CHAPTER I

INTRODUCTION

In the year 1883, Knorr\textsuperscript{1} gave the generic name "pyrazole" to a class of compound which is a five membered unsaturated ring containing two adjacent nitrogen atoms. The dihydropyrazole is called "pyrazoline".

\[
\text{(Pyrazoline)}
\]

Pyrazolines substituted on nitrogen is capable of exhibiting tautomerism indicated by tautomers (a), (b) and (c). The tautomers (a) and (b) are called as $\Delta^2$-pyrazolines and $\Delta^3$-pyrazolines. There is no evidence for the stability of tautomer (c).

\[
\text{(a)} \quad \text{(b)} \quad \text{(c)}
\]

Pyrazoline derivatives have been extensively studied for the past several decades because of their ready accessibility through synthesis, diverse chemical reactivity, broad spectrum of biological activities and variety of industrial applications.\textsuperscript{2-4}

\begin{itemize}
\end{itemize}
Some pyrazolines have been found to be bactericidal\(^5\), fungicidal\(^6\), insecticidal\(^7\) agents. Survey of literature in the recent past reveals that some pyrazolines have been found to possess cerebroprotective effect\(^8\) and antidepressant activity.\(^9\)

The most common method for the synthesis of pyrazolines is the action of hydrazine or substituted hydrazine on \(\alpha,\beta\) unsaturated carbonyl compounds like chalcones or flavanones in different solvents like DMSO, acetic acid, ethanol containing a little HCl.

\[
\begin{align*}
R^1 - C - CH = CH - R^2 & \xrightleftharpoons{R NH_2} \xrightarrow{R NH_2} \\
& \xrightarrow{(1)}
\end{align*}
\]

Under normal conditions, substituted hydrazines and chalcones give hydrazone derivatives. 2,4-dinitrophenylhydrazone of chalcone has been reported by Yaraslwasky\(^{10}\) and Dhar\(^{11}\). The chalcones and hydrazine derivatives undergo cyclization only under vigorous condition to give pyrazolines.

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Aubaguac et al.\textsuperscript{12}, discussed the mechanism of the formation of pyrazoline (2c) from chalcone (2) by 1,2-addition of phenylhydrazine through an adduct intermediate (2a). The rate determining step has been shown to be dehydration of the adduct (2a) to give phenylhydrazone (2b) which has been supported by activation energy calculations\textsuperscript{13} of 1,3,5-triphenylpyrazoline (2c).

2-Hydroxychalcone (3) on treatment with acid gives flavanone (3a). Flavanone (3a) on treatment with phenylhydrazine gives flavanone phenyl hydrazone (3c) which further undergoes thermal rearrangement to yield pyrazoline (3d)\textsuperscript{14-15}.

\begin{itemize}
\end{itemize}
Flavanone on treatment with hydrazine\textsuperscript{16} or phenylhydrazine\textsuperscript{17} under different experimental conditions leads to the formation of pyrazoline (4c)\textsuperscript{16,17} as the main product and flavanoneazine (4b)\textsuperscript{16-18} as a side product. Factors influencing the course of reaction are pH, temperature and amount of hydrazine in the reaction mixture.

\textsuperscript{16} Kalley, F., Janzso, G. and Koezor, I., Tetrahedron, 21 (1965), 3037.
\textsuperscript{17} Kalley, F., Janzso, G. and Koezor, I., Tetrahedron, 23 (1967), 4317.
\textsuperscript{18} Kalley, F. and Janzso, G., Kem Kozl., 42(2) (1974), 213.
Baker et al.\textsuperscript{19}, have reported the formation of 1-phenyl-5-(2-hydroxy-4-methoxyphenyl)-3-methylpyrazolines from 2-hydroxy-4-methoxy styrylmethyl ketone and phenylhydrazone.

Gheorghiu et al.\textsuperscript{20}, attempted to correlate the ease of formation of pyrazoline with stereoisomeric forms of phenylhydrazone. The syn-form (5a) (also called nonprototropic) can readily be converted into pyrazoline (5c). Conversely anti form (5b) (also called prototropic) can not be converted into pyrazoline. It has been known that pyridine\textsuperscript{21} favours the conversion of syn-form to pyrazoline.

\textsuperscript{21} Von Auwers, K. and Muller, Ber. dt. Chem. Ges., 41 (1908), 4230.
Electron donating groups such as hydroxy, alkoxy and amino group on either of the phenyl rings of chalcone makes the phenylhydrazones more labile and it can seldom be isolated.\textsuperscript{22-24} On the other hand, the electron withdrawing group like nitro or halogen stabilizes the hydrazones.\textsuperscript{22-25}

Jamode\textsuperscript{26}, reported the formation and isolation of 2'-hydroxychalcone phenylhydrazone intermediate (6a) and its conversion into 3,5-diaryl-1-phenyl pyrazolines (6b).

\begin{itemize}
\end{itemize}
Borkhade et al., reported the synthesis of 3,5-diaryl-1-phenyl pyrazolines (7b) by the action of phenylhydrazine hydrochloride with 2-hydroxy chalcones (7a) or flavanones (7) in pyridine medium.

