SYNTHETIC STUDIES ON OXOKETENE S,S- AND S,N-ACETALS : DEVELOPMENT OF NEW METHODS FOR NOVEL HETEROCYCLES

ABSTRACT

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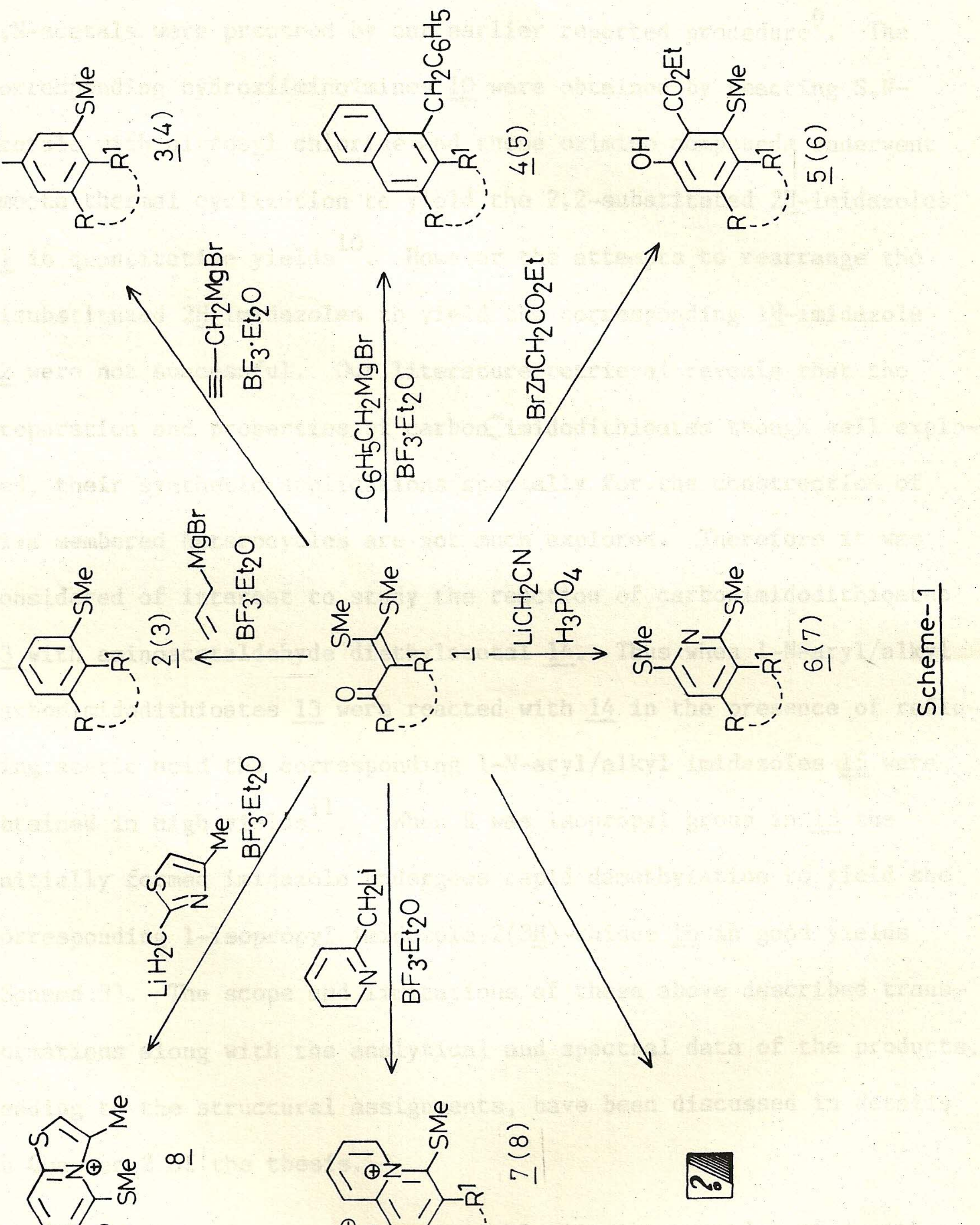
The α-oxoketene dithioacetals 1 have been known since the first report by Kelber in 1910[1]. This class of compounds can be easily prepared by the reaction of active methylene ketones with carbon disulphide in the presence of a suitable base, followed by alkylation. Many efficient methods, essentially using this procedure, have been developed and these substrates (1) are now available from a large variety of active methylene ketones.

