CHAPTER I

INTRODUCTION

Knorr\(^1\), in 1883 gave the name 'Pyrazole' to a class of organic compounds which consists of a five membered ring containing two adjacent nitrogen atoms.

![Pyrazole](image)

The most common method for the synthesis of pyrazoles involves the action of hydrazine or substituted hydrazine on 1,3-dicarbonyl compounds. Monohydrazones is the intermediate in this reaction, which has been occasionally isolated.\(^2\)–\(^8\) Monohydrazones (1a) have been converted to corresponding pyrazoles (1b) thermally or by treating with acid.\(^1\),\(^5\),\(^8\)–\(^11\)

1. Knorr, L.
2. Von Auwers, K. and Schmidt, W.
3. Von Auwers, K. and Stuhlman, H.
4. Von Auwers, K. and Mauss, H.,
5. Woodward, C.F. and Fuson, R.C.,
6. Borsche, W. and Hahn, H.,
7. Panizzi, L.,
8. Von Auwers, K. and Ottens, B.,
9. Michael, A. and Ross, J.,
10. Barot, C.,
11. Von Auwers, K. and Mauss, H.,

Leibig's Ann., 452 (1927), 182.
Leibig's Ann., 537 (1939), 219.
When monosubstituted hydrazine reacts with unsymmetrical diketones (2), give isomeric pyrazoles (2a and 2b). Attempts have been made to determine the identity of the products only in few cases.\(^4\),\(^12\),\(^13\)

The formation of substituted pyrazoles from 1,3 dicarbonyl compounds and substituted hydrazines has been reported by Jacobs\textsuperscript{14} and also by Finar and Simond\textsuperscript{15}. It has been reported that the formation of isomeric pyrazoles depend on steric hinderance, electromeric effects of group and also on the pH of the reaction medium\textsuperscript{15-20}.

Synthesis of pyrazoles by the reaction of hydrazine on acetylenic carbonyl compounds is reported by Bowden and Jones\textsuperscript{21}. The reaction of hydrazine with α-β-acetylenic carbonyl compound (3), gives 1,3 or 1,5-disubstituted pyrazole (3b). Morrachi et al.\textsuperscript{22}, isolated an intermediate hydrazone (3a) which on treatment with triethylamine gives pyrazole (3b).

\[
\begin{array}{c}
\text{O} \\
\text{R - C - C ≡ C - R}^1 \\
\text{N}_2\text{H}_4 \\
\text{R - C - C ≡ C - R}^1 \\
\text{N - NH}_2 \\
\text{Et}_3\text{N}
\end{array}
\]

(3)

(3a)

(3b)

\textsuperscript{14} Jacobs, T.L.,

\textsuperscript{15} Finar, I.L. and Simond, A.B.,

\textsuperscript{16} Knorr, L.,

\textsuperscript{17} Brady, O.L.,

\textsuperscript{18} Rotherberg, R.V.,

\textsuperscript{19} Joshi, S.S. and Gambhir, I.R.,

\textsuperscript{20} Garg, H.G. and Joshi, S.S.,

\textsuperscript{21} Bowden, K. and Jones, E.R.N.,

\textsuperscript{22} Morrachi, S., Ricca, A., and Zararotti, A.,

"Heterocyclic compounds", Edited by R.C. Elderfield (1957), 50.


Pyrazoles are frequently produced when α,β-unsaturated carbonyl compounds substituted at either α or β position with a readily replaceable group, are treated with hydrazine. Only halogens, generally bromine have been examined as the β-substituent\textsuperscript{23}.

\[
\begin{align*}
\text{R}_1 - \text{C} - \text{CH} = \text{C} - \text{R}_2 & \xrightarrow{\text{R}_3 \text{NHNH}_2} \text{R}_3 \text{NHNH}_2 \\
\text{(4)}
\end{align*}
\]

When hydrazine or substituted hydrazine reacts with chalcone dibromides (5) give substituted pyrazoles (5a) of unequivocal structure.\textsuperscript{23-25}

\[
\begin{align*}
\text{HO} & \quad \text{Br} \\
\text{R} & \quad \text{Br} \\
\text{O} & \quad \text{R} \\
\text{Ph} & \quad \text{R} \\
\text{R} & \quad \text{OH} \\
\text{(5)}
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{Ph} & \quad \text{R} \\
\text{R} & \quad \text{Ph} \\
\text{(5a)}
\end{align*}
\]

