CHAPTER I

α-FUNCTIONALIZED THIONO- AND DITHIOACETIC ACID DERIVATIVES AND α-FUNCTIONALIZED KETENE THIOACETALS

Introduction

The chemistry of thionoacetic acid derivatives (1), dithioacetic acid derivatives (2) and thiocetamides (3) is well established. Among higher thionoacetic acid derivatives, the study of α-functionalized thionoacetic acid derivatives (4) has received considerable attention during the last few years.

\[
\begin{align*}
\text{(1)} & \quad Z = 0 \\
\text{(2)} & \quad Z = S \\
\text{(3)} & \quad Z = NR
\end{align*}
\]

An interesting feature of thionoacetic acid derivatives with an electron withdrawing functional group at the α-position is that they exhibit varying tendency to
exist in the enethiol tautomeric form (5). They undergo facile S-alkylation to yield \( \alpha \)-functionalized ketene thioacetals (6). The \( \alpha \)-functionalized thionoacetic acid derivatives (4) and ketene thioacetals (6) have become readily accessible by different synthetic routes and have proved to be versatile starting materials for the synthesis of a wide variety of sulfur containing and non-sulfur containing open-chain and heterocyclic compounds. A brief review of the methods of synthesis of \( \alpha \)-functionalized thionoacetic acid derivatives and ketene thioacetals and their use in heterocycle synthesis is presented, herein.

**Synthesis of \( \alpha \)-Functionalized Thiono- and Dithio-acetic acid Derivatives**

One of the general methods of preparation of \( \alpha \)-functionalized dithioacid derivatives is by the reaction of carbon disulfide with carbanions derived from active methylene compounds. This base catalyzed condensation of active methylene compounds with carbon disulfide has been the subject of many reviews.\(^1\)-\(^{10}\)

A variety of active methylene nitriles, ketones, esters, amides, sulfones, sulfoxides and nitroalkanes have
been reacted with carbon disulfide in the presence of appropriate bases to obtain the corresponding dithiolate salts or the products derived from them.

The reaction of active methylene compounds with carbon disulfide has been performed employing a variety of bases in different solvents. In general, the reaction of carbon disulfide with an active methylene compound (7), in the presence of a base, results in the formation of the dithioacetate anion (8), which is more or less deprotonated by the base employed, and exists in equilibrium with the dianion of 1,1-dimercaptoethylene (9), commonly called as dithiolate. Acidification of the reaction mixture yields the dithioacid (10) and treatment with alkylating agent yields the dithioester (11) or the ketene thioacetal (12).

\[
\text{X-CH}_2\text{-Y} \xrightarrow{\text{CS}_2 \text{ Base}} \text{X} \text{Y} \quad \text{S} \quad \text{S} \quad \text{S} \quad \text{S}^- \\
(7) \quad (8) \quad (9)
\]

\[
\text{HS} \quad \text{RS} \quad \text{R}_2\text{S} \quad \text{SR} \\
(10) \quad (11) \quad (12)
\]
Active methylene nitriles such as malononitrile, cyanoacetate esters, cyanoacetamides, β-ketonitriles, arylacetonitriles and arylsulfonylacetonitriles have been converted to 1,1-dimercapto-2-cyanoethylene derivatives by their reaction with carbon disulfide in the presence of appropriate bases (Table I).

Solvents such as alcohol, benzene, dioxane and dimethylformamide have been used when alkali metal hydroxides or alkoxides are employed as the base. Sodium amide in ether and sodium hydride in dimethylformamide, hexamethylphosphoric triamide, ether or benzene have been employed for effecting the condensation of carbon disulfide with weakly acidic nitriles.

\[
\begin{array}{c}
\text{NC} \\
\text{S} \quad \text{S} \\
\text{Et} \\
\end{array}
\]

(13)

The reaction of malononitrile with carbon disulfide and triethylamine leads to the formation of the bistriethylammonium salt (13; \( \text{Et}^+ = \text{NHEt}_3^- \)) in quantitative yield.
TABLE I

Reaction of carbon disulfide with active methylene nitriles

\[
R - CH_2 - CN + CS_2 \rightarrow \text{Base} \rightarrow \begin{array}{c}
R \\
NC \\
S^- M^+
\end{array}
\]

(14) (15)

<table>
<thead>
<tr>
<th>Active methylene nitrile</th>
<th>Base employed</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malononitrile</td>
<td>NaOH, KOH</td>
<td>12-14, 20, 36</td>
</tr>
<tr>
<td></td>
<td>NaOR</td>
<td>9, 11</td>
</tr>
<tr>
<td></td>
<td>NaNH2</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Liq NH₃, NH₄OH</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Et₃N</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Bu₄NOH</td>
<td>23</td>
</tr>
<tr>
<td>Alkyl cyanoacetates</td>
<td>NaOH, KOH</td>
<td>14, 15, 36</td>
</tr>
<tr>
<td></td>
<td>NaOR</td>
<td>9, 11, 26</td>
</tr>
<tr>
<td></td>
<td>Na</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Bu₄NOH</td>
<td>23</td>
</tr>
<tr>
<td>Cyanoacetamide</td>
<td>KOH</td>
<td>9, 28, 36</td>
</tr>
<tr>
<td></td>
<td>NaOR</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>NH₄OH</td>
<td>19</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Active methylene nitrile</th>
<th>Base employed</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Substituted cyano-acetamides</td>
<td>KOH, NaOR</td>
<td>28, 27</td>
</tr>
<tr>
<td>Cyanothioacetamide</td>
<td>NaOR</td>
<td>21</td>
</tr>
<tr>
<td>Aroyl- and heteroaroyl-acetonitriles</td>
<td>NaOH, KOH, NaH</td>
<td>16, 17, 42, 29-34</td>
</tr>
<tr>
<td>Aryl- and heteroaryl-acetonitriles</td>
<td>NaOR, KOR, NaH</td>
<td>40, 16, 9, 37, 17, 29, 38, 39, 41</td>
</tr>
<tr>
<td>Sulfonylacetonitriles</td>
<td>KOH, NaH</td>
<td>36, 35</td>
</tr>
<tr>
<td>Alkylidene malononitrile</td>
<td>NaOR, Et₃N</td>
<td>44, 43</td>
</tr>
</tbody>
</table>

TABLE – I (continued)
While the diammonium salt \((13; M = \text{NH}_4^+)\) was obtained in the reaction of malononitrile with carbon disulfide in the presence of liquid ammonia, a mixture of products \(16, 17\) and \(18\) was obtained when aqueous ammonia was employed as the base.\(^{19}\)

The tetracethylammonium salt of \(1,1\)-dimercapto-2,2-dicyanoethylene \((13; M = \text{NET}_4^+)\) has been prepared from the dipotassium salt by treatment with tetracethylammonium chloride.\(^{20}\)

The direct formation of diammoniothiomethylene-cyanoacetamide \((19)\) has been observed in the reaction of ethyl cyanoacetate with carbon disulfide and aqueous ammonia.\(^{19}\)
Acidification of the dithiolate salts derived from active methylene nitriles leads to dimeric products and heterocyclic products, such as 1,2-dithiole-3-thione (20) via the unstable α-cyanodithioacetic acid derivatives.\textsuperscript{21} Monomethylation of the dithiolates derived from alkyl-cyanoacetates and cyanoacetamide has yielded the α-cyanodithiocacetates (21-23).

\[
\begin{align*}
\text{O} & \quad \text{S} \\
\text{R-X-C-CH-O-S-CH}_3 & \quad \text{CN} \\
(21) \quad \text{RX} = \text{OCH}_3 \\
(22) \quad \text{RX} = \text{OC}_2\text{H}_5 \\
(23) \quad \text{RX} = \text{NH}_2
\end{align*}
\]

β-Diketones and β-keto esters undergo facile condensations with carbon disulfide. Acetylacetone has been reacted with carbon disulfide in the presence of sodium hydroxide.\textsuperscript{45} Alternatively, sodium salt of acetylacetone has been reacted with carbon disulfide in dimethylformamide and the resulting dithiolate (24) subjected to alkylation reactions.\textsuperscript{46} Benzoylaceton and indan-1,3-dione
have been reacted with carbon disulfide employing sodium hydride as the base.\textsuperscript{29,47} Lawesson and co-workers\textsuperscript{48} have investigated the generation of monoanion salts of dithioacids by the reaction of carbon disulfide with diketones such as acetylacetone, benzoylacetone and dibenzoylmethane by the ion pair extraction technique employing tetra-butylammonium hydroxide. Some of the monoanion salts have also been monoalkylated to obtain the dithioesters (25).

