NEWER SYNTHETIC METHODS FOR NOVEL HETEROCYCLES VIA OXOKETENE- S,S-, S,N- AND N,N-ACETALS

ABSTRACT

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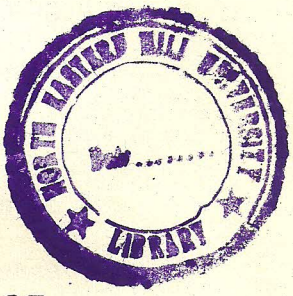

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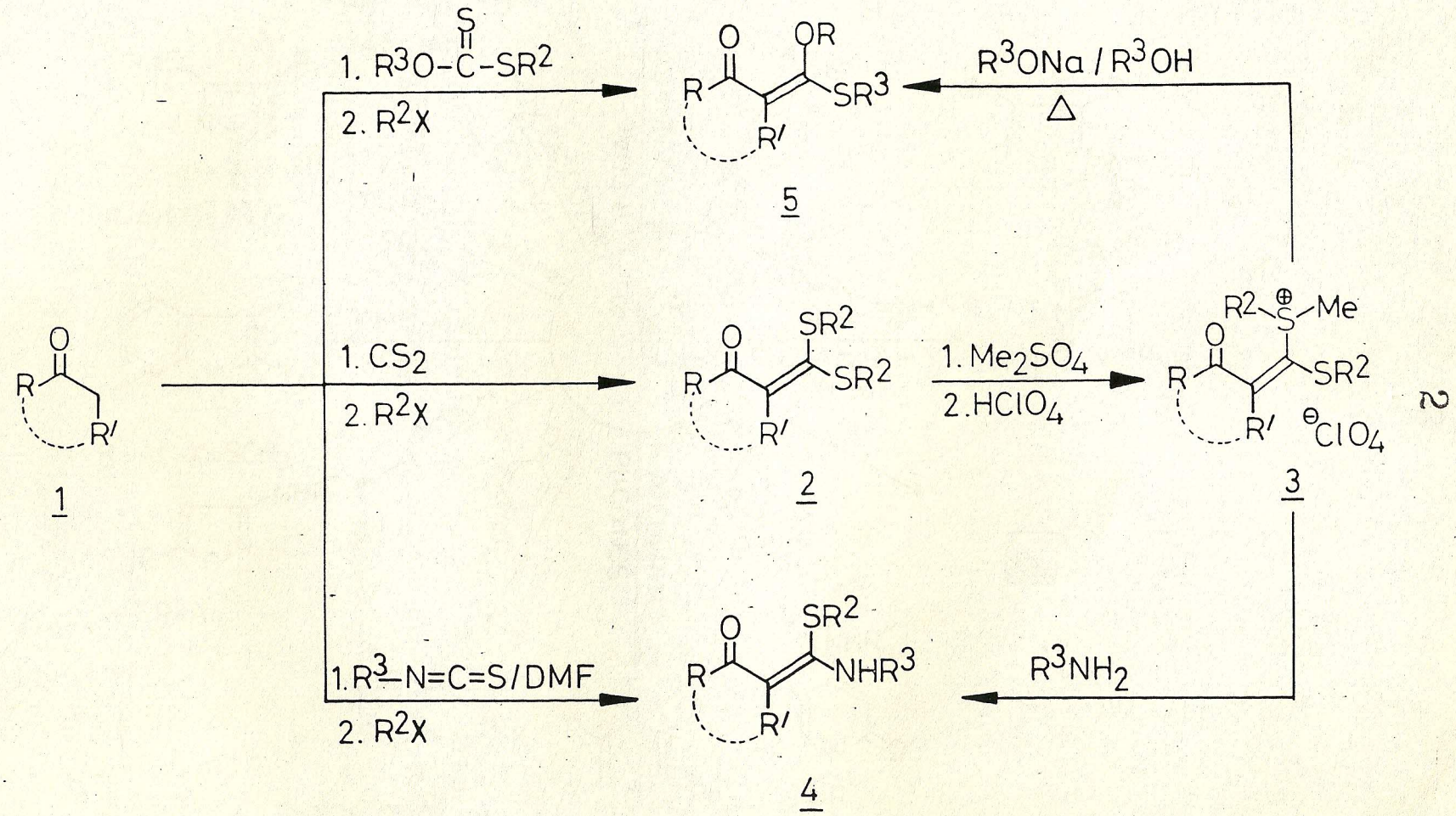
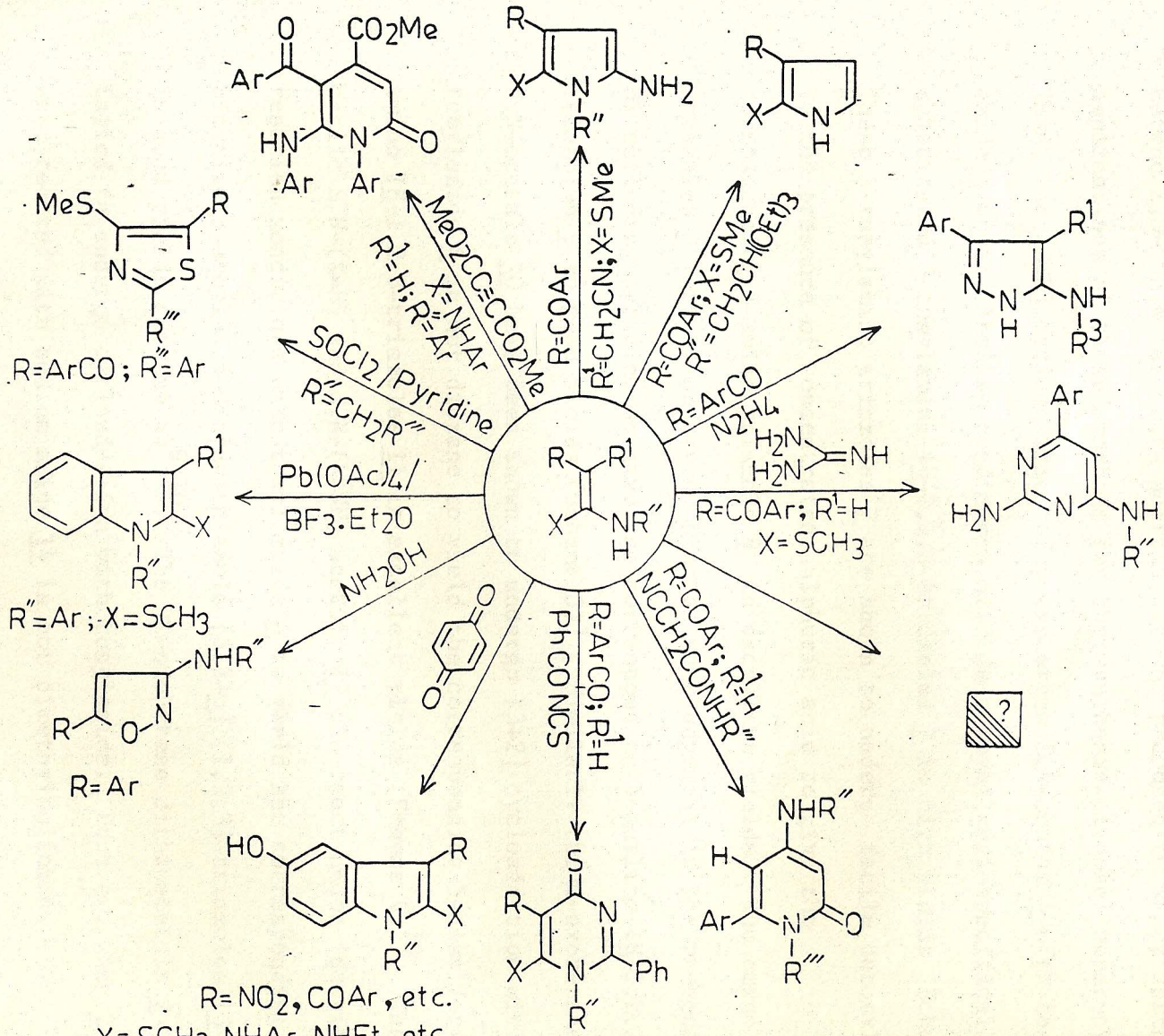
The synthesis of α-oxoketene dithioacetals of the general formula 2 were first reported in 1910 by Kelber and co-workers[1]. A number of these compounds have been subsequently prepared by reacting active methylene ketones with carbondisulphide, in the presence of suitable base followed by alkylation (Scheme 1). Many experimental variations of this method have been developed[2-4] in order to improve the yields of dithioacetals 2 evolving the overall process to a one pot transformation. It is therefore now possible to prepare large structural variants of 2 from widely occuring active methylene ketones. They can also be converted into the corresponding S,N-4[5] and O,S-5[6] acetals, although there are direct methods for the synthesis of S,N-acetals 4 from active methylene compounds 1 (Scheme 1)[7]. The α-oxoketene S,N-acetals are also shown to be useful three carbon precursors for amino heterocycles, when they are reacted with bifunctional nucleophiles[8]. Their usefulness as novel functionalized enaminones has been manifested in their reactions with several electrophilic species like activated double bands, thionyl chloride, nitrosyl chloride etc., to give a number of novel five and six membered heterocycles[8]. Some of the most important transformations achieved in this laboratory have been formulated in Scheme 2 . These methods have been shown to be general for the construction of the corresponding heterocycles with liberal structural variations. These representative transformations manifest immense synthetic potential of S,N and N,N-acetals to construct heterocycles and their further application in this area

