NEWER SYNTHETIC METHODS FOR NOVEL HETEROCYCLES *VIA* OXOKETEN-S,N-ACETALS

ABSTRACT

by

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

DOCTOR OF PHILOSOPHY

To

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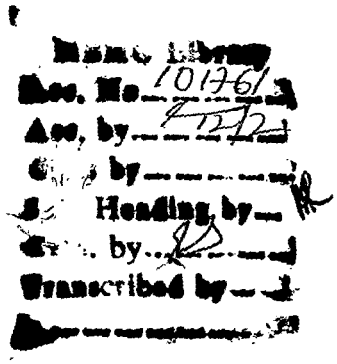
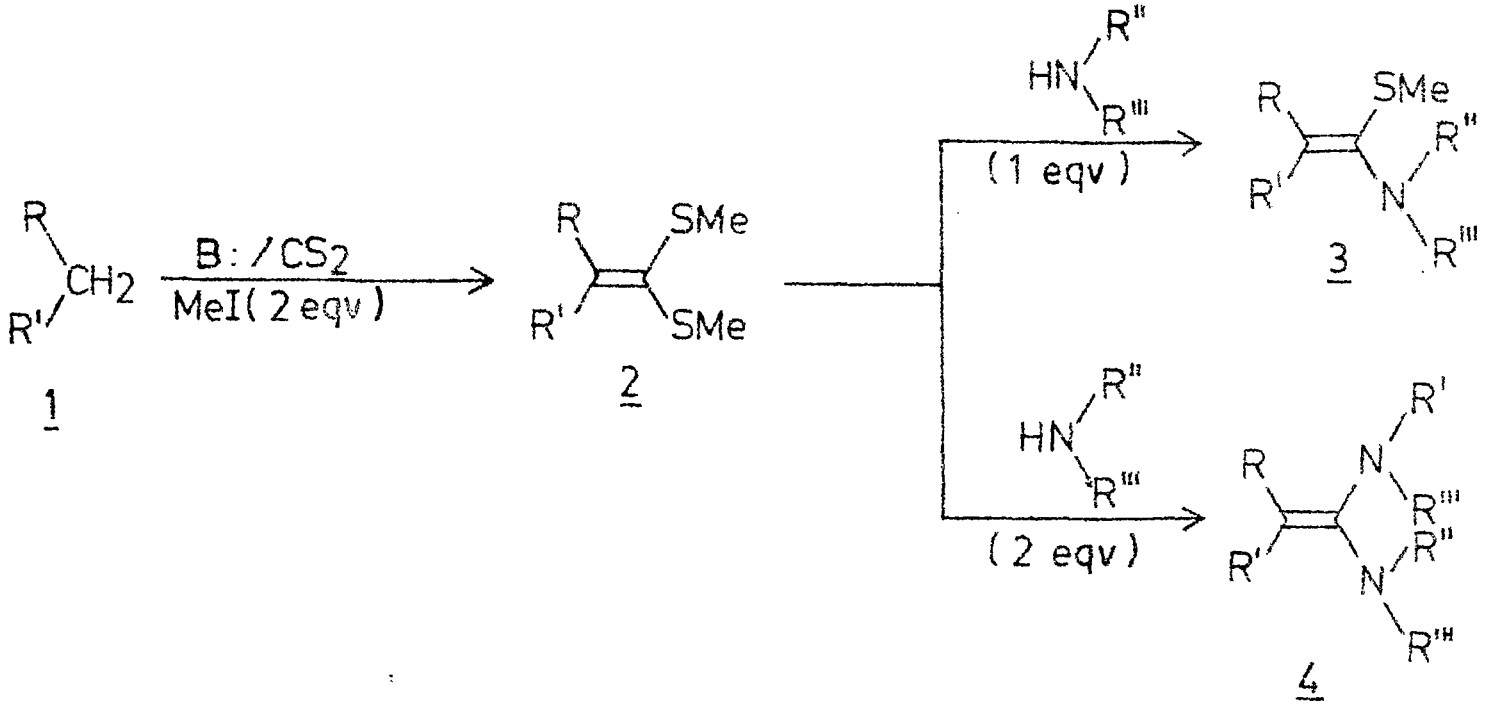


NEWER SYNTHETIC METHODS FOR NOVEL HETEROCYCLES VIA α-OXOKETEN S,N-ACETALS

Earlier work from this laboratory has successfully demonstrated polarized keten dithioacetals 2 as useful synthetic intermediates for the construction of a wide variety of heterocyclic and carbocyclic compounds.[1] These intermediates are easily derived in relatively simpler reaction conditions from a wide variety of active methylene compounds 1 and carbon disulfide in the presence of two equivalent of a suitable base followed by alkylation in one pot reaction (Scheme 1). Unlike the corresponding O,O-acetals, the dithioacetals are stable under mild hydrolytic conditions and thus form an interesting class of useful synthetic intermediates. It is further shown that polarized keten S,N-acetals undergo facile displacement reactions with appropriate nucleophiles to give the corresponding substituted acetals in good yields. Particularly, when the nucleophile is an amine, the displacement can take place either to give the corresponding S,N-acetals 3 or its N,N-acetals 4 depending on the stoichiometry of the amines used or the reaction conditions employed (Scheme 1). Alternatively these S,N-acetals 3a derived from primary amines can also be synthesized in good yields by reactions of corresponding active methylene compounds with alkyl/



1-4, R = ArCO ; AlkylCO ; CN ; CO_2Et ; $CONH_2$; NO_2 etc

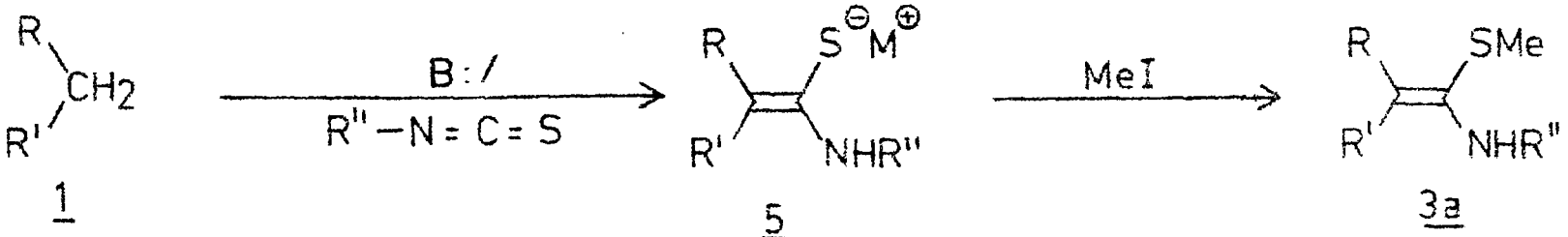
R' = H , alkyl ; aryl ; ArCO ; alkylCO ; CN ; CO_2Et ; NO_2 etc

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

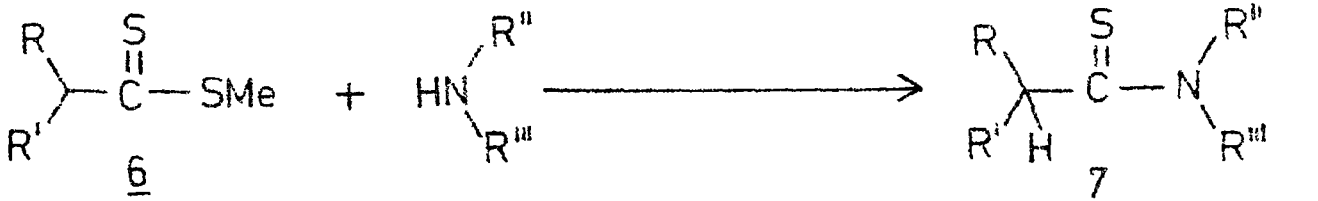
b , R'' = R''' = alkyl , $-(CH_2)_n-$ etc (secondary animines)

Scheme 1

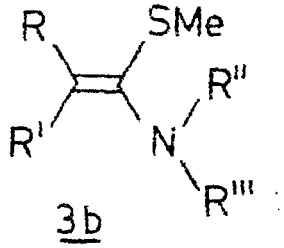
aryl isothiocyanate in the presence of base followed by alkylation (Scheme 2). The keten-S,N-acetals 3b derived from secondary amines are obtained by alkylation of the corresponding thioamides 7 (Scheme 2). These polarized keten S,N- and N,N-acetals also proved to be versatile intermediates for the synthesis of a variety of amino- and mercapto-heterocycles. In some of their reactions, polarized keten S,N-acetals behave as efficient three carbon fragments (those derived from ketones, nitriles and esters) with 1,3-electrophilic centres, which on reaction with bifunctional nucleophiles afford aminoheterocycles (Scheme 3) like aminopyrimidines,[2] aminopyrazoles[3] and aminopyridones.[4] On the otherhand, these intermediates react with a variety of compounds with activated double (triple bonds/E^+) at nucleophilic β-carbon, which on subsequent transformations yield a variety of hietherto inaccessible novel heterocycles (Scheme 3).[5-6] Thus these polarized keten S,N-acetals and N,N-acetals can be considered as novel class of functionalized vinylogous amides or enaminones (those derived from ketones) or polarized enamines (those derived from other active methylene compounds like nitromethane and [illegible] acetonitrle etc). In the present work a systematic investigational study is carried out to further exploit α-oxoketen S,N-acetals as novel functionalized enaminones and efficient three carbon fragments.



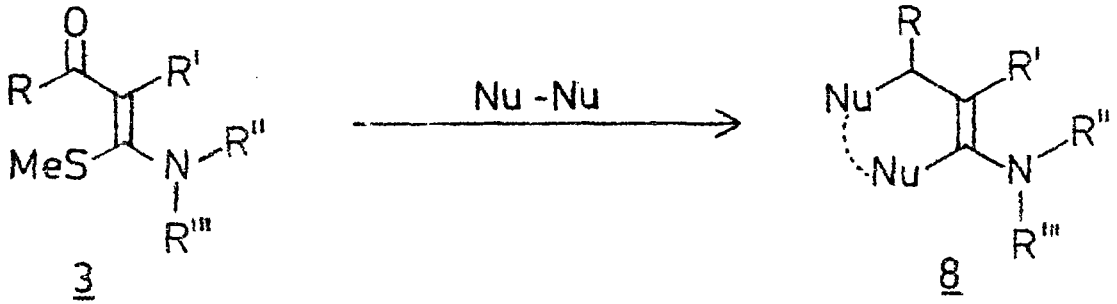
3a , 5 , R'' = aryl or alkyl



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

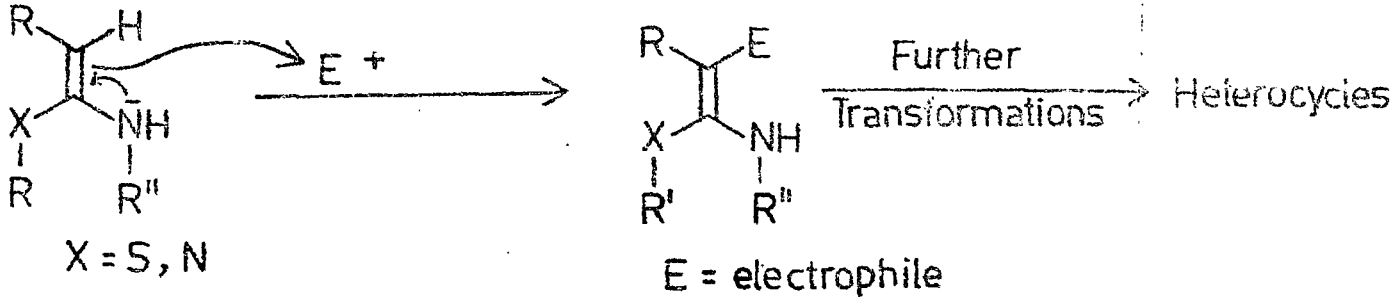


Scheme 2



3 8

S,N-acetals as three carbon fragments for synthesis of aminoheterocycles



S,N- and N,N- as functionalized enamines and enaminones

Scheme 3

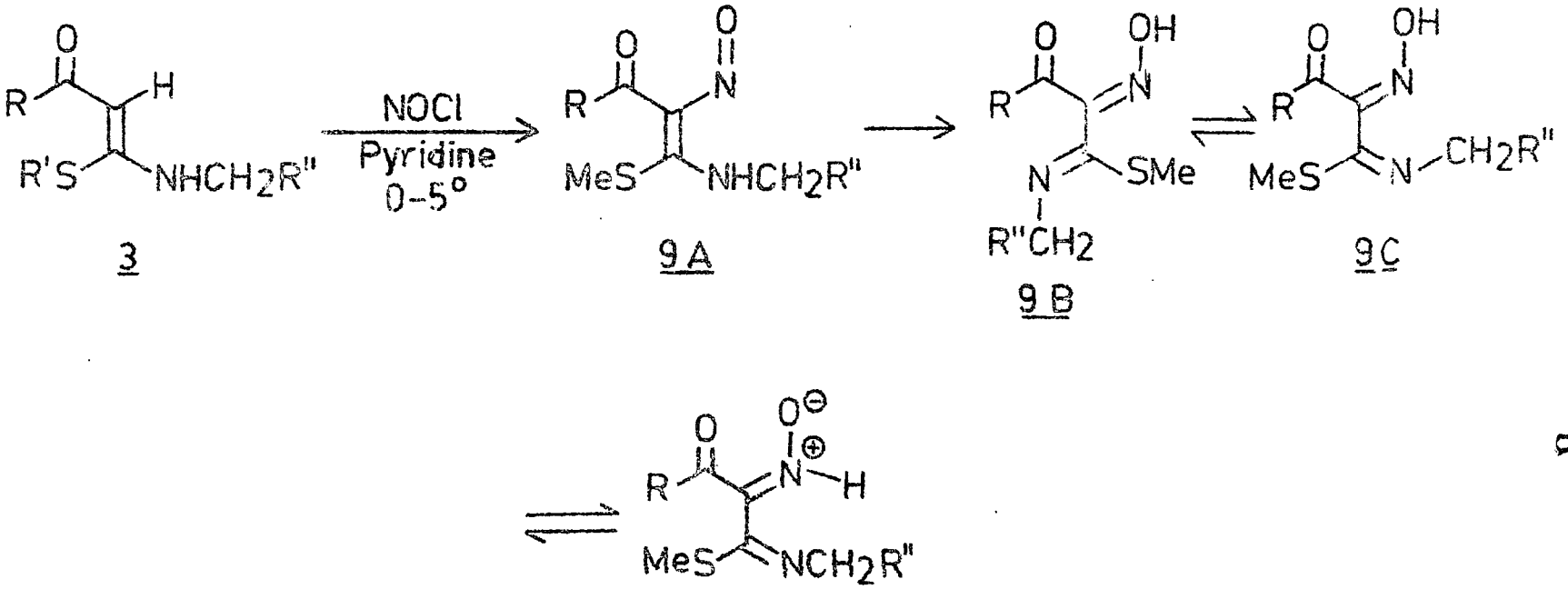
A brief account of the various synthetic transformations of polarized keten-S,S-, S,N- and N,N-acetals achieved in our laboratory is given in the Chapter I.

Synthesis of few selected α-oxoketen-S,N-acetals which were required for subsequent transformation is described in Chapter II. These oxoketen-S,N-acetals were prepared either by displacement method, or by direct method using isothiocyanates. The cyclic ketoketen S,N-acetals were prepared by alkylation of respective thioimides (Scheme 1 and 2).

A novel general approach for imidazole, quinoxaline and thiazole derivatives has been developed via thermal cyclodehydration of novel functionalized nitrosoenaminones* which are obtained by direct nitrosation of α-oxoketen S,N-acetals with nitrosyl chloride. The detailed investigation on these transformations is described in the Chapter III. It is pertinent to note that although a number of purines and alloxazines have been synthesized by cyclocondensation of 4-amino-5-nitrosouracil derivatives,[10] however a similar synthetic operation based on open-chain nitrosoenamines/enaminones (or hydroxyiminoimines) to give imidazole and quinoxaline derivatives has not been

*A. Rahman, H. Ila and H. Junjappa, J.C.S. Chem. Comm., 430 (1984).

investigated earlier. The scant literature on such transformations is primarily due to lack of appropriate open-chain nitrosoenamine enaminone (or hydroxyiminoimine) precursors. We have synthesized a variety of novel class of functionalized nitrosoenaminones or hydroxyiminoimines (9A ⇌ 9D) (Scheme 4) by direct nitrosation of corresponding α-oxoketen S,N-acetals derived from primary aliphatic and aromatic amines (Scheme 4 and 5). Structural studies on these intermediates indicated that they exist in hydroxyiminoimine forms (9B-9D and 10B-10D) (Scheme 4 and 5). These hydroxyiminoimines 9 and 10 proved to be versatile intermediates for the synthesis of imidazole, quinoxaline and thiazole derivatives. Thus thermal cyclodehydration of hydroxyiminoimines derived from primary aliphatic or aralkyl amines under varying conditions afforded the corresponding imidazoles 11 in excellent yields (Scheme 6). Some of the imidazoles could also be synthesized by direct treatment of oxoketen S,N-acetals 3 with nitrosylchloride in refluxing pyridine (Scheme 7). Versatility of these reactions is demonstrated by taking various substituted S,N-acetals (Scheme 7). Mechanistic studies of these thermal cyclodehydrations which involve a 1,5-H Shift have also been incorporated.

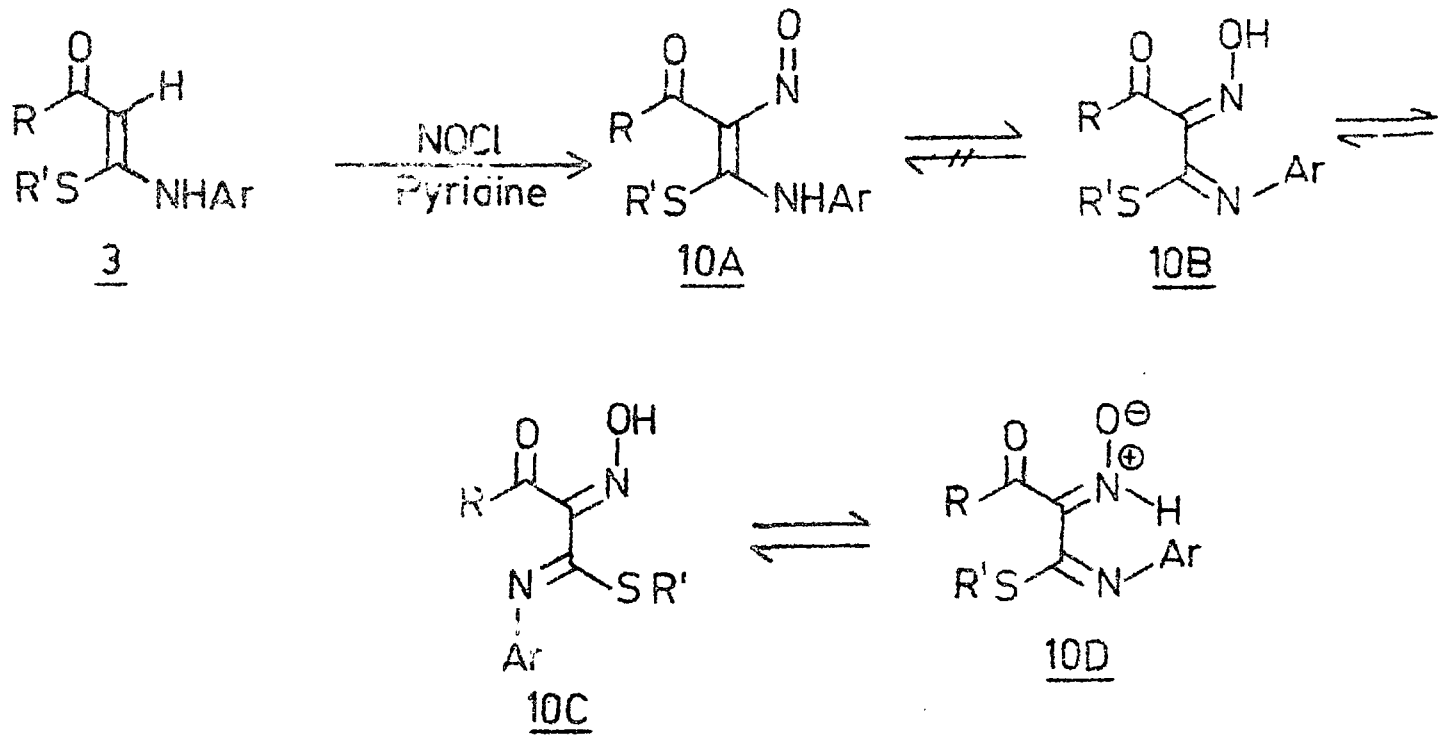


3 9A 9B 9C

9D

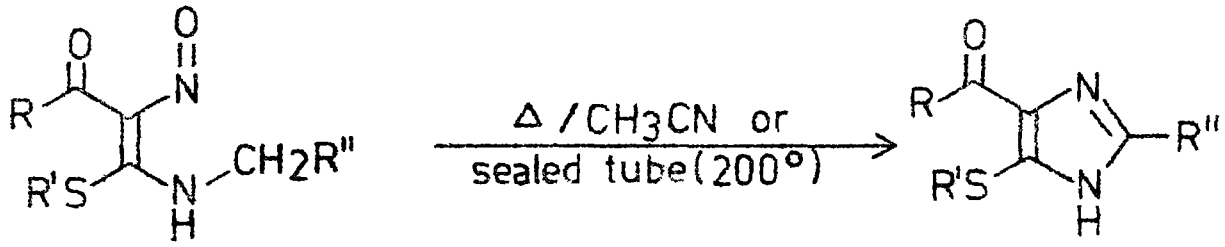
3, 9, R = substituted aryl and alkyl ; R' = Me , Et , $C_6H_5CH_2$;
R" = substituted aryl , Me , Et , CO_2Et etc.

Scheme 4



R = alkyl , aryl ; R' = Me , Et , $C_6H_5CH_2$; Ar = substituted aryl

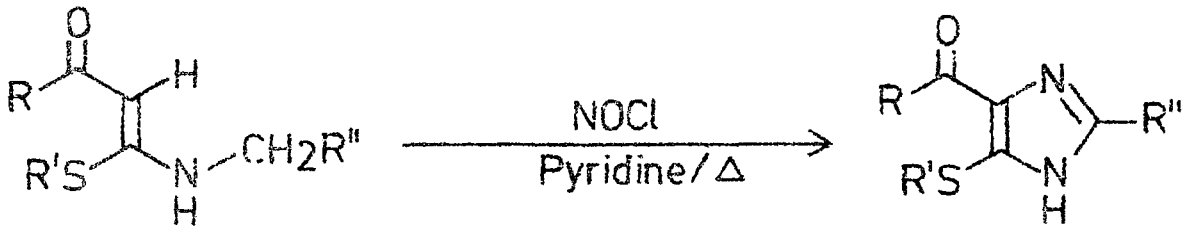
Scheme 5



9 11

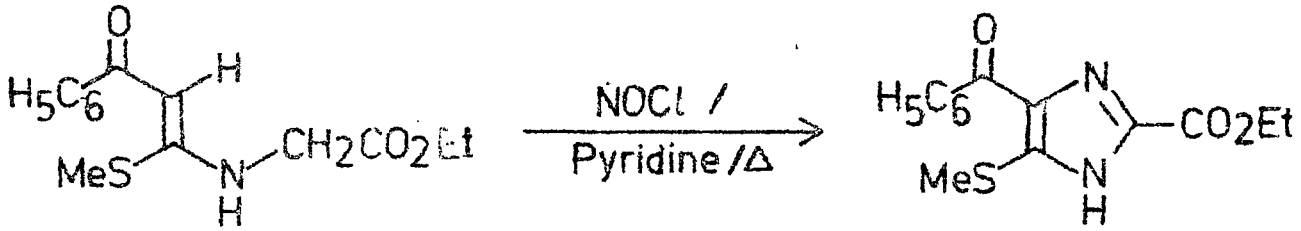
9,11, R = substituted aryl, alkyl ; R' = Me, Et, $C_6H_5CH_2$-;
R" = H, Me, substituted aryl

Scheme 6



3 11

3, 11, R = aryl, alkyl ; R'=Me, Et, $C_6H_5CH_2$;
R" = substituted aryl

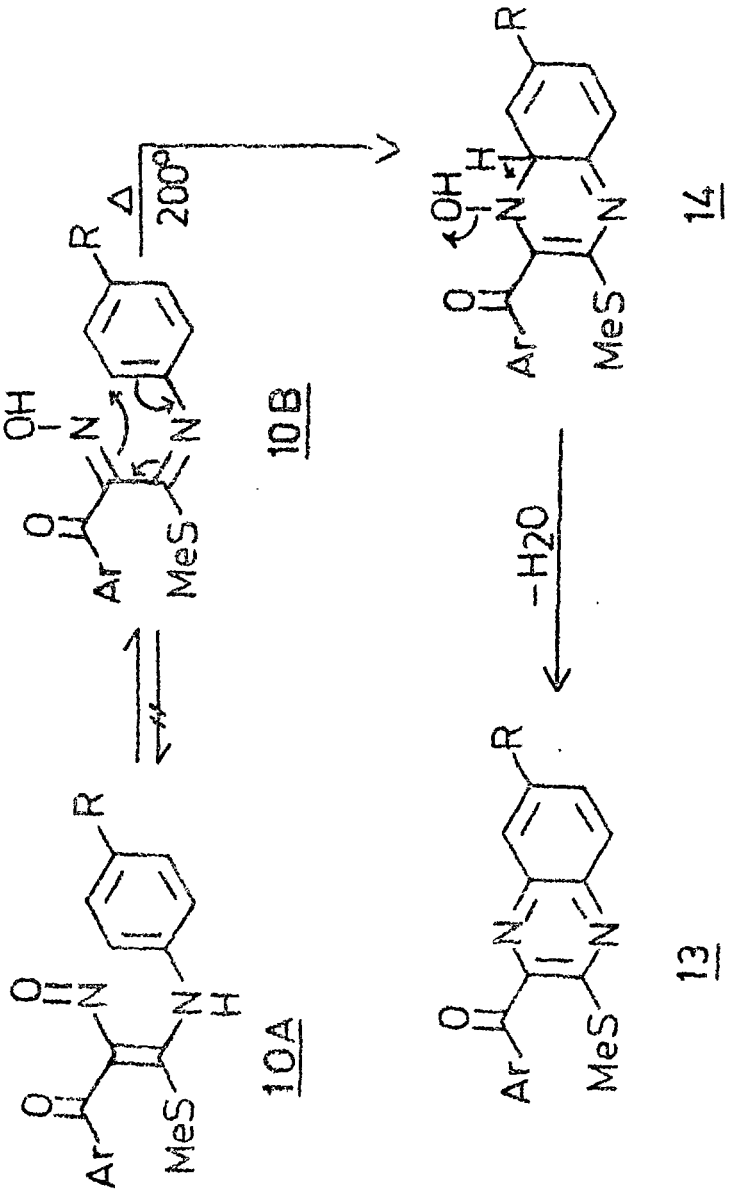


3 12

Scheme 7

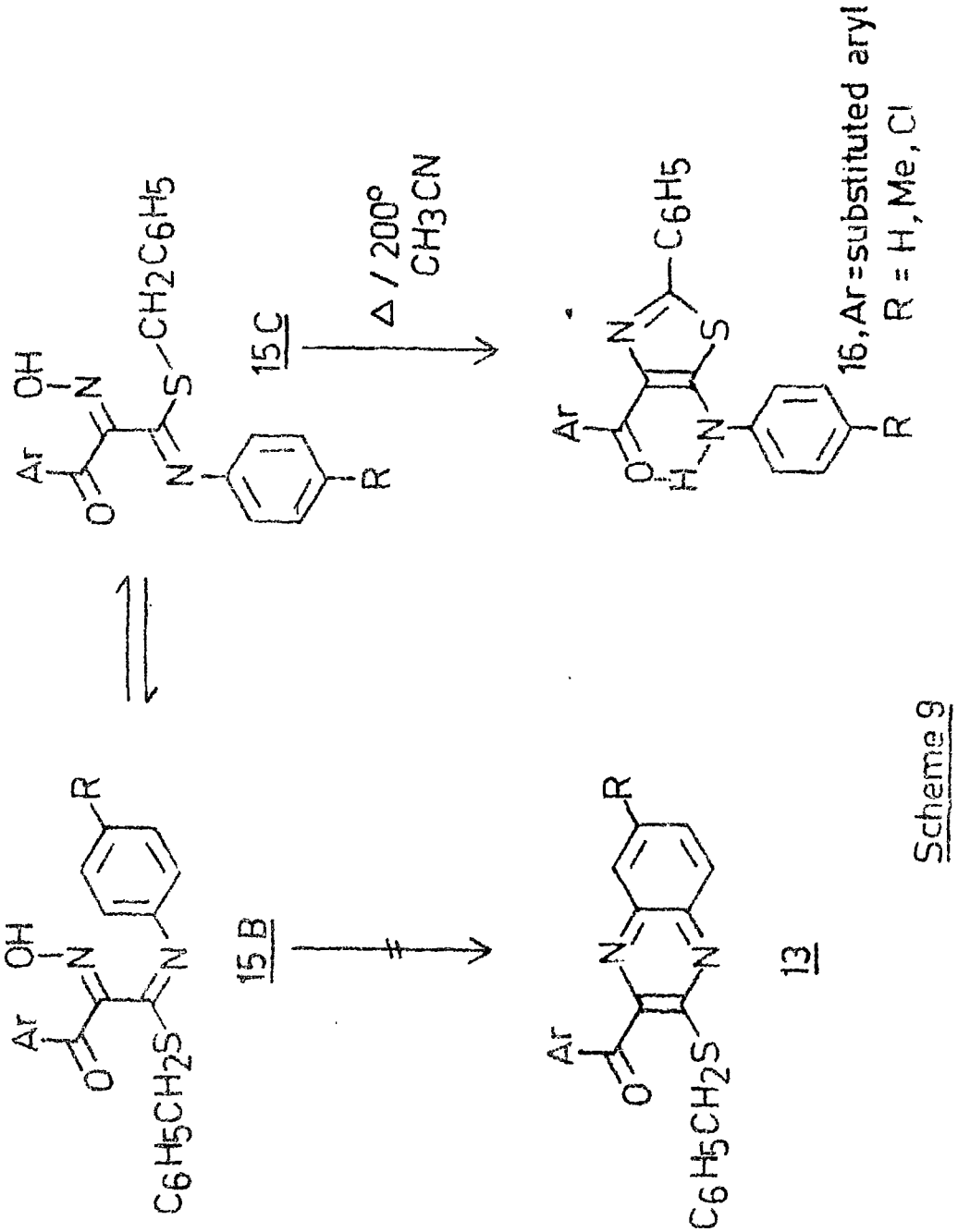
When the hydroxyiminoimines 10 derived from aromatic amines were subjected to thermal cyclodehydration, the corresponding 2-methylthio-3-aroylquinoxalines 13 were obtained in excellent yields (Scheme 8). To best of our knowledge, this is the first report of quinoxaline synthesis from open-chain nitrosoenaminones. Interestingly, however, when the corresponding 5-benzyl-N-anilinohydroxyiminoimine intermediates 15 were subjected to cyclodehydration under similar conditions, the corresponding 2-benzylthioquinoxalines 13 were not obtained, however, the products isolated in good yields were characterized as novel 2-aryl-4-aroyl-5-anilinothiazoles 16 (Scheme 9). The hydroxyiminoimines 9, 10 and 15 are therefore shown to be versatile precursors for novel imidazole, quinoxaline and thiazole derivatives. Mechanism of quinoxaline and thiazole formation and the stereoelectronic factors controlling these transformations are discussed.

Cyclocondensation of α-oxoketen-S,N-alkyl/aralkyl acetals with nitrosobenzene is described in Chapter IV which afforded novel 1-N-aryl 2,5-substituted-4-alkylthioimidazole (17) in excellent yields (Scheme 10). Generality of this method is demonstrated by synthesis of various substituted imidazoles and the mechanism of this cyclocondensation is also discussed.

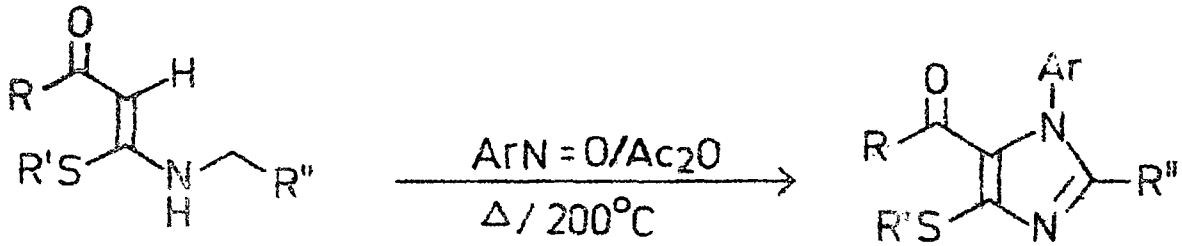


10, 13, 14, Ar = substituted aryl ;
R = H, Me, MeO, Cl

Scheme 8



Scheme 9



3 17

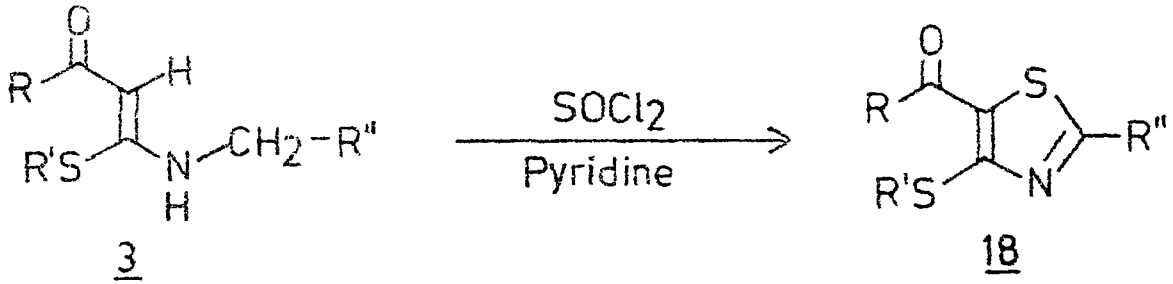
3, 17, R = substituted aryl and alkyl ; R' = Me, Et, $C_6H_5CH_2$; R' = H, Me and aryl ; Ar = C_6H_5 or p-MeC_6H_4

Scheme 10

In the Chapter V of the thesis, a novel method for the synthesis of 2-aryl/carboethoxy-4-alkylthio-5-aroyl/acylthiazoles is reported*, which involves direct annelation of S,N-benzylacetals (3) with thionyl chloride (Scheme 11). It is pertinent to note that 4-alkylthiothiazoles are virtually not known in the literature[11] and this reaction provides a novel route for these heitherto inaccessible 4-alkylthiothiazoles 18 by direct heterocyclization. The method however was not successful for the synthesis of corresponding 2-unsubstituted and 2-alkyl derivatives. Mechanism of these transformations is discussed. Interestingly when the thiazoles 18 were reacted with sodium hydride in DMF, the corresponding debenzoylated thiazoles 19a-d were obtained in excellent yields (Scheme 12). The method therefore is applicable for the synthesis of 5-unsubstituted 4-alkylthiothiazoles also.

In all the reactions described in Chapter III, IV and V, the oxoketen S,N-acetals behave as functionalized vinylogous amide or enaminones which react with nitrosyl chloride, nitrosobenzene and thionyl chloride to yield novel heterocyclic compounds after subsequent transformations. In the last

* A. Rahman, H. Ila and H. Junjappa, Synthesis, 000 (1984).



3 18

3,18 a, R = R" = C_6H_5 ; R' = Me

b, R = p-MeC_6H_4 ; R' = Me ; R" = C_6H_5

c, R = p-$MeOC_6H_4$; R' = Me ; R" = C_6H_5

d, R = p-ClC_6H_4 ; R' = Me ; R" = C_6H_5

e, R = p-$MeOC_6H_4$; R' = Me ; R" = p-ClC_6H_4

f, R = p-$MeOC_6H_4$; R' = Me , R" = p-ClC_6H_4

g, R = p-ClC_6H_4 ; R' = Me ; R" = p-ClC_6H_4

h, R = C_6H_5 ; R' = Me , R" = p-$MeOC_6H_4$

i, R = p-$MeOC_6H_4$; R' = Me ; R" = p-$MeOC_6H_4$

j, R = p-ClC_6H_4 ; R' = Me ; R" = p-$MeOC_6H_4$

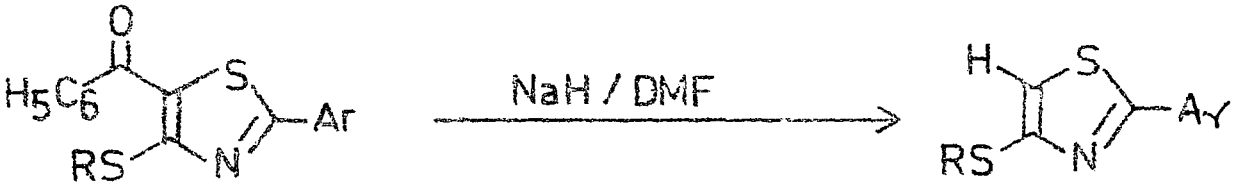
k, R = C_6H_5 ; R' = Et ; R" = C_6H_5

l, R = C_6H_5 ; R' = $-CH_2C_6H_5$; R" = C_6H_5

m, R = p-$MeOC_6H_4$; R' = $-CH_2C_6H_5$; R" = C_6H_5

n, R = Me ; R' = Me ; R" = C_6H_5

Scheme 11



18a , 2e , 2h , 2k

19

a , R = Me ; Ar = C_6H_5
b , R = Me ; Ar = p-ClC_6H_4
c , R = Me ; Ar = p-$MeOC_6H_4$
d , R = Et ; Ar = C_6H_5

Scheme 12

7

Chapter (VI) however, α-oxoketendithioacetals are shown to be versatile 3-carbon fragments for the synthesis of novel 3-aminoisoxazoles* 20 and 21 by reaction with hydroxylamine (Scheme 13 and 14). Thus the reaction of few representative ketoketen S,N-acetals with hydroxylamine afforded the corresponding 3-aryl/alkyl/aralkylaminoisoxazoles 20 in excellent yields (Scheme 13). Similarly the method could also be extended for the synthesis of 3-aminoizoxazoles 21 derived from cyclic secondary amines (Scheme 14). Very few 3-aminoisoxazoles are reported in the literature, which are synthesized by long and circuitous routes.[12] Present procedure provides a facile and simple route for these isoxazoles.

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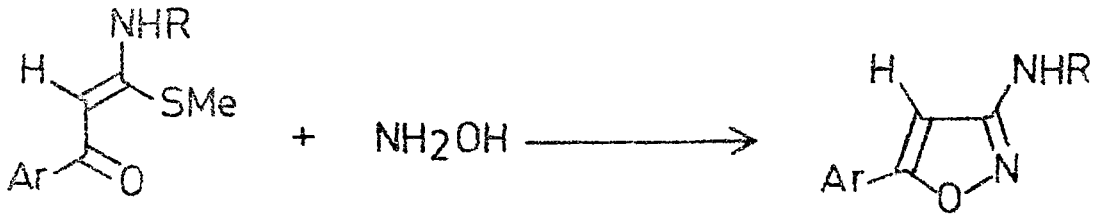
*A. Rahman, R.D. Yadav, H. Ila and H. Junjappa, Synthesis, 000 (1984).



3 20

3, 20 a, Ar = C_6H_5 ; R = C_6H_5

b, Ar = p-MeC_6H_4 ; R = C_6H_5

c, Ar = p-$MeOC_6H_4$; R = C_6H_5

d, Ar = p-ClC_6H_4 ; R = C_6H_5

e, Ar = C_6H_5 ; R = Et

f, Ar = p-$MeOC_6H_4$; R = Et

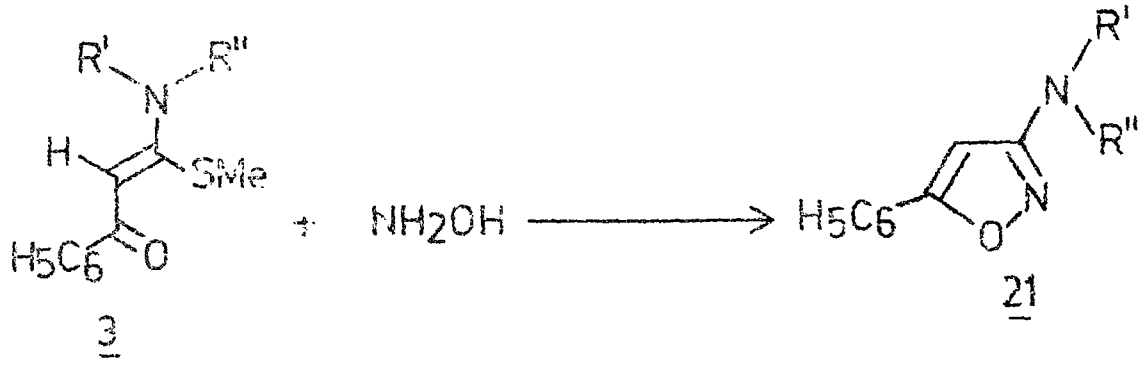
g, Ar = p-ClC_6H_4 ; R = Et

h, Ar = C_6H_5 ; R = $C_6H_5CH_2$

i, Ar = p-ClC_6H_4 ; R = $C_6H_5CH_2$

j, Ar = p-MeC_6H_4 ; R = $C_6H_5CH_2$

Scheme 13



3,21 k, R' = R' = $-(CH_2)_4-$
l, R' = R'' = $-(CH_2)_5-$
m, R' = R'' = $-(CH_2)_2-O-(CH_2)_2-$
n, R' = R'' = $-(CH_2)_2-N(C_6H_5)-(CH_2)_2-$

Schema 14

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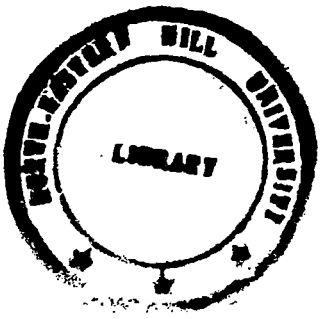

To

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JUNE, 1984

RAH

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 Mr. Azizur-Rahman under my supervision. He 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 : 11th June 1984

H. Ila
(H.ILA)

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Head,
Department of Chemistry

23rd April 1984

This is to certify that Mr. Azizur-Rahman, a Ph.D student of the Department of Chemistry has completed the following courses as part of his Ph.D course programme:-

Course No	Title	Name of the In-charge of the course
CHEM-630	Bio genesis of Natural products.	H. Junjappa
CHEM-608	Bio in-organic Chemistry	J. Subramanian

T.S.B. Narasaraju

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Lastly, I take this opportunity to express my sincere gratitude to my parents for their continued encouragement and patience.

A. Rahman
Azizur-Rahman

C O N T E N T S

P R E F A C E

Earlier work from this laboratory has demonstrated that polarized keten S,N- and N,N-acetals which are easily derived from a variety of active methylene compounds, are versatile intermediates for the synthesis of novel heterocyclic compounds. In the present investigation, a systematic study was undertaken to further exploit α-oxoketen S,N-acetals as novel functionalized enaminones and useful three carbon fragments for construction of a variety of novel heterocyclic ring systems. These studies have resulted in new general methods for the synthesis of novel imidazole,quinoxaline,thiazole and isoxazole derivatives.

In the first chapter, a brief survey of the various synthetic transformations using polarized keten S,S-, S,N- and N,N-acetals achieved in this laboratory is described.

In the second chapter synthesis of few selected polarized keten S,N- and N,N-acetals required for subsequent transformations is described.

The reactions of α-oxoketen S,N-acetals with nitrosyl chloride are discussed in Chapter III. The reactions afford

a novel class open-chain functionalized hydroxyiminoimine intermediates in excellent yields, which are not described earlier. Subsequent thermal cyclodehydration of the hydroxyiminoimines afforded novel imidazole, quinoxaline and thiazole derivatives. The generality and synthetic limitations of these methods and mechanism of these transformations are discussed.

In the next Chapter (IV) a new general method for 1-N-aryl-2-unsubstituted/alkyl/aryl-4-alkylthio-5-aroyl/acylimidazoles has been developed by cyclocondensation of α-oxoketen S,N-alkylacetals with nitrosoarenes.

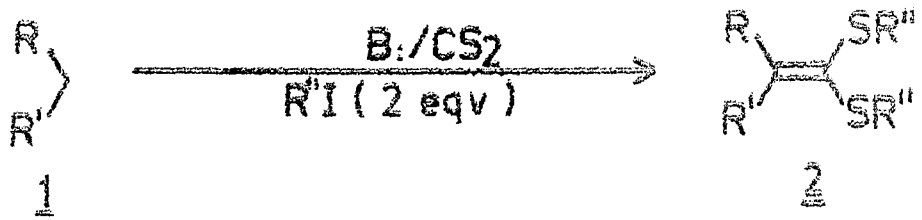
In the fifth chapter annelation of α-oxoketen S,N-acetals with thionyl chloride to give heitherto inaccessible 4-alkylthio-2-aryl/ethoxycarbonyl-5-aroyl/acyl/unsubstituted thiazoles is discussed. The limitations of the method are described.

In all the reactions of α-oxoketen S,N-acetals described in Chapter III, IV and V, the enamine character of these intermediates was exploited. In the last chapter, ketoketen S,N-acetals are shown to be efficient three carbon fragments for the synthesis of novel 3-aminoisoxazoles by reaction with hydroxylamine. The reaction was found to be general for the synthesis of 3-anilino, 3-alkylamino and 3-N-azacycloalkylaminoisoxazoles.

CHAPTER I

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

The polarized keten dithioacetal 2 are among the simplest synthetic intermediates[1,2] which can be prepared by simple methods treating active methylene compounds of general formula 1, with two equivalents of base in the presence of carbon disulfide followed by alkylation (Scheme 1). These acetals 2 are either liquids with well defined boiling points or solids, with sharp melting points which can be purified by conventional purification methods. They are stable at room temperature,under mild acidic and alkaline conditions and can be stored indefinitely without apparent decomposition. On the otherhand, the corresponding O,O-acetals[3] 3 are generally prepared by methods involving more than one step, strictly



1 2

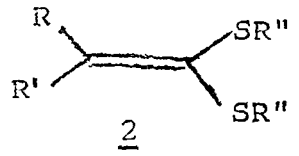
1,2, R=H, Alkyl, Aryl, ArCO, AlkylCO, CO_2R, CN, $CONH_2$, NO_2, Sulphonyl etc

R'= ArCO, alkylCO, H, CO_2R, CN, $CONH_2$, NO_2 etc

R" = alkyl

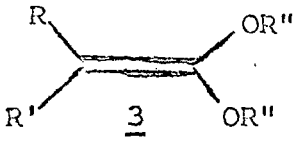
Scheme 1

under moisture free conditions since they undergo rapid hydrolytic cleavage. Besides, active methylene compounds can not be used as starting materials to prepare these compounds employing the same methods used for the corresponding S,S-acetals. Similarly, keten dihalogenides[4] 4 are prepared in the laboratory by chlorinating directly the corresponding keten-S,S-acetals 2, thus making the acetals 2 as primary precursors of keten dihalogenides 4. Similarly the corresponding N,N-acetals 5 are also derived from either one of the analogues 2,3 or 4. Apparently, the polarized keten-S,S-acetals 2, form an important class of 1,3-electrophilic three carbon fragments, which are of potential synthetic value. Despite a large number of reports in the literature on their preparations and physical properties,[6-14] a systematic synthetic investigation on their synthetic utility was not much explored until these studies were initiated in our laboratory.



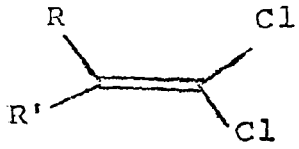
2

Keten-S,S-acetals



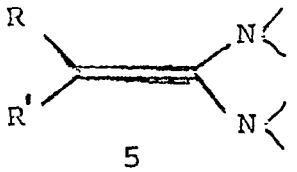
3

Keten-O,O-acetals



4

Keten dihalogenides



5

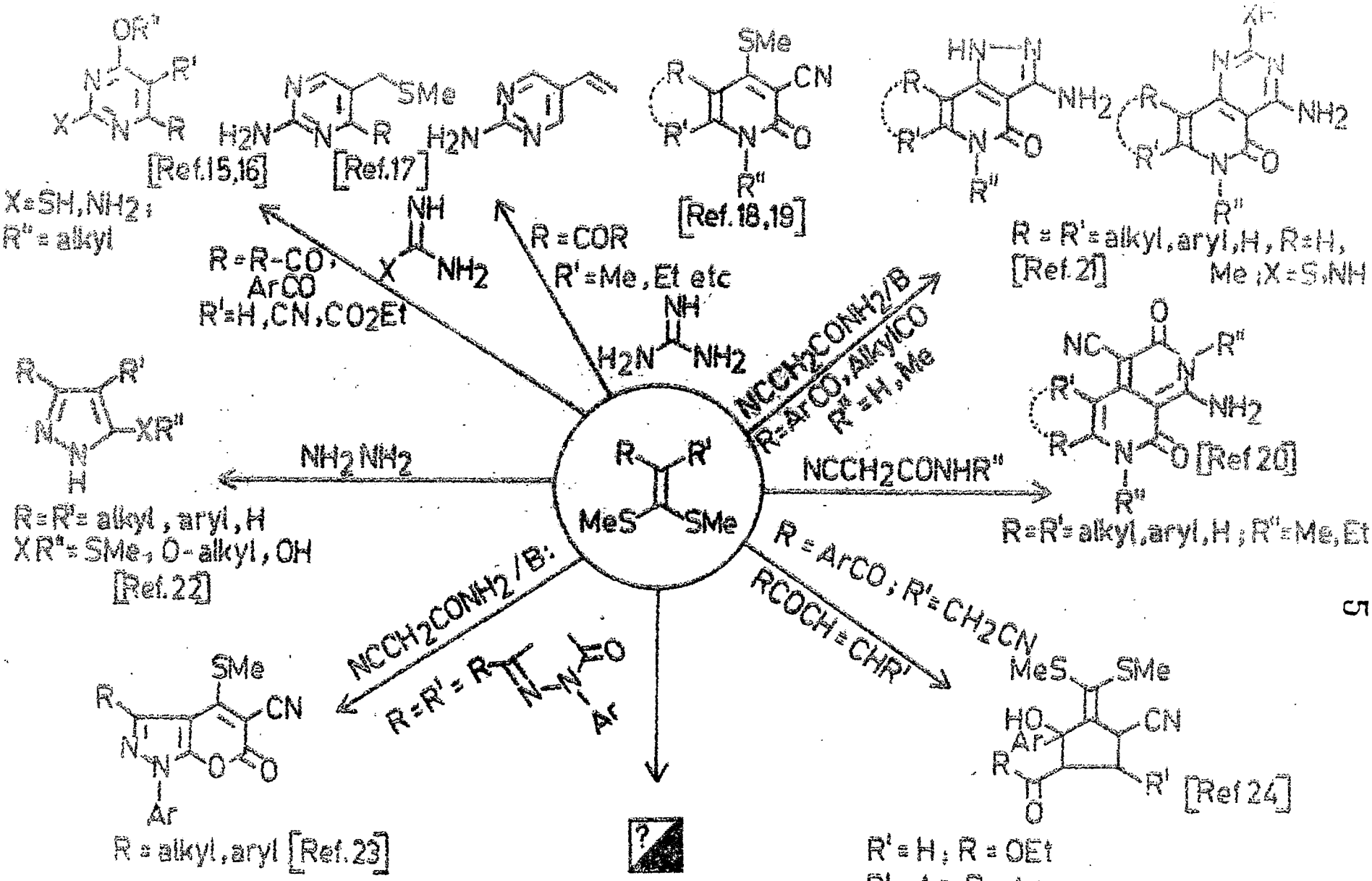
Keten-N,N-acetals

2-5, R=H, alkyl, aryl, nitrile, acyl, aroyl, nitro, sulphonyl etc.

R' = nitrile, acyl, aroyl, sulfonyl, nitro etc.

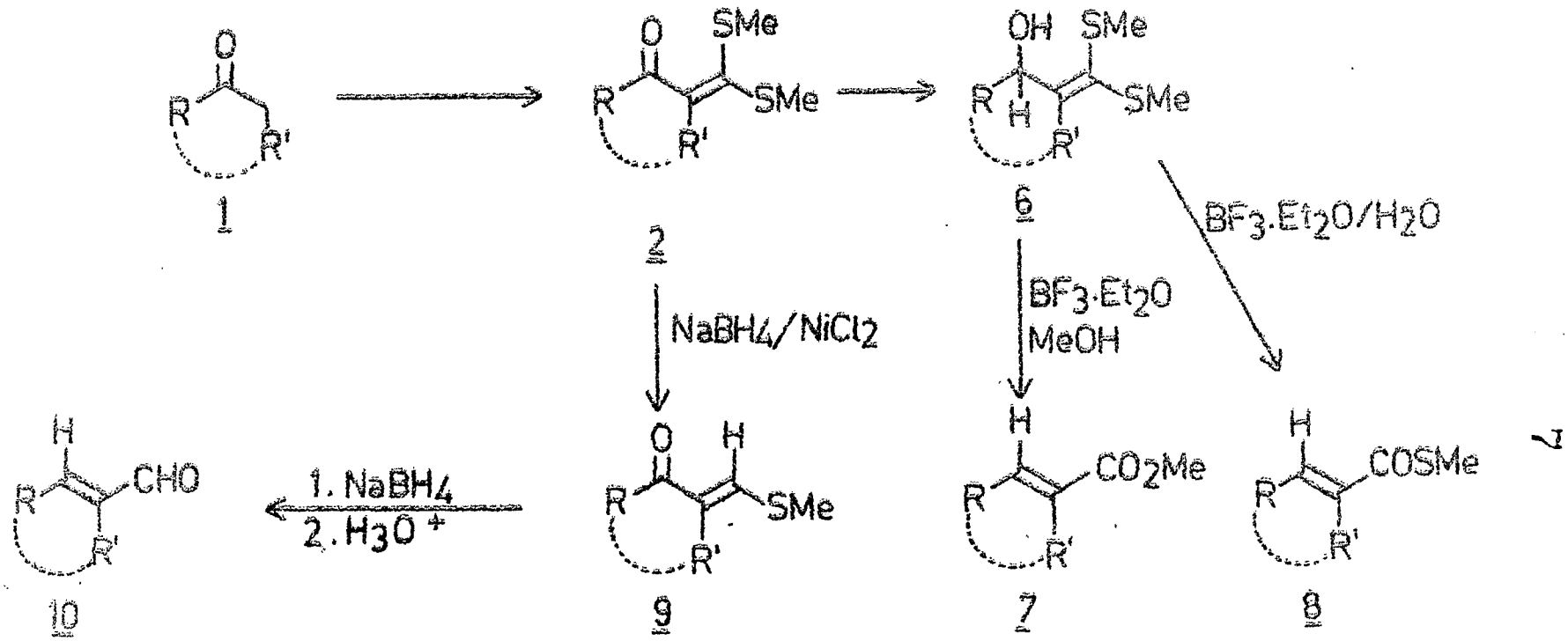
R" = alkyl group.

