2.1 Introduction

The α-oxoketenedithioacetals of general formula 1 have been proved to be versatile intermediates in organic synthesis. They can be easily synthesized by treating active methylene compounds with two equivalents of base and carbondisulfide followed by alkylation. α-Oxoketenedithioacetals are considered as synthetic equivalents of β-ketoesters. Moreover, they provide opportunities for the regioselective and chemoselective formation of new carbon-carbon and carbon-heteroatom bonds. A large number of them with diverse structural features have been prepared by employing minor variations of the general strategy.
The chemistry of α-oxoketenedithioacetals leading to the formation various other valuable reactive intermediates, heterocycles, and aromatic compounds has been studied extensively. Several reviews have appeared on their synthesis and subsequent applications in organic synthesis. They also serve as precursors for the synthesis of the corresponding α-oxoketene-N,S-acetals and aminals by the sequential displacement of either one or both of the methylthio groups. The displacement of methylthio group is also facile with carbon nucleophiles yielding the 1,4 adducts which can be further transformed into novel heterocyclic and aromatic compounds. α-Oxoketenedithioacetals are proven three carbon synthons possessing 1,3-electrophilic centers with differing electrophilic properties, suitable for synthetic manipulations.

2.2 α-Oxoketenedithioacetals: Synthesis

Kelber and co-workers reported the first synthesis α-oxoketenedithioacetals 1. Their procedure involved alkylation of β-oxodithioic acids with alkyl halides under basic conditions.

Later Thuillier and Vialle have developed a more convenient method for their synthesis from ketones. They treated active methylene ketones 2 with carbon disulfide in presence of sodium t-amylate followed by treatment with two equivalents of the alkylation agent (Scheme 1).

Scheme 1

Aliphatic, cyclic and aryl alkyl ketones undergo smooth reaction under these conditions to give the corresponding ketenedithioacetals. α-Oxoketenedithioacetals could be prepared from several heterocyclic compounds having active methylene moiety as well. Subsequently other methods also have been introduced, most of them differing only in the base and the solvent used. Thus, lithium-2,6-di-t-butyl-4-
methylphenoxide\(^4\), lithium dialkylamide\(^4\), sodium hydride\(^6\), potassium \(\rho\)-butoxide\(^7\) and KF/Alumina\(^8\) have been successfully used for the preparation of \(\alpha\)-oxoketenedithioacetals. Besides these, other methods for their preparation also exist. For example, aromatic hydroxy compounds such as phenols and naphthols are converted to the corresponding ketenedithioacetals by their reaction with trithiocarbonium salts (Scheme 2). \(^9\)

\[ \text{Scheme 2} \]

They can also be prepared by the Friedel-Crafts acylation of ketenedithioacetals (Scheme 3). \(^10\)

\[ \text{Scheme 3} \]

Similarly, trithioorthoacetates can be converted to the corresponding \(\alpha\)-oxoketenedithioacetals by Friedel-Crafts type acylation of the intermediate ketene dithioacetals with acid anhydrides or acid chlorides (Scheme 4). \(^11\)
Though there exists several methods for the preparation of α-oxoketenedithioacetals, the reaction of enolate anions derived from the active methylene carbonyl compounds with carbondisulfide followed by alkylation is the method of choice. A large number of α-oxoketenedithioacetals with diverse structural features are known and their chemistry has been studied in detail by different groups.

2.3 α-Oxoketenedithioacetals: Reactivity

α-Oxoketenedithioacetals are considered as synthetic equivalents to β-ketoesters, in which the ester functionality is protected as the ketenedithioacetal group. Alternatively, they can be considered as highly functionalized α,β-unsaturated ketones containing alkylthio substituents that can be displaced with nucleophiles at the β carbon atom. From either point of view, they possess considerable potential for the regioselective and stereoselective construction of new bonds via 1,2 or 1,4 nucleophilic addition reactions. Though the ketenedithioacetal derived from acetone is synthetically equivalent to ethyl acetoacetate, when we consider the donor-acceptor properties of the carbons the acyl ketenedithioacetal have a distinct advantage over the β-ketoester in reactivity. While the α-carbon can undergo, Lewis acid assisted addition to electrophiles, α'-carbon can selectively be deprotonated and added to electrophiles in the presence of base. These reactivity patterns have been exploited in the synthesis of a number of acyclic, cyclic and heterocyclic systems starting from α-oxoketenedithioacetals.

