Dithiocarboxylic esters and Thioamides: Synthesis and Reactivity

2.1 Introduction

Dithio Carboxylic acids and their esters are synthetic intermediates known for a long time. Simple thioamides were also available to organic chemists for several decades. Their chemistry have been extensively studied. There are a number of methods available for their synthesis and most of the methods make use of very cheap starting materials. In this chapter a review of the synthesis and reactivity of simple dithiocarboxylic acids, esters and thioamides is presented, as a background to the chemistry of functionalised dithiocarboxylic esters and thioamides that would be discussed in the coming chapters.

2.2 Dithiocarboxylic Acids and Esters

Dithiocarboxylic acids and esters are widely used in organic synthesis\(^2\) despite their offensive odour and relative instability. The common methods leading to the formation of dithiocarboxylic acids and their esters would be briefly described here. There are several reviews available in the literature on the chemistry of these compounds.

2.2.1 Synthesis of dithiocarboxylic acids and esters

Dithiocarboxylic acids and their esters are valuable intermediates in organic synthesis.\(^1\) They can be obtained by a variety of synthetic procedures.\(^2\) Several methods for the synthesis of simple and functionalized dithioesters are presented here.
2.2.1.1. Thioacylation

Dithiocarboxylates can be prepared from respective thioacyl halides, thioacyl anhydride and thio ketenes by thioacylation. Thioacyl halides undergo facile reaction with thiols in the presence of base to afford alkyl or aryl dithiocarboxylates in high yields (Scheme 1).

\[
\begin{align*}
R^1 \quad S' \quad X' & \quad + \quad R^2 - SH \\
\text{(1)} & \quad \rightarrow \\
& \quad R^1 - S - R^2
\end{align*}
\]

Scheme 1

Similarly bis-thioacyl thioanhydride react with thiols to give corresponding dithiocarboxylates (Scheme 2).

\[
\begin{align*}
R^1 \quad S' \quad S' \quad R^1 & \quad + \quad R^2 - SNa \\
\text{(3)} & \quad \rightarrow \\
& \quad R^1 - S - R^2
\end{align*}
\]

Scheme 2

The reaction of metal salts of dithiocarboxylic acids with phenyl thiochloroformate leads to the formation of the mixed thiocarboxylic thiocarbonic acids 6, which spontaneously undergo intramolecular thioacylation to furnish corresponding phenyl carbodithioates (Scheme 3).

\[
\begin{align*}
R^1 \quad S' \quad S' \quad M & \quad + \quad PhS - Cl \\
\text{(4)} & \quad \rightarrow \\
& \quad [R^1 \quad S' \quad S' \quad Ph] \\
\text{(5)} & \quad \rightarrow \\
& \quad R^1 - S - SPh
\end{align*}
\]

Scheme 3
Thioacyl diphenyl thiophosphinyl sulphides are also valuable thioaclylating agents. Dithiocarboxylates can be obtained from them under mild conditions (Scheme 4). Addition of thiols to thioketenes also afford respective dithioesters (Scheme 5).

\[
\text{Scheme 4}
\]

\[
\text{Scheme 5}
\]

2.2.1.2 Reactions of Organometallic Reagents with Carbondisulphide

A convenient method for the synthesis of dithiocarboxylic acids involve addition of organometallic reagents, such as Grignard reagents, organolithium reagents or organocuprates to carbon disulphide. Subsequent alkylation with alkyl halides afford corresponding dithioesters. Among the various organometallic reagents, Grignard reagents were used widely in the earlier years for the synthesis of dithiocarboxylic acids and their esters. Grignard reagents prepared from various alkyl and aryl halides undergo smooth addition to carbon disulphide while the subsequent alkylation could be carried out with alkyl halides including allyl and propargyl bromides.
In an attempted preparation of α,β-unsaturated dithioesters employing this protocol, the addition of Grignard reagent prepared from 1-bromo propene to carbon disulphide and subsequent alkylation with methyl iodide gave the expected methyl dithiocarboxylate 15 which underwent dimerization involving a 4+2 cycloaddition to afford the substituted thiopyran derivative 16° (Scheme 7).

α,β-Unsaturated iminodithioates are known to undergo conjugate addition with organometallic reagents. Subsequent sulphydrolysis of the intermediate ketene-N,S-acetal obtained with hydrogen sulphide furnish dithiocarboxylates with branched alkyl chains."
The dithioesters could be obtained in better yields by the addition of organo copper reagents to carbondisulphide followed by subsequent alkylation with methyl iodide.\textsuperscript{11}