An interesting synthesis of pyrazoles (6a-e) was reported\textsuperscript{26-29} from epoxides of \( \alpha,\beta \)-unsaturated ketones (6) with hydrazine or phenylhydrazine. With hydrazine, an intermediate 4-hydroxypyrazoline (6a) could sometimes be isolated\textsuperscript{28}, which is readily converted to pyrazole (6c). With phenylhydrazine, the pyrazole (6e) was obtained directly in acetic acid. Dodwardmath R.P. et al.\textsuperscript{27} isolated hydrazone intermediate (6d) which could be converted to pyrazole (6e) by refluxing in acetic acid. Intermediate 5-hydroxypyrazoline (6b) was isolated by Cromwell and Setterquist\textsuperscript{29}.

\begin{equation}
\text{Ar} - \overset{\text{O}}{\text{C}} - \overset{\text{H}}{\text{CH}} - \overset{\text{CH}}{\text{CH}} - \overset{\text{Ar}^1}{\text{O}} \quad \overset{\text{Ph.NHNH}_2}{\rightarrow} \quad \text{Ar} - \overset{\text{CH = CH}}{\text{C}} - \overset{\text{Ar}^1}{\text{Ar}} \quad \overset{\text{NH.NH}_2}{\text{Ph}} \quad \overset{\text{Ph.NNH}_2 / \text{AcOH}}{\rightarrow} \quad \text{Ar} - \overset{\text{NH}_2}{\text{Ph}} \quad \overset{\text{AcOH, Reflux}}{\rightarrow} \quad \text{Ar} - \overset{\text{N}}{\text{Ph}} - \overset{\text{Ar}^1}{\text{Ar}}.
\end{equation}

\textsuperscript{28} Hutchins, W.S., Motuani, D.C., and Wheeler, T.S.
\textsuperscript{29} Cromwell, N.H. and Setterquist, R.A.

Jerzomohsky et al.\textsuperscript{30}, synthesized 4-acetyl-5-(o-hydroxyphenyl)-1,3-diphenylpyrazole (7a) from 3-acetyl flavone (7) and phenylhydrazine.

\begin{center}
\scalebox{0.7}{
\begin{tikzpicture}
  \node at (0,0) {\includegraphics[width=1cm]{fig1}};
  \node at (3.5,0) {\includegraphics[width=1cm]{fig2}};
  \node at (1.75,0) {$\text{Ph.NHNH}_2$};
  \node at (2,0.5) {EtOH};
\end{tikzpicture}
}\end{center}

(7) \hspace{2cm} (7a)

Action of phenyl hydrazine on chromone (8a), thiochromone (8b) or flavone (8c) is one of the best methods for the synthesis of 3-(o-hydroxy phenyl)-5-methyl/phenyl pyrazole (8d).\textsuperscript{31-32}

\begin{center}
\scalebox{0.7}{
\begin{tikzpicture}
  \node at (0,0) {\includegraphics[width=1cm]{fig3}};
  \node at (3.5,0) {\includegraphics[width=1cm]{fig4}};
  \node at (1.75,0) {Ph.NHNH$_2$.HCl};
  \node at (2,0.5) {Pyridine};
\end{tikzpicture}
}\end{center}

(8a) \hspace{2cm} (8) \hspace{2cm} (8b) \hspace{2cm} (8c) \hspace{2cm} (8d)

\begin{itemize}
\item \textsuperscript{30} Jerzomohsky, Zofia, Podwinsky, Bohdon, \textit{Chem. Abstr.}, 70 (1969), 37612x.
\item \textsuperscript{31} Baker, W., Harborne, J.D. and Ollis, W.D., \textit{J. Chem. Soc.}, (1952), 1303.
\end{itemize}
Kessar et al.\textsuperscript{33}, reported the synthesis of some stereoidal pyrazoles like 5-methyl-androsta-4,16-dieno [16,17c] - [3, 2c] dipyrazoles (9a) by the action of 2-hydroxymethylene-5'-methyl-androsta-4,16-dieno-[16,17c] pyrazole (9) with hydrazinehydrate in ethanol medium.

