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The Latest Progress on the Preparation and Biological activity of Pyrazoles

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Abstract: Out of the nitrogen family heterocyclic compounds, Pyrazole is an efficient moiety with a broad region of agrestic and medicinal activities. They pay much attention to the synthesis of drug molecules. In recent decades, many reports have been accomplished for constructing desired pyrazole structures. They exhibit numerous biological activities, namely, they are antifungal, anti-inflammatory, and antimicrobial. Here, we have summarized the published work on pyrazole synthesis and biological activities. The work published between January 2018 and January 2023 on pyrazole derivatives was reviewed accordingly in this article.

Keywords: Pyrazole derivatives; 5-Membered Heterocycles; Biological activities; Nitrogen-containing compounds; Recent Development

1. Introduction

Most known heterocyclic compounds consist of an extensive chemical and medicinal properties region, occupying a large area of stability and reactivity [1].

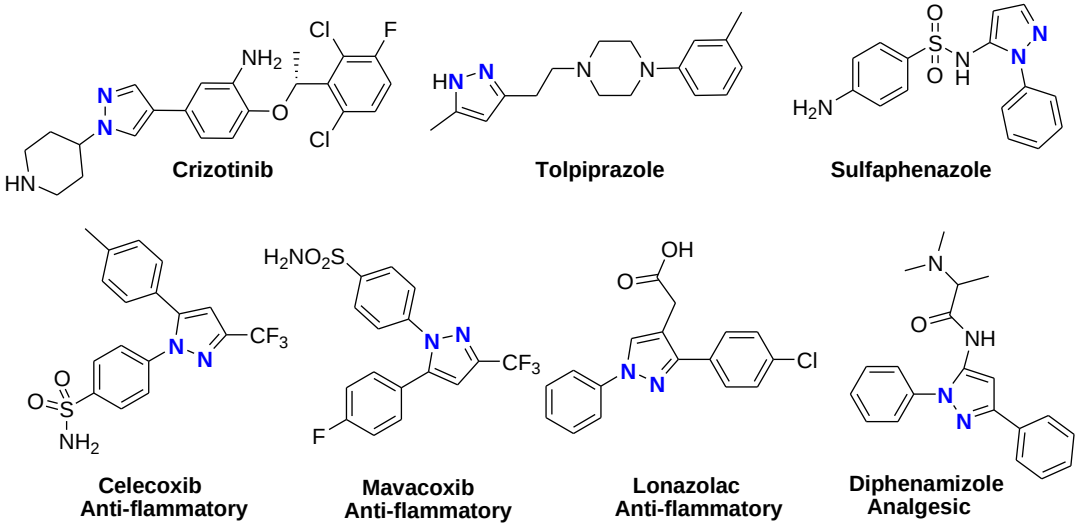


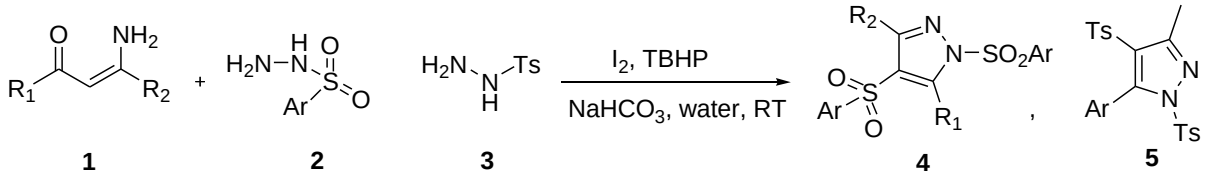
Figure 1. Some examples of biologically active Pyrazole compounds.

Furthermore, they served as reactive intermediates, chiral auxiliaries, protective groups, corrosion inhibitors, and synthetic organic chemistry [2]. Nitrogen-containing five-membered heterocyclic rings generally have a very high concentration of biological activity [3-6]. Examples of biologically active naturally occurring pyrazoles are shown in Fig 1. We mainly use concise reports on pyrazole manufacturing and medicinal activity, which were published between 2018 and 2023. Therefore, it helps the researchers who are working in this field. Synthesis of pyrazoles is included in the first section, whereas biological applications are described in the second section.

2. Synthesis of pyrazole moiety molecules

2.1. From substituted ketones.

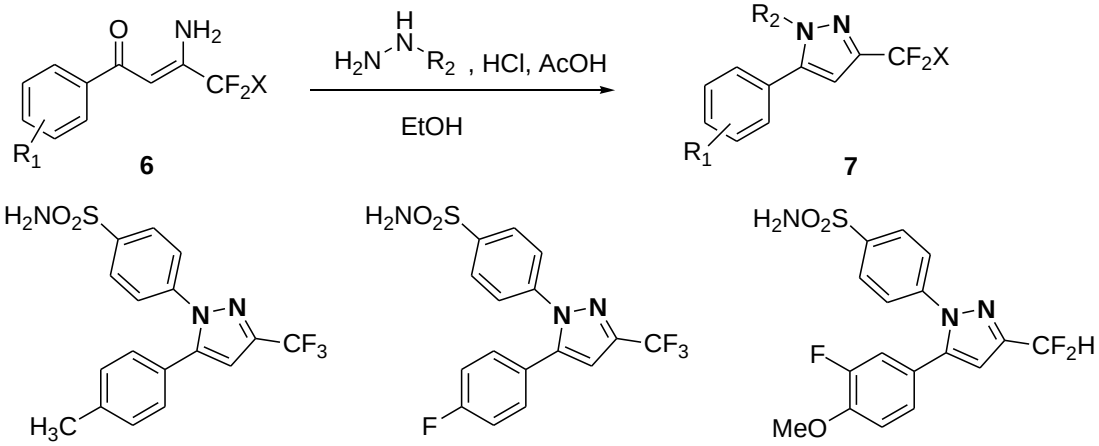
Wan and co-authors have established the tandem reaction for synthesizing Pyrazole from the respective starting precursors **1, 2** and **3** using molecular Iodine in water (Scheme 1) [7]. Unfortunately, aliphatic sulfonyl hydrazine didn't give the final product under standardized reaction conditions. When R1 = R2= ethyl, the reaction has provided a corresponding target product in less yield.



