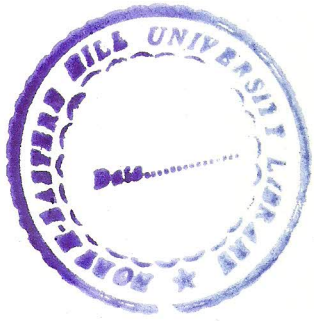
I. SYNTHETIC INVESTIGATION ON AROMATIC AND HETEROAROMATIC ANNELATION REACTION

II. HYDROGEN PEROXIDE/ BORIC ACID OXIDATIONS OF ORGANIC SUBSTRATES



By

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Submitted
in fulfilment of the requirement of the degree of
DOCTOR OF PHILOSOPHY
in
CHEMISTRY
to

NORTH - EASTERN HILL UNIVERSITY
SHILLONG - 793 003
INDIA
1999

The North-Eastern Hill University

Month: June Year:1999

I Miss Amrita Roy, hereby declare that the subject matter of this thesis is the record of work done by me, that the contents of this thesis did not form basis of the award of any previous degree to me or to the best of my knowledge to anybody else, and that the thesis has not been submitted by me for any research degree in any other University/ Institute.

This is being submitted to the North-Eastern Hill University for the Doctor of Philosophy degree in Chemistry.

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Dedicated

To

My Parents

And

Pishimoni

Acknowledgements

I take this opportunity to thank Dr. R. H. Duncan Lyngdoh at the outset for his help and co-operation.

It is a great privilege for me to express my sincere gratitude to Prof. H. Junjappa for his inspiring and dynamic guidance throughout my research career. I wish to express my heart-felt gratitude to Prof.(Mrs.) H. Ila for her invaluable suggestions, guidance and constant encouragement during my research tenure.

It gives me great pleasure to thank Prof. M. K. Mahanti, Head, Department of Chemistry, and all other teachers and non-teaching staff for their help and co-operation.

I also acknowledge the Director and staff of RSIC-Shillong and Director of CDRI, Lucknow for having provided spectral and analytical data.

My special thanks goes to Dr. K. R. Reddy for his helpful suggestions and encouragement.

Financial assistance from CSIR, New Delhi is also acknowledged for senior research fellowship.

I wish to thank all my friends and colleagues both in NEHU, Shillong and IIT, Kanpur with whom I have been associated all these years for their help and moral support.

It is indeed a pleasure to thank Dr. J. R. Suresh for helping me to process my thesis with valuable suggestions.

I am also indebted to Ms. Sanchita for helping me in innumerable ways during my research period. My thanks also goes to Sushmita Dutta, Sushmita Dhar, Rosaline, Guna, Simi and Syam.

It is difficult to translate into words how much I owe to Pramod Mohanta for taking personal care and attention in processing my thesis. I am thankful to him for being with me in hours of need.

Finally I owe my sincere gratitude to my parents who have stood by me throughout my research tenure and have given me moral support and inspiration. I also thank my brother and relatives for their encouragement and support, which has helped me immensely in fulfilling my dream.

Amrita Roy
14.6.99

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PREFACE

Polysubstituted aromatic and heteroaromatic compounds have been the synthetic targets of chemists since an early period. An important approach for the synthesis of these type of compounds involve application of annelation methods, that is; construction of cyclic compounds from open chain precursors. This approach is well applicable for heteroaromatic annelation method for the synthesis of benzoheterocycles. The importance of benzoheterocycles in natural product chemistry as well as pharmacology is the driving force for developing new efficient methods for their construction which, became a part of the on going research programme.

The thesis consists of four chapters.

Chapter I consists of two parts. The first part contains a general introduction on aromatic and heteroaromatic annelation reactions. The second part gives a brief outline of the present investigation.

The second chapter deals with the synthesis of benzo[*a*]quinolizines by the reaction of 6,7-dihydro-3,4-dimethoxy-1-methylisoquinoline with β-oxodithioates in the presence of triethylamine.

The third chapter deals with the synthesis of substituted Indazolone derivatives involving *in situ* generation of pyrazolo-3,4-dienolate as diene reacting with various dienophiles.

The fourth chapter of this thesis deals with the Dakin type oxidation using boric acid and hydrogen peroxide in presence of sulphuric acid for the conversion of aromatic aldehydes and ketones to phenols.

Chapters 2, 3 and 4 are framed with an introduction, followed by results and discussion, conclusion and experimental section. The entire documentation in this thesis is supported by appropriate references at the end of each chapter. The references of the published work of the present investigation are cited in the respective chapters.