2.3.1 Reaction with Binucleophiles

The flexibility of functional group manipulation along with hard-soft dissymmetry and its possible inversion makes α-oxoketenedithioacetals a potential 1,3-electrophilic three-carbon fragment having synthetic importance. Their reactions with a
large number of hetero binucleophiles leading to the formation of a variety of heterocyclic structures are studied.\textsuperscript{1} Thus reactions of 1,3-dinitrogen nucleophiles with \(\alpha\)-oxoketenedithioacetals provide a convenient method for the synthesis of functionalized pyrimidines. Rudorf and Augustin\textsuperscript{12} and Potts\textsuperscript{13} \textit{et al.} have reported the synthesis of pyrimidines by treating amidines with ketenedithioacetals derived from various substituted ketones. For example the ketenedithioacetals 12 derived from \(\alpha\)-cyanoketones on treatment the amidine 13 afford cyano substituted pyrimidines 14 (Scheme 5).

\begin{center}
\begin{align*}
\text{Ketenedithioacetal} & \quad \begin{array}{c}
\text{15} \\
\end{array} \\
\text{prepared from} & \quad \begin{array}{c}
2,6-\text{diacetyl pyridine affords pyrimidine} \\
\text{derivative} & \quad \begin{array}{c}
\text{16} \\
\end{array}
\end{array}
\end{align*}
\end{center}

These pyrimidine derivatives are valuable ligands in organometallic chemistry (Scheme 6).\textsuperscript{14}

\begin{center}
\begin{align*}
\text{Other substituted amidines also have been shown to participate in similar} & \quad \begin{array}{c}
\text{reactions with} \quad \begin{array}{c}
\text{\(\alpha\)-oxoketenedithioacetals. Thus, the reaction of} \\
\text{2-} \\
\end{array}
\end{array}
\end{align*}
\end{center}
thiophenecarboxamidine 17 with the ketenedithioacetal 18, prepared from 2-acetyl thiophene, leads to the formation of the substituted pyrimidine 19 (Scheme 7).13

\[
\begin{align*}
\text{SCH}_3 & & + \\
\text{SCH}_3 & & \text{NH} \\
\text{O} & & \text{NH}_2 \\
\text{N} & & \text{N} \\
\text{SCH}_3 & & \text{SCH}_3 \\
\text{SCH}_3 & & \text{SCH}_3
\end{align*}
\]

Scheme 7

Amidines, which form part of a heterocycle such as, 2-aminopyridine 21 reacts with \(\alpha\)-oxoketenedithioacetals forming annulated pyrimidines 22 (Scheme 8).15

\[
\begin{align*}
\text{NC} & & \text{CH}_3_S & & \text{CH}_3_S \\
\text{OR} & & \text{H}_2\text{N} & & \text{H}_2\text{N} \\
\text{O} & & \text{N} & & \text{N} \\
\end{align*}
\]

Scheme 8

Functionalized pyridones16 could also be prepared from \(\alpha\)-oxoketenedithioacetals. The reaction follows a two step process in which the conjugate addition of the enolates is followed by cyclization. For example, the reaction of cyanoacetamide with \(\alpha\)-oxoketenedithioacetal 23 is shown in Scheme 9. The ketenedithioacetal was treated with cyanoacetamide in presence of sodium isopropoxide in refluxing isopropanol.
Reaction of α-oxoketenedithioacetal with hydrazine hydrate leads to the formation of substituted pyrazoles (Scheme 10).  

