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

ABSTRACT

by
AZIZUR-RAHMAN

DEPARTMENT OF CHEMISTRY
SCHOOL OF PHYSICAL SCIENCES

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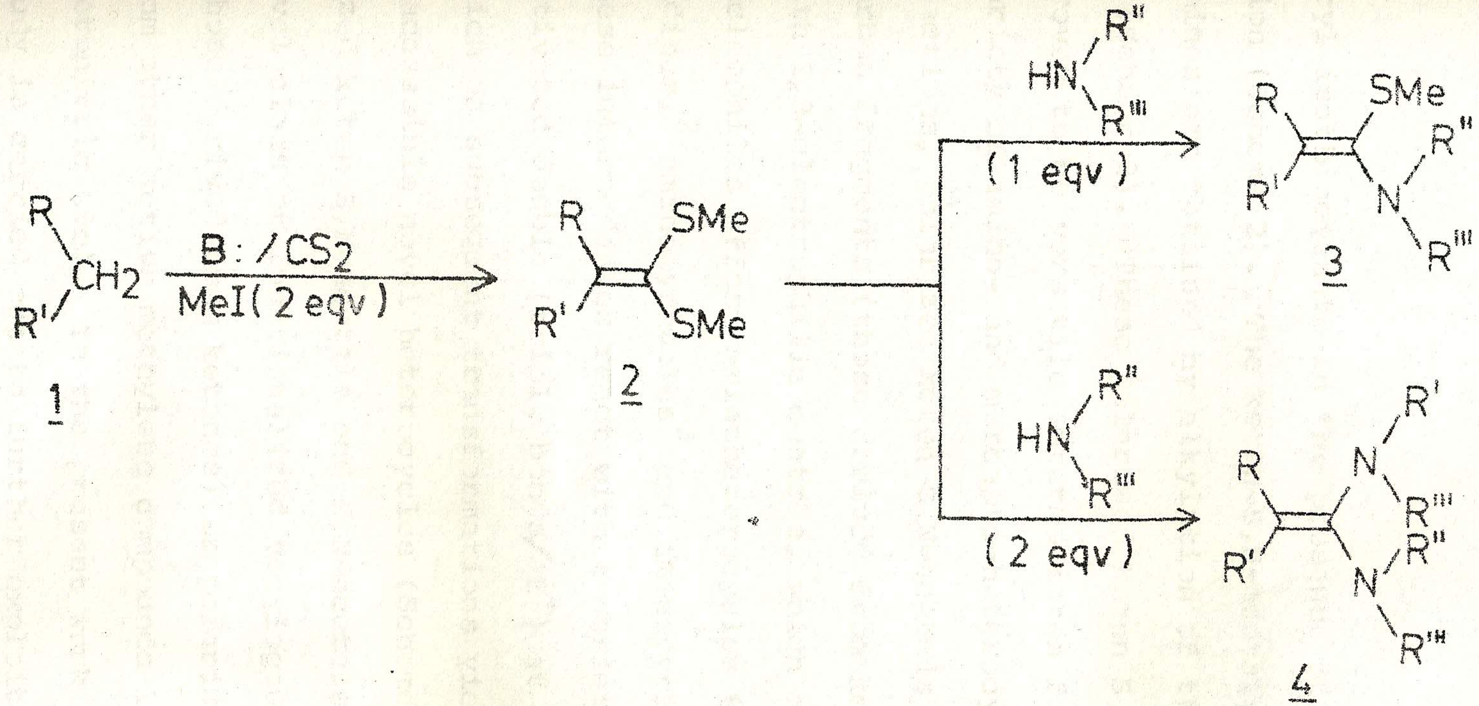
NEWER SYNTHETIC METHODS FOR NOVEL HETEROCYCLES VIA α-OXOKETEN S,N-ACETALS

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 disulfi~~e~~de 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/



