Chapter Three

Reaction of β-Oxodithioesters with Chloromethylene iminium Salts

3.1 Introduction

Though the β-oxo dithioesters can be conveniently prepared from active methylene compounds either by treating them with carbon disulfide in the presence of base followed by alkylation\(^1\) or by direct base catalyzed reaction with trithiocarbonate\(^2\) there further applications in synthesis have not been studied in detail. It is the sulfur atom of the thiocarbonyl group that usually react with the electrophiles. Alkylation of β-oxodithioesters afford α-oxo ketenedithioacetals. This provide a method for the synthesis of α-oxo ketenedithioacetals with different substituents on the sulfur atom. In our knowledge reactions of β-oxodithioesters with other electrophiles other than alkylating agents have not been explored. During the course of the studies on the reactions of iminium salts on sulfur compounds,\(^3\) we have examined the reaction of β-oxo dithioesters with Vilsmeier reagent prepared from POCI\(_3\) and DMF. The chloromethylene iminium salt obtained by the reaction of DMF with POCI\(_3\) is supposed to be the active species in the Vilsmeier-Haack reaction. We have anticipated that the thiocarbonyl group would replace the chlorine of the chloromethylene iminium salt. This would result in the formation of an intermediate species where the thiocarbonyl group is enolized and activated. Other nucleophiles may now add to this intermediate resulting in a substitution reaction and removal of N,N-dimethylthioformamide at the same time. Since chloride ions are present in the Vilsmeier-Haack reaction mixture they can act as the nucleophile. Thus the overall process would result in the selective conversion of the thiocarbonyl group to chlorovinyl moiety.
3.1.1 Vilsmeier Haack Reagent

The reaction of chloromethylene iminium salts formed by the reaction of an N,N-disubstituted formamide with an acid chloride such as POCl₃, phosgene or oxalyl chloride with electron rich aromatic compounds or alkenes is known as the Vilsmeier-Haack reaction. N,N-dimethyl formamide and POCl₃ are the formamide and acid chloride components respectively which are most frequently used in the Vilsmeier-Haack reaction. The formation of the Vilsmeier reagent from POCl₃ and DMF is depicted in scheme 1.

The reaction proceeds via the attack of carbonyl oxygen of the formamide on the acid chloride to form the iminium salt 2 which react further to give the chloromethylene iminium salt 3.

The Vilsmeier-Haack reaction of the electron rich substrates involve iminoalkylation at the electron rich center leading to the formation of an intermediate iminium salt. This intermediate is usually treated with sodium acetate or potassium carbonate in water which would hydrolyze the iminium salt to the corresponding aldehyde. This has made the Vilsmeier-Haack reaction a popular method for the formylation of electron rich substrates.

Other than electron rich substrates, another class of compounds that undergo useful and interesting transformation in the presence of chloromethylene iminium salts are the carbonyl compounds. Simple enolizable ketones undergo a reaction that is commonly referred to as the chloroformylation. The reaction involve transformation of the carbonyl compound to a β-chlorosubstituted α,β-unsaturated aldehyde (Scheme 2).
The \( \beta \)-chloroethylenic aldehyde 6 are usually formed as a mixture of \( E \) and \( Z \) stereoisomers. The nature of the substituents on the starting carbonyl compound would determine which isomer would be formed as the major product. Though formation of \( \beta \)-chloroethylenic aldehydes is known from aliphatic, cyclic and aryl alkyl ketones, multiple iminoalkylations are common, when the carbonyl group is flanked by two methylene or methyl groups that can enolize the ketone. This is exemplified by the reaction of dibenzyl ketone with the Vilsmeier reagent. The iminium salt 8 was formed by the double iminoalkylation of the dibenzyl ketone 7. A 4-pyrone 9 was obtained as the product. Cyclization of the pentadienaldehyde formed by the alkaline hydrolysis of the iminium salt followed by elimination of \( N,N \)-dimethylamine results in the formation of a pyrylium salt which react with water to afford the pyrone 9 (Scheme 3).
The chloroethylenic aldehydes prepared from aryl alkyl ketones are relatively stable and find important applications as synthetic intermediates. For example the macrocyclic pyrylium salt 12 has been prepared by the condensation of the dialdehyde 11 which has been prepared by the Vilsmeier reaction of the diketone 10 with the diketone 10 itself.

