Chapter Two

Functionalized Ketene Dithioacetals in
Organic Synthesis

2.1 Introduction

Ketene dithioacetals having functional groups at α-positions are extremely important multifunctional intermediates in organic synthesis. Functional groups present at the α position are usually electron withdrawing groups, due to the relative ease in their preparation. α-Nitro ketene dithioacetals have been found to be highly versatile synthon for the synthesis of heterocycles. α-Oxo ketene dithioacetals have a carbonyl group in the α-position. Ketene dithioacetals possessing aldehyde, keto, ester or amide functionalities belongs to this class. Any carbonyl compound having an active methylene group can be transformed to corresponding α-oxo ketene dithioacetals under suitable conditions. Since carbonyl group is abundant in organic molecules a large number of α-oxo ketene dithioacetals are also known. α-Oxo ketene dithioacetals also have been used extensively for the construction of heterocycles. Moreover they have been recognized as valuable multifunctional intermediates suitable for selective construction of new carbon-carbon bonds. Ketene dithioacetals with nitrile group at the α-position may also be considered similar to α-oxo ketene dithioacetals, because they also give comparable reaction with nucleophiles. Ketene dithioacetals having pyridinium groups and sulfonyl groups at the α-position have also been synthesized and shown to be valuable intermediates in organic synthesis.
2.2 Synthesis of Functionalized Ketene Dithioacetals

The most popular and convenient method for the preparation of functionalized ketene dithioacetals involves the reaction of an active methylene compound with carbon disulfide in the presence of a suitable base followed by alkylation.

Thuillier and Vialle were the first to develop a high yield synthesis of α-oxo ketene dithioacetals starting from ketones. They have treated ketones with carbon disulfide in the presence of sodium amylate followed by two equivalents of the alkylation agent. Aliphatic, cyclic and aryl alkyl ketones undergo smooth reaction under these conditions to give the corresponding ketene dithioacetals. Several groups have developed alternative methods for the synthesis of ketene dithioacetals from active methylene compounds mostly the difference is in the choice of the base or solvent to match the starting substrate. Lithium 2,6-di-β-buty 1-4-methyl phenoxide, lithium dialkyl amide, sodium hydride, potassium t-butoxide and KF/alumina.

Acyl ketene dithioacetals prepared from aliphatic ketones, such as acetone, ethyl methyl ketone etc have been used for further functionalization. The aldol type condensation of acyl ketene dithioacetals with aromatic aldehydes and substituted cinnnamaldehydes afford cinnamoyl ketene dithioacetals and their higher enyl homologues (Scheme 2).

The ketene dithioacetals derived from ethyl acetoacetate also undergo condensation reactions with aromatic aldehydes. The reaction involve insitu hydrolysis of the ester functionality and decarboxylation to afford cinnamoyl ketene
dithioacetals. Condensation of acyl ketene dithioacetals with N,N-dimethyl formamide diethyl acetal gave the enaminoketones 7 (Scheme 3).

\[
\begin{align*}
\text{Scheme 2} & \\
3 & + \\
4 & \xrightarrow{\text{NaOEt, EtOH}} \\
5 & \text{n=0, 1, 2} \\
& R_1, R_2, R_3 = H, CH_3
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 3} & \\
4 & + \\
6 & \xrightarrow{\text{100°C, Sealed tube, 90-92%}} \\
7 & R_1, R_2, = H, CH_3
\end{align*}
\]
These compounds would have interesting applications since the highly versatile enaminoketone functionality and the ketene dithioacetal moiety are present in the same molecule. It has been found that the enaminoketones 7 undergo chemoselective addition of Grignard reagents to afford alkenoyl ketene dithioacetals 8 (Scheme 4).

\[
\begin{align*}
 &\text{H}_3\text{C}-\text{N} \quad \text{H}_3\text{CS} \quad \text{SC}\text{H}_3 \\
 &\text{1)} \text{R}_3\text{MgBr} \\
 &\text{2)} \text{NH}_4\text{Cl} / \text{H}_2\text{O} \\
 &\text{R}_3=\text{Me, Et, i-Pr, n-Pr etc}
\end{align*}
\]