A few of the important synthetic applications of 2 for the construction of a variety of heterocyclic compounds which are developed in our laboratory are shown in the Scheme 2. The methods thus developed have been shown to be of general synthetic importance, since the choice of the structural variants of active methylene compounds is quite large. Besides, these ketoketen dithioacetals have been shown to be versatile intermediates for 1,3-carbonyl transposition. Thus we have shown


[Ref.15,16]
X=SH,NH2;
R''=alkyl
[Ref.17]
[Ref.18,19]
R=COR
R'=Me,Et etc
R=R-CO,
ArCO
R'=H,CN,CO2Et
[Ref.21]
R=R'=alkyl,aryl,H, R=H,
Me ;X=S,NH
NCCH2CONH2/B
R=ArCO,AlkylCO
R'=H,Me
[Ref.20]
R=R'=alkyl,aryl,H ; R''=Me,Et
NH2NH2
R=R'=alkyl, aryl, H
XR''=SMe, O-alkyl, OH
[Ref.22]
NCCH2CONHR''
NCCH2CONH2/B
R=R'=
[Ref.23]
R=alkyl,aryl
R=ArCO ; R'=CH2CN
RCOCH=CHR'
[Ref.24]
R'=H ; R=OEt
R'=Ar ; R=Ar

Scheme 2

in our earlier work that α,β-ketoketen-S,S-acetals derived from various active methylene ketones undergo selective 1,2-reduction with sodium borohydride to give the corresponding carbinol acetals 6 in nearly quantitative yields (Scheme 3). These carbinol acetals undergo boron trifluoride etherate assisted methanolysis to afford the corresponding α,β-unsaturated esters 7 in good to excellent yields. Thus a highly stereoselective and regiospecific method for homologation of easily available ketones 1 to α,β-unsaturated esters has been developed.[25] The carbinol acetals 6 on treatment with boron trifluoride etherate and water yield the corresponding α,β-unsaturated S-methylesters 8. On the otherhand, ketoketen dithioacetals 2 undergo selective reductive dethiomethylation in the presence of sodium borohydride and nickel (II) chloride to give β-alkylthiomethyleneketones 9 in good yields.[26] These alkylthiomethylene ketones could be converted to α,β-unsaturated aldehyde 10 by 1,2-reduction with sodium borohydride and subsequent hydrolytic rearrangement (Scheme 3). Further, the corresponding arylidene dithioacetals 12 obtained by condensation of aromatic aldehydes and acylketen dithioacetals 11, yielded corresponding methyl 5-aryl-2,4-pentadienoates 14 on



1,2,6–10, R and / or R' = Ar, alkyl, H

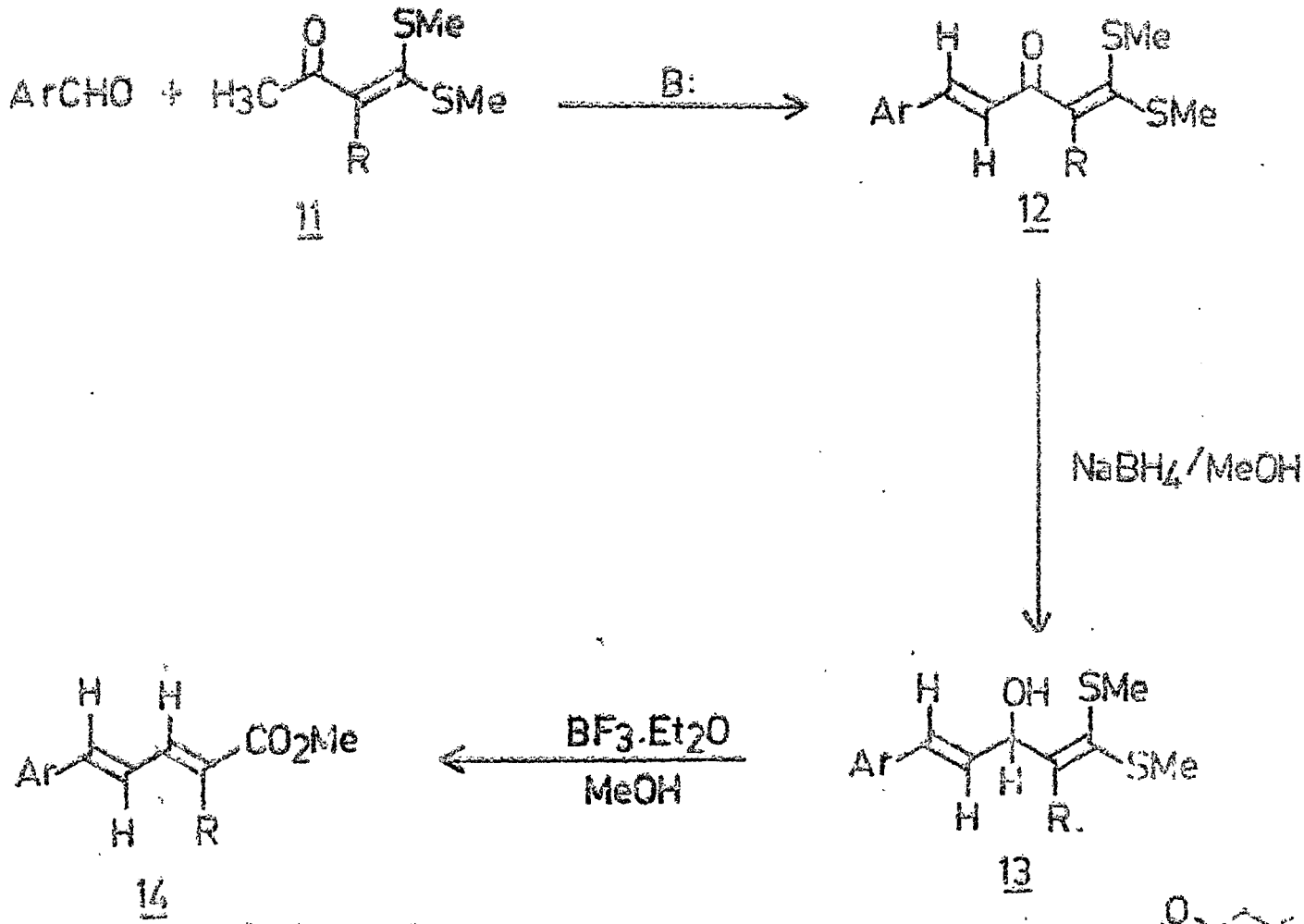
R = R' = $-(CH_2)_n-$

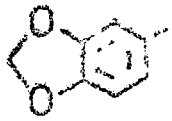
Scheme 3

borohydride reduction and subsequent methanolysis in the presence of boron trifluoride etherate.[27] Thus ketoketen dithioacetals 2 have been shown to be common precursors for α,β-unsaturated-O-methyl, S-methyl esters, α,β-unsaturated aldehydes and methyl-5-aryl pentadienoates.

The ketoketen dithioacetals 15 derived from propiophenone and other higher analogous are shown to undergo interesting 1,3-alkylthio shift to give the rearranged acrylophenones 16 in the presence of base like sodium hydride (Scheme 5).[28] A detailed mechanistic studies on this rearrangement has been already published.[29] Similarly the allylketen dithioacetals 17 are shown to undergo an unprecedented 1,5-alkylthio shift in the presence of sodium hydride and dimethylformamide to give novel dienes 19 (Scheme 5). Mechanistic studies on this rearrangement has shown to involve concerted pathways through the diene intermediate 18 (Scheme 5).[31]

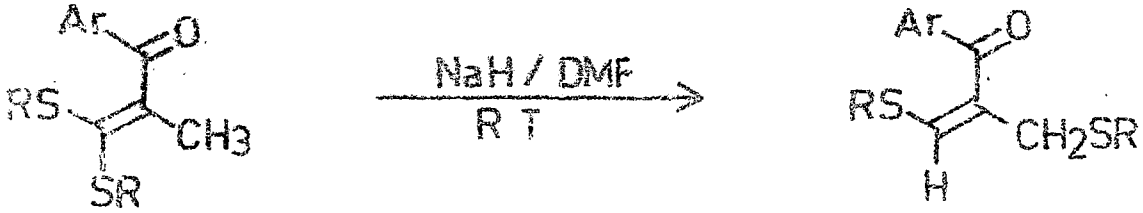
The dithioacetals are also shown to undergo facile displacement reactions with primary and secondary amines to give the corresponding S,N-20 and N,N-acetals 5 depending upon the stoichiometry of the amines used. The S,N-acetals 20 (R"=H)



12-14, Ar = C_6H_5, p-MeC_6H_4, p-ClC_6H_4, p-MeC_6H_4, 

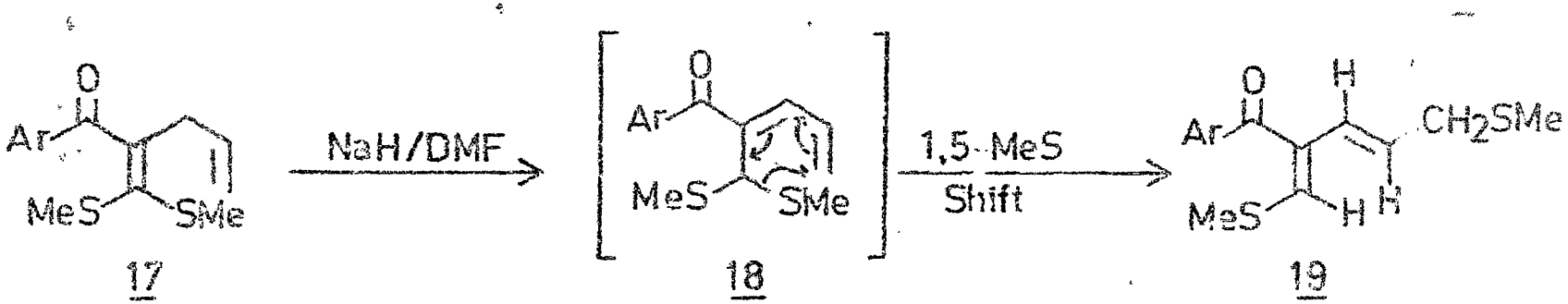
R = H, Me

Scheme 4



15 16

15, 16, Ar = C_6H_5, p-MeC_6H_4, p-ClC_6H_4, p-$MeOC_6H_4$.

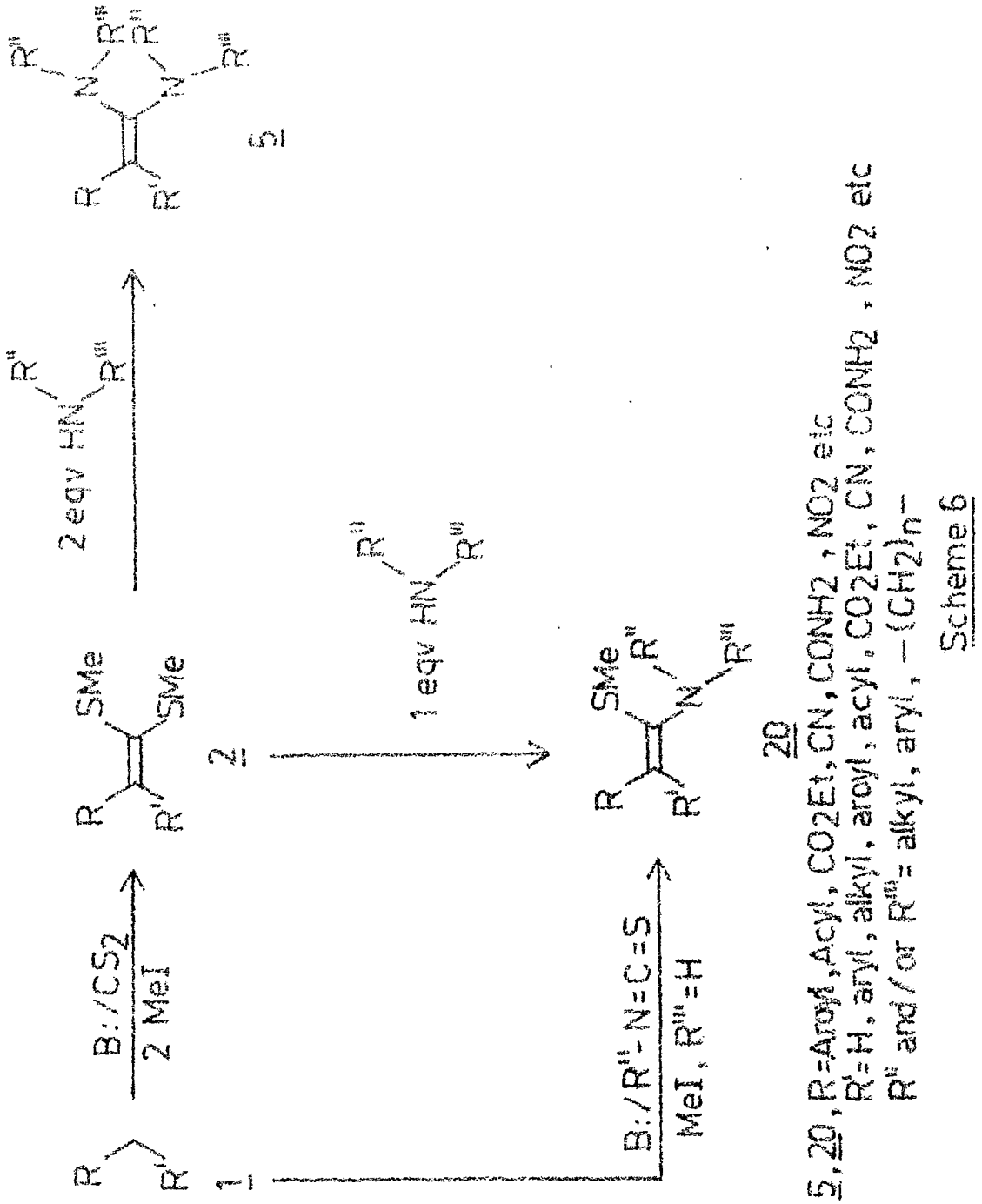


17 18 19

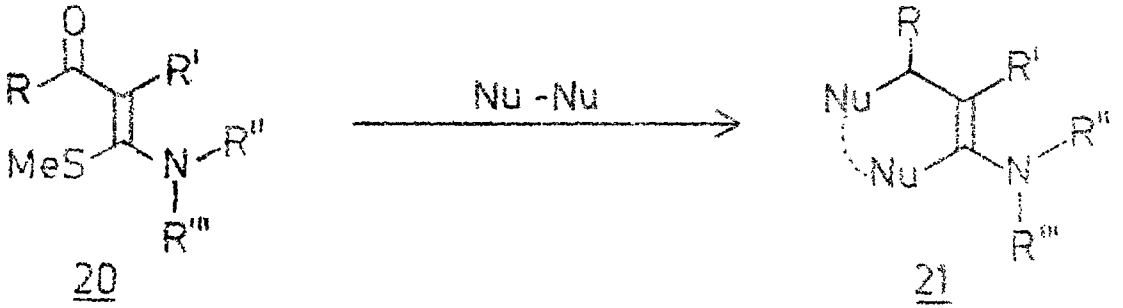
Scheme 5

are best prepared by treating active methylene compounds with appropriate isothiocyanates in the presence of base followed by alkylation (Scheme 6).[32] These S,N- and N,N-acetals represent a novel class of functionalized vinylogous amides or enaminones (those derived from ketones) or enamines (those derived from other active methylene compounds), which proved to be versatile intermediates for the synthesis of a variety of amino- and mercaptoheterocycles (Scheme 7). Some of these transformations achieved in our laboratory are shown in the Scheme 8 and 9. Thus ketoketen S,N-acetals are shown to be useful three carbon fragments for the synthesis of aminoheterocycles by reacting with bifunctional nucleophiles (Scheme 8).[33-35] On the otherhand, the behaviour of polarized S,N- and N,N-acetals as functionalized enaminones or enamines is manifested in the reactions of 5 and 20 with compounds having activated multiple bonds leading to the synthesis of a wide variety of amino and alkylthioheterocycles (Scheme 9).[36-40] Few of the other transformations of these acetals for the synthesis of pyrrolines 30, 2-aminopyrroles 32 and thiazoline derivatives 34 are shown in the Scheme 10.[41-43]

It is evident from these schemes that polarized keten-S,S-S,N- and N,N-acetals which can be prepared in larger quantities

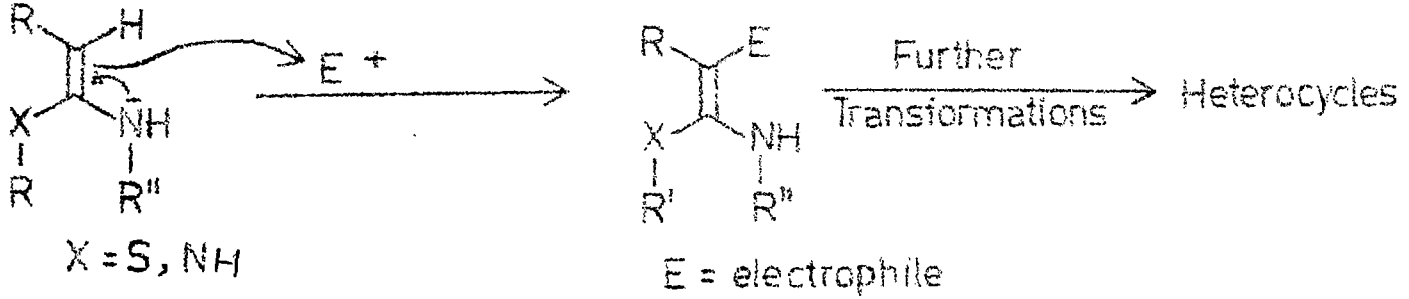

B:/CS2
2 MeI
2 eqv HN
1 eqv HN
B:/R'''-N=C=S
MeI, R'''=H
SMe
SMe
5, 20, R=Aroyl, Acyl, CO2Et, CN, CONH2, NO2 etc
R'=H, aryl, alkyl, aroyl, acyl, CO2Et, CN, CONH2, NO2 etc
R'' and/or R'''= alkyl, aryl, —(CH2)n—

Scheme 6



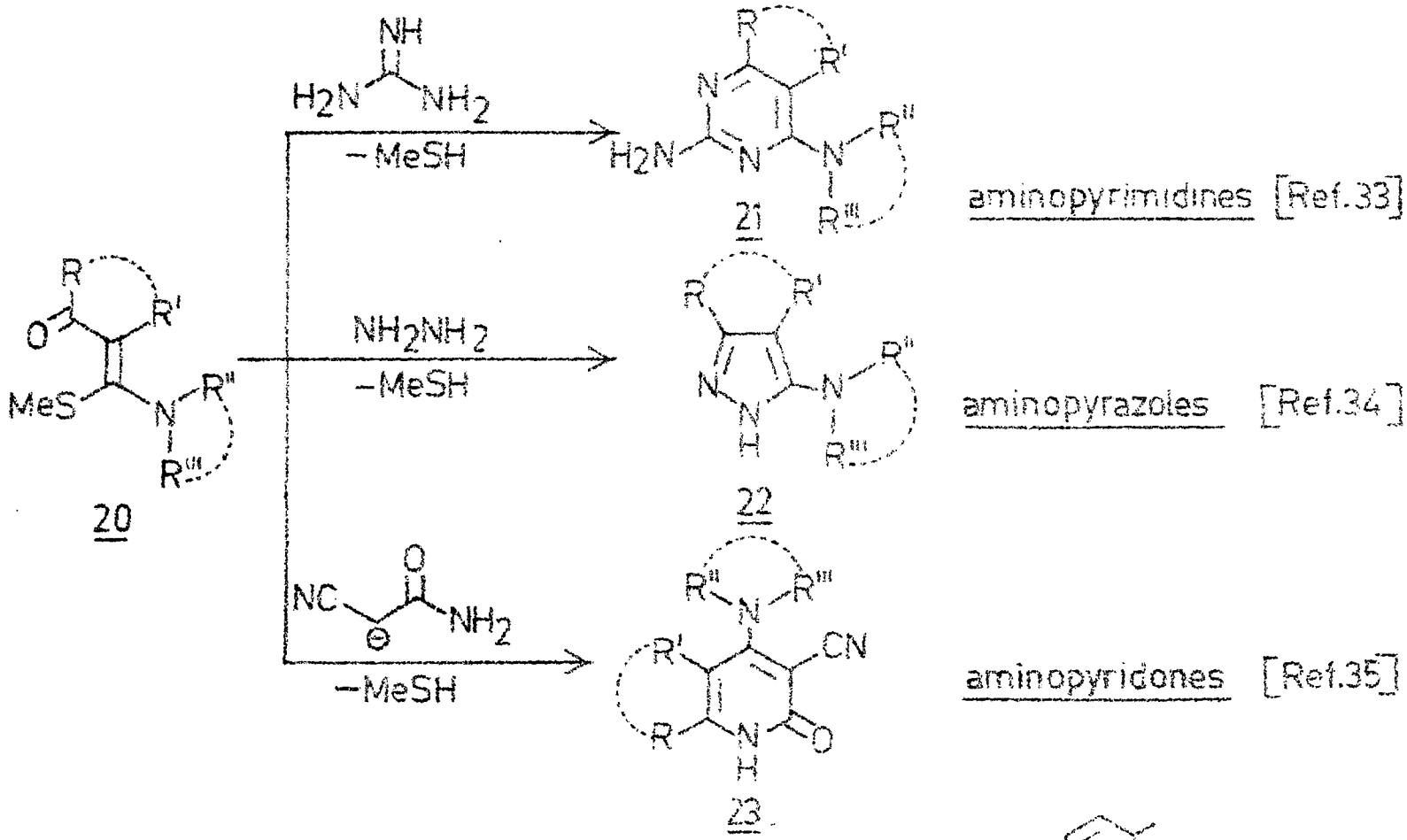
20 21

S,N-acetals as three carbon fragments for synthesis of aminoheterocycles



S,N- and N,N- as functionalized enamines and enaminones

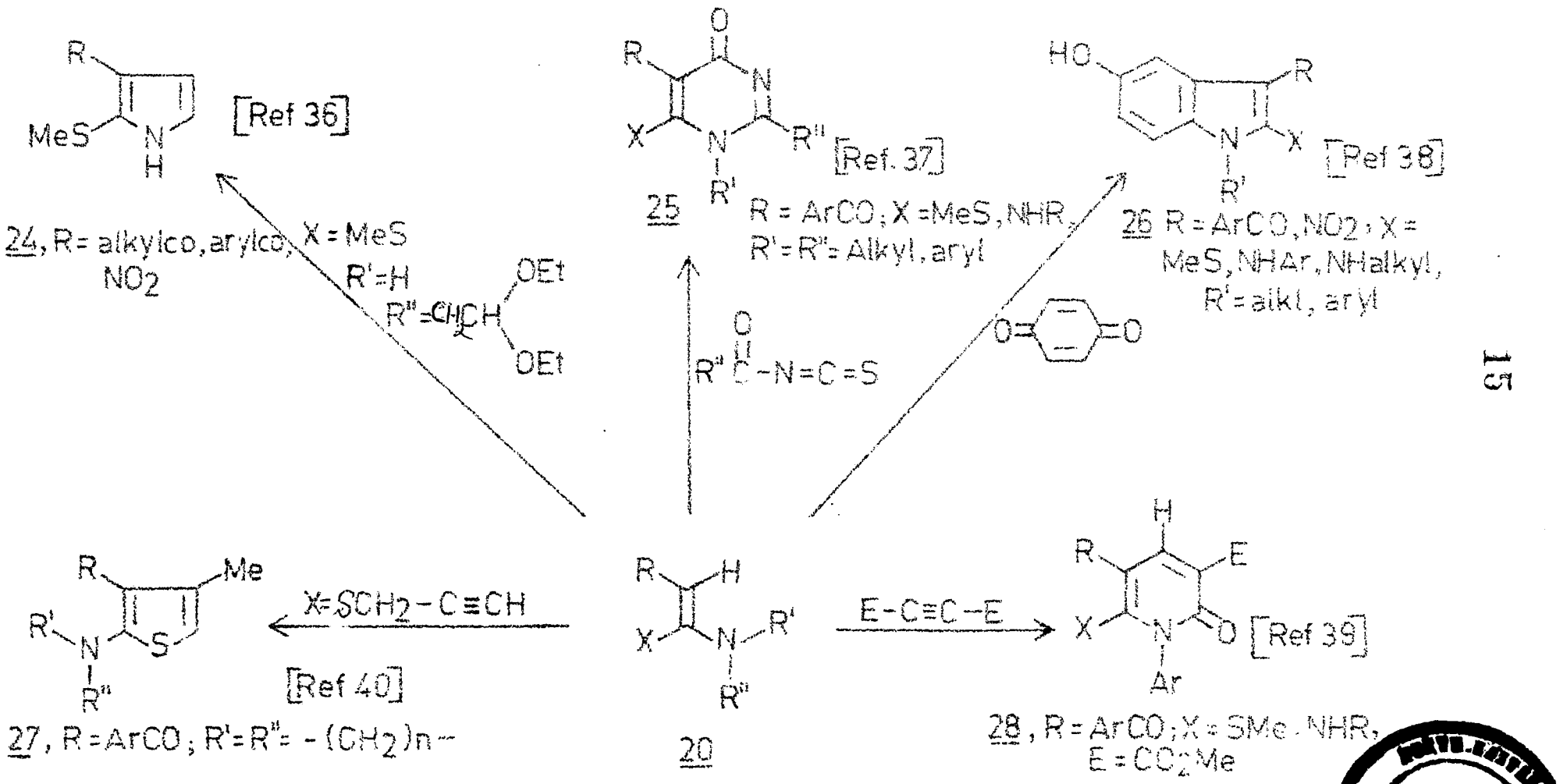
Scheme 7



20-23, R and/or R' = Ar, alkyl, H, $-(CH_2)n-$,

R and/or R''' = Ar, alkyl, H, $-(CH_2)n-$, $-(CH_2)_2-X-(CH_2)_2-$

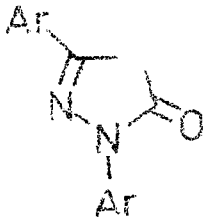
Scheme 8

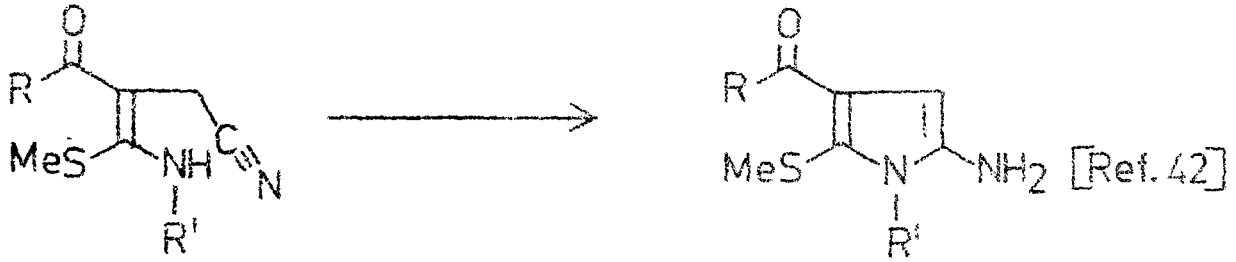

[Ref 36]
24, R = alkylco, arylco, NO2
X = MeS
R' = H
R'' = CH(OEt)2
[Ref. 37]
25
R = ArCO, X = MeS, NHR,
R' = R'' = Alkyl, aryl
[Ref 38]
26 R = ArCO, NO2, X = MeS, NHAr, NHalkyl,
R' = alkl, aryl
X = SCH2 − C≡CH
[Ref 40]
27, R = ArCO; R' = R'' = −(CH2)n−
20
E − C≡C − E
[Ref 39]
28, R = ArCO; X = SMe, NHR,
E = CO2Me

Scheme 9

29 30 [Ref.41]

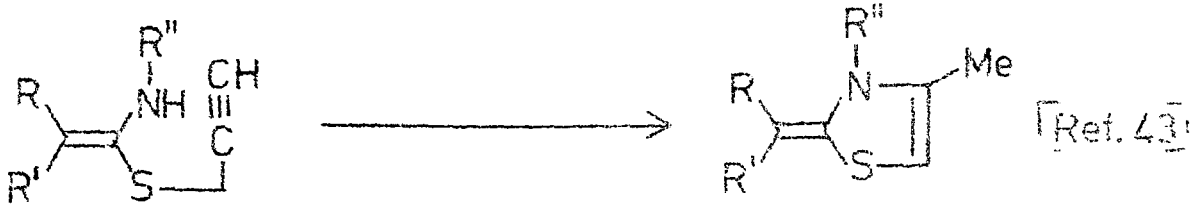
29, 30, R and / or R' = CO_2Me, CN, $CONH_2$,





31 32 [Ref. 42]

31, 32 R = Substituted aryl ; R' = Me , Et , Cyclohexyl etc.



33 34 [Ref. 43]

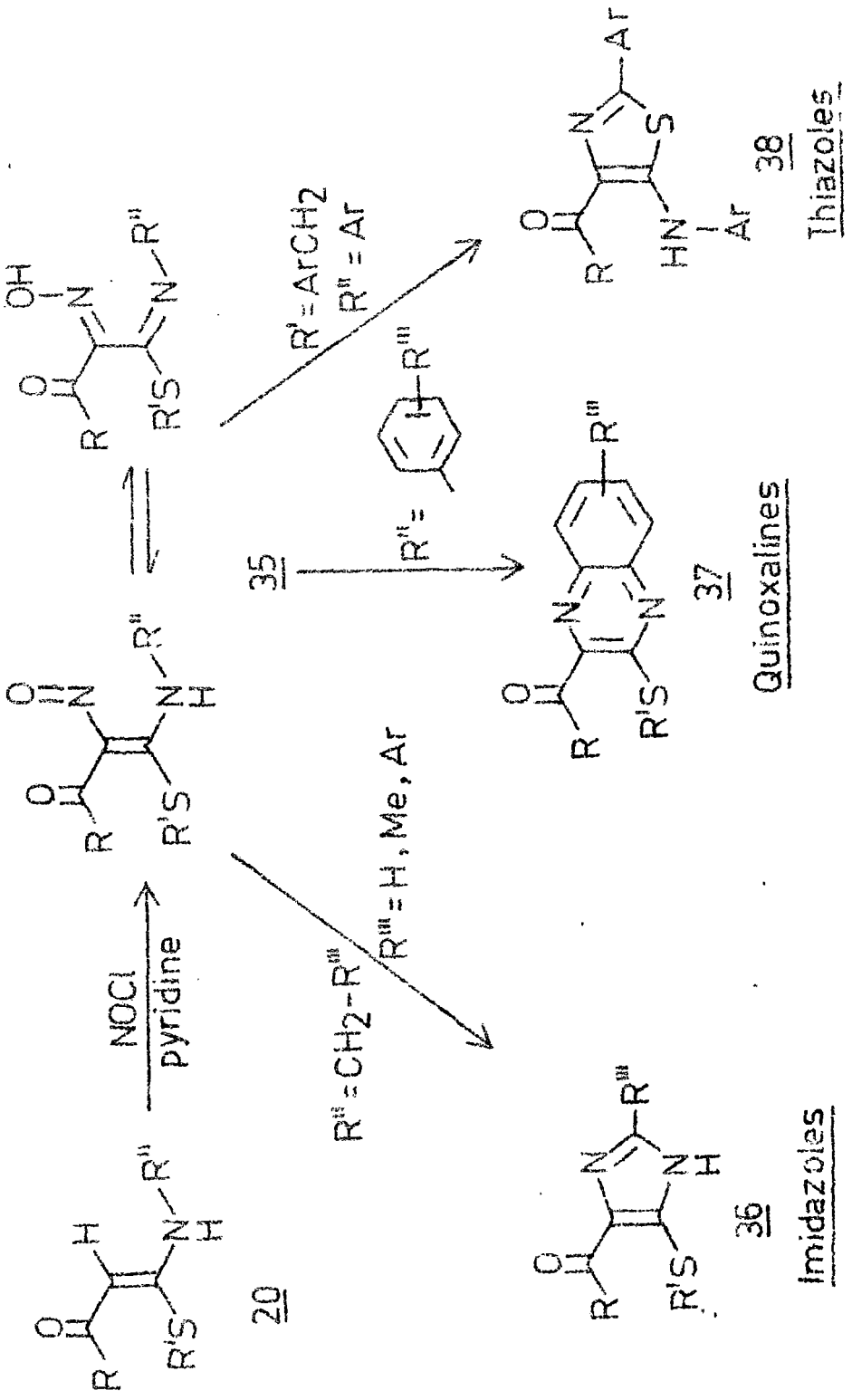
R and / or R' = ArCO , MeCO ; Ar, CN , H R'' = alkyl , aryl

Scheme 10

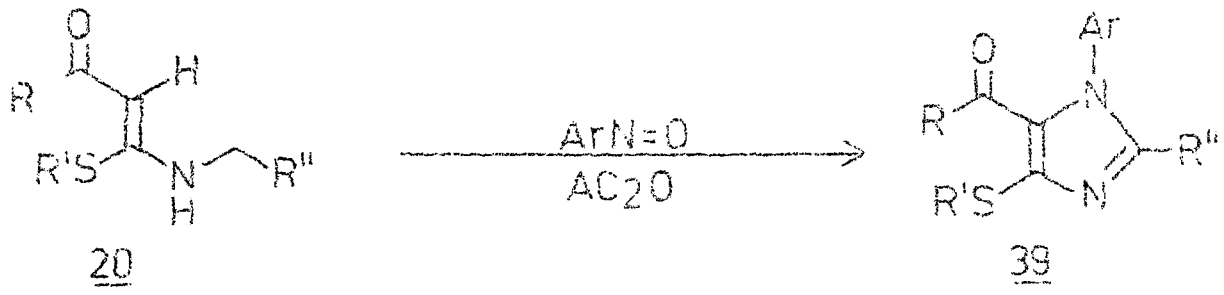
from a variety of active methylene compounds can serve as building blocks for the construction of novel heitherto inaccessible heterocyclic systems. In the present investigation, we have studied electrophilic nitrosation of ketoketen-S,N-acetals 20 with nitrosyl chloride, which afforded nitrosoketen-S,N-acetals (or hydroxyiminoimines) 35 in excellent yields. These nitroso-enaminones 35 again proved to be useful versatile synthons for the construction of a number of heterocyclic systems.[44] Synthesis of these heitherto unknown nitrosoenaminones 35, their structural studies and synthetic transformations leading to new general routes for the imidazole, quinoxaline and thiazole derivatives (Scheme 11) are described in the Chapter III.[44]

In Chapter IV, a novel general route for N-arylimidazole derivatives 39 by reaction of ketoketen-S,N-acetals 20 with nitrosobenzene has been described (Scheme 12).

Annelation of ketoketen S,N-acetals with sulphur leading to a new general method for the synthesis of novel 4-alkyl-thiothiazoles has been achieved[45] by reaction of ketoketen S,N-acetals 20 with thionyl chloride. These results are described in the Chapter V (Scheme 13).


NOCl
pyridine
20
R''=CH2-R'''
R'''=H, Me, Ar
35
R'=ArCH2
R''=Ar
R''=
37
Quinoxalines
38
Thiazoles
36
Imidazoles

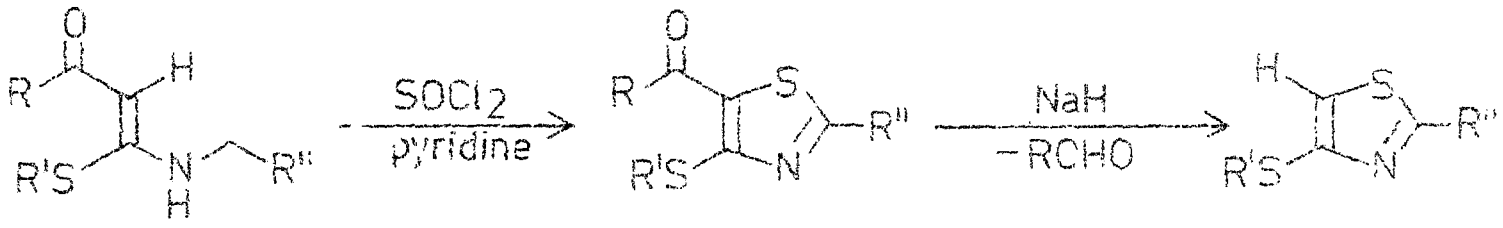
Scheme 11



20 39

20 , 39 , R = aryl , alkyl ; R'=H , Me , Ar
R''= alkyl

Scheme 12

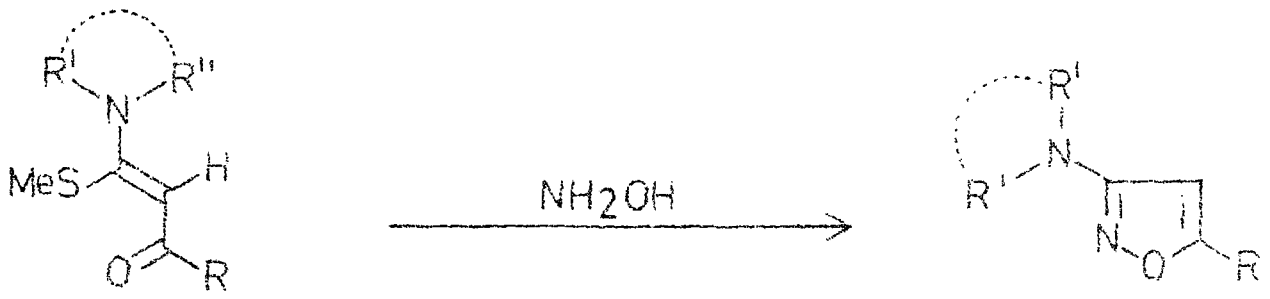


20 40 41

20, 40-41, R = aryl, alkyl; R' = alkyl; R'' = aryl, CO_2Et

Scheme 13

A novel general route for the synthesis of 3-aryl/alkyl-5-cycloalkylamino-5-arylisoxazole by reaction of ketoketen-S,N-acetals with hydroxylamine is described in the Chapter VI.[46]



20 42

20, 42, R = substituted aryl ; R' = alkyl/aryl ; R'' = H ;
R' = R'' = $-(CH_2)_r-$, $-(CH_2)_2-X-(CH_2)_2-$

Scheme 14

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CHAPTER II

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

II. 1 Introduction

A number of polarized keten-S,N- and N,N-acetals required for the present investigation were prepared according to our earlier reported methods.[1] Infact, 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 representative examples of polarized keten S,N- and N,N-acetals were prepared. The various methods used for the preparation of these known as well as unknown keten-S,N- and N,N-acetals and their spectral and analytical data are described in this Chapter.

II.2 Preparation of polarized keten-S,N-acetals

The active methylene compounds used for the preparation of S,N-acetals were either acetophenones, acetone or nitromethane. Following three methods were used for the preparation of polarized ketoketen-S,N-acetals and N,N-acetals and those derived from nitromethane.

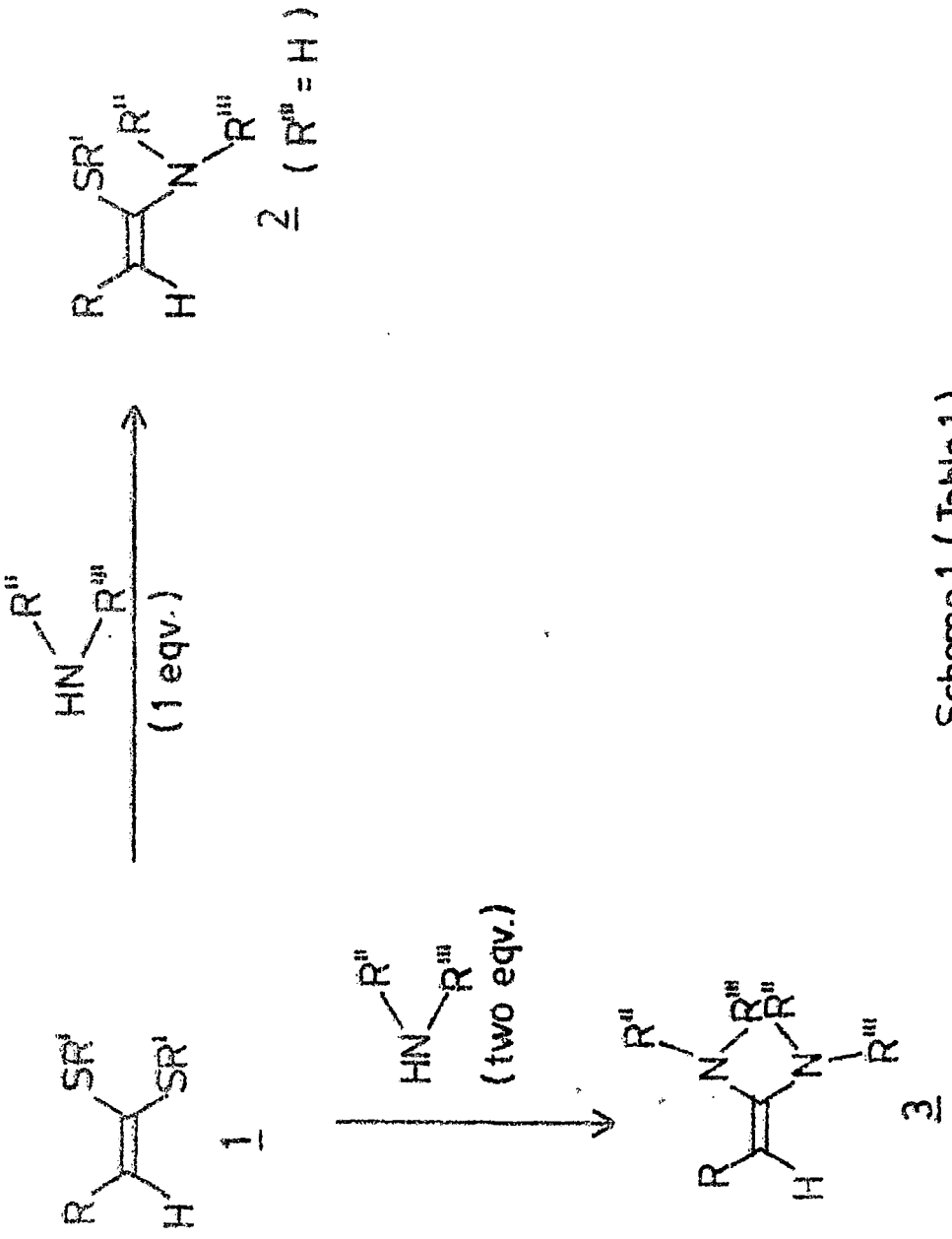
II.2.1 Displacement method

II.2.2 Direct method using isothiocyanates

II.2.3 Thioamide method.

II.2.1 Displacement method

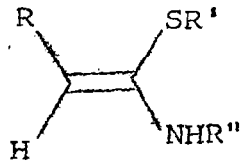
The polarized keten S,S-acetals are known to undergo facile displacement reaction[2-4] with primary or secondary amines to give the corresponding S,N- and N,N-acetals depending upon the reaction conditions and the stoichiometry of the amines used (Scheme 1). This method was found to be useful for the preparation of keten-S,N-acetals derived from primary aliphatic amines. However with primary aromatic amines and secondary amines, a mixture of S,N- and N,N-acetals or only N,N-acetals were obtained.[5] The S,N-acetals (2a-V) prepared by displacement method are given in Table 1. The spectral and



Scheme 1 (Table 1)

TABLE 1

Preparation of Polarized Keten-S,N-acetals by direct displacement method.



2

S No	Starting compound	Product	R	R'	R"
1	1a	2a	C_6H_5CO	Me	$C_6H_5CH_2$
2	1b	2b	p-MeC_6H_4CO	Me	$C_6H_5CH_2$
3	1c	2c	p-$MeOC_6H_4CO$	Me	$C_6H_5CH_2$
4	1d	2d	p-ClC_6H_4CO	Me	$C_6H_5CH_2$
5	1e	2e	C_6H_5CO	Et	$C_6H_5CH_2$
6	1f	2f	C_6H_5CO	$C_6H_5CH_2$	$C_6H_5CH_2$
7	1g	2g	p-$MeOC_6H_4CO$	$C_6H_5CH_2$	$C_6H_5CH_2$
8	1a	2h	C_6H_5CO	Me	p-$ClC_6H_4CH_2$
9	1b	2i	p-ClC_6H_4CO	Me	p-$ClC_6H_4CH_2$
10	1c	2j	p-$MeOC_6H_4CO$	Me	p-$ClC_6H_4CH_2$
11	1a	2k	C_6H_5CO	Me	p-$MeOC_6H_4CH_2$
12	1c	2l	p-$MeOC_6H_4CO$	Me	p-$MeOC_6H_4CH_2$
13	1d	2m	p-ClC_6H_4CO	Me	p-$MeOC_6H_4CH_2$

Table 1 (Contd.)

14	1h	2n	MeCO	Me	$C_6H_5CH_2$
15	1i	2o	NO_2	Me	$C_6H_5CH_2$
16	1a	2p	C_6H_5CO	Me	Me
17	1b	2q	p-MeC_6H_4CO	Me	Me
18	1d	2r	p-ClC_6H_4CO	Me	Me
19	1a	2s	C_6H_5CO	$C_6H_5CH_2$	Et
20	1b	2t*	C_6H_5CO	Me	Et
21	1d	2u*	p-MeC_6H_4CO	Me	Et
22	1f	2v*	p-ClC_6H_4CO	Me	Et

* reported earlier.[1]

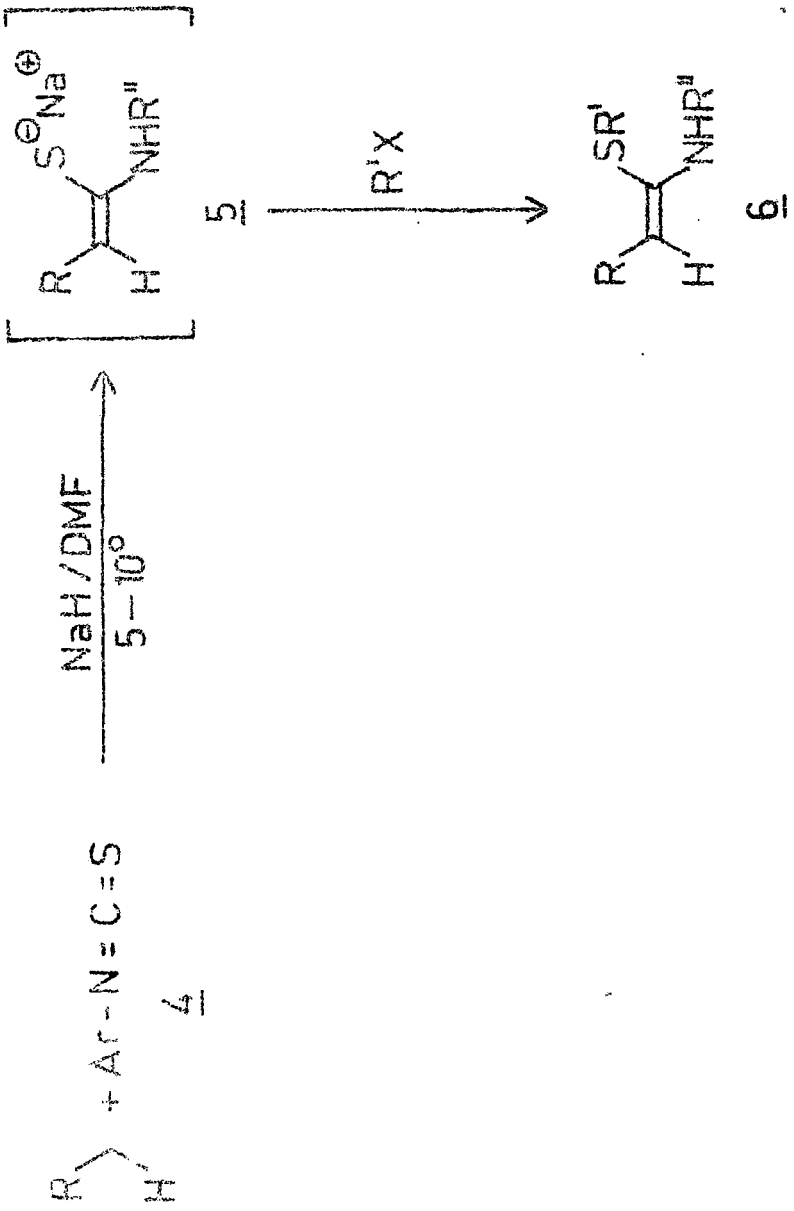
analytical data of the unknown S,N-acetals 2a-s are given in Table 3 and 4 respectively.

II.2.2 Direct method using isothiocyanates

The direct method for the synthesis of S,N-acetals by reacting active methylene compounds with alkyl or aryl isothiocyanate in the presence sodium hydride and dimethylformamide followed by subsequent alkylation with methyl iodide constitutes an alternative method (Scheme 2).[6-10] Some of the keten S,N-acetals which were not satisfactorily obtained by the displacement methods were successfully prepared by this method and are listed in the Table 2. The spectral and analycal data of the keten S,N-acetals 6f-t, which are not reported in the literature are given in the Table 3 and 4 respectively.

II.2.3 Thioamide method[6,10-11]

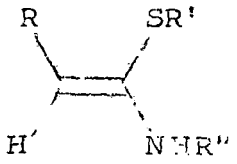
The displacement method failed to yield S,N-acetals derived from cyclic secondary amines. These S,N-acetals were therefore synthesized by an alternate method reported earlier. We have recently reported[12] a facile preparation of dithioester 7 by reacting active methylene ketones with dimethyltrithiocarbonate in the presence of sodium hydride. The



Scheme 2 (Table 2)

TABLE 2

Preparation of Polarized Keten-S,N-acetals by direct method using isothiocyanates.



3

S No	Product	R	R'	R"
1	6a*	C_6H_5CO	Me	C_6H_5
2	6b*	p-MeC_6H_4CO	Me	C_6H_5
3	6c*	p-$MeOC_6H_4CO$	Me	C_6H_5
4	6d*	p-ClC_6H_4CO	Me	C_6H_5
5	6e*	C_6H_5CO	Me	p-ClC_6H_4
6	6f	C_6H_5CO	Et	C_6H_5
7	6g	C_6H_5CO	Me	p-MeC_6H_4
8	6h	p-ClC_6H_4CO	Me	p-MeC_6H_4
9	6i	p-ClC_6H_4CO	Me	p-ClC_6H_4
10	6j	p-$MeOC_6H_4CO$	Me	p-ClC_6H_4
11	6k	p-MeC_6H_4CO	Me	p-ClC_6H_4
12	6l	C_6H_5CO	Me	p-$MeOC_6H_4$
13	6m	p-MeC_6H_4CO	Me	p-$MeOC_6H_4$
14	6n	p-ClC_6H_4CO	Me	p-$MeOC_6H_4$

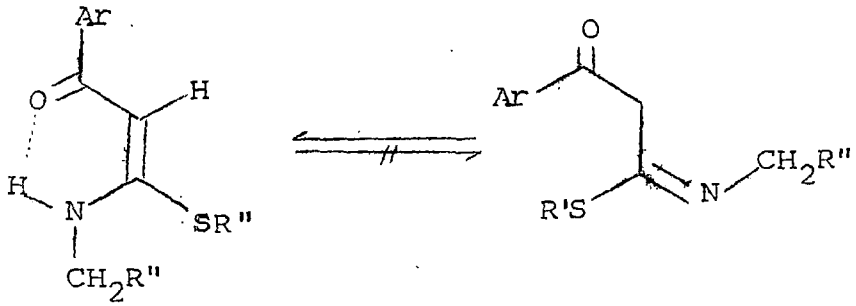
Table 2 (Contd.)