Scheme 4

Acyclic 1,3-dicarbonyl compounds or $\alpha,\beta$-unsaturated carbonyl compounds may undergo cycloaromatization reactions in the presence of Vilsmeier reagent. The reaction often involve multiple iminoalkylations followed by electrocyclic ring closure of the intermediate iminium salts and subsequent elimination of the methyl amine molecules. For example when heptane-3,5-dione was treated with the Vilsmeier reagent prepared from POC13 and DMF the dichloro substituted aromatic aldehyde 14 was formed (Scheme 5).
The chloromethylene iminium salt also find important applications in the synthesis of heterocycles. For example quinoline derivatives 16 are formed when α-substituted acetanilides 15 are allowed to react with the Vilsmeier reagent (Scheme 6). Electron rich substrates on the aromatic ring facilitate the cyclization.  

![Chemical Structure](image1.png)

**Scheme 6**

Meth-Cohn and co-workers have done extensive studies on similar reactions involving amides.

The Vilsmeier-Haack reaction can be performed with inexpensive reagents and lead to the formation of important multifunctional intermediates particularly chloroethylenic aldehydes which are versatile intermediates in organic synthesis. The chloromethylene iminium salts are also valuable reagents for cycloaromatization reactions and heterocyclic synthesis.

### 3.1.2 Reactions of Sulfur Compounds with Chloromethylene iminium Salts

Only a few reports are there in the literature about Vilsmeier reactions on sulfur compounds. An earlier report from our laboratory describes a convenient synthesis of β-alkythioethylenic aldehydes from dithioketals derived from α-methylene ketones under Vilsmeier Haack reaction conditions 17 (Scheme 7).
The reaction is general to dithioketals derived from aliphatic, aromatic and cyclic ketones and E-isomer of the product is formed predominantly. The reaction apparently involves a vinylsulfide intermediate which undergoes further formylation.

Vilsmeier Haack reaction of carbinols derived from 1,2-reduction of acetyl ketene dithioacetals affords 5,5-bis (methyl thio) substituted pentadienaldehydes.

Cyclic ketenedithioacetals also could be transformed similarly to the respective pentadienaldehydes. These pentadienaldehydes can be used for the synthesis of various conjugated polyenaldehydes having bis(methylthio) functionality at the terminal carbon atom. The process involve a Claisen-Schmidt type condensation with aliphatic ketones followed by reduction and subsequent treatment with chloromethyleneiminium salt. One such reaction is depicted in the Scheme 9.
The conjugated polyenaldehydes and ketones prepared by this method have shown to be valuable intermediates in carbonyl group transposition reactions. 

3.2 Results and Discussion

The reactions of β-oxo dithioesters were examined with the chloromethylene iminium salt prepared from POCl₃ and DMF. β-Oxo dithioesters were prepared from active methylene ketones. Base catalyzed Claisen condensation of active methylene ketones with dimethyl trithiocarbonate afford moderate to good yields of β-oxo dithioesters. Substituted acetophenones were treated with sodium hydride in benzene. Dimethyl trithiocarbonate was added slowly to the refluxing mixture.

The dithio esters of α-tetralone and cyclohexanone also could be prepared in a similar fashion.
We have next attempted the preparation of dithioesters from doubly activated active methylene compounds. Thus when ethyl acetoacetate was allowed to react with dimethyl trithiocarbonate in the presence of sodium hydride in benzene the reaction mixture after usual work-up and purification gave an yellow oil. Spectral analysis of this compound revealed that it was not the expected dithioester 35, but the carbethoxy substituted dithioacetate 36. Apparently the initially formed dithioester 35 undergoes deacetylation under the reaction conditions to afford the dithioacetate 36.

\[
\begin{align*}
\text{EtO} & \quad \text{O} \quad \text{O} \quad \text{CH}_3 \\
\text{MeS} & \quad \text{S} \quad \text{SMe} \\
\text{34} & \quad + \quad \text{28} \\
\end{align*}
\]

\[
\begin{align*}
\text{NaH} & \quad \text{DMF, Benzene} \\
\text{35} \\
\end{align*}
\]

\[
\begin{align*}
\text{EtO} & \quad \text{O} \quad \text{O} \quad \text{SMe} \\
\text{36} \\
\end{align*}
\]
Apparently the sodium salt of methanethiol formed in the Claisen condensation of the ethyl acetoacetate with trithiocarbonate acts as the nucleophile in the deacetylation reaction.