Scheme 4

While the polarized ketene dithioacetals having alkyl or benzyl substituents on sulfur can be conveniently prepared by alkylation of the dithiolate anions, phenylthio substituted ketene dithioacetals are obtained by nucleophilic displacement of β-dichloro groups by aryl thiolate anions (Scheme 5).

\[
\begin{align*}
 &\text{NC} \quad \text{O} \quad \text{OC}_2\text{H}_5 \\
 &\text{Cl} \quad \text{Cl} \\
 &\text{PhS} \quad \text{R}_1\text{OH} \\
 &\text{NC} \quad \text{O} \quad \text{OC}_2\text{H}_5 \\
 &\text{PhS} \quad \text{SPh}
\end{align*}
\]

Scheme 5
Aroyl ketene dithioacetals have been synthesized in a similar fashion from bromoethynyl aryl ketones. Another approach towards the synthesis of functionalized ketene dithioacetals involves addition of electron rich substrates such as enamines, enolizable carbonyl compounds, enolates phenols and naphthols to trithiocarbenium salts. Friedel-Crafts type acylation of ketene dithioacetals or trithioorthoacetates also lead to the formation of α-oxo ketene dithioacetals (Schemes 6 and 7).

The reaction of trithiocarbonates with the carbanions derived from N,N-dimethyl amino substituted acetonitriles also afford ketene dithioacetals functionalized at the α-position with nitrile group or sulfoxide group respectively (Scheme 8).
Though the number of methods available for the synthesis of functionalized ketene dithioacetals are not very large, they are sufficient to make these compounds available with diverse structural features. Extensive research has been carried out on the application of these compounds as synthetic intermediates.

2.3 Functionalized Ketene Dithioacetals in Organic Synthesis

The ketene dithioacetal functionality alone has a high potential in organic synthesis, due to its ability to behave as a donor or acceptor in the formation of a new carbon-carbon bonds. The diverse reactivity pattern of ketene dithioacetals and their application in the synthesis of complex molecules have been reviewed by Kolb. In this section, only the reactivity of functionalized ketene dithioacetals, particularly those with electron-withdrawing substituents at the α-position would be discussed.

2.3.1 α-Oxo Ketene Dithioacetals

α-Oxo ketene dithioacetals have been extensively used as three carbon synths in the synthesis of a variety of five membered and six membered heterocycles due to their 1,3-bielectrophilic character. Reactions of hydrazine hydrate with α-oxo ketene dithioacetals lead to the formation of pyrazoles (Scheme 9).
Junjappa and co-workers have recently developed conditions for the regioselective reaction of hydroxyl amine with aryl ketene dithioacetals. They have found that in the pH range 5-9, nucleophilic attack of nitrogen on the carbonyl group is preferred, while at lower pH(2.2) conjugate addition of the nitrogen is favoured. This leads to the selective formation of 3-alkylthio or 5-alkylthio pyrazoles respectively. (Scheme 10).

The reaction of guanidine and amidines with α-oxo ketene dithioacetals lead to the formation of substituted pyrimidines. Pott’s group has extended this method for the synthesis of several pyrimidine derivatives, with diverse structural features. A synthesis of 2,6-thienoyl pyrimidine has been shown in scheme 11.
Similar approaches towards the synthesis of heterocycles involve the reactions of cyanoacetamide anions as well. The reaction of cyanoacetamide with α-oxo ketene dithioacetals in the presence of sodium isopropoxide in isopropanol afford the pyridones 30 (Scheme 12). 74,75
The amidine functionality which is part of a heterocycle can also participate in the reaction with α-oxo ketene dithioacetal leading to the formation of fused pyrimidines. 2-Aminopyridines and 2-aminobenzothiazole have been used for the synthesis of annulated pyrimidines 33 (Scheme 13). 76

![Scheme 13](image)

The enamine functionality of 6-aminouracils and 3-aminopyrazoles also behave as a 1,3-binucleophile in their reaction with α-oxo ketene dithioacetals. 77,69

The reactions of N,N-dimethyl-6-aminouracil with α-oxo ketene dithioacetal have been shown in scheme 14.