15	6o	C_6H_5CO	$C_6H_5CH_2$	C_6H_5
16	6p	p-MeC_6H_4CO	$C_6H_5CH_2$	C_6H_5
17	6q	p-$EtOC_6H_4CO$	$C_6H_5CH_2$	C_6H_5
18	6r	p-ClC_6H_4CO	$C_6H_5CH_2$	C_6H_5
19	6s	C_6H_5CO	$C_6H_5CH_2$	p-MeC_6H_4
20	6t	C_6H_5CO	$C_6H_5CH_2$	p-ClC_6H_4
21	6u	NO_2	Me	C_6H_5

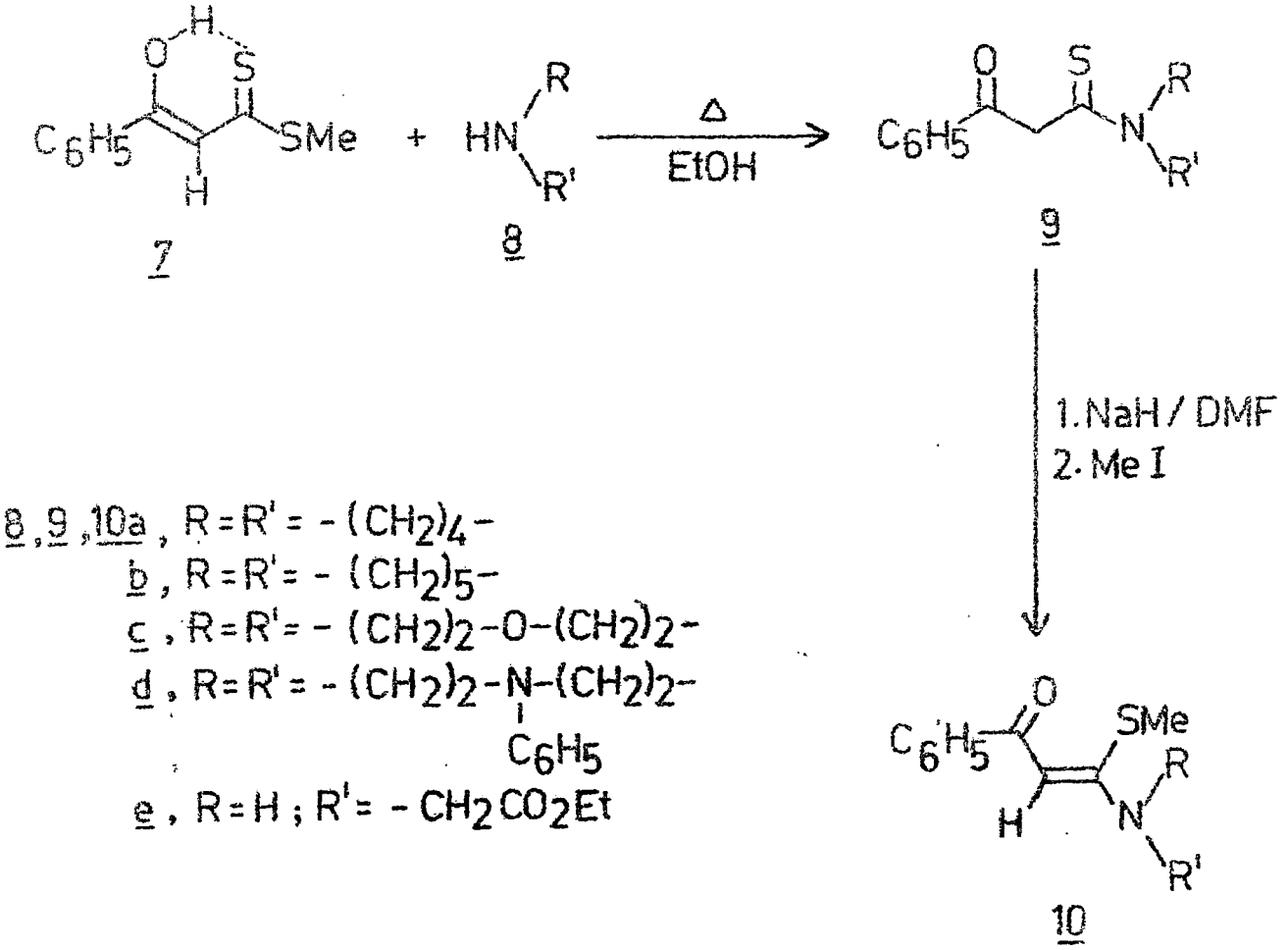
*reported earlier[1]

dithioester thus prepared underwent smooth condensation with piperidine 8a in boiling ethanol to give the corresponding thioamide 9a which was subsequently alkylated with methyl iodide in the presence of sodium hydride to give S,N-acetal 10a in good yield (Scheme 3). The keten-S,N-acetals, 10b-d were similarly prepared (Scheme 3).

The displacement method was also not successful for the preparation of S,N-acetal 10e derived from ethyl glycinate. However, 10e was obtained in good yield by thioamide method (Scheme 3). The spectral data of all the new S,N-alkylacetals 2a-s indicated that they exist in enamino tautomeric form (2A).[13] The benzylic protons in 2a appear as doublet at δ 4.45 due to coupling with NH proton. The doublet collapses to singlet on treatment with D_2O.



2A 2B


7
8
9
10
EtOH
1. NaH / DMF
2. Me I
8, 9, 10a, R = R' = -(CH2)4-
b, R = R' = -(CH2)5-
c, R = R' = -(CH2)2-O-(CH2)2-
d, R = R' = -(CH2)2-N(C6H5)-(CH2)2-
e, R = H; R' = -CH2CO2Et

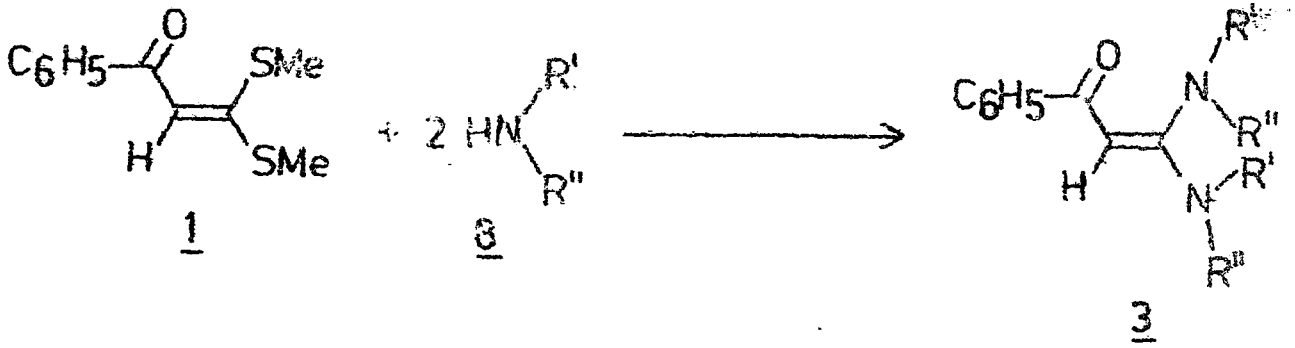
Scheme 3

The carbonyl stretching frequencies in the i.r. spectra of 2a-s appear between 1600-1557 cm^{-1} which further support the enamino form since in imino form the carbonyl frequency appears at 1700 cm^{-1}.

The i.r. and n.m.r. spectral data of S,N-arylacetals 6f-t also show that they exist in enamino tautomeric form (Table 2).

II.3 Preparation of polarized keten N,N-acetals

The ketoketen N,N-acetals required in the present investigation were prepared by displacement method by treating the keten-S,N-acetals with two equivalents of amines under varying conditions (Scheme 4). Thus while 3c was obtained by refluxing 1 with two equivalents of morpholine in ethanol, the corresponding N,N-phenyl acetal 3b was obtained in 64% yield, when acetic acid was used as refluxing medium. The N,N-acetal 3a was obtained in high yield when the corresponding S,S-acetal 1 was heated in sealed tube at 150-60°C with ethylamine.



1 + 2 (8) → 3

8, 3a, R' = H ; R'' = Et

b, R' = H ; R'' = C_6H_5

c, R' = R'' = $-(CH_2)_2-O-(CH_2)_2-$

Scheme 4

II.4 Experimental

M.ps. were determined on a Boetius (German) apparatus and are uncorrected. The i.r. spectra were recorded on Perkin Elmer 297 spectrometer. The 1H-n.m.r. spectra were recorded on a Varian EM-390 spectrometer using TMS as an internal standard and chemical shifts are expressed in δ (ppm).

The starting materials

The commercial samples of acetophenone, p-methylacetophenone nitromethane, acetone, anisaldehyde, p-chlorobenzaldehyde, benzylamine, aniline, p-methylaniline, p-chloroaniline, ethylamine, methylamine pyrrolidine, morpholine, piperidine and N-phenylpiperazine were purified before use.

The dimethyl trithiocarbonate, b.p. 225° (760 mm);[4] phenyl isothiocyanate,[15] p-chlorophenylisothiocyanate,[15] p-methoxyphenylisothiocyanate,[15] p-chlorobenzylamine,[16] p-methoxybenzylamine[16] were prepared by the reported methods.

The keten-S,S-acetals; 3,3-bis(methylthio)-1-phenyl-2-propen-1-one (1a), mp 93°;[17] 3,3-bis(methylthio)-1-(p-methylphenyl)-2-propen-1-one (1b),[17] mp 104-105°; 3,3-bis(methylthio) 1-(p-methoxyphenyl)-2-propen-1-one (1c),[17] mp 100-1°; 3,3-bis

(methylthio)-1-(p-chlorophenyl)-2-propen-1-one (1d),[17] mp 109-110°; 3,3-bis (methylthio)-1-methyl-2-propen-1-one (1h),[18] mp 66-7°, 1,1-bis (methylthio)-2-nitroethylene (1i),[6] mp 125°; 3,3-bis(ethylthio)-1-phenyl-2-propen-1-one (1e), mp 49-50°;[18] 3,3-bis(benzylthio)-1-phenyl-2-propen-1-one (1f), mp 113°[18] and 3,3-bis(benzylthio)-1-(p-methoxyphenyl)-2-propen-1-one (1g);[18] mp 120° were prepared by the reported methods,[17-19] by reacting respective active methylene ketones with one eqv. of CS_2 and two eqv. of t-BuONa in dry benzene followed by alkylation with the respective halides. The nitroketen-S,N-acetal 1i was prepared by methylation of the corresponding dipotassium salt with dimethylsulfate.

The reported methyl benzoyldithioacetate (7);[12] mp 54-55° was prepared by reacting acetophenone with dimethyl trithiocarbonate in the presence of two eqv. of sodium hydride in refluxing benzene.

Preparation of keten-S,N-acetals

Method A: By displcement method

General procedure: A solution of keten-S,S-acetal (0.02 mol) and the appropriate amine (0.025-0.05 mol) (or 40% solution of

either methyl- or ethylamine) in ethanol (50 ml) was refluxed for 5-25 hr. After completion of the reaction (monitored by TLC), solvent was removed and the reaction mixture was diluted with water, extracted with ethyl acetate, dried (Na_2SO_4) and evaporated to give crude S,N-acetals 2a-s which were purified by either crystallization using benzene/hexane mixture (1:1) or by passing through silica gel column (2e, 2h, 2i-n, 2s-v) using hexane/benzene (8:2) as eluent. The S,N-acetals 2a-v were prepared by this method (Table 1). Spectral and analytical data of unreported S,N-acetals 2a-s are given in Table 3 and 4 respectively.

Method B: By the reaction of active methylene compounds with aryl isothiocyanate: General Procedure: 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 dimethyl-formamide (DMF) (50 ml), a solution of active methylene compounds (0.05 mol) in dry DMF (15 ml) was added dropwise during 0.5 hr. A solution of aryl isothiocyanate (0.05 mol) in dry DMF (25 ml) was then added and reaction mixture was further stirred for 1.5-2 hr, followed by subsequent addition of alkyl halide (0.05 mol) in DMF (15 ml). After further stirring for 2 hr,

the reaction mixture was poured over crushed ice, neutrilized with 20% acetic acid, extracted with chloroform (3x75 ml). The chloroform layer was washed with water (3x200 ml), dried (Na_2SO_4) and concentrated to give crude S,N-acetals 6a-u (Table 2), which were purified either by crystallization from benzene/hexane (1:1) or by passing through silica gel column using hexane/benzene (4:1) as eluent. The S,N-acetals 6a-u were prepared by this method (Table 2).

Method C: Thioamide method

Preparation of thioamides(9); A solution of methyl benzoyldithioacetate 7 (0.01 mol) and the appropriate amine 8 (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 9a-e thus obtained, were either purified by crystallization 9a-d or by passing through silica gel column 10e using benzene/hexane (1:1) as eluent. The physical data of reported thioamides 9a-d and physical, spectral and analytical data of unreported thioamide 9e are listed below.

Benzoylthioaceticacidpyrrolidide (9a)[10,11] was obtained as orange solid (benzene:hexane), mp 124-25°; (reported 125-26°). yield 85%.

Benzoylthioaceticacidpiperidide 9b was obtained yellow solid (benzene:hexane) mp 128-30° (Reported 130-31°);[1] yield 80%.

Benzoylthioaceticacidmorpholide 9c was obtained yellow crystalline solid (benzene:hexane); mp 126-27° (Reported 127-29°);[6] yield 78%.

Benzoylthioaceticacid-N-phenylpiperazine 9d was obtained light yellow solid (benzene:hexane); mp 94-95° (Reported 95-97°);[20] yield 79%.

N-(α-carboethoxymethyl)-β-benzoylthioacetamide 9e was obtained pale white needles mp 95-96° (benzene:hexane); yield 52%; i.r. ν max (KBr): 1730 (ester CO); 1669 (aromatic CO); 3500 (NH); n.m.r. (CCl_4); δ 1.30 (t, 3H, $C\underline{H}_3CH_2O$); 3.72 (s, 2H, $C_6H_5COC\underline{H}_2$); 4.0-4.40 (m, 4H, $OC\underline{H}_2CH_3$ and $NH\text{-}C\underline{H}_2CO$); 7.10-7.30 (m, 5H, aromatic); Found: C, 59.32; H, 5.92; N, 5.50; $C_{13}H_{15}NO_3S$ (265) requires C, 58.86; H. 5.66; N, 5.28%.

Preparation of keten-S,N-acetals 10 :

A suspension of thioamide 9 (0.004 mol) and potassium carbonate (0.56g, 0.004 mol) in acetone (30 ml) was refluxed for 3 hr. The solution was cooled and 0.71g (0.005 mol) of

methyl iodide was added with stirring and the reaction mixture was further stirred at room temperature for 3 hr. It was then poured over crushed ice, acidified with 20% acetic acid, extracted with chloroform, dried (Na_2SO_4) and solvent evaporated to give corresponding keten-S,N-acetals 10a-e which were further purified by passing through silica gel column using benzene/hexane (2:1) eluent.

3-Methylthio-3-pyrrolidino-1-phenyl-2-propen-1-one 10a was obtained pale yellow crystalline solid (benzene:hexane); mp 80°; yield 85%; i.r. ν max (KBr): 3280 (ν_{NH}), 1570, 1600 (νCO); n.m.r. (CCl_4): δ 2.00 [br S, 4H, $-(CH_2)_2-$] 2.46 (s, 3H, SCH_3), 3.56 (br S, 4H, $-CH_2-N-CH_2-$); 5.50 (s, 1H, olefinic); 7.10-7.48 (m, 3H, arom); 7.60-7.95 (m, 2H, arom); Found C, 67.76; H, 6.35; N, 5.85; $C_{14}H_{17}NOS$ (247) requires: C, 68.02; H, 6.88; N, 5.85%.

3-Methylthio-3-piperidino-1-phenyl-2-propen-1-one 10b was obtained viscous liquid (TLC single spot); yield 83%; i.r. and n.m.r. spectra same as reported.[1]

3-Methylthio-3-morpholino-1-phenyl-2-propen-1-one 10c was obtained semisolid (TLC single spot); yield 87%; ir and n.m.r. spectra same as reported.[1]

3-Methylthio-3-(N-phenylpiperazino)-1-phenyl-2-propen-1-one 10d was obtained as semisolid (TLC single spot); yield 90% i.r. νmax ($CHCl_3$): 3245 (br, NH), 1600 (νCO); n.m.r. (CCl_4): δ2.43 (s, 3H, SCH_3) 3.10-3.86 (m, $8H_{piperazine}$); 5.93 (s, 1H, olefinic); 6.68-8.12 (m, 10H, aromatic). Found: C, 71.38; H, 6.21; N, 8.57; $C_{20}H_{22}N_2OS$ (338) requires: C, 71.00; H, 6.51; N, 8.28%.

3-Methylthio-3-(α-carboethoxymethyl)amino-1-phenyl-2-propen-1-one 10e was obtained as yellow viscous liquid (TLC single spot); yield 75%; i.r. νmax (KBr): 1620 (aromatic CO), 1730 (ester CO), 3250 (NH); n.m.r. (CCl_4): δ1.30 (t, 3H, $C\underline{H}_3CH_2$-); 2.34 (s, 3H, $SC\underline{H}_3$); 3.82-4.30 (d and q, 4H, $OC\underline{H}_2CH_3$ and NH-$C\underline{H}_2$-); 7.10-7.90 (m, 2H, aromatic); 11.00 (br S, 1H, N$\underline{H}$, exchangeable with D_2O; Found: C, 60.55; H, 6.42; N, 5.50; $C_{14}H_{17}NO_3S$ (279) requires: C, 60.22; H, 6.09; N, 5.02%.

Preparation of keten-N,N-acetals

By direct heating: A solution of keten-S,S-acetal 1 (2.24g, 0.01 mol) and ethylamine (1.40g, 0.025 mol) was heated in a sealed tube (150-160°C) for 6 hr. 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-acetal

3a, which was further purified by column chromatography over silica gel using benzene/hexane (2:3) as eluent, solid (1.4g, 65%), mp 75-77° (reported 76-76°), the n.m.r. and i.r. spectra of 3a was in agreement with that reported.

In refluxing acetic acid:- A solution of keten-S,S-acetal (2.24g, 0.01 mol) and aniline (2.40g, 0.025 mol) in gl. ACOH (20 ml) was refluxed for 8 hr. The solvent was removed under reduced pressure, the reaction mixture was diluted with water and extracted with ethylacetate. The organic layer was dried (Na_2SO_4) and concentrated to give crude N,N-acetal 3b, which was further purified by column chromatography over silica gel using benzene/hexane (3:7) as eluent, yellow solid, mp 130-32° (2.20g, 70%), reported (132-33°), i.r., n.m.r. spectra same as reported.

The corresponding N,N-morpholinoacetal 3c was also prepared in the similar manner except that ethanol was used as solvent instead of acetic acid, white solid (benzene), mp 138-39° (71%), reported (138-40°), i.r. and n.m.r. spectra same as reported.

TABLE 3

Spectral data of products 2a-s and 6f-t

Product	I.R. ν max (cm^{-1})	^{1}H-N.M.R.(CCl_4) δ (ppm)
2a	3255 (NH); 1560 (CO)[a]	2.35 (s, 3H, SCH_3; 4.45 (d, 2H, $NHCH_2$); 5.56 (s, 1H, olefinic); 7.08-7.50 (m, 8H, arom); 7.60-7.90 (m, 2H, arom); 10.40 (br s, 1H, NH).
2b	3267 (NH); 1561 (CO)[a]	2.23 (br s, 6H, SCH_3, CH_3); 4.45 (d, 2H, $NHCH_2$); 5.52 (s, 1H, olefinic); 6.95-7.38 (m, 7H, arom); 7.50-7.72 (m, 2H, arom); 11.40 (br s, 1H, NH).

Table 3 (Contd.)

2c	3245 (NH); 1565 (CO)[d]	2.45 (s, 3H, SCH_3); 3.70 (s, 3H, OCH_3); 4.40 (d, 2H, $NHCH_2$); 5.45 (s, 1H, olefinic); 6.30-7.15 (m, 7H, arom); 7.30-7.70 (m, 2H, arom); 11.35 (br s, 1H, NH).
2d	3250 (NH); 1563 (CO)[a]	2.42 (s, 3H, SCH_3); 4.42 (d, 2H, $NHCH_2$); 5.50 (s, 1H, olefinic); 6.80-7.42 (m, 7H, arom); 7.45-7.80 (m, 2H, arom); 11.35 (br s, 1H, NH).
2e	3235 (NH); 1565 (CO)[a]	1.30 (t, 3H, SCH_2CH_3); 2.82 (q, 2H, SCH_2CH_3); 4.48 (d, 2H, $NHCH_2$); 5.58 (s, 1H, olefinic); 7.0-7.45 (m, 8H, arom); 7.68-7.90 (m, 2H, arom); 10.56 (br s, 1H, NH).
2f	3250 (NH); 1600 (CO)[a]	3.60 (s, 2H, $SCH_2C_6H_5$); 4.30 (d, 2H, $NHCH_2C_6H_5$); 5.85 (s, 1H, olefinic); 6.90-8.00 (m, 15H, arom); 12.00 (br s, 1H, NH).

Table 3 (Contd.)

2g	3238 (NH); 1600 (CO)[a]	3.70 (s, 3H, OCH_3); 4.01 (s, 2H, $SCH_2C_6H_5$); 4.50 (d, 2H, $NHCH_2$); 5.55 (s, 1H, olefinic); 6.50-7.30 (m, 12H, arom); 7.50-7.78 (d, 2H, arom); 13.30 (br s, 1H, NH).
2h	3265 (NH); 1561 (CO)[a]	2.30 (s, 3H, SCH_3); 4.40 (d, 2H, $NHCH_2$); 5.50 (s, 1H, olefinic); 6.60-7.15 (m, 7H, arom); 7.31-7.50 (m, 2H, arom); 11.45 (br s, 1H, NH).
2i	3220 (NH); 1560 (CO)[a]	2.38 (s, 3H, SCH_3); 4.45 (d, 2H, $NHCH_2$); 5.53 (s, 1H, olefinic); 7.01-7.40 (m, 6H, arom); 7.72-7.81 (m, 2H, arom); 10.53 (br s, 1H, NH).
2j	3248 (NH); 1562 (CO)[a]	2.31 (s, 3H, SCH_3); 3.70 (s, 3H, OCH_3); 4.45 (d, 2H, $NH-CH_2$); 5.52 (s, 1H, olefinic); 6.65-7.35 (m, 6H, arom); 7.62-7.82 (m, 2H, arom); 10.58 (br s, 1H, NH).

Table 3 (Contd.)

2k	3268 (NH); 1562 (CO)[a]	2.30 (s, 3H, SCH_3); 3.65 (s, 3H, OCH_3); 4.40 (d, 2H, $NHCH_2$); 5.51 (s, 1H, olefinic); 6.45-7.40 (m, 7H, arom); 7.42-7.80 (m, 2H, arom); 13.45 (br s, 1H, NH).
2l	3232 (NH); 1558 (CO)[a]	2.35 (s, 3H, SCH_3); 3.70 (s, 3H, OCH_3); 3.71 (s, 3H, OCH_3); 4.35 (d, 2H, $NHCH_2$); 5.48 (s, 1H, olefinic); 6.50-7.30 (m, 6H, arom); 7.52-7.81 (m, 2H, arom); 10.86 (br s, 1H, NH).
2m	3245 (NH); 1557 (CO)[a]	2.35 (s, 3H, SCH_3); 3.71 (s, 3H, OCH_3); 4.40 (d, 2H, $NHCH_2$); 5.52 (s, 1H, olefinic); 6.61-7.35 (m, 6H, arom); 7.60-7.81 (m, 2H, arom); 12.75 (br s, 1H, NH).
2n	3200 (NH); 1580 (CO)[b]	1.95 (s, 3H, CH_3); 2.30 (s, 3H, SCH_3); 4.40 (d, 2H, $NHCH_2$); 4.90 (s, 1H, olefinic); 7.20 (br s, 5H, arom); 11.56 (br s, 1H, NH).

Table 3 (Contd.)

2o	1460(NO_2)[c]	2.43 (s, 3H, SCH_3); 4.56 (d, 2H, $NHCH_2$); 6.33 (s, 1H, olefinic); 7.26 (br s, 5H, arom); 13.25 (br s, 1H, NH).
2p	3250 (NH); 1565 (CO)[c]	2.40 (s, 3H, SCH_3); 3.05 (d, 3H, $NHCH_3$); 5.45 (s, 1H, olefinic); 7.13-7.35 (m, 3H, arom); 7.58-7.82 (m, 2H, arom); 11.23 (br s, 1H, NH).
2q	3265 (NH); 1570 (CO)[a]	2.35 (s, 3H, CH_3); 2.41 (s, 3H, SCH_3); 3.06 (d, 3H, $NHCH_3$); 5.56 (s, 1H, olefinic); 7.16 (d, 2H, arom); 7.58-7.83 (d, 2H, arom); 11.35 (br s, 1H, NH).
2r	3250 (NH); 1600, 1570 (CO)[c]	2.43 (s, 3H, SCH_3); 2.90 (d, 3H, $NHCH_3$); 5.00 (s, 1H, olefinic), 7.30 (d, 2H, arom); 7.60-7.82 (d, 2H, arom); 13.56 (br s, 1H, NH).

Table 3 (Contd.)

2s	3245 (br, NH); 1570, 1600 (CO)[d]	1.30 (t, 3H, $CH_2\underline{CH}_3$); 3.60 (q, 2H, $\underline{CH}_2CH_3$); 4.20 (s, 2H, $SC\underline{H}_2C_6H_5$); 5.80 (s, 1H, olefinic); 7.00-7.56 (m, 8H, arom); 7.70-7.96 (m, 2H, arom); 13.58 (br s, 1H, N<u>H</u>).
6f	3280 (br, NH); 1590 (CO)[c]	1.30 (t, 3H, $CH_2\underline{CH}_3$); 2.82 (q, 2H, $\underline{CH}_2CH_3$); 5.80 (s, 1H, olefinic); 7.00-7.50 (m, 8H, arom); 7.55-7.92 (m, 2H, arom); 13.35 (br s, 1H, N<u>H</u>).
6g	3275 (NH); 1570 (CO)[c]	2.38 (br s, 6H, CH_3, $SC\underline{H}_3$); 5.70 (s, 1H, olefinic); 7.10-7.50 (m, 7H, arom); 7.70-7.88 (m, 2H, arom); 13.52 (br s, 1H, N<u>H</u>).
6h	3245 (br, NH); 1590 (CO)[c]	2.33 (s, 6H, $SC\underline{H}_3$, $C\underline{H}_3$); 5.73 (s, 1H, olefinic); 6.90-7.33 (m, 6H, arom); 7.60-7.86 (m, 2H, arom); 11.75 (br s, 1H, N<u>H</u>).

6i	3255 (br, NH); 1600 (CO)	2.36 (s, 3H, SCH_3); 5.73 (s, 1H, olefinic); 7.16-7.46 (m, 6H, arom); 7.80 (d, 2H, arom); 10.30 (br s, 1H, NH).
6j	3285 (br, NH); 1540 (CO)[c]	2.26 (s, 3H, SCH_3); 3.66 (s, 3H, OCH_3); 5.63 (s, 1H, olefinic); 6.70 (d, 2H, arom); 6.90-7.70 (m, 6H, arom); 13.53 (br s, 1H, NH).
6k	3267 (br, NH); 1560 (br, CO)[c]	2.35 (br s, 6H, SCH_3, CH_3); 5.75 (s, 1H, olefinic); 6.90-7.35 (m, 6H, arom); 7.50-7.85 (m, 2H, arom); 12.53 (br s, 1H, NH).
6l	3250 (NH); 1560 (CO)[c]	2.30 (s, 3H, SCH_3); 3.62 (s, 3H, OCH_3); 5.70 (s, 1H, olefinic); 6.75 (d, 2H, arom); 7.00-7.95 (m, 7H, arom); 9.63 (br s, 1H, NH).

Table 3 (Contd.)

6m	3254 (NH); 1590 (CO)[c]	2.30 (s, 6H, SCH_3, CH_3); 3.76 (s, 3H, OCH_3); 5.70 (s, 1H, olefinic); 6.80 (d, 2H, arom); 7.30 (m, 4H, arom); 7.72 (d, 2H, arom); 11.35 (br s, 1H, NH).
6n	3275 (br, NH); 1530 (CO)[c]	2.30 (s, 3H, SCH_3); 3.73 (s, 3H, OCH_3); 5.70 (s, 1H, olefinic); 6.75 (d, 2H, arom); 7.76-7.83 (m, 6H, arom); 13.38 (br s, 1H, NH).
6o	3225 (br, NH); 1550 (CO)[c]	4.08 (s, 2H, $SCH_2C_6H_5$); 5.92 (s, 1H, olefinic); 7.30 (br s, 13H, arom); 7.70-7.85 (m, 2H, arom); 11.58 (br s, 1H, NH).
6p	3238 (br, NH); 1535, 1500 (CO)[c]	2.33 (s, 3H, CH_3); 4.50 (s, 2H, $SCH_2C_6H_5$); 5.90 (s, 1H, olefinic); 7.03-7.35 (m, 12H, arom); 7.60-7.80 (m, 2H, arom); 11.65 (br s, 1H, NH).

Table 3 (Contd.)

6q	3275 (br, NH); 1540 (CO)[c]	1.20 (t, 3H, $OCH_2\underline{CH_3}$); 3.80-4.20 (m, 4H, $OC\underline{H_2}CH_3$, $SC\underline{H_2}C_6H_5$); 5.85 (s, 1H, olefinic); 6.76-7.43 (m, 12H, arom); 7.60-7.83 (m, 2H, arom); 10.50 (br s, 1H, N<u>H</u>).
6r	3266 (br, NH); 1550 (CO)[c]	4.00 (s, 2H, $SC\underline{H_2}C_6H_5$); 5.80 (s, 1H, olefinic); 7.10-8.30 (m, 12H, arom); 7.65 (d, 2H, arom); 12.53 (br s, 1H, N<u>H</u>).
6s	3278 (br, NH); 1530 (CO)[c]	2.26 (s, 3H, $C\underline{H_3}$); 4.00 (s, 2H, $SC\underline{H_2}C_6H_5$); 5.83 (s, 1H, olefinic); 6.90-7.43 (m, 12H, arom); 7.63-7.86 (m, 2H, arom); 11.75 (br, 1H, N<u>H</u>).
6t	3255 (br, NH); 1545 (CO)[c]	4.08 (s, 2H, $SC\underline{H_2}C_6H_5$); 5.93 (s, 1H, olefinic); 7.00-7.55 (m, 12H, arom); 7.66-7.90 (m, 2H, arom); 13.40 (br s, 1H, N<u>H</u>).

[a]in nujol; [b]neat; [c]in KBr; [d]in $CHCl_3$; [e]in CCl_4

TABLE 4

1-Aryl/methyl-3-N-benzyl/alkylamino-3-methyl/ethyl/benzylthio-1-oxo-2-propenes (2a-n, 2p-s); 2-benzylamino-2-methylthio-1-nitroethylenes (2o) and 1-aryl-3-N-arylamino-3-methyl/ethyl/benzylthio-1-oxo-2-propenes (6f-t)

Product[a]	Yield (%)	m.p. (°C)	Molecular formula	Analysis (%)			
				Calc. Found	C	H	N
2a	90	56-57	$C_{17}H_{17}NOS$		72.08	6.01	4.95
			(283)		71.73	5.79	4.71
2b	85	67-68	$C_{18}H_{19}NOS$		72.73	6.40	4.71
			(297)		72.38	6.65	4.92
2c	90	84-85	$C_{18}H_{19}NO_2S$		69.01	6.07	4.47
			(313)		69.37	6.38	4.71
2d	80	95-97	$C_{17}H_{16}ClNOS$		64.25	5.04	4.41
			(317.5)		64.47	5.39	4.66

Table 4 (Contd.)

2e	81	Semi solid	$C_{18}H_{19}NOS$	72.73	6.40	4.71
			(297)	73.22	6.71	4.98
2f	85	55-56	$C_{23}H_{21}NOS$	76.80	5.85	3.90
			(359)	77.35	6.03	4.20
2g	83	84-86	$C_{24}H_{23}NO_2S$	74.04	5.91	3.59
			(389)	74.38	5.73	3.81
2h	80	Semi solid	$C_{17}H_{16}ClNOS$	64.25	5.04	4.41
			(317.5)	64.42	5.38	4.72
2i	90	Semi-Solid	$C_{17}H_{15}Cl_2NOS$	57.95	4.26	3.98
			(352)	57.71	4.48	3.68
2j	81	Semi-Solid	$C_{18}H_{18}ClNO_2S$	62.16	5.18	4.03
			(347.5)	62.41	5.37	4.32
2k	86	65	$C_{18}H_{19}NO_2S$	69.01	6.07	4.47
			(313)	69.42	6.37	4.71

Table 4 (Contd.)

2l	90	77	$C_{19}H_{21}NO_3S$ (343)	66.47 66.72	6.12 6.32	4.08 4.37
2m	90	67-68	$C_{18}H_{18}ClNO_2S$ (347.5)	62.16 62.42	5.18 5.47	4.03 4.39
2n	70	oil	$C_{12}H_{15}NOS$ (221)	65.15 65.42	6.79 7.12	6.33 6.63
2o	89	105-7	$C_{10}H_{12}N_2O_2S$ (224)	53.57 53.10	5.36 5.56	12.50 12.19
2p	89	70	$C_{11}H_{13}NOS$ (207)	63.77 63.10	6.28 6.12	6.76 6.55
2q	83	113-14	$C_{12}H_{15}NOS$ (221)	65.16 65.55	6.79 6.56	6.33 6.21
2r	85	71-72	$C_{11}H_{12}ClNOS$ (241.5)	54.66 54.21	4.97 4.77	5.80 5.95

Table 4 (Contd.)

2s	80	Oil	$C_{18}H_{19}NOS$	72.73	6.40	4.71
			(297)	72.32	6.55	4.56
6f	80	80-82	$C_{17}H_{17}NOS$	72.08	6.00	4.95
			(283)	72.58	6.50	4.73
6g	80	84	$C_{17}H_{16}ClNOS$	72.08	6.00	4.95
			(283)	72.50	6.21	4.89
6h	75	105-6	$C_{17}H_{16}ClNOS$	64.25	5.04	4.40
			(317.5)	64.67	5.31	4.30
6i	85	93-95	$C_{16}H_{13}Cl_2NOS$	56.80	3.85	4.14
			(338)	56.63	3.71	4.25
6j	75	112-14	$C_{17}H_{16}ClNO_2S$	61.17	4.80	4.20
			(333.5)	61.52	4.45	4.57
6k	73	95-96	$C_{17}H_{16}ClNOS$	64.25	5.04	4.40
			(317.5)	64.67	4.89	4.31

Table 4 (Contd.)

6l	75	60-62	$C_{17}H_{17}NO_2S$	68.23	56.85	4.68
			(299)	69.70	57.25	4.65
6m	70	109-10	$C_{18}H_{19}NO_2S$	69.00	6.07	4.47
			(313)	69.50	6.25	4.35
6n	70	114-16	$C_{17}H_{16}ClNO_2S$	61.72	4.84	4.24
			(330.5)	61.35	4.95	4.21
6o	80	106-8	$C_{22}H_{19}NOS$	76.52	5.51	4.06
			(345)	76.85	5.35	3.95
6p	85	120-21	$C_{23}H_{21}NOS$	76.88	5.85	3.90
			(359)	76.50	5.95	3.76
6q	80	99-101	$C_{24}H_{23}NO_2S$	74.04	5.91	3.60
			(389)	74.38	5.78	3.51
6r	80	117-18	$C_{22}H_{18}ClNOS$	69.57	4.74	3.69
			(379.5)	69.23	4.53	3.53

Table 4 (Contd.)

6s	78	98-100	$C_{23}H_{21}NOS$	76.88	5.85	3.90
			(359)	76.35	5.55	3.69
6t	80	134-35	$C_{22}H_{18}ClNOS$	69.57	4.74	3.69
			(379.5)	69.20	4.54	3.53

[a]Crystallization solvent = benzene/hexane.

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CHAPTER III

SYNTHESIS OF NOVEL HYDROXYIMINOIMINES BY DIRECT NITROSATION OF α-KETOKETEN-S,N-ACETALS AND THEIR FURTHER TRANSFORMATIONS:NEW GENERAL SYNTHESES FOR IMIDAZOLE, QUINOXALINE AND THIAZOLE DERIVATIVES*

III.1 Introduction

The chemistry of imidazole[1], quinoxaline[2] and thiazole[3] derivatives has been extensively studied in the recent years in view of the growing applications of these compounds as pharmaceuticals and in industrial processes. The importance of these heterocyclic nuclei in biological processes has also been recognized. Besides, substances with fused imidazole and quinoxaline rings such as purines, pteridines and riboflavins play a very important role in the biochemistry of living cells. Many candidate drugs have been modelled on these

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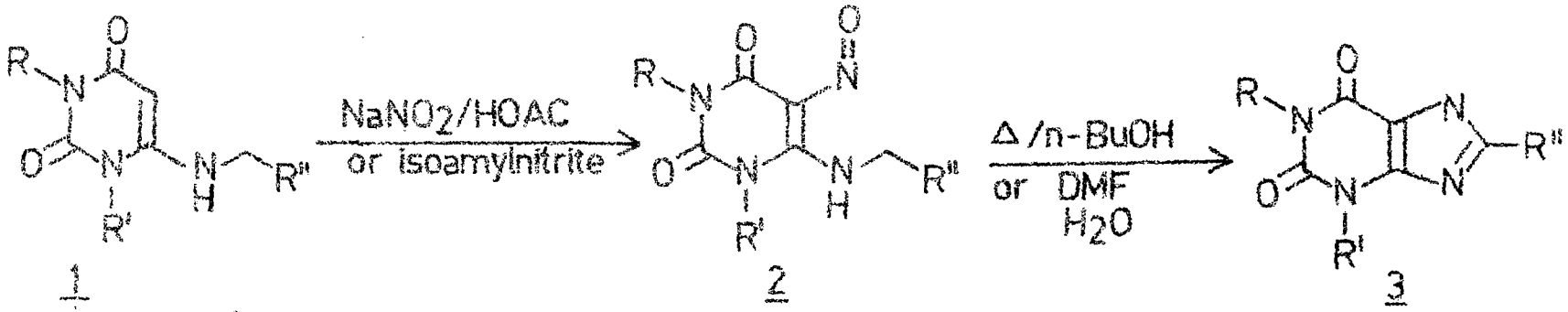
compounds particularly for cancer and virus research. In addition, several antibiotics incorporating these chemical structures have been isolated. Numerous review articles dealing with the chemistry, pharmacology and biology of these heterocyclic compounds have appeared in the recent years.

Among the various routes available for the synthesis of purine and alloxazine derivatives, one approach which has received considerable attention in the recent years, involves annelation of imidazole (or quinoxaline) ring to pyrimidine nucleus by condensation cyclization of 5-nitroso (or nitro) 4-aminopyrimidine derivatives.[4] A variety of xanthine, alloxazine and flavin derivatives have been synthesized by this route. However, a similar synthetic approach based on open-chain nitrosoenamines/enaminones (or hydroxyiminoimines) to give imidazole or quinoxaline derivatives has not been much investigated. The scant literature on such transformation is primarily due to lack of appropriate open-chain nitrosoenamine/enaminone (or hydroxyiminoimine) precursors. In the present chapter, a direct general method for the synthesis of novel functionalized nitrosoenaminones (or hydroxyiminoimine) by reaction of easily available α-keto-keten-S,N-acetals with nitrosyl chloride and their further

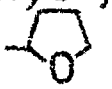
transformations to imidazole, quinoxaline and thiazole derivatives havebeen described. Since the synthetic strategies of these transformations are based on the condensation cyclization reactions of 4-amino-5-nitroso (or nitro) uracil derivatives, a brief discussion on the reactions of 4-amino-uracil derivatives with electrophilic nitroso (or nitro) compounds leading to the synthesis of purine, alloxazine and other condensed heterocycles has also been included.

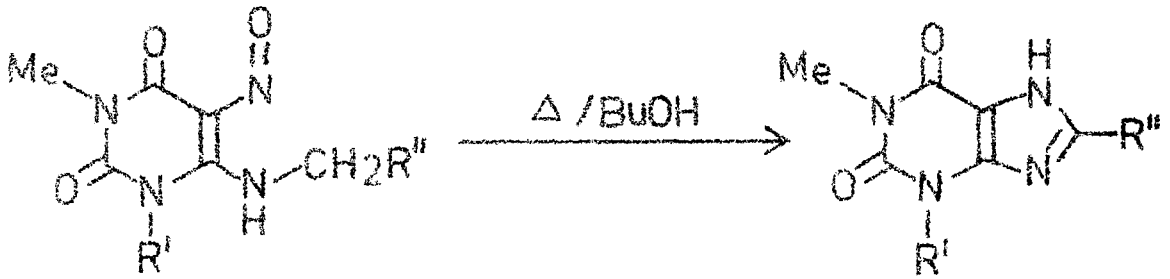
III.2 4-Amino-5-nitrosouracil derivatives as precursors for purines and alloxazines synthesis: A brief survey

4-Aminouracil derivatives of general structure 1 are shown to be highly reactive towards electrophilic substitution at 5-position. Nitrosation of 1 with either sodium nitrite in acetic acid or with isoamyl nitrite yields the corresponding 5-nitroso-4-aminouracil derivatives 2 in excellent yields (Scheme 1).[5,6] Thus a variety of 1,3-disubstituted-4-alkyl/arylamino-5-nitrosouracil derivatives 2 have been synthesized (Scheme 1), which proved to be ubiquitous intermediates for the synthesis of purines, alloxazines, pteridines and other fused pyrimidine heterocycles.



1 2 3

1-3, R and/or R' = H, Me, Et, n-Pr, n-Bu, Benzyl, Phenyl, allyl
R'' = H, Me, Et, Ph; CH_2Ph, CH_2OH, $-CH_2-$ 



2a, R' = Me; R'' = H
b, R' = H; R'' = C_6H_5

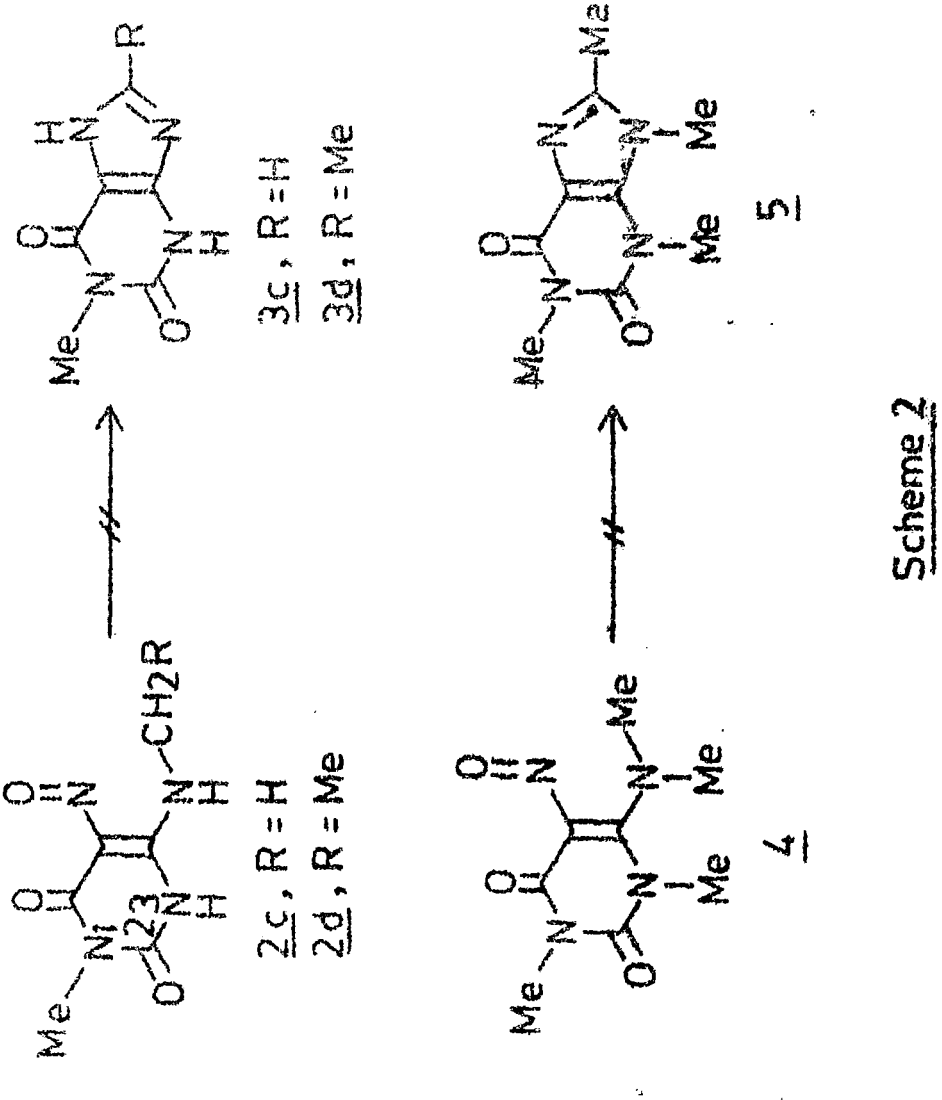
3a, R' = Me; R'' = H
b, R' = H; R'' = C_6H_5

Scheme 1

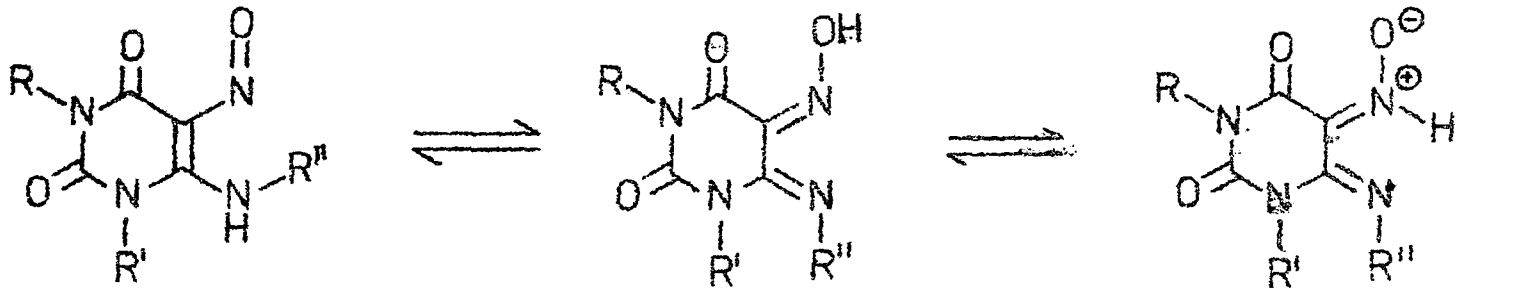
III.2.1 Synthesis of purine derivatives

It was reported earlier that the fading decomposition of 5-nitroso 4-alkylaminouracils during melting point determination was due to imidazole ring formation.[7,8] This reaction has later been developed into a novel general synthesis of purine derivatives. Thus two groups of research workers have reported[5,6] that 4-amino-5-nitrosouracil derivatives 2 carrying CH_2 or CH_3 substituents on the 4-amino group undergo facile thermal cyclodehydration to 8-substituted xanthine derivatives 3 (Scheme 1). It is interesting to note that the methylene group need not be activated; thus the uracil derivative 2a (R"=H,) undergoes facile intramolecular condensation to give xanthine 3a, when refluxed in solvents like n-butanol or dimethylformamide. Pfleiderer has reported that the presence of substituent at N-3 or the activation of methylene group adjascent to nitrogen in the 4-alkylamino side chain is necessary for cyclodehydration of 2 to 3.[6] Thus while 1,3-dimethyl-4-methylamino 5-nitroso uracil 2a and the corresponding 3-unsubstituted 4-benzyl derivative 2b undergo facile thermal cyclization to xanthines 3a and 3b respectively (Scheme 1), the corresponding 3-unsubstituted 4-methylamino-uracil derivative 2c failed to cyclize to 3c even under

drastic conditions (Scheme 2). Further, uracil derivatives with 4-dimethylamino-5-nitrosouracils 4 could not be dehydrated to 8,9-disubstituted xanthine derivatives 5 (Scheme 2).[5] A comparison of the structures 2 and 4 shows that 2 can exist in three tautomeric forms (2A, 2B and 2C) (Scheme 3), while such kind of tautomerism is not possible for 4-disubstituted amino derivative 4. According to Goldner,[5] existance of isonitroso tautomeric form 2c is of considerable importance for cyclodehydration of 5-nitroso-4-amino uracil derivatives (Scheme 3). Thus it has been reported that 2,6-disubstituted 4-benzylamino-5-nitrosopyrimidine 6 does not undergo cyclization inspite of the activation of methylene group (Scheme 3). This failure to cyclization is attributed to the presence of aromatic system in 6, which prevents the formation of isonitroso tautomeric form. Goldner has further shown that cyclization of 2 becomes very facile if the isonitroso form is fixed by alkylation.[9] Thus when the uracil derivative 2a was alkylated with diazomethane at room temperature, no N- or O-alkylated products were isolated and the caffiene 9 was isolated in excellent yield (Scheme 4).[9] The facile transformation of 2a to 9 at room temperature is attributed to the intermediacy of nitrone 8 which undergoes



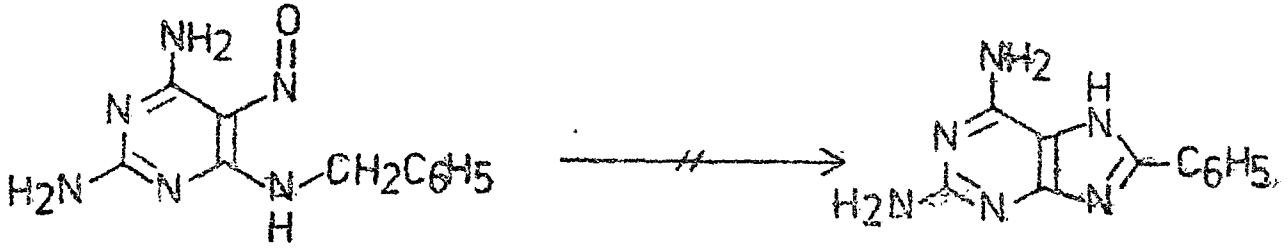
Scheme 2



Nitroso form
2A

Hydroxyimino form
2B

Isonitroso form
2C



6

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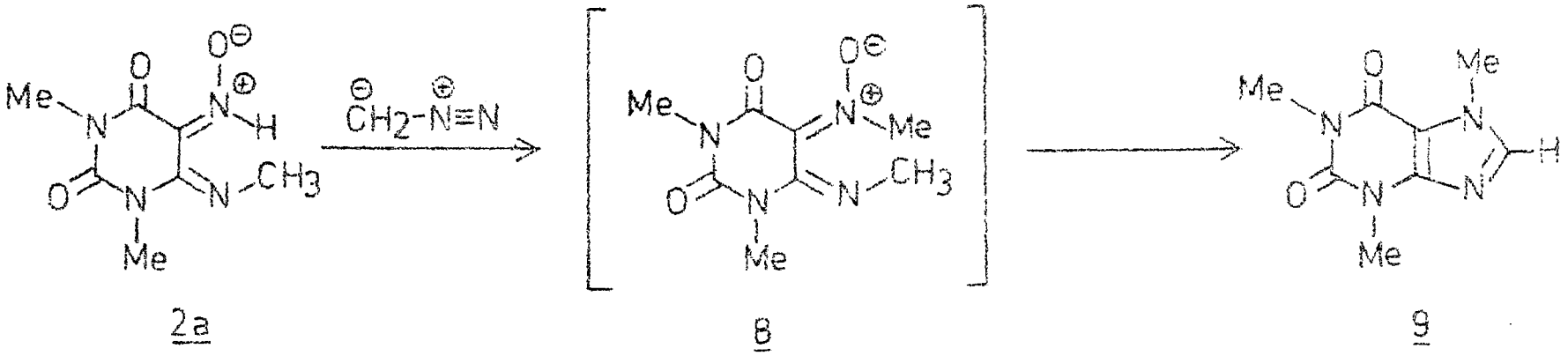
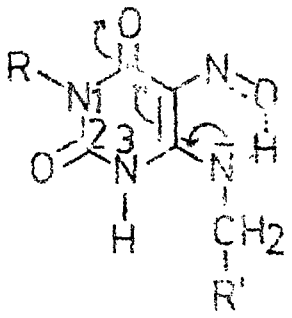
Scheme 3

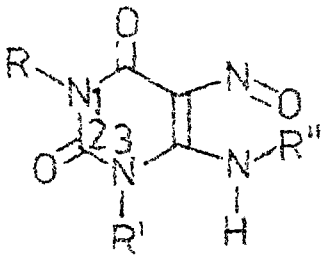
spontaneous cyclization to 9. According to Pfleiderer,[6] however, formation of isonitroso form is not the only factor for the surprising ease with which 1,3-disubstituted-4-alkylamino-5-nitrosouracils 2 undergo dehydration to xanthine derivatives. On the basis of this explanation, 3-unsubstituted uracil derivatives 2c and 2d (Scheme 2) should undergo cyclization as they are capable of existing in isonitroso tautomeric forms, however 2c and 2d could not be dehydrated to the corresponding 3c and 3d even under drastic conditions (Scheme 5). The authors have further emphasized the role of 3-alkyl substituents in these cyclizations. In the absence of N-3 substituents, the planar vinylogous amide system exists in the anti conformation 10 (Scheme 4), which is further stabilized by intramolecular H-bonding with the nitroso group. However in the presence of N-3 substituent, the syn conformation 11 is favoured and due to the presence of three vicinal substituents, the molecule exists in sterically strained conformation which is the driving force for the facile cyclization. The authors have correlated the cyclization temperatures of various 3-N-substituted uracil derivatives with the bulk of 3-N-substituents by differential thermogravimetric methods (Table 1) and found that cyclization temperature decreases in the



2a 8 9



10 (anti)



11 (syn)

Scheme 4

75

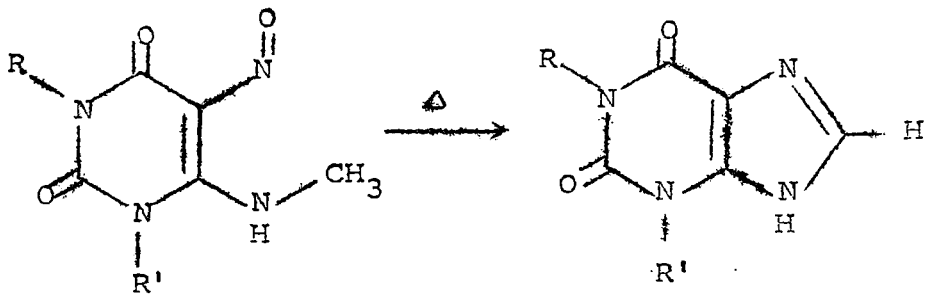
order $C_6H_5 > CH_3 > CH_2C_6H_5 > C_6H_5 > C_2H_5 > CH(Me)(Me) > cyclohexyl > n\text{-}C_4H_9$. The surprisingly high temperature required for the dehydration of 3-N-phenyl uracil derivative indicates that the phenyl group exists in planar vertical configuration in these derivatives.

Dehydrogenation of nitrosouracils 2 under mild conditions is reported to yield 7-hydroxyxanthine derivatives 13 (Scheme 5),[10] which could be converted to xanthines 3 on treatment with phosphorous trichloride and subsequent reductive dehalogenation with Raney Nickel. The formation of 13 apparently involves the dehydrogenated anils 12 as intermediates (Scheme 5).