Incidently the reaction of ethyl acetoacetate with trithiocarbonate followed by deacetylation provide a convenient method for the preparation of the dithioesters of aliphatic esters. The structure of the methyl carbethoxy dithioacetate was confirmed with spectral data. The IR spectrum (Neat, Fig 1) shows the band due to the ethoxy carbonyl group at $\nu$ 1735 cm$^{-1}$. Other prominent bands in the IR spectra were at $\nu$ 1030, 1190, 1310 and 2980 cm$^{-1}$.

The proton NMR spectra (90 MHz, Fig 2) in CDCl$_3$ shows a triplet (J=7Hz) for three protons at $\delta$ 1.25 ppm, due to the methyl group of the ethoxy carbonyl functionality. The methylene group of the carbethoxy group appeared as a quartet (J=7Hz) at $\delta$ 4.21. The singlet at $\delta$ 2.78 and 4.08 ppm were attributed to the methylthio group and the methylene group of the dithioacetate functionality respectively.

The $^{13}$C NMR spectra (22.4 MHz, Fig 3) in CDCl$_3$ shows the peak due to the methylthio group at $\delta$ 2.1 ppm. The methyl carbon of the ethoxy group appeared at $\delta$ 15 ppm while the methylene carbon showed a peak at $\delta$ 56 ppm. The methylene group of the dithioacetal functionality appeared at $\delta$ 61.5 ppm, and the carbonyl group appeared at $\delta$ 167 ppm while the peak at $\delta$ 226 ppm could be due to the thiocarbonyl group.

The GCMS of methyl carbethoxy dithioacetate (Fig 4) showed the molecular ion peak as the base peak at m/z 178 (100%). Other prominent peaks were at m/z
Fig. 1 1R Spectrum (neat) of compound 36
Fig. 2 $^1$H NMR Spectrum (90 MHz) of compound 36
Fig. 3 $^{13}$C NMR Spectrum (22.4 MHz) of compound 36
Fig. 4 Mass Spectrum (GCMS) of compound 36
133(20.4%, M'-OEt), 131(40.1%, M'-SMe), 103(20.1%) and 91(30.1%) due to the ion (CSSMe)⁻.

It has been mentioned by Junjappa et al.² that the doubly activated active methylene compounds such as ethyl cyanoacetate, diethyl malonate and malononitrile do not give the dithiocarboxylates under these conditions. Though we have made some efforts in this direction a satisfactory method could not be developed for their synthesis.

### 3.2.1 A Synthesis of β-Methylthio α,β-Unsaturated Ketones

α-Oxo ketenedithioacetals 38 are highly versatile, multifunctional synthetic intermediates.¹¹ They are conveniently prepared from active methylene ketones on treatment with carbon disulfide, in the presence of a base followed by alkylation.

\[
\begin{align*}
\text{O} & \quad \text{Base} \quad \text{CS}_2 \quad \text{RX} \\
\text{37} & \quad \text{38}
\end{align*}
\]

*Scheme 15*

One important aspect of the chemistry of these intermediates involve regio and stereo selective addition of nucleophiles to them. Nucleophiles may directly add to the carbonyl group leading to the formation of allylic carbonols or addition could be in a conjugate fashion replacing one of the alkylthio group selectively. Extensive studies have been carried out in this area and products obtained by the nucleophilic addition have been shown to undergo valuable transformations.

Acyl ketene N,S-acetals are also valuable intermediates particularly in the synthesis of heterocycles.¹¹ They may be obtained by the reaction of active methylene ketones with aryl or alkyl isothiocyanates in the presence of base followed by alkylation.¹²
Alternatively acyl ketene N,S-acetal may be prepared by selective substitution of one of the alkylthio group by an amine. Acyl ketene N,S-acetal can also be prepared conveniently from β-oxo dithiocarboxylates. Substitution of the alkylthio group by an amine afford the corresponding β-oxo thioamide. Alkylation of the enolates derived from β-oxo thioamides on treatment with base afford acyl ketene N,S-acetals.

Recently Junjappa and co-workers have generalized methods for the synthesis of acyl ketene O,S-acetals and have explored their applications as potential synthetic intermediates. The preparation of O,S-acetals involve alkylation of thiolate anions derived from β-oxo thionoesters.

