Chapter 4

Studies on the Reactions of $\alpha$-Formylketene Dithioacetals with Hydroxylamine Hydrochloride: Synthesis of Three Different Isoxazoles

4.1 Introduction

Isoxazoles are a class of heterocyclic compounds having a remarkable number of applications and have been demonstrated as highly versatile building blocks for pharmaceutically active compounds.\(^1\) Isoxazoles possess a wide range of biological activities such as hypoglycemic, analgesic, anti-inflammatory, anti-bacterial and HIV-inhibitory activity. Therefore the substituted isoxazoles has been a focal point in medicinal chemistry over the years. Some isoxazole derivatives display agrochemical properties, namely herbicidal and soil fungicidal activities and have applications as pesticides and insecticides.\(^2\) Isoxaflutole, an isoxazole derivative of trifluoromethylphenyl ketone is developed for the selective pre-emergence control of both grass and broad-leaved weeds in maize and sugar cane. Isoxazoles have also been used as dyes, electric insulating oils, high temperature lubricants etc., while polyisoxazoles have applications as semiconductors.\(^3\) Muscimol A and Ibotenic acid B are two psychoactive constituents of the mushrooms Amanita muscaria and A. pantherina. They belong to a group of 3-hydroxyisoxazoles that are known to display remarkable central nervous system (CNS) activity.\(^4\)

\[ \text{Isoxaflutole} \quad \text{Muscimol A} \quad \text{Ibotenic acid} \]
The key feature of these heterocycles is that they possess the typical properties of an aromatic system but contain a weak nitrogen-oxygen bond, which under certain reaction conditions, particularly in reducing or basic conditions, is a potential site of ring cleavage. The isoxazole ring has become a major tool as a masked enaminone or 1,3-diketone by cleavage of their weak N-O bond when the β-imino ketone functionality becomes obvious. Thus isoxazoles are very useful intermediates for the synthesis of heterocycles as the ring stability allows manipulation of substituents to give functionally complex derivatives, at the same time it is easily cleaved when necessary. The construction of the isoxazole ring can be achieved by either 1,3-dipolar cycloaddition of alkenes and alkynes with nitrile oxide or by the reaction of hydroxylamine with a three carbon atom component.

Junjappa et al have investigated in detail the reaction of hydroxylamine with α-oxoketene dithioacetals using different reaction conditions to afford alkylthio isoxazoles. In this chapter we summarize the important general methods for the synthesis of substituted isoxazoles. This brief review is followed by our work on the reaction of 2-aryl-3,3-bis(alkylsulfanyl) acrylaldehydes and hydroxylamine hydrochloride under different conditions to afford a variety of functionalized isoxazoles in good yields.

### 4.2 Isoxazoles: General Methods of Synthesis

In 1888 Claisen first reported a general synthesis of isoxazoles by the condensation-cyclization of 1,3-diketones with hydroxylamine which was further modified in 1962 by Quilico (Scheme 1).

$$\begin{array}{c}
\text{CH}_3\text{COCH}_2\text{COCH}_3 \quad \text{NH}_2\text{OH} \quad \text{H}_3\text{C} \quad \text{N} \quad \text{O} \quad \text{CH}_3
\end{array}$$

1 \rightarrow 2

Scheme 1

The above reaction, using unsymmetrical 1,3-diketone or their derivatives with hydroxylamine resulted in two possible isomeric
Isoxazoles 4 and 5 (Scheme 2) which reduced the yield of the reactions and in many cases the separation of the isomers was difficult. However the regiospecificity of the reaction could be controlled by the nature of substitutes R and R₁ or by controlling the pH of the reaction medium.⁹

\[
\text{RCOCH}_2\text{COR}^1 \xrightarrow{\text{NH}_2\text{OH}} \begin{array}{c}
\text{N} = \text{O} \\
\text{R} \quad \text{R}^1
\end{array} + \begin{array}{c}
\text{N} = \text{O} \\
\text{R}^1 \quad \text{R}
\end{array}
\]

Scheme 2

Norman et al observed that the regiospecificity was increased by the use of sodium acetate in the above reaction.¹⁰ Norman et al reported that the reaction of steroidal β-ketoaldehyde 6 with hydroxylamine hydrochloride in acetic acid afforded a mixture of 3- and 5- substituted isoxazoles 7 and 8, while the reaction in the presence of sodium acetate / acetic acid buffer provided exclusively the 5-substituted isomer 8 (Scheme 3).

\[
\begin{array}{c}
\text{RO} \\
\text{OH}
\end{array} \xrightarrow{\text{NH}_2\text{OH}} \begin{array}{c}
\text{RO} \\
\text{OH}
\end{array} + \begin{array}{c}
\text{RO} \\
\text{N} \quad \text{O}
\end{array}
\]

Scheme 3

Jones et al observed that an electron-withdrawing group such as ethoxycarbonyl at the α-carbon atom of ethoxyvinyl ketones enhanced the electrophilicity of the β-carbon atom and thus increasing the regiospecificity of the reaction. They treated 9 with hydroxylamine to afford exclusively 5-substituted isoxazole-4-carboxylates 10 (Scheme 4).¹¹

\[
\begin{array}{c}
\text{Et} \\
\text{COOEt}
\end{array} \xrightarrow{\text{NH}_2\text{OH}} \begin{array}{c}
\text{Et} \\
\text{N} \quad \text{O}
\end{array}
\]