![Scheme 14](image)
Some binucleophiles such as 1,2 or 1,3 diamines, aminoalcohols and aminothiols undergo conjugate addition displacing both the alkylthio groups leading to the formation of α-oxo ketene aminals, O, N-acetals and N, S-acetals respectively. Scheme 15 shows the reaction of 2-mercaptoethylamine with α-oxo ketene dithioacetals.

\[ \text{Scheme 15} \]

Displacement of one or both of the alkylthio groups of the ketene dithioacetal also afford α-oxoketene N,S-acetals or aminals respectively. There are some reactions which transform acyl ketene dithioacetals directly to functionalized heterocycles. For example the reaction of α-oxo ketene dithioacetals with \( \text{P}_4\text{S}_{10} \) offer a convenient procedure for the synthesis of 3-thione-1,2-dithiols 38 (Scheme 16).

\[ \text{Scheme 16} \]
Several functionalized ketene dithioacetals having active methylene group attached to at least one of the sulfur atom undergo intramolecular aldol type condensation to afford thiophene derivatives. Alkylation of the dithiolate dianions obtained by the reaction of active methylene ketones with carbon disulfide in the presence of a base with α-haloketones, esters or nitriles is shown in (Scheme 17). \[27,78,90-92\]

\[\text{RS} \quad \begin{array}{c} \text{R}^1 \quad \text{O} \quad \text{R}^2 \\ \hline \text{RS} \quad \text{Y} \quad \text{R}^1 \quad \text{O} \quad \text{R}^2 \end{array} \]

39

\[\text{RS} \quad \begin{array}{c} \text{R}^1 \quad \text{O} \quad \text{R}^2 \\ \hline \text{RS} \quad \text{Y} \quad \text{R}^1 \quad \text{O} \quad \text{R}^2 \end{array} \]

40

\[\text{Y=CN, CO}_2\text{Et, R-C}=\text{O}\]

Scheme 17

α-Oxo ketene dithioacetals have also been found to afford thiophene derivatives 41 on treatment with Simmons-Smith reagent (Scheme 18). The authors have proposed that the reaction involve an intermediate ylide, resulting from the reaction of the carbenoid methylene with the methylthio group. \[93\]

\[\begin{array}{c} \text{H}_3\text{CS} \\ \hline \text{H}_3\text{CS} \end{array} \quad \begin{array}{c} \text{R}^1 \quad \text{O} \\ \hline \text{R}^1 \quad \text{O} \end{array} \]

20

\[\text{Zn-Cu, CH}_2\text{I}_2 \quad \text{Et}_2\text{O, THF} \]

\[\text{H}_3\text{CS} \quad \text{SCH}_3 \quad \text{H}_3\text{CS} \quad \text{SCH}_3 \]

41

Scheme 18
Besides the synthesis of heterocycles, several valuable transformations have been reported on α-oxo ketene dithioacetals. One class of reactions involve nucleophilic addition of hydride or carbon nucleophiles to the carbonyl carbon of the α-oxo ketene dithioacetal followed by Lewis acid or protic acid catalyzed solvolysis. The overall transformation involve a reductive or alkylative 1,3-carbonyl group transposition (Scheme 19).

\[
\begin{align*}
\text{O} & \quad \text{SCH}_3 \\
R & \quad \text{SCH}_3 \\
\text{NaBH}_4 & \quad \text{EtOH} \\
\text{OH} & \quad \text{SCH}_3 \\
\text{BF}_3\cdot\text{Et}_2\text{O} & \quad \text{MeOH} \\
\end{align*}
\]

