SYNTHETIC AND MECHANISTIC INVESTIGATIONS ON POLARIZED KETENE DITHIOACETALS FOR THE DEVELOPMENT OF NEWER SYNTHETIC METHODS

By

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DOCTOR OF PHILOSOPHY

To

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INDIA
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DEDICATED
To
My beloved parents

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Grams : NEHU

North-Eastern Hill University
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Head,
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This is to certify that the work described in this thesis has been carried out by Mr. **Laitonjam Warjeet Singh** under my supervision. He has satisfactorily completed the pre-Ph.D. courses 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: 15th June, 1987

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15/1/87

L. Warjeet Singh

CONTENTS

PREFACE

The work described in this thesis is part of an ongoing research programme in our laboratory since last ten years. It is aimed at developing newer synthetic methods for both heterocyclic and carbocyclic compounds utilizing polarized ketene dithioacetals as synthetic intermediates. The versatility of these intermediates which are easily available in one pot reaction from any kind of active methylene compounds for synthesis of heterocyclic and carbocyclic compounds has been already established in the earlier works.

The thesis is divided into four chapters. The first chapter deals with the introductory account of the recent work carried out in this field both by our research group and other workers. In the second chapter of the thesis, α-cinnamoyl and α-(5-aryl-2,4-butadienoyl)ketene dithioacetals which are easily obtained by base catalyzed condensation of α-acetylketene dithioacetals with benzaldehydes and cinnamaldehydes, have been explored as three carbon fragments for synthesis of styryl and 4-aryl-1,3-butadienyl pyrimidines and pyridones by their reactions with guanidine and cyanoacetamide anion respectively.

In chapter three of the thesis, an attempt has been made to utilize enolate anions derived from α-alkanoylketene dithioacetals as four carbon fragments with an electrophilic and nucleophilic terminal carbon atoms, which have been subjected to cyclocondensation with heteromultiple bonds with a view to getting six membered heterocycles. Thus synthesis of novel substituted 6-amino-2-methylthio-4H-thiopyran-4-ones and 2-aryl-6-methylthio-4H-pyran-4-ones has been developed by base catalyzed cyclocondensation of acylketene dithioacetals with aryl isothiocyanates and methyl benzoates respectively. A novel cycloaromatization leading to substituted 4-hydroxyacetophenone was also observed during these studies.

