Chapter 3

Reactions of Polyvinyl and N-Methyl Pyrrolidone Bromine Complexes with Dithioacetals and Ketene Dithioacetals

3.1 Introduction

Even though the concept of immobilizing reagents on a support material as in catalytic hydrogenation and in numerous other heterogeneous reactions that occur at the interface of a solid was known a century ago, the subject has got widespread acceptance after Merrifield’s solid-phase peptide synthesis. A wide range of polymeric reagents was developed for use in organic synthesis and those based on cross-linked polymers have become more popular due to the ease of handling. The reaction can often be driven to completion by using excess of reagent without the fear of separating the unspent reagents or the polymeric byproducts from the product mixture. A polymeric reagent is a system that combines the unique properties of conventional reactive moieties bound to it and those of high molecular weight polymer. The reactivity of a functional group bound to a polymer backbone varies form a solution phase synthesis and depends on the nature of the polymer backbone, the conformation of the polymer chain, the microenvironment of the reactive functional groups, the relative occurrence of the functional groups in the chain, the stereochemistry around the functional group, the overall topology of the macromolecular matrix and the solvent and swelling characteristics.
3.2 Polymer-supported halogen complexes

The halogen-containing reagents based on polymers such as polystyrenes, polyacrylamides, poly(vinylpyrrolidene)s, poly(vinylpyridine)s and poly(vinylpyridin-styrene)s were developed for oxidation, addition as well as halogenation reactions. Kesset and co-workers have reported oxidation of primary and secondary alcohols to aldehydes and ketones using polyvinylthioazolium hydrotribromide 1 in aqueous sodium hydroxide. The resin was easily synthesized by radical copolymerisation of 4-methyl-5-vinylthiazole, styrene and divinylbenzene followed by treatment with HBr and bromine.

![Chemical Structure](image)

Pillai et al. reported polystyrene-supported t-butyl hypochlorite and hypobromite to effect oxidation of alcohols to carbonyl compounds and for halogenation. The same group has shown the utilities of chloramine-T and bromamine-T supported on polystyrene in the oxidation of alcohols and halogenation of ketones. Polystyrene-supported benzyltriethylammonium dichloroiodate and dibromoiodate were reported as polymeric anionic oxidants. A polymeric reagent electrochemically produced from cross-linked poly(4-vinylpyridine)-supported hydrobromide was found to oxidize secondary alcohols to corresponding ketones. Pillai et al. developed bromo derivatives of poly(vinylpyrrolidone)s as reagents for the oxidation of alcohols. A series of polymeric oxidants 2, 3 and 4 based on a co-polymer of acrylamide and divinylbenzene for oxidizing primary and secondary alcohols to aldehydes and ketones, respectively were developed by Sreekumar et al. They could succeed in binding the active functions $\mathrm{ICl}_2^-$, $\mathrm{ICl}_4$ and $\mathrm{IBr}_2^-$ on these acrylamide-based supports.
Polyacrylamide-bromine complexes were developed by Pillai et al. for oxidation, bromination and addition reactions and observed that highly polar solvents enhanced reaction rate in the case of NNMBA cross-linked reagents. The same reagents were also used in the bromination of carbonyl compounds. Zupan reported the use of poly(4-vinylpyridinium-styrene)-supported dichlorooiodate for the addition reactions of alkenes.

Polymer-bound bromides have been prepared for use in the bromination of variety of aromatic molecules. The polymer used was based upon cross-linked co-polystyrene-4-vinyl(N-hexylpyridinium bromide), which was treated with chlorine or bromine to give the two reagents 5 and 6. Both reagents displayed regioselective para-bromination for a range of substituted benzenes.

Bromine complexes with various polymers bearing basic units (pyridine, piperidine and pyrazine) were investigated by the same group and the role of polymer matrices on reactivity was tested by three types of organic reactions: electrophilic addition, aromatic substitution and free radical substitution. Pyridine complex was most reactive in all the three types of reactions. Sinisterra described the use of poly (N-bromoacrylamide)s as heterogeneous reagents for alpha halogenation of ketones. Zabicky has developed complexes of bromine and bromine chloride with poly(4-vinylpyridine)s 7 to use in the addition reactions with alkenes and alkynes.
The complexes of bromine with poly(vinylpyridine-styrene)\textsuperscript{17}, poly(vinylpyridine N-oxide-styrene) and poly(vinylpyridiniumbromide-styrene)\textsuperscript{18} were used in addition reactions of double bond-containing compounds. These reagents showed stereospecificity in the addition.

A facile bromomethoxylation of alkenes using a new polymer supported brominechloride resin \textbf{8} under microwave condition has been reported recently\textsuperscript{19}. Reactions using this resin were regioselective, following Markovnikov's addition rules, and also chemoselective in which only isolated double bonds were bromomethoxylated, keeping the conjugated double bonds inert to the reaction conditions.