\begin{center}
\begin{tikzpicture}

\node[draw,shape=circle,fill=white,minimum size=1cm] (A) at (0,0) {
\includegraphics[width=0.5\textwidth]{fig1.pdf}};

\node[draw,shape=circle,fill=white,minimum size=1cm] (B) at (4,0) {
\includegraphics[width=0.5\textwidth]{fig2.pdf}};

\node at (2,0) {Ethanol};

\end{tikzpicture}
\end{center}

Borkhade et al.\textsuperscript{34}, reported the synthesis of pyrazoles (10b) from o-hydroxydibenzoyl methanes (10) or chalconedibromides (10a) and phenyl hydrazine in pyridine medium.

\begin{center}
\begin{tikzpicture}

\node[draw,shape=circle,fill=white,minimum size=1cm] (A) at (0,0) {
\includegraphics[width=0.5\textwidth]{fig3.pdf}};

\node[draw,shape=circle,fill=white,minimum size=1cm] (B) at (4,0) {
\includegraphics[width=0.5\textwidth]{fig4.pdf}};

\node at (2,0) {Ph.NNH\textsubscript{2} Pyridine};

\end{tikzpicture}
\end{center}

\begin{itemize}
\end{itemize}
Mutreja et al.\textsuperscript{35}, reported the synthesis of 1-H/substituted-5-aryl-3-methyl-4-(N-substituted \(\gamma\)-sulphamylbenzeneazo) pyrazoles (11) by the reaction of 1-methyl-3-(\(\alpha\)-naphthyl) and 1-methyl-3-(5',6',7',8'-tetrahydronaphth-2'-yl)-2-(N-substituted-p-sulphamylbenzeneazo) propane-1,3-diones with hydrazine hydrate/benzoic acid hydrazide/p-nitrobenzoic acid hydrazide.

\[
\text{HN=NSO}_{2}\text{NR}_{1}
\]

(11)

Krentzberger\textsuperscript{36}, reported aminocyanopyrazoles (12,12a) by the reaction of EtOCH : C(CN)\(_2\) with \(R\_n\text{C}_6\text{H}_{11-n}\text{NHNH}_2\) cyclized by guanidine.

\[
\text{R}_n\text{NCN}\text{NH}_2
\]

(12)

\[
\text{NH}_2
\]

(12a)


\textsuperscript{36} Krentzberger, Chem. Abstr., \textbf{92} (1980), 198346h.
Gaggad H.L.\textsuperscript{37}, synthesized 1-phenyl-3-(2-hydroxyphenyl)-5-styryl pyrazoles (13b) from 2-hydroxybenzoylcinnamoyl methanes (13) and styryl chromones (13a) with phenylhydrazine hydrochloride in ethanol and pyridine medium respectively.

\begin{align*}
\text{(13a)} & \quad \xrightarrow{\text{Ph.NHNNH}_2\text{HCl}} \\
& \quad \xrightarrow{\text{EtOH}} \\
\text{(13b)} & \quad \xrightarrow{\text{Ph.NHNNH}_2\text{HCl}} \\
& \quad \xrightarrow{\text{Pyridine}}
\end{align*}

Wadodkar and Joshi\textsuperscript{38}, reported the synthesis of 3,5-diaryl pyrazoles (14a) and 3,5-diaryl-1-phenylpyrazoles (14b) by the reaction of 3-iodoflavanones (14) with hydrazinehydrate in ethanol and phenylhydrazine in pyridine medium respectively.

\begin{align*}
\text{(14)} & \quad \xrightarrow{\text{N}_2\text{H}_4\text{H}_2\text{O}} \\
& \quad \xrightarrow{\text{EtOH}} \\
\text{(14a)} & \quad \xrightarrow{\text{Ph.NHNNH}_2\text{HCl}} \\
& \quad \xrightarrow{\text{Pyridine}} \\
\text{(14b)} &
\end{align*}


Band et al., reported the synthesis of 3-coumaryl-5-aryl-1-phenylpyrazoles (15) by the action of 1-coumaryl-3-arylpropane-1,3-diones with phenylhydrazine hydrochloride in acetic acid.

