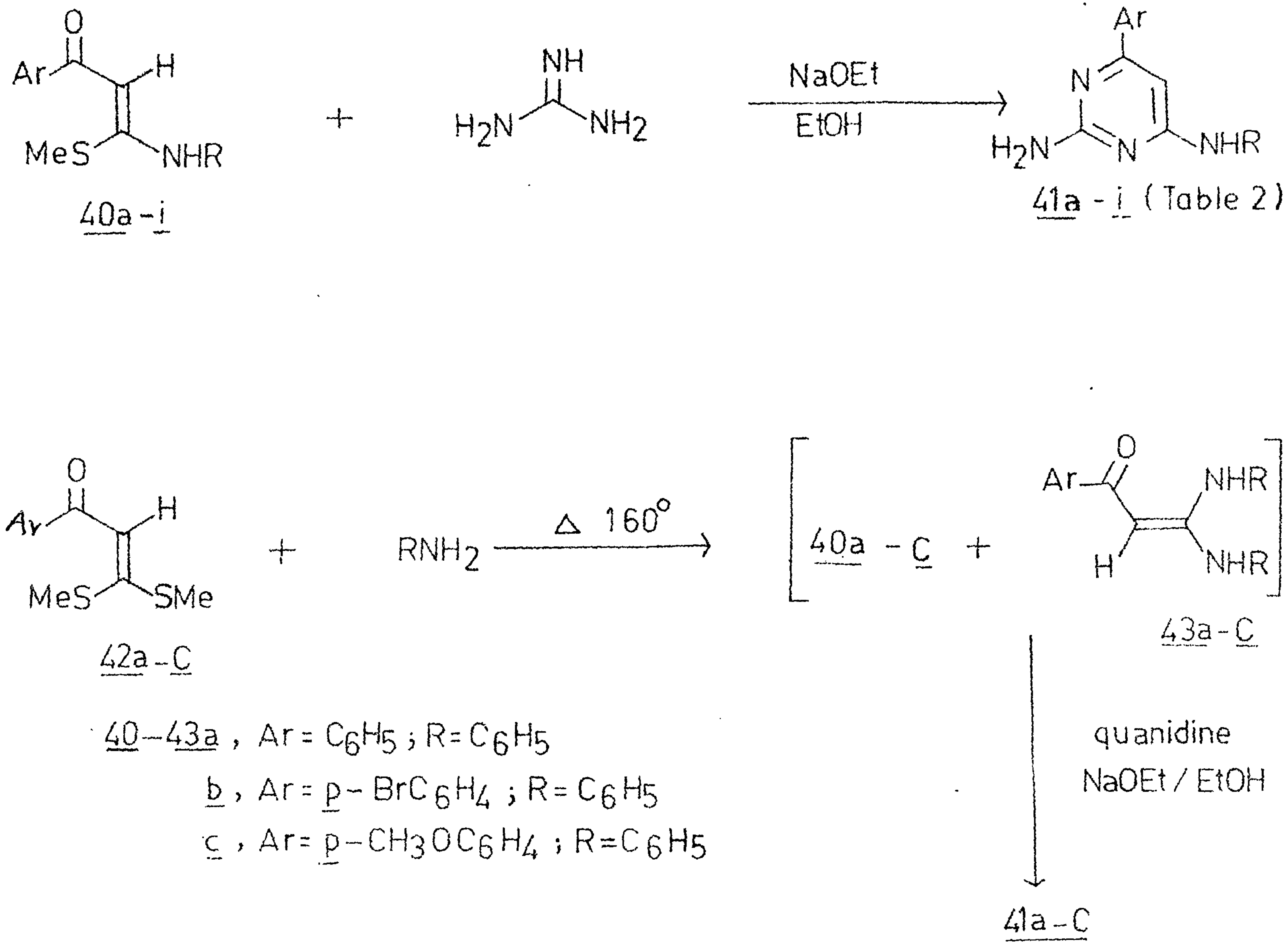


37

NO	R^1	R^2
37a	C_6H_5	H
37b	p-$CH_3C_6H_4$	H
37c	p-$CH_3OC_6H_4$	H
37d	p-clC_6H_4	H
37e	p-F-C_6H_4	H
37f	$-(CH_2)_2-O-(CH_2)_2-$	

assigned to the pyrimidines **37a-f** were confirmed on the basis of their analytical and spectral data described in table 7 and table 3 respectively. When the ketoketen-S,N-acetal **40a** (Scheme 12) (Table 2) was similarly reacted with guanidine nitrate under identical conditions, the corresponding aminopyrimidine **41a** was formed in 35% yield. Similarly, **40b-i** gave the corresponding **41b-i** in 34-50% overall yields, under identical conditions. The structures assigned to these pyrimidines were in conformity with their analytical (Table 8) and spectral data (Table 4). The alternative synthesis of **41a** in one pot reaction by generating the corresponding S,N-acetal **40a** *in situ*, resulted in poor yield (18%). However, it was found that the N,N-acetal was also formed in comparable yield which was recovered unreacted, and the yield of the pyrimidine therefore, varied according to the S,N-acetal formation *in situ*. When S,N-propylacetal **40j** (Scheme 13) was reacted with guanidine nitrate in the presence of ethanolic sodium ethoxide, a mixture of 4-n-propylaminopyrimidine **41j** (15%) and 4-ethoxypyrimidine **45** (30%) was formed. The exchange reaction, however, was not observed on similarly reacting **40j** in the presence of sodium *t*-butoxide when **41j** was formed exclusively in 47% yield. Its analytical and spectral data are

Scheme 12

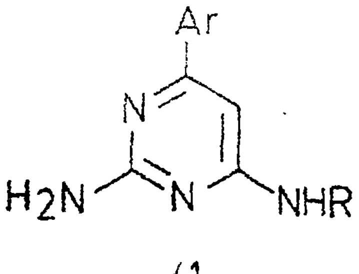


40–43a , Ar = C_6H_5 ; R = C_6H_5

b , Ar = p – BrC_6H_4 ; R = C_6H_5

c , Ar = p – $CH_3OC_6H_4$; R = C_6H_5

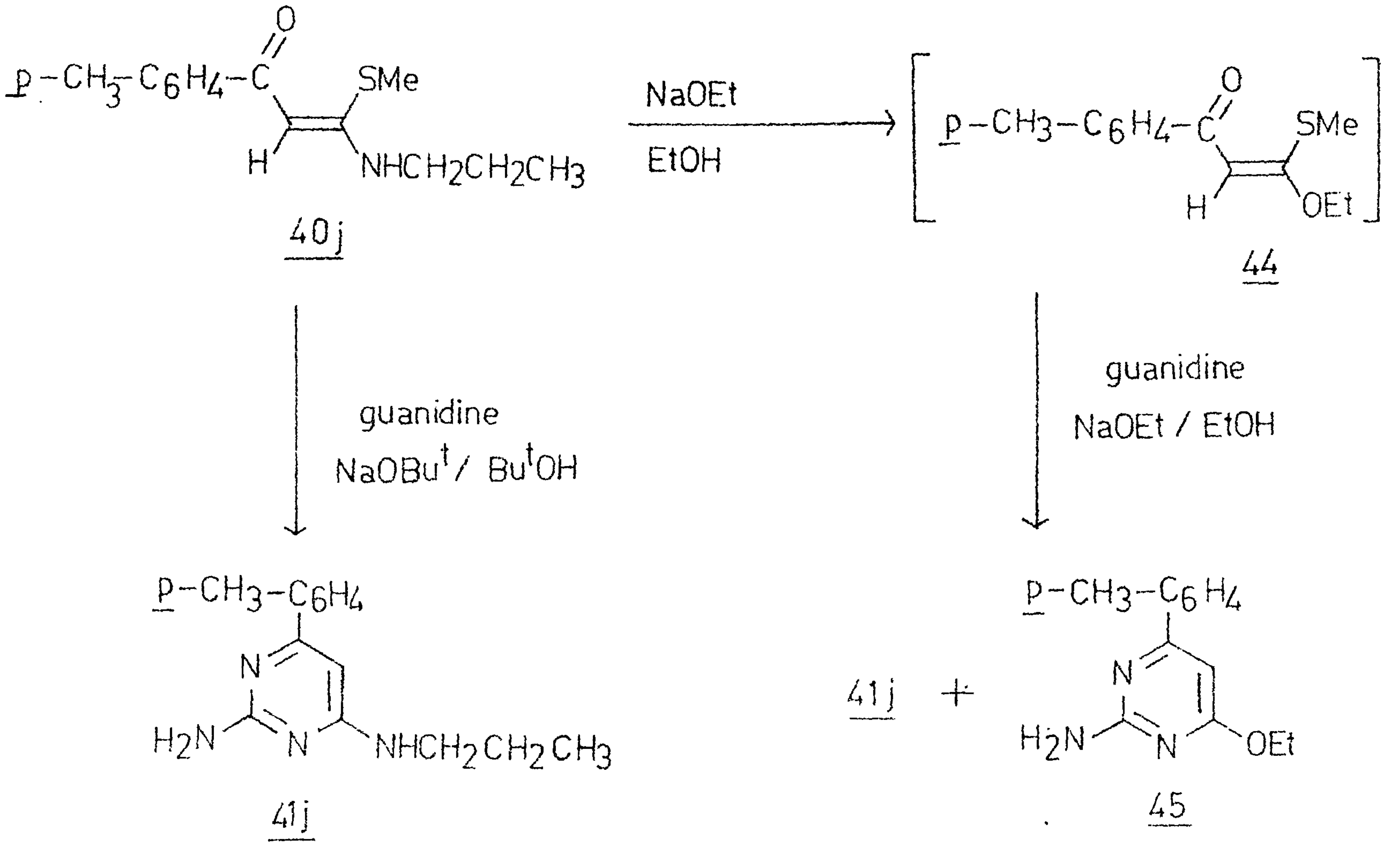
Table 2



41

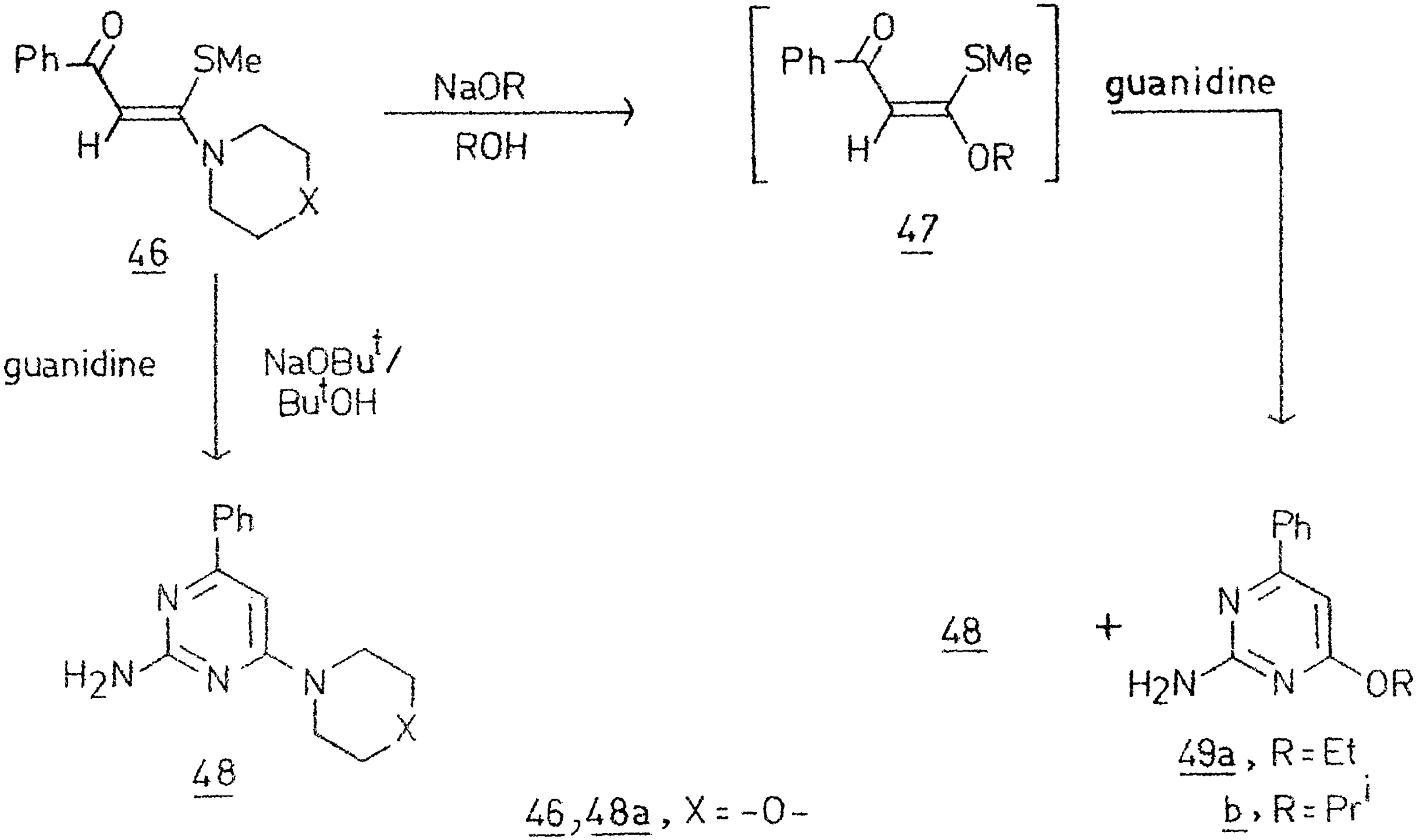
NO	Ar	R
41a	C_6H_5	C_6H_5
41b	p - BrC_6H_4	C_6H_5
41c	p - $CH_3OC_6H_4$	C_6H_5
41d	p - ClC_6H_4	C_6H_5
41e	C_6H_5	p-ClC_6H_4
41f	C_6H_5	C_2H_5
41g	p - $CH_3OC_6H_4$	C_2H_5
41h	p - ClC_6H_4	C_2H_5
41i	C_6H_5	$CH_2C_6H_5$

Scheme 13


p-CH3-C6H4-C
O
SMe
H
NHCH2CH2CH3
40j
NaOEt
EtOH
p-CH3-C6H4-C
O
SMe
H
OEt
44
guanidine
NaOBu^t / Bu^tOH
guanidine
NaOEt / EtOH
p-CH3-C6H4
N
H2N
N
NHCH2CH2CH3
41j
41j +
p-CH3-C6H4
N
H2N
N
OEt
45

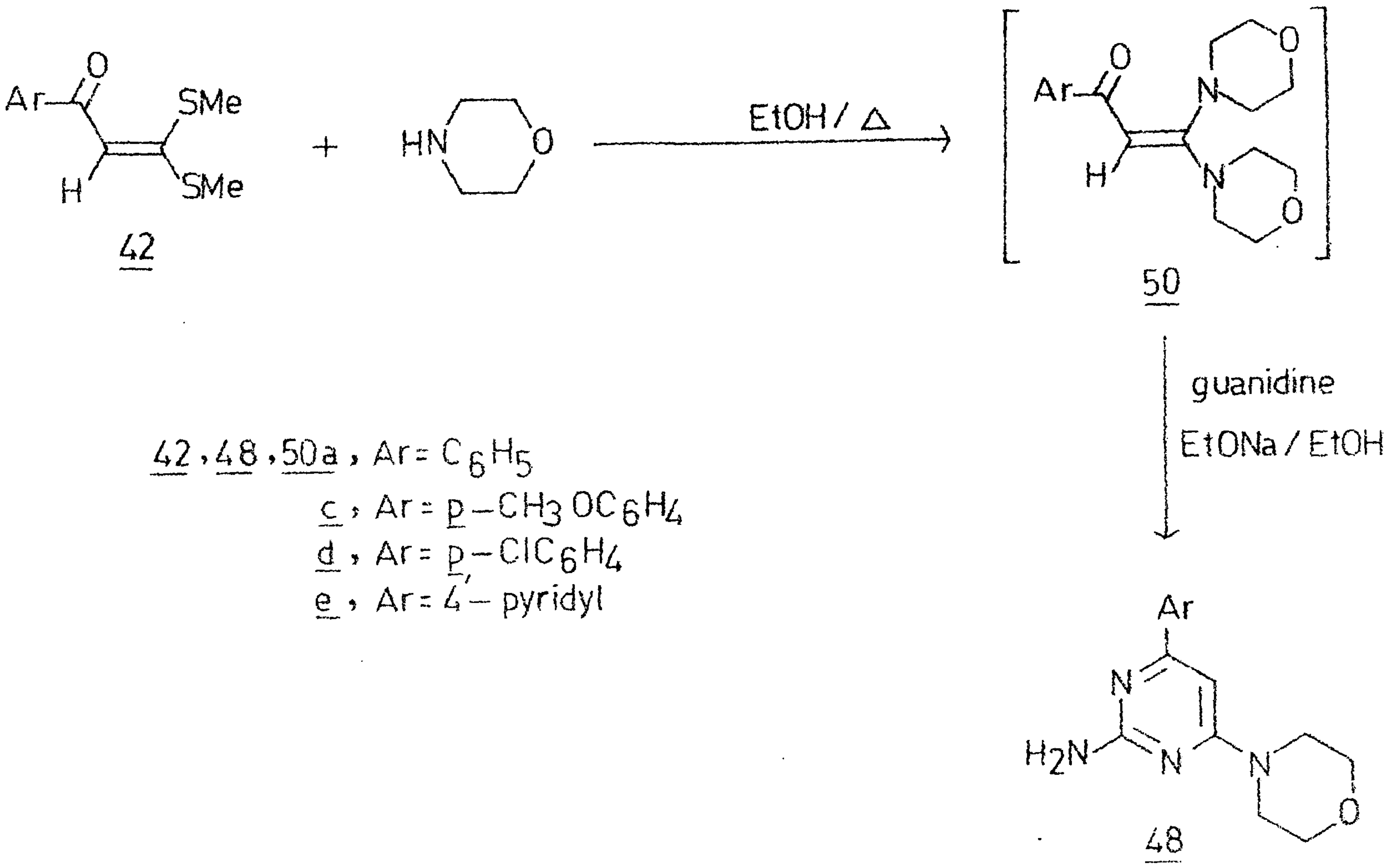
described in table 8 and table 4 respectively and are in conformity with the structures assigned. Similarly, the ketoketen-S,N-morpholinoacetal **46a** (Scheme 14) when reacted with guanidine nitrate in boiling ethanolic sodium ethoxide, a mixture of 4-morpholinopyrimidine **48a** (26%) and 4-ethoxypyrimidine **49a** (20%) was formed. Also the reaction in the presence of sodium isopropoxide in boiling isopropanol yielded a mixture of **48a** (33%) and **49b** (11%). However, **46a** reacted with guanidine nitrate in the presence of sodium *t*-butoxide, to yield only the aminopyrimidine **48a** in 46% yield. Similarly, **46b** with guanidine in the presence of sodium *t*-butoxide gave **48b** in 44% yield. Alternatively, the N,N-acetal **50a** (Scheme 15) generated *in situ* (TLC), by reacting **42a** with morpholine was also found to react with guanidine in the presence of sodium ethoxide to yield the corresponding pyrimidine **48a** in 28% yield. **48a** was found to be identical (mp, mmp, superimposable IR) with that obtained from **46a**. Similarly, **42c-e** were used to generate *in situ*, the corresponding **50c-e** and were found to react with guanidine nitrate in the presence of sodium ethoxide to yield the corresponding aminopyrimidines **48c-e** in 20-31% overall yields. As a typical example

Scheme 14



46, 48a, X = –O–
b, X = –CH$_2$–

Scheme 15

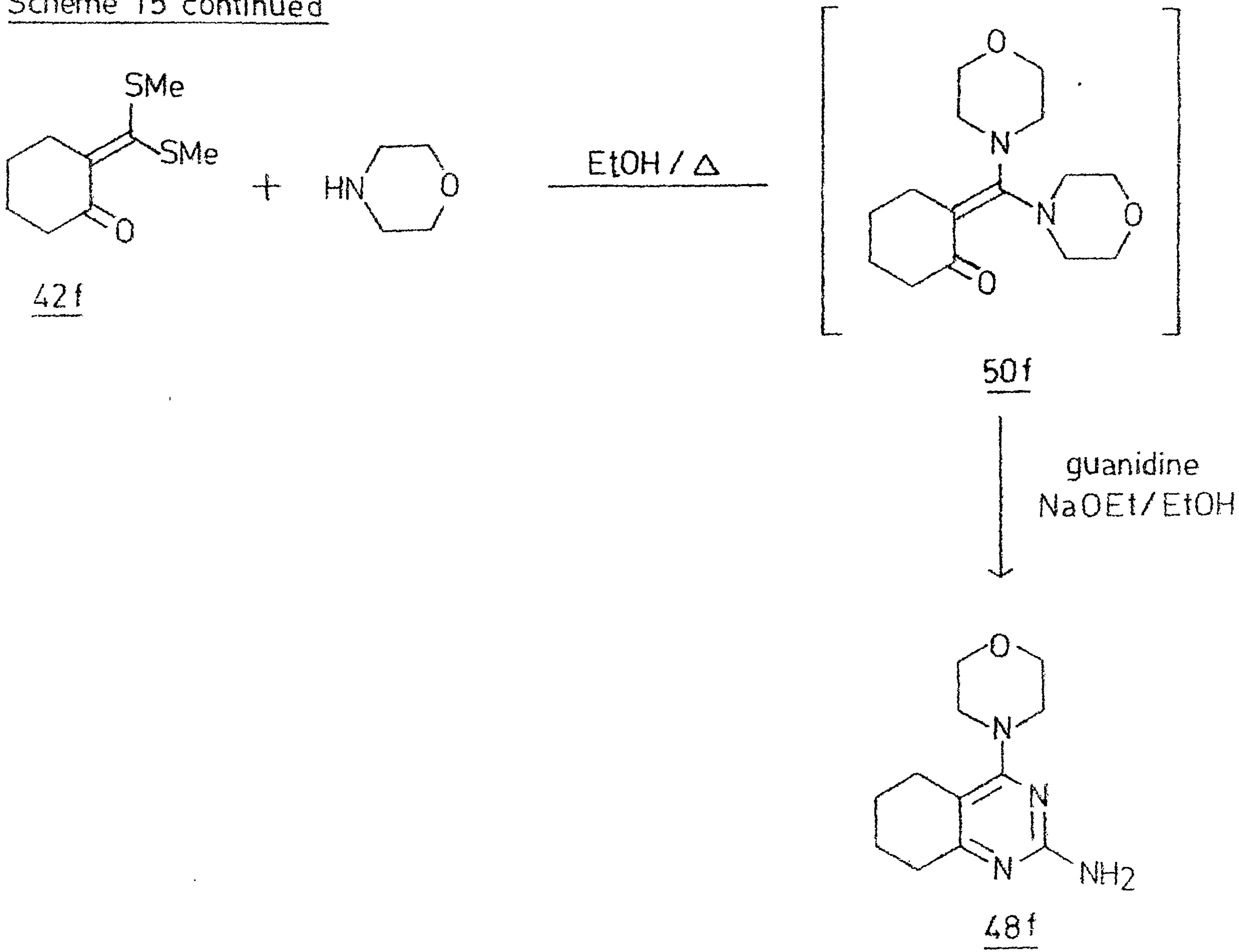


42, 48, 50a, Ar = C_6H_5
c, Ar = p–$CH_3OC_6H_4$
d, Ar = p–ClC_6H_4
e, Ar = 4′– pyridyl

for the synthesis of fused pyrimidines, the keten-S,S-acetal 42f derived from cyclohexanone, when reacted with morpholine, gave the corresponding N,N-acetal, generated *in situ* (TLC), which on subsequent treatment with guanidine nitrate in boiling ethanolic sodium ethoxide yielded the corresponding pyrimidine 48f in 20% yield. The pyrimidines 48a-f were characterised by their analytical (Table 9) and spectral data (Table 5), which were found to be in conformity with the structures assigned.

Apparently, since the keten-S,N-acetals proved to be versatile three carbon fragments for the synthesis of aminopyrimidines from the aforementioned examples, it was considered attractive to attempt the reaction of the functionalized S,N-acetals 51[9] (Scheme 16) with guanidine under similar conditions to yield the corresponding aminopyrimidines 52, which can be cyclized to pyrrolo-[2,3-*d*]-pyrimidines 53. Although, the formation of aminopyrimidines 52 was confirmed under usual reaction conditions, conversion of 52 to 53 under various conditions was not successful. Experiments towards developing a method for the synthesis of 53 from 51 are still in progress. The structures of 52 were confirmed by their analytical (Table 10) and spectral data (Table 6).

Scheme 15 continued

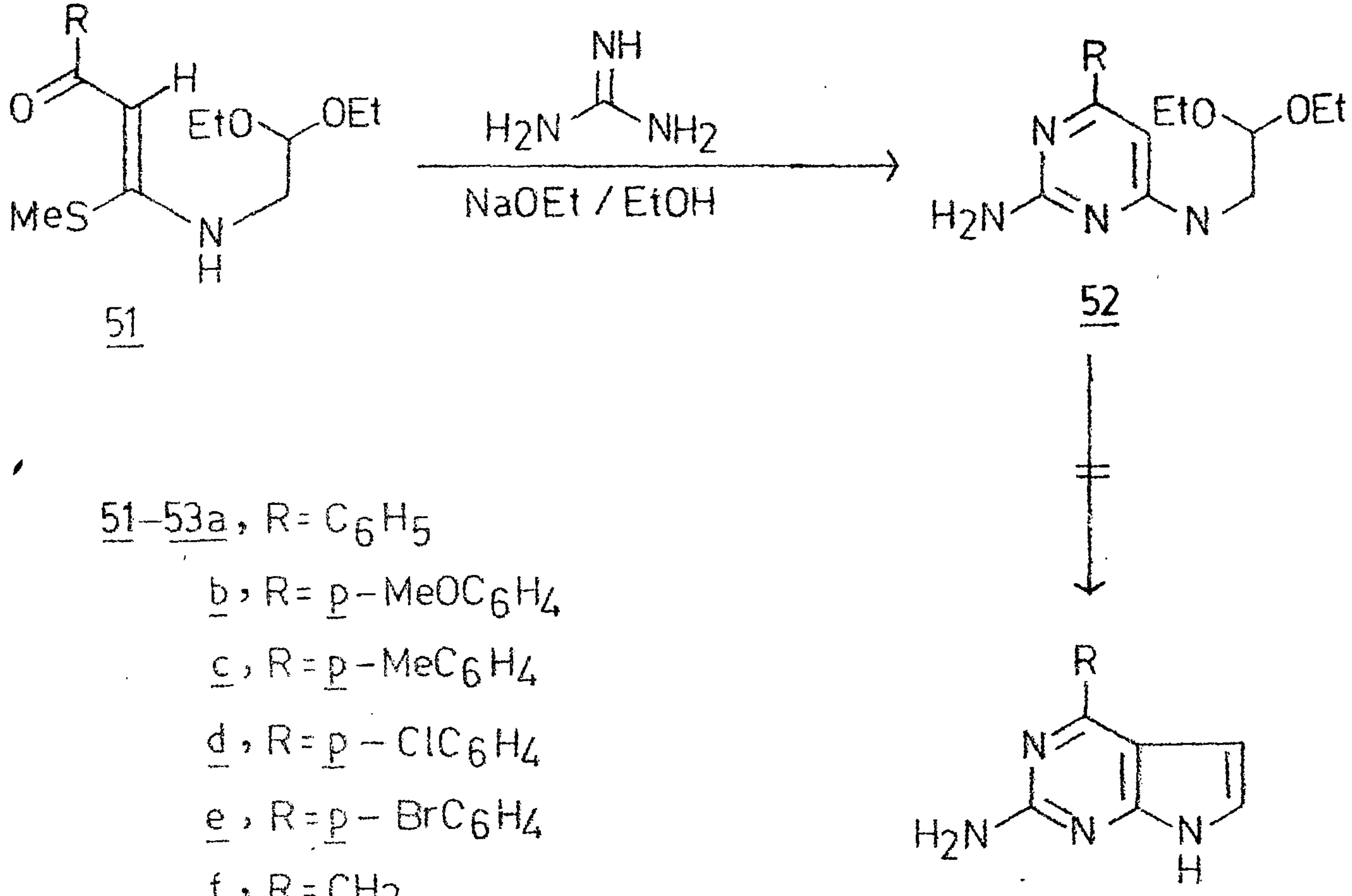


42f

50f

48f

Scheme 16



51

52

53

51–53a, R = C_6H_5

b, R = p-$MeOC_6H_4$

c, R = p-MeC_6H_4

d, R = p-ClC_6H_4

e, R = p-BrC_6H_4

f, R = CH_3

TABLE 3

Spectral data of products 37(a-f)

Product	IR(cm^{-1})^a	^1H-NMR(δ/ppm)^b
37a	3420,3270, 3155 (ν_{NH},ν_{NH_2}); 2200 (ν_{CN}); 1660 (ν_{CO}); 1635, 1585 (δ_{NH_2})	6.75-7.26 (m, 5H_{arom}); 8.66 (br s, 1H, $N\underline{H}$).
37b	3280, 3220, 3140 (ν_{NH}, ν_{NH_2}); 2215 (ν_{CN}); 1650 (ν_{CO}); 1600, 1540 (δ_{NH_2})	Insoluble.
37c	3425, 3265, 3150 (ν_{NH}, ν_{NH_2}); 2215 (ν_{CN}); 1662 (ν_{CO}); 1600, 1560 (δ_{NH_2})	3.51 (s, 3H, $OC\underline{H}_3$); 6.80 (A_2B_2.dd, 4H_{arom}); 8.56 (br s, 1H, $N\underline{H}$).

Table 3 (Contd.)

37d	3480, 3310, 3280, 3200, 3130 (ν_{NH}, ν_{NH_2}); 2200 (ν_{CN}); 1668 (ν_{CO}); 1640, 1600 ($\overset{\delta}{\cancel{\nu}}_{NH_2}$)	Insoluble.
37e	3475, 3292, 3200, 3123 (ν_{NH}, ν_{NH_2}); 2204 (ν_{CN}); 1670 (ν_{CO}); 1624, 1600 (δ_{NH_2})	6.56-7.05 (m, 4H$_{arom}$); 8.43 (br s, 1H, N$\underline{H}$).
37f	3280, 3175, 3100 (ν_{NH}, ν_{NH_2}); 2180 (ν_{CN}); 1670 (ν_{CO}); 1655, 1580 (δ_{NH_2})	3.66 (s, 8H, morpholine CH$_2$).

[a] IR medium = KBr.

[b] NMR solvent = TFA.

TABLE 4

Spectral data of products 41(a-j)

Product	IR(cm^{-1})	^{1}H-NMR(δ /ppm)
41a	3400, 3270, 3130 (ν_{NH},ν_{NH_2}); 1620, 1590 (δ_{NH_2})[a]	5.22 (s, 2H, N$\underline{H}_2$); 6.61 (s, 1H, $\underline{H}$-5); 7.00-7.70 (m, 8H$_{arom}$); 7.73-7.96 (m, 2H$_{arom}$).[c]
41b	3370, 3320, 3280 (ν_{NH}, ν_{NH_2}); 1618, 1590 (δ_{NH_2})[a]	5.00 (br s, 2H, N$\underline{H}_2$); 6.38 (s, 1H, $\underline{H}$-5); 7.15-7.78 (m, 9H$_{arom}$).[c]
41c	3450, 3380, 3170 (ν_{NH}, ν_{NH_2}); 1628 1600 (δ_{NH_2})[a]	3.71 (s, 3H, OC$\underline{H}_3$); 5.08 (br s, 2H, N$\underline{H}_2$); 6.35 (s, 1H, $\underline{H}$-5); 6.70-7.33 (m, 7H$_{arom}$); 7.76 (dd, 2H$_{arom}$).[c]

Table 4 (Contd.)

41d	3410, 3270, 3160 (ν_{NH}, ν_{NH_2}); 1610, 1592 (δ_{NH_2})[b]	6.30 (s, 1H, $\underline{H}$-5); 7.05–7.70 (m, $9H_{arom}$).[d]
41e	3400, 3220, 3150 (ν_{NH}, ν_{NH_2}); 1638, 1590 (δ_{NH_2})[a]	5.21 (br s, 2H, $N\underline{H}_2$); 6.26 (s, 1H, $\underline{H}$-5); 7.08–7.35 (m, $7H_{arom}$); 7.75–7.85 (m, $2H_{arom}$).[c]
41f	3320, 3280 (ν_{NH}, $_{NH_2}$); 1645, 1590 (δ_{NH_2})[a]	1.30 (t, 3H, $CH_2C\underline{H}_3$); 3.55 (q, 2H, $C\underline{H}_2CH_3$); 5.16 (br, 2H, $N\underline{H}_2$); 6.50 (s, 1H, $\underline{H}$-5); 7.66–8.03 (m, $3H_{arom}$); 8.16–8.48 (m, $2H_{arom}$).[c]

Table 4 (Contd.)

41g	3440, 3340, 3200 (ν_{NH}, ν_{NH_2}); 1650, 1592 (δ_{NH_2})[a]	1.20 (t, 3H, $CH_2C\underline{H}_3$); 3.30 (q, 2H, $C\underline{H}_2CH_3$); 3.80 (s, 3H, $OC\underline{H}_3$); 4.72 (br, 2H, $N\underline{H}_2$); 6.07 (s, 1H, $\underline{H}$-5); 6.88 (dd, $2H_{arom}$); 7.84 (dd, $2H_{arom}$).[c]
41h	3500, 3320, 3260 (ν_{NH}, ν_{NH_2}); 1628, 1605 (δ_{NH_2})[b]	1.28 (t, 3H, $CH_2C\underline{H}_3$); 3.50 (br q, 2H, $C\underline{H}_2CH_3$); 6.21 (s, 1H, $\underline{H}$-5); 7.28-7.92 (m, $4H_{arom}$).[d]
41i	3500, 3290, 3250 (ν_{NH}, ν_{NH_2}); 1630, 1595, 1575 (δ_{NH_2})[a]	4.55 (d, 2H, $NHC\underline{H}_2$); 5.02 (br, 2H, $N\underline{H}_2$); 6.20 (s, 1H, $\underline{H}$-5); 7.20-7.52 (m, $8H_{arom}$); 7.88 (dd, $2H_{arom}$).[c]

Table 4 (Contd.)

