4.1 INTRODUCTION

The isoxazole (1a) is a five membered heterocyclic ring system containing both oxygen and nitrogen atoms at the adjacent positions (1,2-positions). They are isomers of oxazole (1b) wherein the hetero atoms occupy 1,3-positions. The oxazole nucleus may be regarded as a furan nucleus in which −CH= grouping has been replaced by −N= grouping.

\[
\begin{align*}
\text{(1a)} & & \text{(1b)} \\
N_2 & \text{(1a)} & O & \text{(1b)} \\
\text{1} & \text{2} & \text{3} & \text{4}
\end{align*}
\]

Isoxazole derivatives have been reported to possess antibacterial\(^1\), antitubercular\(^2\), antiviral\(^3\) and antifungal\(^4\) activity.

Penicillin derivatives (2) containing isoxazole ring, isoxazole carbonyl penicillins synthesised by Eguchi et al.\(^5\) were antibacterial \emph{Pseudomonas aeruginosa}.

\[
\begin{align*}
R_1 & \text{CONHCHR.COIN} \\
R_2 & \text{CONHCHR.COIN} \\
& \text{(2)} \\
& (R, R_1, R_2 = \text{H, alkyl, aryl etc.})
\end{align*}
\]

Love et al.\(^6\) reported the use of 4-nitro-isoxazoles (3) as corrosion inhibitors for fuels and lubricants.

\[
\begin{align*}
\text{(3)} \\
R & \text{NO}_2
\end{align*}
\]

Isoxazole (4) has been observed to have antiviral activity\(^7\) against Herpes type 2 virus.
The most common method for the synthesis of 3,5-disubstituted isoxazoles\(^8\) (5d) involves the condensation of 1,3-dicarbonyl compounds (5) and hydroxylamine hydrochloride in pyridine or ethanol solvent. The reaction proceeds via the formation of intermediate \(\beta\)-diketone-oxime (5a), its tautomer (5b) and 5-hydroxy isoxazoline (5c) which has been isolated\(^9\) from the reaction mixture.

Asymmetrical 1,3-dicarbonyl compounds on reaction with hydroxylamine hydrochloride form isomeric isoxazoles. However, the formation of isomeric isoxazole depends upon the reactivity of the 1,3-dicarbonyl compounds.

In the enolic form of the diketone (6), if \(R_1 = H\) and \(R_2 = \text{alkyl group}\) then the inductive effect of the alkyl will make carbon atom-3 less
positive and therefore, the nucleophilic attack of \( \text{NH}_2\text{OH} \) will be on carbon atom-1 to give 5-substituted isoxazole (6a), as the major product.\(^{10-11}\)

\[
\begin{align*}
\text{R}_1 & \quad \text{H} \\
\text{C} & \quad \text{C} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H}
\end{align*}
\]

(6)

The formation of only one isoxazole has been reported\(^{12,13}\) when \( \text{R}_1 \) and \( \text{R}_2 \) are substituted phenyl groups with sufficient difference in substituents for carbon atom-1 to be sufficiently positive so that the reaction occurs only at this position.

Substituted isoxazoles are synthesised from the enol ethers of 1,3-dicarbonyl compounds by the reaction with hydroxylamine in alkaline or acidic medium. Thus, a mixture of isomeric 3-methyl isoxazoles (7a) and 5-methyl isoxazoles (7b) are obtained by the action of hydroxylamine hydrochloride on hydroxy methyleneacetone in alcoholic sodium hydroxide solution, while the alkyl ether of hydroxymethylene acetone (7c) in acetic acid gave only 3-methyl isoxazole\(^{14,15}\) (7d).

\[
\begin{align*}
\text{NH}_2\text{OH}/\text{Alc. NaOH} & \quad \overset{(7a)}{\longrightarrow} \quad \text{CH}_3 - \text{C} - \text{CH} = \text{C} - \text{H} \\
\text{NH}_2\text{OH}/\text{AcOH} & \quad \overset{(7b)}{\longrightarrow} \quad \text{CH}_3 - \text{C} = \text{CH} - \text{C} - \text{H} \\
\text{NH}_2\text{OH}/\text{AcOH} & \quad \overset{(7c)}{\longrightarrow} \quad \text{CH}_3 - \text{C} - \text{CH} = \text{C} - \text{H}
\end{align*}
\]
Weygand et al\textsuperscript{16} have reported the formation of only one isoxazole (8d) from the two isomeric methyl ethers of anisoylacetophenone (8, 8a) and hydroxylamine hydrochloride in acid medium. This is due to the fact that enol form of β-diketone (8b-c) is formed by the hydrolysis of enol ethers in acid medium, which is then converted into isoxazole.

\[
\begin{align*}
&\text{OCH}_3
\end{align*}
\]

\[
\begin{align*}
&\text{OCH}_3
\end{align*}
\]

\[
\begin{align*}
&\text{OCH}_3
\end{align*}
\]

\[
\begin{align*}
&\text{OCH}_3
\end{align*}
\]

\[
\begin{align*}
&\text{OCH}_3
\end{align*}
\]

In alkaline medium, this reaction proceeds by 1,4 addition. This is supported by the isolation of β-hydroxyl amine-chalcone (9b) in neutral solution which is converted into isoxazole (9c) by the treatment with acid or alkali. Eistert and Markel\textsuperscript{17} suggested that, it is 1,2-addition rather than 1,4-addition.
Isoxazoles from acetylenic ketones have also been reported. However, the products differ with the reaction medium.\textsuperscript{16} Thus, p-anisoyl-phenylacetylene (10) reacts with hydroxylamine hydrochloride in acid medium to give isoxazole (10a) and in basic medium isoxazole (10b) and benzoyl-p-methoxyphenyl acetylene (10c) gives isoxazole (10b) in basic medium.
Depending upon the experimental conditions, here both 1,4 and 1,2 type of addition are possible. 1,4-addition is a Michael addition and hence proceeds in the alkaline medium. In the acid medium, the oxime is first formed by 1,2-addition which forms the isoxazole by cyclisation and rearrangement.\(^{18}\)

Acetylene treated with fuming nitric acid form isoxazoles\(^{19,20}\) in the presence of acetone. Fulminic acid is the reactive intermediate which forms 3-substituted isoxazoles.\(^{20-24}\)

