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 metation 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 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 \(\alpha\)-oxoketene dithioacetals (as 3-carbon 1,3-electrophilic species). Therefore, it is considered appropriate to give a brief introduction to \(\alpha\)-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.

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 \( \beta \)-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 \( \alpha \)-oxoketene dithioacetals,\(^9\) it was shown in our laboratory that these \( \alpha \)-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 boron trifluoride-etherate to afford \( \alpha,\beta \)-unsaturated methyl esters 5 in good yields\(^{22}\) (Scheme-1). The overall transformation can be viewed as homologation of active methylene ketones at the \( \alpha \)-position involving a 1,3-carbonyl transposition.

Methylmagnesium iodide was shown to react with \( \alpha \)-oxoketene dithioacetals to afford the carbinol acetals 3 by 1,2-addition in good yields (Scheme-1)\(^{23}\). The BF\(_3\).Et\(_2\)O assisted methanolysis of these carbinol acetals afforded the corresponding \( \beta \)-methyl-\( \alpha,\beta \)-unsaturated esters 6. The course of addition of higher alkyl Grignard reagents (\( R = \text{Et}, \text{n-Pr}, \text{n-Bu} \)) to \( \alpha \)-oxoketene
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 BF₃.Et₂O²³ (Scheme-1).

Allyl magnesium bromide was also reacted with 1 to give the corresponding carbinol acetal 8 in high yields²⁴. Interestingly when these carbinol acetals were treated with BF₃.Et₂O 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 \( \alpha \)-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 \( \alpha \)-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 \( \alpha \)-oxoketene dithioacetals to afford the intermediate carbinols which on treatment with BF\(_3\),Et\(_2\)O 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 \( \alpha \)-oxoketene dithioacetals followed by BF\(_3\),Et\(_2\)O-assisted cyclization to afford the corresponding substituted naphthalenes (scheme-3).
Scheme 3
When $\alpha$- and $\beta$-naphthylmethylmagnesium halides were reacted with $\alpha$-oxoketene dithioacetals it afforded after cycloaromatization, the corresponding phenanthrenes and polycondensed aromatic compounds\(^{29}\) (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 $\alpha$-oxo-
ketene dithioacetals yielded the corresponding benzisoxazoles\textsuperscript{30}, quinazolines\textsuperscript{31}, indazolones\textsuperscript{32} and quinolizinium salts\textsuperscript{33} respectively. Recently, [a]annelated carbazoles\textsuperscript{34}, [b]annelated carbazoles\textsuperscript{35}, indoles\textsuperscript{36} and benzothiophenes\textsuperscript{37} have been achieved by extending this aromatic annelation methodology (Scheme-5).

The classical synthetic approaches for benzo-heterocycles 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 benzo-heterocyclic 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).
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).
References


   
   
   
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