The reaction of α-ketenedithioacetals with hydroxylamine is an example where the electrophilicity of the carbonyl carbon and the β-carbon of the α-oxoketenedithioacetal could be altered by employing appropriate reaction conditions. Junjappa and co-workers have successfully demonstrated that α-oxoketenedithioacetals could be transformed to either 3-alkylthio or 5-alkylthio isoxazoles by simply choosing reagent combinations of appropriate pH. Thus, the 5-alkylthioisoxazole 28 can be obtained by the reaction of hydroxylamine hydrochloride with α-oxoketenedithioacetals in the presence of barium hydroxide or sodium methoxide at the pH range 5 to 9. On the other hand in the presence of sodium acetate-acetic acid, the β-carbon is more electrophilic and the reaction yields 3-alkylthio isoxazole 29 (Scheme 11).
The enamine moiety of amino uracils and amino pyrazoles also act as 1,3 binucleophiles in their reactions with α-oxoketenedithioacetals. Thus the reactions of N,N-dimethyl-6-aminouracil 30 with α-oxoketenedithioacetals 31 afford pyrido[2,3-d]pyrimidine derivatives 32 (Scheme 12).19

1,4-Binucleophiles such as ethylene diamine, ethanolamine and 2-aminoethanethiol sequentially displace both the alkylthio groups of α-oxoketenedithioacetals leading to the formation of imidazolidines, oxazolidines, and thiazolidines respectively (Scheme 13).20 Addition of amines to ketenedithioacetals afford the corresponding N, S acetal which could be converted in to the ketene aminals by reaction with a second equivalent of the amine.17,21
2.3.2 1,2-Addition Reactions of Carbon Nucleophiles

An interesting aspect of the α-oxoketenedithioacetal chemistry is their application in the synthesis of substituted aromatic compounds. The Grignard reagents prepared from allyl magnesium bromide undergo selective 1,2-addition to α-oxoketenedithioacetals. The intermediate carbinol acetal 37 on cycloaromatization in the presence of boron trifluoride etherate in refluxing benzene leads to the formation of benzenoids 38 (Scheme 14).
Dieter and co-workers have also reported similar results on the addition of methallyl magnesium bromide to \( \alpha \)-oxoketenedithioacetals followed by cycloaromatization employing HBF\(_4\) in aqueous THF.\(^{23}\) Junjappa's method for the preparation of highly substituted aromatic compounds has been further extended to cinnamoyl ketenedithioacetals as well for the synthesis of substituted stilbenes. Substituted cinnamoyl ketenedithioacetals 39 also undergo selective addition of allyl magnesium bromide on to the carbonyl group. Cycloaromatization of the intermediate carbinol acetal 40 upon treatment with a Lewis acid such as boron trifluoride etherate gave the corresponding alkylthio substituted stilbene 41 in good yields (Scheme 15).\(^{24}\)
By using benzyl magnesium chloride, the cycloaromatization route was extended for the preparation of substituted naphthalenes as well.\textsuperscript{25} Propargyl magnesium bromide also reacts in 1,2 fashion giving the intermediate carbinol, which undergo benzoannulation on treatment with BF\textsubscript{3} etherac\textsubscript{26}.

Dieter's group have also developed a method for the synthesis of substituted phenols starting from \(\alpha\)-oxoketenedithioacetals. The addition of trimethyl silyl substituted allyl lithium \textsuperscript{43} to the ketenedithioacetal \textsuperscript{42} derived from cyclohexanone gave the \(\alpha,\beta\)-unsaturated thiolester \textsuperscript{44}, which could be cyclized to the phenol \textsuperscript{45} in 56\% yield on treatment with dimethyl methylthio sulfonium fluoroborate in CH\textsubscript{2}Cl\textsubscript{2} (Scheme 16).\textsuperscript{27}


Scheme 16

Other than organomagnesium reagents, nucleophilic addition reactions of other functionalized carbanions to α-oxoketenedithioacetals also have studied in detail. They include reactions with Reformatsky reagents, with enolates derived from esters and ketones and with imine anions prepared from hydrazones etc. An interesting transformation of α-oxoketenedithioacetals to substituted salisylates involves a sequential addition of two molecules of the Reformatsky reagent prepared from ethyl bromoacetate followed by in situ cyclisation and aromatization. Similar reactions have been further extended to cinnamoyl ketenedithioacetals also (Scheme 17).