Acetylenic compounds also on treatment with nitrolic acid formed isoxazoles.\(^{25}\) Nitrile oxide first formed by the elimination of nitrous acid then reacts with phenyl acetylene yielding isoxazole (11c).

\[
\begin{align*}
\text{CH}_3 & - \text{C} - \text{C} - \text{NO}_2 \quad \text{CH}_3 & - \text{C} - \text{C} \equiv \text{N} \quad \rightarrow \quad \text{O} \\
\text{O} & \quad \text{NOH} & \quad \text{O} \\
(11) & \quad & (11a) \\
\end{align*}
\]

\[
\begin{align*}
\text{C}_6\text{H}_5 - \text{C} \equiv \text{CH} \\
\text{N} & \quad \ominus \\
(11b) & \quad (11c) \\
\end{align*}
\]
Schlubach and Repenning\textsuperscript{26} have reported the synthesis of 3,5-diaryl isoxazoles (12a) from acetylene and nitrolic acid or aciphenyl-nitromethane in presence of boron trifluoride.

\[
\begin{align*}
\text{Ph} - \text{CH} = \text{N} & \rightarrow \text{O} \quad - \text{H}_2\text{O} \\
& \text{OH} \\
\text{(12)} & \quad [\text{Ph} - \equiv \text{C} \equiv \equiv \text{N} \rightarrow \text{O}] \\
& \quad \downarrow \\
& \text{CH} \equiv \text{C} - \text{Ph} \\
& \quad \text{(12a)}
\end{align*}
\]

Chalcone epoxide\textsuperscript{27} (13) have also been used in the synthesis of 3,5-diaryl isoxazoles (13d) by the action of hydroxyl amine hydrochloride on the epoxide in various media. Epoxide oxime (13a) or 3,5-diaryl-4-hydroxy isoxazolines (13b) are the intermediates which are readily converted into isoxazoles. It was later proved that 5-hydroxy isoxazolines (13c) is the intermediate rather than (13b).

\[
\begin{align*}
\text{Ph} - \text{CH} - \text{CH} - \text{C} - \text{Ar} & \quad \parallel \quad \text{O} \\
& \text{NH}_2\text{OH.HCl/Dioxane} \quad 2 \text{hrs, 70°C} \\
& \quad \downarrow \\
& \text{(13)} \quad \quad \text{(13b)} \quad \text{+} \quad \text{(13c)} \\
\text{Ph} - \text{CH} - \text{CH} - \text{C} - \text{Ar} & \quad \parallel \quad \text{NOH} \\
& \quad 30 \text{ min.} \quad 66°C \\
& \quad \downarrow \\
& \text{NH}_2\text{OH.HCl} \quad \text{Na}_2\text{CO}_3 \\
& \quad \quad \downarrow \\
& \text{(13a)} \quad \quad \text{(13b)} \\
\text{Ph} - \text{CH} - \text{CH} - \text{C} - \text{Ar} & \quad \parallel \quad \text{NOH} \\
& \quad \quad \text{AcOH + H}_2\text{SO}_4 \\
& \quad \quad 25 \text{ min.} \\
& \quad \quad \downarrow \\
& \quad \text{(13b)}
\end{align*}
\]

2,4,6-Triphenyl pyrilium salts\textsuperscript{28} (14) yield 3,5-diaryl isoxazoles (14a) when treated with hydroxylamine hydrochloride. The same isoxazoles could also be obtained from the same reactants by photoelimination reaction\textsuperscript{29}.
Flavones, thiochromones\textsuperscript{30} and chromones\textsuperscript{31} (15) have been used in the synthesis of 3,5-diaryl isoxazoles and 3-aryl-5-methyl isoxazoles (15a) respectively when treated with hydroxylamine hydrochloride in pyridine medium.

It is found that the direct synthesis of 3,5-diethyl isoxazole (16a) from 3,5-dinitroheptane (16) can be effected when treated with KOH.\textsuperscript{32}

\[ \text{C}_2\text{H}_5 - \text{CH} - \text{CH}_2 - \text{CH} - \text{C}_2\text{H}_5 \xrightarrow{\text{KOH}} \text{C}_2\text{H}_5 \]

\[ \text{NO}_2 \]

\[ \text{NO}_2 \]

\[ \text{(16)} \]

\[ \text{(16a)} \]

\(\alpha\)-Acetyl-\(\beta\)-nitrostilbenes (17) on chemical and electrochemical reduction gave trisubstituted isoxazoles\textsuperscript{33} (17a).

\[ \text{O}_2\text{N} - \text{C.} \text{Ph} : \text{C.} \text{Ph} - \text{COR} \xrightarrow{} \]

\[ \text{(17)} \]

\[ \text{(17a)} \]

\(\alpha\)-Bromostyrene (18) or \(\omega\)-nitrostyrene (18a) reacts with phenyl nitrile oxide (18b) to form 5-bromo isoxazoline (18c) and 4-nitro isoxazoline (18d) as the intermediates. These isoxazolines on treatment with alkali followed by heating yields isoxazole\textsuperscript{34} (18e).
Borkhade et al\textsuperscript{35} have synthesised 3,5-diaryl isoxazoles (19d) from 1,3-propanediones (19), flavones (19a), chalcone dibromides (19b) and chalcones (19c) by the action of hydroxylamine hydrochloride in pyridine medium. Borkhade proposed mechanism for this reaction is based on that proposed by Ghiya and Marathe\textsuperscript{36}.
The reaction of chalcone dibromide (20) with hydroxylamine hydrochloride in the presence of alkali provided an unambiguous synthesis of isoxazole\textsuperscript{12,16,37-39} (20d). Similarly α-bromochalcone (20a) obtained from chalcone dibromide by elimination of HBr, which on reaction with hydroxyl amine hydrochloride in the presence of alkali and further on cyclisation gives isoxazole\textsuperscript{12,39,40} (20d). Definite mechanism has not been reported so far for these reactions, though it appears to proceed through 1,2-addition leading to the formation of intermediate oximes. 4-Bromo isoxazoline (20c) undergoes dehydrobromination in alkali to form isoxazole.