<u>1</u>-<u>4</u> , R = ArCO ; AlkylCO ; CN ; CO_2Et ; $CONH_2$; NO_2 etc

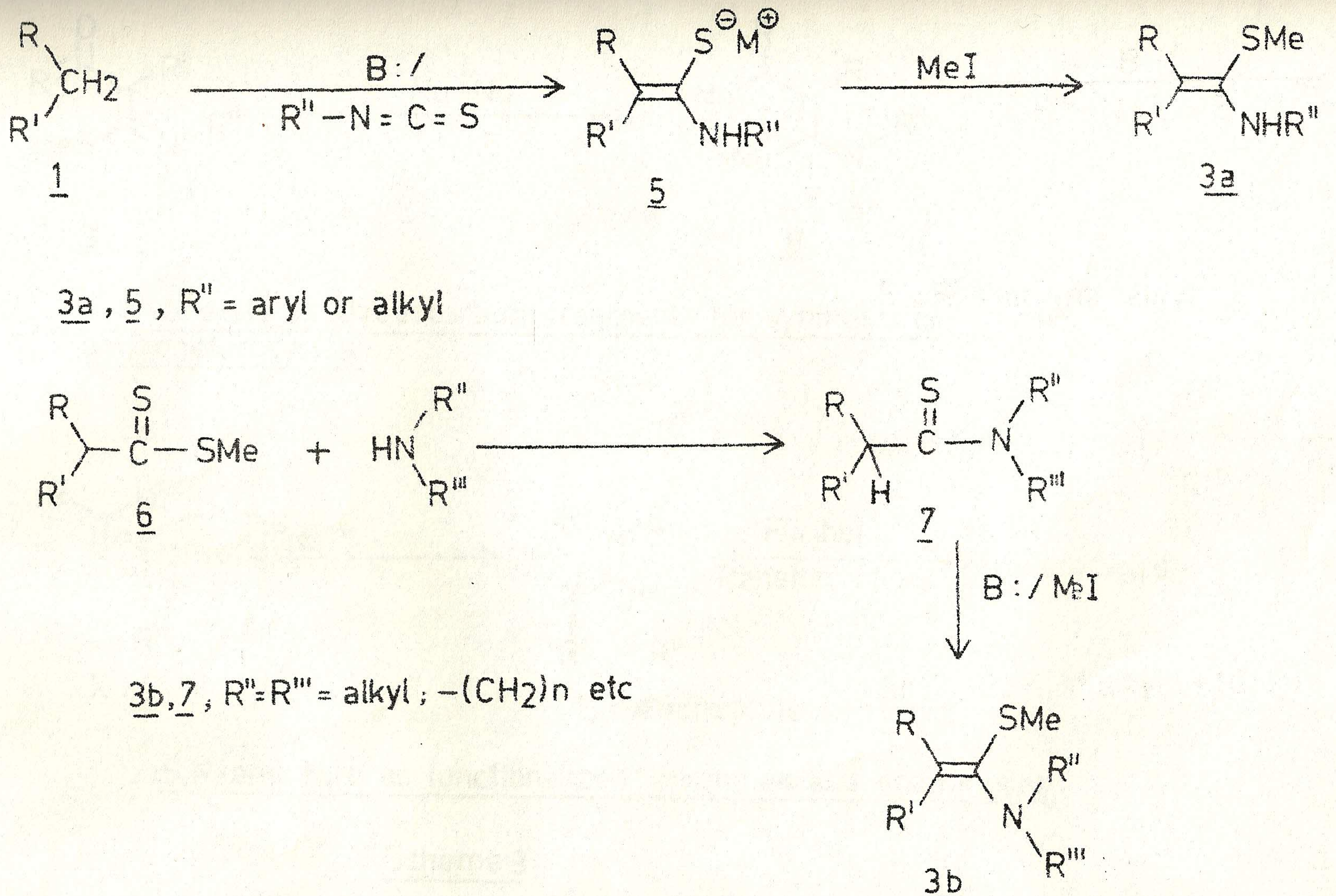
R' = H , alkyl ; aryl ; ArCO ; alkylCO ; CN ; CO_2Et ; NO_2 etc

<u>3</u>-<u>4a</u> ; R'' = aryl ; alkyl ; R''' = H (primary amines)

<u>b</u> , R'' = R''' = alkyl , – $(CH_2)_n$–etc (secondary animines)

Scheme 1

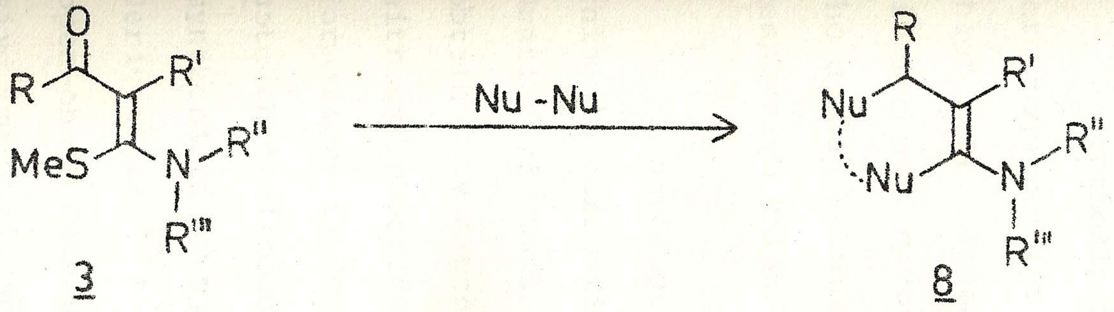
aryl isothiocyanate in the presence of base followed by alkylation (Scheme 2). The keten-S,N-acetals <u>3b</u> derived from secondary amines are obtained by alkylation of the corresponding thiomides <u>7</u> (Scheme 2). These polarized keten S,N- and N,N-acetals also proved to be versatile intermediates 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, nitrles 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 α-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.