Terminal alkynes are also used in the synthesis of dithioesters. The substituted acetylene is first treated with butyl lithium and then with elemental sulfur to furnish the corresponding lithium alkyne thiolates which on subsequent addition of two equivalents of thiol affords the dithioesters. An example starting with methyl acetylene is shown in Scheme 9.\textsuperscript{12}

\begin{equation}
\begin{align*}
\text{H}_3\text{C} & \equiv \equiv \text{H} \quad \xrightarrow{1.\text{BuLi}} \quad \text{H}_3\text{C} - \equiv \equiv \text{S}_{\text{Li}} \quad \xrightarrow{\text{MeSH}} \quad \text{H}_3\text{C} \equiv \equiv \text{SMe} \\
20 & \quad 21 & \quad 22
\end{align*}
\end{equation}

Scheme 9

The addition of organo cuprates across the triple bond affords vinyl substituted cuprates. Addition of these intermediates to carbon disulphide followed by alkylation provide a convenient method for the preparation of $\alpha,\beta$-unsaturated dithioesters \textsuperscript{26} (Scheme 10).

\begin{equation}
\begin{align*}
[\text{R}^1\text{CuBr}]\text{MgCl} + \text{R}^2 & \equiv \equiv \text{H} \quad \rightarrow \quad \text{R}^2 \quad \xrightarrow{1.\text{CS}_2} \\
23 & \quad 24 & \quad 25 & \quad 26
\end{align*}
\end{equation}

Scheme 10

Recently Hoppe and co-workers have shown that chiral organolithium reagents prepared from the N,N-diisopropyl carbamate of (S)-1-phenyl ethanol react with electrophiles with retention or inversion of stereochemistry depending on the nature of the electrophile. Electrophiles which would have a strong interaction with the lithium cation,
such as those having alkoxy or carbonyl group, react with retention of configuration, while electrophiles having an energetically low LUMO, such as acid chlorides, heterocoumulenes and soft electrophiles react with inversion of configuration. Dithiocarboxylation proceeds with inversion of configuration, since carbon disulphide is a soft electrophile.\textsuperscript{41} This method provide access to chiral dithioesters (Scheme 11).

Organolithium reagents derived from suitable aromatic substrates undergo facile addition to carbon disulphide leading to the formation of substituted aromatic dithiocarboxylic acids. $\alpha$-Hydroxynaphthyl lithium \textsuperscript{30}, for instance on addition to carbon disulphide gave the dithiocarboxylic acid \textsuperscript{31} (Scheme 12).\textsuperscript{32} Several aromatic substrates are known to undergo similar addition to carbon disulphide.\textsuperscript{33}
2.2.1.3 Sulfurization

Several functional groups can be transformed into dithiocarboxylic acids or dithioesters by sulfurization. For instance, the conversion of aldehydes to corresponding dithiocarboxylic acids can be accomplished by hydrogen polysulphide or by ammonium polysulphide\textsuperscript{13b,13}.

Addition of thiols to nitriles afford thioiminoesters. Treatment of thioiminoesters in ether or pyridine with dry hydrogen sulphide furnish corresponding dithioesters in good yields\textsuperscript{14} (Scheme 13).

\[ \text{CN} \xrightarrow{\text{EtSH}} \text{NH.HCl} \xrightarrow{\text{K}_2\text{CO}_3} \]

\[ \text{32} \quad \text{33} \quad \text{34} \quad \text{35} \]

Scheme 13

Alternatively thioiminoesters could be obtained by the addition of Grignard reagents to aryl isothiocyanates followed by alkylation with methyl iodide. Subsequent treatment of the iminoesters thus obtained with hydrogen sulphide in acetonitrile afford the corresponding dithioesters. For example, addition the Grignard reagent prepared from 1,3-pentadienylbromide to phenyl isothiocyanate followed by alkylation with methyl iodide affords the methyl thioiminoester 37 which on subsequent treatment with hydrogen sulphide gave the dithioester 38\textsuperscript{13} (Scheme 14).

\[ \alpha,\beta\text{-unsaturated amides also could be converted to the corresponding } \alpha,\beta\text{-unsaturated dithioesters, though the procedure involves several steps (Scheme 15).} \]
Scheme 14

\[ \text{H}_3\text{C} \equiv \text{C} - \text{CH}_2\text{MgBr} + \text{Ph}-\text{N} = \text{C}=\text{S} \xrightarrow{1. \text{THF}} \xrightarrow{2. \text{CH}_3\text{I}} \text{H}_3\text{C} \equiv \text{C} - \text{CH}_2\text{NPh} \]

\[ \xrightarrow{\text{H}_2\text{S}} \text{CH}_3\text{CN} \xrightarrow{} \text{H}_3\text{C} \equiv \text{C} - \text{SMe} \]