\[ \text{NH}_2\text{OH.HCl/OH}^- \downarrow \text{Cyclisation} \rightarrow \text{R R } \text{Br} \text{O} \text{R R } \text{Br} \text{N} \text{BrR} \text{R } \text{O} \text{H} \rightarrow \text{R R } \text{Br} \text{O} \text{R R } \text{Br} \text{N} \text{BrR} \text{R } \text{O} \text{H} \]

Thakar et al\textsuperscript{41} have synthesised 3-(2'-furyl or 2'-thienyl)-5-(2'-hydroxyphenyl) isoxazoles (21a) by reaction of 1,3-propanediones (21) with hydroxyl amine hydrochloride in methanol.

\[ \text{R R } \text{Br} \text{O} \text{R R } \text{Br} \text{N} \text{BrR} \text{R } \text{O} \text{H} \rightarrow \text{R R } \text{Br} \text{O} \text{R R } \text{Br} \text{N} \text{BrR} \text{R } \text{O} \text{H} \]
Elkasaby and Salem$^{42}$ have reported the synthesis of 3,5-diaryl isoxazoles (23a) from chalcones (23) by different routes as given below.

The o-hydroxy dibenzoyl methanes (24) and 3-iodoflavanones (24b) when treated with hydroxyl amine hydrochloride in DMF/Pyridine yielded isoxazoles$^{43}$ (24a).

Perkin$^{44}$ synthesised 3-(4’-chlorophenyl)-5-(4”-methoxyphenyl) isoxazole (25) by treating p-ClC$_6$H$_4$.CMe.NOH with BuLi at 0°C followed
by the cyclization of intermediate with p-MeOC₆H₄CO₂Me in THF containing HCl.

![Diagram of compound 25]

Jamode⁴⁵ have synthesised several 3-(o-hydroxy aryl)-5-aryl isoxazoles (26c) by the action of hydroxyl amine hydrochloride in ethylene diamine on dibenzoyl methanes (26), flavones (26a) and 3-bromoflavones (26b).

![Diagram of compounds 26, 26a, 26b, and 26c]

Chincholkar et al reported the synthesis of isoxazoles⁴⁶ (27a) and isomeric isoxazoles⁴⁷ (27b) by the action of hydroxyl amine hydrochloride on 3-arylfлавones (27) in pyridine and methanol medium respectively.
Sankyo Co. Ltd.\textsuperscript{48} synthesised isoxazoles (28) by the addition of \(\text{Cu(OAc)}_2\) to \(\text{Pd(OAc)}_2\) in \(\text{Me}_2\text{SO}_4\) followed by heating with 3-(p-Tosyloxy)-5-methyl isoxazole in benzene.

\[
\text{(28)}
\]

Kakade\textsuperscript{49} synthesised isomeric 3-phenyl-5-(2"-hydroxy substituted phenyl)-isoxazoles (29a) from 1-(2"-hydroxy substituted phenyl)-3-phenyl-1,3-propanediones (29) and hydroxylamine hydrochloride in dimethylsulphoxide in presence of sodium acetate.

\[
\begin{array}{c}
\text{OH} \\
\text{R} \\
\text{O} \\
\text{R}_1 \\
\text{R} \\
\text{O} \\
\text{N} \\
\text{R}_3 \\
\text{R}_2 \\
\text{N=N=Cl} \\
\text{R}_4 \\
\end{array}
\xrightarrow{\text{NH}_2\text{OH.HCl}}
\begin{array}{c}
\text{OH} \\
\text{R} \\
\text{O} \\
\text{R}_1 \\
\text{R} \\
\text{O} \\
\text{N} \\
\text{R}_3 \\
\text{R}_2 \\
\text{N = N=Cl} \\
\text{R}_4 \\
\end{array}
\]

\[
\text{(29)}
\rightarrow
\text{(29a)}
\]

Mittal and Singhal\textsuperscript{50} synthesised isoxazoles (30b) from different substituted benzene diazonium chlorides (30) coupled with some reactive methylene compounds and then were condensed with hydroxyl amine hydrochloride.

\[
\begin{array}{c}
\text{N=N=Cl} \\
\text{R}_3 \\
\text{R}_2 \\
\text{R}_4 \\
\end{array}
\xrightarrow{\text{R}_1 \text{COCH}_2 \text{COCH}_3}
\begin{array}{c}
\text{R}_3 \\
\text{R}_2 \\
\text{N = N=Cl} \\
\text{R}_4 \\
\end{array}
\rightarrow
\begin{array}{c}
\text{N = N} \\
\text{R}_3 \\
\text{R}_2 \\
\text{R}_4 \\
\text{O} \\
\text{CH}_3 \\
\end{array}
\xrightarrow{\text{NH}_2\text{OH.HCl}}
\begin{array}{c}
\text{N = N} \\
\text{R}_3 \\
\text{R}_2 \\
\text{R}_4 \\
\text{O} \\
\text{N} \\
\text{CH}_3 \\
\end{array}
\]

\[
\text{(30)}
\rightarrow
\text{(30a)}
\rightarrow
\text{(30b)}
\]
Nair\textsuperscript{51} has reported the synthesis of isomeric isoxazoles (31a and 31b) from 1-(2'-furyl)-3-(2"-hydroxyphenyl)-1,3-propanedione (31) with hydroxylamine hydrochloride in pyridine and methanol.

\[ \text{R} \quad \begin{array}{c}
\text{O} \\
\text{OH} \\
\text{R} \\
\text{O} \\
\text{O} \\
\text{H} \\
\text{C}_5\text{H}_5\text{N} \\
\end{array} \quad \xrightarrow{\text{NH}_2\text{OH.HCl}} \quad \begin{array}{c}
\text{OH} \\
\text{N} \\
\text{O} \\
\text{R} \\
\text{O} \\
\text{H} \\
\end{array} \quad (31a) \]

\[ \text{R} \quad \begin{array}{c}
\text{O} \\
\text{OH} \\
\text{R} \\
\text{O} \\
\text{O} \\
\text{H} \\
\text{MeOH} \\
\end{array} \quad \xrightarrow{\text{NH}_2\text{OH.HCl}} \quad \begin{array}{c}
\text{OH} \\
\text{N} \\
\text{O} \\
\text{R} \\
\text{O} \\
\text{H} \\
\end{array} \quad (31b) \]