\textbf{Sodium salt of ethyl acetoacetate reacts normally with carbon disulfide.}\textsuperscript{49} However, the reaction of carbon disulfide with ethyl acetoacetate in the presence of sodium ethoxide leads to deacylated dithiocarboxylate intermediates which yield dithiomalonate (26) on methylation.\textsuperscript{50} The reaction of carbon disulfide with sodium salt of ethyl \textit{\alpha}-methylacetoacetate has also been investigated.\textsuperscript{51}
Ethyl benzoylacetate has been reacted with carbon disulfide in the presence of sodium hydride in dimethylformamide.\textsuperscript{29} The reaction of dialkyl malonates with carbon disulfide has been investigated by many workers.\textsuperscript{1,8,9,11,23,52-55} Some monoanilides of malonic ester have recently been reacted with carbon disulfide employing sodium hydride as the base. Treatment of the dithiolate intermediates with one mole of methyl iodide, followed by acidification of the reaction mixture has yielded the corresponding dithioesters.\textsuperscript{56}

A variety of $\alpha$-methylene ketones have been reacted with carbon disulfide in the presence of appropriate bases (Table II). The dithiolates have generally been employed \textit{in situ}, in reactions with alkylating agents. The dithiolate salts (27) obtained by the reaction of ketones with carbon disulfide on acidification, frequently, yield isolable $\beta$-keto dithioacids (28).\textsuperscript{10,15,61}

The synthesis of $\beta$-ketodithioesters by the alkylation of $\beta$-ketodithioacid derivatives has also been
TABLE II

Reaction of carbon disulfide with α-methylene ketones

\[ \text{Base} \quad \text{employed}\]

<table>
<thead>
<tr>
<th>α-Methylene ketones</th>
<th>Base employed</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>NaOR</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>NaH</td>
<td>58</td>
</tr>
<tr>
<td>Higher aliphatic ketones</td>
<td>NaOR</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>NaNH(_2)</td>
<td>60,61</td>
</tr>
<tr>
<td></td>
<td>NaH</td>
<td>58</td>
</tr>
<tr>
<td>Cycloalkanones</td>
<td>KOH</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>NaOR, KOR</td>
<td>39,48,66,</td>
</tr>
<tr>
<td></td>
<td>Na(_2)NH</td>
<td>78,80</td>
</tr>
<tr>
<td></td>
<td>NaH</td>
<td>58,67</td>
</tr>
<tr>
<td></td>
<td>LiMDBP</td>
<td>64</td>
</tr>
<tr>
<td>Acetophenones</td>
<td>KOH</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>NaOR, KOR</td>
<td>10,15,66,69,</td>
</tr>
<tr>
<td></td>
<td>NaNH(_2)</td>
<td>72,74,77,81</td>
</tr>
<tr>
<td></td>
<td>NaH</td>
<td>58,71</td>
</tr>
<tr>
<td></td>
<td>LiMDBP</td>
<td>64</td>
</tr>
<tr>
<td>Desoxybenzoins</td>
<td>KOH</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>NaNH(_2)</td>
<td>9,60</td>
</tr>
<tr>
<td></td>
<td>NaH</td>
<td>58</td>
</tr>
<tr>
<td>Heteroaryl methyl ketones</td>
<td>NaH</td>
<td>76</td>
</tr>
</tbody>
</table>

* R = t-butyl, t-amyl

LiMDBP = Lithium 4-methyl-2,6-di-t-butylphenoxide
reported.\textsuperscript{73,74} Gompper and Schafer\textsuperscript{72} have described the preparation of α-benzoyldithioacetates by the treatment of the dithiolate salts derived from acetophenone and carbon disulfide with an equivalent of an acid, followed by an equivalent of an alkylating agent. Larsson and Lawesson\textsuperscript{10} have studied the generation of monoanionic salts of benzoyldithioacetic acids employing tetrabutylammonium hydroxide for their monoalkylation to obtain the dithioesters (29). Carbon disulfide has also been reacted with certain α-methylene aldehyde,\textsuperscript{82} esters,\textsuperscript{58,83} amides\textsuperscript{70,79} and lactones\textsuperscript{84} in the presence of appropriate bases.

The reaction of cyclic ketones with ammonia and carbon disulfide has been shown to yield the β-imino-dithiocarboxylates or products derived from them.\textsuperscript{62,85-88} The isolation of free imino or enaminodithiocarboxylic acid (30) or (31) by acidification of the reaction mixture
The reaction of 3-methyl-1-phenylpyrazol-5-one with carbon disulfide and ammonia has been found to yield the corresponding 5-iminopyrazole-4-dithiocarboxylate derivatives.\textsuperscript{89}

Enamines undergo reactions with carbon disulfide yielding either $\alpha,\beta$-unsaturated $\beta$-aminodithiocarboxylic acids\textsuperscript{87,90} or 1,4-dipolar compounds\textsuperscript{91}, depending on the nature of the enamine. The formation of iminodithiocarboxylate from the reaction of imines with carbon disulfide is reported by Mayer and Jentzsch.\textsuperscript{92} Japanese workers\textsuperscript{93} have studied the reaction between carbon disulfide and $\beta$-iminonitriles in the presence of a strong base such as sodium t-butoxide. $\beta$-Iminodithioacids (32) along with a variety of other by-products such as thiazines, pyridothiazines and diazocines have been isolated depending on the reaction conditions employed and the nature of the starting material. However, iminodithioacids (32) and esters derived
from them (33) have been obtained from the reaction of
\[
\begin{array}{c}
\text{NC} \quad \text{S} \\
\text{R} \quad \text{NH} \\
\text{SH}
\end{array}
\]
(32)
\[
\begin{array}{c}
\text{NC} \quad \text{S} \\
\text{R} \quad \text{NH} \\
\text{SR}
\end{array}
\]
(33)
\[\beta\text{-iminonitriles with carbon disulfide under appropriate}

conditions.}^{94,95}

Some enamino heterocycles, such as 6-aminopyrimidines, undergo base catalysed condensation with carbon
disulfide to yield the corresponding 6-aminopyrimidine-5-
dithiocarboxylic acid salts, which on alkylation, yield the
corresponding dithioesters.}^{96} \text{Carbon disulfide reacts with}
\[\beta\text{-iminosulfones to give a variety of products, depending on}

the reaction conditions.}^{97} \text{Other substrates such as}
tetrahydrothiophan-2-one,}^{98} \text{1,2-dithiole-3-thiones,}^{99} \text{cyclic}
hydrazides,}^{100} \text{barbituric acids,}^{101} \text{hydantoins,}^{101}
N-substituted rhodanines,}^{102} \text{arylsulfonylacetonilides,}^{103}
sulfoxides,}^{104} \text{sulfones}^{104-106} \text{and nitroalkanes}^{72,107}
\text{have been reacted with carbon disulfide, under appropriate}

conditions, to obtain dithiocarboxylic acid derivatives.
The reaction of carbon disulfide with certain nitrogen, sulfur and phosphorous ylides has also been studied.\textsuperscript{108-113} Dithiocarboxy betaines (34) resulting from the condensation of carbon disulfide with pyridinium ylides have been subjected to alkylation and cyclization reactions.

![Chemical Structure]

(34)

An alternative approach to \( \alpha \)-functionalized thionoesters and dithioesters (35) involves the direct condensation of an active methylene compound with thionocarbonic acid derivatives. This approach, however, has found only limited applicability.

\[
\text{R-X-C=S} \quad \overset{\text{Lg}}{+} \quad \text{Z-CH}_2-Y \quad \rightarrow \quad \text{R-X-S} \quad \overset{\text{Lg}}{+} \quad \text{Z-CH}_2-Y \quad \quad (35)
\]

\( X = O, S, N\text{R} \)

Lg= Leaving group

Z,Y= electron withdrawing group

Hartke and Gunther\textsuperscript{114} have reacted acetonitrile anion generated from acetonitrile and n-butyllithium with 0,S-dialkyl thionocarbonates and dialkyl trithiocarbonates.
to obtain the enethiolate salts (36) from which the alkyl cyanothionoacetate (37; X=0) has been isolated in the free form by acidification.

\[
\begin{align*}
SLi & \quad S \\
RX-C=CH-CN & \quad RX-C-CH_2-CN \\
(36) & \quad (37)
\end{align*}
\]

The condensation of thionocarbonic esters with malononitrile\textsuperscript{115} and cyanoacetic esters\textsuperscript{116} has been performed employing potassium ethoxide as the base to obtain the corresponding potassium enethiolates (38) and (39). Free thionoesters (40; X=0) and dithioesters (40; X=S) have been obtained by acidification of the corresponding enethiolates (39).

\[
\begin{align*}
\text{NC} & \quad \text{RO}_2\text{C} \\
\text{CN} & \quad \text{CN} \\
\text{RX-S} & \quad \text{RX-S} \\
(38) & \quad (39) \\
\text{RO}_2\text{C} & \quad \text{CN} \\
(40)
\end{align*}
\]

Nilsson\textsuperscript{117} has studied the reaction of malononitrile with alkyl and aryl chlorodithioformates and 0-alkyl and 0-aryl chlorothionoformates for the synthesis of the
corresponding thioacid derivatives (38). The reactions were effected in dimethylformamide employing sodium hydride as the base. The sodium dithiolates thus obtained have been employed in situ for alkylation reactions.

The reaction of O-aryl chlorothionoformates with enamines\textsuperscript{118} and trithiocarbonate-S,S-dioxides with malonic esters\textsuperscript{119} has yielded the corresponding thiono- and dithioester derivatives.