Amberlyst-A26 resin in its tribromide form effects para-bromination of phenols with high yields and selectivity; the resin is easily recovered by filtration and can be reconverted into the tribromide form by addition of bromine\textsuperscript{20}. Poly(4-methyl-5-vinylthiazolium) hydrotribromide (P4M5VTHT), incorporating 45\% of bromine, was found to be a stable, and effective brominating reagent for various unsaturated ketones and olefines\textsuperscript{21}. The aminomethylpolystirene-supported (diacyloxy)iodobenzene ragent \textbf{9} has been used for the oxidaton of hydroquinones and phenols to the corresponding quinones\textsuperscript{22}. Thus, Mukaiyama aldol reactions were performed at -78 °C in dichloromethane afford the products in very good yields.
A polymeric derivative of the coupling reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) 10 has been prepared and utilized in amidation by Desai and later utilised by Adamczyk et al. for the generation of thiol esters 13. (Scheme 1).^{13}

\[
\begin{align*}
\text{R'OH} + \text{R'SH} & \underset{\text{CHCl}_3}{\overset{10}{\longrightarrow}} \text{RSR'}^+ \\
11 & \quad 12 & \quad 13
\end{align*}
\]

Scheme 1

### 3.3 General methods for the synthesis of thiolesters

For the preparation of some synthetic intermediates such as β-oxothiolesters, to be used in the total synthesis of alkaloids such as rigidin and related molecules, we needed to develop an efficient method for the partial hydrolysis of α-oxoketene dithioacetals. β-Oxothiolesters are valuable synthons in organic synthesis. β-Oxothiolesters have got a distinct advantage over simple thiolesters due to the presence of multiple reactive sites. Due to the relative weakness of the overlapping of the C (2p) and S (3s) orbitals to carbon-sulfur double bond, (C=S+R,) of thiol ester when compared with (C=O+R) in carboxylic esters, the α-hydrogen acidity is enhanced and processes like enolate formation and Claisen condensation are favored. They are mild acyl transfer agents that undergo transesterification reactions with various heteronucleophiles. They can be transformed into ketones and has been utilized in the total synthesis of natural products like fuligorubin.^{24} Recently application of this functional group has been extended into the synthesis of proteins by chemical legation of benzyl thiolesters^{25} and as a latent carboxylic acid in the macrolactonization applicable to the dilactonic pyrrolizidine alkaloids.^{26}
Inspite of the wide utility of β-oxothiolcarboxylates in organic synthesis, there are only limited methods available in the literature for their synthesis. An economically and environmentally viable method for the synthesis of this molecule is still desirable. Our research group has recently developed a new synthesis of β-oxothiolesters from α-oxoketene dithioacetals.\textsuperscript{27} The conventional ways to prepare thiolester 15 in fair to good yields include the reaction of acid chlorides 14 with thallous 2-methylpropane-2-thiolate (Scheme 2).\textsuperscript{28}

![Scheme 2]

Thiolesters 17 were prepared in good yields by reacting thioacetylenes 16 with \textit{p}-toluenesulfonic or trifluoroacetic acid in dichloromethane in the presence of silica (Scheme 3).\textsuperscript{29}

![Scheme 3]

Recently palladium catalyzed thiocarbonylation of prochiral 1,3-conjugated dienes 18 with thiols and carbon monoxide has been developed as an efficient method for the synthesis of optically active β,γ-unsaturated thiolesters 19 (Scheme 4).\textsuperscript{30} Using a similar approach the same group has successfully thiocarbonylated enynes, allenes with thiols to afford thiolesters.\textsuperscript{31}
Aldehydes 20 were converted into thiolesters 21 by a Tishchenko-type reaction using diisobutylaluminium chalcogenoate (Scheme 5). The method is effective for the synthesis of thiolesters from aromatic as well as aliphatic aldehydes except pivalaldehyde. In another approach \( \alpha \)-oxotrithioorthoesters generated from methyl carboxylate in presence of NBS in THF or HgO in aqueous HBF₄ in THF afforded \( \alpha \)-oxothiolcarboxylates.

\[ \text{Scheme 5} \]

\[ \begin{align*}
& \text{PhCHO} \\
\rightarrow & \text{Bu₂AlSBn} \\
& \text{PhC(}=\text{S})(\text{SBn})
\end{align*} \]

\( \beta \)-Ketothioesters have got a distinct advantage over simple thiolesters as synthons owing to the presence of multiple reactive sites. In spite of the wide utility of \( \beta \)-ketothioesters in organic synthesis, there are only limited methods available in the literature for their synthesis. Synthesis of \( \beta \)-ketothioester usually starts with another thioester. Ethyl acetothiolacetate 23 has been prepared in low yield by the self-condensation of ethyl thiolacetate 22 in presence of sodium (Scheme 6).

\[ \text{Scheme 6} \]

\[ \begin{align*}
& \text{CH₃C}(\text{S})\text{C₂H₅} \\
\rightarrow & \text{Base} \\
& \text{CH₃C}(\text{S})\text{C₂H₅}
\end{align*} \]
Similar reaction was studied by Wilson and Hess\textsuperscript{36} under different conditions and has shown that best results could be obtained when isopropyl magnesium chloride or magnesium chloroethyl mercaptide was used as the base. This method has limited practical utility as a method for the preparation of \(\beta\)-dithiolesters, since thiolesters do not undergo clean crossed Claisen condensations. \(\beta\)-Ketothiolesters 26 are formed by the addition of enolates derived from ketones 24 to acylating agents such as S,S-dimethyl dithiocarbonate 25.\textsuperscript{17}

![Scheme 7](image1)

Diketene 27 can be converted into \(\beta\)-ketobromothiolester 28 by bromination followed by treatment with butanethiol in 73% yield (Scheme 8).\textsuperscript{38}

![Scheme 8](image2)

The same product was prepared in 76% yield by acylation of Meldrum’s acid 29 with bromoacetyl bromide 30 followed by reaction of t-butanethiol.\textsuperscript{39} The bromothiolester 28 was used in the preparation of t-butyl-4-diethyl phosphono-3-oxobutanethiote 31 (Scheme 9),\textsuperscript{40} a valuable reagent for Wittig-Homer reaction.