41j	3410, 3318, 3290 (ν_{NH}; ν_{NH_2}); 1615, 1594 (δ_{NH_2})[b]	0.90 (br.t, 3H, $CH_2C\underline{H}_3$); 1.10–1.70 (m, 2H, $CH_2C\underline{H}_2CH_3$); 2.34 (s, 3H, $C\underline{H}_3Ar$); 2.56–3.35 (br.m, 2H, $NHC\underline{H}_2$); 5.59 (br.s, 2H, $N\underline{H}_2$); 6.00 (s, 1H, $\underline{H}$-5), 7.38 (A_2B_2.dd, $4H_{arom}$).[c]

---

[a] in KBr; [b] in nujol;

[c] in $CDCl_3$; [d] in TFA.

TABLE 5

Spectral data of products 48(a–f)

Product	IR (cm^{-1})	^1H–NMR (δ /ppm)
48a	3470, 3275, 3135 (ν_{NH_2}); 1620, 1575 ((δ_{NH_2})[a]	3.45–3.93 (m, 8H, morpholine $C\underline{H}_2$); 4.96 (br.s, 2H, $N\underline{H}_2$); 6.26 (s, 1H, $\underline{H}$–5); 7.28–7.53 (m, $3H_{arom}$); 7.76–7.96 (m, $2H_{arom}$).[c]
48b	3360, 3330, 3220 (ν_{NH_2}); 1638, 1598 (δ_{NH_2})[b]	1.60 (br.s, 6H, –$(C\underline{H}_2)_3$–); 3.55 (br s, 4H, –$C\underline{H}_2$–N–$C\underline{H}_2$–); 4.87 (br, 2H, $N\underline{H}_2$); 6.26 (s, 1H, $\underline{H}$–5); 7.00–7.60 (m, $3H_{arom}$); 7.80 (m, $2H_{arom}$).[c]

Table 5 (Contd.)

Product	IR(cm^{-1})	^{1}H-NMR(δ/ppm)
48c	3328, 3170 (ν_{NH_2}); 1630, 1580 (δ_{NH_2})^a	3.48-3.78 (m, 8H, morpholine $C\underline{H}_2$); 3.81 (s, 3H, $OC\underline{H}_3$); 4.96 (br s, 2H, $N\underline{H}_2$); 6.20 (s, 1H, $\underline{H}$-5); 6.90 (dd, $2H_{arom}$); 7.83 (dd, $2H_{arom}$).^{c}
48d	3405, 3270, 3135 (ν_{NH_2}); 1622, 1580 (δ_{NH_2})^a	3.63 (s, 8H, morpholino $C\underline{H}_2$); 6.11 (s, 1H, $\underline{H}$-5); 7.10 (br s, $4H_{arom}$).^{d}
48e	3385, 3265, 3125 (ν_{NH_2}); 1630, 1570 (δ_{NH_2})^a	3.65 (br s, 8H, morpholino $C\underline{H}_2$); 6.51 (br.s, 1H, $\underline{H}$-5); 7.85-8.20 (br m, 2H, $\underline{H}$-3', $\underline{H}$-5'); 9.23-9.53 (m, 2H, $\underline{H}$-2', H-6').^{d}

Table 5 (Contd.)

Product	IR(cm^{-1})	^{1}H-NMR(δ /ppm)
48f	3425, 3325, 3130 (ν_{NH_2}); 1640, 1600 (δ_{NH_2})^a	1.58 (br s, 6H, $-(C\underline{H}_2)_3-$); 2.28 (br.s, 6H, $-C\underline{H}_2-$ and $-C\underline{H}_2-N-C\underline{H}_2-$); 3.78 (s, 4H, $-C\underline{H}_2-O-C\underline{H}_2$); 7.18 (br, 2H, $N\underline{H}_2$).^{d}

^{a} in KBR; ^{b} in nujol; ^{c} in CDCl$_3$; ^{d} in TFA.

TABLE 6

Spectral data of products 52 (a-f)

Product	IR(cm^{-1})^{a}	^{1}H-NMR(δ /ppm)^{b}
52a	3330, 3260, 3130 (ν_{NH}, ν_{NH_2}); 1655, 1640, 1600 (δ_{NH_2})	1.15 (t, 6H, $OCH_2C\underline{H}_3$); 3.33-3.80 (m, 6H, $NC\underline{H}_2+OC\underline{H}_2CH_3$); 4.53 (t, 1H, $-C\underline{H}$); 5.34 (br, 2H, $N\underline{H}_2$); 5.60 (br.t, 1H, $N\underline{H}$); 6.03 (s, 1H, $\underline{H}$-5); 7.03-7.34 (m, 3H$_{arom}$); 7.60 (dd, 2H$_{arom}$).
52b	3490, 3388, 3290 (ν_{NH}, ν_{NH_2}); 1620, 1600, 1590 (δ_{NH_2})	1.16 (t, 6H, $OCH_2C\underline{H}_3$); 3.33-3.73 (m, 6H, $NC\underline{H}_2+OC\underline{H}_2CH_3$); 3.76 (s, 3H, $OC\underline{H}_3$); 4.60 (t, 1H, $-C\underline{H}$); 4.91 (br s, 2H, $N\underline{H}_2$); 5.13 (br, 1H, $N\underline{H}$); 6.05 (s, 1H, $\underline{H}$-5); 6.85 (dd, 2H$_{arom}$; 7.76 (dd, 2H$_{arom}$).

Table 6 (Contd.)

Product	IR(cm^{-1})[a]	^1H-NMR(δ/ppm)[b]
52c	3358, 3200 (ν_{NH}, ν_{NH_2}); 1650, 1590 (δ_{NH_2})	1.16 (t, 6H, $OCH_2C\underline{H}_3$); 2.31 (s, 3H, $C\underline{H}_3Ar$); 3.33–3.83 (m, 6H, $NC\underline{H}_2+OC\underline{H}_2CH_3$); 4.53 (t, 1H, $-C\underline{H}$); 5.00 (br s, 2H, $N\underline{H}_2$); 5.25 (br, 1H, $N\underline{H}$); 6.05 (s, 1H, $\underline{H}$-5); 7.10 (dd, $2H_{arom}$); 7.70 (dd, $2H_{arom}$).
52d	3300, 3140 (ν_{NH}, ν_{NH_2}); 1640, 1610, 1592 (δ_{NH_2})	1.18 (t, 6H, $OCH_2C\underline{H}_3$); 3.36–3.93 (m, 6H, $NC\underline{H}_2+OC\underline{H}_2CH_3$); 4.63 (t, 1H, $-C\underline{H}-$); 5.01 (br, 2H, $N\underline{H}_2$); 5.21 (br t, 1H, $N\underline{H}$); 6.11 (s, 1H, $\underline{H}$-5); 7.36 (dd, $2H_{arom}$); 7.83 (dd, $2H_{arom}$).

Table 6 (Contd.)

Product	IR(cm^{-1})[a]	^{1}H-NMR(δ /ppm)[b]
52e	3375, 3250, 3150 (ν_{NH}, ν_{NH_2}); 1630, 1605, 1585 (δ_{NH_2})	1.16 (t, 6H, $OCH_2C\underline{H}_3$); 3.25–3.72 (m, 6H, $NC\underline{H}_2$+$OC\underline{H}_2CH_3$); 4.45 (t, 1H, –C$\underline{H}$·); 5.13 (s, 2H, $N\underline{H}_2$); 5.40 (br t, 1H, N$\underline{H}$); 7.33 (dd, 2H$_{arom}$); 7.63 (dd, 2H$_{arom}$).
52f	3420, 3318, 3245, 3150 (ν_{NH} ν_{NH_2}); 1645, 1600, 1585 (δ_{NH_2})	1.16 (t, 6H, $OCH_2C\underline{H}_3$); 2.13 (s, 3H, $C\underline{H}_3CO$); 3.23–3.73 (m, 6H, $NC\underline{H}_2$+$OC\underline{H}_2CH_3$); 4.53 (t, 1H, –C$\underline{H}$·); 4.83 (br s, 2H, $N\underline{H}_2$); 5.10 (br s, 1H, N$\underline{H}$); 5.58 (s, 1H, $\underline{H}$-5).

[a] IR medium = KBr. [b] NMR solvent = $CDCl_3$.

EXPERIMENTAL

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

The starting materials

The commercial samples of aniline, p-chloroaniline, p-fluoroaniline, p-toluidine, p-anisidine, morpholine and piperidine were purified before use.

The keten-S,S-acetals 38 and 42a-f were prepared by reported methods.[11-14]

The unreported keten-S,N-acetals 35a-f, 40a-j and 46a-b were prepared as described in chapter 2.

The keten-S,N-acetals: 3-(2-diethoxyethylamino)-3-methylthio-1-phenyl-2-propen-1-one (51a),[15] viscous semisolid; 3-(2-diethoxyethylamino)-3-methylthio-1-(p-methoxyphenyl)-2-propen-1-one (51b),[15] viscous oil; 3-(2-diethoxyethylamino)-3-methylthio-1-(p-methylphenyl)-2-propen-1-one (51c), mp 62-3°;[15] 3-(2-diethoxyethylamino)-3-methylthio-1-(p-chlorophenyl)-2-propen-1-one

(51d),[15] viscous oil; 3-(2-diethoxyethylamino)-3-methylthio-1-(p-bromophenyl)-2-propen-1-one (51e),[15] dark yellow oil; 3-(2-diethoxyethylamino)-3-methylthio-1-methyl-2-propen-1-one (51f),[15] viscous oil were prepared according to the reported procedure.

General method for the preparation of 2-amino-4-arylamino-(or-morpholino)-5-cyano-6-oxo-1,6-dihydropyrimidines (37a-f):

A solution of keten-S,S-acetal 38 (0.01 mol) and amine 39a-f (0.01 mol) in absolute ethanol (35 ml) was refluxed for 4 hr. When the reaction was complete (TLC), the reaction mixture was added to a suspension of guanidine nitrate (1.22 g, 0.01 mol) and sodium ethoxide prepared by dissolving sodium (0.46 g, 0.02 mol) in refluxing ethanol (35 ml) in absolute ethanol. The combined reaction mixture was refluxed for 12 hr and concentrated under reduced pressure to give a viscous residue, which was diluted with ice cooled water and acidified with 4N-HCl (15 ml). The crude oxopyrimidines were filtered and purified by crystallization from acetic acid (Table 7).

Alternatively, a solution of pure keten-S,N-acetal 35a-f (0.01 mol), guanidine nitrate (1.22 g, 0.01 mol) and sodium ethoxide (0.02 mol) in 70 ml of absolute ethanol was refluxed for 8-14 hr (Table 7). The reaction was worked up as described above to yield crude oxopyrimidines 37a-f.

Preparation of 2-amino-4-N-aryl/alkylamino-6-arylpyrimidines (41a-i) and 2-amino-4-(2-diethoxyethylamino)-6-aryl/methylpyrimidines (52a-f):

(a) General procedure:

A solution of keten-S,N-acetal 40a-i (0.01 mol) in absolute ethanol was added to a suspension of guanidine nitrate (1.22 g, 0.01 mol) and sodium ethoxide (from 0.01 mol of sodium) in absolute ethanol (50 ml). The reaction mixture was then heated under reflux for 18-30 hr (appropriate time given in table 8) and after removal of solvent under reduced pressure, the residue was diluted with ice-cold water and extracted with chloroform (2 x 100 ml). The chloroform layer was dried (Na_2SO_4) and evaporated to give crude pyrimidines 41a-i which were purified by crystallization from dichloromethane and hexane mixture (Table 8).

The pyrimidines 52a-f were similarly obtained by column chromatography (silica gel) of the residue obtained after work-up of the reaction mixture, using benzene/ethyl acetate (7:3) as eluent. Further crystallization from dichloromethane/hexane mixture yielded pure 52a-f (Table 10).

(b) By *in situ* generation of S,N-acetals (40a-c):

A mixture of keten-S,S-acetal 42a-c (0.01 mol) and aniline (0.011 mol) was heated at 160°C for 15 hr (monitored by TLC). The reaction mixture was dissolved in absolute ethanol (15 ml) and added to a suspension of guanidine nitrate (1.22 g, 0.01 mol) and sodium ethoxide (obtained from 0.01 mol of sodium) in absolute ethanol (25 ml) and the combined reaction mixture was refluxed for 21-25 hr. The reaction was worked-up as described above and the crude residue was column chromatographed over silica gel. Elution with 5% ethyl acetate in benzene gave the unreacted N,N-acetals 43a-c, while further elution with 15% ethyl acetate in benzene gave the pyrimidines 41a-c (Table 8).

Preparation of 2-amino-4-N-propylamino-6-(p-methylphenyl)-pyrimidine (41j)

(a) In sodium ethoxide and ethanol :

A solution of S,N-propylacetal 40j (2.49 g, 0.01 mol) in absolute ethanol (10 ml) was added to a suspension of guanidine nitrate (1.22 g, 0.01 mol) and sodium ethoxide (from 0.01 mol of sodium) in absolute ethanol (50 ml) and the reaction mixture was refluxed for 26 hr (TLC). Work-up of the reaction as described above, yielded a viscous residue (two spots on TLC), which was column chromatographed on silica gel. Elution with 10% ethyl acetate in benzene gave 4-ethoxypyrimidine 45 (0.69 g, 30% yield), mp 160-61°C (reported mp 163-64°,[6] superimposable IR and NMR spectra). Further elution with 15% ethyl acetate in benzene gave the pyrimidine 41j (0.36 g, 15% yield) (Table 8).

(b) In sodium t-butoxide and t-butanol :

A solution of S,N-propylacetal 40j (2.49 g, 0.01 mol) in dry t-butanol (10 ml) was added to a suspension of guanidine nitrate (1.22 g, 0.01 mol) and sodium t-butoxide (from 0.01 mol of sodium) in 50 ml of t-butanol and the reaction mixture was refluxed for 28 hr. The pyrimidine 41j obtained after usual work-up was purified by passing through silica gel column and using benzene/hexane (3:1) as eluent (Table 8).

Preparation of 2-amino-4-morpholino/piperidino-5,6-substituted-pyrimidines (48a-f)

(a) In refluxing sodium ethoxide and ethanol:

A solution of S,N-acetal 46a (2.6 g, 0.01 mol) in absolute ethanol (10 ml) was added to a suspension of guanidine nitrate (1,22 g, 0.01 mol) and sodium ethoxide (from 0.01 mol of sodium) in absolute ethanol (50 ml) and the reaction mixture refluxed for 20 hr. After usual work-up of the reaction, the residue obtained (two spots on TLC) was column chromatographed over silica gel. Elution with 10% ethyl acetate in benzene gave 4-ethoxypyrimidine 49a (0.4 g, 20% yield), mp 151°C (reported mp 152°,[6] superimposable IR and NMR spectra). Further elution with ethyl acetate/benzene (1.5:10) yielded the morpholinopyrimidine 48a (0.66 g, 26% yield). The reaction of S,N-acetal 46b with guanidine nitrate yielded ethoxypyrimidine 49a and 4-piperidinopyrimidine 48b in 22% and 25% yields respectively.

(b) In sodium isopropoxide and isopropanol

Reaction of **46a** (2.6 g, 0.01 mol), guanidine nitrate and sodium isopropoxide in isopropanol under similar conditions as described in sodium ethoxide and ethanol, yielded 0.25 g (11%) of 4-isopropoxypyrimidine **49b**, m.p. 137° (reported mp 139°, superimposable IR and NMR spectra) and 0.84 g (33%) of 4-morpholinopyrimidine **48a**.

(c) In sodium *t*-butoxide and *t*-butanol:

A solution of S,N-acetals **46a** and **46b** (0.01 mol) in dry *t*-butanol (10 ml) was added to a suspension of guanidine nitrate (1.22 g, 0.01 mol) and sodium *t*-butoxide (from 0.01 mol of sodium) in *t*-butanol (50 ml) and refluxed for 16 and 10 hr respectively. The crude pyrimidines **48a** and **48b** obtained after usual work-up as described above, were purified by crystallization from ethanol (Table 9).

(d) By *in situ* generation of N,N-acetals:

Keten-N,N-morpholinoacetals **50a** and **50c**-*f* were generated *in situ*, by refluxing a solution of the corresponding keten-S,S-acetals **42a** and **42c**-*f* (0.01 mol) and morpholine (0.022 mol) in absolute ethanol (20 ml) for 4 hr. The reaction mixture was then added to a suspension of guanidine nitrate (1.22 g, 0.01 mol) and sodium ethoxide (from 0.01 mol of sodium) in absolute ethanol (20 ml). After further refluxing for 18–21 hr, the reaction mixture was worked-up as usual when crude pyrimidines 48a and 48c–f were obtained, which were crystallized from ethanol (Table 9).

TABLE 7

2-Amino-4-(N-arylamino)/morpholino-5-cyano-6-oxo-1,6-dihydropyrimidines (37a-f)

Product[a]	Reflux[b] time(hr)	Yield[c] (°C)	m.p.	Molecular formula	Analysis (%) Calc. Found	C	H	N
37a	12	57	340	$C_{11}H_9N_5O$		53.14	3.96	30.83
				(227.2)		58.38	4.12	30.65
37b	8	51	360[d]	$C_{12}H_{11}N_5O$		59.75	4.56	29.04
				(241.3)		59.52	4.65	29.38
37c	14	54	326-	$C_{12}H_{11}N_5O_2$		56.03	4.28	27.23
				(257.3)		56.41	4.58	27.57
37d	6	57	364-	$C_{11}H_8ClN_5O$		50.47	3.05	26.76
			366	(261.7)		50.39	3.37	26.25

Table 7 (Contd.)

37e	9	53	368-	$C_{11}H_8FN_5O$	53.87	3.26	28.57
			370	(245.2)	54.07	3.49	28.87
37f	8	47	327[d]	$C_9H_{11}N_5O_2$	48.64	5.40	31.53
				(221.2)	48.81	5.70	31.82

---

[a] Crystallization solvent = AcOH.

[b] Corresponds to the reaction starting from S,N-acetals 35a-f.

[c] The yields are those from S,N-acetals 35a-f.

[d] Decomposed.

TABLE 8

2-Amino-4-N-aryl/alkylamino-6-arylpyrimidines (41a-j)

Product[a]	Reflux[b] time(hr)	Yield[c] (%)	m.p. (°C)	Molecular formula	Analysis (%) Calc. Found	C	H	N
41a	21	35(18)[d]	159[e]	$C_{16}H_{14}N_4$		73.28	5.34	21.37
				(262.3)		73.57	5.75	21.67
41b	25	45(19)[d]	147-	$C_{16}H_{13}BrN_4$		56.30	3.81	16.42
			148	(341.2)		55.95	3.62	16.09
41c	24	34(21)[d]	167	$C_{17}H_{16}N_4O$		69.86	5.47	19.17
				(292.3)		69.61	5.04	19.42
41d	28	47	141-	$C_{16}H_{13}ClN_4$		64.75	4.38	18.88
			142	(296.7)		64.31	4.71	18.62

Table 8 (Contd.)

41e	25	50	138^{f}	$C_{16}H_{13}ClN_4$	64.75	4.38	18.80
				(296.8)	64.92	4.61	18.57
41f	18	40	148-	$C_{12}H_{14}N_4$	67.29	6.54	26.16
			149	(214.3)	67.59	6.81	26.47
41g	26	44	153	$C_{13}H_{16}N_4O$	80.32	6.55	22.95
				(244.3)	80.67	6.85	22.75
41h	25	46	146-	$C_{12}H_{13}ClN_4$	57.94	5.23	22.53
			147	(248.7)	57.75	5.54	22.85

Table 8 (Contd.)

41i	30	43	128	$C_{17}H_{16}N_4$	73.91	5.79	20.28
				(276.3)	73.67	5.55	20.47
41j	28[g]	47[g]	Viscous	$C_{14}H_{18}N_4$	69.39	7.48	23.12
			liquid	(242.3)	68.04	7.15	22.85

[a] Crystallization solvent = CH_2Cl_2:hexane.

[b] Reaction time for method a, general procedure.

[c] The yields described are those from method a, general procedure.

[d] The yields in parentheses correspond to those obtained by *in situ* generation of S,N-acetals 40a-c.

[e] M.S.:m/e = 262 (M^+); Lit.[16] m.p. 305°C.

[f] M.S.:m/e = 296 (M^+, ^{35}Cl); Lit.[16] m.p. 304°C.

[g] Reaction time and yield correspond to method b, using Bu^tONa and Bu^tOH.

TABLE 9

2-Amino-4-morpholino/piperidino-6-aryl/(4-pyridyl)-pyrimidines (48a-e) and 2-amino-4-morpholino-5,6-tetramethylenepyrimidine (48f)

Product[a]	Reflux[b] time (hr)	Yield[c] (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis (%) C	H	N
48a	19(16)[d]	28(46)[e]	170	$C_{14}H_{16}N_4O$		65.62	6.25	21.87
				(256.3)		65.47	6.48	21.55
48b	-(10)[d]	-(44)[e]	138-	$C_{15}H_{18}N_4$		70.86	7.08	22.04
			139	(254.3)		70.65	7.37	22.50
48c	20	31	214-	$C_{15}H_{18}N_4O_2$		62.93	6.29	19.58
			215	(286.3)		62.71	6.47	19.37

Table 9 (Contd.)

48d	21	30	184-185	$C_{14}H_{15}ClN_4O$ (286.8)	57.87 57.56	5.16 5.41	19.27 19.42
48e	20	20	199	$C_{13}H_{15}N_5O$ (257.3)	60.70 60.57	5.83 5.45	27.23 27.51
48f	18	20	326-328	$C_{12}H_{18}N_4O$ (234.3)	61.53 61.81	7.69 7.92	23.93 23.51

[a] Crystallization solvent = EtOH. [b] Corresponds to method d.

[c] The yields are those from method d, by *in situ* generation of N,N-morpholinoacetals 50.

[d] Reflux time in parentheses corresponds to method c using Bu^tONa in Bu^tOH.

[e] The yields in parentheses correspond to those obtained by method c from from S,N-acetals 46a and 46b.

TABLE 10

2-Amino-4-(2-diethoxyethylamino)-6-aryl/methylpyrimidines 52(a-f)

Product[a]	Reflux[b] time(hr)	Yield (%)	m.p. (°C)	Molecular formula	Analysis (%) Calc. Found C	H	N
52a	12	27	125-	$C_{16}H_{22}N_4O_2$	63.57	7.28	18.54
			126	(302)	63.41	6.84	18.24
52b	12	30	82-	$C_{17}H_{24}N_4O_3$	61.44	7.22	16.86
			83	(332)	61.07	7.43	16.52
52c	13	25	112	$C_{17}H_{24}N_4O_2$	64.55	7.59	17.72
				(316)	64.11	7.28	17.55
52d	12.5	30	118-	$C_{16}H_{21}ClN_4O_2$	57.05	6.24	16.64
			119	(336.5)	56.81	5.96	16.41

Table 10 (Contd.)

52e	14	30	115	$C_{16}H_{21}BrN_4O_2$	50.39	5.51	14.69
				(381)	50.07	5.32	14.38
52f	11	26	139-	$C_{11}H_{20}N_4O_2$	55.00	8.33	23.33
			140	(240)	55.35	8.58	23.49

---

[a] Crystallization solvent = CH_2Cl_2:hexane

[b] Reaction solvent = EtOH.

REFERENCES

1. P.B. Russel and G.H. Hitchings, J. Amer. Chem. Soc. 73, 3763 (1951).
2. L.N. Ferguson, Chem. Soc. Reviews, 4, 289 (1975).
3. (a) D.J. Brown, 'The Pyrimidines' (edited by A. Weissberger), Chapter IX, pp. 306, Interscience, New York (1962) and references therein.
   (b) D.J. Brown, 'The Pyrimidines' (edited by A. Weissberger), Supplement I, Chapter IX, pp. 230, Interscience, New York (1970) and references therein.
4. E.A. Arutyunyan, V.I. Gunar, E.P. Gracheva, S.I. Zav'talov, 'Izv. Akad. Nauk SSSR Ser. Khim.' 1969, 655; Chem. Abstr. 71, 30453 (1969).
5. E.B. Pederson, D. Carlsen, Synthesis, 844 (1978).
6. S.M.S. Chauhan and H. Junjappa, Synthesis, 880 (1974).
7. S.M.S. Chauhan and H. Junjappa, Tetrahedron, 32, 1779, 1811 (1976).
8. S.M.S. Chauhan and H. Junjappa, Synthesis, 798 (1975).
9. A. Kumar, H. Ila and H. Junjappa, J. Chem. Soc. Chem. Comm. 593 (1976).
10. V. Amarnath, R. Madhav, Synthesis, 837 (1974).

11. J. Sandström and I. Wennerbeck, Acta Chem. Scand. 24, 1191 (1970).

12. A. Thuillier and J. Vialle, Bull. Soc. Chim. France, 1398 (1959).

13. R.R. Rastogi, A. Kumar, H. Ila and H. Junjappa, J. Chem. Soc. Perkin Trans. I, 549 (1978).

14. A. Thuillier and J. Vialle, Bull. Soc. Chim. France, 2194 (1962).

15. A. Kumar, Ph.D. Thesis, CDRI, Lucknow, 1977 (Submitted to Agra Univ., Agra), Chapter IIIb.

16. G.H. Hitchings, P.B. Russel, U.S. Patent 2691655 (1954); Chem. Abstr. 49, 11726 (1955).

CHAPTER 4

REACTION OF α-KETOKETEN-S,N-ACETALS WITH CYANOACETAMIDE : A NEW GENERAL METHOD FOR SUBSTITUTED AND FUSED 4-(N-ALKYLAMINO-, N-ARYLAMINO-, OR N-MORPHOLINO)-3-CYANO-2(1H)-PYRIDONES*

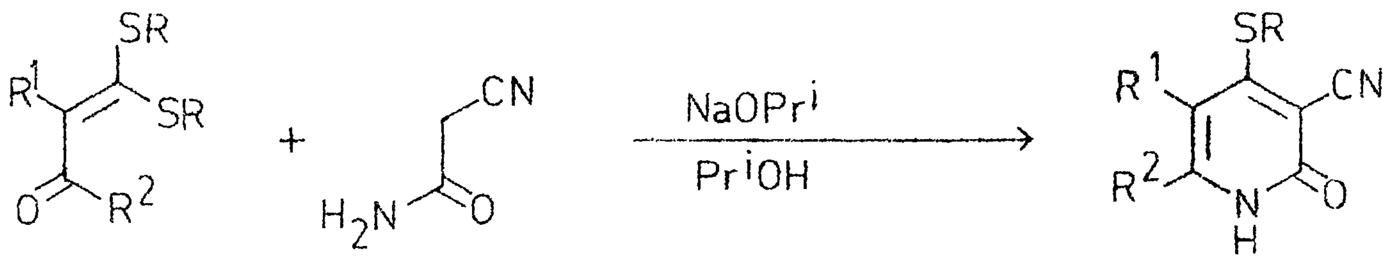
4.1 Introduction

In the preceding chapter, the synthetic utility of polarized keten-S,N- and N,N-acetals for the synthesis of 2,4-diaminopyrimidines was described. In our earlier work[1,2] it was shown that the keten-S,S-acetals 1 (Scheme 1) undergo facile condensation with cyanoacetamide (2a) in the presence of sodium isopropoxide to give 3-cyano-4-alkylthio-5,6-substituted-2(1H)-pyridones (3) in excellent yields. It was further shown that the ketoketen-S,S-acetals reacted with N-methylcyanoacetamide (2b) (Scheme 2) to give the corresponding 2,7-naphthyridin-1,6(2H,7H)-diones 5 instead of the expected pyridones 4. The yield of 5 was quantitative when two equivalents of N-methylcyanoacetamide was used. The

---

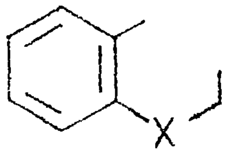
* V. Aggarwal, G. Singh, H. Ila and H. Junjappa, Synthesis, 214 (1982).

Scheme 1

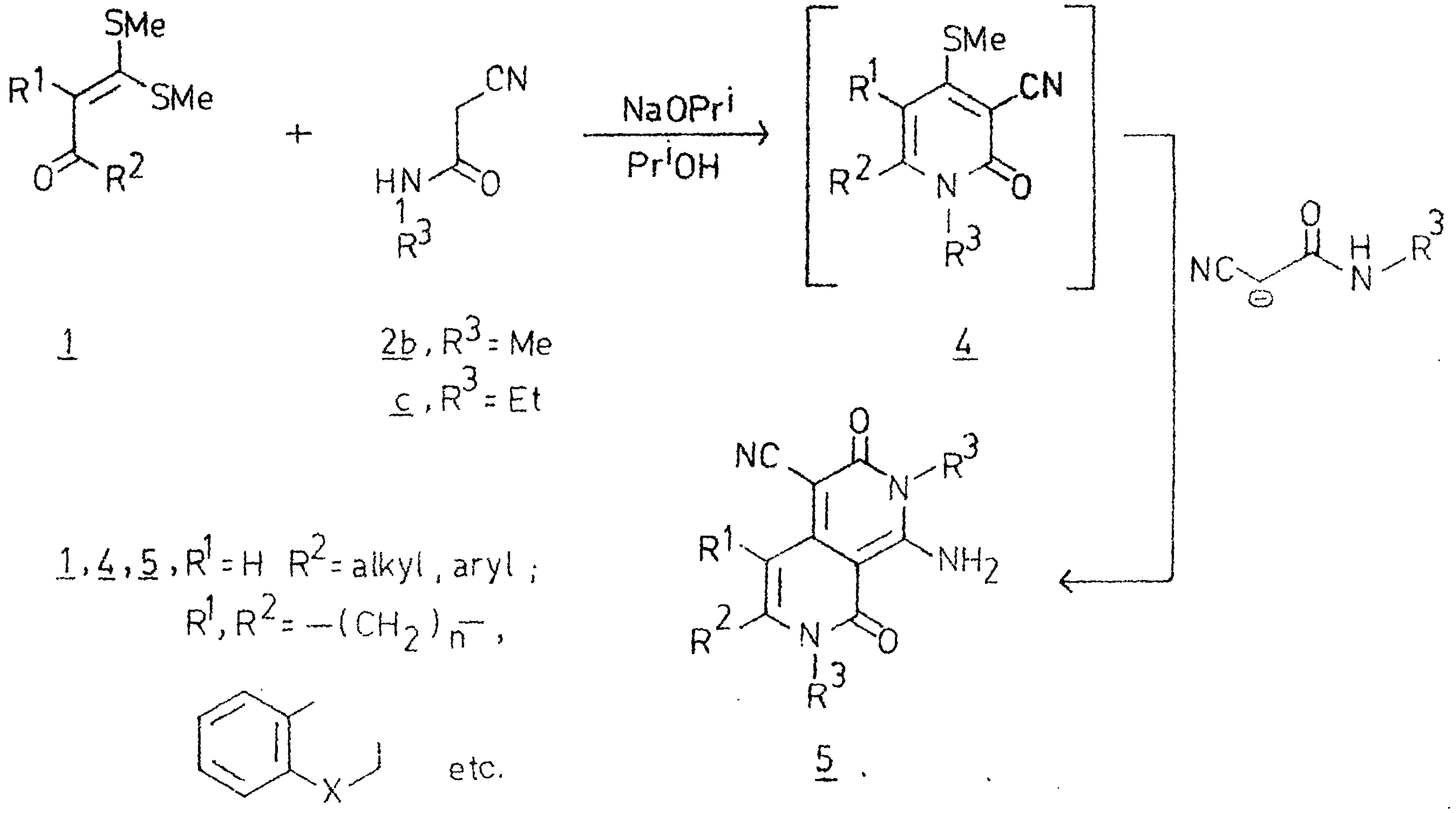


1 2a 3

R = alkyl ; R^1 = H ; R^2 = aryl , alkyl ;

$R^1, R^2 = -(CH_2)_n-$, 

Scheme 2

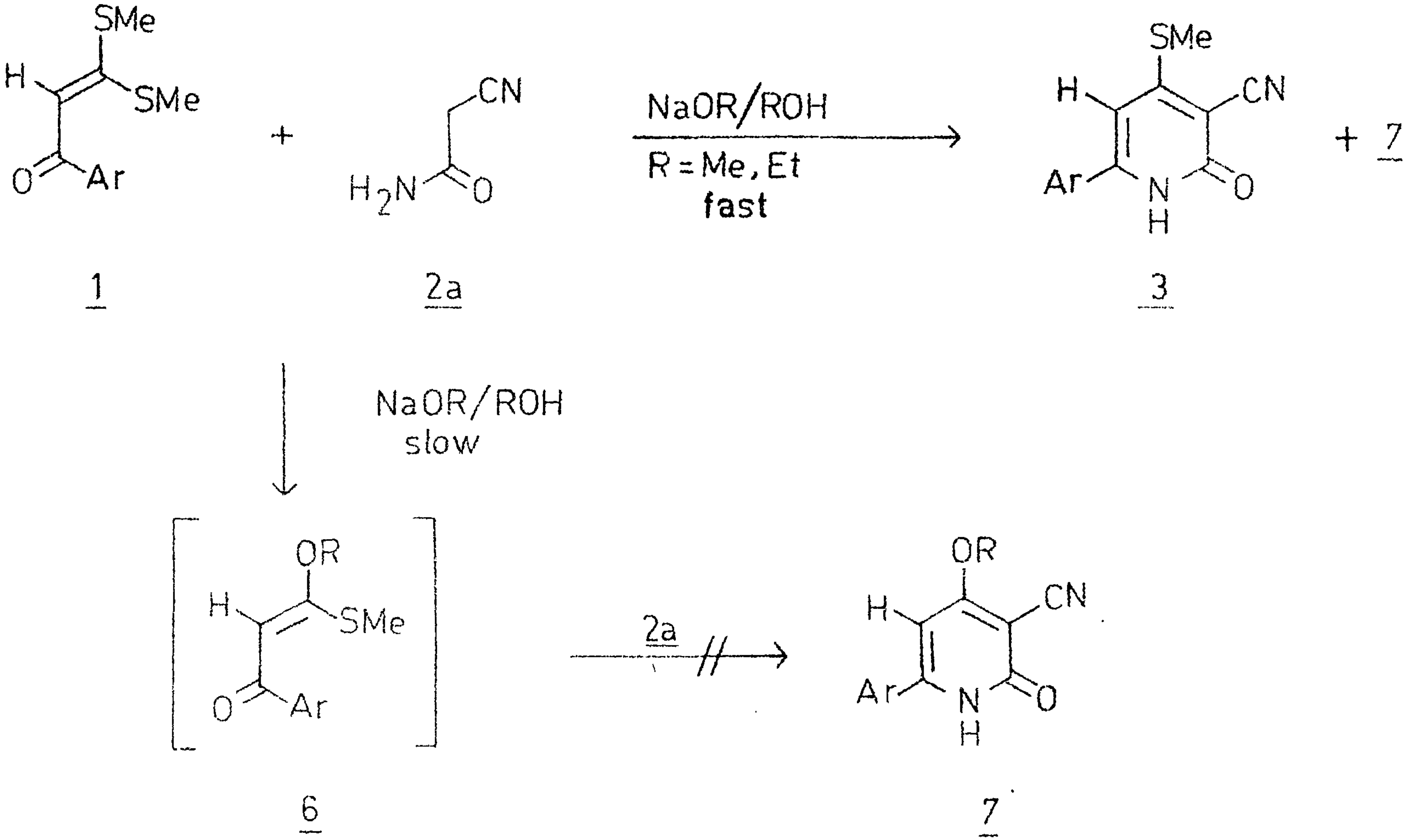

SMe
R^1
SMe
O
R^2
+
CN
HN
O
R^3
$NaOPr^i$
Pr^iOH
SMe
R^1
CN
R^2
N
O
R^3
NC
O
H
N
R^3
$\ominus$
NC
O
N
R^3
R^1
NH_2
R^2
N
O
R^3
X
1
2b, R^3 = Me
c, R^3 = Et
4
5
1, 4, 5, R^1 = H R^2 = alkyl, aryl;
R^1, R^2 = $-(CH_2)_n-$,
etc.

method was found to be general as exemplified by several structural variants.[3] When the reaction of keten-S,S-acetal 1 with cyanoacetamide was carried out in the presence of sodium ethoxide (Scheme 3),[2] a small amount of 4-ethoxy-2(1H)-pyridone 7 along with 3 was formed. Efforts to further improve the yield of 7 were not successful, probably due to competition of carbanion derived from cyanoacetamide with alkoxide ions.