CHAPTER-I

AROMATIC AND HETEROAROMATIC ANNELATION: A BRIEF INTRODUCTION

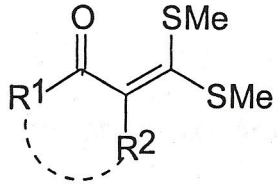
The invention of efficient methods for the synthesis of substituted aromatic compounds has been the interest of chemists since the time of the earliest synthetic organic investigations in the 19th century. Classical approaches to substituted aromatic compounds exploited readily available benzene derivatives and relied on electrophilic and nucleophilic substitution reactions. In recent years, directed metalation reactions have joined the classical substitution methods as another means for the introduction of substituents onto preexisting aromatic rings.

A second approach to highly substituted aromatic compounds involves the application of annelation methods in which the aromatic system is assembled from acyclic precursors[1] and the substitution pattern of the aromatic

ring, is governed by the functionalities and the structure of the starting materials. Annelation strategies enjoy several advantages over substitution strategies, especially when applied to the preparation of highly substituted target molecules. It provides access to substitution patterns that cannot be easily obtained by the classical electrophilic and nucleophilic aromatic substitutions and also facilitates the efficient assembly of highly substituted aromatics that would require long, multistep routes using classical substitution methodology.

The most commonly employed synthetic strategies for the construction of aromatic compounds from open chain precursors are methods based on Diels-Alder chemistry[2] and condensation of 1,3-carbonyl compounds with appropriate 3-carbon fragments.[1] A number of approaches have been developed on the basis of carbonyl condensation reactions for the synthesis of benzene derivatives and their condensed analogs[3,4]. Recently few other methods have been developed which include use of Fisher vinyl carbenes[5], ring expansion of cyclobutenones[6] and cycloaddition of quinodimethane intermediates[7]. In our laboratory, a new method has been developed for the construction of aromatic compounds starting from open chain precursors.[8] This strategy consists of [3+3] annelation approach involving use of α-oxoketene dithioacetals (as 3-carbon 1,3-electrophilic species). Therefore, it is considered appropriate to give a brief introduction to α-oxoketene dithioacetals at this juncture.

The α-oxoketene dithioacetals[9] of general formula **1** are among the simplest synthetic intermediates in organic synthesis which can be conveniently prepared from any active methylene compound by treatment with base, carbon disulfide followed by alkylation. They have been recognized as useful building blocks in many synthetic operations.