Thus α,β-unsaturated ketones having hetero substituents at the α-position are attractive intermediates in organic synthesis. We thought that β-oxo dithiocarboxylates could be a valuable substrate for the synthesis of α,β-unsaturated ketones with various substituents at the β-position. If the thiocarbonyl group could be activated using a suitable electrophilic reagent, subsequent nucleophilic substitution at the β-carbon would provide access to α,β-unsaturated ketones substituted at the β-position.

We have examined the reactions of β-oxo dithiocarboxylates with chloromethylene iminium salt prepared from POCl₃ and DMF. Thus p-chlorobenzoyl dithioacetate 29c was
allowed to react with 1.5 equivalent of Vilsmeier reagent. The reaction mixture was stirred at room temperature for twenty hours. The product obtained after usual work up and purification by chromatography in 60% (1.48g) yield was identified to be 3-chloro-3-methylthio-1-(4'-chlorophenyl)-2-propene-1-one 43c. The structure of 43c was suggested on the basis of the spectral data. The IR (KBr) spectrum (Fig 5) of the compound shows band due to carbonyl group at $v = 1640$ cm$^{-1}$, other bands are at $v = 1570, 1470$ and $1375$ cm$^{-1}$.

The proton NMR (90 MHz CDCl$_3$) (Fig 6) shows a singlet of three hydrogens at $\delta = 2.35$ ppm due to CH$_3$ group and singlet of one hydrogen (vinyllic) at $\delta = 6.65$ and multiplet of four hydrogen (aromatic) at $\delta = 7.00-7.95$ ppm. Two small singlets present near the methyl signal could be due to stereoisomers. The correct stereochemistry of the product has not been identified clearly.

GCMS (Fig 7) of the compound shows parent ion peak at m/z 246 (11.3%), and base peak at m/z 139 (100%). Other prominent peaks are at (m/z) 231 (34%), 179 (5.5%), 168 (8.8%), 115 (11.7%), 111 (44.7%), 85 (8.8%), 75 (44.4%), 57 (7.7%) and 51 (11.1%).

Other substituted benzoyl dithioacetates also behaved similarly to afford the corresponding β-chlorovinyl ketones 43a-b in moderate to good yields (Scheme 18).

The mechanism of the reaction apparently involves the initial attack of the thiocarbonyl group to the chloromethylene iminium salt. This leads to the formation of an intermediate iminium salt 46 which is essentially a ketene dithioacetal, of which one of the sulfur substituent is activated. However, our efforts to isolate this intermediate were not successful. The chloride ion present in the reaction mixture adds to the β-carbon resulting in the elimination of the N,N-dimethyl thioformamide.

We have next attempted the reactions of β-oxo dithiocarboxylates derived from aliphatic ketones with chloromethylene iminium salt. When the β-oxo dithiocarboxylate 44, prepared by the reaction of ethyl methyl ketone with trithiocarbonate, was treated with the Vilsmeier reagent prepared from POCl$_3$ and DMF at room temperature only an intractable mixture of products could be obtained.
Fig. 5  IR Spectrum (KBr) of compound 43c
Fig. 6 $^1$H NMR Spectrum (90 MHz) of compound 43c
Fig. 7 Mass Spectrum (GCMS) of compound 43c
The reactions of β-oxo dithiocarboxylates derived from cyclic ketones, with chloromethylene iminium salt were also examined. The dithiocarboxylate 47 prepared from β-tetralone react with the Vilsmeier reagent prepared from POCl₃ and DMF, to afford the expected β-chloro β-methylthio enone 48 in 72% yield (Scheme 20).
The structure of 48 was confirmed with the help of spectral data. The IR spectrum (KBr, Fig 8) of 48 showed a band due to the carbonyl group at ν 1620 cm\(^{-1}\). The other prominent bands in the IR spectrum were at ν 1580, 1480 and 1330 cm\(^{-1}\). The proton NMR spectrum (90MHz, CDCl\(_3\), Fig 9) shows a singlet at δ 2.20 ppm for three protons. This is due to the methylthio group. The methylene protons of the tetralone moiety appeared as a multiplet, integrating for four protons, between δ 2.70 and 3.20 ppm. The four aromatic protons also appeared as a multiplet between δ 7.00 and 8.10 ppm. The \(^{13}\)C NMR (224MHz, CDCl\(_3\), Fig 10) shows a peak at δ 18.56 ppm due to the methylthio group. Aromatic and vinylic carbons showed peaks at δ 127.30, 128.15, 129.37, 133.15, 134.13, 142.63 and 148.14 ppm. The carbonyl group showed a signal at δ 185.64 ppm. The GCMS (Fig 11) of 48 showed the molecular ion peak at m/z 238(22.2%). The other prominent peaks in the mass spectra were at 223(88.8%), 221(11.3%), 187(11.6%), 159(22.2%), 141(11.2%), 128(67.1%), 115(100%), 105(11.4%), 90(89.5%), 79(45.2%), 63(66.8%), 51(45.1%).