In view of the facile methods available for the synthesis of keten-S,N-acetals as described in chapter 2, it was intended to investigate the reaction of S,N-acetals with cyanoacetamide and its derivatives, with a view to developing a new general method for the synthesis of hitherto inaccessible 4-aminopyridones. Our literature survey of 4-aminopyridones revealed that there is no satisfactory general method available for their synthesis. The methods suffer from multiplicity of steps resulting in overall poor yields, coupled with lack of generality in their structural variations. They can be grouped into four categories which are described as follows:

Thus, when cyanoacetamide was treated with phosphorous oxychloride, it underwent self-condensation to

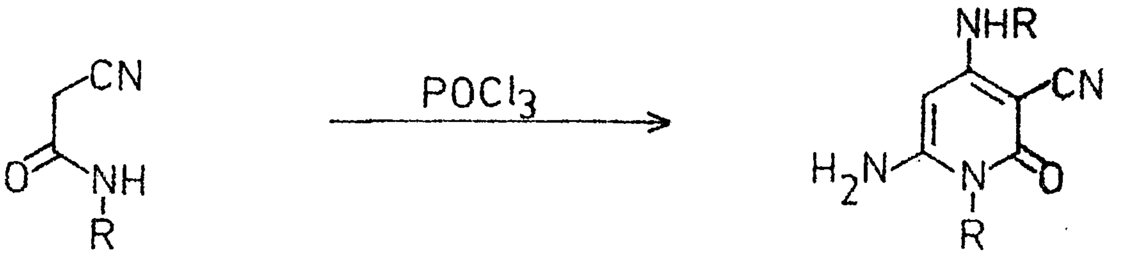
Scheme 3



SMe
H
SMe
O
Ar
1
+
CN
H$_2$N
O
2a
NaOR/ROH
R = Me, Et
fast
SMe
H
CN
Ar
N
H
O
3
+ 7
NaOR/ROH
slow
OR
H
SMe
O
Ar
6
2a
OR
H
CN
Ar
N
H
O
7

give 3-cyano-4,6-diamino-2(1H)-pyridone (8)[4] (Scheme 4) in 80% yield. However, the method is limited to variations only in cyanoacetamide. The second method (Scheme 5)[5] involves ring transformation of 1,3-dialkyl/aryl-5-substituted-6-(2-dimethylaminovinyl)uracils (9) in the presence of sodium hydroxide to yield pyridones 10. The intermediate 9 requires several steps for its preparation, resulting in overall poor yields. In the third method, the synthesis of 3-cyano-4-N,N-dimethylamino-2(1H)-pyridone (14) was achieved in a sequence of reactions as shown (Scheme 6).[6] Thus, when diethylacetal of N,N-dimethylacetamide (11) and cyanoacetamide were condensed, the corresponding enaminoamide 12 was formed. Subsequent treatment of 12 with diethylacetal of N,N-dimethylformamide, gave the corresponding condensation product 13, which on heating gave 14. In the fourth method, the key intermediate for the synthesis of aminopyridones 17 is reported[7] to be 4-chloropyridone 16 (Scheme 7), which was in turn obtained from the reaction of the corresponding 4-hydroxypyridone 15 and phosphorous oxychloride. Although, the method can be used to prepare a variety of 4-amino-and 4-substituted-aminopyridones, it requires a method for the synthesis of 4-hydroxypyridones with good yields.

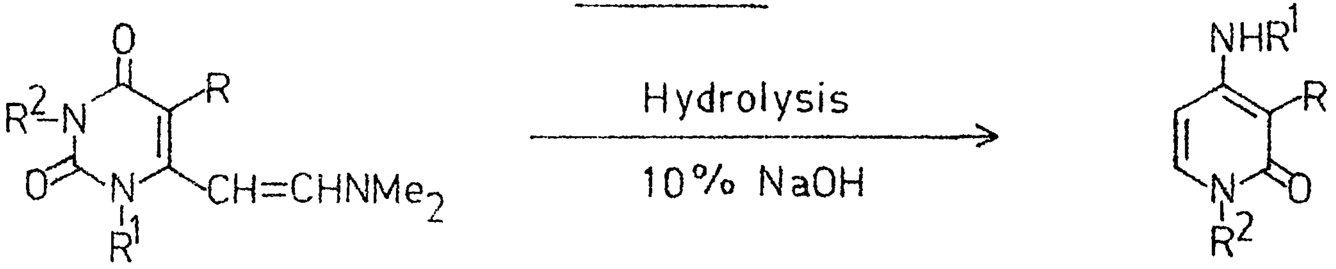
Scheme 4



2

8, R = H, alkyl

Scheme 5

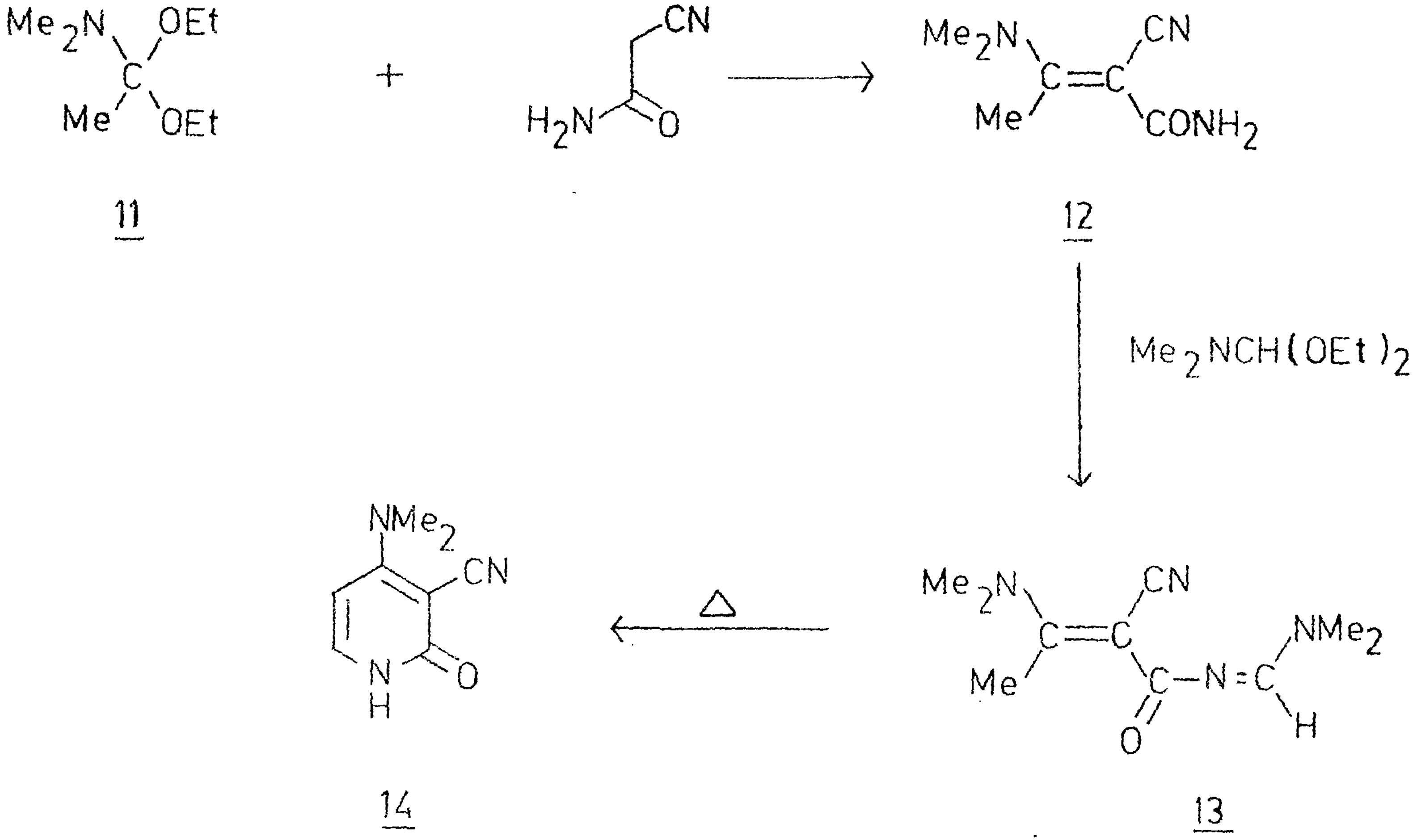


9

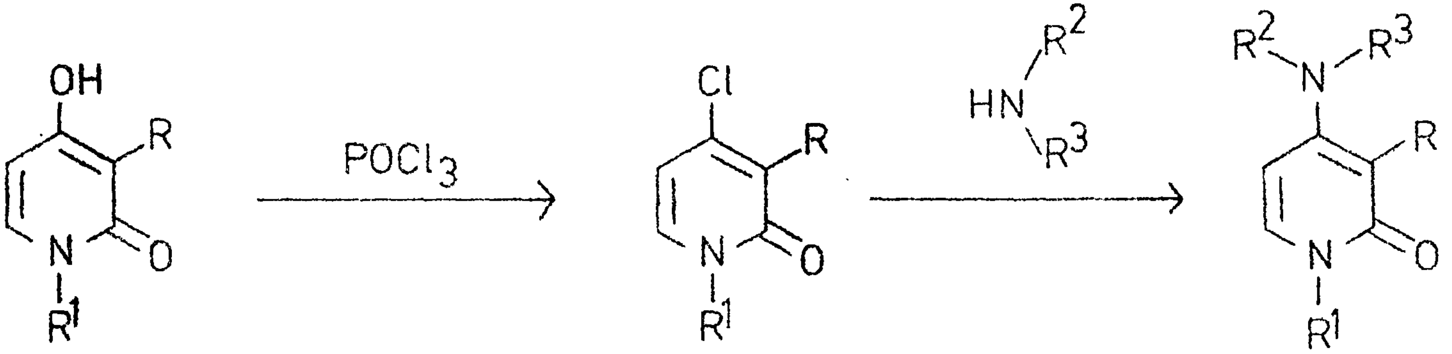
10

9, 10, R = H, CN, NO$_2$;
R^1 = Me, Ph, Bz;
R^2 = Me, Ph

Scheme 6

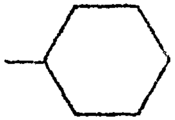

Me2N
OEt
C
Me
OEt
11
+
CN
H2N
O
Me2N
CN
C=C
Me
CONH2
12
Me2NCH(OEt)2
NMe2
CN
N
H
O
14
△
Me2N
CN
C=C
NMe2
Me
C—N=C
O
H
13

Scheme 7

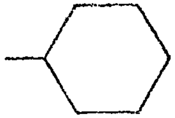


15 16 17

15 – 17, R = H, CN, NO_2 ;

R^1 = Me, Et, Ph, 

R^2 = H, Me,

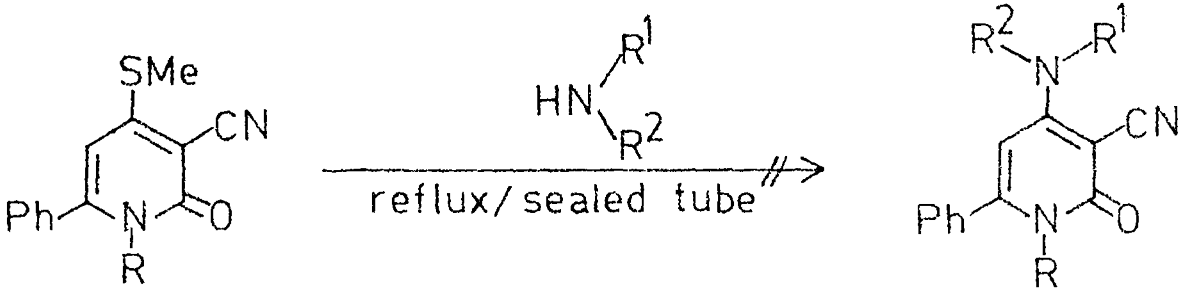
R^3 = Me, iso – Bu, allyl, ph, .

Evidently, the scope with which structural variations can be introduced in the synthesis of keten-S,N-acetals from a wide variety of open-chain as well as cyclic ketones, makes these class of compounds excellent starting materials as three carbon fragments for the synthesis of 4-aminopyridones. A systematic study of the reaction of cyanoacetamide and its derivatives with a few selected keten-S,N-acetals is therefore, undertaken in the present investigation with a view to developing a new general one step synthesis of 4-aminopyridones.

4.2 Results and discussion

Attempts were made to react 3-cyano-4-methylthio-6-phenyl-2(1H)-pyridone (3) with primary and secondary amines under various condtions to prepare the corresponding 4-aminopyridones 18 (Scheme 8), however, the pyridone 3 was recovered unreacted. In our earlier work we had shown[8] that 3 undergoes facile condensation with hydrazine to give the corresponding pyrazolo-[4,3-c]-pyridone, probably due to the driving force involving the ring closure. It became necessary therefore, that the construction of aminopyridones has to be through the reaction of keten-S,N-acetals and cyanoacetamide or its N-alkyl derivatives.

Scheme 8



3

18

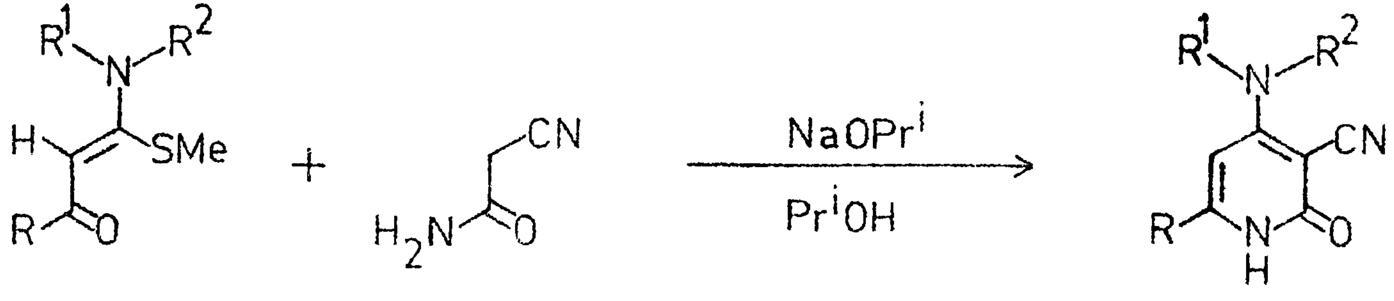
3, 18, R = H, Me;

18, R^1 = n-Pr, Ph, R^2 = H;

$R^1, R^2 = -(CH_2)_2-O-(CH_2)_2-$

Thus, S,N-acetal 19a (Scheme 9) (Table 1) when reacted with cyanoacetamide (2a) (equimolar quantities) in the presence of sodium isopropoxide in refluxing isopropanol, yielded the corresponding 3-cyano-4-anilino-6-phenyl-2(1H)-pyridone (18a) in 64% yield. The structure of 18a was established by its analytical (Table 3) and spectral data (Table 2). Thus, its mass spectrum displayed a molecular ion peak at M^+ 287 ($C_{18}H_{13}N_3O$), while its IR spectrum showed an absorption band at 3230 cm^{-1} (ν_{NH}) and a sharp absorption band at 2220 cm^{-1} (ν_{CN}). The strong bands at 1640, 1620 cm^{-1} (ν_{CO}) are characteristic of 2(1H)-pyridones. Further confirmation of the structure was derived from its NMR spectrum. A singlet at δ 6.60 was assigned to H-5 proton and a broad multiplet around δ 7.20-7.66 was assigned to ten aromatic protons of the two phenyl groups. Similarly, 19b-k reacted with 2a under identical conditions to give the corresponding 18b-k in 55 to 77% overall yields. The analytical (Table 3) and spectral data (Table 2) of 18b-k are described which, are in conformity with the structures assigned. The reaction of 2a was then extended to cyclic S,N-acetal 20a (Scheme 10), derived from tetralone, when the corresponding fused pyridone 21a

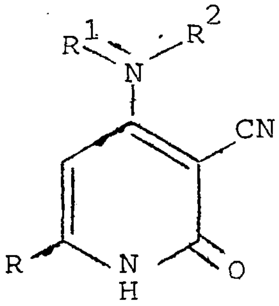
Scheme 9



19a-k   2a   18a-k

(Table 1)

TABLE 1



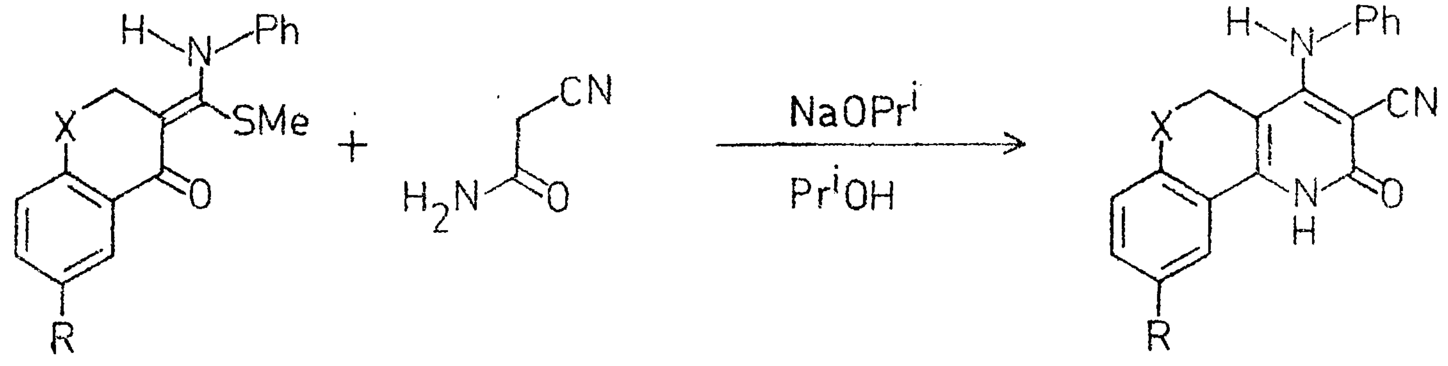
18

Product	R	R^1	R^2
18a	C_6H_5	C_6H_5	H
18b	p-ClC_6H_4	C_6H_5	H
18c	p-$CH_3OC_6H_4$	C_6H_5	H
18d	C_6H_5	C_2H_5	H
18e	p-ClC_6H_4	C_2H_5	H
18f	p-$CH_3OC_6H_4$	C_2H_5	H
18g	C_6H_5	n-C_3H_7	H
18h	C_6H_5	$CH_2C_6H_5$	H
18i	C_6H_5	$CH_2CH(OC_2H_5)_2$	H
18j	CH_3	C_2H_5	H
18k	p-$CH_3C_6H_4$	$-(CH_2)_2-O-(CH_2)_2-$	

was formed in 60% yield. Similarly, 20b and 2a gave 21b in 53% yield. The analytical (Table 3) and spectral data (Table 2) of 21a and 21b were found to be in accordance with the structures assigned.

It was earlier observed in this laboratory,[3] that the keten-S,S-acetals 1 (Scheme 2) when reacted with 2b in the presence of sodium isopropoxide in refluxing isoporpanol, 2,7-naphthyridin-1,6(2H,7H)-diones 5 were formed instead of the corresponding pyridones. However, the reaction of 2b with 19a (Scheme 11) under identical conditions, yielded only 3-cyano-4-anilino-6-phenyl-N-methyl-2(1H)-pyridone (22a) in 58% yield and no trace of the corresponding naphthyridindione was observed. Similarly, 19b and 19c gave the corresponding aminopyridones 22b and 22c in 66 and 50% yields respectively, instead of the naphthyridines. The analytical and spectral data of these pyrimidines are described in table 3 and table 2 respectively. However, when the keten-S,N-ethylacetal 19d (Scheme 12) was reacted with 2b under identical conditions, only the corresponding naphthyridindione 23a was isolated. 23a thus obtained, was identical (mp, mmp, superimposable IR) with that

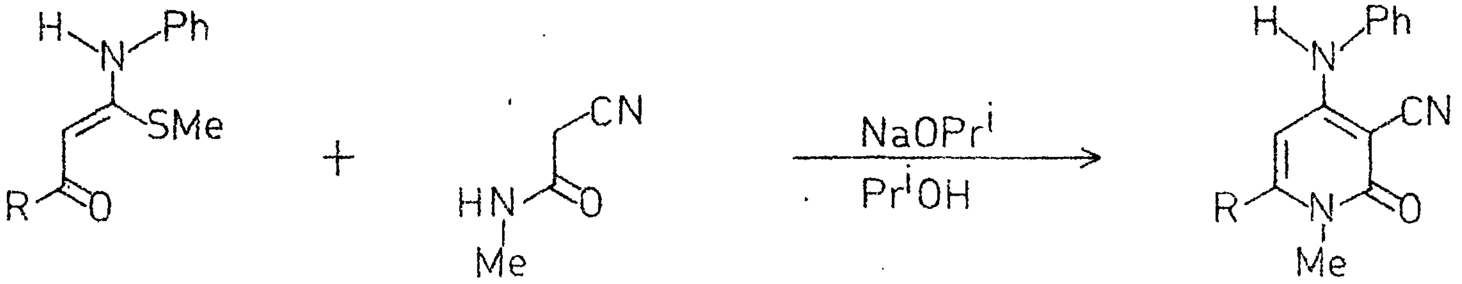
Scheme 10



20 2a 21

20, 21a, R = H , X = –CH$_2$– ;
b, R = Me , X = –S–

Scheme 11

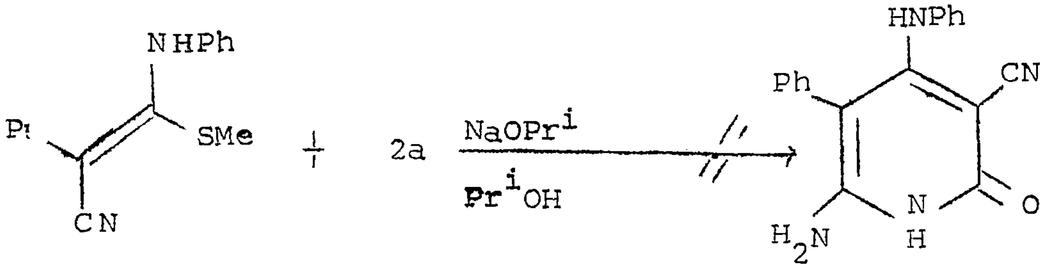


19a-c 2b 22a-c

19 22a $R = C_6H_5$
b $R = p\text{-}ClC_6H_4$
c $R = p\text{-}CH_3OC_6H_4$

obtained from the corresponding S,S-acetal and 2b. Also 23b and 23c were similarly obtained by reacting the corresponding 19e and 19f with 2b and were found to be identical with the reported naphthyridindiones.

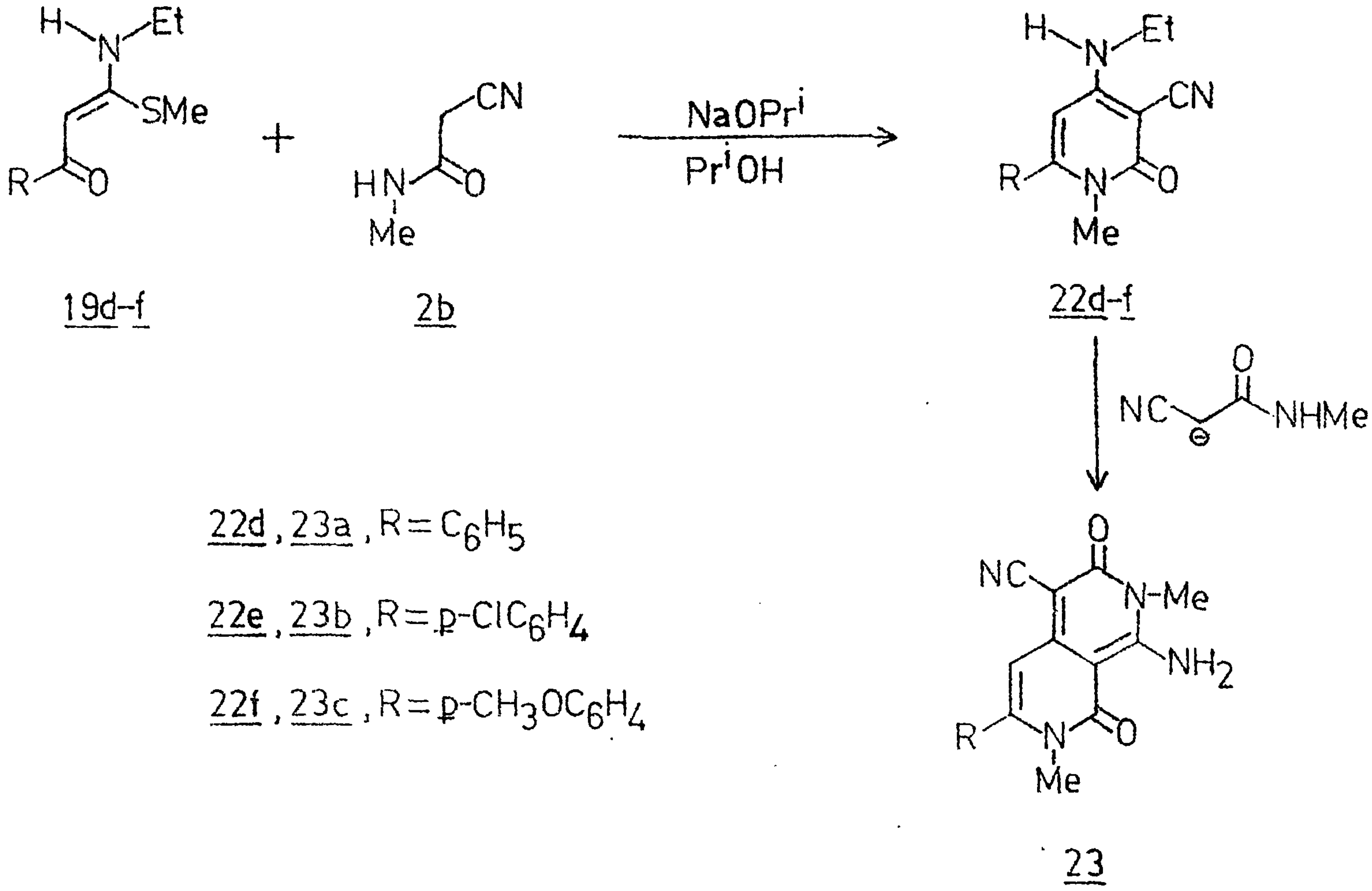
The keten-N,N-acetals 24a-c (Scheme 13), when reacted with 2a and 2b under identical conditions, the expected aminopyridones 25a-c were not formed, indicating that the β-carbon in N,N-acetals is not sufficiently electrophilic to react with sodio derivative of cyanoacetamide. Also the aminopyridone 27 was not formed when the corresponding S,N-acetal 26 and 2a were refluxed in alcoholic sodium isopropoxide.[2]



26

27

Scheme 12

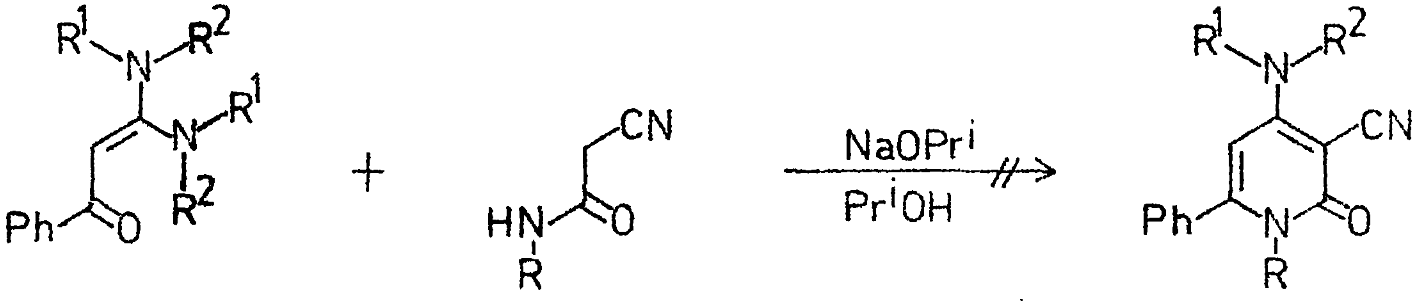


22d, 23a, R = C_6H_5

22e, 23b, R = p-ClC_6H_4

22f, 23c, R = p-$CH_3OC_6H_4$

Scheme 13



24 2a,b 25

24, 25a, $R^1 = H$, $R^2 = Et$

b, $R^1 = H$, $R^2 = Ph$

c, $R^1, R^2 = -(CH_2)_2-O-(CH_2)_2-$

TABLE 2

Spectral data of products 18 (a-k), 21 (a-b) and 22 (a-c)

Product	IR(cm^{-1})^{a}	^{1}H-NMR(δ/ppm)^{b}	M.S. m/e(M^{+})
18a	3230 (ν_{NH}); 2220 (ν_{CN}); 1640, 1620 (ν_{CO} and pyridone ring)	6.60 (s, 1H, H-5); 7.20-7.66 (m, 10H$_{arom}$).	287
18b	3280 (ν_{NH}); 2215 (ν_{CN}); 1648, 1625 (ν_{CO} and pyridone ring)	6.56 (s, 1H, H-5); 7.16-7.70 (m, 9H$_{arom}$).	-
18c	3280 (ν_{NH}); 2202 (ν_{CN}); 1630, 1612 (ν_{CO} and pyridone ring)	4.00 (s, 3H, OCH_3); 6.63 (s, 1H, H-5); 7.00-7.80 (m, 9H$_{arom}$).	-

Table 2 (Contd.)

Product	IR(cm^{-1})^{a}	^{1}H-NMR(δ /ppm)^{b}	M.S. m/e(M^{+})
18d	3324 (ν_{NH}); 2220 (ν_{CN}); 1630, 1612 (ν_{CO} and pyridone ring)	1.28 (t, 3H, $CH_2C\underline{H}_3$); 3.45 (q, 2H, $C\underline{H}_2CH_3$); 6.40 (s, 1H, $\underline{H}$-5); 7.42 (br s, 5H$_{arom}$).	239
18e	3290 (ν_{NH}); 2220 (ν_{CN}); 1640, 1625 (ν_{CO} and pyridone ring)	1.43 (t, 3H, $CH_2C\underline{H}_3$); 3.63 (q, 2H, $C\underline{H}_2CH_3$); 6.60 (s, 1H, $\underline{H}$-5); 7.46-7.80 (m, 4H$_{arom}$).	-
18f	3322 (ν_{NH}); 2220 (ν_{CN}); 1620, 1610 (ν_{CO} and pyridone ring)	1.28 (t, 3H, $CH_2C\underline{H}_3$); 3.50 (br q, 2H, $C\underline{H}_2CH_3$); 3.80 (s, 3H, $OC\underline{H}_3$); 6.48 (s, 1H, $\underline{H}$-5); 7.32 (A_2B_2 dd, 4H$_{arom}$).	-

Table 2 (Contd.)

Product	IR(cm^{-1})^a	^1H-NMR(δ /ppm)^b	M.S. m/e(M^+)
18g	3310 (ν_{NH}); 2205 (ν_{CN}); 1620, 1610 (ν_{CO} and pyridone ring)	1.05 (t, 3H, $CH_2C\underline{H}_3$); 1.84 (q, 2H, $C\underline{H}_2CH_3$); 3.50 (t, 3H, $NHC\underline{H}_2$); 6.57 (s, 1H, $\underline{H}$-5); 7.60 (s, $5H_{arom}$).	-
18h	3335 (ν_{NH}); 2200 (ν_{CN}); 1630, 1615 (ν_{CO} and pyridone ring)	4.68 (d, 2H, $NHC\underline{H}_2$); 6.60 (s, 1H, $\underline{H}$-5); 7.38 (br.s, $5H_{arom}$); 7.50 (br.s, $5H_{arom}$).	301
18i	3370 (ν_{NH}); 2200 (ν_{CN}); 1640, 1625 (ν_{CO} and pyridone ring	1.40-1.70 (br t, 6H, two $OCH_2C\underline{H}_3$); 4.43-4.81 (br m, 6H, two $OC\underline{H}_2CH_3$+ $NHC\underline{H}_2$); 6.54 (s, 1H, $\underline{H}$-5); 7.02 (br. t, 1H, -CH=); 7.72 (s, $5H_{arom}$).	327

Table 2 (Contd.)