Scheme 4
Functionalized ketene dithioacetals are good sources of substituted isoxazoles. Gompper and Topfl reported that conjugated ketene dithioacetals derived from active methylene compounds produced isoxazoles by the sequential substitution of one of the alkylthio groups by the amino group on the hydroxylamine followed by intramolecular addition of O-atom to the carbonyl group.\textsuperscript{12} Junjappa and Ila had prepared various isoxazoles regioselectively from ketene dithioacetals 11 by varying the substituents and pH of the reaction medium. They synthesized 3 or 5-alkylthio isoxazoles 12 or 13 selectively by changing the pH of the reaction medium (Scheme 5).\textsuperscript{13}

\begin{center}
\textbf{Scheme 5}
\end{center}

The reaction was extended to cinnamoylketene dithioacetals 14 and their enyl homologues to produce the expected regioisomers 15 and 16 (Scheme 6).\textsuperscript{14}
Asish De and coworkers also have reported regio-controlled preparation of isoxazoles from ketene dithioacetals. They synthesized 18 and 19 from ketene dithioacetal 17 by the treatment of 17 with hydroxylamine hydrochloride at different pH of the reaction medium (Scheme 7).  

![Scheme 7](image)

Rudorf and Augustin prepared isoxazoles 21 by the reaction of cyano-α-oxoketene dithioacetals 20 and hydroxylamine using calcium hydroxide as base (Scheme 8).  

![Scheme 8](image)

Mellor et al reported the synthesis of isoxazole-4-carboxaldehyde 25 from cyclic ketene dithioacetals. The dithioacetal 22 was reduced to the diketone 23 with magnesium in methanol, which was reacted with hydroxylamine hydrochloride to afford isoxazole derivative 24, which on deprotection with N-bromosuccinimide to give isoxazole-4-carbaldehyde 25 (Scheme 9).
Li et al synthesized isoxazolylimidazoles 27 and 28 by cyclo-condensation of α-oxo-β-imidazolylketene dithioacetal 26 with hydroxylamine using barium hydroxide as base (Scheme 10).¹⁸

Petrillo et al cyclized, vinyloximes 30 obtained from the reduction of 4-aryl-1,1-bis(methylthio)-3-nitro-1,3-butadienes 29 to isoxazoles 31, making use of an acidic ion-exchange resin as catalyst (Scheme 11).¹⁹

Junjappa and co workers prepared substituted isoxazoles 33 and 34 that have a masked aldehyde functionality from 1,1-bis(methoxy)-4,4-bis(methylsulfanyl)-3-buten-2-one 32 by cyclocondensation with hydroxylamine (Scheme 12).²⁰
The results of our work on the synthesis of different isoxazoles from 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes are described below.

### 4.3 Results and Discussion

The 1,3-dipolar addition reaction of asymmetric bifunctional heteronucleophiles like hydroxylamine with 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes could generate various isomeric heterocycles due to the difference in the electrophilicities of the different centers in the 3 carbon unit. Varying the substrate-reagent stoichiometry and temperature of the reaction medium, we could synthesize three different isoxazoles like (aryl)[5-(methylsulfanyl)-4-isoxazolyl]methanones 36, 3-(methylsulfanyl)-5-phenyl-4-isoxazolecarbonitriles 37 and 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oximes 38 in good yields (Scheme 13).
4.3.1 Synthesis of \([5-(methylsulfanyl)-4-isoxazolyl(aryl)]methanones from 2-aroyl-3,3-bis(alkylsulfanyl) acrylaldehydes\)

Treatment of 2-benzoyl-3,3-bis(alkylsulfanyl)acrylaldehyde \(35\) with one equivalent of hydroxylamine hydrochloride in the presence of 2 equivalents of \(K_2CO_3\) in acetonitrile at 60 °C gave \([5-(methylsulfanyl)-4-isoxazolyl](phenyl) methanone \(36e\) in 65% yield. The reaction was extended to other substituted acrylaldehydes to get corresponding isoxazoles in 50-90 % yields (Scheme 14).

In order to examine the effect of pH on the product formation, the 3,3-bis(methylsulfanyl)-2-(4-methoxybenzoyl)acrylaldehyde \(35b\) was treated with one equivalent of hydroxylamine hydrochloride and 2 equivalents of \(K_2CO_3\) in methanol and water at room temperature. The reaction mixture was acidified with glacial acetic acid to attain a pH 2-3 and then the mixture was refluxed for 5h. The product formed in this reaction was (4-methoxyphenyl)[5-(methylsulfanyl)-4-isoxazolyl] methanone \(36b\), same as the one in the former method. The later reaction proved that pH change had little effect on the nature of the product formed in the reaction between 2-benzoyl-3,3-bis(alkylsulfanyl)acrylaldehyde and one equivalent of hydroxylamine hydrochloride.

![Scheme 14](image-url)
The FABMS (Figure 1) of 36a shows the molecular ion peak at m/z = 254 and 255 corresponding to a molecular formula C_{11}H_8ClNO_2S. The IR spectrum (Figure 2) of 36a shown absorbance at 1677 cm\(^{-1}\) due to carbonyl group. The \(^1\)H NMR spectrum of the compound (Figure 3) reveals a singlet at δ 2.47 for SMe group, two multiplets at δ 7.45 - 7.50 and δ 8.02 - 8.07 for phenyl protons and a sharp singlet at δ 8.69 for one proton of the isoxazole ring. The \(^{13}\)C NMR spectrum (Figure 4) of 36a shows resonance at δ 11.9 due to SMe, δ 115.7 due to 4C of isoxazole, δ 124.46, 129.0, 130.2 and 138.2 due phenyl carbons, two signals at δ 150.4 and 168.1 due to 3C and 5C of isoxazole ring and at δ 184.10 due to the carbonyl carbon. Analysis; Calculated: C, 52.08; H, 3.18; N, 5.52; S, 12.61; Found: C, 52.3; H 3.2; N, 5.68; S, 12.79.