Scheme 19

Junjappa’s group have successfully achieved a selective reduction of the carbonyl group using an excess of sodium borohydride in refluxing absolute ethanol. Subsequent solvolysis in the presence of boron trifluoride etherate in refluxing methanol gave the α,β-unsaturated esters 43 in good yields with high stereoselectivity. Similar 1,3-cabonyl group transpositions leading to the formation of α,β-unsaturated thiol esters or carboxylic acids were also observed with HBF₄ in the presence of mercury salts. Reductive transpositions were further extended to the preparation of conjugated pentadienoates and heptatrienoates. The reductive carbonyl group transposition methodology has also been used for the synthesis of γ-butyrolactone derivatives. The α,β-unsaturated ester 46 prepared from the ketene dithioacetal 44 with an α-allyl substituent underwent cyclization to the α-ylidene-γ-butyrolactone 47 (Scheme 20).
1,2-Addition of organometallic reagents such as Grignard reagents or organolithium reagents also give similar carbinols which undergo carbonyl group transposition under solvolytic conditions. Thus the addition of methyl magnesium iodide to α-oxo ketene dithioacetal on subsequent solvolysis afford the α,β-unsaturated ester 49 depending on the reaction conditions (Scheme 21).\textsuperscript{100,101}

The Grignard reagents derived from higher homologues of alkyl halides underwent sequential 1,4 and 1,2-addition to the α-oxo ketene dithioacetal. The subsequent carbonyl group transposition reaction lead to the formation of α,β-unsaturated ketones.\textsuperscript{101}
There are several reports on the reaction of functionalized carbanions to the carbonyl group of the α-oxo ketene dithioacetals. Reformatsky reagents,\textsuperscript{102} enolates derived from esters and ketones\textsuperscript{103-105} and the lithium salts prepared from hydrazone are used as the nucleophiles. The intermediate γ-hydroxy ketones are highly functionalized and undergo further useful transformations. Scheme 22 illustrates a synthesis of substituted pyrones 53 employing such intermediates.

Selective reduction of α-oxo ketene dithioacetals resulting in the removal of one of the alkylthio group leading to the formation of vinylogous thiol esters is a valuable transformation. Junjappa’s group have used a combination of nickel chloride and sodium borohydride to achieve this objective.\textsuperscript{106} In a recent report they have disclosed that zinc in the presence of zinc chloride and tetramethyl ethylene diamine (TMEDA)
in refluxing ethanol has been found to be very efficient in the selective displacement of one of the methylthio groups of α-oxo ketene dithioacetal (Scheme 23).  

\[
\begin{align*}
\text{O} & \quad \text{SCH}_3 \\
\text{R}^1 & \quad \text{SCH}_3 \\
\text{R}^2 & \\
\text{R}^3 & \quad \text{OBut}^t \\
\text{R}^4 & & \text{THF} \quad \text{-78°C} & \text{HBF}_4 & \text{THF}
\end{align*}
\]

\[29 + 51 \rightarrow 52 \rightarrow 53\]

Scheme 22

By varying the amount of ZnCl$_2$-TMEDA, further reduction of the double bond or complete reduction of the ketene dithioacetal functionality to a methyl group are also

\[
\begin{align*}
\text{O} & \quad \text{SCH}_3 \\
\text{R}^1 & \quad \text{SCH}_3 \\
\text{R}^2 & & \text{Zn, ZnCl}_2$-$\text{TMEDA} & \text{EtOH, Reflux}
\end{align*}
\]

\[29 \rightarrow 54\]

Scheme 23
possible. Selective reduction of the double bond in \( \alpha \)-oxo ketene dithioacetals could also be achieved by treating them with magnesium in methanol.\(^{108,109}\)

One of the extensively studied aspects of \( \alpha \)-oxo ketene dithioacetal chemistry is the addition of allylic or propargylic carbanions selectively to the carbonyl group followed by Lewis-acid catalyzed cycloaromatization reactions. The addition of allyl or methallyl magnesium bromide to \( \alpha \)-oxo ketene dithioacetals and subsequent cycloaromatization in the presence of BF\(_3\).Et\(_2\)O or HBF\(_4\) lead to the formation of substituted benzenes 57 (Scheme 24).\(^{110,111}\)

![Diagram of the reaction](image)

