SYNTHETIC STUDIES ON HETEROCYCLES USING OXOKETENE - S,S-, S, N - AND O,S-ACETALS

ABSTRACT

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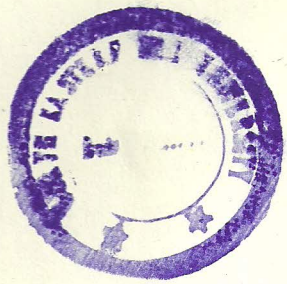

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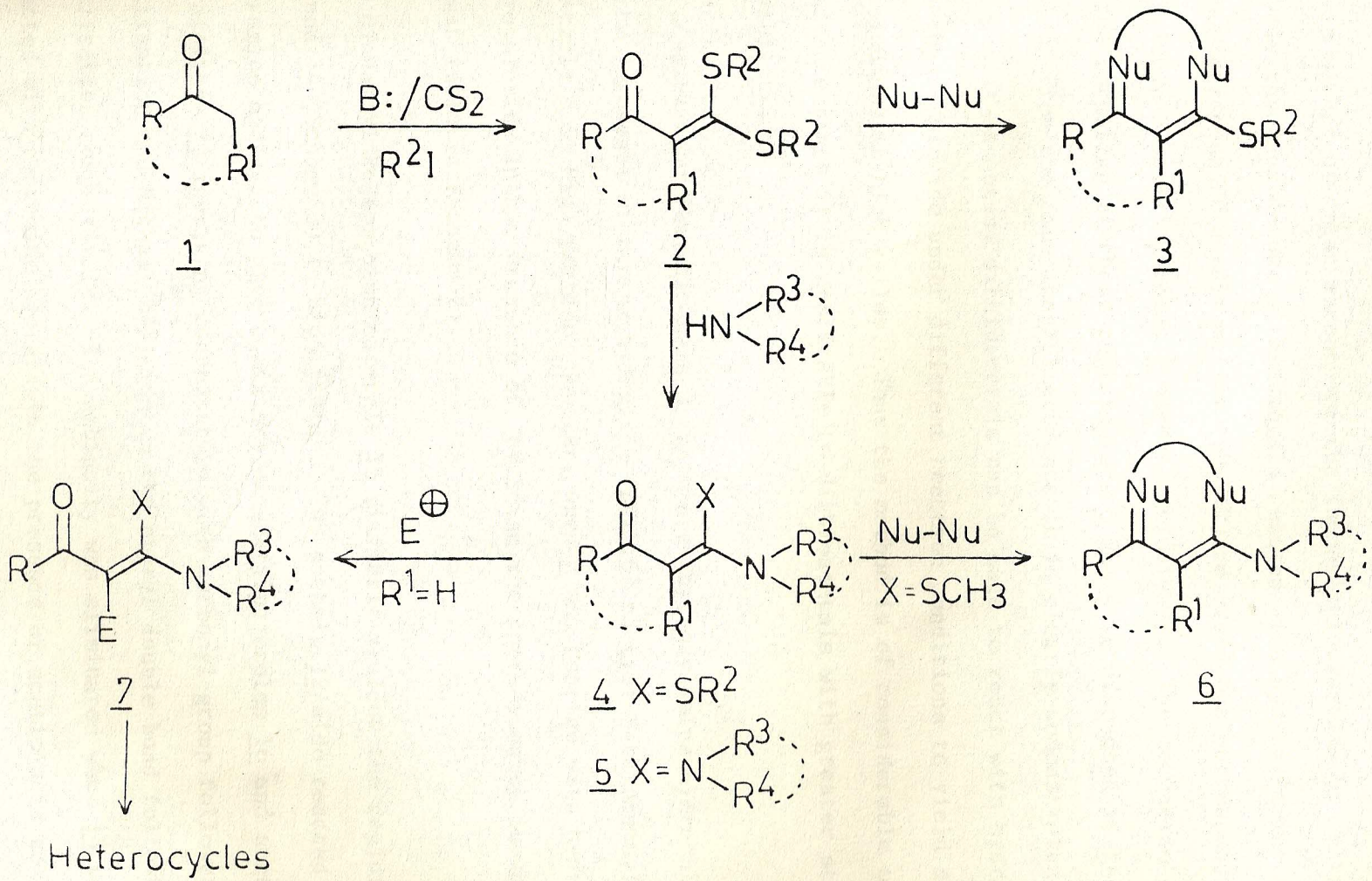
The α-oxoketene dithioacetals of general formula 2 were first reported by Kelber and co-workers[1] in 1910. Improved methods for the synthesis of these compounds have been subsequently developed[2-4], and they can now be prepared, often in one pot reaction by treating the enolate anions with carbon disulphide followed by alkylation. They can also be converted into the corresponding S,N[5], N,N[6]- and O,S-acetals[7] although there are direct methods for the synthesis of S,N-acetals from active methylene compounds[8-11]. The α-oxoketene dithioacetals posses 1,3-electrophilic centres with a discrete dissymmetry in their electrophilic property, which makes these compounds follow regiospecific attack by nucleophiles depending on their nucleophilicity. Their 1,3-electrophilic reactivity has been extensively exploited for the construction of regio-selective new C-C bonds involving either 1,2 or 1,4-nucleophilic addition leading to a diverse product range.

