A REVIEW ON SYNTHETIC APPROACHES OF PYRAZOLINE DERIVATIVES

Sarita A. Shinkar, Vaybhav J. Shetty and Deepali M. Jagdale*

1Bharati Vidyapeeth’s College of Pharmacy, Sector 8, CBD Belapur, Navi Mumbai, Maharashtra, India- 400614.

ABSTRACT
Pyrazolines as a scaffold have come into prominence in the field of medicinal chemistry this is due to the fact that the scaffold has a rich and diverse range of activities, another important reason for the popularity of this scaffold is its ease of synthesis. Various analogues of the scaffold show different activity and have different route of synthesis. The mode of synthesis of these various analogues has not been dealt thoroughly in the literature. This article mainly focuses on the synthesis of different Pyrazoline derivatives. Thus this review will be helpful for all researchers who are attempting to synthesize various derivatives of Pyrazoline in their research work.

KEYWORDS: Synthesis, Pyrazoline, chalcone, phenyl hydrazine, Claisen-Schmidt reaction.

INTRODUCTION
Pyrazoline is an unsaturated compound containing three carbon atoms and two nitrogen atoms in adjacent positions. It consists of only one endocyclic double bond in the structure. It is a reduction product of pyrazole, which is further reduced to pyrazolidine. Pyrazoline and pyrazolidine are stronger bases than pyrazole. Depending on the position of the double bond three partially reduced forms of pyrazoline structure are possible namely 1-pyrazoline, 2-pyrazoline and 3-pyrazoline which exist in equilibrium with each other. 2-Pyrazoline exhibits the monoamino character and hence is more stable than the rest of the reduced forms. 2-Pyrazoline seems to be the most frequently studied form of pyrazoline owning to the fact that there is a plethora of information available in the literature. This abundance in information
can be accounted for by the fact that 2-pyrazolines have a considerably easy route of synthesis and rich biological activity.

The repertoire of activities of the pyrazoline scaffold include Anti-bacterial, Anti-allergic, Anticonvulsant, Anti-diabetic, Anti-implantation, Anti-inflammatory, Antitumor, Antineoplastic, Antimicrobial, Analgesic, Cardiovascular, Diuretic, Fungicidal, Herbicidal, Hypoglycaemic, Insecticidal and Tranquilizer etc.

Considering the various activities of pyrazolines, it comes as no surprise that the pyrazolines are scaffold of interest among the research community. In the present article we have attempted to discuss in detail various synthetic approaches for creation of various Pyrazoline derivatives.

**DERIVATIVE 1**

3, 5-di-aryl N-substituted carbonyl pyrazoline derivatives

**Method 1:** Sarkar B.K. *et al.* 2011\(^1\) (Fig.1) synthesized 3,5-di-aryl N-substituted carbonyl Pyrazoline derivative by the method 1. In this method the substituted chalcone were obtained by placing the solution of sodium hydroxide (40%) in water and rectified spirit. The flask was then immersed in water bath and the substituted ketone and substituted aldehyde was added into it. In the above solution hydrazine hydrate was added drop wise in RBF. This reaction mixture was then heated under reflux for 6 hrs followed by addition of ice cold water. The mixture was kept overnight at a temperature of 8°C. The precipitate that was obtained was filtered, washed with distilled water and dried. After re-crystallization with ethanol 3,5-di-aryl N-substituted carbonyl Pyrazoline derivative was obtained.

**Method 2:** Sahoo A. *et al.* 2011\(^2\) (Fig.1) synthesized 3,5-di-aryl N-substituted carbonyl Pyrazoline by using chalcone. This chalcone was then reacted with hydrazine hydrate to form an intermediate. To this intermediate, benzoil chloride and pyridine were added and the mixture was refluxed for 3 hrs to obtain the final product of 3,5-di-aryl N-substituted carbonyl Pyrazoline derivative.

**Method 3:** Rossella F. *et al.* 2010\(^3\) (Fig.1) synthesized 3,5-di-aryl N-substituted carbonyl Pyrazoline derivative by reacting substituted ketone with isopropyl bromide, K\(_2\)CO\(_3\) and acetone at room temperature to form ketone derivative. This derivative was again treated with substituted aldehyde, barium hydroxide, water and ethanol (96%) to form chalcone
derivative. Which was further reacted with hydrazine, acetic acid and dry ethanol at 78\(^0\)C to form 3,5-di-aryl N-substituted carbonyl Pyrazoline derivative.