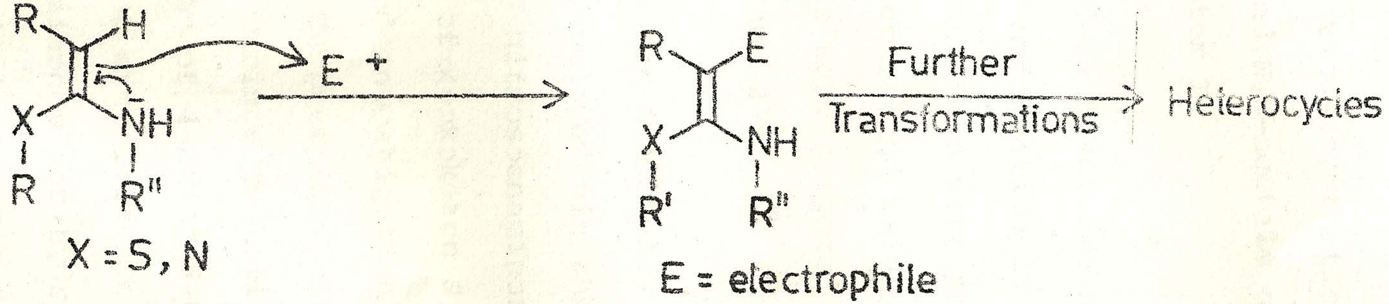
3a , 5 , R'' = aryl or alkyl

3b, 7 ; R''=R''' = alkyl ; –(CH2)n etc

Scheme 2



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 thiomides (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

