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Recent advances in the synthesis of bis(pyrazolyl)methanes and their applications

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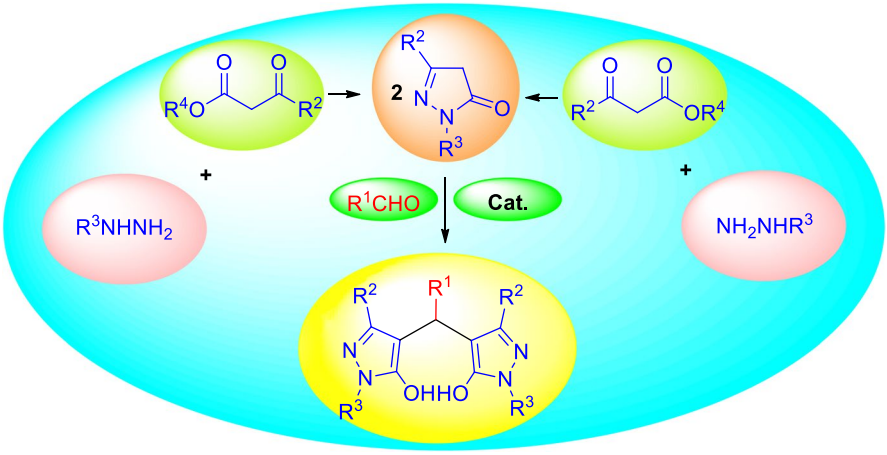
Abstract

Pyrazole and its derivatives are an important class of heterocyclic compounds, present in several biologically and medicinally active compounds. Compounds containing 2,4-dihydro-3*H*-pyrazol-3-one structural motif, including 4,4′-(arylmethylene)-bis-(1*H*-pyrazol-5-ols), have attracted interest because they exhibit a wide range of biological activities and as the chelating and extracting reagents for different metal ions. There are two main strategies to the synthesis of bis(pyrazolyl)methane derivatives. The first involves the one-pot pseudo three-component reactions of 3-methyl-5-pyrazolone derivatives and aldehydes, and the second approach is the one-pot pseudo five-component reactions of *β*-keto esters, hydrazins and aldehydes. This review includes the recent investigation in the multi-component synthesis and their applications of bis(pyrazolyl)methanes and describes the literature reports for the period of 2014 to early 2021.

Graphic abstract



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Keywords Bis(pyrazolyl)methane · Bispyrazole · Hydrazine · β-Keto ester · Multicomponent reaction

Introduction

Heterocyclic compounds are widely distributed in nature and are essential to life. Pyrazole derivatives are an important class of heterocyclic compounds having a 5-membered ring structure with three carbon atoms and two neighbor nitrogen atoms. There are several applications of pyrazole core-based organic molecules in various areas including pharmacy and agro-chemical industries. 2,4-Dihydro-3*H*-pyrazol-3-one derivatives including 4,4′-(arylmethylene)-bis-(1*H*-pyrazol-5-ols), have attracted interest because they exhibit a wide range of biological activities such as anti-malarial [1], anti-inflammatory [2, 3], anti-nociceptive [4], antipyretic [5], antifungal [6], anti-virals [7], antidepressant [8], antibacterial [9, 10], antitumor [11], antioxidant [12] and anti-filarial agents [13]. In addition, these derivatives are applied as fungicides [14], analgesic [15], pesticides [16], insecticides [17], and as the chelating and extracting reagents for different metal ions [18–20]. There are two main strategies to the synthesis of bis(pyrazolyl)methane derivatives. The first involves the one-pot pseudo three-component reactions of two equivalents of 3-methyl-5-pyrazolone derivatives and one equivalent of aldehydes, and the second approach is the one-pot pseudo five-component reactions of two equivalents of β-keto esters, two equivalents of hydrazins and one equivalent of aldehydes.

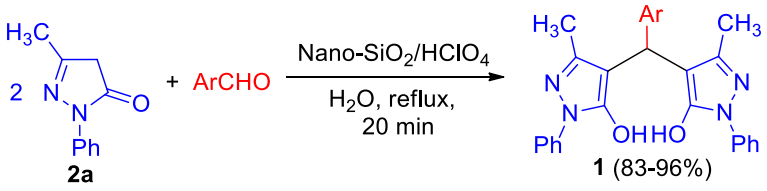
Prior to 2014, bis(pyrazolyl)methanes were synthesized under different conditions and using various catalysts including piperidine catalyzed the reaction of pyrazolone with *p*-methoxybenzaldehyde [21], reaction of arylidene anilines with pyrazolone [22], solid-state Michael addition of pyrazolone to 4-arylidene-5 pyrazolones [23], reaction of pyrazolones with phenacylpyridinium salt in refluxing glacial acetic acid containing ammonium acetate [24], treatment of 4-[2-cyano-2-ethoxycarbonyl-1-(aryl)ethyl]-3-methyl-1-phenylpyrazolin-5-ones with pyrazolone [25], ring opening of bis-pyrazolo[5,4-b]-4*H*-pyranes with KOH (10%) in refluxing EtOH [10], reaction of aldehydes and pyrazolones in the presence of sodium dodecyl sulfate in aqueous media [26], treatment of aryl aldehydes and 1-phenyl-3-trifluoromethylpyrazol-5-one in aqueous media without catalyst [27], electrochemically induced catalytic reaction of pyrazolone with aromatic aldehydes using NaBr as an electrolyte [28]. Also, synthesis of bis(pyrazolyl)methanes has been accomplished via one-pot three-component reaction of pyrazolones with aromatic aldehydes using various conditions and catalysts such as ceric ammonium nitrate (CAN) [7], solvent- and catalyst-free at 120–130 °C [29], silica-bonded s-sulfonic acid [30], cellulose sulfuric acid [31], piperidine under ultrasound irradiation [32], diammonium hydrogen phosphate [33], poly(ethylene glycol)-bound sulfonic acid (PEG-SO_3H) [34], sulfuric acid ([3-(3-silicapropyl)sulfanyl]propyl)ester [35], catalyst-free in refluxing H_2O [36], silica sulfuric acid (SSA) [37], PEG-400 and catalyst-free [38], ionic liquid [HMIM]HSO_4 under ultrasonic irradiation [39], *N*-(3-silicapropyl)-*N*-methylimidazolium hydrogen sulfate ([Sipmim]HSO_4) [40], 3-aminopropylated silica gel [41], 1,3,5-tris(hydrogensulfato) benzene (THSB) [42], 1,3-disulfonic acid

imidazolium tetrachloroaluminate {[Dsim]$AlCl_4$} [43], LiOH. H_2O in water [44], xanthan sulfuric acid (XSA) [45], phosphomolybdic acid [46], 2-hydroxyethylammonium acetate (2-HEAA) as a task-specific ionic liquid [47], ammonium acetate [48], silica-bonded *N*-propyltriethylenetetramine (SBNPTT) [49], melamine trisulfunic acid [50], ionic liquid 1-sulfopyridinium chloride {[pyridine–SO_3H]Cl} [51], poly(4-vinylpyridine)-supported Brønsted ionic liquid ([P_4VPy-BuSO_3H]HSO_4) [52] and [Cu(3,4-tmtppa)]$(MeSO_4)_4$ [53]. Moreover, pseudo five-component synthesis of bis(pyrazolyl)methanes has been carried out under different conditions and catalysts such as silica-bonded *N*-propylpiperazine sulfamic acid (SBPPSA) under solvent-free conditions [54], catalyst-free in refluxing H_2O [55], pyridine trifluoroacetate [56], AcOH at room temperature [57], microwave irradiation (300 W) [12], sulfonated rice husk ash (RHA-SO_3H) under solvent-free conditions [58] and catalyst-free under ultrasonic irradiation [59]. However, a review article on the synthesis of these compounds has been published by Gouda until the end of 2013 [60]. In this review, we want to cover the recent synthetic methodologies and their applications of bis(pyrazolyl)methane derivatives and describe the literature reports for the period of 2014 to early 2021.

Synthesis of bispyrazoles via one-pot pseudo three-component reactions

In 2014, Sadeghi and Ghorbani Rad synthesized a series of 4,4′-(arylmethylene) bis(1*H*-pyrazol-5-ols) **1** in 83–96% yields via stirring of 3-methyl-1-phenyl-2-pyrazoline-5-one (**2a**) with various aromatic aldehydes in the presence of nano-SiO_2/$HClO_4$ as a catalyst in water under reflux within 20 min (Scheme 1) [61].

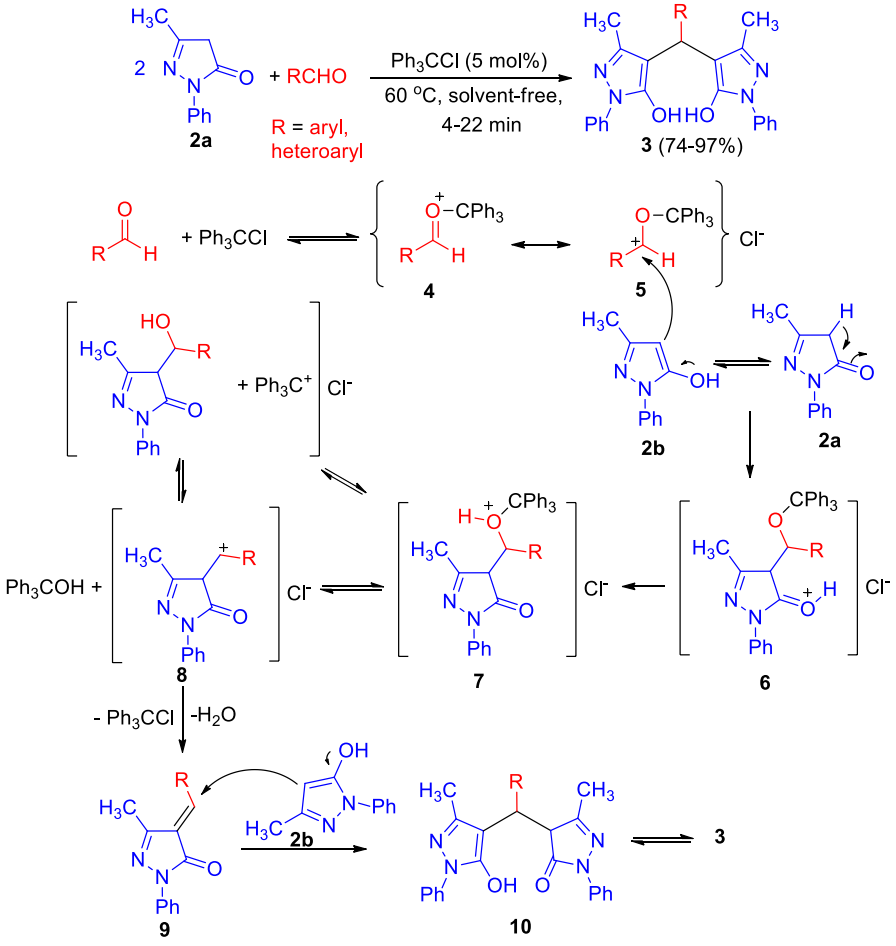
Next, synthesis a series of bis(pyrazolyl)methanes in 85–94% yields was accomplished via a one-pot pseudo three-component condensation reaction of **2a** with aromatic aldehydes using ZnO nanoparticles as a recyclable and highly efficient catalyst in EtOH-H_2O under reflux conditions for 15–30 min. The reaction with aliphatic aldehydes did not take place. In the proposed mechanism, firstly, the *α,β*-unsaturated adduct is generated by the Knoevenagel condensation reaction between aromatic aldehyde and **2a.** Then, Michael addition of **2a** to the *α,β*-unsaturated adduct followed by 1,3-proton shift gives the desired products**.** In this reaction, ZnO NPs act as a Lewis acid catalyst with high surface area by activating the carbonyl group of the aldehyde [62].



