Chapter 1

Introduction

Dithio carboxylic acids and their esters are valuable reactive intermediates in synthetic organic chemistry. They can be easily prepared from inexpensive starting materials. Functionalized dithiocarboxylates are used in the synthesis of a variety of heterocycles.\textsuperscript{1-4} They are useful precursors for the synthesis of thioamides and $\alpha$-oxoketene-$S,N$-acetals. Functionalized ketene-$S,N$-acetals and corresponding thioketones are versatile three carbon fragments exhibiting enamine character as well.\textsuperscript{5-9} They can also undergo variety of other valuable synthetic transformations leading to synthesis of hetrocyclic compounds.\textsuperscript{10-21} An overview of general methods of preparation and important applications of $\alpha$-oxoketene-$S,N$-acetals and $\beta$-enaminothioketones are reviewed in the chapter two of the thesis. We have examined the reactions of functionalized ketene-$S,N$-acetals, enaminothioketones and $\beta$-oxodithiocarboxylates and the results of these reactions are described in Chapters three, four and five of the thesis.

1.1 $\alpha$-Oxoketene-$S,N$-acetals

Usually $\alpha$-oxoketene-$S,N$-acetals are prepared from active methylene ketones. The reaction of enolate anion derived from active methylene ketones 1
with aryl isothiocyanate 2 and subsequent alkylation afford α-oxoketene-S,N-acetal 3 (Scheme 1).\(^{22,23}\)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{R}^1 & \quad \text{R}^2 \\
\text{1} & \quad \text{2} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{1.Base} & \quad \text{2.Mel} \\
\text{3} & \quad \text{3}
\end{align*}
\]

Scheme 1

An alternative method for the synthesis of α-oxoketene-S,N-acetals involves the reaction of α-oxoketene-S,S-acetal with primary or secondary amines.\(^{24-26}\) However this reaction requires vigorous reaction conditions and results in α-oxoketene-S,N-acetal along with α-oxoketene-N,N-acetal. Recently this method has been modified using lithioamino anions.\(^{27}\) Alkylation of β-oxothioamide, prepared from β-oxodithioesters 4 with methyl iodide also result in the formation of α-oxoketene-S,N-acetals 6 in good yield (Scheme 2).\(^{24}\)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{SMe} & \quad \text{N} \quad \text{N} \\
\text{R}^1 & \quad \text{R}^2 \\
\text{4} & \quad \text{5} & \quad \text{6}
\end{align*}
\]

Scheme 2

α-Oxoketene-S,N-acetals are three carbon synthons with 1,3-bielectrophilic character. Their reactions with binucleophiles like guanidine and cyanoacetamide give corresponding pyrimidines and pyridones respectively. As the α-position of the ketene-S,N-acetal moiety can act as a nucleophile, they can also function as enaminoketones. For example Junjappa et al reported the reaction of S,N-acetal 3
with bromoacetaldehyde diethylacetal 7 in hot DMF to afforded N-substituted pyrroles 8 (Scheme 3).\textsuperscript{28}

\[
\begin{array}{c}
\text{MeS}^\text{N}^\text{H} \\
\text{R}^1 \\
\text{R}^2 \\
\text{H} \\
\text{MeS}^\text{N}^\text{H} \\
\text{R}^1 \\
\text{R}^2 \\
\text{EtO}^\text{OEt} \\
\text{Br} \\
\text{N} \\
\text{MeS}^\text{N}^\text{H} \\
\text{R}^1 \\
\text{R}^2 \\
\end{array}
\xrightarrow{\text{DMF, Heat}}
\begin{array}{c}
\text{MeS}^\text{N}^\text{H} \\
\text{R}^1 \\
\text{R}^2 \\
\text{O} \\
\text{MeS}^\text{N}^\text{H} \\
\text{R}^1 \\
\text{R}^2 \\
\end{array}
\]

Scheme 3

In continuation with the ongoing research on these intermediates, in the Chapter three of the thesis, we have described the reactions of α-oxoketene-S,N-acetals with Lawesson’s reagent and Vilsmeier Haack reagent leading to the formation of functionalized 1,2-dithiol-3-thiones and 3-benzoyl-2-hydroxy quinolines respectively.