When 1,3-dimethyl-5-nitroso-4-secondaryalkylaminouracils 14 were subjected to cyclodehydration, novel 8,8-disubstituted xanthines 15 were formed which undergo facile thermal rearrangements to 7,8-disubstituted xanthines 16. Dehydrogenation of 14 under mild conditions is reported to afford 8H-xanthine-7-N-oxide 18 via intermediate anil 17 (Scheme 6). The xanthine-N-oxide 18 isomerizes to fused oxadiazines 19 under thermal conditions (Scheme 6).[11]

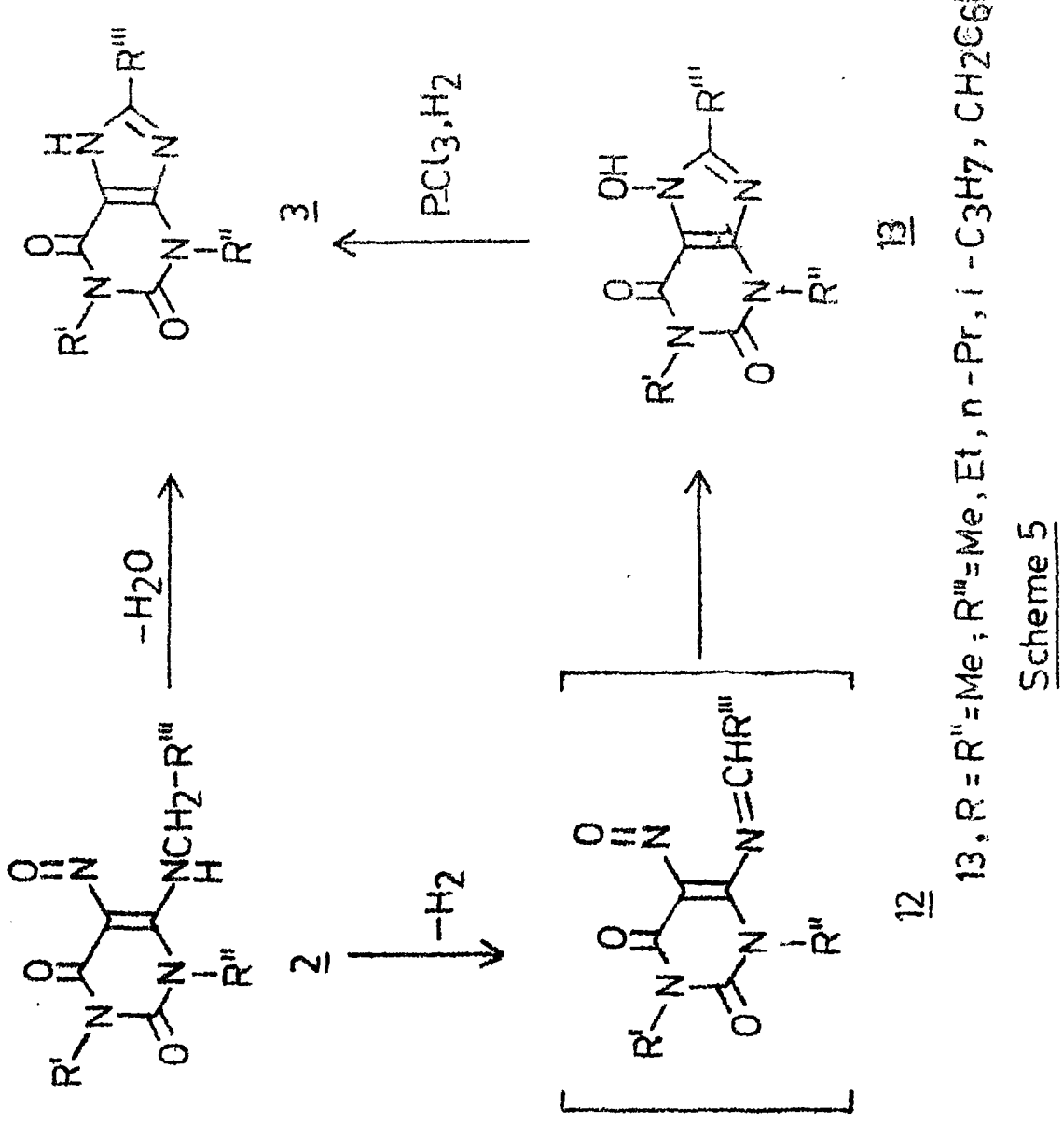
TABLE 1

Thermogravimetric estimation of cyclodehydration temperatures for 1,3-disubstituted 4-methylamino-5-nitrosouracils

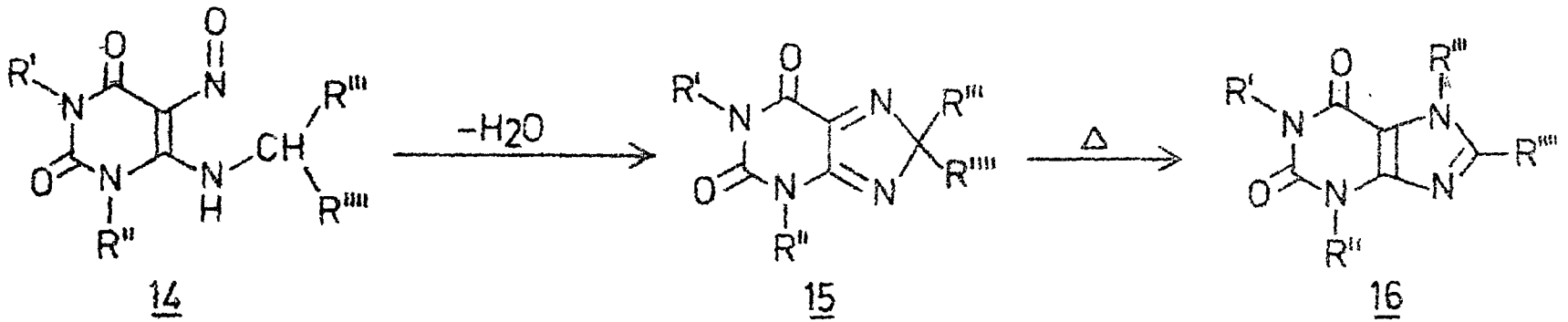


2 3

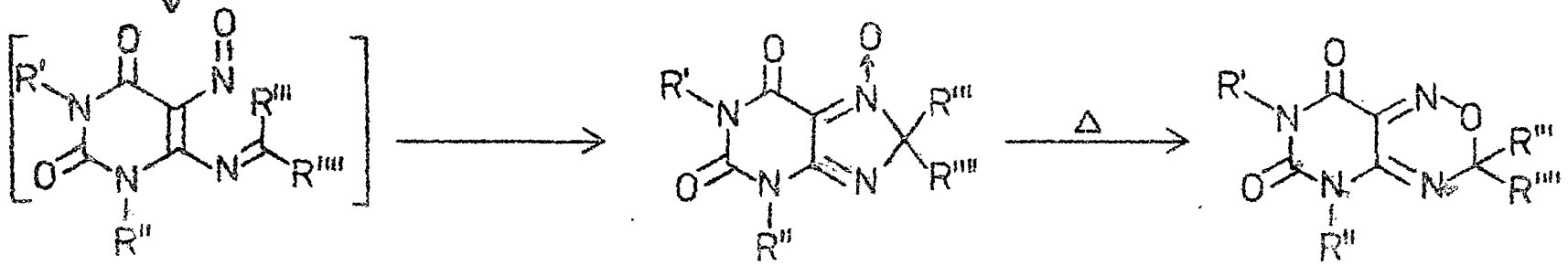
R	CH_3	C_6H_{11}	$CH(CH_3)_2$	CH_3	CH_3	CH_3	C_6H_5
R'	$n\text{-}C_4H_9$	C_6H_{11}	$CH(CH_3)_2$	C_2H_5	$CH_2C_6H_5$	CH_3	C_6H_5
°C	61	80	84	93	99	131	188



Scheme 5



14 15 16



17 18 19

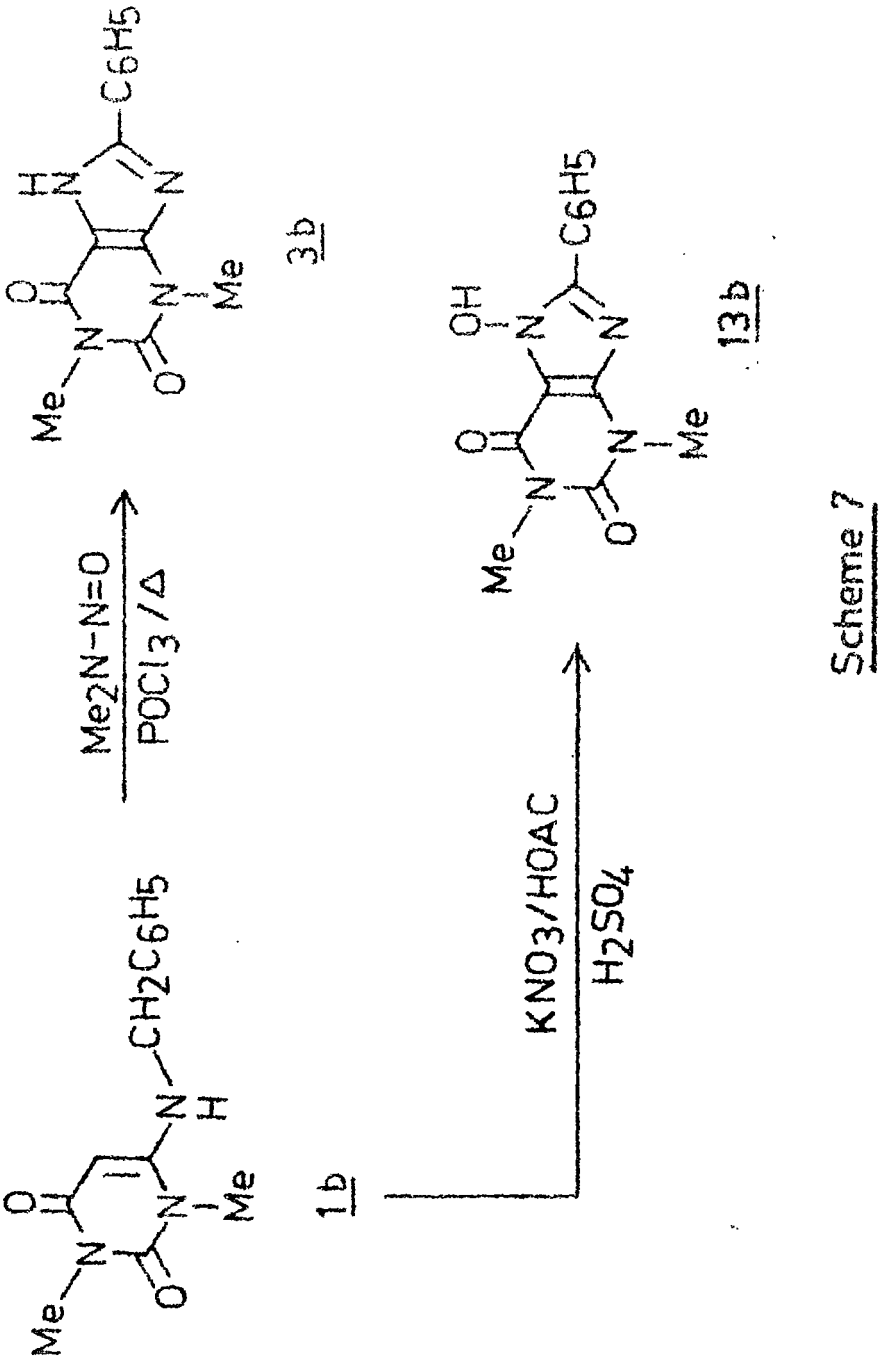
9–14, R' and/or R'' = alkyl, H or aryl
R''' and R'''' = Me, Et, Ph or –(CH2)5–

Scheme 6

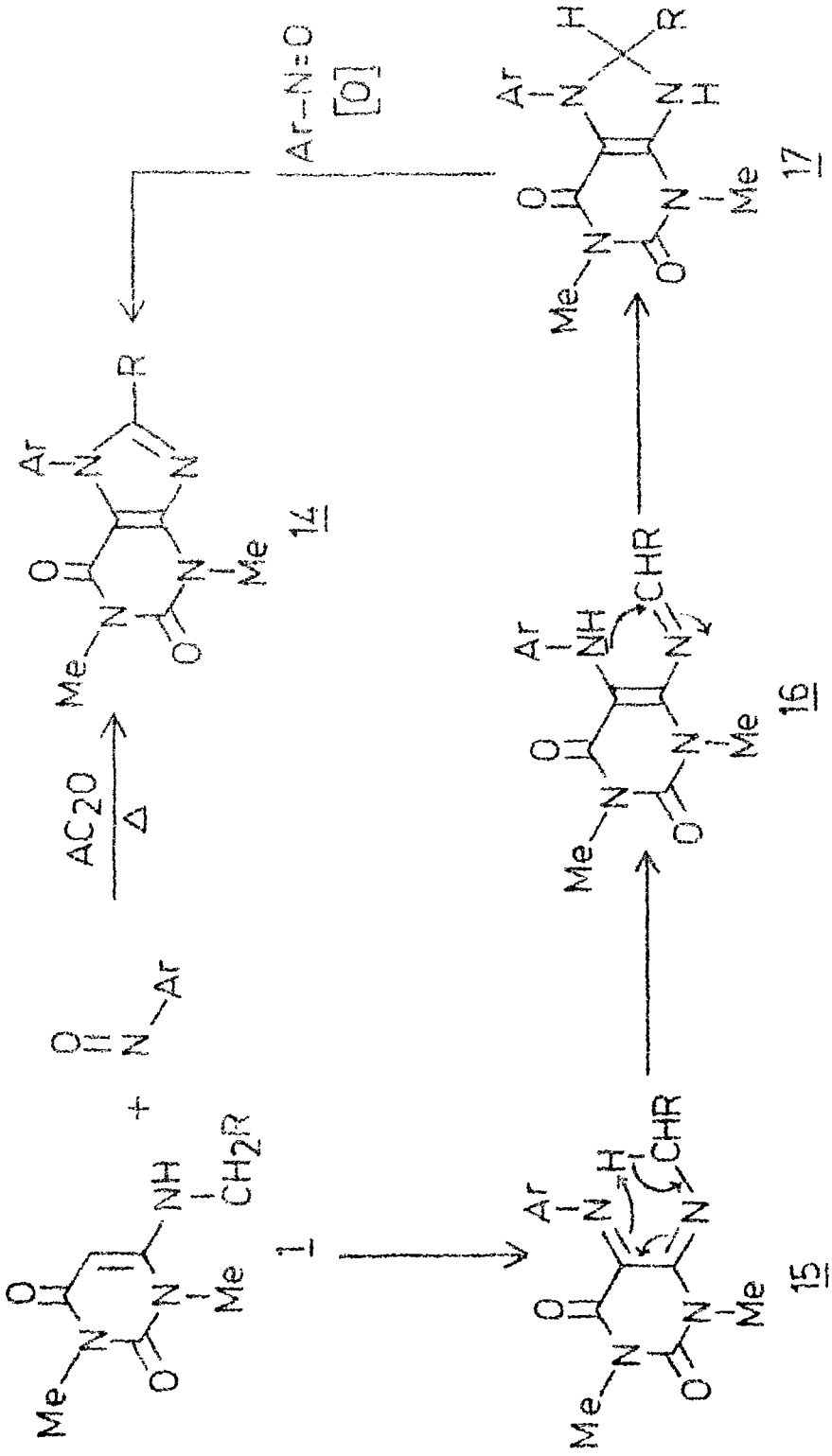
Recently Yoneda has reported direct synthesis of theophylline 3b by treatment of 1b with N-nitrosodimethylamine and phosphorous oxychloride (Scheme 7).[12] The reaction apparently involves ring nitrosation followed by cyclization. Nitration of 4-benzylaminouracil 1b with potassium nitrate and acetic acid/H_2SO_4 similarly affords 7-hydroxyxanthine 13b (Scheme 7).[13]

Electrophilic nitrosation and cyclization of 4-aminouracil derivatives 1 has also been achieved with nitrosobenzene in the presence of acetic anhydride which affords 7-arylxanthines 14 in excellent yields (Scheme 8).[14] The reaction proceeds through the intermediacy of 5-hydroxylamino derivative which suffers dehydration in the presence of acetic anhydride to give the diimine 15. Prototropic rearrangement of 15 gives monoimine 16, which is ideally disposed for intramolecular cyclization to 17. Subsequent dehydrogenation of 17 by excess of nitrosobenzene would then afford the 7-aryltheophylline 14 (Scheme 8).

Taylor has reported the synthesis of 8-phenyltheophylline derivatives 21 by treatment of 4-amino-5-nitrosouracil derivatives with benzaldehyde in refluxing dimethylformamide

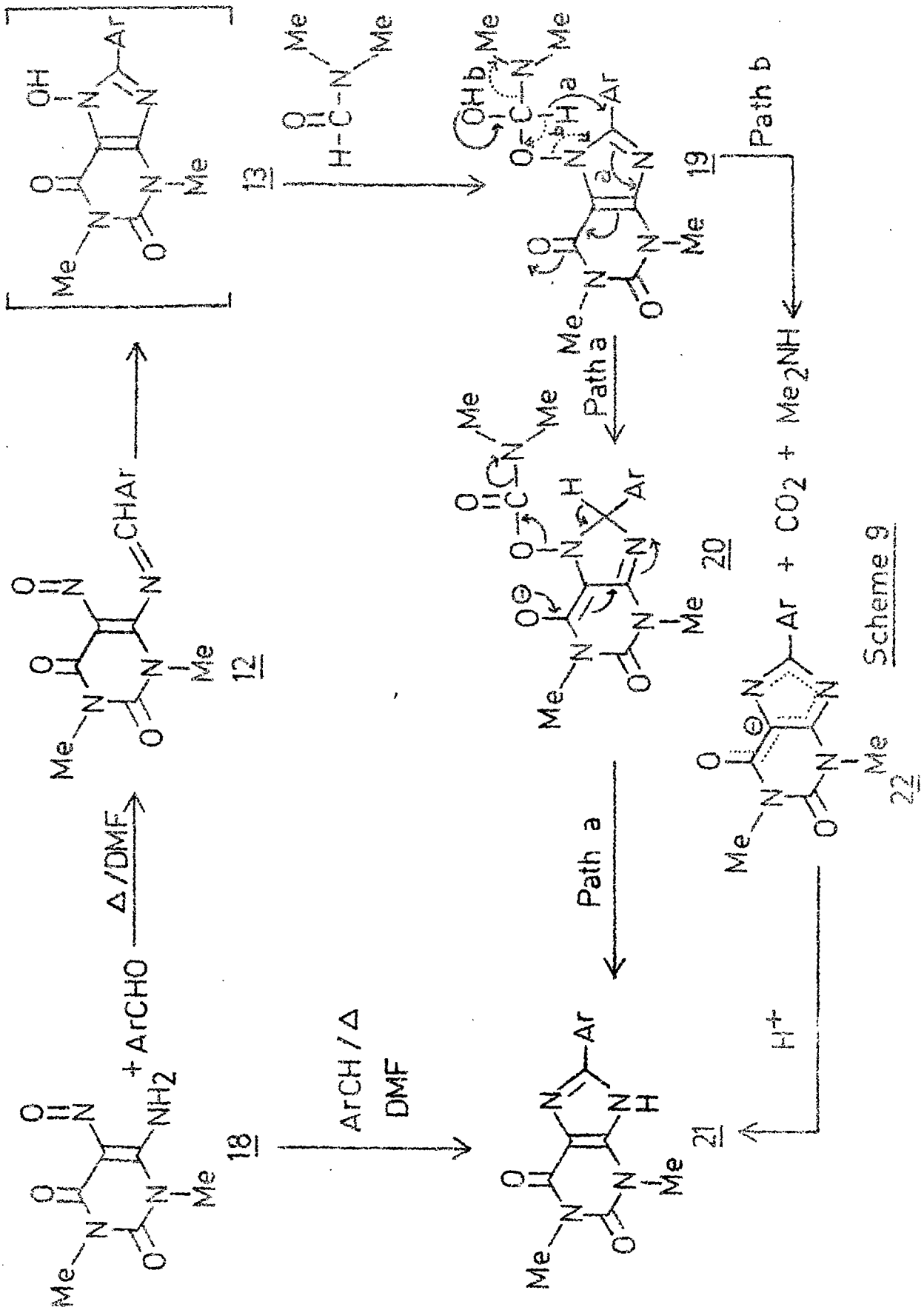


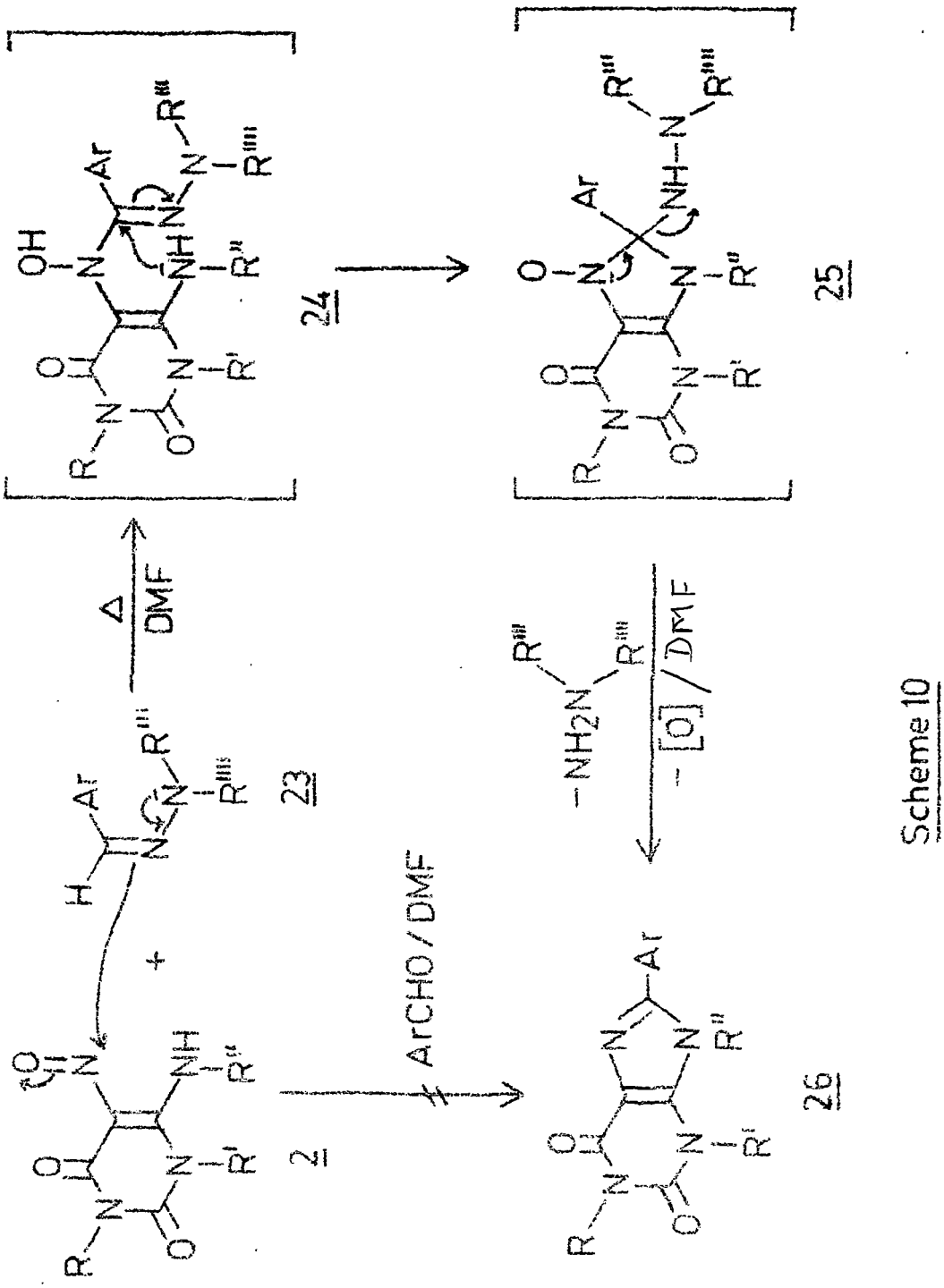
Scheme 7



Scheme 8

(Scheme 9).[15] The reaction has been shown to involve 7-hydroxyxanthines 13 as intermediates which undergo an unusual Leukart type reduction by dimethylformamide to give 21. The intermediate complex 19 can undergo an intramolecular oxidation reduction sequence either by transfer of a hydride ion to 8-position of purine ring (path a) or by direct collapse to 21, CO_2 and dimethylamine (path b) via a cyclic transition state involving 6-carbonyl group (Scheme 9). The corresponding 4-N-alkylderivatives 2 (Scheme 10) however did not yield the 8-aryl-9-substituted theophylline derivatives 26 on treatment with benzaldehyde under similar conditions. However when 2 were reacted with various substituted hydrazones of aldehydes, corresponding xanthines 26 were formed in good yields (Scheme 10).[16] This new purine synthesis is rationalized by assuming intermolecular nucleophilic attack of electron rich α-carbon of hydrazone 23 on nitroso group of 2 to form hydroxylamine intermediate 24, followed by intramolecular cyclization by addition of ortho amino substituents to imine carbon of the intermediate. Elimination of hydrazine and deoxygenation of purine 7-oxide by hydrazine could yield the purine 26 (Scheme 10).


+ ArCHO
Δ /DMF
+ NH2
18
12
ArCH / Δ
DMF
13
Path a
Path b
19
20
21
22
H+
Ar + CO2 + Me2NH
Scheme 9



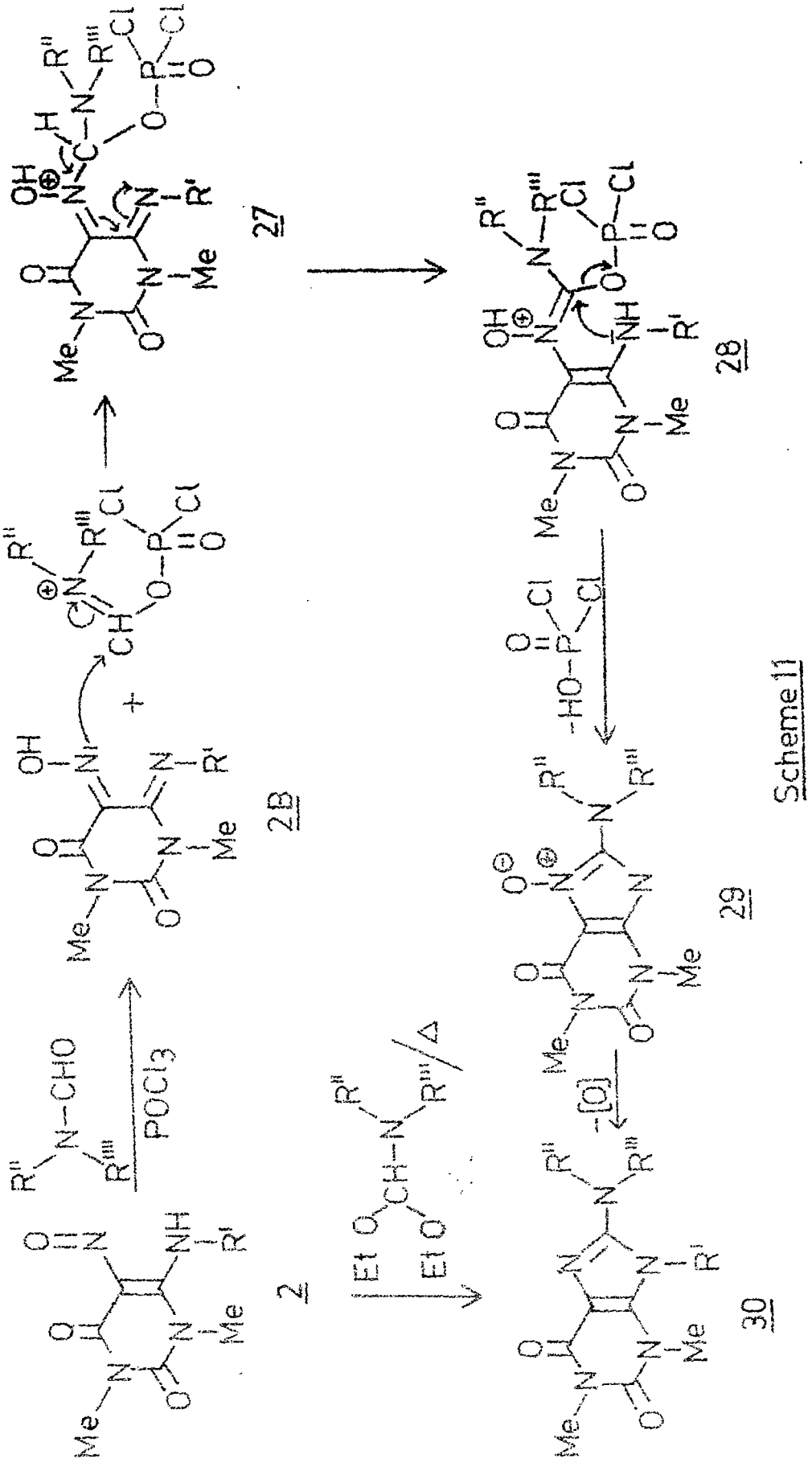
Scheme 10

In an interesting variation of above reaction, Yoneda and coworkers have reported the synthesis of 8-disubstituted-amino purines 30 by reaction of 4-amino-5-nitrosouracil derivatives 2 with Vilsmeier's reagent (Scheme 11).[17] Thus when 2 was treated with phosphorous oxychloride in dimethyl-formamide at 150°C the corresponding 8-dimethylaminotheophy-lline 30 (R"=R"=Me) was obtained in excellent yield. The proposed mechanisms for the formation of 30 through initial nucleophilic attack of hydroxyimino form 2B on Vilsmeier's reagent and subsequent intramolecular cyclization to 29 by elimination of dichlorophosphoric acid is shown in the Scheme 11.[18] Deoxygenation of purine 7-N-oxide 29 probably by dimethylformamide leads to the purine 30.

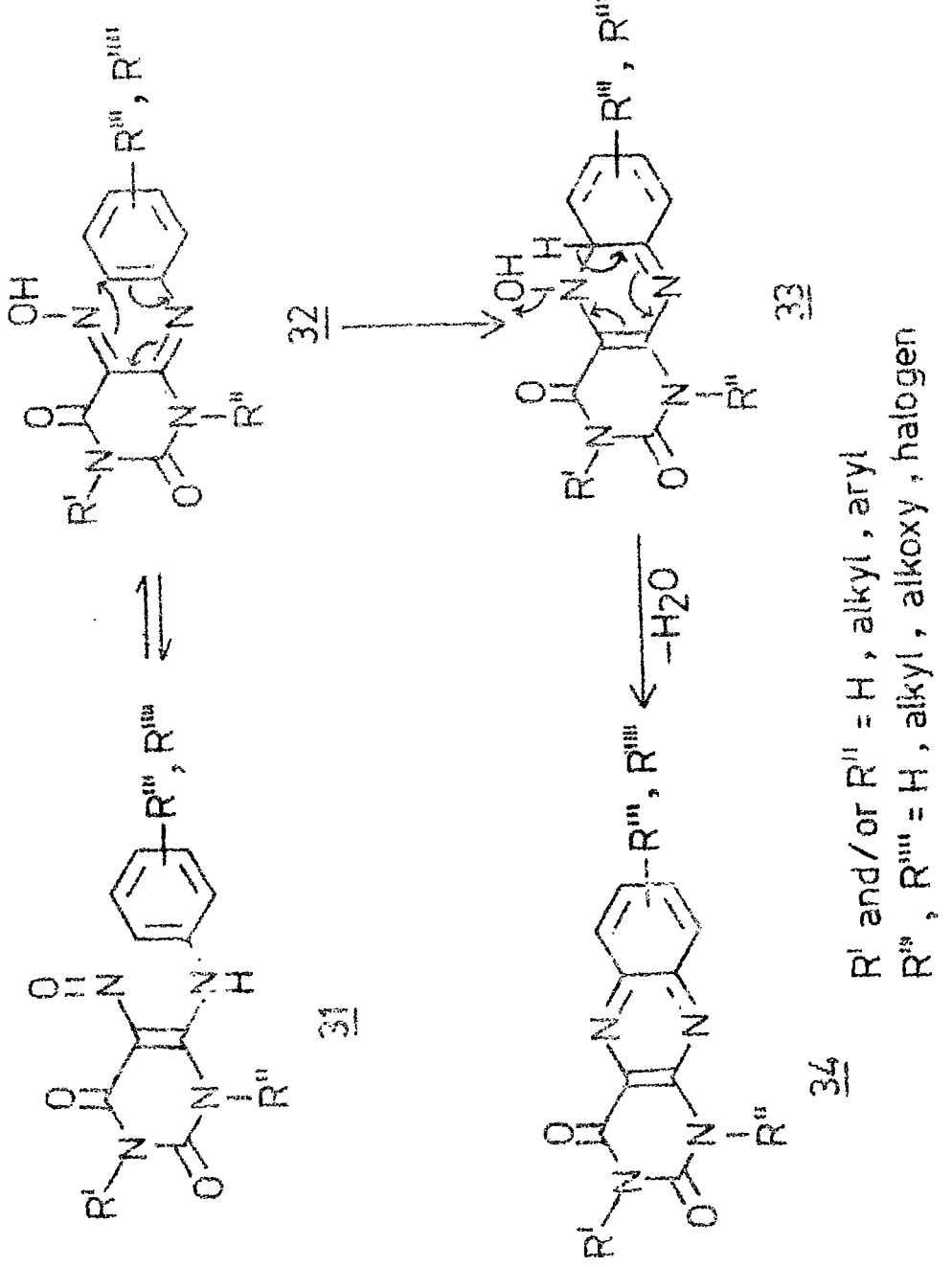
The reaction of excess of dimethylformamide diethyl-acetal with 4-amino-5-nitroso derivatives has also been reported to afford the corresponding 8-dimethylaminopurine derivatives 30 in good yields (Scheme 11).[19]

III.2.2 Synthesis of alloxazine and flavin derivatives

Goldner has reported a new general synthesis of alloxazine derivatives 34 (Scheme 12) by nitrosation of 4-anilino 1,3-dialkyluracils and subsequent thermal cyclo-dehydration of 4-anilino-5-nitrosouracil derivatives 31



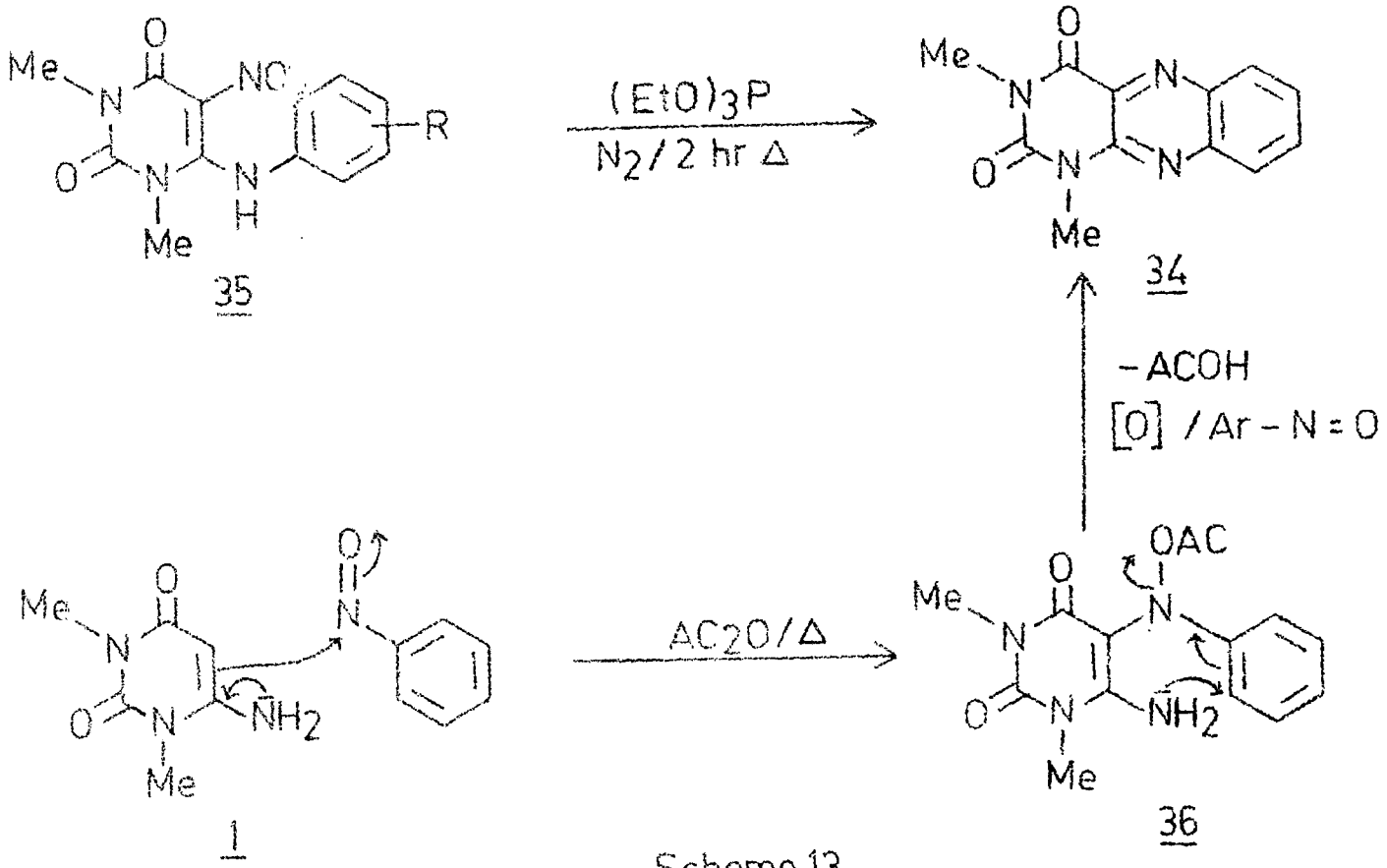
Scheme 11



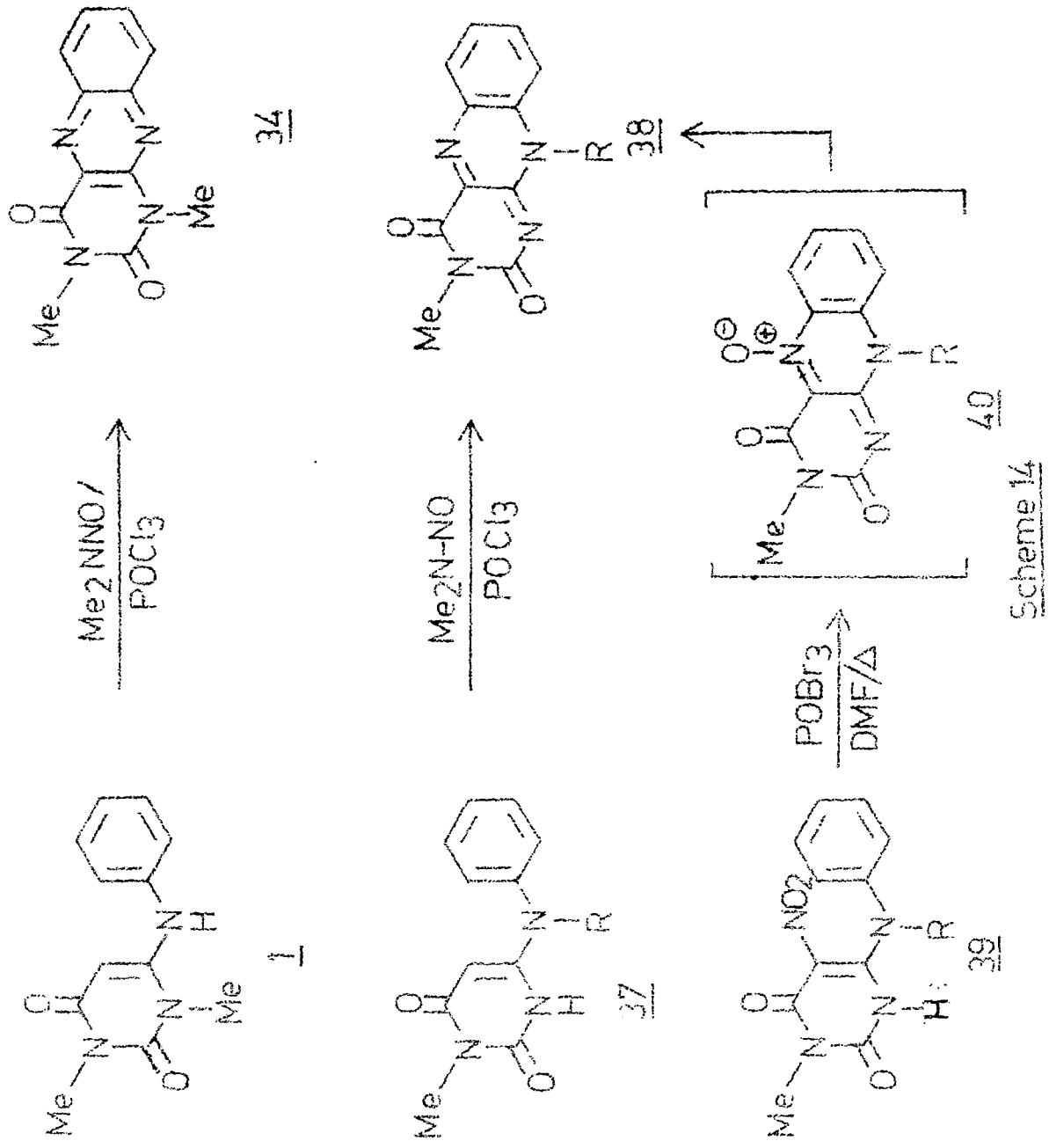
Scheme 12

(Scheme 12).[20] Taylor has synthesized alloxazine 34 by reduction of 4-anilino-5-nitrosouracil derivative 35 with triethylphosphite and by electrophilic nitrosation of 4-aminouracil 1 with nitrosobenzene in the presence of acetic anhydride (Scheme 13).[21] The former reaction appears to involve nitrene intermediate, while in the latter reaction, the hydroxyimino intermediate 36 after cyclodehydration, undergoes dehydrogenation with excess of nitrosobenzene to give the alloxazine 34 (Scheme 13).[21]

Alloxazine 34 has also been obtained by direct nitrosation and cyclization of 4-anilinouracil 1 (Scheme 14) with N-nitrosodimethylamine in the presence of phosphorous oxychloride.[22] This reaction has been further utilized for the synthesis of flavin derivatives 38 by treatment of 4-(N-alkyl-N-anilino) uracils 37 or by treatment of corresponding 5-nitroderivatives 39 with Vilsmeier-Haack reagent (Scheme 14).[23] The conversion of 39 to 38 probably involves the initial formation of flavin-5-oxide 40 by dehydrative cyclization of 39 followed by subsequent loss of oxygen by dimethylformamide (Scheme 14).[24,25]


Me
N
O
NO
R
N
H
Me
35
(EtO)3P
N2 / 2 hr Δ
Me
N
O
N
N
Me
34
-ACOH
[O] / Ar - N = O
Me
N
O
N
NH2
Me
1
AC2O/Δ
OAC
Me
N
O
N
NH2
Me
36

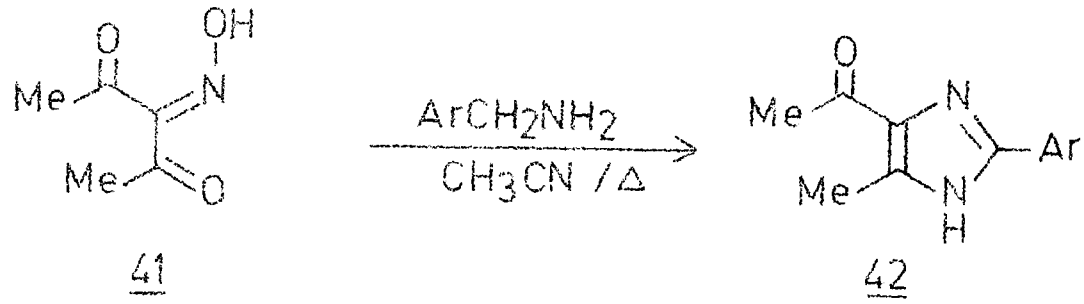
Scheme 13



Scheme 14

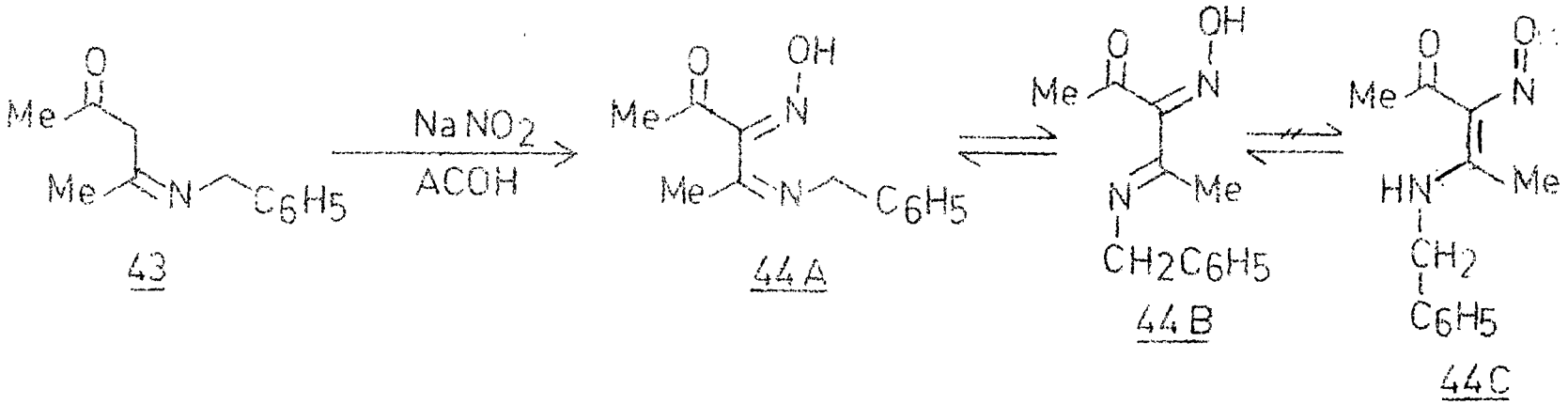
III.3 Synthesis of novel functionalized hydroxyiminoimines by direct nitrosation of α-ketoketen S,N-acetals and their further transformations: New general routes to imidazole, quinoxaline and thiazole derivatives

From the above discussion it is apparent that 4-amino-5-nitroso/nitrouracil derivatives 2 are useful intermediates for the synthesis of purine, alloxazine and flavin derivatives. Our literature survey at this stage revealed that a similar synthetic approach based on open-chain nitrosoenamines/enaminones (or hydroxyiminoimines) to give imidazole or quinoxaline derivatives has not been investigated. The only related reference reported in the literature involves the synthesis of 4-acetyl-2-aryl-5-methylimidazoles 42 by annelation of 3-hydroxyimino-2,4-dione 41 with benzylamines (Scheme 15).[26,27] The scant literature on such transformations is primarly due to the lack of appropriate open-chain nitrosoenamine/enaminone (or hydroxyiminoimines) precursors. Despite, the report of the preparation of few 1,2-hydroxyiminoimine derivatives by condensation of α-hydroxyiminoketones with appropriate amines,[27] an alternate general approach for these precursors, by electrophilic nitrosation of open-chain or cyclic enamines or enaminones has not been reported.[28,29] There is



41 42

41, 42, Ar = Substituted aryl



43 44A 44B 44C

Scheme 15

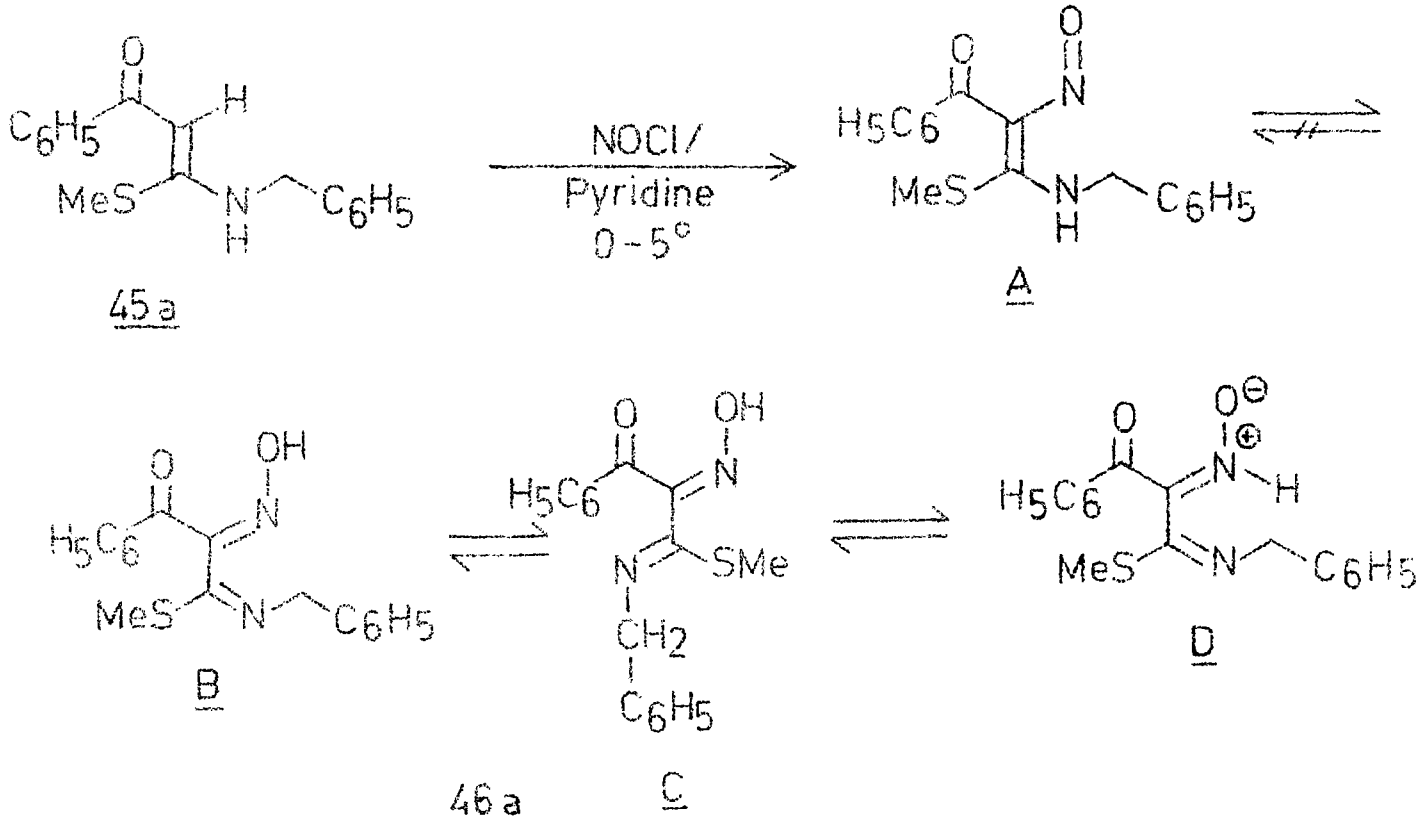
only one report[30] of the preparation of methyl (β-benzylimino-α-oximinopropyl)ketone 44 by nitrosation of the corresponding imine 43 (or enaminone) with sodium nitrite and acetic acid (Scheme 15). In the previous chapters we have shown that polarized ketoketen-S,N- and N,N-acetals represent a novel class of functionalized enaminones, which react with a variety of electrophilic compounds to yield novel mercapto and amino-heterocyclic compounds. In the present chapter we have carried out nitrosation of these compounds with nitrosyl chlorides which affords a facile general route to novel class of functionalized hydroxyiminoimines. Further cyclodehydrations of these hydroxyiminoimine derivatives afford novel imidazole, quinoxaline and thiazole derivatives. Thus novel general routes to these heterocyclic rings systems have been developed and the results are described in this chapter.

III.3.1 Synthesis of novel functionalized hydroxyiminoimines and their structural studies.