Product	IR(cm^{-1})^{a}	^{1}H-NMR(δ/ppm)^{b}	M.S. m/e(M^{+})
18j	3412 (ν_{NH}); 2200 (ν_{CO}); 1640, 1625 (ν_{CO} and pyridone ring)	1.36 (t, 3H, $CH_2C\underline{H}_3$); 2.48 (s, 3H, $C\underline{H}_3Ar$); 3.50 (q, 2H, $C\underline{H}_2CH_3$); 6.30 (s, 1H, $\underline{H}$-5).	-
18k	2200 (ν_{CN}); 1620, 1608 (ν_{CO} and pyridone ring)	2.40 (s, 3H, $C\underline{H}_3Ar$); 4.00 (br s, 4H, $-C\underline{H}_2-N-C\underline{H}_2-$); 4.04 (br s, 4H, $-C\underline{H}_2-O-C\underline{H}_2-$); 6.54 (s, 1H, $\underline{H}$-5); 7.42 (A_2B_2 dd, 4H$_{arom}$).	295
21a	3250 (ν_{NH}); 2220 (ν_{CN}); 1602, 1590 (ν_{CO} and pyridone ring)	2.82-3.38 (br m, 4H, $-C\underline{H}_2C\underline{H}_2-$); 7.30-8.00 (m, 9H$_{arom}$).	313

Table 2 (Contd.)

Product	IR(cm^{-1})^{a}	^{1}H-NMR(δ/ppm)^{b}	M.S. m/e(M^{+})
21b	3250 (ν_{NH}); 2214 (ν_{CN}); 1605, 1590 (ν_{CO} and pyridone ring)	2.50 (s, 3H, C$\underline{H}_3$Ar); 3.74 (s, 2H, SC$\underline{H}_2$); 7.24-7.76 (m, 8H$_{arom}$).	345
22a	3280 (ν_{NH}); 2205 (ν_{CN}); 1638, 1610 (ν_{CO} and pyridone ring.	3.52 (s, 3H, NC$\underline{H}_3$); 6.45 (s, 1H, $\underline{H}$-5); 6.92-7.68 (m, 10H$_{arom}$).	301
22b	3270 (ν_{NH}); 2210 (ν_{CN}); 1640, 1632 (ν_{CO} and pyridone ring)	3.56 (s, 3H, NC$\underline{H}_3$); 6.40 (s, 1H, $\underline{H}$-5); 7.16-7.70 (m, 9H$_{arom}$).	-

Table 2 (Contd.)

Product	IR(cm^{-1})^a	^{1}H-NMR (δ/ppm)^b	M.S. m/e(M$^+$)
22c	3285 (ν_{NH}); 2205 (ν_{CN}); 1640, 1608 (ν_{CO} and pyridone ring)	3.52 (s, 3H, NC$\underline{H}_3$); 3.98 (s, 3H, OC$\underline{H}_3$); 6.38 (s, 1H, $\underline{H}$-5); 7.00-7.55 (br m, 9H$_{arom}$).	331

[a] IR medium = nujol mull. [b] NMR solvent = TFA.

EXPERIMENTAL

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

The starting materials

The commercial samples of aniline and morpholine were purified before use.

N-Methylcyanoacetamide (2b), mp. 98-99°C was prepared by the condensation of ethyl cyanoacetate with methylamine.

Reaction of 3-cyano-4-methylthio-6-phenyl-2(1H)-and N-methyl-2-(1H)-pyridone 3 with amines : Attempted preparation of 4-aminopyridones 18 by exchange method:

A suspension of pyridone 3 (0.01 mol) and amine (0.01 mol) (aniline, morpholine or propylamine) in 50 ml of ethanol was refluxed for 8-20 hr. After evaporation of the solvent and washing with ethanol the pyridone 3 was recovered unchanged (mp, mmp, superimposable IR).

In an alternate reaction, a mixture of pyridone 3 (0.01 mol) and amine (0.01 mol) (aniline, morpholine or propylamine) was heated in a sealed tube at 140-150° for 2-5 hr. Work-up of the reaction mixture yielded a tarry residue from which neither the starting pyridone 3 nor the aminopyridone 18 could be recovered.

Similarly, when equimolar quantities of 3 and amine (aniline or morpholine) were heated at 150-160° in the absence of any solvent, work-up of the reaction mixture by washing with ethanol, yielded only the starting pyridone 3 (mp, mmp, superimposable IR).

The keten-S,N-acetals 19a-k, 20a-b and 26 and N,N-acetals 24a-c required, were prepared as described in chapter 2.

General method for the preparation of 4-N-aryl(or alkyl)amino/morpholino-3-cyano-5,6-substituted-N-unsubstituted/N-methyl-2(1H)-pyridones (18a-k, 21a-b and 22a-c):

To a solution of sodium isopropoxide (prepared by dissolving 0.23 g, 0.01 mol of sodium in 40 ml of dry isopropanol) in isopropanol, cyanoacetamide/N-methylcyanoacetamide (0.01 mol) was added and the mixture was shaken for 5-10 min. The appropriate keten-S,N-acetal 19 (0.01 mol) was then added and the reaction mixture was refluxed for 8-35 hr (Table 3). Evaporation of the solvent yielded bright organge sodium salt,which was diluted with water (20-30 ml) and filtered. The residue obtained was acidified with dil. HCl (30%) to give the crude pyridones 18a-h, 18j-k, 21a and 21b as pale yellow amorphous solids which were crystallized from acetic acid (Table 3). Treatment of the filtrate with dil. HCl did not yield more pyridones. In a few cases (20a and 20b) the sodium salt partly dissolved in water and treatment of both the residue and the filtrate yielded the corresponding pyridones. 21a and 21b.

In case of pyridone 18i and N-methylpyridones 22a-c, the residue obtained after work-up of the reaction mixture was neutralized with dil. AcOH to give the crude pyridones, which were crystallized from acetic acid (Table3).

General method for the preparation of 8-amino-5-cyano-2,7-dimethyl-2,7-naphthyridin-1,6(2H,7H)-diones (23a-c):

The S,N-acetals 19d-f (0.01 mol) and N-methylcyanoacetamide 2b (0.02 mol) were reacted as described above. Neutralization of the residues obtained after work-up with acetic acid gave crude naphthyridines 23a-c as pale yellow solids which were crystallized from acetic acid. IR and NMR of 23a-c were superimposable with those of authentic sample.[3] (mp, mmp).

Reaction of keten-N,N-acetals 24a-c with cyanoacetamide and N-methylcyanoacetamide :

A suspension of keten-N,N-acetal 24a (0.01 mol), cyanoacetamide/N-methylcyanoacetamide (2) (0.01 mol) and sodium isopropoxide (0.01 mol) in 50 ml of dry isopropanol was refluxed for 3-4 hr. Work-up of the reaction mixture as described above, yielded a residue which on crystallization yielded the unreacted N,N-acetal 24a (mp, mmp, superimposable IR). The N,N-acetals 24b and 24c were similarly recovered unreacted under identical condtions.

Reaction of S,N-acetal 26 (0.01 mol) with cyanoacetamide (2a, 0.01 mol) under similar condtions yielded after work-up, a tarry residue from which the pyridone 27 could not be isolated.

TABLE 3

4-N-Aryl(or alkyl)amino/morpholino-3-cyano-5,6-substituted-N-unsubstituted/N-methyl-2(1H)-pyridones 18 (a-k), 21 (a-b) and 22 (a-c)

Product[a]	Reflux time(hr)	m.p. (°C)	Yield (%)	Molecular formula	Calc. Found	Analysis (%)		
						C	H	N
18a	8	315-317	64	$C_{18}H_{13}N_3O$ (287.3)	Calc.	75.26	4.53	14.63
					Found	75.54	4.63	14.39
18b	12	>355	71	$C_{18}H_{12}ClN_3O$ (321.8)	Calc.	67.18	3.73	13.06
					Found	66.82	3.90	12.88
18c	18	308-310	62	$C_{19}H_{15}N_3O_2$ (317.3)	Calc.	71.92	4.73	13.24
					Found	71.69	4.68	12.80

Table 3 (Contd.)

18d	9	303-	55	$C_{14}H_{13}N_3O$	70.29	5.44	17.57
		305		(239.3)	70.47	5.38	17.70
18e	20	263-	62	$C_{14}H_{12}ClN_3O$	61.42	4.38	15.35
		265		(273.7)	61.65	4.29	15.18
18f	24	282-	59	$C_{15}H_{15}N_3O_2$	66.91	5.57	15.61
		283		(269.3)	66.71	5.64	15.15
18g	30	273-	58	$C_{15}H_{15}N_3O$	71.14	5.92	16.60
		275		(253.3)	70.78	6.11	16.85
18h	30	295-	67	$C_{19}H_{15}N_3O$	75.74	4.98	13.95
		297		(301.3)	75.83	5.05	14.23

Table 3 (Contd.)

18i	35	220	60	$C_{18}H_{21}N_3O_3$	66.05	6.42	12.84
				(327.4)	66.44	6.27	13.01
18j	16	257-	63	$C_{19}H_{11}N_3O$	61.01	6.21	23.72
		260		(177.2)	60.83	6.08	23.44
18k	12	288-	57	$C_{17}H_{17}N_3O_2$	69.15	5.76	14.23
		290		(295.3)	69.33	5.80	14.10
21a	20	302-	60	$C_{20}H_{15}N_3O$	76.67	4.79	13.41
		303		(313.3)	76.38	4.90	13.66
21b	8	264-	53	$C_{20}H_{15}N_3OS$	69.56	4.34	12.17
		266		(345.4)	69.71	4.22	11.97

Table 3 (Contd.)

22a	20	312-	58	$C_{19}H_{15}N_3O$	75.74	4.98	13.95
		314		(301.3)	75.83	5.01	14.02
22b	22	265-	66	$C_{19}H_{14}ClN_3O$	67.95	4.17	12.51
		266		(335.8)	68.11	4.35	12.67
22c	15	240-	50	$C_{20}H_{17}N_3O_2$	72.50	5.13	12.68
		241		(331.4)	72.83	4.99	12.58

---

[a] Crystallization solvent = AcOH.

REFERENCES

1. R.R. Rastogi, H. Ila and H. Junjappa, J. Chem. Soc. Chem. Comm. 645 (1975).
2. R.R. Rastogi, A. Kumar, H. Ila and H. Junjappa, J. Chem. Soc. Perkin Trans. I, 549 (1978).
3. R.R. Rastogi, A. Kumar, H. Ila and H. Junjappa, J. Chem. Soc. Perkin Trans. I, 554 (1978).
4. (a) H. Junek and A. Schmidt, Monatsch. Chem. 98, 1097 (1967); Chem. Abstr. 67, 82055^{s} (1967).

   (b) J.N. Phillips, Aust. P 491554; Chem. Abstr. 89, 109114^{d} (1978).
5. S. Senda, K. Hirota, T. Asao and Y. Abe, Heterocycles, 9, 739 (1978); Chem. Abstr. 89, 109349^{j} (1978).
6. V.G. Granik, N.B. Marchenko, T.F. Vlasona, R.G. Glushkov, Khim. Geterotsikl. Soedin, 1509 (1976); Chem. Abstr. 86, 139783^{b} (1977).
7. S. Senda and K. Hirota, Japan Kokai, 76,118,768; Chem. Abstr. 86, 189720^{z} (1977).
8. A. Kumar, H. Ila and H. Junjappa, J. Chem. Soc. Perkin Trans. I, 857 (1978).

CHAPTER 5

REACTION OF POLARIZED KETEN-S,N- AND N,N-ACETALS WITH BENZOYL ISOTHIOCYANATE : SYNTHESIS OF NOVEL 1-N-ARYL (ALKYL)-2-PHENYL-5-AROYL-6-METHYLTHIO (N-ALKYLAMINO)-4-THIOXOPYRIMIDINES*

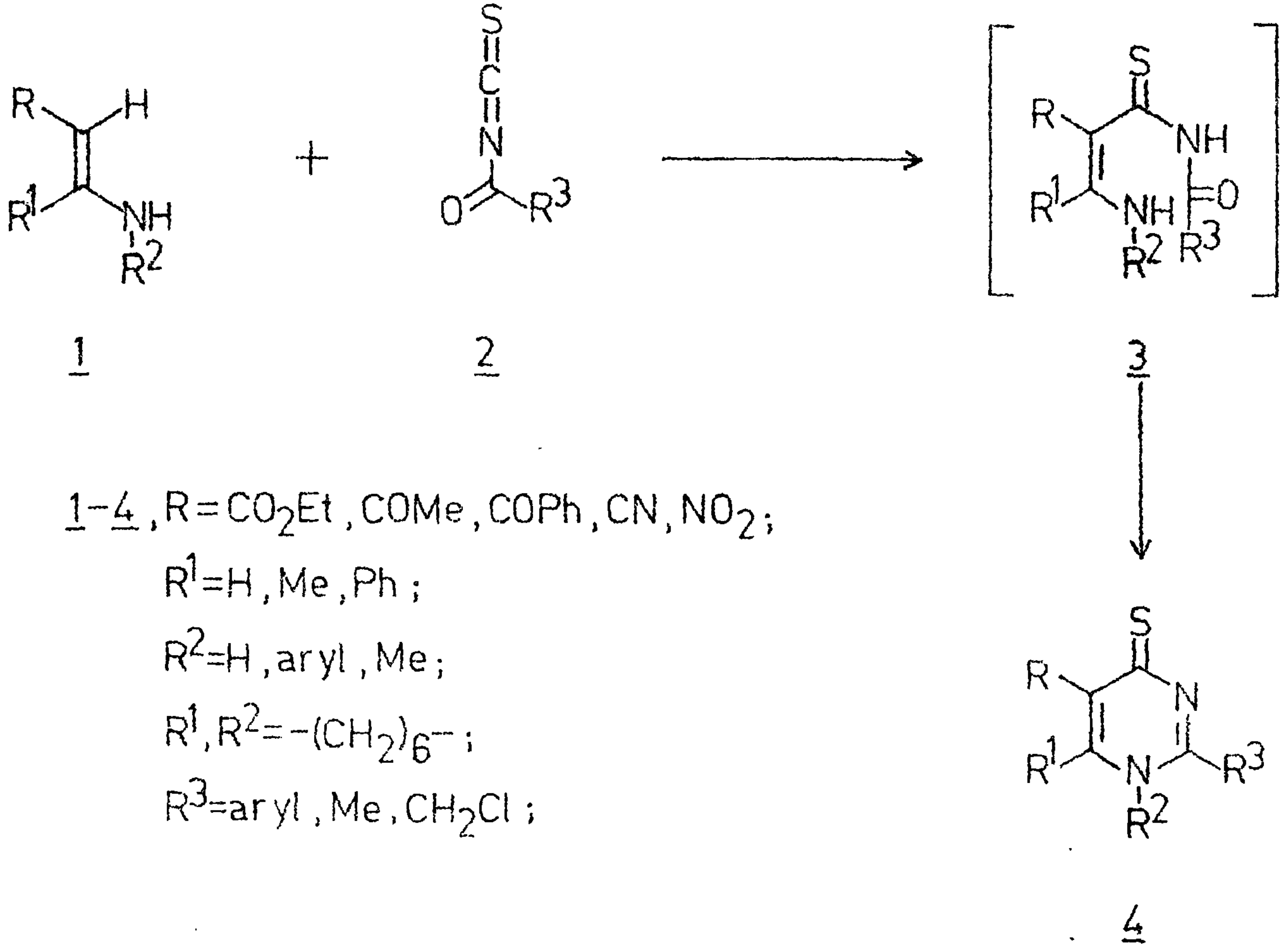
5.1 Introduction

α-Ketoketen-S,N- and N,N-acetals have been shown to be versatile intermediates and found to behave predictably towards binucleophiles, providing new general methods for the synthesis of 2,4-diaminopyrimidines and 4-amino-2(1H)-pyridones in moderate to excellent yields. These reactions constitute characteristic behaviour of S,N- and N,N-acetals as three carbon fragments. However, their reactivity as enamine components, towards electron-deficient reactants has been totally neglected.[1-4] Classical enamine components derived from β-ketoesters and 1,3-diketones, have been reported[3-15] to react with benzoyl isothiocyanate to give 4-thioxopyrimidines 4 and 9 (Scheme 1) in good yields. One of the serious limitations of this method involves, that the product

---

*V. Aggarwal, H. Ila and H. Junjappa, *Synthesis*, 65 (1982).

Scheme 1



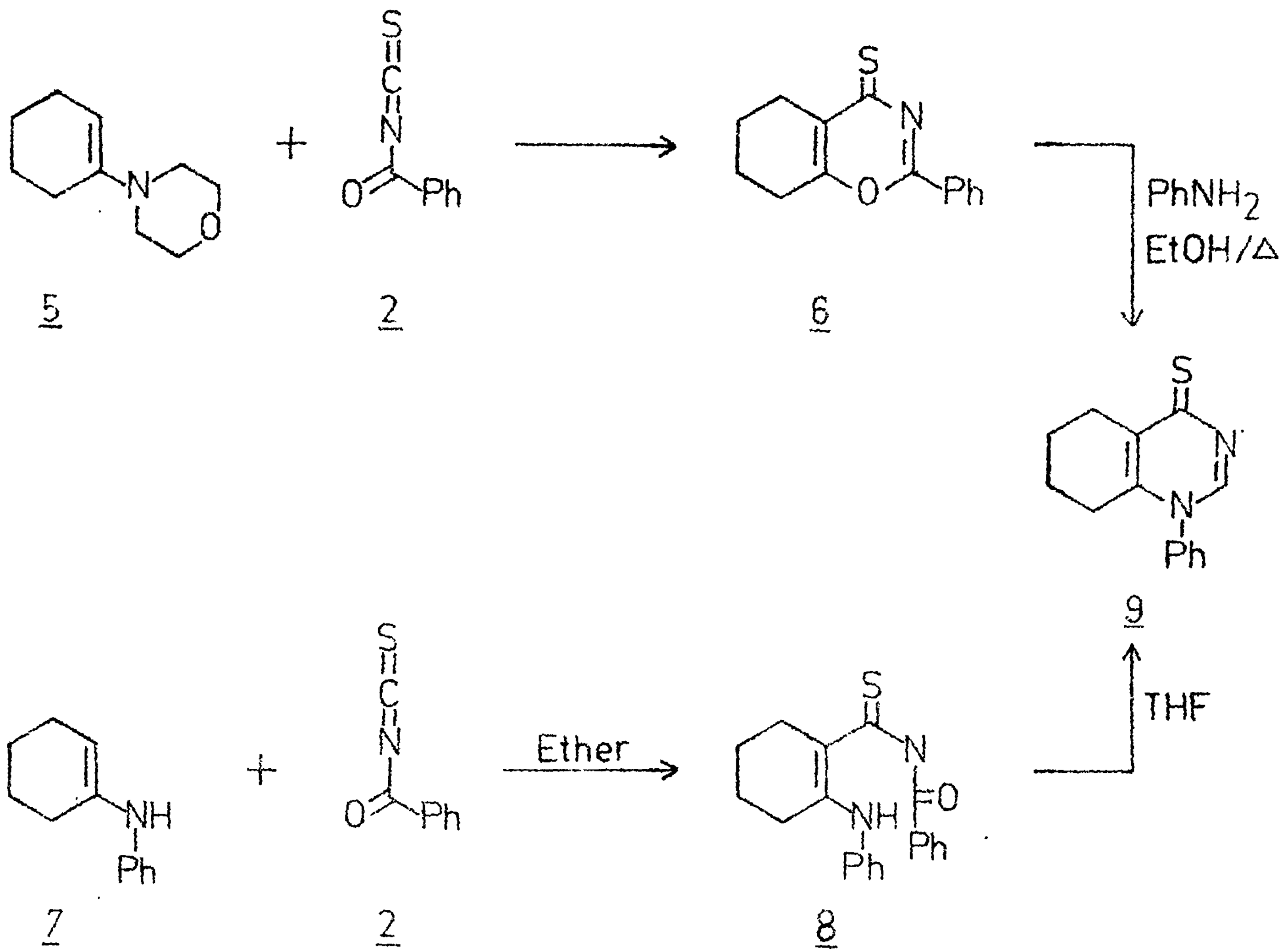
$\underline{1}$–$\underline{4}$, R = CO_2Et, COMe, COPh, CN, NO_2;
R^1=H, Me, Ph ;
R^2=H, aryl, Me;
R^1,R^2= –$(CH_2)_6$– ;
R^3=aryl, Me, CH_2Cl ;

pyrimidine carries an alkyl or aryl group at 6-position of the ring making it unsuitable for subsequent structural elaboration for fused ring construction. There is only one report[14] of the reaction of ethyl β-amino-β-ethoxyacrylate (1, $R=CO_2Et$; $R^1=OEt$; $R^2=H$) and β-amino-β-ethoxyacrylophenone (1, $R=PhCO$; $R^1=OEt$, $R^2=H$) with ethoxycarbonyl isothiocyanate to yield the corresponding 6-ethoxy-4-thioxopyrimidine (4)($R=CO_2Et$, PhCO; $R^1=OEt$; $R^2=H$; $R^3=OH$) in good yields. It was anticipated that similar reactions of keten-S,N- and N,N-acetals with benzoyl isothiocyanate should provide a more versatile entry to the synthesis of usefully functionalised thioxopyrimidines. Further, the pyrimidines thus obtained will be particularly useful for the synthesis of purines and their derivatives. A few of the acetals (Chapter 2) have been selected to react with benzoyl isothiocyanate and the results of these reactions are presented here.

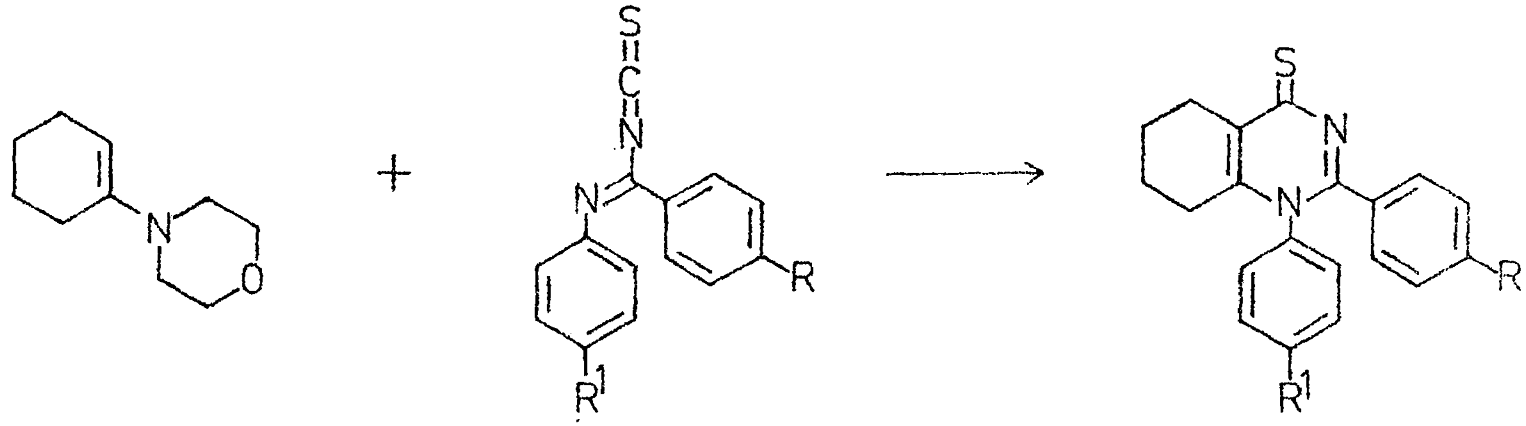
5.2 Results and discussion

When S,N-anilinoacetal 11a and 2 (Scheme 2) (Table 1) were refluxed in ether for 18 hr, the corresponding 4-thioxopyrimidine 13a was formed in 80% yield. The structure of 13a was confirmed by its analytical (Table 6)

Scheme 1 contd.



Scheme 1 contd.



5 10 9

9,10, R = H, Me, Cl, OMe; R^1 = H, F

and spectral data (Table 3). Thus, its mass spectrum showed a molecular ion peak at M^+ 414 and was analysed for $C_{24}H_{18}N_2OS_2$. Its IR spectrum showed characteristic absorption band at 1665 cm^{-1} (ν_{CO}) and a weak band at 1595 cm^{-1} ($\nu_{C=N}$). Its structure was further confirmed by its NMR spectrum. A singlet at δ1.60 (3H) was assigned to three protons of the methylthio group. The broad multiplet around δ7.06 to 7.50 and a double doublet at δ7.86 were assigned to thirteen and two aromatic protons respectively. Similarly, 11b and 11c reacted with 2 to give the corresponding 13b and 13c in 78 and 76% yields respectively. However, S,N-ethylacetal 11d and N,N-diethyl acetal 11h in refluxing ether, gave only the corresponding open-chain adducts 12d (80%) and 12h (75%). When the above reaction mixture was refluxed in tetrahydrofuran, the desired pyrimidines 13d and 13h were obtained in 68 and 42% yields respectively. Similarly, 11e-g and 11i-j were reacted with 2 in refluxing tetrahydrofuran, to give the corresponding pyrimidines 13e-g and 13i-j in 35 to 70% overall yields. The analytical and spectral data of 13b-j are described in table 6 and table 3 respectively, which are in support of the structures assigned.

Scheme 2

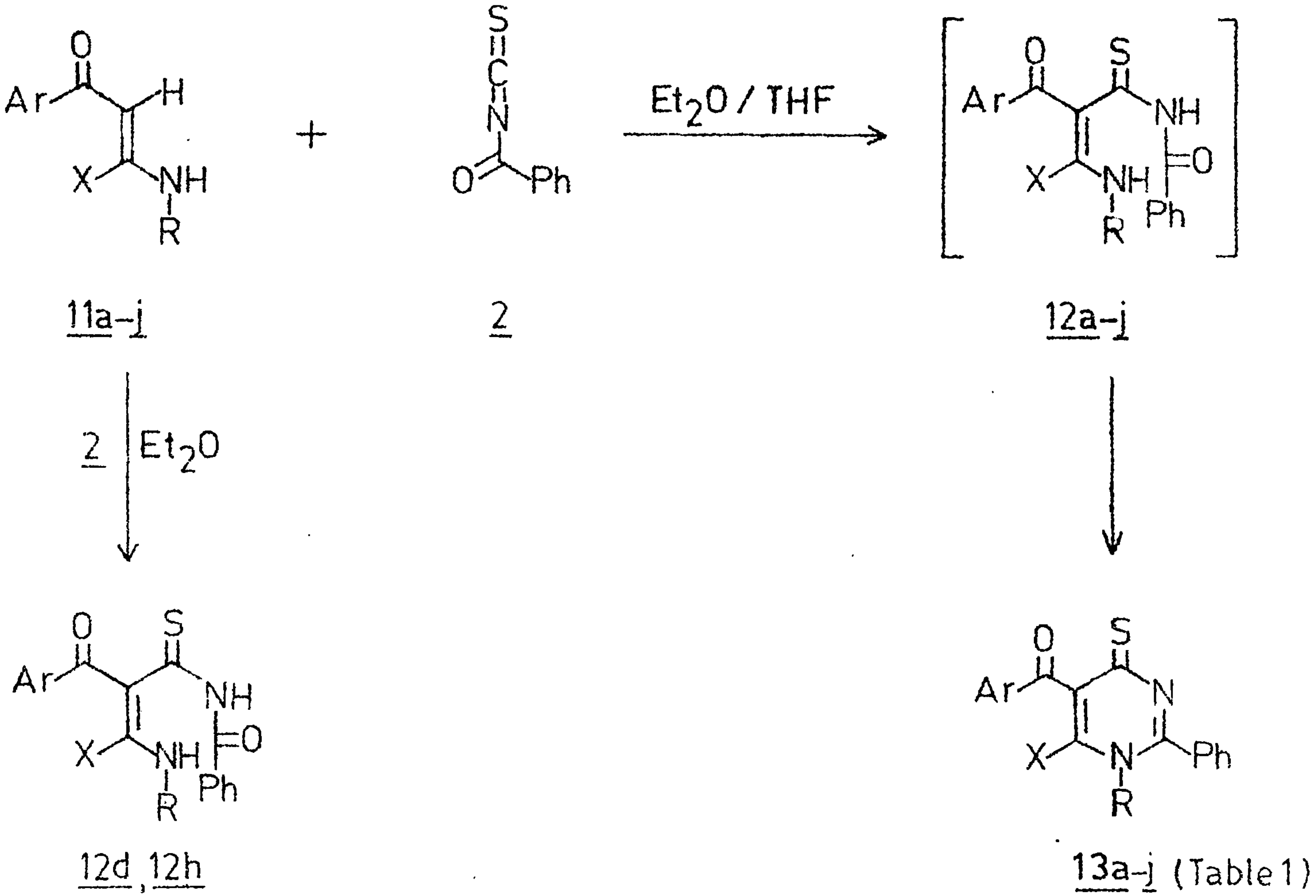
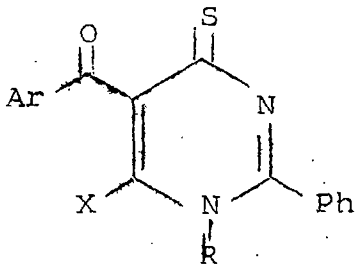

Ar
X
NH
R
H
O
+
S
C
N
O
Ph
Et2O / THF
11a–j
2
12a–j
2
Et2O
12d, 12h
13a–j (Table 1)

TABLE 1

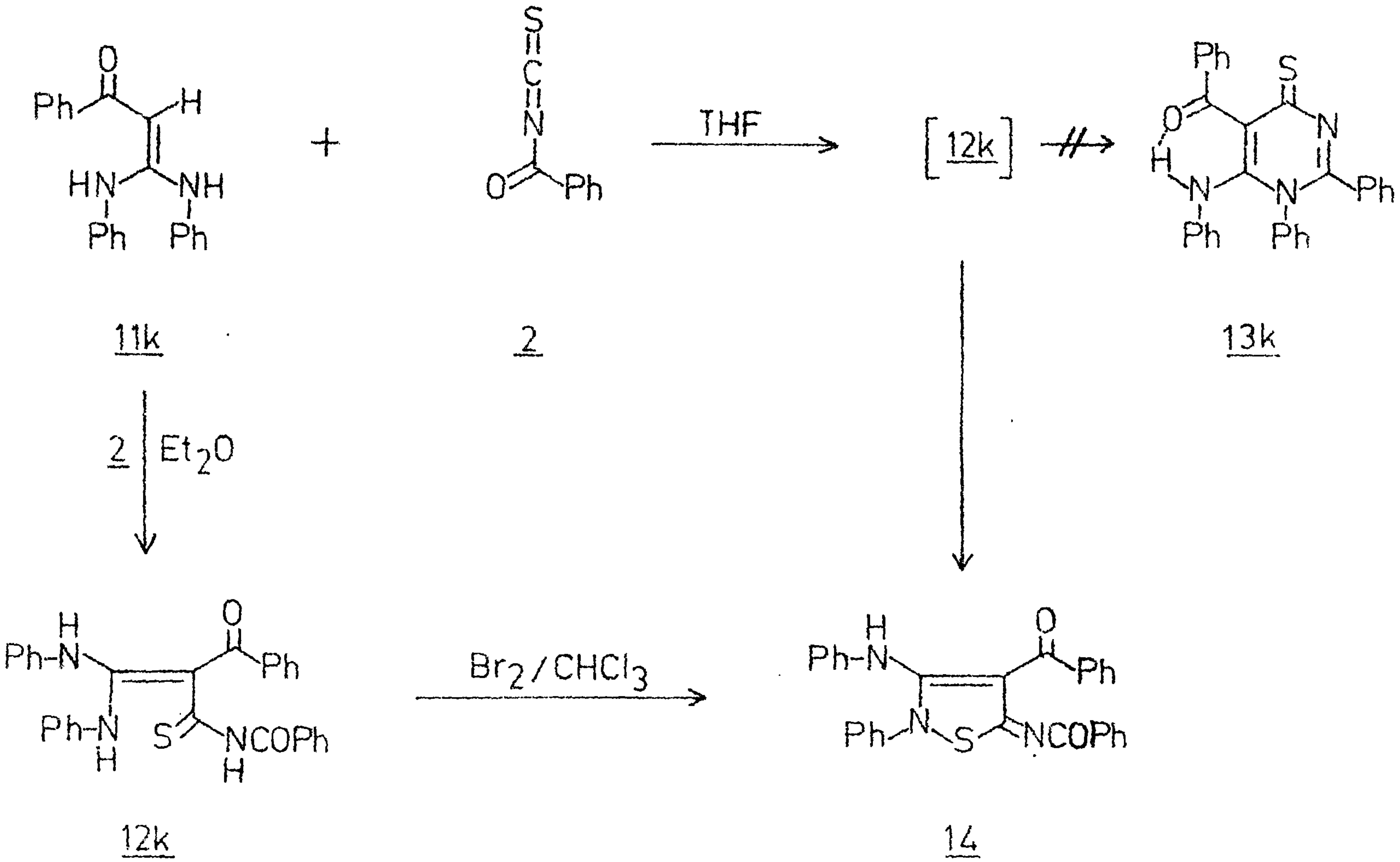


13

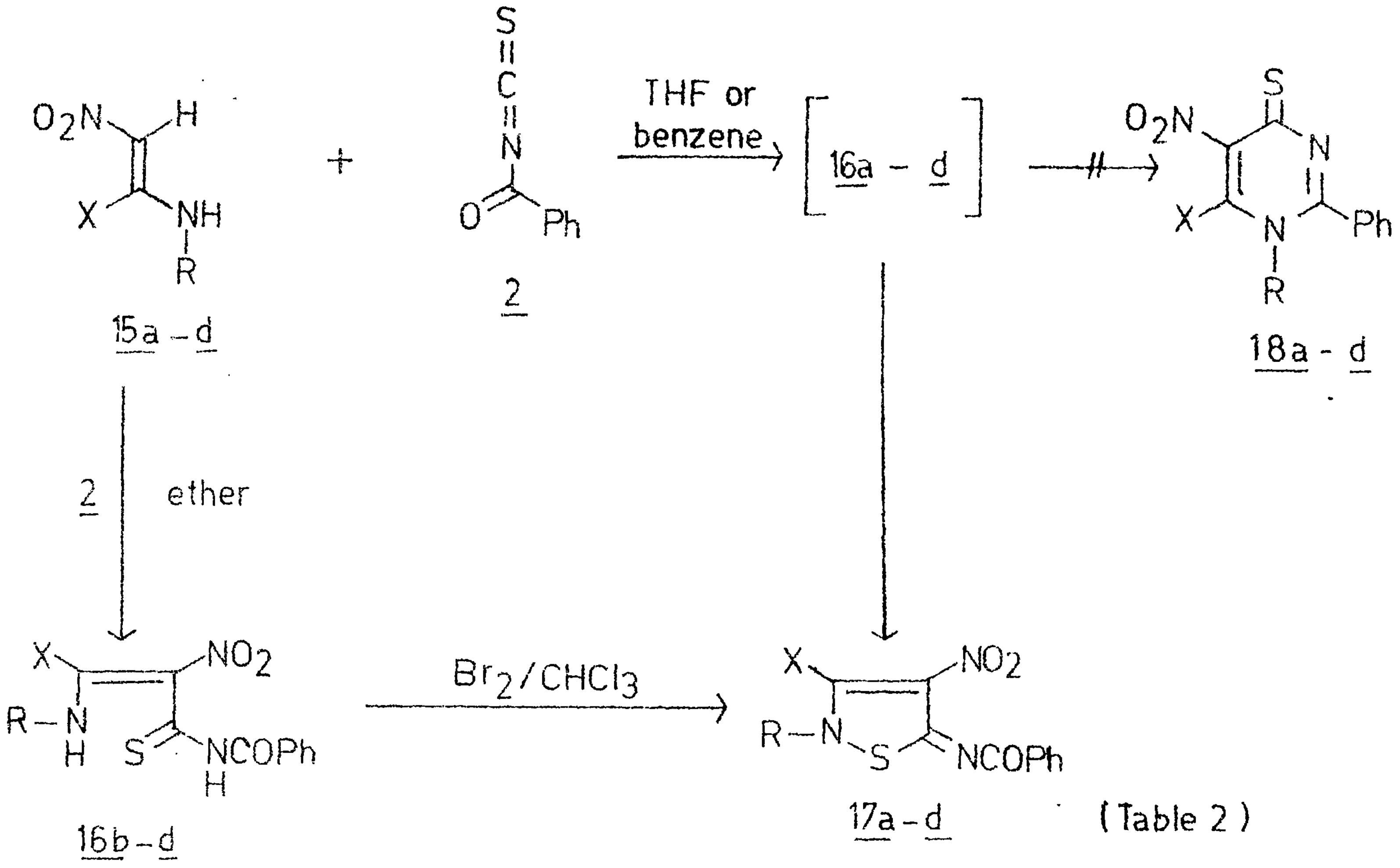
Product	Ar	X	R
13a	C_6H_5	SCH_3	C_6H_5
13b	*p*-ClC_6H_4	SCH_3	C_6H_5
13c	*p*-$CH_3OC_6H_4$	SCH_3	C_6H_5
12d, 13d	C_6H_5	SCH_3	C_2H_5
13e	*p*-ClC_6H_4	SCH_3	C_2H_5
13f	*p*-$CH_3OC_6H_4$	SCH_3	C_2H_5
13g	*p*-$CH_3C_6H_4$	SCH_3	C_2H_5
12h, 13h	C_6H_5	NHC_2H_5	C_2H_5
13i	*p*-ClC_6H_4	NHC_2H_5	C_2H_5
13j	*p*-$CH_3OC_6H_4$	NHC_2H_5	C_2H_5