\[
\begin{align*}
\text{O} & \quad \text{CH}_3 \\
\text{OH} & \quad \text{N} = \text{N} - \text{SO}_2 \text{NHR}_4 \\
\text{R}_1 & = \text{CH}_3, \ H \\
\text{R}_2 & = \text{H}, \ \text{CH}_3 \\
\text{R}_3 & = \text{OCH}_3 \\
\text{R}_4 & = \text{Pyrimidin-2-yl}, \ 4,6\text{-dimethoxypyrimidin-2-yl} \\
\text{R}_5 & = \text{tolyl}
\end{align*}
\]

Ahluwalia et al., reported the synthesis of 1-substituted-5-aryl-3-methyl-4-(N\textsuperscript{1}-substituted p-sulphamylbenzeneazo) pyrazoles, (17).

Where, \( R_1 = \text{CH}_3, \ H \)  \\
\( R_2 = \text{H, CH}_3 \)  \\
\( R_3 = \text{OCH}_3 \)  \\
\( R_4 = \text{Pyrimidin-2-yl, 4,6-dimethoxypyrimidin-2-yl} \)  \\
\( R_5 = \text{tolyl} \)


Ahluwalia et al.,\textsuperscript{40} reported the synthesis and antimicrobial activities of some new 1-substituted-3-methyl-5-(2′-naphthyl)-4-[p-(substituted sulphamyl) benzeneazo] pyrazoles (17a) by the action of 2-arylazo-1-methyl-3-(2′-naphthyl) propane-1,3-diones (17) with substituted hydrazine in acetic acid medium.

![Chemical structure](image)

\[ (17) \]

Burner et al.,\textsuperscript{41} synthesized 3-substitutedphenyl-1H-pyrazoles (18) as a novel herbicide.

![Chemical structure](image)

\[ (18) \]

Jamode and Tayade\textsuperscript{42}, reported the synthesis of 3,5-diaryl-1-phenyl pyrazoles (19a) from aroyloxyacetophenones (19) and phenyl hydrazine hydrochloride in alcoholic medium.

\begin{itemize}
\item \textsuperscript{41} Burner, H.G., Karvas, M., Nebel, Kurt and Pissiotas, G., PTC Int. Appl. WO 97 00, 246 (Cl C07D231/18), 1997, 228.
\end{itemize}
The synthesis of (3-oxo-2,3-dihydropyridazine-6-yl) pyrazole (20), which was found useful for prevention and/or treatment of ischemic heart diseases (angina), migraine and parkinson's diseases have also been reported.\textsuperscript{43}

Shingare et al.\textsuperscript{44} reported the synthesis of some new coumarino pyrazoles (21b) by condensation of coumarinoacidhydrazide (21) with diketones (21a).

\begin{align*}
\text{R} &= \text{Cl, Me;} \\
\text{R'} &= \text{H, p-Me, p-OMe, m-Cl}
\end{align*}

\textsuperscript{43} Astushi, A., Satoru, K. and Hiromichi, I., Chem. Abstr., 126(15), (1997), 17616c.

\textsuperscript{44} Shingare, M.S., Bhawar, S.B., Chavan, V.P. and Mane, A.S., Indian J. Heterocyclic Chem., 9(2) (1999), 135.
Talley et al.\textsuperscript{45}, reported the synthesis of pyrazolylsulfonamide (22), commonly known as celecoxib which is a nonstereoidal, antiinflammatory drug.

\begin{center}
\includegraphics[width=0.2\textwidth]{22.png}
\end{center}

Zhu et al.\textsuperscript{46}, reported the synthesis of 1-naphthyl-3-methyl-1-H-pyrazole-5-carboxamide (23).

\begin{center}
\includegraphics[width=0.2\textwidth]{23.png}
\end{center}

Thakare N.R.\textsuperscript{47}, reported the synthesis of 1-pyridoylH/carboxamido-3-(4-methyl-7-hydroxy-8-coumaryl)-5-arylpyrazole (24a) from diketone (24).

\begin{center}
\includegraphics[width=0.6\textwidth]{24_24a.png}
\end{center}

\textsuperscript{46} Zhu, Bing Yan, Jia,, Chem. Abstr., 134 (2001), 252334d.