Basinski and Jerzmanowska\textsuperscript{52} have reported the synthesis of two isomeric isoxazoles (32b-c) from \(\omega\)-formyl-o-hydroxy acetophenone (32) or chromone (32a) with hydroxylamine hydrochloride in ethanol.

\[ \begin{array}{c}
\text{OH} \\
\text{O} \\
\text{C} \\
\text{O} \\
\text{O} \\
\text{H} \\
\end{array} \quad (32) \]

\[ \begin{array}{c}
\text{OH} \\
\text{N} \\
\text{O} \\
\text{R} \\
\text{O} \\
\text{H} \\
\text{EtOH} \\
\end{array} \quad + \quad \begin{array}{c}
\text{OH} \\
\text{N} \\
\text{O} \\
\text{R} \\
\text{O} \\
\text{H} \\
\text{EtOH} \\
\end{array} \quad (32b) \]

\[ \begin{array}{c}
\text{OH} \\
\text{O} \\
\text{C} \\
\text{O} \\
\text{O} \\
\text{H} \\
\end{array} \quad (32a) \]

The two isomeric isoxazoles along with other products (33a and 33b) have been reported\textsuperscript{53,54} from o-hydroxy chalcones (33) and hydroxylamine hydrochloride in presence of NaOH.
Steven et al\textsuperscript{55} have synthesised isoxazoles (34) by the action of Ph.CClNOH with H\textsubscript{2}C.Cl\textsubscript{2} and Et\textsubscript{3}N followed by NaOCH\textsubscript{2}Ph treatment.

\[
\begin{array}{c}
\text{HO} \\
\text{OCH\textsubscript{2}Ph} \\
\text{N} \\
(34)
\end{array}
\]

Grabowask\textsuperscript{56} reported chlorosubstituted isoxazoles (35) from ClC\textsubscript{6}H\textsubscript{4}CH.NOH with MeCOCH\textsubscript{2}COOEt in the presence of NaOCl and NaOH.

\[
\begin{array}{c}
\text{Cl} \\
\text{Me} \\
\text{O} \\
\text{N} \\
\text{COOEt} \\
(35)
\end{array}
\]

Gaggad et al\textsuperscript{57} have reported the preparation of 3-(2"-hydroxyphenyl)-5-styryl isoxazole (36a) from 1-(2"-hydroxyphenyl)-5-phenyl-4-pentene-1,3-diones (36) by the action of hydroxylamine hydrochloride in pyridine.
Kashima et al\textsuperscript{58} reported the selective synthesis of 3,5-disubstituted isoxazoles (37) by the cyclocondensation of \( \beta \)-substituted enones with hydroxylamine hydrochloride in presence of \( \text{K}_2\text{CO}_3 \), \( \text{Et}_3\text{N} \) or \( \text{NaOMe} \).

\[
\begin{array}{c}
\text{R}_1 \ \ | \ \ N \ | \ \ O \\
\text{R}_2
\end{array}
\]

(37)

Reaction of 2-hydroxydibenzoyl methane and hydroxylamine hydrochloride in various solvents such as pyridine, ethylenediamine, aqueous DMF, methanol containing excess of KOH etc. has been studied\textsuperscript{59} and reported the formation of 3-(2"'-hydroxy-5"'-methylphenyl)-5-(4'-methoxy-phenyl)-isoxazole (38) and 3-(\( \alpha \)-hydroxylamino-4-methoxystyryl)-5-methyl benzene isoxazole (38a).

\[
\begin{array}{c}
\text{O}_\text{H} \\
\text{O}_\text{CH}_3
\end{array}
\]

(38)

\[
\begin{array}{c}
\text{O}_\text{CH}_3 \\
\text{NH.OH}
\end{array}
\]

(38a)

Oda Kengo\textsuperscript{60} have reported the synthesis of isoxazole (39) by the action of 3-(3-chlorophenyl)-4-chloro-5-acetoxy-2-isoxazoline on 1,8-diazobicyclo(5, 4-O) undecane in THF.

\[
\begin{array}{c}
\text{X}_n \\
\text{Y}
\end{array}
\]

(39)

\( \text{X} = \text{halo, haloalkyl, haloalkoxy etc.} \)
\( \text{Y} = \text{halo, Ar, etc.} \)
\( n = 1-5 \)
Malyula et al.\textsuperscript{61} synthesised substituted isoxazoles (40a) by halogenation of the corresponding derivatives (X=H) by Cl, Br, I-KI and dehydrohalogenation of resulting intermediate (40) in dioxane or MeOH.

\[
\begin{align*}
\text{(40)} & \quad \text{R} \quad \text{N} \quad \text{O} \quad \text{R} \quad \text{Ph} \quad \text{NO} \quad \text{2} \quad \text{X} \quad \text{O} \\
\text{MeOH or dioxane} & \quad \text{HX} \\
\rightarrow & \\
\text{(40a)} & \\
\end{align*}
\]

Isomeric 5-(2”-hydroxyphenyl)-3-styryl isoxazoles\textsuperscript{62} (41a) have been synthesised from 1-(2”-hydroxyphenyl)-5-phenyl-4-pentene-1,3-diones (41) and hydroxylamine hydrochloride in ethanol.

\[
\begin{align*}
\text{(41)} & \quad \text{R} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{OH} \quad \text{R} \quad \text{1} \\
\text{EtOH} & \quad \text{NH}_2\text{OH.HCl} \\
\rightarrow & \\
\text{(41a)} &
\end{align*}
\]

Thakare\textsuperscript{63} have synthesised 3-methyl-4-aryloxy-5-(2”-hydroxyphenyl)-isoxazoles (42a) and 3-methyl-4-(2”-hydroxyaryl)-5-aryl isoxazole (42b) from 3-aryloxy-2-methyl chromones (42) by the action of hydroxylamine hydrochloride in ethanol containing aqueous KOH and pyridine respectively.
Chiriano\textsuperscript{64} reported the formation of isoxazoles (43) from $R_1\text{CH}:\text{CH}_2$, H.CO.CO$_2$H, HONO$_2$ and Cl.

\[
\text{R}_1 = \text{CH}_2\text{OH}, \text{ Ph}, \text{CH}_2\text{Br}, \text{CH(OH)}\text{Me}, \\
\text{CH(OH)Ph, C}_5\text{H}_11
\]

(43)

Synthesis of 4-amino-3-(p-chlorophenyl)-5-(\(\beta\)-aminoethylthio) isoxazole (44) has been reported\textsuperscript{65} by the treatment of NaOEt, EtOH, HCl-ether with 4-(p-chlorophenyl)-3-methyl furoxane and condensing with Li(CH$_2$)$_2$NH$_2$.