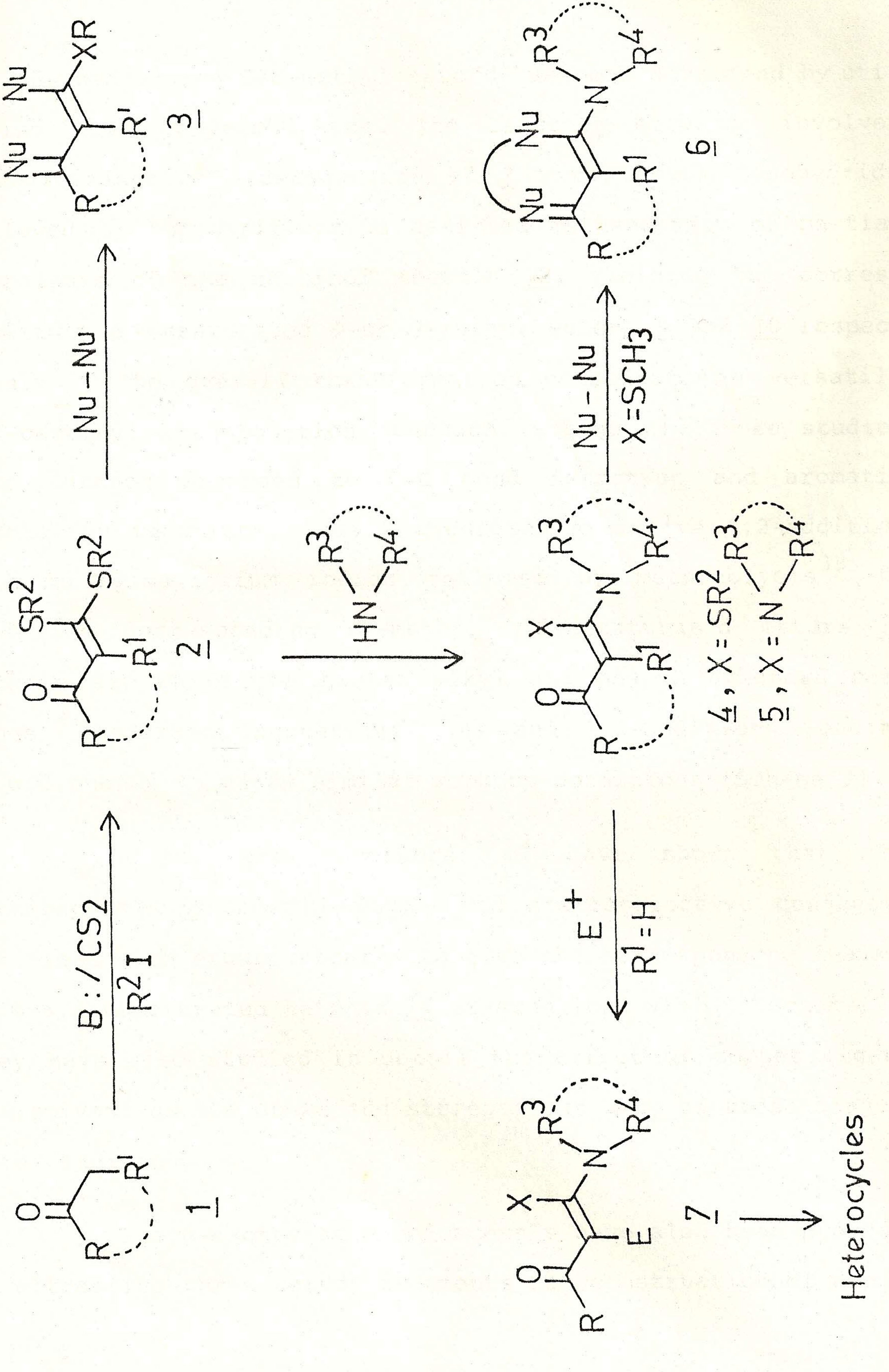
In chapter four of the thesis, anionic [3+2] cyclizations of 1,1-bis(methylthio)-2-aroyl-3-cyanoallyl anion with heteromultiple and activated double bonds have been studied with a view to developing novel methods for five membered heterocyclic and carbocyclic ring systems. Thus the base catalyzed reaction of 4-aryl-3-[bis(methylthio)methylene]-4-oxobutanenitriles with aryl isothiocyanates, 4-chlorobenzaldehyde, benzonitrile, chalcone, benzylideneacetone and ethyl acrylate to give various expected and unexpected products have been described in this chapter. The structural assignment of all the new products has been estgablished with the help of spectral and analytical data. Finally cyclocondensation of these intermediates with hydrazine to give novel pyridazinone derivatives have been described.

CHAPTER I

INTRODUCTION

During the last ten years, the α-oxoketene dithioacetals[1] 2 have emerged as versatile, 1,3-electrophilic three carbon synthons, used in the synthesis of a variety of heterocyclic and carbocyclic compounds. They are among the simplest synthetic intermediates which can be easily prepared[2-9] in one pot reaction by treating, structurally diverse active methylene ketones 1 with two equivalents of base in the presence of carbon disulfide followed by alkylation (Scheme 1). The dithioacetals 2 thus formed exhibit well defined physical properties which can be purified by conventional purification methods. They are generally stable at room temperature both under mild acidic and alkaline conditions and can be stored indefinitely without apparent decomposition. These intermediates have been extensively explored in this laboratory for developing general synthetic methods for a number of five and six membered heterocycles[10-18] 3 by reacting them with bifunctional nucleophiles like guanidine, hydrazine hydrate, hydroxylamine and cyanoacetamide anion etc. Further, displacement of alkylthio groups by one or two equivalents of primary or secondary alkyl/arylamines, yields the corresponding α-oxoketene S,N[19]-(4) and N,N[20]-acetals (5), which have also proved to be useful intermediates for the construction of a variety of heterocyclic ring systems (Scheme 1). While the α-oxoketene S,N-acetals are shown to be useful three carbon precursors for aminoheterocycles[21-23] when they are reacted with bifunctional nucleophiles, their usefulness as novel functionalized enaminones has been manifested in their reactions with several electrophilic species like activated double bonds, heteromultiple bonds, thionyl chloride, nitrosyl chloride and nitrosobenzene to give a number of novel five and six membered heterocycles[24-35] (Scheme 1). All these reactions have been discussed in a recent review[36].