Scheme 15

\[ \text{H}_3\text{C}_6\text{N} - \text{CH}_3 \xrightarrow{(\text{C}_2\text{H}_5)_2\text{OBf}_4} \text{H}_3\text{C}_6\text{N} - \text{CH}_3 \xrightarrow{\text{H}_2\text{S}} \text{H}_3\text{C}_6\text{N} - \text{CH}_3 \]

\[ \text{H}_3\text{C}_6\text{N} - \text{CH}_3 \xrightarrow{} \text{H}_3\text{C}_6\text{N} - \text{CH}_3 \]

\[ \text{H}_3\text{C}_6\text{O} \text{C}_2\text{H}_5 + \text{NH} \xrightarrow{} \text{H}_3\text{C}_6\text{N} \]

\[ \text{H}_3\text{C}_6\text{N} \xrightarrow{\text{CH}_3\text{I}} \text{H}_3\text{C}_6\text{N} \xrightarrow{\text{H}_2\text{S}} \text{H}_3\text{C}_6\text{S}\text{H}_3 \]

\[ \text{H}_3\text{C}_6\text{N} - \text{CH}_3 \xrightarrow{\text{CH}_3\text{I}} \text{H}_3\text{C}_6\text{N} - \text{CH}_3 \xrightarrow{\text{H}_2\text{S}} \text{H}_3\text{C}_6\text{S}\text{H}_3 \]
The amide was first alkylated with triethyl oxonium fluoborate to furnish the ethoxy substituted iminium salt 40 which on treatment with hydrogen sulphide at -15°C gave the thionoester 41. Ethoxy group was then replaced by pyperidine to afford the thioamide 42. Subsequent alkylation with methyl iodide gave the methylthio substituted iminium salt 43 which was subjected to treatment with hydrogen sulphide at low temperature to furnish the dithiocinnimate 44. 

The synthesis of functionalized dithioesters usually involve the reaction of functionalized carbanions with carbon disulphide followed by alkylation. Carbanions derived from a wide variety of substrates undergo addition to carbon disulphide resulting in the formation of the respective dithiocarboxylic acids.

Derivatives of malonic acid 16, phenols, naphthols, hydroxyquinolines 17, aldehydes 18 ketones 19,16b,16c, nitromethane 20, pyrrole, indole, pyridine, quinoline and their derivatives 21, ketimines of cyclic ketones 22 and pyrazolone derivatives 23 are among the substrates that undergo base catalyzed addition to carbon disulphide leading to the formation of dithiocarboxylic acids.

2.2.1.4 Reactions of enolates with carbodisulfide

β-Oxo dithiocarboxylic acids and their esters are prepared by the reaction of enolate anion derived from enolizable ketones on treatment with a strong base with carbon disulphide. Aliphatic and cyclic ketones react with carbon disulphide in the presence of sodium t-pentoxide to furnish the corresponding β- oxo dithiocarboxylic acids 24 (Scheme 16).
Substituted acetophenones undergo addition to carbon disulphide in the presence of potassium t-butoxide leading to the formation of β-hydroxy dithiocinnamic acids which could be alkylated to the respective β-oxo dithioesters 50 by an ion-pair technique\(^{25}\) (Scheme 17).

Other active methylene compounds such as diethyl malonate, methyl cyanoacetate, malononitrile, acetyl acetone, benzoyl acetone and dibenzoyl methane also react similarly giving the corresponding functionalized dithioesters.

Konen and co-workers have described a method for the conversion of long chain carboxylic acids to dithioesters. For example nonanoic acid was first converted to the lithium enolate, which on reaction with carbon disulphide followed by alkylation with methyl iodide and subsequent decarboxylation gave methyl dithiooctanonate 53\(^{29}\) (Scheme 18).
Addition of sodium phenoxide to carbon disulphide at high temperature (155-170°C) in DMF also leads to the formation of dithiocarboxylic acids. For example 3,5-di-\textit{t}-butyl dithiosalicylic acid can be prepared by this method.\textsuperscript{34}

\begin{equation}
\begin{aligned}
\text{ONa} & \quad \text{CS}_2\text{DMF} \\
\text{54} & \quad \text{155-170°C} \\
\text{OH} & \quad \text{S} \\
\text{55} & \quad \text{SH}
\end{aligned}
\end{equation}

\textbf{Scheme 19}

\subsection{2.2.1.5 Reactions of Enolates with Dimethyl trithiocarbonate}

Junjappa and co-workers have developed a convenient general method for the synthesis of functionalized dithioesters from active methylene compounds. This method works well with aliphatic, cyclic, and aryl alkyl ketones. The reaction involves treatment of the carbanions derived from active methylene compounds in the presence of a base such as NaH in DMF, with dimethyl trithiocarbonate.\textsuperscript{26} The synthesis of \textit{β}-oxo dithioesters employing this protocol is depicted in Scheme 20.

\begin{equation}
\begin{aligned}
\text{R}^1\text{C}=\text{O} & \quad + \quad \text{MeS=SMe} \\
\text{45} & \quad \text{NaH} \\
\text{56} & \quad \text{DMF} \\
\text{R}^2\text{C}=\text{O} & \quad \text{MeS=SMe} \\
\text{57} & \quad \text{R}^2
\end{aligned}
\end{equation}

\textbf{Scheme 20}

This method has been further extended to the preparation of dithioesters of sulphones and sulphotides.\textsuperscript{27} Methyl chlorodithioformates also undergo similar reactions with enolates to afford corresponding dithioesters.\textsuperscript{28}
2.2.1.6 Formation of α-Oxodithioesters

While β-oxo dithioesters could be conveniently prepared from enolizable carbonyl compounds, direct methods leading to the formation of α-oxo dithioesters are rare. The reaction of benzaldehyde with carbon disulphide in the presence of potassium cyanide, followed by alkylation with diazomethane gave the methyl ester of benzoyl dithiocarboxylic acid\(^{30}\) (Scheme 21).