1 **2** **3** **4** **5**

Scheme 1

Later, a different method for the synthesis of celecoxib (**7a**), mavacoxib (**7b**), and deracoxib (**7c**) was developed by Wan *et al*. **(Scheme 2)** [8]. The reaction was reported in ethanol. In addition, they have developed a regioselective of the reaction and obtained the products with high yield.



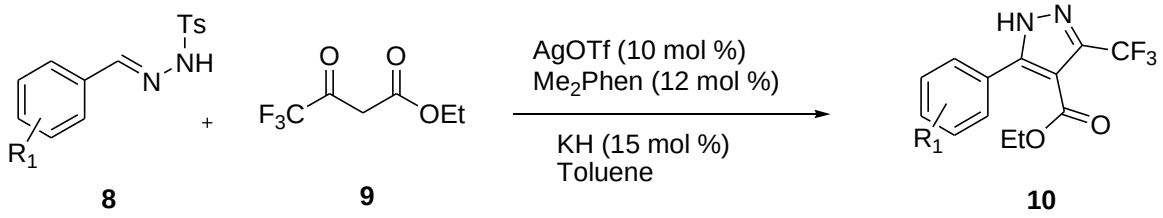
6 **7**

Celecoxib (7a) **Mavacoxib (7 b)** **Deracoxib (7c)**

Scheme 2

2.2. From diketocompounds.

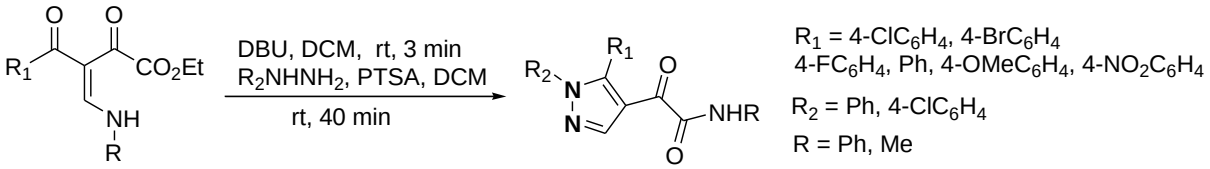
Trifluoromethylated pyrazole derivatives **10** have been reported from the reaction between tosyl hydrazones and diketones. In this methodology, addition, cyclization, elimination, and [1,5]-H shift were involved consecutively using silver (Scheme 3) [9]. They also tested the reaction with other catalysts; however, some reactions gave lower yields or no reaction.



8 **9** **10**

Scheme 3

Poletto *et al*. described selectively substituted pyrazoles from the reaction between the secondary β-enamine diketone and arylhydrazines in a one-pot synthetic strategy under moderate reaction conditions (Scheme 4) [10].

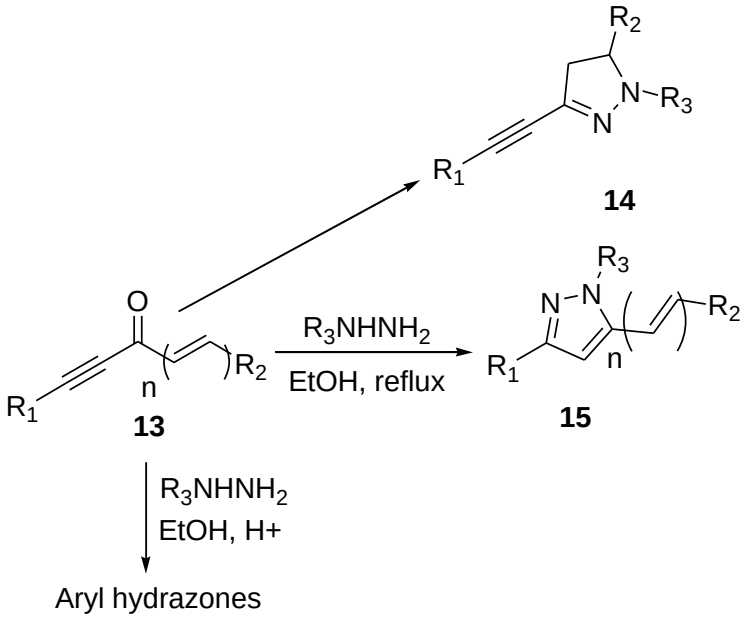


11 **12**

Scheme 4

2.3. Pyrazoles from acetylenic ketones.

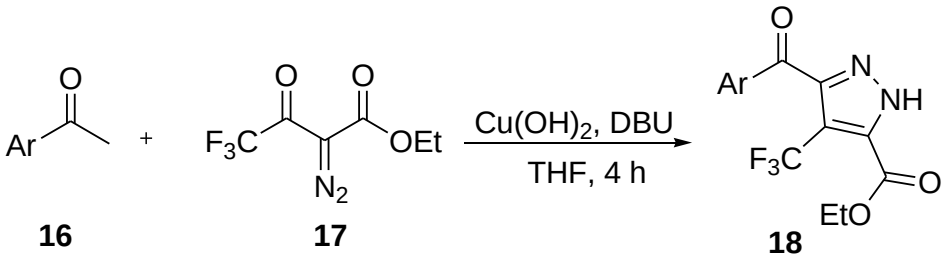
Enynones **13** have provided the final Pyrazole derivatives **14** and **15** through condensation followed by cyclization under reflux conditions (Scheme 5) [11]. All the final products are obtained in good to high yield.