**Fig.1. 3,5-diaryl-N-substituted carbonyl pyrazoline derivatives**

**Reagents and conditions:** (a) 10\% KOH, Ethanol; (b) Isoniazid, DMF; (c) NH\(_2\)NH\(_2\), C\(_2\)H\(_5\)OH; (d) C\(_6\)H\(_5\)COCl, THF, Stirring, 0.5-1 hr; (e) 3-methyl-but-2-enyl bromide, K\(_2\)CO\(_3\), acetone; (f) Benzaldehyde, Ba(OH\(_2\))\(_2\)H\(_2\)O EtOH 96 \% 30\(^0\)C; (g) NH\(_2\)NH\(_2\), CH\(_3\)COOH, EtOH dry 78\(^0\)C.

**DERIVATIVE 2**

**3,5-diaryl N-thiocarbamoyl Pyrazoline derivative**

**Method 1:** Rossella F. *et al.* 2010\(^3\) (Fig.2) synthesized 3,5-diaryl N-thiocarbamoyl Pyrazoline derivative by reacting substituted ketone with isopropyl bromide, K\(_2\)CO\(_3\) and acetone at room temperature to form ketone derivative. This derivative was again treated with substituted aldehyde, barium hydroxide, water and ethanol (96\%) to form chalcone derivative. Which was further reacted with thiosemicarbazide, dry ethanol at 78\(^0\)C to form 3,5-diaryl N-thiocarbamoyl Pyrazoline derivative.

**Method 2:** Monica J. *et al.* 2011\(^4\) (Fig.2) synthesized 3,5-diaryl N-thiocarbamoyl Pyrazoline derivative by refluxing chalcone derivative with hydrazine hydrate (99\%) and ethanol for 3 hrs to form intermediate product which was further reacted with ethanol and phenyl isothiocyanate and refluxed for 30-45 minutes to form the final product of 3,5-diaryl N-thiocarbamoyl Pyrazoline derivative.
Method 3: Franco C. et al. 2008\(^{[5,6]}\) (Fig.2) synthesized 3,5-di-aryl N-thiocarbamoyl Pyrazoline derivative in which chalcone is synthesized by Claisen-Schmidt condensation reaction, by refluxing the substituted aryl or hetero aryl ketones and substituted aryl or hetero aryl aldehyde in presence of KOH and ethanol. This product was treated with thiosemicarbazide (molar ratio 1:2) in KOH/ethanol to afford the desired product.

![Diagram of 3,5-diaryl-N-thiocarbamoyl Pyrazoline derivative](image)

**Fig.2. 3,5-diaryl-N-thiocarbamoyl Pyrazoline derivative**

**Reagents and conditions:** (a) 3-methyl-but-2-enyl bromide, K\(_2\)CO\(_3\), acetone, rt; (b) Benzaldehyde, Ba(OH)\(_2\)-8H\(_2\)O EtOH (96 %) 30\(^\circ\)C; (c) NH\(_2\)NHCS NH\(_2\), EtOH dry, 78\(^\circ\)C; (d) KOH, Ethanol; (e) KOH, Ethanol, NH\(_2\)NHCS NH\(_2\); (f) NH\(_2\)NH\(_2\) H\(_2\)O (99%), C\(_2\)H\(_5\)OH, reflux for 3 hrs; (g) R2- C\(_6\)H\(_4\)NCS, C\(_2\)H\(_5\)OH, reflux for 30-45 mins.

**DERIVATIVE 3**

**1,3,5-trisubstituted Pyrazoline derivative**

**Method 1:** Chovatia Y. S. et al. 2010\(^{[7,13]}\) (Fig.3) synthesized 1,3,5-tri-substituted Pyrazoline derivative by reaction of chalcone with substituted hydrazine. The chalcone was synthesized by two methods. In first reaction they reacted KOH with a mixture of aldehyde and ketone for 1 hr. In second method they triturated KOH pellets mixed with aldehyde and ketone. This
chalcone was refluxed with substituted hydrazine in presence of concentrated H$_2$SO$_4$ to get 1,3,5-tri-substituted Pyrazoline derivative.