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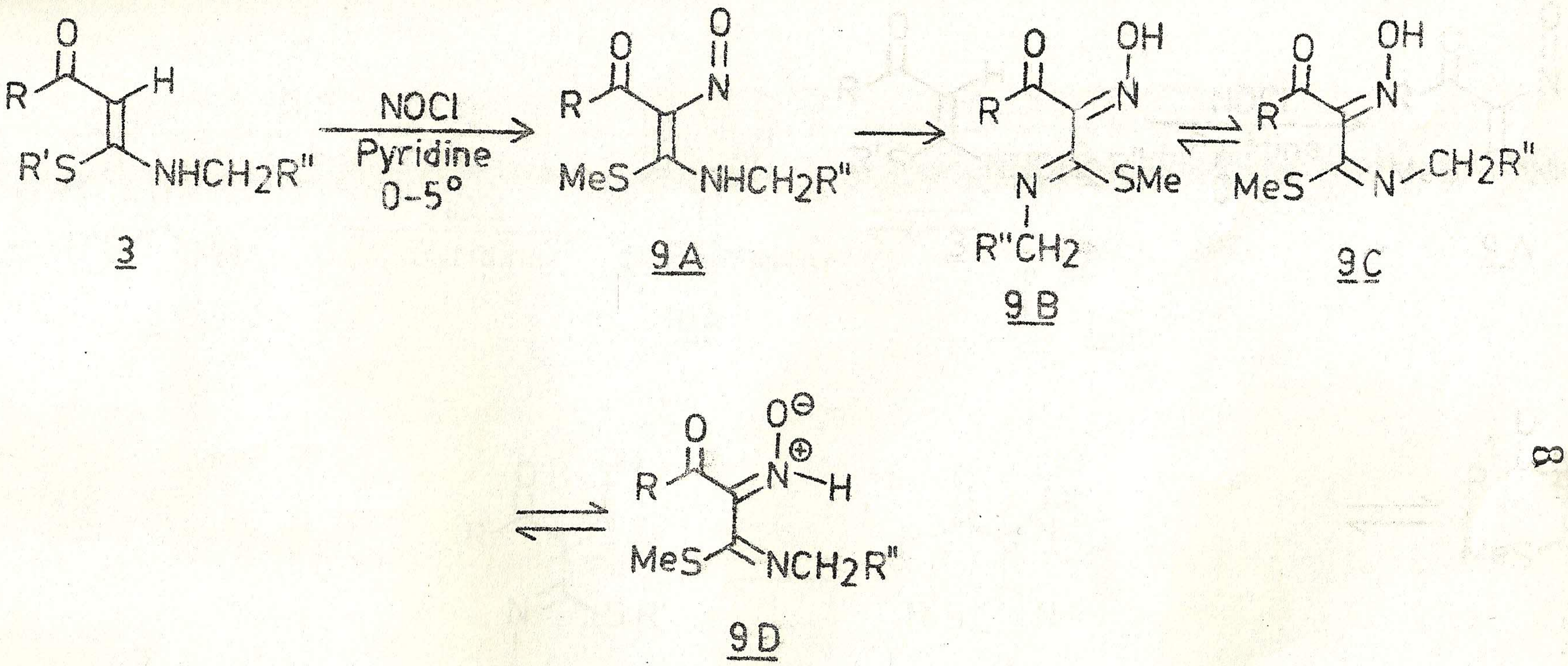
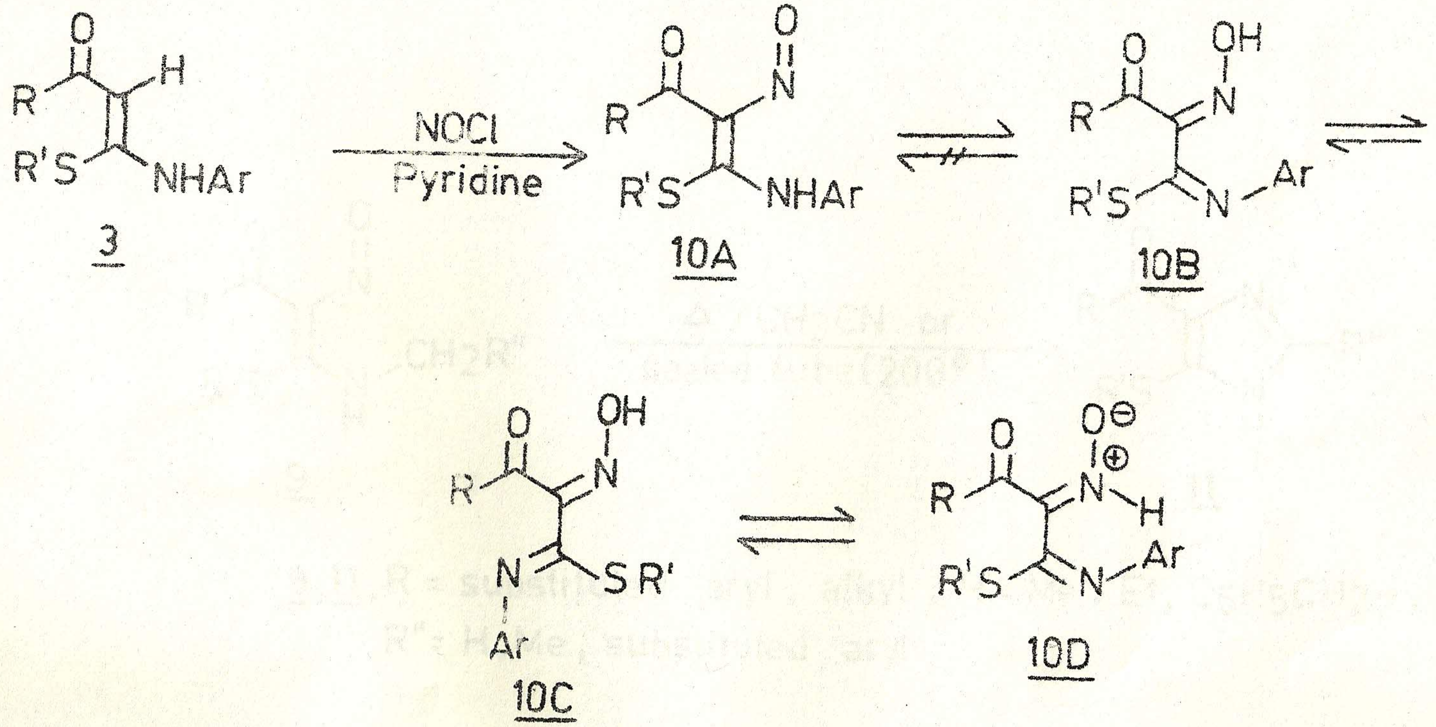
*A. Rahman, H. Ila and H. Junjappa, J.C.S. Chem. Comm., 430 (1984).

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 $\rightleftharpoons$ 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.



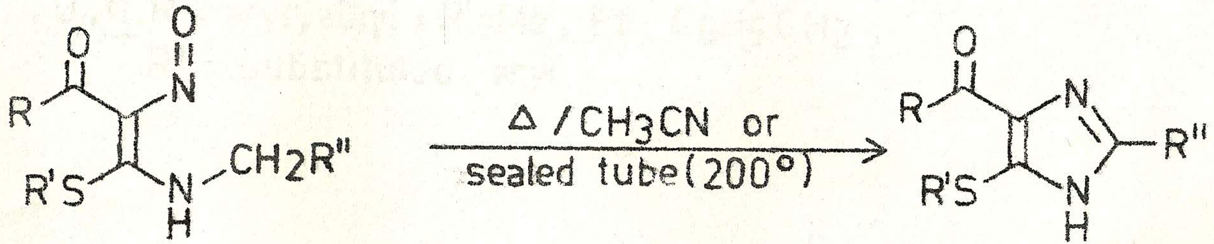
3,9,R= substituted aryl and alkyl ; R' = Me , Et, $C_6H_5CH_2$;
R" = substituted aryl , Me , Et , CO_2Et etc.