The dithiocarboxylates 49 obtained from the reaction of cyclohexanone with trithiocarbonate was treated with the Vilsmeier reagent prepared from POCl\(_3\) and DMF next. The reaction was carried out at room temperature for 20h. The product isolated as a yellow oil in 38% yield after usual work up and purification by column chromatography was identified as the 2-chloro-3-(1'-chloro-1'methylthio) methylene cyclohex-1-ene-1-carbaldehyde 50 on the basis of spectral data (Scheme 21).
Fig. 8 IR Spectrum (KBr) of compound 48
Fig. 9 $^1$H NMR Spectrum (90 MHz) of compound 48
Fig. 10 $^{13}$C NMR Spectrum (22.4 MHz) of compound 48
Fig. 11 Mass Spectrum (GCMS) of compound 48
The IR spectrum (KBr) of 50 showed a band due to the carbonyl group at ν 1650 cm⁻¹ while a band due to unsaturation appeared at ν 1540 cm⁻¹. The proton NMR spectrum of 50 (90MHz, CDCl₃) showed a multiplet between δ 1.65 and 1.85 ppm due to two methylene protons. The multiplet due to the four allylic methylene protons appeared between δ 2.20 and 2.60 ppm. The singlet due to the methylthio group (3H) was merged with the multiplet between δ 2.20 and 2.60 ppm.

The formation of pentadienaldehydes similar to 50 is not uncommon in the reaction of substrates containing alicyclic ketone moieties with chloromethylene iminium salts. When cyclohexanone was treated with a large excess of Vilsmeier reagent, followed by the addition of sodium perchlorate solution, the 3-chloropentamethinium salt 51 could be isolated which on further alkyline hydrolysis afforded the penta dienaldehyde 52.

Scheme 21

Scheme 22
Earlier studies from our laboratory also gave similar results. When cyclohexanone in DMF in the presence of Lewis acid and butane thiol was treated with POCl₃ the pentadienaldehyde 52 was formed in high yield (Scheme 23).

![Scheme 23](image)

When the Vilsmeier reaction of cyclohexanone was carried out with the reagent prepared from POCl₃ and DMF, in the presence of a Lewis acid such as boron trifluoride etherate, treatment of the reaction mixture with mercapto ethanol, before the usual alkaline workup gave the pentadienaldehyde 54 in good yield as an yellow crystalline solid.

![Scheme 24](image)

In the reaction of the dithiocarboxylate derived from cyclohexanone, the initial activation of the thiocarbonyl group and replacement with chloride ion must have resulted in the formation of the β-chloro β-methylthio enone 55 which should have undergone further iminoalkylation to afford the 3,5-dichloro pentamethinium salt 56 which is the precursor of the isolated pentadienaldehyde 50 (Scheme 25).
Our results described here indicate that β-oxo dithiocarboxylates, which do not have protons that can participate in enolization at the γ-position can be effectively transformed into the corresponding β-chloro, β-methylthio α,β-unsaturated ketones. While the dithioesters derived from alicyclic ketones underwent subsequent iminoalkylation reactions and acyclic aliphatic substrates did not give any useful reaction.