The α-oxoketene dithioacetals have been shown to be an excellent three carbon synthon possessing 1,3-electrophilic centres with differing electrophilicty, which has been extensively exploited for the regioselective construction of new bonds via 1,2- or 1,4-nucleophilic additions leading to a number of organic synthesis[2]. For example, the α-oxoketene dithioacetals 1 (Scheme 1) have been shown to undergo exclusive 1,2-addition with allylmagnesium bromide to yield the corresponding carbinol acetals which on $BF_3.Et_2O$ assisted cationic cyclization yield the substituted and fused benzene derivatives 2[3]. The approach is extended for the synthesis of other benzenoids 3-5[4-6]. The method is further shown to be extremely versatile and found general application for synthesizing pyridines 6[7], quinolizinium salts 7[8] and thiazolo pyridinium compounds 8.

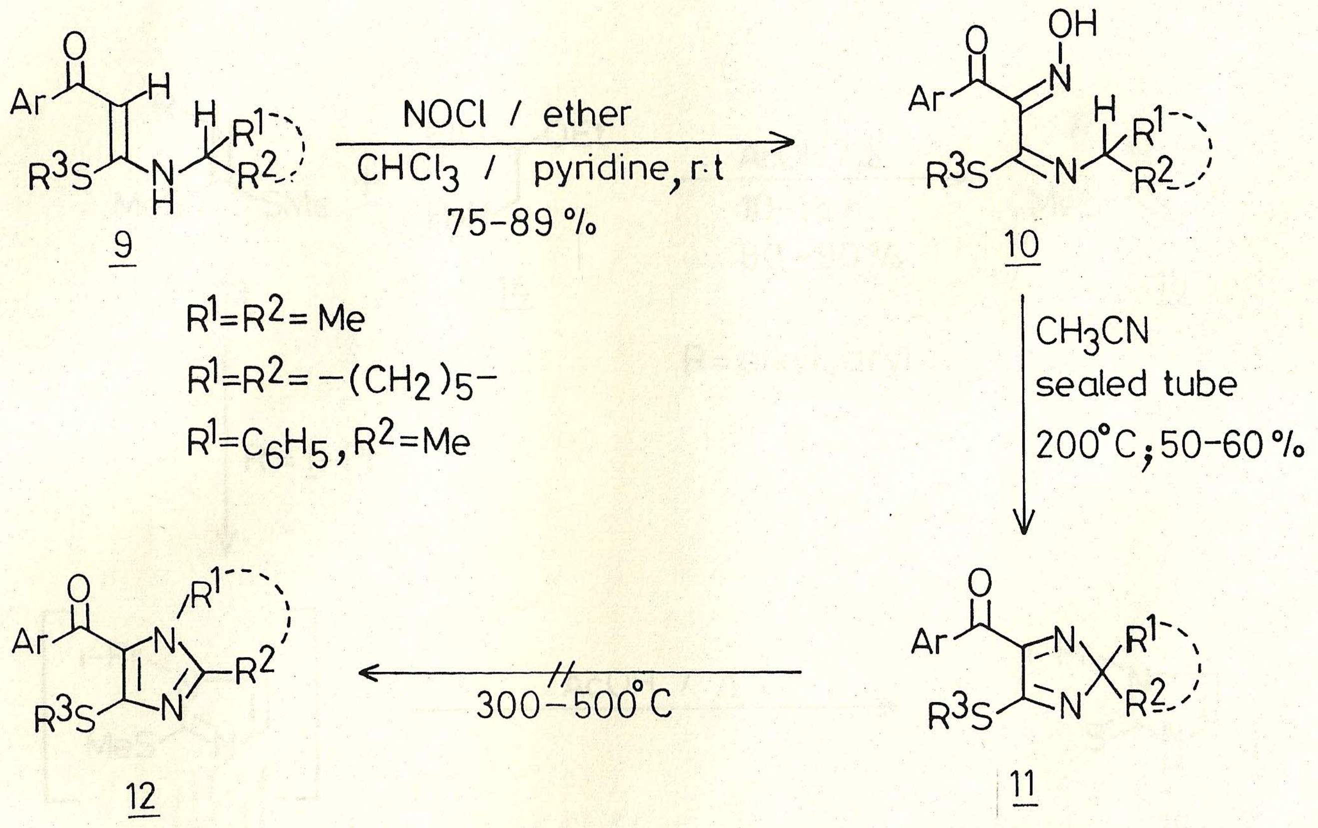
In the light of all these studies and as a part of our ongoing research, it was proposed to study the reaction of α-oxoketene dithioacetals to develop further new methodologies to construct various biologically important heterocycles. It was therefore considered of interest to


