REVIEW

The work presented in this thesis deals with the synthesis and properties of 2-imidazolin-5-ones. As a background to these investigations a critical survey of the literature on the synthesis of 2-imidazolin-5-ones is quite appropriate. The following review so prepared deals with synthesis of 2,4-disubstituted imidazolin-5-ones.

Synthesis of Unsaturated 2-Imidazolin-5-ones

Imidazolinones with an exocyclic double bond at the 4\textsuperscript{th} position is usually called unsaturated 2,4-disubstituted 2-imidazolin-5-ones. They are also known as unsaturated 2,4-disubstituted 5(4H)-imidazolones and unsaturated 2,4-disubstituted 5-ketodihydro glyoxalines. They are usually called unsaturated 2-imidazolin-5-ones for convenience.

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{O} \\
\text{R} \text{2} \\
\text{R} \text{1}
\end{array}
\]

The synthesis of unsaturated 2-imidazolin-5-one was first reported in 1899 by Ruheman and Cunnington.\textsuperscript{8,9} They synthesised 2-phenyl-4-benzylidene-2-imidazolin-5-one by condensing phenylpropionic ester with benzamidine hydrochloride in presence of sodium ethoxide. But no other unsaturated 2-imidazolin-5-one have been prepared by this method.
At present there are four general methods for the synthesis of unsaturated 2-imidazolin-5-ones namely azlactone, imidine-glyoxal, imidic acid ester-glycine ester and amidine-haloacetic ester method.

**Azlactone method**

Azlactones may be considered as anhydrides of alpha-acylamino acids. Erlenmeyer\textsuperscript{10-18} prepared 2-phenyl-4-arylidene-2-imidazolin-5-ones starting from azlactone. On heating a mixture of benzaldehyde and hippuric acid in presence of fused sodium acetate and acetic anhydride, the azlactone of alpha benzoylaminocinnamic acid is formed. This azlactone readily affords alpha benzoylaminocinnamic acid amide on heating with conc.ammonia in presence of alcohol. The amide then cyclises to give 2-phenyl-4-benzylidene-2-imidazolin-5-ones, under the influence of hot dilute sodium hydroxide solution.

The method was further extended by various workers\textsuperscript{19-30} to synthesise 1,2,4-trisubstituted-2-imidazolin-5-ones.
In 1935 Ekeley and Ronzio\textsuperscript{31} developed a method for the synthesis of 2-aryl-4-arylidene-2-imidazolin-5-one by condensing aromatic aldehydes with aromatic amidine-glyoxal addition products. Actually they thought that the condensation products obtained were either diarylpyrimidones or 2-aryl-4-aryloylglyoxalones. For example on treating a mixture of glyoxal and benzamidine hydrochloride with potassium hydroxide, a labile basic substance is formed. It may be represented either as an open chain compound or preferably as a 2-phenyl-4,5-dihydroxy-2-imidazoline.
On condensing aromatic aldehydes with this substance in the presence of NaOH or KOH good yields of 2-phenyl-4-arylidene-2-imidazolin-5-ones are obtained. The reaction may be formulated in the manner illustrated below using the more possible 4,5-dihydroxy-2-imidazoline structure for the benzamidine-glyoxal complex. It is assumed that the dihydroxyimidazoline loses one molecule of water under the influence of the base to form 2-phenyl-2-imidazolin-5-one containing a highly active methylene group.

The 2-phenyl-2-imidazolin-5-one thus formed readily undergoes condensation with the aldehyde to give the final product.

Ekeley and co-workers\textsuperscript{31,32} prepared numerous 2-aryl-4-arylidene-2-imidazolin-5-ones by this method using addition product of glyoxal with different aromatic amidines like benzamidine, p-toluamidine, m-toluamidine, etc.

In 1948 Cornforth\textsuperscript{33,34} prepared 5-imidazolones by the reaction between benzamidine hydrochloride and monosubstituted glyoxals.
The 4(5)-imidazolones which have a methylene group adjacent to the carbonyl group form benzylidene derivatives and also couple with diazonium salts.