Scheme 17

The addition of lithioacetonitrile to α-oxoketenedithioacetals follows a 1,2-addition pathway. The intermediate carbinol acetals formed on treatment with
phosphoric acid undergo ring closure to afford substituted pyridine derivatives 48 (Scheme 18).

Junjappa and co-workers have extended their cycloaromatization methodology for the synthesis of a variety of benzoheterocycles. Here, α-oxoketenedithioacetals are allowed to react with allylic anions which form part of a heterocyclic system. The allylic anion undergo either a 1,2-addition or a 1,4-addition followed by cycloaromatization. For example, when 3-methyl-5-lithiomethylisoxazole 49 was treated with α-oxoketene-dithioacetals and the intermediate carbinols were allowed to undergo cycloaromatisation on treatment with boron trifluoride etherate, the corresponding substituted benzisoxazoles 50 were formed in good yields (Scheme 19).32,33 This method has been further extended of a large variety of substituted benzoheterocycles.33
Dieter and co-workers have developed several methods for the synthesis of substituted 2-pyrons from α-oxoketenedithioacetals. Addition of enolates derived from esters and ketones to α-oxoketenedithioacetal followed by acid catalyzed cyclization is highly useful in the synthesis of substituted pyrones. A typical example for this strategy is given in Scheme 20. The method involves 1,2 nucleophilic addition of ester or ketone enolate anions to ketenedithioacetals followed by acid assisted 1,3-carbonyl group transposition to give the δ-keto-α,β-unsaturated acids or esters. They were subjected to enol lactonization to the respective pyrones.

This reaction gives better results when cyclic ketenedithioacetals are allowed to react with ester or ketone enolates. Reaction with acyclic ketenedithioacetals suffered from lower yields of pyrons. An alternative method involves the 1,2-addition of
enolates derived from hydrazone and the resulting carbinol was hydrolyzed and rearranged to pyrons by a sequential treatment with Cu(OAc)$_2$ and HBF$_4$/HgO or treatment with trifluoroacetic acid.$^{29}$

### 2.3.3 1,4-Addition Reactions of Carbon Nucleophiles

1,4-Addition reactions of carbon nucleophiles to $\alpha$-oxoketenedithioacetals follow an addition-elimination pathway resulting in the substitution of the alkylthio group or cyclization of the intermediate depending on the nature of the ketenedithioacetal and the nucleophile. Active methylene compounds undergo addition to oxoketenedithioacetals through enolate anions. Potassium enolate derived from active methylene ketones prefer conjugate addition to polarised ketenedithioacetals. If the starting ketenedithioacetal has an ester functionality at the $\alpha$-position, the adduct on subsequent cyclization afford substituted 2-pyrons (Scheme 21).$^{35}$ Enolate anions derived from heterocyclic compounds that posses active methylene moiety have also been shown to participate in similar reactions leading to the formation of heteroannulated pyron derivatives.$^{36}$

\[
\begin{align*}
\text{X} = \text{CN, CO}_2\text{Et; R}', R'' & = \text{aryl, alkyl, cyclic} \\
53 & \rightarrow 54 \\
& \text{Scheme 21}
\end{align*}
\]

Potts and co-workers have studied the conjugated addition of active methylene ketones to $\alpha$-oxoketenedithioacetals in the presence of potassium t-butoxide in THF. The 1,5-enediones formed in these reactions have been subsequently exploited for the synthesis of substituted pyridines. Scheme 22 shows an application of this methodology for the synthesis of oligopyridines 57.
Organocopper reagents add to α-oxoketenedithioacetals stereoselectively, giving the 1,4-addition products. Thus, the ketenedithioacetal 42 reacts with two equivalents of methylcopperlithium to afford the α-alkylidene ketone 58 (Scheme 23).