Scheme 5

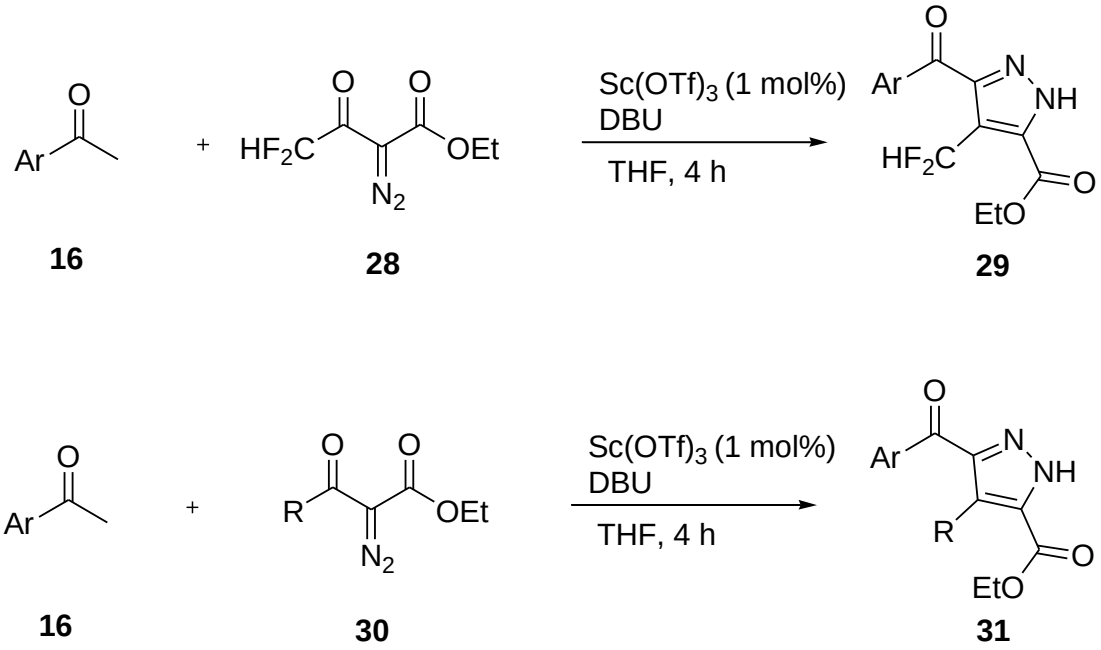
2.3. From diazoester.

The methodology for synthesizing pyrazole derivatives from acetophenone 16 and substituted diazoester 17 (Scheme 6) [12] has been illustrated. The final products were formed from the reaction between the ketones and diazoester through cyclization. Dialkyl ketones failed to provide the corresponding final products using bases like DBU and Et_3N. It might be a reason for less activity of α-hydrogen of ketones.



Scheme 6

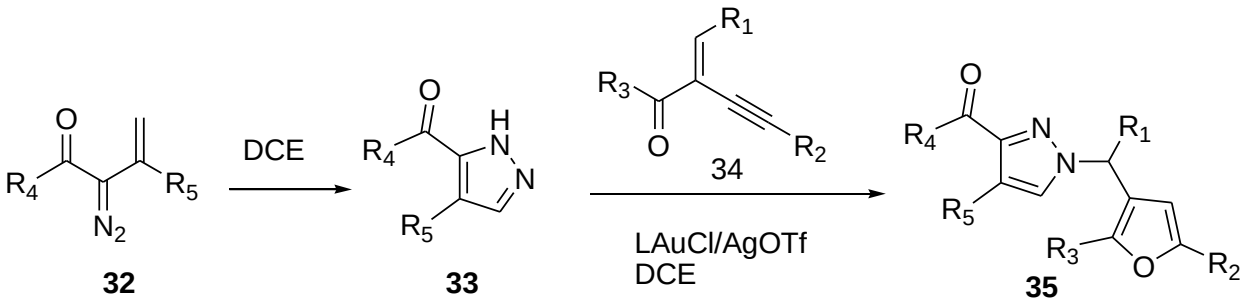
The synthetic approach has been accomplished by Chen *et al*. [13] for the construction of pyrazole moiety molecules **29** and **31** using scandium triflate as a catalyst in the presence of THF solvent (Scheme 7). Other metal catalysts, such as Sc(OTf)3, were inefficient for this method. Unfortunately, other bases like Et3N, t-BuOK, K2CO3, and K3PO4 did not produce the expected product.



Scheme 7

2.4. From vinyldiazo ketones.

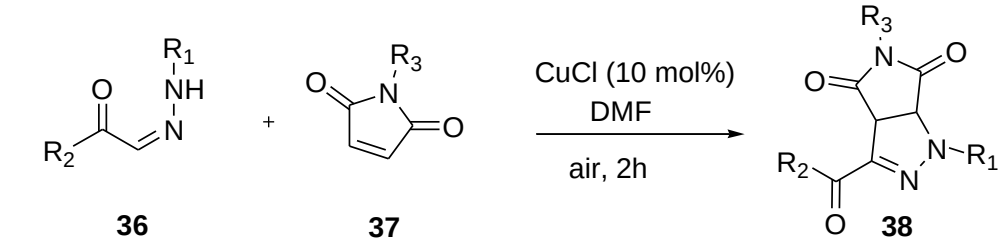
The method for the manufacturing of pyrazole derivatives was established (**Scheme 8**) [14]. This method involves two stages. Vinyldiazo ketones undergo heating in the presence of DCE solvents to produce 1*H*-pyrazoles **33** in the first stage, while, in the second stage, the compound **33** was treated with enynones 34 using silver triflate catalyst to get target product pyrazole-based triarylmethanes **35** in good yield.



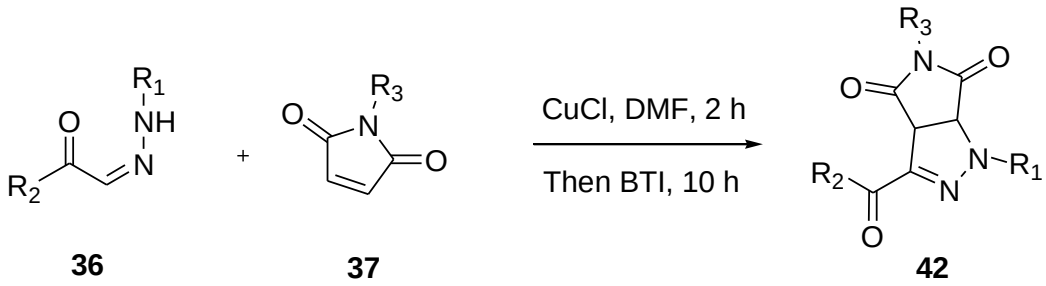
Scheme 8

2.5. From hydrazones.

Zhu and coauthors [15] have investigated method for the construction of pyrazole compounds from **36** and **37** *via* oxidative coupling reaction **(Scheme 9)**. As per their optimization Cu (I) sources have shown better catalytic activity than Cu (II) sources. On the other hand, remaining metal slats ($Pd(OAc)_2$, Ag_2CO_3, $Mn(OAc)_3$, and $FeCl_3$) were inefficient for this method.