(44)

Sharan\textsuperscript{66} synthesised isoxazoles (45) having fungicidal activity towards \textit{Asparagillus niger}, by the condensation of substituted aldehydes with 8-acetyl-7-hydroxy-4-methyl coumarin followed by cyclisation with NH$_2$OH.

(45)

Isomeric isoxazoles (46 and 46a) have been synthesised\textsuperscript{67} from unsymmetrical \(\beta\)-diketones, 1-aryl-3-tolylpropane-1,3-diones and 1-aryl-butane-1,3-diones by the action of hydroxylamine hydrochloride.
Hagiwara Yuichi et al\textsuperscript{68} reported the synthesis of 3,4-di-(4'-4"'-methoxyphenyl)-5-methyl isoxazole (47) and its use in the preparation of anti-inflammatory, analgesic and antipyretic drugs. It is also reported to inhibit prostaglandin formation by blocking cyclooxygenase.

\begin{center}
\includegraphics[width=0.5\textwidth]{47.png}
\end{center}

Nagana Mitsuo et al\textsuperscript{69} reported the synthesis of 3-(2',3'-dihydroxy propoxy) isoxazoles (48) and their use as the central muscle relaxants.

\begin{center}
\includegraphics[width=0.5\textwidth]{48.png}
\end{center}

\(\alpha, \beta\)-Unsaturated ketoxime derivatives on oxidation yielded (3,4-diaryl isoxazol-5-yl) acetic acid\textsuperscript{70} (49).

\begin{center}
\includegraphics[width=0.5\textwidth]{49.png}
\end{center}

Hagiwara Yuichi et al\textsuperscript{71} have synthesised 3,4-di-(4'-4"'-methoxy phenyl)-5-alkyl isoxazole (50) from 5-hydroxyimino-4,5-di-(4',4"'-methoxy phenyl)-3-pentenoate and hydrochloric acid by stirring in methanol at 60°C. These isoxazoles are used as anti-inflammatory, analgesic and antipyretic drugs.

\begin{center}
\includegraphics[width=0.5\textwidth]{50.png}
\end{center}

Rajput\textsuperscript{72} have been reported the formation of 3,5-diaryl isoxazoles (51c) from 1,3-propanediones (51), flavones (51a) and chalcone dibromides (51b) by the action of hydroxylamine hydrochloride in ethanol as the reaction solvent containing piperidine.
A convenient method for the preparation of 3,5-diaryl isoxazoles (52) was given by Wei Xudong et al.\textsuperscript{73} These were prepared by the oxidation of HON:CR\textsubscript{1}CH:CHR\textsubscript{2} with a new metal complex oxidant, tetrakis (pyridine) Cobalt(II) dichromate (TPCD).

\[
\begin{align*}
\text{(51)} & \\
\text{(51a)} & \\
\text{(51b)} & \\
\text{(51c)} & \\
\end{align*}
\]

where,

\begin{align*}
R_1 &= \text{Ph, } 3\text{-ClC}_6\text{H}_4, \ 4\text{-ClC}_6\text{H}_4, \ 3\text{-BrC}_6\text{H}_4, \ 3,4\text{-methyleneedioxy phenyl, } \text{Ph.CH:CH, } 4\text{-BrC}_6\text{H}_4, \\
R_2 &= 4\text{-BrC}_6\text{H}_4, \ 4\text{-O}_2\text{NC}_6\text{H}_4
\end{align*}

Raghuwanshi\textsuperscript{74} used DMSO-I\textsubscript{2} system for the oxidation of isoxazolines (53) in the synthesis of isoxazoles (53a).

\[
\begin{align*}
\text{(53)} & \\
\text{(53a)} & \\
\end{align*}
\]

Shibata Yasushi et al\textsuperscript{75} synthesised triazolylisoxazole derivatives (54) from β-(dimethylamino) acrylophenone by the action of hydroxylamine
hydrochloride in ethanol containing small amount of p-MeC₆H₄SO₃H. These derivatives are used in the preparation of insecticides and acaracides.

Talley et al⁷⁶ reported isoxazole (55) compounds as cyclooxygenase inhibitors.

Damale et al⁷⁷ have reported the synthesis of 3-(2"-hydroxy phenyl)-5-(nitrosubstituted phenyl)-isoxazoles (56a) and 3-(nitrosubstituted phenyl)-5-(2"-hydroxyphenyl)-isoxazoles (56b) as the isomeric isoxazoles from 1,3-propanediones (56) by the action of hydroxylamine hydrochloride in ethanol as the reaction solvent.

Chattopadhyay et al⁷⁸ have synthesised 4-amino-5-benzoyl isoxazole-3-carboxamide (57a) directly from oximino cyanoacetamide (57) and benzylamine via corresponding oximinates.
Heda et al. have synthesised 1,3-diaryl-2-iodo-propane-1,3-dione (58a) and 4-iodo-3,5-diaryl isoxazoles (58b) from various propane-1,3-diones (58) condensing with hydroxylamine hydrochloride in ethanol. It exhibits microbial activity.

Synthesis and antifungal activity of substituted 5,6-hydroxy-3-methyl-4,5-benzisoxazoles (59) have been reported by Kumbhare et al.

Gajbhiye et al. have reported bis-isoxazoles (60c) synthesised by the reaction of bis-chalcone dibromide (60b) with hydroxylamine hydrochloride in pyridine medium.
Thakare et al. have reported the synthesis of 3-(2”-hydroxy substituted phenyl)-5-(2'-furyl)-isoxazoles (61a) and isomeric 3-(2'-furyl)-5-(2”-hydroxy substituted phenyl)-isoxazoles (61b) from 1-(2'’-hydroxy substituted phenyl)-β-(2'-furyl) acrylophenone dibromides (61) and hydroxylamine hydrochloride in pyridine and methanol in KOH as the solvent respectively.
Synthesis of 3,5-diaryl-4-aroyl isoxazoles (62a) from chloro-substituted 3-aroyl flavones (62) on treatment with hydroxylamine hydrochloride in DMF containing small amount of piperidine have been reported by Patil et al.\textsuperscript{83}

Synthesis of 2-bromo-β-diketone derivatives (63a) and 4-bromoisoxazoles (63b) have been reported\textsuperscript{84,85} by using IBr/dioxane and hydroxylamine hydrochloride in ethanol solvent respectively from 1,3-diaryl propane dione (63).
Synthesis of some new oxygen, nitrogen heterocyclics\textsuperscript{86} such as 5-hydroxy-4,5-diaryl isoxazoles (64a) have been reported from $\alpha$-formyldeoxybenzoin (64) condensed with hydroxylamine hydrochloride in methanol/pyridine medium.