**Method 2:** Maleki B. et al. 2009$^{[8]}$ (Fig.3) synthesized 1,3,5-tri-substituted Pyrazoline derivative in which they treated the generally synthesized chalcone with ethanol (96%), in which the substituted hydrazine and methanoic acid was added at room temperature. The reaction was heated and refluxed for 10-35 mins. During heating the 1,2 addition reaction occurred with H$^+$ ions to form intermediate product which undergoes cyclization reaction to form the Pyrazoline derivative. The ethanol was separated under reduced pressure and the residue was recrystallized from ethanol.

![Diagram of chemical reaction](image)

**Fig.3. 1,3,5-trisubstituted Pyrazoline derivative**

**Reagents and conditions:** (a) Ethanol, KOH; (b) R-NHNH$_2$; (c) CH$_3$COOH; (d) CH$_3$COOH

R = H, Ph

**DERIVATIVE 4**

*N-sulphonyl 3,5 disubstituted Pyrazoline derivative*

**Method 1:** In Sahoo A. et al. 2011$^{[2,13]}$ (Fig.4) synthesized the derivative N-(aryl sulphonyl)-3,5-di-substituted Pyrazoline derivative using chalcone. This chalcone was then reacted with excess of hydrazine hydrate and ethanol and refluxed for 3-6 hr to form an intermediate product. This intermediate product was then treated with p-toluene sulfonyl chloride and
tetrahydrofuran, for 0.5 to 1.0 hr to get the N-(aryl sulphonyl)-3,5-di-substituted Pyrazoline derivative.

![Chemical structure](image)

Fig.4. N-sulphonyl 3,5 disubstituted Pyrazoline derivative

**Reagents and conditions:** (a) \(\text{NHNH}_2 \cdot \text{H}_2\text{O} (80\%)\), \(\text{C}_2\text{H}_5\text{OH}\), reflux for 3-6 hr; (b) \(\text{C}_8\text{H}_4\text{SO}_2\text{Cl}\), THF, Stirring, 0.5 - 1 hr.

**DERIVATIVE 5**

*N-hydroxy-1-carboxyimidamide Pyrazoline derivative*

**Method 1:** In Sahoo A. *et al.* 2011\(^{[2]}\) (Fig.5) synthesized the derivative N-hydroxy-1-carboxyimidamide Pyrazoline by using chalcone which obtained by Claisen-Schmidt condensation reaction. This chalcone was then reacted with thiosemicarbazide and ethanol for 8-10 hr to form an intermediate product. This was then treated with methyl iodide and hydroxyl amine in methanol while stirring for 6 to 12 hr to get the N-hydroxy-1-carboxyimidamide Pyrazoline derivative.

![Chemical structure](image)

Fig.5. N-hydroxy-1-carboxyimidamide Pyrazoline derivative

**Reagents and conditions:** (a) \(\text{C}_2\text{H}_5\text{OH}\), Thiosemicarbazide, \(\text{H}_2\text{O} (80\%)\), reflux for 3-6 hrs; (b) \(\text{CH}_3\text{I/ NH}_2\text{OH}\), Stirring, 6 - 12 hrs.

**DERIVATIVE 6**

*3,4,5-trimethyl-N-substituted Pyrazoline derivative*

**Method 1:** Elkanzi N. A. A. *et al.* 2013 and Rahman M.A. *et al.* 2010 \(^{[9, 10]}\) (Fig.6) synthesized 3,4,5-trimethyl-1-benzyl Pyrazoline derivative by mesityl oxide and hydrazine
hydrate. The mesityl oxide undergoes condensation reaction with acrylonitrile to obtain intermediate product (Y-acetyl-Y-isopropylidenebutyronitrile). Which was again condensed with hydrazine hydrate in boiling alcohol to yield 3,4,5-trimethyl-N-substituted Pyrazoline derivative.

**Method 2**: Elkanzi N. A. A. *et al.* 2013[9] (Fig.6) synthesized 3,4,5-trimethyl-1-benzyl Pyrazoline derivative by the reaction of hydrazine hydrate with ketone in alcohol which gave the Pyrazoline derivative.