Recently, the utility of these intermediates has been extended to reactions involving C-H and C-C bond formations leading to the synthesis of open chain and cyclic sulfur free compounds. Thus a new stereo-and regioselective synthesis

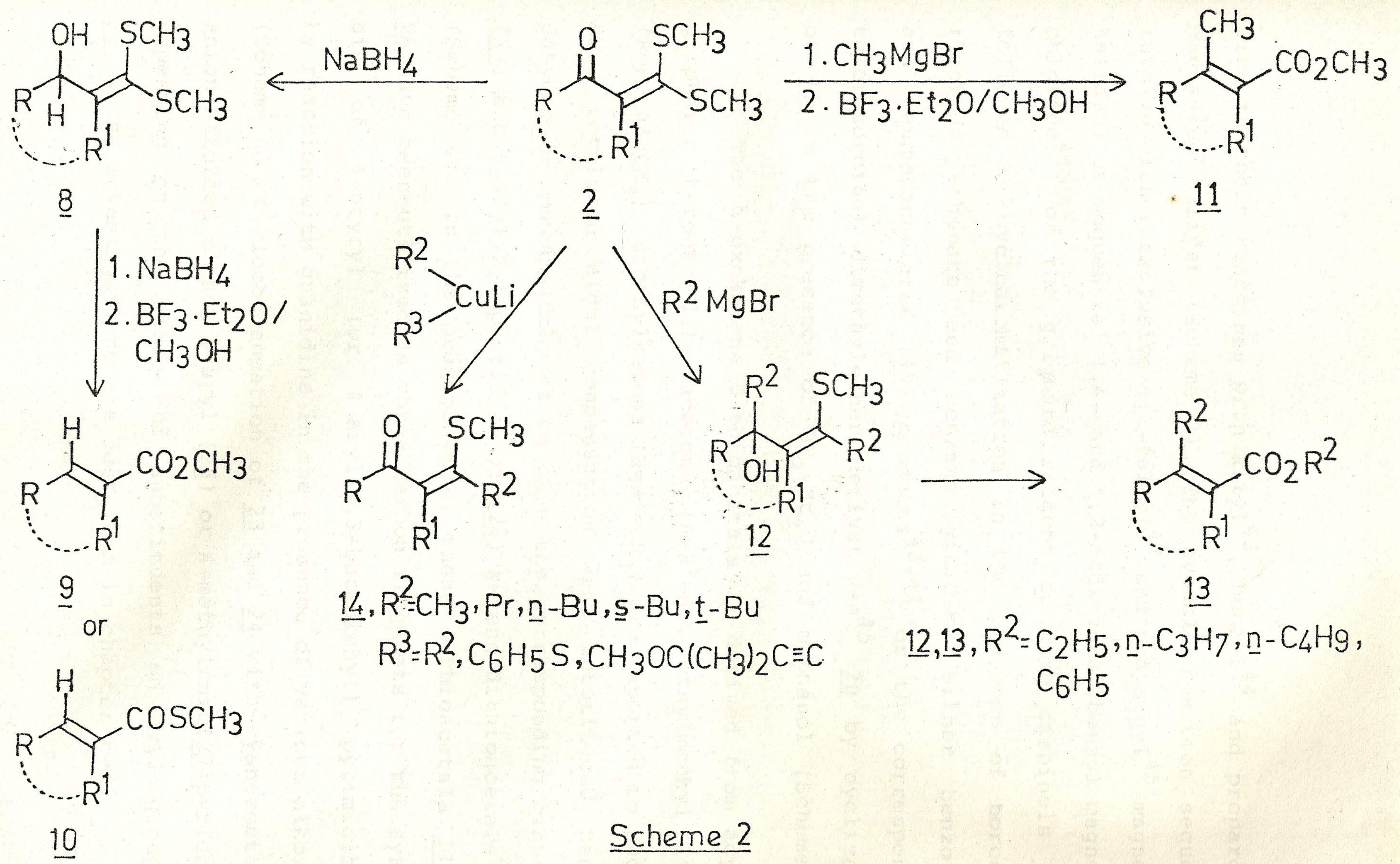

1
B:/CS₂
R²I
2
Nu-Nu
3
HN R³ R⁴
Nu-Nu
X=SCH₃
6
4, X = SR²
5, X = N R³ R⁴
E⁺
R¹=H
7
Heterocycles

Scheme 1

of α,β-unsaturated O/S-methyl esters has been developed by utilizing these intermediates. The reaction sequence involves a regioselective 1,2-reduction of 2 with sodium borohydride followed by borontrifluoride assisted methanolysis or partial hydrolysis of the carbinol acetals 12, yielding the corresponding α,β-unsaturated O-or S-methyl esters 9 and 10 respectively[37]. The overall transformation constitutes a versatile 1,3-carbonyl transposition reaction (Scheme 2). These studies were further extended to C-C bond formation