Mulwad and Hegde\textsuperscript{87} synthesised 3,5-dimethyl-4-[6'-coumarinyl] azoisoxazoles (65a) by refluxing 1,3-dimethyl-propane-1,3-dione-2-[6'-coumarinyl] hydrazone (65), sodium acetate and hydroxylamine hydrochloride in presence of ethanol and few drops of water.

Synthesis and characterisation of some new 3,5-diaryl substituted isoxazoles (66a) from chalcones (66) condensed with hydroxylamine hydrochloride in presence of aqueous KOH have been reported by Murthy et al.\textsuperscript{88}
Desai and Tilve\textsuperscript{89} reported a novel and convenient method for the synthesis of 3,5-diaryl isoxazoles (67a) by oxidative cyclisation of $\alpha,\beta$-unsaturated oxime of chalcones (67) on treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in methanol at room temperature.

\[
\begin{align*}
\text{Ar}_1 - \text{C} = \text{C} - \text{Ar}_2 & \xrightarrow{\text{DDQ, MeOH, rt}} \text{N} = \text{O} \\
(67) & \to (67a)
\end{align*}
\]

Popat et al\textsuperscript{90} reported the synthesis and biological activity of 3-substituted aryl-5-(3'-bromo/chloro phenyl) isoxazole derivatives (68a) by condensing 1-substituted aryl-3-(3'-bromo/chlorophenyl)-2-propen-1-ones (68) with hydroxylamine hydrochloride using sodium acetate in acetic acid and ethanol solvent.

\[
\begin{align*}
\text{CHO} + \text{H}_3\text{C} - \text{C} - \text{O} & \xrightarrow{40\% \text{ Alkali}} \text{CHO} \\
\text{(68)} & \to (68a)
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2\text{OH.HCl, AcONa} & \xrightarrow{\text{AcOH/EtOH}} \text{N} = \text{O} \\
(68a) & \to (68a)
\end{align*}
\]

(X = Br, Cl)
Synthesis and biological evaluation of some tri and tetra substited isoxazoles\textsuperscript{91,92} (69a) have been synthesied by the reaction between 3-acetyl flavones (69) with various reagents such as hydrazine hydrate, phenyl hydrazine and hydroxylamine hydrochloride in different media like ethanol or acetic acid and NaOH in methanol or pyridine.

\begin{equation}
\begin{array}{c}
\text{R}_1 \quad \text{R}_2 \quad \text{O} \\
\text{O} \\
\text{Ac}
\end{array}
\begin{array}{c}
\text{NH}_2\text{NH}_2\text{H}_2\text{O/PhNHNH}_2/ \\
\text{NH}_2\text{OH.HCl}
\end{array}
\begin{array}{c}
\text{R}_1 \quad \text{R}_2 \quad \text{O} \\
\text{N} \\
\text{Ac}
\end{array}
\end{equation}

\textbf{(69) \rightarrow (69a)}

Om Prakash et al\textsuperscript{93} synthesised and reported antimicrobial activity of 3-(2',4'-dichloro-5-fluorophenyl)-5-aryl isoxazoles (70a) starting from substituted chalcone dibromides (70) refluxed in ethanol, hydroxylamine hydrochloride and 30\% KOH.

\begin{equation}
\begin{array}{c}
\text{Cl} \\
\text{F} \\
\text{Br} \\
\text{Br}
\end{array}
\begin{array}{c}
\text{R}
\end{array}
\begin{array}{c}
\text{O} \\
\text{Cl}
\end{array}
\begin{array}{c}
\text{F} \\
\text{N}
\end{array}
\begin{array}{c}
\text{R}
\end{array}
\begin{array}{c}
\text{O}
\end{array}
\begin{array}{c}
\text{R}
\end{array}
\end{equation}

\textbf{(70) \rightarrow (70a)}

Synthesis and antimicrobial activity of 2-(5-aryl-3-isoxazolyl)-3-phenyldindoles\textsuperscript{94} (71a) have been reported from 2-[[3-(p-methoxy phenyl)-2,3-dibromopropanoyl] -3-phenylandoles (71) reacted with hydroxylamine hydrochloride in presence of aqueous KOH.

\begin{equation}
\begin{array}{c}
\text{Ph} \\
\text{R}_1 \\
\text{N} \\
\text{H} \\
\text{O} \\
\text{Br}
\end{array}
\begin{array}{c}
\text{Br}
\end{array}
\begin{array}{c}
\text{R}
\end{array}
\begin{array}{c}
\text{NH}_2\text{OH.HCl}
\end{array}
\begin{array}{c}
\text{Ph} \\
\text{R}_1 \\
\text{N} \\
\text{H} \\
\text{O} \\
\text{Br}
\end{array}
\begin{array}{c}
\text{Br}
\end{array}
\begin{array}{c}
\text{R}
\end{array}
\end{equation}

\textbf{(71) \rightarrow (71a)}
Recently, Sauers et al\textsuperscript{95} reported the synthesis of 3-acetyl-5-methyl-isoxazoles (72c) by Jones oxidation of 5-hydroxy hex-3-yne-2-one (72) to hex-3-yne-2,5-diones (72c), which on nitrosation with alkoxy amine followed by acid catalysed cyclisation produces intermediate oxime (72b) and 3-acetyl-5-methyl isoxazoles (72c).

\[
\begin{align*}
\text{O} & \quad \text{O} \quad \text{O} - \text{H} \\
\text{(72)} & \quad \xrightarrow{\text{Jones Oxidation}} \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{(72a)} & \quad \\
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{(72c)} & \quad \xleftarrow{- \text{R.OH}} \text{H}^+, \text{Cyclisation} \\
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{(72b)} & \quad \text{(R = H, CH}_3\text{)} \\
\end{align*}
\]