α-Sulfonyl dithioacetic esters have been synthesized by the successive treatment of α-methylene sulfones with sodium hydride and dimethyl trithiocarbonate.\textsuperscript{105}

The reaction of diazoalkanes with thionoformates yields higher thionoesters. The α-carbethoxy thionoacetate (41) and the α-benzoylthionoacetate (42) have also been obtained by the reaction of carbethoxy and benzoyl diazomethane with ethyl thionoformate.\textsuperscript{120}

\begin{align*}
\text{S} & \quad \text{O} & \quad \text{S} \\
\text{H}_5\text{C}_2\text{O}_2\text{C-CH}_2\text{OC}_2\text{H}_5 & \quad \text{C}_6\text{H}_5\text{C-CH}_2\text{C-OOC}_2\text{H}_5
\end{align*}

(41) \quad (42)

2,4-Dimethylene-1,3-dithietanes can be formally
regarded as thiolketene dimers. Their reaction with nucleophiles often leads to the formation of thiocarbonyl derivatives. Thus, the reaction of thiols with 2,4-dibenzylmethylene-1,3-dithietane leads to the formation of benzoyldithioacetates. The dithietane (43) on reaction with ethanol yields the thionoester (44).

\[
\begin{align*}
\text{H}_3\text{CO}^+ & \quad \text{S} \quad \text{COOCH}_3 \\
\text{H}_3\text{C}_2\text{O}_2\text{C} & \quad \text{S} \quad \text{COO}_2\text{C}_2\text{H}_5 \\
\text{(43)} & \quad \text{(44)}
\end{align*}
\]

Bridges and Whitham have found that the treatment of S-phenacyl- or acetonyldithiocarbonates (45) with a base such as sodium hydride leads to the formation of the corresponding \(\beta\)-ketothionoester (47) by the ring contraction of the episulfide intermediate (46).

\[
\begin{align*}
\text{R-CH}_2\text{S-C-OEt} & \quad \text{R-CH-S-C-OEt} \\
\text{(45)} & \quad \text{(46)}
\end{align*}
\]

\[
\begin{align*}
\text{R-CH}_2\text{C-OEt} & \\
\text{(47)}
\end{align*}
\]
The thiohydrolysis of iminoethers and iminothioethers has also been found applicable for the preparation of some α-functionalized thionoesters and dithioesters. Thus, nitriles, such as ethyl cyanoacetate, benzoylacetonitrile and phenylsulfonylacetonitrile have been converted to the corresponding iminoethers or iminothioethers (48) and further thiohydrolysed to the α-functionalized thiono- or dithioesters (49). Similarly, thiono- and dithiomalonates (51) have been prepared from malononitrile via the iminoether or iminothioether intermediates (50).

\[
\begin{align*}
\text{NH} & \quad \text{S} \\
\text{R-CH}_2-\text{C-} & \quad \text{R-CH}_2-\text{C-} \\
\text{XR}_1 & \quad \text{XR}_1 \\
(48) & \quad (49)
\end{align*}
\]

\[
\begin{align*}
\text{R} & = \text{CO}_2\text{Et}, \text{COPh}, \text{SO}_2\text{Ph} ; \quad \text{X} = 0 \text{ or } S \\
\text{NH} & \quad \text{NH} \\
\text{R}_1\text{X-C-CH}_2-\text{C-} & \quad \text{R}_1\text{X-C-CH}_2-\text{C-} \\
\text{XR}_1 & \quad \text{XR}_1 \\
(50) & \quad (51)
\end{align*}
\]

The base promoted Claisen ester condensation of thiono- and dithioacetates has been employed to obtain
thioacetyl-thiono-and dithioacetates.\textsuperscript{124,126,127}

Amine exchange reaction has found application in the synthesis of some N-substituted enaminodithioacid derivatives.\textsuperscript{87}

Some $\alpha$-functionalized thiono- and dithioesters have been studied by UV, IR and NMR spectral methods, so as to ascertain the structure and tautomeric behaviour of such compounds.

Hartke and Meissner\textsuperscript{116} have established the existence of a solvent and temperature dependent equilibrium between the thionoester form (53) and the chelated Z-enethiol form (54) by the NMR study of $\alpha$-cyanomonothionomalonic esters (53; $X=0$, $R=\text{Me}$, $\text{Et}$). The E-isomeric form (52) could not be detected. They also found that the dithioester (53; $X=S$, $R=\text{Me}$) exists almost exclusively in the enethiol form (54).

\begin{align*}
\begin{array}{ccc}
\text{NC} & \text{OR} \\
\text{HS} & \text{XR} & (52) \\
\end{array} & \begin{array}{ccc}
\text{NC} & \text{OR} \\
\text{RX} & \text{S} & (53) \\
\end{array} & \begin{array}{ccc}
\text{NC} & \text{OR} \\
\text{RX} & \text{H} & (54) \\
\end{array}
\end{align*}

NMR studies have revealed the existence of the
dithioester (23) in the intramolecularly hydrogen bonded methyl l-amino-l-hydroxy-2-cyanodithioacrylate form (23b).\textsuperscript{128}

The existence of $\alpha$-aroyl-dithioacetic acids (55a; XR=SH), $\alpha$-thionoesters (55a; X=O) and $\alpha$-dithioesters (55a; X=S) in the intramolecularly hydrogen bonded $\beta$-hydroxy-thiono cinnamic acid form (55b) has been established by spectral studies.\textsuperscript{10,34,72,123,129,130}

\textbf{Synthesis of $\alpha$-Functionalized Thioacetamide Derivatives}

A variety of $\alpha$-functionalized thioamides such as (56) or their enethiol tautomers (57) have been prepared by thiocarbamoylation of the carbanions derived from active methylene compounds or by the functional group transfor-
The condensation of isothiocyanates with carbanions derived from active methylene compounds, to obtain N-mono substituted thioamides or their derivatives is a reaction of general applicability and has been the subject of some reviews. A variety of C-H acidic compounds such as malononitrile, cyanoacetic esters, cyanoacetamides, dialkyl malonates, β-ketonitriles, β-diketones and β-ketoesters undergo this nucleophilic addition to isothiocyanates to yield thioamide derivatives (Table III).

The reaction of isothiocyanates with C-H acidic compounds has been performed by employing sodium alkoxides as the base. Alternatively, the anionic salts of active methylene compounds have directly been reacted with isothiocyanates. Strong bases, such as sodium t-butoxide, sodium t-amyl oxide, potassium t-butoxide, sodium amide and sodium hydride, have been used for the condensation of
TABLE III

Reaction of isothiocyanates with active methylene compounds

<table>
<thead>
<tr>
<th>Active methylene compound</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malononitrile</td>
<td>132</td>
</tr>
<tr>
<td>Alkyl cyanoacetates</td>
<td>133-140</td>
</tr>
<tr>
<td>Cyanoacetamide</td>
<td>141</td>
</tr>
<tr>
<td>N-Substituted cyanoacetamides</td>
<td>139,140,142,143</td>
</tr>
<tr>
<td>Cyanoacetyl hydrazides</td>
<td>140,144,145</td>
</tr>
<tr>
<td>( \beta )-Ketonitriles</td>
<td>31,34,146,147</td>
</tr>
<tr>
<td>Heterocyclic acetonitriles</td>
<td>40,149</td>
</tr>
<tr>
<td>Arylsulfonyl acetonitrile</td>
<td>148</td>
</tr>
<tr>
<td>Cyanomethyl pyridinium ylides</td>
<td>151-154</td>
</tr>
<tr>
<td>Cyanomethyl phosphonates</td>
<td>150</td>
</tr>
<tr>
<td>Alkylidene malononitriles</td>
<td>155</td>
</tr>
<tr>
<td>( \beta )-Diketones</td>
<td>146,156-164,176</td>
</tr>
<tr>
<td>( \beta )-Ketoesters</td>
<td>165-167,177</td>
</tr>
<tr>
<td>Malonic esters</td>
<td>143,158,168-173</td>
</tr>
<tr>
<td>Acetoacetanilides</td>
<td>174,175</td>
</tr>
<tr>
<td>Malonoanilides</td>
<td>56,143,174</td>
</tr>
<tr>
<td>( \alpha )-Methylene ketones</td>
<td>178,179</td>
</tr>
<tr>
<td>Heterocyclic methyl ketones</td>
<td>76</td>
</tr>
</tbody>
</table>
isothiocyanates with weakly acidic compounds.

The isolation of α-functionalized thigacetamides (59-62), by the acidification of the enethiolate salts obtained in these condensations, has been found successful in a number of cases. 146,147,178

\[
\begin{align*}
\text{(59)} & \quad \text{(60)} \\
\text{(61)} & \quad \text{(62)}
\end{align*}
\]

β-Diketones, such as dimedone, have been reacted with isothiocyanates in the presence of triethylamine. 146,156,157

The thioamides (63), (64) and (65) are obtained in the reaction of acetylacetone with isothiocyanates depending upon the base employed and the reaction conditions. 159-164

\[
\begin{align*}
\text{(63)} & \quad \text{(64)} & \quad \text{(65)}
\end{align*}
\]

The reaction between enamines and isothiocyanates
has been studied by many workers. The reaction of enamines with isothiocyanates normally leads to the formation of \(\alpha,\beta\)-unsaturated \(\beta\)-aminothioamides. The tertiary enamines derived from \(\alpha\)-methylene ketones, \(\alpha\)-aldehydes, \(\beta\)-diketones and \(\beta\)-ketoesters and related compounds undergo smooth reaction with isothiocyanates to yield the corresponding thioamides (66) and (67).

\[
\begin{align*}
R_4 \quad \text{S} \quad \text{NHR} \\
\text{R}_3 \quad \text{NR}_1 \text{R}_2
\end{align*}
\]

A variety of primary and secondary enamines derived from \(\beta\)-ketoesters, \(\beta\)-diketones and related compounds have been reacted with isothiocyanates to obtain \(N\)-substituted thioamides (68). \(N\)-Sulfonylthioamides have been obtained by the reaction of enamines with sulfonyl isothiocyanates. The reaction between acyl isothiocyanates and primary, secondary and tertiary enamines yield the open chain \(N\)-acylthioamides (69).
or cyclic products such as pyrimidines, pyridines or oxazines depending upon the nature of the reactants and the reaction conditions employed.