This method offers an opportunity to construct aromatic compounds starting from aliphatic precursors. Besides the substitution pattern of the products could be designed by choosing the appropriate starting substrates. This method has been further extended to the synthesis of stilbenes.\(^{112}\) Similar reactions with benzyl magnesium chloride give napthaannulation, but benzyl Grignard undergo sequential 1,4 and 1,2-addition to \( \alpha \)-oxo ketene dithioacetal. This results in the formation of naphthalene derivatives substituted with a benzyl group rather than the methylthio group.\(^{113}\)
The propargyl magnesium bromide gave exclusive 1,2-addition products with α-oxo ketene dithioacetals. Subsequent cycloaromatization in the presence of borontrifluoride etherate in methanol gave methoxy substituted benzene derivatives 60 (Scheme 25).\textsuperscript{114}

\begin{化学式}
\begin{align*}
&\text{O} \quad \text{SCH}_3 \\
&\text{R}^1 \quad \text{R}^2 \quad \text{SCH}_3 \\
&\text{R}^1 \quad \text{H-C-C} \quad \text{MgBr} \\
&\text{R}^2 \quad \text{OH} \quad \text{R}^1 \\
&\text{SCH}_3
\end{align*}
\end{化学式}

\begin{化学式}
\begin{align*}
&\text{OCH}_3 \\
&\text{R}^1 \quad \text{R}^2 \quad \text{SCH}_3
\end{align*}
\end{化学式}

Scheme 25

Similar reactions have also been reported with lithioacetonitrile while the treatment of the intermediate β-hydroxy nitrile with boron trifluoride etherate gave the nitrile substituted diene, cyclization involving intramolecular migration of methylthio group could be achieved in the presence of phosphoric acid (Scheme 26).\textsuperscript{115}

Benzoheterocycles are conventionally prepared by starting with a suitable aromatic substrate and constructing the desired heterocycles on that. An alternate approach would be to start with a suitable heterocyclic precursor on which an aromatic ring could be
annulated. The reaction of 3-methyl-5-lithio-methyl isoxazole with α-oxo ketene dithioacetals followed by cycloaromatization gave benzisoxazoles 64 in good yields (Scheme 27).\textsuperscript{114,117}

\[ \text{Scheme 26} \]

\[ \text{Scheme 27} \]
Similar cyclizations have been reported with other allyl anions as well. The allyl anions derived from 2-picoline, $\beta$-pyrrolidino crotonate, 1,3,6-trimethyl uracil and 2,3-dimethyl-1-phenylpyrazoline-5-one have been found to undergo nucleophilic addition to $\alpha$-oxo ketene dithioacetals and subsequent cyclization leading to the formation of quinolizinium salts, amino substituted benzene derivatives, quinazoline derivatives and indazolone derivatives respectively.

A rather unusual reaction of Reformatsky reagents involves the addition of a second molecule of reagent to the initial adduct followed by cyclization, leading to the formation of substituted salicylates (Scheme 28).

![Scheme 28]

The addition of Methyl Grignard on $\alpha$-oxo ketene dithioacetals followed by dehydration lead to the formation of sulfur substituted butadienes which are valuable intermediates for cycloaddition reactions. Similar dienes can also be obtained by Wittig reaction. These dienes have been shown to undergo facile (4+2) cycloaddition reactions with electron deficient dienes (Scheme 29).

Several nucleophilic reagents have been found to undergo conjugate addition with functionalized ketene dithioacetals. Ketene dithioacetals having two electron withdrawing groups at the $\alpha$-position are particularly susceptible to conjugate additions.
The chemo and stereoselective addition of organocuprates to α-oxo ketene dithioacetals has been explored in much detail.\textsuperscript{18,126-129} The high chemo and stereoselectivity, that could be achieved in this reaction is evident in the example highlighted in the scheme 30.

There are a number of reports on the conjugate addition of functionalized nucleophiles to polarized ketene dithioacetals which involve subsequent cyclizations leading to the formation of a variety of heterocycles. For example the anion generated from α-pyridyl acetonitrile adds to the ketene dithioacetal 72 prepared from ethyl cyanoacetate followed by cyclization to quinolizones 73 (Scheme 31).\textsuperscript{130}
A large number of similar transformations are available in the literature. Conjugate additions of enolates to the polarized ketene dithioacetals derived from ethyl cyanoacetate or diethyl malonate undergo further cyclization leading to the formation of substituted 2-pyrone 76 (Scheme 32). 