III.3.1.1 Results and discussion

All the keten-S,N- and N,N-acetals required for the present investigation were prepared by one of the methods described in the chapter II. When a solution of ketoketen-S,N-acetal 45a (R = C_6H_5; R' = Me; R" = C_6H_5) in ethanol was

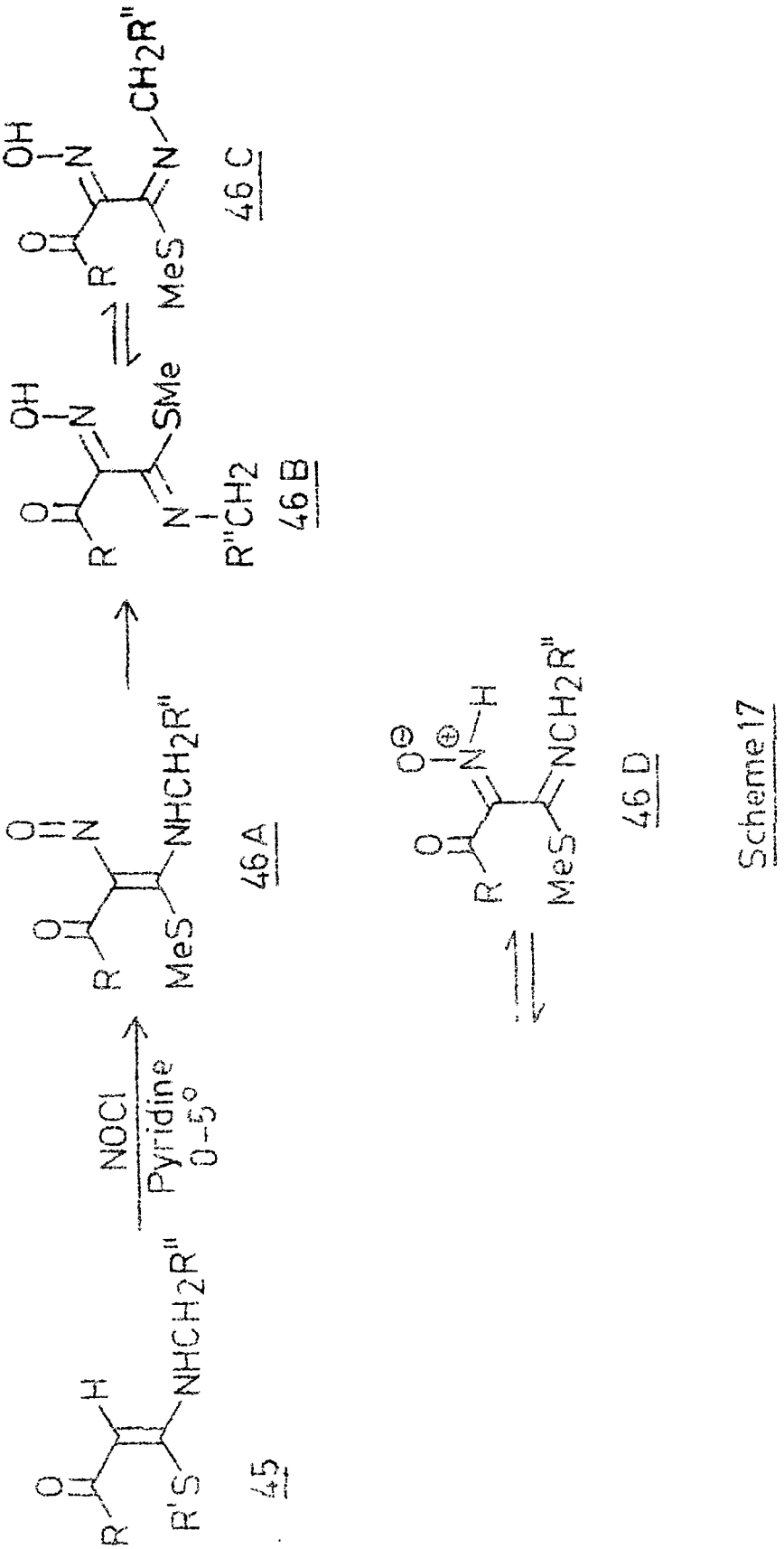
stirred at room temperature with equimolar quantities of isoamylnitrite in alcohol, the starting material was recovered unchanged. The keten-S,N-acetal 45a similarly remained unreacted even on prolonged refluxing in ethanol in the presence of isoamylnitrite. Alternatively, when the nitrosation of 45a was attempted with sodium nitrite in acetic acid at room temperature, analysis of the reaction mixture after work-up revealed, that a mixture of several products was formed, although the starting material had completely disappeared. On the otherhand, when a solution of 45a (0.01 mol) in ether was stirred with nitrosyl chloride (0.012 mol in ether) in the presence of pyridine at 0-5°, a colorless amorphous compound was obtained in 80% yield after work-up which was characterized as phenyl (α-oximino-β-benzylimino-β-methylthio) ketone 46a on the basis of spectral and analytical data (Scheme 16). Thus 46a analysed for $C_{17}H_{16}N_2O_2S$ and its mass spectrum showed weak molecular ion peak at m/e 312 (M^+). Its infrared spectrum (KBr) exhibited strong bands at 3480 (Br, OH) 1592 and 1642 (C=N and CO) cm^{-1}. Further structural proof for 46a was obtained from its ^1H-n.m.r. spectrum ($CDCl_3$-DMSO-d_6) which showed two singlets (total 3H, 2:1 ratio) at δ2.32 and 2.42 for SMe group in



Scheme 16

different environment, and another two singlets (total 2H, 1:2 ratio, $C_6H_5C\underline{H}_2$) at δ 4.38 and 4.55. The aromatic protons appeared as multiplets at δ 6.85-7.55 (m, 8H, Ar) and δ 7.62-8.11 (m, 2H, Ar). Its ultraviolet spectrum showed absorption maxima at λmax (MeOH): 242 (logϵ, 4.23) nm [λMax (MeOH) for 45a 245, 342 (logϵ, 2.35, 4.58)] nm. The hydroxyiminoimine structure (B and C) (Scheme 16) for 46a was assigned on the basis of its ultraviolet spectrum and the n.m.r. signal for the benzylic protons, which appears as a singlet,[31] while in the corresponding S,N-acetal 45a the signal due to benzylic protons appeared as doublet (δ 4.45, J=6Hz) owing to coupling with the NH proton. However the appearance of two signals for the MeS and benzylic protons in the n.m.r. spectrum of 46a is probably due to the existance of two geometrical isomers (S-cis B and S-trans C).

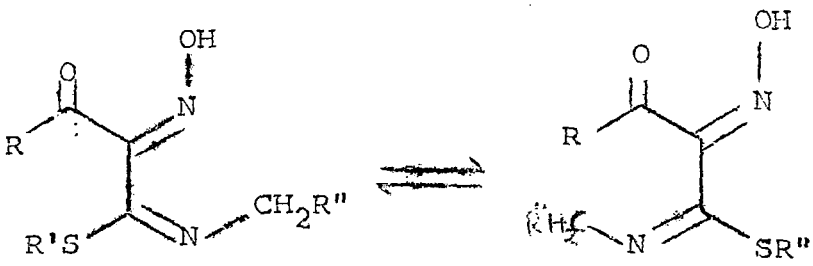
The reaction of other ketoketen-S,N-acetals 45b-j derived from primary alkylamines with nitrosyl chloride similarly yielded the corresponding hydroxyiminoimine derivatives 46b-j in 76-81% overall yields (Scheme 17, Table 2). All of these hydroxyiminoimines 46b-j were characterized



Scheme 17

TABLE 2

Synthesis of N-alkylhydroxyiminoimine derivatives (46a-j)



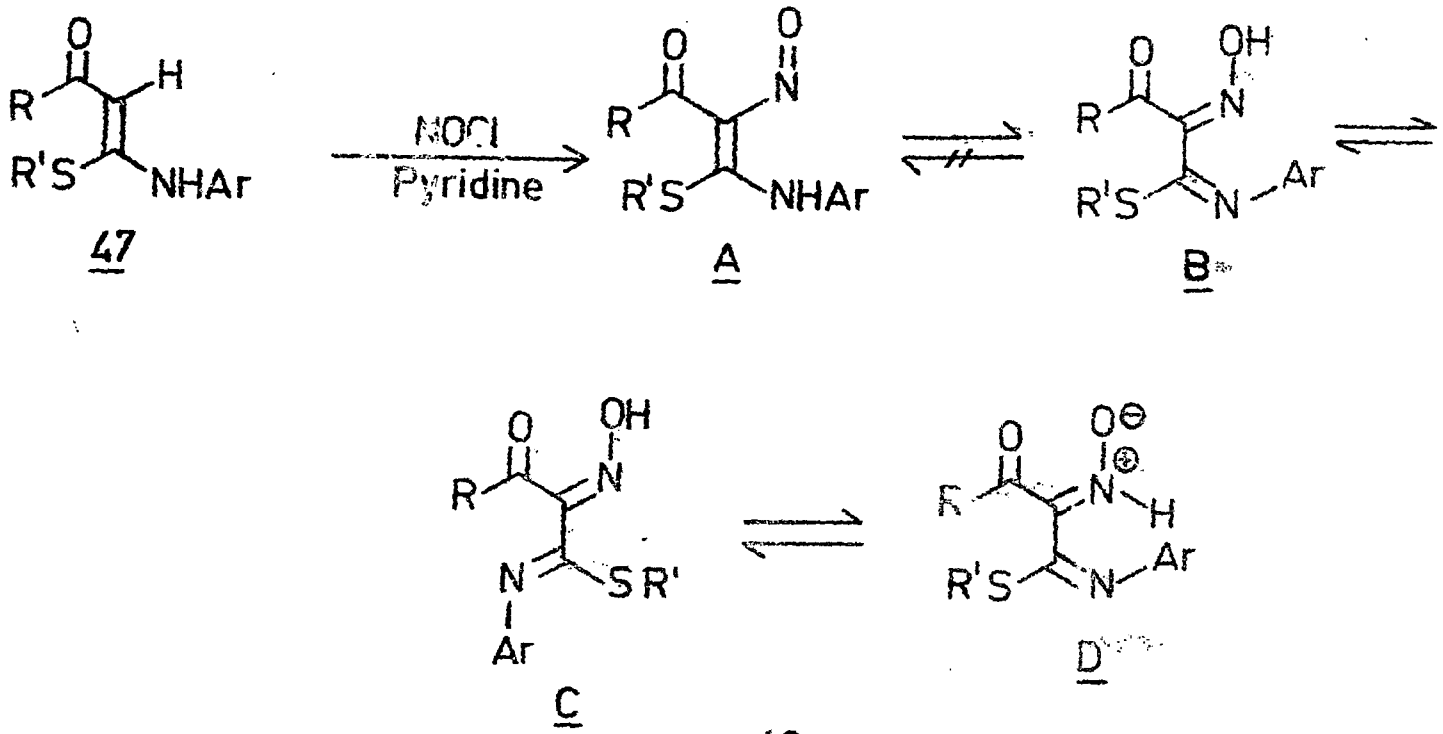
46

S. No	Starting compound	Product	R	R'	R"
1	45a	46a	C_6H_5	Me	C_6H_5
2	45b	46b	Me	Me	C_6H_5
3	45c	46c	C_6H_5	$C_6H_5CH_2$	C_6H_5
4	45d	46d	C_6H_5	Me	H
5	45e	46e	p-MeC_6H_4	Me	H
6	45f	46f	p-ClC_6H_4	Me	H
7	45g	46g	C_6H_5	Me	Me
8	45h	46h	p-MeC_6H_4	Me	Me
9	45i	46i	p-ClC_6H_4	Me	Me
10	45j	46j	C_6H_5	$C_6H_5CH_2$	Me

with the help of spectral and analytical data (Table 8 and 12). The u.v. and n.m.r. spectra of 46b-j indicated that they exist in hydroxyiminoimine tautomeric forms (46B and 46C).

When the ketoketen-S,N-acetal 47a derived from aniline was subjected to nitrosation under identical conditions, corresponding hydroxyimine 48a was obtained in 80% yield (Scheme 18, Table 3), which was characterized with the help of spectral and analytical data (Table 8 and 12). The ultra-violet spectrum of 48a [λmax (MeOH): 244] nm supported the hydroxyiminoimine tautomeric structure. The other N-aryliminohydroxyiminoimines 48b-s were similarly obtained in 75-81% overall yields under identical conditions (Table 3). The spectral and analytical data of 48a-s are given in Table 8 and 12. The ultraviolet spectrum of 48a-s indicates hydroxyimino tautomeric structures.

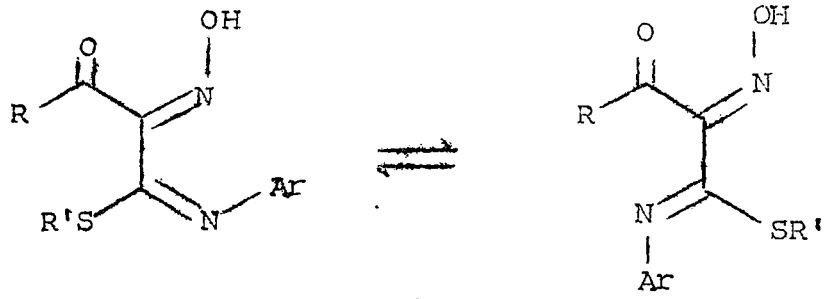
Attempted nitrosation of nitroketen-S,N-acetal 49 was not successful (Scheme 19) and the starting material was recovered unchanged, even when the nitrosation was carried out at higher temperature in refluxing chloroform. When the



Scheme 18

TABLE 3

Synthesis of N-aryl hydroxyiminoimine derivatives(48a-h).



48

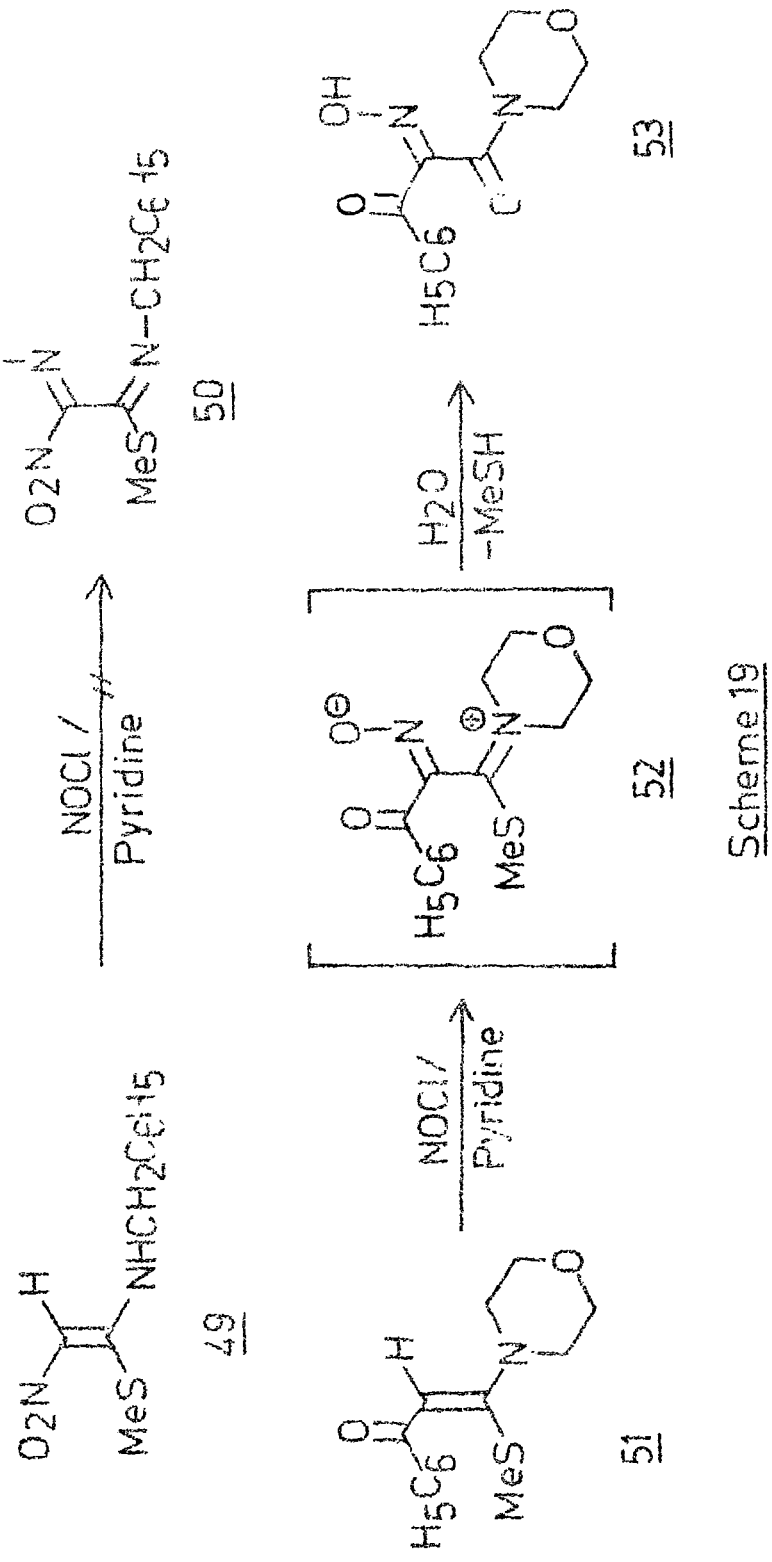
S. No	Starting compound	Product	R	R'	Ar
1.	47a	48a	C_6H_5	Me	C_6H_5
2.	47b	48b	p-MeC_6H_4	Me	C_6H_5
3.	47c	48c	p-$MeOC_6H_4$	Me	C_6H_5
4.	47d	48d	p-ClC_6H_4	Me	C_6H_5
5.	47e	48e	C_6H_5	Me	p-MeC_6H_4
6.	47f	48f	C_6H_5	Me	p-$MeOC_6H_4$
7.	47g	48g	C_6H_5	Me	p-ClC_6H_4
8.	47h	48h	p-MeC_6H_4	Me	p-$MeOC_6H_4$

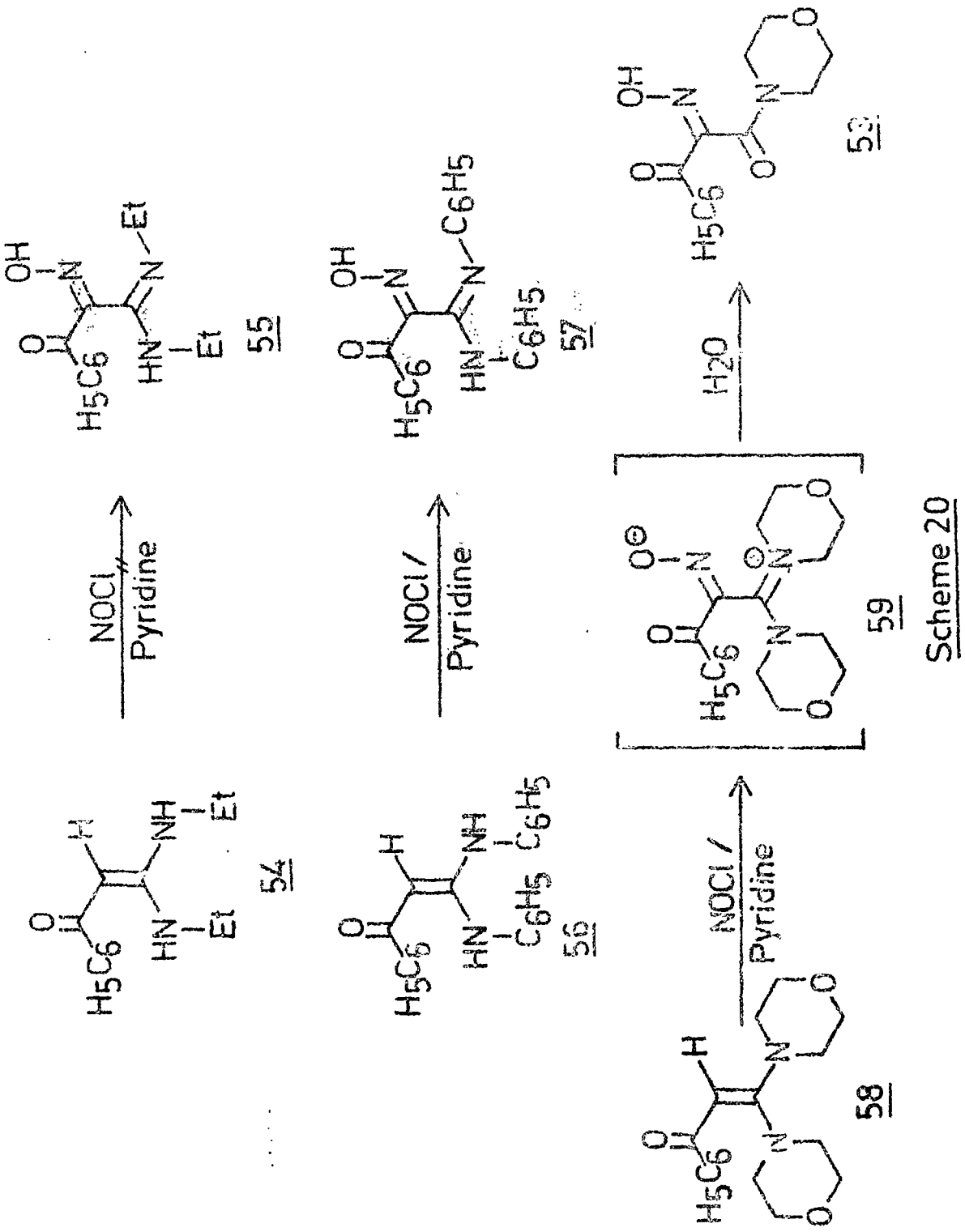
Table 3 (Contd.)

9.	47i	48i	p-MeC_6H_4	Me	p-ClC_6H_4
10.	47j	48j	p-$MeOC_6H_4$	Me	p-ClC_6H_4
11.	47k	48k	p-ClC_6H_4	Me	p-MeC_6H_4
12.	47l	48l	p-ClC_6H_4	Me	p-$MeOC_6H_4$
13.	47m	48m	C_6H_5	Et	C_6H_5
14.	47n	48n	C_6H_5	$CH_2C_6H_5$	C_6H_5
15.	47o	48o	p-MeC_6H_4	$CH_2C_6H_5$	C_6H_5
16.	47p	48p	p-$EtOC_6H_4$	$CH_2C_6H_5$	C_6H_5
17.	47q	48q	p-ClC_6H_4	$CH_2C_6H_5$	C_6H_5
18.	47r	48r	C_6H_5	$CH_2C_6H_5$	p-MeC_6H_4
19.	47s	48s	C_6H_5	$CH_2C_6H_5$	p-ClC_6H_4

corresponding S,N-morpholinoacetal 51 was subjected to nitrosation under identical conditions, the product isolated in 60% yield was characterised as α-oximinomorpholinide 53 on the basis of spectral and analytical data. Apparently, the intermediate hydroxyimine 52 undergoes facile hydrolysis during work-up to give 53 (Scheme 19).

Nitrosation of the corresponding ketoketen-N,N-acetals (54, 56 and 58) was next investigated. The corresponding N,N-ethylacetal 54, however, failed to yield the corresponding hydroxyiminoimine 55 even under drastic conditions and the starting material was recovered unchanged (Scheme 20). Interestingly, the corresponding N,N-phenylacetal underwent facile nitrosation to give the hydroxyiminoimine 57 in good yield (Scheme 20). The spectral and analytical data of 57 was in conformity with the assigned structure. However, it is not possible to give any rational explanation at this stage for the observed different behaviour of N,N-acetals 54 and 56. Nitrosation of the corresponding N,N-morpholinoacetal 58 under reported conditions yielded α-oximinomorpholinide 53 (Scheme 20) which was also obtained from nitrosation of S,N-acetal 51 (Scheme 19). Apparently, the


NOCl / Pyridine
H2O
-MeSH
NOCl / Pyridine
49
50
51
52
53
Scheme 19



Scheme 20

nitrosoenaminones 52 and 59 derived from secondary amines undergo facile hydrolysis during work-up to give hydrolysed oximinoketone 53. These observations are in conformity with the earlier report of facile hydrolysis of 4-dimethylamino-5-nitrosouracil derivatives 4 (Scheme 2) to 1,3-dimethyl-5-nitrosobarbituric acid.[5]

III.3.1.2 Structural studies

Despite the wide applications of 4-amino-5-nitroso-pyrimidine derivatives for purine and alloxazine synthesis, there is still no real knowledge on the predominating tautomeric states of these derivatives.[31] It is still uncertain whether they exist in nitroso or oximino or both tautomeric forms.[32] Nitrosopyrimidines are coloured compounds. Explanation of the various colors along the lines of "Strained Structure" associated with isonitroso-ketonitroso-hydroxy tautomerism in the molecules are described in the several papers, but the overall picture is still not clear.[31] The n.m.r. spectral studies on the only reported acyclic nitrosoenamine 44 support the hydroxyimino structures 44A and 44B on the basis of splitting pattern of benzylic protons signal.[31] The nitrosoenaminones 46a-j and 48a-s

prepared in the present investigation by nitrosation of α-ketoketen S,N-acetals with nitrosyl chloride are all colorless compounds with u.v. absorption maxima in the range of λmax (MeOH): 242 nm- 269 nm; which supports the hydroxyimino structures B & C (Scheme 16 and 17), since most of the nitroso monomeric compounds show weak absorption between λmax 630 - 790 nm.[33] The splitting pattern of N-alkyl protons (see discussion in section III.3.1.1) in the n.m.r. spectrum of N-alkyliminohydroxyimines 46a-j (Table 8) also supports the hydroxyiminoimine tautomeric structures for these intermediates. The ultraviolet spectra of aryliminohydroxyiminoimines 48a-s also indicate the presence of hydroxyiminoimine tautomeric forms. However it is not possible to draw definite conclusion about predominant tautomeric forms in these derivatives and further work is in progress in this direction.

III.3.1.3 Conclusion

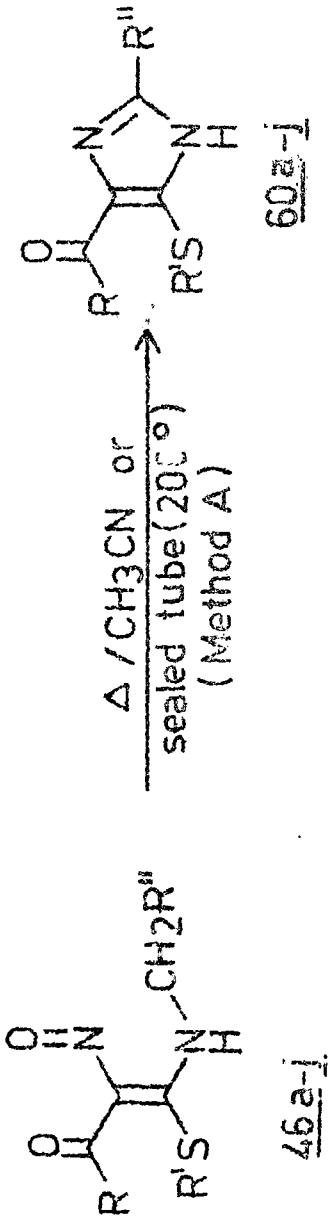
A novel class of functionalized nitrosoenaminones or hydroxyiminoimines have been synthesized by direct nitrosation of polarized ketoketen-S,N-acetals with nitrosyl chloride. The spectral studies on these compounds indicate that they exist in predominent hydroxyiminoimine tautomeric

forms. Their further synthetic transformations to imidazole, quinoxaline and thiazole derivatives are described below.

III.3.2 A novel general route to 2-aryl/alkyl/ethoxycarbonyl/unsubstituted-4-aroyl/acyl-5-alkylthioimidazoles by thermal cyclodehydration of aryl/alkyl (α-oximino-β-aryl/alkylimino-β-alkylthio)ketones

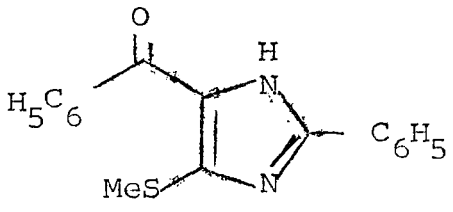
III.3.2.1 Results and discussion

With a variety of functionalized hydroxyiminoimines 46a-j and 48a-s in hand, we next intended to study the thermal cyclodehydration of these intermediates with a view to develop novel general routes for imidazole and quinoxaline derivatives. Interestingly, when the hydroxyiminoimine 46a was heated at its melting point for 0.5 hr, the recovered compound was not the starting material 46a, on the otherhand a light yellow compound, m.p. 215°C, was obtained in 80% yield. The same compound was also obtained in 78% yield, when the hydroxyiminoimine 46a was refluxed for 3 hr in acetonitrile. The product was characterized as 2-phenyl-4-benzoyl-5-methylthioimidazole 60a on the basis of spectral and analytical data (Scheme 21). It showed molecular ion peak at m/z 294 (100%, M^+) in its mass spectrum and analysed for $C_{17}H_{14}N_2OS$. It's infra-red spectrum (KBr)



Scheme 21 (Table 4)

exhibited absorption peaks at 3240 (NH) and 1600 (conjugated CO) cm^{-1}. Further structural proof for 60a was obtained from its n.m.r. spectrum ($CDCl_3$/DMSO-d_6), which showed disappearance of signal due to benzylic protons present in the n.m.r. spectrum of hydroxyiminoimine 46a. A singlet at δ 2.55 (3H) was assigned to MeS protons, while the aromatic protons appeared as three multiplets at δ 7.45 (6H), 7.88 (2H) and 8.15 (2H) respectively. A low field broad signal at δ12.85 (exchangeable with D_2O, 1H) was assigned to imidazole NH proton. The tautameric structure 61 was ruled out on the basis of u.v. spectrum of 60a, which showed absorption maxima



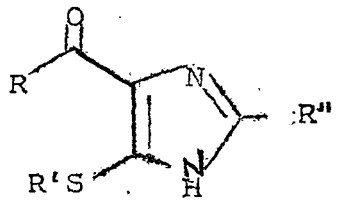
61

at λmax (MeOH): 270, 350 (logϵ , 4.54, 4.23) nm pointing to a β-aminoenone moiety; λmax (MeOH) for 45a: 245, 342

(log ϵ, 2.35, 4.58) nm. The corresponding α-acetylhydroxyiminoimine 46b and S-benzylhydroxyiminoimine 46c (Table 2), similarly underwent facile cyclodehydration in refluxing acetonitrile to give the corresponding 2-aryl-4-acetyl-5-methylthioimidazole 60b and 5-benzylthioimidazole 60c (Scheme 21) (Table 4) in 58% and 82% yields, respectively. The corresponding N-methyliminohydroxyimine 46d, on the otherhand remained unchanged when refluxed for prolonged time in acetonitrile (12 hr). However when 46d was subjected to cyclodehydration at higher temperature (200°C in sealed tube/ CH_3CN), the corresponding 2-unsubstituted-4-benzoyl-5-methylthioimidazole (60d) was obtained in 55% yield. Apparently the methylene group in 46d is not activated and the cyclodehydration to imidazole 60d requires more drastic conditions than 46a in which the methylene group is activated by an aryl group. The other substituted N-methylimino 46e-f and N-ethylimino 46g-j hydroxyiminoimines similarly underwent cyclodehydration at higher temperature (200° in sealed tube) to give the corresponding 2-unsubstituted (60e-f) and 2-methyl (60g-j) imidazoles in 52-60% overall yields (Method A) (Table 4). The spectral and analytical data (Table 9 and 13)

TABLE 4

2-Aryl/methyl/unsubstituted-4-aroyl/acyl-5-alkylthioimidazoles prepared*



60

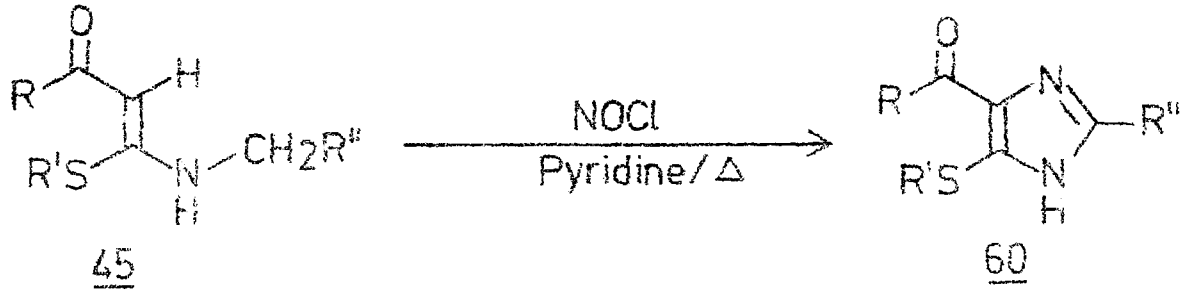
S. No	Starting compound	Product	R	R'	R"
1.	46a	60a	C_6H_5	Me	C_6H_5
2.	46b	60b	Me	Me	C_6H_5
3.	46c	60c	C_6H_5	$C_6H_5CH_2$	C_6H_5
4.	46d	60d	C_6H_5	Me	H
5.	46e	60e	p-MeC_6H_4	Me	H
6.	46f	60f	p-ClC_6H_4	Me	H
7.	46g	60g	C_6H_5	Me	Me
8.	46h	60h	p-MeC_6H_4	Me	Me
9.	46i	60i	p-ClC_6H_4	Me	Me
10.	46j	60j	C_6H_5	$C_6H_5CH_2$	Me

* By method A

of all imidazoles 60b-j were in conformity with the assigned structures.

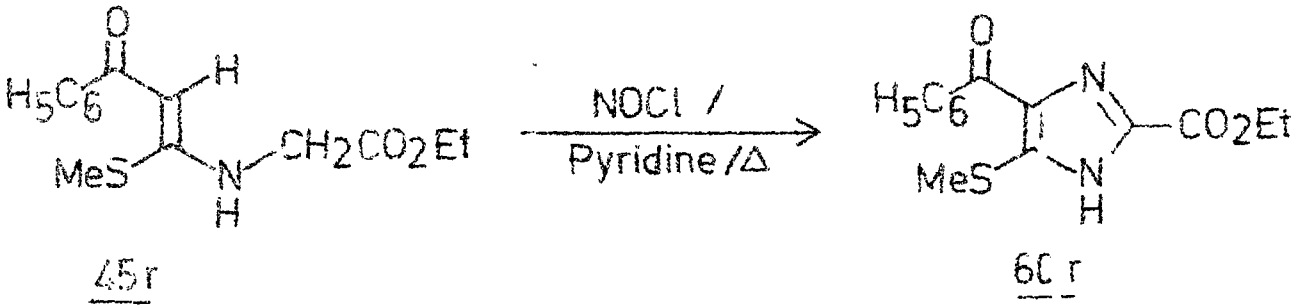
Interestingly, the 2-phenylimidazole 60a could also be prepared directly in one step in 75% yield (m.p., i.r. and n.m.r. spectra in agreement with 60a obtained by Method A), when a mixture of S,N-acetal 45a (0.01 mol) and nitrosyl chloride (0.012 mol in 5 ml of dry ether) was refluxed in pyridine for 2.5 hr (Method B) (Scheme 22). The reaction was found to be general and other substituted 2-aryl imidazoles (60k-m) (60o-q) 5-ethylthio-(60n) imidazoles were obtained in 70-82% overall yields (Table 5). Method B thus provides a direct entry to 2-arylimidazoles without the need for the isolation of corresponding hydroxyiminoimine intermediates 46. However this direct method was not successful for the preparation of 2-unsubstituted (60d-f) and 2-methyl (60g-j) imidazoles and attempted reaction of S,N-methyl 45d and S,N-ethyl 45g acetals with nitrosyl chloride under similar conditions (Method B) yielded only intractable reaction mixture from which the corresponding imidazoles 60d and 60g could not be isolated.

When the S,N-acetal 45r derived from ethylglycinate (preparation given in the Chapter II) was reacted with



45 60

Scheme 22 (Table 5)

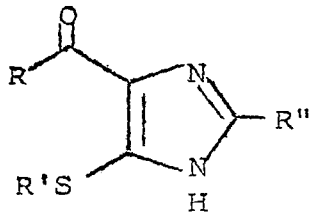


45r 60r

Scheme 23

TABLE 5

2-Aryl/ethoxycarbonyl-4-aroyl-5-alkylthioimidazoles prepared (Method B)* (Scheme 22)



60

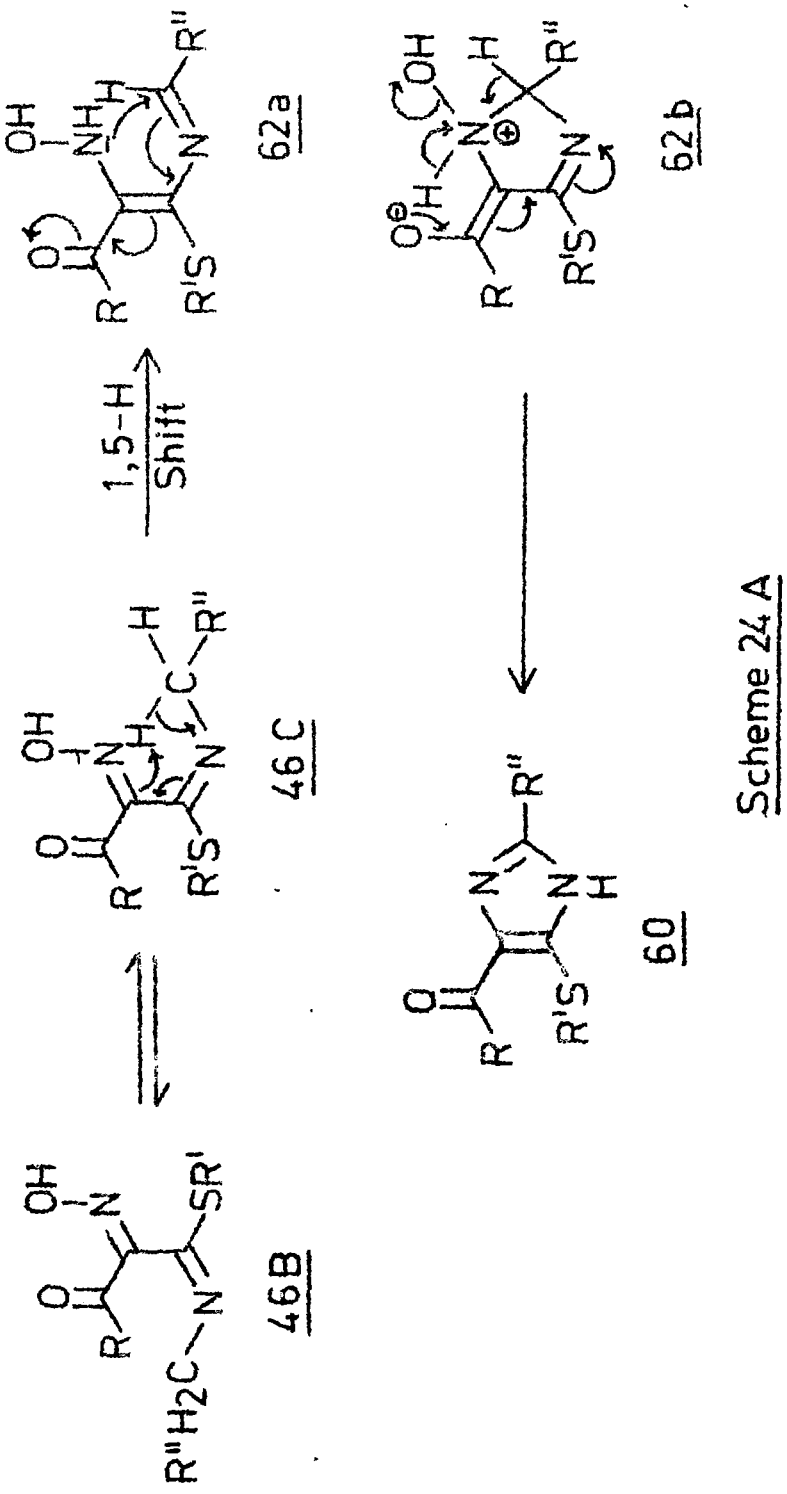
S. No	Starting Compound	Product	R	R'	R"
1.	45a	60a	C_6H_5	Me	C_6H_5
2.	45k	60k	p-MeC_6H_4	Me	C_6H_5
3.	45l	60l	p-$MeOC_6H_4$	Me	C_6H_5
4.	45m	60m	p-ClC_6H_4	Me	C_6H_5
5.	45n	60n	C_6H_5	Et	C_6H_5
6.	45o	60o	C_6H_5	Me	p-$MeOC_6H_4$
7.	45p	60p	p-ClC_6H_4	Me	p-$MeOC_6H_4$
8.	45q	60q	C_6H_5	Me	p-ClC_6H_4
9.	45r	60r	C_6H_5	Me	CO_2Et

*By direct treatment of nitrosyl chloride with S,N-acetals.

nitrosyl chloride in refluxing pyridine (Method B), the corresponding 2-carbethoxyimidazole 60r was obtained in 55% yield. The structures of all imidazoles 60k-r prepared by method B were confirmed by their spectral and analytical data which are given in the Table 9 and 13, respectively.

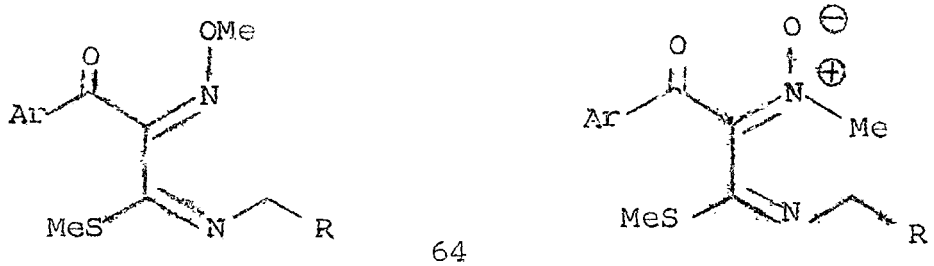
III.3.2.2 Mechanism of imidazole formation

The mechanism of imidazole formation from the hydroxyiminoimines 46 is shown in the Scheme 24A. The hydroxyiminoimine 46C in its S-cis configuration is favourably disposed for a thermal 1,5-proton shift to give substituted enaminoimine intermediate 62a. Intramolecular nucleophilic attack of hydroxyimino group at imine carbon and subsequent elimination of water in the intermediate 62b affords the imidazole 60. The imine carbon in the intermediate 62a is very susceptible to nucleophilic attack due to delocalization of electrons over carbonyl group as shown. No attempts were made to isolate any of these intermediates. Interestingly when the hydroxyiminoimine 46a was reacted with methyl iodide in refluxing acetone the corresponding 1-N-methyl-2-aryl-4-methylthio-5-aroylimidazole 63a was obtained in 70% yield



Scheme 24 A

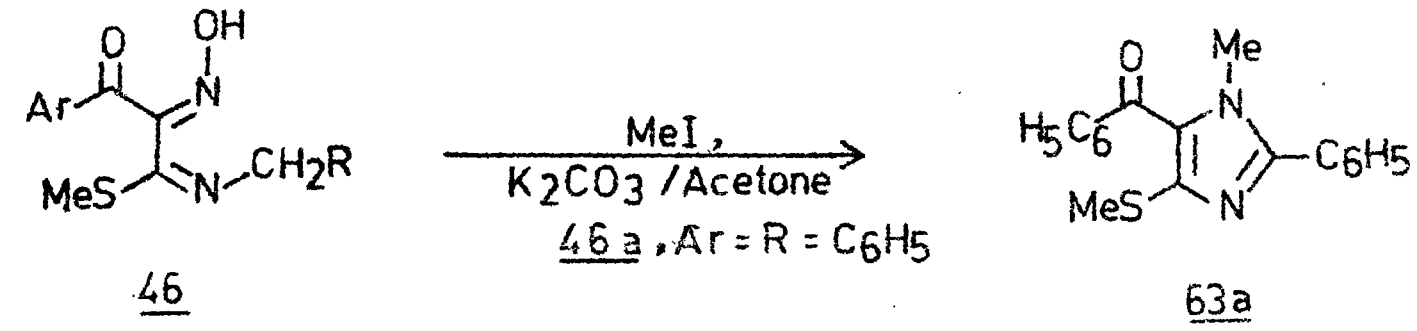
(Scheme 24B) and none of the corresponding O-methyl or N-methylhydroxyiminoimines 64a or 64a' were isolated. The structure of 63a was confirmed with the help of spectral and



64

64a, a' Ar = R=C_6H_5
b, b' Ar = p-ClC_6H_4; R=H
c, c' Ar = C_6H_5; R=Me

analytical data (experimental). However when the corresponding N-methylhydroxyiminoimine 46f was reacted with methyl iodide under identical conditions, the corresponding 1-N-methyl-2-unsubstituted imidazole 63b was not formed (Scheme 24B), the product isolated after work-up was found to be a mixture of N- and O-alkylated hydroxyiminoimines 64b and 64b' from spectral and analytical data. Similarly the corresponding N-ethylhydroxyiminoimine 46g yielded a mixture of N- and O-alkylated hydroxyiminoiminines 64c and 64c'. These results indicate that fixing of isonitroso structures by alkylation (64a'-c') does not facilitate the cyclization to the corresponding imidazoles as observed in the alkylative cyclization of 4-N-methylamino-5-nitrosouracils 2a (Scheme 4) to the corresponding N-methyl



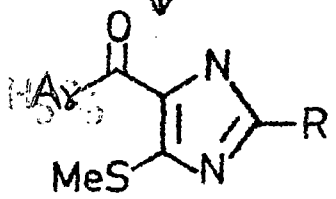
46

46a , Ar = R = C_6H_5

63a

46f , Ar = p ClC_6H_4 ; R = H

46g , Ar = C_6H_5 ; R = Me



63b , R = H

c , R" = Me

Scheme 24B

purines 9 in the presence of either diazomethane or methyl iodide (Scheme 4). On the otherhand, cyclization of 46 to imidazoles 60 is facilitated either by activation of N-methyl-enecamino group by an aryl group (46a-c) or by increasing the cyclization temperature (46d-j). These studies indicate the importance of tautomeric hydroxyiminoimine intermediate 62a (Scheme 24A) in the cyclization of 46 to 60 formed by a thermal 1,5-H shift in the hydroxyimine 46c. However, our attempts to isolate such intermediate (62a) were not successful and further work is in progress to study the concerted nature of this 1,5-H shift.

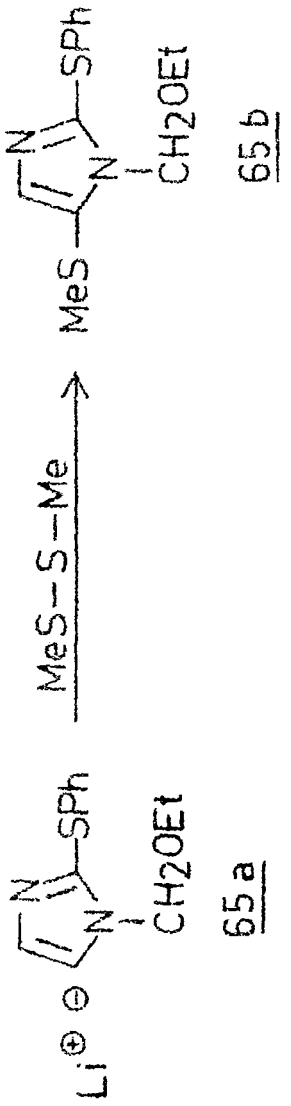
III.3.2.3 Conclusion

A novel general route for 2-aryl/alkyl/ethoxycarbonyl-4-aroyl/acyl-5-alkylmercaptoimidazoles has been developed by thermal cyclodehydration of novel functionalized hydroxyiminoimines 46 which could be easily prepared by nitrosation of easily available S,N-acetals 45. The imidazoles 60a, 60k-r could also be prepared directly from the corresponding S,N-acetals 45 without the isolation of hydroxyiminoimines intermediates 46. It is pertinent to note that very few 4(5)-alkylthioimidazoles are reported in the literature, which

are usually prepared either by alkylation of the corresponding imidazole-4(5) thiones in presence of base or by nucleophilic displacement of 4(5)-halogenoimidazoles by alkyl mercaptans.[34-38] Recently a few of the 5-methylthioimidazole derivatives (65b) have been synthesized by reaction of the corresponding imidazol-5-ylithium derivatives (65a) (prepared by metallation of the corresponding 5-haloimidazoles) with dimethyldisulfide (Scheme 25).[39] The present method provides a simple high yield route for the preparation of 5-alkylthioimidazole derivatives from easily available starting materials having build-in alkylthio groups.

III.3.3 Thermal cyclodehydration of phenyl (α-hydroxyimino-β-N-arylimino-β-alkylthio) ketones: A novel general routes to 2-methylthio-3-aroylquinoxalines and 2-aryl-4-aroyl-5-arylaminothiazoles

After considerable success achieved in the synthesis of imidazole derivatives by thermal cyclodehydration of novel N-alkyl-α-hydroxyiminoimines 46a-j, we next investigated thermal cyclodehydration of the corresponding N-aryl hydroxyiminoimines 48a-s (Table 3) with a view to develop a facile general route for quinoxaline synthesis from these intermediates. Thus the corresponding β-N-arylimino-β-methylthiohydroxyimines 48a-l



65 a

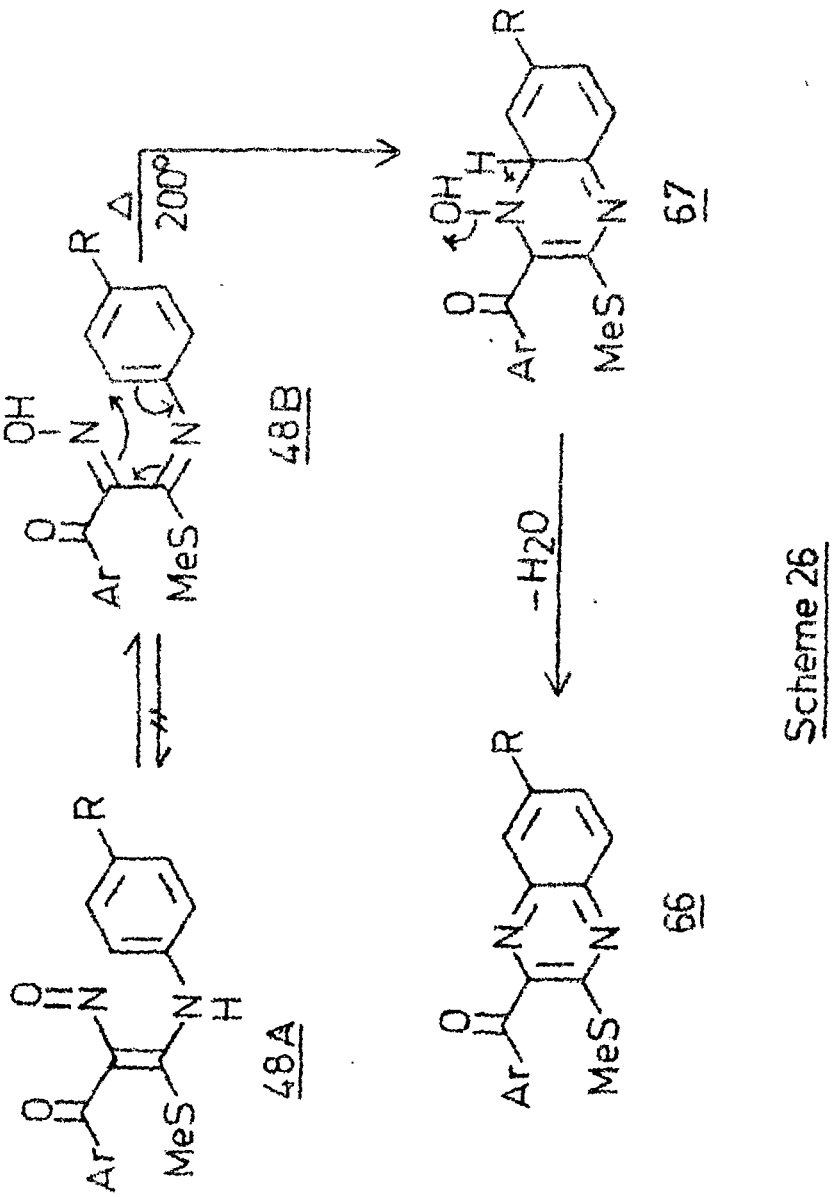
65 b

Scheme 25

yielded the expected quinoxalines 66a-l (Table 6) in good yields. However, cyclodehydration of the corresponding S-benzylthiohydroxyiminoimines (48n-s) (Table 3) took different course and the corresponding 2-aryl-4-aroyl-5-anilinothiazoles (68) (Table 7) were obtained instead of the quinoxaline derivatives. These results are presented here.