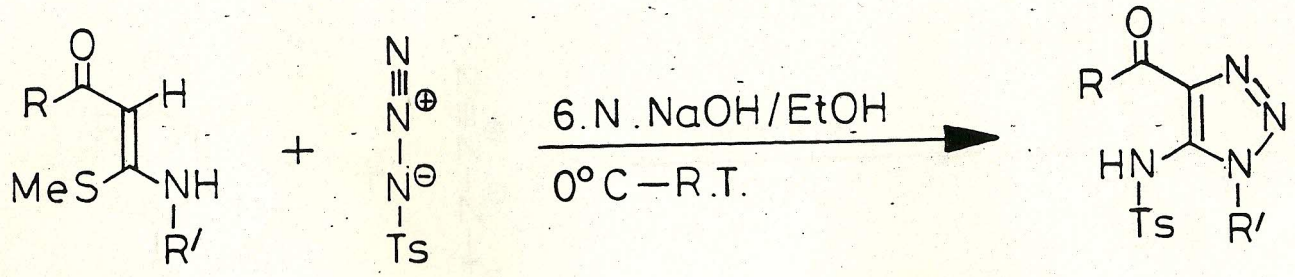

1. R3O-C(=S)-SR2
2. R2X
R3ONa / R3OH
Δ
1. CS2
2. R2X
1. Me2SO4
2. HClO4
1. R3-N=C=S / DMF
2. R2X
R3NH2
1
2
3
4
5

Scheme 1

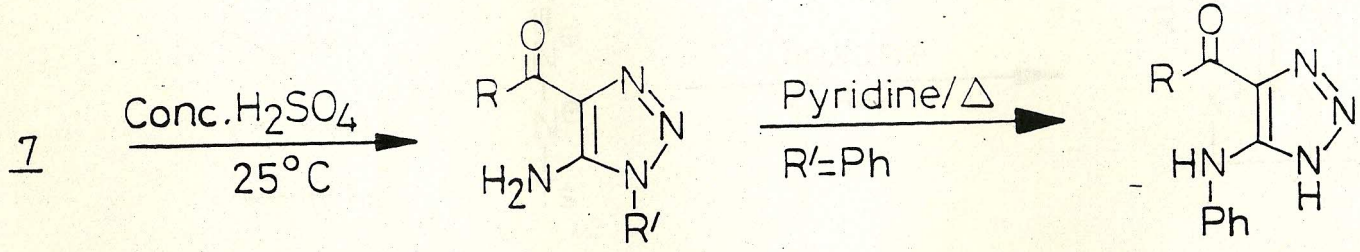

R=ArCO ; R''=Ar
R''=Ar ; X=SCH3
R=Ar
R=NO2, COAr, etc.
X=SCH3, NHAr, NHEt etc.
MeO2CC=CCO2Me
X=NHAr
R1=H; R''=Ar
SOCl2/Pyridine
R''=CH2R'''
Pb(OAc)4/
BF3.Et2O
NH2OH
R=COAr
R1=CH2CN; X=SMe
PhCONCS
R=ArCO; R1=H
R=COAr; X=SMe
R''=CH2CH(OEt)3
R=ArCO
N2H4
R=COAr; R1=H
X=SCH3
R=COAr; R1=H
NCCH2CONHR'''
?