SMe
SMe
O
R
R1
1
2(3)
3(4)
4(5)
5(6)
6(7)
7(8)
8
MgBr
BF3·Et2O
CH2MgBr
C6H5CH2CH2MgBr
BrZnCH2CO2Et
LiCH2CN
H3PO4
CH2Li
LiH2C
Me
OMe
CH2C6H5
OH
CO2Et
BF4⊖
⊕

Scheme-1

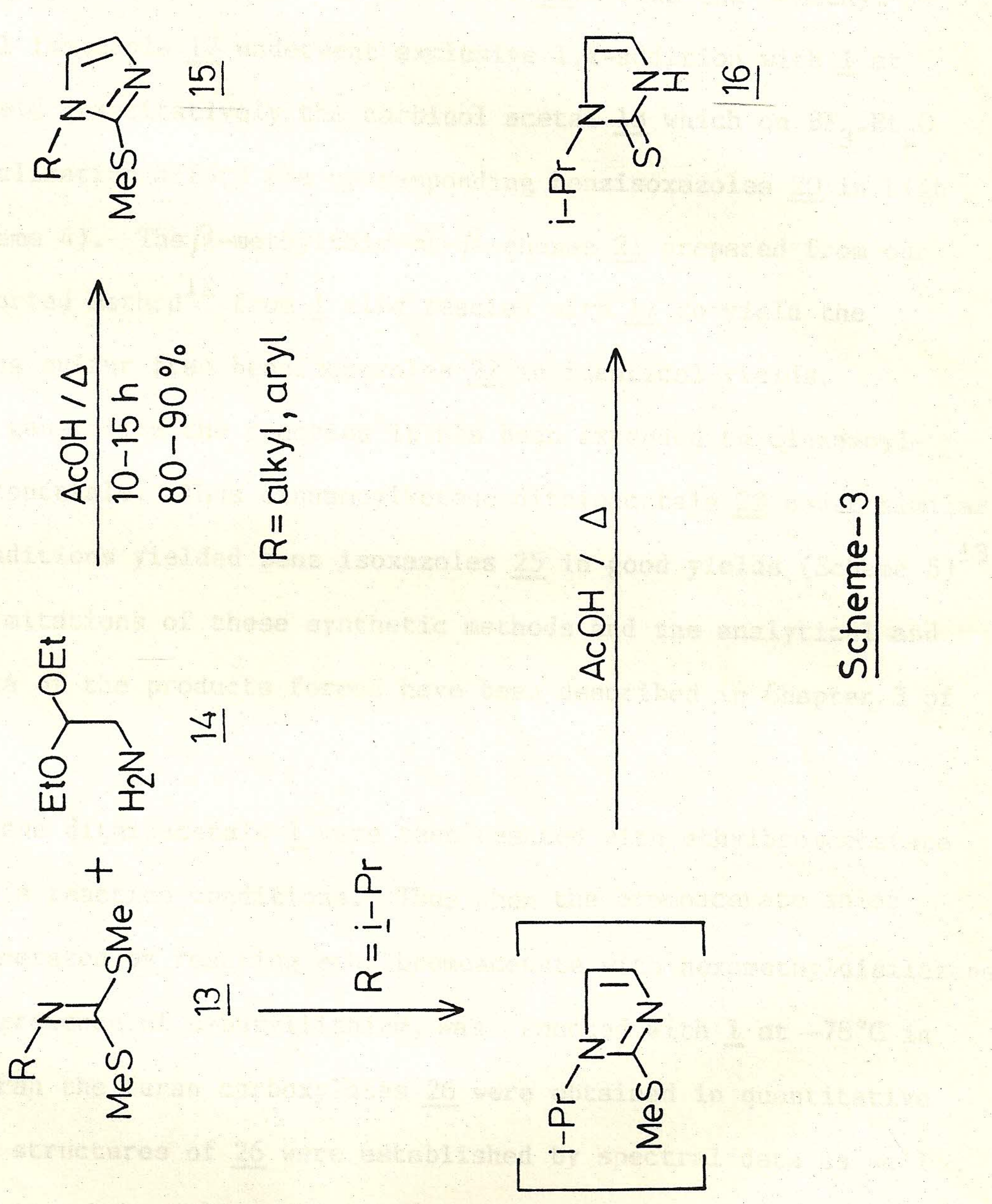
study the reaction of nitrosyl chloride with corresponding S,N-acetals 9 (Scheme 2) derived from alkylamines and cyclic alkylamines and these S,N-acetals were prepared by our earlier reported procedure[9]. The corresponding hydroxiiminoimines 10 were obtained by reacting S,N-acetals with nitrosyl chloride and these oximino compounds underwent smooth thermal cyclization to yield the 2,2-substituted 2*H*-imidazoles 11 in quantitative yields[10]. However the attempts to rearrange the disubstituted 2*H*-imidazoles to yield the corresponding 1*H*-imidazole 12 were not successful. Our literature retrieval reveals that the preparation and properties of carbonimidodithioates though well explored, their synthetic applications specially for the construction of five membered heterocycles are not much explored. Therefore it was considered of interest to study the reaction of carbonimidodithioates 13 with aminoacetaldehyde diethylacetal 14. Thus when 1-N-aryl/alkyl carbonimidodithioates 13 were reacted with 14 in the presence of refluxing acetic acid the corresponding 1-N-aryl/alkyl imidazoles 15 were obtained in high yields[11]. When R was isopropyl group in 13 the initially formed imidazole undergoes rapid demethylation to yield the corresponding 1-isopropyl imidazole-2(3*H*)-thione 16 in good yields (Scheme 3). The scope and limitations of these above described transformations along with the analytical and spectral data of the products, leading to the structural assignments, have been discussed in details in Chapter 2 of the thesis.

In continuation of our interest in exploring the reaction of 1 with various allyl and azaallylanions it was considered of interest to extend



Ar
R3S
9
NOCl / ether
CHCl3 / pyridine, r.t
75-89 %
10
R1=R2= Me
R1=R2= −(CH2)5−
R1=C6H5, R2=Me
CH3CN
sealed tube
200°C; 50-60 %
11
300−500°C
12