The ketene aminal, 1,1-dipiperidinoethylene, reacts with isothiocyanates to yield the corresponding 1:1 or 1:2 adducts (70) depending upon the reaction conditions.

\[ \text{R}_2\text{N} \quad \begin{array}{c} \text{S} \\ \text{NHR} \end{array} \quad \text{R}_2\text{N} \quad (70) \quad \text{R}_1 \]

\[ \text{R}_1 = \text{H} \text{ or } \text{RNHC} = \text{PiPeridino} \]

Other \( \alpha \)-functionalized ketene acetals and aminals such as, acylketene \( S,N \)-acetals, acylketene aminals, thioacylketene aminals and nitroketene aminals, have been reacted with alkyl, aryl or acyl isothiocyanates to obtain open-chain thioamides or cyclic compounds.

Certain \( \beta \)-iminonitriles, imines, hydrazones of simple ketones, acetophenone anils and enaminoi heterocycles such as, 6-aminopyrimidines, have been reacted with isothiocyanates to obtain the corresponding C-thiocarbamoylated products.
Phenyl isothiocyanate reacts with nitromethane and benzoylnitromethane in the presence of sodium hydride to yield the salts of the thioamides (71; \( R=\text{H} \))\(^{72} \) and (71; \( R=\text{COC}_6\text{H}_5 \))\(^{221} \).

\[
\begin{aligned}
\text{R} & \text{S} \quad \text{N} \\
\text{O}_2\text{N} & \quad \text{NHPh}
\end{aligned}
\]

(71)

\( R = \text{H}, \text{PhCO} \)

Phenylacetylene,\(^{197,222} \) dimethyl sulfoxide, dimethyl sulfone\(^{223} \) and other sulfones containing an activated methylene group, such as arylsulfonylaceto-phenones and arylsulfonylacetanilides,\(^{224,225} \) afford thioamide derivatives on their reaction with isothiocyanates.

The use of other thiocarbamoylating agents in place of isothiocyanates in the reaction with carbanions should, in principle, lead to the formation of thioamides. Nilsson and co-workers\(^{117,226} \) have reacted \( N,N \)-disubstituted thiocarbamoyl chlorides (72) or \( C \)-sulfonyl thioformamides (73)

\[
\begin{aligned}
\text{S} & \\
\text{R}_1\text{R}_2\text{N-C-Cl} & \quad \text{S} \\
& \quad \text{R}_1\text{R}_2\text{N-C-SO Ar}
\end{aligned}
\]

(72) \hspace{1cm} (73)

with carbanions of active methylene compounds to obtain the
corresponding thioamide intermediates (56). Alkyl N-aryldithiocarbamates have been employed for the thiocarbamoylation of some active methylene compounds.  

\[
\begin{align*}
\ce{R1R2N-C-CH-X} \\
(56)
\end{align*}
\]

N-substituted \(\alpha\)-cyanothioamide derivatives (75) or enethiol tautomers have been prepared by the reaction of hydrosulfides with \(\alpha\)-cyanoketene S,N-acetal derivatives (74; \(X=\text{SR}\)) or 3-halo-3-aminoacrylonitriles (74; \(X=\text{halo}\))  

\[
\begin{align*}
\ce{R-CN} & \quad \ce{R-CN} \\
(74) & \quad (75)
\end{align*}
\]

2-Acyl-1-chloro-1-aminoethylenes have been reacted with hydrogen sulfide to obtain the corresponding thioamide derivatives.  

The reaction of dithietanes (76) \(^{231,232}\) and trithiacyclopentanes (77) \(^{233}\) with aliphatic and aromatic
amines has yielded a variety of α-cyanothioamides (78) or their salts.

Some acylmethylenedithietanes and dithiolanes have been reacted with amines to obtain β-ketothioamides.

The reaction of carbon subsulfide with arylamines yields malonodithioanilides.

Reaction of certain α-functionalized dithioacids or dithioesters with amines leads to the formation of the corresponding thioamides. Thus, the reactions of primary or secondary amines with benzoyldithioacetic acid or its ester yields benzoyl thioacetamides.

Ring opening reaction of 1,2-dithiolium salts with amines has served as a useful method of synthesis of enaminothioacid derivatives such as the enaminothionoesters, (80; Y=0) enaminodithioesters (80; Y=S) and enaminothioamides (80; Y=NR).
Enaminodithioesters (80; Y=S) have been obtained by the action of Grignard reagents, R–MgX, on isothiazoline-5-thiones (81). Enaminothioamides have been prepared from the reaction of amines with β-ketothioamides, acetylenic thioamides and by the reaction of an amine with 1,2-dithiole-3-thione in the presence of triphenyl phosphite.

Deacylation of 2,2-diacyl thioacetamides and hydrolysis of β-imino or enaminothioamides have been employed for the synthesis of β-oxothioamides. Cyanothioacetanilides have been obtained by the hydrolysis and decarboxylation of the corresponding α-carbalkoxy cyanothioacetanilides. Malonic acid monothioanilide has, similarly, been prepared by the hydrolysis and
decarboxylation of isothiocyanate adducts of diethyl malonate or thionomalonates. Some α-functionalized primary thioamides (82) have been synthesized by the hydrosulfurization of α-functionalized nitriles. The addition of hydrogen sulfide has been effected with a variety of nitriles such as malononitrile, methyl-, t-butyl-, benzyl cyanoacetates, substituted cyanoacetanilides, cyanothioacetanilides, and α-cyanomalonothioanilides. Methyl- and ethyl cyanoacetates have been converted to thioamides by reaction with 0,0-diethyl dithiophosphoric acid.

\[
\begin{align*}
\text{R-CH}_2\text{C}=\text{N} & \xrightarrow{\text{H}_2\text{S}} \text{R-CH}_2\text{C-NH}_2 \\
\text{R=CN, CO}_2\text{Me, CO}_2\text{C}_3\text{H}_7, \text{CO}_2\text{CH}_2\text{Ph, CONHR, CSNHR} \\
\end{align*}
\]

Malonitrile has been converted to malonodithioamide (82; R=CSNH₂) by reaction with hydrogen sulfide under appropriate conditions or by the hydrogen sulfide transfer reaction of malononitrile with thioacetamide. This has also been obtained as the product of reaction between dimethylaminomalononitrile and hydrogen sulfide. α-Benzyl malononitrile on reaction with
hydrogen sulfide yields the corresponding benzyl malonodithioamide. \(^{253}\)

Certain \(\beta\)-imino- or enaminonitriles have been converted to the corresponding thioamides (83) by the reaction with hydrogen sulfide.\(^{199,256-258}\)

\[
\begin{align*}
S \\
R=CH=\text{CH}-\text{NH}_2 \\
\text{NR}_1\text{R}_2 \\
\end{align*}
\]

(83)

Ethoxyethylidemalononitrile,\(^{247}\) dimethylamino-methylene-malononitrile\(^{257}\) and \(3\)-alkoxy-\(^{259}\), \(3\)-alkylthio-\(^{260}\) and \(3\)-dialkylamino-\(3\)-amino-\(2\)-cyanoacrylonitriles\(^{261}\) have been reacted with hydrogen sulfide to obtain the corresponding thioamides. \(\alpha\)-Carbethoxycyanothioacetamide has been obtained by the sulfurization of \(\alpha\)-carbethoxy-cyanoacetamide with phosphorous pentasulfide.\(^{250}\) The reaction of \(1\)-chloro-\(1\)-amino-\(2\)-cyanoethylenes or \(1\)-amino-\(1\)-methylthio-\(2\)-cyanoethylenes with hydrosulfides, the reaction of ammonia with \(2,4\)-dicyanomethylene-\(1,3\)-dithietanes and the reaction of hydrazine with \(3,6\)-biscyanomethylene-\(1,4,2,5\)-dithiadiazines has been employed for the
synthesis of primary cyanothioacetamide derivatives with an electron withdrawing functional group at α-position.\textsuperscript{228,229,232,262}

Tautomeric behaviour of some α-functionalized thioamides has been studied. Spectral studies have indicated that the thioamides (84) exist as their enethiol tautomers (85).\textsuperscript{137,263}

\begin{equation}
\begin{array}{c}
\text{R'O} \\
\text{R'N}\text{H} \\
\text{CN} \\
\text{S} \\
\end{array}
\end{equation}

(84)

\begin{equation}
\begin{array}{c}
\text{R'O} \\
\text{R'N}\text{H} \\
\text{CN} \\
\text{SH} \\
\end{array}
\end{equation}

(85)

The keto-enol and thione-enethiol tautomerism in a variety of β-Ketothioamides (86) has been studied by many workers. In general, the intramolecularly hydrogen bonded keto or enol thione forms (86 or 87) have been found to predominate over other tautomeric forms.\textsuperscript{178,179,234}

\begin{equation}
\begin{array}{c}
\text{R_1} \\
\text{R_2} \\
\text{S} \\
\text{N} \\
\text{H} \\
\end{array}
\end{equation}

(86)

\begin{equation}
\begin{array}{c}
\text{R_1} \\
\text{R_2} \\
\text{R_3} \\
\text{S} \\
\text{H} \\
\end{array}
\end{equation}

(87)

The existence of tautomeric equilibrium between the
forms (88) and (89) has been established by the NMR studies of thioacetanilide. The NMR spectral study of thioamides (90) and (91) has revealed that while (90) exists solely as the enol tautomer, (91) exists as a mixture of keto and enol tautomers in a ratio of 61:39 in solution.