3.2.2 Reaction of Methyl carbethoxy dithioacetate with Chloro methylene iminium Salt

It has been mentioned earlier that when ethyl acetoacetate was treated with dimethyl trithiocarbonate, the reaction was accompanied by deacetylation resulting in the formation of a carbethoxydithioacetate. We have examined the reaction of this carbethoxydithioacetate with the chloromethylene iminium salt prepared from POCl₃ and DMF, expecting the formation of β-chloro β-methylthio acrylate. The methylcarbethoxy dithioacetate 36 was treated with the Vilsmeier reagent at room temperature and the mixture stirred for 20h. After usual alkaline work up with saturated potassium carbonate solution and extraction with diethyl ether, the organic layer was dried and evaporated and the residue was column chromatographed over silicagel, using hexane ethylacetate mixture (20:1) as eluent.
The product isolated as an orange crystalline solid in 78% yield was identified as Diethyl-6-methylthio-2-dithiopyrone-3.5-dicarboxylate 57, on the basis of spectral data. In the IR spectrum of 57 (KBr, Fig 12) two bands at \( \nu = 1692 \) and \( 1725 \text{ cm}^{-1} \) were assigned to the carbonyl groups. The finger print region showed bands at \( \nu = 1550, 1455, 1350, 1285, 1195, 1165 \) and \( 1060 \text{ cm}^{-1} \).

The proton NMR spectrum (CDCl\( _3 \), 90MHz, Fig 13) of this compound showed a triplet (\( J = 6 \text{ Hz} \)) at \( \delta = 1.4 \text{ ppm} \) integrating for six protons. This is due to the two methyl groups of the two carbethoxy substituents. The four methylene protons of the carbethoxy group appeared as a quartet (\( J = 6 \text{ Hz} \)) at \( \delta = 4.38 \text{ ppm} \). The three protons of the methylthio group was present at \( \delta = 2.65 \text{ ppm} \) as a singlet while the peak at \( \delta = 8.15 \text{ ppm} \) was due to the proton at the 4-position of the thiopyrone ring.

The \( ^{13} \text{C} \) NMR spectrum (CDCl\( _3 \), 22.4MHz, Fig 14) showed two peaks at \( \delta = 14.05 \) and \( 14.23 \text{ ppm} \) due to the methyl group in the carbethoxy substituents. The methyl thiogroup appeared at \( \delta = 16.64 \text{ ppm} \). The methylene carbons of the carbethoxy group showed two peaks at \( \delta = 61.96 \) and \( 62.02 \text{ ppm} \). The C-4 carbon of the dithiopyron ring was present at \( \delta = 137.09 \text{ ppm} \). The quarternary carbon of the dithiopyron ring were present at \( \delta = 118.11, 133.54 \) and \( 149.90 \). The signals due to the carbonyl groups of the carbethoxy substituents could not be clearly distinguished from the noise. The peak at \( \delta = 212.72 \text{ ppm} \) is assigned to the thiocarbonyl group.

The EIMS of the compound 57 (Fig 15) showed the molecular ion peak at \( m/z 318 \) (94.1%). The base peak was at \( m/z 246 \) resulting from the loss of one carbethoxy group.
Fig. 12 IR Spectrum (KBr) of compound 51
Fig. 13 $^1$H NMR Spectrum (90 MHz) of compound 51
Fig. 14 $^{13}$C NMR Spectrum (22.4 MHz) of compound 51
group from the parent compound. Mass spectra also showed peaks at m/z 217 (33.2%), 197 (35.8%), 185 (30.6%) and 69 (66.2%).

The reaction leading to the formation of the dithiopyrone 57 apparently involves the initial activation of the thiocarbonyl group. Addition of the thiocarbonyl group to the chloromethylene iminium salt should lead to the formation of the iminium ion. Reaction of the dithioacetate 36 with this iminium salt gives the divinyl sulfide 60. Iminoalkylation of the divinyl sulfide 60 followed by cyclization of the resultant iminium salt and subsequent elimination of the dimethyl amine would lead to the formation of the dithiopyrone 57 which has been isolated.

\[
\begin{align*}
36 & \quad \text{POCl}_3 \quad \text{DMF} & 58 & \quad \text{POCl}_3 \quad \text{DMF} & 60 & \quad \text{Cl}^- \\
\end{align*}
\]

\[
\begin{align*}
57 & \quad \text{Scheme 27}
\end{align*}
\]
Fig. 15 Mass Spectrum (EIMS) of compound 51
The reaction of β-oxo dithiocarboxylic acids with α,β-unsaturated ketones or aldehydes having a leaving group at the β-position are known to afford dithiopyrone derivatives.\textsuperscript{16}

### 3.3 Conclusion

In conclusion, the reaction of β-oxo dithioesters with Vilsmeier reagent provides β-chloro-β-methylthio substituted α,β-enones which are potential multifunctional intermediates in organic synthesis. To the best of our knowledge, this is the first report on the synthesis of this class of compounds. Other α,β-unsaturated ketones having heterosubstituents at the β-position such as α-oxoketene acetals α-oxoketene dithioacetals N,S-acetals, aminals and β-chlovinyl ketones are versatile intermediates in organic synthesis.