![Chemical structure](image_url)

**Fig.6. 3,4,5-trimethyl-N-substituted pyrazoline derivative**

**Reagents and conditions:** (a) CH₂=CHCN; (b) NHNH₂.H₂O; (c) NHNH₂.H₂O

**DERIVATIVE 7**

**2,3,5-triphenyl pyrazoline derivative**

**Method 1**: Chimenti *et al.* 2006[11] (Fig.7) Synthesised 2,3,5-triphenyl pyrazoline derivative by the reaction of substituted chalcone and p-chlorophenyl hydrazine hydrochloride which gives the corresponding Pyrazoline derivative.

**Method 2**: 1,3,5-Triaryl-2-pyrazolines (Li *et al.*, 2007)[15] (Fig.7) have been prepared through the reaction of chalcone and phenyl hydrazine hydrochloride in the presence of sodium acetate-acetic acid aqueous solution under ultrasound irradiation.
Fig.7. 1,3,5-triphenyl pyrazoline derivative

Reagents and conditions: (a) KOH/EtOH; (b) p-chloro-phenyl hydrazine hydrochloride, AcOH OR (a) KOH/EtOH; (b) CH$_3$COONa, CH$_3$COOH.H$_2$O, PhNH.NH$_2$.HCl

DERIVATIVE 8
1,3,5-triphenyl Pyrazoline amine derivative

Method: Shivakumar M.H. et al. 2013$^{[14]}$ (Fig.8) Synthesised a mixture of substituted acetaminophen and benzaldehyde in presence of ethanol and NaOH solution. The mixture of acrylamide in presence of ethanol and few drops of glacial acetic acid and refluxed it for 4-6 hrs. The reaction mixture was poured into cold water and the product obtained was separated, filtered and recrystallised.

Fig.8. 1,3,5-triphenyl Pyrazoline amine derivative

Reagents and conditions: (a) Ethanol, 20% NaOH (b) Ph-NH.NH$_2$

DIFFERENT ACTIVITIES OF PYRAZOLINE DERIVATIVES
There are different pyrazoline derivatives which have diverse activities as mentioned in following table.

Table 1: Activities of different derivatives.

<table>
<thead>
<tr>
<th>Fig No.</th>
<th>Name of Derivative</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3,5-diaryl-N-substituted carbonyl Pyrazoline derivative</td>
<td>Antimicrobial$^{[4,10]}$ Antibacterial$^{[10]}$</td>
</tr>
<tr>
<td>2</td>
<td>3,5-diaryl-N-thiobcarbomoyl Pyrazoline derivative</td>
<td>Antiepileptic$^{[10]}$ Anti-inflammatory$^{[10]}$ Antimicrobial$^{[5,10]}$ Antitubercular$^{[10,14]}$</td>
</tr>
<tr>
<td>3</td>
<td>1,3,5-trisubstituted Pyrazoline derivative</td>
<td>Antioxidant$^{[10,12]}$</td>
</tr>
<tr>
<td></td>
<td>Structure Description</td>
<td>Biological Activity</td>
</tr>
<tr>
<td>---</td>
<td>----------------------------------------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>4</td>
<td>N-sulphonyl 3,5 disubstituted Pyrazoline derivative</td>
<td>Antidiabetic</td>
</tr>
<tr>
<td>5</td>
<td>N-hydroxy-1-carboxyimidamide Pyrazoline derivative</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MAO inhibitor</td>
</tr>
<tr>
<td>6</td>
<td>3,4,5-trimethyl-N-substituted pyrazoline derivative</td>
<td>Antiamoebic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>7</td>
<td>2,3,5-triphenyl pyrazoline derivative</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Photoluminescence</td>
</tr>
<tr>
<td>8</td>
<td>2,3,5-triphenyl Pyrazoline amine derivative</td>
<td>Antitubercular</td>
</tr>
</tbody>
</table>

**CONCLUSION**

A comprehensive study of the various processes involved in creation of the various pyrazoline derivatives have been mentioned above. Also the procedures mentioned above are simple and can be performed with basic facilities available in laboratories. This is done with the hope that any researcher attempting to synthesise a pyrazoline scaffold can do so by choosing an appropriate process which fulfils all major criterion of an efficacious chemical reaction such as - economy, minimisation in formation of byproducts, frugal use of toxic chemicals etc.

**REFERENCES**