![Scheme 9](image3)
The phosphono-3-oxobutanethioate \( \text{32} \) was used by Ley and Woodward for the synthesis of \( \gamma,\delta \)-unsaturated \( \beta \)-ketothiolesters \( \text{33} \) by Wittig-Horner reaction (Scheme 10).\(^{11}\) The compound finds application in the total synthesis of natural products.\(^{42}\)

![Scheme 10](image)

**3.4 Results and Discussion**

Solid-supported reagents have been utilized for a large number of diverse and interesting chemical manipulations. One of the main difficulties encountered by a synthetic chemist while developing a supported reagent is the time needed to synthesize the expensive polymer backbones. If we utilize commercially available polymer supports for developing new reagents, then it will be economic as well as time saving. Thus we have brominated the commercially available polyvinylpyrrolidene (PVP) and the resulting polymer supported bromine reagent (PVP-Br\(_2\)) was utilized for the efficient conversion of \( \alpha \)-oxoketene dithioacetals to \( \beta \)-oxothiolesters.

**3.4.1 Partial hydrolysis of \( \alpha \)-oxoketenedithioacetals to thiolesters using bromine complexed on polyvinyl pyrrolidone**

Bromine is \( \text{CCl}_4 \) was added to commercially available polyvinyl pyrrolidone taken in \( \text{CCl}_4 \) and kept at room temperature for 4 h. The resulting polymer supported bromine reagent was filtered and excess bromine was evaporated by aeration and kept in an airtight bottle. When aroylketenedithioacetals \( \text{34} \) prepared from substituted acetophenones were allowed to react with four equivalents of the reagent based on bromine capacity of the resin in chloroform at 60 °C for 3-4 h with occasional shaking, the corresponding thiolesters \( \text{35} \) were obtained in
excellent yield. Thus α-oxoketene dithioacetal 34a, prepared from acetophenone was heated with the resin in chloroform and after the completion of the reaction, as indicated by the TLC, the reaction mixture was cooled and filtered. The resin was washed with chloroform and the filtrate together with the chloroform washings were evaporated under vacuum to get β-ketothiolester 35a as a pale yellow liquid. This on further purification by filtering through a short column packed with silica gel using hexane to afford the thiolester in 80% yield. The structure of the compound has been confirmed by comparing its IR, 1H NMR, 13C NMR and MS data with that already reported in literature.27

We have compared the efficiency of the commercially available non-cross linked polyvinyl pyrrolidone (PVP) with co polymers of pyrrolidone for the above transformation. Different polymers of N-vinyl pyrrolidone having 2% cross-linking agents like hexanediol diacrylate (HDODA), tetraethyleneglycol diacrylate (TTEGDA), N,N'-methylene-bis-acrylamide (NNMBA) and divinylbenzene (DVB) were selected for the study. These polymers were prepared by suspension polymerization. The microporous polymer beads (200-300 mesh) were treated with bromine in CCl4 after swelling in the same solvent for 2h. The polymer bromine complex formed was filtered and excess bromine was removed by aeration. The bromine capacity, given in Table 1, of these reagents was estimated following the Schoeniger method43 in which 50 mg of the complex was added to ice-cooled dimethylformamide and 1 g of potassium iodide was added to the suspension. The liberated iodine was titrated with 0.5 N sodium thiosulphate solution. The bromine capacity of each polymer depends on their swelling properties which in turn depends on nature of cross linking agent used. Thus more hydrophobic DVB cross-linked resin showed least efficiency and HDODA cross linked resin showed maximum efficiency in adsorbing bromine.

When the ketene dithioacetal derived from acetophenone 34a was treated with polyvinylpyrrolidone-bromine complexes having various cross-
linking agents, the corresponding thiolester 35a was formed in excellent yields. The efficiency of different polymer bromine complexes for converting ketene dithiocetal 34a to 35a are also summarized in Table 1. The result shows a linear relationship between bromine capacity of the polymer and their efficiency for converting 1a to 2a.

**Table 1:** Effect of different cross linking agents on brominated vinyl pyrrolidone polymers for converting 34a to 35a

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Cross linking agent used</th>
<th>Bromine Capacity (mmol/gm)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HDODA</td>
<td>5.1</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>TTEGDA</td>
<td>4.9</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>NNMBBA</td>
<td>4.8</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>DVB</td>
<td>3.3</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>Non Cross linked</td>
<td>4.5</td>
<td>80</td>
</tr>
</tbody>
</table>

Comparing the efficiencies of non-crosslinked polyvinylpyrrolidone bromine complex with cross-linked ones, there is little difference in their efficiencies for the partial hydrolysis of ketene dithiaoactals. Therefore we have used bromine complex of the commercially available less expensive polyvinyl pyrrolidone(PVP-Br2) for the conversion of other substituted ketene dithiaoactals to the corresponding thiolesters. The reaction was found to be general for other substituted benzoylketene dithiaoactals 34b-e giving the corresponding β-oxothiolesters (35b-e) in excellent yields (Scheme 11). The compounds were characterized by comparing their spectral data with literature reports.27
The acylketene dithioacetals prepared from aliphatic acyclic ketones 36a-f (Scheme 12) also underwent partial hydrolysis leading to the formation of thiolesters effectively. Thus, the acylketene dithioacetal 36a prepared from ethyl methyl ketone on treatment with PVP-Br<sub>2</sub> complex in chloroform and heated at 60 °C for 3 h followed by filtering through a short silica column affords the thiolester 37a in 95% yield as pale yellow liquid.