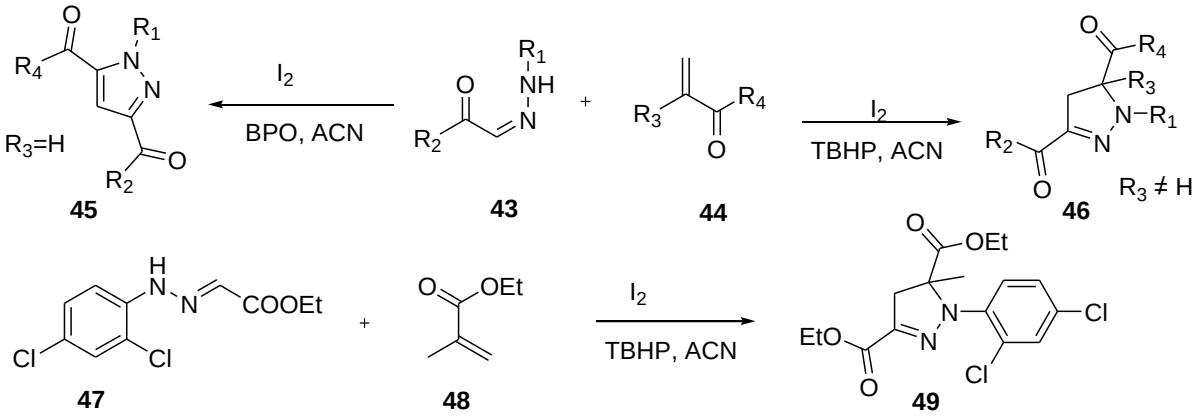


Scheme 9



Scheme 10

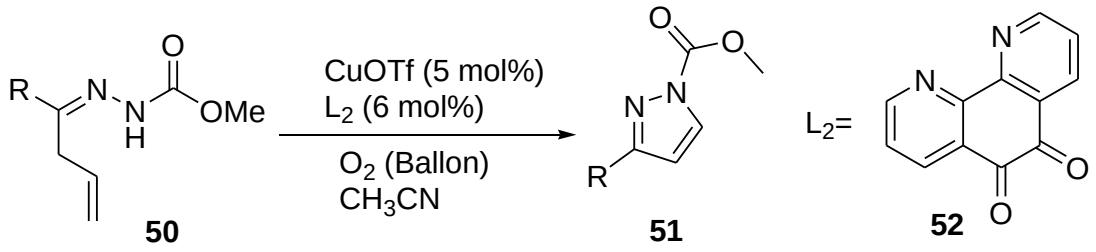
Iodine catalyzed preparation of pyrazole derivatives has been accomplished from the reaction between aldehyde hydrazones and electron-deficient olefins (**Scheme 11**) [16] under mild reaction conditions. Out of the used solvents DMF gave target product in quantitative yield, in contrast, the solvent CH_3CN produced final product in less yield. Based on their optimization, BPO found to be a good oxidant than others. In addition, other iodinating reagents (NaI, NIS, or TBAI) were not effective like I_2.



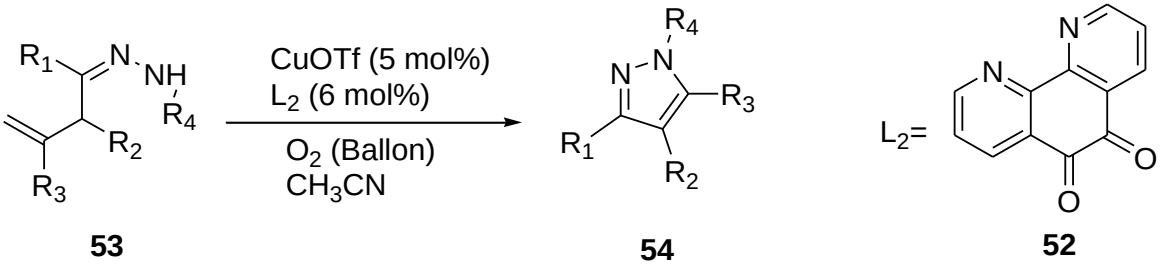
Scheme 11

Fan and co-workers [17] have reported one-pot copper-catalyzed aerobic cyclization for the construction0-98trl of pyrazole derivatives (**51** and **54**) (Scheme 12 and 13). β and γ-unsaturated hydrazones provided final products in good yield under optimized reaction

conditions. During their optimization they could find CuOTf was efficient than other employed copper catalysts.