Scheme 1 Nano-SiO_2/$HClO_4$ catalyzed synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) **1**

After that, Zare and co-workers developed preparation of bis(pyrazolyl)methanes **3** in 74–97% yields via condensation of **2a** with aryl/heteroary aldehydes catalyzed by trityl chloride (Ph_3CCl) as a homogeneous organocatalyst under mild and solvent-free conditions at 60 °C for 4–22 min. In a reasonable mechanism as illustrated in Scheme 2, resonance forms **4** and **5** can first be produced from aryl aldehyde and Ph_3CCl in a reversible reaction. They act as an activated aldehyde, reacting with tautomer **2b** of **2a** providing **6**, which converts to **7** by proton transfer. Intermediate **7** can interconvert to **8** by loss of Ph_3COH. **8** and Ph_3COH then react to yield benzylidene intermediaite **9**, Ph_3CCl, and H_2O. Then, **9** react with another molecule of **2b** to generate **10**. In the last step, tautomerization of **10** affords the desired products **3** [63].

Later, two efficient and green methods for the synthesis of bispyrazoles in 90–96% yields in the absence of any catalyst or solvent were developed by



Scheme 2 Ph_3CCl catalyzed synthesis of bis(pyrazolyl)methanes **3**

heating (at 120 °C) for 10 min or microwave irradiation at 60 °C (300 W) for 3 min of intimate mixtures of **2a** and aldehydes in 2:1 mol ratio [64].

In addition, ammonium acetate is employed as a catalyst for the condensation reaction of 1-aryl-3-alkyl-1*H*-pyrazol-5-ol (alkyl = CF_3, CH_3) with aromatic or aliphatic aldehydes. This condensation reaction was performed by grinding at room temperature for 5–10 min giving 4,4′-aryl or alkyl methylene-bis(1*H*-pyrazol-5-ols) in 80–95% yields. In the proposed mechanism, the reaction proceeds via Knoevenagel-type condensation of aldehyde with pyrazole using NH_4OAc to afford benzylidene intermediaite, followed by Michael addition of another molecule of pyrazole to yield the desired products. These compounds were tested in vitro antibacterial activity against S. aureus, X. protophormiae, P. aeruginosa and B. licheniformis. Among them**,** CF_3 group-containing compounds show excellent antibacterial activity and CH_3 group containing compounds were not active [48].

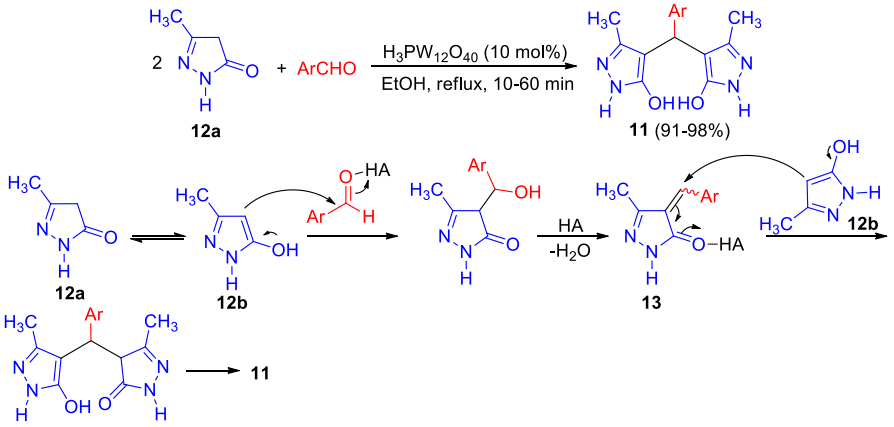
Further, bispyrazole derivatives were synthesized in 83–93% yields in the presence of aqueous extract of fruit (biosurfactant) as a biobased green acidic catalyst from the reaction between aryl aldehydes and **2a** at 60 °C. At first, Knoevenagel condensation proceeded rapidly for 2 min to give orange coloured arylidenepyrazolones which were converted to the target products within 15–60 min via Michael step [65].

In 2015, Eskandari et al. described synthesis of bispyrazoles in 85–92% yields via condensation of **2a** with aromatic aldehydes catalyzed by Mohr's salt in EtOH:H_2O (1:1) under reflux conditions for 20–30 min. In addition, the reaction with aliphatic aldehydes did not take place [66].

Moreover, 2-carbamoylhydrazine-1-sulfonic acid and carbamoylsulfamic acid as nano-structure organocatalysts were applied for the solvent-free synthesis of bis(pyrazolyl)methanes in 83–98% yields by the reaction of several aromatic aldehydes with **2a** at 60 °C for 10–210 min. The probable mechanism includes the creation of benzylidene intermediaite via the nucleophilic addition of **2a** to aryl aldehyde, followed through dehydration. Next, the second molecule of **2a** adds in the Michael addition approach to yield the corresponding products [67].

After that, a rapid and environmentally friendly method was developed for the preparation of bis(pyrazolyl)methanes in 86–97% yields by condensing **2a** with various aldehydes catalyzed by CsF in de-ionized water at ambient temperature for 5–10 min. In the reasonable mechanism, CsF probably plays two important roles, first it increases the electrophilicity of the carbonyl carbon of the aldehyde, and secondly the fluoride counter ion works as a base generating the enolate of pyrazolone [68].

Later, 12-tungstophosphoric acid ($H_3PW_{12}O_{40}$) is employed as a catalyst for the synthesis of 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ols) **11** in 91–98% yields by the reaction of two equivalents of 3-methyl-1*H*-pyrazol-5(4*H*)-one (**12a**) with aromatic aldehydes in refluxing EtOH for 10–60 min. Considering the Brønsted acidic nature of $H_3PW_{12}O_{40}$ = HA, a plausible mechanism is depicted in Scheme 3. It is believed that **12b** (first equivalent of enolic form of **12a**) reacts initially with aryl aldehyde to give the intermediate **13**, which then reacts with second equivalent of **12b** to afford the desired products **11** [69].



Scheme 3 $H_3PW_{12}O_{40}$ catalyzed synthesis of bis(pyrazolyl)methanes **11**

Nanomagnetite-Fe_3O_4 is applied as a recyclable nanomagnetite catalyst for the preparation of bis(pyrazolyl)methane derivatives in 74–95% yields via the condensation reaction of **2a** with aryl aldehydes at 70 °C under solvent-free conditions for 3–9 min. In the suggested mechanism, at first, **2a** converts to the other tautomer **2b** in the presence of nonamagnetite-Fe_3O_4. Nucleophilic addition of **2b** on activated of carbonyl group of aldehyde affords benzylidene intermediaite. Additions of another molecule of **2b** to benzylidene adduct followed by tautomerization and aromatization gives the target products [70].

Elinson and co-workers reported preparation of bis(pyrazolyl)methanes in 93–99% yields by the reaction of aromatic aldehydes and **2a** in refluxing EtOH under catalyst-free conditions for 5 min. The plausible mechanism involves ionization of **2a** leads to the formation of pyrazole anion. This process can be thermally activated. Then, Knoevenagel condensation reaction of pyrazole anion with aryl aldehyde affords benzylidene intermediate. Subsequently, benzylidene intermediate and another equivalent of **2a** undergo Michael addition yields bispyrazole anion, which then undergoes intramolecular tautomeric transformation results the desired products [71].

Further, synthesis of bispyrazoles in 84–95% yields was accomplished by the condensation of **2a** with aromatic aldehydes catalyzed by $SbCl_5/SiO_2$ NPs as a recyclable catalyst in refluxing water within 20 min [72].

Karami and co-workers noted that treatment of various aromatic aldehydes with **2a** catalyzed by ZnO NWs as a recyclable catalyst in EtOH:H_2O (1:1) under reflux conditions for 15–30 min gave bis(pyrazolyl)methane derivatives in 84–90% yields. The reaction with aliphatic aldehydes was unsuccessful. It seems that the problem in the case of aliphatic ones is likely to be enolyzed. In the plausible mechanism, α,β-unsaturated adduct is obtained via reaction of **2a** with aldehyde. Then, 1,4-addition of **2b** on α,β-unsaturated adduct followed by [1, 3]-sigmatropic proton shift affords the corresponding products [73].

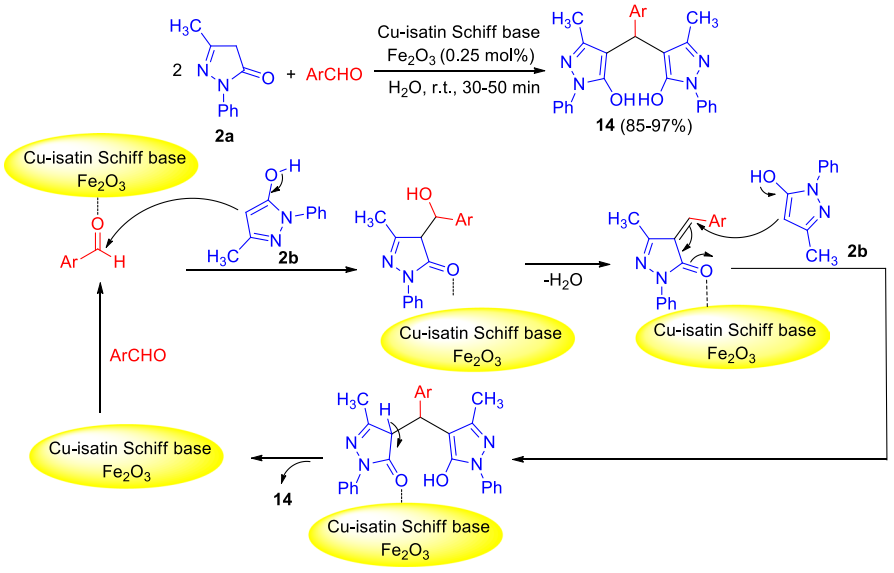
In 2016, Cu-isatin Schiff base supported on γ-Fe_2O_3 is prepared and employed as a recyclable catalyst for the synthesis of bis-derivative **14** in 85–97% yields by the reaction of aromatic and aliphatic aldehydes with **2a** in H_2O at room temperature for 30–50 min. A possible mechanism for the formation of **14** is depicted in Scheme 4. Firstly, compound **2b** reacts with aldehyde followed by dehydration to give benzylidene intermediaite, which is then react with the second molecule of **2b** through Michael addition to afford bispyrazoles **14** [74].

Next, nano-magnetic Fe_3O_4-based vanadic acid [MNPs@$VO(OH)_2$] was used as a solid acid catalyst for the synthesis of bispyrazole derivatives **15** in 72–96% yields via the reaction **2a** with of aromatic and heteroaromatic aldehydes in 4–5 drops ethanol at 40 °C for 5–45 min. A proposed mechanism for the preparation of **15** is illustrated in Scheme 5. Initially, the reaction between **2b** and aldehyde affords intermediate **16**. Then, intermediate **16** and the second molecule of **2b** undergo Michael addition to give the desired products **15** [75].