![Scheme 21](image)

Didier and Frederic have recently reported another approach for the synthesis of α-oxo dithioesters from aryl methyl ketones. The intermediate pyridinium salts obtained from methyl ketones on treatment with pyridine and iodine, react with sulfur in the presence of triethyl amine to afford the α-oxo dithiocarboxylates, which on further alkylation to furnish the corresponding dithioesters.\(^{31}\)

![Scheme 22](image)
The conversion of aryl methyl ketones to the corresponding $\alpha$-oxo dithiocarboxylates can also be achieved by their treatment with ethyl disulphide in the presence of a base such as sodium $t$-butoxide. This reaction has been illustrated for substituted acetophenone in Scheme 23\textsuperscript{40}.

![Scheme 23]

**2.2.1.7 Friedel Crafts Type Reactions**

Electron rich aromatic substrates undergo Friedel-Crafts type reaction with carbon disulphide to furnish aromatic dithiocarboxylic acids. Trimethyl silyl methyl dithiobenzoate \textsuperscript{64} has been prepared from benzene following this method as shown in Scheme 24\textsuperscript{35}.

![Scheme 24]

Similarly pyrrole derivatives also undergo reaction with carbon disulphide\textsuperscript{36} to give substituted pyrrole dithiocarboxylic acids.

**2.2.1.8 Reactions Involving 3-Thioxo-1,2-dithiol**

3-Thioxo-1,2-dithiol \textsuperscript{65} is a valuable substrate for the synthesis of functionalized dithioesters. The reaction of morpholine with 3-thioxo-1,2-dithiol in chloroform followed by alkylation leads to the formation of 3-morpholino dithioacrylate \textsuperscript{67} (Scheme 25).
Alternatively the alkylation of 3-thioxo-1,2-dithiol can be performed before the reaction with amine. For example, the reaction of methyl iodide with 65 gave the salt 68 which on further reaction with amines gave β-amino dithioacrylic esters. \(^{37}\)

Scheme 25

\[
\begin{align*}
\text{Scheme 26} \\
\text{Scheme 27}
\end{align*}
\]
Other substituted thioxodithiole salts also react similarly with amines to afford β-amino substituted α,β-unsaturated dithioesters. For example amino substituted cyclopentenyl dithioesters are obtained as shown in scheme above.\textsuperscript{38}

### 2.2.1.9 Reactions of Dithioenolates

Aliphatic dithiocarboxylic acids on treatment with two equivalents of butyl lithium afford the corresponding dilithium dithioenolates 72 which undergo smooth addition to aldehydes and ketones leading to the formation of β-hydroxy dithiocarboxylic acids\textsuperscript{73}. Subsequent alkylation with methyl iodide followed by dehydration furnish α,β-unsaturated dithioesters 75. A synthesis of methyl-3,3-dimethyl dithioacrylate by this protocol is depicted in Scheme 28.\textsuperscript{39}

\[
\text{BuLi} \quad \xrightarrow{} \quad \text{SLi} + \quad \text{O} \quad \xrightarrow{} \quad \text{H}_3\text{C} \quad \xrightarrow{} \quad \text{CH}_3
\]

\[
\text{H}_3\text{C} \quad \text{OH} \quad \xrightarrow{\text{MeI}} \quad \text{SMe} \quad \xrightarrow{\text{COO}_2^\text{Me}} \quad \text{B}_3\text{N}_2\text{B}_2\text{O} \quad \text{H}_3\text{C} \quad \text{CH}_3
\]

Scheme 28

### 2.2.2 Reactions of dithiocarboxylic acids and esters

Dithiocarboxylic esters can be easily transformed to the corresponding lithium or sodium enethiolate. The thioenolates are valuable intermediates used in the construction of new carbon carbon bonds. The thioclaisen rearrangements involving these intermediates have also attracted attention from several groups. The dithiocarboxylic acids and esters are also useful intermediates in the synthesis of heterocycles.
2.2.2.1 Reactions of enethiolates

Deprotonation of dithioesters can be accomplished quantitatively by strong bases such as lithium diisopropyl amide. Sulphur has a high aptitude for stabilizing negative charge, which supports the enthiolate structure to the deprotonated species rather than the α-metalated structure. Enethiolates have some advantages over the analogous enolates. They have good thermal stability and do not undergo equilibration with proton donors. Another important feature is that formation of enethiolate is highly stereospecific cis-Isomer is formed exclusively.