Fig 1  FABMS Spectrum of (4-chlorophenyl)[5-(methylsulfanyl)-4-isoxazolyl]methanone 36a
**Fig-2** IR Spectrum of (4-chlorophenyl)[5-(methylsulfanyl)-4-isoxazolyl]methanone 36a

**Fig-3** $^1$H NMR Spectrum of (4-chlorophenyl)[5-(methylsulfanyl)-4-isoxazolyl]methanone 36a
4.3.2. Synthesis of 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbonitriles from 2-arylo-3,3-bis(alkylsulfanyl)acrylaldehydes

Treatment of 2-arylo-3,3-(alkylsulfanyl)acrylaldehydes 35 with 2 equivalents of hydroxylamine hydrochloride in acetonitrile at 85 °C for 10 h. We were curious to know whether the keto carbonyl group would involve in the reaction leading to the formation of isoxazoloisoxazoles. Although both the carbonyl groups in the acrylaldehydes were reactive towards hydroxylamine, the product formed suggested that after the aldoxime formation, a \(N,S\)-acetal intermediate was formed by a second molecule of hydroxylamine. This intermediate underwent cyclization reaction with the second carbonyl group producing an isoxazole oxime 38. This isoxazole
Isoxazoles

oxime eliminated a water molecule at 85 °C to afford 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbonitriles 37 in 30 - 56% yields (Scheme 15).

\[
\begin{array}{cccc}
35 & 2\text{NH}_2\text{OH}.\text{HCl} / 4\text{K}_2\text{CO}_3./\text{CH}_3\text{CN} & \text{Heat} 85\,^\circ\text{C}, 10\text{h} & 37 \\
\end{array}
\]

<table>
<thead>
<tr>
<th>35, 37</th>
<th>R</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>4-CH₃</td>
<td>43</td>
</tr>
<tr>
<td>b</td>
<td>4-H</td>
<td>30</td>
</tr>
<tr>
<td>c</td>
<td>4-Br</td>
<td>56</td>
</tr>
<tr>
<td>d</td>
<td>4-OCH₃</td>
<td>41</td>
</tr>
</tbody>
</table>

**Scheme-15**

The EIMS spectrum of 37a (Figure 5) shows molecular ion peak at 231 corresponding to 5-(4-methylphenyl)-3-(methylsulfanyl)-4-isoxazolecarbonitrile having molecular formula C₁₂H₁₀N₂O₅S. In the IR spectrum of 37a peak due to the nitrile group is visible at 2229 cm⁻¹ (Figure 6). ¹H NMR spectrum (Figure 7) of 37a has a singlet of three protons at δ 2.44 due to methyl protons and another singlet at δ 2.67 for three protons of SMe, two doublets at δ 7.36 - 7.33 (J = 9 Hz) and δ 7.94 - 7.91 (J = 9 Hz) are due to phenyl protons. ¹³C NMR spectrum (Figure 8) of 37a further confirms the predicted structure. It shows resonance at δ 12.0 (SMe) and δ 21.5 (CH₃), δ 116.5 (CN), δ 126.8 (4C isoxazole), δ 127.7, δ 128.4 and δ 129.8, δ 144.7 due to phenyl carbons and δ 162.2 and δ 174.6 due to 3C and 5C of isoxazole ring. Analysis; Calculated: C, 61.09 %; H, 3.73 %; N, 12.95 %; S, 14.83 %. Found: C, 61.68 %; H, 3.53 %; N, 13.08 %; S, 14.00 %. All the data supported the predicted structure for 37a as 3-(methylsulfanyl)-5-phenyl-4-isoxazolecarbonitrile.
Fig 5  Electrospray MS spectrum of 5-(4-methylphenyl)-3-(methylsulfanyl)-4-isoxazolecarbonitrile 37a

Fig 6  IR Spectrum of 5-(4-methylphenyl)-3-(methylsulfanyl)-4-isoxazolecarbonitrile 37a
Fig 7 $^1$H NMR Spectrum of 5-(4-methylphenyl)-3-(methylsulfanyl)-4-isoxazolecarbonitrile 37a

Fig 8 $^{13}$C NMR of 5-(4-methylphenyl)-3-(methylsulfanyl)-4-isoxazolecarbonitrile 37a
4.3.3 Synthesis of 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oximes from 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes

In order to get the expected isoxazoloisoxazoles in the above reaction, we have to prevent the dehydration reaction of 38. In order to accomplish this, the 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes 35 were treated with 2 equivalents of hydroxylamine hydrochloride in the presence of 4 equivalents of potassium carbonate in acetonitrile at room temperature for 10h. The reaction afforded only 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oximes 38 in 22-54% yields (Scheme 16). As in the case of pyrimidines, in this case also the stability of the molecules 38 prevented the annulation reaction to produce isoxazoloisoxazoles.

\[
\begin{align*}
\text{R} & | \text{Yield} \\
\hline
\text{35, 38} & |	ext{35, 38} & \text{R} & \text{Yield} \\
\hline
\text{a} & 4-\text{CH}_3 & 54 \\
\text{b} & 4-\text{Br} & 43 \\
\text{c} & 4-\text{OCH}_3 & 22 \\
\text{d} & 4-\text{H} & 42 \\
\end{align*}
\]