Synthesis and characterisation of some new isoxazoles\textsuperscript{96} (73b) derived from benzosuberones (73a) reacted with hydroxylamine hydrochloride in presence of ethanolic sodium hydroxide solution.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{(73)} & \quad + \quad \text{R} - \text{C} - \text{H} \xrightarrow{\text{Alc. KOH}} \text{H}_3\text{C} \\
\text{(73a)} & \quad \text{R} \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{N} \quad \text{O} \\
\text{(73b)} & \quad \text{R} \\
\end{align*}
\]
4.2 ORIGIN OF THE PROBLEM, PROBLEM AND SUMMARY OF THE WORK:

ORIGIN OF THE PROBLEM

Isoxazoles are commonly synthesised from 1,3-dicarbonyl compounds\(^8\), chalcone dibromides, \(\alpha\)-bromo chalcones\(^{16,37-39}\), flavones\(^{101,102}\) and chromones\(^{103}\) by the action of hydroxylamine hydrochloride in the solvent like pyridine or methanol. Nair\(^{51}\) reported the formation of isomeric isoxazoles from 1,3-propanediones and hydroxylamine hydrochloride in pyridine and methanol medium. Chincholkar et al\(^{46,47}\) also prepared isomeric isoxazoles from 3-aroyl flavones and hydroxylamine hydrochloride in solvents pyridine and methanol. Kakade\(^{49}\) reported the formation of isoxazoles from dibenzoyl methanes and hydroxylamine hydrochloride in DMSO solvent in presence of sodium acetate.

Ethylene diamine\(^{45}\) is used as the reaction medium in the preparation of isoxazoles by the action of hydroxylamine hydrochloride on dibenzoyl methanes, flavones and 3-bromo flavanones. Wadodkar\(^{43}\) reported the preparation of isoxazoles from o-hydroxy dibenzoyl methanes and 3-iodo-flavanones by the reaction with hydroxylamine hydrochloride in DMF or pyridine. Krishnamohanrao et al\(^4\) reported the synthesis of isoxazoles from 2'-hydroxy chalcone dibromide in an alkaline medium and \(\beta\)-diketones by the treatment with hydroxylamine hydrochloride with or without the addition of alkali. Methanol\(^{41}\) has been used as a solvent in the synthesis of 3,5-disubstituted isoxazoles from 1,3-propanediones and hydroxylamine hydrochloride. Borkhade and Marathey\(^{35}\) have synthesised isoxazoles from \(\beta\)-diketones, flavones and 3-bromo flavanones on treatment with hydroxylamine hydrochloride in pyridine medium.
Literature survey showed that, aqueous KOH in ethanol as a solvent has not so far been reported in the synthesis of isoxazoles. It was therefore, thought of interest to attempt the synthesis of 3,5-diaryl isoxazoles by the action of hydroxylamine hydrochloride containing small amount of aqueous KOH in ethanol as a solvent with 2''-hydroxy chalcone dibromides or flavones.

**PROBLEM**

The work presented in this chapter of the thesis deals with the synthesis of some new nitrosubstituted-3,5-diaryl isoxazoles from chalcone dibromides (obtained by bromination of chalcones) and hydroxylamine hydrochloride containing small amount of aqueous KOH in ethanol as a solvent and also by the reaction between flavones, hydroxylamine hydrochloride containing small amount of aqueous KOH in ethanol medium. It has been revealed that the use of ethanol solvent containing few drops of aqueous potassium hydroxide in the reaction medium increases the rate of reaction and reduced the reflux time with good yield of the products. Acetyl isoxazoles, thioisoxazoles and acetyl thioisoxazoles were synthesised. The probable mechanism for isoxazole formation has been proposed.

The formation of compounds (XVIIIa-d), (IXa-d), (XXa-d) and (XXIa-d) can be explained by the reaction scheme as given in Scheme-4.
Scheme - 4

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SUMMARY OF THE WORK

SECTION - A

2-Hydroxy acetophenones (Ia-c):

p-Cresyl acetate (Ia), b.p. 212°C was prepared from p-cresol, acetic anhydride and a pinch of fused sodium acetate by acetylation. 2-Hydroxy-5-methyl acetophenone (Ib), m.p. 58°C was prepared from p-cresyl acetate by the Fries migration using anhydrous AlCl₃. Nitration of 2-hydroxy-5-methyl acetophenone (Ib) with the nitrating mixture gave 2-hydroxy-3-nitro-5-methyl acetophenone (Ic), m.p. 140°C.

SECTION - B

2'-Hydroxy chalcones (IIa-d):

2'-Hydroxy chalcones (IIa-d) have been synthesised by the condensation of approximate amount of 2-hydroxy-3-nitro-5-methyl acetophenone (Ic) with calculated amount of aromatic aldehydes in ethanol in the presence of aqueous NaOH (40%). Thus, 1-(2'-hydroxy-3'-nitro-5'-methylphenyl)-3-phenyl-2-propen-1-one (IIa), m.p. 158°C; 1-(2'-hydroxy-3'-nitro-5'-methylphenyl)-3-(4'-methoxyphenyl)-2-propen-1-one (IIb), m.p. 210°C; 1-(2'-hydroxy-3'-nitro-5'-methylphenyl)-3-(3'-nitrophenyl)-2-propen-1-one (IIc), m.p. 225°C and 1-(2'-hydroxy-3'-nitro-5'-methylphenyl)-3-(3',4'-methylenedioxyphenyl)-2-propen-1-one (IId), m.p. 257°C were prepared.

SECTION - C

2-(Substituted phenyl)-6-methyl-8-nitroflavones (XIIa-d):

2-(Substituted phenyl)-6-methyl-8-nitroflavones (XIIa-d) has been obtained by refluxing 1-(2'-hydroxy-3'-nitro-5'-methylphenyl)-3-(substituted phenyl)-2-propen-1-one (IIa-d) in DMSO solvent containing 1,2
crystals of iodine. Thus, 2-phenyl-6-methyl-8-nitroflavone (XIIa), m.p. 217°C; 2-(4’-methoxyphenyl)-6-methyl-8-nitroflavone (XIIb), m.p. 185°C; 2-(3’-nitrophenyl)-6-methyl-8-nitroflavone (XIIc), m.p. 179°C and 2-(3’,4’-methylene dioxyphenyl)-6-methyl-8-nitroflavone (XIIId), m.p. 175°C were obtained.