The reaction of ketoketen N,N-dianilinoacetal 11k with 2 (Scheme 3) in refluxing ether yielded the open-chain adduct 12k in 82% yield. When 11k and 2 were refluxed in tetrahydrofuran, the expected thioxopyrimidine 13k was not formed and a yellow solid obtained after prolonged refluxing was identified as isothiazoline 14 on the basis of its spectral (Table 5) and analytical data (Table 8). Thus its mass spectrum displayed a molecular ion peak at M^+ 475 ($C_{29}H_{21}N_3O_2S$), while its IR spectrum showed an absorption band at 3175 cm^{-1} (ν_{NH}) and a broad band between 1600-1500 cm^{-1} characteristic of isothiazolines.[6,8-10] The structure of isothiazoline 14 was further confirmed by oxidative cyclization[6,8-10] of open-chain adduct 12k with bromine when 14 was obtained in 52% yield (mp, mmp and superimposable IR). Similarly, nitroketen-S,N-acetal 15a (Scheme 4) (Table 2) reacted with 2 in refluxing benzene to give the corresponding isothiazoline 17a (39% yield), rather than the thioxopyrimidine 18a. The isothiazolines 17b-d were similarly prepared in refluxing tetrahydrofuran from the corresponding 15b-d and 2 in 46-55% overall yields. Alternatively, these were also prepared by oxidative cyclisation (bromine in chloroform) of the corresponding adducts

Scheme 3

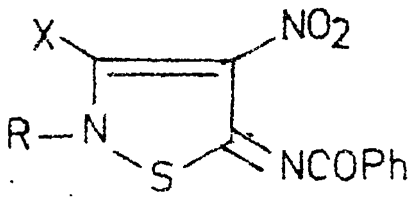


Scheme 4



15a – d
2
THF or benzene
16a – d
18a - d
2
ether
16b – d
Br2/CHCl3
17a – d
(Table 2)

Table 2



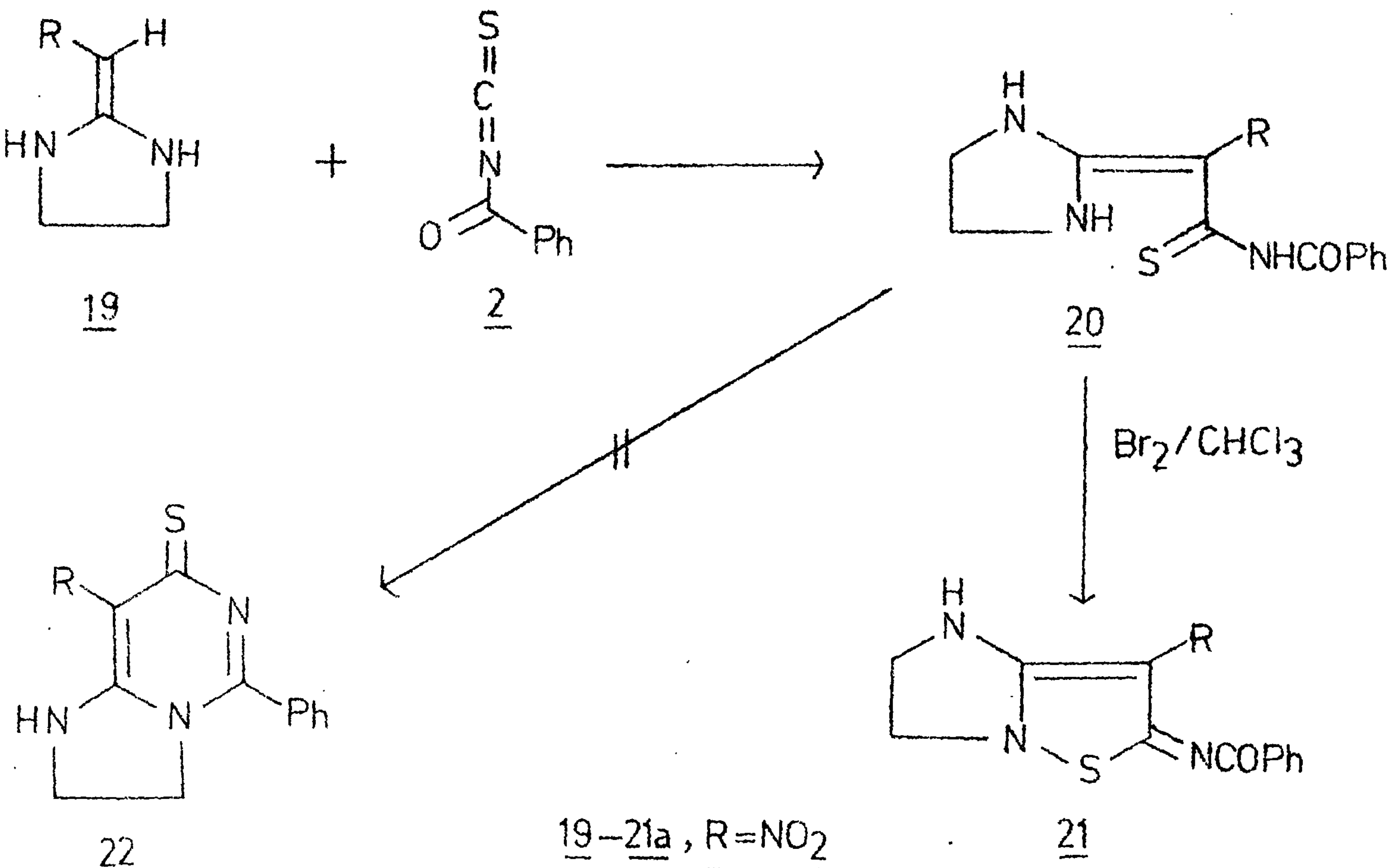
17

Product	X	R
17a	SCH_3	C_6H_5
16b, 17b	SCH_3	C_2H_5
16c, 17c	NHC_2H_5	C_2H_5
16d, 17d	NHC_6H_5	C_6H_5

16b-d, obtained by reacting 15b-d and 2 in refluxing ether. The analytical and spectral data of the adducts 12d, 12h, 12k and 16b-d are described in table 7 and table 4 respectively and the data of isothiazolines 17a-d are described in table 8 and table 5 respectively, which are in conformity with the structures assigned. Interestingly, the cyclic keten-N,N-acetals 19a and 19b (Scheme 5) reacted with 2 to give the corresponding open-chain adducts 20a (87%) and 20b (77%), which underwent oxidative cyclisation in the presence of bromine in chloroform to give fused isothiazolines 21a (70%) and 21b (74%) respectively. Their analytical (Table 8) and spectral data (Table 5) are in conformity with the structures assigned.

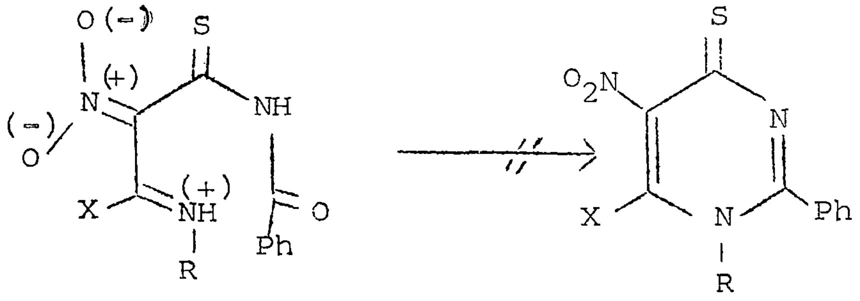
Thus, from the above results it is apparent, that while ketoketen-S,N-phenyl, S,N-ethyl and N,N-diethylacetals react with benzoyl isothiocyanate to give the respective 1-N-ethyl/phenyl-4-thioxo-5-aroyl-6-methylthio/anilino/ethylaminopyrimidines in good yields, the corresponding N,N-diphenylacetal 11k gives an open-chain adduct 12k which on refluxing in tetrahydrofuran is converted to isothiazoline 14. Although, it is not

Scheme 5



$\underline{19}$–$\underline{21}$a, R=NO$_2$
b, R=COC$_6$H$_5$

possible to give a definite explanation for these observations, however, it appears that because of steric crowding in 13k, due to the presence of three adjacent phenyl groups, the oxidative cyclization pathway to 14 is preferred over dehydrative cyclization. The failure of intermediate open-chain adducts 16a-d, derived from nitroketen-S,N- and N,N-acetals, to undergo cyclization to thioxopyrimidines 18a-d is probably due to greater delocalization of lone pair on nitrogen of aryl/alkylamino group over nitro group (A) which prevents nucleophilic attack of amino group at benzamido group.



A

18

TABLE 3

Spectral data of products <u>13</u> (<u>a</u>-<u>j</u>)

Product	IR(cm^{-1})	^1H-NMR(δ/ppm)	M.S. m/e(M^+)
<u>13a</u>	1665 (ν_{CO}); 1595 ($\nu_{C=N}$)^a	1.60 (s, 3H, $SC\underline{H}_3$); 7.06-7.50 (m, $13H_{arom}$); 7.86 (dd, $2H_{arom}$).^{c}	414
<u>13b</u>	1673 (ν_{CO}); 1585 ($\nu_{C=N}$)^a	1.58 (s, 3H, $SC\underline{H}_3$); 6.84-7.12 (m, $12H_{arom}$); 7.54 (dd, $2H_{arom}$).^{c}	-
<u>13c</u>	1660 (ν_{CO}); 1600 ($\nu_{C=N}$)^a	1.62 (s, 3H, $SC\underline{H}_3$); 3.52 (s, 3H, $OC\underline{H}_3$; 6.64 (d, $2H_{arom}$); 6.98 (br s, $10H_{arom}$); 7.50 (dd, $2H_{arom}$).^{c}	-

Table 3 (Contd.)

13d	1665 (ν_{CO}); 1595 ($\nu_{C=N}$)[a]	1.01 (t, 3H, $CH_2C\underline{H}_3$); 2.06 (s, 3H, $SC\underline{H}_3$); 4.20 (q, 2H, $C\underline{H}_2CH_3$); 7.25–7.58 (m, 8H_{arom}); 7.66–7.90 (dd, 2H_{arom}).[c]	366
13e	1670 (ν_{CO}); 1585 ($\nu_{C=N}$)[a]	1.01 (t, 3H, $CH_2C\underline{H}_3$); 2.10 (s, 3H, $SC\underline{H}_3$); 4.13 (q, 2H, $C\underline{H}_2CH_3$); 7.10 (d, 2H_{arom}); 7.35 (br s, 5H_{arom}); 7.60 (d, 2H_{arom}).[c]	–
13f	1660 (ν_{CO}); 1595 ($\nu_{C=N}$)[a]	1.00 (t, 3H, $CH_2C\underline{H}_3$); 2.11 (s, 3H, $SC\underline{H}_3$); 3.56 (s, 3H, $OC\underline{H}_3$); 4.10 (q, 2H, $C\underline{H}_2CH_3$); 6.66 (d, 2H_{arom}); 7.30 (br s, 5H_{arom}); 7.58 (dd, 2H_{arom}).[c]	396

Table 3 (Contd.)

13g	1660 (ν_{CO}); 1600 ($\nu_{C=N}$)^{a}	1.00 (t, 3H, $CH_2C\underline{H}_3$); 2.05 (br.s, 6H $SC\underline{H}_3+CH_3$); 4.05 (q, 2H, CH_3); 6.90 (d, $2H_{arom}$); 7.28 (br s, $5H_{arom}$); 7.44 (dd, $2H_{arom}$).^{c}	–
13h	3230 (br, ν_{NH}); 1625 (ν_{CO}); 1590 ($\nu_{C=N}$)^{b}	0.60 (t, 3H, $CH_2C\underline{H}_3$); 0.80 (t, 3H, $CH_2C\underline{H}_3$); 3.05 (br q, 4H, two $C\underline{H}_2CH_3$); 7.00–7.28 (m, $8H_{arom}$); 7.55 (dd, $2H_{arom}$).^{c}	363
13i	3220 (br, ν_{NH}); 1625 (ν_{CO}); 1580 ($\nu_{C=N}$)^{a}	0.95–1.60 (two br t, 6H, $CH_2C\underline{H}_3$); 3.10–3.90 (two br q, 4H, $C\underline{H}_2CH_3$); 7.20–8.35 (m, $9H_{arom}$).^{c}	–

Table 3 (Contd.)

13j	3230 (br, ν_{NH}); 1625 (ν_{CO}); 1605 ($\nu_{C=N}$)[a]	1.14–1.55 (two br t, 6H, $CH_2C\underline{H}_3$); 3.32–3.78 (two br q, 4H, $C\underline{H}_2CH_3$); 3.96 (s, 3H, $OC\underline{H}_3$); 6.98–7.50 (m, 2H_{arom}); 7.55–7.80 (m, 5H_{arom}); 8.02 (dd, 2H_{arom}).[c]	–

---

[a] in nujol; [b] in KBr; [c] in TFA.

TABLE 4

Spectral data of products 12d, 12h, 12k, 16b-d, 20a and 20b

Product	IR(cm^{-1})	^1H-NMR(δ/ppm)
12d	3140 (ν_{NH}); 1680 (ν_{CO}amide); 1668 (ν_{CO}keto)[a]	1.30 (t, 3H, $CH_2C\underline{H}_3$); 2.43 (s, 3H, $SC\underline{H}_3$); 3.42 (br q, 2H, $C\underline{H}_2CH_3$); 5.60 (br s, 1H, N$\underline{H}$); 7.22-8.18 (br m, 10H_{arom}).[c]
12h	3250, 3150 (ν_{NH}); 1690 (ν_{CO}amide); 1625 (ν_{CO}keto)[a]	1.05 (t, 6H, two $CH_2C\underline{H}_3$); 3.25 (br q, 4H, two $C\underline{H}_2CH_3$); 7.28-7.61 (m, 8H_{arom}); 8.00 (dd, 2H_{arom}).[c]
12k	3350-3200 (br, ν_{NH}); 1688 (ν_{CO}amide); 1600 (ν_{CO}keto)[a]	6.24-9.32 (m, 20H_{arom}).[d]

Table 4 (Contd.)

16b	3200 (br, ν_{NH}); 1693 (ν_{CO})^b	1.58 (t, 3H, $CH_2C\underline{H}_3$); 2.71 and 2.80 (two s, total 3H, $SC\underline{H}_3$); 3.85 and 4.61 (two q, total 2H, $C\underline{H}_2CH_3$); 7.50-8.20 (m, $5H_{arom}$).^{d}
16c	3220, 3210 (br, ν_{NH}); 1695 (ν_{CO})^b	1.42 (two br t, 6H, $CH_2C\underline{H}_3$); 3.55 (two br q, 4H, $C\underline{H}_2CH_3$); 7.50-8.20 (m, $5H_{arom}$).^{d}
16d	3470, 3400 (br, ν_{NH}); 1688 (ν_{CO})^a	7.00-10.60 (m, $15H_{arom}$).^{d}
20a	3200 (ν_{NH}); 1692 (ν_{CO})^a	3.83 (s, 4H, $-C\underline{H}_2C\underline{H}_2-$); 7.38-8.02 (m, $5H_{arom}$); 9.50-9.78 (br, 2H, $N\underline{H}$).^{e}

Table 4 (Contd.)

20b	3375 (ν_{NH}); 1690 (ν_{CO}amide); 1610 (ν_{CO}keto)^{a}	3.57 (s, 2H, NHC$\underline{H}_2$-); 3.74 (s, 2H, NHC$\underline{H}_2$-); 6.94-7.70 (m, 10H$_{arom}$).^{d}

---

[a] in KBr; [b] in nujol; [c] in CDCl$_3$; [d] in TFA; [e] in DMSO-d$_6$.

TABLE 5

Spectral data of products 17 (a-d), 21a, 21b and 14

Product	IR(cm^{-1})	^1H-NMR(δ/ppm)	M.S. m/e(M^+)
17a	1590, 1530 (ν_{CO}, $\nu_{C=N}$)[a]	1.76 (s, 3H, $SC\underline{H}_3$); 7.16-7.51 (m, 8H_{arom}); 7.61-8.00 (m, 2H_{arom}).[d]	371
17b	1590, 1535 (ν_{CO}, $\nu_{C=N}$)[a]	1.40 (t, 3H, $CH_2C\underline{H}_3$); 2.52 (s, 3H, $SC\underline{H}_3$); 4.12 (q, 2H, $C\underline{H}_2CH_3$); 7.28-7.64 (m, 3H_{arom}); 8.28-8.44 (m, 2H_{arom}).[c]	323

Table 5 (Contd.)

17c	3265 (ν_{NH}); 1600, 1532 (ν_{CO}, $\nu_{C=N}$)[a]	1.30 (t, 3H, $CH_2C\underline{H}_3$); 1.33 (t, 3H, $CH_2C\underline{H}_3$); 3.48 (br q, 2H, $C\underline{H}_2CH_3$); 3.80 (q, 2H, $C\underline{H}_2CH_3$); 7.20-7.60 (m, $3H_{arom}$) 8.20-8.45 (m, $2H_{arom}$); 8.80 (br t, 1H, $N\underline{H}$).[c]	320
17d	3200 (br, ν_{NH}); 1590, 1560 (ν_{CO}, $\nu_{C=N}$)[b]	6.60-10.28 (m, $15H_{arom}$).[d]	416

Table 5 (Contd.)

21a	3370 (ν_{NH}); 1620 (ν_{CO})^{b}	4.08 (s, 4H, $-C\underline{H}_2C\underline{H}_2-$); 8.20 (br.s, 5H$_{arom}$).^{d}	-
21b	3340 (ν_{NH}); 1610, 1602 (ν_{CO})^{b}	4.21 (s, 4H, $-C\underline{H}_2C\underline{H}_2-$); 7.72 (br s, 10H$_{arom}$).^{d}	-
14	3175 (ν_{NH}; 1600-1500 (ν_{CO}, $\nu_{C=N}$)^{b}	6.12-8.06 (m, 20H$_{arom}$).^{d}	475

---

^{a} in KBr; ^{b} in nujol; ^{c} in CDCl$_3$; ^{d} in TFA.

EXPERIMENTAL

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

The starting materials

Benzoyl isothiocyanate (2), bp 119° (10 mm) was prepared by the reported method.[16]

The keten-S,N-(11a-g, 15a-b) and N,N-acetals (11h-j, 15c-d, 19a-b) required were prepared as described in chapter 2.

General method for the preparation of 1-phenyl(or ethyl)-2-phenyl-5-aroyl-6-methylthio(or N-ethylamino)-4-thioxopyrimidines (13a-j)

A solution of 11a-j (0.01 mol) and benzoyl isothiocyanate (2; 2.03 g, 0.0125 mol) in dry ether or peroxide free and dry tetrahydrofuran (15 ml) was either stirred at room temperature (11d-g) or refluxed (11a-c and 11h-j) for the stated time (Table 6). The crude products separated out as bright yellow or orange solid, which were filtered, washed with ether and further purified by crystallization from either ethyl acetate (13a-c) or ether: chloroform mixture (13d-g) (Table 6). In the reaction of 11h-j with 2, no solid was separated and the residue obtained after evaporation of the solvent was passed through a silica gel column. Elution with ethyl acetate: benzene (1:1) yielded pure pyrimidines 13h-j, which were further purified by crystallization from chloroform/hexane mixture (Table 6).

β-Methylthio(or N-ethylamino/anilino)-β-N-ethylamino/anilino-α-benzoylthiocarbamoyl-α-benzoyl/nitro-ethyle ethylenes (12d, 12h, 12k and 16b-d); 2-(benzoyl/nitro-benzoylthiocarbamoylmethylene)-imidazolidines (20a and 20b) : General Procedure:

A solution of keten-S,N-/N,N-acetal 11d, 11h, 11k, 15b-d and 19a-b (0.01 mol) and benzoyl isothiocyanate

(2) (2.03 g, 0.0125 mol) in ether/THF was refluxed for 0.5–10 hr. The open chain adducts separated out as orange copious precipitates were crystallized from chloroform (Table 7).

2,3-Substituted-4-benzoyl/nitro-5-benzoylamino-Δ^3-isothiazolines (14, 17a-d, 21a and 21b) : General procedure :

Method A : The isothiazolines 14 and 17a-d were obtained by refluxing the respective S,N- and N,N-acetals 11k and 15a-d; (0.01 mol) and benzoyl isothiocyanate (2; 2.03 g, 0.0125 mol) in either benzene (15a) or dry, peroxide free-tetrahydrofuran (11k and 15b-d) for 45 to 54 hr (Table 8). The isothiazolines 17a-d were separated as light brown solids which were further purified by crystallisation from mathanol: benzene mixture (17a-c) and chloroform (17d) (Table 8). The isothiazoline 14 was obtained by column chromatography of the reaction mixture over silica gel. Elution with hexane : benzene (3:1) gave pure 14 as light brown solid which were further purified by crystallization from chloroform (Table 8).

Method B : To an ice-cooled solution of the open-chain adducts 12k, 16b-d and 20a-b (0.001 mol) in dry chloroform (5 ml), bromine (160 mg, 0.001 mol) in dry chloroform (5 ml) was added dropwise during 10-15 min. After stirring at room temperature for 0.5 to 4 hr (monitored by t.l.c.), the reaction mixture was neutralised with 2N-NaOH solution, diluted with water (20 ml), and extracted with chloroform (2x20 ml), The chloroform layer was dried (Na_2SO_4) and evaporated to give crude isothiazolines, which were crystallized from methanol/benzene (17b-c and 21a-b or chloroform (14 and 17d) as light brown solids (Table 8).

TABLE 6

1-N-Ethyl/phenyl-2-phenyl-5-aroyl-6-methylthio/N-ethylamino-4-thioxopyrimidines (13a-j)

Product	Reaction[a] time(hr)	Yield (%)	Cryst. solvent	m.p. (°C)	Molecular formula	Calc. Found	Analysis(%) C	H	N
13a	18	80	EtOAc	158-	$C_{24}H_{18}N_2OS_2$		69.56	4.34	6.76
				160	(414)		69.21	4.64	6.82
13b	24	78	EtOAc	185-	$C_{24}H_{17}ClN_2OS_2$		64.28	3.79	6.24
				186	(448.5)		64.71	4.02	6.30
13c	20	76	EtOAc	149-	$C_{25}H_{20}N_2O_2S_2$		67.56	4.50	6.30
				150	(444)		67.31	4.71	6.41

Table 6 (Contd.)

13d	20	68	Et_2O:	202	$C_{20}H_{18}N_2OS_2$	65.57	4.91	7.65
			$CHCl_3$		(366)	65.32	4.74	7.32
13e	22	70	Et_2O:	200-	$C_{20}H_{17}ClN_2OS_2$	59.92	4.24	6.99
			$CHCl_3$	201	(400.5)	59.30	4.32	7.07
13f	26	68	Et_2O:	172-	$C_{21}H_{20}N_2O_2S_2$	63.63	5.05	7.07
			$CHCl_3$	174	(396)	63.22	4.84	7.19
13g	20	67	Et_2O:	193-	$C_{21}H_{20}N_2OS_2$	66.31	5.26	7.36
			$CHCl_3$	195	(380)	66.60	5.35	7.55

Table 6 (Contd.)

13h	24	42	$CHCl_3$:	179-	$C_{21}H_{21}N_3O_3$	69.42	5.78	11.57
			hexane	181	(363)	69.04	5.61	11.32
13i	10	35	$CHCl_3$:	159-	$C_{21}H_{20}ClN_3OS$	63.39	5.03	10.56
			hexane	161	(397.5)	63.77	4.88	10.29
13j	32	38	$CHCl_3$:	151-	$C_{22}H_{23}N_3O_2S$	67.17	5.85	10.68
			hexane	152	(393)	66.83	5.71	10.58

---

[a] Reaction solvents = ether (13a-c) and THF (13d-j).

TABLE 7

β-Anilino/N-ethylamino(or methylthio)-β-anilino/N-ethylamino-α-benzoylthiocarbanoyl-α-benzoyl/nitroethylenes (12d, 12h, 12k and 16b-d); 2-(benzoyl/nitrobenzoylthiocarbanoyl) methylene - imidazolidines 20 (a, b)

Product[a]	Reaction solvent	Reaction time(hr)	Yield (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis(%) C	H	N
12d	ether	0.5	80	125-	$C_{20}H_{20}N_2O_2S_2$		62.94	5.24	7.28
				126	(384.5)		62.48	4.95	7.73
12h	ether	0.5	75	129-	$C_{21}H_{23}N_3O_2S$		66.11	6.08	11.01
				130	(381.5)		66.42	6.43	11.42
12k	ether	10	82	126-	$C_{29}H_{23}N_3O_2S$		72.93	4.85	8.80
				127	(477.6)		72.35	4.53	8.48

Table 7 (Contd.)

16b	ether	8	77	125–	$C_{13}H_{15}N_3O_3S_2$	48.00	4.61	12.92
				127	(325.4)	47.74	4.33	13.20
16c	ether	2	78	130–	$C_{14}H_{18}N_4O_3S$	52.17	5.59	17.39
				131	(322.4)	51.80	5.41	17.58
16d	ether	15	75	148–	$C_{22}H_{18}N_4O_3S$	63.15	4.30	13.39
				150	(418.5)	62.81	4.19	13.50
20a	ether/	4	87	145–	$C_{12}H_{12}N_4O_3S$	49.32	4.11	19.18
	THF			146	(292.3)	49.87	4.60	19.43
20b	ether/	3	77	155	$C_{19}H_{17}N_3O_2S$	64.96	4.84	11.97
	THF				(351.4)	64.35	4.32	11.43

---

[a] Crystallization solvent = $CHCl_3$.

TABLE 8

2-N-Ethyl/phenyl-3-anilino/N-ethylamino(or methylthio-4-benzoyl/nitro-5-benzoylimino-Δ^3-isothiazolines (14 and 17a-d); 2,3-fused-4-benzoyl/nitro-5-benzoylimino-Δ^3-isothiazolines 21 (a-b)

Product[a]	Reaction solvent	Reaction time(hr)	Yield[b] (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis(%) C	H	N
17a	benzene	54	39	210–212	$C_{17}H_{13}N_3O_3S_2$ (371.4)	Calc.	54.98	3.50	11.32
						Found	55.36	3.38	11.19
17b	THF	54	55(60)[c]	151–153	$C_{13}H_{13}N_3O_3S_2$ (323.4)	Calc.	48.29	4.02	13.00
						Found	48.55	3.81	13.18
17c	THF	45	52(59)[c]	173–174	$C_{14}H_{16}N_4O_3S$ (320.4)	Calc.	52.50	5.00	17.50
						Found	52.84	4.87	17.63

Table 8 (Contd.)

17d	THF	52	46(55)[c]	257-	$C_{22}H_{16}N_4O_3S$	63.46	3.84	13.46
				258	(416.5)	63.79	3.91	13.62
21a	-	-	(70)[c]	210-	$C_{12}H_{10}N_4O_3S$	49.64	3.47	19.29
				211	(290.3)	49.22	3.15	18.58
21b	-	-	(74)[c]	192-	$C_{19}H_{15}N_3O_2S$	65.31	4.32	12.02
				193	(349.4)	64.77	4.02	11.61
14	THF	45	35(52)[c]	196-	$C_{29}H_{21}N_3O_2S$	73.26	4.42	8.89
				198	(475.6)	73.51	4.27	8.99

---

[a] Crystallization solvent = methanol:benzene (17a-c, 21a and 21b) and $CHCl_3$ (14 and 17d).

[b] The yields described are those from method A.

[c] The yields in parentheses are those from method B.

REFERENCES

1. (a) D.J. Brown in, 'The Pyrimidines', Chapter VIII, pp. 272-282; Chapter VII, pp. 251; Chapter VI, pp. 206, Interscience Publisheres, New York (1962).
   (b) D.J. Brown in, 'The Pyrimidines', Supplement I, Chapter VIII, pp. 202, Interscience Publisheres, New York (1970).
2. D.J. Brown, E. Hoerger, and S.F. Mason, J. Chem. Soc. 211 (1955).
3. M.E. Keuhne in, 'Enamine Synthesis, Structure and Reactions', Chapter 8, (edited by A.G. Cook) Mercer Dekker Inc. (1969).
4. H. Ulrich in, 'Cycloaddition Reactions of Heterocumulenes', (edited by A.T. Blomquist) Chapter V, pp. 220, Academic Press, New York (1967).
5. G. de Stevens, B. Smolinsky, L. Dorfman, J. Org. Chem. 29, 1115 (1964).
6. J. Goerdeler, H.W. Pohland, Chem. Ber. 96, 526 (1963).
7. J. Goerdeler, Angew. Chem. 75, 941 (1963).
8. J. Goerdeler and U. Keuser, Chem. Ber. 97, 2209, 3106 (1964).

9. J. Goerdeler and J. Gnad, Chem. Ber. 98, 1531 (1965).

10. J. Goerdeler and H. Pohland, Chem. Ber. 94, 2950 (1961).

11. S. Rajappa, R. Sreenivasan and B.G. Advani, Ind. J. Chem. 15B, 297 (1977).

12. R.W.J. Carney, J. Wojtkunski, G. de Stevens, J. Org. Chem. 29, 2887 (1964).

13. H.M. Blatter and H. Lukaszewski, J. Org. Chem. 31, 722 (1966).

14. R.W. Lamon, Tetrahedron Letters, 3957 (1970).

15. S. Hünig and K. Hübner, Chem. Ber. 95, 937 (1962).

16. (a) Handbook of preparative Inorganic Chemistry by G. Brauer, Vol.1, Acad. Press, New York (1963).
(b) T.B. Johnson and L.H. Chernoff, J. Amer. Chem. Soc., 167 (1912).

