PART IV

SYNTHESIS
OF
SUBSTITUTED 3, 5-DIARYL-4-AROYL ISOXAZOLES

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INTRODUCTION

Isoxazoles are five membered heterocyclic compounds containing nitrogen and oxygen hetero atoms at the adjacent positions. They are isomers of oxazoles where in the heteroatoms occupy 1, 3-positions.

![Isoxazole and Oxazole Structures](image)

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

Penicillin derivatives containing isoxazole ring, isoxazole-carbonyl penicillins\(^1\) synthesised by Eguchi et. al.\(^5\) were antibacterial *Pseudomonas aeruginosa*.

![Penicillin Derivative Structure](image)

Where \(R_1, R_2 = H, \text{aryl, alkyl etc.}\)

Love et. al.\(^6\) reported the use of 4-nitro-isoxazoles (2) as corrosion inhibitors for fuels and lubricants.
Isoxazole (3)\(^7\) has been observed to have antiviral activity against Herpes type 2 virus.

\[
\begin{array}{c}
\text{Et} \\
\text{MeO-} \\
\text{O(CH\textsubscript{2}}\text{\textsubscript{6}} \\
\text{Et}
\end{array}
\]

(3)

The most common method for the synthesis of 3, 5-disubstituted isoxazoles\(^8\) involved the condensation of 1, 3-dicarbonyl compounds and hydroxylamine hydrochloride. The reaction proceeds via the formation of intermediate \(\beta\)-diketone-oxime (4a), its tautomer (4b) and 5-hydroxy-isoxazoline (4c) which has been isolated\(^9\) from the reaction mixture.

\[
\begin{array}{c}
\text{R}-\text{C}-\text{CH}_2-\text{C}-\text{R'} \\
\text{O} \\
\text{O}
\end{array}
\]

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

\[
\begin{array}{c}
\text{CH}_2-\text{C}-\text{R'} \\
\text{R}-\text{C} \\
\text{N} \\
\text{O}
\end{array}
\]

(4a)

\[
\begin{array}{c}
\text{CH} \\
\text{R} \\
\text{N} \\
\text{OH}
\end{array}
\]

(4b)

\[
\begin{array}{c}
\text{HO} \\
\text{R} \\
\text{N} \\
\text{OH}
\end{array}
\]

(4c)

Asymmetrical 1, 3-dicarbonyl compounds on reaction with hydroxyl amine 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, if \( R_1 = H \) and \( R_2 = \text{alkyl group} \) then the inductive effect of the alkyl group will make \( C_g \) atom less positive and therefore the nucleophilic attack of \( \text{NH}_2\text{OH} \) will be on \( C_1 \) atom to give 5-substituted isoxazole as the major product.\(^{10,11}\)

The formation of only one isoxazole has been reported\(^{12,13}\) when \( R_1 \) and \( R_2 \) are substituted phenyl groups with a sufficient difference in substituents for one carbon atom to be sufficiently positive.

Substituted isoxazoles are obtained from the enol ethers of 1, 3-dicarbonyl compounds by the reaction with hydroxylamine in acidic or alkaline medium. Thus, a mixture of isomeric 3-methyl and 5-methyl isoxazoles is obtained from hydroxy methylene acetone and hydroxyl amine hydrochloride in alcoholic alkali solution whereas the alkyl ether of hydroxymethylene acetone in acetic acid gave only 3-methyl isoxazole.\(^{14,15}\)

Weygand et. al.\(^{74}\) have also reported the formation of only one isoxazole from the two isomeric methyl ethers of anisoylaceto phenone and hydroxylamine hydrochloride in acid medium. This is due to the fact that
enol form of β-diketone is formed by the hydrolysis of enol ethers in acid medium which is then converted into isoxazole.

In alkaline medium, this reaction proceeds by 1, 4-addition. This is supported by the isolation of β-hydroxylamine chalcone in neutral solution which is converted into isoxazole by the treatment with acid or alkali. Eistert and Markel\textsuperscript{16} 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. Thus, p-anisoylphenyl acetylene (9) reacts with hydroxylamine hydrochloride in acid medium to give isoxazole (9a) and in basic medium isoxazole (9b) and benzoyl-p-methoxyphenyl acetylene (9c) gives isoxazole (9b) in acid and isoxazole (9a) in basic medium. Depending upon the experimental conditions, here both 1, 4- and 1, 2-type of additions 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.

Acetylenes treated with fuming nitric acid form isoxazoles in the presence of acetone.
Acetylenic compounds also on treatment with nitrolic acid formed isoxazoles. Nitrileoxide first formed by the elimination of nitrous acid then reacts with acetylene yielding isoxazole.

\[
\begin{align*}
\text{(10)} & : 
\begin{array}{c}
\text{CH}_3-\text{C} \equiv \text{C}-\text{NO}_2 \\
\text{O} \quad \text{N} \cdot \text{OH}
\end{array} \\
\text{(10a)} & : 
\begin{array}{c}
\text{CH}_3-\text{C} \equiv \text{C}-\text{N} \equiv \text{O} \\
\text{O}
\end{array} \\
\text{(10b)} & : 
\begin{array}{c}
\text{H}_3\text{COC} \\
\text{N} \equiv \text{C} \cdots \text{C} \equiv \text{CPh}
\end{array} \\
\text{(10c)} & : 
\begin{array}{c}
\text{H}_3\text{COC} \\
\text{C} \cdots \text{CPh}
\end{array}
\]