III.3.3.1 Results and discussion

When β-phenylimino-β-methylthio-α-hydroxyimino-ketone 48a (Table 3) was subjected to cyclodehydration in refluxing acetonitrile, the imine 48a was recovered unchanged even after prolonged refluxing. However when the solution of 48a in acetonitrile was heated in a sealed tube (200°C) for 2.5 hr, work-up of the reaction mixture yielded a bright yellow crystalline solid (65%), which was characterized as 2-methyl-thio-3-benzoylquinoxaline 66a on the basis of (Scheme 26) spectral and analytical data (Table 10 and 14). Thus the product 66a showed molecular ion peak at m/z 280 (M^+) and analysed for $C_{16}H_{12}N_2OS$. Its infra-red spectrum (KBr) exhibited strong intensity peak at 1668 cm^{-1} which was assigned to aromatic carbonyl group. Its n.m.r. spectrum showed signal

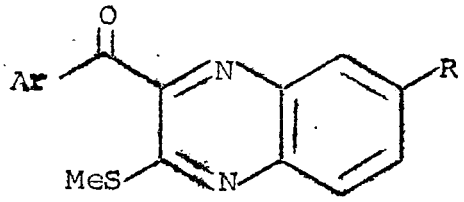


Scheme 26

due to MeS group protons at δ 2.54 (s, 3H), while the aromatic protons appeared as two multiplet at δ 7.0-7.81 (5H) and 7.82-8.20 (4H) which were in conformity with the assigned structure. Presence of absorption maxima at λmax (MeOH): 242, 267 (Sh) and 362 (logϵ, 4.30, 4.25, 3.62) nm further supports the presence of quinoxaline chromaphore [λmax(cyclohexane) for 2-methylthioquinoxaline 240, 270, 360 (logϵ, 4.4, 4.42, 3.85)] nm .[40] The other substituted β-aryl imino-β-methylthio-α-hydroxyiminoketones 48b-l similarly underwent facile cyclodehydration under identical conditions to give the corresponding quinoxalines 66b-l in 48-65% overall yields (Table 6). The spectral and analytical data (Table 10 and 14) of 66b-l were in conformity with the assigned structures. Recently at the time of writing this work, it was found that the quinoxaline 66a was formed in improved yield (70%), when the corresponding hydroxyiminoimine 48a was refluxed in acetic anhydride for 5 hr. Thus the cyclodehydration step is facilitated in the presence of acetic anhydride. When the corresponding β-ethylthio-β-phenyliminohydroxyimine 48m was subjected to cyclodehydration under identical conditions, the desired 2-ethylthioquinoxaline 66m was not obtained. Work-up

TABLE 6

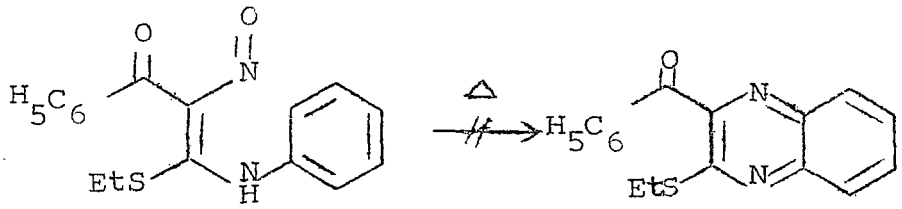
Synthesis of 6-substituted-2-methylthio-3-aroyl quinoxalines (66)



66

S. No	Starting compound	Product	Ar	R
1.	48a	66a	C_6H_5	H
2.	48b	66b	p-MeC_6H_4	H
3.	48c	66c	p-$MeOC_6H_4$	H
4.	48d	66d	p-ClC_6H_4	H
5.	48e	66e	C_6H_5	Me
6.	48f	66f	C_6H_5	MeO
7.	48g	66g	C_6H_5	Cl
8.	48h	66h	p-MeC_6H_4	MeO
9.	48i	66i	p-MeC_6H_4	Cl
10.	48j	66j	p-$MeOC_6H_4$	Cl
11.	48k	66k	p-ClC_6H_4	Me
12.	48l	66l	p-ClC_6H_4	MeO

of the reaction mixture yielded a light brown solid, m.p. 160-61°, which could not be identified on the basis of its spectral data. Its n.m.r. spectrum showed absence of ethylthio group and only signals due to aromatic protons were

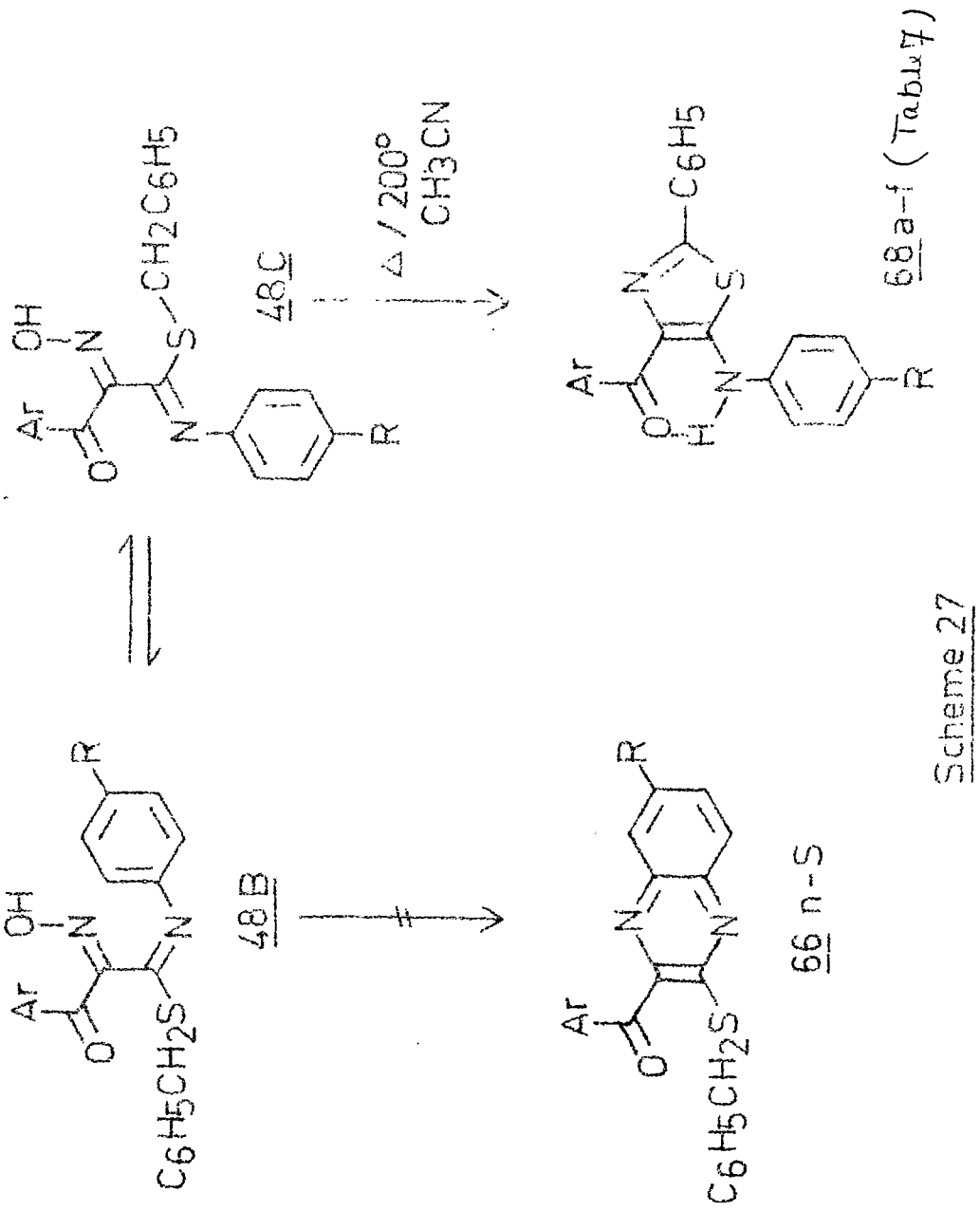


48m 66m

present between δ 7.0-8.25. Its i.r. spectrum (KBr) exhibited sharp peaks at 3350, 1600 and 1660 cm^{-1} probably due to NH and carbonyl group.

Similarly, when the corresponding S-benzylhydroxyiminoimine 48n (Table 3) was subjected to thermal cyclodehydration under reported conditions the desired 2-benzylthio-3-benzoylquinoxaline 66n (R=H) was not obtained. However, the work-up of the reaction mixture yielded a yellow crystalline compound (55%) which was characterized as 2-phenyl-4-benzoyl-5-anilinothiazole (68a) (R=H) (Scheme 27)

(Table 7) on the basis of spectral and analytical data. Thus the thiazole 68a exhibited molecular ion peak at m/z 356 and it was analysed for $C_{22}H_{16}N_2OS$ showing that 68a is formed by elimination of one equivalent of water from hydroxyiminoimine 48n. However, the characteristic high intensity carbonyl peak between 1660-1675 cm^{-1} present in all 3-aroylquinoxalines (66a-l) was absent in the infra-red spectrum (KBr) of 68a which showed two peaks at 1600 and 1588 cm^{-1} due to H-bonded carbonyl stretching frequency and N-H bending vibrations. The weak broad bonds at 3240 cm^{-1} were assigned to H-bonded N-H stretching vibrations. Further support for the thiazole 68a was obtained from its n.m.r. spectrum ($CDCl_3$), which showed absence of signal for benzylic protons between δ 4-5 showing that benzylthiomethylene protons are involved in the reaction. The aromatic protons were present as three multiplets at δ7.0-7.65 (9H); 7.65-8.22 (4H) and 8.25-8.58 (2H) while a low field broad signal (1H) at δ15.2 (exchangeable with D_2O) was assigned to H-bonded NH proton. Its ultra-violet spectrum showed absorption maxima at λmax (MeOH): 240, 345, 388 (logϵ, 4.78, 4.77, 4.70) nm which shows the presence of enaminone moiety [λmax for 47n (MeOH): 275, 360 (logϵ, 4.29, 4.59)]$_{n-m}$. The reaction was found to be general with all

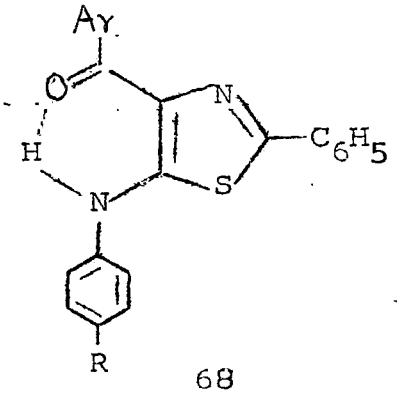

Ar
OH
N
O
S
CH2C6H5
N
R
48C
Δ / 200°
CH3CN
C6H5
68a-f (Table 7)
48B
66 n-S
C6H5CH2S

Scheme 27

N-aryliminobenzylthio hydroxyimines 48o-s which gave the corresponding 2-phenyl-4-aroyl-5-arylaminothiazoles 68b-f in 48-56% overall yields (Table 7) (Scheme 27). The spectral and analytical data of 68b-f were in conformity with the assigned structures (Table 11 and 15). The probable mechanism of thiazoles 68 formation from the corresponding hydroxyimino-imines 48 is shown in the scheme 28. It appears that the S-trans hydroxyiminoimine 48c exists in equilibrium with dipolar structures like 69 and 70 under thermal conditions. The ylid intermediate 70 is stabilized due to delocalization of carbanion over aryl group and over empty d orbitals of sulphur. Subsequent anionotropic rearrangement in 70 gives the intermediate 71, which undergoes facile intramolecular cyclization and dehydration to afford thiazoles 68 via N-hydroxyimidazole intermediate 72. It is pertinent to note that the corresponding N-benzylimino-S-benzylthio (46c) and N-ethylimino-S-benzylthio (46j) hydroxyimines (Table 2) undergo facile cyclodehydration to give the expected 2-aryl-5-benzylthio-(60c) and 2-methyl-5-benzylthio (60j) imidazoles (Table 4, Scheme 29) and no trace of the corresponding 5-benzylamino 73a or 5-ethylamino 73b thiazoles was isolated from the respective reaction mixtures (Scheme 29). However,

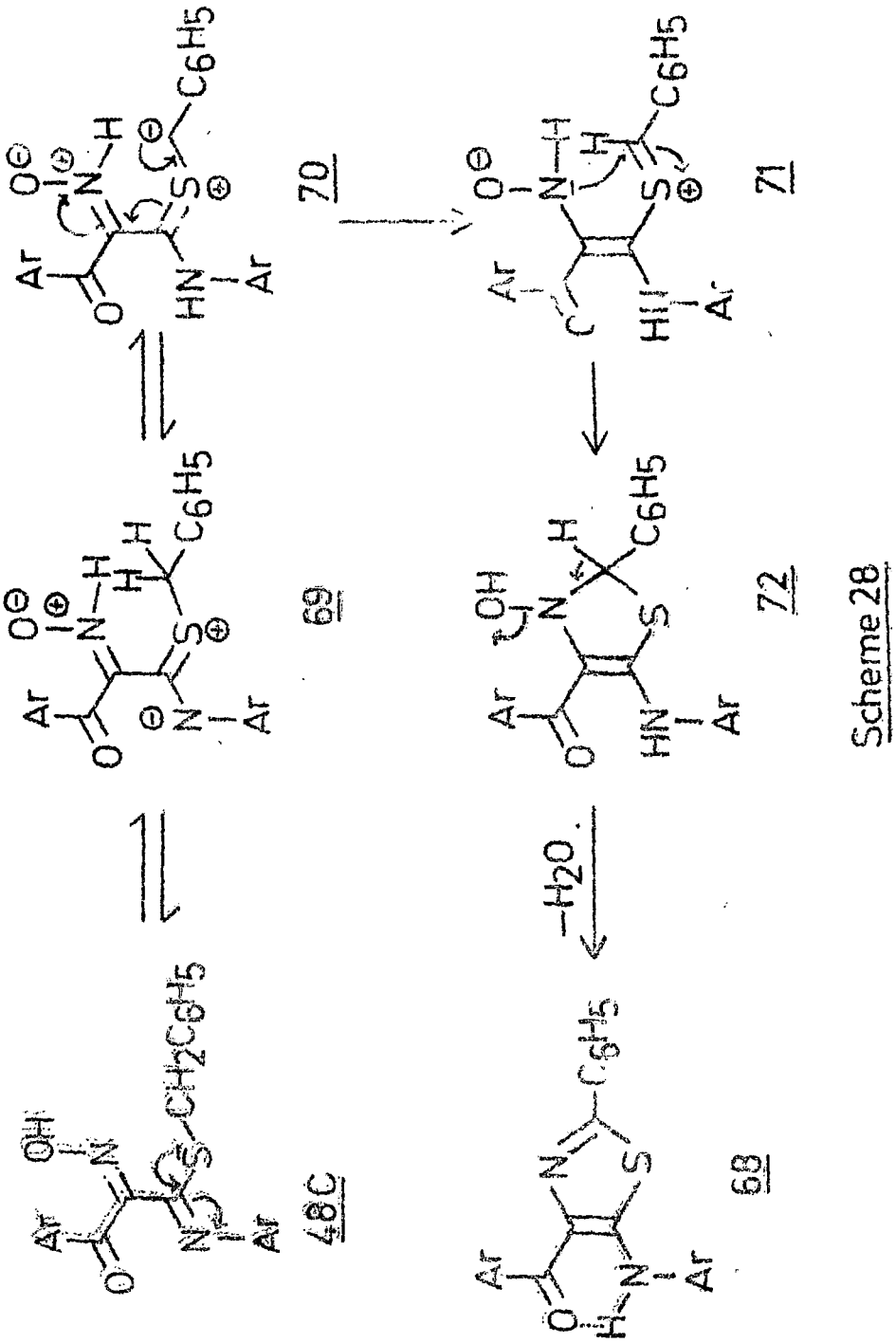
TABLE 7

2-Phenyl-4-aroyl-5-arylaminothiazoles prepared (68a-f).

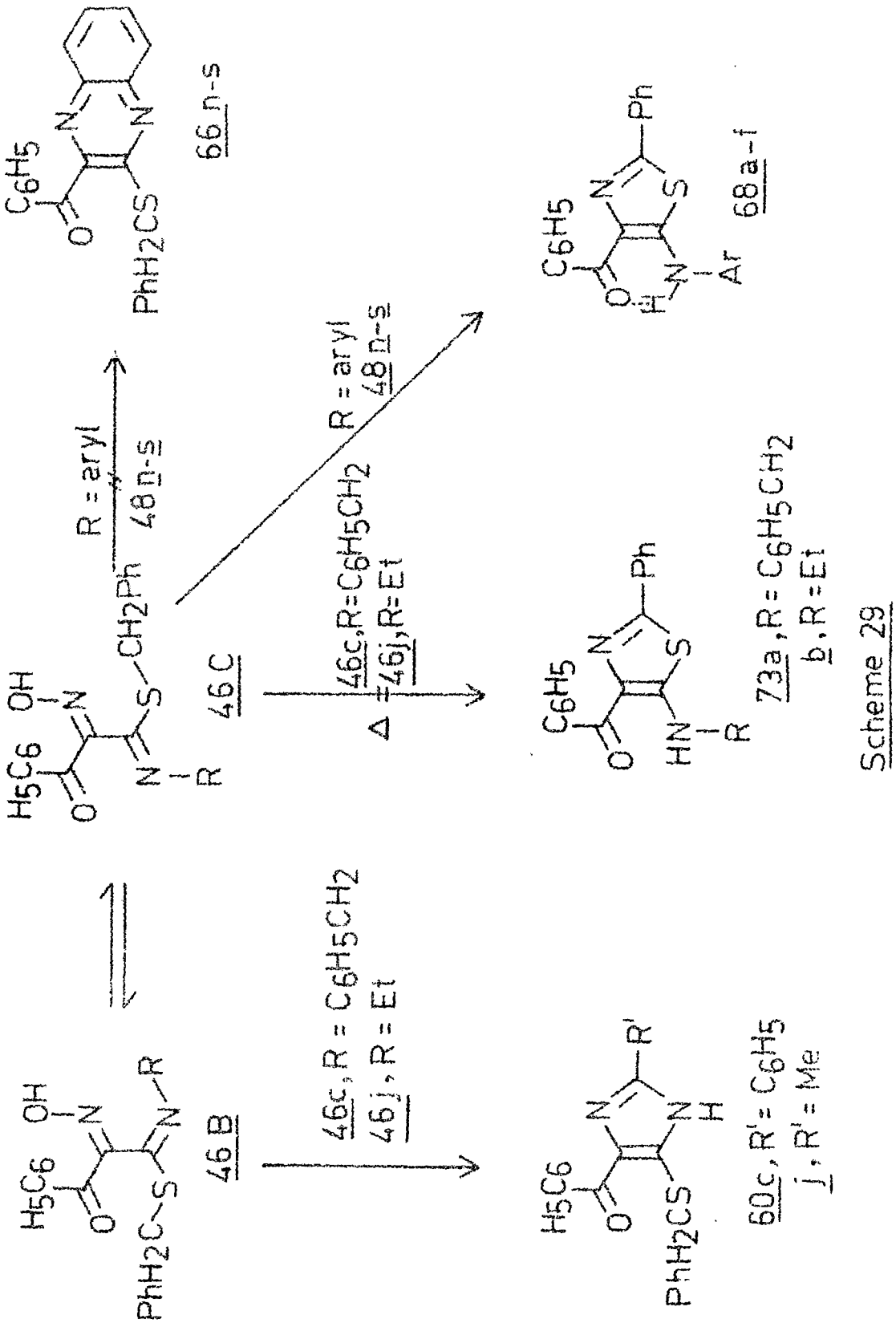


68

S. No	Starting compound	Product	Ar	R
1.	48n	68a	C_6H_5	H
2.	48o	68b	p-MeC_6H_4	H
3.	48p	68c	p-$EtOC_6H_4$	H
4.	48q	68d	p-ClC_6H_4	H
5.	48r	68e	C_6H_5	Me
6.	68s	68f	C_6H_5	Cl

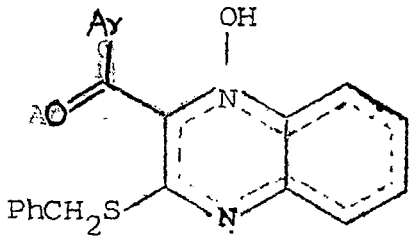


Scheme 28



Scheme 29

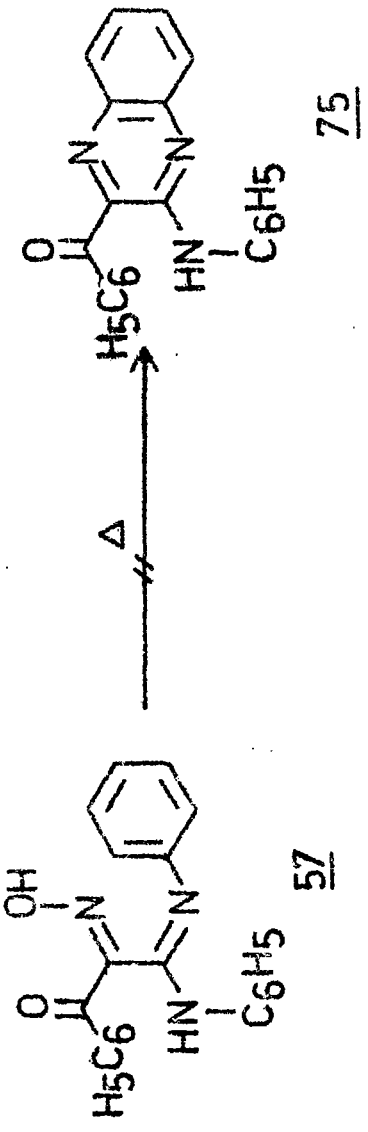
in the case of N-arylimino-S-benzylthiohydroxyimines (48n-s), the expected quinoxalines 66n-s (Scheme 29) are not formed and cyclodehydration takes different course to give the corresponding 5-anilino-thiazoles 68a-f. The probable explanation for this unexpected behaviour of N-arylimino-S-benzylthiohydroxyimines (48n-s) during cyclodehydration lies in the presence of bulkier benzylthio group ortho to the aroyl group which prevents the formation of planar transition state 74 required for six electron electrocyclization to give quinoxalines 66n-s, thus resulting in different course of reaction by



74

cyclodehydration at methylene carbon of benzylthio group to give thiazoles 68a-f (Scheme 29).

Attempted thermal cyclodehydration of hydroxyimino-imine 57 derived from N,N-anilinoacetal 56 (Scheme 20) did not yield the expected 2-anilinoquinoxaline 75 (Scheme 30),



Scheme 30

however the reaction mixture after work-up afforded a white solid which could not be identified.

III.3.3.2 Conclusion

A facile general route for 2-methylthio-3-aroyl-quinoxalines 66 have been developed by thermal cyclodehydration of novel N-phenylimino-S-methylthiohydroxyimines 48. Although the alloxazines and pteridines have been synthesized by cyclo-dehydration of 1,3-disubstituted 4-arylamino-5-nitrosouracil derivatives (Section III.2.2), to our knowledge, this is the first report of quinoxaline synthesis by cyclodehydration of N-aryl hydroxyiminoimine intermediate. Very few 2-methyl-thioquinoxalines are reported in the literature, which are prepared by methylation of the corresponding quinoxaline 2-thiones.[40] The present method provides a simple and conve-nient route for 2-methylthioquinoxalines from easily available starting materials having build in methylthio group. The method is not successful for the preparation of higher 2-alkylthioquinoxalines and reaction takes different course in the case of N-arylimino-S-benzylthiohydroxyimines (43n-s) which on thermal cyclodehydration afford novel 4-aroyl-5-anilinothiazoles (68a-f). To our knowledge, 5-anilinothia-zoles are not reported in the literature and the present

method provides a novel approach to 2-aryl-4-aroyl-5-anilino thiazoles by cyclocondensation of benzylicthiomethylene and hydroxyimino group.

Thus from these results it is obvious that hydroxy-iminoimines 46 and 48 are versatile intermediates for synthesis of novel functionalized heterocycles like imidazoles, quinoxalines and thiazoles. Further synthetic transformations based on these novel intermediates are in progress.

III. 4 Experimental

M.ps were determined on a 'Boetius' (German) apparatus and are uncorrected. The i.r. spectra were recorded on Perkin-Elmer 297 spectrometer, while the u.v. spectra were obtained on Beckman 26 spectrophotometer. The ^{1}H-n.m.r. spectra were recorded on a Varian EM-390 spectrometer using TMS as an internal standard and chemical shifts are expressed in δ (ppm).

The starting materials

The commercial samples of pyridine, acetonitrile and acetic anhydride were purified before use.

The keten-S,N-(45a-j, 47a-s, 49, 51) and N,N-acetals (54, 56, 58) were prepared as described in Chapter II.

Attempted nitrosation of 45a with isoamylnitrite

A solution of 45a (1.4g, 0.005 mol) in alcohol (25 ml) was refluxed with isoamyl nitrite (0.50g, 0.005 mol) for 15 hr, work-up of the reaction mixture yielded 1.2g (85%) of 45a, m.p. 55-57° (mixed m.p., superimposable i.r. and n.m.r. spectra).

Attempted nitrosation of 45a with sodium nitrite

To an ice cooled and stirred solution of 45a (1.4g, 0.005 mol) in acetic acid (20 ml), 0.4g (0.006 mol) of sodium nitrite was added in fractions and reaction mixture was stirred for 1 hr. The reaction mixture was then poured over water, extracted with chloroform (2x100 ml), dried (Na_2SO_4) and evaporated to give a dark residue which showed several spots on T.L.C. plate, from which no pure compounds could be isolated on column chromatography over silica gel.

General method for the preparation of hydroxyiminoimines (46a-j, 48a-s, 57):

To an ice cooled and well stirred solution of either S,N-(45a-j, 47a-s) or N,N-acetal 56 (0.01 mol) in dry pyridine (2 ml) and dry ether (25 ml), nitrosyl chloride (0.012 mol in 5 ml ether) was added and the reaction mixture was further stirred for 10-15 min. It was then diluted with ice cold water (50 ml), extracted with chloroform (3x50 ml). The chloroform layer was washed with water(3x100 ml) to remove excess of pyridine, dried (Na_2SO_4) and evaporated to give crude solid hydroxyiminoimines 46a-j, 48a-s, 57 (Table 2 and 3),

which were purified by crystallization using benzene (46a-c, 48a-s, 57) and chloroform (46d-j). Spectral and analytical data of 57 is given below, while of 46a-j, 48a-s are given in Tables 8 and 12 respectively.

Phenyl (α-oximino-β-bis (anilino)-ketone (57) m.p. 178-7°° was obtained in 82% yield; i.r. ν max (KBr): 3235 cm^{-1} (br, NH), 1595, 1660 cm^{-1} (νCN and CO); u.v. λmax (MeOH): 262 (logϵ, 4.53) nm; n.m.r. ($CDCl_3$DMSO-d_6): δ 6.72-7.60 (m, 15H, arom); Found: C, 73.11; H, 4.82; N, 11.93; Calc. for $C_{21}H_{17}N_3O_2$(343): C, 73.47; H, 4.96, N, 12.24%.

Attempted nitrosation of keten-S,N-acetal 49 and Keten-N,N-acetal 54

When a solution of either 49 (1.12g, 0.005 mol) or N,N-acetal 54 (1.10g, 0.005 mol) in 20 ml of ether was stirred with nitrosyl chloride (0.006 mol in 3 ml of ether) at 0-5° for 15 min, work-up of the reaction mixture yielded either 49, m.p. 105-7° (0.93g, 85%) or 54, m.p. 75-77° (0.94g, 83%) (mixed m.p., superimposable i.r. and n.m.r. spectra). When the reaction mixture was stirred for longer time (5-6 hr), the starting material 49 and 54 remained unchanged (TLC).

Attempted nitrosation of 49 or 54 in refluxing chloroform for 7 hr under identical conditions yielded only starting material 49, m.p. 105-7° or 54, m.p. 74-76 (mixed m.p., superimposable i.r. and n.m.r. spectra).

Nitrosation of keten-S,N-acetal 51

A solution of 51 (1.30g, 0.005 mol) in ether (20 ml) was stirred with nitrosyl chloride (0.006 mol in 20 ml of ether) for 15 min, work-up of the reaction mixture (as described in general procedure) yielded a white solid (0.80g, 60%), m.p. 169-70°, which was characterized as phenyl -oximino-benzoylaciticacidmorpholide (53); M^+ 262; i.r. ν_{max} (KBr): 3400 cm^{-1} (br, OH), 1620 cm^{-1} (CO); n.m.r. ($CDCl_3$): δ3.20-3.60 (br S, 8H, morpholino); 6.90-7.48 (m, 3H, arom); 7.60-7.90 (m, 2H, arom); Found: C, 59.12; H, 5.68; N, 10.28; Calc. for $C_{13}H_{14}N_2O_3$ (262): C, 59.54; H, 5.34; N, 10.68%.

Nitrosation of keten-N,N-acetal 58

Keten N,N-acetal 58 (1.50g, 0.005 mol) under identical conditions as 51 yielded 0.9g (70%) of 53 (m.p. 168-70°) (mixed m.p. superimposable i.r., n.m.r. spectra).

Synthesis of 2-phenyl-4-benzoyl-5-methylthioimidazole (60a):

1.40g (0.005 mol) of 46a was heated at 150° in an oil bath for 0.5 hr. The solid was then dissolved in hot acetic acid which on cooling gave 1.20g (80%) of 60a. Spectral and analytical data of 60a is given in text as well as in Table 9 and 13 respectively.

General method for the synthesis of 2-aryl-4-aroyl/acetyl-5-methyl/benzylthioimidazoles (60a-c) (Method A):

A solution of hydroxyiminoimines 46a-c (0.01 mol) in acetonitrile (25 ml) was refluxed for 3 hr. The solvent was removed on water bath and crude imidazoles 60a-c thus obtained were crystallized from acetic acid. Spectral and analytitcal data of 60a-c are given in Table 9 and 13 respectively.

General procedure for the synthesis of 2-unsubstituted/methyl-4-aroyl-5-methyl/benzylthioimidazoles (60d-j) (Method A):

A solution of hydroxyiminoimines 46d-j (0.01 mol) in acetonitrile (25 ml) was heated in a steel bomb at 200° for 0.5 hr. The reaction mixture after cooling was poured over water (100 ml), extracted with chloroform (2x100 ml), dried (Na_2SO_4) and concentrated to give crude imidazoles 60d-j,

which were further purified by column chromatography over silica gel using ethylacetate/hexane (1:3) as eluent. Spectral and analytical data of 60d-j are given in Table 9 and 13 respectively.

General method for the Synthesis of 2-aryl/ethoxycarbonyl-4-aroyl-5-alkylthioimidazoles (60a, 60k-r)

(Method B) : To an ice cooled solution of keten-S,N-acetal 45a, 45k-r (0.01 mol) in pyridine (40 ml), nitrosyl chloride (0.012 mol in 5 ml of dry ether) was added, the reaction mixture was stirred for 10 min and then refluxed for 2.5 hr. The reaction mixture after cooling was poured over water, extracted with chloroform (2x50 ml). The chloroform layer was washed with water (3x150 ml), dried (Na_2SO_4) and concentrated to give crude imidazoles 60a, 60k-r, which were purified by column chromatography over silica gel using benzene/hexane (2:3) as eluent. Spectral and analytical data of 60a, 60k-r are given in Table 9 and 13 respectively.

Methylation of hydroxyiminoimine 46a: Synthesis of 1-N-methyl-2-aryl-4-methylthio-5-benzoylimidazole (63a)

To a suspension of hydroxyiminoimine 46a (1.55g, 0.005 mol) and potassium carbonate (1.35g, 0.01 mol) in dry acetone

(20 ml), 1.05g (0.075 mol) of methyl iodide was added and the reaction mixture was refluxed for 3 hr. It was then diluted with ice cold water (60 ml), acidified with 20% acetic acid, extracted with chloroform (2x40 ml), dried (Na_2SO_4) and evaporated to give crude viscous liquid, which was purified by column chromatography over silica gel using benzene/hexane (2:3) as eluent to give 1.0g (70%) of 63a as light yellow crystalline solid (benzene); m.p. 93-95°; νmax (KBr); 1660 cm^{-1} (CO); n.m.r. ($CDCl_3$); δ2.48 (s, 3H, SCH_3); 3.88 (s, 3H, CH_3); 7.13-7.88 (m, 10H, arom); Found: C, 70.63; H, 4.75; N, 8.73; Calc. for $C_{18}H_{16}N_2OS$ (308): C, 70.13; H, 5.19; N, 9.09%.

Methylation of 46f

A suspension of 46f (1.37g, 0.005 mol), potassium carbonate (1.35g, 0.01 mol) and methyl iodide (1.05g, 0.0075 mol) in dry acetone (20 ml) was refluxed for 4 hr. Work-up of the reaction mixture as described for methylation of 63a, afforded a white solid (0.65g, 50%), m.p. 82-86°, which was found to be a mixture of 64b and 64b'; (1:1); i.r. ν max (KBr): 1660 cm^{-1} n.m.r ($CDCl_3$): δ2.50 (s, 1.5H, SCH_3); 2.52 (s, 1.5H, SCH_3); 3.25 (s, 3H, NCH_3); 3.50 (s, 1.5H, NCH_3); 4.0 (s, 1.5H, OCH_3); 7.0-8.15 (m, 8H, arom).

; Found: C, 50.35; H, 4.73; N, 9.63; Calc. for $C_{12}H_{13}ClN_2O_2S$ (284.5); C, 50.62; H, 4.57; N, 9.84%.

Methylation of 46g

A suspension of 46g (1.25g, 0.005 mol), potassium carbonate (1.35g, 0.01 mol) and methyl iodide (1.05g, 0.0075 mol) in dry acetone (20 ml) was refluxed for 4 hr. Work-up of the reaction mixture as described above afforded a viscous semisolid, 0.73g (60%) which found to be a mixture (1:1) of 64c and 64c'; i.r. ν_{max} (CCl_4): 1660 cm^{-1}; n.m.r. ($CDCl_3$): δ 1.0-1.45 (m, 3H, CH_3CH_2); 2.20 (s, 1.5H, SCH_3); 2.30 (s, 1.5H, SCH_3); 3.15-3.55 (m, 3.5H, CH_3CH_2 and $N-CH_3$); 4.05 (s, 1.5H, CH_3O); 7.15-8.25 (m, 10H, arom); Found: C, 59.43; H, 6.35; N, 10.34; Calc. for $C_{13}H_{16}N_2O_2S$ (264): C, 59.09; H, 6.06; N, 10.61%.

Cyclodehydration of hydroxyiminoimines 48a-l: General method for preparation of 2-methylthio-3-aroylquinoxalines (66a-l)

A solution of hydroxyiminoimines 48a-l (0.01 mol) in 25 ml of CH_3CN was heated in a sealed tube (200°C) for 2.5 hr. Reaction mixture was cooled, poured over ice cold water (100 ml), extracted with chloroform (2x70 ml), dried (Na_2SO_4) and evaporated to give crude quinoxalines 66a-l (Table 6), which

were purified by column chromatography over silica gel using benzene/hexane (1:4) as eluent. Spectral and analytical data of 66a-l are given in Table 10 and 14 respectively.

In another experiment, a solution of hydroxyiminoimine 48a (1.50g, 0.005 mol) in acetic anhydride (30 ml) was refluxed for 5 hr. Acetic anhydride was removed under reduced pressure and crude quinoxaline 66a was purified by column chromatography over silica gel using benzene/hexane (1:4) as eluent, yellow solid, 1.00g (70%) m.p. 109-10° (mixed m.p., superimposible i.r. and n.m.r. spectra).

Attempted cyclodehydration of phenyl (α-oximino-β-phenylimino-β-ethylthio)ketone (48m):

Hydroxyiminoimine 48m (1.55g, 0.005 mol) under identical conditions as described in general procedure yielded 1.20g of light brown solid (benzene), m.p. 160-61°; i.r. max (KBr); 3350, 1600, 1660 cm^{-1}; n.m.r. ($CDCl_3$); 7.0-8.25 (m, aromatic protons).

Attempted cyclodehydration of phenyl[(α-oximino-β-bis(anilino)] ketone (57)

Thermal cyclodehydration of 1.2g (0.005 mol) of 57 under identical conditions as described in general procedure

for preparation of quinoxalines, yielded 0.80g of white crystalline solid (benzene); m.p. 163-64°; i.r. ν_{max} (KBr) 3350, 1660, 1600 cm^{-1}; n.m.r. ($CDCl_3$+DMSO-d_6): δ6.90-8.13 (m, aromatic protons).

Cyclodehydration of hydroxyiminoimines 48n-s: General method for the preparation of 2-phenyl-4-aroyl-5-aryl-aminothiazoles (68a-f)

A solution of hydroxyiminoimines 48n-s (0.01 mol) in acetonitrile (25 ml) was heated in a sealed tube (200°C) for 2.5 hr. Reaction mixture was cooled, poured over water, extracted with chloroform (3x50 ml), dried (Na_2SO_4) and evaporated to give crude thiazoles 68a-f (Table 7), which were purified by column chromatography over silica gel using benzene/hexane (1:3) as eluent. Spectral and analytical data of 68a-f are given in Table 11 and 15 respectively.

TABLE 8

Spectral data of products 46a-j; 48a-s

Product	I.R.(KBr) νmax (cm^{-1})	U.V.(MeOH) λmax (logϵ)nm	^{1}H-N.M.R. δ(ppm)
46a	3480 (br,OH); 1642, 1592	242 (4.23)	2.32 and 2.42 (two singlets, 3H, 2:1 ratio, SCH_3); 4.38 and 4.55 (two singlets, 2H, 1:2 ratio, $NCH_2C_6H_5$); 6.85-7.55 (m, 8H, arom), 7.62-8.11 (m, 2H, arom).[b]
46b	3450 (br, OH); 1695, 1615	230 (4.15)	2.20 (s, 3H, CH_3); 2.40 (s, 3H, SCH_3) 4.60 (s, 2H, $NCH_2C_6H_5$); 7.60 (br s, 5H, arom).[b]
46c	3450 (br, OH); 1665, 1595	244 (4.32)	4.58 (br s,4H, $SCH_2C_6H_5$, $NCH_2C_6H_5$); 6.59-7.75 (m, 15H, arom).[b]

Table 8 (Contd.)

46d	3425 (br, OH); 1658, 1600	250 (4.08)	2.30 (s, 3H, SCH_3); 3.26 (s, 3H, CH_3); 7.13-7.64 (m, 3H, arom); 7.76-8.10 (m, 2H, arom).[b]
46e	3415 (br, OH); 1640, 1600	269 (4.09)	2.26 (s, 3H, CH_3); 2.36 (s, 3H, SCH_3); 3.10 and 3.26 (two singlets, 3H, 1:2 ratio, NCH_3); 6.98-7.92 (m, 4H, arom).[a]
46f	3412 (br, OH); 1650, 1600	265 (4.07)	2.30 (s, 3H, SCH_3); 3.28 (s, 3H,NCH_3); 7.20-7.98 (dd, 4H, arom).[a]
46g	3460 (br, OH); 1655, 1590	250 (4.12)	1.30 (t, 3H, CH_3CH_2); 2.30 and 2.40 (two singlets, 3H, 2:1 ratio, SCH_3); 3.36 (q, 2H,NCH_2CH_3); 7.38-7.62 (m, 3H, arom); 7.80-8.08 (m, 2H, arom).[a]
46h	3450 (br, OH); 1650, 1590	268 (4.17)	1.26 (t, 3H, CH_3CH_2); 2.26 (s, 3H, CH_3); 2.35 (s, 3H, SCH_3); 3.43 (q, 2H,NCH_2CH_3); 7.30-7.98 (m, 4H, arom).[a]

Table 8(Contd.)

46i	3455 (br, OH); 1672, 1585	265 (4.15)	1.26 (t, 3H, $C\underline{H}_3CH_2$); 2.24 (s, 3H, $SC\underline{H}_3$); 3.40 (q, 2H, $NC\underline{H}_2CH_3$); 7.03-7.98 (dd, 4H, arom).[a]
46j	3435 (br, OH); 1658, 1600	242 (4.28)	1.28 (t, 3H, $C\underline{H}_3CH_2$); 3.50 (br q, 2H, $NC\underline{H}_2CH_3$); 3.95 (s, 2H, $SC\underline{H}_2C_6H_5$); 7.10-7.58 (m, 8H, arom); 7.80-7.81 (m, 2H, arom).[b]
48a	3440 (br, OH); 1658, 1580	244 (4.24)	2.20 and 2.55 (two singlets, 2H, 1:2 ratio, $SC\underline{H}_3$); 6.79-7.52 (m, 8H, arom); 7.90-8.16 (m, 2H, arom).[b]
48b	3450 (br, OH); 1650, 1585	246 (4.27)	2.30 (s, 3H, $C\underline{H}_3$); 2.33 and 2.60 (two singlets, 3H, 1:2 ratio, $SC\underline{H}_3$); 6.68-7.44 (m, 9H, arom).[b]

Table 8 (Contd.)

48c	3450 (br, OH); 1655, 1605	243 (4.23)	2.30 and 2.60 (two singlets, 3H, 1:2 ratio, $SC\underline{H}_3$); 3.82 (s, 3H, $OC\underline{H}_3$); 6.51-7.10 (m, 7H, arom); 7.46-7.61 (m, 2H, arom).[b]
48d	3445 (br, OH); 1670, 1598	242 (4.21)	2.10 and 2.43 (two singlets, 3H, 1:1 ratio, $SC\underline{H}_3$); 6.70-7.90 (m, 9H, arom).[b]
48e	3450 (br, OH); 1658, 1610	244 (4.27)	2.16 (s, 3H, $C\underline{H}_3$); 2.30 and 2.53 (two singlets, 3H, 2:1 ratio, $SC\underline{H}_3$); 6.68-8.10 (m, 9H, arom).[b]
48f	3450 (br, OH); 1655, 1605	240 (4.21)	2.23 and 2.48 (two singlets, 3H, 1:2 ratio, $SC\underline{H}_3$); 3.76 (s, 3H, $OC\underline{H}_3$); 6.56-7.20 (m, 7H, arom); 7.31-7.61 (m, 2H, arom).[b]

Table 8 (Contd.)

48g	3450 (br, OH); 1650, 1608	242 (4.27)	2.42 (s, 3H, SCH_3); 6.70-8.21 (m, 9H, arom).[b]
48h	3455 (br, OH); 1651, 1608	249 (4.20)	2.30 (s, 3H, CH_3); 2.46 (s, 3H, SCH_3); 3.62 (s, 3H, OCH_3); 6.43-7.90 (m, 8H, arom).[b]
48i	3450 (br, OH); 1663, 1594	242 (4.27)	2.23 (s, 3H, CH_3); 2.53 (s, 3H, SCH_3); 6.58-6.73 (m, 8H, arom).[b]
48j	3450 (br, OH); 1670, 1595	244 (4.29)	2.29 and 2.56 (two singlets, 3H, 1:2 ratio, SCH_3); 3.70 (s, 3H, OCH_3); 6.56-8.22 (m, 8H, arom).[b]
48k	3450 (br, OH); 1665, 1595	242 (4.29)	2.23 (s, 3H, CH_3); 2.53 (s, 3H, SCH_3); 6.56-8.16 (m, 8H, arom).[b]

Table 8 (Contd.)

48l	3448 (br, OH); 1670, 1595	245 (4.25)	2.26 and 2.58 (two singlets, 3H, 1:2 ratio, $SC\underline{H}_3$); 3.68 (s, 3H, $OC\underline{H}_3$); 6.56-8.15 (m, 8H, arom).[b]
48m	3450 (br, OH); 1660, 1585	245 (4.24)	1.33 (t, 3H, $CH_2C\underline{H}_3$); 3.20 (q, 2H, $C\underline{H}_2CH_3$); 6.73-8.10 (m, 10H, arom).[b]
48n	3445 (br, OH); 1660, 1580	244 (4.39)	4.43 (s, 2H, $C\underline{H}_2C_6H_5$); 6.63-7.63 (m, 15H, arom).[b]
48o	3448 (br, OH); 1660, 1582	244 (4.37)	2.40 (s, 3H, $C\underline{H}_3$); 3.60 (s, 2H, $C\underline{H}_2C_6H_5$); 7.00-8.60 (m, 14H, arom).[b]
48p	3446 (br, OH); 1618, 1615	245 (4.35)	1.43 (t, 3H, $OCH_2C\underline{H}_3$); 4.16 (q, 2H, $OC\underline{H}_2CH_3$); 4.22 (s, 2H, $C\underline{H}_2C_6H_5$); 6.74-8.13 (m, 14H, arom).[b]

Table 8 (Contd.)

48q	3450 (br, OH), 1660, 1595	245 (4.39)	4.48 (s, 2H, $C\underline{H}_2C_6H_5$); 6.70-7.98 (m, 14H, arom).[b]
48r	3440 (br, OH); 1663, 1580	244 (4.35)	2.22 (s, 3H, $C\underline{H}_3$); 4.43 (s, 2H, $C\underline{H}_2C_6H_5$); 6.66 -7.64 (m, 14H, arom).[b]
48s	3450 (br, OH); 1660, 1595	245 (4.38)	4.48 (s, 2H, $C\underline{H}_2C_6H_5$); 6.72-7.58 (m, 14H, arom).[b]

[a] in $CDCl_3$; [b] in $CDCl_3$/DMSO-d_6.

TABLE 9

Spectral data of products 60a-r

Product	I.R. ν_{max} (cm^{-1})	^{1}H-N.M.R. δ(ppm)	M.S. m/e(M^+)
60a	3240 (NH); 1600 (CO)[a]	2.55 (s, 3H, SCH_3); 7.10-7.60 (m, 6H, arom); 7.68-8.28 (m, 4H, arom); 12.85 (br s, 1H, NH, exchangeable with D_2O).[d]	294
60b	3250 (NH); 1620 (CO)[a]	2.45 (s, 3H, CH_3); 2.66 (s, 3H, SCH_3); 7.20-7.43 (m, 3H, arom); 8.06-8.24 (m, 2H, arom); 12.10 (br s, 1H, NH, exchangeable with D_2O).[d]	231

Table 9 (Contd.)

60c	3240 (NH); 1595 (CO)[a]	3.51 (s, 2H, $CH_2C_6H_5$); 6.10-7.83 (m, 15H, arom).[e]	370
60d	3225 (NH); 1610 (CO)[b]	2.38 (s, 3H, SCH_3); 7.15-7.41 (m, 4H, arom); 7.55-7.85 (m, 2H, arom), 11.70 (br s, 1H, NH, exchangeable with D_2O).[f]	218
60e	3220 (NH); 1605 (CO)[a]	2.36 (br s, 6H, CH_3, SCH_3 ; 6.75-7.30 (m, 3H, arom); 7.35-7.93 (m, 2H, arom), 11.80 (br s, 1H, NH, exchangeable with D_2O).[f]	232
60f	3215 (NH); 1603 (CO)[a]	2.56 (s, 3H, SCH_3); 7.12-7.62 (m, 3H, arom); 7.66-8.10 (m, 2H, arom); 13.60 (br s, 1H, NH, exchangeable with D_2O).[f]	

Table 9 (Contd.)

60g	3230 (NH); 1602 (CO)[a]	2.46 (s, 6H, CH_3, SCH_3); 7.31-7.59 (m, 3H, arom); 7.60-7.83 (m, 2H, arom); 13.60 (br s, 1H, NH, exchangeable with D_2O).[g]	232
60h	3225 (NH); 1600 (CO)[a]	2.45 (br s, 9H, CH_3, CH_3, SCH_3); 7.19 (d, 2H, arom); 7.48 (d, 2H, arom); 13.66 (br s, 1H, NH, exchangeable with D_2O).[g]	246
60i	3225 (NH); 1605 (CO)[a]	2.46 (s, 6H, CH_3, SCH_3); 7.36 (d, 2H, arom); 7.70 (d, 2H, arom); 13.50 (br s, 1H, NH, exchangeable with D_2O).[g]	266, 268
60j	3235 (NH); 1630, 1580 (CO)[a]	1.28 (s, 3H, CH_3); 4.46 (s, 2H, $CH_2C_6H_5$); 7.13-8.20 (m, 10H, arom); 11.55 (br s, 1H, NH, exchangeable with D_2O).[d]	-
60k	3240 (NH); 1600 (CO)[a]	2.03 (s, 3H, CH_3); 2.10 (s, 3H, SCH_3); 6.75-7.68 (m, 9H, arom).[e]	308

Table 9 (Contd.)

60l	3250 (NH); 1593 (CO)[a]	2.50 (s, 3H, SCH_3); 3.80 (s, 3H, OCH_3); 5.00 (br s, 1H, NH, exchangeable with D_2O); 6.86-8.20 (m, 9H, arom).[g]	324
60m	3255 (NH); 1595 (CO)[a]	2.12 (s, 3H, SCH_3); 6.68-7.60 (m, 9H, arom).[e]	328, 330
60n	3240 (NH); 1595 (CO)[a]	0.75 (t, 3H, CH_2CH_3); 2.50 (q, 2H, CH_2CH_3); 6.90-7.68 (m, 10H, arom).[e]	308
60o	3250 (NH); 1600 (CO)[a]	2.15 (s, 3H, SCH_3); 3.58 (s, 3H, OCH_3); 6.74 (d, 2H, arom); 7.21-7.30 (m, 3H, arom); 7.50-7.68 (m, 4H, arom).[e]	324
60p	3250 (NH); 1591 (CO)[a]	2.14 (s, 3H, SCH_3); 2.55 (s, 3H, OCH_3); 6.78 (d, 2H, arom); 7.15 (d, 2H, arom); 7.30-7.68 (m, 4H, arom).[e]	357, 359

Table 9 (Contd.)

60q	3250 (NH); 1600, 1580(CO)[a]	2.15 (s, 3H, SCH_3); 7.00-7.60 (m, 9H, arom).[e]	328, 330
60r	3240 (NH); 1715 (Ester CO); 1625 (CO)[c]	0.91 (t, 3H, CH_2CH_3); 2.44 (s, 2H, SCH_3); 4.20 (q, 2H, CH_2CH_3); 7.20-7.50 (m, 3H, arom); 7.80-8.08 (m, 2H, arom); 12.35 (br s, 1H, NH, exchangeable with D_2O).[f]	290

[a] in KBr; [b] in $CHCl_3$; [c] neat; [d] in $CDCl_3$/DMSO-d_6; [e] in TFA; [f] in CCl_4; [g] in $CDCl_3$.

TABLE 10

Spectral data of products 66a-l

Product	I.R. νmax (cm^{-1})	U.V.(MeOH) λmax (logϵ)nm	^{1}H-N.M.R. δ(ppm)	M.S. m/e(M^+)
66a	1668 (CO)[a]	242, 267 (Sh), 362 (4.30, 4.25, 3.62)	2.54 (s, 3H, SCH_3); 7.00-7.81 (m, 5H, arom); 7.82-8.20 (m, 4H, arom).[c]	280
66b	1668 (CO)[b]	250, 275 (Sh), 374 (4.27, 4.29, 3.65)	2.35 (s, 3H, CH_3); 2.50 (s, 3H, SCH_3); 6.72-7.40 (m, 6H, arom); 7.50-8.10 (m, 2H, arom).[d]	-

Table 10 (Contd.)

66c	1660 (CO)[a]	243, 275, 375 (4.27, 4.29, 3.65)	2.62 (s, 3H, SCH_3); 3.85 (s, 3H, OCH_3); 6.85 (d, 2H, arom); 7.50-7.80 (m, 2H, arom); 7.80-8.15 (m, 4H, arom).[c]	310
66d	1668 (CO)[a]	242, 268 (Sh), 352 (4.29, 4.27, 3.62).	2.68 (s, 3H, SCH_3); 7.21-8.15 (m, 8H, arom).[c]	314, 316
66e	1665 (CO)[b]	254, 280 (Sh), 376 (4.31, 4.28, 3.60).	2.40 (s, 3H, CH_3); 6.82-7.46 (m, 6H, arom); 7.63-8.01 (m, 2H, arom).[c]	
66f	1670 (CO)[a]	258, 278 (Sh), 376 (4.33, 4.26, 3.63).	2.56 (s, 3H, SCH_3); 3.86 (s, 3H, OCH_3); 7.10-7.53 (m, 4H, arom); 7.66-8.08 (m, 4H, arom).[c]	

Table 10 (Contd.)

66g	1668 (CO)[a]	247, 270 (Sh), 365 (4.32, 4.30, 3.64)	2.65 (s, 3H, $SC\underline{H}_3$); 7.15-8.10 (m, 8H, arom).[c]	314, 316
66h	1663 (CO)[a]	256, 274 (Sh), 374 (4.34, 4.33, 3.62)	2.40 (s, 3H, $C\underline{H}_3$); 2.56 (s, 3H, $SC\underline{H}_3$); 3.90 (s, 3H, $OC\underline{H}_3$); 7.05-7.46 (m, 5H, arom); 7.87 (d, 2H, arom).[c]	-
66i	1675 (CO)[a]	240, 278, 365 (4.33, 4.36, 3.62)	2.53 (s, 3H, $C\underline{H}_3$); 2.63 (s, 3H, $SC\underline{H}_3$); 7.13-8.20 (m, 7H, arom).[d]	328, 330
66j	1676 (CO)[a]	259, 276 (Sh), 374 (4.33, 4.26, 3.61)	2.63 (s, 3H, $SC\underline{H}_3$); 3.92 (s, 3H, $OC\underline{H}_3$); 6.95-7.56 (m, 5H, arom); 7.62-8.20 (m, 2H, arom).[c]	344, 346

Table 10 (Contd.)

66k	1672 (CO)[a]	244, 285, 368 (4.30, 4.24, 3.62)	2.53 (s, 3H, $C\underline{H}_3$); 2.60 (s, 3H, $SC\underline{H}_3$); 7.15-8.30 (m, 7H, arom).[c]	328, 330
66l	1672 (CO)[a]	255, 278 (Sh), 380 (4.36, 4.25, 3.60)	2.58 (s, 3H, $SC\underline{H}_3$); 3.90 (s, 3H, $OC\underline{H}_3$); 6.90-8.15 (m, 7H, arom).[c]	344, 346

[a] in KBr; [b] in $CHCl_3$; [c] in $CDCl_3$; [d] in CCl_4.

TABLE 11

Spectral data of product 68a-f

Product	I.R.(KBr) νmax (cm^{-1})	U.V. (MeOH) λmax (logε)nm	^{1}H-NMR ($CDCl_3$) δ(ppm)	M.S. m/e(M^+)
68a	3240 (NH); 1600, 1588 (CO)	240, 345, 388 (4.78, 4.77, 4.70)	7.00-7.65 (m, 9H, arom); 7.65-8.22 (m, 4H, arom); 8.25-8.58 (m, 2H, arom); 15.2 (br s, 1H, NH, exchangeable with D_2O).	356
68b	3245 (br, NH); 1608, 1590 (CO)	258, 342, 385 (4.73, 4.75, 4.73)	2.50 (s, 3H, CH_3); 7.10-7.61 (m, 10H, arom); 7.70-8.10 (m, 2H, arom); 8.20-8.48 (m, 2H, arom); 13.50 (br s, 1H, NH, exchangeable with D_2O).	370

Table 11 (Contd.)

68e	3243 (NH); 1608, 1590 (CO)	255, 345, 380 (4.72, 4.75, 4.73)	1.45 (t, 3H, $CH_2\underline{CH}_3$); 4.05 (q, 2H, $\underline{CH}_2CH_3$); 6.75-7.63 (m, 10H, arom); 7.80-8.10 (m, 2H, arom); 8.60 (d, 2H, arom); 10.15 (br s, 1H, N<u>H</u>, exchangeable with D_2O).	-
68d	3250 (NH); 1588 (CO)	252, 343, 385 (4.78, 4.74, 4.71)	7.14 (m, 10H, arom); 7.70-7.90 (m, 2H, arom); 8.60 (d, 2H, arom); 13.35 (br s, 1H, N<u>H</u>, exchangeable with D_2O).	-
68e	3255 (NH); 1596, 1558 (CO)	258, 342, 385 (4.72, 4.74, 4.69)	2.47 (s, 3H, $\underline{CH}_3$); 7.03-7.66 (m, 10H, arom); 7.73-8.00 (m, 2H, arom); 8.20-8.43 (m, 2H, arom); 12.65 (br s, 1H, N<u>H</u>, exchangeable with D_2O)	-

Table 11 (Contd.)

68f	3250 (NH); 1595, 1585 (CO)	243, 343, 385 (4.73, 4.74, 4.72)	7.08-7.62 (m, 10H, arom); 7.65-7.93 (m, 2H, arom); 8.23-8.50 (m, 2H, arom); 14.53 (br s, 1H, NH, exchangeable with D_2O).

TABLE 12

Aryl/alkyl (α-oximino-β-aryl/alkylimino-β-alkylthio)ketones (46a-j, 48a-s)

Product[a]	Yield (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis (%) C	H	N
46a	80	140-41	$C_{17}H_{16}N_2O_2S$ (312)		65.38 65.89	5.13 5.30	8.97 8.65
46b	78	153-55	$C_{12}H_{14}N_2O_2S$ (250)		57.60 57.22	5.60 5.33	11.20 11.45
46c	76	156-58	$C_{23}H_{20}N_2O_2S$ (388)		71.13 70.66	5.15 5.38	7.21 6.7
46d	80	150-51	$C_{11}H_{12}N_2O_2S$ (236)		55.93 56.60	5.08 5.31	11.86 11.71
46e	79	163-64	$C_{12}H_{14}N_2O_2S$ (250)		57.60 57.92	5.60 5.41	11.20 11.43

Table 12 (Contd.)