and aromatic annelation reactions. Thus 2 undergoes exclusive 1,2-addition with methylmagnesium iodide followed by methanolysis[38] to give the corresponding β-methyl α, β-unsaturated esters 11 (Scheme 2), while the higher alkyl and phenyl grignard reagents[38] underwent sequential 1,4- and 1,2-additions leading to α,β-enones 13 under similar work up conditions (Scheme 2).

Dieter and coworkers[39-42] have shown that the dithioacetals 2 undergo chemo- and stereoselective conjugate additions with organocuprates to give the corresponding β-alkylthio-α,β-unsaturated ketones 14 in excellent yields (Scheme 2). They have also studied in detail the effect of copper ligand and solvent on the chemo and stereoselectivity of these conjugate additions.

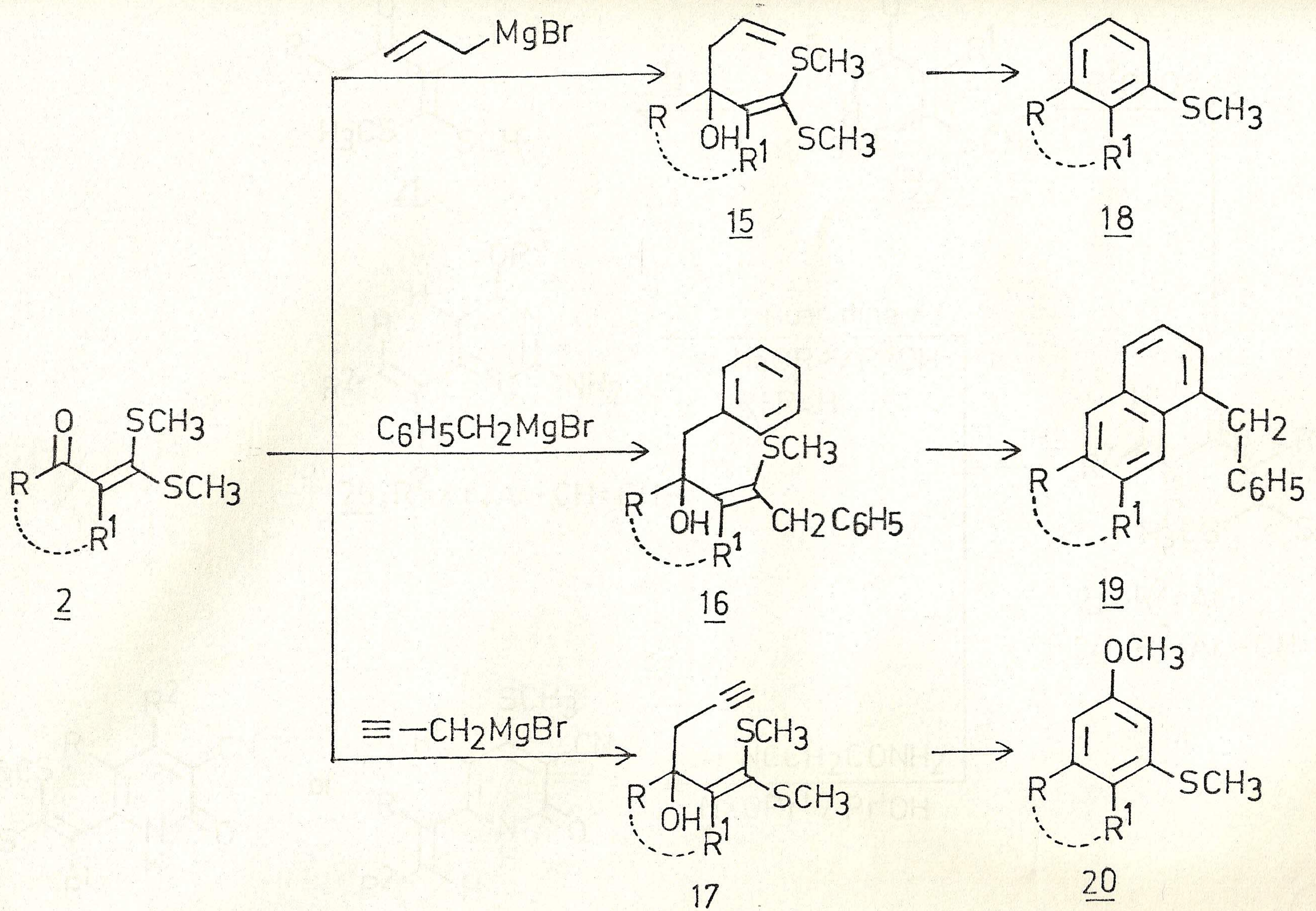
The α-oxoketene dithioacetals have also been proved to be attractive three carbon fragments for construction of aromatic


