5.1 Introduction

Enaminothioketones are useful intermediates and have been utilized for the synthesis of a variety of heteroatom containing compounds.\textsuperscript{1-5} We have investigated some of the reactions of $\beta$-enaminothioketones, which are also referred to as enaminothiones. $\beta$-Enaminothioketones are 1,3-biselectrophilic three carbon fragments and valuable synthons for the syntheses of heterocyclic compounds especially for the syntheses of thiophenes\textsuperscript{6,7} and thiopyrans.\textsuperscript{8-10} However, relatively fewer methods are known for the preparation of functionalized $\beta$-enaminothioketones. They have not been extensively studied so far, even though they are potential intermediates in heterocyclic syntheses. This might be due to the difficulty of access to this class of compounds. We have prepared $\beta$-enaminothioketones 2 by the thionation reaction of $\alpha$-oxoketene-S,N-acetal 1 with Lawesson's reagent (Scheme 1) and the results are described in the chapter three of the thesis. In the present chapter the reactions of $\beta$-enaminothioketone with alkylating
agents like methyl iodide and phenacyl bromide resulting the formation of thiolesters and functionalized aminothiophenes are described.

\[
\begin{array}{c}
\text{agents like methyl iodide and phenacyl bromide resulting the formation of thiolesters and functionalized aminothiophenes are described.}
\end{array}
\]

Scheme 1

5.2 Thioesters from ketene dithioacetals and dithioesters

\[\alpha\text{-Oxoketene dithioacetals are considered as protected } \beta\text{-ketoesters and hence their complete hydrolysis should give the corresponding } \beta\text{-ketoesters. Partial hydrolysis of ketene dithioacetals to } \beta\text{-ketothiolester is known to proceed in presence of mineral acid and water.}\]

\[\alpha\text{-Oxoketene dithioacetals undergo 1,2 reduction with NaBH}_4\text{ to give the allylic alcohols in good yields.}^{11b}\text{ These carbionial acetals on treatment with p-toluenesulfonic acid gave of } \alpha,\beta\text{-unsaturated thiolesters 4(Scheme2).}\]

\[
\begin{array}{c}
\text{Later Dieter found that HBF}_4\text{ in THF could be effectively used to get unsaturated thiolesters together with methyl sulfide.}
\end{array}
\]
Oxidation reaction of functionalized dithioesters with phenyl selenic anhydride afforded thiolesters (Scheme 3)\(^{13}\)

\[
\begin{align*}
\text{5.3 General Methods for the Preparation of Functionalized Aminothiophenes} \\
\text{Literature survey revealed that there are only a few reports on the syntheses of functionalized aminothiophenes. They are valuable precursors in pharmaceutical chemistry. Kirsch et al. recently reported the syntheses of functionalized aminothiophenes from 1,3 diketones. For example, the reaction of 1,3-diketone 7 with isothiocyanates in the basic medium, followed by a condensation with bromoacetate or chloroacetonitrile afforded aminothiophene 9 in good yield via a Dieckmann-type condensation of the intermediate ketene-S,N-acetal 8 (Scheme 4).}^{11}
\end{align*}
\]

In 1998 Kim et al. reported the synthesis of 2-acyl and 2-aryl-2-(alkylamino)-5-aryliothiophenes 11 and 12 by the reaction of thioaroylketene S,N-acetals with 1,3-dicarbonyl compounds in the presence of mercury(II)acetate (Scheme 5).\(^7\)
3-Aminothiophene-2-carboxylic ester derivatives 14 are made by the reaction of potassium 3-ethoxy-3-oxopropanoate with isothiazolium salts or by reaction with 2-ethoxy-2-oxo ethylidenedimethyl sulfuran (Scheme 6). \(^\text{16}\)

In our laboratory the reaction of \(\beta\)-oxothioamides with alkylating agents like \(\alpha\)-haloketones afforded an intermediate ketene-S,N-acetal which undergoes intermolecular cyclization involving the enamine moiety to afford corresponding aminothiophene derivatives (Scheme 7). \(^\text{17}\)
There are some reports in the literature which describes alkylation of β-oxodithioesters and β-oxothioamides with α-haloketones. These reactions involve the alkylation at the thiolate anion followed by an intramolecular nucleophilic attack of enolates on carbonyl group or a nitrite. For example Gompper and Schafer have reported the reaction of the dianion of the dithioic acid derived from methyl cyanoacetate with α-chloroacetamide. The reaction proceeds under acidic condition and the intermediate formed from the initial alkylation undergo cyclization which involves addition to the nitrile group (Scheme 8).