Aldol reactions of enethiolates derived from dithiocarboxylates were mentioned earlier in connection with the preparation of α,β-unsaturated dithioesters. Addition of enethiolates generated from dithioesters to aldehydes at low temperature (to avoid retro-aldol reaction) provide good yields of β-hydroxy dithioesters. The reaction is highly stereospecific and cis-enethiolate give the syn-aldol. As mentioned earlier dehydration of β-hydroxydithioesters give α,β-unsaturated dithiocarboxylates.

Lithium enethiolates are reactive towards α,β-unsaturated carbonyl compounds. The addition takes place in Michael fashion to afford δ-keto dithioesters which find further application in synthesis. The Michael reaction of the enethiolates derived from dithiocarboxylates proceed stereospecifically, under kinetically controlled conditions. Thus the addition of cis-enethiolate to E-enone furnishes the anti-adduct.

Epoxides also react with enethiolates generated from dithioesters, though the reaction is sluggish. However it is the sulphur end of the ambident nucleophile that opens the epoxide ring.
The reaction of ene-thiolates with alkylating agents also furnish products with alkylation at sulphur. Base catalysed alkylation of dithioesters lead to the formation of the corresponding ketene dithioacetals. Alkylation of the thiolate anion derived from dithioesters or dithiocarboxylic acids with functionalized alkylating agents may lead to the formation of heterocycles. Several such reactions involving β-oxo dithioesters and β-oxo dithiocarboxylic acids are described along with similar reactions involving β-oxo thioamide (vide supra).

Alkylation of dithiocarboxylic acids with allylic halides furnish S-allyl dithiocarboxylates. The lithium enethiolates derived from these S-allyl dithiocarboxylates undergo a facile 3,3-sigmatropic shift leading to the formation of lithium salt of α-allyl dithiocarboxylic acids.

S-Alkenyl dithioesters are also formed in this reaction as a result of the base catalyzed migration of the double bond. S-Allyl α-oxo ketenedithioacetals also undergo base catalyzed thio-Claisen rearrangement. This method has been used for the synthesis of α-allyl ketene dithioacetals as shown in scheme 33.
2.2.2.2 Synthesis of 2H-thiopyran-2-thiones

Pradere and co-workers have described the reactions of β-oxo dithiocarboxylic acids with α-acetylenic ketones and β-chlorovinyl aldehydes. Substituted 2H-thiopyran-2-thiones 93 and 95 are obtained respectively from these reactions (Scheme 34 and Scheme 35)
\[ R' = \text{Aryl or Alkyl}; \quad R^1 = \text{Aryl or Alkyl} \]

Scheme 34

\[ R^1 = \text{Aryl or Alkyl}; \quad R^2 = \text{Aryl or Alkyl}. \]

\[ R^1 = \text{Aryl}, \quad R^2 = \text{Aryl}. \]

Scheme 35

\( \beta \)-Chlorovinyl ketones also react similarly with \( \beta \)-oxo thiocarboxylic acids to afford 2H-thiopyran-2-thione derivatives.\(^{56} \) The reaction of dimethyl acetylene dicarboxylate with \( \beta \)-oxo thioamides also afford 2H-thiopyran-2-one derivatives.\(^{57} \) Acyl dithioacetate react with dithiolium salts to give 3-acyl substituted 2H-thiopyran-2-one derivatives.\(^{58} \) (Scheme 36)

![Chemical structures](image)
2.2.2.3 Formation of Other Heterocycles

β-Oxodithioesters react with functionalized electrophiles leading to the formation of several heterocycles particularly thiophene derivatives. These reactions would be described along with similar reactions of β-oxo thioamides. A few examples of reactions leading to the formation of other heterocyclic systems are described here. β-Oxo dithiocarboxylic acids can be transformed into substituted 3-thioxo-1,2-dithiols on treatment with trimethyl silyl sulfide in presence of N-chlorosuccinimide and imidazole.59

![Scheme 37](image)

![Scheme 38](image)
The dithioester 108 derived from dimedone 101 undergo selective addition of aniline to one of the carbonyl group to afford the β-phenylamino substituted α,β-unsaturated dithioester 103 which cyclize to 104 on heating in diphenyl ether.60

2.2.2.4 Oxidation Reactions

Oxidation reactions of sulfur compounds lead to the formation of corresponding sulfoxides or sulfones depending on the reaction conditions. Oxidation of functionalized dithioesters should provide access to functionalized sulfones or sulfoxides which are valuable intermediates in organic synthesis. Aliphatic dithioesters can be oxidized to sulphines by treating them with m-chloroperbenzoic acid in methylene chloride. However these sulphines have been found to undergo facile rearrangement to corresponding dithioperoxy esters at room temperature.42

\[
\text{Scheme 39}
\]

Oxidation of dithiocarboxylates with benzene selinic anhydride furnish thiol esters as the products.43

\[
\text{Scheme 40}
\]
2.3 Thioamides

Thioamides are also among very common intermediates in organic synthesis while thiocarbonyl compounds are unstable in general these amides are fairly stable. They are widely used in the synthesis of heterocycles and as synthetic intermediates.\textsuperscript{103, 70a, 93b}

2.3.1 Synthesis of thioamides

Thioacylation reactions, addition of nucleophiles to isothiocyanates\textsuperscript{104, 93a, 75a} and thionation of amides\textsuperscript{105} are among the most common methods used in the synthesis of thioamides. A survey of some of the important methods is presented here.