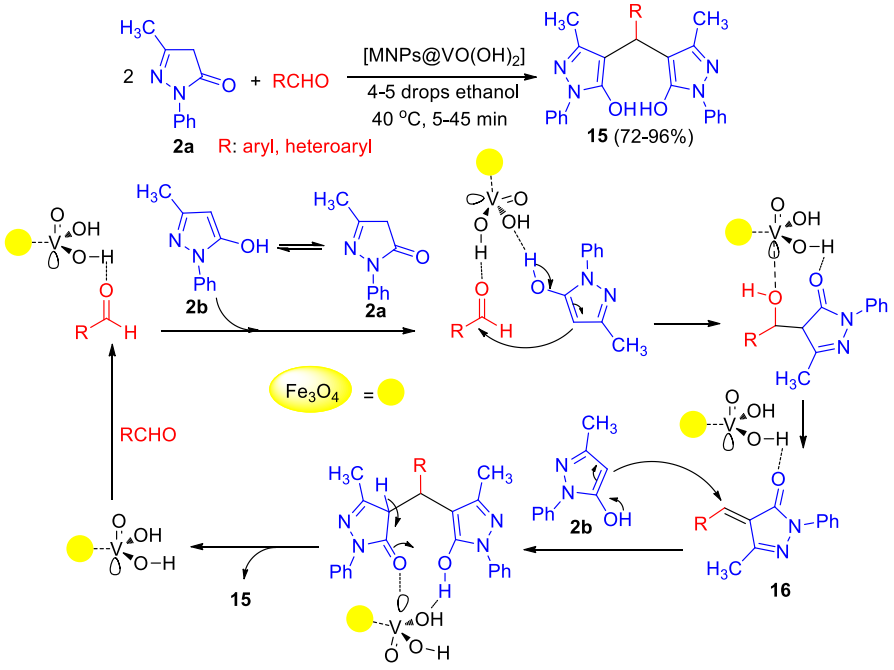
Pawar and co-workers described catalyst-free green synthesis of bispyrazoles in 80–91% yields by the reaction of aromatic aldehydes with **2a** in ethylene glycol at 90 °C for 1–2 h. In this method, all the reactions proceeded smoothly and the corresponding products were purified by simple recrystallization without further purification [76].

Furthermore, alum ($KAl(SO_4)_2$ $12H_2O$) as a reusable catalyst was applied to synthesize bis(pyrazolyl)methanes in 81–95% yields via the reaction of **2a** with carbonyl compounds (aromatic/heteroaromatic aldehydes or *N*-alkyl substituted isatin derivatives) at 60 °C under solvent-free conditions for 15–300 min [77].

The [Amb]L-prolinate was prepared from the immobilization of L-prolinate anion onto amberlite IRA900OH and used as an organocatalyst for the synthesis of



Scheme 4 Cu-isatin Schiff base-γ-Fe_2O_3 catalyzed synthesis of bispyrazoles **14**



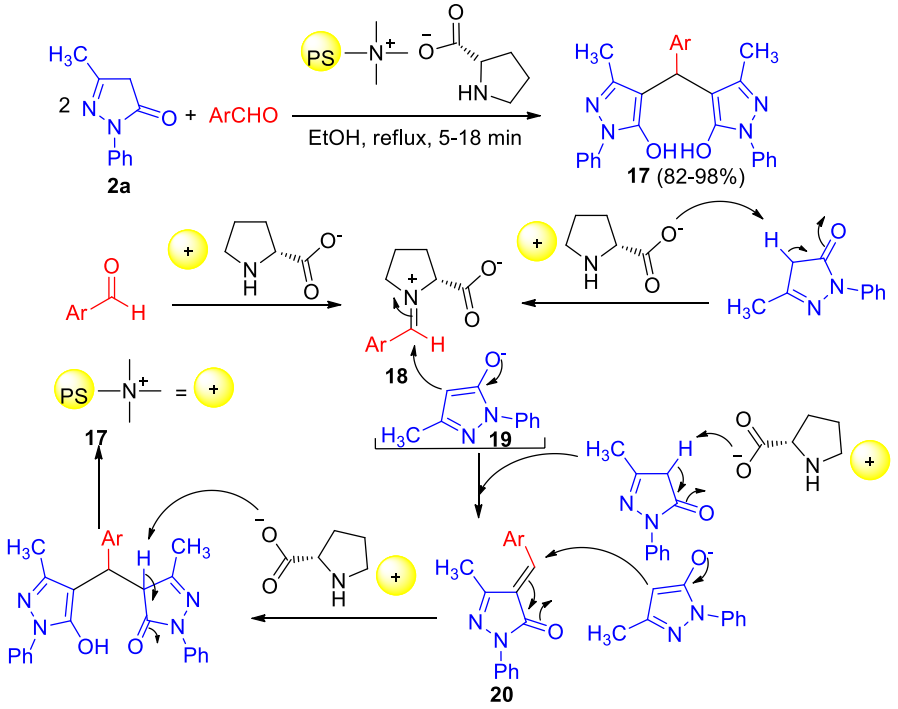
Scheme 5 [MNPs@$VO(OH)_2$] catalyzed synthesis of bis-derivatives **15**

bispyrazoles **17** by the condensation reaction of **2a** with aromatic aldehydes**.** The reaction was performed in EtOH under reflux conditions for 5–18 min giving the corresponding products **17** in 82–98% yields. A reasonable mechanism for the synthesis of **17** is depicted in Scheme 6. Initially, an iminium carboxylate **18** is obtained via reaction of aldehyde with L-prolinate anion of catalyst. Next, L-prolinate anion abstracts a proton from **2a** to form the enolate intermediate **19**. Subsequent Michael addition of enolate **19** to the iminium carboxylate **18** affords intermediate **20**. Finally, Michael addition of the second molecule of **19** to **20** leads to the formation of the corresponding products **17** [78].

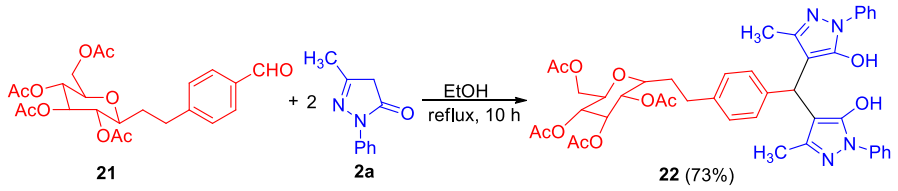
Moreover, a Knoevenagel condensation reaction of 1-(2,3,4,6-tetra-*O*-acetyl-1-*β*-D-glucopyranose)-2-(4-formylphenyl)-ethane (**21**) with **2a** in EtOH under reflux conditions for 10 h gave bispyrazole derivative **22** in 73% yield instead of a benzylidene-pyrazolinone derivative (Scheme 7) [79].

In 2017, Mosaddegh et al. reported synthesis of bispyrazoles in 81–98% yields via the reaction of **2a** with aromatic aldehydes using $Ce(SO_4)_2.4H_2O$ as a reusable catalyst in H_2O:EtOH (1:1) solution at reflux for 5–25 min. The plausible mechanism for this reaction involves formation of benzylidene intermediate of nucleophilic addition of **2b** to aromatic aldehyde followed by elimination of one molecule of water. Subsequently, Michael addition of the second molecule of **2b** to benzylidene adducts to afford the desired products [80].

4-Sulfophthalic acid (4-H_3SPA) solution 50 wt% in H_2O is employed as a catalyst for the preparation of bis(pyrazolyl)methanes in 88–97% yields by condensing **2a**



Scheme 6 Synthesis of bis(pyrazolyl)methanes **17** catalyzed by [Amb]L-prolinate

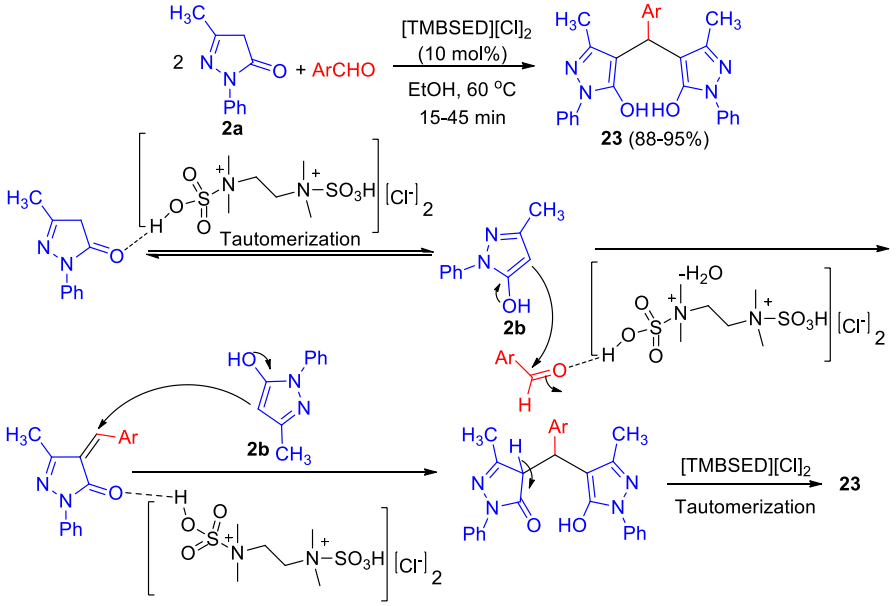


Scheme 7 Synthesis of bispyrazole derivative **22**

with aryl and heteroaryl aldehydes under aqueous conditions at room temperature within 10–20 min [81].

After that, Saghanezhad and co-workers succeeded in preparation of bis(pyrazolyl)methanes in 80–92% yields via the reaction of aromatic aldehydes and **2a** using caffeine-H_3PO_4 (7.5 mol%) as an efficient recyclable catalyst at 80 °C under solvent-free conditions within 55–75 min [82].

Moreover, N^1,N^1,N^2,N^2-tetramethyl-N^1,N^2-bis(sulfo)ethane-1,2-diaminium chloride ([TMBSED][Cl]$_2$) as an acidic ionic liquid catalyst was applied for the synthesis of bis(pyrazolyl)methanes **23** in 88–95% yields by the condensation reaction of **2a** with aromatic aldehydes in EtOH at 60 °C within 15–45 min. The plausible mechanism for the preparation of **23** is illustrated in Scheme 8 [83].

