CHAPTER 1

INTRODUCTION

Oxazole is a five-membered ring system containing both oxygen and nitrogen atoms in the 1,3-positions. Isoxazole is isomeric with oxazole with oxygen and nitrogen atoms in the 1,2 positions. The isoxazole nucleus can be regarded as furan nucleus in which -CH= has been replaced by -N=.

![Oxazole 1](image1) ![Isoxazole 2](image2)

Isoxazole derivatives possess antibacterial, antitubercular, antiviral and antifungal properties. These compounds are also effective as antipyretics analgesics, antiinflammants and anticonvulsants. Some 4-nitroisoisoaxozoles were shown to be corrosion inhibitors for fuels and lubricants.

3,5-Disubstituted isoxazoles are synthesised by the action of hydroxylamine on 1,3-dicarbonyl compounds also known as diacylmethane derivatives. The process probably involves the intermediates. β-diketone oxime (5) its tautomer
When unsymmetrical 1,3-dicarbonyl compounds (8) are allowed to react with hydroxyamine hydrochloride, two isomeric isoxazoles (9) and (10) can form and their proportion depends on the reactivity of 1,3-dicarbonyl compounds.

The inductive effect of R and R' is important in deciding the proportion of two isoxazoles in the products. For example, in R.CO.CH$_2$.CHO (11) the inductive effect of an alkyl group makes adjacent carbon less electropositive. Therefore, the nucleophilic reagent hydroxylamine attacks an aldehyde carbon to give 5-substituted isoxazole (12) as a major product$^9,10$. 

\[
\text{R-C-CH}_2\text{-CHO} \rightarrow R\text{-C-CH}_2\text{-C-H} \rightarrow \begin{array}{c}
\text{R} \\
\text{N} \\
\text{HO}
\end{array}
\]

\[
\text{R-C-CH}_2\text{-C-R'} \\
\text{N} \\
\text{O}
\]
It has been reported that only single isoxazole could be isolated from a diketone (8) when both R and R' were substituted phenyl groups with a sufficient difference in substituents\textsuperscript{11,12}.

Contrary to the above results, Basinski and Jerzmanowska\textsuperscript{13} have reported the formation of two isomeric isoxazoles (13) and (14) from W-formyl-o-hydroxyacetophenone (15) chromone and its derivatives with hydroxylamine.

\[
\begin{align*}
\text{(15)} & \rightarrow \text{(13)} + \text{(14)}
\end{align*}
\]

The two isoxazoles were differentiated on the basis of colour reaction with neutral ferric chloride. The isoxazole (13) gave colour reaction with neutral ferric chloride solution while isoxazole (14) did not give colour reaction. This difference in the reactivity was attributed to difference in strength of intramolecular hydrogen bonds\textsuperscript{13}.

Similarly Paries et al.\textsuperscript{14} have also reported the formation of two isomeric isoxazole derivatives (18) and (19) along with oxime (17) as a minor product from the nucleophilic attack of hydroxylamine on 2-oxo-\[3,4-b\]\-y-pyrone (16). The products were identified by C-13 NMR studies (Scheme 2).
Witczak\textsuperscript{15,16} has reported the formation of two isomeric isoxazoles along with other products from o-hydroxychalcones by the action of hydroxylamine hydrochloride in presence of sodium hydroxide (Scheme 3).

Acetylenic ketones also gave isoxazoles on treatment with hydroxylamine. Formation of isoxazoles may, however, proceed in two ways depending on the reaction medium (acidic or alkaline). An example of this reaction can be discussed p'-Anisoylphenylacetylene (20) was converted into isoxazole (21) in acid medium and isomeric isoxazole (22) in basic medium. Similarly benzoylanisylacetylene (23) was reacted with hydroxylamine in acid and basic media to yield isomeric isoxazoles (22) and (21).
Hence 1,4- or 1,2-addition is found to depend on experimental conditions. The 1,4-addition can be regarded as a Michael addition to \(\alpha,\beta\)-unsaturated compounds. This is possible in alkaline medium. In acid medium the normal oxime is first formed by 1,2-addition and then it is cyclised to corresponding isoxazole \(^{17}\) (Scheme 4).

Roth and Schwarz \(^{18}\) have reported the formation of 3,3-diarylisoazole (25) from chalcone epoxide (24) and hydroxylamine hydrochloride in different media and proposed the
formation of the epoxide oxime, (26) or 3,5-diaryl-4-hydroxyisoxazoline, (27) as an intermediate which can be converted into isoxazole, (25) (Scheme 5).

![Chemical Diagram](image)

Reiche and Neubauer\(^{19}\) have proved that 5-hydroxy-5-arylisoxazoline, (27) is the intermediate in the formation of isoxazole from chalcone epoxide.

Recently Sammour et al.\(^{20}\) and Hamed et al.\(^{21}\) have also reported the formation of 3,5-diarylisoazole, (28) by the reaction of chalcone epoxide, (29) with hydroxylamine.