<table>
<thead>
<tr>
<th>Product 37</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>95</td>
</tr>
<tr>
<td>b</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>92</td>
</tr>
<tr>
<td>c</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>88</td>
</tr>
<tr>
<td>d</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>98</td>
</tr>
<tr>
<td>e</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>93</td>
</tr>
<tr>
<td>f</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CO</td>
<td>90</td>
</tr>
</tbody>
</table>
The thiolester 37a was characterized by spectral data. Proton NMR spectrum of 37a (300 MHz, CDCl₃, Fig. 1) shows a three proton doublet at δ 3.39 with a coupling constant 7 Hz corresponding to methyl group. A three-proton singlet at δ 2.23 ppm is due to methyl sulfanyl group and another three proton singlet at δ 2.35 ppm corresponds to the acetyl protons. A one proton quartet at 3.76 ppm with a coupling constant 7 Hz is due to methynic proton.

The structure was further confirmed by ¹³C NMR spectrum. The ¹³C spectrum of 37a (75.4 MHz, CDCl₃, Fig. 2) shows peaks at δ 11.65 and at δ 13.29 corresponds to methylthio group and methyl group adjacent to methynic carbon respectively. The peak at δ 28.12 ppm is due to methyl carbon adjacent to carbonyl group and that at δ 61.69 ppm is due to the methynic carbon. The thiolester carbonyl carbon appears at δ 196.80 ppm and the acetyl carbonyl appears at δ 202.35. The mass spectrum (EIMS, Fig 3) shows molecular ion peak at m/z 146. Other prominent peaks are at 129, 97, 83, 57 and 55.

Figure 1 ¹H NMR (300 MHz, CDCl₃) Spectrum of Compound 37a
Thiolesters 37b-f was generated by the partial hydrolysis of the corresponding ketene dithioacetals 36 on reaction with the PVP-Br₂ resin under similar conditions as pale yellow liquids in 88-92% yields. All new compounds were characterized with the help of spectral data and the details are given in the
experimental section. Attempts to synthesize thiol ester from cinnamoyl ketene dithioacetal also afforded an unstable yellow solid.

3.4.2 Deprotection of dithioacetals and dithioketals

As an extension of the previous work on partial hydrolysis of ketene dithioacetals, we have treated the protected formyl ketene dithioacetal derived from α-formyl acetophenone ketenedithioacetal with four fold excess of PVP bromine complex in chloroform. We expected that the formyl group will remain protected and the ketendithioacetal moiety would undergo partial hydrolysis. Surprisingly by treatment of protected α-formyl ketene dithioacetal gave the parent aldehyde on treatment with PVP-Br₂. This motivated us to examine whether bromine complexed polymer reagent is effective for the deprotection of dithioacetals and dithioketals.

Carbonyl group protection from nucleophilic attack is an important process during many multi step synthetic transformations. Cyclic thioacetals and ketals have been widely used as carbonyl protecting group because of their stability under acidic and basic conditions and the ease of their introduction and removal. Numerous methods have been developed for the cleavage of thioacetals and ketals to the parent carbonyl derivatives. These include hydrolysis in the presence of different transition-metal ions, oxidation of sulfur to a higher oxidation state, hydrolysis and use of alkylating agents. Thioacetals have been deprotected by the combined use of molecular oxygen and catalytic amounts of Bi(NO₃)₃.5H₂O. Non-metallic reagents such as trimethylloxonium tetrafluoroborate, trifluorosulphonate and oxides of nitrogen have also been used for deprotection. Different naturally occurring clay supported reagents have recently gained considerable attention as a reagent for the cleavage of thioacetals and ketals because of its selectivity to the functional group and economical, practical and recent environmental demands. Natural kaolinitic clay has been utilized by Bandgar et al. for the selective cleavage of thioacetals, under solventless conditions. Due to its
specific activity in the regeneration of aldehydes, the methodology is useful for the chemoselective removal of a thioacetal in the presence of a thiol (Scheme 13). Phenolic, methylenedioxy, and methoxy groups tolerate the reaction conditions.\(^5\)

![Scheme 13](image)

Clay supported nitrates have been successfully utilized to cleave cyclic and acyclic thioacetal derived from aldehydes and ketones. Clayfen was employed by Varma et al. to deprotect thioacetal derivatives 40 under solvent-free conditions and with the help of microwaves. Only draw back is substrates having free phenolic moieties undergo some ring nitration (Scheme 14).\(^5\)

![Scheme 14](image)

Clayan was also reported by Meshram to be good catalyst/reagent for this deprotection reaction, carried out in dichloromethane\(^5\) or under solventless conditions using microwave irradiation.\(^6\) Although both methods tolerate common groups such as esters and ethers, they fails in the selective cleavage of thioacetals in the presence of acetonides.