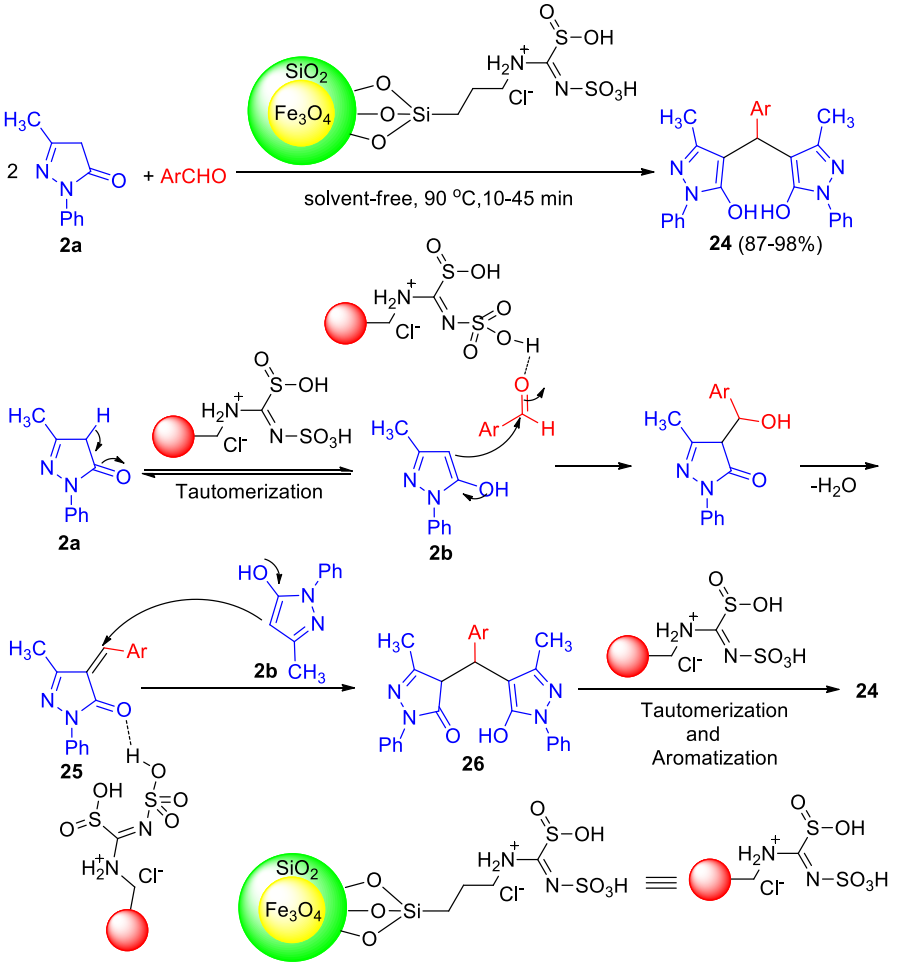


Scheme 8 The production of bis(pyrazolyl)methanes **23** promoted by $[TMBSED][Cl]_2$

Bispyrazoles **24** were synthesized in 87–98% yields by using $\{Fe_3O_4@SiO_2@(CH_2)_3$-thiourea dioxide-$SO_3H/HCl\}$ as a recyclable solid acid catalyst from the reaction between **2a** and aromatic aldehydes at 90 °C under solvent-free conditions within 10–45 min. A possible mechanism for the formation of **24** is outlined in Scheme 9. At first, **2a** converts to its enol form (**2b**) through interaction with the nanomagnetic catalyst and attacks the activated aldehyde to give intermediate **25** via dehydration. Then, treatment of the second molecule of **2b** with **25** to give the intermediate **26**, which undergo tautomerization and aromatization leads to the corresponding products **24** [84].

Furthermore, an efficient and eco-friendly protocol was introduced for the synthesis of bispyrazoles in 87–97% yields by the condensation reaction of **2a** with aryl aldehydes using boehmite nanoparticles (BNPs) (an aluminum oxide hydroxide (γ-AlOOH) mineral) as a recyclable catalyst at 80 °C under solvent-free conditions for 8–35 min. In the suggested mechanism, BNPs formulate electrophilic activation of the aldehyde to increase the rate of formation of the benzylidine intermediate. Subsequently, it accelerates the rate of the Michael addition of a second equivalent of **2b** on the benzylidine adducts for the formation of the desired products [85]**.**

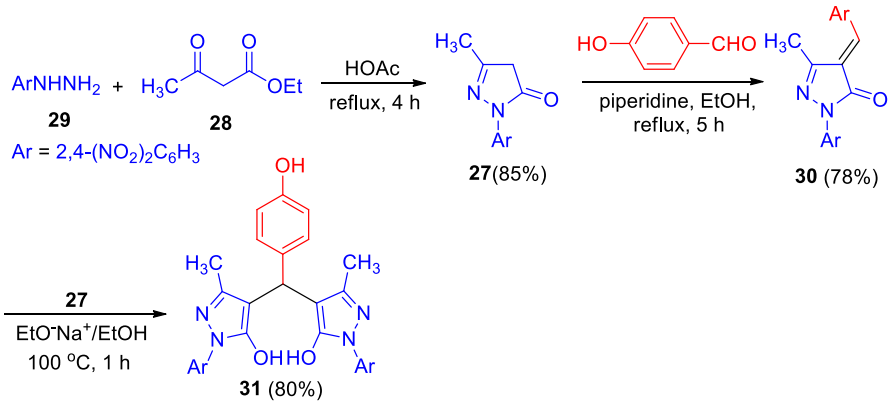
Also, 1-(2,4-dinitrophenyl)-3-methyl-1H-pyrazol-5(4H)-one (**27**) in 85% yield was prepared using ethylacetoacetate (**28**) and 2,4-dinitrophenylhydrazine (**29**) in HOAc under reflux conditions for 4 h. Then, Knoevenagel condensation reaction of **27** with *p*-hydroxybenzaldehyde in refluxing EtOH using piperidine for 5 h afforded the pyrazolone derivative **30** in 78% yield. Pyrazolone **30** reacted with pyrazolone **27** in the presence of sodium ethoxide in ethanol at 100 °C for 1 h to give 4,4′-((4-hydroxyphenyl)methylene)



Scheme 9 {Fe_3O_4@SiO_2@$(CH_2)_3$-thiourea dioxide-SO_3H/HCl} catalyzed synthesis of bis(pyrazolyl) methanes **24**

bis(1-(2,4-dinitrophenyl)-3-methyl-1*H*-pyrazol-5-ol) (**31**) in 80% yield (Scheme 10) [86].

In 2018, Mohammed Khan and co-workers reported that preparation of bis(pyrazolyl)methane derivatives in good to excellent yields by condensing **2a** with different aldehydes catalyzed by CsF as catalyst in ethanol at ambient temperature for 2–3 h. In this reaction, CsF plays two important roles. Firstly, it increases the positive charge on the carbonyl carbon of the aldehyde, and secondly the fluoride ion works as a base producing the enolate of pyrazolone. As a result, the formation of carbon–carbon double bond by condensation with the aldehydes forms an intermediate 1,4-Michael type substrate serving for a 1,4-attack by the second fluoride-generated enolate of the pyrazolone resulting



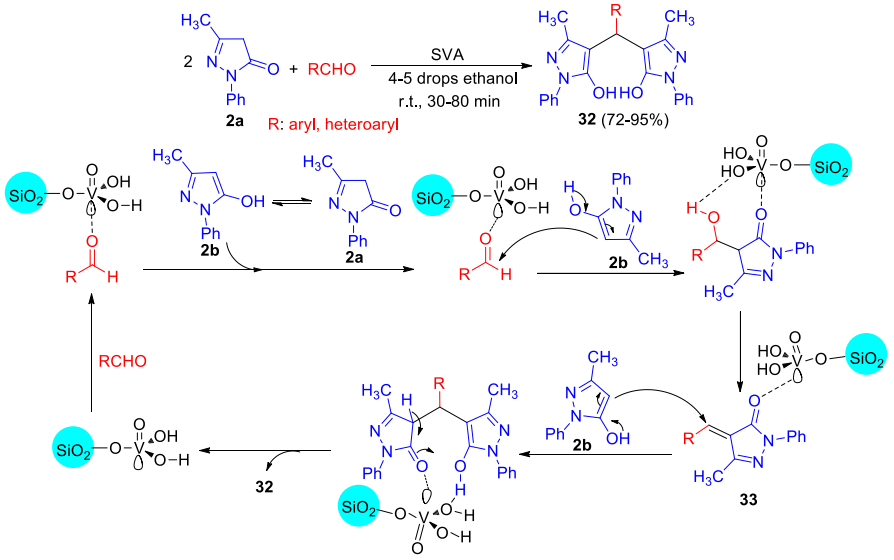
Scheme 10 Preparation of bis(pyrazolyl)methane **31**

in the formation of the corresponding *bis*-pyrazoles. These compounds demonstrated diverse in vitro DPPH radical scavenging activities with IC_{50} values ranging between 55.2 ± 1.2–149.6 ± 1.7 μM, as compared to standard BHT (butylated hydroxytoluene) ($IC_{50} = 128.8 \pm 2.1$ μM). Further chemical modifications and research work on these molecules may result in clinically useful antioxidants [87].

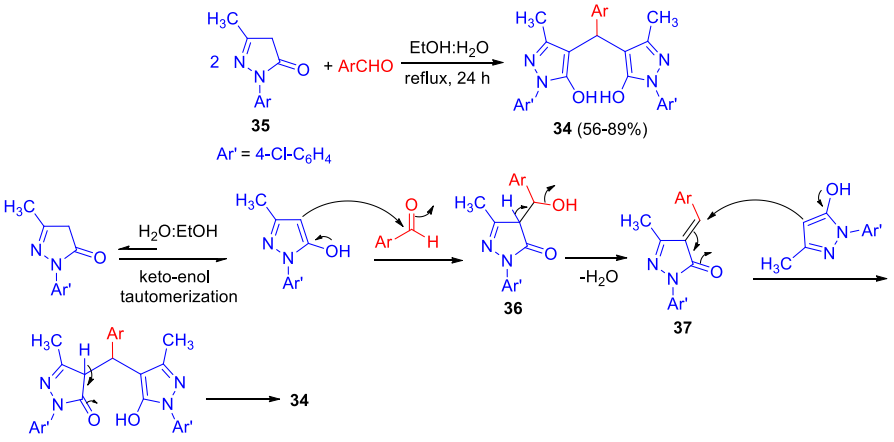
Later, silica vanadic acid with Lewis and Bronsted acid sites is employed as a recyclable catalyst for the Knoevenagel–Michael reaction of **2a** with aromatic aldehydes. This reaction was performed in 4–5 drops ethanol at room temperature within 30–80 min resulting bispyrazoles **32** in 72–95% yields. A reasonable mechanism for the formation of **32** is shown in Scheme 11. The catalyst activates the aldehyde group for nucleophilic attack by **2b** to yield **33**, which is then treated with the second molecule of **2b** to produce the target products **32** [88].

Graphene oxide/Fe_3O_4/L-proline nano-hybrid is synthesized and used as a catalyst for the preparation of bis(pyrazolyl)methanes in 87–98% yields by the reaction of **2a** with aryl aldehydes in refluxing EtOH for 5–15 min. GO/Fe_3O_4/L-proline catalyst was separated simply by using an external magnet and employed in six runs for the synthesis of the desired products [89].

Bis(pyrazolyl)methanes **34** are obtained in 56–89% yields by the reaction of 1-(4-chlorophenyl)-3-methyl-1*H*-pyrazol-5-ol (**35**) with aryl aldehydes in the absence of catalyst in EtOH:H_2O (1:3) under reflux conditions for 24 h. In the proposed mechanism as indicated in Scheme 12, nucleophilic carbon of pyrazolone in enol form attacks the electrophilic carbonyl carbon of benzaldehyde thus resulting in the formation of an intermediate **36**. Successful removal of water molecule from intermediate **36** formed the another *α,β*-unsaturated intermediate **37**. This intermediate **37** still has an electrophilic center at *β*-position, thus another attack of the second molecule of pyrazolone at *β*-position leads to the formation of **34**. Synthetic *bis*-pyrazolones **34** were evaluated for their oxidative burst inhibitory effect of zymosan stimulated whole blood phagocytes by using luminol enhanced chemiluminescence technique. All molecules demonstrated the potent ROS inhibition activity in



Scheme 11 Silica vanadic acid catalyzed synthesis of bis(pyrazolyl)methanes **32**



Scheme 12 Green synthesis of bis(pyrazolyl)methanes **34**

the range of $IC_{50} = 1.2 \pm 0.1$–48.8 ± 3.9 M as compared to the standard ibuprofen ($IC_{50} = 54.2 \pm 9.2$ M) [90].