CHAPTER 6

POLARIZED KETEN-S,N- AND N,N-ACETALS AS NOVEL ENAMINE COMPONENTS FOR THE NENITZESCU 5-HYDROXYINDOLE SYNTHESIS*

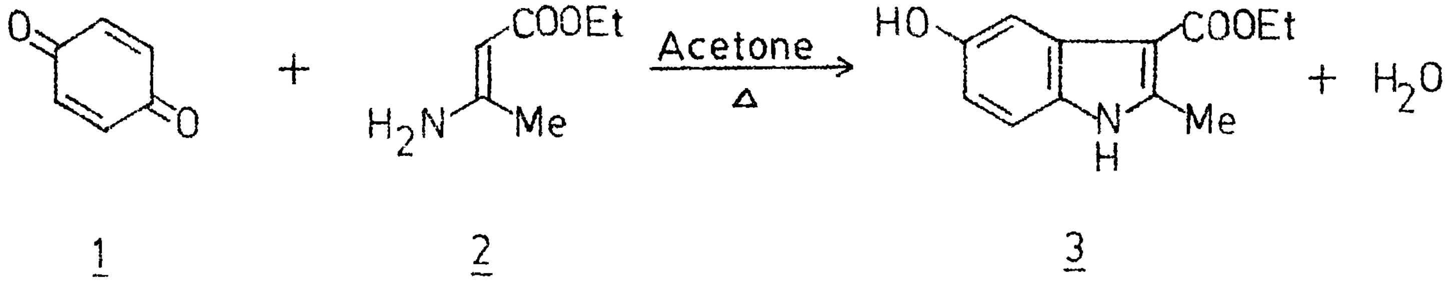
6.1 Introduction

The reaction of p-benzoquinone with ethyl 3-aminocrotonate (2) in refluxing acetone to yield ethyl 5-hydroxy-2-methylindole-3-carboxylate (3) (Scheme 1) was discovered by Nenitzescu[1] in 1929. The method however, did not find its use for over three decades, until the importance of indole derivatives containing 5-hydroxy group was discovered, having physiologically important properties. The interest in melanin and related substances and the discovery of 5-hydroxytryptamine (serotonin) as a vasoconstrictor, initiated the reviewed interest in the chemistry of 5-hydroxyindole derivatives. Although, the final yields of 5-hydroxyindoles in Nenitzescu indole synthesis are comparatively low, the simplicity of reactants involved and the ease with which the reaction occurs,

---

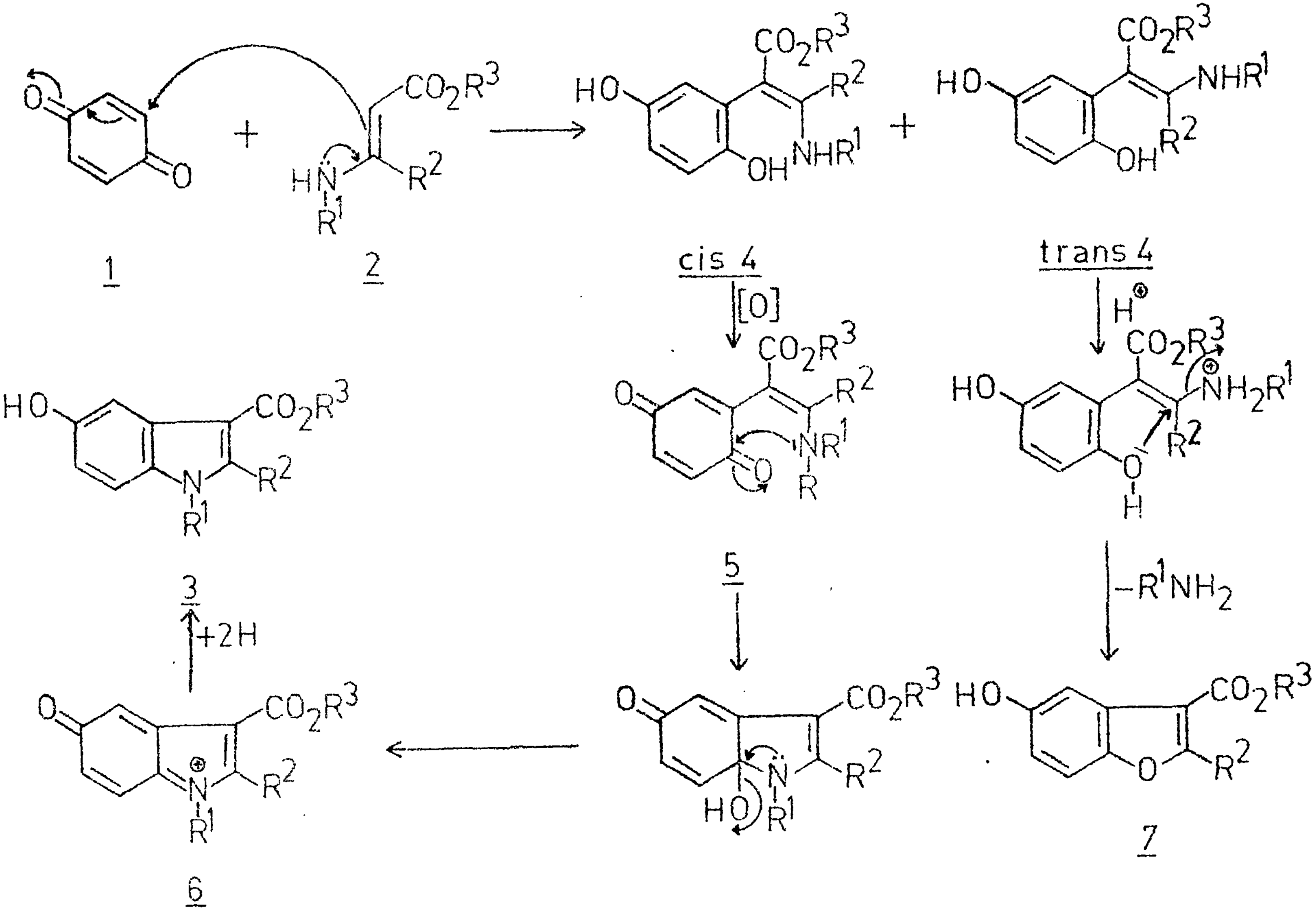
* V. Aggarwal, A. Kumar, H. Ila and H. Junjappa, Synthesis, 157 (1981).

Scheme 1



makes the method attractive. Since 1950, much interest is shown in this method and consequently the synthesis of a large number of 5-hydroxyindole derivatives has been reported.[2-6] All the reactions reported for the synthesis of 5-hydroxyindoles require the choice of two kinds of reactants (a) an enamine component (b) the 1,4-benzoquinone component. The enamine components used in this reaction have been mainly derived from the reaction of ammonia or primary amines with β-ketoesters, 1,3-diketo diketones and 1,3-cyclicdiones. One of the serious limitations of the use of these enamines is their β-substituents (alkyl, phenyl, or carbalkoxy), which are carried to the 2-position of the product indole and cannot be subsequently removed except when it is carbalkoxy group. There is only one report[7] of the preparation of 2-ethoxy-5-hydroxyindole by the reaction of ethyl β-amino-β-ethoxyacrylate with 1,4-benzoquinone. The mechanism of the reaction of an enamine with 1,4-benzoquinone is shown in Scheme 2 .[7-14] The enamine through its α-carbon adds Michaelwise to 1,4-benzoquinone with the formation of hydroquinone adduct 4. The two geometrical isomers of the adduct, cis-4 and trans-4, can cyclize either to indole 3 or furan 7[7,9] respectively. The

Scheme 2



cis-4 isomer was shown to undergo subsequent oxidation either by the starting quinone or by quinonimmonium intermediate 6 to give the quinone adduct 5, which undergoes intramolecular cyclisation via 6 to the indole 3.

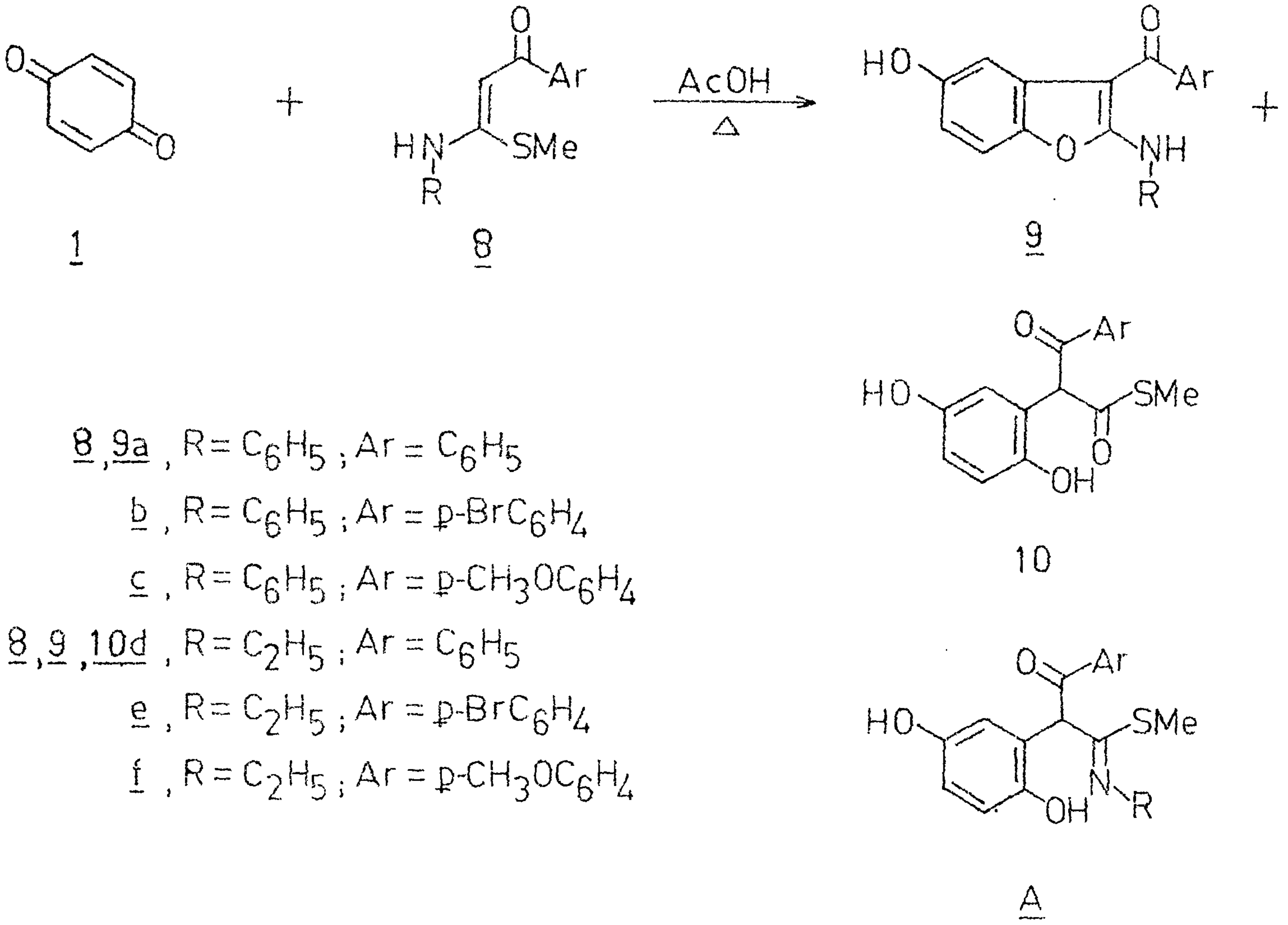
It is evident from the mechanism of Nenitzescu indole synthesis that the keten-S,N- and N,N-acetals should also function as useful enamine components, providing an important synthetic variation in 5-hydroxyindoles. The synthesis of these acetals from diverse active methylene compounds (Chapter 3) constitutes a wide scope for liberal structural variation.

6.2 Results and discussion

Investigation of the reaction of a few selected polarized keten-S,N- and N,N-acetals with 1,4-benzoquinone was undertaken, with a view to studying the scope of synthetic applications of these acetals as enamine components in the Nenitzescu indole synthesis.

Thus, when 1,4-benzoquinone and the S,N-acetal 8a (Scheme 3) were refluxed in glacial acetic acid, the compound 9a (24% yield) was obtained, which was identified as 2-anilino-3-benzoyl-5-hydroxybenzofuran rather than the corresponding indole.[15-17] The structure of 9a was confirmed by its analytical (Table 4) and spectral (Table 1) data. Thus, its mass spectrum showed a molecular ion peak at M^+ (329) and was analysed for $C_{21}H_{15}NO_3$. Its IR showed weak bands at 3280 cm^{-1}(ν_{OH}) and 3200 cm^{-1}(ν_{NH}) and a broad band at 1635 cm^{-1} which was attributed to carbonyl stretching vibrations. Further confirmation of the structure was obtained from its NMR spectrum. Thus, the doublet at δ 5.95 with coupling constant J=2.5 Hz, was assigned to 4-H proton, accounting for meta coupling. The double doublet at δ 6.43 was assigned to 6-H proton with coupling constants, J=8.5 Hz and 2.5 Hz, accounting for ortho and meta couplings respectively. Similarly, the doublet at δ 6.80 (J=8.5 Hz), accounting for ortho coupling was assigned to 7-H proton. The broad signal between δ 7.00-7.30 (10H) was assigned to the aromatic protons of the two phenyl rings. Similarly, 1 when reacted with 8b and 8c under identical conditions, yielded the corresponding 9b and 9c in 26% and 24% yields respectively. Their analytical and spectral data are described in table 4 and table 1 respectively. However, no trace of indole was observed in these reactions. When R in 8 was

Scheme 3



$\underline{8}$, $\underline{9a}$, R = C_6H_5 ; Ar = C_6H_5

$\underline{b}$, R = C_6H_5 ; Ar = p-BrC_6H_4

$\underline{c}$, R = C_6H_5 ; Ar = p-$CH_3OC_6H_4$

$\underline{8}$, $\underline{9}$, $\underline{10d}$, R = C_2H_5 ; Ar = C_6H_5

$\underline{e}$, R = C_2H_5 ; Ar = p-BrC_6H_4

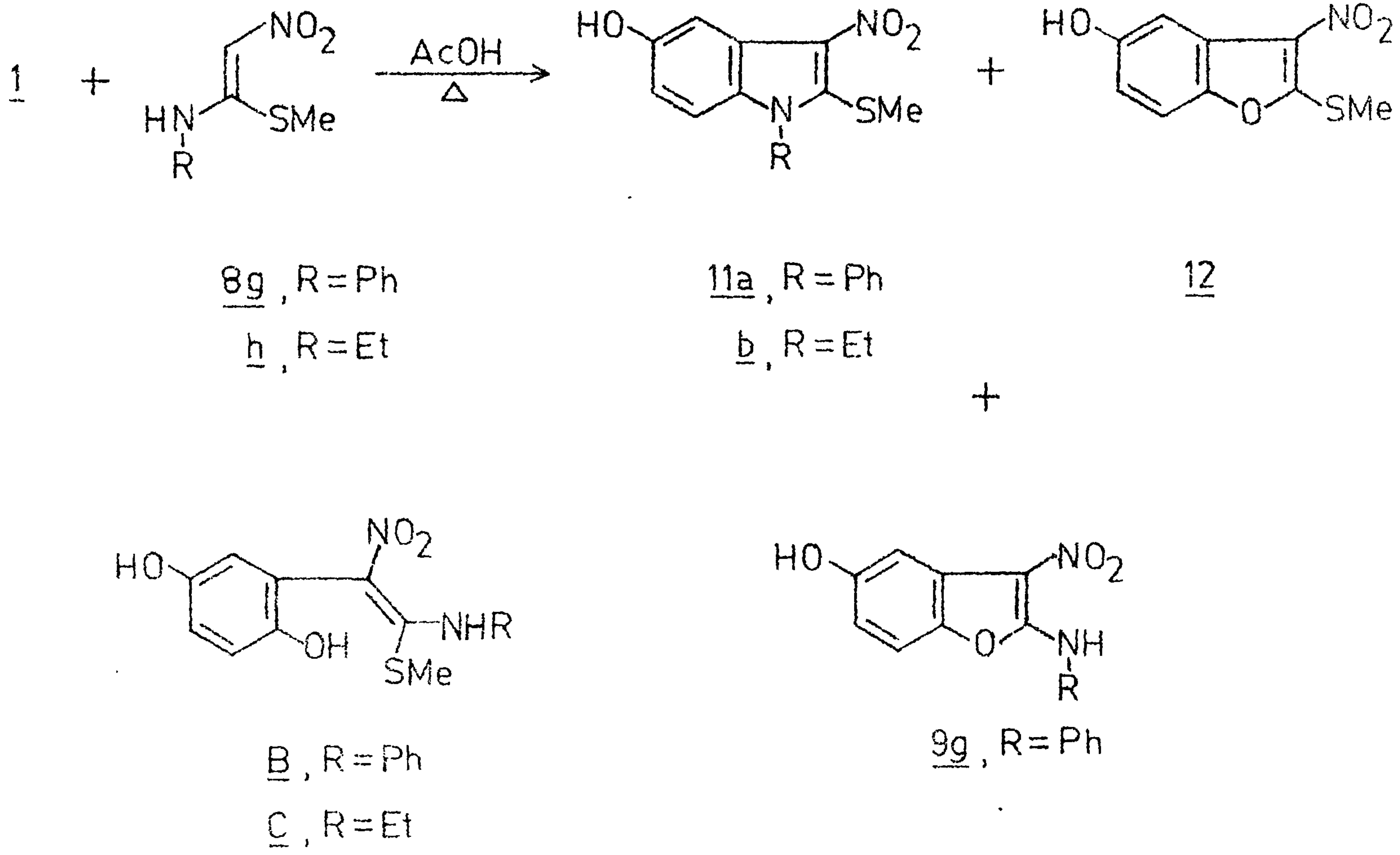
$\underline{f}$, R = C_2H_5 ; Ar = p-$CH_3OC_6H_4$

changed from phenyl to ethyl, there was no change in the course of reaction except that an open chain compound 10 was formed in addition to the corresponding benzofurans. Thus, when 1 was reacted with 8d in refluxing acetic acid, a mixture of benzofuran (9d) (22%) and the corresponding hydroquinone adduct (10d) (21%) was obtained, which were subsequently separated by column chromatography. Similarly, 1 when reacted with 8e and 8f in refluxing glacial acetic acid, gave the corresponding benzofurans 9e (27%) and 9f (23%), along with the corresponding hydroquinone adducts 10e (19%) and 10f (16%), which are formed by hydrolysis of the imine intermediate A. The analytical (Table 4) and spectral (Table 1) data of 9d-f are in conformity with their structures assigned. Also, the analytical (Table 4) and spectral (Table 2) data of 10d-f are in accordance with the assigned structures.

However, when 1 was reacted with nitroketen-S,N-acetal 8g (Scheme 4) in refluxing glacial acetic acid, a mixture of three products was obtained which were separated by column chromatography. The inseparable 11a and 12 were eluted together and were subsequently separated by fractional crystallization in 19% and 20%

yields respectively. The third compound 9g was isolated in pure form from the column in 11% yield. The synthesis of 1-phenyl-2-thiomethyl-3-nitro-5-hydroxyindole (11a) constitutes a novel variant of Nenitzescu indole synthesis, wherein, the enamine component is derived from nitromethane. The structure of 11a was confirmed by its analytical (Table 6) and spectral (Table 3) data. Its mass spectrum showed a molecular ion peak at M$^+$ 300 ($C_{15}H_{12}N_2O_3S$). Its IR spectrum showed a band at 3300 cm^{-1} (ν_{OH}) and two sharp bands at 1590 cm^{-1} and 1352 cm^{-1}, characteristic stretching vibrations for nitro group. Its structure was further confirmed by its NMR spectrum. The singlet at δ2.31 (3H) was assigned to methylthio protons. The doublet at δ 6.44 (1H) with coupling constant J=2.0 Hz was attributed to 4-H, accounting for its meta coupling. The double doublet at δ 6.96 was assigned to 6-H with characteristic ortho (J=8.5 Hz) and meta (J=2.0 Hz) couplings. The multiplet at δ7.66 (5H) was assigned to the aromatic protons of the N-phenyl ring. The doublet at δ8.04 (J=8.5 Hz) was due to 7-H proton. The broad singlet at δ 9.70 (1H) accounted for the hydroxy proton. The structures of 9g and 12 were similarly assigned on the basis of their analytical and spectral data as described in table 4

Scheme 4



8g, R = Ph
h, R = Et

11a, R = Ph
b, R = Et

12

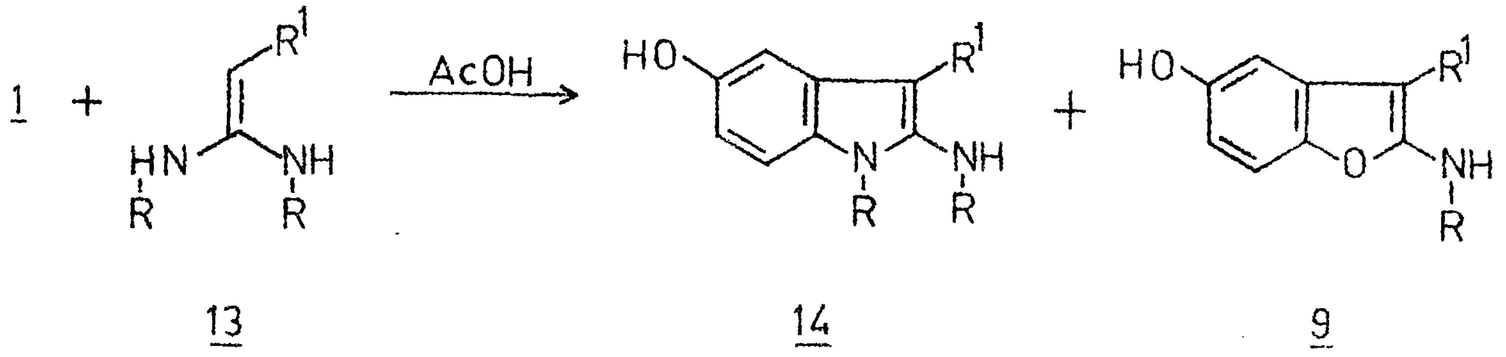
B, R = Ph
C, R = Et

9g, R = Ph

and table 1 respectively. The benzofurans 12 and 9g are formed by elimination of either anilino or methylthio group respectively from the Michael adduct B. However, when 1 was reacted with 8h under similar conditions, the corresponding indole 11b was formed in 19% yield, along with only 2-methylthiobenzofuran 12 (16%) with no trace of the corresponding 2-N-ethylaminobenzofuran. It appears that in the presence of acetic acid the protonated ethylamino group in the adduct C preferentially acts as a leaving group over its mercapto counterpart, thus yielding 2-methythiobenzofuran rather than its 2-N-ethylamino analogue. The analytical (Table 6) and spectral (Table 3) data of 11b is described.

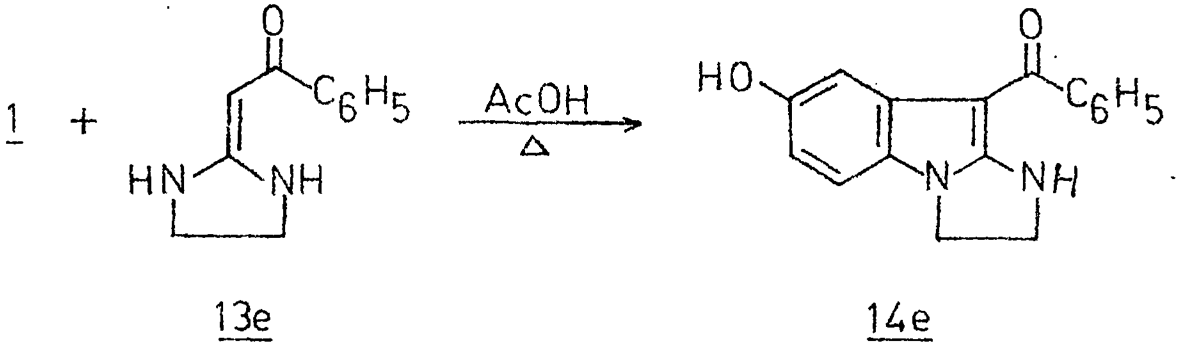
When the reaction of 1 was extended to the keten-N,N-acetals 13 (Scheme 5), derived from acetophenone and nitromethane under similar conditions, a mixture of indole 14 and benzofuran 9 was obtained, which were separated by column chromatography. Thus, 1 and 13a, when refluxed in glacial acetic acid, the corresponding indole 14a was obtained in 21% yield, while the benzofuran 9a was obtained in 15% yield. Similarly, 1 and 13b gave the corresponding indole

Scheme 5



13, 14a, R = Ph ; R^1 = COPh
b, R = Et ; R^1 = COPh
c, R = Ph ; R = NO_2
d, R = Et ; R = NO_2

9a, R = Ph ; R^1 = COPh
d, R = Et ; R^1 = COPh
g, R = Ph ; R^1 = NO_2
h, R = Et ; R = NO_2



14b in 33% yield along with benzofuran 9d in only 6% yield. Interestingly, when 1 was reacted with nitroketen-N,N-diphenylacetal 13c, the corresponding indole 14c was obtained in 70% yield while the complementary benzofuran 9g was obtained in only 6% yield. The yield of the indole 14d lowered to 21%, when nitroketen-N,N-diethylacetal 13d was reacted with 1, while that of the corresponding benzofuran 9h increased to 29%. The structures of the indoles 14a-d and the benzofurans 9a, 9d, 9g and 9h were fully in conformity with their analytical (Table 6 and 4 respectively) and spectral data (Table 3 and 1).

When this reaction was extended to cyclic keten-N,N-acetal 13e, the tricyclic indole 14e was obtained in 9% yield. Its analytical and spectral properties are given in table 6 and table 3 respectively.

Apparently, the keten-S,N- and N,N-acetals derived from various active methylene compounds, have behaved like the family of enamines in their chemical reactivity towards 1,4-benzoquinone. The application of N,N-acetals to yield 2-amino-3-nitro-5-hydroxyindoles, is the first report of 2-amino-3-nitro-indole synthesis through Nenitzescu reaction. These indoles are of particular interest, since the nitro group can be reduced to yield 2,3-diamino-indoles, which are excellent precursors for the construction of various heterocylces on the basis of *o*-phenylenediamine. Thus, in one of the examples 14c, attempted reduction with hydrogen over Raney-Ni (Scheme 6) yielded a compound, which was assigned the structure 16 tentatively, on the basis of its IR and mass spectrum. The elucidation of the final structure of compound 16 is in progress.

Scheme 6

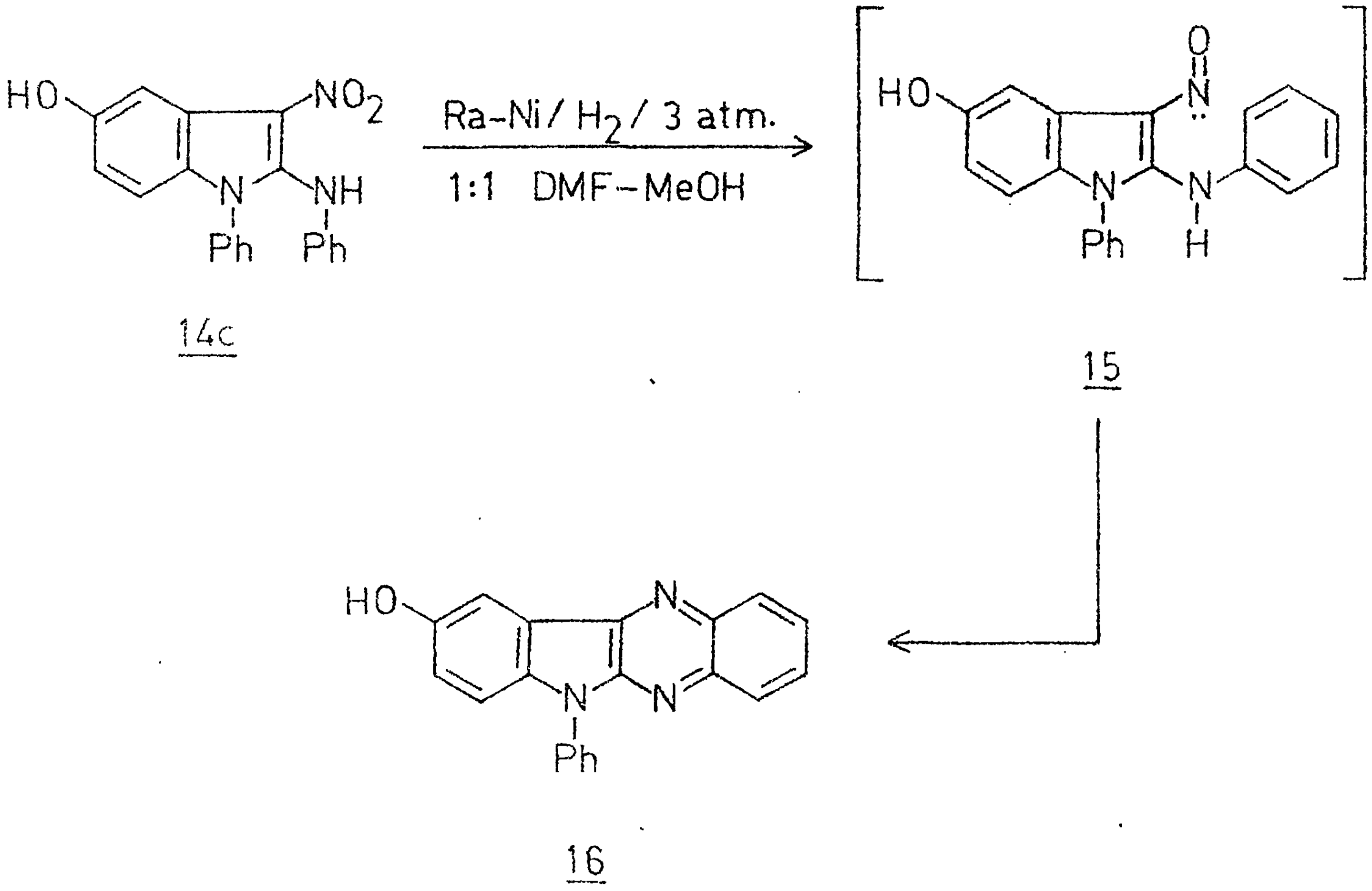

HO
NO2
NH
N
Ph
Ph
14c
Ra-Ni / H2 / 3 atm.
1:1 DMF–MeOH
HO
O
N:
N
N
Ph
H
15
HO
N
N
N
Ph
16

TABLE 1

Spectral data of benzofurans 9 (a-h) and 12

Product	IR(cm^{-1})	^{1}H-NMR(δ/ppm)	M.S. m/e(M^+)
9a	3280 (ν_{OH}); 3200 (ν_{NH}); 1635 (ν_{CO})^a	5.95 (d, 1H, H-4, J=2.5 Hz); 6.43 (dd, 1H, H-6, J=8.5 Hz, 2.5 Hz); 6.80 (d, 1H, H-7, J=8.5 Hz); 7.00-7.30 (m, 10H_{arom}).^{c}	329
9b	3375 (ν_{OH}); 3250 (ν_{NH}); 1620 (ν_{CO})^b	6.08 (d, 1H, H-4, J = 2.0 Hz); 6.23 (dd, 1H, H-6, J = 8.5 Hz, 2.0 Hz); 7.00 (d, 1H, H-7, J= 8.5 Hz); 7.10-7.80 (m, 9H_{arom}).^{c}	408

Table 1 (Contd.)

9c	3225 (ν_{OH}); 3175 (ν_{NH}); 1628 (ν_{CO})[b]	4.01 (s, 3H, OC$\underline{H}_3$); 6.68 (d, 1H, $\underline{H}$-4, J = 2.5 Hz); 6.94 (dd, 1H, $\underline{H}$-6, J = 9.0 Hz, 2.5 Hz); 7.20 (d, 1H, $\underline{H}$-7, J = 9.0 Hz); 7.22-7.92 (m, 9H$_{arom}$).[c]	-
9d	3260 (ν_{OH}); 3190 (ν_{NH}); 1635(ν_{CO})[a]	1.05 (t, 3H, CH$_2$C$\underline{H}_3$); 3.53 (br q, 2H, C$\underline{H}_2$CH$_3$); 5.98 (d, 1H, $\underline{H}$-4, J=2.5 Hz); 6.55 (dd, 1H, $\underline{H}$-6, J= 8.5 Hz, 2.5 Hz); 6.91 (d, 1H, $\underline{H}$-7, J = 8.5 Hz); 7.06-7.40 (m, 5H$_{arom}$).[c]	281

Table 1 (Contd.)

9e	3210 (ν_{OH}); 3160 (ν_{NH}); 1625 (ν_{CO})[b]	1.16 (t, 3H, $CH_2C\underline{H}_3$); 3.58 (br q, 2H, $C\underline{H}_2CH_3$); 5.98 (d, 1H, $\underline{H}$-4, J = 2.5 Hz); 6.48 (dd, 1H, $\underline{H}$-6, J = 8.5 Hz, 2.5 Hz); 6.80 (d, 1H, $\underline{H}$-7, J = 8.5 Hz); 7.23 (A_2B_2 dd, $4H_{arom}$).[c]	360
9f	3220 (ν_{OH}); 3160 (ν_{NH}); 1645 (ν_{CO})[a]	1.55 (t, 3H, $CH_2C\underline{H}_3$); 3.88 (br q, 2H, $C\underline{H}_2CH_3$); 4.06 (s, 3H, $OC\underline{H}_3$); 6.60 (d, 1H, $\underline{H}$-4, J = 2.5 Hz); 6.92 (dd, 1H, $\underline{H}$-6, J = 8.5 Hz, 2.5 Hz); 7.32 (d, 1H, $\underline{H}$-7, J = 8.5 Hz), 7.48 A_2B_2 dd, $4H_{arom}$).[c]	–

Table 1 (Contd.)

9g	3340 (ν_{OH}); 3175 (ν_{NH}); 1510, 1355 (ν_{NO_2})^b	6.66 (dd, 1H, H-6, J = 8.5 Hz, 2.5 Hz); 7.11–7.80 (m, 7H$_{arom}$); 9.50 (s, 1H, OH); 10.90 (br s, 1H, NH).^{d}	270
9h	3275 (ν_{OH}); 3260 (ν_{NH}); 1595, 1385 (ν_{NO_2})^b	1.26 (t, 3H, CH_2CH_3); 3.60 (q, 2H, CH_2CH_3); 6.60 (dd, 1H, H-6, J = 9.0 Hz, 3.0 Hz); 7.26 (d, 1H, H-4, J = 3.0 Hz); 7.30 (d, 1H, H-7, J = 9.0 Hz); 9.28–9.50 (br, 2H, NH and OH).^{d}	222

Table 1 (Contd.)

12	3365 (ν_{OH}); 1518 1365 (ν_{NO_2})[a]	2.76 (s, 3H, SC$\underline{H}_3$); 6.82 (dd, 1H, $\underline{H}$-6, J = 8.5 Hz, 2.5 Hz); 7.32 (d, 1H, $\underline{H}$-4, J = 2.5 Hz); 7.45 (d, 1H, $\underline{H}$-7, J = 8.5 Hz); 9.75 (s, 1H, O$\underline{H}$).[d]	225

---

[a] in nujol; [b] in KBr;

[c] in TFA; [d] in DMSO-d_6.