An oxidant like metal nitrates supported on silica gel has been widely used by several groups for the thioacetals deprotection. Thus SiO\(_2\)/Cu(NO\(_3\))\(_2\)\(^7\)
or SiO₂·Fe(NO₃)₃⁵⁸ reagent combination regenerates the corresponding ketones 43 and aldehydes from 1,3-dithiolanes 42 and 1,3-dithianes (Scheme 15).

![Scheme 15](image)

Similarly, the reagent combinations like oxone on alumina⁵⁹ or dimethyl sulfoxide and silica gel chloride⁶⁰ also affords aldehydes from thioacetals. The development of newer methodologies for dethioacetalization process is still an active area of research as evident by the increasing number of publications found in recent literature.⁴⁴

As an extension of the previous work on partial hydrolysis of ketene dithioacetals, we have treated the protected formyl ketene dithioacetal 45 derived from 44 with PVP bromine complex in chloroform. Surprisingly the expected thiolester 46 was not formed. From spectral and analytical data the structure of the product was confirmed to be α-formyl ketene dithioacetal 45 (Scheme 16).

![Scheme 16](image)

This observation motivated us to further investigate the utility of the reagent as dethioacetalizing agent. We have prepared different cyclic thioacetals and ketals from the respective aldehydes and ketones by reacting it with 1,2-ethane dithiol in presence of catalytic amount of TiCl₄. Initially benzaldehyde dithioacetal deprotection was studied as a model experiment. The
dithioacetal was treated with four-fold excess of PVP-Br₂ reagent in chloroform at 60 °C for 3 hours. TLC showed complete disappearance of the starting dithioacetal. GCMS analysis of the crude reaction mixture showed formation of benzaldehyde in 88% yield. We have further generalized the process by selecting dithioacetals derived from different substituted benzaldehydes. The results are summarized in Scheme 17.

Scheme 17

Further studies on deprotection process were conducted using dithioketals. Dithioketals derived from acetophenone and p-bromoacetophenone were studied. The reagent was found to be less efficient for the deprotection of dithioketals.
3.4.3 Bromine in N-methyl 2-pyrrolidone: a new selective brominating reagent

After the studies on bromine complexes on polyvinylpyrrolidone for the partial hydrolysis of \( \alpha \)-oxoketenedithioacetals to thioesters, we examined the behavior of bromine complexed to N-methyl pyrrolidone itself. Bromine is a highly versatile reagent, which can undergo wide variety of reactions like addition, substitution \textit{etc.} and the selectivity depends on the reaction conditions and the brominating reagent used. Selective bromination at a particular reaction sight in presence of other reactive centers without any protection or deprotection is a challenging goal in many synthetic programs. The bromides thus generated are potential precursor for carbon-carbon bond forming reactions \textit{via} cross coupling reactions such as Heck, Suzuki, Stille \textit{etc.} leading to complex target molecules.

Treatment of aniline 49 with \( \eta \)-butyllithium and then trimethyltin chloride gave the tin amide (PhNH-SnMe\(_3\)) \textit{in situ}. Without isolation of the tin amide, reaction with bromine and workup with aqueous fluoride ion gave p-bromoaniline 50 in 76% yield, with no dibromoaniline or o-bromoaniline (Scheme 18). This constitutes a good general method for the regioselective bromination of aromatic amines.\(^6^1\)

\[
\text{49} \quad \text{1. n-BuLi, THF, -78 °C} \\
\text{2. R3SnCl, THF, -78 °C} \\
\text{3. Br2, -75 °C, rt} \\
\text{4. aqueous KF} \\
\text{76%} \\
\]

\textbf{Scheme 18}

\( \eta \)-Bromoalkanones were synthesized by the reaction of alkanones with hexamethylenetetramine-bromine complex and basic alumina in solvent free conditions under microwave irradiation.\(^6^2\) Reactions of mono-substituted aromatics of moderate activity with bromine in the presence of stoichiometric amounts of \textit{zeolite} NaY proceed in high yield and with high selectivity to the
corresponding para-bromo products. The zeolites can easily be regenerated by heating and can be reused. Furia and coworkers have reported that vanadium bromoperoxide catalyses the oxidation of bromide ion by hydrogen peroxide to a bromine equivalent intermediate which is useful in bromination reactions (Scheme 19).63

![Scheme 19]

Nucleophilic 1,2-addition of bromine by perbromide reagents was reported recently. Pyridinium perbromide (PPB) and trimethyl(phenyl) ammoniumperbromide (TMPAP) were used for mild and selective bromination of $\alpha,\beta$-unsaturated ketones 53. TMPAP has been used for addition of bromine selectively at $\alpha,\beta$-unsaturated carbonyl group even in the presence of other carbon-carbon double bonds affording 54 in good yields (Scheme 20).64

![Scheme 20]

Sekiya and co-workers developed 2-bromo-2-cyano-N,N-dimethyl acetamide (BCDA) as a brominating reagent. It brominates $\alpha$-carbon of ketone 55 with high selectivity of mono bromination affording 56 (Scheme 21).65