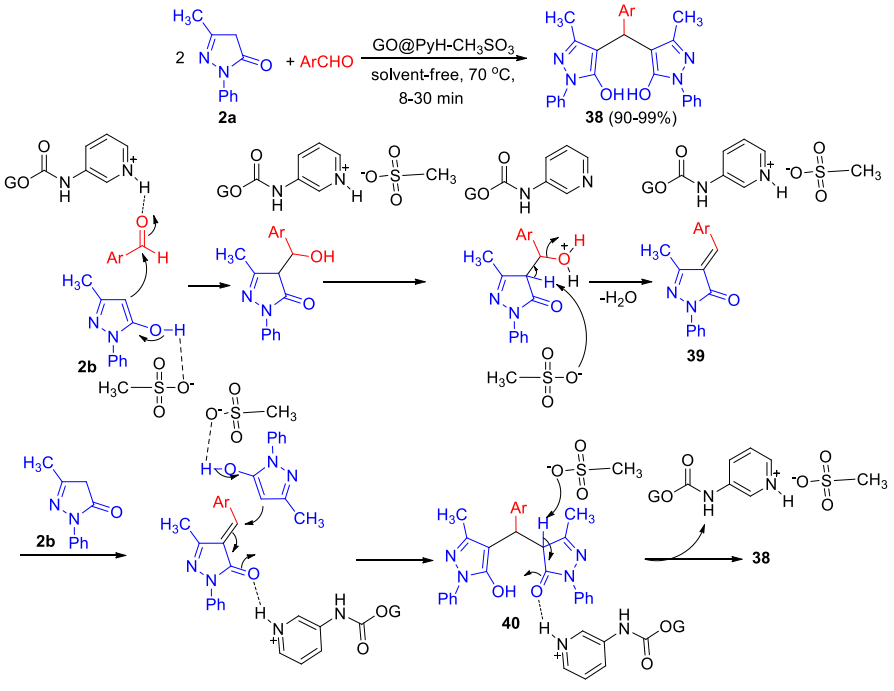
In 2019, Ghorbani-Choghamarani and his group reported that preparation of bis(pyrazolyl)methanes in good yields (75–92%) was accomplished by the treatment of **2a** with aromatic aldehydes using Ni-guanidine@MCM-41NPs as a recyclable catalyst in CH_3CN at 80 °C for 15–60 min [91].

In 2020, Rostami and Kordrostami developed a strategy for the preparation of bispyrazole derivatives **38** in 90–99% yields by the condensation reaction of **2a** with

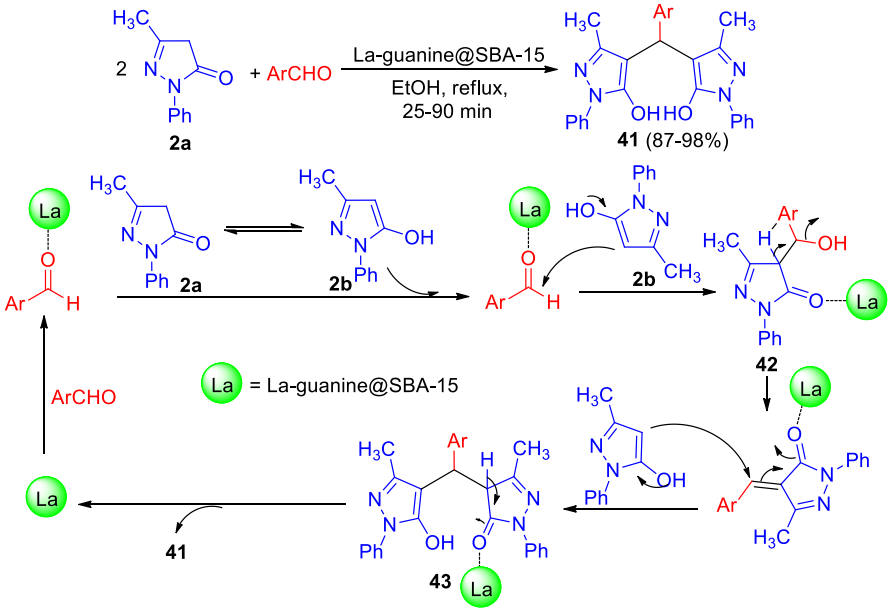
aromatic aldehydes using graphene oxide functionalized pyridine-methanesulfonate (GO@PyH-CH_3SO_3) as a recyclable nano-catalyst at 70 °C under solvent-free conditions for 8–30 min. The possible mechanism for the synthesis of **38** is illustrated in Scheme 13. According to the mechanism, at first, aldehyde was activated by acidic proton, while **2b** was activated by methane sulfonate group. Nucleophilic addition of **2b** to aldehyde followed by water elimination resulted benzylidene intermediate **39**. Then, Michael addition of second molecule of **2b** to the activated intermediate **39** explored the intermediate **40**; by eliminating the second water molecule, the products were obtained [92].

Furthermore, More and co-workers have shown the reaction of **2a** with aromatic and heteroaromatic aldehydes using chitosan-SO_3H (CTSA) as a biodegradable polymeric catalyst at 70 °C under solvent-free conditions for 15–70 min afforded bis(pyrazolyl)methanes in 79–96% yields. For the formation of the products, chitosan sulfonic acid increases the electrophilic character of aldehyde via proton donor. Firstly, **2a** converts to its enol form (**2b**) and attacks the activated aldehyde with catalyst to yield benzylidene intermediate via dehydration. Then, the intermediate and second equivalents of **2b** undergo Michael addition to yield the desired products [93].

After that, guanine-La complex supported onto SBA-15 is employed as a recoverable nanocatalyst for the formation of bispyrazoles **41** in 87–98% yields by the reaction of **2a** with aryl aldehydes in refluxing EtOH within 25–90 min. The suggested reaction mechanism for the synthesis of **41** is outlined in Scheme 14. At first,



Scheme 13 GO@PyH-CH_3SO_3 catalyzed synthesis of bis(pyrazolyl)methanes **38**



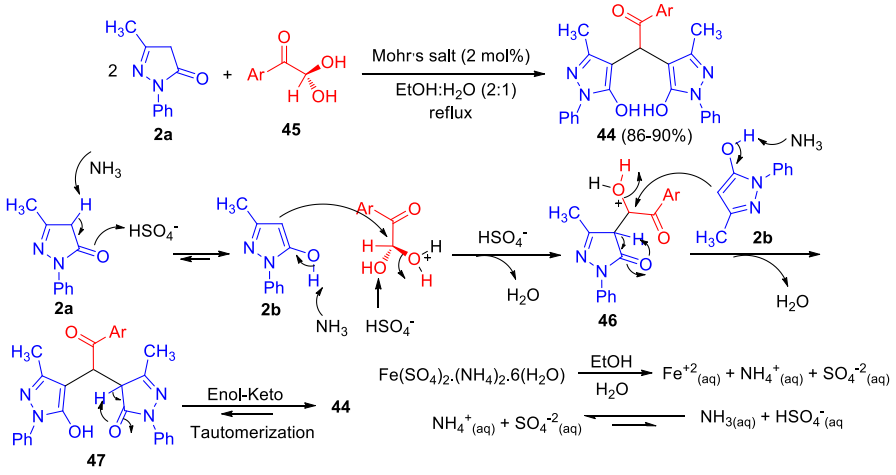
Scheme 14 La-guanine@SBA-15 catalyzed preparation of bis(pyrazolyl)methanes **41**

the intermediate **42** is generated by the Knoevenagel condensation of aldehyde and **2b** using La-guanine@SBA-15 nanocatalyst. Then, Michael addition of the second mol of **2b** to **42** affords intermediate **43**, which undergo tautomerization **to** give the desired products **41** [94].

Moreover, MCM-41-supported nanoscale guanine bonded with Zr (IV) was synthesized and used as an efficient, chemoselectivity and recyclable catalyst system for the preparation of bis(pyrazolyl)methanes in 88–98% yields by using aromatic aldehydes and **2a** in ethanol under refluxing within 10–45 min. The suggested reaction mechanism is similar to the proposed mechanism in Scheme 14. Initially, benzylidene intermediate is generated from the Knoevenagel condensation of aldehyde with **2b** and dehydration using Zr-guanine-MCM-41 nanocatalyst. In the next step, bispyrazole derivatives are obtained via Michael addition of the second molecule of **2b** to the benzylidene intermediate followed by tautomerization [95].

Eskandari and Karami reported a practical synthesis of bispyrazole derivatives **44** in 86–90% yields via the reaction of **2a** with arylglyoxal derivatives **45** using the environmentally benign catalyst, Mohr's salt in EtOH:H_2O (2:1) under reflux conditions. A suggested mechanism for the synthesis of **44** is illustrated in Scheme 15. At first, **2a** is tautomerized to **2b** in the presence of Mohr's salt. Then, nucleophilic addition of **2b** to the arylglyoxal led to the formation of intermediate **46** via elimination of one molecule of water. Treatment of the second mole of **2b** with **46** yielded intermediate **47** via loss of one molecule of water. Finally, **47** experiences an enol-keto tautomerization gave compounds **44** [96].

Recently, Heredia-Moya and co-workers reported synthesis of bispyrazoles in 60–99% yields by a three-component reaction of **2a** with aryl aldehydes catalyzed



Scheme 15 Mohr's salt catalyzed synthesis of bispyrazoles **44**

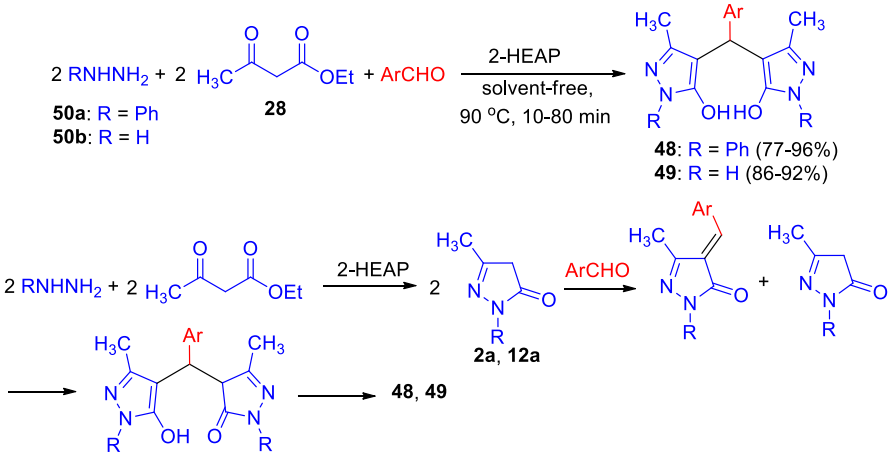
by NaOAc in 70% EtOH at ambient temperature for 10–480 min. All synthesized compounds were evaluated for antioxidant activity by the *N*,*N*-diphenyl-*N*′-picrylhydrazyl (DPPH) assay. Several derivatives proved to be cytotoxic in the RKO cell line. In particular, bispyrazole containing two hydroxyl groups in the positions of 3, 4 on aromatic ring proved to be a very potent scavenger with an IC_{50} of 6.2 ± 0.6 µM and exhibited an IC_{50} of 9.9 ± 1.1 µM against RKO cell [97].

Synthesis of bispyrazoles via one-pot pseudo five-component reactions

In 2014, one-pot pseudo five-component synthetic method for the 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ol)s **48** and **49** in 77–96% yields was developed by the reaction of aryl aldehydes, ethyl acetoacetate (**28**) and phenylhydrazine (**50a**) or hydrazine hydrate (**50b**) using 2-hydroxy ethylammonium propionate as catalyst at 90 °C under solvent-free conditions within 10–80 min. In the suggested mechanism, the first step involves the generation of pyrazolones **2a** and **12a** by the condensation of **50** with **28**. Subsequently, reaction of aldehyde with two equivalents of pyrazolone to afford bis(pyrazolyl)methanes **48** and **49** via tandem Knoevenagel–Michael reaction as depicted in Scheme 16 [98].