Simple thioamides can be prepared by thioacylation of amines. Thiocarboxylates, 3H-1,2-dithiol-3-ones, dithiocarboxylates, thioamides, thioketenes and carbon disulfide are the commonly used substrates for the thioacylation reaction with amines. A few examples of the synthesis of thioamides involving thioacylation protocol are described here.

Nucleophilic attack of ammonia or secondary amines on O-alkylthiocarboxylate 110 provide thioamides. A large number of reports describe synthesis of thioamides employing this method.\textsuperscript{61} However under some conditions for example when the reaction was carried out in polar protic solvents such as ethanol some unwanted side reactions are favoured. If the reaction is performed at high temperature there is a possibility of the rearrangement of the O-alkylthiocarboxylates to the S-alkylthiocarboxylates thus resulting in the formation of of simple amides rather than thioamides.\textsuperscript{61a} Besides when primary amine is used there is a tendency to form amidines or imidates instead of the the thioamides.\textsuperscript{61b}

\begin{equation}
\begin{array}{c}
\begin{array}{c}
\text{HS} \\
\text{OR} \\
\text{R}^1
\end{array}
\begin{array}{c}
\text{HN}R^2 R^3
\end{array}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\begin{array}{c}
\text{HS} \\
\text{NR}^2 R^3 \\
\text{R}^1
\end{array}
\end{array}
\end{equation}

Scheme 41
The S-S bond cleavage of 3H-1,2-dithiol-3-ones 112 by nucleophiles such as Grignard reagent affords malonic acid monothioamide 113.62

Active methylene compounds, for example camphor react with carbon disulfide in the presence of excess base to provide dianions of dithiocarboxylic acid 115 which on neutralization with HCl and addition of primary amines yield 3-oxonorbornane thiocarboxamide 116 with undefined stereochemistry 63 (Scheme 43).

A Friedel-Crafts type reaction involving electron rich aromatic substrates with thiocarbamoyl chloride lead to the formation of aryl substituted thioamides 64. Thus the reaction of anisol with N,N-dimethyl thiocarbamoyl chloride 118 afford the corresponding thioamide 119 in 77% yield. (Scheme 44)
Carbanions derived from active methylene compounds undergo condensation reaction with thiacarbamoyl chloride to afford functionalized thioamides (Scheme 45).\textsuperscript{65}

Dithiocarboxylates react with amines faster than the corresponding O-alkyl thiocarboxylates.\textsuperscript{66} This pronounced reactivity may lead to the in situ reaction of the dithioester generated by the thiolysis of thioimidate with liberated ammonia to give a primary thioamide.

Transamidation is another method for the formation of thioamides by which another thioamide is treated with amines and the reactivity depends on the nucleophilicity.
of the incoming amine and the leaving group ability of the amine to be replaced. Thus some N-thioacylated heterocycles such as benzoxasole derivative, succinimide and azoles etc. are exceptionally good substrates for transamidation.

![Diagram](image)

**Scheme 47**

In some reactions thioamides are converted to other thioamides by C-C bond forming reactions. For example, when N,N-Dimethyl thioformamide was treated with lithium diisopropyl amide to afford the corresponding C-lithiated species, which on subsequent treatment with electrophiles gave thioamide (Scheme 48).

![Diagram](image)

**Scheme 48**

The reaction of N,N-diisopropyl carbamoyl or N,N-dimethyl thiocarbamoyl chloride with excess of lithium powder and catalytic amount of naphthalene in the presence of a carbonyl compound at -78° to -20°C undergo Barbier type reaction give the corresponding α-hydroxyamides or thioamides in 40-80% yields.
Treatment of the thioenolates derived from thioamides with electrophiles also afford novel functionalized thioamides. For example, the thioenolates obtained from 134 on treatment with aldehydes lead to the stereoselective formation of the β-hydroxy thioamide as the erythro isomer.\textsuperscript{72}

\[
\begin{align*}
\text{R}^2\text{S} & \quad \text{(i) LDA} \\
\text{NMe}_2 & \quad \text{(ii) R}^4\text{CHO}
\end{align*}
\]