Schlubach and Repenning reported the synthesis of 3, 5-diaryl isoxazole from acetylene and nitrolic acid or aciphenyl-nitromethane in the presence of boron trifluoride.

\[
\begin{align*}
\text{(11)} & : 
\begin{array}{c}
\text{Ph-CH}=\text{N} \\
\text{OH}
\end{array} \\
\text{(11a)} & : 
\begin{array}{c}
\text{Ph-CH}=\text{N} \\
\text{O}
\end{array} \\
\text{(11b)} & : 
\begin{array}{c}
\text{Ph-CH}=\text{N} \\
\text{O}
\end{array} \\
\text{(11c)} & : 
\begin{array}{c}
\text{Ph-CH}=\text{N} \\
\text{O}
\end{array}
\]

Chalcone epoxide have also been used in the synthesis of 3, 5-diaryl isoxazoles by the action of hydroxylamine hydrochloride on the epoxide in various media. Epoxide oximes or 3, 5-diaryl-4-hydroxy isoxazolines are the intermediates which are readily converted into isoxazole. It was latter proved that 5-hydroxyisoxazoline is the intermediate rather than (12b).
2, 4, 6-Triphenylpyrylium salts\textsuperscript{23} yield 3, 5-isoxazole when treated with hydroxylamine hydrochloride. The same isoxazoles could also be obtained from the same reactants by photoelimination reaction.\textsuperscript{24}

It is found that the direct synthesis of 3, 5-diethyl isoxazole from 3, 5-dinitroheptane can be effected on treatment with KOH.\textsuperscript{25}

Flavones and thichromones\textsuperscript{26} and also chromones\textsuperscript{27} have been used in the synthesis of 3, 5-diaryl-isoxazoles and 3-aryl-5-methyl-isoxazole respectively.
Borkhade and Marathey\textsuperscript{75} obtained 3-(2-hydroxy-5-methylphenyl)-5-phenyl-isoxazoline; 3-(2-hydroxy-3-bromo-5-methylphenyl)-5-phenyl-isoxazoline and 3-(2'-hydroxy-3-bromo-5-methylphenyl)-5-phenyl isoxazole by the reaction of 2'-hydroxy-5'-methylchalcone dibromide with hydroxylamine hydrochloride in pyridine medium. Borkhade proposed mechanism for this reaction is based on that proposed by Ghiya and Marathey.\textsuperscript{28}

\[
\begin{align*}
&\text{OH} \\
&C-\text{CH} = \text{CH} \\
&\text{H}_3\text{C} \quad \text{(16)} \\
&\text{Br} \quad \text{Br} \\
&\text{C}_6\text{H}_4\text{N} \\
&\text{OH} \\
&C-\text{CH} = \text{CH} \\
&\text{H}_3\text{C} \quad \text{(16a)} \\
&\text{Br} \\
&\text{C}_6\text{H}_4\text{N} \\
&\text{OH} \\
&C-\text{CH} = \text{CH} \\
&\text{H}_3\text{C} \quad \text{(16b)} \\
&\text{Br} \\
&\text{C}_6\text{H}_4\text{N} \\
&\text{OH} \\
&C-\text{CH} = \text{CH} \\
&\text{H}_3\text{C} \quad \text{(16c)} \\
&\text{Br} \\
&\text{C}_6\text{H}_4\text{N}
\end{align*}
\]

\(\alpha\)-Acetyl-\(\beta\)-nitrostilbene on chemical and electrochemical reduction gave trisubstituted isoxazoles.\textsuperscript{29}
Perkin\textsuperscript{30} synthesised 3-(4-chlorophenyl)-5-(4-methoxyphenyl)-isoxazole by the treatment of \(\text{P-ClC}_6\text{H}_4\text{CO}_2\text{Me}\) with \(\text{BuLi}\) at 0\(^\circ\text{C}\) followed by the cyclisation of intermediate with \(\text{P-MeOC}_6\text{H}_4\text{CO}_2\text{Me}\) in THF containing HCl.

Elkasaby and Salem\textsuperscript{31} have reported the synthesis of 3, 5-diaryl isoxazoles from chalcones by different routes as given below.
Thakare et al.\textsuperscript{32} have synthesised 3-(2'-furyl or 2'-thienyl)-5-(2-hydroxyphenyl)-isoxazoles by reaction of 1, 3-propanediones with hydroxylamine hydrochloride in methanol.

![Chemical structure](attachment:image)

The o-hydroxydibenzoylmethanes and 3-iodoflavanones when treated with hydroxylamine hydrochloride in DMF/pyridine yielded isoxazoles.\textsuperscript{33}

![Chemical reactions](attachment:image)

Jamode\textsuperscript{76} have synthesised several 3-(o-hydroxyaryl)-5-arylisoazoles by the action of hydroxylamine hydrochloride in ethylenediamine on dibenzoylmethanes, flavones and 3-bromoflavanones.
Chincholkar et. al. reported the synthesis of isoxazoles (23a) and isomeric isoxazoles (23b) by the action of hydroxylamine hydrochloride on 3-arylfianavanones in pyridine and methanol medium respectively.