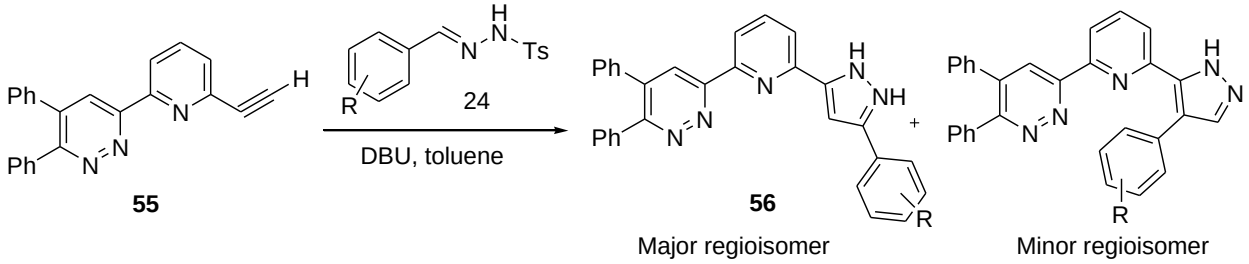


Scheme 12



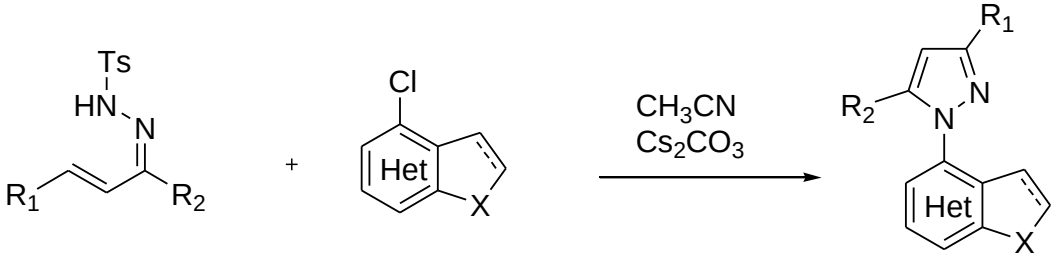
Scheme 13

Cycloaddition was used to synthesize pyrazole derivatives **56** using DBU in the presence of Toulene (Scheme 14) [18]. The desired products were produced from the starting precursors in good to excellent.



Scheme 14

Zheng and co-workers [19] have demonstrated base-promoted Pyrazole moieties **59** from starting materials **57** and **58** in the presence of Acetonitrile solvent (Scheme 15).

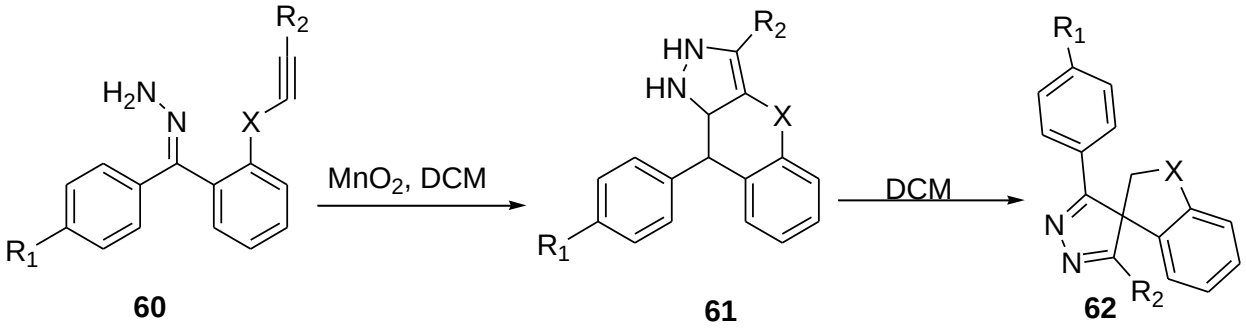


Scheme 15

2.5. From diazo intermediates and alkynes.

Dimirjian and colleagues [20] have developed a methodology for manufacturing Pyrazoles **62** through intramolecular reaction (Scheme 16). Notably, Manganese dioxide and

DCM solvents are good for this reaction. The final products **62** was obtained through 1,3-dipolar intramolecular cycloadditions.

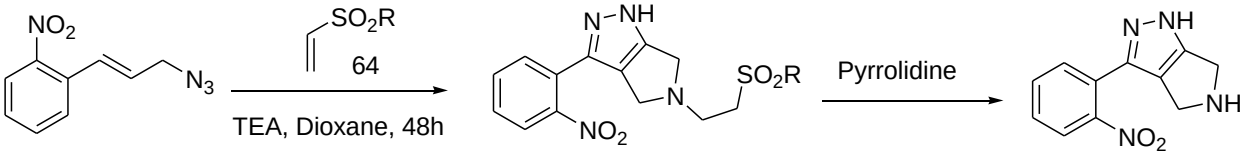


60 **61** **62**

Scheme 16

2.6. From vinyl sulfone.

Pyrazoles derivatives **66** have also been constructed from cinnamyl azides and vinyl sulfones through a cascade reaction under moderate reaction conditions (Scheme 17) [21]. In this work, dioxane was found to be more effective than other solvents. As per base optimization, Triethyl amine was superior to other diisopropyethylamine (DIPEA) and diisopropanolamine (DIPA).

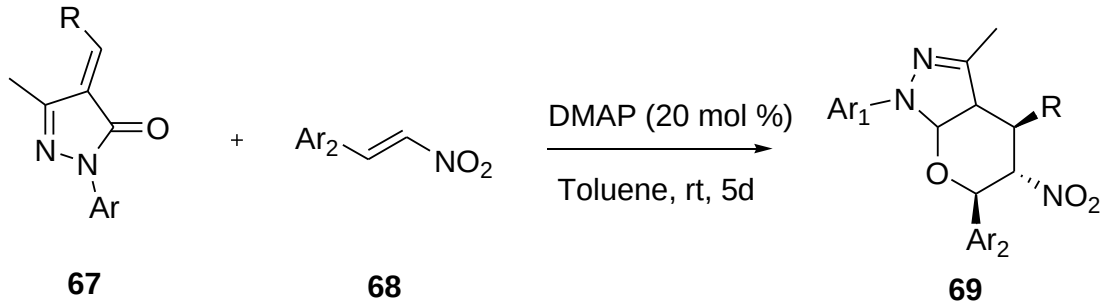


63 **65** **66**

Scheme 17

2.7. Pyrazoles from nitro-olefins.

The method for the construction of pyrazoles **69** is accomplished under moderated conditions. Domino cross-coupling is involved in this reaction (Scheme 18) [22]. In this method, they developed stereochemistry of the fused pyrazoles.