The spectral studies on the isothiocyanate adducts of primary, secondary and tertiary enamines derived from $\beta$-ketoesters, $\beta$-diketones indicate the existence of these thioamides in the intramolecularly hydrogen bonded chelated forms (92) and (93).
NMR study has revealed the intramolecular hydrogen bonded structure (94) for the isothiocyanate adducts derived from dimedone and its enamines.\textsuperscript{157}

\begin{equation}
\begin{array}{c}
\text{X-H} \\
\text{S} \\
\text{O-H} \\
\text{N} \\
R
\end{array}
\end{equation}

\textbf{Synthesis of }\alpha\text{-Functionalized ketene }S,S\text{-and }O,S\text{-acetals}

\alpha\text{-Functionalized ketene dithioacetals are represented by the formula (12) where, }X\text{ or }Y\text{ is an electron withdrawing group such as }\text{CN}, \text{CO}_2\text{R}, \text{COR}, \text{SO}_2\text{R}, \text{NO}_2\text{, etc. One of the most general methods for the preparation of such dithioacetals with an alkyl substituent on the sulfur atom, is by the alkylation of the dithiolate anion}

\begin{equation}
\begin{array}{c}
X \\
R_2S \\
\text{SR}_1 \\
Y
\end{array}
\end{equation}

resulting from the base catalyzed condensation of active
TABLE IV

Preparation of ketene S,S-acetals by alkylation of
dithiolates derived from active methylene compounds.

\[
\begin{align*}
X & \quad \text{CH}_2 \quad CS_2, \text{ Base} \quad Y \\
\text{X} & \quad 2RX \quad \rightarrow \quad \text{X} \quad \text{SR} \quad \text{Y} \quad \text{SR}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Active methylene Compound</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malononitrile</td>
<td>9,11,14,19,22,28,260</td>
</tr>
<tr>
<td>Alkyl cyanoacetates</td>
<td>9,11,14,19,23,25,28,264</td>
</tr>
<tr>
<td>Cyanoacetamide</td>
<td>9,19,24,28,29,37</td>
</tr>
<tr>
<td>N-Substituted cyanoacetamides</td>
<td>28</td>
</tr>
<tr>
<td>β-Ketonitriles</td>
<td>29-34</td>
</tr>
<tr>
<td>Arylacetonitriles</td>
<td>9,29,37,39</td>
</tr>
<tr>
<td>Heteroarylacetonitriles</td>
<td>41,42</td>
</tr>
<tr>
<td>Arylsulfonylacetonitrile</td>
<td>35</td>
</tr>
<tr>
<td>Alkylidene malononitrile</td>
<td>44</td>
</tr>
<tr>
<td>β-Diketones</td>
<td>29,46-48,265</td>
</tr>
<tr>
<td>β-Ketoesters</td>
<td>29,49</td>
</tr>
<tr>
<td>Malonic esters</td>
<td>11,14,23,29,53</td>
</tr>
<tr>
<td>Malonanilides</td>
<td>56</td>
</tr>
<tr>
<td>α-Methylene ketones</td>
<td>10,39,48,57-59,61,64</td>
</tr>
<tr>
<td></td>
<td>66-68,76,80</td>
</tr>
<tr>
<td>α-Methylene aldehydes</td>
<td>82</td>
</tr>
<tr>
<td>Arylacetic esters</td>
<td>58</td>
</tr>
<tr>
<td>Cyclic esters</td>
<td>79</td>
</tr>
<tr>
<td>Nitromethane</td>
<td>72</td>
</tr>
</tbody>
</table>
methylene compounds with carbon disulfide (Table IV). While the alkylation with two equivalents of an alkylating agent to obtain symmetrical dithioacetals has been routinely performed, the alkylation with two different alkylating agents, sequentially, to obtain unsymmetrically substituted dithioacetals has been reported only in a few cases.

$\alpha$-Acetyldimethane dithioacetal has been obtained by the alkylation of the condensation product of acetylacetone with carbon disulfide in the presence of sodium ethoxide as a base.$^{29}$ Dicyanoketene dithioacetals (95) have been prepared by the alkylation of enethiolates derived by the reaction of malononitrile with dimethyl trithiocarbonate$^{115}$ or chlorodithioformate.$^{117}$ Silver salt of malononitrile has been condensed with dimethyl trithiocarbonate to obtain

$$
\begin{align*}
\text{NC} & \quad \text{CN} \\
\text{R}_2\text{S} & \quad \text{SR}_1
\end{align*}
$$

(95)

the dicyanoketene dithioacetal ($95; R_1 = R_2 = \text{Me}$).$^{11}$

Alkylation of $\alpha$-functionalized dithioesters with an equivalent of an alkylating agent and a base leads to
the formation of α-functionalized ketene dithioacetals.\textsuperscript{1,50,72,106,122}

Cyclic ketene dithioacetals (96) have been prepared by the reaction of active methylene compounds with dithiolium salts.\textsuperscript{71,72,266}

\[
\begin{array}{c}
\text{X} \\
\text{Y}
\end{array}
\]

(96)

α-Acylketene dithioacetals (99) have been obtained by the reaction of 1,1-dichloro-2-acylethylenes (97) or 1-halo-2-acylacetylenes (96) with thiols.\textsuperscript{267-270}

\[
\begin{array}{c}
\text{R-C-CH=C}^\text{Cl} \\
\text{R-C-CH=O}^\text{Br} \\
\text{R-C-CH=O}^\text{SR_1}
\end{array}
\]

(97) \quad (98) \quad (99)

The ketene dithioacetal (100) has been reacted with diphenyl ketene,\textsuperscript{271} oxalyl chloride,\textsuperscript{272} or phenyl isocyanate\textsuperscript{271} to obtain the corresponding α-substituted ketene dithioacetals (101).

\[
\begin{array}{c}
\text{H} \\
\text{H} \\
\text{EtS} \\
\text{EtS}
\end{array}
\]

(100) \quad \begin{array}{c}
\text{H} \\
\text{R} \\
\text{EtS} \\
\text{EtS}
\end{array}

(101) \quad R = \text{Ph}_2\text{CH}, \text{ClCO}, \text{PhNH}

Schafer and Gewald\textsuperscript{273} have reported the prepara-
tion of dicyanoketene $O,S$-acetals (102) by the alkylation of the dianions derived from the reaction of malononitrile with carbonyl sulfide.

$$\text{NC} \quad \text{CN} \quad \text{R}_2\text{O} \quad \text{SR}_1$$ (102)

Dicyanoketene $O,S$-acetals (102) have also been obtained by the alkylation of enethiolates resulting from the reaction of malononitrile with xanthate esters$^{115}$ and $O$-alkyl- or $O$-aryl chlorothionoformates.$^{117}$

The methylation of monothionomalonic ester has given the corresponding $\alpha$-carbalkoxy-ketene, $O,S$-acetal (103).$^{125}$ The reaction of thiols with $0,0$-acetals has been employed for the preparation of some ketene $O,S$-acetals.$^{274}$

$$\text{SCH}_3 \quad \text{R}_1\text{O}_2\text{S}\text{-CH}=\text{O} \quad \text{O}_2\text{R}$$ (103)

**Synthesis of $\alpha$-Functionalized ketene $S,N$-acetals**

Alkylation of the thioamide salts, resulting from the base catalyzed condensation of isothiocyanates with
### TABLE V

Preparation of ketene S,N-acetals by alkylation of thioamides derived from active methylene compounds and isothiocyanates.

\[
\begin{array}{c}
\begin{array}{c}
\text{X} \\
\text{CH}_2 \\
\text{Y}
\end{array}
\end{array}
\begin{array}{c}
\text{R}_1\text{NCS/Base}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{X} \\
\text{CH}_2 \\
\text{Y}
\end{array}
\end{array}
\begin{array}{c}
\text{SR} \\
\text{NH-R}_1
\end{array}
\]

(104)

<table>
<thead>
<tr>
<th>Active methylene compounds</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkyl cyanoacetates</td>
<td>134, 275</td>
</tr>
<tr>
<td>(\beta)-Ketonitriles</td>
<td>31, 34</td>
</tr>
<tr>
<td>Heterocyclic Acetonitriles</td>
<td>149</td>
</tr>
<tr>
<td>Cyanomethyl pyridinium salts</td>
<td>153</td>
</tr>
<tr>
<td>Cyanomethyl phosphoric esters</td>
<td>150</td>
</tr>
<tr>
<td>Malonic esters</td>
<td>55, 134, 172</td>
</tr>
<tr>
<td>Malonanilides</td>
<td>56</td>
</tr>
<tr>
<td>Nitromethane</td>
<td>72</td>
</tr>
</tbody>
</table>
active methylene compounds, yields ketene S,N-acetals (104) (Table V).