Sankyo Co. Ltd. synthesised by the addition of Cu(OAc)$_2$ to Pd (OAc)$_2$ in Me$_2$SO$_4$ followed by heating with 3-(p-Tosyloxy)-5-methylisoxazole in benzene.
Kakade\(^\text{76}\) synthesised isomeric 3-phenyl-5-(2-hydroxyphenyl)-isoxazoles from 1-(2-hydroxyphenyl)-3-phenyl-1, 3-propanediones and hydroxylamine hydrochloride in dimethylsulphoxide in presence of sodium acetate.

Mittal and Singhal\(^\text{76}\) synthesised isoxazoles from different substituted benzene diazonium chlorides coupled with some reactive methylene compounds and then condensed with hydroxylamine hydrochloride.

Nair\(^\text{77}\) has reported the synthesis of isomeric isoxazoles from 1-(*2'-furyl)*-3-(2''-hydroxyphenyl)1-, 3-propanedione in pyridine and methanol.
Steven et. al.\textsuperscript{38} have synthesised isoxazoles by the action of Ph.CClNOH with $\text{H}_2\text{C}:\text{Cl}_2$ and Et$_3$N followed by NaOCH$_2$Ph treatment.

Grabowask et. al.\textsuperscript{39} prepared chlorosubstituted isoxazoles from ClC$_6$H$_4$CH.NOH and MeCOCH$_2$COOEt in the presence of NaOCl and NaOH.

Gaggad et. al.\textsuperscript{40} have reported the preparation of 3-(2-hydroxyphenyl)-5-styryl isoxazole from 1-(2-hydroxyphenyl)-5-phenyl-4-pentene-1, 3-diones by the action of hydroxylamine hydrochloride in pyridine.
Kashima et. al.\(^4\) reported the selective synthesis of 3, 5-disubstituted isoxazoles by the cyclocondensation of \(b\)-substituted enones with \(\text{NH}_2\text{OH.HCl}\) in the presence of \(\text{K}_2\text{CO}_3\), \(\text{Et}_3\text{N}\) or \(\text{NaOMe}\).

Reaction of 2-hydroxydibenzoylmethane and hydroxylamine hydrochloride in various solvents such as pyridine, ethylenediamine, aqueous DMF, methanol containing excess of KOH etc. has been studied\(^4\) and reported the formation of 3-(2-hydroxy-5-methylphenyl)-5-(4-methoxy phenyl)-isoxazole (31a) and 3-(\(\alpha\)-hydroxylamino-4-methoxystyryl)-5-methyl benzene isoxazole (31b).

\[
\begin{align*}
(31a) & \quad \text{O} \quad \text{H} \\
(31b) & \quad \text{H} \quad \text{N} = \text{O} \quad \text{OH}
\end{align*}
\]

Oda Kengo et. al.\(^4\) have reported the synthesis of isoxazole by the action of 3-(3-chlorophenyl)-4-chloro-5-acetoxy-2-isoxazoline on 1, 8-diazobicyclo (5, 4-0) undecane in THF.

\[
\begin{align*}
(32) & \quad \text{Xn} \\
(33) & \quad \text{X} \quad \text{Y}
\end{align*}
\]

Malyula et. al.\(^4\) synthesised substituted isoxazoles by halogenation of the corresponding derivatives (\(X=H\)) by Cl, Br, I-KI and dehydrohalogenation of the resulting intermediate in dioxane or MeOH.

\[
\begin{align*}
(33) & \quad \text{N} \quad \text{O} \quad \text{X} \\
(33a) & \quad \text{N} \quad \text{O} \quad \text{X}
\end{align*}
\]
Isomeric 5-(2'-hydroxyphenyl)-3-styrylisoxazoles\textsuperscript{45} have been synthesised from 1-(2'-hydroxyphenyl)-5-phenyl-4-pentent-1, 3-diones and hydroxylamine hydrochloride in ethanol.

3-Methyl-4-aryloxy-5-(2-hydroxyphenyl)-isoxazoles and 3-methyl-4-(2-hydroxybenzoyl)-5-aryl isoxazoles have been synthesised\textsuperscript{46} from 3-aryloxy-2-methylchromones by the action of hydroxylamine hydrochloride in ethanol containing aqueous KOH and pyridine respectively.

Chiriano et. al.\textsuperscript{47} reported the formation of isoxazoles from $R_1 C=CH_2$, H.COCO$_2$H, HONO$_2$ and HCl.

Synthesis of 4-amino-3-(p-chlorophenyl)-5-(b-aminoethylthio)-isoxazoles has been reported\textsuperscript{48} by the treatment of NaOEt.EtOH, HCl-Ether with 4-(p-chlorophenyl)3-methyl furoxane and condensing with Li(CH$_2$)$_2$NH$_2$. 
Sharan\textsuperscript{49} synthesised isoxazoles having fungicidal activity towards Aspergillus niger, by the condensation of substituted aldehydes with 8-acetyl-7-hydroxy-4-methyl coumarin followed by cyclisation with $\text{NH}_2\text{OH}$.