1

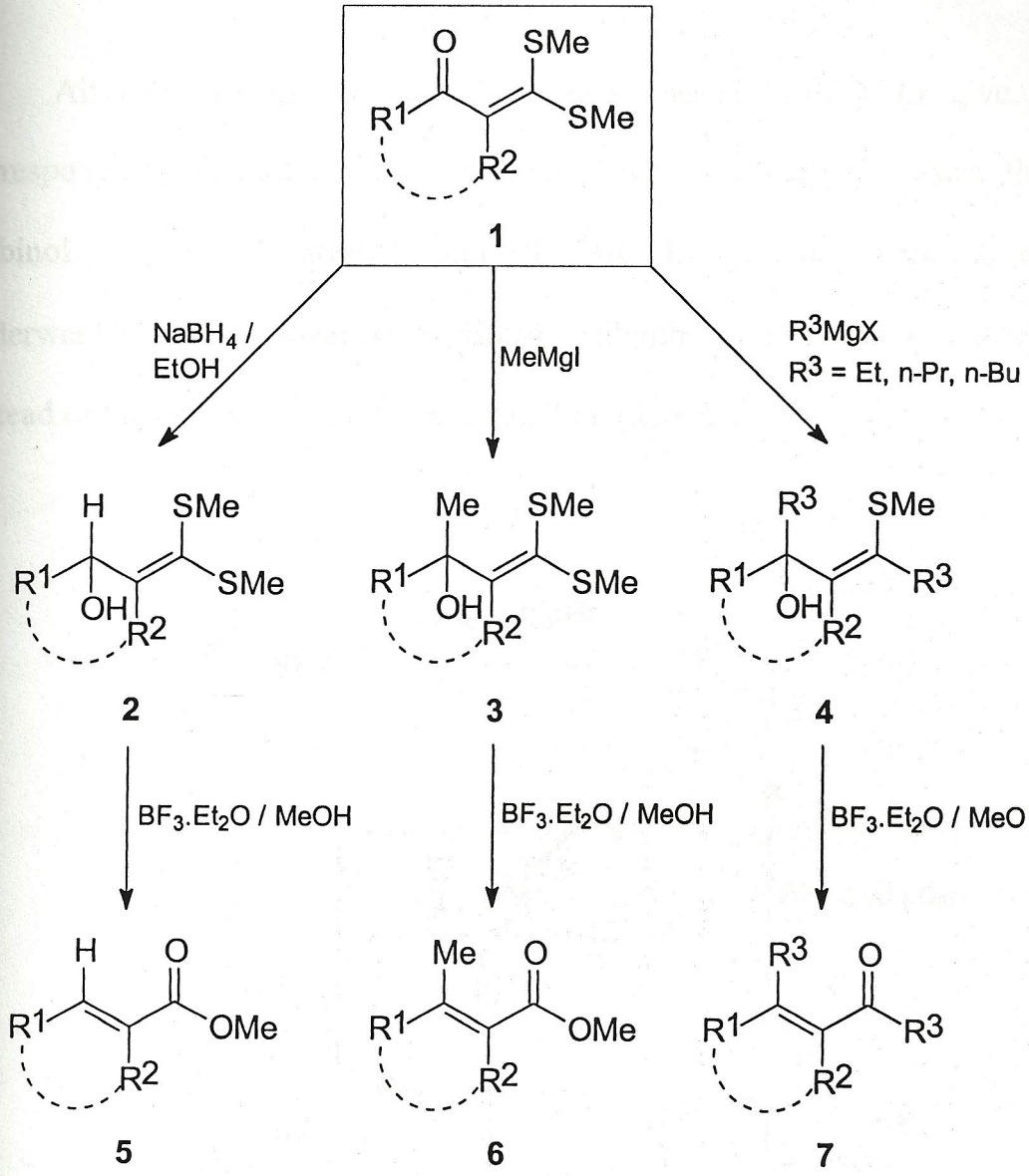
The first synthesis of α-oxoketene dithioacetal was reported by Kelber and co-workers in 1910[10-12]. However, the chemistry of these intermediates remained unexplored, until Thuillier and co-workers[13-16] prepared these compounds in high yields in one pot reaction by reacting the active methylene ketones with carbon disulfide in the presence of sodium amylate followed by alkylation. Later on several modifications in the reaction conditions have been made for obtaining higher yields of α-oxoketene dithioacetals.[17-21]

The oxoketene dithioacetals can be visualized as masked β-ketoesters in which the ester functionality is manifested as a ketene dithioacetal moiety. Alternatively, they may be considered as α,β-unsaturated ketones containing a highly functionalized β-carbon. The α-oxoketene dithioacetals have been

shown to be excellent three carbon fragments possessing 1,3-electrophilic centres with differing electrophilic properties. These intermediates possess considerable potential in the stereo- and regioselective construction of bonds either by a 1,2-nucleophilic addition to carbonyl group or 1,4-conjugate addition to the β-carbon of the enone system. They are primary precursors for the corresponding O,S-, N,S- and N,N-acetals.[9]

As a part of systematic study on various reactivity profiles of α-oxoketene dithioacetals,[9] it was shown in our laboratory that these α-oxoketene dithioacetals undergo sodium borohydride reduction in 1,2-fashion to give the corresponding carbinol acetal **2.** These carbinol acetals are shown to undergo smooth methanolysis in the presence of borontrifluoride-etherate to afford α,β-unsaturated methyl esters **5** in good yields[22] (Scheme-1). The overall transformation can be viewed as homologation of active methylene ketones at the α -position involving a 1,3-carbonyl transposition.