Scheme 16

The FABMS (Figure 9) of 5-(4-methylphenyl)-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oxime 38a shows the molecular ion peak at 249 corresponding to C_{12}H_{12}N_{2}O_{2}S. IR spectrum (Figure 10) of 38a shows a broad peak at 3339 cm^{-1} corresponding to oxime OH and a sharp peak at 937 cm^{-1} due to N-O stretching vibration of oxime. No prominent peak for
carbonyl grouping the IR spectrum. \(^1\)H NMR spectrum (CDCl\(_3\)) (Figure 11) of 38a shows two singlets at \(\delta\) 2.43 and \(\delta\) 2.63 for CH\(_3\) protons and SCH\(_3\) protons respectively. The aromatic protons shown resonance at \(\delta\) 7.31 - 7.34 and \(\delta\) 7.54 - 7.77 as multiplets. The two singlets at \(\delta\) 7.65 and \(\delta\) 8.23 are attributed to aldoxime and -OH protons respectively.

**Fig 9** FABMS of 5-(4-methylphenyl)-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oxime 38a

**Fig 10** IR Spectrum of 5-(4-methylphenyl)-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oxime 38a
Fig 11  $^1$H NMR Spectrum of 5-(4-methylphenyl)-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oxime 38a

4.3.4 Mechanisms for the formation of substituted isoxazoles from 2-aryle-3,3-bis(alkylsulfanyl)acrylaldehydes

Generally the reaction of asymmetric bifunctional heteronucleophiles like hydroxylamine with $\alpha$-oxoketene dithioacetals 39 generates two regioisomic heterocycles 40 and 41 depending on the electrophilicities of the 1 and 3-carbon centers of the dithioacetals, the nucleophilicities of the heteroatoms in the bifunctional nucleophiles and the pH of the reaction medium (Scheme 17).21
Junjappa et al have investigated in detail the reaction of hydroxylamine with α-oxoketene dithioacetals using different reaction conditions to afford highly regioselective 3 or 5 alkylthio isoxazoles in high yield. They have ascertained the actual structures of isoxazoles prepared from acylketene-O,S-acetals from their mass spectral data (Scheme 18). The structure of isoxazole 43 was confirmed from its mass spectral data which showed the base peak at m/z = 144 (100%) and another peak at m/z = 116 (50%) along with the molecular ion peak m/z = 175 (M⁺). The two peaks at m/z = 144 and 116 were assigned to (M⁺-OMe) and (M⁺- CO₂Me), suggesting that the methoxy group is adjacent to the ring oxygen atom. In another reaction also Junjappa et al ascertained the formation of 3-cyclopropyl and 5-cyclopropyl isoxazoles from their mass spectral data. They were able to confirm the structures of the two isomers from the mass spectral fragmentation pattern arising from the loss of the substituents at the 5-position of the isoxazole ring. Similar inferences have been drawn by Hauser et al and Bowie and coworkers for establishing the structures of the two regio isomers of isoxazoles.
Based on the above observations and on the detailed study of the analytical data, we suggest the following mechanisms for the formation of different isoxazoles.

4.3.5. **Mechanism for the formation of (aryl)[5-(methylsulfanyl)-4-isoxazolyl]methanones**

When 2-arylo-3,3-bis(alkylsulfanyl)acrylaldehydes were treated with one equivalent of hydroxylamine hydrochloride at 60 °C, the amino group on the hydroxylamine reacted with the more reactive aldehyde group in order to form the corresponding aldoxime intermediate 44. An intramolecular conjugate addition reaction of the hydroxyl group on the aldoxime to the ketene dithioacetal moiety followed by the elimination of an alkylsulfanyl group resulted in the formation of (aryl)[5-(methylsulfanyl)-4-isoxazolyl]methanones 36 (Scheme 19). The FABMS of 36a (Fig 1), proved the SMe group at the 5th position in the isoxazole ring. (M⁺) peak at 254 and (M⁺ - SMe) at 206.

![Scheme 19]

4.3.6 **Mechanism for the formation of 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbonitriles and 5-Aryl-3-(methylsulfanyl)-4-isoxazolcarbaldehyde oximes**

5-Aryl-3-(methylsulfanyl)-4-isoxazolecarbonitriles 37 were formed by the reaction of 2-arylo-3,3-bis(alkylsulfanyl)acrylaldehydes with 2 equivalents
of hydroxylamine hydrochloride in acetonitrile at 85 °C. Under this reaction condition the aldoxime intermediate 44 undergoes conjugate addition-substitution reaction with the second molecule of hydroxylamine to produce 47 prior to the intramolecular cyclization. Once the intermediate 47 is formed the stereochemistry of the molecule may be more favorable for the cyclization involving the benzyol group present in the aldoxime to get 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oximes 38. At a higher temperature the 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oximes underwent a dehydration reaction to afford 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbonitriles 37 (Scheme 20). The spectral values were also in agreement with the proposed structure.

The proposed mechanism was further supported by the isolation of the intermediate 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oximes 38 by treating 2-aryloyl-3,3-bis(alkylsulfanyl)acrylaldehydes with 2 equivalents of hydroxylamine hydrochloride in acetonitrile at room temperature.