Ketene S,N-acetals (105) have also been obtained by the alkylation of enethiolates, resulting from the reaction of active methylene compounds with thiocarbamoylating agents, such as N,N-disubstituted thiocarbamoylchlorides or C-sulfonyl thioformamides.117,226

\[ \text{R} \text{N}^+ \text{X} \text{SR} \]

(105)

The reaction of active methylene compounds with 1-chloro- and 1-methylthioiminium salts (106)30,276,277 and N-methyl- and N-tosyliminodithiocarbonates (107)278,279 and related compounds,280 leads to the direct formation of \( \alpha \)-functionalized ketene S,N-acetals. Episulfide ring

\[ \text{R}_1 \text{N}^+ \text{Y} \text{SR} \]

(106)

\[ \text{R} \text{N} \text{NSMe} \]

(107)

\( \text{Y} = \text{Cl}, \text{SCH}_3 \)
contraction of 2-phenacylthiothiazolium salts has yielded cyclic ketene S,N-acetals.\textsuperscript{281}

The reaction of \(\alpha\)-functionalized ketene S,S- and O,S-acetals with primary and secondary amines has been one of the general methods of preparation of the corresponding ketene S,N-acetals. The reaction course depends on the nature of the substituents present at the \(\alpha\)-position of the ketene S,S-acetal, the nature of the amine and the reaction conditions employed. While a few ketene S,S-acetals are unreactive towards amines, some \(\alpha\)-functionalized ketene thioacetals react with amines to yield directly the aminals (108).

\[
\begin{align*}
Y & \quad X \\
RS & \quad SR \\
\text{HN} & \quad R_1 \\
R_2 & \quad R_2
\end{align*}
\]

Normal displacements were observed in the reactions between amines and ketene dithioacetals derived from malonitrile,\textsuperscript{282,283} ethyl-\textsuperscript{284,285} and methyl-\textsuperscript{282} cyanoacetates, benzoylacetonitrile,\textsuperscript{30,286,287} phenylsulfonylacetonitrile,\textsuperscript{35}
heterocyclic acetonitriles,\textsuperscript{41} acetylacetone,\textsuperscript{30,46} indandione,\textsuperscript{47} \(\alpha\)-methylene ketones,\textsuperscript{67,288} malonanilides,\textsuperscript{56} nitromethane\textsuperscript{288,289} and heterocyclic amides.\textsuperscript{290}

Ammonia and a variety of aliphatic and aromatic primary amines and aliphatic secondary amines have generally been employed for the displacement of the methylthio group in ketene dithioacetals. Aziridine has been reported to yield the corresponding \(S,N\)-acetals.\textsuperscript{291,292}

The dicyanoketene \(S,N\)-acetal (109) have been obtained by the reaction of corresponding amines with \(O\)-aryl dicyanoketene \(O,S\)-acetals.\textsuperscript{117}

\[
\begin{align*}
\text{NC} & \quad \text{CN} \\
\text{R}_2\text{N} & \quad \text{SR}
\end{align*}
\]

(109)

Some \(2\)-acyl-1,1-dichloroethylenes (97) have been converted to \(\alpha\)-acylketene \(S,N\)-acetals (110) by sequential reaction with an amine and a thiol or alternatively, with a thiol followed by an amine.\textsuperscript{230,268}

\[
\begin{align*}
\text{R-C-H} & \quad \text{Cl} \\
\text{C} & \quad \text{Cl} \\
\text{R} & \quad \text{C-H} & \quad \text{Cl} \\
\text{R} & \quad \text{C-H} & \quad \text{C-NR}_2\text{R}_2 & \quad \text{SR}
\end{align*}
\]

(97) (110)
Electrophilic substitution reactions with ketene S,N-acetals possessing a replaceable α-hydrogen atom has yielded some α-functionalized ketene S,N-acetals. The preparation of N,N-disubstituted S,N-acetals by the alkylation of N-monosubstituted S,N-acetals has been reported.

\[
\begin{align*}
\text{R}_1\text{R}_2\text{N} & \quad \text{O} \\
\text{XR} & \quad \text{R}_3 \\
\text{SR} & \quad \text{(111)}
\end{align*}
\]

The ring opening reaction of 3-alkylthio- or arylthioisoxazolium salts leads to the formation of acylketene S,N-acetals. Some 3-chloroisoxazolium salts have been converted directly to acylketene S,N-acetals by the treatment with thiols.

\[
\begin{align*}
\text{Ar} & \quad \text{O} \\
\text{CH}_3 & \quad \text{SR} \\
\text{Y} = \text{SR, Cl} \\
\text{(112)} \\
\text{(113)}
\end{align*}
\]

Physical and spectroscopic techniques have been employed to study the geometric isomerism as well as
barrier to rotation around C=C in $\alpha$-functionalized ketene thioacetals and related compounds. $^{29,30,55,299,300-302}$

These $\alpha$-functionalized ketene thioacetals possess electron donating acetal substituents on C-1 and electron withdrawing substituents on C-2 and therefore, represent polarized ethylenes with a push-pull system. The NMR signal coalescence studies indicate a low free energy barrier for rotation around C=C in such systems. $^{29,55}$

$\alpha$-Functionalized ketene S,N-acetals of the type (114a) can exist in the imino tautomeric form (114b) or

\[
\begin{align*}
X & \quad \quad \quad \quad Y \\
H-N & \quad \quad \quad SR_1 \\
\quad & \quad \quad R
\end{align*}
\]

(114a)

\[
\begin{align*}
X & \quad \quad \quad \quad Y \\
N & \quad \quad \quad SR_1 \\
\quad & \quad \quad R
\end{align*}
\]

(114b)

other tautomeric forms involving the functional group present on the $\alpha$-carbon atom. The IR and NMR spectral studies have frequently been employed for the determination of tautomeric nature of such compounds.

Tautomeric equilibrium between thiomidates (115b) and ketene S,N-acetals (115a) has been found to be dependent upon the nature of the substituents. $^{303}$
imidate form (115b) predominates in substrates possessing hydrogen, alkyl or aryl substituents at the α-position. Those possessing electron withdrawing substituents, such as 116, exist as a mixture of thioimidate (116b) and ketene S,N-acetal (116a) tautomers. The tautomeric equilibrium between (116a) and (116b) has been found to be dependent upon the polarity, hydrogen bonding ability of the solvent and temperature. Some of the molecules 115 (X=CN; Y=CN, CO₂R, C₆H₅SO₂) were found to exist mainly in the ketene S,N-acetal form (115a). The existence of analogous tautomerism between some iminomethane disulfides and aminovinyl disulfides has earlier been demonstrated. IR and NMR spectral studies have indicated that
some potentially tautomerizable α-acylketene S,N-acetals (117)\textsuperscript{287} and α-nitroketene S,N-acetals (118)\textsuperscript{72} exist in the ketene S,N-acetal form. However, the nitroketene S,N-acetal (119a) has been shown to exist preferentially in the hydrazone form (119b)\textsuperscript{306}.

Use of α-Functionalized Thiono- and Dithioacetic acid Derivatives and α-Functionalized Ketene Thioacetals in Heterocycle syntheses

α-Functionalized thionoacetic acid derivatives and ketenethioacetals undergo a variety of useful synthetic transformations. Their use in the synthesis of heterocycles has been of special interest. The nucleophilicity of the sulfur atom in these functionalized thionoacid
derivatives forms the basis of a variety of reactions leading to sulfur containing heterocycles.

The formation of 2,4-bismethylene-1,3-dithietanes (120) or 3,5-bismethylene-1,2,4-trithiacyclopentanes (121) has been observed by many workers in the preparation and reaction of dithiolates with oxidizing agents or acylating agents\(^1,9,15,19,60,68,75,93,122,208,232,307-311\).

\[ 
\begin{align*}
\text{X, Y} &= \text{electrons withdrawing group} \\
(120) &
\end{align*}
\]

The reaction of dithiolates with 1,1-dihalocarbons, like dihalogenoalkanes and phosgene yield the corresponding dithietane derivatives (122).\(^1,9,20,48,61,312-314\)

\[ 
\begin{align*}
(122) &
\end{align*}
\]

\[ R_1, R_2 = \text{alkyl, aryl; } R_1 - R_2 = 0 \]

The direct formation of 1,2-dithiole-3-thiones (123)

\[ 
\begin{align*}
(123) &
\end{align*}
\]

in the reaction of active methylene compounds or enamines
with carbon disulfide and sulfur or by the reaction of
\(\alpha\)-acylketene dithiolates with phosphorous pentasulfide
has been reported.\(15,19,21,69,82,315,316\)

2-Methylene-1,3-dithiolanes (124) and dithiins
(125) have been prepared by the reaction of dithiolates
with 1,2- and 1,3-dihaloalkanes.\(9,14,15,35,61,67,76\)

\[
\begin{array}{c}
\text{S} & \text{S} \\
(124) & (125)
\end{array}
\]

Similarly, the reaction of dithiolates with 1,2-dihaloal-
kenes,\(36,317\) \(\alpha\)-halocarbonyl compounds\(14,71,72\) and pro-
pargyl halides\(14,48\) yield 2-methylene-1,3-dithioles (126).

\[
\begin{array}{c}
R_1 & R_2 \\
(126)
\end{array}
\]

The formation of benzodithioles (127) benzoxa-
thioles (128) and related heterocycles have been observed

\[
\begin{array}{c}
\text{OH} & \text{OH} \\
(127)
\end{array}
\]

in the reactions of \(\alpha\)-cyanodithiocarboxylates with
p-quinones, 2,3-dichloroquinones, p-nitrochlorobenzenes, and 2,3-dichloroquinoxalines.