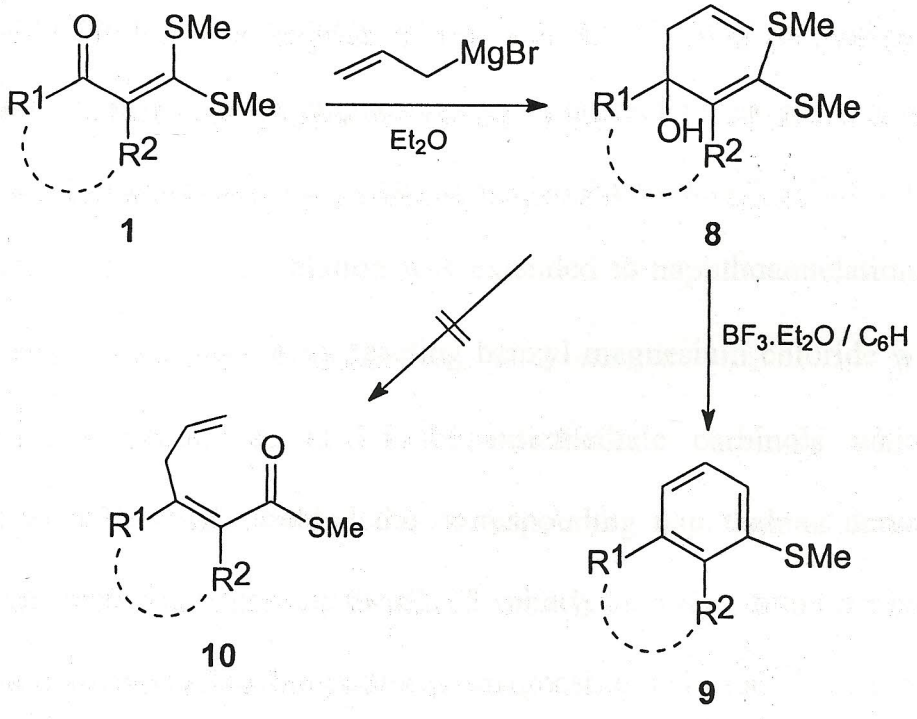
Methylmagnesium iodide was shown to react with α-oxoketene dithioacetals to afford the carbinol acetals **3** by 1,2-addition in good yields (Scheme-1)[23]. The $BF_3.Et_2O$ assisted methanolysis of these carbinol acetals afforded the corresponding β-methyl-α,β-unsaturated esters **6.** The course of addition of higher alkyl Grignard reagents (R = Et, *n*-Pr, *n*-Bu) to α-oxoketene


O
SMe
R1
SMe
R2
1
NaBH4 /
EtOH
MeMgI