46f	81	141-42	$C_{11}H_{11}ClN_2O_2S$	48.80	4.06	10.35
			(270.5)	48.38	4.45	10.63
46g	80	160-61	$C_{12}H_{14}N_2O_2S$	57.60	5.60	11.20
			(250)	58.20	5.32	10.88
46h	81	146-48	$C_{13}H_{16}N_2O_2S$	59.10	6.06	10.61
			(264)	59.42	6.28	10.33
46i	81	146-47	$C_{12}H_{13}ClN_2O_2S$	50.62	4.57	9.84
			(284.5)	50.40	4.80	9.53
46j	81	146-48	$C_{18}H_{18}N_2O_2S$	66.25	5.52	8.59
			(326)	66.71	5.22	8.23
48a	80	129-30	$C_{16}H_{14}N_2O_2S$	64.43	4.70	9.40
			(298)	64.79	4.41	9.12

Table 12 (Contd.)

48b	79	146-47	$C_{17}H_{16}N_2O_2S$	65.38	5.13	8.97
			(312)	64.50	4.61	8.77
48c	78	144-46	$C_{17}H_{16}N_2O_3S$	62.20	4.88	8.54
			(328)	62.48	4.99	8.23
48d	79	168-70	$C_{16}H_{13}ClN_2O_2S$	57.74	3.91	8.42
			(332.5)	57.41	3.59	8.11
48e	80	133-35	$C_{17}H_{16}N_2O_2S$	65.38	5.13	8.97
			(312)	65.69	5.41	8.63
48f	77	163-65	$C_{17}H_{16}N_2O_3S$	62.20	4.88	8.54
			(328)	62.53	4.43	8.24
48g	79	145-46	$C_{16}H_{13}ClN_2O_2S$	57.74	3.91	8.42
			(332.5)	58.20	4.64	8.63

Table 12 (Contd.)

48h	77	135-37	$C_{18}H_{18}N_2O_3S$	63.15	5.26	8.18
			(342)	63.51	4.96	7.80
48i	76	145-46	$C_{17}H_{15}ClN_2O_2S$	58.87	4.33	8.08
			(346.5)	58.70	4.24	7.64
48j	76	166-68	$C_{17}H_{15}ClN_2O_3S$	56.28	4.14	7.72
			(362.5	56.67	4.51	7.41
48k	75	150-52	$C_{17}H_{15}ClN_2O_2S$	58.87	4.33	8.08
			(346.5)	58.43	4.20	7.69
48l	75	166-67	$C_{17}H_{15}ClN_2O_3S$	56.28	4.14	7.72
			(362.5)	56.61	4.34	8.13
48m	81	150-52	$C_{17}H_{16}N_2O_2S$	65.38	5.13	8.97
			(312)	65.10	4.97	9.03

Table 12 (Contd.)

48n	80	136-38	$C_{22}H_{18}N_2O_2S$	70.59	4.81	7.49
			(374)	70.35	4.68	7.13
48o	81	132-35	$C_{23}H_{20}N_2O_2S$	71.13	5.15	7.22
			(388)	71.63	5.41	7.56
48p	78	183-85	$C_{24}H_{22}N_2O_3S$	68.90	5.26	6.70
			(418)	68.45	5.43	6.58
48q	80	146-48	$C_{22}H_{17}ClN_2O_2S$	64.63	4.16	6.85
			(408.5)	64.21	4.43	6.63
48r	79	134-35	$C_{23}H_{20}N_2O_2S$	71.13	5.15	7.22
			(388)	71.56	5.43	7.03
48s	79	150-52	$C_{22}H_{17}ClN_2O_2S$	64.63	4.16	6.85
			(408.5)	64.21	4.53	6.49

[a]crystallization solvent = benzene/hexane (46a-c, 46j, 48a-s) and chloroform (46d-i).

TABLE 13

2-Aryl/methyl/unsubstituted-4-aroyl/acyl-5-alkylthioimidazoles (60a-j); 2-aryl/ethoxycarbonyl-4-aroyl-5-alkylthioimidazoles (60k-r).

Product[a]	Yield (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis (%) C	H	N
60a	78	215	$C_{17}H_{14}N_2OS$		69.39	4.75	9.52
			(294)		68.83	4.48	9.23
60b	58	208-10	$C_{12}H_{12}N_2OS$		62.07	5.17	12.07
			(232)		62.48	5.43	12.29
60c	82	228-29	$C_{23}H_{18}N_2OS$		74.59	4.86	7.57
			(370)		74.98	4.61	7.28
60d	55	Viscous Semi-Solid	$C_{11}H_{10}N_2OS$		60.55	4.59	12.84
			(218)		60.13	4.31	12.4[illegible]

Table 13 (Contd.)

60e	52	Semi-Solid	$C_{12}H_{12}N_2OS$	62.07	5.17	12.07
			(232)	62.48	5.38	12.37
60f	53	Semi-Solid	$C_{11}H_9ClN_2OS$	52.28	3.56	11.09
			(252.5)	52.69	3.13	11.28
60g	60	169-70	$C_{12}H_{12}N_2OS$	62.07	5.17	12.07
			(232)	61.63	4.87	11.98
60h	58	152-53	$C_{13}H_{14}N_2OS$	63.41	5.69	11.38
			(246)	62.89	5.97	11.63
60i	57	150-52	$C_{12}H_{11}ClN_2OS$	54.00	4.13	10.51
			(266.5)	54.51	4.37	10.21
60j	52	225-27	$C_{18}H_{16}N_2OS$	70.12	5.19	9.09
			(308)	69.83	5.42	9.37

Table 13 (Contd.)

60k	76	220	$C_{18}H_{16}N_2OS$	70.13	5.19	9.09
			(308)	69.64	5.43	9.38
60l	77	204-5	$C_{18}H_{16}N_2O_2S$	66.67	4.94	8.64
			(324)	66.23	4.63	8.81
60m	75	234-35	$C_{17}H_{13}ClN_2OS$	62.10	3.96	8.52
			(328.5)	62.35	3.63	8.38
60n	81	206-7	$C_{18}H_{16}N_2OS$	70.13	5.19	9.09
			(308)	70.53	4.93	9.38
60o	70	180-82	$C_{18}H_{16}N_2O_2S$	66.67	4.94	8.64
			(324)	66.31	4.29	8.39
60p	76	208-9	$C_{18}H_{15}ClN_2O_2S$	60.25	4.18	7.81
			(338.5)	60.66	4.43	7.53

Table 13 (Contd.)

60q	72	220-21	$C_{17}H_{13}ClN_2OS$ (328.5)	62.10 62.51	3.96 3.61	8.52 8.28
60r	55	Viscous liquid	$C_{14}H_{14}N_2O_3S$ (290)	57.93 57.61	4.83 4.51	9.66 9.39

[a] crystallization solvent = acetic acid (60a, 60c, 60k-q) and chloroform (60b,60g-j)

TABLE 14

2-Methylthio-3-aroylquinoxalines (66a-l)

Product[a]	Yield (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis (%) C	H	N
66a	65	109	$C_{16}H_{12}N_2OS$ (280)		68.57 68.11	4.29 4.63	10.00 10.38
66b	55	Semi-solid	$C_{17}H_{14}N_2OS$ (294)		69.39 68.83	4.76 4.38	9.52 9.21
66c	60	154-55	$C_{17}H_{14}N_2O_2S$ (310)		65.81 66.43	4.51 4.31	9.03 9.44
66d	67	150	$C_{16}H_{11}ClN_2OS$ (314.5)		61.05 61.49	3.50 3.21	8.90 8.63
66e	50	Semi-solid	$C_{17}H_{14}N_2OS$ (294)		69.39 69.88	4.76 4.51	9.52 9.23

Table 14 (Contd.)

66f	56	150-51	$C_{17}H_{14}N_2O_2S$	65.81	4.51	9.03
			(310)	65.38	4.22	9.38
66g	55	195-96	$C_{16}H_{11}ClN_2O_2S$	61.05	3.50	8.90
			(314.5)	61.48	3.21	8.63
66h	50	143-44	$C_{16}H_{16}N_2O_2S$	66.67	4.94	8.64
			(324)	67.13	4.58	8.33
66i	48	170-71	$C_{17}H_{13}ClN_2O_2S$	62.10	3.96	8.52
			(328.5)	61.53	3.63	8.31
66j	60	152-53	$C_{17}H_{13}ClN_2O_2S$	59.22	3.77	8.12
			(344.5)	58.88	3.43	8.48
66k	50	170-72	$C_{17}H_{13}ClN_2OS$	62.10	3.96	8.52
			(328.5)	61.73	3.59	8.87
66l	65	154-55	$C_{17}H_{13}ClN_2O_2S$	59.22	3.77	8.12
			(344.5)	59.61	3.53	8.44

[a]crystallization solvent = benzene/hexane.

TABLE 15

2-Phenyl-4-aroyl-5-arylaminothiazoles (68a-f).

Product[a]	Yield (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis (%) C	H	N
68a	55	144-45	$C_{22}H_{16}N_2OS$		74.16	4.49	7.87
			(356)		73.63	4.22	7.51
68b	50	138-40	$C_{23}H_{18}N_2OS$		74.59	4.86	7.57
			(370)		74.11	4.48	7.21
68c	52	146-47	$C_{24}H_{20}N_2O_2S$		72.00	5.00	7.00
			(400)		72.48	4.73	7.33
68d	56	195	$C_{22}H_{15}ClN_2OS$		67.61	3.84	7.17
			(390.5)		67.21	3.63	7.48
68e	48	157-58	$C_{23}H_{18}N_2OS$		74.59	4.86	7.57
			(370)		74.98	4.53	7.88
68f	50	163-65	$C_{22}H_{15}ClN_2OS$		67.61	3.84	7.17
			(390.5)		67.12	3.43	7.45

[a] crystallization solvent = benzene/hexane.

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CHAPTER IV

CYCLOCONDENSATION OF KETOKETEN-S,N-ACETALS WITH NITROSOBENZENE: A FACILE GENERAL ROUTE TO 1-N-ARYL-2-ARYL/ALKYL/UNSUBSTITUTED-4-ALKYLTHIO-5-AROYL/ACYLIMIDAZOLES

IV.1 Introduction

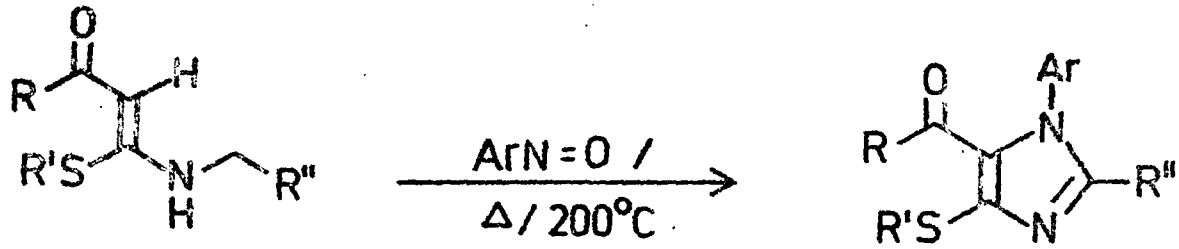
In the Chapter III, we have successfully achieved annelation of ketoketen-S,N-acetals with nitrosyl chloride which affords novel imidazole, quinoxaline and thiazole derivatives via acyclic N-alkyl/N-aryliminohydroxyimine intermediates. We further intended to extend thia approach for the synthesis of title imidazoles by cyclocondensation of ketoketen-S,N-benzyl/alkylacetals with nitrosobenzene. Electrophilic nitrosation of 4-alkylaminouracils with nitrosobenzene and subsequent cyclization to 7-arylaxanthines (14) (Scheme 8, Chapter III) has been reported by Taylor and

co-workers.[1] The same authors have also synthesized alloxazine derivatives (34) (Scheme 13, Chapter III) by cyclocondensation of 1,3-dimethyl 4-aminouracil with nitrosobenzene.[2] However there is no report of the reaction of cyclic enamines or enaminones with nitrosobenzene to give N-arylimidazoles. In the present investigation, we have successfully carried out the cyclocondensations of polarized ketoketen-S,N-alkyl-acetals with nitrosobenzenes, which afford the title imidazoles in excellent yields. These results are presented in this chapter.

IV.2 Results and discussion

The S,N-acetals 1a-m required in the present investigation were prepared by one of the methods described in Chapter II. When a solution of S,N-acetal 1a in acetic anhydride was refluxed for 15 hr with equimolar quantity of nitrosobenzene, the starting material was recovered unchanged. However when 1a (0.01 mol) and nitrosobenzene (0.013 mol) in acetic anhydride were heated in a sealed tube (200°C) for 1 hr the corresponding 1-N-phenyl-2-phenyl-4-methylthio-5-benzoylimidazole 2a was obtained in 30% yield. Improved yields (85%) of imidazole 2a were obtained when nitrosobenzene

was taken in excess (0.03 mol for 0.01 mol of 1a). The structure of 2a was confirmed with the help of spectral and analytical data. The elemental analysis of 2a agreed with the molecular formula $C_{23}H_{18}N_2OS$, while its mass spectrum exhibited molecular ion peak at m/z 370 (M^+) which showed that 1a has condensed with nitrosobenzene with elimination of one mol of water. Its infra red spectrum (KBr) showed aromatic carbonyl frequency at 1638 cm^{-1}. Further confirmation of its structure was obtained from its n.m.r. spectrum ($CDCl_3$). The characteristic benzylic protons and olefinic proton signals present in the n.m.r. spectrum of 1a, at 4.45 (d, 2H) and 5.56 (s, 1H) respectively were absent in the n.m.r. spectrum of 2a, thus indicating that α-carbon and aminomethylene carbon atoms of 1a are involved in cyclocondensation with nitrosobenzene. The signal due to MeS protons was present at 2.50 (s, 3H) while the aromatic protons appeared as two multiplets at 7.05-7.53 (13H) and 7.6-7.83 (2H). Its ultraviolet spectrum exhibited absorption maxima at max (MeOH): 259, 347 (log , 4.37, 3.89) nm. The reaction of other S,N-benzyl acetals 1b-f with nitrosobenzene similarly yielded the corresponding 1-N-aryl-4-methylthio(2b-d)and 4-ethylthio 2e and 4-benzylthio(2f)imidazoles in 80-85%

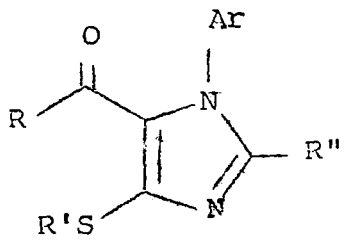


1 2

Scheme 1 (Table 1)

TABLE 1

1-N-Aryl-2-aryl/alkyl/unsubstituted-4-alkylthio-5-aroyl/acyl-imidazoles prepared



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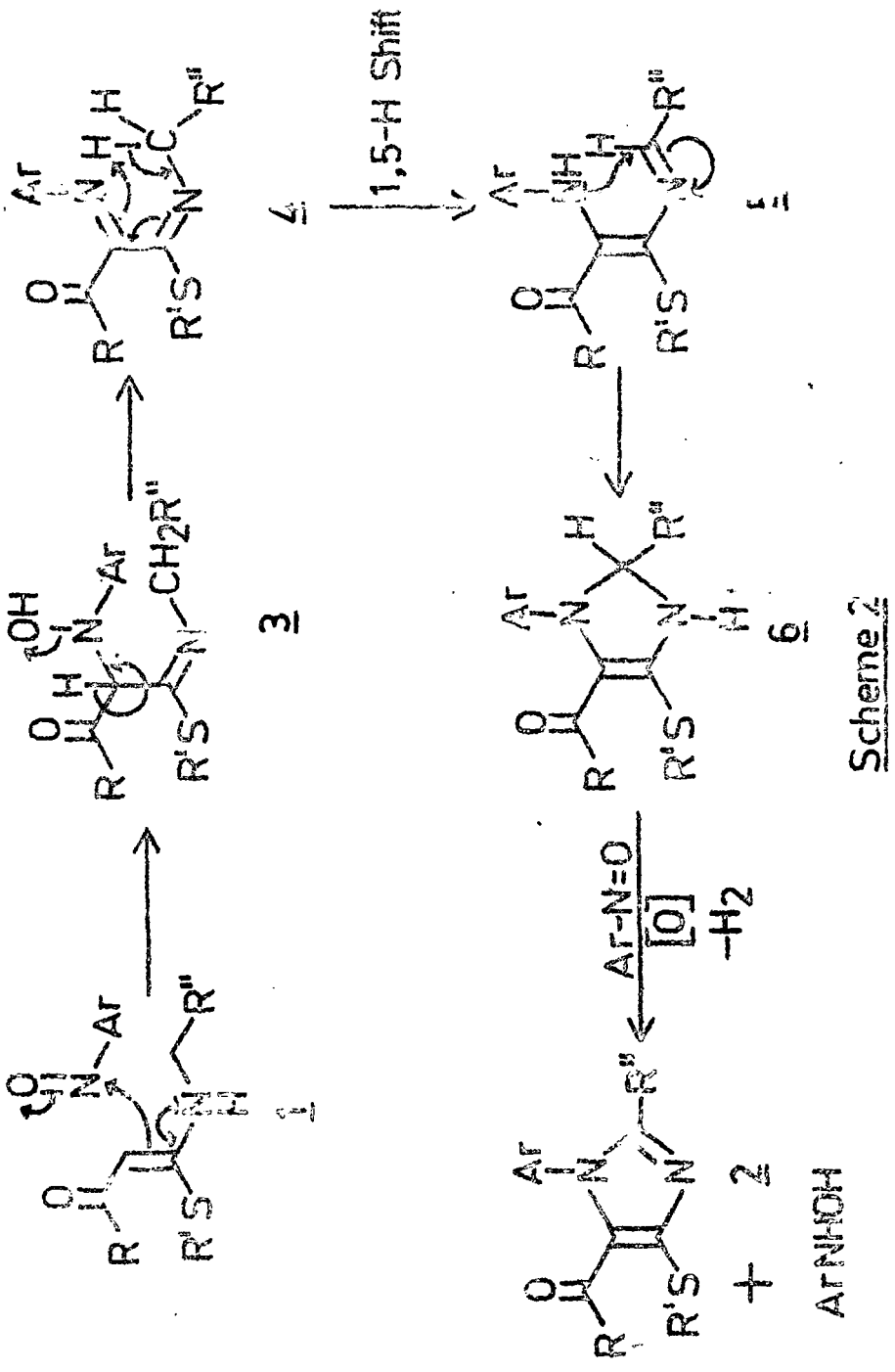
S No	Starting compd.	Product	R	R'	R"	Ar
1	1a	2a	C_6H_5	Me	C_6H_5	C_6H_5
2	1b	2b	p-MeC_6H_4	Me	C_6H_5	C_6H_5
3	1c	2c	p-MeOC_6H_4	Me	C_6H_5	C_6H_5
4	1d	2d	p-ClC_6H_4	Me	C_6H_5	C_6H_5
5	1e	2e	C_6H_5	Et	C_6H_5	C_6H_5
6	1f	2f	C_6H_5	$C_6H_5CH_2$	C_6H_5	C_6H_5
7	1g	2g	Me	Me	C_6H_5	C_6H_5
8	1h	2h	C_6H_5	Me	H	C_6H_5
9	1i	2i	p-MeC_6H_4	Me	H	C_6H_5

Table 1 (Contd.)

10	1j	2j	p-ClC_6H_4	Me	H	C_6H_5
11	1k	2k	C_6H_5	Me	Me	C_6H_5
12	1l	2l	p-MeC_6H_4	Me	Me	C_6H_5
13	1m	2m	p-ClC_6H_4	Me	Me	C_6H_5
14	1a	2n	C_6H_5	Me	C_6H_5	p-MeC_6H_4
15	1h	2o	C_6H_5	Me	H	p-MeC_6H_4
16	1k	2p	C_6H_5	Me	Me	p-MeC_6H_4

overall yields. The S,N-benzylacetal 1g derived from acetone similarly yielded 5-acetylimidazole 2g in good yield. The reaction was equally successful with the corresponding S,N-methyl (1h-j) and S,N-ethyl (1k-m) acetals having unactivated methylene protons. Thus when S,N-methylacetal 1h was reacted with nitrosobenzene under identical conditions, corresponding 2-unsubstituted-1-N-arylimidazole 2h was obtained in 75% yield. The other substituted 1-N-aryl-2-unsubstituted 2i-j and 1-N-aryl-2-methyl 2k-m imidazoles were similarly obtained in 72-80% overall yields. Similarly the reaction of S,N-benzylacetal 1a, S,N-methylacetal 1h, S,N-ethylacetal 1k with p-nitrosotoluene yielded the corresponding 1-N-p-tolylimidazoles 2n-p in 70-84% overall yields (Table 1). The structures of all new 1-N-arylimidazoles 2b-p were confirmed with the help of spectral and analytical data, which are given in Table 2 and 3, respectively.

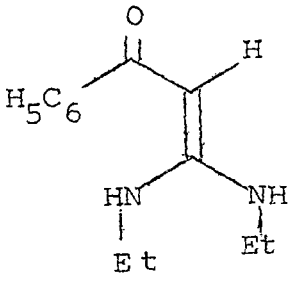
The mechanism of N-aryl imidazole 2 formation from 1 and nitrosobenzene is shown in the Scheme 2, which is very similar to that suggested by Taylor for the formation of 7-arylxanthines by the reaction of 1-3-dimethyl-6-alkylaminouracil with nitrosobenzene. Thus β-hydroxylaminoimine intermediate 3 formed by nucleophilic attack of β-carbon of S,N-acetal to



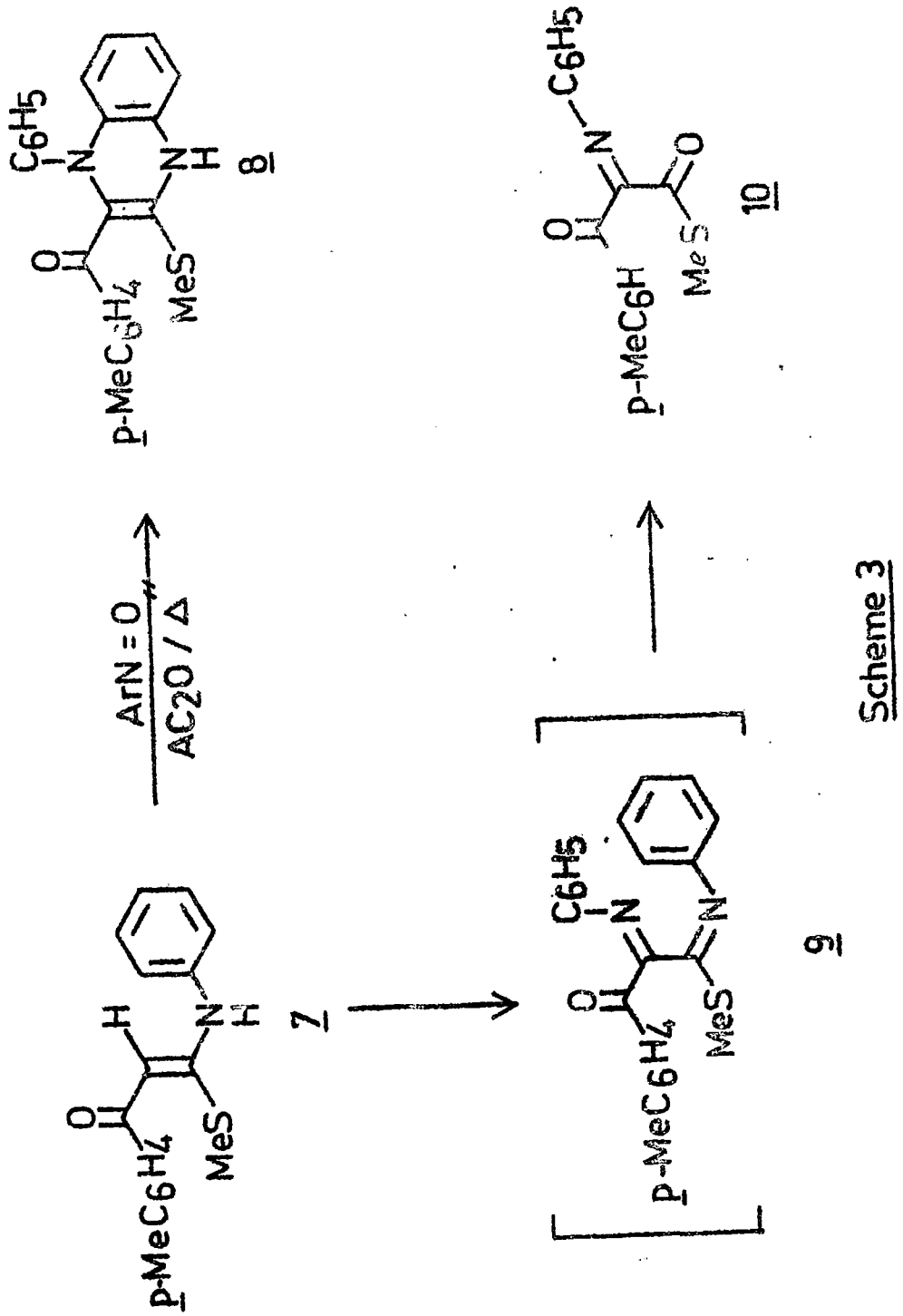
Scheme 2

nitrosobenzene suffers dehydration in the acetic anhydride medium to give the diimine 4, which on 1,5-proton shift gives the monoimine 5, which is ideally disposed for intramolecular cyclization to dihydroimidazole 6. Subsequent dehydrogenation by excess of arylnitroso compound would then lead to 1-N-arylimidazoles 2 and arylhydroxylamine.

When the corresponding S,N-anilinoacetal 7 was reacted with 2 eqv. of nitrosobenzene the expected dihydroquinoxaline 8 was not formed. The product thus isolated was characterized as imine 10 (Scheme 3). Apparently, the diimine intermediate 9 suffers hydrolysis during work-up to give 10. When the corresponding N,N-ethylacetal 11 was reacted with nitrosobenzene under identical conditions, the starting material 11 was recovered unchanged after 2.5 hr. However on prolonged heating (10 hr) intractable reaction mixture was obtained.



11


C6H5
N
NH
O
p-MeC6H4
MeS
8
ArN=O
Ac2O / Δ
7
C6H5
N
N
O
p-MeC6H4
MeS
9
C6H5
N
O
O
p-MeC6H
MeS
10

Scheme 3

IV. 3 Conclusion

A novel general approach for 1-N-aryl-2-aryl/alkyl/unsubstituted-4-alkylthio-5-aroyl/acylimidazoles has been developed by cyclocondensation of corresponding α-ketoketen S,N-benzyl and alkylacetals with nitrosobenzene. The reaction yields the imidazoles 2 under simple reaction conditions from easily available S,N-acetals in excellent yields. Although several approaches to N-arylimidazoles[2] are available in the literature, to our knowledge this is the first report of use of acyclic enaminones for the synthesis of N-arylimidazoles by electrophilic nitrosation with nitrosobenzene.

IV.4 Experimental

M.ps. were determined on a 'Boetius' (German) apparatus and are uncorrected. The i.r. spectra were recorded on Perkin-Elmer 297 spectrometer, while the u.v. spectra were obtained on Beckman 26 spectrophotometer. The n.m.r. spectra were recorded on a Varian EM-390 spectrometer using T.M.S. as internal standard and the values are expressed in δ(ppm).

The starting materials

Commercial acetic anhydride was purified before use by distillation.

Nitrosobenzene and nitroso-p-toluene were prepared by the reported method.[4]

The keten-S,N-acetals (1a-m) were prepared as described in Chapter II.

General method for the preparation of 1-N-aryl-2-aryl/alkyl/unsubstituted-4-alkylthio-5-aroyl/acylimidazoles (2a-p)

A solution of S,N-acetal 1 (0.01 mol) and nitroso-benzene/nitroso-p-toluene (0.03 mol) in 25 ml of acetic anhydride was heated in a sealed tube (200°C) for 1 hr. Acetic anhydride was removed under reduced pressure and the residue diluted with water (50 ml), extracted with chloroform

(3x250 ml), dried (Na_2SO_4) and evaporated to give crude imidazoles (2a-p) (Table 1), which were purified by column chromatography over silica gel using benzene/hexane (2:3) as eluent. Spectral and analytical data of imidazoles 2a-p is given in Table 2 and 3, respectively.

Reaction of keten-S,N-acetal 7 with nitrosobenzene

A solution of 2.83gm (0.01 mol) of S,N-acetal 7 and 2.14gm (0.02 mol) of nitrosobenzene was refluxed in acetic anhydride for 2.5 hr, work-up of the reaction mixture yielded starting material, m.p. 75-76° (mixed m.p., superimposible i.r. and n.m.r. spectra. In another attempt the reaction mixture was heated in a sealed tube (200°C) for 1 hr. Acetic anhydride was removed under reduced pressure, diluted with water (50 ml), extracted with chloroform, dried (Na_2SO_4) and evaporated to give crude viscous liquid 10 (Scheme 3), which was purified by column chromatography over silica gel to give white crystalline solid (Benzene); m.p. 113-14°C; i.r. ν_{max} (KBr): 1665, 1600 cm^{-1}; n.m.r. ($CDCl_3$): 2.06 (s, 6H, CH_3, SCH_3); 6.93-7.60 (m, 9H, arom); Found: C, 68.35, H, 5.29; N, 4.40; Calc. for $C_{17}H_{15}NO_2S$ (297): C, 68.69; H, 5.05; N, 4.71%.

Reaction of keten-N,N-acetal with nitrosobenzene: Attempted preparation of 1-N-aryl-2-methyl-4-ethylamino-5-aroyl imidazole

N,N-ethylacetal 11 under identical conditions as described in general procedure yielded starting material, m.p. 75-77° (mixed m.p., superimposable i.r. and n.m.r. spectra).

TABLE 2

Spectral data of products 2a-p

Product	IR (KBr) νmax (cm^{-1})	^{1}H-N.M.R.($CDCl_3$) δ (ppm)	M.S. m/e(M^+)
2a	1638 (CO)	2.50 (s, 3H, SCH_3); 7.03-7.53 (m, 13H, arom); 7.60-7.83 (m, 2H, arom).	370
2b	1636 (CO)	2.40 (s, 3H, CH_3); 2.56 (s, 3H, SCH_3); 7.30-7.40 (m, 12H, arom); 7.70 (d, 2H, arom).	384
2c	1638, 1605 (CO)	2.46 (s, 3H, SCH_3); 3.75 (s, 3H, OCH_3); 6.70-7.30 (m, 12H, arom); 7.78 (d, 2H, arom).	—

Table 2 (Contd.)

2d	1635 (CO)	2.56 (s, 3H, SCH_3); 7.00-7.46 (m, 12H, arom); 7.58 (d, 2H, arom).	404, 405
2e	1632 (CO)	1.30 (t, 3H, SCH_2CH_3); 3.10 (q, 2H, SCH_2CH_3); 7.03-7.50 (m, 13H, arom); 7.60-7.80 (m, 2H, arom).	384
2f	1635 (CO)	4.34 (s, 2H, $CH_2C_6H_5$); 7.15-7.60 (m, 20H, arom).	—
2g	1660 (CO)	2.13 (br s, 6H, SCH_3 and CH_3); 6.80-7.63 (m, 10H, arom).	—
2h	1645 (CO)	2.50 (s, 3H, SCH_3); 7.06-7.75 (m, 11H, arom).	294
2i	1650, 1632 (CO)	2.36 (s, 3H, CH_3); 2.46 (s, 3H, SCH_3); 7.00-7.36 (m, 8H, arom); 7.60 (d, 2H, arom).	308

Table 2 (Contd.)

2j	1620 (CO)	2.50 (s, 3H, SCH_3); 7.06-7.43 (m, 8H, arom); 7.60 (d, 2H, arom).	328, 330
2k	1635 (CO)	2.23 (s, 3H, CH_3); 2.40 (s, 3H, SCH_3); 7.03-7.43 (m, 8H, arom); 7.50-7.66 (m, 2H, arom).	308
2l	1628 (CO)	2.30 (s, 3H, CH_3); 2.33 (s, 3H, CH_3); 2.46 (s, 3H, SCH_3); 7.03-7.46 (m, 7H, arom); 7.59 (d, 2H, arom).	322
2m	1630 (CO)	2.28 (s, 3H, CH_3); 2.50 (s, 3H, SCH_3); 7.03-7.46 (s, 7H, arom); 7.58 (d, 2H, arom).	344,
2n	1615 (CO)	2.28 (s, 3H, CH_3); 2.50 (s, 3H, SCH_3); 6.83-7.50 (m, 12H, arom); 7.63-7.80 (m, 2H, arom).	384

Table 2 (Contd.)

2o	1621, 1595 (CO)	2.35 (s, 3H, $C\underline{H}_3$); 2.53 (s, 3H, $SC\underline{H}_3$); 6.92-7.76 (m, 10H, arom)	308
2p	1635 (CO)	2.26 (s, 3H, $C\underline{H}_3$); 2.35 (s, 3H, $C\underline{H}_3$); 2.46 (s, 3H, $SC\underline{H}_3$); 7.22-7.80 (m, 9H, arom).	—

TABLE 3

1-N-Aryl-2-aryl/alkyl/unsubstituted-4-alkylthio-5-aroyl/acylimidazoles (2a-p).

Product[a]	Yield (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis (%) C	H	N
2a	85	151-52	$C_{23}H_{18}N_2OS$		74.59	4.86	7.57
			(370)		77.12	4.53	7.25
2b	83	160-61	$C_{24}H_{20}N_2OS$		75.00	5.21	7.29
			(384)		75.35	5.43	7.61
2c	84	148-49	$C_{24}H_{20}N_2O_2S$		72.00	5.00	7.00
			(400)		72.45	4.75	7.33
2d	85	195-96	$C_{23}H_{17}ClN_2OS$		68.23	4.20	6.92
			(404.5)		68.65	4.51	6.60

Table 3 (Contd.)

2e	80	134-35	$C_{24}H_{20}N_2OS$	75.00	5.21	7.29
			(384)	75.41	5.00	7.67
2f	82	181-83	$C_{29}H_{22}N_2OS$	78.02	4.93	6.28
			(446)	77.41	4.58	6.57
2g	78	105	$C_{18}H_{16}N_2OS$	70.13	5.19	9.09
			(308)	70.34	5.43	9.28
2h	75	119-20	$C_{17}H_{14}N_2OS$	69.39	4.76	9.52
			(294)	69.03	4.59	9.29
2i	72	161	$C_{18}H_{16}N_2OS$	70.13	5.19	9.09
			(308)	70.43	5.32	8.89
2j	75	142-43	$C_{17}H_{13}ClN_2OS$	62.10	3.96	8.52
			(328.5)	61.85	3.69	8.35

Table 3 (Contd.)

2k	80	129-30	$C_{18}H_{16}N_2OS$	70.13	5.19	9.09
			(308)	69.83	5.03	9.38
2l	77	105-7	$C_{19}H_{18}N_2OS$	70.81	5.59	8.70
			(322)	70.60	5.35	8.55
2m	78	145-46	$C_{18}H_{15}ClN_2OS$	63.07	4.38	8.18
			(342.5)	63.23	4.13	8.31
2n	84	125-26	$C_{24}H_{20}N_2OS$	75.00	5.21	7.29
			(384)	74.78	5.01	7.63
2o	70	138-40	$C_{18}H_{16}N_2OS$	70.13	5.19	9.09
			(308)	70.61	4.73	8.68
2p	72	125-26	$C_{19}H_{18}N_2OS$	70.81	5.59	8.70
			(322)	70.33	5.78	8.97

[a] crystallization solvent = benzene/hexane.

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CHAPTER V

REACTIONS OF POLARIZED KETOKETEN-S,N-ACETALS WITH THIONYL CHLORIDE: A NOVEL GENERAL ROUTE TO 5-AROYL/ACYL-2-ARYL/ETHOXYCARBONYL-4-ALKYLTHIOTHIAZOLES BY DIRECT HETEROCYCLIZATION*

V.1 Introduction

In the previous chapters we have successfully achieved the annelation reactions of polarized keten-S,N-acetals with nitrosyl chloride and nitrosobenzene, which provide novel routes for the construction of imidazole, quinoxaline and thiazole derivatives. We further anticipated on similar grounds that polarized keten S,N-acetals of general structure 1 should undergo electrophilic C-sulfination and subsequent ring closure in the presence of thionyl chloride to afford novel thiazole derivatives 2(Scheme 1). Our literature survey at this stage revealed

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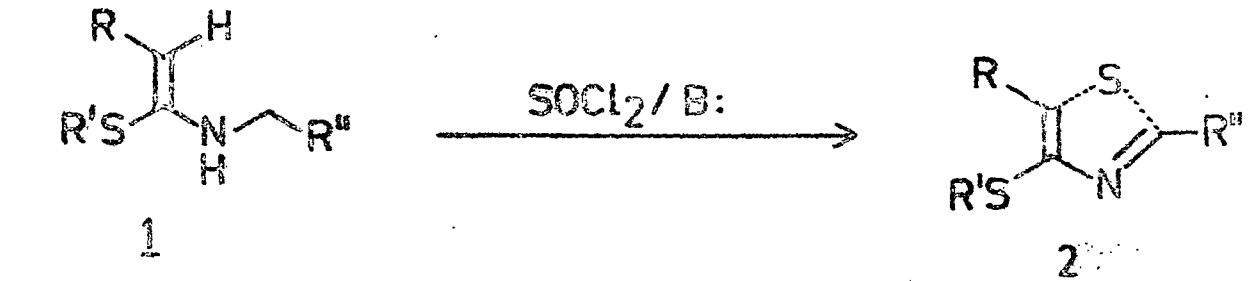
*A. Rahman, H. Ila and H. Junjappa, Synthesis, 000 (1984).



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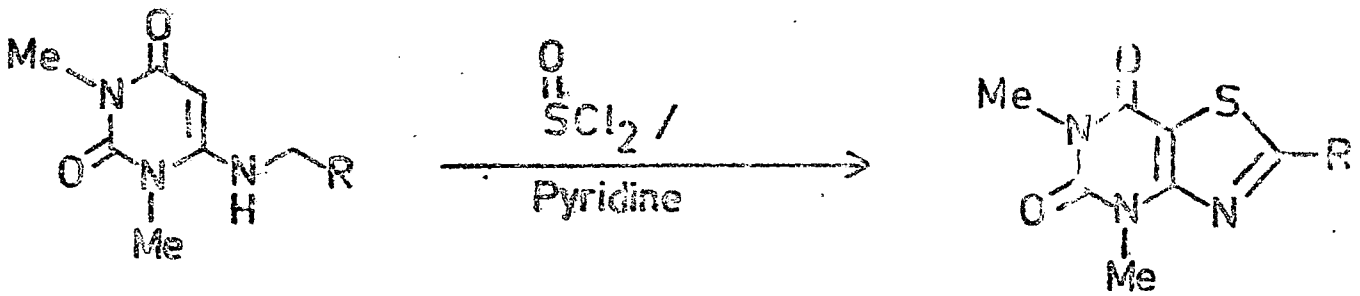


3 4

3, 4a, R = C_6H_5
b, R = H
c, R = Me
d, R = CF_3

Scheme 1

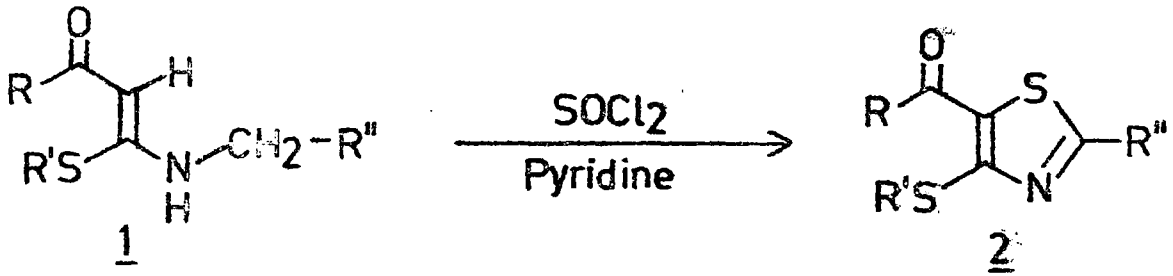
that C-sulfination of appropriately substituted active methylene compounds to give thiophenes and isothiazole derivatives is known in the literature,[1] however, no examples of electrophilic C-sulfination of enamines or enaminones are reported. The only related reference available in the literature[2] describes the synthesis of fused thiazolo [4,5-d] pyrimidine derivatives 4 by reaction of thionyl chloride with 4-alkylamino-1,3-dimethyluracil 3 (Scheme 1). In the present chapter, we have discussed the results of our studies on the reactions of polarized ketoketen-S,N-acetals with thionyl chloride, which provide a novel general route to hitherto inaccessible 4-alkylthio-5-aroyl/acyl/unsubstituted-2-aryl/ethoxycarbonyl thiazoles.

V. 2 Results

When the S,N-benzylacetal 1a was reacted with excess of thionyl chloride in pyridine at 0-5° for 3 hr, work-up and column chromatography of the reaction mixture yielded a yellow solid (60%), which was characterized as 2-phenyl-4-methylthio-5-benzoylthiazole (2a) on the basis of spectral and analytical data (Scheme 2). It showed molecular ion peak (M^+) at m/Z 311 and was analysed for $C_{17}H_{13}NOS_2$. The strong band at

1618 cm^{-1} in the i.r. spectrum of 2a was attributed to the aromatic carbonyl group. Further structural proof for 2a was derived from its n.m.r. spectrum, which showed the disappearance of the characteristic doublet at δ 4.45 and singlet at δ 5.56 (due to benzylic and olefinic protons respectively) presently in the n.m.r. spectrum of 1a. The singlet at δ 2.70 (3H) was assigned to the 4-MeS protons. The aromatic protons appeared as broad multiplet at δ 7.28-7.68 (6H) and 7.68-8.05 (4H). Similarly the other S,N-benzyl acetals 1b-m reacted with thionyl chloride under identical conditions to give the corresponding thiazoles 2b-m in 57-65% overall yields under similar conditions. The S,N-acetal 1n derived from acetone yielded the thiazole 2n in only 21% yield. Further attempts to increase the yield of 2n were not successful probably due to further reaction of acyl group with thionyl chloride.

Under similar reaction conditions, the S,N-alkyl-acetals 1o and 1p failed to react with thionyl chloride to give the corresponding 2-unsubstituted 2o and 2-methylthia-zoles 2p (Scheme 3). In both the cases, intractable polymers were obtained. Apparently, the activation of aminomethylene protons is necessary for thiazole formation. It is pertinent



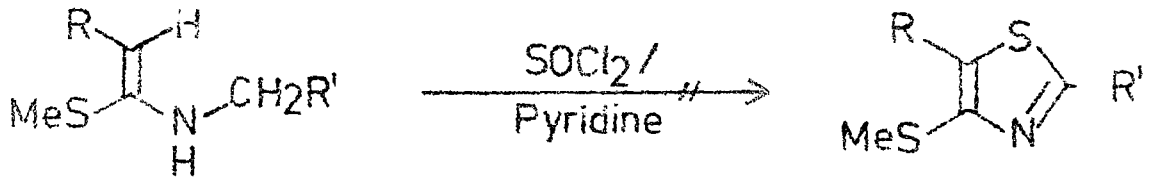
1,2 , a, R = R" = C_6H_5 ; R' = Me
b, R = p-MeC_6H_4 ; R' = Me ; R" = C_6H_5
c, R = p-$MeOC_6H_4$; R' = Me ; R" = C_6H_5
d, R = p-ClC_6H_4 , R' = Me ; R" = C_6H_5
e, R = p-$MeOC_6H_4$; R' = Me ; R" = p-ClC_6H_4
f, R = p-$MeOC_6H_4$; R' = Me ; R" = p-ClC_6H_4
g, R = p-ClC_6H_4 ; R' = Me ; R" = p-ClC_6H_4
h, R = C_6H_5 ; R' = Me , R" = p-$MeOC_6H_4$
i , R = p-$MeOC_6H_4$; R' = Me ; R" = p-$MeOC_6H_4$
j , R = p-ClC_6H_4 ; R' = Me ; R" = p-$MeOC_6H_4$
k , R = C_6H_5 ; R' = Et , R" = C_6H_5
l , R = C_6H_5 ; R' = $-CH_2C_6H_5$; R" = C_6H_5
m , R = p-$MeOC_6H_4$; R' = $-CH_2C_6H_5$; R" = C_6H_5
n , R = Me ; R' = Me ; R" = C_6H_5

Scheme 2

to note however, that the corresponding 4-methylamino-(3b) and 4- ethylamino(3c)-1,3-dimethyluracils underwent facile cyclization under similar conditions to yield the corresponding 2-unsubstituted and 2-methyl thiazolopyrimidines 4b and 4c in good yields (Scheme 1).

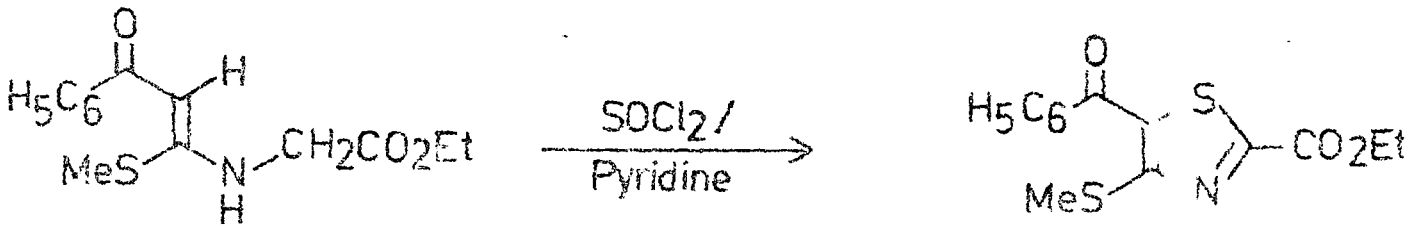
When the S,N-acetal 1q derived from ethyl glycinate was reacted with thionyl chloride in pyridine, corresponding 2-ethoxycarbonylthiazole 2q was obtained in 30% yield. The yield could not be improved further under varying conditions.

Treatment of nitroketen S,N-acetal 1r with thionyl chloride under identical conditions did not yield the desired thiazole. However, a yellow viscous liquid was obtained in 45% yield, which could not be identified. Interestingly, when the thiazole 2a was stirred with sodium hydride in dimethylformamide for 5 hr, after work-up, a viscous semi-solid was obtained which was characterized as 2-phenyl-4-methylthiothiazole 5a on the basis of spectral and analytical data (Scheme 4) (Table 2 and 3). Thus the thiazole 2a undergoes facile debenzoylation in the presence of sodium hydride. The other thiazoles 2e, 2h and 2k similarly underwent facile



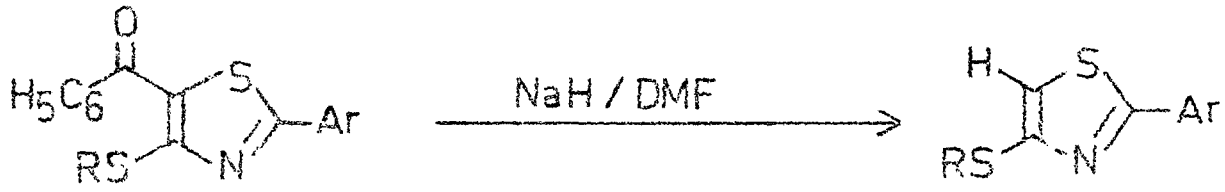
1 2

1,2,o , R = C_6H_5CO ; R' = H
p , R = C_6H_5CO ; R' = Me
r , R = NO_2 ; R' = C_6H_5



1q 2q

Scheme 3



2a , 2e , 2h , 2k

5

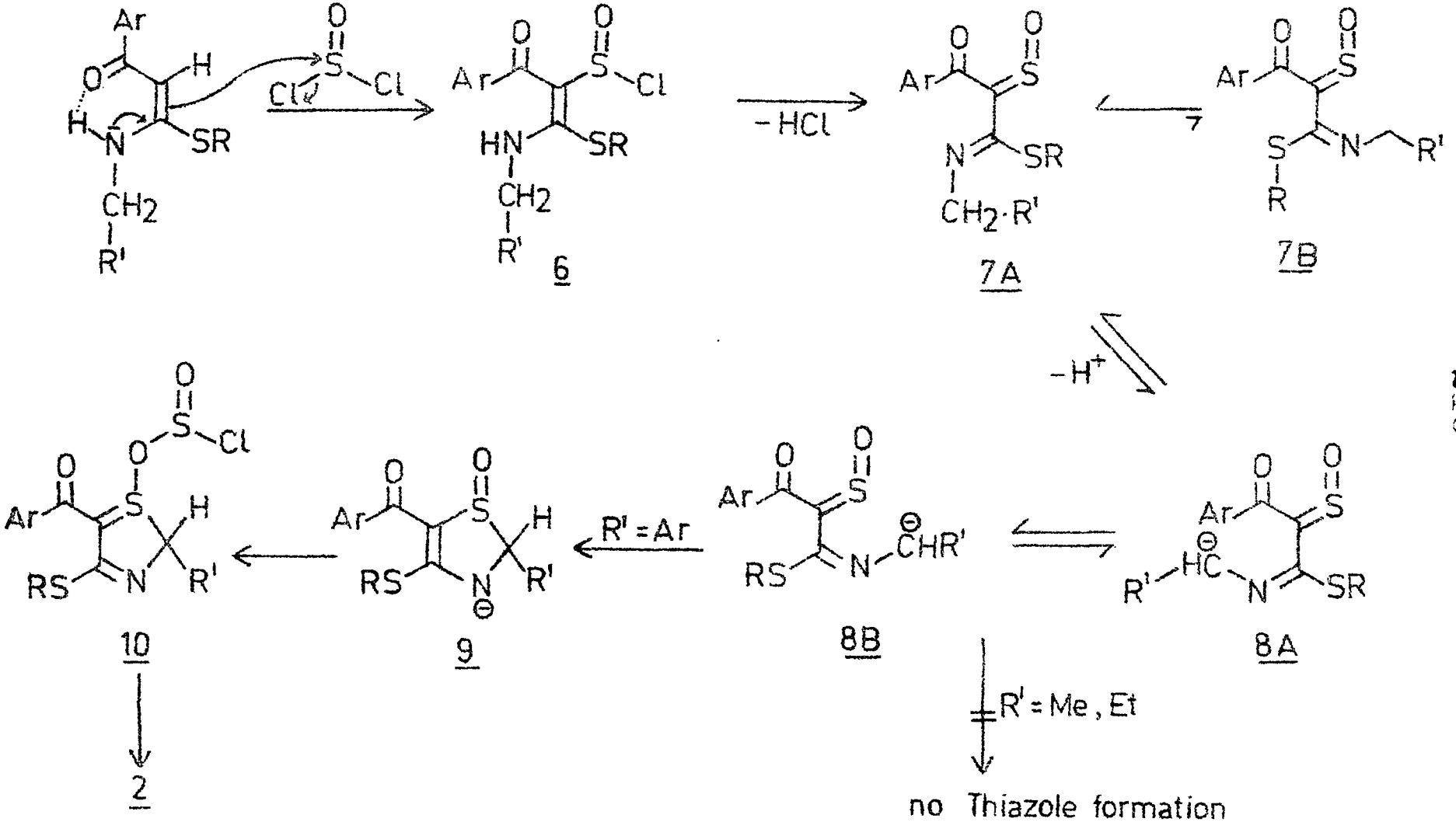
a , R = Me ; Ar = C_6H_5
b , R = Me ; Ar = p-ClC_6H_4
c , R = Me ; Ar = p-$MeOC_6H_4$
d , R = Et ; Ar = C_6H_5

Scheme 4

debenzoylation under identical conditions to give the corresponding 5-unsubstituted 4-alkylthiothiazoles 5b-d in 70-75% overall yields (Scheme 4), thus providing a novel and convenient route for 2-aryl-4-alkylthio-5-unsubstituted thiazoles.

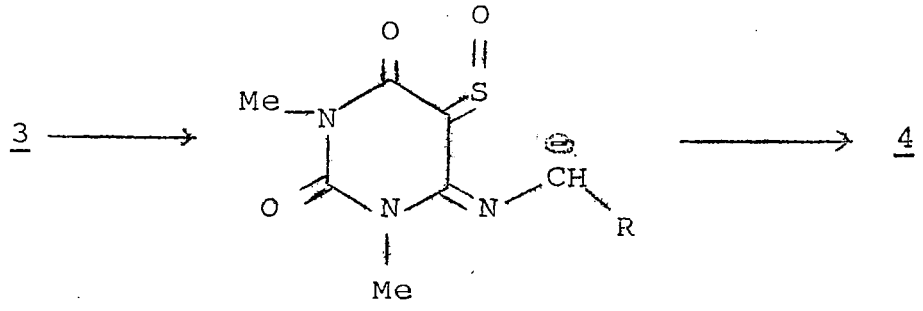
V.3 Mechanism for thiazole formation

Mechanistically, the formation of thiazole 2 from S,N-acetals 1 appears to be similar to that proposed by Goldman for thiazolo[4,5-d]pyrimidine 4 formation from 3.[2] The sulfene intermediate 7 formed from the intermediate 6 (Scheme 5) undergoes cyclization after proton abstraction via anion 8 to give the corresponding thiazoline S-oxide 9. Further reaction of 9 with thionyl chloride affords the corresponding thiazoles 2 via Pummerer intermediate 10. Attempts to isolate any one of the intermediates 6-10 were not successful, while the reaction of 1a with thionyl chloride in absence of pyridine yielded mixture of several unidentifiable products. The failure of S,N-acetals 1o (R'=H) and 1p (R'=Me) to undergo cyclization to the corresponding 2o and 2p is probably due to decreased acidity of N-alkyl protons in 1o and 1p resulting in the slower rate of


Ar
H
O
H
N
SR
CH2
R'
Cl
S
Cl
6
HN
- HCl
7A
7B
CH2·R'
- H+
8A
8B
CHR'
R' = Ar
9
10
2
RS
R' = Me , Et
no Thiazole formation

Scheme 5

anion 8 formation. However the corresponding 4-methylamino 3b and 4-ethylamino 3c uracil derivatives undergo facile cyclizations to the corresponding 4b and 4c under similar conditions (Scheme 1). The reason for this observed difference in the reactivities of 1o (or 1p) and 3b (or 3c) can be traced in the geometrically flexible nature of the anion 8. The enaminone moiety in the uracil derivative 3 is retained in a rigid ring system, so that the sulfene moiety and the N-alkyl anion in the intermediate 11 have favourable geometry (with syn sulfeno and alkylamino group) for cyclization to thiazolopyrimidine 4. However, in the case of acyclic S,N-acetals 1, the sulfene intermediate 7 exists probably in more stable S-trans conformation 7A. When R'=aryl, the anion



11 (R= Ar, H, Me)

8A is stable enough to equilibriate to anion 8B (S-cis) having favourable geometry for cyclization to thiazole 2. However when R'=Me or Et, the anion 8A undergoes faster proton abstraction rather than equilibriation to 8B thus leading to different course of reaction.(Scheme 5).