1.2 β-Enaminothioketones

β-Enaminothioketones 10 are usually prepared by thiocarbonylation of enamiones 9 with suitable thionating agent like phosphorous pentasulfide, hydrogen sulfide\textsuperscript{29} or 2,4-bis(p-methoxyphenyl)-1,3-dithiadiphosphetane-2,4-disulfide (Scheme 4).\textsuperscript{30}

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{NR}^2 \\
\text{R}^1 \\
\text{R}^2 \\
\text{NR}^2 \\
\text{H}_2\text{S} \\
\text{R}^1 \\
\text{R}^2 \\
\text{NR}^2 \\
\end{array}
\xrightarrow{\text{H}_2\text{S}}
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{NR}^2 \\
\text{R}^1 \\
\text{R}^2 \\
\text{NR}^2 \\
\end{array}
\]

Scheme 4
Recently Kim et al reported a method for the preparation of $\beta$-enaminothiones by the reaction of isothiazolium salt with NaBH$_4$ in a mixture of chloroform and ethanol at room temperature.$^{31}$ Ring opening reaction of 1,2-dithiolium salt with amine or hydrogen sulfide also affords $\beta$-enaminothioketones.$^{32}$

Similar to $\alpha$-oxoketene-S,N-acetals, $\beta$-enaminothioketones can act as enamines and are used in the synthesis of heterocyclic compounds.$^{33}$ A review of their methods of preparation and synthetic applications have been described in the Chapter two of the thesis.

1.3 $\beta$-Oxodithiocarboxylates

$\beta$-Oxodithiocarboxylates usually prepared by the thiocarbonylation of active methylene ketones with dialkyl trithiocarbonates or chlorodithioformates. For example a convenient method of preparation for the $\beta$-oxodithioester 4 involves the condensation of active methyleneketones 1 with dimethyl trithiocarbonate 11 in the presence of base (Scheme 5).$^{34}$

![Scheme 5](image)

We have also developed convenient methods for the synthesis of these valuable intermediates. Nair et al have reported the solvolysis of substituted $\alpha$-ketenedithioacetals catalyzed by Lewis or protic acid to afford respective esters or thioesters.$^{35}$ Similarly the sulfhydrolysis of benzoyl ketene dithioacetals lead
to the formation of methyl benzoyl dithioacetate in good yields. We have also found that demethylation reaction of α-oxoketene dithioacetals employing a strong base such as dimethyl anion also leads to the formation of β-oxodithiocarboxylates.\textsuperscript{36}

β-Oxodithiocarboxylates are valuable three carbon synthons in the synthesis of a variety of heterocycles. Earlier studies from our laboratory have shown that they can be transformed into related multifunctional intermediates.\textsuperscript{37} In continuation with the ongoing research work in our laboratory we have developed a convenient method for the synthesis of β-oxodithiocarboxylates and they have effectively used in the preparation of functionalized thiophenes.\textsuperscript{38}

1.4 **Reactions of α-oxoketene-S, N-acetals with Lawesson’s Reagent**

The dimer of p-methoxyphenylthionophosphine sulfide is commonly known as Lawesson’s reagent \textsuperscript{15} which is considered as the best known thionating reagent.\textsuperscript{30} We have investigated the thionation reaction of 1,3-electrophilic α-oxoketene-S,N-acetal with Lawesson’s reagent (LR). Our aim was to prepare β-enaminothioketones, which can be further transformed into heterocyclic compounds. However, the reaction led to the formation corresponding 1,2-dithiol-3-thiones \textsuperscript{13} as the major product along with β-enaminothioketones \textsuperscript{14} and β-oxodithio carboxylates \textsuperscript{15} (Scheme 6).
The S, N-acetal derived from cyclic ketone such as α-tetralone 17 gave only the corresponding β-oxodithioester 18 (Scheme 7).
1.5 Reaction of α-Oxoketene-S,N-acetal with Vilsmeier-Haack Reagent

Vilsmeier-Haack reaction is an important formylation reaction for the facile preparation of aldehydes from electron rich aromatic compound.\(^{39,40}\) In recent years studies on the reaction of enolizable carbonyl compounds with Vilsmeier-Haack reagent have resulted in a variety of useful transformations leading to heterocyclic synthesis. Our group has also made contributions to explore the synthetic utility of this reagent in organic synthesis.\(^{40,41}\) In literature there are many reports on the Vilsmeier-Haack formylation on hetero atoms like oxygen, nitrogen, sulfur etc. leading to the formation of heterocyclic compounds. So we were interested to examine the reactivity of aroyl ketene-S,N-acetal towards Vilsmeier-Haack reagent. When benzoyl ketene-S,N-acetal 12 was treated with two equivalent of Vilsmeier-Haack reagent, functionalized quinoline 19 was obtained. (Scheme 8)

\[
\begin{align*}
\text{O} & \quad \text{SMe} \\
\text{H} & \quad \text{N} \\
\text{O} & \quad \text{POCl}_3 \\
\text{DMF} & \quad \text{12} \quad \text{19}
\end{align*}
\]

Scheme 8

Reaction of α-oxoketene-S,N-acetal, synthesized from cyclic ketone such as α-tetralone 20, afforded N-formyl α-oxoketene-S,N-acetal 21 in good yield (Scheme 12).
1.6 Synthesis of β-Oxodithiocarboxylates