R3MgX
R3 = Et, n-Pr, n-Bu
H
SMe
R1
SMe
OH
R2
2
Me
SMe
R1
SMe
OH
R2
3
R3
SMe
R1
R3
OH
R2
4
BF3.Et2O / MeOH
BF3.Et2O / MeOH
BF3.Et2O / MeO
H
O
R1
OMe
R2
5
Me
O
R1
OMe
R2
6
R3
O
R1
R3
R2
7

Scheme 1

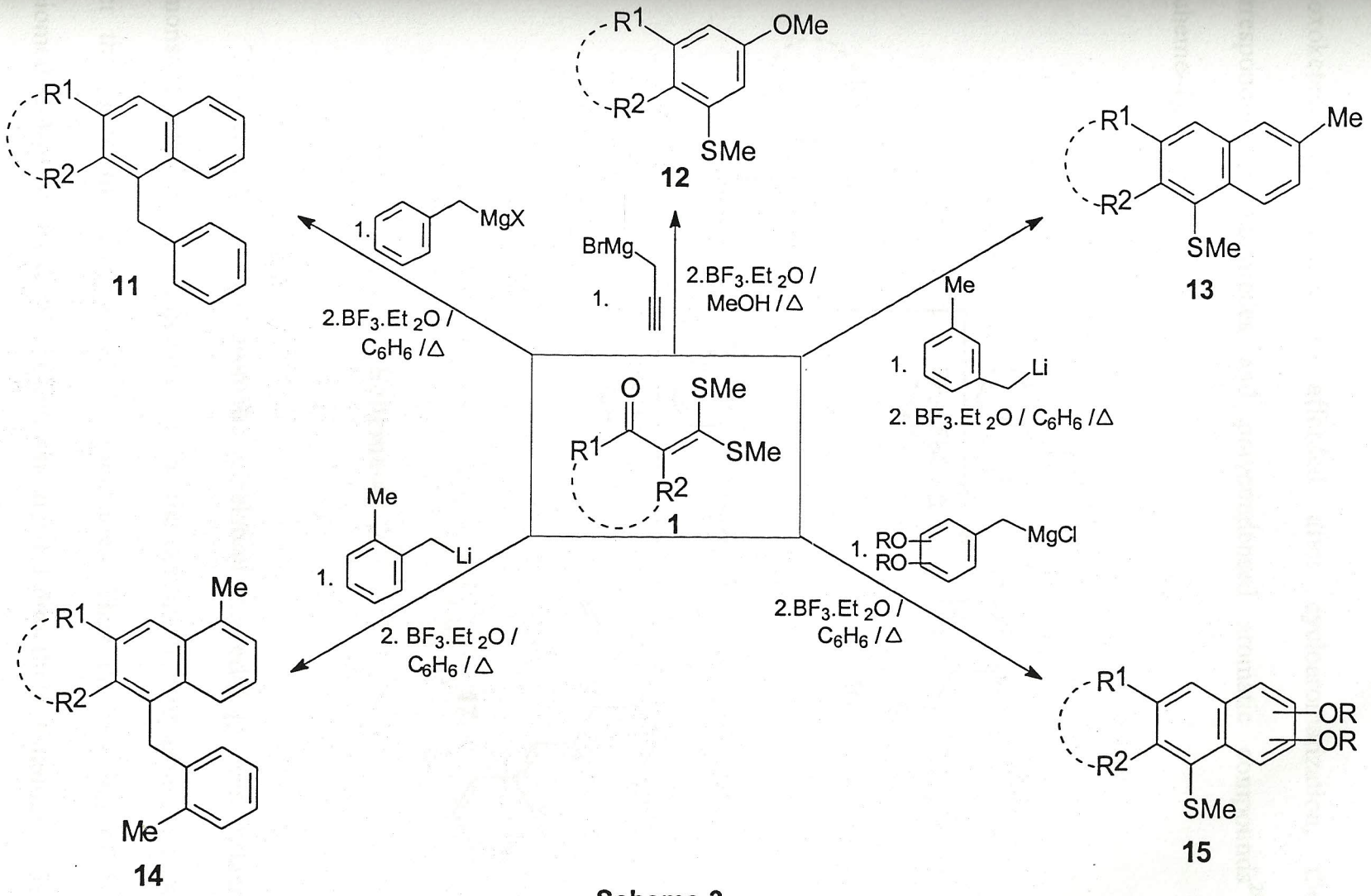
dithioacetals followed a sequential 1,4- and 1,2-addition pattern to afford carbinols **4** which are shown to afford α,β-unsaturated ketones **7** after subsequent hydrolysis in the presence of $BF_3.Et_2O$[23] (Scheme-1).