Scheme 50

Enolizable thioamides may be transformed to the corresponding enaminothioketones by heating with N,N-dimethyl formamide O, N-acetal. The reaction involves a sequence of electrophilic attack and elimination.\textsuperscript{73}

\[
\begin{align*}
\text{R} & \quad \text{(Me}_2\text{N})_2\text{CHO} - \text{Bu} \\
\text{NMe}_2 & \quad \text{Me}_2\text{N}
\end{align*}
\]

Scheme 51

The S-silylated derivatives of thioamides react with electrophiles in the presence of Lewis acids. The addition of the silyl enol thioether 137 with Schiff base yields β-amino thioamides 138 as a mixture of diastereomers.\textsuperscript{74}
Thioketenes, though highly unstable, can be generated by a variety of methods and are valuable intermediates in synthesis. Amines give a smooth reaction with thioketenes to afford thioamides under mild non-reducing conditions. Sensitive functional groups such as cyano, nitro or sulfonyl residues remain unaffected. Scheme 53 shows the reaction of a secondary amine with α-nitrothioketene.

Alkynyl thiolates react with excess of diethyl amine to generate the thioketene which would be trapped by the diethyl amine itself to afford the thioamide (Scheme 54).
Amides can be directly transformed to thioamides on treatment with thionating agents like Lawesson's reagent\textsuperscript{106} or phosphorous pentasulfide.\textsuperscript{107,108} Thioamides can be obtained conveniently by the thiolysis of imidoyl chlorides. Scheme 55 shows the formation of N-sulfonyl thioamides from the corresponding imidoyl chloride as well.\textsuperscript{77} The imidoyl chlorides can be prepared from the corresponding amides on treatment with phosgene.

\begin{equation}
\begin{array}{c}
\text{Cl} \\
\text{Ar} \\
\text{NSO}_2\text{Ar} \\
\text{145} \\
\end{array} + \begin{array}{c}
\text{Na}_2\text{S}, 50-60°C \\
\text{H}_2\text{O, Dioxane} \\
\end{array} \rightarrow \begin{array}{c}
\text{S} \\
\text{Ar} \\
\text{NSO}_2\text{Ar} \\
\text{146} \\
\end{array}
\end{equation}

Scheme 55

The chlorosubstituted iminium salts, derived from amides and lactams on treatment with \textit{POCl}_3, triphosgene or oxalyl chloride, can be transformed to corresponding thioamides or thiolactams on treatment with hexamethyl disilathiane. Secondary and tertiary amides and lactams gave good to excellent yields in this reaction while the yields of primary thioamides were poor.\textsuperscript{78}

\begin{equation}
\begin{array}{c}
\text{N} \\
\text{Me} \\
\text{147} \\
\end{array} \xrightarrow{\text{CO}_2\text{Cl}_2} \begin{array}{c}
\text{N} \\
\text{Cl} \\
\text{Me} \\
\text{148} \\
\end{array} \xrightarrow{T\text{MS}_2\text{S}} \begin{array}{c}
\text{N} \\
\text{Me} \\
\text{149} \\
\end{array}
\end{equation}

Scheme 56

The reaction of benzimidium chloride 150 with dithiocarbamate 151 yields the thioimidate 152 as the primary product which on rearrangement give the thioacylated thiobenzamide 153 in quantitative yield.\textsuperscript{79}
Thiolysis of imidates is of limited application in the synthesis of thioamides. Imidates are usually prepared from nitriles. But nitriles can be directly transformed to thioamides in one step. However for the synthesis of thiolactams, the corresponding lactams are first converted to imidates and then subjected to thiolysis.\(^8^0\)

Benzyl triethyl ammonium tetrathiomolybdate has also been shown to be an effective sulfur transfer agent, useful in the conversion of amides and lactams to the corresponding thioamides and thiolactams through their chlorosubstituted iminium salt intermediates.\(^8^1\)

\(^{8^1}\) N,N-Disubstituted amidines 157 can be transformed into tertiary thioamide 158 on treatment with hydrogen sulfide in the presence of pyridine. However thiolysis of N-mono substituted amidines give a mixture of thioamides.
Thioamides can be prepared from nitriles by thiolysis under acid catalyzed or base catalyzed conditions. Aromatic or heteroaromatic nitriles react with hydrogen sulfide in the presence of triethyl amine or pyridine to give the thioamides in excellent yields. However base catalyzed solvolysis of aliphatic nitriles often give low yields. Better yields are obtained when the reaction is carried out in the presence of phase transfer catalysts and under high pressure of hydrogen sulfide.

\[
\begin{align*}
R-CN & \xrightarrow{H_2S} \text{H or Base} \rightarrow \text{R-NH}_2 \\
159 & \rightarrow 160 \\
\text{Scheme 60}
\end{align*}
\]

A reagent prepared by reacting phosphorous decasulfide with sodium sulfide (1:1 ratio) has been found to be very efficient for the rapid conversion of nitriles to thioamides, at -20°C.