Similarly, the α-oxoketene S,N- and N,N-acetals exhibit 1,3-electrophilicity substantially inversed so that the β-carbon becomes more electrophilic than the oxo carbon. The nucleophilic reagents therefore preferentially add in the 1,4 fashion, in these systems.

The discriminating 1,3-electrophilicity in the α-oxoketene dithioacetals and the S,N-acetals was exploited in the present investigation as a key theme to develop novel routes for the synthesis of heterocycles. Thus, the α-oxoketene dithioacetals 2 when reacted[12] with hydroxylamine hydrochloride in the presence of sodium methoxide (pH=9) the corresponding 5-alkylthio-3-arylisoxazoles 8 were formed exclusively confirming the

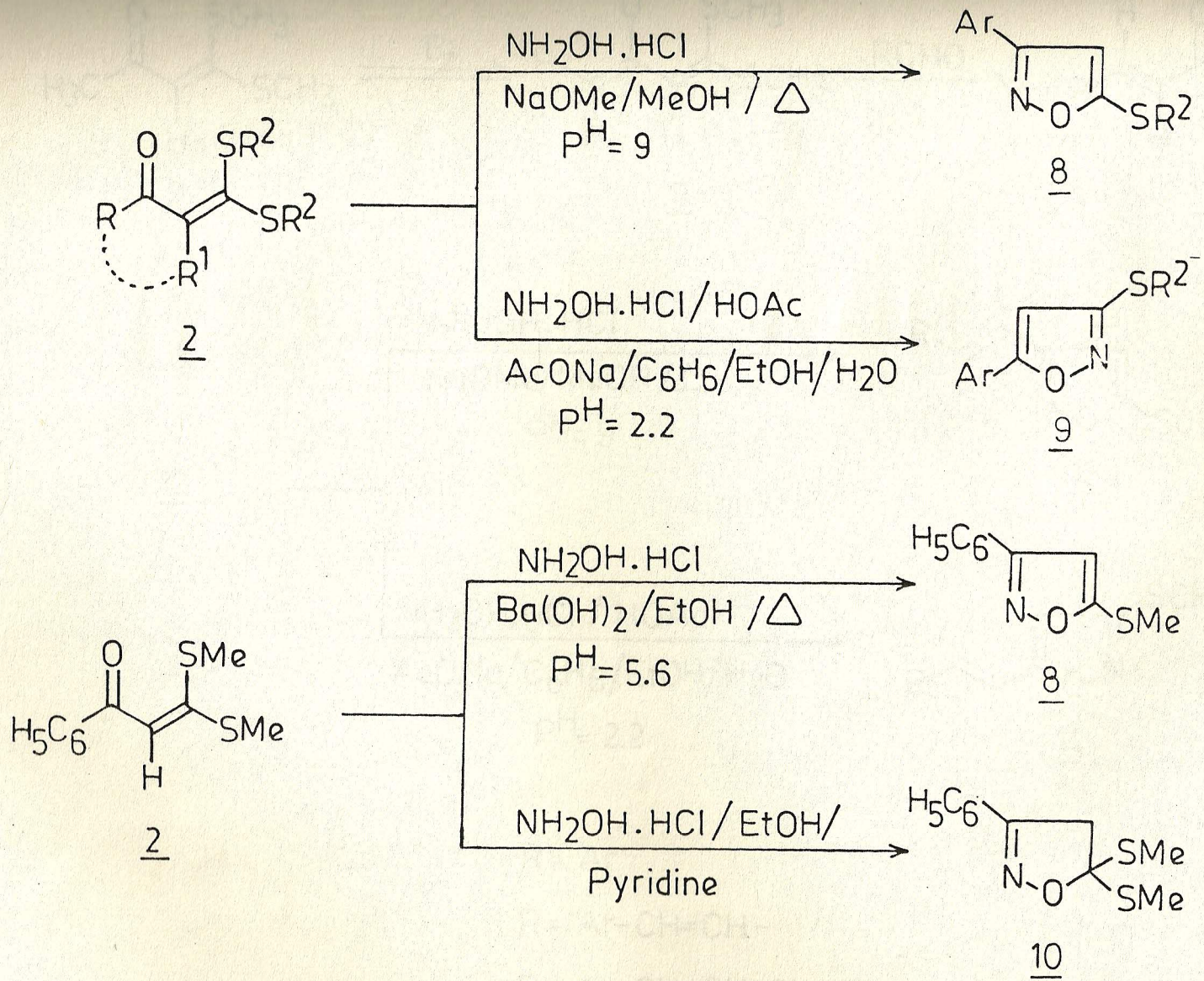

B:/CS2
R2I
Nu-Nu
HN
R3
R4
E⊕
R1=H
X=SCH3
Nu-Nu
1
2
3
4 X=SR2
5 X=N
6
7
Heterocycles

Scheme 1

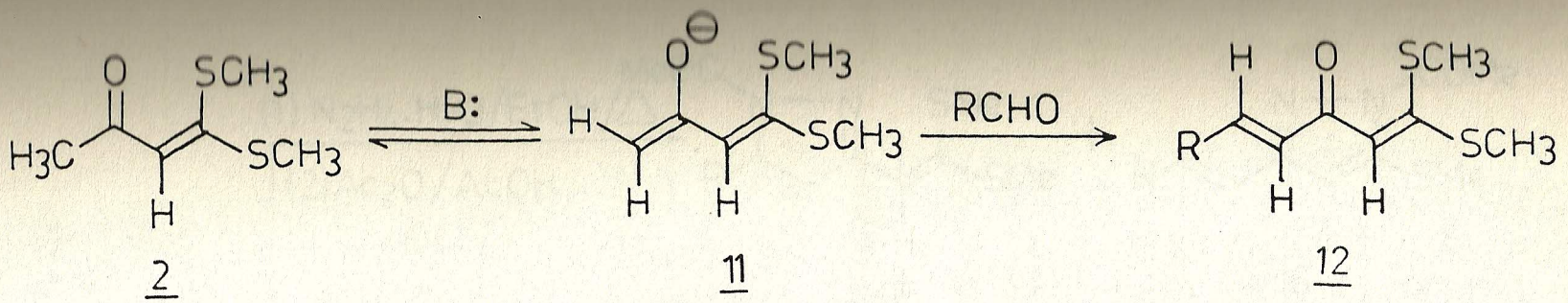
oxime formation as the first step. The high regioselectivity in this case is marked by clear absence of the isomeric isoxazoles 9. Alternatively the α-oxoketene dithioacetals reacted with hydroxylamine hydrochloride under acidic medium (pH=2.2) to yield the corresponding 3-alkylthio-5-arylisoxazoles 9 almost exclusively. The mechanism governing the formation of these regioisomers 8 and 9 is discussed in the thesis. From the experimental evidence it is clearly demonstrated that the α-oxoketene dithioacetals can be made to react with hydroxylamine hydrochloride under different reaction conditions to yield different regioisomers in high yeilds. Thus the method is of considerable synthetic importance since it is applicable to dithioacetals with greater structural flexibility.

The α-oxoketene dithioacetals 2 react with hydroxylamine hydrochloride in the presence of barium hydroxide (pH=5.6) to give 5-thiomethylisoxazole 8 in high yields. However, when 2 was reacted with hydroxylamine hydrochloride in the presence of pyridine the corresponding isoxazoline 10 was isolated (Scheme 2).