![Scheme-20](image)

**4.4 Conclusion**

In this chapter we have described general facile methods for the regioselective synthesis of various isoxazoles from α-formylketene dithioacetals. 5-Alkylthio isoxazoles 36 with a benzyol substitution further
enhances their synthetic potential. Moreover it is proved that 5-alkylthio isoxazoles have anthelmintic activity.\textsuperscript{25} The isoxazoles generated in the other two reactions \textbf{37} and \textbf{38} are also valuable precursors for new heterocyclic compounds. When we tried the regioselective synthesis of the other isomer of \textbf{36} [3-(methylsulfanyl)-4-isoxazolyl](aryl)methanones by changing the pH of the medium, we expected the protonation of the carbonyl group in acid medium preventing the initial oxime formation, as observed by Junjappa \textit{et al}.\textsuperscript{7} On the other hand no protonation of formyl group took place and the acid medium reaction also afforded the same product as \textbf{36}. In general, these convenient protocols are highly useful for the synthesis of different isoxazoles from a single starting compound, \(\alpha\)-formylketene dithioacetals.

\textbf{4.5. Experimental}

Melting points were determined on Buchi 530 melting point apparatus and were uncorrected. The IR spectra were on KBr pellets on a Schimadzu IR-470 spectrometer and the frequencies are reported in cm\(^{-1}\). The \(^1\)H NMR spectra were recorded on a Brucker WM (300 MHz) spectrometer using TMS as internal standard and CDCl\(_3\) or acetone-\(d_6\) as solvents. The \(^{13}\)C NMR spectra were recorded on a Brucker WM 300 (75.47 MHz) spectrometer using CDCl\(_3\) or acetone-\(d_6\) as solvent. Both \(^1\)H NMR and \(^{13}\)C NMR values are expressed as \(\delta\) (ppm). The CHN analyses were done on an Elementar VarioEL III Serial Number 11042022 instrument. The FAB mass spectra were recorded on a JOEL SX 102/DA-6000 Mass Spectrometer / Data System using Argon as the FAB gas. The EIMS spectra were recorded on a MICROMASS QUATTRO 11 triple quadrupole mass spectrometer. Anhydrous sodium sulfate was used as drying agent. All purified compounds gave a single spot upon TLC analyses on silica gel 7GF using an ethyl acetate / hexane mixture as eluent. Iodine vapors or KMnO\(_4\) solution in water was used for detecting spots on TLC.
All commercially available reagents were purified before use. The aroyl ketene dithioacetals and α-formylketene dithioacetals were prepared by the known procedure.\textsuperscript{26}

4.5.1. Synthesis of (Aryl)[5-(methylsulfanyl)-4-isoxazolyl]methanones from 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes

**General Procedure**

The appropriate 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehyde \textsuperscript{35} (2 mmol) was dissolved in acetonitrile (20 mL) at room temperature. To the above solution hydroxylamine hydrochloride (0.14 g, 2 mmol) followed by K\textsubscript{2}CO\textsubscript{3} (0.55 g, 4 mmol) were added and the reaction mixture was heated to 60 °C for 5 h. It was cooled and poured into ice-cold water. The semisolid obtained was extracted with ethyl acetate (3 x 25 mL), dried with anhydrous sodium sulfate and purified using column chromatography with hexane as the eluent. Recrystallized from hexane.

![Chemical Structure](image)

\textit{(4-Chlorophenyl)[5-methylsulfanyl]-4-isoxazolyl]methanone} was obtained from 3,3-bis(methylsulfanyl)-2-(4-chlorobenzoyl) acrylaldehyde by reacting with one equivalent hydroxylamine hydrochloride at 60 °C; yield 70\% (0.35 g); white solid; mp; 98 - 100 °C.; IR (KBr \textit{\nu}_{\text{max}}) = 1674, 1550, 1362 cm\textsuperscript{-1}; \textit{\textit{1}}H NMR (300 MHz, CDCl\textsubscript{3}) \textit{\delta} = 2.47 (s, 3H, SCH\textsubscript{3}), 7.45 - 7.50 (m, 2H, ArH), 8.02 - 8.06 (m, 2H, ArH), 8.69 (s, 1H, 3C isoxazole proton); \textit{\textit{13}}C NMR (75.47 MHz, CDCl\textsubscript{3}) \textit{\delta} = 11.9 (SCH\textsubscript{3}), 115.7 (4C isoxazole), 124.4 (4C ArH), 129.0 (3,3’C ArH), 130.2 (2, 2’ C ArH), 138.0 (1C ArH), 150.0 (3C isoxazole), 168.1 (5C isoxazole), 184. (CO) ppm; FABMS m/z (%): 254 (100), 206 (65), 165 (5), 107 (5); Anal. Calcd: C, 52.08; H, 3.18; N, 5.52; S, 12.64. Found: C, 52.3; H, 3.2; N, 5.68; S, 12.79.
(4-Methoxyphenyl)[5-methylsulfanyl]-4-isoxazolyl]

methanone was obtained from 3,3-bis(methylsulfanyl)-2-(4-methoxybenzoyl)acrylaldehyde by reacting with one equivalent hydroxylamine hydrochloride at 60 °C; yield 70% (0.35 g); white solid; mp: 100 - 102 °C; IR (KBr νmax) = 1658, 1608, 1515, 1263 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 2.41 (s, 3H, SCH₃), 3.78 (s, 3H, OMe), 6.929 - 6.9 (d, J = 8.7 Hz, 2H, ArH), 8.024 - 7.99 (d, J = 9Hz, 2H, ArH), 8.584 (s, 1H, 3CH isoxazole proton); ¹³C NMR (75.47 MHz, CDCl₃) δ = 11.7 (SCH₃), 55.3 (OMe), 114.4 (3,3’C ArH), 114.5 (4C isoxazole), 113.4 (1C ArH), 126.7 (2,2’C ArH), 150.4 (3C isoxazole), 163.4 (4C ArH), 169.1 (5C isoxazole), 184.0 (CO) ppm; FABMS m/z (%) 250 (100), 202 (95), 155 (50), 120 (45), 107 (50), 89 (45); Anal. Calcd: C, 57.82; H, 4.45; N, 5.62; S, 12.86. Found: C, 56.84; H, 4.65; N, 5.52; S, 12.15.