Scheme 2

is still an ongoing research activity in this laboratory. In continuation of these studies and as a part of the research on polarized ketene S,S-, S,N- and N,N- acetals, it was proposed to study further applications of these synthons for the synthesis of novel heterocycles. Thus, the [3+2] cycloaddition of α-oxoketene S,N-acetal 4 with tosyl azide 6 under alkaline conditions affords a novel regiospecifically substituted 5-tosylamino 1H-1,2,3-triazoles 7 in high yields (Scheme 3)[9]. These 5-tosylamino triazoles 7 are shown to undergo facile detosylation in the presence of concentrated sulphuric acid to give the corresponding 5-amino triazole 8 in excellent yields. The amino triazoles 8 further underwent Dimroth rearrangement in the presence of refluxing pyridine to give the corresponding 5-anilino-1H-1,2,3-triazoles 9 in good yields (Scheme 3)[9]. Similarly the α-oxoketene N,N-acetals 10 have been shown to undergo [3+2] cycloaddition with tosylazide 6 in hot dioxane to yield the corresponding 5-alkyl/aryl-amino 1H-1,2,3-triazoles 11 in excellent yields (Scheme 4)[10]. The cyclic S,N-(X=S) and N,N-(X=NH) acetals 12 did react under identical reaction conditions with tosyl azide 6 to yield the corresponding bicyclic 3-aroyl-5,6-dihydrothiazolo [3,2-c] [1,2,3]-triazoles 13 in good yields (Scheme 4)[9,10]. The α-oxoketene dithioacetals 2 failed to undergo cycloaddition with tosylazide. However, when 2 were reacted with sodium azide 14 in hot dimethylsulfoxide the corresponding 5-methylthio-1H-1,2,3-triazoles 15 were obtained in good yields (Scheme 5)[11]. It is apparent that the method for the synthesis of triazoles is highly versatile, since a large number