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The synthesis of 3,5-diaryl-1-phenylpyrazolines (8a) from flavanones (8) and phenylhydrazine hydrochloride in DMF\textsuperscript{28} solvent, has been reported.

![Chemical structure](image)

Therapeutically active 3-amino-1-phenyl and substituted phenyl-2-pyrazolines\textsuperscript{29} were synthesized from alkenenitriles and phenylhydrazine. These pyrazolines are found to be anti-inflammatory, bactericidal, pharmaceutical and fungicidal agents.

![Chemical structure](image)

Ozawa et al.\textsuperscript{30}, reported the synthesis of the following pyrazolines (10) which have been found to be effective in killing houseflies.

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Hammouda et al.\textsuperscript{31}, synthesized new heterocyclic compounds in which pyrazole moiety bears isoxazole (11a) and pyrazoline ring (11b) from 4-cinnamoyl-1,5-diphenyl-3-methylpyrazole (11).

Reddy et al.\textsuperscript{32}, reported the synthesis of 3-arylsulphonyl-2-pyrazolines (12a) via cycloaddition of diazomethane to aryl vinylsulphones (12) in presence of triethylamine at 0°C.

\[
\begin{align*}
\text{ArSO}_2\text{CH} &= \text{CH}_2 + \text{CH}_2\text{N}_2 \\
&\xrightarrow{\text{Et}_2\text{N}, 0^\circ\text{C}} \quad \begin{array}{c}
\text{Ar} \\
\text{O} \\
\text{S}
\end{array} \\
\begin{array}{c}
\text{N}
\end{array} \\
\begin{array}{c}
\text{H}
\end{array} \\
\text{N}
\end{align*}
\]

Pyrazolines (13) possessing insecticidal properties have been reported.\textsuperscript{33}

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

3,5-diphenyl-1-(3,5-dichloro) salicyloylpyrazolines have been synthesized by the action of 5,2-R (OH) \text{C}_6\text{H}_3\text{COCH}:\text{CH} \text{C}_6\text{H}_3\text{R}_1\text{R}_2 with 3,5,2-
\text{Cl}_2(\text{OH}) \text{C}_6\text{H}_2\text{CONH}\text{NH}_2 in DMF solvent.\textsuperscript{34}

\[
\begin{array}{c}
\text{R} \\
\text{R}^1 \\
\text{R}^2
\end{array} \\
\begin{array}{c}
\text{OH} \\
\text{OH} \\
\text{Cl}
\end{array} \\
\begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array}
\]


Chem. Abstr. 98(2) (1983), 16679n.
Anti-implantation activity of 4,5-trans/cis-1-acetyl-3,5-diaryl-4-phenylpyrazolines (15) has been reported by Suratkumar and Rastogi.\textsuperscript{35}

![Chemical Structure](image)

(20)

Sayed et al.\textsuperscript{36}, reported the synthesis of new 4-aryl-5-arylmethyl-2-pyrazolines (16a) by action of diazomethane on chalcones (16).

$$\text{Ar}_1 - \text{CH} = \text{CH} - \text{COAr}_2 \xrightarrow{\text{CH}_2\text{N}_2, 0^\circ\text{C}, 48\text{ hrs.}} \text{H}_2\text{N}_2\text{COAr}_2$$

(16)

![Chemical Structure](image)

(16a)

Gawande et al.\textsuperscript{37}, reported the synthesis of thiazolyl pyrazolines (17a) by the action of acrylothiazoles (17) with hydrazine hydrate in ethanol-acetic acid medium.

![Chemical Structure](image)

(17)

![Chemical Structure](image)

(17a)

\textsuperscript{35} Suratkumar & Nivas Rastogi; \hfill \textsuperscript{Indian J. Chem., 26B (1987), 968-71.}
\textsuperscript{36} Svea, G.H. and Kjssen, H., \hfill \textsuperscript{Indian J. Chem., 19B (1980), 980.}
\textsuperscript{37} Gawande, N.G. and Shingare, M.S., \hfill \textsuperscript{Indian J. Chem., 26B (1987), 351.}
Iyer et. al.\textsuperscript{38}, reported the synthesis of pyrazolines (18a) from acrylophenones (18) by reaction with hydrazinehydrate in ethanolic medium and found to possess antifertility activity.

Ankhiwala and Naik\textsuperscript{39}, synthesized substituted pyrazolines (19) by the action of Ph.NHNNH\textsubscript{2} on corresponding chalcone.