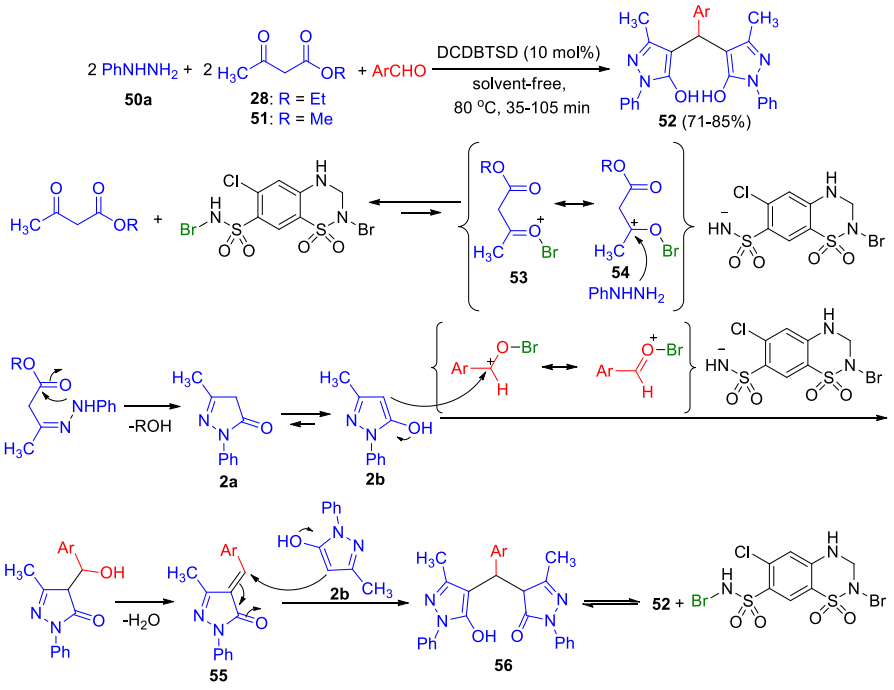
After that, Safaei-Ghomi and his group reported that preparation of bis(pyrazolyl) methanes in 80–92% yields using $ZnAl_2O_4$ nanoparticles by pseudo five-component reaction of **50b**, **28** and aromatic aldehydes in water at 60 °C within 14–28 min [99].

Next, *N*,2-dibromo-6-chloro-3,4-dihydro-2*H*benzo[e][1,2,4]thiadiazine-7-sulfonamide-1,1-dioxide (DCDBTSD) is employed as a homogeneous catalyst for the condensation reaction of **28** or methyl acetoacetate (**51**) with **50a** and aromatic aldehydes. This reaction is performed at 80 °C under solvent-free conditions for 35–105 min, resulting bispyrazoles **52** in 71–85% yields. In the



Scheme 16 Synthesis of bis(pyrazolyl)methanes **48** and **49** using 2-hydroxy ethylammonium propionate

proposed mechanism, *β*-keto ester and the catalyst generate intermediates **53** and **54** (Scheme 17). Then, intermediate **2a** is obtained by nucleophilic addition of **50a** to **53** and **54** via elimination of one molecule of alcohol, which is tautomerize to **2b**.

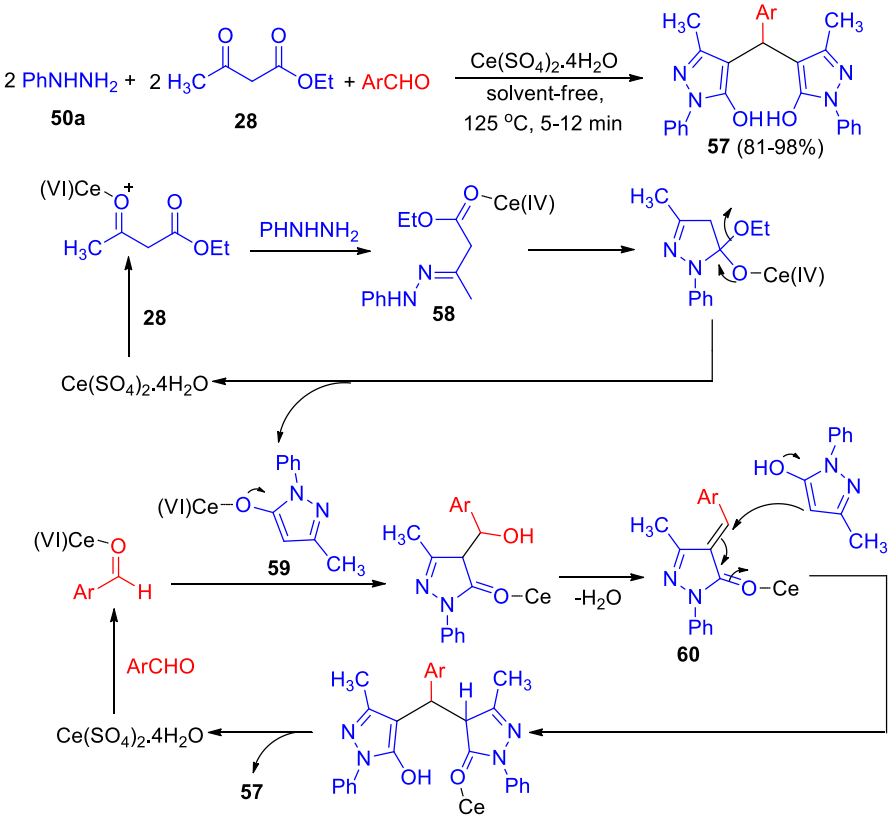


Scheme 17 DCDBTSD catalyzed synthesis of bispyrazoles **52**

Intermediate **55** is produced via condensation of **2b** with **53** or **54**. Subsequently, Michael addition of another intermediate **2b** to **55** leads to intermediate **56**, which undergoes tautomerization to afford the desired products **52** [100].

In 2015, Hassankhani described an efficient method for the one-pot synthesis of bis(pyrazolyl)methanes **57** in 81–98% yields by condensation of aromatic aldehydes, **28** and **50a** in the presence of $Ce(SO_4)_2.4H_2O$ as a recoverable catalyst under solvent-free conditions at 125 °C for 5–12 min. A reasonable mechanism is shown in Scheme 18. Initially, the reaction between **28** and **50a** affords phenylhydrazone **58**, which then cyclizes to give the intermediate **59**. Nucleophilic addition of 1-phenyl-3-methyl-5-pyrazolone to aldehyde leads to benzylidene **60** via elimination of one mole of H_2O. Finally, Michael addition of the second molecule of 1-phenyl-3-methyl-5-pyrazolone to intermediate **60** affords the corresponding products **57** [101].

Sulfonated nanohydroxyapatite functionalized with 2-aminoethyl dihydrogen phosphate (HAP@AEPH_2-SO_3H) was used as a reusable solid acid catalyst for the solvent-free synthesis of bispyrazoles **61** in 80–98% yields by the one-pot reaction of **28, 50a,b** and aromatic/heteroaromatic aldehydes at 80 °C within 2–10 min. A

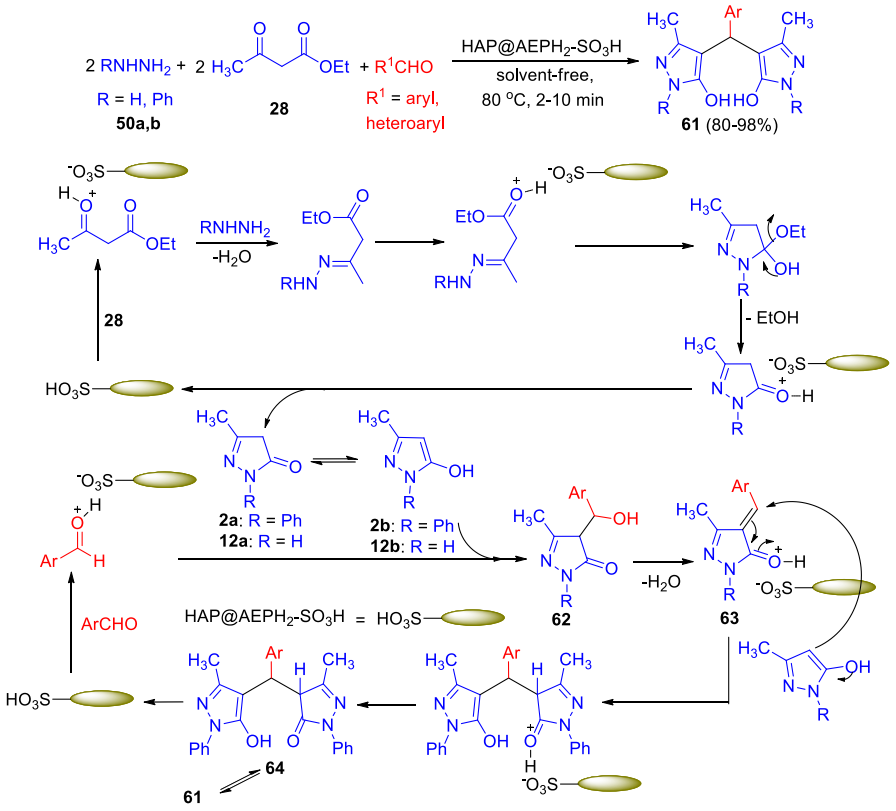


Scheme 18 $Ce(SO_4)_2$ $4H_2O$ catalyzed preparation of bis(pyrazolyl)methanes **57**

possible mechanism for the formation of **61** is outlined in Scheme 19. The reaction involves the initial formation of pyrazolones **2a** and **12a** (which are in equilibrium with theirs other tautomeric forms **2b** and **12b**) by the reaction between the protonated form of **28** and **50a** or **50b**. Then, in acidic media, condensation of the intermediates **2b** and **12b** with aldehyde to give adduct **62** and subsequent dehydration, leads to the formation of **63**. Michael addition of **63** to **2b/12b** produces two tautomeric forms **64** and **61** followed by release of the acidic catalyst [102].