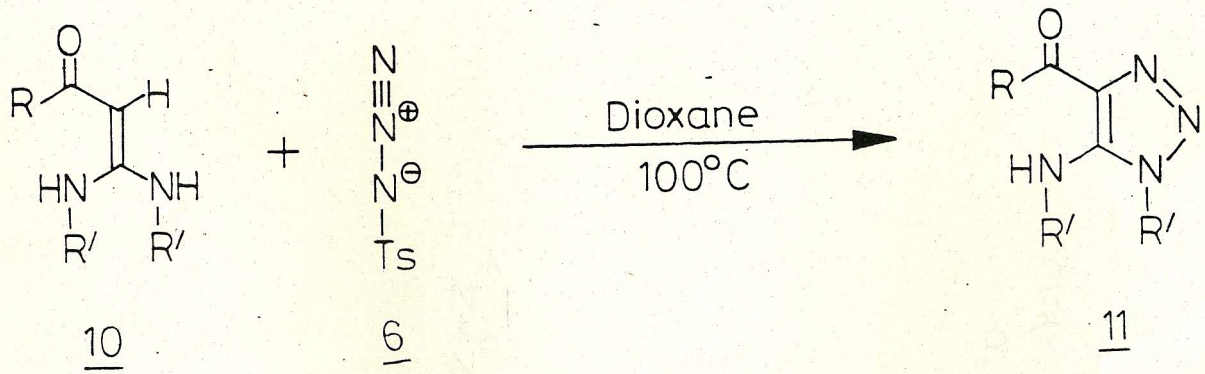


4 6 7

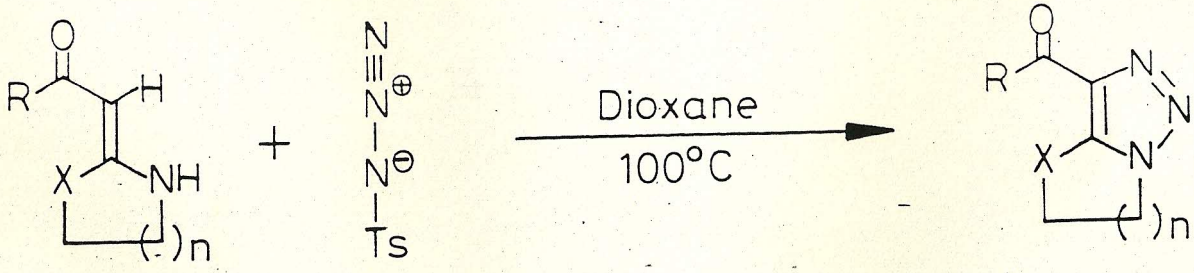


8 9

Scheme 3

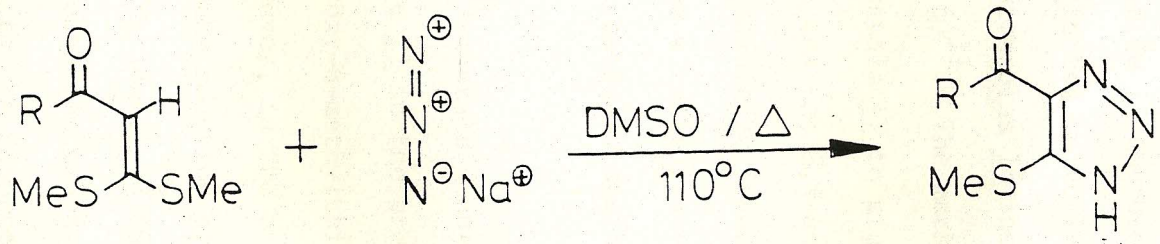


10 6 11



12 6 13

Scheme 4



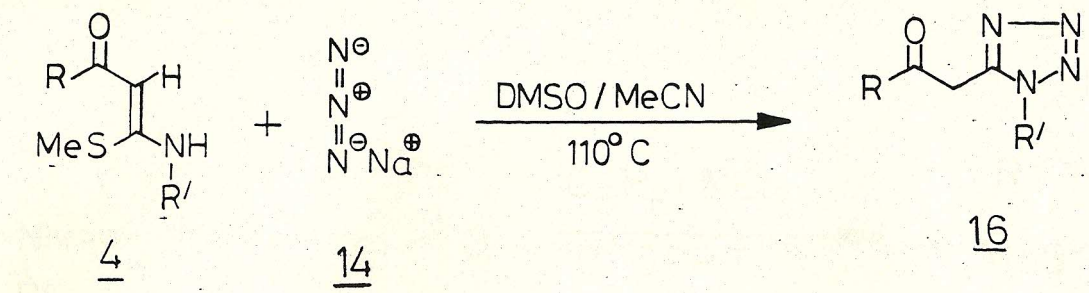
2 14 15

Scheme 5

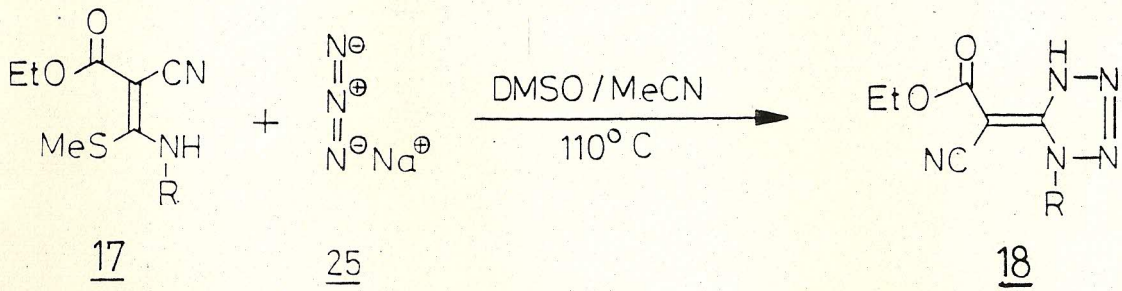
of active methylene ketones can play as primary precursors through the corresponding S,N-acetals. Interestingly, the S,N-acetals 4 did react with sodiumazide 14 through different pathway involving cyclization of initially formed imidoylazide intermediates to give a novel 1,5-substituted tetrazoles 16 instead of the corresponding 5-amino triazoles (Scheme 6)[11]. The method has been extended to many structural variants of S,N-acetals 17 to study the reactivity towards sodiumazide 14. The exception was the S,N-acetal 19 derived from malononitrile, which gave the tetrazole 20 formed by cycloaddition of the azide ion with one of the nitrile groups (Scheme 6)[11]. The scope and limitations of the tetazole synthesis have been critically discussed in Chapter II.