β-Oxodithioesters have been shown to be a class of highly versatile and widely used intermediates in organic synthesis. Generally they are prepared by refluxing active methylene ketones with trithiocarbonate in benzene or toluene in the presence of sodium hydride as the base. The reaction was comparatively difficult, as it requires continuous heating for five to ten hours. Moreover, the yield of the reaction was varied depending on the reaction condition. So we modified the procedure using a solvent mixture of hexane/DMF (4:1 ratio) for the reaction β-oxodithioesters in good yield. The reaction is attractive and is devoid of offensive smell of methanethiol as well as refluxing in carcinogenic aromatic hydrocarbon solvents.
1.7 Reactions of Functionalized β-Oxodithioesters with Phenacyl Bromide

Earlier reports from our laboratory have shown that the reaction of β-oxodithioesters with α-haloketones in the presence of sodium hydride as the base leads to the formation of an intermediate ketene dithioacetal, which can undergo cyclization reactions leading to a variety of substituted thiophenes.\textsuperscript{37} It has been demonstrated that the mode of cyclization of the intermediate ketene dithioacetal largely depends on the structure of the substrates. However, now we report a selective intramolecular aldol condensation reaction of the intermediate ketene dithioacetal, leading to the formation of functionalized thiophenes in good yields. When β-oxodithioester 25 is allowed to react with phenacyl bromide in NaOH/EtOH media, functionalized thiophenes 26 were formed in good yield via in situ cyclization reaction of the intermediate ketene dithioacetal. (Scheme 11).

\[ \text{O} \quad \text{SMe} \quad \text{O} \quad \text{Ph} \quad \text{Br} \]

\[ \text{R}_1 \text{C} = \text{C} \text{R}_2 \quad \text{NaOH/EtOH} \quad \text{MeS} \]

\[ \text{O} \quad \text{R}^1 \quad \text{Ph} \]

\[
\begin{array}{|c|c|c|c|}
\hline
\text{25, 26} & \text{R}_1 & \text{R}_2 & \text{Yield (\%)} \\
\hline
\text{a} & \text{C}_6\text{H}_5 & \text{H} & 60 \\
\text{b} & \text{4-ClC}_6\text{H}_4 & \text{H} & 62 \\
\text{c} & \text{CH}_3 & \text{H} & 58 \\
\text{d} & & & 62 \\
\text{e} & & & 60 \\
\hline
\end{array}
\]

Scheme 11
1.8 Reactions of Functionalized β-Oxodithioesters with Bromoacetone

We have also examined the alkylation reactions of β-oxodithioesters with bromoacetone. The reaction was similar to the above described reactions affording functionalized acetyl thiophenes 27 in good yields.

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th></th>
<th>R_1</th>
<th>R_2</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>C_6H_5</td>
<td>H</td>
<td>68</td>
</tr>
<tr>
<td>b</td>
<td>4-ClC_6H_4</td>
<td>H</td>
<td>72</td>
</tr>
<tr>
<td>c</td>
<td></td>
<td></td>
<td>66</td>
</tr>
<tr>
<td>d</td>
<td></td>
<td></td>
<td>69</td>
</tr>
</tbody>
</table>

Scheme 12
1.9 Reaction of Functionalized β-Enaminothioketones with Phenacyl Bromide

As a part of our studies to explore the synthetic potentiality, 3-methylthio-3-anilino-1-phenyl thioxopropene was allowed to react with bielectrophile such as phenacyl bromide in the presence of a base such as sodium hydride and it afforded aminothiophene 29. Similar strategy was extended to other substituted analogues also (Scheme 13). In this reaction, we expected alkylation on the thiocarbonyl moiety leading to the formation of methylthio substituted α-oxoketene-S,N-acetal intermediate and the additional electrophilic center of the phenacythio moiety available in the intermediate ketene dithioacetal lead to the formation of the expected thiophene.

![Scheme 13](image)

1.10 Reaction of Functionalized β-Enaminothioketones with Methyl Iodide

We have examined the alkylation reaction of β-enaminothioketones 17 with methyl iodide. In the presence of base the reaction afforded thiolesters 30 as the main product (Scheme 14). The reaction was extended to chlorophenyl enaminothioketone also. This strategy deserve some attention due to the formation of synthetically important thiolesters which is otherwise difficult to synthesise.
Conclusions

We have investigated the synthetic utility of α-oxoketene-S,N-acetals, β-enaminothioketones and β-oxodithioesters leading to the formation of functionalized heterocycles. The reaction of α-oxoketene-S,N-acetals with Lawesson’s reagent affords 3H-1,2-dithiole-3-thiones along with β-enamionthioketones and functionalized dithioesters in a one pot process. Benzoyl-S,N-acetal on treatment with Vilsmeier-Haack reagent affords functionalized quinolines, while the α-oxoketene-S,N-acetal derived from α-tetralone afforded N-formylated product. In Chapter four of the thesis we have described a convenient method for the synthesis of β-oxodithioesters and their application in the synthesis of functionalized thiophenes. When β-enaminothioketones are treated with various alkylating agents like methyl iodide and phenacyl bromide, substituted thioesters and amino substituted thiophenes respectively are formed.

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