This method have been further extended to the synthesis of 2-pyrone derivatives annulated to other heterocyclic systems as well. The 1,5-diketones formed on the conjugate addition of enolates to α-oxo ketene dithioacetals have been found to cyclize to the pyrilium salts which could be then transformed into pyridine derivatives on treatment.
with ammonium salts. One example shown in scheme 33 illustrates the preparation of a valuable base.

![Scheme 33: Preparation of a valuable base](image)

### 2.3.2 Nitro Ketene Dithioacetals

The simple nitro ketene dithioacetals is prepared in high yield by the alkylation of the dithiolate dianion obtained by the reaction of nitromethane with carbon disulfide in the presence of a base. The nitro ketene dithioacetals are valuable two carbon synthons particularly useful in the synthesis of heterocycles which should have a nitro or amino substituent. While the α-carbon acts as a donor, the β-carbon behaves as an acceptor. Functionalized nucleophiles add to the β-carbon, of the nitro ketene dithioacetals and the adducts formed could be cyclized subsequently. Scheme 34 shows the reaction of anthranilic ester with nitro ketene dithioacetal. The initial addition of two molecules of anthranilic ester leads to the formation of an intermediate quinolone derivative. Further cyclization to the diazepinone could be accomplished in the presence of Raney nickel/hydrazine.

The reaction of amines with nitro ketene dithioacetals lead to the formation of corresponding N,S-acetals or aminals. Scheme 35 shows a synthesis of pyrrole derivatives from nitro ketene N,S-acetals. The amino acetaldehyde diethylacetal adds to the nitro ketene dithioacetal to afford an intermediate ketene N,S-acetal which on further cyclization give the nitro substituted pyrrole.
Scheme 34

Scheme 35
Carbanions generated from active methylene compounds also add to nitro ketene-S,S-acetals. Scheme 36 shows the reaction of 3-cyanomethyl indole-2-carboxylate leading to the formation of carbazole derivatives 88.153

\[
\begin{align*}
&\text{O}_2\text{N-} \quad + \quad \text{H}_3\text{CS-SCH}_3 \\
&\text{H}_3\text{CS-SCH}_3 \\
&\text{H}_3\text{CS-SCH}_3 \\
&\text{CN} \\
&\text{H} \\
&\text{OC}_2\text{H}_5 \\
&\text{H} \\
&\text{OH} \\
&\text{NO}_2 \\
&\text{H} \\
&\text{H} \\
&\text{SCH}_3 \\
&\text{CN} \\
&\text{80} \\
&\text{87} \\
&\text{88}
\end{align*}
\]

Scheme 36

The reaction of pyridinium-N-ylides with nitro ketene dithioacetals is accompanied by cyclization and denitration leading to the formation of the indolizine derivative 90 (Scheme 37).154

\[
\begin{align*}
&\text{O}_2\text{N-} \quad + \quad \text{Ph-CON-NO}_2 \\
&\text{H}_3\text{CS-SCH}_3 \\
&\text{Ph-CON-NO}_2 \\
&\text{Ph} \\
&\text{H}_3\text{CS} \\
&\text{90}
\end{align*}
\]

Scheme 37

2.4 Conclusions

Functionalized ketene dithioacetals are important synthetic intermediates in organic chemistry. They can be prepared with virtually any functional group at the α-positions.
They have a wide spectrum of reactivity. They have found applications in almost every field of organic synthesis such as selective formation of new carbon-carbon bonds, functional group manipulations, carbonyl group migrations, aromatic annihilation reactions, synthesis of a large variety of heterocycles and synthesis of complex natural products. The sulfur substituents present in the products are also useful for further synthetic transformations.

2.5 References


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Kobayashi, G.; Matsuda, Y.; Natsuki, R.; Tominaga, Y. *Yakugaku Zasshi* 1972, 92, 713.