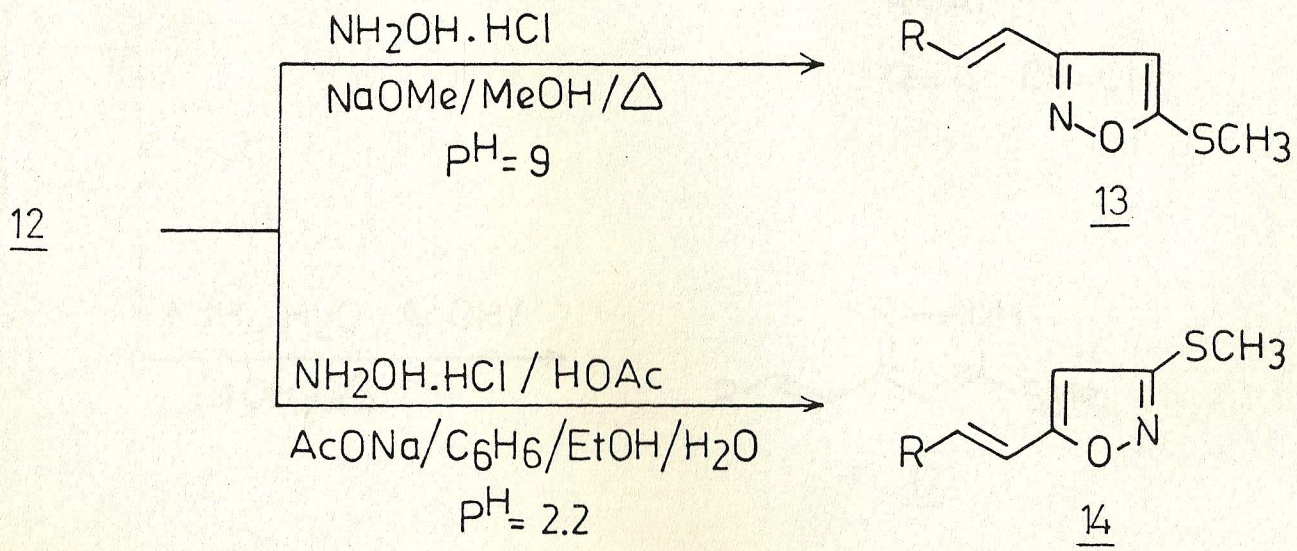
The cinnamoyl ketene dithioacetals 12 similarly yielded the regioisomers 13 and 14 (Scheme 3) in high yields. The acetals 12 also reacted with hydrazine hydrate to give a mixture of acetylpyrazoles 16 and acetylpyrazolines 15 involving condensation with carbonyl group followed by cyclisation and Michael addition on the styryl double bond followed by cyclisation respectively. The ambiguity was eliminated when 16 was reacted with hydrazine hydrate in the presence of acetic acid to yield styryl pyrazoles 17 exclusively (Scheme 4).


NH2OH.HCl
NaOMe/MeOH / △
PH= 9
NH2OH.HCl/HOAc
AcONa/C6H6/EtOH/H2O
PH= 2.2
2
8
9
NH2OH.HCl
Ba(OH)2/EtOH /△
PH= 5.6
NH2OH.HCl/EtOH/
Pyridine
2
8
10