SECTION - D

2"-Hydroxy chalcone dibromides (XIIIa-d):

2"-Hydroxy chalcone dibromides (XIIIa-d) were prepared by the bromination of 2"-hydroxy chalcones (IIa-d) on treatment with 25% (w/v) bromine in acetic acid reagent. Thus, 1-(2"-hydroxy-3"-nitro-5"-methyl phenyl)-3-phenyl-2,3-dibromo-propan-1-one (XIIIa), m.p. 123°C; 1-(2"-hydroxy-3"-nitro-5"-methyl phenyl)-3-(4’-methoxy phenyl)-2,3-dibromo-propan-1-one (XIIIb), m.p. 138°C; 1-(2"-hydroxy-3"-nitro-5"-methyl phenyl)-3-(3’-nitrophenyl)-2,3-dibromo-propan-1-one (XIIIc), m.p. 221°C and 1-(2"-hydroxy-3"-nitro-5"-methyl phenyl)-3-(3’,4’-methylene dioxyphenyl)-2,3-dibromo-propan-1-one (XIIIId), m.p. 189°C were prepared.

SECTION - E

3,5-Diaryl isoxazoles (XVIIIa-d):

3,5-Diaryl isoxazoles (XVIIIa-d) have been synthesied from 1-(2"-hydroxy-3"-nitro-5"-methyl phenyl)-3-(substituted phenyl)-2,3-dibromo-propan-1-one (XIIIa-d) by treating them with hydroxylamine hydrochloride and aqueous KOH in ethanol. Thus, 3-(2"-hydroxy-3"-nitro-5"-methylphenyl)-5-phenyl-isoxazole (XVIIIa), m.p. 141°C; 3-(2"-hydroxy-3"-nitro-5"-methylphenyl)-5-(4’-methoxyphenyl)-isoxazole (XVIIIb), m.p. 209°C; 3-(2"-hydroxy-3"-nitro-5"-methylphenyl)-5-(3’-nitrophenyl)-isoxazole (XVIIIc), m.p. 216°C and 3-(2"-hydroxy-3"-nitro-5"-methylphenyl)-5-(3’,4’-methylene dioxyphenyl)-isoxazole (XVIIIId), m.p. 201°C were synthesised.
The same 3,5-diaryl isoxazole (XVIIIa-d) were also synthesised from 2-(substituted phenyl)-6-methyl-8-nitroflavones (XIIa-d) on treatment with hydroxylamine hydrochloride and aqueous KOH in ethanol.

SECTION - F

3-(2"-Acetoxy-3"-nitro-5"-methylphenyl)-5-(substituted phenyl)-isoxazoles (XIXa-d) :

3-(2"-Hydroxy-3"-nitro-5"-methylphenyl)-5-(substituted phenyl)-isoxazole (XVIIIa-d) on refluxed with acetic anhydride and a pinch of fused sodium acetate gave 3-(2"-acetoxy-3"-nitro-5"-methylphenyl)-5-(substituted phenyl)-isoxazoles (XIXa-d). Thus, 3-(2"-acetoxy-3"-nitro-5"-methylphenyl)-5-phenyl-isoxazole (XIXa), m.p. 219°C; 3-(2"-acetoxy-3"-nitro-5"-methylphenyl)-5-(4'-methoxyphenyl)-isoxazole (XIXb), m.p. 190°C; 3-(2"-acetoxy-3"-nitro-5"-methylphenyl)-5-(3'-nitrophenyl)-isoxazole (XIXc), m.p. 127°C and 3-(2"-acetoxy-3"-nitro-5"-methylphenyl)-5-(3',4'-methylenedioxyphenyl)-isoxazole (XIXd), m.p. 145°C were prepared.

SECTION - G

3,5-Diaryl thioisoxazoles (XXa-d) :

3,5-Diaryl thioisoxazoles (XXa-d) have been synthesied from 3-(2"-hydroxy-3"-nitro-5"-methylphenyl)-5-(substituted phenyl)-isoxazole (XVIIIa-d) by treating them with phosphorus pentasulphide in pyridine. Thus, 3-(2"-hydroxy-3"-nitro-5"-methylphenyl)-5-phenyl-thioisoxazole (XXa), m.p. 155°C; 3-(2"-hydroxy-3"-nitro-5"-methylphenyl)-5-(4'-methoxyphenyl)-thioisoxazole (XXb), m.p. 111°C; 3-(2"-hydroxy-3"-nitro-5"-methylphenyl)-5-(3'-nitrophenyl)-thioisoxazole (XXc), m.p. 139°C and 3-(2"-hydroxy-3"-nitro-5"-methylphenyl)-5-(3',4'-methylene dioxyphenyl)-thioisoxazole (XXd), m.p. 148°C were synthesised.
SECTION - H

3-(2''-Acetoxy-3''-nitro-5''-methylphenyl)-5-(substituted phenyl)-thioisoxazoles (XXIa-d):

3-(2''-Hydroxy-3''-nitro-5''-methylphenyl)-5-(substituted phenyl)-thioisoxazoles (XXa-d) on refluxed with acetic anhydride and a pinch of fused sodium acetate gave 3-(2''-acetoxy-3''-nitro-5''-methylphenyl)-5-(substituted phenyl)-thioisoxazoles (XXIa-d). Thus, 3-(2''-acetoxy-3''-nitro-5''-methylphenyl)-5-phenyl-thioisoxazoles (XXIa), m.p. 195°C; 3-(2''-acetoxy-3''-nitro-5''-methylphenyl)-5-(4'-methoxyphenyl)-thioisoxazoles (XXIb), m.p. 154°C; 3-(2''-acetoxy-3''-nitro-5''-methylphenyl)-5-(3'-nitrophenyl)-thioisoxazoles (XXIc), m.p. 135°C and 3-(2''-acetoxy-3''-nitro-5''-methylphenyl)-5-(3',4'-methylenedioxyphenyl)-thioisoxazoles (XXId), m.p. 117°C were prepared.