The synthetic development of pyrazole nucleus: From reflux to microwave

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ABSTRACT

Pyrazole belongs to the “diazole” class of heterocycles and is the most important moiety found in a large number of pharmaceutical agents. One of the earliest methods of pyrazole synthesis is refluxing the contents over hot water bath for few hours with constant stirring leading to the synthesis of a single compound in a particular yield. Overcoming the disadvantages of reflux method, newer technologies like one pot multicomponent synthesis, solution free synthesis, solid support synthesis, microwave and ultrasound synthetic technologies along with solution phase and solid phase combinatorial synthetic procedures are being adopted with the advantages of getting compounds in high yields in a lesser time duration. In the present review, an attempt has been made to describe the various development stages in the synthesis of pyrazole analogues.

Keywords: Pyrazole, 1,2-diazoles, Synthesis, Combinatorial chemistry, Solid phase synthesis.

INTRODUCTION

Pyrazoles owing to the presence of two neighbourhood nitrogen atoms, are also known as 1,2-diazoles. It has been the topic of medicinal research for the millions of researchers all over the world because of its large number of pharmacological activities. Some of the pyrazole possessing drugs like celecoxib [1], antipyrene, analgin, allopurinol, butazoline, phenylbutazone, oxyphenbutazone, novalgin [2], pyrazofurin [3], ramifenazole [4], indisteron [5], apixaban, fipronil, rimonabant [6] and many more are already in market. Structures of some of these drugs have been shown in Fig. 1.
1. **Reflux Method**: One of the oldest, common and mostly acceptable procedure for synthesis of pyrazole is reflux method where the reaction is performed between 1,3-diketo compound e.g. diethyl malonate or ethylacetoacetate with hydrazine hydrate (Scheme 1) in ethanol or hydrazine halides [7].

![Chemical diagrams](image)

**Figure 1. Few pyrazole based drugs available in the market.**

![Scheme 1](image)
2. **One pot multicomponent synthesis:** In 2009, Shestopalov *et al.* reported a new method for the synthesis of 6-Amino-2,4-dihydropyrano[2,3-c]pyrazol-5-carbonitrile by reacting all four reactants in a single pot i.e. β-ketoesters, aromatic aldehydes, hydrazine hydrate, malononitrile for 10-15 minutes taking triethylamine as base (Scheme 2). It was interesting to see that the method not only reduced the reaction time between substrates but also produced the target compounds in high yields [8].

\[
\begin{align*}
\text{NH}_2\cdot\text{NH}_2\cdot2\text{H}_2\text{O} & + \text{R}_1\text{C}(\text{O})\text{C}_2\text{H}_5 \quad \text{Reflux} \\
\text{R}_2\text{-CHO} & + \text{H}_2\text{C} = \text{C}(-\text{CN})_2 \quad \text{C}_2\text{H}_5\text{OH} \\
& \quad \text{Triethylamine}
\end{align*}
\]

Scheme 2.

3. **Microwave assisted solvent free synthesis:** Gupta *et al.* in 2001, synthesized fused pyrazoles or pyrazolo[3,4-c]quinoline derivatives under microwave irradiation taking β-chlorovinylaldehyde and hydrazine hydrate (Scheme 3) as reactants [9].

\[
\begin{align*}
\text{N} & \text{CHO} \quad \text{Microwave} \\
\text{Cl} & \quad \text{irradiations} \\
\text{R}_1\text{-NHNH}_2 & \quad 300\text{W}
\end{align*}
\]

Scheme 3.

4. **Ultrasound promoted synthesis:** Ultrasound machines are now a days not limited to hospitals. The statement was proved by Rahman *et al.* in 2009, when he reported a new method of pyrazole synthesis using ultrasound radiations condensing together in a reaction vessel N-phenylbenzenecarbohydrazonyl chloride and an alcoholic solution of 1-aryl-2-(phenylsulphonyl)ethanone at room temperature (Scheme 4) under ultrasonic irradiations with constant stirring [10].
5. Solid phase combinatorial synthesis: Dodd et al. described an effective resin bound solid support synthetic method, synthesizing 5-N-arylamino and 5-N-alkylamino pyrazoles. Immobilized γ-ketoamide was taken as the starting material which was then reacted at 50-55°C with immobilized resin bound alkylhydazine and lawesson’s reagent in a vessel containing THF solution (Scheme 5). After the completion of the reaction, resin-bound 5-aminopyrazoles were generated and further purified and tested for their analytical profile [11].

Below is some work done for the synthesis of pyrazoles by different techniques (Table 1).