Benzoxathioles (128) have also been obtained by the reaction of methylthiomercaptomethylenenitriles with p-quinones.

\[
\text{(128)}
\]

1,3,5-Dithiazines (129) and 1,3-thiazines (130) have been obtained by the reaction of dithiolates, derived from cyanoacetic esters and acetoacetic esters, with formaldehyde and a primary amine.

\[
\text{(129)}
\]

\[
\text{(130)}
\]

A variety of \(\alpha\)-functionalized primary thioamides, such as cyanothioacetamide derivatives, react normally with \(\alpha\)-haloketones, \(\alpha\)-halonitriles and \(\alpha\)-haloesters to yield the corresponding thiazoles (131).
N-Substituted thioamides derived from active methylene compounds have been reacted with \(\alpha\)-haloketones, esters, \(\alpha\)-halonitriles, 1,2-dihaloalkanes and oxalyl chloride to obtain 2-methylenethiazoline and thiazolidine derivatives (132-135).

\[\text{Structure (132)}\]

\[\text{Structure (133)}\]

\[\text{Structure (134)}\]

\[\text{Structure (135)}\]

The formation of oxathiole (136) in the reaction of certain thioamide derivatives with \(\alpha\)-haloketones has been observed. Thiazolines (137) have been obtained from the reaction of dithioesters with aziridine.

\[\text{Structure (136)}\]

\[\text{Structure (137)}\]

N-Arylthioamides can yield benzothiazole deriva-
tives (138) on oxidation. Such benzothiazole formation has been observed in the oxidation reactions of N-arylthioamides derived from aryl isothiocyanates and active methylene compounds such as ethyl cyanoacetate, benzoylacetonitrile, dimedone, enamine of dimedone, acetylacetone, diethyl malonate and cyanomethylphosphonates.

\[ \text{138} \]

The oxidation of some N-substituted thioamides derived from active methylene nitriles gives thiazoline (139) or 1,2,4-thiadiazoline (140).

\[ \text{139} \]
\[ \text{140} \]

The oxidative cyclization of phenyl isothiocyanate adduct of cyanomethylpyridinium chloride yields imidazopyridinium ylide (141).

\[ \text{141} \]
3,5-Diamino- and 3,5-diarylamino-1,2-dithiolium salts (142) have been obtained by the oxidation of malonodithioamide and malonodithioanilides.\(^{253,329}\)

\[
\begin{align*}
\text{RNH} & \quad \text{NHR} \quad X^- \\
\text{NH} & \quad \text{S} \\
\quad & \quad \text{R1}
\end{align*}
\]

(142)

The oxidative cyclization of thionoacid derivatives with \(\beta\)-imino (143a) or enamino function (143b) has been one of the fruitful and generally applicable synthetic method for a variety of isothiazole derivatives (144).\(^{330-337}\)

\[
\begin{align*}
\text{R1} & \quad \text{R2} & \quad \text{R3} \\
\text{NH} & \quad \text{NH} & \quad \text{NH2} \\
\text{X} & \quad \text{X} & \quad \text{X} \\
\end{align*}
\]

(143a) (143b) (144)

Dithioacid\(^{12,13,18,338-345}\) and thioamide (145)\(^{320,346,347}\) derivatives obtained from active methylene nitriles have

\[
\begin{align*}
\text{R2} & \quad \text{CN} \\
\text{R1} & \quad \text{SH} \\
\quad & \quad X = S, NR'
\end{align*}
\]

(145)

been cyclized to a variety of isothiazoles (146) by
reaction with sulfur, halogens, hydrogen peroxide and chloramine.

\[
Y = \text{SH, Cl, Br, OH, NH}_2
\]

(146)

The reaction of a variety of \( \alpha \)-functionalized thionoacid derivatives (147) with an active halomethyl compound has extensively been used for the synthesis of thiophenes (148). Thienothiophenes (150) have been obtained by the reaction of dithiolates (149) derived from certain active methylene compounds with active halomethyl compounds.
Functionalized ketene S,S- and S,N-acetals are prone to nucleophilic attack at the acetal carbon and therefore, their reaction with 1,2-, 1,3- or 1,4-binucleophilic compounds often leads to the formation of heterocyclic compounds. A variety of ketene S,S-acetals, especially bismethylthio ketene acetal derivatives have been reacted with ethylenediamine, o-phenylenediamine, ethanolamine, o-aminophenol and o-aminothiophenol to obtain imidazolines (151; X=NH), \[35, 47, 56, 72, 282, 286\] benzimidazolines (152; X=NH), \[35, 47, 359\] oxazolines (151; X=0), \[282, 284\] benzoazolines (152; X=0) \[35, 359\] and benzothiazolines (152; X=S). \[56, 358\] Reaction of \(\alpha\)-nitroketene dithioacetal with o-phenylenediamine and o-aminothiophenol has been found to yield bisbenzimidazole and bisbenzothiazole, respectively. \[359\]
The reaction of some aminothiazolium salts (153) with ketene dithioacetals yields thiazoloimidazoles (154).

\[
\begin{align*}
R - N X^- & \quad \text{(153)} \\
\text{NH}_2 & \quad \text{(154)}
\end{align*}
\]

The ketene thioacetals with a cyano, keto, ester or amide function at the \(\alpha\)-position are formally 1,3-dicarbonyl compounds and their reactions with 1,2-binucleophilic reagents, such as hydrazines or hydroxylamine leads to the formation of pyrazoles and isoxazoles, respectively, and the reaction with 1,3-binucleophilic species such as amidines guanidines, ureas and thioureas yields pyrimidines.

A variety of pyrazoles have been obtained by the reaction of hydrazines with dimethylthiomethylene derivatives of active methylene compounds.\(^26,30,35,67,274,360-371\) The reaction of hydrazines, hydrazides and semicarbazides with dimethylthiomethylene derivatives of malononitrile,\(^360,368,369\) cyanoacetic esters,\(^26,360,361,366,367,370\)
cyanoacetamide\textsuperscript{360} and arylsulfonylacetonitriles\textsuperscript{35} gives the corresponding alkylthio substituted aminopyrazoles (155). Similarly, ketene S,S-acetals derived from ketones,\textsuperscript{67,274,363,364} \(\beta\)-ketonitriles,\textsuperscript{30,362} \(\beta\)-ketoesters and \(\beta\)-diketones,\textsuperscript{30,365,371} afford the corresponding substituted pyrazole derivatives (156). Pyrazole derivatives have also been obtained by the reaction of some \(\beta\)-iminodithiocarboxylic acids with hydrazines.\textsuperscript{372}

\[ \begin{align*}
Y & \quad \text{(155)} \\
R_1 & \quad \text{(156)} \\
\end{align*} \]

Aminopyrazoles (157) have been obtained by the

\[ \begin{align*}
\text{(157)} \\
\end{align*} \]

reaction of hydrazine with appropriate \(\alpha\)-acylketene
S,N-acetals. However, the reaction of hydrazines with some acylketene S,N-acetals has been found to yield 3-alkylthiopyrazoles instead of the expected 3-aminopyrazoles.

Pyrazole derivatives have been obtained by the reaction of hydrazines with α-functionalized thioacetamides. Thus, 3,5-diaminopyrazoles have been prepared by the reaction of hydrazine with cyanothioacetanilides373 and malonodithioanilides.374,375 Reaction of hydrazine with the thioamide (84) yields hydrazinium salt which cyclizes to the diaminopyrazole (158) on heating.376 Diaminopyrazole (158; R=Ph) has also been obtained by the reaction of anilinomethylthiomethylene cyanoacetic esters with hydrazine.285

3-Amino-5-arylamino-4-arylopyrazole formation has been observed in the reaction of certain α-arylcyanothioacetanilides with hydrazine in the presence of mercuric oxide.34 Pyrazoles have also been synthesized by the reaction of hydrazines with β-ketothioamides209,377 and thioamides derived by the reaction of isothiocyanates
with enamines\textsuperscript{209}, acetylenes\textsuperscript{378} and active methylene esters.\textsuperscript{150}

Reaction of hydroxylamine with dimethylthiomethylene derivatives of malononitrile, methyl cyanoacetate and benzoyl-acetonitrile has yielded the isoxazoles, (159; \(R_1=\text{CN}, R_2=\text{NH}_2\))\textsuperscript{360}, (159; \(R_1=\text{CO}_2\text{Me}, R_2=\text{NH}_2\))\textsuperscript{360} and (159; \(R_1=\text{CN}, R_2=\text{Ph}\))\textsuperscript{362} respectively. Ethyl dimethylthiomethyleneacetoacetate yields the 3-methyl-4-carbethoxy-5-methylthioisoxazole.\textsuperscript{371} N-Substituted 3-aminoisoxazoles (160) have been obtained by the reaction of hydroxylamine with appropriate acylketene S,N-acetals\textsuperscript{46,362}. N-substituted \(\alpha\)-acyl thioacetamides\textsuperscript{159} and acetylenic thioamides.\textsuperscript{378}

\begin{align*}
\text{NHR} & \quad \text{EtO}_2\text{C} \quad \text{CH}_3 \\
\text{EtO}_2\text{C} & \quad \text{CH}_3
\end{align*}

The reaction of diethyl \(\alpha\)-acyethylthionomalonate with hydroxylamine has yielded the isoxazole (161).\textsuperscript{122} The reaction of methyl \(\alpha\)-benzoyldithioacetate with
hydroxylamine has been reported to give benzoylacetonitrile instead of isoxazoles.\textsuperscript{72}

The direct formation of pyrimidines in the reaction of primary or secondary enamines and enaminoid compounds with acyl isothiocyanates, or the synthesis of pyrimidines by the intramolecular cyclization of the open chain adducts formed from acyl isothiocyanates and enamines has been the subject of many investigations.\textsuperscript{141,190,201,202,206,211,379,380} The reaction of imidoyl isothiocyanates with active methylene compounds, such as cyanoacetic esters and dialkyl malonates, also leads to the direct formation of pyrimidine derivatives.\textsuperscript{381}

The thioamides (162) derived from enamines\textsuperscript{209} and ketones,\textsuperscript{209} and \(\alpha\)-acyl-ketene \(S,S\)- and \(S,N\)-acetals (163) derived from benzoyl-acetonitrile,\textsuperscript{382}

\[
\begin{align*}
\text{(162)} & \quad X = S,NR, \\
& \quad YR_4 = OH,NR_5R_6
\end{align*}
\]

acetophenones,\textsuperscript{39,383} aryl-acetones\textsuperscript{66} and cyclic ketones\textsuperscript{39,47}
yield pyrimidines (164) when condensed with amidines, guanidines and related compounds.