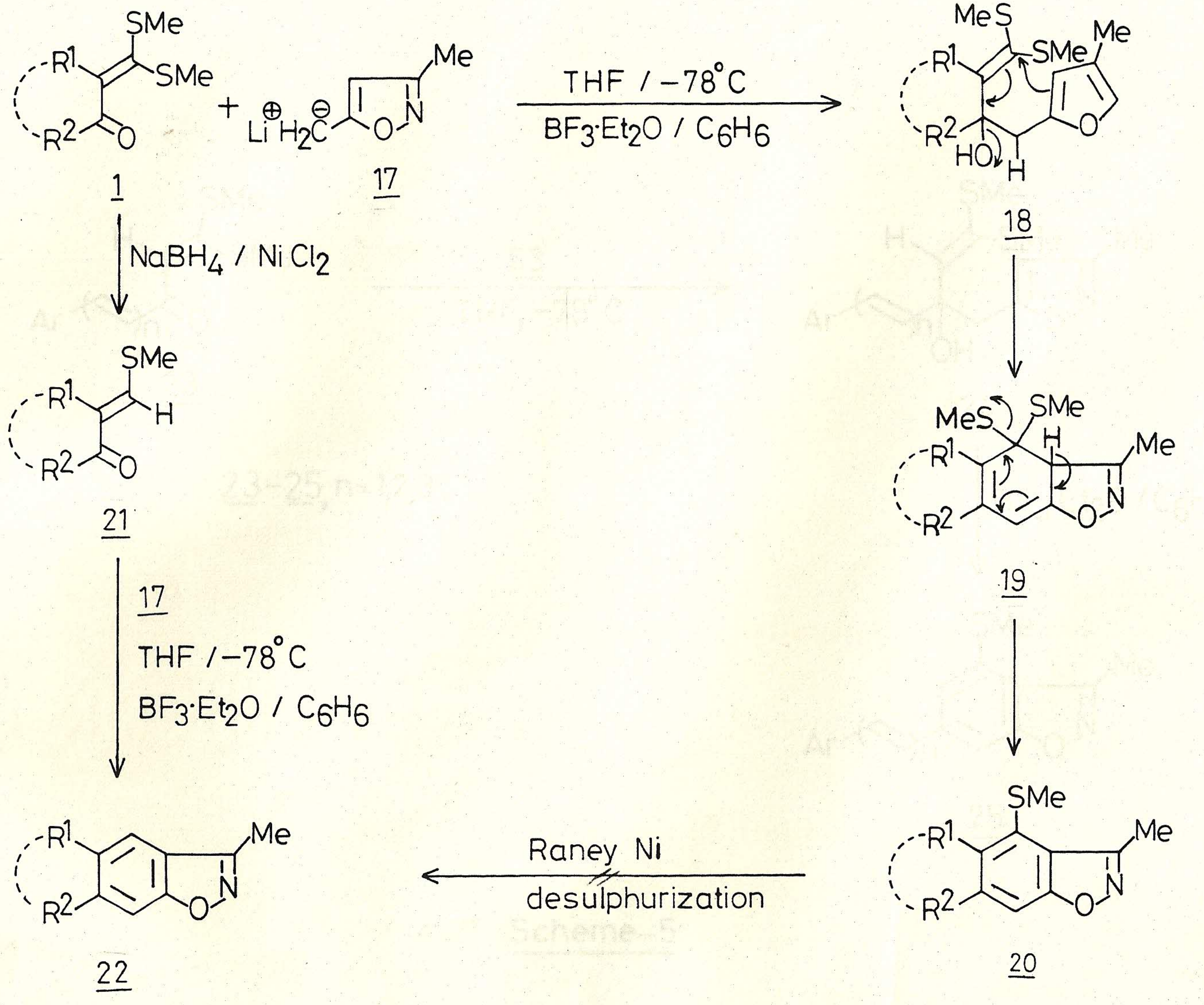
Scheme–2



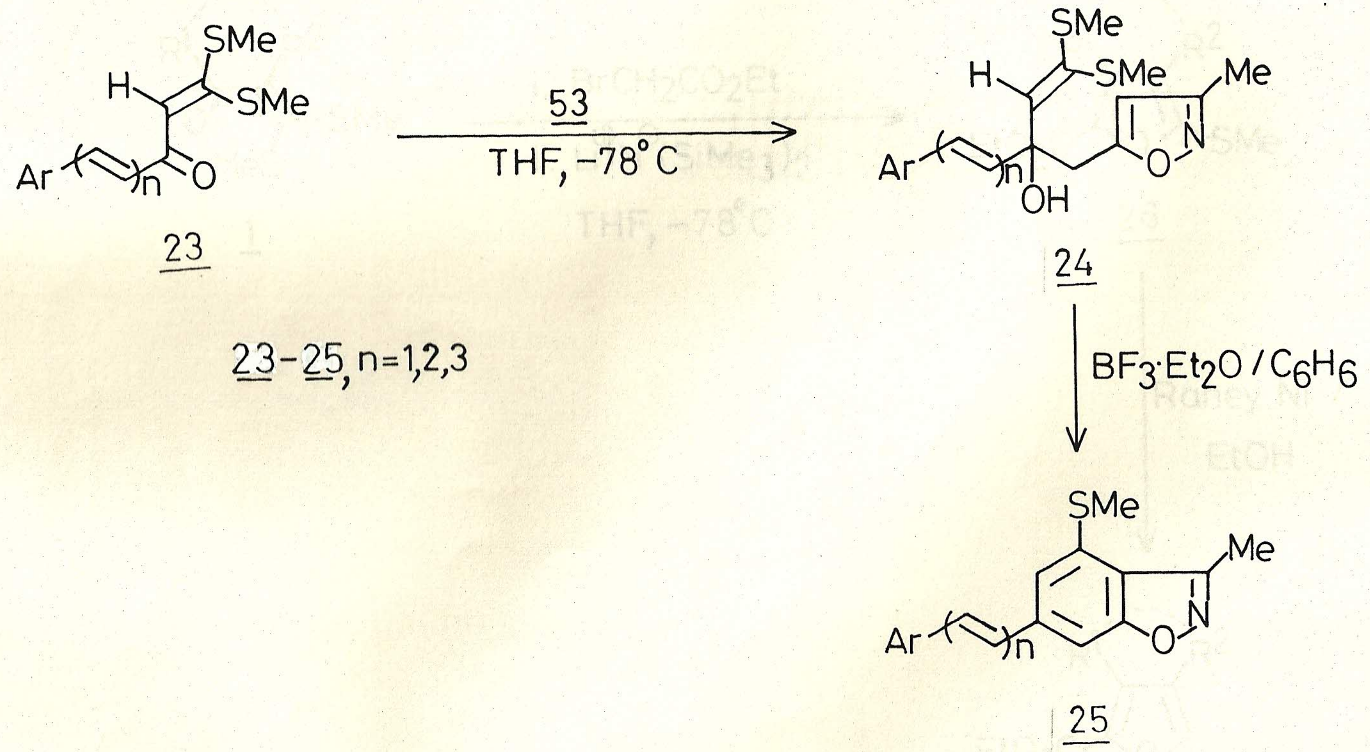
Scheme-3

the aromatic annelation approach for the synthesis of heteroaromatics. Therefore in the present investigation 3-methyl-5-lithiomethyl isoxazole 17 was selected as an allylanion system to extend the aromatic annelation approach for the synthesis of benzisoxazoles 20. Thus the 3-methyl-5-lithiomethyl isoxazole 17 underwent exclusive 1,2-addition with 1 at -78°C to yield quantitatively the carbinol acetal 18 which on $BF_3.Et_2O$ assisted cyclization afford the corresponding benzisoxazoles 20 in high yields (Scheme 4). The β-methylthio-α-β-enones 21 prepared from our earlier reported method[12] from 1 also reacted with 17 to yield the corresponding sulfur free benzisoxazoles 22 in identical yields. In order to generalize the reaction it has been extended to cinnamoylketene dithioacetals. Thus cinnamoylketene dithioacetals 23 under similar reaction conditions yielded benz isoxazoles 25 in good yields (Scheme 5)[13]. Scope and limitations of these synthetic methods and the analytical and spectral data of the products formed have been described in Chapter 3 of the thesis.

The α-oxoketene dithioacetals 1 were then reacted with ethylbromoacetate under Darzen's reaction conditions. Thus when the bromoacetate anion which was generated by reacting ethylbromoacetate with hexamethyldisilazane at -78°C in presence of n-butyllithium, was reacted with 1 at -78°C in tetrahydrofuran the furan carboxylates 26 were obtained in quantitative yields. The structures of 26 were established by spectral data as well as by subjecting them to Raney Nickel desulfurization to the known furan derivatives 27 in some cases (Scheme 6)[14]. Interestingly when the reaction was extended to cinnamoylketenedithioacetals 23 the products 28 and 29 were obtained (Scheme 7). The results of these reactions and the analytical and spectral data of the compounds are discussed in details in Chapter 4 of the thesis.