(3-Methoxyphenyl)[5-methylsulfanyl]-4-isoxazolyl]

methanone was obtained from 3,3-bis(methylsulfanyl)-2-(3-methoxybenzoyl)acrylaldehyde by reacting with one equivalent hydroxylamine hydrochloride at 60 °C; white solid; yield 65% (0.32 g); mp 80 – 82 °C; IR (KBr νmax) = 2930, 1658, 1566, 1473, 1296 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 2.47 (s, 3H, SCH₃), 3.88 (s, 3H, OMe), 7.07 (m, 1H , ArH), 7.38 (m, 1H, ArH), 7.64 - 7.67 (m, 2H, ArH), 8.69 (s, 1H, isoxazole); ¹³C NMR (75.47 MHz, CDCl₃) δ = 11.9 (SCH₃), 55.4 (OMe), 113.7 (4C isoxazole), 115.7 (2C ArH), 118.2 (4C ArH), 121.2 (6C ArH), 127.0 (5C ArH), 129.9 (1C ArH), 150.4 (3C isoxazole), 159.5 (3C ArH), 169.0 (5C isoxazole), 184.0 (CO) ppm; EIMS m/z (%) 250 (2), 202 (40), 135 (100), 107 (45), 102 (54); Anal. Calcd: C, 57.82; H, 4.45; N, 5.62; S, 12.86. Found: C, 57.87; H, 4.48; N, 5.61; S, 12.36.
(3,4-Dimethoxyphenyl)[5-methylsulfanyl]-4-isoxazolyl methanone was obtained from 3,3-bis(methylsulfanyl)-2-(3,4-dimethoxybenzoyl)acrylaldehyde by reacting with one equivalent hydroxyamine hydrochloride at 60 °C; yield 90% (0.5 g); white solid; mp: 80 - 82 °C. IR (KBr ν max) = 2935, 1662, 1604, 573, 1485, 1276 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 2.48 (s, 3H, SMe), 3.96 (s, 3H, OMe) and 3.98 (s, 3H, OMe), 6.99 - 6.96 (d, J = 9 Hz, 1H, ArH), 7.77 (s, 1H, ArH), 7.85 (m, 1H, ArH), 8.69 (s, 1H, Isoxazole); ¹³C NMR (75.47 MHz, CDCl₃) δ = 11.9 (SCH₃), 56.0 (OMe) and 56.1 (OMe), 110.7 (4C isoxazole), 111.5 (2C ArH), 114.6 (5C ArH), 118.6 (6C ArH), 122.7 (1C ArH), 148.7 (3C isoxazole), 150.6 (3C ArH), 152.2 (4C ArH), 168.9 (5C isoxazole), 184.1 (CO) ppm; EIMS m/z (%) 280 (15), 232 (50), 204 (20), 177 (50) 165 (80); Anal: Calcd: C, 55.90; H, 4.69; N, 5.01; S, 11.48. Found: C, 55.47; H, 4.89; N, 5.23; S, 11.54.

[5-(Methylsulfanyl)-4-isoxazolyl](phenyl)methanone was obtained from 2-benzoyl-3,3-bis(alkylsulfanyl) acrylaldehydes by reacting with one equivalent hydroxyamine hydrochloride at 60 °C; yield 65% (0.28 g); white solid; mp 68 - 70 °C; IR (KBr ν max) = 1662, 1596, 1577 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 2.68 (s, 3H, SCH₃), 7.2 (s, 1H ArH), 7.51 - 7.48 (d, J = 9 Hz, 2H, ArH), 8.07 - 8.04 (d, J = 9 Hz, 2H, ArH), 8.71 (s, 1H, isoxazole) ppm; EIMS m/z (%) 220 (5), 172 (3), 167 (40), 150 (10), 105 (100); Anal: Calcd: C, 60.26; H, 4.14; N, 6.39; S, 14.62. Found: C, 59.87; H, 4.34; N, 6.39; S, 15.02.
(4-Bromophenyl)[5-methylsulfanyl]-4-isoxazolyl] methanone was obtained from 3,3-bis(methylsulfanyl)-2-(4-bromobenzoyl) acrylaldehyde by reacting with one equivalent hydroxylamine hydrochloride at 60 °C.; yield 50% (0.27 g); white solid; mp 84 - 86 °C; IR (KBr $\nu_{\text{max}}$) = 1662, 1589, 1554, 1461 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 2.48 (s, 3H, SCH$_3$), 7.47 - 7.51 (m, 2H, ArH), 8.03 - 8.07 (m, 2H, ArH), 8.70 (s, 1H, isoxazole) ppm; FABMS: m/z (%) 300 (M + 2, 98), 298 (M$^+$, 98), 252 (98), 251 (96), 185 (100), 183 (100), 149 (60), 105 (52); Anal. Calcd: C, 44.31; H, 2.70; N, 4.70; S, 10.75. Found: C, 45.01; H, 3.97; N, 4.46; S, 10.57.