Isomeric isoxazoles have been synthesised\textsuperscript{50} 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{51} reported the synthesis of 3, 4-di-(4-methoxy phenyl)-5-methyl isoxazole and its use in the preparation of anti-inflammatory, analgesic and anti-pyretic drugs. It is also reported to inhibit prostaglandin formation by blocking cyclooxygenase.
Nagana Mitsuo et. al.\textsuperscript{52} reported the synthesis of 3-(2, 3-dihydroxy propoxy)-isoxazoles and their use as the muscle reluctants.

\[
\begin{align*}
\text{CH}_2\text{OH}&.\text{CH(OH)}_.\text{CH}_2\text{O} \\
\text{R}_1, \text{R}_2
\end{align*}
\]

$\alpha, \beta$-Unsaturated ketoxime derivatives on oxidation yielded isoxazol-5-yl -acetic acid.\textsuperscript{53}

\[
\begin{align*}
\text{R, } \text{CH}_2\text{COOH} \\
\text{CH, } -<0>^\text{CH}-<0>-\text{Oe.}
\end{align*}
\]

Hagiwara Yuichi et. al.\textsuperscript{54} synthesised 3, 4-di-(4-methoxyphenyl)-5-methyl isoxazole from 5-hydroxyimino-4, 5-di-(4-methoxyphenyl)-3-pentenoate and hydrochloric acid by stirring in methanol at 60°C.

\[
\begin{align*}
\text{CH}_2\text{O}_.\text{N}_.\text{O_.} \\
\text{R}_1, \text{R}_2
\end{align*}
\]

These isoxazoles are used as anti-inflammatory, analgesics and antipuretics.

Rajput\textsuperscript{79} gave the formation of 3, 5-diaryl isoxazoles from 1, 3-propanediones flavones and chalconedibromides by the action of hydroxylamine hydrochloride in ethanol as the reaction solvent containing piperidine.
A convenient method for the preparation of 3, 4-diarylloxazoles was given by Wei Xudong et al.\textsuperscript{55} These were prepared by the oxidation of HON:(RCH:CHR\textsubscript{2}) with a new metal complex oxidant, tetrakis (pyridine) Cobalt (II) dibromate (TPCD).

Raghuwanshi\textsuperscript{60} used DMSO-I\textsubscript{2} system for the oxidation of isoxazolines in the synthesis of isoxazoles.
Chattopadhyay et al.\textsuperscript{56} reported the synthesis of 4-amino-5-benzoyl isoxazole-3-carboxamide directly from oximino cyanoacetamide and benzylamine via the corresponding oximinates.

\begin{equation}
\begin{array}{c}
\text{R-CN} \\
\text{ON}
\end{array}
\quad \xrightarrow{\text{Ph.CH$_2$NH$_2$, Ph.O.CO.CH$_2$Br}}
\quad
\begin{array}{c}
\text{R-C} \\
\text{NH$_2$, CO.Ph}
\end{array}
\end{equation}

Shibata Yashshi et al\textsuperscript{57} synthesised triazolylisoxazoles derivatives from \(\beta\)-(dimethylamino)-acrylophenone by the action or hydroxyl amine hydrochloride in ethanol containing small amount of \(\text{P-Me.C$_6$H$_4$SO$_2$.H}\). These derivatives are used in the preparation of insecticides and acaracides.

\[
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{N} \\
\text{N-Me} \\
\text{F}
\end{array}
\]

Talley John\textsuperscript{58} reported isoxazole compounds as cycloxygenase inhibitors.

\[
\begin{array}{c}
\text{Cl} \\
\text{Cl} \\
\text{CO$_2$.H} \\
\text{N} \quad \text{O} \\
\text{Me} \quad \text{SO$_2$.NH$_2$}
\end{array}
\]

Damale et. al.\textsuperscript{59} have reported the synthesis of 3-(2'-hydroxyphenyl)-5-(nitrosubstitutedphenyl)-isoxazoles and isomeric isoxazoles, 3-(nitro-substitutedphenyl)-5-(2'-hydroxyphenyl)-isoxazoles.
Heda et. al. synthesized 4-iodo-3, 5-(substituted diphenyl) isoxazoles by condensing 2-iodopropane, 1, 3-dion hydroxylamine hydrochloride and phenyl hydrazine in ethano. It exhibit antimicrobial activity.

Ravindra et. al. reported the synthesis and antifungal activity of substituted 5, 6-hydroxy-3-methyl-1, 2-benzisoxazoles.

Gajbhiye et. al. have been reported bis-isoxazoles synthesised by the reaction of bis-chalconedibromide with hydroxylamine hydrochloride in pyridine medium.
Thakare et al.\textsuperscript{63} reported the synthesis of 3-(substituted-2"'-hydroxyphenyl)-5-(2'-furyl)-isoxazoles and isomeric 3-(2'-furyl)-5-(substituted-2"'-hydroxyphenyl)-isoxazoles from b-(2'-furyl)-acrylphenone dibromides and hydroxylamine hydrochloride in pyridine and methanol medium respectively.
Patil K. N. et al.\textsuperscript{64} have reported the synthesis of 3,5-diaryl-4-aryloxyisoxazoles from Chloro substituted 3-aryloxygenone on treatment with NH$_2$OH/HCl.

\[ \text{NH}_2\text{OH / HCl / aq. KOH} \]

\[ \text{Methanol / Pyridine} \]

(54a) \hspace{2cm} (54b)