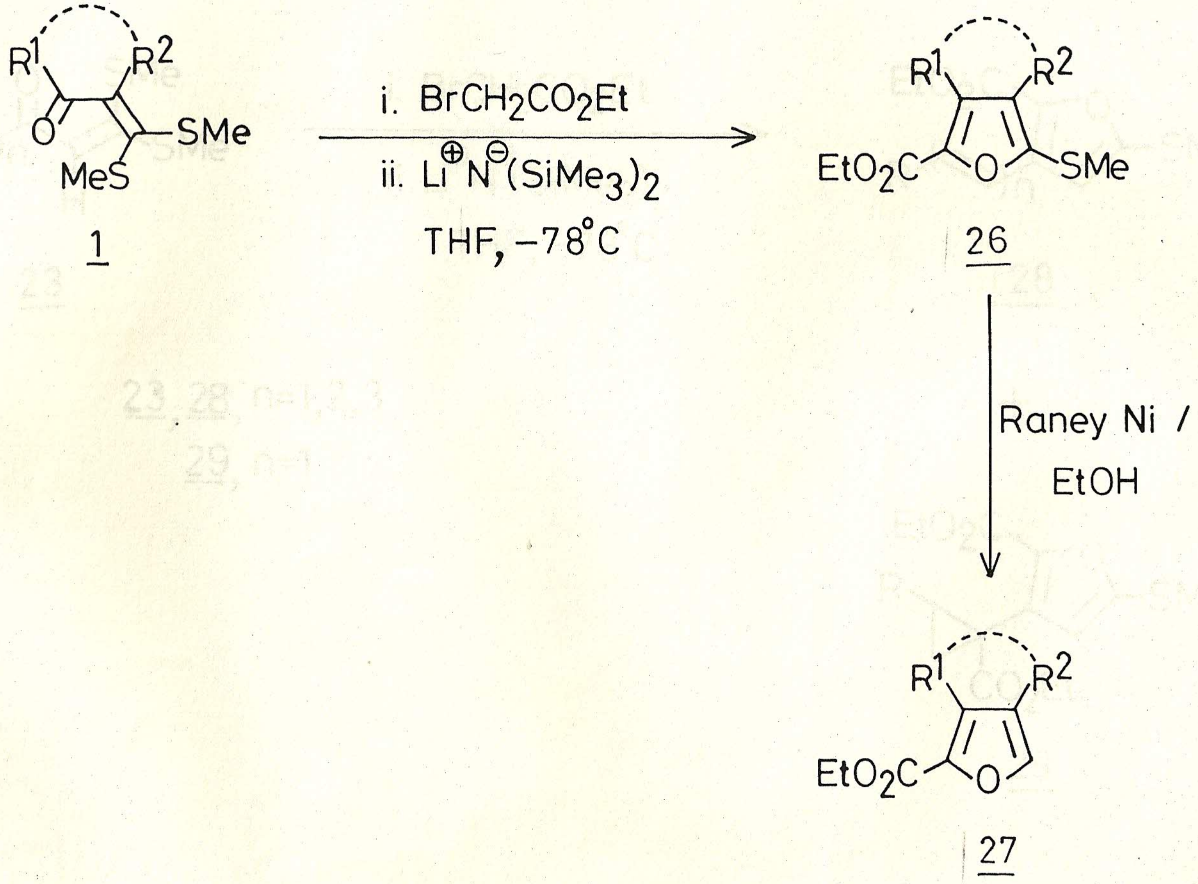

SMe
SMe
R1
R2
O
1
+
Li⊕ H2C⊖
Me
O
N
17
THF / –78°C
BF3·Et2O / C6H6
MeS
SMe
Me
R1
R2
HO
H
O
18
NaBH4 / NiCl2
SMe
R1
H
R2
O
21
MeS
SMe
H
Me
R1
R2
O
N
19
17
THF / –78°C
BF3·Et2O / C6H6
SMe
R1
Me
R2
O
N
20
Raney Ni
desulphurization
R1
Me
R2
O
N
22