Scheme 22

Organocopper reagents add to α-oxoketenedithioacetals stereoselectively, giving the 1,4-addition products. Thus, the ketenedithioacetal 42 reacts with two equivalents of methylcopperlithium to afford the α-alkylidene ketone 58 (Scheme 23).

Scheme 23

2.3.4 Miscellaneous Reactions Leading to Heterocycles

Reaction with phosphorus pentasulfide leads to the formation of 3-thione-1,2-dithiols 60 (Scheme 24).
If an active methylene moiety is attached to sulfur atom of the α-oxoketenedithioacetals, they can be converted into thiophene derivatives in the presence of a suitable base. The reaction proceeds through the initial deprotonation of the alkylthio group followed by intramolecular condensation involving carbonyl group (Scheme 25).

\[ \text{Scheme 24} \]

Thiophenes are also formed from the reaction of α-oxoketenedithioacetals with Simmons-Smith reagent. The reaction proceeds through the intermediate formation of an ylide by the addition of the carbenoid methylene to the alkylthio group (Scheme 26).

\[ \text{Scheme 25} \]

\[ \text{Scheme 26} \]
Aziridines undergo substitution reaction with the alkylthio group giving the 6-azirido acetics, which in the presence of KI undergo ring expansion to afford the corresponding 2-thiomethyl 3,3-disubstituted pyrrolines 66. The reaction of the cyclic ketenedithioacetal 64, derived from pyrazoline, with aziridine is shown in Scheme 27.

Scheme 27

2.3.5 Solvolysis and Hydrolysis of α-Oxo and α-Hydroxyketenedithioacetals:

α-Oxoketenedithioacetals are considered as protected β-ketoesters and hence their complete hydrolysis should give the corresponding β-ketoesters. Partial hydrolysis of ketenedithioacetals to β-thiolesters in low yields is known to proceed in presence of mineral acid and water (Scheme 28).

Scheme 28

Shahak and co-workers have reported the complete solvolysis of ketenedithioacetal 68 to the respective β-ketoester 69 in the presence of PTSA and ethanol (Scheme 29).
The reductive and alkylative 1,3-carbonyl group transpositions involving α-oxoketenedithioacetals have been extensively studied. The general procedure for these reactions include 1,2-nucleophilic addition of borohydride, Grignard or organo lithium reagents to ketenedithioacetals followed by acid assisted solvolysis of the resulting carbinol acetals.

α-Oxoketenedithioacetals undergo 1,2-reduction with sodium borohydride to give the allylic alcohols in good yields. These carbinol acetals on treatment with p-toluenesulfonic acid gave low yields of α,β-unsaturated thiolesters along with β-methylthio thiolesters 71, formed by the conjugate addition of methanethiol to the initially formed α,β-unsaturated thiolester (Scheme 30).

Further developments in this area came from Junjappa’s group, who reported that treatment of the allylic alcohol, obtained by the 1,2-reduction of α-oxoketenedithioacetals, with boron trifluoride etherate in methanol afforded α-unsaturated methylester 72 in good yields (Scheme 31).
Later Dieter\textsuperscript{27,43} found that HBF\textsubscript{4} in THF could be effectively used to get high yields of the unsaturated thiolester together with the methyl sulfide.

The effectiveness and stereoselectivity of HBF\textsubscript{4} or BF\textsubscript{3} assisted solvolysis is attributed to a six membered transition state 73 formed by the complexion of boron to oxygen and sulfur. The proposed involvement of a cyclic transition state also rules out the possibility of an intramolecular 1,3-migration of the alkylthio group leading to the formation of the $\beta$-alkylthio substituted product.