Scheme 4



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

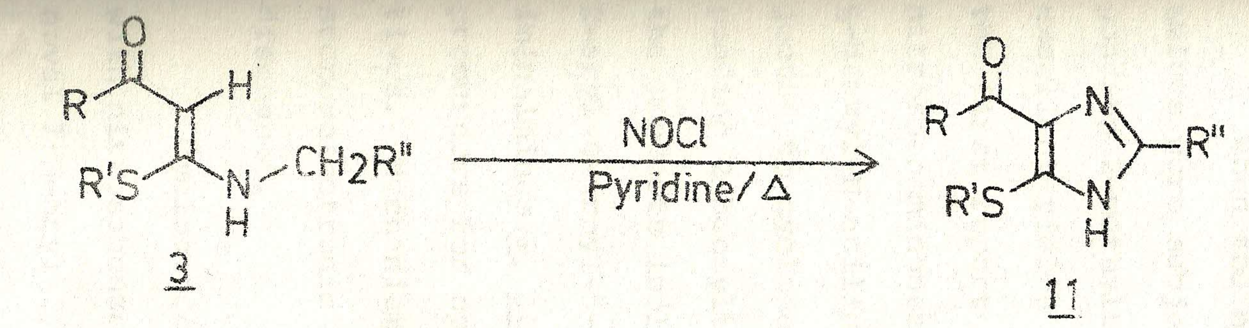
Scheme 5



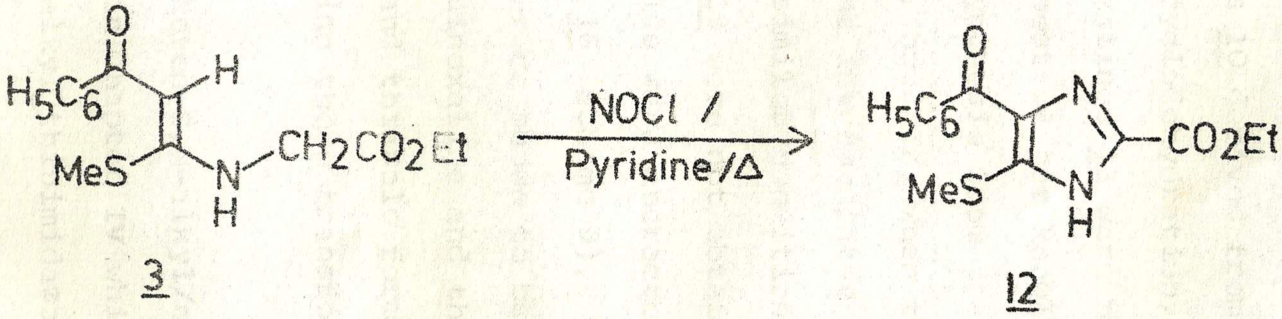
9 11

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

Scheme 6



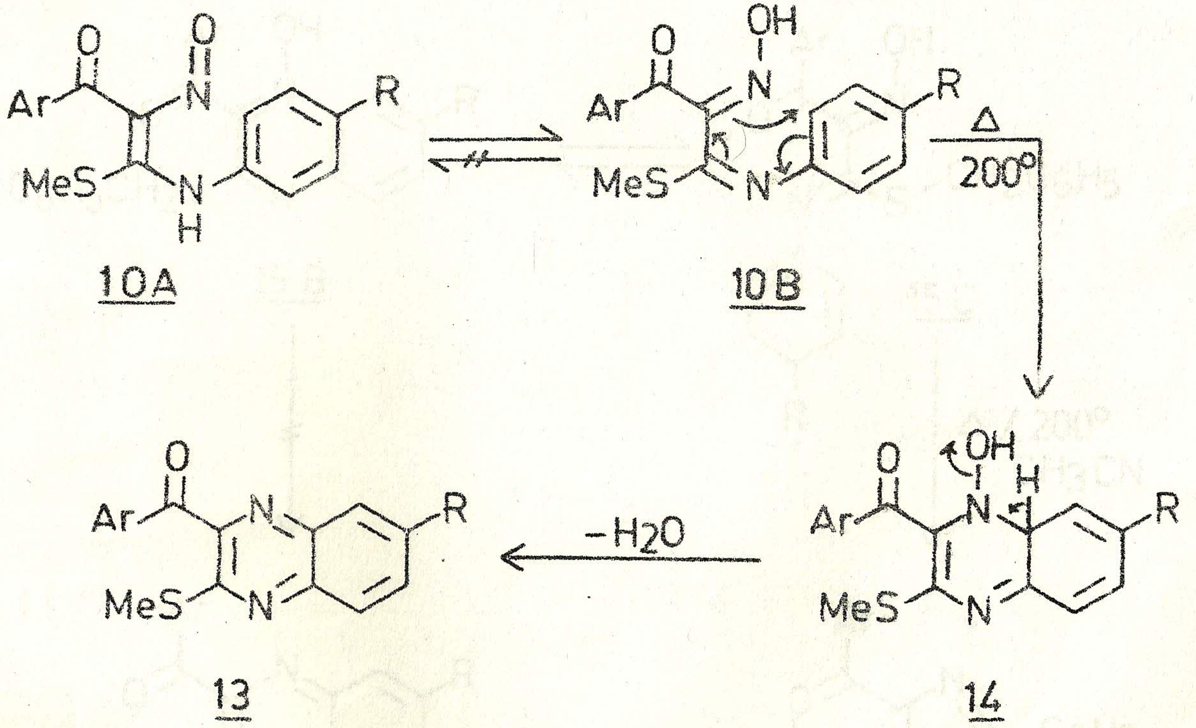
3, 11, R = aryl, alkyl ; R' = Me, Et, $C_6H_5CH_2$;
R" = substituted aryl



Scheme 7

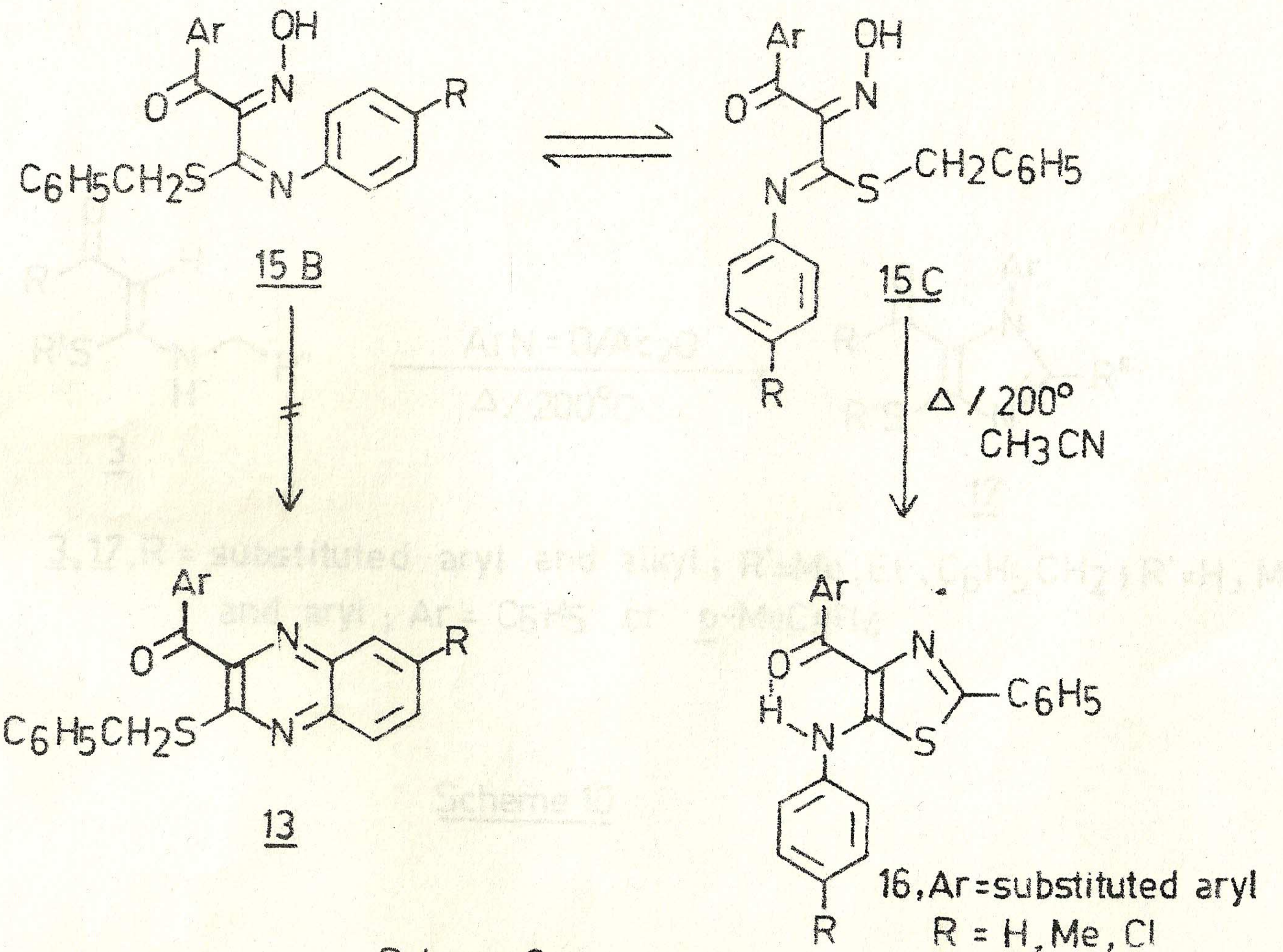
When the hydroxyiminoimines 10 derived from aromatic amines were subjected to thermal cyclodehydration, the corresponding 2-methylthio-3-aroylquinoxalines 13 were obtained in excellent yields (Scheme 8). To best of our knowledge, this is the first report of quinoxaline synthesis from open-chain nitrosoenaminones. Interestingly, however, when the corresponding S-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.