Scheme 2



2 11 12

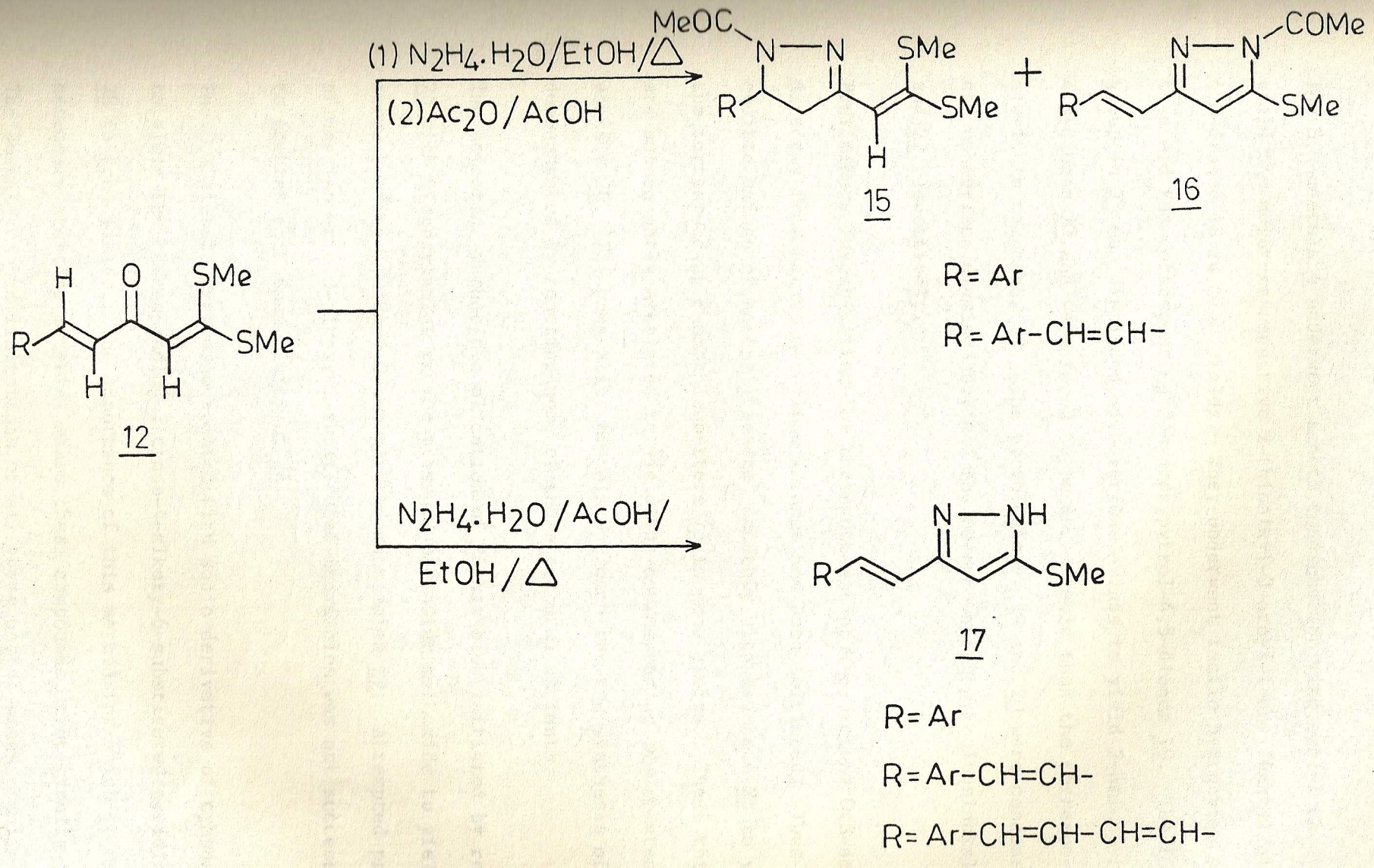


R = Ar

R = Ar-CH=CH-

R = Ar-CH=CH-CH=CH-

Scheme 3



12 15 16 17

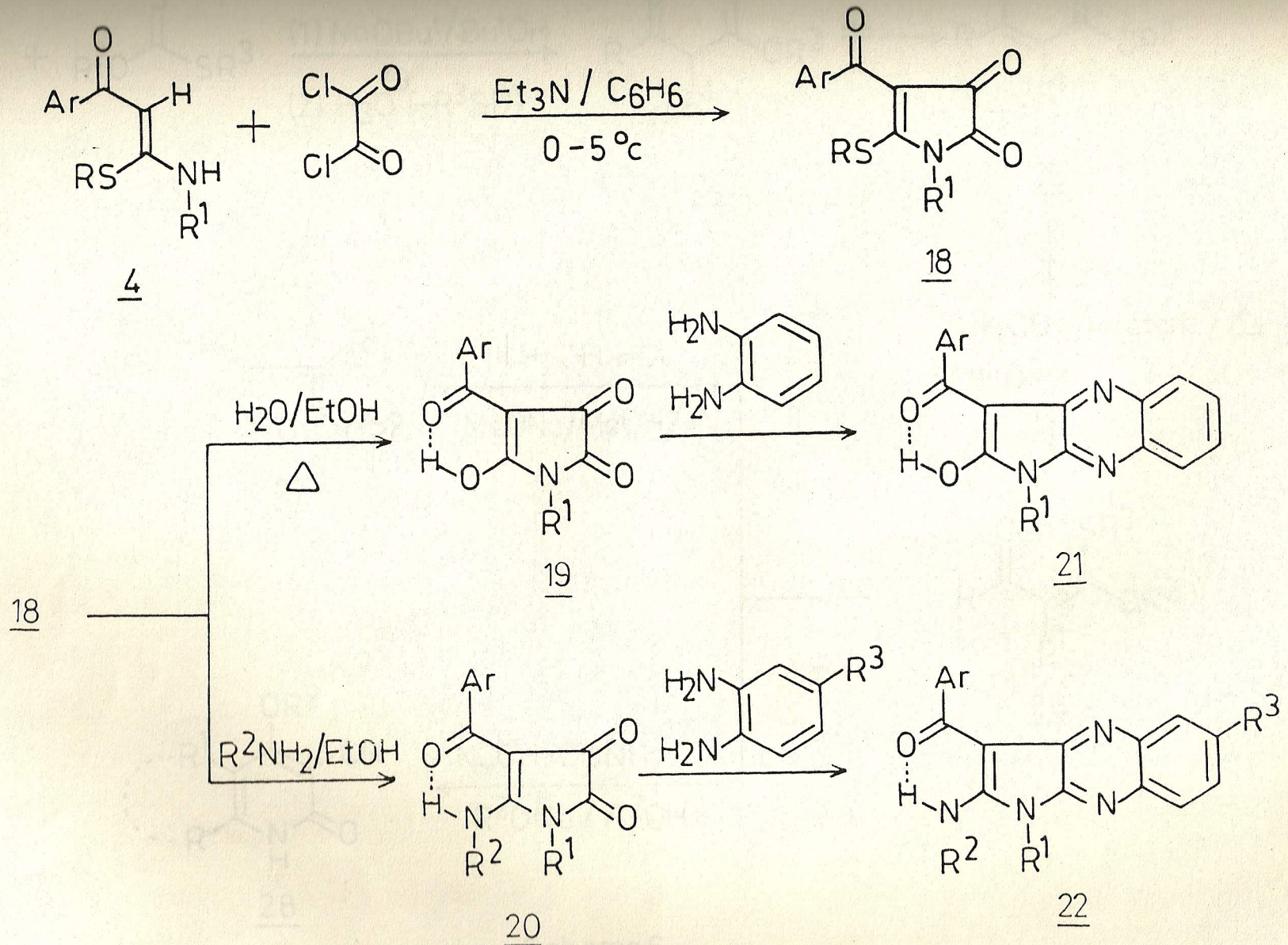
Scheme 4

The S,N-acetals 4 underwent smooth condensation with oxalyl chloride to yield the moisture sensitive 2-thioalkyl-3-aroyl-1-aryl/benzyl/alkylpyrrol-4,5-diones 18 in high yields. They underwent facile hydrolytic cleavage to yield the corresponding 2-hydroxypyrrol-4,5-diones 19. The thiomethyl group in 23 was displaced with various amines to yield 2-aminopyrrole-4,5-diones 20 and were found to be more stable than the corresponding alkylthio compounds 18. The pyrrolediones 19 and 20 were condensed with orthophenylene diamine to yield the corresponding pyrroloquinoxalines 21 and 22 respectively.