Allyl magnesium bromide was also reacted with **1** to give the corresponding carbinol acetal **8** in high yields[24]. Interestingly when these carbinol acetals were treated with $BF_3.Et_2O$ in refluxing benzene, they underwent cycloaromatization to afford methylthio substituted aromatics **9** instead of the observed carbonyl transposition (Scheme-2)[24].



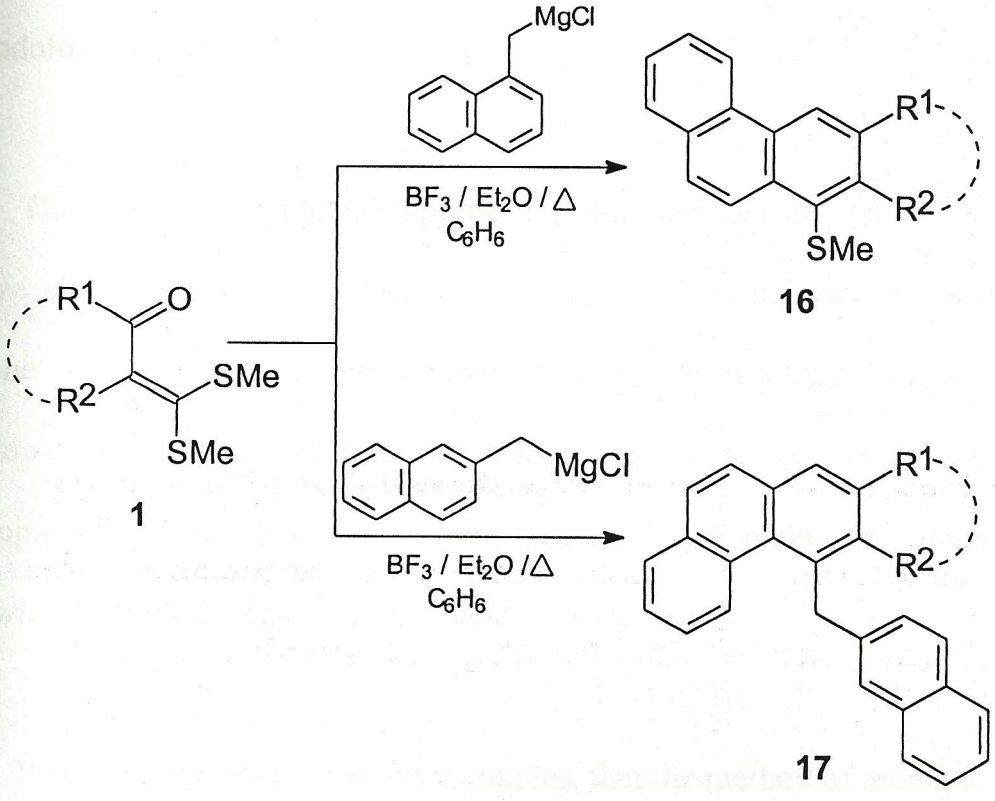
Scheme-2

Thus, a new [3+3] aromatic annelation methodology via α-oxoketene dithioacetals was discovered in our laboratory and this protocol has emerged as an area of great synthetic potential. This new [3+3] aromatic annelation methodology has been extensively investigated to establish its general applicability. The method is a major discovery involving highly functionalized open chain precursors to afford appropriately substituted aromatics in a simple two step sequence. The reaction was found to be general with a large number of α-oxoketene dithioacetals derived from both cyclic, acyclic ketones as well as equally large number of allylic anions making its synthetic scope unlimited. Thus this method was extremely versatile when extended to methyl allyl magnesium bromide, crotyl magnesium bromide and propargyl magnesium bromide to afford the substituted benzoannelated products[8,25]. Subsequently this method of aromatic annelation was extended to naphthoannelation. This transformation was achieved by reacting benzyl magnesium chloride with α-oxoketene dithioacetals to afford the intermediate carbinols which on treatment with $BF_3.Et_2O$ yielded the corresponding naphthalene derivatives through benzene ring participation[26]. Similarly *o*-xylyl lithium, *m*-xylyl lithium[27] and methoxy substituted benzyl magnesium chlorides[28] were reacted with α-oxoketene dithioacetals followed by $BF_3.Et_2O$-assisted cyclization to afford the corresponding substituted naphthalenes (scheme-3).


R1
R2
OMe
SMe
12
11
1. MgX
2.BF3.Et2O / C6H6 /Δ
BrMg
1.
2.BF3.Et2O / MeOH /Δ
Me
SMe
13
1. Li
2. BF3.Et2O / C6H6 /Δ
O
SMe
SMe
R1
R2
1
Me
1. Li
2. BF3.Et2O / C6H6 /Δ
1. RO RO MgCl
2.BF3.Et2O / C6H6 /Δ
OR
OR
15
14

Scheme-3

When α- and β-naphthylmethylmagnesium halides were reacted with α-oxoketene dithioacetals it afforded after cycloaromatization, the corresponding phenanthrenes and polycondensed aromatic compounds[29] (Scheme-4).