![Chemical Diagram](image)

A direct and most suitable method for the synthesis of 3,5-diarylisoazole, (29) and 3-aryl-5-methyl-isoazoles, (29b) and (29c) of definite structure is by the action of
thiochromones (30b),\textsuperscript{22} and chromones,(30c)\textsuperscript{23}.

\[
\begin{array}{c}
\text{NH}_2\text{OH.HCl} \\
\text{Pyridine}
\end{array}
\rightarrow
\begin{array}{c}
\text{30} \\
\text{39}
\end{array}
\]

\begin{itemize}
\item a : R = Ar; X = O
\item b : R = CH\textsubscript{3}; X = S
\item c : R = CH\textsubscript{3}; X = O
\end{itemize}

Contrary to above results, Witczak and Krolikowska\textsuperscript{24} have reported the formation of isomeric isoxazole (31) along with flavone oxime (32) by the action of hydroxylamine on flavone, (33).

\begin{itemize}
\item 33
\item 32
\end{itemize}

Jermanowska and Basinski\textsuperscript{25} have reported the formation of both 3-(2-hydroxyphenyl) isoxazole, (34) and 5-(2-hydroxyphenyl)-isoxazole, (35) from chromone, (36 or \(\omega\)-formyl-\(\omega\)-hydroxyacetophenone, (37) in acetic medium with hydroxylamine with 1:2 ratio.
At pH 6-7 and 1:1 reactant ratio on oxime (38) is formed and in alkaline medium a mixture of products (39) and (40) is obtained 36 and 37.

\[
\text{36 OR 37} \xrightarrow{\text{NH}_2\text{OH/ 6-7 PH}} \text{38}
\]

Wadodkar \(^{26}\) has used dimethylformamide as a medium for preparation of isoxazoles, (41) from dibenzoylmethanes, (42) by the action of hydroxylamine hydrochloride. The isoxazoles, (43) were also prepared from 3-iodoflanonones, (44) with hydroxylamine in pyridine medium.

\[
\text{44} \xrightarrow{\text{NH}_2\text{OHHCl/ Pyridine}} \text{43}
\]

Very recently Kakde \(^{27}\) has prepared 3-aryl-5-(2-hydroxylaryl)-isoxazoles, (45) from 2-hydroxydibenzoylmethanes, (46) by
treatment with hydroxylamine hydrochloride in presence of sodium acetate in dimethyl sulphoxide.

\[ \text{NH}_2\text{NR}_2\text{HCl} \xrightarrow{\text{DMSO}} \]

Chincholkar and Jamode\(^{28}\) have reported the synthesis of 3-(2-hydroxyaryl)-4-aryl-5-arylisoxazoles, \(^{47}\) by the interaction of 3-arylflavones, \(^{48}\) and hydroxylamine hydrochloride in pyridine medium.

\[ \text{NH}_2\text{OH.HCl} \xrightarrow{\text{Pyridine}} \]

They have also reported\(^{29}\) the synthesis of 3-aryl-4-aryl-5-(2-hydroxyaryl)isoxazoles, \(^{49}\) by the condensation of 3-arylflavones, \(^{50}\) and hydroxylamine hydrochloride in methanol.
The other methods reported for synthesis of isoxazoles can be discussed in brief.

3,5-Diarylisoxazoles of equivocal structure have been synthesised from 2,4,6-triphenyl-pyridinium salts by the action of hydroxylamine. The same isoxazoles can also be obtained from the same reactants by photoelimination reaction.

\[
\text{Ph} \quad \text{NH}_2\text{OH/\H}^+ \quad \text{PhCOCH}_3
\]

1,4,6-Trisubstituted pyrimidines underwent ring transformation with hydroxylamine to afford 3,5-disubstituted isoxazoles in high yields.

\[
\text{Me} \quad \text{NH}_2\text{OH} \quad \text{Me}
\]

Isoxazole can be prepared by the action of hydroxylamine hydrochloride on 1,1,3,3-tetraethoxypropane.
Elkasaby and Salem\textsuperscript{34,35} have prepared isoxazoles by treating chalcones with hydroxylamine and brominating-dehydrobrominating the resulting isoxazolines by N-bromosuccinimide and bases respectively (Scheme 6).

![Scheme 6]

4-Chloro, 4-bromo, 4-iodo isoxazoles are readily prepared by direct halogenation of the corresponding isoxazoles, from 4-isoxazolediazonium salts by the sandmeyer reaction or by reaction of hydroxylamine with 4-halo-\(\beta\)-dicarbonyl compounds\textsuperscript{36,37}.

The reaction of 4-bromo or 4-iodo-isoxazoles with ethylmagnesium bromide gave the 4-MgBr reagent by the exchange of reaction while the 4-chloro derivative undergoes reductive cleavage\textsuperscript{37} (Scheme 7).

![Scheme 7]
Problem and Origin of Problem.

Isoxazoles are generally prepared by the action of hydroxylamine on chalcone dibromides, $\beta$-diketones$^{38,39}$ acetylenic ketones$^{40}$ and flavones$^{41,42}$ 4-aryl isoxazoles and pyrazoles have also been synthesised by many workers$^{43,44}$.

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Keeping in view the work done so far by different workers in the field of bromo substituted isoxazoles, 4-bromoisoxazole synthesis was taken up for study starting with the following two compounds.

1) 3-Bromo flavones (as prepared and studied earlier in Part I of thesis) and 2) $\alpha$-Bromo, 1,3-diketones (1,3-diaryl, 2-bromo-propan-1,3-dione)