![Scheme 21]
NBS is used for allylic bromination in solvents such as CC\textsubscript{4} or CH\textsubscript{2}Cl\textsubscript{2} etc. and considered as a selective brominating agent. In presence of water NBS selectively oxidizes secondary alcohol. NBS has used in aqueous 1,2-dimethoxyethane for generation of HOBr. Pure NBS effects side chain oxidation of aromatic hydrocarbons. Some cases it is used fore decarboxylation of \(\alpha\)-amino acids and dicarboxylic acids. Z-Selective \(\beta\)-bromination of N-formyl \(\alpha,\beta\)-dehydro amino acid esters 57 was investigated by Nunami and coworkers (Scheme 22).\textsuperscript{56}

![Scheme 22](image)

Junjappa et al. have reported the bromination of \(\alpha\)-aryyl ketene-S,S-acetals 59 using N-bromosuccinimide (1.2 equiv.) as the brominating reagent. The bromination occurred at the \(\alpha\)-position of the ketenedithioacetal group afford 60 in high yields (Scheme 23).\textsuperscript{57}

![Scheme 23](image)

To gain an insight into the reaction of polyvinylpyrrolidone bromine complex, we have carried out the reaction of \(\alpha\)-oxoketene dithioacetals with N-methyl pyrrolidone bromine complex. The ketene dithioacetal (1 mmol) was dissolved in excess NMP (10 mL) containing bromine (1.1 mmol) and stirred at room temperature for 3 hours. Subsequent aqueous work up, extraction with diethyl ether and filtration through a short silica gel column using hexane
afforded a pale yellow oil in 95% yield (Scheme 24). This compound was identified as 2-bromo-3,3-bis(methylsulfanyl)-1-phenyl-2-propen-1-one 34a by comparing the spectral data with literature values. Ketene dithioacetal derived from substituted acetophenones also afforded the corresponding bromo derivatives 61b-e in excellent yields.

**Scheme 24**

\[
\begin{array}{c}
\text{Product 61} \\
\text{a} & \text{H} & 97 \\
\text{b} & \text{Cl} & 95 \\
\text{c} & \text{Br} & 98 \\
\text{d} & \text{Me} & 92 \\
\text{e} & \text{OMe} & 90
\end{array}
\]

We have extended the reaction to substituted 1,3-dithiolane 2-ylidenes 51 derived from substituted acetophenones. The reactions were examined with N-methyl pyrrolidone bromine complex. The reaction proceeded as expected to afford 1-bromo-1-(1,3-dithiolan-2-yliden)-1-aryl-1-ethanone 63 in excellent yields (Scheme 25).

**Scheme 25**

<table>
<thead>
<tr>
<th>Product 52</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>92</td>
</tr>
<tr>
<td>b</td>
<td>Cl</td>
<td>94</td>
</tr>
<tr>
<td>c</td>
<td>CH₃</td>
<td>90</td>
</tr>
</tbody>
</table>
A mechanism for the selective bromination of ketene dithioacetals in the presence of bromine in N-methyl pyrrolidone may be depicted as follows (Scheme 26).

![Scheme 26](image)

Thus we have developed a simple procedure and a new reagent for bromination and may substitute the expensive NBS for α-bromination of ketene dithioacetals as well as other bromination reactions. Our group is currently investigating the usefulness of this new reagent as a selective brominating agent.

3.5 Experimental

Melting points are uncorrected and were obtained on a Buchi-530 melting point apparatus. IR spectra were recorded on Shimadzu IR-470 spectrometer and the frequencies are reported in cm\(^{-1}\). Proton NMR spectra were recorded on a Bruker DRX-300 (300 MHz), Bruker WM 300 (300 MHz) or on a Bruker AMX 400 (400 MHz) spectrometer in CDCl\(_3\). Chemical shifts are expressed in parts per million downfield from internal tetramethyl silane. Coupling constants \(J\) are given in Hz. Electron impact mass spectra were obtained on a Finnigen-Mat 312 instrument and GCMS spectra were recorded in Shimadzu 5050 instrument.
All reagents were commercially available and were purified before use. The previously reported ketene dithioacetals were prepared by the known procedure and anhydrous sodium sulphate was used as drying agent. All purified compounds gave a single spot upon TLC analyses on silicagel 7GF using an ethyl acetate/hexane mixture as eluent. Iodine vapors or KMnO₄ solution in water was used as developing agent for TLC.

3.5.1 General procedure for the preparation of β-oxothiolcarboxylates 35 and 37

To the acylketene dithioacetal (5 mmol) dissolved in chloroform (50 mL), the bromine complexed resin (PVP-Br₂, 3.8 g, 20 mmol) was added followed by few drops of water. The mixture was kept at 60 °C for 2-4 h with occasional shaking. When the reaction was complete (TLC), the mixture was filtered and the reagent was washed with chloroform (3 x 10 mL). The combined organic layer was then washed with cold saturated sodium bicarbonate solution (2 x 30 mL) followed by water (2 x 50 mL). The filtrate together with the chloroform washings were evaporated under vacuum to afford β-ketothiolesters 35 or 37 which were further purified by passing through a short column packed with silicagel using hexane.