NaBH4
1. CH3MgBr
2. BF3·Et2O/CH3OH
1. NaBH4
2. BF3·Et2O/CH3OH
R2MgBr
R2 CuLi R3
8
2
11
9
or
10
12
13
14, R2=CH3, Pr, n-Bu, s-Bu, t-Bu
R3=R2, C6H5S, CH3OC(CH3)2C≡C
12,13, R2=C2H5, n-C3H7, n-C4H9, C6H5

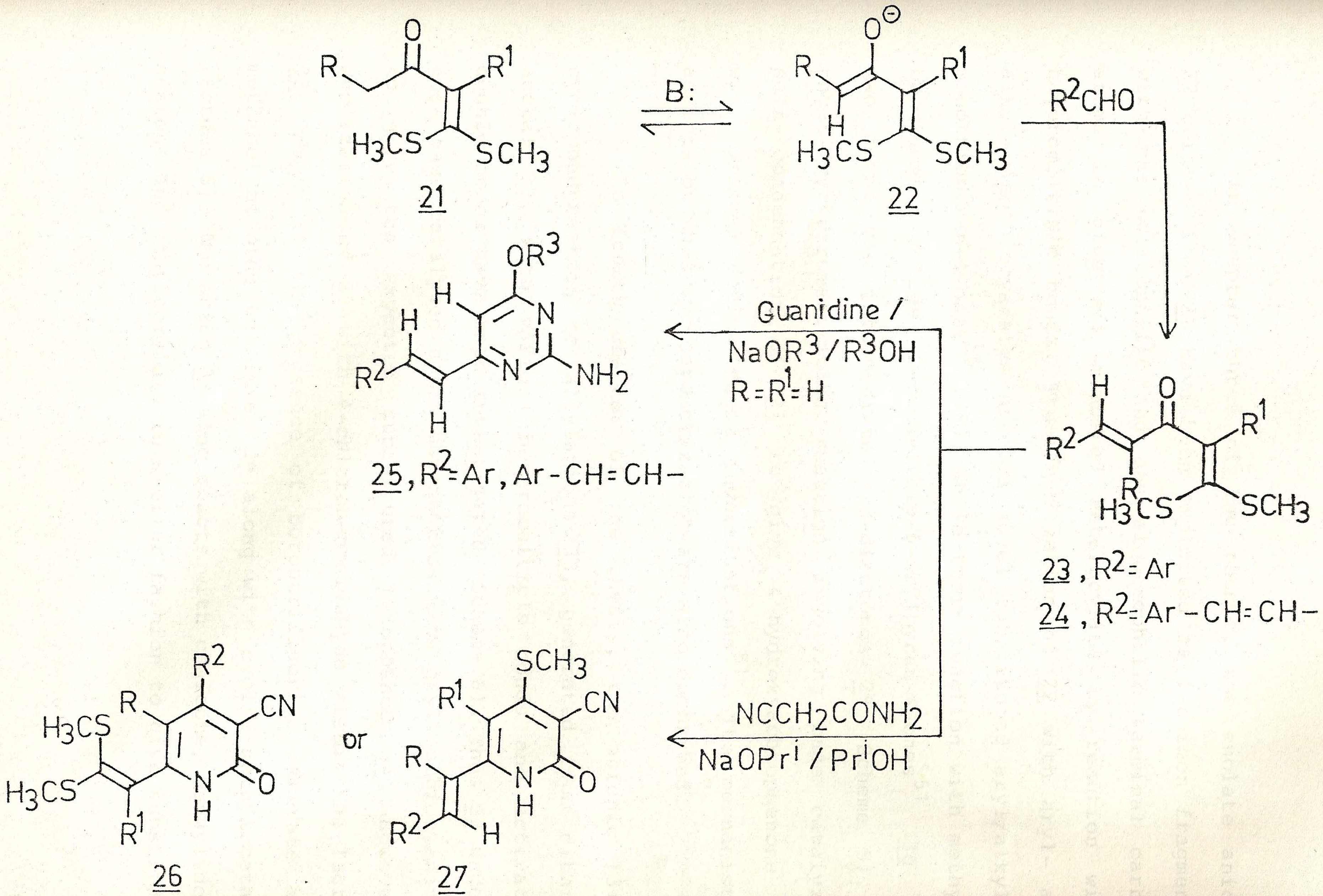
Scheme 2

ring in their reactions with allyl[43], benzyl[44] and propargyl[45] magnesium halides (Scheme 3). The overall reaction sequences involve either exclusive 1,2-(allyl[43] and propargyl[45] magnesium halides) or sequential 1,4- and 1,2-additions (benzyl magnesium chloride[44]) of the grignard reagent to give carbinols 15-17 followed by cycloaromatization in the presence of borontrifluoride etherate and benzene yielding either benzo-(18) and naphthoannelated (19) products[43,44] or the corresponding thioresorcinol dimethylether derivatives[45] 20 by cyclization of 17 in the presence of $BF_3.Et_2O$ and methanol (Scheme 3).

The α-oxoketene dithioacetals 21 derived from acyclic aliphatic ketones like acetone (R=R'=H), ethylmethyl ketone (R=H, R'=CH_3), diethylketone (R=R'=CH_3) are reported to undergo base catalyzed aldol condensation with substituted benzaldehydes or cinnamaldehydes to give the corresponding cinnamoyl (23) and 5-aryl-2,4-pentadienoyl (24) ketene dithioacetals[46,47] (Scheme 4). In the present work, these dithioacetals 23 and 24 have been utilized as three carbon fragments for the synthesis of 4-styryl (or 4-aryl-1,3-butadienyl) pyrimidines[48] by reaction with guanidine in the presence of various alkoxides (Scheme 4). Cyclocondensation of 23 and 24 with cyanoacetamide anion afforded either 4-aryl (26) or 4-methylthio(27)pyridones[49] depending on the nature of substituents on aryl group in 23. These investigations are described in chapter two.