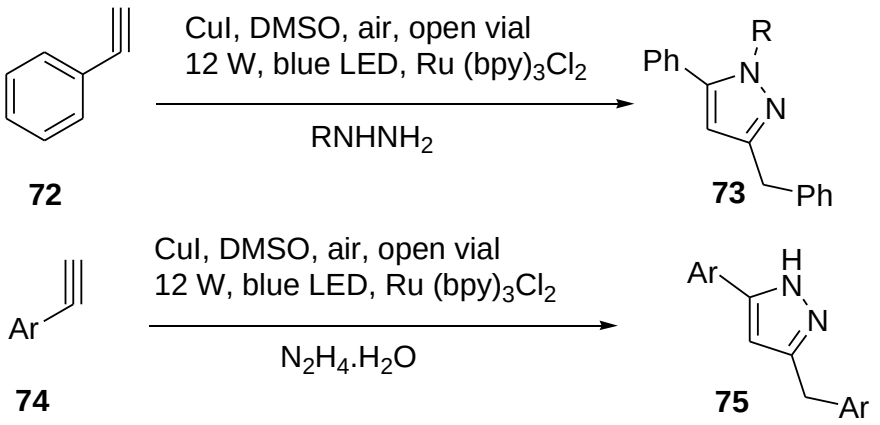


67 **68** **69**

Scheme 18

2.8. From alkynes.

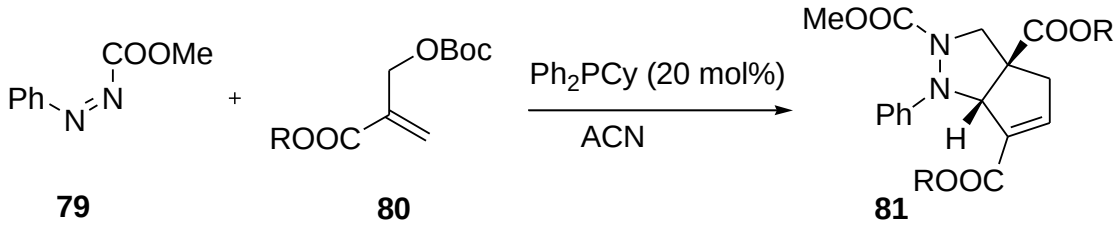
Polysubstituted pyrazoles **73** and **75** construction was promoted by visible light using CuI as a catalyst (Scheme 19) [23]. This method mainly consists of coupling/annulation reactions. Other catalysts (CuCl, $CuCl_2$, $Cu(OTf)_2$, and $Cu(OAc)_2$) have shown lower catalytic activity.



Scheme 19

2.9. Pyrazoles from Morita−Baylis−Hillman (MBH) carbonates.

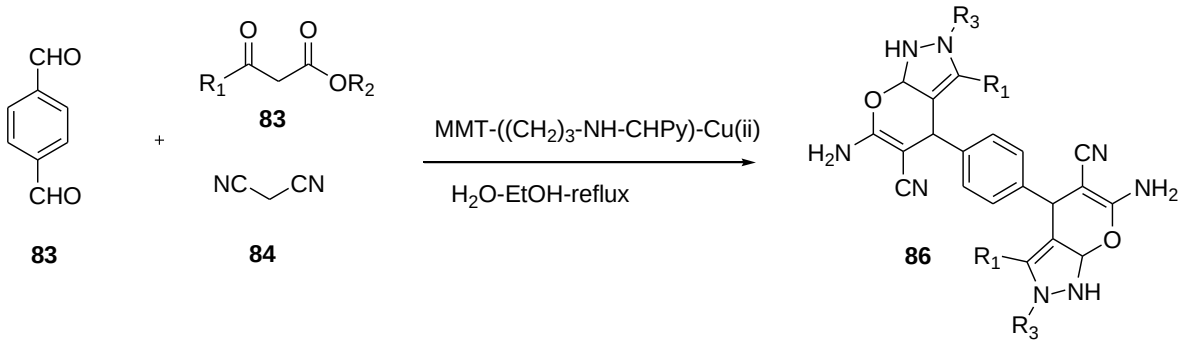
The synthetic pyrazole method is described by a phosphine-catalyzed domino cross-coupling reaction between diazenes and carbonates (Scheme 20) [24]. The starting precursors undergo the reaction to get the desired molecules in excellent yields.



Scheme 20

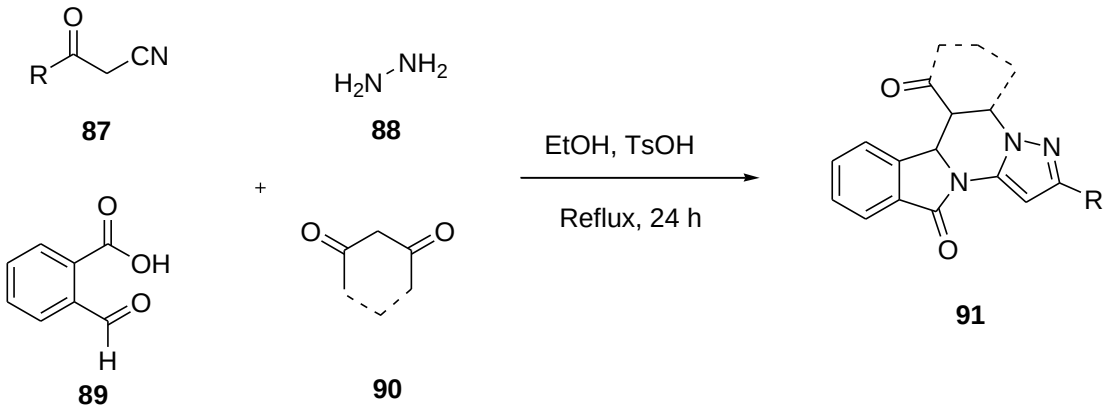
2.10. Multicomponent strategies.

A heterogeneous multicomponent reaction has been established for the construction of Pyrazoles using secondary support (MMT K10) (Scheme 21) [25]. They have also done catalyst recovery and reuse studies for this reaction and observed no loss activity for 5 cycles.