Saraf\textsuperscript{40}, reported the synthesis of new 5-phenyl-3-(2-methyl-4-oxy-4H-1-benzopyran-3-yl)-\Delta^2-pyrazoline-1-carboximides (20a) from 3-cinnamoyl-2-methyl chromones (20) and semicarbazide hydrochloride in ethanol containing a little acetic acid.

\textsuperscript{40} Saraf, B.D., "Reactivity of 1-(2-hydroxyphenyl)-5-phenyl-4-pentene-1,3,diones", Ph.D. Thesis Amravati University, Amravati. (1988).
Formation of 4-bromo-3-(2'-hydroxyphenyl)-1,5-diphenylpyrazolines (21a) from 3-(2-hydroxy phenyl)-1,5-diphenylpyrazolines (21) on treatment with NBS in CCl₄ medium has been reported by Wadodkar and Joshi.¹¹

Kalsi et al.⁴² reported the synthesis of pyrazoline (22a) by action of diazomethane on dehydrocostus lactone (22) which is a sesquiterpenoid obtained from costus roots.

Shingare et al.\textsuperscript{43}, synthesized the pyrazolines (23a) and (23b) by the action of hydrazinehydrate and phenylhydrazine on chalcone (23).

\textbf{(23a)}

\textbf{(23b)}

Ammar et al.\textsuperscript{44}, synthesized some halogenated sulfonamides with pyrazoline moiety (24) from corresponding chalcone and hydrazinehydrate in ethanol containing acetic acid.

\textbf{(24)}

here \(X = \text{Cl or Br}\)


\textsuperscript{44} Chem. Abstr., 102 (1985), 18478n.
Hussain M.I. et al.\textsuperscript{45}, reported the synthesis of N-(acetyl/phenyl-5-aryl pyrazoline-3-yl)phenylaryl sulfonamides (25a/25b) from chalcone (25).

\[
\begin{align*}
\text{Me} & \quad \text{SO}_2\text{NH} \quad \text{C} \quad \text{CH = CH - Ar} \\
\text{(25)}
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2\text{NH}_2\text{H}_2\text{O} & \quad \text{Ph.NHNH}_2 \\
\text{EtOH/ACOH} & \\
\text{Me} & \quad \text{SO}_2\text{NH} \quad \text{Ar} \quad \text{C} \quad \text{COCH}_3 \\
\text{(25a)}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{SO}_2\text{NH} \quad \text{Ar} \quad \text{Ph} \\
\text{(25b)}
\end{align*}
\]

Parekh H. et al.\textsuperscript{46}, reported the synthesis of 3-(4-phenylsulphonamido phenyl)-5-aryl-1-acetyl/phenylpyrazolines (26a)/(26b) from chalcone (26).

\[
\begin{align*}
\text{Ph} & \quad \text{SO}_2 - \text{NH} \quad \text{C} \quad \text{CH = CH - Ar} \\
\text{(26)}
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2\text{NH}_2\text{H}_2\text{O} & \quad \text{Ph.NHNH}_2 \\
\text{AcOH} & \\
\text{Ph} & \quad \text{SO}_2 - \text{NH} \quad \text{Ar} \quad \text{C} \quad \text{COCH}_3 \\
\text{(26a)}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{SO}_2 - \text{NH} \quad \text{Ar} \quad \text{Ph} \\
\text{(26b)}
\end{align*}
\]

\textsuperscript{45} Hussain, M.I. and Kumar Ashok; \textsuperscript{46} Parekh, H., Dave, U., Upadhyay, J.

Chem. Abstr., 107 (1987), 51773q;

J. Indian Chem. Soc., 68(7) (1991), 413;

Some chloro-substituted pyrazolines (27a) have been synthesized by the action of 2-substituted chalcones (27) on phenylhydrazone hydrochloride in ethanol containing few drops of piperidine.48

Ankhiwala et al.49, reported the synthesis of 1-phenyl-3,5-diaryl-2-pyrazolines (28) from Ph.NHNH₂.HCl and chalcones.

Fernandes Y.J., et al.50, reported the synthesis of 3-(3-phenyl-sulphonamidophenyl)-5-arylpyrazoline (29).

R = H, Ac or Ph

Ganguli et al. reported the synthesis of 3,5-diarylpyrazolines (29a) from chalcone (30).

\[
\begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{C} - \text{CH} = \text{CH} - \text{Ar}
\end{array} \\
\text{SO}_{2}\text{NH}
\end{array} \quad \xrightarrow{\text{X = H, Ac or Ph}} \quad \begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{C} - \text{CH} = \text{CH} - \text{Ar}
\end{array} \\
\text{SO}_{2}\text{NH}
\end{array}
\]

Patel P. et al. synthesized the 1-acetyl/H-3,5-diarylpyrazolines (31).