\[
\begin{align*}
R-CN & \xrightarrow{(P_8S_9)Na_2} \rightarrow \text{R-NH}_2 \\
159 & \rightarrow 160 \\
\text{Scheme 61}
\end{align*}
\]

Heating of nitriles 159 with dithiocarbamate 160 gives good yields of N,N-dimethyl thioamide 161.

\[
\begin{align*}
R-CN & + \overset{\oplus}{\text{Me}_2\text{NH}_2\text{Me}_2\text{NCS}_2} \xrightarrow{\text{C}_6\text{H}_6 \text{or Xylene}} \text{R-NMe} \backslash \text{Me} \\
159 & \rightarrow 160 \rightarrow 161 \\
\text{Scheme 62}
\end{align*}
\]
Thioacetamide 162 is a convenient source of $\text{H}_2\text{S}$. An equilibrium is established which is shifted to the right if the liberated acetonitrile is removed by distillation.$^{88}$

\[
\begin{array}{cccc}
\text{R} & & \text{H}_3\text{C} & \text{NH}_2 \\
\text{===N} & + & \xrightarrow{\text{HCl} \ \text{DMF}} \text{S} & \xrightarrow{100 \ ^\circ \text{C}} \text{S} \\
159 & & 162 & \text{R} \text{NH}_2 \\
& & \text{MeCN} & 163
\end{array}
\]

**Scheme 63**

Successive reactions of Grignard's Reagents with carbondisulfide, 1-trifluoro methyl sulfonyl triazole and amines afford the corresponding N,N-disubstituted thio amides in good yields (Scheme 64).$^{89}$

\[
\begin{array}{cccc}
\text{RMgBr} & + & \text{CS}_2 & \rightarrow \\
& & \text{S} & \text{SMgBr} \\
164 & & 165 & \text{R} \text{NR}_2 \\
& & \text{TFMST} & 166
\end{array}
\]

**Scheme 64**

Transition metal catalysed cross-coupling reaction of Grignard's reagents with N-N dimethylthiocarbamoyl chloride provide a very simple method for the synthesis of various thioamides (Scheme 65).$^{90}$

\[
\begin{array}{cccc}
\text{Cl} & \text{NR}_2 & + & \text{RMgBr} \\
\text{==S} & \xrightarrow{\text{Transition metal}} \text{S} & \text{R} \text{NR}_2 \\
166
\end{array}
\]

**Scheme 65**
2.3.2 Reactions of thioamides

Thiocarbonyl compounds are usually unstable due to the inefficient overlap of \( \pi \)-orbitals in the carbon-sulfur double bond. But thioamides are fairly stable due to the delocalization of C=S bond resulting from the resonance interaction between the \( \pi \)-bond and the non-bonding electron pair on nitrogen (Scheme 66).

They have been widely used as synthetic intermediates and in heterocyclic synthesis. A few examples to illustrate the reactivity patterns of thioamides would be discussed here.

Alkylation of thioamides using dialkoxy carbenium salts introduces the alkyl group selectively on the sulfur leading to the formation of thioamides. The reaction of diethoxy carbenium tetrafluoroborate with thiobenzamide has been shown in scheme 67.

Thioamides having tertiary amino substituents can be alkylated with methyl iodide as well. It has been shown that the intermediate formed on alkylation can be transformed into carboxylic esters on basic hydrolysis (Scheme 68).
A classic example, on the application of thioamides in organic synthesis, is Eschenmoser’s sulfide contraction, which also involve an initial alkylation on the sulfur. An example, illustrating the reaction of bromomalonate with the thioamide 170 to give vinylogous urethanes 172 has been shown in scheme 69.

Though triphenyl phosphine is usually used to facilitate removal of sulfur, the sulfur extrusion is spontaneous in some cases. A reaction of tertiary amino substituted thioamides with benzene sulfonyl isocyanate leads to a formal (2+2) cycloaddition followed by fragmentation and removal of COS resulting in the N-protonated amidines (Scheme 70). Though this would appear to be a convenient method for the synthesis of amidines, the harsh condition needed to deprotect the benzene sulfonyl group may often destroy the iminoderivatives.
Deprotonation at the methylene group adjacent to nitrogen is particularly facile due to co-ordination offered by the sulfur to the metal atom. Several thioamides could be conveniently deprotected by $\text{S-BuLi}$. Subsequent addition to electrophiles followed by hydrolysis would afford substituted amines (Scheme 71).

Thioamides can be transformed in nitriles by a variety of methods. They include dehydration by diphosphorous tetraiodide ($\text{P}_2\text{I}_4$), Oxidation with benzene telluric anhydride and treatment with phosgene followed by a base such as pyridine. Thioamides can also be converted to corresponding amines by desulfurization with sodium borohydride in the presence of a Ni(ii) salt. Reaction of functionalized thioamides leading to the formation of heterocycles have been discussed in chapter 4.
2.4 References


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