Safaei-Ghomi et al. noted that a solution of **28** with **50b** by using $CuCr_2O_4$ as a recyclable nano-catalyst in water at ambient temperature was stirred for 15 min, then aromatic aldehydes was added and the mixture was stirred at 50 °C for 10 min to give the desired products in 84–95% yields. Also**,** the catalyst can be reused at least five times without any obvious change in its catalytic activity. Presumably, the reaction mechanism includes formation of pyrazolone **12b** from **50b** and **28**, which is then reacts with aldehyde to give arylidene intermediate. Treatment of arylidene intermediate with another molecule of **12b** leads to the target products [103]**.**

After that, Na^+-MMT-[pmim]HSO_4 is synthesized and used as a recyclable Brönsted acidic ionic liquid catalyst for the solvent-free synthesis of bis(pyrazolyl)

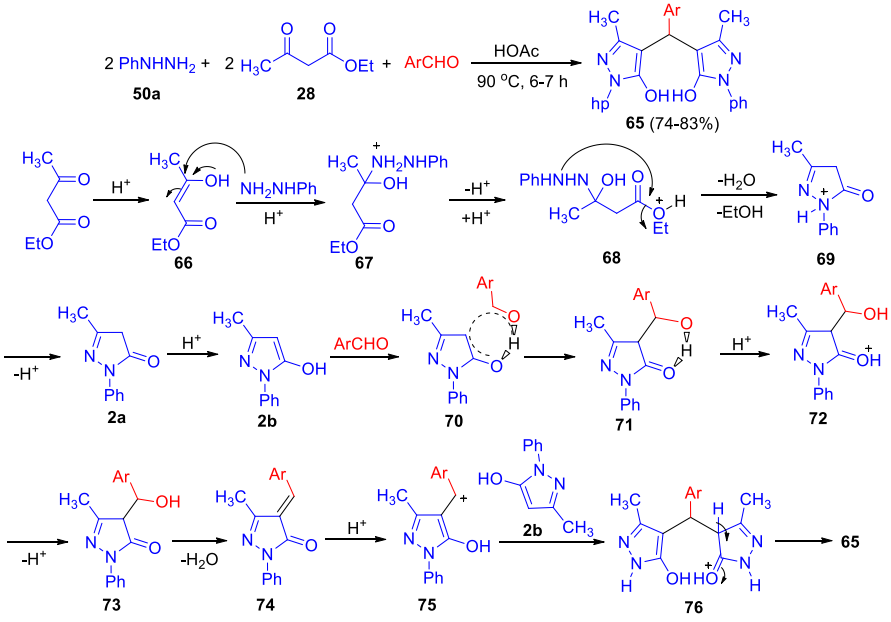


Scheme 19 Preparation of bis(pyrazolyl)methanes **61** using HAP@$AEPH_2$-SO_3H

methanes in 87–93% yields by the one-pot condensation of **28**, **50a** and aryl aldehydes at 100 °C for 10–45 min. The results showed that the reaction proceed via the in situ generation of **2a,** which in reaction with aldehydes produce the target products [104].

Furthermore, solvent-free one-pot three-component condensation of aromatic aldehydes, **28** and **50** was performed at 90 °C within 20–45 min using $[Et_3NH][HSO_4]$ as a reusable catalyst, giving bis(pyrazolyl)methanes in 79–97% yields. The proposed mechanism involves $[Et_3NH][HSO_4]$ catalyzed synthesis of **2a** and **12a** by the condensation of **28** with **50a,b**. Next, the activated carbonyl is attacked by the nucleophilic pyrazolones to produce the Knoevenagel adducts. The subsequent addition of these fragments to pyrazolones gives the desired products [105].

In 2016, Gouda et al. succeeded in preparation of bispyrazoles **65** in 74–83% yields via the one-pot pseudo five-component reaction of **28**, **50a** and aryl aldehydes in acetic acid at 90 °C for 6–7 h. The suggested mechanism for the synthesis of **65** is shown in Scheme 20. Protonation of **28** by acetic acid produces the enol **66**. Electrophilic attraction of **50a** to the enol **66** gives the ammonium salt **67**; hydronium ion transfer takes place to yield the oxonium ion **68**. Cyclization of **68** gives the pyrazolium ion **69** which loss proton to convert into pyrazole **2a**. Protonation of **2a** by AcOH generates the enol **2b** which reacts with the aldehydic carbonyl to give six-membered cyclic transition state **70** and increases the electrophilicity of the aldehyde carbonyl group and makes it more susceptible to nucleophilic attack in an intramolecular fashion to afford the intermediate **71**. Subsequently, intermediate **71** abstracts the proton from AcOH and produces the enolate aldol cation **72**



Scheme 20 Synthesis of bispyrazoles **65** in AcOH

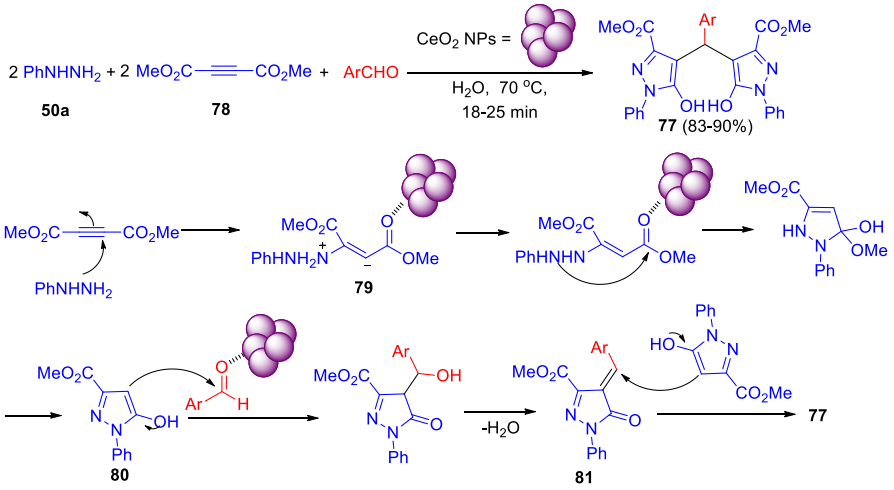
which interacts with **2a** to generate the enol form **2b** to complete the catalytic cycle. The aldol **73** on dehydration results in the formation of 4-arylidene-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **74** which is reacted with AcOH to generate the cation **75**, condensation with **2b** to afford *bis*-enolate cation **76**, which subsequently loss proton and form the corresponding products **65.** Moreover, some of the synthesized compounds were screened for their antioxidant activity using 2,2′-azino-*bis*(3-ethyl benzothiazoline-6-sulfonic acid (ABTS) method; all the investigated compounds showed similar and higher antioxidant activity than ascorbic acid and exhibited high protection against DNA damage induced by the bleomycin iron complex [106].

Moreover, *N*-methylimidazolium perchlorate ([MIm]ClO_4) was prepared and used as recyclable catalyst for the preparation of bis(pyrazolyl)methanes in 77–94% yields via the condensation reaction of **28**, **50a,b** and aromatic/heteroaromatic aldehydes at 50 °C under solvent-free conditions for 20–60 min. In the proposed mechanism, pyrazolone would be anticipated from the very fast condensation between **50a** and **50b** with **28** catalyzed by [MIm]ClO_4. The activated carbonyl group of the aldehyde again by the catalyst condenses with two equivalents of pyrazolone through a pyrazolenone intermediate via a tandem Knoevenagel–Michael reaction resulting in the formation of the corresponding products [107].

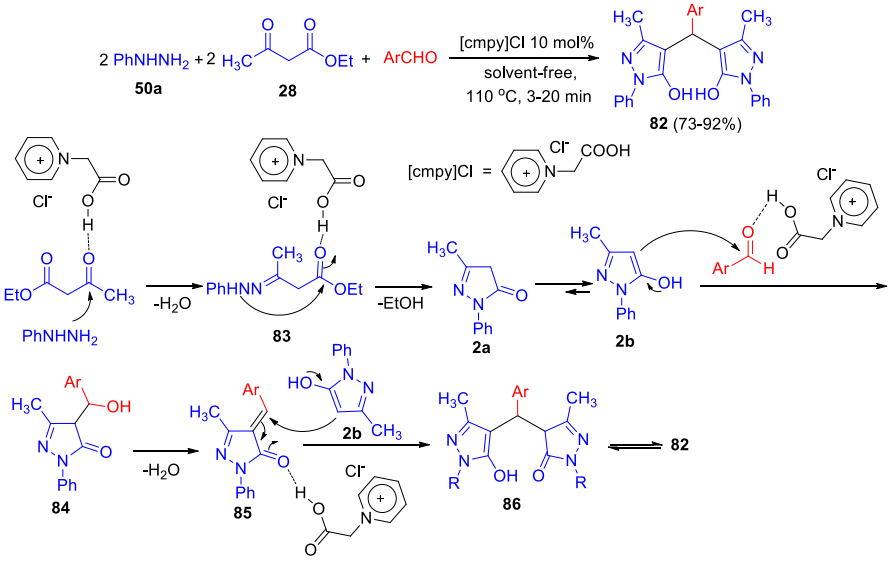
Microwave irradiation of 3-substituted isoxazole-5-carbaldehydes and 4-chlorophenyl hydrazine or **50b** over solid support SiO_2 at 70 °C under solvent-free conditions within 8–12 min gave 4-substituted pyrazolones in 78–97% yields. The mechanism of formation of bispyrazoles involves generating of intermediate hydrazone via nucleophilic addition of hydrazine to *β*-keto ester. Subsequently, intramolecular nucleophilic attack of amino group to carbonyl by removing of a molecular ethanol followed by cyclization to yield **12a** and **35**. Then, intermediates **12a** and **35** interconverted the stable intermediates (enol forms). Afterwards, arylidene intermediates are formed by the nucleophilic addition of enol forms of intermediates **12b** and **35** to 3-substituted isoxazole-5-carbaldehydes followed by dehydration. Michael addition of the second molecule of enol forms of intermediates **12b** and **35** to arylidene intermediate**,** which is then tautomerize to the desired products [108].

After that, CeO_2 nanoparticles are employed as a recyclable catalyst for the formation of C-tethered bis(pyrazolyl)methanes **77** in 83–90% yields by pseudo five-component condensation reaction of **50a**, dimethyl acetylenedicarboxylate (**78**) and aryl aldehydes in water at 70 °C within 18–25 min. The mechanism of these domino reactions is proposed in Scheme 21. Firstly, the condensation reaction of **78** and **50a** led to the formation of 1,3-dipole intermediate **79**, which subsequently underwent proton transfer and aminolysis of the ester group, resulting the pyrazolones **80** in situ. The pyrazolone derivative was treated with aryl aldehydes, leading to arylidene pyrazolones **81**. Then, the arylidene pyrazolones were further reacted with pyrazolones produced in situ to yield the final bis(pyrazolyl)methanes [109].

Acetic acid functionalized pyridinium salt (1-(carboxymethyl)pyridinium chloride {[cmpy]Cl}) is employed as a reusable catalyst for the condensation reaction of **50a**, **28**, and aryl aldehydes. This reaction was performed at 110 °C under solvent-free conditions for 3–20 min, resulting bis(pyrazolyl)methanes **82** in 73–92% yields. In a possible mechanism, compound **28** is activated by the catalyst (Scheme 22). Then, intermediate **83** is obtained by the reaction of **50a** with **28** followed by



Scheme 21 Synthesis of C-tethered bis(pyrazolyl)methanes **77** using CeO_2 NPs



Scheme 22 Solvent-free synthesis of bispyrazoles **82** using [cmpy]Cl

removing of H_2O. By intramolecular attack in intermediate **83** and removing of EtOH, compound **2a** is obtained. Afterwards, **2a** converts to **2b** after tautomerization. Intermediate **84** is formed via the condensation of **2b** with an activated aldehyde by the catalyst, which is then converted to **85** by removing of H_2O. **85** as Michael acceptor is reacted with another intermediate **2b** to give **86**, which is tautomerize to the target products **82** [110].

Moreover, 4-(succinimido)-1-butane sulfonic acid (SBSA) as a reusable Brönsted acid catalyst catalyzes the condensation of **28**, **50a,b** and aryl aldehydes under solvent-free conditions at 60 °C for 20–55 min, affording bis(pyrazolyl)methanes in 82–92% yields. In the suggested mechanism for the formation of the products, pyrazolone would be anticipated from the very fast condensation between **50** and **28** in the presence of SBSA. Then, the activated carbonyl group of the aldehyde condensed with two equivalents of pyrazolone, resulting bis(pyrazolyl)methanes [111].