Scheme-4

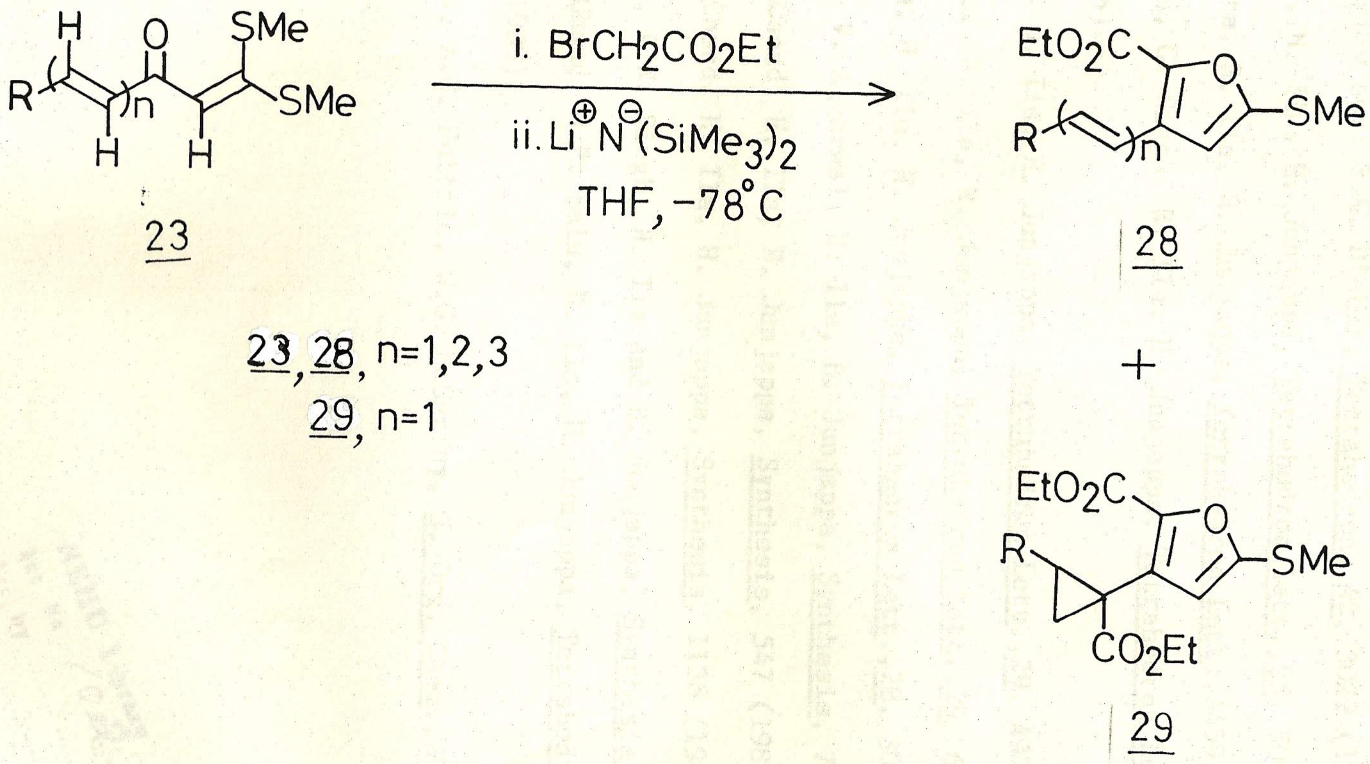


23-25, n=1,2,3

Scheme-5


R1
R2
SMe
MeS
O
1
i. BrCH2CO2Et
ii. Li⊕N⊖(SiMe3)2
THF, -78°C
R1
R2
EtO2C
O
SMe
26
Raney Ni /
EtOH
R1
R2
EtO2C
O
27

Scheme-6



$\underline{23}$, $\underline{28}$, n=1,2,3
$\underline{29}$, n=1

Scheme–7

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