Amravati University
ORIGIN OF THE PROBLEM

3, 5-Diarylisoxazoles are usually synthesised by the action of hydroxylamine on 1, 3-dicarbonyl compounds. 3, 5-Diaryl-isoxazoles are reported to be formed from flavones, chromones, chalconedibromides or α-bromochalcones. Rao and Rao reported the synthesis of isoxazoles from 2'-hydroxychalconedibromides in an alkaline medium and from B-diketones by treatment with NH₂OH.HCl with or without the addition of alkali. Borkhade and Marathey have synthesised isoxazole from B-diketone, flavone, 3-bromoflavanone on treatment with NH₂OH.HCl in pyridine medium. Ethylenediamine is used as the reaction medium in the preparation of 3, 5-diarylisoxazoles by the action of NH₂OH.HCl on B-diketones, flavones and 3-bromoflavanones. Wadodkar reported the formation of 3, 5-diarylisoxazoles from o-hydroxydibenzoyl-methanes and 3-iodoflavanones by reaction with NH₂OH.HCl in DMF. Methanol has been used as solvent in the synthesis of 3, 5-disubstituted isoxazoles from 1, 3-propanediones and NH₂OH.HCl. 3-Aroylflavones have been used for the first time in the synthesis of isomeric 3, 5-diaryl-4-aroylisoxazoles in pyridine and methanol media. Nair reported further synthesis of 3-(2'-hydroxyphenyl)-4-(2'-furoyl)-5-aryl isoxazoles and 3-(2''-hydroxyphenyl)-4-(2''-furoyl)-5-methyl isoxazoles from 3-aroyl-2-aryl chromones and 3-aroyl-2-methyl chromones by the action of NH₂OH.HCl in pyridine medium.

Literature survey has thus prompted us for the present study involving the use of DMF solvent containing few drops of piperdine as a medium for the synthesis of some new substituted 3, 5-diaryl-4-aroyl isoxazoles from some new substituted 3-aroyl flavones.
PROBLEM

The present work deals with the synthesis of some new substituted 3, 5-diaryl-4-aryloxy isoxazoles from some new substituted 3-aryloxy flavones and \( \text{NH}_2\text{OH.HCl} \) in DMF solvent containing few drops of piperidine as a medium. It has been revealed that the use of DMF solvent containing few drops of piperidine as a medium increases the rate of reaction and so reduced the reflux time from 3 hours to 1:30 hours with very good yield of the products.

The structures have been confirmed on the basis of elemental analysis and spectral studies (IR, UV, NMR). The probable mechanism has also been discussed.

SCHEME
SUMMARY OF THE WORK

STARTING MATERIALS

2-hydroxy acetophenones (1a-b), 2-benzoyloxy acetophenones (2a-b), 1, 3-propanediones (3a-b) and 3-aryl flavanones (4a-d) were prepared by the procedures as described in chapter III of part I of this thesis. Also 3-aryl flavones (5a-d) were prepared by the procedure as described in chapter III of Part III.

Some new substituted-3, 5-diaryl-4-aryloyl Isoxazoles (9a-d)

Some new substituted-3, 5-diaryl-4-aryloyl Isoxazoles (9a-d) where synthesised on refluxing of 3-aryloyl flavones (5a-d) and hydroxyl amine hydrochloride in DMF solvent containing few drops of piperidine for 1.3 hrs. Thus, the following 3, 5-diaryl-4-aryloyl Isoxazoles were synthesised.

- 3-(2'-hydroxy-5'-chloro phenyl)-4-(4'-chloro benzoyl)-5-(4'-N, N-dimethyl amino phenyl) Isoxazole (9a); m. p. 208°C.
- 3-(2'-hydroxy-5'-chloro phenyl)-4-(4'-chloro benzoyl)-5-(3', 5'-dimethoxy-4'-hydroxy phenyl) Isoxazole (9b); m. p. 206°C.
- 3-(2'-hydroxy-3'-nitro-5'-methyl phenyl)-4-(4'-chloro benzoyl)-5-(4'-N, N-dimethyl amino phenyl) Isoxazole (9c); m. p. 199°C.
- 3-(2'-hydroxy-3'-nitro-5'-methyl phenyl)-4-(4'-chlorobenzoyl)-5-(3', 5'-dimethoxy-4'-hydroxy phenyl) Isoxazole (9d); m. p. 191°C.

The structure of (9a) was confirmed on the basis of elemental analysis, chemical properties and spectral analysis (IR, UV, PMR). The probable mechanism for the formation of isoxazole have been discussed.
From the historical account of the literature, it is observed that the reaction of chalconedibromide with different nitrogen nucleophiles like hydroxylaminehydrochloride, hydrazinehydrochloride and semicarbazide in alkaline medium provides different nitrogen heterocyclic compounds. Borkhade\(^{84}\) used pyridine as a basic medium for the synthesis of isoxazoles from chalconedibromides or dibenzoylmethanes. Use of pyridine has also been reported in the synthesis of isoxazoles from acetylenic ketones\(^{92}\) or flavones\(^{86}\) by the reaction with NH\(_2\)OH.HCl. Use of methanol\(^{90}\) has been reported in the synthesis of 3-(2'-furyl-or 2'-thienyl)-5-(2-hydroxyphenyl) isoxazoles with NH\(_2\)OH.HCl. 3-Iodoflavanones\(^{81}\) have been used as starting materials for the synthesis of isoxazoles. 3-Aroyl flavones\(^{93}\) have been used for the synthesis of isomeric 3, 5-diaryl-4-aryl isoxazoles in pyridine and methanol media. Nair\(^{95}\) reported further, synthesis of 4-furoyl-3, 5-diarylisoxazoles and 4-furoyl-3-aryl-5-methyl-isoxazoles from 3-aryloyl-2-arylchromones and 3-aryloyl-2-methyl-chromones in pyridine medium by the action of NH\(_2\)NH.HCl.