**Imidic acid ester – Glycine ester method**

In 1907 Finger\(^{35}\) obtained 2-methyl-2-imidazolin-5-one by condensing glycine ester with acetimidic acid ester at room temperature. The 2-methyl-2-imidazolin-5-one condensed with two molecules of benzaldehyde to form 2-benzylidene-methyl-4-benzylidene-2-imidazolin-5-one.

![Chemical structure of 2-methyl-2-imidazolin-5-one and its derivatives](image)

Finger and Zeh\(^{36}\) prepared 2-benzyl-2-imidazolin-5-one by condensing phenylacetimidic ester and glycine ester. This imidazolone condenses with benzaldehyde in presence of alkali to give 2-benzyl-4-benzylidene-2-imidazoline-5-ones.

![Chemical structure of 2-benzyl-2-imidazolin-5-one and its derivatives](image)
In 1953 Kjaer prepared 2-phenyl-2-imidazolin-5-ones in 18.8% yield by condensing benzimidic acid ester with glycine ester in presence of anhydrous ether in nitrogen atmosphere. The product was recrystallised from benzene in an oxygen free atmosphere followed by sublimation. He obtained 2-phenyl-4-benzylidene-2-imidazolin-5-one by condensing benzaldehyde with 2-phenyl-2-imidazolin-5-one.

1-Naphthaldehyde, furfuraldehyde, isatin and pyruvic acid were also condensed with 2-phenyl-2-imidazolin-5-one and obtained the corresponding unsaturated 2-imidazolin-5-ons.

In 1953 Lehr and coworkers obtained 2-substituted 4-isopropylidene-2-imidazolin-5-ones instead of the expected 2-substituted 2-imidazolin-5-ones when imidic acid esters were condensed with glycine ester using acetone as solvent. Glycine ester and imidic acid ester first condense to form 2-substituted 2-imidazolin-5-one which in turn reacts with acetone to form 2-substituted-4-isopropylidene-2-imidazolin-5-one.
Lehr and coworkers\textsuperscript{38} prepared a large number of unsaturated 2-imidazolin-5-ones by refluxing aliphatic and aromatic ketones, acetoacetic ester, levulinic ester and acetophenone with a mixture of imidic acid ester and glycine ester. Benzene was used as solvent in the case of high boiling ketones while in the case of low boiling ketones excess of ketones themselves were the solvents. The structure of these compounds were confirmed by synthesising one of them namely 2-benzyl-4-cyclohexylidene-2-imidazolin-5-one by the simultaneous reaction of phenylacetimidic acid ester, glycine ester and cyclohexanone and also by the condensation of the preformed 2-benzyl-2-imidazolin-5-one with cyclohexanone.

In 1962 Kidwai and Devasia\textsuperscript{39} prepared a number of unsaturated 2-imdiazolin-5-ones by condensing aldehydes (aromatic aldehydes and isobutyraldehyde) with a mixture of an imidic acid ester and glycine ester in the presence of benzene at room temperature. When benzimidic acid ester was used they obtained very high yields of 2-phenyl-4-arylidene-2-imidazolin-5-ones. Phenylacetimidic acid ester and acetimidic acid ester are other imidic acid esters used by them.
They further improved this method by condensing aromatic aldehydes directly with a mixture of the hydrochlorides of an imidic acid ester and glycine ester in presence of sodium bicarbonate in benzene at 72°C. Thus they prepared a few 2-phenyl-4-arylidene-2-imidazolin-5-ones in very high yields.

In 1975 Devasia and Pillai\textsuperscript{40} prepared a few 2-phenyl-4-arylidene-2-imidazolin-5-ones employing the above methods of Kidwai and Devasia.

It is relevant to mention here that saturated 2,4-disubstituted-2-imidazolin-5-ones were prepared by condensing benzimidic acid ester with amino acid esters.\textsuperscript{41}
Imidazolinones having hypotensive activity were synthesised\textsuperscript{42} by cyclocondensation of various imidic acid esters with glycine ethyl ester.