TABLE 2

Spectral data of products 10 (d-f)

Product	IR(cm^{-1})	^{1}H-NMR(δ/ppm)	M.S. m/e(M$^+$)
10d	3400, 3390 (ν_{OH}); 1710, 1670 (ν_{CO})^a	2.18 (s, 3H, SCH$_3$); 3.67 (s, 1H, CHCO); 6.55-7.20 (m, 3H$_{arom}$); 7.85 (m, 5H$_{arom}$).^{c}	-
10e	3400, 3380 (ν_{OH}); 1720, 1670 (ν_{CO})^a	2.30 (s, 3H, SCH$_3$); 3.84 (s, 1H, CHCO); 6.85-7.05 (m, 3H$_{arom}$); 7.97 (A$_2$B$_2$ dd, 4H$_{arom}$).^{c}	381

Table 2 (contd.)

10f	3400 (ν_{OH}); 1715, 1675 (ν_{CO})[b]	2.28 (s, 3H, $SC\underline{H}_3$); 3.97 (s, 3H, $OC\underline{H}_3$); 3.75 (s, 1H, $C\underline{H}CO$); 6.74–7.10 (m, $3H_{arom}$); 7.80 (m, $5H_{arom}$).[c]	–

---

[a] in KBr; [b] in nujol; [c] in TFA.

TABLE 3

Spectral data of indoles 14 (a-e) and 11 (a,b)

Product	IR(cm^{-1})	^{1}H-NMR(δ/ppm)	M.S. m/e(M$^+$)
14a	3240 (ν_{OH}); 3160 (ν_{NH}); 1590 (ν_{CO})^a	6.56 (d, 1H, $\underline{H}$-4, J = 2.0 Hz); 6.74 (br s, 5H$_{arom}$); 6.82 (dd, 1H, $\underline{H}$-6, J = 8.5 Hz, 2.0 Hz); 7.20-7.60 (m, 11H, 10H$_{arom}$+ $\underline{H}$-7); 8.86 (br s, 1H, N$\underline{H}$); 9.52 (s, 1H, O$\underline{H}$).^{c}	404
14b	3350 (ν_{OH}); 3130 (ν_{NH}); 1595 (ν_{CO})^b	1.36 (t, 3H, $CH_2C\underline{H}_3$); 1.50 (t, 3H, $CH_2C\underline{H}_3$); 3.58 (q, 2H, $C\underline{H}_2CH_3$); 4.12 (q, 2H, $C\underline{H}_2CH_3$); 6.16	308

Table 3 (Contd.)

		(d, 1H, H-4, J = 2.5 Hz); 6.53 (dd, 1H, H-6, J = 8.0 Hz, 2.5 Hz); 6.92 (d, 1H, H-7, J = 8.0 Hz); 7.28-7.72 (m, $5H_{arom}$); 8.00 (br, 1H, OH); 9.13 (br t, 1H, NH).[c]	
14c	3400 (ν_{OH}); 3130 (ν_{NH}); 1570, 1365 (ν_{NO_2})[b]	6.38 (d, 1H, H-4, J = 2.5 Hz); 6.81 (dd, 1H, H-6, J = 8.5 Hz, 2.5 Hz); 7.00 (m, $5H_{arom}$); 7.94 (d, 1H, H-7, J = 8.5 Hz); 8.50 (br s, 1H, NH); 9.65 (s, 1H, OH).[c]	345

Table 3 (Contd.)

14d	3400 (ν_{OH}); 3240 (ν_{NH}); 1540, 1340 (ν_{NO_2})[a]	1.31 (t, 6H, two $CH_2C\underline{H}_3$); 3.72 (br.q, 2H, $C\underline{H}_2CH_3$); 4.20 (q, 2H, $C\underline{H}_2CH_3$); 6.67 (dd, 1H, $\underline{H}$-6, J = 8.0 Hz, 2.5 Hz); 7.21 (d, 1H, $\underline{H}$-7, J=8.0 Hz); 7.45 (d, 1H, $\underline{H}$-4, J = 2.5 Hz); 8.50-8.83 (br, 1H, N$\underline{H}$); 9.11 (s, 1H, O$\underline{H}$).[c]	249
14e	3380 (ν_{OH}); 3075 (ν_{NH}); 1520 (ν_{CO})[b]	3.97 (s, 4H, $-C\underline{H}_2C\underline{H}_2-$); 6.36 (dd, 1H, H-6, J = 9.0 Hz, 3.0 Hz); 6.62 (d, 1H, $\underline{H}$-4, J = 3.0 Hz); 6.82 (d, 1H, $\underline{H}$-7, J = 9.0 Hz); 7.48 (m, $5H_{arom}$); 8.57 (s, 1H, O$\underline{H}$).[c]	278

Table 3 (Contd.)

11a	3300 (ν_{OH}); 1590 1352 (ν_{NO_2})^b	2.31 (s, 3H, SC$\underline{H}_3$); 6.44 (d, 1H, $\underline{H}$-4, J = 2.0 Hz); 6.96 (dd, 1H, $\underline{H}$-6, J = 8.5 Hz, 2.0 Hz); 7.66 (m, 5$\underline{H}_{arom}$); 8.04 (d, 1H, $\underline{H}$-7, J = 8.5 Hz); 9.70 (br.s, 1H, O$\underline{H}$).^{c}	300
11b	3330 (ν_{OH}); 1510 1350 (ν_{NO_2})^a	1.32 (t, 3H, CH$_2$C$\underline{H}_3$); 2.60 (s, 3H, SC$\underline{H}_3$); 4.44 (q, 2H, C$\underline{H}_2$CH$_3$); 7.00 (dd, 1H, $\underline{H}$-6, J = 8.0 Hz, 2.5 Hz); 7.05 (d, 1H, $\underline{H}$-4, J = 2.5 Hz); 8.04 (d, 1H, $\underline{H}$-7, J = 8.0 Hz); 9.80 (s, 1H, O$\underline{H}$).^{c}	252

---

[a] in nujol; [b] in KBr; [c] in DMSO-d_6.

EXPERIMENTAL

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

The starting materials

The commercial sample of p-benzoquinone was purified by crystallization from acetic acid.

The keten-S,N-acetals 8a-h and N,N-acetals 13a-e required, were prepared as described in chapter 2.

Preparation of 2-anilino/N-ethylamino-3-aroyl-5-hydroxybenzofurans (9a-f); 2-(-aroyl-thiocarbomethoxy)methyl-1,4-hydroquinones(10d-f) from ketoketen-S,N-acetals 8a-f: General Procedure:

A mixture of keten-S,N-acetal 8 (0.01 mol) and 1,4-benzoquinone (1) (1.3 g, 0.012 mol) in gl. AcOH

(50 ml) was heated under reflux for 0.5 to 1 hr. Removal of the solvent under reduced pressure gave tarry residues, which were column chromatographed over silica gel. Elution with 1% ethyl acetate in benzene gave the benzofurans 9a-f, which were further purified by crystallization from ethyl acetate/hexane (Table 4). Further elution with 5% ethyl acetate in benzene gave the adducts 10d-f, which were further purified by crystallization from ethyl acetate/benzene (Table 5).

Preparation of 2-anilino/methylthio-3-nitro-5-hydroxybenzofurans (9g and 12); 1-N-ethyl/phenyl-2-methylthio-3-nitro-5-hydroxyindoles (11a and 11b) from nitroketen-S,N-acetals 8g-h: General Procedure.

A mixture of S,N-acetal 8 (0.01 mol) and 1,4-benzoquinone (1) (1.3 g, 0.012 mol) in gl. AcOH (50 ml) was refluxed for 0.5 hr and the solvent removed under reduced pressure to give tarry residues which were column chromatographed over silica gel. The residue obtained from the reaction of 8g with 1 was eluted with 1% ethyl acetate in benzene to yield a mixture of 11a and 12 as a yellow solid, which were separated by fractional crystallization (ethyl acetate/hexane). Further elution with 5% ethyl acetate in benzene gave the furan 9g (Table 4).

The residue obtained from 8h and 1, on elution with 1% ethyl acetate in benzene gave the furan 12 (Table 4) and further elution with 5% ethyl acetate in benzene gave the indole 11b (Table 6), which were further purified by crystallization from ethyl acetate/hexane and ethyl acetate/benzene respectively.

Preparation of 2-anilino/N-ethylamino-3-benzoyl/nitro-5-hydroxybenzofurans (9a, 9d, 9g and 9h); 1,2-disubstituted-3-benzoyl/nitro-5-hydroxyindoles (14a-e) from keten-N,N-acetals 13a-e : General Procedure:

A mixture of keten-N,N-acetal 13 (0.01 mol) and 1 (1.3 g, 0.012 mol) in gl. AcOH (50 ml) was refluxed for 0.5 hr and the solvent removed under reduced pressure to give tarry residues which were column chromatographed.

Elution with 1% ethyl acetate in benzene gave benzofurans 9a, 9d, 9g and 9h and further elution with 5% ethyl acetate in benzene gave the corresponding indoles 14a-d. The residue obtained from 13e and 1, gave the cyclic indole 14e on elution with ethyl acetate/chloroform (1:4). The furans 9a, 9d, 9g and 9h (Table 4) and indoles 14a-e (Table 6) were further purified by crystallization.

Hydrogenation of 3-nitroindole 14c: To a solution of indole 14c (0.69g, 0.002 mol) in DMF/MeOH (1:1), Reney-Ni (1.5g) was added and the mixture was hydrogenated over hydrogen at 48 p.s.i. for 4 hr. After completion of the reaction (when no more hydrogen was absorbed), Raney-Ni was filtered off and the filtrate diluted with water (to remove DMF), extracted with ethyl acetate, dried (Na_2SO_4) and concentrated to give an orange coloured solid which on crystallization from ethyl acetate/methanol yielded pure 16, 0.41 g (66%), m.p. 271-274°C; M.S.:(m/e):M^+, 311; IR ν_{max}(nujol):3220 (OH) cm^{-1}, 1662 (w,C=N) cm^{-1}, 1612 (s,C=C) cm^{-1}; Found: C, 76.70%; H, 3.86%; N, 13.18%; Calc: C, 77.17%; H, 4.18%; N, 13.50%.

The fused quinoxaline 16 was insoluble in $CDCl_3$, DMSO-d_6, $(CD_3)_2C=O$ and TFA, therefore, its NMR spectrum could not be recorded.

TABLE 4

2-Anilino/N-ethylamino/methylthio-3-aroyl/nitro-5-hydroxybenzofurans

9 (a-h) and 12

Product[a]	Yield[b] (%)	m.p. (°C)	Molecular formula		Analysis (%)		
				Calc. Found	C	H	N
9a	24(15)	234-	$C_{21}H_{15}NO_3$		76.59	4.56	4.25
		235	(329.3)		76.43	4.62	4.22
9b	26	228-	$C_{21}H_{14}BrNO_3$		61.76	3.43	3.43
		230	(408.3)		61.68	3.39	3.41
9c	24	210	$C_{22}H_{17}NO_4$		73.53	4.76	3.89
			(359.3)		73.16	4.48	3.45

Table 4 (Contd.)

9d	22(6)	184	$C_{17}H_{15}NO_3$	72.59	5.33	4.92
			(281.3)	72.63	5.46	4.89
9e	27	225-	$C_{17}H_{14}BrNO_3$	56.66	5.38	5.38
		228	(360.2)	56.79	5.42	5.37
9f	23	211	$C_{18}H_{17}NO_4$	69.44	5.49	4.49
			(311.3)	69.13	5.21	4.19
9g	11(6)	209-	$C_{14}H_{10}N_2O_4$	62.22	3.79	10.37
		210	(270.2)	62.33	3.69	10.31

Table 4 (Contd.)

9h	–(29)	231–	$C_{10}H_{10}N_2O_4$	54.05	4.50	12.61
		233	(222.2)	54.27	4.66	12.70
12	20^{c}(16)	232–	$C_9H_7NO_4S$	48.00	3.11	6.22
		235	(225.2)	48.12	3.04	6.25

---

[a] Crystallization solvent = EtOAc:hexane.

[b] The yields are those obtained from S,N-acetals 8a-g, while those in parentheses are from N,N-acetals 13a-d.

[c] Yield from S, N-acetal 8g, while that in parentheses is obtained from S,N-acetal 8h.

TABLE 5

2-(Aroyl-thiocarbomethoxy)methyl-1,4-hydroquinones 10 (d-f)

Product[a]	Yield (%)	m.p. (°C)	Molecular formula	Calc.Found	Analysis(%) C	H
10d	21	130-	$C_{16}H_{14}O_4S$		63.56	4.67
		131	(302.3)		63.21	4.33
10e	19	183	$C_{16}H_{13}O_4SBr$		50.39	34.38
			(381.3)		49.92	33.97
10f	16	136-	$C_{17}H_{16}O_5S$		61.44	4.85
		138	(332.3)		61.17	4.39

[a] Crystallization solvent = EtOAc:benzene.

TABLE 6

1,2-Disubstituted-3-benzoyl/nitro-5-hydroxyindoles 14 (a-e) and 11 (a,b)

Product	Yield (%)	Cryst. solvent	m.p. (°C)	Molecular formula	Calc. Found	Analysis(%) C	H	N
14a	21	EtOAc	263-	$C_{27}H_{20}N_2O_2$		80.19	4.95	6.93
			265	(404.5)		80.22	4.80	6.88
14b	33	$CHCl_3$:	165-	$C_{19}H_{20}N_2O_2$		74.02	6.49	9.09
		hexane	167	(308.4)		74.15	6.39	8.98
14c	70	EtOAc:	220	$C_{20}H_{15}N_3O_3$		69.56	4.37	12.17
		hexane		(345.3)		69.54	4.31	12.01

Table 6 (Contd.)

14d	21	EtOAc	220	$C_{12}H_{15}O_3$	57.83	6.02	16.86
				(249.3)	57.87	5.92	16.83
14e	9	EtOAc:	291-	$C_{17}H_{14}N_2O_2$	73.38	5.03	10.07
		$CHCl_3$	293	(278.3)	73.13	4.99	9.92
11a	19	EtOAc:	220	$C_{15}H_{12}N_2O_3S$	60.00	4.00	9.33
		hexane		(300.3)	59.89	3.93	9.18
11b	19	EtOAc:	211-	$C_{11}H_{12}N_2O_3S$	52.38	4.76	11.11
		benzene	212	(252.2)	52.42	4.66	11.21

REFERENCES

1. C.D. Nenitzescu, Bull. Soc. Chim. Romania, 11, 37 (1929); Chem. Abstr. 24, 110 (1930).
2. G.R. Allen, Jr., in 'Organic Reactions', Vol. 20 (edited by W.G. Dauben), pp. 337, John Wiley Intersciences, New York (1973).
3. U. Kuckländer, Tetrahedron, 29, 921 (1973).
4. J.B. Patrick, E.K. Saunders, Tetrahedron Letters 4009 (1979).
5. U. Kuckländer, Tetrahedron, 31, 1631 (1975).
6. U. Kuckländer, Liebigs Ann. Chem. 129, 140 (1978).
7. R.J.S. Beer, H.F. Devenport, and A. Robertson, J. Chem. Soc., 1262 (1953).
8. D. Raileanu, M. Palaghita, and C.D. Nenitzescu, Tetrahedron, 27, 5031 (1971).
9. D. Raileanu and C.D. Nenitzescu, Rev. Roum. Chim. 10, 339 (1965); Chem. Abstr. 63, 9903^{f} (1965).
10. G.R. Allen, Jr., and M.J. Weiss, Chem. Ind. (London), 117 (1966).

11. G.R. Allen, Jr., C. Pidacks and M.J. Weiss, J. Amer. Chem. Soc. 88, 2536 (1966).

12. G.R. Allen, Jr., and M.J. Weiss, J. Org. Chem. 33, 198 (1968).

13. U. Kuckländer, Tetrahedron, 28, 5251 (1972).

14. R.K. Brown, in 'Indoles', Part I (edited by W.J. Houlihan), pp. 413, John Wiley-Interscience, New York (1972).

15. K.C. Brannock, R.D. Burpitt, H.E. Davis, H.S. Pridgen and J.G. Thweatt, J. Org. Chem. 29, 2579 (1964).

16. G. Domschke, J. Prakt. Chem. 32, 114 (1966).

17. K. Ley and R. Nast, Angew. Chem. Int. Ed. Engl., 6, 174 (1967).

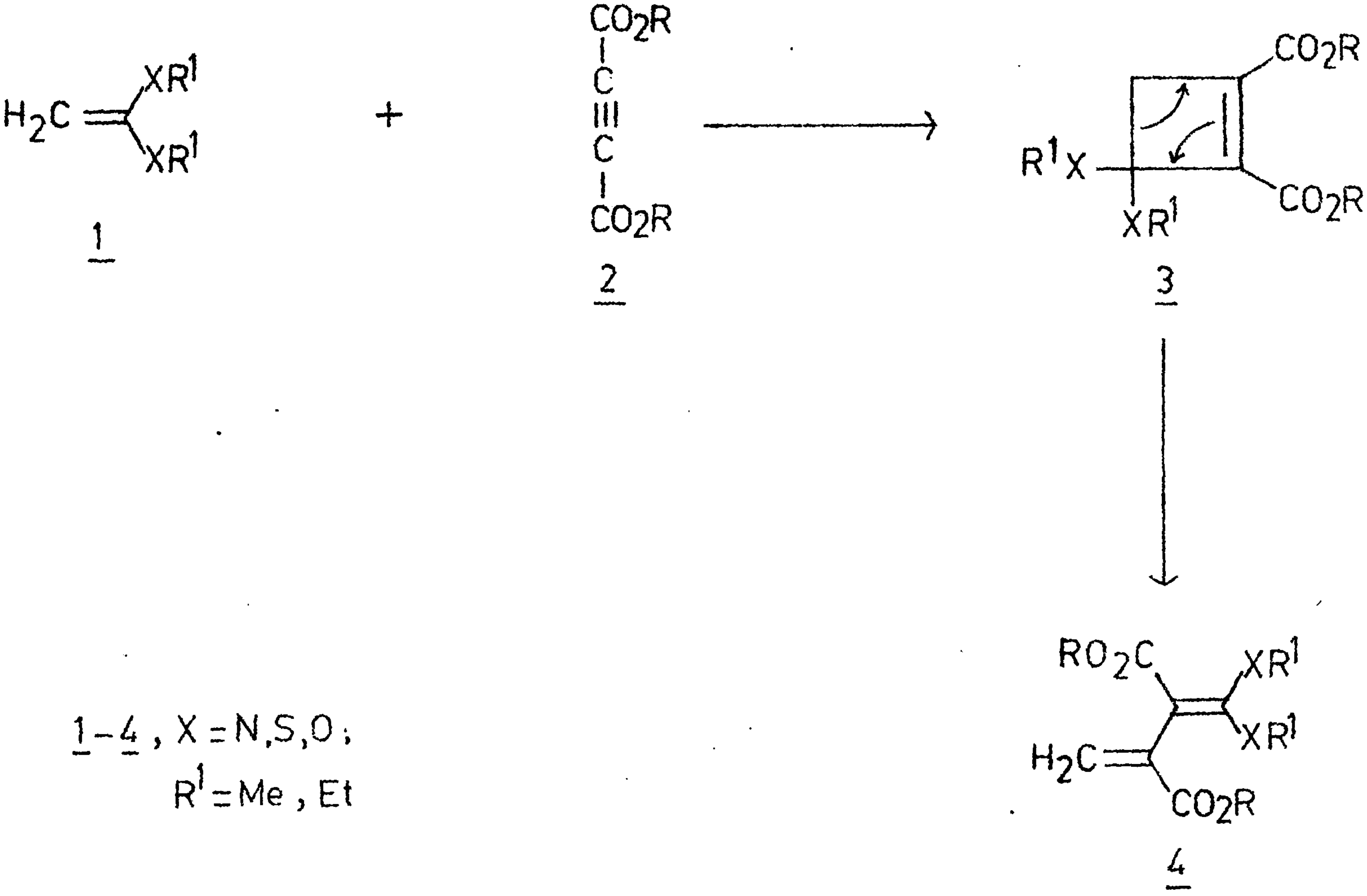
CHAPTER 7

REACTION OF POLARIZED KETEN-S,N- AND N,N-ACETALS WITH DIMETHYL ACETYLENEDICARBOXYLATE

7.1 Introduction

The chemical reactivity of keten-S,N- and N,N-acetals with 1,4-benzoquinone has been shown in the preceding chapter to give 5-hydroxyindoles, demonstrating that these S,N- and N,N-acetals exhibit properties like those of enamines used in the Nenitzescu indole synthesis. In principle, the keten-S,N- and N,N-acetals should undergo all the reactions, that enamines are known to have undergone. As exemplified in scheme 1, simple keten acetals react[1-6] with acetylenedicarboxylate to give a *trans*-butadiene 4, arising from rearrangement of the cyclobutene 3, which is known to be formed through (2+2) cycloaddition of 1 and 2. A similar reaction of enamines,

Scheme 1

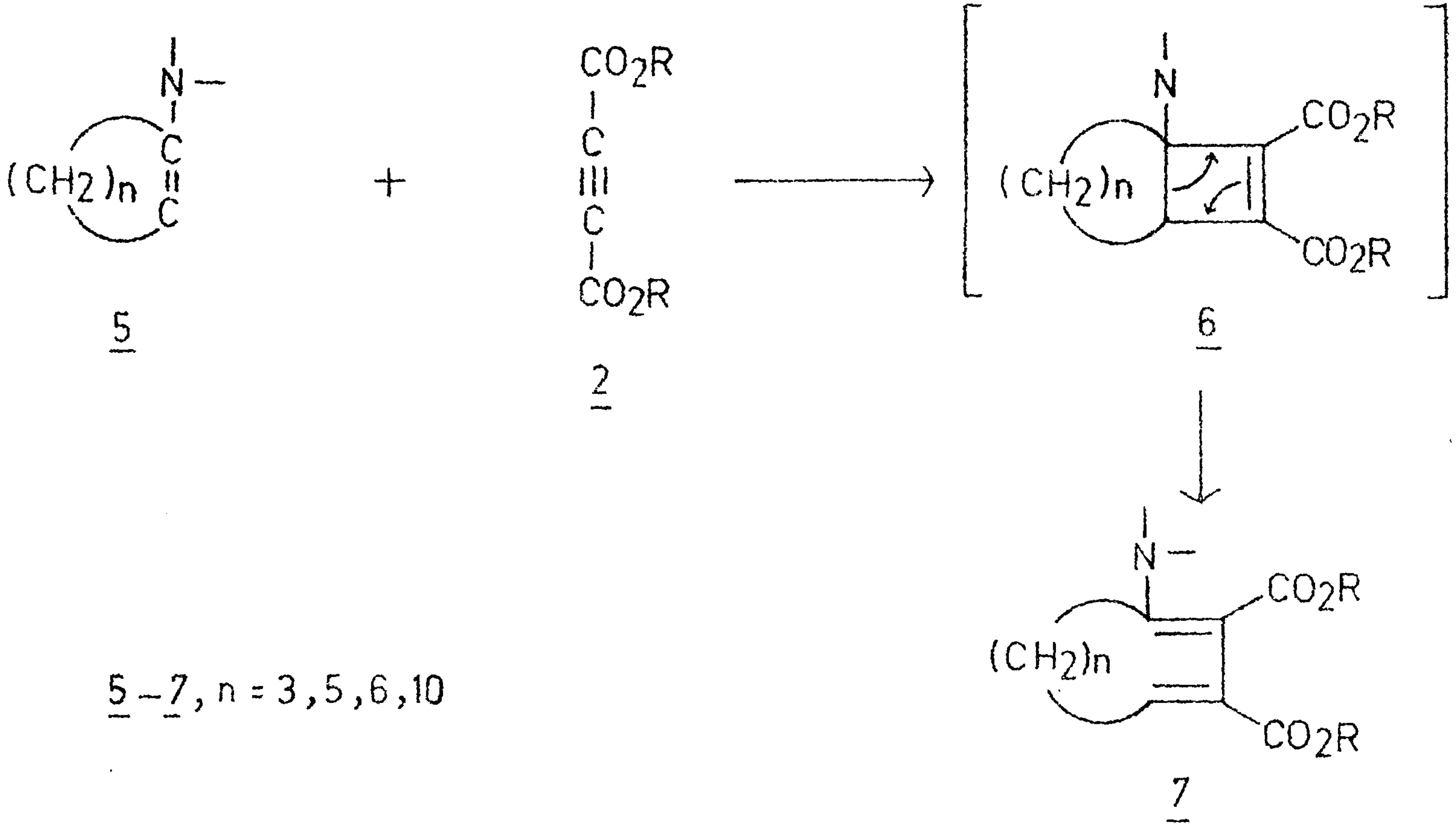


$\underline{1}$–$\underline{4}$, X = N,S,O;
R^1 = Me, Et

derived from cyclic ketones, with acetylenedicarboxylates resulted in ring enlargement by two carbon atoms via the intermediate cyclobutene adducts 6 (Scheme 2).[7,8] Enamines derived from β-diketones and β-keto esters were found to differ considerably from the simple enamines in their reactivities towards 2. In one of the reactions, the enamine 8 (Scheme 3) was reacted with 2, when the initially formed diene 10 underwent cyclization to give the dimethyl phthalate 11 in 60% yield. However, when the same system with one or two labile hydrogens, like 12a and 12b were reacted with 2 (Scheme 4),[8] 12a gave the expected 13a formed via cyclobutene route, while in the case of 12b, the open chain adduct 13b was converted to the cyclic amide 14 on treatment with water. Although, spectral data supported the structures 13a and 13b, the authors have not completely ruled out the possibility of structures 15a and 15b respectively, formed via Michael route. It was not possible to differentiate between 13 and 15 by spectral and analytical data.

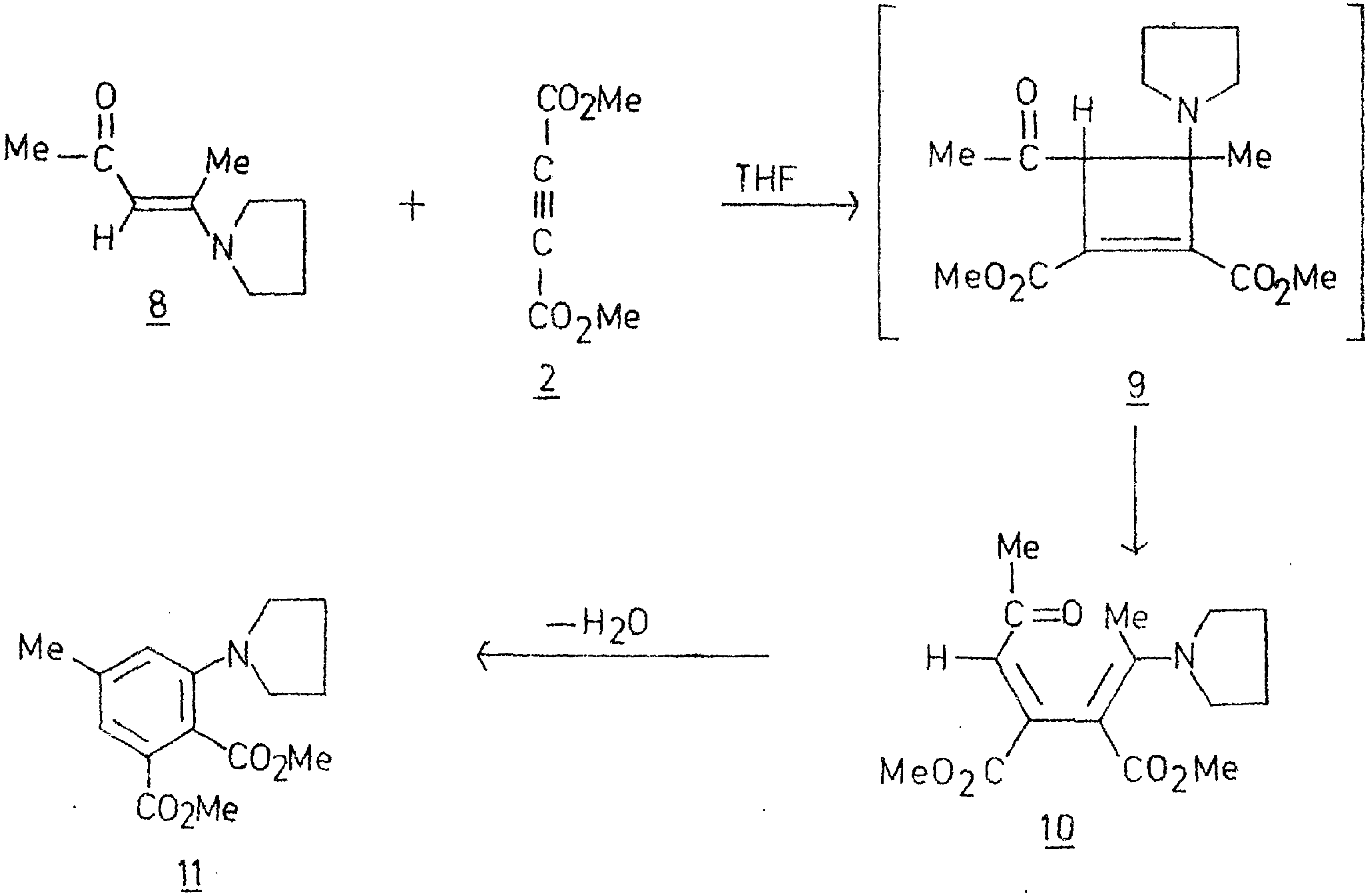
Although, there are number of examples of (2+2) cycloaddition of simple ketene acetals, the reactivity

Scheme 2

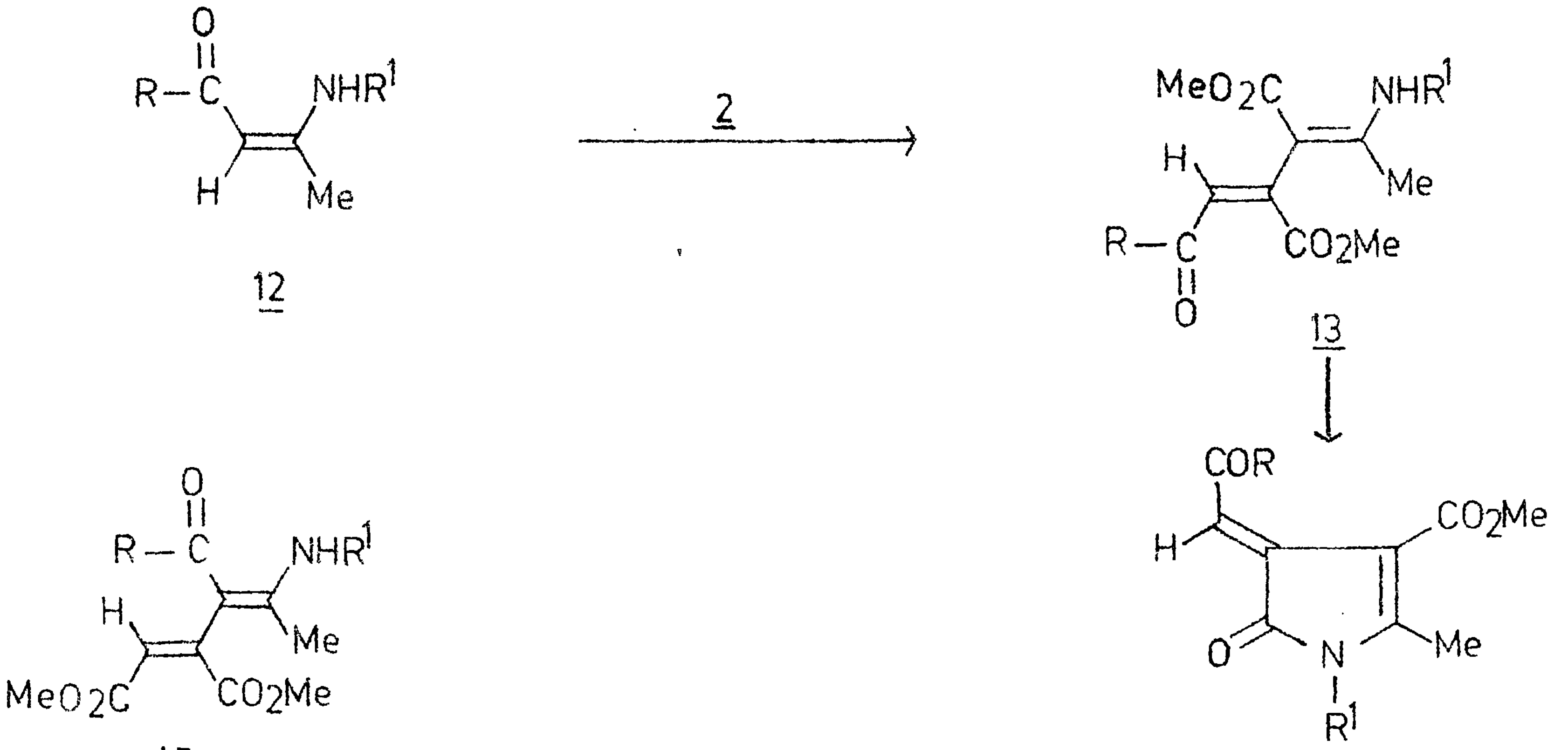


5–7, n = 3,5,6,10

Scheme 3



Scheme 4



12

13

14, R= Me ; R^1= H

15

12 , 13 , 15a , R = OEt ; R^1=Ph

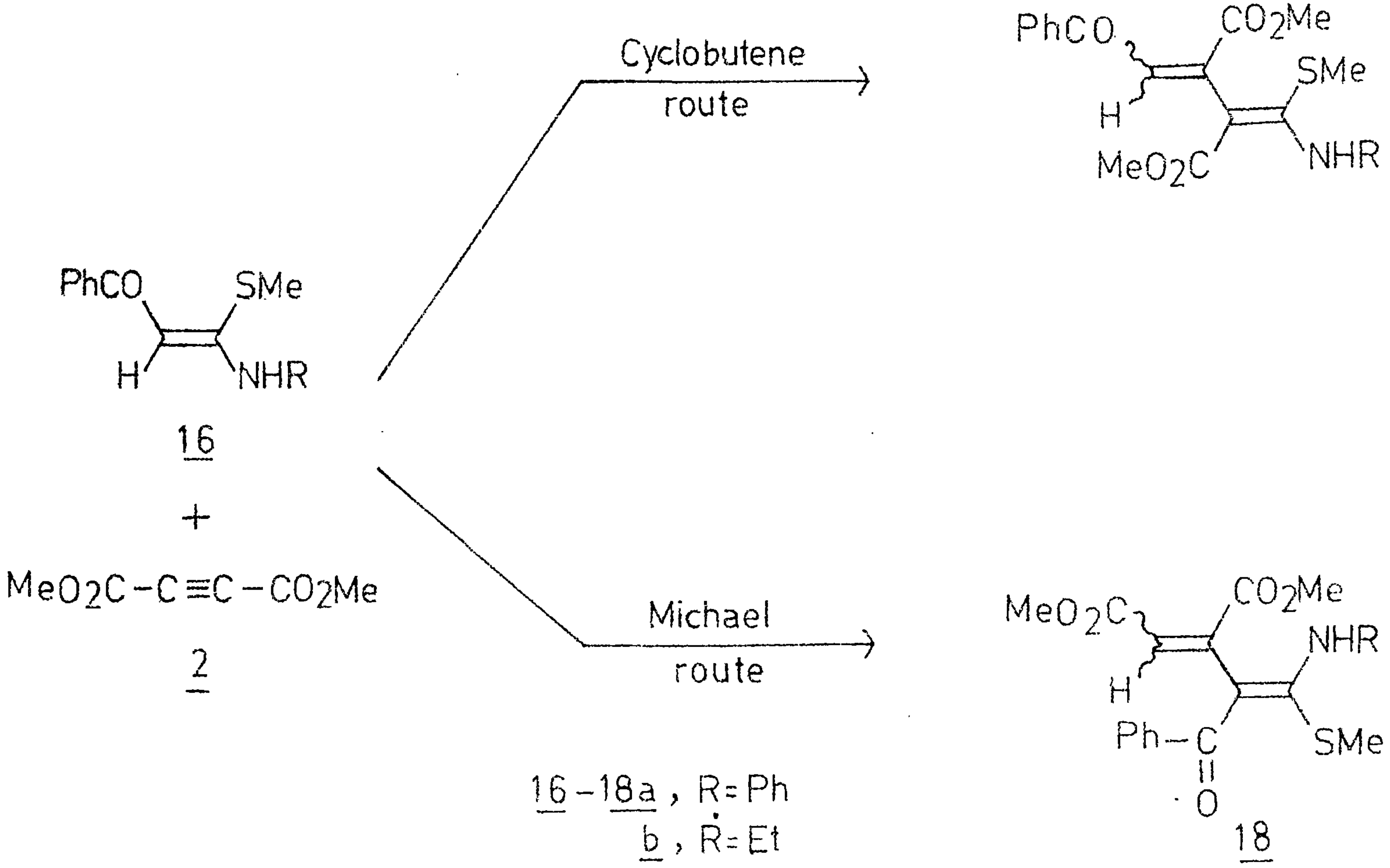
12 – 15b , R = Me ; R^1 = H

of polarized keten-S,N- and N,N-acetals towards acetylenedicarboxylates has been totally neglected and no study so far has been reported in the literature. It was therefore, contemplated that the reaction of keten-S,N- and N,N-acetals with dimethyl acetylenedicarboxylate would lead to the formation of hitherto inaccessible heterocycles and a few keten-S,N- and N,N-acetals have been chosen for the present investigation (Chapter 2).