Here, this part deals with the use of DMF solvent containing few drops of piperidine, for the first time, as a medium, for the synthesis of 3, 5-diaryl-4-aryl isoxazoles (9a-d) from chlorosubstituted 3-aryloylfavones (5a-d) on treatment with NH\(_2\)OH.HCl.

All the compounds have been characterised on the basis of chemical properties and elemental and spectral analysis. The melting points are uncorrected. The infrared spectrum was recorded on "Nujol" spectrophotometer. The proton magnetic resonance spectrum was recorded
on UV-VB spectrophotometer-119. The UV-VIS, spectrum was recorded on "Perkin-Elmer 202" spectrophotometer. The carbon and hydrogen analysis was carried out on "Carlo-Erba 1106" analyser. The nitrogen estimation was carried out on "Coleman-N-analyser 29". The elemental and spectral analysis was carried out at RSIC, Punjab University, Chandigarh, Pune University, Pune. Vidyabharti Mahavidyalaya, Amravati. The chemicals used were synthesised was tested by TLC.

**PREPARATION OF THE STARTING MATERIALS**

2-hydroxy acetophenones (1a-b), 2-benzoyloxy acetophenones (2a-b), 1, 3-propanediones (3a-b) and 3-aroyl flavanones (4a-d) were prepared by the procedures as described in chapter III of part I of this thesis. Also 3-aroyl flavones (5a-d) were prepared by the procedure as described in Chapter III Part III

**Synthesis of Some new substituted 3,5-diaryl-4-Aroyl isoxazoles (9a-d) from 3-aroyl flavones (5a-d)**

Isoxazoles have been usually obtained from chalconedibromide and diketone94 and also from acetylenic ketones92 or flavones with NH₂OH.HCl. Methanol97 and pyridine have been used as reaction media. 3-aroylflavones93 have been used for the synthesis of isomeric isoxazoles in pyridine and methanol media. Nair95 used 3-furoylchromones for the synthesis of 4-furoylisoxazoles in pyridine medium.

In this part, some new substituted 3, 5-diaryl-4-aroyl isoxazoles (9a-d) have been synthesised from 3-aroyl flavones (5a-d) and NH₂OH.HCl in DMF solvent containing few drops of piperidine. Piperidine enhances the basicity of NH₂OH and increases the rate of the reaction and yields of the isoxazoles.
GENERAL PROCEDURE FOR THE PREPARATION OF SOME NEW SUBSTITUTED-3, 5-DIARYL-4-AROYL ISOXAZOLES (9a-d)

A mixture of some new substituted 3-aroyl flavones (5a-d) (0.01 mol) and hydroxyl amine hydrochloride (0.02 mol) in DMF (10 ml) containing a few drops of piperidine, was refluxed for 1.3 hrs. The reaction mixture was cooled. After cooling the reaction mixture was acidified with dilute HCl (1:1). The solid product thus separated was filtered, washed with sodium bicarbonate solution 2% and then with water. Finally it was crystallised from ethanol acetic acid mixture (80:20), yield 70%.

Experiment No. 15
Action of NH₄OH.HCl on 4'-(N,N-dimethyl amino)-3-(4'-chloro benzoyl)-6-chloro flavone (5a):

Formation of 3-(2'-hydroxy-5'-chloro phenyl)-4-(4'-chloro benzoyl)-5-(4'N,N-dimethyl amino phenyl) Isoxazole (9a):

4'-(N,N-dimethyl amino)-3-(4'-chloro benzoyl)-6-chloro flavone (5a) (0.01 mol) and hydroxyl amine hydrochloride (0.02 mol) was refluxed in DMF (10 ml) containing few drops of piperidine for 1.3 hrs. The reaction mixture was cooled and then decomposed by acidified water. The product thus obtained was separated and washed with sufficient water. It was
crystallised from ethanol acetic acid mixture (80:20) to obtain white crystalline solid compound (9a), m.p. 208°C.

PROPERTIES AND CONSTITUTION OF THE COMPOUND (9a)

1. The compound (9a) showed no colouration with ethanolic FeCl₃ solution, but it was soluble in NaOH giving yellow coloration indicating the presence of phenolic -OH group.

2. TLC: Solvent (CCl₄) height : 4.5 cm.
   Solute height : 2.1 cm.
   Rf value : 0.46

3. The analytical data of the compound (9a), the molecular formula was found to be C₃₄H₂₈Cl₂N₂O₇.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>% C</th>
<th>% H</th>
<th>% N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
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<td>6.15</td>
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<tr>
<td>Calculated</td>
<td>63.57</td>
<td>3.97</td>
<td>6.18</td>
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</table>

Spectral analysis of the compound (9a)

IR, UV and PMR spectra of the compound (9a) were recorded and showed the following results (IR: Spectrum No. 19, UV: Spectrum No. 20, PMR: Spectrum No. 21).