V. 4 Discussion

The present method provides a novel general route for 2-aryl-4-alkylthio-5-aroyl/acyl/unsubstituted thiazoles in good yields. It is pertinent to note that the chemistry of 2-mercaptothiazoles and their S-alkyl/aryl derivatives is well established[3a] and these compounds have long been established as fundamentally important accelerators for vlcanization of rubber.[4] Besides they are known to exhibit herbicidal, insecticidal, antibacterial and CNS activity.[3b] A few of the 5-mercaptothiazoles and their 5-S-alkyl/aryl derivatives are also reported in the literature.[3c,3d] Surprizingly 4-mercaptothiazoles and their S-alkyl/aryl derivatives are virtually not known[3c] and to our knowledge, 5-nitro-4-butylthio-2-acetamidothiazole,[5] an intermediate in the preparation of azo-dye, and 4-phenylthiothiazole (13, R=H)[6] prepared by the nucleophilic displacement of 4-bromothiazole by thiophenolat ion(Scheme 6) are the only two examples found in the

literature. This is apparently due to the lack of suitable precursors leading to 4-alkyl/arylthio derivatives. The most general methods for the synthesis of either 2- or 5-alkyl/arylthiothiazoles include (a) one of the varients of direct heterocyclization[7,8] (b) alkylation of the corresponding 2- or 5-mercaptothiazoles with appropriate alkyl halides[3e,9] (c) nucleophilic displacement of 2- or 5-halogenothiazoles by the appropriate alkyl/arylthio anions,[3c,10] which has been most commonly used. Since very few of the 4-mercaptothiazoles are reported in the literature, the second method is not much applicable for the synthesis of 4-alkylthiothiazole. Similarly, 4-halogenothiazoles are also not easily accessible although they are known to undergo facile nucleophilic displacement by alkyl and aryl mercaptans at the rates comparable with those of 2-halogenothiazoles.[6] The preparation of 4-halogenothiazole is only achieved by partial dehalogenation of the corresponding 2,4- or 4,5-dihalogenothiazoles with zinc[10] (Scheme 6). This is primarily due to the fact that direct halogenation of substituted thiazoles lead preferentially to 5-halogenoderivatives.* [11]

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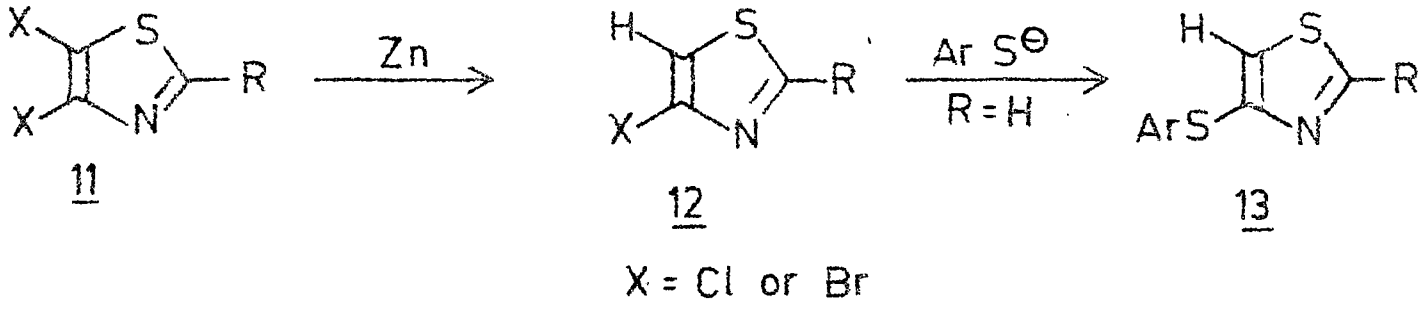
*When 5-position is substituted by an activating group as in 2-methyl-5-ethoxythiazole, the bromination takes place at 4-position.



Scheme 6

The present method therefore provides a novel and simple route for hitherto unreported 5-aroyl/acyl/unsubstituted-4-alkylthiothiazoles by direct heterocyclization in good yields.

V. 5 Experimental

M.ps. were determined on a 'Boetius' (German) apparatus and are uncorrected. The i.r. spectra were recorded on Perkin-Elmer 297 spectrometer. The n.m.r. 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 thionyl chloride (Merck) and pyridine (BDH) were distilled before use. The corresponding S,N-acetals were prepared as described in Chapter II.

General method for the preparation of 2-aryl/ethoxylcarbonyl-4-alkylthio-5-aroyl/acylthiazoles 2a-n, 2q

To an ice cooled solution of S,N-acetal 1 (0.01 mol) in dry pyridine (8 ml), excess of freshly distilled thionyl chloride (40 ml) was added slowly during 0.5 hr and the reaction mixture was further stirred for 2 hr. The whole reaction mixture was poured over crushed ice, slowly neutralized with solid sodium bicarbonate and the reaction mixture was allowed to warm up at room temperature. It was then extracted with chloroform (3x100 ml), washed with

water (3x150 ml), dried (Na_2SO_4) and evaporated to give orange yellow viscous residue, which was purified by column chromatography over neutral alumina. Elution with benzene/hexane (1:4) gave the pure thiazoles as bright yellow solids 2a-n (Scheme 2) or viscous liquid 2q (Scheme 2). The spectral and analytical data of 2a-n and 2q are given in Table 1 and 3 respectively.

Attempted reaction of keten-S,N-acetals 1o, 1p and 1r with thionyl chloride:

The S,N-acetals 1o, 1p and 1r . were reacted with thionyl chloride under similar conditions as described under general procedure. Work-up of the reaction mixture as described, yielded dark residues, which showed several spots on T.L.C. and no identifiable product could be isolated from the reaction mixture.

General method for the preparation of 2-aryl-4-alkylthio-5-unsubstituted-thiazoles (5a-d):

To a suspension of sodium hydride (0.3g, 0.006 mol, 50% suspension) in 20 ml of dry dimethylformamide, 0.004 mol of respective thiazoles 2a, 2e, 2h and 2k in 5 ml of

dimethylformamide was added slowly and the reaction mixture was further stirred at 65-70° for 4-5 hr. It was then poured over ice cold water, neutrilized with 20% acetic acid and extracted with chloroform (2x100 ml). The chloroform layer after drying and evaporation yielded the thiazoles 5a-d as viscous liquids (5a) and (5d) (Scheme 4) or low melting solids (5b) and (5c) (Scheme 4), which were pure enough for spectral data. They were further purified for microanalysis by passing through small alumina column using benzene/hexane (1:4) as eluent. The spectral and analytical data of 5a-d are given in Table 2 and 3 respectively.

TABLE 1

Spectral data of products 2a-n, 2q

Product	I.R. νmax (cm^{-1})	^{1}H-N.M.R. ($CDCl_3$) δ (ppm)	M.S. m/e (M^+)
2a	1618 (CO)[a]	2.70 (s, 3H, SMe); 7.28-7.68 (m, 6H, arom); 7.68-8.05 (m, 4H, arom).	311
2b	1621 (CO)[c]	2.32 (s, 3H, CH_3); 2.75 (s, 3H, SCH_3); 7.05-7.98 (m, 9H, arom).	325
2c	1620 (CO)[c]	2.75 (s, 3H, SCH_3); 3.90 (s, 3H, OCH_3); 6.90 (d, 2H, arom); 7.30-7.65 (m, 3H, arom); 7.66-8.12 (m, 4H, arom).	341
2d	1621 (CO)[a]	2,68 (s, 3H, SCH_3); 7.1-7.68, 5H, arom); 7.70-8.0 (m, 4H, arom).	347,345

Table 1 (Contd.)

2e	1626 (CO)[c]	2.68 (s, 3H, SCH_3); 7.20-7.55 (m, 5H, arom); 7.65-7.98 (m, 4H, arom).	347, 345
2f	1615 (CO)[c]	2.60 (s, 3H, SCH_3); 3.79 (s, 3H, OCH_3); 6.65-6.85 (d, 2H, arom); 7.15-7.35 (d, 2H, arom); 7.58-6.91 (m, 4H, arom).	377, 375
2g	1610 (CO)[c]	2.68 (s, 3H, SCH_3); 7.28-7.49 (d, 4H, arom); 7.62-7.92 (m, 4H, arom).	380
2h	1615 (CO)[a]	2.65 (s, 3H, SCH_3); 3.80 (s, 3H, OCH_3) 6.81 (d, 2H, arom); 7.20-7.45 (m, 3H, arom) 7.61-7.92 (m, 4H, arom).	341
2i	1610 (CO)[a]	2.62 (s, 3H, SCH_3); 3.80 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); 6.83 (d, 4H, arom); 7.82 (dd, 4H, arom).	371

Table 1 (Contd.)

2j	1626 (CO)[c]	2.65 (s, 3H, SCH_3); 3.75 (s, 3H, OCH_3); 6.68-6.90 (d, 2H, arom); 7.0-7.40 (d, 2H, arom); 7.0-7.40 (d, 2H, arom); 7.60-7.98 (m, 4H, arom).	377, 375
2k	1612 (CO)[c]	1.15 (t, 3H, CH_3CH_2S); 2.99 (q, 2H, CH_3CH_2S); 6.85-7.20 (m, 6H, arom); 7.32-7.70 (m, 4H, arom).	325
2l	1615 (CO)[c]	4.40 (s, 2H, $SCH_2C_6H_5$); 7.0-7.51 (m, 11H, arom); 7.52-7.95 (m, 4H, arom).	387
2m	1610 (CO)[c]	3.75 (s, 3H, OCH_3); 4.49 (s, 2H, $SCH_2C_6H_5$); 6.80 (d, 2H, arom); 7.0-7.52 (m, 8H, arom); 7.63-8.0 (m, 4H, arom).	417

Table 1 (Contd.)

2n	1670 (CO)[c]	2.50 (s, 3H, $C\underline{H}_3$); 2.71 (s, 3H, $SC\underline{H}_3$); 7.26-7.51 (m, 3H, arom); 7.76-8.10 (m, 2H, arom).	249
2q	1724 (ester CO) 1660 (CO)[b]	1.30 (t, 3H, $OCH_2C\underline{H}_3$); 2.01 (s, 3H, $SC\underline{H}_3$); 4.04 (q, 2H, $OC\underline{H}_2CH_3$); 7.16-7.48 (m, 3H, arom); 7.50-7.71 (m, 2H, arom).	307

[a] in nujol mull; [b] neat; [c] in KBr.

TABLE 2

Spectral data of products 5a-d

Product	I.R. $\nu_{max}(cm^{-1})$	^{1}H-N.M.R. ($CDCl_3$) δ (ppm)	M.S. m/e (M^+)
5a	1620 (s) 1500 (m) 1470 (s) 1260 (s)[a]	2.55 (s, 3H, SCH_3); 6.68 (s, 1H, H-5); 7.10-7.50 (m, 3H, arom); 7.65-8.10 (m, 2H, arom).	207
5b	1260 (s) 1505 (m) 1470 (s) 1265 (s)[b]	2.38 (s, 3H, SCH_3); 6.61 (s, 1H, H-5); 7.0-7.80 (dd, A_2B_2, 4H, arom)	243, 241

Table 2 (Contd.)

5c	1615 (s) 1525 (m) 1470 (s) 1260 (s)[b]	2.42 (s, 3H, $SC\underline{H}_3$); 3.65 (s, 3H, $OC\underline{H}_3$); 6.59 (s, 1H, <u>H</u>-5); 6.70 (d, A_2B_2, 2H, arom); 7.75 (d, A_2B_2, 2H, arom).	237
5d	1615 (s) 1500 (m) 1462 (s) 1265 (s)[a]	0.90 (t, 3H, $C\underline{H}_3CH_2S$); 2.62 (q, 2H, $S\text{-}C\underline{H}_2CH_3$); 6.45 (s, 1H, <u>H</u>-5); 6.68-7.20 (m, 3H, arom); 7.30-7.80 (m, 2H, arom).	221

[a] neat; [b] in KBr.

TABLE 3

2-Aryl/ethoxycarbonyl-4-alkylthio-5-aroyl/acylthiazoles (2a-n, 2q); 2-aryl-4-alkylthio-5-unsubstituted-thiazoles (5a-d)

Product[a]	Yield (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis (%) C	H	N
2a	60	95-96	$C_{17}H_{13}NOS_2$		65.59	4.18	4.50
			(311)		65.32	4.28	4.35
2b	58	116-17	$C_{18}H_{15}NOS_2$		66.46	4.62	4.31
			(325)		66.10	4.28	4.68
2c	61	160	$C_{18}H_{15}NO_2S_2$		63.34	4.40	4.11
			(341)		66.65	4.78	4.43
2d	60	143	$C_{17}H_{12}ClNOS$		65.07	3.82	4.46
			(313.5)		59.38	3.71	4.42
2e	57	127-28	$C_{17}H_{12}ClNOS$		65.07	3.82	4.46
			(313.5)		65.52	3.42	4.23

Table 3 (Contd.)

2f	60	150	$C_{18}H_{14}ClNO_2S_2$	57.52	3.73	3.73
			(375.5)	57.30	3.45	3.82
2g	61	157	$C_{17}H_{11}Cl_2NOS_2$	53.68	2.90	3.68
			(380)	53.28	3.38	3.91
2h	58	170-71	$C_{18}H_{15}O_2NS_2$	63.34	4.40	4.11
			(341)	63.15	4.72	4.47
2i	62	139-40	$C_{19}H_{17}NO_3S_2$	61.46	4.58	3.77
			(371)	61.81	4.81	3.92
2j	60	199	$C_{18}H_{14}ClNO_2S_2$	57.52	3.73	3.73
			(375.5)	57.40	3.91	3.82
2k	63	30-32	$C_{18}H_{15}NOS_2$	66.46	4.62	4.31
			(325)	66.72	4.91	4.85
2l	60	128	$C_{23}H_{17}NOS_2$	71.32	4.40	3.62
			(387)	71.05	4.75	3.95

Table 3 (Contd.)

2m	65	106-7	$C_{24}H_{19}NO_2S_2$ (417)	69.06 68.71	4.56 4.91	3.36 3.82
2n	21	137-38	$C_{12}H_{11}NOS_2$ (249)	57.83 57.45	4.42 4.81	5.62 5.93
2q	30	Oil	$C_{14}H_{13}NO_3S_2$ (307)	54.72 54.48	4.23 4.67	4.56 4.83
5a	70	Oil	$C_{10}H_9NS_2$ (207)	57.97 53.21	4.35 4.82	6.76 6.91
5b	72	53-54	$C_{10}H_8ClNS_2$ (241.5)	49.68 49.38	3.31 3.75	5.80 5.93
5c	75	57-58	$C_{11}H_{11}NOS_2$ (237)	55.70 55.68	4.64 4.91	5.91 6.12
5d	72	Semi-Solid	$C_{11}H_{11}NS_2$ (221)	59.73 59.55	4.97 5.18	6.33 6.75

[a] Crystallization solvent = benzene/hexane.

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CHAPTER VI

REACTION OF POLARIZED KETOKETEN-S,N-ACETALS WITH HYDROXYLAMINE: A FACILE GENERAL ROUTE FOR SYNTHESIS OF 5-ARYL-3-N-ARYL/ALKYL/N-AZACYCLOALKYLAMINOISOXAZOLES*

VI.1 Introduction

In the previous chapters we have exploited enaminone character of polarized ketoketen-S,N-acetals, which undergo initial electrophilic attack at β-carbon by nitrosyl chloride, nitrosobenzene or thionyl chloride to give either stable (nitrosoketen-S,N-acetals) or unstable intermediates. Subsequent transformations of these intermediates yield a variety of novel heterocycles like imidazole, quinoxaline and thiazole derivatives. Earlier work from this laboratory has demonstrated that ketoketen-S,N-acetals of general structure 1 are efficient three carbon fragments for the construction

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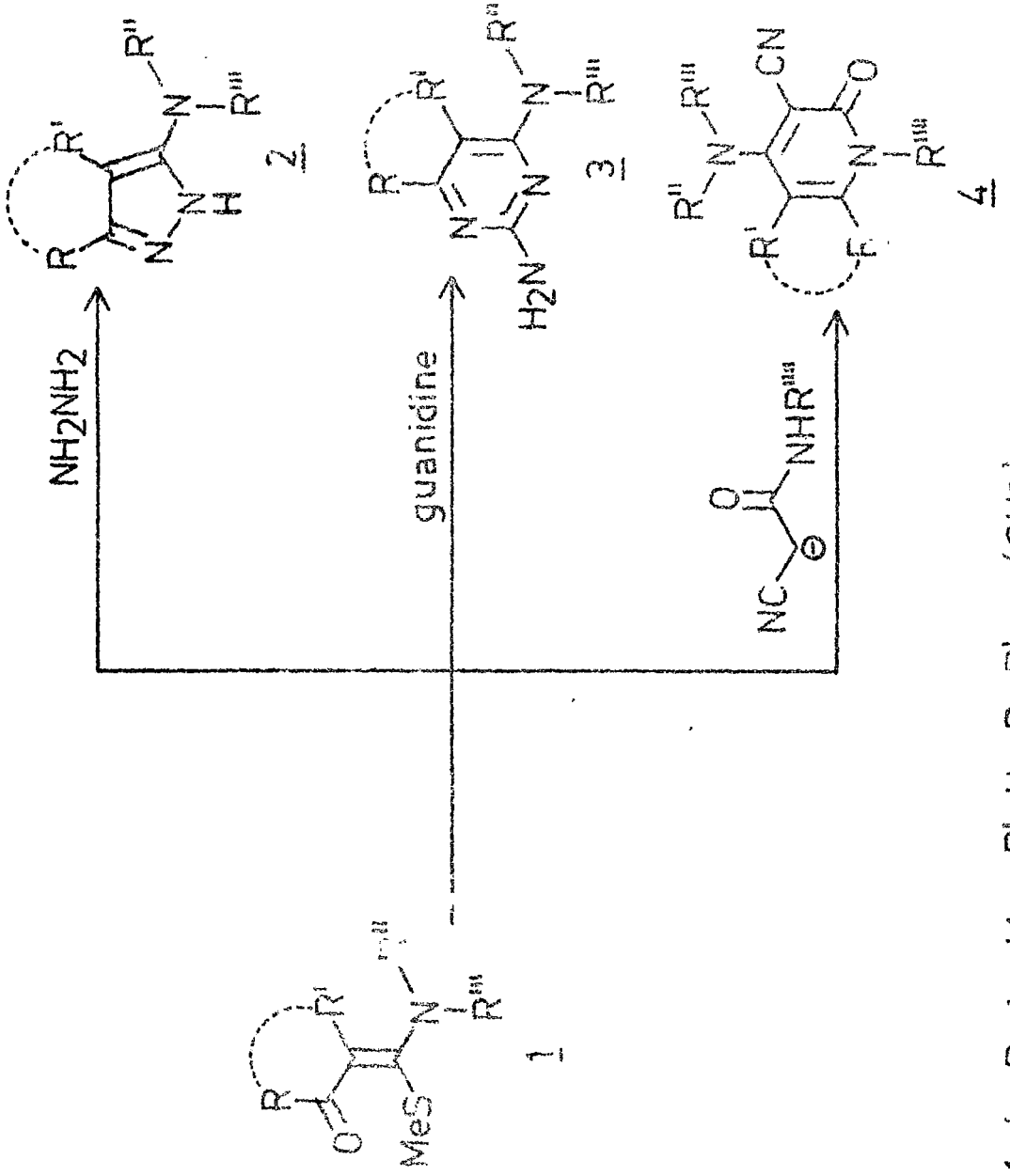
*A. Rahman, R.D. Yadav, H. Ila & H. Junjappa, Synthesis, 000, (1984).

of aminoheterocycles like 5-aminopyrazoles[1] 2, 6-aminopyrimidines 3[2] and 4-aminopyridones 4[3] on reactions with bifunctional nucleophiles like hydrazine, guanidine and cyanoacetamide anion, respectively (Scheme 1). In continuation with these studies, it was intended to study the reaction of a variety of ketoketen-S,N-acetals with hydroxylamine in order to develop a general synthetic route to 3-aminoisoxazoles. Our literature survey at this stage revealed that doubly activated keten-S,N-acetals 5a and 5b have been reacted with hydroxylamine to give the corresponding anilinoisoxazoles 6a and 6b, respectively (Scheme 2).[4,5] In the present work a systematic investigation of reaction of hydroxylamine with a variety of ketoketen-S,N-acetals derived from aromatic, aliphatic and cyclic secondary amines have been carried out, which led to a facile general route for the synthesis of 3-amino-5-aryl-isoxazoles.

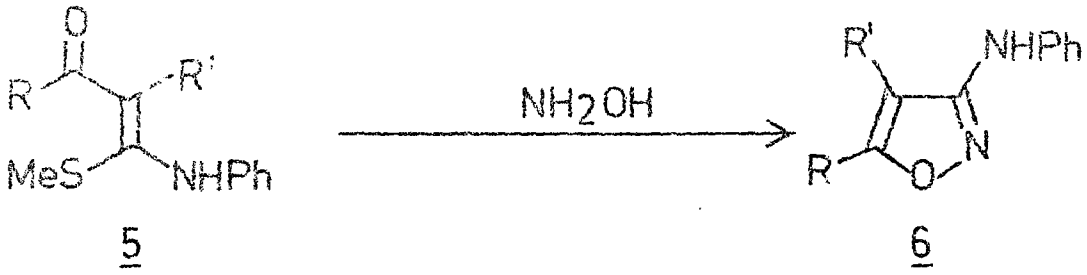
VI.2 Results

The ketoketen-S,N-acetals required for the investigation were prepared according to the general procedures described in Chapter II. Few representative examples of ketoketen-S,N-acetals derived from primary aromatic amines



1-4 , R= Ar, Me ; R'= H ; R= R' = -(CH2)n-
R''= Aryl , alkyl ; R'''= H ; R''= R''' = -(CH2)n-

Scheme 1

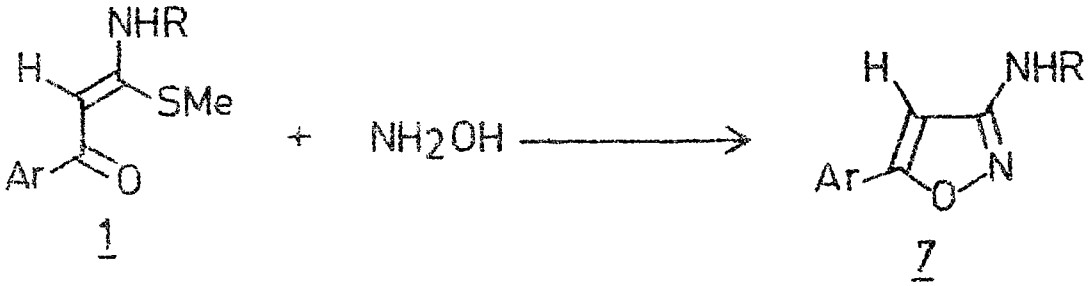


5 6

5, 6a, R = Me ; R' = MeCO
b, R = Ph ; R' = CN

Scheme 2

1a-d, aliphatic amines 1e-g, benzylamines 1h-j and cyclic secondary amines 1k-n were selected to study the generality of the reaction (Schemes 3 and 9). When a suspension of S,N-anilinoacetal 1a, hydroxylamine hydrochloride and sodium acetate was refluxed for prolonged time (20 hr), starting material 1a was recovered unchanged. However when S,N-anilinoacetal 1a was refluxed with 1.2 eqv. of free hydroxylamine (generated separately by treatment with KOH) in ethanol, work-up of the reaction mixture yielded pale white needles m.p. 143-44°; in 88% yield, which was characterized as 3-anilino-5-phenylisoxazole 7a on the basis of spectral and analytical data. Thus 7a showed molecular ion peak at m/z 236 (M^+) and it was analysed for $C_{15}H_{12}N_2O$. Its i.r. spectrum (KBr) exhibited a sharp band at 3340 cm^{-1} (ν_{NH}) and strong bands at 1600 and 1620 cm^{-1} ($\nu_{C=N}$ and δ_{NH}). Further proof for its structure was obtained from its n.m.r. spectrum ($CDCl_3$/DMSO-d_6), which showed a signal at δ 6.25 (s, 1H) due to H-4 proton, while the aromatic protons were present as broad multiplet at δ 6.70-7.85 (10H). The anilino NH-proton appeared as broad singlet at δ 8.0 (1H, exchangeable with D_2O). The isoxazole 7a has been reported earlier (reported mp 142-143° and 145-146°), which is synthesized by



1, 7a, Ar = C_6H_5 ; R = C_6H_5
b, Ar = p-MeC_6H_4 ; R = C_6H_5
c, Ar = p-$MeOC_6H_4$; R = C_6H_5
d, Ar = p-ClC_6H_4 ; R = C_6H_5
e, Ar = C_6H_5 ; R = Et
f, Ar = p-$MeOC_6H_4$; R = Et
g, Ar = p-ClC_6H_4 ; R = Et
h, Ar = C_6H_5 ; R = $C_6H_5CH_2$
i, Ar = p-ClC_6H_4 ; R = $C_6H_5CH_2$
j, Ar = p-MeC_6H_4 ; R = $C_6H_5CH_2$

Scheme 3

the routes shown in the schemes 4 and 5.[6,7] However, the authors have not reported spectral data for this compound except u.v. spectrum (reported λmax 258 and 211 nm), which is in agreement with the u.v. spectrum [λmax (MeOH) 211 (logϵ = 4.11) and 258 (logϵ = 4.09)] of 3-anilinoisoxazole prepared by us. Interestingly, the corresponding 5-anilino-3-phenylisoxazole 16 prepared by the reaction of 3-morpholinoacrylicacidthioamide 14 with hydroxylamine (Scheme 6) is also reported to have mp 145-146°.[8] However, 16 shows absorption maxima at λ max (EtOH): 256 (logϵ 4.29) and 293 nm (4.09). Besides, the 4-H proton in 16 is reported to appear at higher field at δ 4.3 (s, 1H)* (δ H-4 in 7a = 6.25) probably due to delocalization of lone pair of amino group as shown which increases electron density at 4 position in 16. Hydrolysis of 16 with mild acid is reported to yield 3-phenyl

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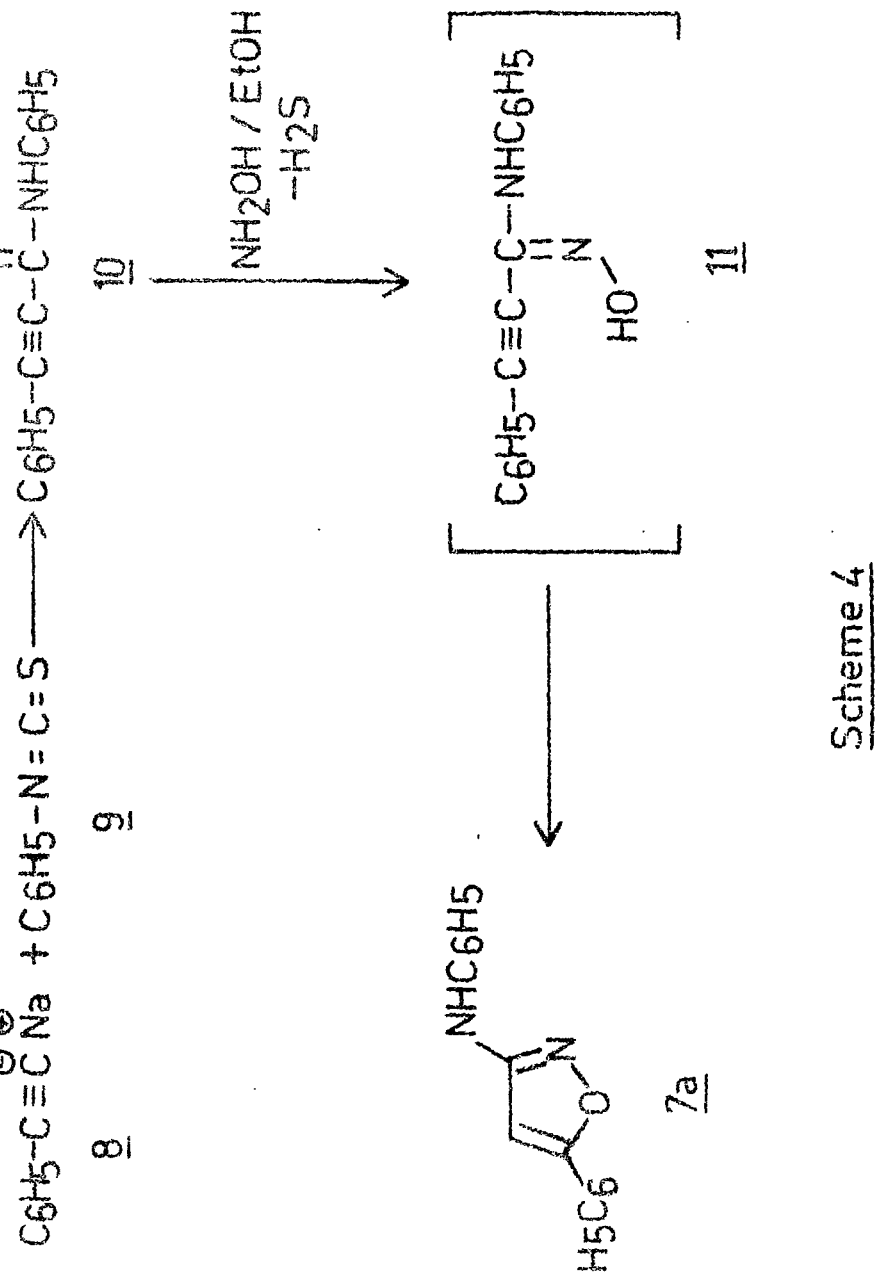
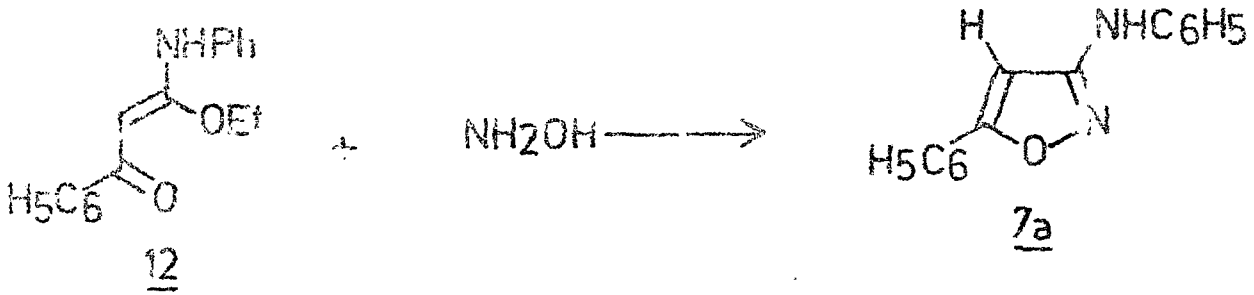
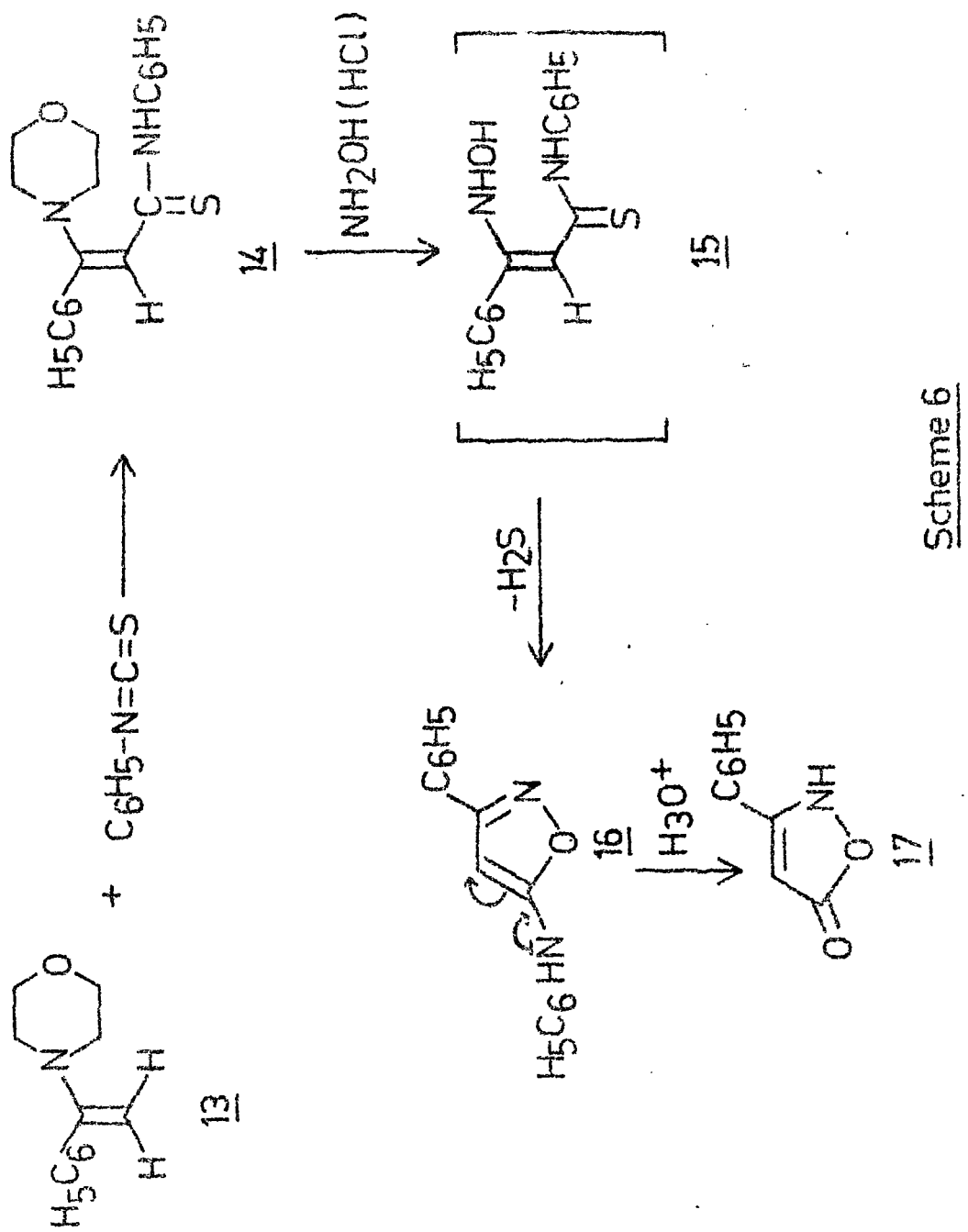
*The authors have reported two singlets at δ 4.3 (s, 1H) and δ 5.84 (s, 1H) in the n.m.r. spectrum of 16, however they have not assigned these chemical shifts to specific protons. We believe that they have got a mixture of 3- and 5-phenylisoxazoles 7a and 16 and the signal at δ 5.84 is due to H-4 proton of 3-anilinoisoxazole 7a. The band at 256 nm in u.v. spectrum of 16 is also probably corresponds to u.v. spectrum of 7a.


C6H5-C≡C⊖ Na⊕ + C6H5-N=C=S
8
9
C6H5-C≡C-C(=S)-NHC6H5
10
NH2OH / EtOH
-H2S
C6H5-C≡C-C(=N-OH)-NHC6H5
11
NHC6H5
H5C6
7a

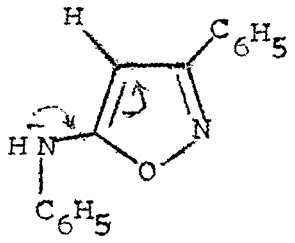
Scheme 4



Scheme 5

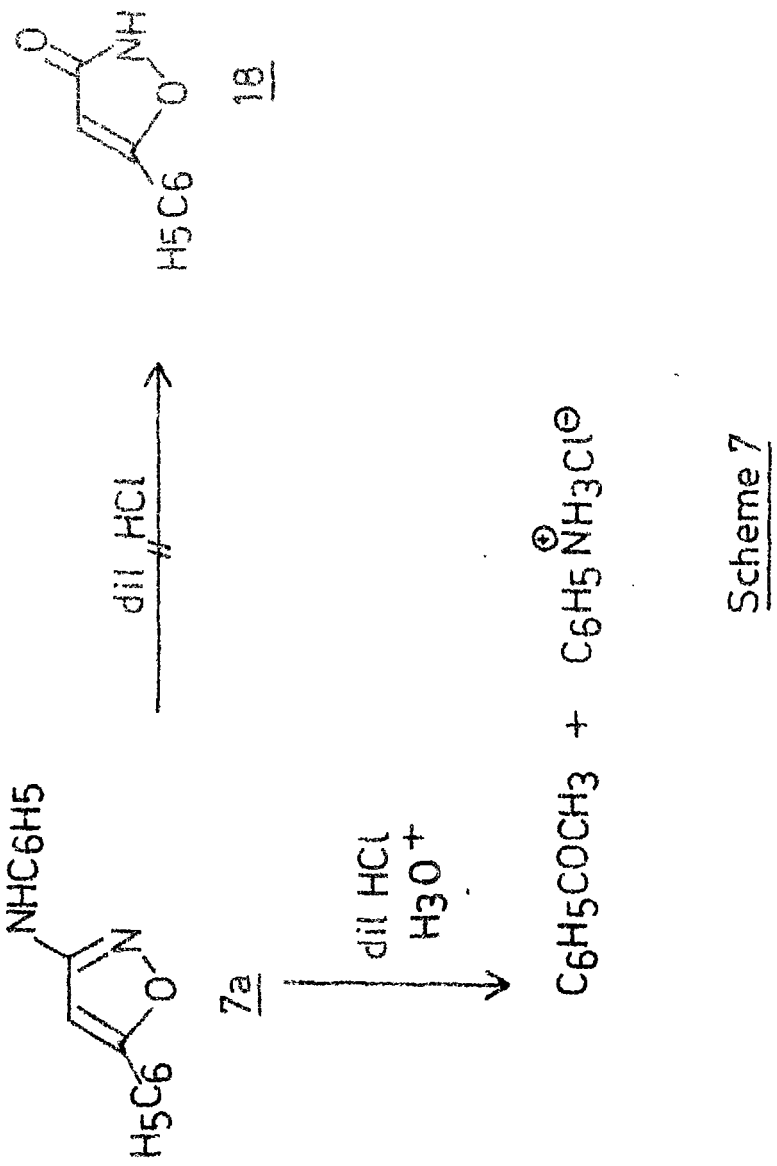


Scheme 6

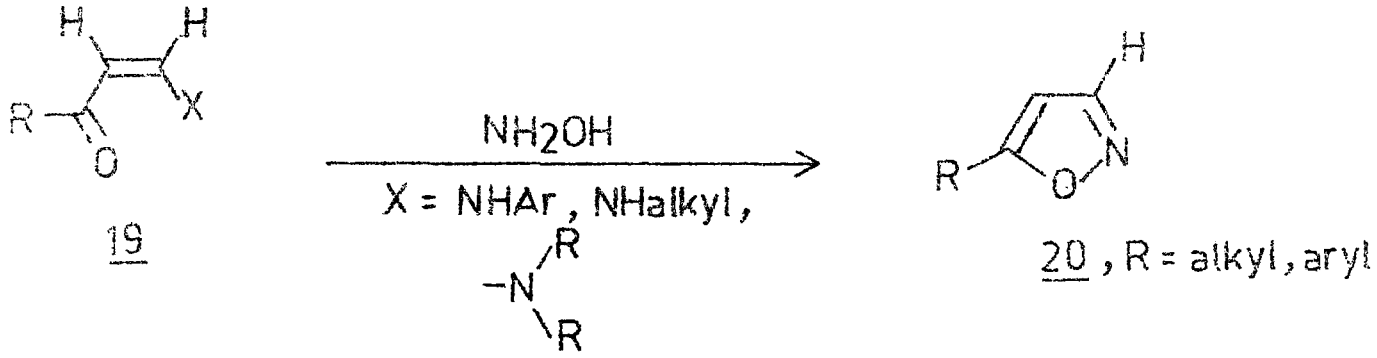


16

isoxazoline-5-one 17 (Scheme 6).[8] However our attempts to isolate 5-phenylisoxazoline-3-one 18 by mild hydrolysis of 7a were not successful and the only products isolated from the reaction mixture were characterized as acetophenone and aniline hydrochloride. The acetophenone is apparently formed by complete degradation of isoxazole 7a (Scheme 7). On the basis of these arguments, 7a is characterized as 3-anilino-5-phenylisoxazole. The structure of 7a is further supported by earlier studies on the reaction of hydroxylamine with various, β-substituted vinylketones 19 (X=Cl, OAr and NR_2) which gave exclusively 5-aryl/alkylisoxazole 20 (Scheme 8) when X is either aryl-, alkyl- or dialkylamino substituent.[9] The other anilinoacetals 1b-d similarly yielded the respective 3-anilinoisoxazoles 7b-d in 75-85% overall yields (Scheme 3). The corresponding 3-ethylaminoisoxazoles 7e-g were similarly obtained in 75-92% overall yields from the corresponding S,N-ethylacetals 1e-g (Scheme 3). When the corresponding S,N-benzylacetals 1h-j were reacted with hydroxylamine under


NHC6H5
H5C6
7a
dil HCl
H3O+
C6H5COCH3 + C6H5NH3Cl⊖
dil HCl
18
H5C6

Scheme 7

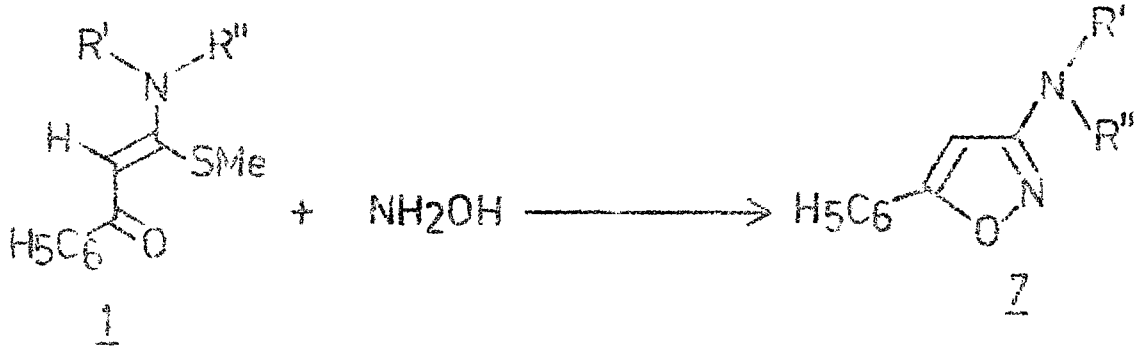


Scheme 8

identical conditions the corresponding 3-benzylaminoisoxazoles 7h-j were obtained in 56-92% overall yields (Scheme 3). Thus the reaction is found to be general for the synthesis of 3-aryl and 3-alkylaminoisoxazoles. When the reaction was extended to keten-S,N-acetals derived from cyclic secondary amines 1k-n (Scheme 9), the respective 3-pyrrolidino-(7k) 3-piperidino- (7l) 3-morpholino-(7m) and 3-(N-phenyl)piperazino-(7n) isoxazoles were obtained in excellent yields (Scheme 9). All the isoxazoles were characterized with the help of spectral and analytical data (Tables 1 and 2).

VI.3 Discussion

A facile general route for the preparation of 3-aryl/alkyl/cycloalkylaminoisoxazoles has been developed from the easily available α-ketoketen-S,N-acetals 1 under simple reaction conditions. It is pertinent to note that very few 3-substituted aminoisoxazoles are reported in the literature. The reported synthesis of few 3-anilinoisoxazoles involves the reaction of hydroxylamine with phenylpropiolthioanilides (10) (Scheme 4), which affords the corresponding 3-anilino isoxazoles in poor yields (Scheme 4).[6] The isoxazole 7a has also been obtained by reaction of benzoylketen-N,O-acetal 12



1, 7 k, R' = R'' = $-(CH_2)_4-$

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

m, R' = R'' = $-(CH_2)_2-O-(CH_2)_2-$

n, R' = R'' = $-(CH_2)_2-N(C_6H_5)-(CH_2)_2-$

Scheme 9

with hydroxylamine (Scheme 5).[7] Both methods are of limited synthetic value for liberal structural variations, since the former method requires preparation of thioanilides 10 from substituted arylacetylenes. Similarly the benzoylketen-O,N-acetal 12 is not easily accessible, besides it is not very stable under atmospheric conditions. Except these few 3-anilinoisoxazoles, no examples of 3-alkylamino and 3-N-azacycloalkylaminoisoxazoles are reported in the literature. The present method therefore provides an efficient general route for 3-substituted aminoisoxazoles, which has wide scope for liberal structural variations.

VI. 4 Experimental

M.ps. were determined on a 'Boetius' (German) apparatus and are uncorrected. The i.r. spectra were recorded on Perkin-Elmer 297 spectrometer, while the u.v. spectra were obtained on Beckmann 26 spectrophotometer. The n.m.r. spectra were recorded on Varian EM-390 spectrometer using TMS as internal standard and the values are expressed in δ (ppm).

The keten-S,N-acetals 1a-n were prepared as described in Chapter II.

General method for the preparation of 5-aryl-3-N-aryl/alky/N-azacycloalkylaminoisoxazoles (7a-n)

A solution of S,N-acetal 1a-n (0.01 mol) and hydroxylamine (generated from 0.04 mol of hydroxylamine hydrochloride and 0.04 mol of potassium hydroxide in 5 ml of water, neutral to litmus) in ethanol (25 ml) was refluxed for 3-4 hr. The mixture was poured into ice-cold water. The aqueous layer was extracted with chloroform (3x25 ml), and the chloroform layer was dried with Na_2SO_4, and evaporated to give isoxazoles 7a-n (Schemes 3 and 9), which were crystallized from ethanol. Spectral and analytical data of isoxazoles 7a-n are given in Table 1 and 2, respectively.

Acid hydrolysis of 3-anilino-5-phenylisoxazole (7a)

A solution of isoxazole 7a (2.36gm, 0.01 mol) in 50 ml of methanol and 5 ml of hydrochloric acid (12%) was refluxed for 1 hr. Reaction mixture was cooled, methanol was removed under reduced pressure, diluted with water (50 ml) and extracted with chloroform. Chloroform layer was dried (Na_2SO_4) and concentrated to give dark viscous liquid, which was further purified by column chromatography over silica gel. The viscous liquid thus obtained (0.9g, 75%) was identified as acetophenone (superimposable i.r. and n.m.r.).

Aqueous layer was basified with 4 ml of sodium hydroxide (10%), extracted with chloroform, dried (Na_2SO_4) and evaporated to give dark colored liquid, which was dissolved in ether and heated with dry HCl, a white solid, was obtained which was characterized as aniline hydrochloride (super imposable i.r.).

TABLE 1

Spectral data of products 7a-n

Product	I.R. ν_{max} (cm^{-1})[a]	^{1}H-N.M.R. δ(ppm)	M.S. m/e (M^+)
7a	3340, 1620 1600	6.25 (s, 1H, H-4); 6.7-7.85 (m, 10H, arom); 8.0 (br s, exchangeable with D_2O, NH).[c]	236
7b	3380, 1625, 1600	2.31 (s, 3H, CH_3); 6.28 (s, 1H, H-4); 6.71-7.72 (m, 9H, arom); 8.30 (br s, exchangeable with D_2O, 1H, NH).[c]	250
7c	3410, 1624, 1602	3.78 (s, 3H, OCH_3); 6.22 (s, 1H, H-4); 6.68-7.75 (m, 9H, arom and NH).[c]	-

Table 1 (Contd)

7d	3400,1625, 1600	6.30 (s, 1H, H-4); 6.75-7.82 (m, 9H, arom); 8.62 (br s, exchangeable with D_2O, 1H, NH).[c]	272, 270
7e	3265, 1625, 1600	1.22 (t, 3H, CH_3CH_2-); 3.25 (br q, 2H, CH_3CH_2); 3.98 (br s, 1H, NH); 5.86 (s, 1H, H-4); 7.15-7.48 (m, 3H, arom); 7.51-7.82 (m, 2H, arom).[b]	-
7f	3275, 1628, 1600	1.21 (t, 3H, CH_3CH_2-); 3.22 (q, 2H, CH_3CH_2-); 3.70 (s, 3H, OCH_3); 3.78 (br S, 1H, NH); 5.80 (s, 1H, H-4); 6.60-7.70 (m, A_2B_2, 4H, arom).[b]	-

Table 1 (Contd.)

7g	3280, 1628, 1600	1.21 (t, 3H, $C\underline{H}_3CH_2$); 3.25 (br q, 2H, $CH_3C\underline{H}_2$-); 3.75 (br S, 1H, N$\underline{H}$); 5.81 (s, 1H, $\underline{H}$-4); 7.21-7.73 (m, A_2B_2, 4H, arom).[b]	-
7h	3300, 1622	4.35 (br S, 3H, $C_6H_5C\underline{H}_2$ and N$\underline{H}$); 5.92 (s, 1H, $\underline{H}$-4); 7.11-7.45 (br S, 8H, arom); 7.43-7.75 (m, 2H, arom).[b]	-
7i	3320, 1630	4.30 (br S, 3H, $C_6H_5C\underline{H}_2$ and N$\underline{H}$); 5.90 (s, 1H, $\underline{H}$-4); 7.10-7.48 (m, 7H, arom); 7.50-7.71 (m, 2H, arom).[b]	-
7j	3320, 1630	2.32 (s, 3H, $C\underline{H}_3$); 4.20 (br S, 1H, N$\underline{H}$); 4.35 (br S, 2H, $C_6H_5C\underline{H}_2$); 5.91 (s, 1H, $\underline{H}$-4); 7.05-7.41 (m, 7H, arom); 7.41-7.71 (m, 2H, arom).[b]	-

Table 1 (Contd.)

7k	1630, 1610, 1595	1.77-2.22 (m, 4H, pyrrolidino); 3.18-3.51 (m, 4H, pyrrolidino); 5.95 (s, 1H, H-4); 7.21-7.48 (m, 3H, arom); 7.51-7.82 (m, 2H, arom).[b]	-
7l	1620, 1595, 1580	1.5-1.75 (m, 6H, piperidino); 3.13-3.30 (m, 4H, piperidino); 5.98 (s, 1H, H-4); 7.23-7.40 (m, 3H, arom); 7.51-7.70 (m, 2H, arom).[b]	-
7m	1625, 1595, 1550	3.18-3.41 (m, 4H, morpholino); 3.65-3.92 (m, 4H, morpholino); 6.08 (s, 1H, H-4); 7.25-7.52 (m, 3H, arom); 7.61-7.82 (m, 2H, arom).[b]	-
7n	1625, 1595, 1545	2.21-2.65 (m, 8H, piperazino); 6.18 (s, 1H, H-4); 6.95-7.48 (m, 8H, arom); 7.50-7.85 (m, 2H, arom).[b]	-

[a] in KBr; [b] in $CDCl_3$; [c] in $CDCl_3$/DMSO-D_6

TABLE 2

5-Aryl-3-N-aryl/alkyl/N-azacycloalkylaminoisoxazoles (7a-n)

Product[a]	Yield (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis (%) C	H	N
7a	88	143-44	$C_{15}H_{12}N_2O$		76.27	5.08	11.86
			(236)		76.50	5.28	11.53
7b	80	186	$C_{16}H_{14}N_2O$		76.80	5.60	11.20
			(250)		76.41	5.31	11.42
7c	75	174	$C_{16}H_{14}N_2O_2$		72.18	5.26	10.53
			(266)		72.39	5.51	10.80
7d	85	194	$C_{15}H_{11}ClN_2O$		66.54	4.07	10.35
			(270.5)		66.81	4.29	10.38
7e	75	101	$C_{11}H_{12}N_2O$		70.21	6.38	14.89
			(188)		70.32	6.47	14.71

Table 2 (Contd.)

7f	69	78-80	$C_{12}H_{14}N_2O_2$	66.06	6.42	12.84
			(218)	66.38	6.71	12.50
7g	92	141	$C_{11}H_{11}ClN_2O$	59.33	4.94	12.58
			(222.5)	59.32	4.73	12.81
7h	56	136	$C_{16}H_{14}N_2O$	76.80	5.60	11.20
			(250)	77.11	5.81	11.38
7i	86	116	$C_{16}H_{13}ClN_2O$	67.48	4.56	9.84
			(284.5)	67.77	4.82	9.75
7j	92	121	$C_{17}H_{16}N_2O$	77.27	6.06	10.61
			(264)	77.52	6.28	10.91
7k	90	95	$C_{13}H_{14}N_2O$	72.90	6.54	13.08
			(214)	73.10	6.75	12.98

Table 2 (Contd.)

7l	88	85	$C_{14}H_{16}N_2O$	73.68	7.02	12.28
			(228)	73.91	7.35	12.41
7m	87	155	$C_{13}H_{14}N_2O_2$	67.83	6.09	12.17
			(230)	67.92	6.32	12.31
7n	80	127	$C_{19}H_{19}N_3O$	74.75	6.23	13.77
			(305)	74.42	6.31	13.57

[a] crystallization solvent = ethanol.

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