\[
\text{S-Methyl-3-oxo-3-phenylpropanethioate (35a)}
\]
Pale yellow liquid; Yield: 1.9 g (97%). Spectral data has been previously reported.²⁷

\[
\text{S-Methyl-3-oxo-3-(4-chlorophenyl)propanethioate (35b)}
\]
Pale yellow liquid; Yield: 2.1 g (95%). Spectral data has been previously reported.²⁷
S-Methyl-3-oxo-3-(4-bromophenyl)propanethioate (35c)
Pale yellow liquid; Yield: 2.4 g (92%), Spectral data has been previously reported.27

S-Methyl-3-oxo-3-(4-methylphenyl)propanethioate (35d)
Pale yellow liquid; Yield: 1.5 g (88%), Spectral data has been previously reported.27

S-Methyl-3-oxo-3-(4-methoxyphenyl)propanethioate (35e)
Pale yellow liquid; Yield: 1.8 g (91%), Spectral data has been previously reported.27

S-Methyl-2-methyl-3-oxobutanethioate (37a) Pale yellow liquid; Yield: 1.4 g (95%). 1H NMR (300 MHz, CDCl3) δ = 1.38 (d, 3H, J = 7 Hz, CH3CH), 2.23 (s, 3H, SCH3), 2.35 (s, 3H, CH3), 3.76 (q, 1H, J = 7 Hz, CH3CH); 13C NMR (75.47 MHz, CDCl3) δ = 11.70, 21.84, 28.12, 61.69, 196.80, 202.35 ppm.; EIMS m/z (%) 146 (M+, 15), 129 (27), 115 (18), 97 (69), 83 (82), 57 (88), 55 (100).

S-Methyl-2-methyl-3-oxopentanethioate (37b)
Pale yellow liquid, Yield: 1.5 g (96%). 1H NMR (300 MHz, CDCl3) δ = 1.37 (t, 3H, J = 7 Hz, CH3CH2), 2.33 (d, j = 7 Hz, 3H, CH3), 2.34 (s, 3H, SCH3), 2.57 (q, 2H, J = 7 Hz, CH2CH3), 3.76 (q, 1H, J = 7Hz, CH). 13C NMR (75.47 MHz, CDCl3) δ = 8.05, 12.32, 14.08, 35.12, 61.47, 198.42, 205.76 ppm. EIMS m/z (%) 160 (M+, 22), 131 (15), 113 (68), 104 (100), 75 (92), 57 (88).
S-Methyl-2-ethyl-3-oxohexanethioate (37c)  Pale yellow liquid; Yield: 1.7 g (96%). IR (neat) $\nu_{\text{max/cm}^{-1}} = 1697, 1667, 1595, 1448, 1169, 955$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta = 0.88$ (t, 3H, $J = 7$ Hz, $CH_3$), 0.99 (t, 3H, $J = 7$ Hz, $CH_3$), 1.66 (m, 2H, $CH_2$), 2.25 (m, 2H, $CH_2$), 2.34 (t, 2H, $CH_2$), 2.37 (s, 3H, SCH$_3$), 2.47 (t, 1H, $J = 7$ Hz, $CH$). $^{13}$C NMR (75.47 MHz, CDCl$_3$) $\delta = 9.72$ (SCH$_3$), 13.46 (CH$_3$), 13.96 (CH$_3$), 20.14, 22.63, 40.16, 43.76, 199.11 (carbonyl) and 225.71 (carbonyl) ppm. EIMS m/z (%) 188 (M$^+$, 17), 187 (32), 158 (28), 129 (29), 115 (22), 99 (48), 85 (100).

S-Methyl-3-oxobutanethioate (37d)

Pale yellow liquid; Yield: 1.2 g (95%). Spectral data has been previously reported.$^{27}$

S-Methyl-2-methyl-3-oxo-3-phenylpropanethioate (37e)

Pale yellow liquid; Yield: 1.8 g (93%). IR (neat) $\nu_{\text{max/cm}^{-1}} = 1725, 1626, 1456, 851$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta = 1.55$ (d, 3H, $J = 7$Hz, $CH_3CH$), 2.29 (s, 3H, SCH$_3$), 4.68 (q, 1H, $J = 7$ Hz, $CH_3CH$), 7.38-7.62 (m, 3H, aromatic), 7.99 (d, 2H, $J = 7$ Hz, aromatic); $^{13}$C NMR (75.47 MHz, CDCl$_3$) $\delta = 11.86, 13.72, 56.35, 128.01, 128.79, 131.24, 133.59, 194.87, 196.90$ ppm. EIMS m/z (%) 208 (M$^+$, 8), 191 (12), 161 (25), 149 (7), 105 (100).

S-Methyl-2-acetyl-3-oxobutanethioate (37f)

Pale yellow liquid; Yield: 1.5 g (90%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta = 2.13$ (s, 6H, $CH_3$), 2.72 (s, 3H, SCH$_3$). EIMS m/z (%) 175 (M$^+$+1, 22), 143 (34), 101 (99), 85 (25).
2-Benzoyl-3,3-bis(methylsulphonyl)acrylaldehyde 60
yellow colored oil. Yield: 2.4 g (98%). Spectral data has been previously reported.69

3.5.2 General procedure for the dethioacetalization

To the dithioacetal or dithioketal (10 mmol) dissolved in chloroform (50 ml.), the bromine complexed resin (PVP-Br₂), 40 mmol (7.5 g) was added followed by few drops of water. The mixture was kept at 60 °C for 3 h with occasional shaking. The reaction mixture was filtered and the reagent was washed with chloroform (3 x 10 mL). The combined organic layer was then washed with cold saturated sodium bicarbonate solution (2 x 30 mL) followed by water (2 x 50 mL). The filtrate together with the chloroform washings were evaporated under vacuum to afford the respective aldehydes or ketones which were further purified by passing through a short column packed with silica gel using hexane. The structures of known compounds were confirmed by comparing the analytical results with the reported values.