Scheme 8

Substituted α-cyanoketones were treated with carbon disulfide in the presence of base and the intermediate dithiolate anions were reacted with methyl iodide and α-haloketeones, esters or α-halonitriles to afford the respective thiophenes (Scheme 9).

Scheme 9
When doubly activated compounds such as acetyl acetone and ethyl acetoacetate were reacted in a similar fashion, aminothiophene derivatives 23 were obtained (Scheme 10).\(^{17}\)

\[
\begin{align*}
\text{O} & \text{O} \quad \text{H}_3\text{C} \quad \text{C} \quad \text{CH}_3 \\
\text{1. PhNCS/ NaH/ DMF} & \quad \text{2. PhCOCH}_2\text{Br} \\
\text{22} & \quad \text{23}
\end{align*}
\]

**Scheme 10**

5.4 Results and Discussion

The reaction of functionalized \(\beta\)-enaminothioketone with alkylating agent such as methyl iodide in presence of base such as sodium hydride was examined first. Again \(\beta\)-enaminothioketones were allowed to react with \(\alpha\)-haloketone such as phenacyl bromide under similar reaction condition. Finally we have done a few reactions on alkylation reaction of functionalized \(\beta\)-enaminothioketones which also gave the the expected products.

5.4.1 Reaction of \(\beta\)-Enaminothioketones with Methyl iodide: Formation of 3-Aryl-1,3-bis(methylthio) prop-2-ene-1-ones

\(\beta\)-Enaminothioketones can be readily obtained by the thionation reaction of \(\alpha\)-oxoketene-S,N-acetal with Lawesson’s reagent. We have examined the alkylation reaction of \(\beta\)-enaminothioketones using methyl iodide as the alkylating agent in presence of sodium hydride as the base. The reaction resulted in the formation of an intermediate imine which on hydrolysis afforded corresponding
thiolesters $24$ (Scheme 11). The structure of the compound $24$ was confirmed by $^1$H NMR, $^{13}$C NMR and mass spectral data.\textsuperscript{12-15}

The mechanism of the reaction involves simple alkylation of $\beta$-enaminothioketones with methyl iodide leading to the formation of an imine and the hydrolysis of the intermediate to afford the thiolesters (Scheme 12).

![Diagram](image)

Scheme 11

<table>
<thead>
<tr>
<th>24</th>
<th>R</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Cl</td>
<td>80</td>
</tr>
<tr>
<td>b</td>
<td>Me</td>
<td>64</td>
</tr>
</tbody>
</table>

Scheme 12
5.4.2 Reaction of β-Enaminothioketones with α-Haloketones: Formation of 2-Benzoyl-3-phenylamino-5-phenylthiophene

Next we have treated β-enaminothioketones with phenacyl bromide in presence of sodium hydride as the base. In this reaction we expected not only the formation of an intermediate imine, but also the formation of functionalized thiophenes as a result of subsequent cyclization. The analytical results proved the structure of the compounds as the expected substituted thiophenes (Scheme 13). The yield of the reaction was 52-62 %.

The mechanism for the formation of functionalized aminothiophene from β-enaminothioketones can be rationalized as follows (Scheme 14). The alkylation reaction of the β-enaminothioketone by phenacyl bromide on thiocarbonyl group, affords an imine 26. Under basic conditions, nucleophilic
attack on carbon atom of the imine by the enolate generated at the phenacylthio group results in a cyclic intermediate 28 which on elimination of the methylthio group undergoes aromatization to afford 2-arylated-3-phenylamino-5-phenylthiophene 25a in good yield.