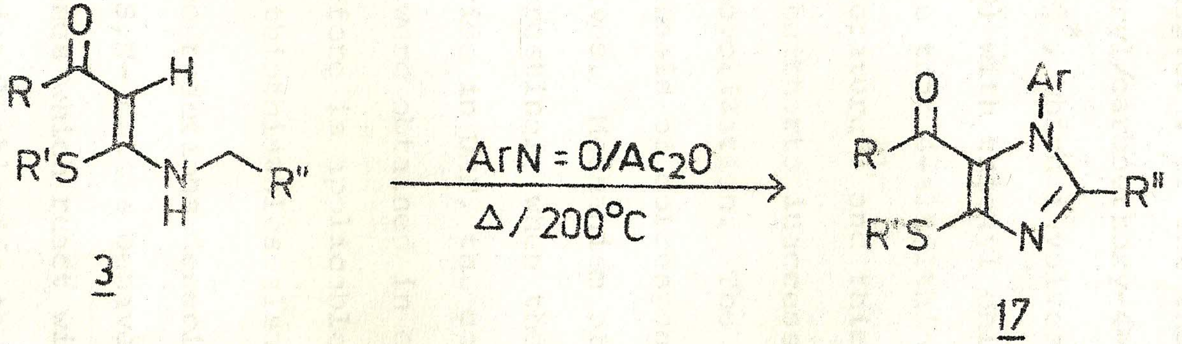


$\underline{10}$, $\underline{13}$, $\underline{14}$, Ar = substituted aryl ;
R = H , Me , MeO , Cl

Scheme 8


Ar
OH
R
C6H5CH2S
15 B
15 C
CH2C6H5
Δ / 200°
CH3CN
13
16, Ar = substituted aryl
R = H, Me, Cl
C6H5

Scheme 9



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

<u>Scheme 10</u>

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 or thionyl chloride to yield novel heterocyclic compounds after subsequent transformations. In the last

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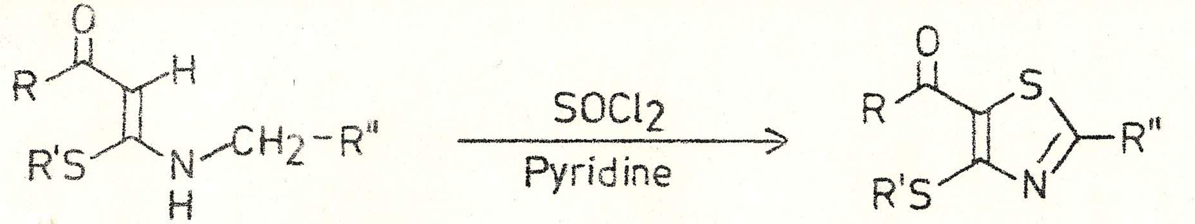
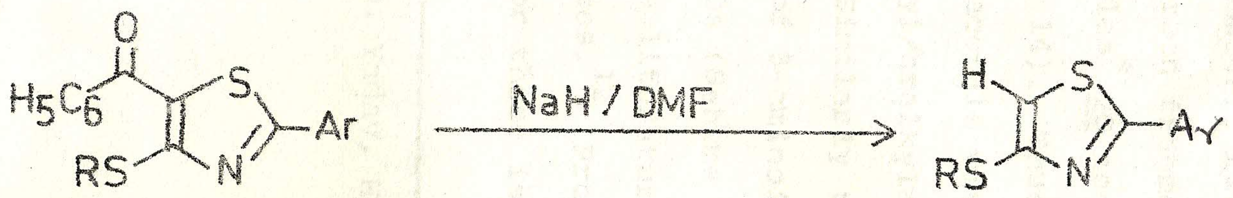
* A. Rahman, H. Ila and H. Junjappa, Synthesis, 000 (1984).