In 1994 Griffiths and coworkers\textsuperscript{43} prepared imidazolones by the cyclocondensation of glycine ester hydrochloride (e.g., glycine methyl ester hydrochloride) with imidic ester (e.g., pentanimidic acid methyl ester) in presence of base (e.g., sodium hydroxide). These imidazolones were chlorinated with phosphorus oxychloride or through chloride to get their chloroderivatives which on treatment with DMF and POCl\textsubscript{3} yielded their formyl derivatives.

These compounds are useful as pharmaceuticals and agrochemicals.

**Amidine-Haloacetic Ester method**

In 1976 Devasia\textsuperscript{44} developed the amidine-chloroacetic ester method for the synthesis of unsaturated 2-imidazolin-5-ones. He obtained moderately good yields of 2-phenyl-4-arylidene-2-imidazolin-5-ones by condensing aromatic aldehydes with a mixture of benzamidine hydrochloride and ethyl

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chloroacetate in the presence of sodium bicarbonate in n-propanol at reflux temperature. As in the cases of amidine-glycerol and imidic acid ester-glycine ester methods, 2-phenyl-2-imidazolin-5-one with a highly active methylene group may be formed as intermediate and the aldehyde condense with it to form the final product.

Devasia and Shafi\textsuperscript{46} synthesised 4-arylidene-2-phenyl-2-imidazolin-5-ones by condensing aromatic aldehydes with a mixture of chloroacetyl chloride and benzamidine in presence of sodium bicarbonate.

Devasia and Shafi\textsuperscript{46} prepared a large number of unsaturated 2,4-disubstituted 2-imidazolin-5-ones employing the known amidine-haloacetic ester method.
In 1985 Shafi\textsuperscript{47} prepared 2-aryl-4-arylidene-2-imidazolin-5-ones in quantitative yield by condensing aromatic aldehydes with benzamidine and ethyl iodoacetate in presence of sodium bicarbonate.

\[
\text{Ar-CHO} + \text{H}_2\text{N}-\text{NH}_2 + \text{COOC_2H_5} + \text{NaHCO}_3 \rightarrow \text{Ar}-\text{N} = \text{N}\text{Ph}
\]

**Other Methods**

Husain and coworkers\textsuperscript{48} synthesised new imidazolinones by heating amine with PhSO\textsubscript{2}NHC(:NH)NHHCN, water and concentrated hydrochloric acid at 130-140\textdegree C.

\[
\text{PhSO}_2\text{NHC(:NH)NHHCN + H}_2\text{O + Con. HCl} \rightarrow \text{Product}\n\]

In 1985 Ashare and coworkers\textsuperscript{49} synthesised 4-(arylmethylene)-1,2-diphenyl-2-imidazolin-5-ones by the reaction between hippuric acid, phenyl isothiocyanate and aromatic aldehydes.

\[
\text{PhCONHCOOH} + \text{CONHPh} + \text{PhCNS} \xrightarrow{\text{Pyridine 160-170 °C}} \text{Product}\n\]
In 1991 Saxena and coworkers\textsuperscript{30} prepared novel imidazole congeners as antiinflammatory agents. A number of furylmethylene imidazolone derivatives were prepared from furfuraldehyde and aroyl glycine via Mannich or cyclisation reactions of intermediate imidazolones and tested their anti-inflammatory activity. It was found that they were strongly active.

In 1999 Sobha and Shafi\textsuperscript{51} synthesised 2-imidazolin-5-ones by heating benzoylglycine amide and aromatic aldehyde with saturated aqueous potassium carbonate solution for 3 hrs. They got 2-imidazolin-5-ones in 44-60\% yields.

![Reaction Scheme]

Shafi and Basheer\textsuperscript{52} synthesised novel spiro imidazolinones from divinyl ketone, glycine ethyl from ester and benzimidic acid methyl ester. The reaction is carried out in presence of pyridine.