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Work Done</th>
<th>Structure</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>New “green” approaches to the synthesis of pyrazole derivatives</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>[12]</td>
</tr>
<tr>
<td>2.</td>
<td>Solid phase synthesis of variably substituted pyrazoles</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>[13]</td>
</tr>
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3. Ultrasound promoted synthesis of substituted pyrazoles

4. Greener and rapid access to bio-active heterocycles: room temperature synthesis of pyrazoles and diazepines in aqueous medium

5. Fully automated polymer-assisted synthesis of 1,5-biaryl pyrazoles

6. Green one pot solvent free synthesis of pyrano[2,3-c] pyrazoles and pyrazol[1,5-a] pyrimidines

7. Solid phase synthesis of 5-substituted amino pyrazoles

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8. Microwave assisted one-pot synthesis of pyrazolone derivatives under solvent-free conditions

![Pyrazolone Derivative](image1)

9. Microwave Assisted Synthesis of N-Azacycloalkanes, Isoindole, Pyrazole, Pyrazolidine, and Phthalazine Derivatives

$$\text{R}_1 \quad \text{R}_2 \quad \text{R}_3$$

10. Three-component, one pot reaction for the combinatorial synthesis of 1,3,4-substituted pyrazoles

![Three-component Reaction](image2)

11. Solid phase synthesis of pyrazolo-pyridines from polymer-bound alkyne and azomethine imines

![Solid Phase Synthesis](image3)

12. Solid phase synthesis of amino acid derived N-unsubstituted pyrazoles via sydnones

![Solid Phase Synthesis](image4)
13. Convenient synthesis of tridentate 2,6-di(pyrazol-1-yl)-4-carboxy pyridine and tetridentate 6,6’-di(pyrazol-1-yl) -4,4’-dicarboxy-2,2’-bipyridine ligands

14. Solid phase synthesis of novel 7,8-functionalized pyrazolo[1,5-a][1,3,5]-2-oxo-4-thioxotriazine derivatives via cyclization reactions of dithiocarboxy resin bound pyrazoles

15. Water mediated construction of trisubstituted pyrazoles/isoxazoles library using ketene dithioacetals

16. Cellulose beads: a new versatile solid support for microwave-assisted synthesis. Preparation of pyrazole and isoxazole libraries

17. Synthesis and phosphorescent properties of blue emissive iridium complexes with tridentate pyrazolyl ligands
18. Synthesis of fully substituted pyrazoles via regio and chemo-selective mettualtions

19. Cyclization of 3-diazoalkenes to pyrazoles

20. Reactions of diazo compounds with nitro olefins-the preparation of pyrazoles

21. Synthesis of pyrazole derivatives and their evaluation as photosynthetic electron transport inhibitors
22. Synthesis, crystal structure and biological evaluation of novel 2-(5-(hydroxyl methyl)-3-phenyl-1H-pyrazol-1-yl 1-phenyl ethanol derivatives

23. Regioselective synthesis of 1,3,5- and 1,3,4,5-substituted pyrazoles via acylation of N-Boc-N-substituted hydrazones

24. Pd-catalyzed Negishi coupling of pyrazole triflates with alkyl zinc halides

25. Substituted biaryl pyrazoles as sodium channel blockers
26. Expeditious synthesis of 1,3,4-trisubstituted pyrazoles from Baylis-Hillman adducts

27. Synthesis of 3- and 5-formyl-4-phenyl-1H-pyrazoles: promising head units for the generation of asymmetric imine ligands and mixed metal polynuclear complexes

28. Regioselective synthesis of 1-aryl-3,4-substituted/annulated-5-(methyl thio) pyrazoles and 1-aryl-3-(methylthio)-4,5 substituted/annulated pyrazoles

29. Zinc-catalyzed synthesis of pyrazolines and pyrazoles via hydro hydrazination
30. Synthesis of new pyrazole and pyrimidine steroidal derivatives

![Chemical Structure of Steroidal Derivatives](image)

31. Synthesis of some fused pyrazoles

![Chemical Structure of Fused Pyrazoles](image)

32. A novel synthesis of 1,3,5-trisubstituted pyrazoles through a spiropyrazoline intermediate via a tandem 1,3-dipolar cycloaddition/elimination

![Chemical Structure of Trisubstituted Pyrazoles](image)

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![Chemical Structure of 3-Amino Pyrazoles](image)
34. Synthesis of new class of pyrazole based diaryl heterocycles

35. Synthesis and pharmacological activity of substituted pyrazoles

36. Synthesis of novel fused heterocycles based on pyrano[2,3-c] pyrazole
37. Synthesis of some new pyrrolidino [3,4-c] pyrazolines, pyrazoles and pyrazolo [3,4-d] pyridazines

38. Synthesis of some novel pyrazoles

Synthesis and study of chlorosubstituted 4-aryl/alkoyl pyrazoles and isoxazoles and their impact on phytotic growth of some vegetable crop plants

CONCLUSION

This study presents some newer approaches useful for the synthesis of pyrazole nucleus. Huge collection of research articles cited in this review describes the different stages of developments in the synthesis of pyrazole moiety. Novel methods of pyrazole synthesis like solid phase synthesis, solution free synthesis, water mediated synthesis, one pot multicomponent synthesis, microwave and ultrasound mediated synthetic procedures are preferred now a days due to their several advantages over the longer duration reflux method which is also inferior in case of product yield. This article can serve as a better tool for the researchers and can provide fresh ideas in the minds of several medicinal chemists to develop new molecules possessing pyrazole scaffold.

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REFERENCES