Scheme 14

Similar mechanism is also possible for the formation of 25b. The structure of the compound 25a was confirmed by \(^1\)H NMR, IR and mass spectral data. The structure of the compound 25b was confirmed on the basis of comparison of spectral and physical data with reported values.\(^7\)\(^,\)\(^26\)

5.5 Conclusions

The functionalized \(\beta\)-enaminothioketones obtained by the thionation reaction of \(\alpha\)-oxoketene-S,N-acetals with Lawesson's reagent was allowed to
react with suitable alkylation agents such as methyl iodide and phenacyl bromide and the reactions afforded 3-aryl-1,3-bis(methylthio)-prop-2-ene-1-one 24 and functionalised aminothiophenes 25 in good yields.

5.6 Experimental

General experimental details are given in chapter three.

5.6.1 General Procedure for the Preparation of 3-aryl-1,3-bis(methylthio)prop-2-ene-1-ones

To an ice cold and well stirred suspension of sodium hydride (480 mg, 10 mmol, 50% suspension) in dry benzene (20 mL) substituted β-enaminothioketones 2 (5 mmol) were added, followed by methyl iodide (5 mmol) and the mixture was stirred for 24 hours. Then it was worked up and extracted with diethyl ether (3 × 50 mL). The organic layer was dried over anhydrous sodium sulfate and was evaporated to give a viscous residue. The residue was column chromatographed over silica gel (60-120 mesh) using hexane-ethylacetate (20:1) as eluent to get the thiolesters 24.

1,3-Bis(methylthio)-3-(4-chlorophenyl)prop-2-ene-1-one 24a was obtained from the reaction of β-enaminothioketone 2a (5 mmol) with methyl iodide as yellow crystalline solid. Yield 1g(80%); mp: 102 – 103 °C. 1H NMR (400 MHz, CDCl₃) δ = 2.54 (s, 3H, SCH₂), 2.57 (s, 3H, SCH₂) 6.71 (s, 2H), 7.41 (d, 2H, J = 8 Hz, Ar) 7.85 (d, 2H, J = 8 Hz, Ar) EIMS m/z (%): 260 (M⁺+2, 9), 258 (M⁺, 20), 245 (32), 243 (100), 199 (5), 197 (17), 141 (24) 139 (82), 111 (35), 75 (32)
5.6.2 General procedure for the preparation of 2-Aroyl-3-phenyl amino-5-phenyl thiophenes and 2-aroyl-3-methylamino-5-phenylthiophenes

To a well stirred suspension of sodium hydride (480 mg, 10 mmol, 50% suspension) in 30 mL dry benzene, β-enaminothioketone (5 mmol) was added. After 15 minutes phenacyl bromide (0.96 g, 5 mmol) was added and stirred the mixture was stirred at room temperature for 48 hours, poured over ice (50 mL) and extracted with benzene (50 mL x 3). The organic layer was dried by using anhydrous Na₂SO₄ and stripped the solvent under vacuum. The crude residue was column chromatographed over silica gel (60-120 mesh) using a mixture of hexane-ethylacetate (20:1) as the eluent to get the aminothiophene 25 in good yield.

2-Benzoyl-3-phenylamino-5-phenyl thiophene 25a was obtained from the reaction of β-enaminothioketone 2a (5 mmol) with phenacyl bromide as an yellow crystalline solid Yield 1.1g (62%) mp. 181-182 °C. IR (KBr) νmax = 1720, 1600, 1250, 1H NMR (300 MHz), CDCl₃ δ = 4.56 (s, 1H, NH), 7.1 (s, 1H, Ar), 7.5 (m, 9H, Ar) 8.0 (m, 3H, Ar), 8.16 (m, 3H, Ar), EIMS m/z = 355 (M⁺, 75), 322 (30.6), 251 (43), 129 (86), 105 (100), 77 (85)

2-Benzoyl-(3-methylamino-5phenylthiophene)25b was obtained from the reaction of β-enaminothioketone 2b (5 mmol) with phenacyl bromide as an yellow crystalline solid yield (0.76g, 52%) mp. 108-109 °C (lit 108-109 °C)
5.7 References


2. Gaemas, J.-P.; Lees, M.; Reliquet, A.; Reliquet, F.; Quiniou, H.; Phosphorus and Sulfur. 1980, 8, 351