The α-oxoketene S,N-acetals 4 have been reacted with one equivalent of malonyl chloride 21 in the presence of a base to give novel 1,5-substituted 4-hydroxy-6-methylthio-2(1H) pyridones 22 in good yields (Scheme 7)[12]. However, in the presence of excess of malonyl chloride 21 (3 equivalent) the reaction proceeds further to give the corresponding pyrano[3,2-c] pyridones 23 in moderate yields (Scheme 7)[12]. The synthetic approach described for 22 and 23 is one of the simplest routes as compared to the reported methods. The scope and limitations of the methods are discussed in Chapter III.

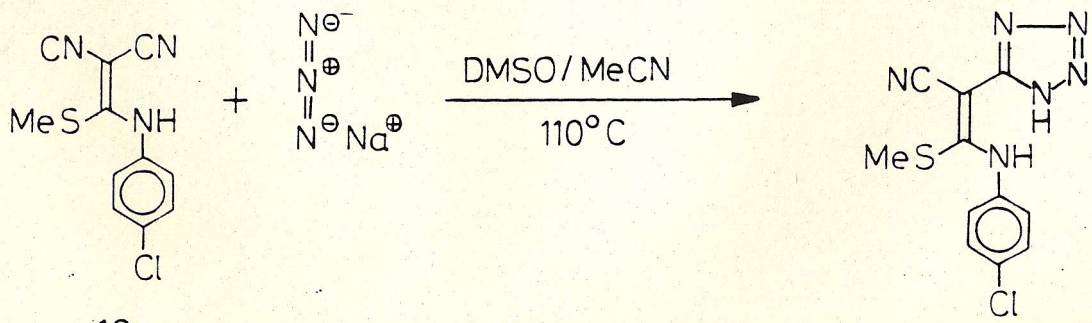
The hydroxyiminoimines 24 were reacted with hydrazine hydrate with a view to develop a new methodology for the 4,5-diaminopyrazoles. Thus, when hydroxyiminoimines 24 reacted with one equivalent of hydrazine hydrate at room temperature, afforded a corresponding 4-nitroso-3(5)-