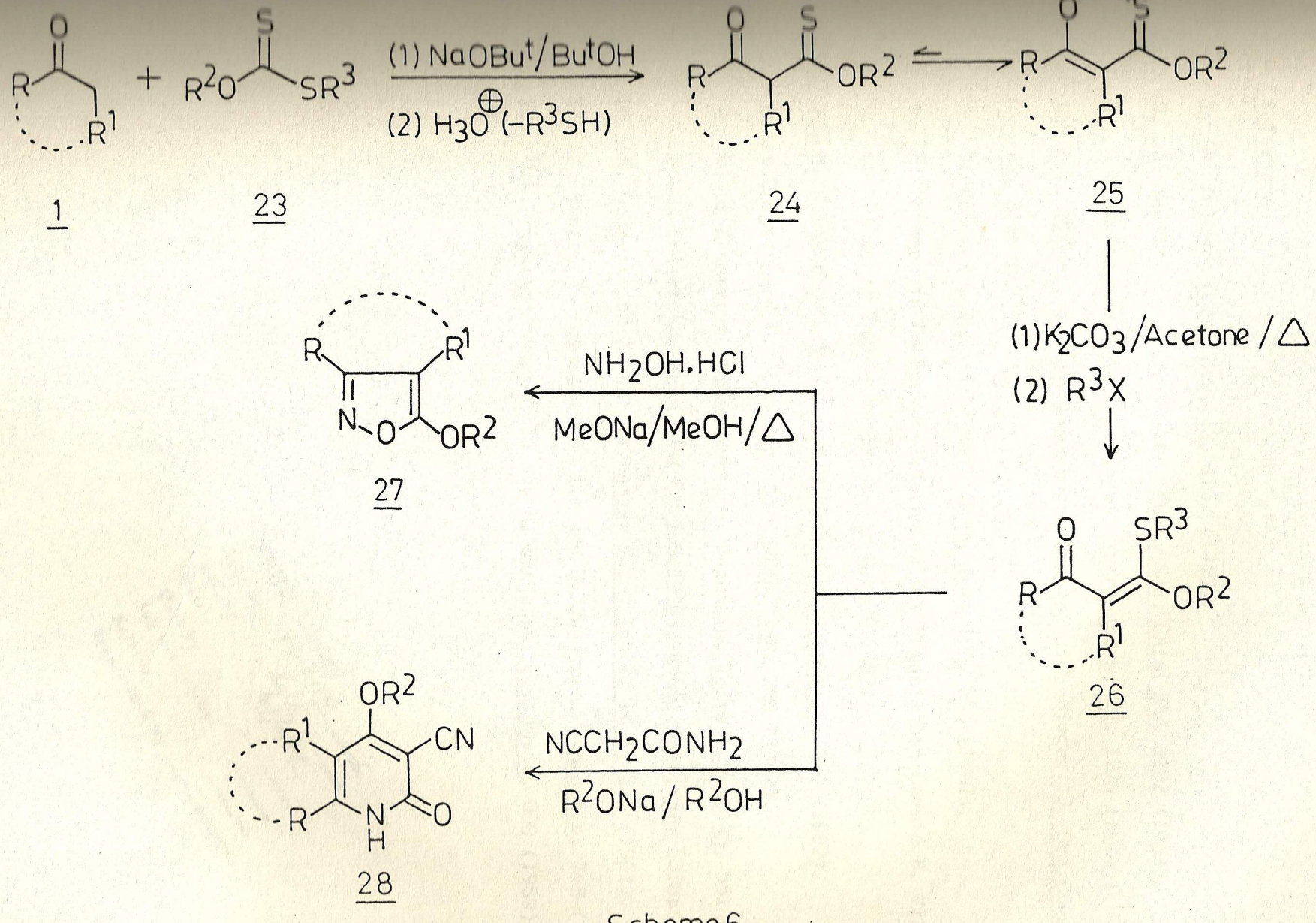
Preliminary investigation for the synthesis of α-oxoketene O,S-acetals directly from active methylene ketones has been initiated. Thus the enolate anions of ketone 1 reacted smoothly with xanthate 23 to yield the corresponding β-oxothionoesters 25 in good yields. These thionoesters are subsequently alkylated to yield the corresponding α-oxoketene O,S-acetals 26. The generality of this approach for the synthesis of 26 is demonstrated by reacting some of the structural variants.

The selected synthetic application of 26 has been initiated by reacting 26 with hydroxylamine in the presence of sodium methoxide to yield the corresponding 5-alkoxy-3-substituted isoxazoles 27. Attempted preparation of the isomeric 3-alkoxy-5-substituted isoxazoles was not successful due to greater acid sensitivity of 26.

The O,S-acetals were also reacted with sodio derivative of cyanoacetamide to yield the corresponding 3-cyano-4-alkoxy-6-substituted pyridin-1H-2(one) 28 in good yields. The importance of this method for which 26 as a necessary starting material makes these compounds strategically important. The advantages and limitations of all these useful transformations are described in the thesis.



Scheme 5



1 23 24 25 26 27 28

Scheme 6

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