Scheme 21

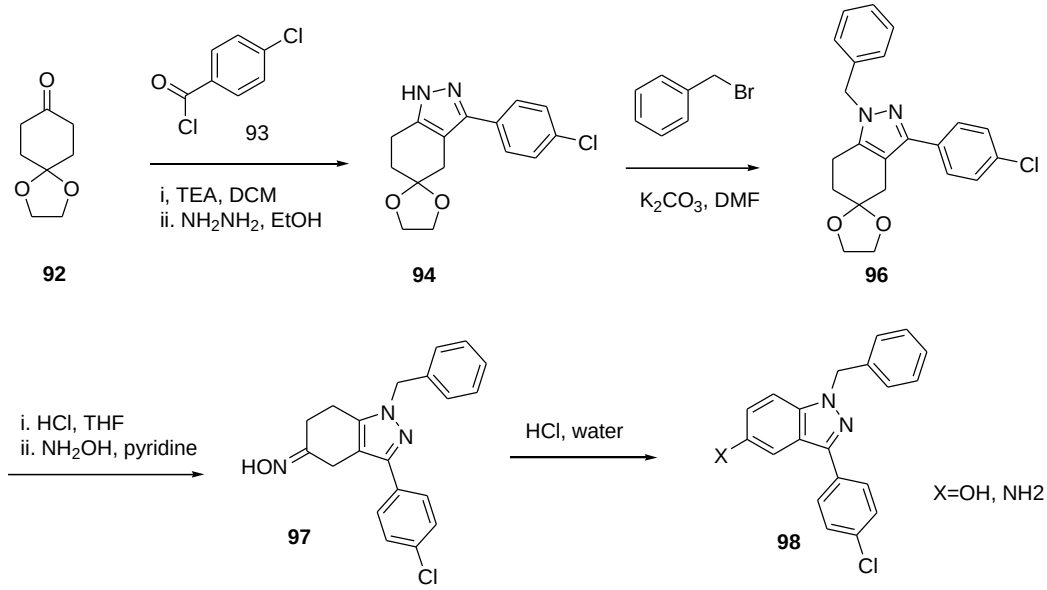
A new *N*-fused pyrazole derivative **91** has been accomplished by Alizadeh-Kouzehrash *et al*. in a pot multi-component reaction (Scheme 22) [26] using 4-toluenesulfonic in greenery solvent EtOH at 80 °C. The control experiment confirmed that no final product was observed without a catalyst.



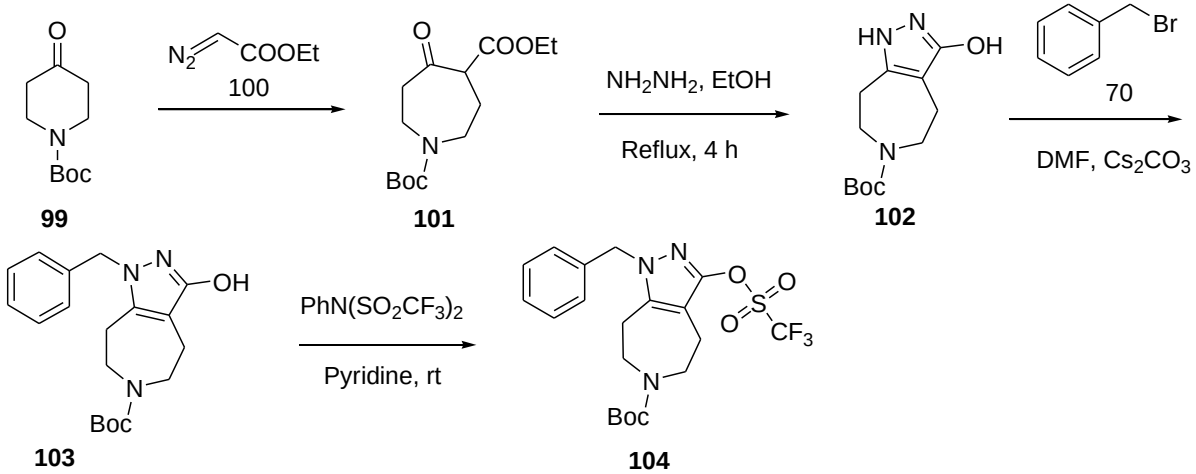
Scheme 22

2.11. Miscellaneous.

Dvorak and co-workers developed a method for the preparation of Pyrazole through a multi-step reaction (Scheme 23) [27]. The same group has also described an approach for constructing pyrazoletriflate moieties at room temperature (Scheme 24).



Scheme 23



Scheme 24

3. Biological activity of pyrazole derivatives.

3.1. Anti-inflammatory.

1,3,4,5-tetrasubstituted pyrazole (Figure 2) molecules have been reported for their anti-inflammatory effect by Bhale *et al*. According to reports, compound 105 exhibit inhibition (93.80%), which is better than other compounds. El-Karim and co-workers have evaluated the anti-inflammatory activity of the compounds **106a-f**. Based on the values, they have confirmed that the desired compounds have effective anti-inflammatory activity and are considered good potent candidates. Furthermore, 106b–e compounds have expressed good potent analgesic and long-acting analgesia activity [28-29].

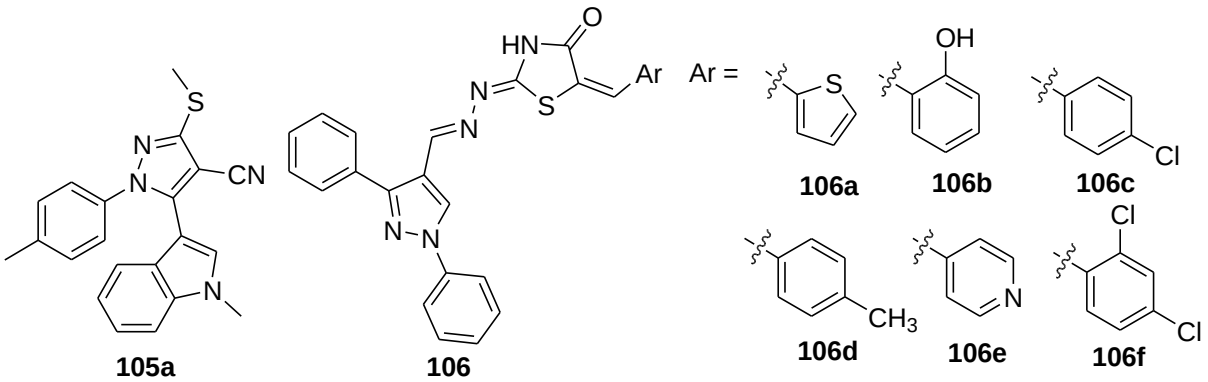


Figure 2

3.2. Anticancer activity.

Karim and co-workers have tested the anticancer activity of desired compounds against a normal Vero cell line. In this regard, compound **105b** expressed reliable cytotoxicity (Figure 3) [30]. Pyrazole-benzimidazole hybrids' anticancer activity has been evaluated by Sivaramakarthikeyan and others [31-33]; they revealed that the compound (**107a**) has shown effective activity. Later, Akhtar *et al*. [30, 34] have studied anticancer activity on Pyrazole-Pyrazole hybrid molecules. They point out that the compound bearing para methoxy at pyrazole nucleus **108 a** was better than other molecules.