3 18

3,18 a, $R = R'' = C_6H_5$; $R' = Me$
b, $R = p\text{-}MeC_6H_4$; $R' = Me$; $R'' = C_6H_5$
c, $R = p\text{-}MeOC_6H_4$; $R' = Me$; $R'' = C_6H_5$
d, $R = p\text{-}ClC_6H_4$; $R' = Me$; $R'' = C_6H_5$
e, $R = p\text{-}MeOC_6H_4$; $R' = Me$; $R'' = p\text{-}ClC_6H_4$
f, $R = p\text{-}MeOC_6H_4$; $R' = Me$, $R'' = p\text{-}ClC_6H_4$
g, $R = p\text{-}ClC_6H_4$; $R' = Me$; $R'' = p\text{-}ClC_6H_4$
h, $R = C_6H_5$; $R' = Me$, $R'' = p\text{-}MeOC_6H_4$
i, $R = p\text{-}MeOC_6H_4$; $R' = Me$; $R'' = p\text{-}MeOC_6H_4$
j, $R = p\text{-}ClC_6H_4$; $R' = Me$; $R'' = p\text{-}MeOC_6H_4$
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, $R = p\text{-}MeOC_6H_4$; $R' = -CH_2C_6H_5$; $R'' = C_6H_5$
n, $R = Me$; $R' = Me$; $R'' = C_6H_5$

Scheme 11



18a, 2e, 2h, 2k

NaH / DMF

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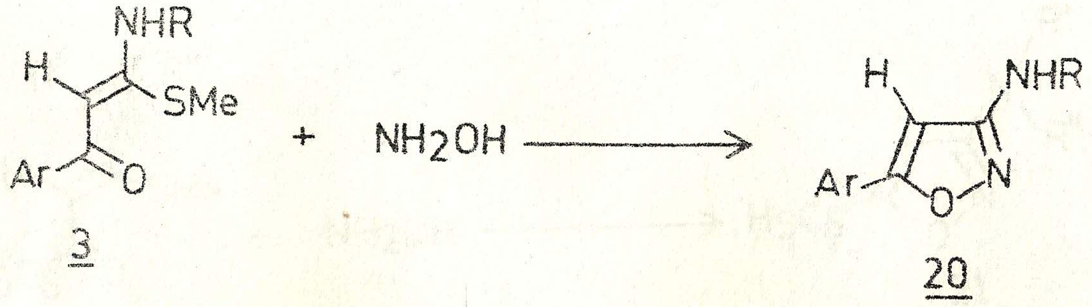
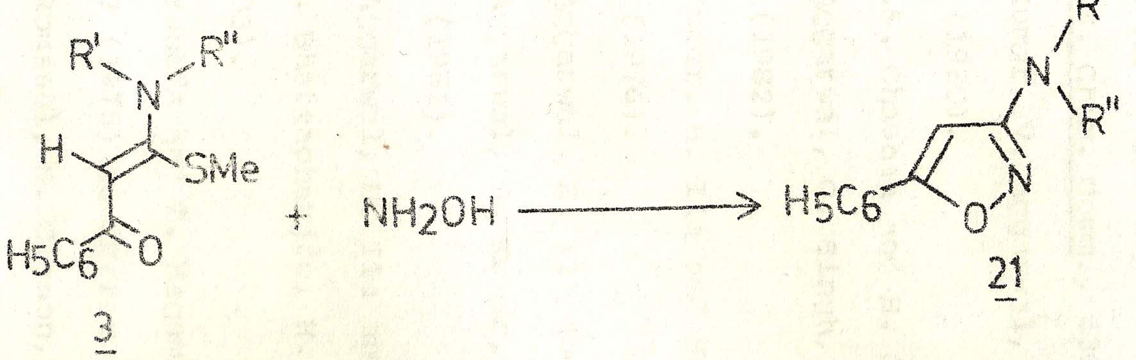
[*] A. Rahman, R.D. Yadav, H. Ila and H. Junjappa, *Synthesis*, 000 (1984).



3, 20 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



$\underline{3},\underline{21}$ $\underline{k}$, $R' = R' = -(CH_2)_4-$

$\underline{l}$, $R' = R'' = -(CH_2)_5-$

$\underline{m}$, $R' = R'' = -(CH_2)_2-O-(CH_2)_2-$

$\underline{n}$, $R' = R'' = -(CH_2)_2-\underset{C_6H_5}{\underset{|}{N}}-(CH_2)_2-$

Scheme 14

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