[5-(Benzylsulfanyl)-4-isoxazolyl](phenyl)methanone was obtained from 2-benzoyl-3,3-bis(benzylsulfanyl) acrylaldehydes by reacting with one equivalent hydroxylamine hydrochloride at 60 °C; yield 60% (0.35 g); white solid; mp 110 - 112 °C; IR (KBr $\nu_{\text{max}}$) = 1643, 1596, 1562 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 4.41 (s, 2H, SCH$_2$-), 7.44 - 7.52 (m, 6H, ArH), 7.56 - 7.66 (m, 2H, ArH), 7.76 - 7.79 (m, 2H, ArH), 8.74 (s, 1H, isoxazole); $^{13}$C NMR (75.47 MHz, CDCl$_3$) $\delta$ = 35.5 (SCH$_2$Ph), 108.1 (4C isoxazole), 119.3, 127.5, 128.4, 128.8, 129.2, 133.1, 136.2, 140.6, 138.0, 160.7 (3C isoxazole), 162.5 (5C isoxazole), 186.7 (CO) ppm.
4.5.2. Synthesis of 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbonitriles from 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes

**General procedure**

The appropriate 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehyde 35 (2 mmol) was dissolved in acetonitrile (20 mL). To this solution hydroxylamine hydrochloride (0.28 g, 4 mmol) followed by and K$_2$CO$_3$ (1.1 g, 8 mmol) were added and the reaction mixture was refluxed at 85 °C for 10 h. It was cooled and poured into ice-cold water. The semisolid obtained was extracted with ethyl acetate (3 x 25 mL), dried with anhydrous sodium sulfate and purified by column chromatography using hexane as the eluent. Recrystallized from ethyl acetate / hexane solution.

5-(4-Methylphenyl-3-(methylsulfanyl)-4-isoxazolecarbonitrile was obtained from 3,3-bis(methylsulfanyl)-2-(4-methylbenzoyl)acrylaldehyde by the reaction of two equivalents of hydroxylamine at 85 °C; yield 43% (0.19g); white solid; mp 96-98 °C; IR (KBr $\nu_{\text{max}}$) = 2993, 2223, 1604, 1562, 1427 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 2.44 (s, 3H, Me), 2.67 (s, 3H, SCH$_3$), 7.36 - 7.33 (d, J = 9 Hz, 2H, ArH), 7.94 - 7.91 (d, J = 9 Hz, 2H, ArH). $^{13}$C NMR (75.47 MHz, CDCl$_3$) $\delta$ = 12.0 (SMe), $\delta$ 21.5 CH$_3$, 116.5 (CN) 126.8 (4C isoxazole), 127.7, 128.4 and 129.8, 144.7 (ArH carbons) and 162.2 (3C, isoxazole) 174.6 (5C isoxazole) ppm; EIMS m/z (%) 231 (20), 216 (5), 208 (25), 202 (30), 149 (23), 119 (100), 102 (50); Anal.: Calcd.: C, 61.09; H, 3.73; N, 12.95; S, 14.83. Found: C, 61.38; H, 3.63; N, 13.08; S, 14.60.
3-(Methylsulfanyl)-5-phenyl-4-isoxazolecarbonitrile was obtained from 2-benzoyl-3,3-bis(methylsulfanyl) acrylaldehyde by the reaction of two equivalents of hydroxylamine at 85 °C; yield 30% (0.12 g); white solid; mp 110-112 °C; IR (KBr \( \nu_{\text{max}} \)) = 2229, 1604, 1568, 1496 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta = 2.68 \) (s, 3H, SCH\(_3\)), 7.72 - 7.62 (m, 3H, ArH), 8.01 - 8.05 (m, 2H, ArH); \(^{13}\)C NMR (75.47 MHz, CDCl\(_3\)): \( \delta = 13.6 \) (SCH\(_3\)), 111.1 (CN), 124.7 (4C isoxazole), 126.8 (3,3'C ArH), 129.4 (2,2'C ArH), 132.8 (4C ArH), 162.3 (3C isoxazole), 174.4 (5C isoxazole) ppm; Anal: Calcd: C, 61.09; H, 3.73; N, 12.95; S, 14.83. Found: C, 61.68; H, 3.53; N, 13.08; S, 14.50.

5-(4-Bromophenyl-5-(methylsulfanyl)-4-isoxazolecarbonitrile was obtained from 3,3-bis(methylsulfanyl)-2-(4-bromobenzoyl)acrylaldehyde by the reaction of two equivalents of hydroxylamine at 85 °C; yield 56% (0.33 g); white solid; mp 148 - 150 °C; IR (KBr \( \nu_{\text{max}} \)) = 2927, 2233, 1600, 1558, 1488 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta = 2.69 \) (s, 3H, SCH\(_3\)), 7.72 - 7.69 (d, J = 9Hz, 2H, ArH), 7.92 - 7.89 (d, J = 9Hz, 2H, ArH) ppm; FABMS m/z (%) 297 (100), 295 (98), 226 (2), 185 (40), 183 (40), 120 (5), 107 (8); Anal: Calcd.: C, 44.76; H, 2.39; N, 9.49. Found: C, 45.01; H, 2.29; N, 9.57.
5-(4-methoxyphenyl-3-(methylsulfanyl)-4-isoxazolecarbonitrile was obtained from 3,3-bis(methylsulfanyl)-2-(4-methoxybenzoyl)acrylaldehyde by the reaction of two equivalents of hydroxylamine at 85 °C; yield 41% (0.2 g); white solid; mp 142 °C; IR (KBr $\nu_{\text{max}}$) = 2923, 2229, 1610, 1585, 1508 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 2.67 (s, 3H, SMe), 3.90 (s, 3H, OCH$_3$), 7.05 -7.02 (d, J = 9 Hz, 2H, ArH), 8.01 -7.98 (d, J = 9 Hz, 2H, ArH) ppm; Anal: Calcd.: C, 58.52; H, 4.09; N, 11.37. Found: C, 58.82; H, 4.29; N, 11.57.