### 3.4 Experimental

Melting points are uncorrected and were obtained on a Buchi-530 melting point apparatus. Infrared spectra were measured with a Shimadzu IR-470 spectrometer and are given as cm\textsuperscript{-1}. Proton NMR spectra were recorded on a varian 390 (90 MHz), Bruker WM 250 (250 MHz), or on a Bruker WM 200 (200 MHz) spectrometer in CDCl\textsubscript{3}. Carbon-13 NMR spectra were recorded on a Bruker WM 250 (62.9 MHz) or on a Bruker WM 200 (50.8 MHz) spectrometer in CDCl\textsubscript{3}. Chemical shifts are reported in parts per million (ppm) downfield from internal tetra methyl silane. Coupling constants \(J\) are given in Hz. Electron impact mass spectra were obtained on a Finnigen-Mat 312 instrument.

#### 3.4.1 Reaction of β-oxodithioesters with Vilsmeier reagent: General procedure.

To the Vilsmeier reagent prepared from POCl\textsubscript{3} (1.5 ml, 15 mmol) and dry DMF (10 ml) the dithioester (10 mmol) was added at 0-5 °C and the mixture was allowed to stir at room temperature for 20 h. It was then poured over cold saturated potassium carbonate solution (100 mL) and was extracted with diethyl ether (3 x 30 mL). The ether layer was evaporated under vacuum and the residue was chromatographed on silicagel using a mixture of hexane and ethyl acetate (20:1) as the eluent.
3-Chloro-3-methylthio-1-phenyl-2-propene-l-one (43a)
Isolated as yellow crystalline solid recrystallized from a mixture of hexane and dichloromethane (30:1) (1.5g 70% yield); m.p 69°C.; IR (KBr, v cm⁻¹) 1620, 1510, 1225.; ¹H NMR (90 MHz, CDCl₃) δ 2.65 (s, 3H), 7.35 (s, 1H), 7.40-8.20 (m, 5H) ppm.; EI MS (m/z) 212 (35.6%), 197 (85.6%), 135 (28.5%), 105 (100%), 77 (78.8%).

3-Chloro-3-methylthio-1-(4'-chlorophenyl)-2-propene-l-one (43b)
Isolated as yellow crystalline solid recrystallized from dichloromethane (1.54g 68% yield); m.p 110°C.; IR (KBr, v cm⁻¹) 1655, 1600, 1490.; ¹H NMR (90 MHz, CDCl₃) δ 2.35 (s, 3H), 2.55 (s, 3H), 7.15 (s, 1H), 7.25 (d, J= 8 Hz, 2H), 7.80 (d, J=8Hz, 2H) ppm.; GCMS (m/z) 226 (11.1%), 213 (11.2%), 211 (33.3%), 179 (8.8%), 148 (8.8%), 135 (11.2%), 120 (9.9%), 119 (100%), 99 (5.5%), 91 (44.6%), 77 (6.6%), 65 (4.4%), 51 (11.1%).

3-Chloro-3-methylthio-1-(4'-methylphenyl)-2-propene-l-one (43c)
Isolated as yellow crystalline solid recrystallized from dichloromethane (1.48g 60% yield); m.p 160°C.; IR (KBr, v cm⁻¹) 1640, 1570, 1470, 1375.; ¹H NMR (90 MHz, CDCl₃) δ 2.35 (s, 3H), 6.65 (s, 1H), 7.00-7.95 (m 4H ppm.; GCMS (m/z) 246 (11.3%), 231 (34%), 179 (5.5%), 168 (8.8%), 139 (100%), 115 (11.7%), 111 (44.7%), 85 (8.8%), 75 (44.4%), 57 (7.7%), 51 (11.1%).
3,4-Dihydro-1[2-(1'-chloro-1'-methylthio)methylene]napthalene (48) Isolated as yellow crystalline solid, (1.79g 72 % yield); Mp 101°C; IR (KBr, vcm⁻¹) 1620, 1580, 1480, 1300.; ¹H NMR (90 MHz, CDCl₃) δ 2.20 (s, 3H), 2.70-3.20 (m, 4H), 7.00-8.10 (m, 4H) ppm.; ¹³C NMR (100.6 MHz, CDCl₃) δ 18.56, 28.66, 30.26, 127.30, 128.15, 129.37, 133.15, 134.13, 142.63, 148.14, 185.64 ppm. GCMS (m/z) 238 (22.2%), 223 (88.8%), 221 (11.3%), 187 (11.6%), 159 (22.2%), 141 (11.2%), 128 (67.1%), 115 (100%), 105 (11.4%), 90 (89.5%), 79 (45.2%), 63 (66.8%), 51 (45.1%).