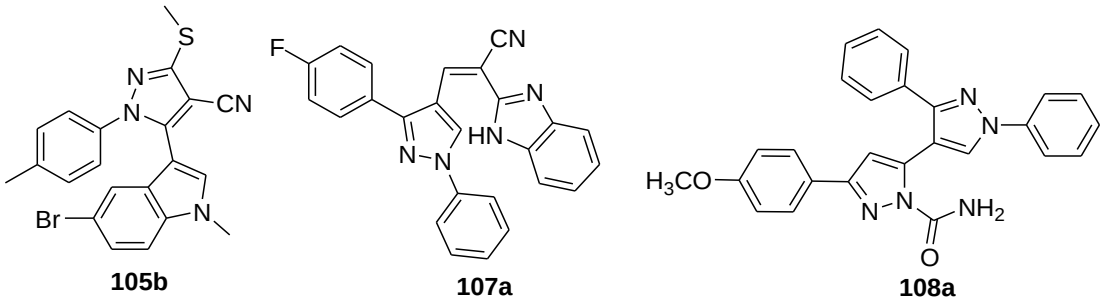


Figure 3

3.3. Antibacterial activity.

Nayak *et al*. [35] have illustrated **109** as promising antibacterial agents (Figure 4). Design and synthesis of novel Pyrazole containing imidazole have been established in one pot three-component reaction by Ebenezer *et al*. [36], and it was also evaluated for biological study.

In this regard, they found that all prepared molecules (zone of inhibition 9 mm) exhibited good bacterial activity. When compared with standard ciprofloxacin, all the compounds have exhibited good activity except for MRSA. Further, the synthesis and antibacterial activity of Pyrazoloquinoline derivatives have been evaluated using the Agar diffusion method [37] **2021**]. The synthesized compounds like **111a** and **111b** expressed percentages of activity of 112% and 95% (Streptococcus pneumoniae) and 86% and 83%, respectively (Bacillus subtilis), compared to the standard control. On the other hand, the compound (halogenated Pyrazole) **111b** exhibited enhanced activity compared to gentamicin (109%); however, they didn't observe any activity in Pseudomonas aeruginosa. Later, a new group of poly-substituted indole pyrazole molecules with antibacterial activity was investigated by targeting DNA gyrase [38]. Among the compounds, **112** showed good antibacterial activity against four drug-resistant E. coli bacteria strains.

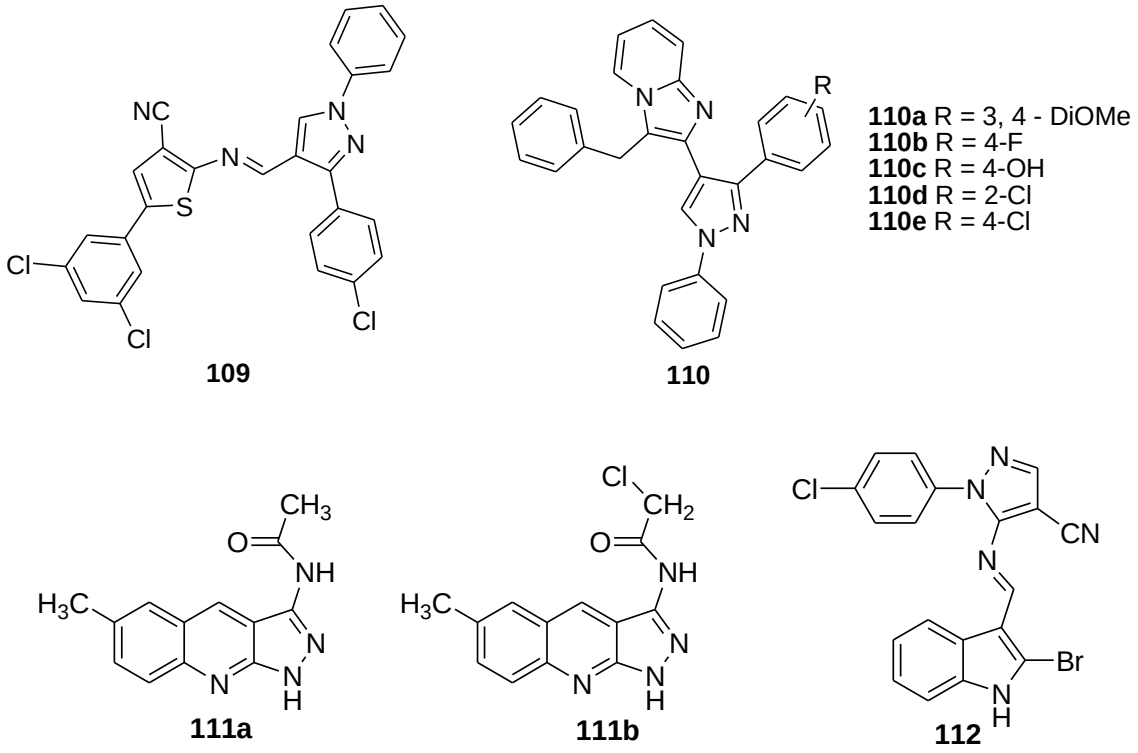


Figure 4

4. Conclusions

Pyrazoles are one of the nitrogens containing heterocyclic compounds, and they are an efficient class for drug development. Furthermore, they treat different infections of clinical privacy and serve as an intermediate for developing new pharmacological agents. This review has revealed different methodologies for the synthesis of pyrazoles and their biological study, such as anti-inflammatory, anticancer, and antibacterial. This review will benefit the upcoming researchers for exploring pyrazole moieties investigation.

Acknowledgments

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Conflicts of Interest

The authors declare no conflict of interest.

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