MgBr
C6H5CH2MgBr
≡—CH2MgBr
O
SCH3
SCH3
R
R1
OH
CH2C6H5
CH2
C6H5
OCH3
2
15
16
17
18
19
20

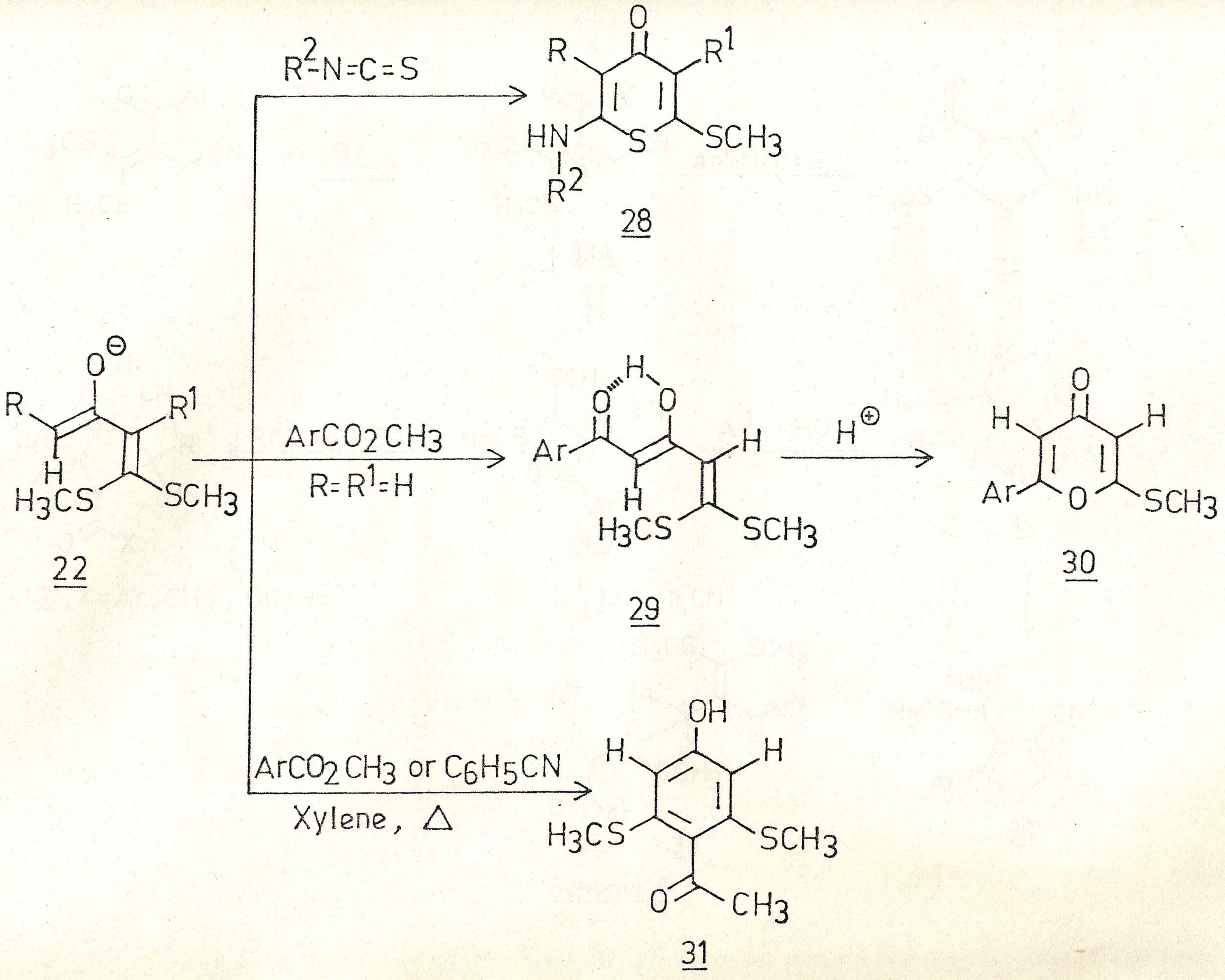
Scheme 3


21
B:
22
R²CHO
23, R²= Ar
24, R²= Ar-CH=CH-
Guanidine /
NaOR³/R³OH
R=R¹=H
25, R²=Ar, Ar-CH=CH-
NCCH₂CONH₂
NaOPrⁱ / PrⁱOH
26
or
27