2-Chloro,3-(1'-chloro-1'-methylthio)methylene-1-cyclohex-1-ene-1-carbaldehyde (50) Isolated as yellow oil (0.9g 38% yield) IR (KBr, vcm⁻¹) δ 1650, 1540.; ¹H NMR (90 MHz, CDCl₃) δ 1.65-1.85 (m, 2H), 2.20-2.60 (m, 7H), 10.20 (s, 1H) ppm.

3.4.2 Methyl carbethoxy dithioacetate (36)

To a well stirred suspension of sodium hydride (2.5g, 50%, 0.05mol) in dry benzene (100mL), dimethyl trithiocarbonate (3.8g, 0.027mol) was added and the mixture is refluxed with stirring for 10minutes. A solution of ethyl acetoacetate (4.45g, 0.025mol) in dry benzene (25mL) is slowly added drop wise over a period of 1-2h. The mixture is further refluxed for 3h. Then allowed to cool and poured into ice-cold water (250mL). The aqueous layer is separated and washed with benzene (200mL) acidified with 3N HCl or 20% acetic acid and extracted with chloroform (2x150mL). The extract is dried with sodium sulfate and evaporated to gave the product (single spot on TLC). Further purification was achieved by column chromatography on silicagel (60g) using hexane as eluent.
Methyl carbethoxy dithioacetate (36) Isolated as yellow oil, (1.79g 73 % yield); IR (neat, vcm⁻¹) 2980, 1735, 1030, 1190, 1310 cm⁻¹; ¹H NMR (90 MHz, CDCl₃) δ 1.25 (t, 3H, J=7Hz), 2.78 (s, 2H), 4.08 (s, 3H), 4.21 (q, 2H, J=7Hz) ppm.; ¹³C NMR (22.4 MHz, CDCl₃) δ 15, 21, 56, 61.5, 167, 226, ppm. GCMS (m/z) 178 (100%), 133 (20.4%), 131 (40.1%), 103 (20.1%), 91 (30%).

3.4.3 Diethyl-6-methylthio-2-dithiopyrone-3,5-dicarboxylate (57)

To the Vilsmeier reagent prepared from POCl₃ (1.5 mL, 15mmol) and dry DMF (10mL) methyl carbethoxy dithioacetate (1.78g, 10mmol) was added at 0-5°C and the reaction mixture was stirred at room temperature for 20h. It was then worked up using cold saturated potassium carbonate solution (100 mL) and was extracted with diethyl ether (3 x 30 mL). The ether layer was evaporated under vacuum and the residue was chromatographed on silicagel using a mixture of hexane and ethyl acetate (20:1) as eluent.

Diethyl-6-methylthio-2-dithiopyrone-3,5-dicarboxylate (57) as an orange crystalline solid, (2.48g 78 % yield); IR (KBr. v cm⁻¹) 1725, 1692, 1550, 1455, 1350, 1285, 1195, 1165, 1060. cm⁻¹.; ¹H NMR (90 MHz, CDCl₃) δ 1.4 (t, 6H, J=6Hz), 2.65 (s, 3H), 4.38 (q, 4H, J=6Hz), 8.15 (s, 1H) ppm.; ¹³C NMR (22.4 MHz, CDCl₃) δ 14.05, 14.23, 16.64, 61.96, 62.02, 118.11, 133.54, 137, 149 90, 212.72 ppm. EIMS (m/z) 318 (94.1%), 246 (100%), 217 (33.2%), 197 (35.8%), 185 (30.6%), 158 (23.6%), 69 (72.1%).
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