The reductive 1,3-carbonyl group transposition methodology was further extended to cinnamoyl ketenedithioacetals as well. Thus the ketenedithioacetal 74 on 1,2-reduction with sodium borohydride and subsequent methanolysis gave the 5-aryl pentadienoate 75 (Scheme 32).\textsuperscript{44} Similarly pentadienoyl ketenedithioacetal 76 also yielded the corresponding heptatrienoates 77 (Scheme 33).\textsuperscript{45}
However, the carbinol acetal obtained by the 1,2-reduction of the alkenyl ketenedithioacetal 78 did not give the expected dienester, instead the cyclopentenone derivatives 79 were isolated after boron trifluoride assisted methanolyis (Scheme 34).46

Under similar conditions, 2,4-dimethyl-7-aryl-2,4,6-heptatrienoyl ketenedithioacetals afforded the styryl cyclopentenones.

The formation of cyclopentenones results from an electrocyclic ring closure of the intermediate pentadienoyl cation. The presence of methyl substituents at the 2 and 4
positions force the cation to form a ‘U’ conformation, which is the stereochemical requirement for the cyclization.

α-Oxo, α-alkenyl ketenedithioacetals 80 were also subjected to 1,2-reduction followed by methanolysis under boron trifluoride assisted conditions. These reactions resulted in the formation of α-ylidene-γ-δ-unsaturated esters 81, which are subsequently converted to the γ-butyrolactones 82 (Scheme 35).47

\[
\text{Scheme 35}
\]

α-oxoketenedithioacetals are also subjected to 1,2-addition of organometallic reagents and further solvolytic studies resulted in the formation a number of interesting intermediates. Often the initial adducts formed were subjected to additional synthetic manipulations leading to the formation of a variety of useful products. Junjappa and Ila have studied the reaction of methylmagnesium iodide with α-oxoketenedithioacetal to afford the carbinol acetal 83 which on BF₃ assisted methanolysis gave the corresponding β-methyl α,β-unsaturated esters 84, exclusively as E isomers (Scheme 36).48
However, the carbinol acetal derived from the addition of methyl Grignard to aroylketenedithioacetals 85, having an α-alkyl substituent gave the corresponding 2-alkyl-3-methyl indenones 86 under the solvolysis conditions (Scheme 37).

![Chemical structures](image)

Scheme 36

The proposed mechanism for the formation of the indenone involves a boat like transition state 87. Under solvolytic condition, this will lead to the Z-cinnamate 88 wherein the phenyl and the ester groups are cis to each other which would subsequently cyclize to the indenone 86 (Scheme 38). This transition state is preferentially formed when the α-position of the ketenedithioacetal is substituted with a bulky group.
Similarly, a-allyl substituted aroyl ketenedithioacetal 89 gave the corresponding 2-allyl indene 90 under similar conditions (Scheme 39).47

\[ R' = \text{alkyl, aryl} \]

Scheme 38

Similarly, \( \alpha \)-allyl substituted acyl ketenedithioacetal 89 gave the corresponding 2-allyl indene 90 under similar conditions (Scheme 39).47

Scheme 39

The \( \alpha \)-allyl substituted acyl ketenedithioacetals 91 where the aromatic participation is absent, gave the enesters 92 on the addition of methyl Grignard
followed by Lewis acid assisted methanolysis (Scheme 40). The enesters 92 could be subsequently cyclized to the butyrolactones under acid catalyzed conditions.

The addition of Grignard reagents derived from higher alkyl halides to α-oxoketenedithioacetals was also studied. Here, the reaction proceeds by a successive 1.4 and 1,2 addition leading to the formation of the carbinol acetals 94. This under BF$_3$ catalyzed methanolysis gave the corresponding α,β-unsaturated ketones 95 (Scheme 41).
possibility of easy functional group manipulation makes them an important building block in organic chemistry.

2.4 References


44. Myrboh, B.; Asokan, C. V.; Ila, H.; Junjappa, H. *Synthesis* 1984, 50