4.5.3. 5-Aryl-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oximes from 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes

General procedure

The appropriate 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehyde 35 (2 mmol) was dissolved in acetonitrile (20 mL) at room temperature. To the above solution hydroxylamine hydrochloride (0.28 g, 4 mmol) followed by K$_2$CO$_3$ (1.1 g, 8 mmol) were added and the reaction mixture was stirred for 10h. It was poured into ice cold water and the semisolid obtained was extracted with ethyl acetate (3 x 25 mL). Dried with anhydrous sodium sulfate and the solvent was evaporated off. The crude product was purified by column chromatography using hexane / ethyl acetate (8:2) as the eluent. Recrystallized from ethyl acetate / hexane solution.
5-(4-methylphenyl)-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oxime was obtained from 3,3-bis(methylsulfanyl)-2-(4-methylbenzoyl)acrylaldehyde by the reaction of two equivalents of hydroxylamine at room temperature; yield 54% (0.26 g); white solid; mp 174 - 176 °C; IR (KBr \nu_{\text{max}}) = 3339, 1628, 1432 cm^{-1}; ^1H NMR (300 MHz, CDCl$_3$) \delta = 2.43 (s, 3H, CH$_3$), 2.63 (s, 3H, SCH$_3$), 7.31 - 7.33 (m, 2H, ArH), 7.54 - 7.76 (m, 2H, ArH), 7.65 (s, 1H aldoxime), 8.23 (s, 1H, OH proton.) ppm; FABMS m/z (%) 249 (100), 188 (1), 167 (2), 119 (48), 107 (5), 89 (5).

5-(4-bromophenyl)-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oxime was obtained from 3,3-bis(methylsulfanyl)-2-(4-bromobenzoyl)acrylaldehyde by the reaction of two equivalents of hydroxylamine at room temperature; yield 43% (0.26 g); white solid; mp 186 - 188 °C; IR (KBr \nu_{\text{max}}) 3336, 1643, 1596, 1488 cm^{-1}; ^1H NMR (300 MHz, CDCl$_3$ + DMSO-d$_6$): \delta = 2.58 (s, 3H, SCH$_3$), 7.58 - 7.61 (m, 2H, ArH), 7.67 - 7.70 (m, 2H, ArH), 8.13 (s, 1H, aldoxime), 11.43 (s, 1H, OH proton); $^{13}$C NMR (75.47 MHz, CDCl$_3$): \delta = 13.9 (SCH$_3$), 111.4 (4C isoxazole), 118.4 (4C ArH), 129.1 (2,2'C ArH), 132.4 (3,3'C ArH), 140.9 (1C ArH), 156.1 (3C isoxazole), 162.8 (aldoxime carbon.), 172.4 (5C isoxazole) ppm; FABMS m/z (%) 315 (M + 2, 50), 313 (M$^+$, 50), 279 (20), 259 (20), 219 (60), 149 (80), 123 (40), 107 (60).
5-(4-methoxyphenyl)-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oxime was obtained from 3,3-bis(methylsulfanyl)-2-(4-methoxybenzoyl)acrylaldehyde by the reaction of two equivalents of hydroxylamine at room temperature; yield 22% (0.11 g); white solid; mp 180 - 182 °C; IR (KBr \( \nu_{\text{max}} \)) = 3321, 1643, 1608, 1512 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) = 2.63 (s, 3H, SCH\(_3\)), 3.88 (s, 3H, OCH\(_3\)), 7.04 - 7.01 (d, \( J = 9 \) Hz, 2H, ArH), 7.63 - 7.60 (d, \( J = 9 \) Hz, 2H, ArH), 7.79 (b, 1H, aldoxime), 8.21 (s, 1H, OH proton) ppm; FABMS m/z (%) 265 (98), 242 (5), 180 (5), 121 (80), 107 (40), 88 (20).

3-(methylsulfanyl)-5-phenyl-4-isoxazolecarbaldehyde oxime was obtained from 2-benzoyl-3,3-bis(methylsulfanyl)acrylaldehyde by the reaction of two equivalents of hydroxylamine at room temperature; yield 42% (0.19g); white solid; mp 182 - 184 °C; IR (KBr \( \nu_{\text{max}} \)) = 3331, 1639, 1566, 1450 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) = 2.68 (s, 3H, SCH\(_3\)), 7.51 - 7.55 (m, 3H, ArH), 7.60 - 7.69 (m, 3H, two ArH and one aldoxime proton), 8.23 (s, 1H, OH proton); \(^13\)C NMR (75.47 MHz, CDCl\(_3\)): \( \delta \) = 13.8 (SCH\(_3\)), 108.6 (4C isoxazole), 126.8 (4C ArH), 127.5 (2,2’C ArH), 128.9 (3,3’C ArH), 130.6 (1C ArH), 139.6 (3C isoxazole), 159.8 (aldoxime carbon), 167.6 (5C isoxazole) ppm.


4.6 References