\[
\begin{array}{c}
\text{R}_1 \text{X} \\
\text{R}_2 \\
\text{R}_3 \\
\text{X} = \text{S, NR}^* \\
\end{array}
\]

(164)

\(\alpha\)-Cyanoketene thioacetals (165) when reacted with amidines, guanidines and related compounds yield the corresponding 4-aminopyrimidines (166).\(^{35,39,384-389}\)

\[
\begin{array}{c}
\text{R} \text{CN} \\
\text{CH}_3 \text{S} \text{SCH}_3 \\
\text{X} = \text{S or NR} \\
\end{array}
\]

(165)

\[
\begin{array}{c}
\text{R} \text{NH}_2 \\
\text{CH}_3 \text{S} \text{N} \text{R}_1 \\
\end{array}
\]

(166)

\(\alpha\)-Cyano-\(\alpha\)-carbalkoxy ketene S,S- and S,N-acetals (167; \(X=\text{S or NR}\)) yield 4-oxo-5-cyanopyrimidines (168; \(X=\text{S, NR}\)).\(^{383,387,388}\) However, 4-amino-5-carbalkoxypyrimidines (170; \(X=\text{NR}\)) have been obtained by the cyclization of the isolated \(\alpha\)-cyanovinylamidine inter-

\[
\begin{array}{c}
\text{R'} \text{O}_2 \text{C} \text{CN} \\
\text{RX} \text{SCH}_3 \\
\end{array}
\]

(167)

\[
\begin{array}{c}
\text{R'} \text{O}_2 \text{C} \text{NH} \\
\text{RX} \text{N} \text{R}_1 \\
\end{array}
\]

(168)
mediate \((169; X=NR)\) under appropriate conditions.\(^{389}\)

\[
\begin{align*}
\text{R'}O_2C & \quad \text{CN} & \quad \text{NH}_2 \\
\text{RX} & \quad N \quad \text{R}_1 \\
\end{align*}
\]

Condensed pyrimidines have been prepared by the reaction of ketene thioacetal \(165\) \((R=CN, \text{CO}_2\text{Me})\) with 2-aminopyridine and 2-aminobenzothiazoles.\(^{282}\)

The formation of 5-alkylthiomethylpyrimidines \((172)\) along with other byproducts has been observed in the base catalyzed condensation of ketene dithioacetal \((171)\) with guanidine. The formation of \(172\) has been explained on the basis of the initial isomerization and thioallylic rearrangement of \(171\).\(^{66,390,391}\)

\[
\begin{align*}
\text{R}_2 & \quad \text{R}_1 \\
\text{RS} & \quad \text{SR} \\
\end{align*}
\]

The reaction of amidines with ethoxycarbonylthiono-
acetates has yielded 4-hydroxy-6-mercaptopyrimidines.\textsuperscript{392}

Pyrimidines (174) have been obtained by the reaction of ketene $S,N$-acetal (173) with orthoesters and acid anhydrides\textsuperscript{46} or by acylation and cyclization reactions with the ketene $S,N$-acetal (175).\textsuperscript{393}

\begin{align*}
(173) & \quad \begin{array}{c}
\text{NC} \\
\text{CH}_3\text{S} \\
\text{NH}_2 \\
\text{NH}_2
\end{array} \\
(174) & \quad \begin{array}{c}
\text{NC} \\
\text{CH}_3\text{S} \\
\text{N} \\
\text{NH} \\
\text{R}
\end{array} \\
(175) & \quad \begin{array}{c}
\text{NC} \\
\text{CH}_3\text{S} \\
\text{N} \\
\text{CN} \\
\text{NH}_2
\end{array}
\end{align*}

Benzodiazepines (176) along with other products have been obtained in the condensation of $\alpha$-acyldithioacetic acid derivatives with o-phenylenediamine.\textsuperscript{394}

\begin{align*}
(176) & \quad \begin{array}{c}
\text{N} \\
\text{R} \\
\text{N} \\
\text{SH}
\end{array}
\end{align*}

1,3-Thiazine derivatives (177) and (178) have been obtained from mercaptomethylthiomethyleneacyanocacetamide\textsuperscript{395,396} and $\beta$-iminodithiocarboxylate.
intermediates 62, 85, 86, 88, 372, 397 by the reaction with acid derivatives and carbonyl compounds.

\[
\text{NC} \quad \text{O} \quad \text{N-H} \quad \text{R}_2 \\
\text{CH}_3 \text{S} \quad \text{S} \quad \text{R}_1
\]

(177)

\[
\text{R}_4 \quad \text{NH} \quad \text{R}_2 \\
\text{S} \quad \text{S} \quad \text{R}_1
\]

(178)

The condensation of \( \alpha \)-acylketene thioacetals with thioamides in the presence of acids yields thiazinium salts (179). 269

\[
\text{R}_3 \quad \text{R}_2 \\
\text{R}_4 \quad \text{N} \quad \text{X}^- \\
\text{S} \quad \text{S} \quad \text{R}_1
\]

(179)

The synthesis of pyridines (180) and (181) by the reaction of dithioacetals (165; \( R=\text{CONH}_2 \)) with primary enamines 398 or by the cyclization of the intermediates (182) 399 obtained by the reaction of enamines
with ketene dithioacetals (165; \( R=CN \)) have been described.  

3-Cyanopyridin-2-ones (183) and condensed pyridine derivatives have been obtained by the condensation of \( \alpha \)-cyano-, \( \alpha \)-acylketone S,S- and S,N-acetals with cyanoacetamides and cyanoacetylhydrazones.  

\[
\text{\begin{align*}
R_2
\end{align*}}
\]

\( \text{(183)} \)

Acetophenone condenses with dimethylthiomethylene benzoylacetetonitrile in the presence of alkali to yield 2-hydroxy-3-benzoyl-4-methylthio-6-phenylpyridine. \(^{402}\) \( \text{2-Cyanomethylpyridine}^{405} \) and 1-phenyl-3-amino-pyrazolin-5-one \(^{282}\) yield condensed pyridines in the reactions with \( \alpha \)-functionalized ketene thioacetals.

Aminopyridine derivatives (185), (186) are obtained as products of reaction between tertiary enamines (184)

\( \text{(184)} \)

\( \text{(185)} \)

\( \text{(186)} \)

and benzoyl isothiocyanate. \(^{207,208}\)
Some N-phenyl ketene S,N-acetals (187) have been intramolecularly cyclized to 4-chloroquinolines (188) and 4-oxoquinoline derivatives (189). The formation of benzothiopyrans and quinolin-4-ones (190) has been observed in the reaction of o-chlorobenzoylacetonitrile with carbon disulfide and isothiocyanates.

The reaction of carbon disulfide with acetone derivatives is known to yield thiopyran-4-one derivatives (191) under certain conditions. Treatment of dimethylthio-
methylene cinnamoylacetonitrile with acid leads to the thiopyranone (192) by S-dealkylation. The formation of thiopyran derivatives has been observed in the thio-Claissen rearrangement of S-propargyl α-acylketene dithioacetals.

Pyrrolone derivatives (194) have been prepared by the cyclization of 193 resulting from the reaction of nitromethane with α-cyanoketene dithioacetals.

\[
\begin{align*}
\text{(191)} & \quad \text{(192)} \\
\text{(193)} & \quad \text{(194)}
\end{align*}
\]

α-Methylene thionoacetic acid derivatives (195) and α-monofunctionalized ketene thioacetals (196) undergo some heterocyclization reactions involving the α-methylene or methine carbon atom.
Pyrroles (198) have been prepared by the intramolecular cyclization of S,N-acetals (197) derived from ketene dithioacetals and 2,2-diethoxyethylamine.  

\[
\begin{align*}
\text{RX} & \quad \text{Y} \\
\text{S} & \\
(195) & \\
\end{align*}
\]

\[
\begin{align*}
\text{RX} & \quad \text{Y} \\
\text{SR} & \\
(196) & \\
\end{align*}
\]

Nitrothiophenes (199) have been obtained by the intramolecular cyclization of intermediates resulting from the reaction of α-halocarbonyl compounds with dithioacid, ester and amides derived from nitromethane.  

\[
\begin{align*}
\text{EtO} & \quad \text{H} & \quad \text{Y} \\
\text{EtO} & \quad \text{SR} \\
(197) & \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{Y} \\
\text{SR} & \\
(198) & \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_1 & \quad \text{NO}_2 \\
\text{R}_2 & \quad \text{XR} \\
(199) & \\
\end{align*}
\]

\[X = S, \text{NH}\]

The reaction of nitroketene S,N-acetal (118) with
oxalyl chloride or chlorocarbonyl sulfenyl chloride has yielded the nitropyrrrole derivative (200) and the nitrothiazole derivative (201).

\[
\begin{align*}
\text{(118)} & \\
\text{(200)} & \\
\text{(201)}
\end{align*}
\]

3-Nitroquinolines (202) and 3-nitrothienopyrimidines (203) have been synthesized by the reaction of \( \alpha \)-nitroketene S,S- and S,N-acetals with \( \alpha \)-aminobenzophenones and 2-amino-3-benzoylthiophenes.

\[
\begin{align*}
\text{(202)} & \\
\text{(203)}
\end{align*}
\]

2-Mercapto-3-cyanopyridines (204) have been obtained by the condensation of \( \beta \)-dicarbonyl compounds with cyanothioacetamide.

\[
\text{(204)}
\]