(a) The IR Spectrum of the compound no. (9a) (Spectrum No. 19) was recorded in Nujol and showed the following absorption bands: 98-102
7. Frequency cm⁻¹ | Intensity | Correlation
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>3448</td>
<td>(v, b)</td>
<td>O-H stretching</td>
</tr>
<tr>
<td>1751-1612</td>
<td>m</td>
<td>C=O stretching</td>
</tr>
<tr>
<td>1377</td>
<td>s</td>
<td>C-O stretching in phenol</td>
</tr>
<tr>
<td>1569</td>
<td>s</td>
<td>C=N stretching</td>
</tr>
<tr>
<td>609</td>
<td>s</td>
<td>C-Cl stretching</td>
</tr>
<tr>
<td>1612-1569</td>
<td>s</td>
<td>C=N-O stretching</td>
</tr>
<tr>
<td>1461-1569</td>
<td>s</td>
<td>C=C stretching</td>
</tr>
</tbody>
</table>

(b) The UV spectrum of the compound no. (9a) (Spectrum No. 20) was recorded in CHCl₃ showed λmax 323 nm corresponding to n --> π* transition.

(c) The proton NMR spectrum of the compound (9a) (Spectrum No. 23) was recorded in CDCl₃. The observed chemical shift can be correlated as follows: 97-105

<table>
<thead>
<tr>
<th>Chemical shift δ ppm</th>
<th>Nature of peak</th>
<th>No. of protons</th>
<th>Types of protons</th>
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<tr>
<td>2.85</td>
<td>s</td>
<td>6H</td>
<td>AR·N(CH₃)₂</td>
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<tr>
<td>6.7-8.16</td>
<td>m</td>
<td>11H</td>
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<tr>
<td>11.92</td>
<td>s</td>
<td>1H</td>
<td>-OH</td>
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From the chemical properties, analytical results and spectral analysis, compound (9a) was assigned the structure 3-(2'-hydroxy-5'-chloro phenyl)-4-(4'-chloro benzoyl)-5-(4'N,N-dimethyl amino phenyl) isoxazoles (9a)
Peaktable of B-8.IRS, 29 Peaks
Threshold: 100, Noise: 2, File Range Selection

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<td>609.5</td>
<td>94.008</td>
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<tr>
<td>4</td>
<td>657.7</td>
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POINT PICK
323.2  1.596

PEAK PICK
323.2  1.596
368.8  0.748
396.4  0.734

\[ \text{Chemical Structure} \]

Spectrum No. 20

SYBTRONICS 119

As already explained, it has been observed that the electron donating group such as N(CH$_3$)$_2$ at 4'-position of the side phenyl ring at position 2 in flavone causes an increase in the yield. This may be attributed to the increase in electron density on oxygen of carbonyl group due to the increase in electron density on oxygen of carbonyl group due to electron flow from N(CH$_2$)$_2$ group. This increased electron density accelerates the process of 1:2-addition of NH$_2$OH.HCl which results in the molecule of an intermediate adduct. This then loses the molecule of water to give oxime which undergoes cyclization to give isoxazole (9a). The mechanism is given below.

**Reaction Mechanism :-**
Experiment No. 16
Action of NH$_3$.OH.HCl on (3',5'-dimethoxy-4'-hydroxy)-3-(4'-chloro benzoyl)-6-chloro flavone (5b):

Formation of 3-(2'-hydroxy-5'-chloro phenyl)-4-(4'-chloro benzoyl)-5-(3', 5'-dimethoxy-4'-hydroxy phenyl) Isoxazole (9b):

(3', 5'-dimethoxy-4'-hydroxy)-3-(4'-chloro benzoyl)-6-chloro flavone (5b) (0.01 mol) and Hydroxyl amine hydrochloride (0.02 mol) was refluxed in DMF (10 ml) containing few drops of piperidine for 1.3 hrs. The reaction mixture was cooled and then decomposed by acidified water. The product thus obtained was separated and wash with sufficient water. It was crystallised from ethanol acetic acid mixture (80:20) to obtain white crystalline solid compound (9b), m.p.206°C.

PROPERTIES AND CONSTITUTION OF THE COMPOUND (9b)
1. The compound (9b) showed no colouration with ethanolic FeCl$_3$ solution, but it was soluble in NaOH giving yellow coloration indicating the presence of phenolic -OH group.

2. TLC: Solvent (CCl$_4$) height : 4.5 cm.
Solute height : 2.1 cm.
Rf value : 0.46
3. The analytical data of the compound (9b), the molecular formula was found to be \( \text{C}_{24}\text{H}_{17}\text{Cl}_{2}\text{NO}_6 \).

<table>
<thead>
<tr>
<th>Analysis</th>
<th>% C</th>
<th>% H</th>
<th>% N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
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<td>2.83</td>
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<tr>
<td>Calculated</td>
<td>59.25</td>
<td>3.49</td>
<td>2.88</td>
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</table>

4. On the basis of analytical and chemical properties, the compound (9b) was assigned the structure as 3-(2'-hydroxy-5'-chloro phenyl)-4-(4'-chloro benzoyl)-5-(3', 5'-dimethoxy-4'-hydroxy phenyl) Isoxazole (9b):

![Structure of (9b)](image)

Experiment No. 17

**Action of \( \text{NH}_2\text{OH.HCl} \) on 4'-(N,N-dimethyl amino)-3-(4'-chloro benzoyl)-6-methyl-8-nitro flavone (5c)**