4 14 16

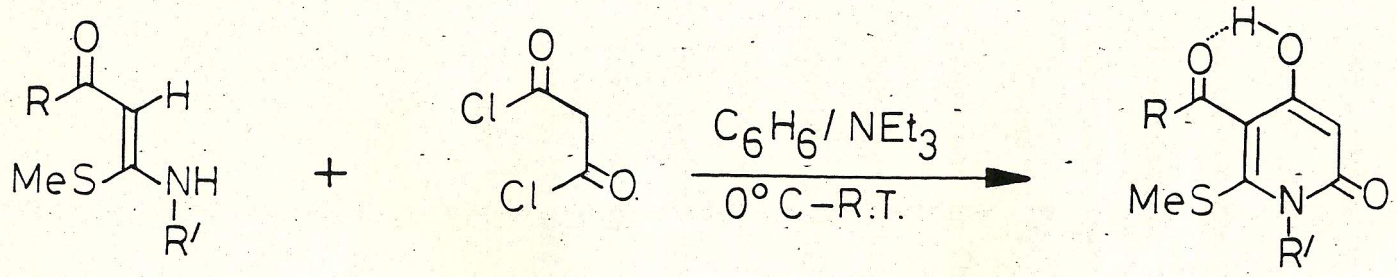


17 25 18

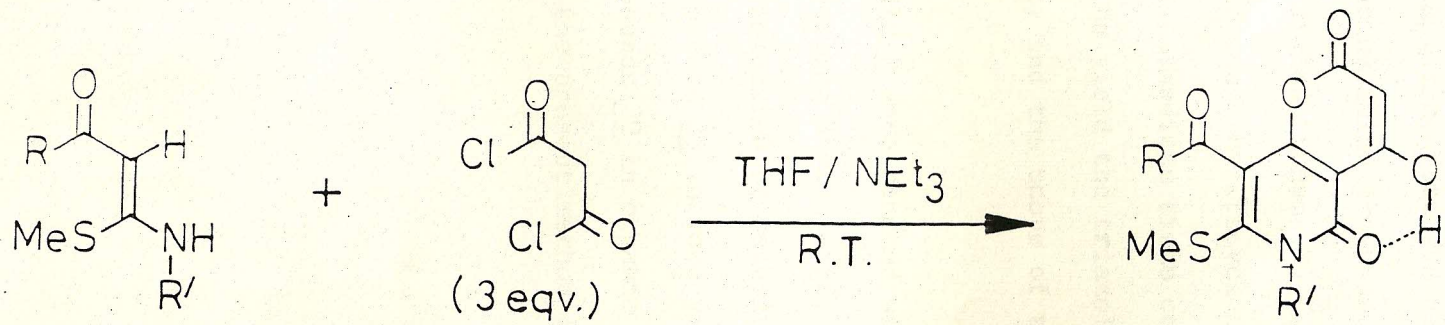


19 25 20

Scheme 6



4 + 21 → 22

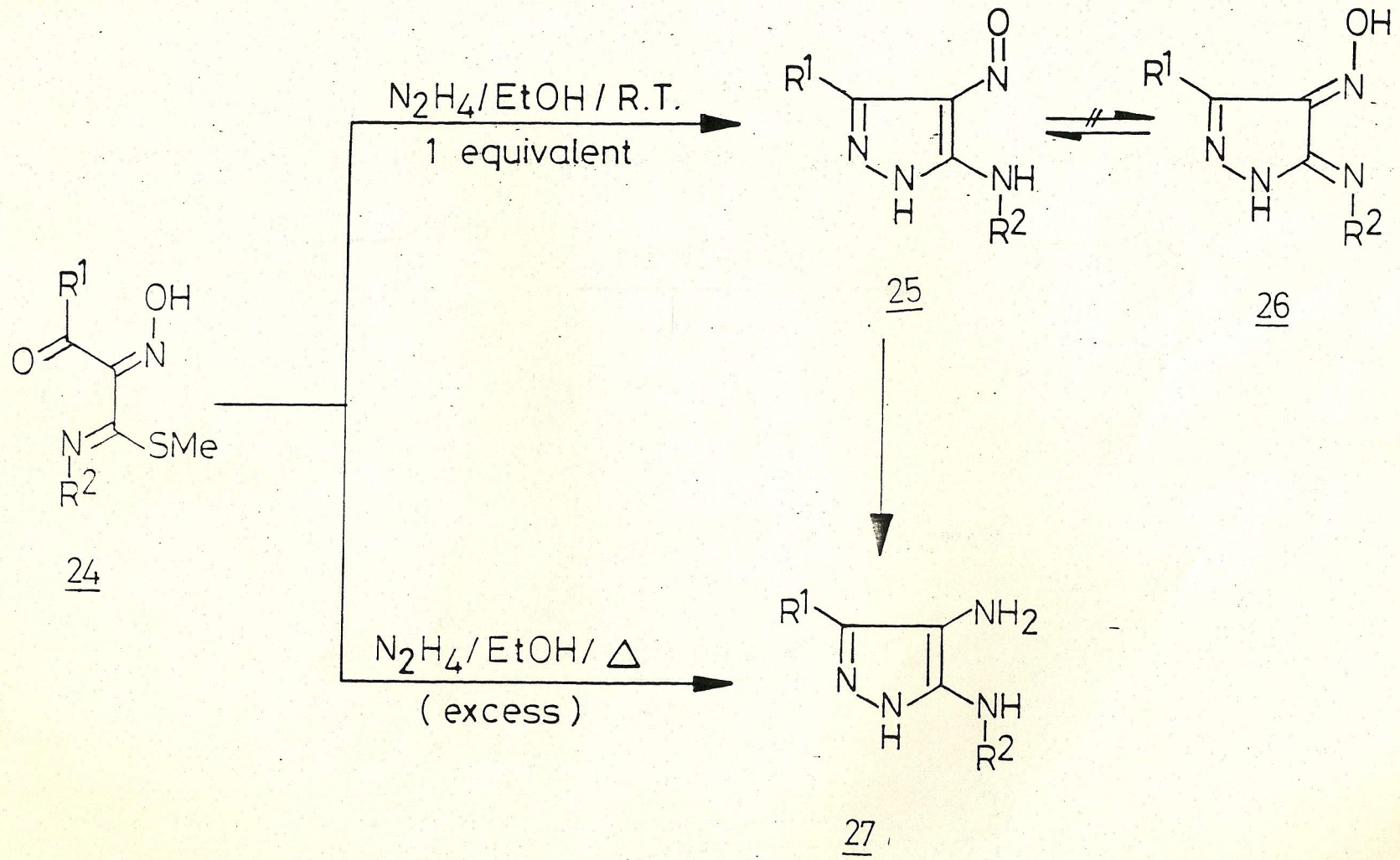


4 + 21 (3 eqv.) → 23

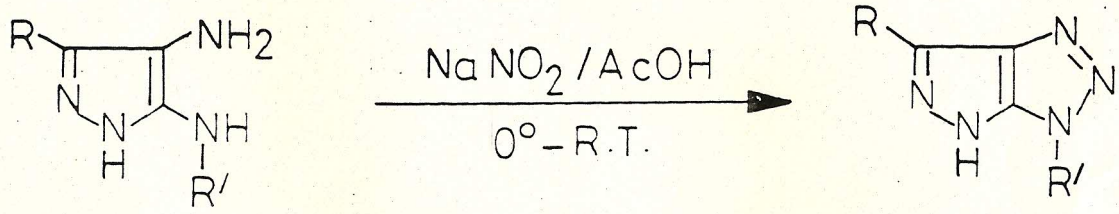
Scheme 7

aryl 5(3)-alkyl/aryl aminopyrazoles 25 in excellent yields (Scheme 8)[13]. However, when excess of hydrazine hydrate was used the 4-nitroso group was reduced to the corresponding amino group and diamino pyrazole 27 were formed in quantitative yields (Scheme 8)[13], which are of synthetic value for the construction of fused heterocycles. Thus, 27 underwent diazotization to yield the intermediate diazo compound which underwent intramolecular ring closure to yield the triazolo[3,4-d] pyrazoles 28 (Scheme 9)[13]. The generality and the scope of the present method is discussed in Chapter IV.

When α-oxoketene dithioacetals 2 were reacted with sodium cyanoborohydride in the presence of boiling acetic acid, underwent facile 1,4-reduction followed by elimination of methylthio group to yield the desired vinylogous thiolesters 29 in good yields (Scheme 10)[14]. The importance of these compounds 29 in organic synthesis, the generality and the scope of the present method is discussed in the Chapter V.

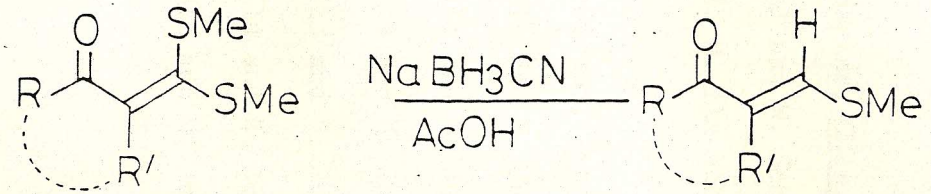


Scheme 8



27 28

Scheme 9



2 29

Scheme 10

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