Benzaldehyde 48a yield 8.5 g (85%), bp 66 °C/12 Torr (reported bp, 62 °C/10 Torr).70

p-Chlorobenzaldehyde 48b yield 1.3 g (92%), mp 46-48 °C (reported mp 47 °C).70

p-Methoxybenzaldehyde 48c yield 1.2 g (90%), bp 133-135 °C/12 Torr (reported bp, 134-135 °C/12 Torr).70
3.5.3 Bromination of 3, 3-bis (methylsulfanyl)-1-aryl-2-propen-1-one

To an ice cold N-methylpyrrolidone (7 mL, 70.8 mmol), bromine (10 mmol) was added and stirred well for 5 min. The appropriate ketenedithioacetal (10 mmol) was added to it and stirring continued for further 0.5 h, allowing the temperature to come to room temperature during this period. The reaction mixture was then poured into ice-cold water, extracted with diethyl ether. The organic phase was washed with saturated sodium bicarbonate solution and dried over anhydrous Na2SO4. Evaporation of the solvent afforded the crude product which was further purified by column chromatography over silica gel using hexane ethyl acetate (9:1) as the eluent.

2-bromo-3,3-bis(methyl sulfanyl)-1-phenyl-2-propen-1-one 61a was obtained from by the reaction of 3, 3-bis (methylsulfanyl)-1-phenyl-2-propen-1-one (10 mmol) with bromine as brown oil; yield 2.9 g (97%). Spectral data has been previously reported.67
2-bromo-3,3-bis(methyl sulfanyl)-1-(4-chlorophenyl)-2-propen-1-one 61b was obtained by the reaction of 3, 3-bis (methyl sulfanyl)-1-(4-chlorophenyl)-2-propen-1-one (10 mmol) with bromine as pale yellow oil. Yield 3.2 g (95%). Spectral data has been previously reported.\(^6\)

2-bromo-3, 3-bis (methyl sulfanyl)-1-(4-bromo-phenyl)-2-propen-1-one 61c was obtained by the reaction of 3, 3-bis (methylsulfanyl)-1-(4-bromo-phenyl)-2-propen-1-one (10 mmol) as pale brown oil. Yield 3.7 g (98%). Spectral data has been previously reported.\(^6\)

2-bromo-3, 3-bis (methyl sulfanyl)-1-(4-methyl phenyl)-2-propen-1-one 61d was obtained by the reaction of 3, 3-bis (methyl sulfanyl)-1-(4-methyl phenyl)-2-propen-1-one (10 mmol) with bromine as pale yellow oil. Yield 2.9 g (92%). Spectral data has been previously reported.\(^6\)

2-bromo-3, 3 bis (methyl sulfanyl)-1-(4-methoxy phenyl)-2-propen-1-one 61e was obtained by the reaction of 3, 3-bis (methyl sulfanyl)-1-(4-methoxy phenyl)-2-propen-1-one (10 mmol) with bromine as brown oil. Yield 3 g (90%). Spectral data has been previously reported.\(^6\)

1-bromo-1-(1,3-dithiolan-2-yliden)-1-phenyl-1-ethanone 63a was obtained by the reaction of (1,3-dithiolan-2-yliden)-1-phenyl-1-ethanone (10 mmol) with bromine as pale brown oil. Yield 2.7 g (92%)

EIMS: (m/z, %) = 302(m+14), 300 (m+14), 272 (6), 224 (16), 196 (18), 105 (100).
2-bromo-2-(1,3-dithiolan-2-yliden)-1-(4-chloro phenyl)-1-ethanone \(63b\) was obtained by the reaction of (1,3-dithiolan-2-yliden)-1-(4-chloro phenyl)-1-ethanone (10 mmol) with bromine as pale yellow oil. Yield 3.1 g (94%). EIMS (m/z, %) = 336 (m+2, 32), 334 (m+, 20), 310 (6), 308 (16), 306 (15), 256 (10), 226 (6), 228(6), 222 (20), 224(27), 197 (8), 139 (89), 113 (32), 111 (100).

1-bromo-1-(1,3-dithiolan-2-yliden)-1-(4-methyl phenyl)-1-ethanone \(63c\) was obtained by the reaction of (1,3-dithiolan-2-yliden)-1-(4-methyl phenyl)-1-ethanone (10 mmol) with bromine as pale brown oil. Yield 2.8 g (90%). EIMS: (m/z, %) 316 (m+2, 16), 314 (m+, 16), 288 (12), 236 (23), 208 (21), 210 (7), 119 (91), 91 (100).

References


10 George, B.K.; Pillai, V.N.R. Macromolecules 1988, 21, 1867.


(b) Xiao, W. -J.; Vasapollo, G.; Alper, H.; J. Org. Chem. 1999, 64, 2080.


63 Conte, V; Furia, F. D; Moro, S. Tetrahedron lett. 1994, 35, 7429.