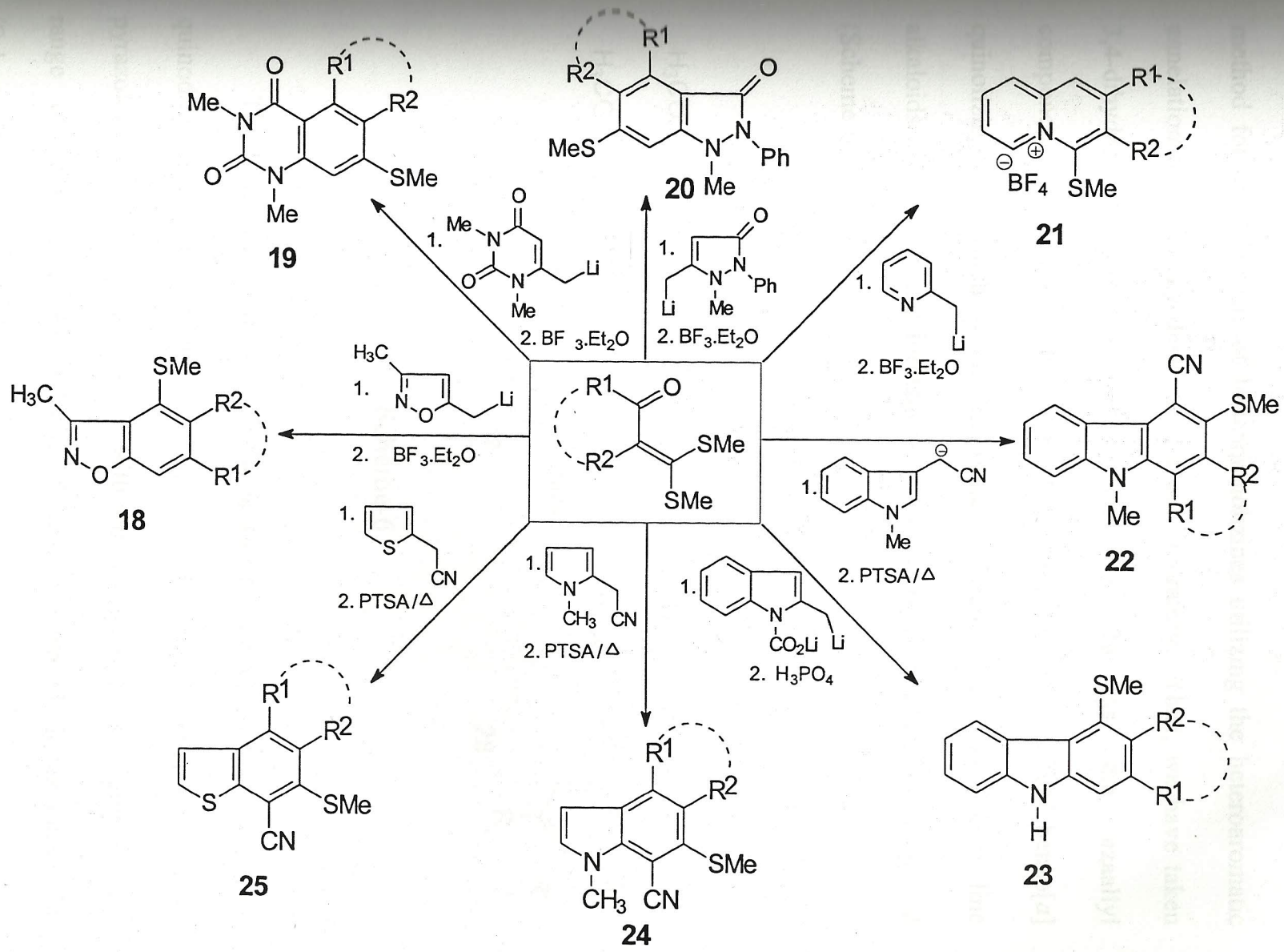
Scheme-4

The versatility of this aromatic annelation methodology was further demonstrated by applying this strategy for the construction of aromatic ring over the preconstructed heterocyclic molecules. Thus the reaction of 5-lithiomethyl-3-methylisoxazole, 6-lithiomethyl-1,3-dimethylpyrimidine, 3-lithiomethyl-2-methyl-1-phenyl-5-pyrazolone and 2-picoline with α-oxo-

ketene dithioacetals yielded the corresponding benzisoxazoles[30], quinazolines[31], indazolones[32] and quinolizinium salts[33] respectively. Recently, [a]annelatedcarbazoles[34], [b]annelated carbazoles[35], indoles[36] and benzothiophenes[37] have been achieved by extending this aromatic annelation methodology (Scheme-5).

The classical synthetic approaches for benzoheterocycles usually involve elaboration of a heterocyclic ring onto an appropriately substituted benzene ring. However, the aromatic annelation strategy of building functionalized benzene ring onto preconstructed heterocycles resulted in the development of new synthetic methodology for target molecules which are otherwise difficult to achieve by classical approaches.

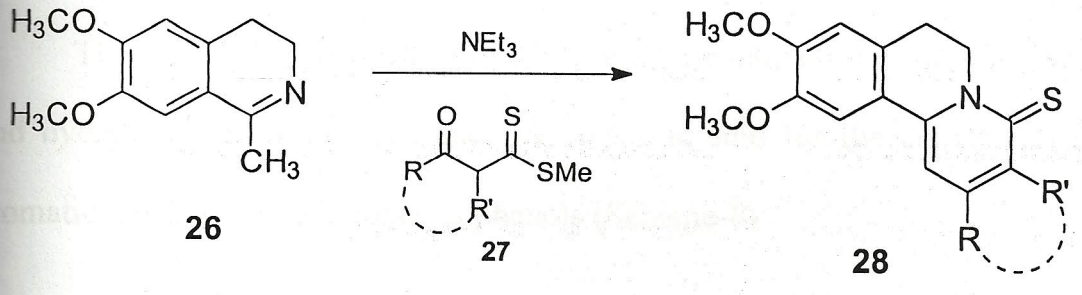
It is apparent from the above examples, that the method of aromatic and heteroaromatic annelation is not only applicable for the synthesis of condensed aromatics but this new strategy has been found to be highly successful for the construction of aromatic ring over the preconstructed heterocyclic molecules providing a new synthetic dimension to the entire chemistry of benzoheterocyclic compounds and their condensed variants.