\[
\begin{array}{c}
\begin{array}{c}
\text{Cl} \\
\text{SO}_{2}\text{NH}
\end{array} \\
\text{Ar}
\end{array} \quad \text{R = H or Ac}
\]

Koregaonkar et al. reported the synthesis of 3-(3-(4-chlorophenyl)-sulphonamidophenyl)-5-arylpurazolines (32) from chalcones.

\[
\begin{array}{c}
\begin{array}{c}
\text{Cl} \\
\text{SO}_{2}\text{NH}
\end{array} \\
\text{Ar}
\end{array} \quad \text{R = H or Ac}
\]

---

52. Patel, P., Koregaonkar, S., Parekh, H., \( \text{Farmaco, 51}(1) \) (1996), 59.
55. \( \text{Chem. Abstr., 127} \) (1997), 17610r.
Barot\textsuperscript{54}, has synthesized 1-H-3-(2'-hydroxy-4'-ethoxy-5'-bromophen-1-yl)-5-substituted phenyl-2-pyrazolines (33) and their derivatives (33a-d).

Sorathiya et al.\textsuperscript{55} reported the synthesis of 3-(4-(2',5'-dibromophenyl-sulphonamido)-phenyl)-3-aryl-1-H/acetyl/phenylpyrazolines (34).

\[\text{R} = \text{H, Ac, Ph}\]

(34)

Raghuwanshi et al.\textsuperscript{56} synthesized some nitropyrazolines (35) and (35a).

(35)

(35a)

Deshmukh et al.\textsuperscript{57} reported some chlorosubstituted-\(\Delta^2\)-pyrazolines (36a) from 2'-hydroxy-3'-5'-dichlorochalcones (36) and phenylhydrazine in DMSO.

(36)

(36a)


Jamode et al.\textsuperscript{58}, reported 3,5-diaryl-4-benzoyl-1-pyridoyl-Δ²-pyrazolines (37) from 3-arylflavanones and isoniazide in pyridine medium.

Sayed A.Z. et al\textsuperscript{59}, synthesized some new pyrazolines (38) from aminomethoxychalcones.

\[
R = 4\text{-aminophenyl, 4-acetamidophenyl}
\]

\[
R^1 = \text{H, Ph, aroyl, sulphonyl, acetyl, etc.}
\]

Kinhikar\textsuperscript{60}, reported some new bis-pyrazolines (39).

\[
R = \begin{array}{c}
\text{CO-} \\
\text{N}
\end{array}
\]


\textsuperscript{60} Kinhikar Ravi,
Udo Bauer et al.\textsuperscript{61} reported novel route for synthesis of N-substituted-2-pyrazolines using polymer supported reagents (PS-DIEA) and scavengers.

\[ \text{R}^2\text{COCI} \quad \text{PS-DIEA} \]

\[ \text{R}^3\text{NHCOCl} \quad \text{PS-DIEA} \]

\[ \text{R}^3\text{SOCl} \quad \text{PS-DIEA} \]

\[ \text{O} \quad \text{N} \quad \text{N} \quad \text{H} \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \]

\[ \text{(40b)} \]

\[ \text{O} \quad \text{S} \quad \text{O} \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \]

\[ \text{(40c)} \]

\[ \text{O} \quad \text{N} \quad \text{S} \quad \text{O} \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \]

\[ \text{(40d)} \]

\[ \text{O} \quad \text{N} \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \]

\[ \text{(40e)} \]

Thakare N.R.\textsuperscript{62}, reported the synthesis of 3-coumaryl-5-aryl pyrazolines (41).

![Chemical structure of 3-coumaryl-5-aryl pyrazolines (41)](image)

E. Palaska et al\textsuperscript{63}, reported the synthesis of 3,5-diarylpyrazoline (42).

![Chemical structure of 3,5-diarylpyrazoline (42)](image)

Recently, synthesis of 1-isonicotinoyl-5-phenyl-3-pyridin-2-yl) pyrazoline (43a) from pyrazoline (43) has been reported by Grazia Mamolo et al\textsuperscript{64}.

![Chemical reaction of 1-isonicotinoyl-5-phenyl-3-pyridin-2-yl) pyrazoline (43a)](image)

\textsuperscript{62} Thakare, N.R.,

\textsuperscript{63} Palaska, E., Aytemir, M., Uzbay, T., Erol, D.,

\textsuperscript{64} Mamolo, M.G., Zampieri, D., Falagiani, V., Luciano Vio, Elena Banfi:


IL Farmaco, 56 (2001), 593.
Recently, Parikh A.R. et. al.\textsuperscript{65}, reported the synthesis of pyrazoline (44a) from chalcone (44).

\begin{equation}
\text{Ar} - \text{CH} = \text{HC} \xrightarrow{\text{NH}_2\text{NH}_2\text{H}_2\text{O}} \text{Ar} - \text{N} = \text{N} - \text{Ar} \quad \text{(44a)}
\end{equation}