7.2 Results and discussion

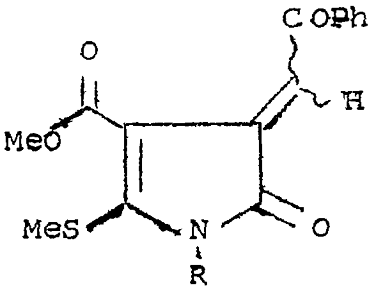
It was anticipated that ketoketen-S,N- and N,N-acetals will react with dimethyl acetylenedicarboxylate to give products formed either via Michael route or via cyclobutene route. Thus, when S,N-acetal 16a (Scheme 5) was reacted with equimolar quantities of dimethyl acetylenedicarboxylate (2) in benzene at room temperature, work-up of the reaction mixture yielded a viscous semisolid 17a (or 18a) in 57% yield, which was characterized as 1:1 adduct on the basis of spectral (Table 2) and analytical data (Table 4).

Scheme 5

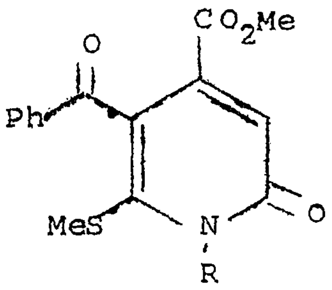


16–18a, R=Ph
b, R=Et

Thus, the product analysed for $C_{22}H_{21}NO_5S$ and its IR spectrum showed absorption bands at 1735, 1720 and 1670 cm^{-1} due to two carbomethoxy groups and one aromatic carbonyl group respectively, while a weak broad band between 3450-3300 cm^{-1} was assigned to the $-N\underline{H}$ group. Its NMR spectrum exhibited two singlets at δ 1.65 and δ 1.90, (integrating for three protons) due to protons of the $-SC\underline{H}_3$ group. The signal due to two $-CO_2C\underline{H}_3$ groups appeared as a broad singlet (6H) between δ 3.38-3.91, while the broad band between δ 6.70-8.80 (12H) was assigned to ten aromatic protons, one vinylic proton and one -NH proton. From the above data, it is not possible to distinguish between structures 17a and 18a formed via cyclobutene and Michael route respectively. It appears, that in the present case both pathways are operative and the product isolated is a mixture of 17a and 18a. Similarly, the S,N-ethylacetal 16b when reacted with 2 yielded a mixture of the isomers 17b and 18b. Its analytical and spectral data is given in table 4 and table 2 respectively. Attempts to identify 17 and 18 by cyclizing them to 19 and 20 respectively, in the presence of



19

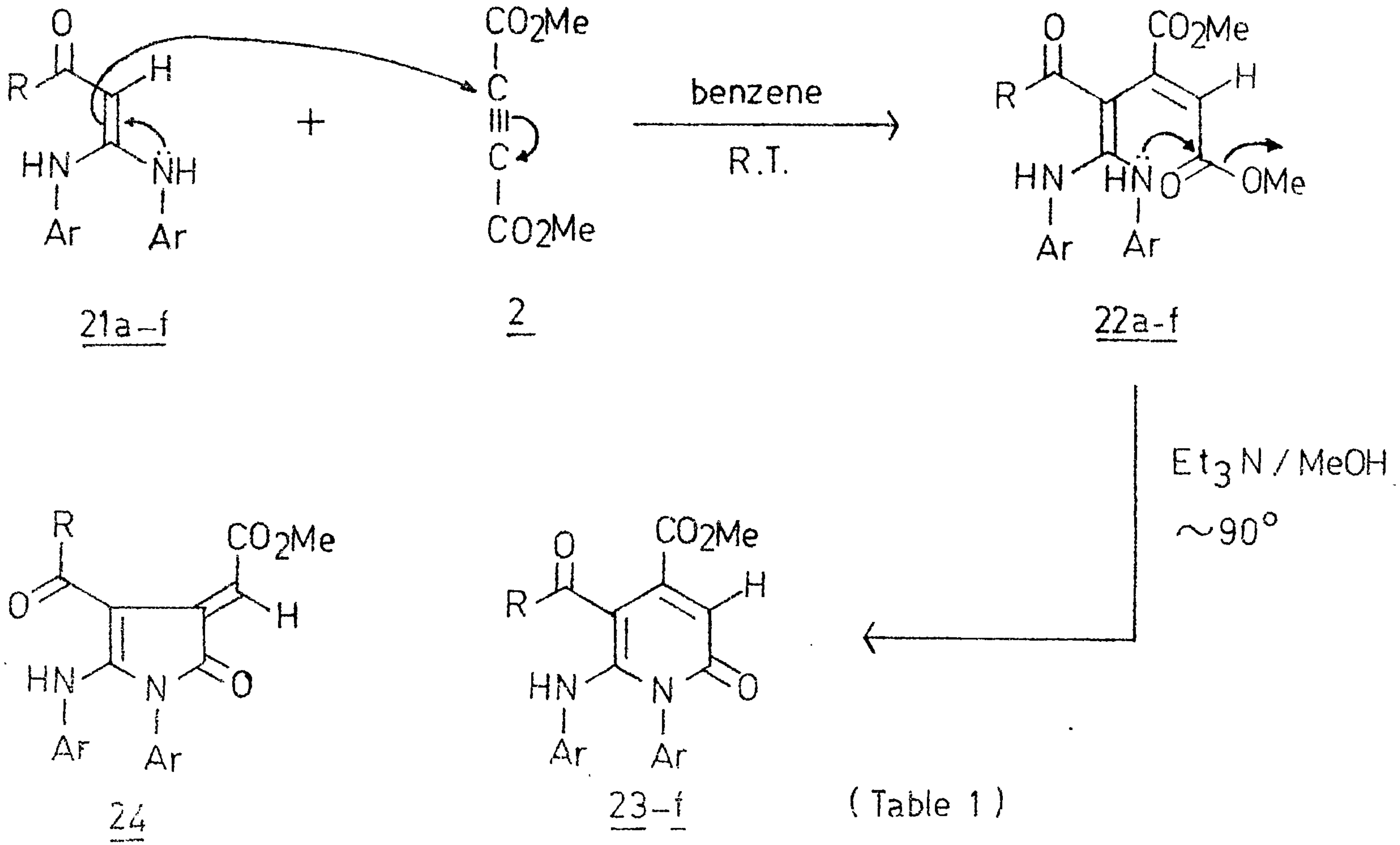


20

triethylamine in methanol were not successful and in both the cases, a mixture of several products was obtained, from which no identifiable product could be isolated.

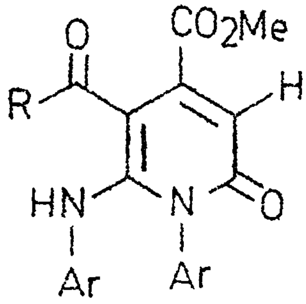
The α-carbon in the N,N-acetal 21 (Scheme 6) is apparently more nucleophilic than in the S,N-acetals 16, due to the presence of two amino groups at β-carbon. Therefore, it is expected that 21 should react with 2 via Michael pathway rather than via cyclobutene. Thus, when 21a was reacted with 2 at room temperature in benzene, the open-chain Michael adduct 22a was obtained in 83% yield. When

Scheme 6



22a was refluxed in methanol in the presence of triethylamine, it underwent smooth cyclization to give 1-N-phenyl-4-carbomethoxy-5-benzoyl-6-anilino-2(1H)-pyridone (23a) in 66% yield. Similarly, the keten-N,N-acetals 21b-f (Table 1) reacted with 2 to give the corresponding 22b-f in 78-88% overall yields, all of which yielded the corresponding pyridones 23b-f in 59-67% overall yields. The structure of 22a was elucidated on the basis of its spectral data (Table 2). Thus, its IR spectrum exhibited weak bands at 3420 cm^{-1} and 3340 cm^{-1} which were assigned to the two -NH stretching vibrations. The bands at 1740 and 1720 cm^{-1} were assigned to the carbonyl frequencies of the two ester groups while the band at 1660 cm^{-1} was attributed to the carbonyl frequency of the keto group. The structure of 22a was further confirmed by its NMR spectrum ($CDCl_3$) which showed a singlet(δ3.60, 6H) for the two carbomethoxy groups. The multiplet around δ6.16-6.93 accounting for seven protons, was assigned to five aromatic protons merged with one vinylic and one -NH proton. The other aromatic protons (10H)

Table 1

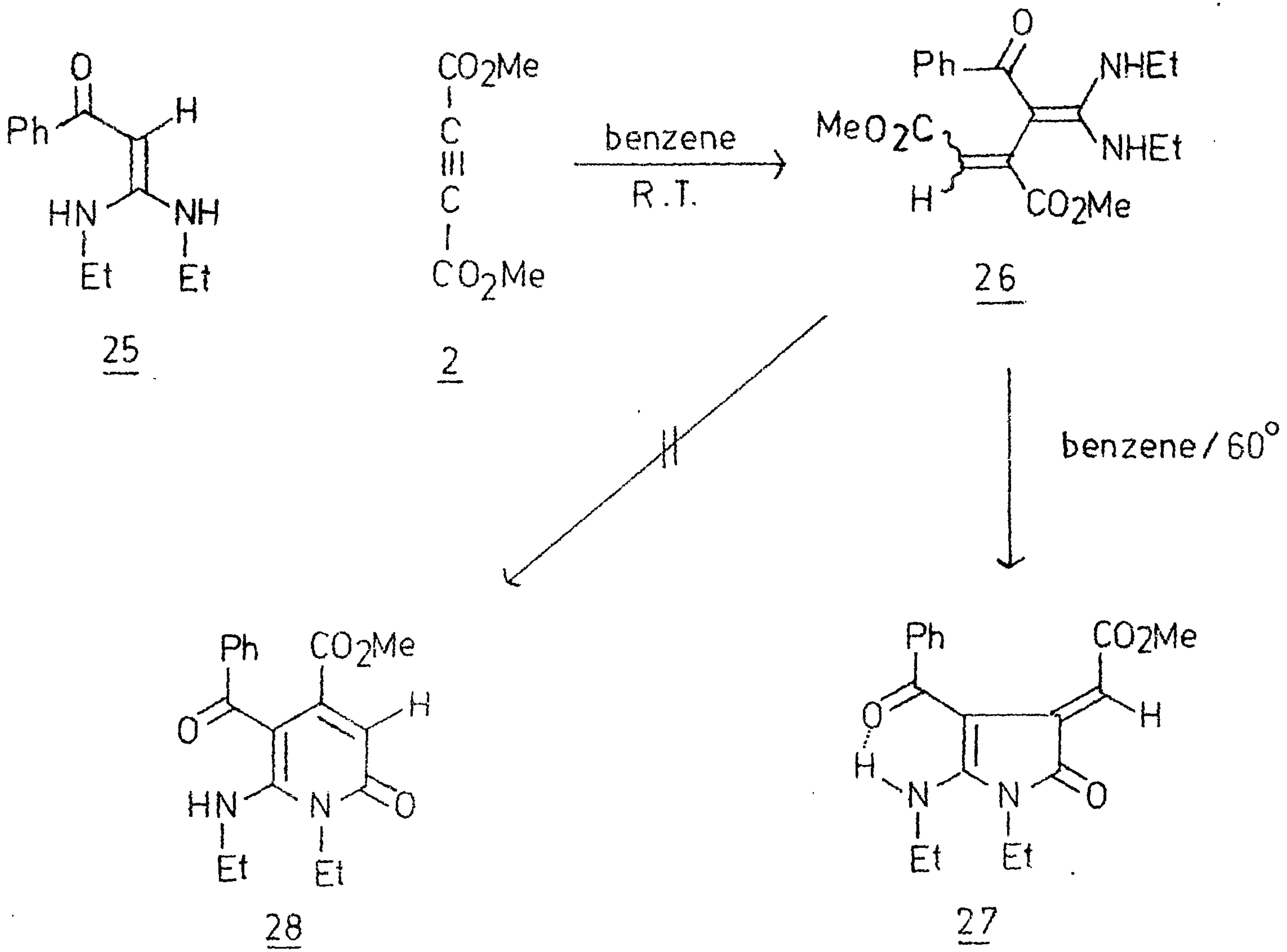


23

Starting material	Product	R	Ar
22a	23a	C_6H_5	C_6H_5
22b	23b	p-$CH_3OC_6H_4$	C_6H_5
22c	23c	p-ClC_6H_4	C_6H_5
22d	23d	p-$CH_3OC_6H_4$	p-ClC_6H_4
22e	23e	p-$CH_3OC_6H_4$	p-$CH_3C_6H_4$
22f	23f	p-$CH_3C_6H_4$	p-$CH_3OC_6H_4$

appeared as a broad multiplet around δ 7.00-7.65 while the other -N<u>H</u> proton appeared at δ 12.00. The spectral data of pyridone <u>23a</u> (Table 3) was appreciably distinguishable from that of <u>22a</u> thus, confirming its cyclic nature. Its mass spectrum showed molecular ion peak at M^+ 424 ($C_{26}H_{20}N_2O_4$). The IR spectrum showed a strong band at 3340 cm^{-1} (ν_{NH}) and a band at 1740 cm^{-1}, which was assigned to the ester carbonyl group. The keto carbonyl was assigned to the band at 1648 cm^{-1}, while the band at 1680 cm^{-1} was attributed to the amide carbonyl group. Its structure was further confirmed by its NMR spectrum (TFA). The singlet at δ 3.61 (3H) accounting for three protons of the carbomethoxy group, confirmed the participation of other ester group in intramolecular cyclization. The <u>H</u>-3 proton appeared as a singlet at δ 6.62, while the broad multiplets around 6.8-7.3 (5H) and δ 7.2-7.8 (10H) accounted for fifteen aromatic protons. All the Michael adducts <u>22b-f</u> and the corresponding pyridones <u>23b-f</u> showed analytical (Table 4 and 5 respectively) and spectral data (Table 2 and 3), which were in conformity with the structures assigned. However, it should be noted at this stage that the possibility of the formation of five-membered amide 24 on treatment of 22 with triethylamine in methanol cannot be completely ruled out, although the five-membered amide (24) with an exocyclic double bond, appears to be less stable as compared to six-membered pyridone (23). Also the vinylic proton in 24 will appear at lower field ($\sim\delta$ 7.0) due to deshielding by the amide carbonyl group. Interestingly, the Michael adduct 26, obtained from the reaction of N,N-diethylacetal 25 and 2 (Scheme 7), was not very stable and on longer heating in benzene at 60°C, it was converted to a greenish yellow viscous solid, which was tentatively assigned the five-membered amide structure 27 on the basis of spectral and analytical data. The Michael adduct 26 exhibited absorption bands at 1718, 1692 and 1620 cm^{-1} in its IR spectrum (Table 2) due to two ester carbonyl and one aromatic carbonyl groups respectively, while in the IR spectrum (Table 3) of 27, the

Scheme 7


Ph
O
H
HN
NH
Et
Et
25
CO2Me
C
C
CO2Me
2
benzene
R.T.
Ph
O
NHEt
MeO2C
NHEt
H
CO2Me
26
benzene / 60°
Ph
CO2Me
O
H
HN
N
O
Et
Et
28
Ph
CO2Me
O
H
H
N
N
O
Et
Et
27

absorption frequencies at 1740, 1715 and 1644 cm^{-1}, were assigned to ester, amide and aromatic carbonyl groups respectively. Both the products 26 and 27 showed strong bands at 3300 and 3320 cm^{-1} respectively due to -NH group. The NMR spectrum of 26 (Table 2) showed broad triplets between δ 0.90-1.40 due to two methyl groups (-NHCH$_2$C$\underline{H}_3$), while two singlets δ 3.40 (3H) and δ 3.70 (3H) and a broad quartet (4H) around δ 3.30-3.60 were assigned to two carbomethoxy groups and four methylene protons of the two ethylamino groups respectively. The broad multiplet between δ 7.20-7.90 (6H) accounted for five aromatic protons and one vinylic proton. In the NMR spectrum (Table 3) of 27, the signal due to two methyl groups (-NCH$_2$C$\underline{H}_3$) appeared as a broad triplet between δ 0.90-1.63, while a singlet at δ 3.15 (3H) and a broad quartet around δ 3.50-4.00 accounted for three carbomethoxy protons and four methylene protons (-NC$\underline{H}_2$CH$_3$) respectively. The aromatic protons and exocyclic vinyl proton were present as a broad multiplet (6H) between δ 7.12-8.13. The presence of only one

TABLE 2

Spectral data for products 17a, 17b (or 18a, 18b) 22 (a–f) and 26

Product	IR(cm^{-1})	^{1}H–NMR(δ /ppm)
17a(or 18a)	3450–3300 (w, ν_{NH}); 1735, 1720 (ν_{CO}ester); 1670 (ν_{CO}keto)[a]	1.65, 1.90 (two s, total 3H, SC$\underline{H}_3$); 3.38–3.91 (br s, 6H, COOC$\underline{H}_3$); 6.70–8.80 (m, 12H, 10H$_{arom}$+ 1$\underline{H}$ vinylic + N$\underline{H}$).[b]
17b(or 18b)	3380 (w, ν_{NH}); 1740, 1705 (ν_{CO}ester); 1660 (ν_{CO}keto)[a]	1.02–1.32 (br t, 3H, CH$_2$C$\underline{H}_3$); 2.24, 2.35 (two s, total 3H, SC$\underline{H}_3$); 3.38–3.97 (m, 8H, C$\underline{H}_2$CH$_3$ + two COOC$\underline{H}_3$); 5.20 (br, 1H, N$\underline{H}$); 6.90–7.66 (br m, 6H, 5H$_{arom}$+ 1H vinylic).[b]

Table 2 (Contd.)

Product	IR(cm^{-1})	^{1}H–NMR(δ/ppm)
22a	3420, 3340 (w, ν_{NH}); 1740, 1720 (ν_{CO}ester); 1660 (ν_{CO}keto)[a]	3.60 (s, 6H, COOC$\underline{H}_3$); 6.16–6.93 (m, 6H, 1$\underline{H}$ vinylic + 5H$_{arom}$); 7.00–7.65 (m, 10H$_{arom}$).[b]
22b	3430, 3360 (w, ν_{NH}); 1734, 1724 (ν_{CO}ester); 1668 (ν_{CO}keto)[a]	3.50 (s, 3H, COOC$\underline{H}_3$); 3.58 (s, 3H, COOC$\underline{H}_3$); 3.80 (s, 3H, OC$\underline{H}_3$); 6.21–7.66 (br m, 15H, 1$\underline{H}$ vinylic + 14H$_{arom}$).[b]
22c	3440, 3360 (w, ν_{NH}); 1738, 1730 (ν_{CO}ester); 1665 (ν_{CO}keto)[a]	3.58 (s, 6H, COOC$\underline{H}_3$); 6.22–7.60 (br m, 15H, 1$\underline{H}$ vinylic + 14H$_{arom}$).[b]

Table 2 (Contd.)

Product	IR(cm^{-1})	^1H-NMR(δ /ppm)
22d	3440, 3340 (w, ν_{NH}) 1745, 1730 (ν_{CO} ester); 1635 (ν_{CO} keto)[a]	3.48 (s, 3H, $COOC\underline{H}_3$); 3.60 (s, 3H, $COOC\underline{H}_3$); 3.85 (s, 3H, $OC\underline{H}_3$); 6.14-7.65 (br m, 13H, $12H_{arom}$+ $1H_{vinylic}$).[b]
22e	3390, 3320 (w, ν_{NH}); 1735, 1730 (ν_{CO} ester); 1660 (ν_{CO} keto)[a]	2.10 (s, 3H, $C\underline{H}_3$); 2.35 (s, 3H, $C\underline{H}_3$); 3.50 (s, 3H, $COOC\underline{H}_3$); 3.56 (s, 3H, $COOC\underline{H}_3$); 3.81 (s, 3H, $OC\underline{H}_3$); 7.20-7.40 (br.m, 13H, $12H_{arom}$ + $1\underline{H}_{vinylic}$).[b]
22f	3440 (w, ν_{NH}); 1745, 1730 (ν_{CO} ester); 1665 (ν_{CO} keto)[a]	2.32 (s, 3H, $C\underline{H}_3$); 3.43 (s, 6H, $COOC\underline{H}_3$); 3.58 (s, 3H, $OC\underline{H}_3$); 3.70 (s, 3H, $OC\underline{H}_3$); 6.22 (s, 3H, $2H_{arom}$+$1\underline{H}_{vinylic}$); 6.68-7.48 (br.m, $10H_{arom}$).[b]

Table 2 (Contd.)

Product	IR (cm^{-1})	^1H-NMR (δ/ppm)
26	3300 (ν_{NH}); 1718, 1692 (ν_{CO} ester); 1620 (ν_{CO} keto)[a]	0.90–1.40 (two br.t, 6H, two $CH_2C\underline{H}_3$); 3.40, 3.70 (br m, 6H, two $COOC\underline{H}_3$); 3.30–3.60 (br.q, 4H, two $C\underline{H}_2CH_3$); 7.20–7.90 (br m, 6H, $5H_{arom}$ + $1\underline{H}_{vinylic}$); 9.58 (br s, 1H, $N\underline{H}$).[c]

[a] in nujol; [b] in $CDCl_3$; [c] in TFA.

TABLE 3

Spectral data of products 23 (a-f) and 27

Product	IR(cm^{-1})	^{1}H-NMR(δ/ppm)	M^{+} (m/e)
23a	3340 (s,ν_{NH}); 1740 (ν_{CO} ester); 1680 (ν_{CO} amide); 1648 (ν_{CO} keto)[a]	3.61 (s, 3H, COOC$\underline{H}_3$); 6.62 (br, 1H, $\underline{H}$-3); 6.80-7.30 (m, 6H, 5H$_{arom}$); 7.20-7.80 (br m, 10H$_{arom}$).[c]	424
23b	3330 (s, ν_{NH}); 1738 (ν_{CO}ester); 1680 (ν_{CO}amide); 1632 (ν_{CO}keto)[a]	3.70 (s, 3H, COOC$\underline{H}_3$); 3.95 (t, 3H, OC$\underline{H}_3$); 6.55-8.20 (br.m, 15H, 14H$_{arom}$+ $\underline{H}$-3).[c]	—

23c	3310 (s, ν_{NH}); 1730 (ν_{CO} ester); 1685 (ν_{CO} amide); 1630 (ν_{CO} keto)[a]	3.74 (s, 3H, $COOC\underline{H}_3$); 6.52–7.98 (br.m, 15H, 14H_{arom}+ $\underline{H}$-3).[c]	**458.5**
23d	3380, 3300 (ν_{NH}); 1735 (ν_{CO} ester); 1685 (ν_{CO} amide) 1660 (ν_{CO} keto)[a]	3.68 (s, 3H, $COOCH_3$); 3.94 (s, 3H, $OC\underline{H}_3$); 6.38–7.88 (br m, 13H, 12H_{arom}+$\underline{H}$-3).[c]	-
23e	3320 (ν_{NH}); 1732 (ν_{CO} ester); 1685 (ν_{CO} amide); 1618 (ν_{CO} keto)[a]	1.50 (s, 3H, $C\underline{H}_3$); 1.72 (s, 3H, $C\underline{H}_3$); 3.05 (s, 3H, $COOC\underline{H}_3$); 3.30 (s, 3H, $OC\underline{H}_3$); 5.76–7.06 (br m, 13H, 12H_{arom}+ $\underline{H}$-3).[c]	482

Table 3 (Contd.)

23f	3320 (ν_{NH}); 1725 (ν_{CO}ester); 1675 (ν_{CO}amide); 1610 (ν_{CO}keto)[a]	2.40 (s, 3H, CH_3); 3.31 (s, 3H, $COOCH_3$); 3.68 (s, 3H, OCH_3); 3.71 (s, 3H, OCH_3); 6.32-7.68 (br m, 13H, $12H_{arom}$+ H-3).[c]	498
27	3320 (ν_{NH}); 1740 (ν_{CO}ester); 1715 (ν_{CO}amide); 1644 (ν_{CO}keto)[a]	0.90-1.63 (br.t, 6H, two CH_2CH_3); 3.15 (s, 3H, $COOCH_3$); 3.50-4.00 (two br q, 4H, CH_2CH_3); 7.12-8.13 (m, $5H_{arom}$+ $1H_{vinylic}$).[b]	-

---

[a] in nujol; [b] in $CDCl_3$; [c] in TFA.

carbomethoxy group in the NMR spectrum of 27 confirms the intramolecular cyclization of 26, however, further work is in progress to confirm the structure of 27.

EXPERIMENTAL

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

The starting materials

The keten-S,N- (16a, 16b) and N,N-acetals (21a-f, 25) required, were prepared as described in chapter 2.

Reaction of S,N-acetals 16a-b and N,N-acetals 21a-f with dimethyl acetylenedicarboxylate (2) : General Procedure :

A solution of keten-N,N-acetal 21a-f (0.01 mol) or S,N-acetal 16a-b (0.01 mol) and 2 (2.6 g, 0.013 mol) in dry benzene (40 ml) was stirred at room temperature for 0.25-20 hr (Table 4) (monitored by TLC). The solvent was removed and the crude adducts 22a-f were crystallized from ether/hexane mixture as bright yellow solids (Table 4).

The adducts 17a and 17b (or 18a and 18b) were purified by column chromatography over silica gel. Elution with benzene/hexane (1:1) yielded pure 17a and 17b as viscous semisolids (TLC, single spot).

Preparation of 1-N-aryl-2(1H)-pyridones 23a-f : General Procedure

A solution of the adduct 22a-f (0.005 mol) and triethylamine (8 ml) in absolute methanol (25 ml) was heated at 80-90°C for 6 hr (checked by TLC). The solvent was removed under pressure, the residue diluted with water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated to give crude pyridones 23a-f, which were crystallized from chloroform/hexane mixture (Table 5).

Reaction of N,N-diethylacetal 25 with 2

A solution of 25 (1.09 g, 0.005 mol) and 2 (1.2g, 0.006 mol) in dry benzene (25 ml) was stirred at room temperature for 15 min. The adduct 26 separated as greenish yellow solid (1.62 g, 90%), which was filtered immediately and washed with hexane. Attempts to further purify 26 were not successful. When 26 (0.36g, 0.001 mol) was heated in benzene at 60° for 1 hr, it was converted to 27 as greenish yellow viscous semi-solid (0.24 g, 75%) which was purified by trituration with hexane. Attempts to further purify 27 were not successful. IR, NMR and analytical data of 26 and 27 were recorded immediately after isolation.

TABLE 4

1-Methylthio-1-anilino/N-ethylamino-2,3(3,4)-dicarbomethoxy-4(2)-benzoyl-1,3-butadienes (17a-b or 18a-b); 1,1-bis(N-aryl/ethylamino)-2-aroyl-3,4-dicarboethoxy-1,3-butadienes (22a-f and 26)

Product	Reaction time(hr)	Yield (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis(%) C	H	N
17a(or	20	57	Viscous	$C_{22}H_{21}NO_5S$		64.23	5.10	3.40
18a)			Semi solid	(411)		64.52	5.27	3.61
17b(or	15	59	Viscous	$C_{18}H_{21}NO_5S$		59.50	5.78	3.85
18b)			Semi solid	(363)		59.71	5.92	3.77
22a	5	83	102-	$C_{27}H_{24}N_2O_5$		70.05	5.26	6.14
			103	(456)		69.68	5.08	6.33

Table 4 (Contd.)

22b	7	82	130	$C_{28}H_{26}N_2O_6$ (486)	69.13 69.68	5.34 5.08	5.76 5.61
22c	15	80	104	$C_{27}H_{23}ClN_2O_5$ (490.5)	66.05 66.39	4.68 4.48	5.70 5.97
22d	10	78	155- 157	$C_{28}H_{24}Cl_2N_2O_6$ (555)	60.54 60.19	4.32 4.20	5.04 5.37
22e	8	88	104- 105	$C_{30}H_{30}N_2O_6$ (514)	70.03 69.84	5.83 6.01	5.44 5.53

Table 4 (Contd.)

22f	10	85	Viscous	$C_{30}H_{30}N_2O_7$	67.92	5.66	5.28
			semi solid	(530)	68.35	5.80	5.07
26[a]	0.25	90	95-	$C_{19}H_{24}N_2O_5$	63.33	6.66	7.77
			97	(360)	64.12	7.80	7.21

---

[a] The analytical data of 26 was not completely agreeing with the calculated value, since an analytical sample of 26 could not be obtained because of its unstable nature.

TABLE 5

1-N-Aryl-4-carbomethoxy-5-aroyl-6-N-arylamino-2(1H)-pyridones 23 (a-f);

1-N-ethyl-2-oxo-3-(carbomethoxy)methylene-4-benzoyl-5-N-ethylaminopyrroline(27)

Product	Yield (%)	m.p. (°C)	Molecular formula	Analysis (%) Calc. Found	C	H	N
23a	66	231	$C_{26}H_{20}N_2O_4$		73.58	4.71	6.60
			(424)		73.80	4.63	6.84
23b	64	227	$C_{27}H_{22}N_2O_5$		71.36	4.84	6.16
			(454)		71.01	4.59	5.98
23c	61	211-	$C_{26}H_{19}ClN_2O_4$		68.04	4.14	6.10
		212	(458.5)		67.77	4.00	5.92

Table 5 (Contd.)

23d	59	225	$C_{27}H_{20}Cl_2N_2O_5$	61.95	3.82	5.35
			(523)	62.33	4.07	5.21
23e	65	189-	$C_{29}H_{26}N_2O_5$	72.19	5.39	5.80
		91	(482)	71.73	5.50	5.62
23f	67	143-	$C_{29}H_{26}N_2O_6$	69.87	5.22	5.62
		144	(498)	70.29	5.48	5.79
27[a]	75	Semi-	$C_{18}H_{20}N_2O_4$	65.85	6.09	8.53
		solid	(328)	66.04	5.63	9.01

---

[a] could not be further purified.

REFERENCES

1. R. Gompper, Ang. Chem. Int. Ed. 8, 312 (1969).
2. K.C. Brannock, R.D. Burpitt, and J.G. Thweatt, J. Org. Chem. 28, 1697 (1963).
3. S. Karlsson and J. Sandstrom, Acta Chem. Scand. Ser.B, B32, 141 (1978); Chem. Abstr. 89, 23352^{t} (1978).
4. S.M. McElvain and H. Cohen, J. Amer. Chem. Soc. 64, 260 (1942).
5. R. Okazaki, A. Kitamura, and N. Inamoto, J. Chem. Soc. Chem. Comm. 257 (1975).
6. M.O. Oka, A. Kitamura, R. Okazaki and N. Inamoto, Bull. Chem. Soc. Japan, 51, 301 (1978).
7. K.C. Brannock, R.D. Burpitt, V.W. Goodlett and J.G. Thweatt, J. Org. Chem. 28, 1464 (1963).
8. C.F. Huebner, L. Dorfman, M.M. Robison, E. Donoghue, W.G. Pierson and P. Strachan, J. Org. Chem. 28, 3134 (1963).

VITAE

Born on 3rd October 1954, Miss Veena Aggarwal passed her Higher Secondary Examination from Delhi in 1971. After successful completion of B.Sc.(honours) in 1974 and M.Sc. (Chemistry) in 1976 from Delhi University, she registered as Junior Research Fellow for Ph.D programme in the Department of Chemistry, North-Eastern Hill University, Shillong in November 1977. She is presently continuing as Senior Research Fellow in the same department.