Scheme - 5

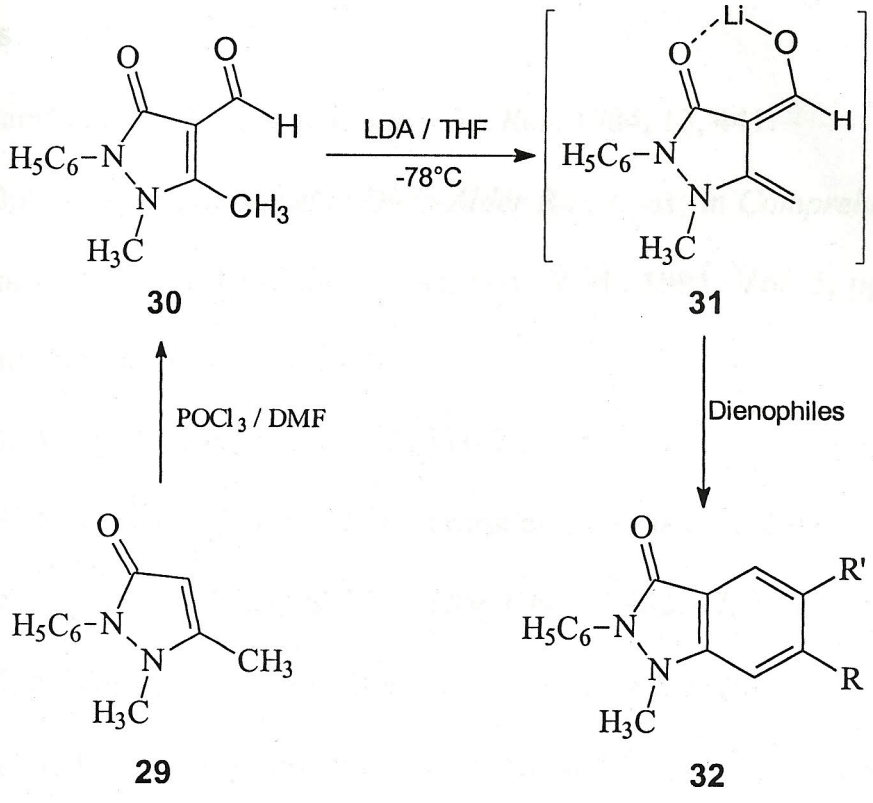
The work presented in this thesis

In the present investigation it was proposed to develop a new efficient method for the synthesis of benzoquinolizines utilizing the heteroaromatic annelation methodology developed in our laboratory. Thus, we have taken 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline **26** as the azaallyl component and reacted with various β-oxodithioates **27** to afford benzo[*a*] quinolizines **28** which forms the basic skeleton of various isoquinoline alkaloids. The scope and limitations of this work is discussed in chapter 2 (Scheme-6).



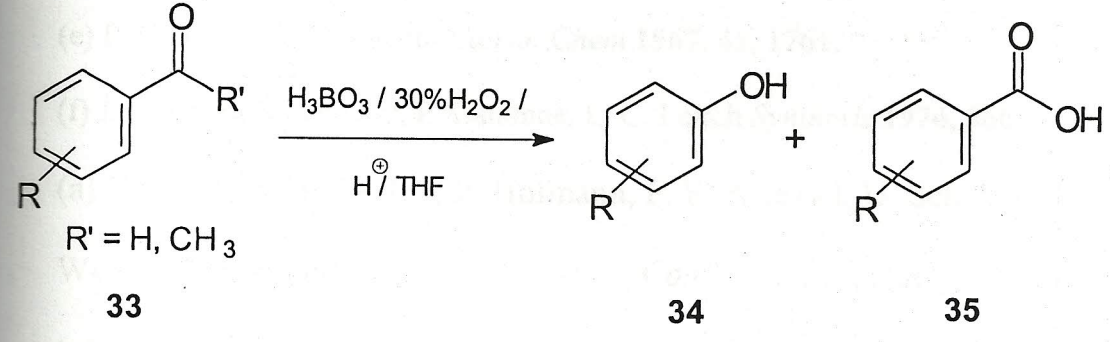
Scheme-6

The third chapter deals with the *in situ* generation of heterocyclic *o*-quinodimethane intermediate **31** from 4-formyl-2,3-dimethyl-1-phenyl pyrazolin-5-one **30** and its reaction with various dienophiles to give a wide range of regiospecifically substituted and condensed indazolones **32** (Scheme-7).



Scheme -7

The fourth chapter deals with the Dakin type oxidation using boric acid and hydrogen peroxide in presence of sulphuric acid for the conversion of aromatic aldehydes and ketones to phenols (Scheme-8).



Scheme-8

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