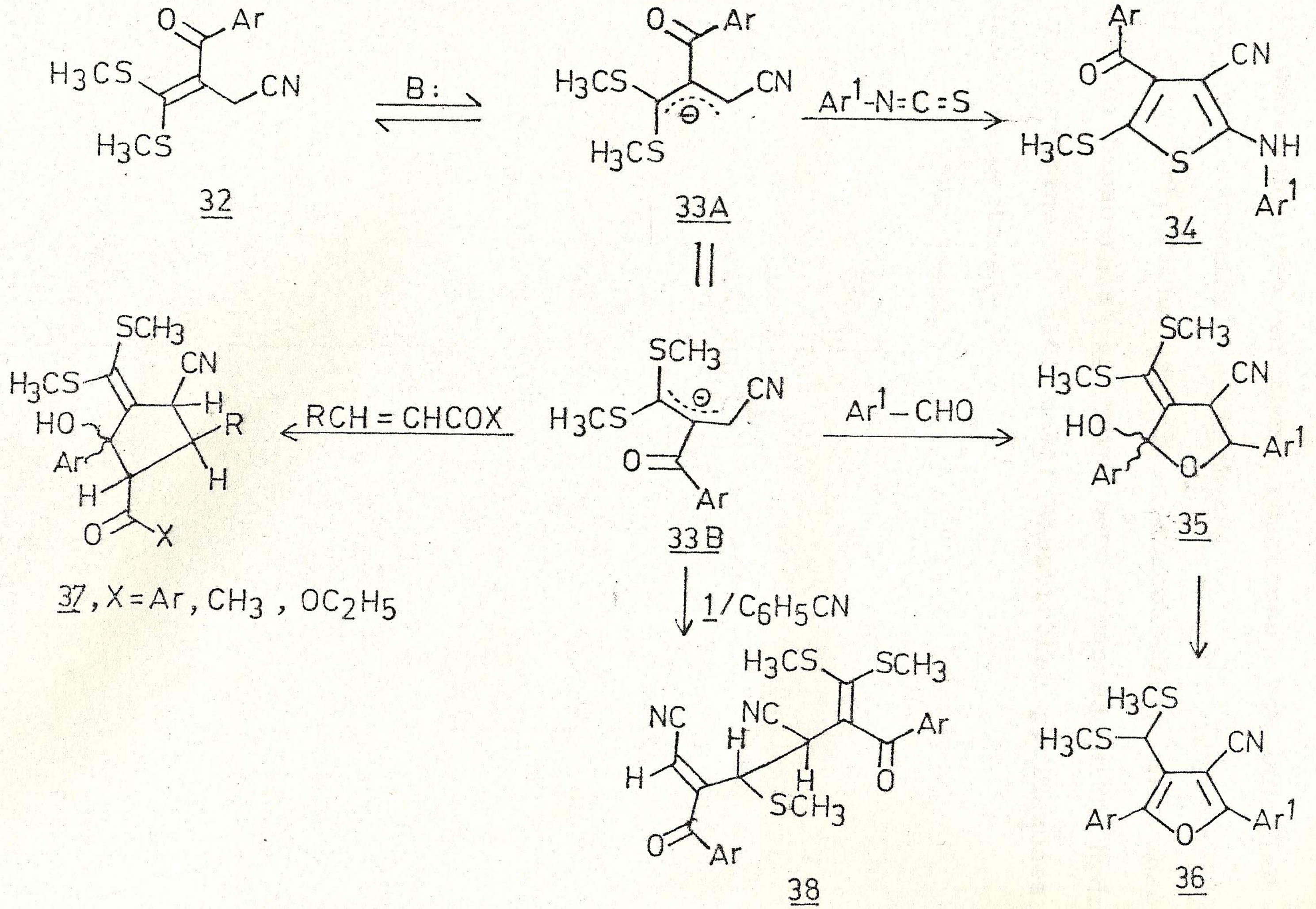
Scheme 4

In chapter three of the thesis, the enolate anions 22 derived from 21 have been exploited as 4-carbon fragments with one nucleophilic and one electrophilic terminal carbon atoms to give six membered heterocycles by reaction with heteromultiple bonds. Thus cyclization of 22 with aryl- and alkyl- isothiocyanates affords novel substituted aryl/alkylaminothiopyran-4-ones[50] (28), while their reaction with methylbenzoates yields 2-methylthio-6-arylpyran-4-ones[51] 30 in two steps via intermediate 1,3-diketones 29 (Scheme 5). A novel cycloaromatization reaction involving base catalyzed self condensation of 21 to give 4-hydroxyacetophenone 31 was observed during these investigations[51]. The mechanistic aspects of this cycloaromatization are also described.

In fourth chapter of the thesis, the anionic [3+2] cyclocondensation of allyl anions 33, generated from dithioacetal 32, with various heteromultiple bonds and activated double bonds have been investigated (Scheme 6). Thus 33 undergoes base catalyzed cyclocondensation with arylisothiocyanates to give the expected substituted thiophenes 34. However, cyclization of 33 with 4-chlorobenzaldehyde yields the lactol 35, which in the presence of borontrifluoride etherate and methanol affords the furan 36 along with cyclic methylacetals (Scheme 6). The anion 33 also reacts with chalcone, benzylidene acetone and ethylacrylate in similar fashion to give substituted


R^2-N=C=S
28
22
$ArCO_2CH_3$
R=R^1=H
29
$H^{\oplus}$
30
$ArCO_2CH_3$ or C_6H_5CN
Xylene, Δ
31

Scheme 5


32
B:
33A
Ar1-N=C=S
34
33B
RCH = CHCOX
Ar1–CHO
35
37, X = Ar, CH3 , OC2H5
1/C6H5CN
38
36

Scheme 6

cyclopentane derivatives 37. However it failed to undergo cyclocondensation with benzonitrile and only dimeric products 38 were obtained in these reactions. The detailed structural and stereochemical assignments of all the products formed in these reactions have been discussed in this chapter. Also, the dithioacetals 32 have been reacted with hydrazine and hydroxylamine to give novel substituted pyridazinones and amidoxime respectively.

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