**Formation of 3-(2'-hydroxy-3'-Nitro-5'-methyl)-4-(4'-chloro benzoyl)-5-(4'-N,N-dimethyl amino phenyl) Isoxazole (9c)**

4'-(N,N-dimethyl amino)-3-(4'-chloro benzoyl)-6-methyl-8-nitro flavone (5c) (0.01 mol) and Hydroxyl amine hydrochloride (0.02 mol) was refluxed in DMF (10 ml) containing few drops of piperidine for 1.3 hrs. The reaction mixture was cooled and then decomposed by acidified water. The product thus obtained was separated and wash with sufficient water. It was crystallised from ethanol acetic acid mixture (80:20) to obtain white crystalline solid compound (9c), m.p. 199°C.
PROPERTIES AND CONSTITUTION OF THE COMPOUND (9c)

1. The compound (9c) showed no colouration with ethanolic FeCl₃ solution, but it was soluble in NaOH giving yellow coloration indicating the presence of phenolic -OH group.

2. TLC: Solvent (CCl₄) height : 4.5 cm. 
   Solute height : 1.9 cm. 
   Rf value : 0.42

3. The analytical data of the compound (9c), the molecular formula was found to be C₂₅H₂₀ClN₃O₆.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>% C</th>
<th>% H</th>
<th>% N</th>
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</thead>
<tbody>
<tr>
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<td>4.55</td>
<td>8.77</td>
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<tr>
<td>Calculated</td>
<td>62.82</td>
<td>4.60</td>
<td>8.79</td>
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</table>

4. On the basis of analytical and chemical properties, the compound (9c) was assigned the structure as 3-(2'-hydroxy-3'-Nitro-5'-methyl phenyl)-4-(4'- chloro benzoyl)-5-(4'-N,N-dimethyl amino phenyl) Isoxazol (9c):
Experiment No. 18
Action of NH$_2$OH.HCl on (3',5'-dimethoxy-4'-hydroxy)-3-(4'-chlorobenzoyl)-6-methyl-8-nitro flavone (5d).

Formation of 3-(2'-hydroxy-3'-Nitro-5'-methyl phenyl)-4-(4'-chlorobenzoyl)-5-(3',5'-dimethoxy-4'-hydroxy phenyl) Isoxazole (9d):

(3',5'-dimethoxy-4'-hydroxy)-3-(4'-chlorobenzoyl)-6-methyl-8-nitro flavone (5d) (0.01 mol) and Hydroxyl amine hydrochloride (0.02 mol) was refluxed in DMF (10 ml) containing few drops of piperidine for 1.3 hrs. The reaction mixture was cooled and then decomposed by acidified water. The product thus obtained was separated and wash with sufficient water. It was crystallised from ethanol acetic acid mixture (80:20) to obtain white crystalline solid compound (9d), m.p. 191°C.

PROPERTIES AND CONSTITUTION OF THE COMPOUND (9d)

1. The compound (9d) showed no colouration with ethanolic FeCl$_3$ solution, but it was soluble in NaOH giving yellow coloruation indicating the presence of phenolic -OH group.

2. **TLC**:
   - Solvent (CCl$_4$) height : 4.5 cm.
   - Solute height : 1.3 cm.
   - Rf value : 0.28
3. The analytical data of the compound (9d), the molecular formula was found to be $\text{C}_{25}\text{H}_{19}\text{ClN}_{2}\text{O}_8$.

<table>
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<th>Analysis</th>
<th>% C</th>
<th>% H</th>
<th>% N</th>
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<tbody>
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<td>5.67</td>
<td>5.44</td>
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<td>3.72</td>
<td>5.48</td>
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</table>

4. On the basis of analytical and chemical properties, the compound (9d) was assigned the structure as 3-(2'-hydroxy-3'-Nitro-5'-methyl phenyl)-4-(4'-chloro benzoyl)-5-(3', 5'-dimethoxy-4'-hydroxy phenyl) Isoxazole (9d):

![Structural formula of compound (9d)](image)

**Probable Mechanism:**

The addition of Hydroxylamine to a carbonyl group involves the nucleophilic attack by nitrogen on it. Protonation of carbonyl oxygen makes carbonyl carbon more susceptible to a nucleophilic attack. In carbonyl compounds the addition will be favoured by high acidity. But, if the solution is too acidic, hydroxylamine can also undergo protonation to form the ion $\text{NH}_3\text{OH}$ which lacks unshared electron pair and is no longer nucleophile. Thus, the conditions under which the addition proceeds favourably are the results of the compromise; the solution must be acidic enough for an appreciable fraction of carbonyl compound to be protonated, but not so acidic that the concentration of free nitrogen is too low.

DMF with piperidine as a medium might be satisfying the necessary conditions required for nucleophilic addition. The formation of probable intermediate mono-oxime involves the attack of nucleophile $\text{NH}_3\text{OH}$ on carbonyl compound to form the adduct. This is followed by acid/base catalysed dehydration of the latter to yield oxime.
Based on these facts, the probable mechanism by which the formation of isoxazole from 3-arylfavones and \( \text{NH}_2\text{OH}. \text{HCl} \) in DMF/Piperidine takes place can be rationalised as under.

The formation of isoxazole involves 1:2-addition of \( \text{NH}_2\text{OH}. \text{HCl} \) to carbonyl function giving an adduct. This then loses water molecule to give mono-oxime. The mono-oxime under experimental conditions cyclizes to isoxazole.
REFERENCES

21. Schlubach, H. H. and Repenning, K. Liebig,