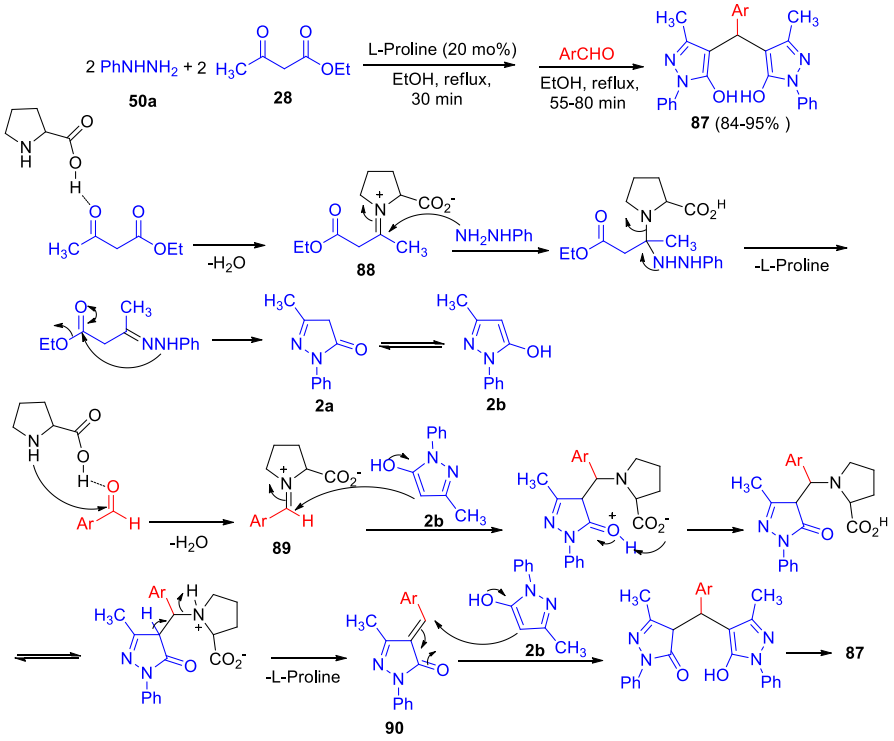
In 2017, Hazeri and his group reported that preparation of bispyrazoles in 75–93% yields were accomplished by the condensation reaction of **28**, **50b** and aryl/heteroaryl aldehydes in the presence of Ag/TiO_2 nano-thin films as a recyclable catalyst in EtOH:H_2O (2:1) at 70 °C for 25–55 min. In this reaction, treatment of aryl aldehyde with the acidic sites of Ag-TiO_2 gives the activated carbonyl group which is followed by nucleophilic attack of **12a** to afford arylidene intermediate. Michael addition of another pyrazolone to arylidene intermediate leads to the target products [112].

A convenient approach for the preparation of bispyrazoles in 56–93% yields by an efficient one-pot condensation reaction of aromatic/aliphatic aldehydes, **50a** and β-ketoesters (**28** and ethyl benzoylacetate) by using K_2CO_3 in CH_3CN at ambient temperature for 1–4.5 h is described. It was found that aromatic aldehydes with electron withdrawing substituent afforded the corresponding products in high yield and in short reaction times. When the reaction was carried out with aromatic aldehydes containing moderately strong electron donating groups, the target products obtained with lower yield. Moreover, aliphatic aldehydes reacted with **50a** and β-keto ester under similar condition to yield the target compounds in good to moderate yields [113].

An environmentally friendly method has been developed for the synthesis of bis(pyrazolyl)methanes in good yields (76–93%) by condensation reaction of aromatic/heteroaromatic aldehydes, **50b** and **28** using aspirin as a green catalyst in EtOH/H_2O at 60 °C for 20–55 min. The proposed mechanism for this reaction involves formation of pyrazolone **12a** of **28** and **50b**. Then, Knoevenagel condensation of the activated carbonyl group of the aldehyde with pyrazolone to give the arylidene pyrazolone**,** which undergoes Michael addition with another pyrazolone to afford the desired products [114].

L-proline as an organocatalyst has been employed for the preparation of bis(pyrazolyl)methanes **87** in 84–95% yields via the reaction of aromatic/heteroaromatic aldehydes, **50a** and **28** in refluxing EtOH for 55–80 min. A suggested mechanism for the formation of **87** is shown in Scheme 23. Initially, nucleophilic reaction of L-proline on the **28** followed by dehydration affords intermediate **88**, which is treated with **50a** followed by removing L-proline to produce **2b**. In the next step, nucleophilic addition of **2b** to intermediate **89** to afford arylidene **90**, which undergo Michael addition with the second molecule of **2b** to give the desired products **87**. Bispyrazole containing thiophene-2-yl ring, emerged as the most interesting compound in this series exhibiting excellent DPPH radical scavenging activity and found to be more potent than the standard drug BHT used [115].

Furthermore, immobilized lanthanum (III) triflate on graphene oxide ($La(OTf)_2$-grafted-GO) as a reusable catalyst is synthesized and used for the

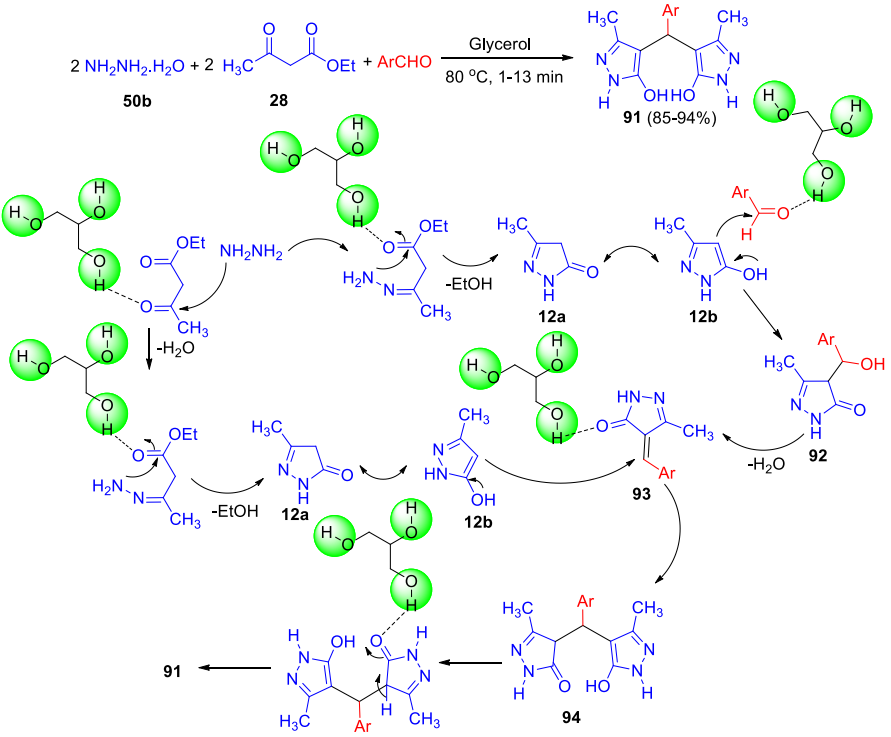


Scheme 23 Synthesis of bis(pyrazolyl)methanes **87** using L-proline

one-pot five-component synthesis of bispyrazoles in 70–98% yields by the reaction of **50a**, **28** and aryl/heteroaryl aromatic at 100 °C under solvent-free conditions for 10–45 min. In this reaction, the carbonyl groups in **28** are activated by the acidic functional groups of the catalyst to react with **50a** to give pyrazolone. Next, the activated aldehydes by the catalyst undergo a tandem reaction with the activated pyrazolones by basic sites to generate the corresponding products [116].

Lalitha and co-workers succeeded in the preparation of bispyrazoles **91** in 85–94% yields via the reaction of **50b**, **28** and aromatic aldehydes in glycerol at 80 °C for 1–13 min. A possible mechanism for the formation of **91** is presented in Scheme 24. Firstly, intermediate **12a** is obtained by the condensation of **28** with **50b**, which is converted into **12b** by tautomerisation. Aromatic aldehyde is activated by the glycerol through the hydrogen bonding followed by nucleophilic attack of **12b** at the carbonyl group to give intermediate **92.** Intermediate **92** is converted to the Knoevenagel adduct **93** by dehydration. Adduct **93** as a Michael acceptor is activated by glycerol. Then, **93** undergo Michael addition with another molecule of **12b** to yield intermediate **94**, which is converted into the target products **91** by tautomerization [117].

Sulfonated honeycomb coral (HC-SO_3H) as a green, high stability and reusability of the catalyst was used for the solvent-free synthesis of bispyrazoles **95** in 82–98% yields by the reaction of **50a,b**, aryl aldehydes and **28** at 70 °C within

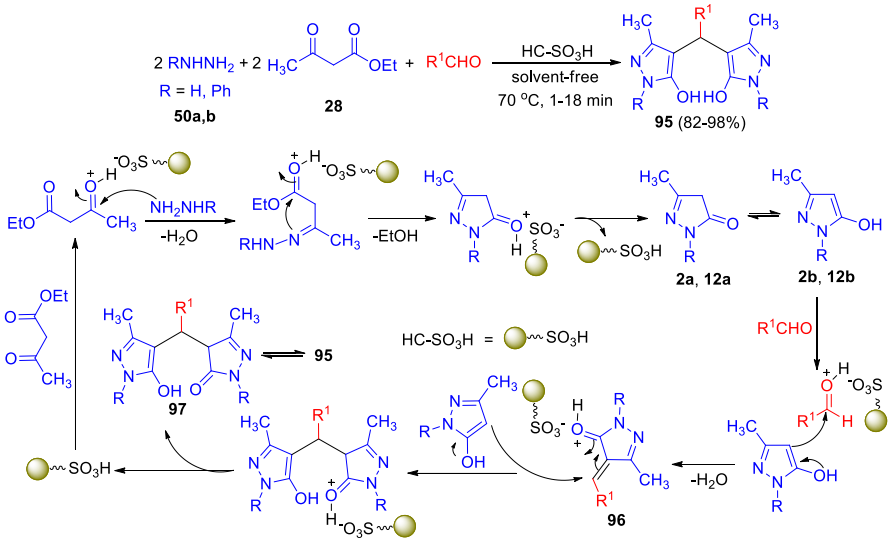


Scheme 24 Glycerol assisted synthesis of bis(pyrazolyl)methanes **91**

1–18 min. In this reaction, allylic aldehydes such as cinnamaldehyde and heteroaromatic aldehydes such as pyridine carboxaldehydes led to the expected products. A possible mechanism for the formation of **95** is outlined in Scheme 25. According to this mechanism, treatment of **50** and protonated form of **28**, eventually leads to the formation of pyrazolones **2a** and **12a**, which are in equilibrium with their tautomeric forms **2b** and **12b**. In the next step, the condensation reaction between intermediates **2b** or **12b** and aldehyde in the acidic condition, followed by dehydration, gives intermediate **96**. Michael addition reaction between **2b** or **12b** and **96** leads to the product **97**, which is converted into the corresponding products **95** by tautomerization [118].

Microwave irradiation of **50a** with dimethyl acetylenedicarboxylate (**78**) and aromatic aldehydes in the presence of bis(1(3-methoxysilylpropyl)-3-methylimidazolium) copper tetrachloride tethered to colloidal silica nanoparticles as a recyclable catalyst in H_2O at 50 °C for 10–15 min gave bispyrazoles in 82–96% yields [119].

In addition, Mn-[4-chlorophenyl-salicylaldimine-methylpyranopyrazole]Cl_2 ([Mn-4CSMP]Cl_2) as nano-Schiff base complex catalyst is synthesized and used for the preparation of bis(pyrazolyl)methanes in 59–95% yields by the condensation reaction of **50a**, **28** and various aryl aldehydes at 100 °C under solvent-free conditions for 20–80 min [120].

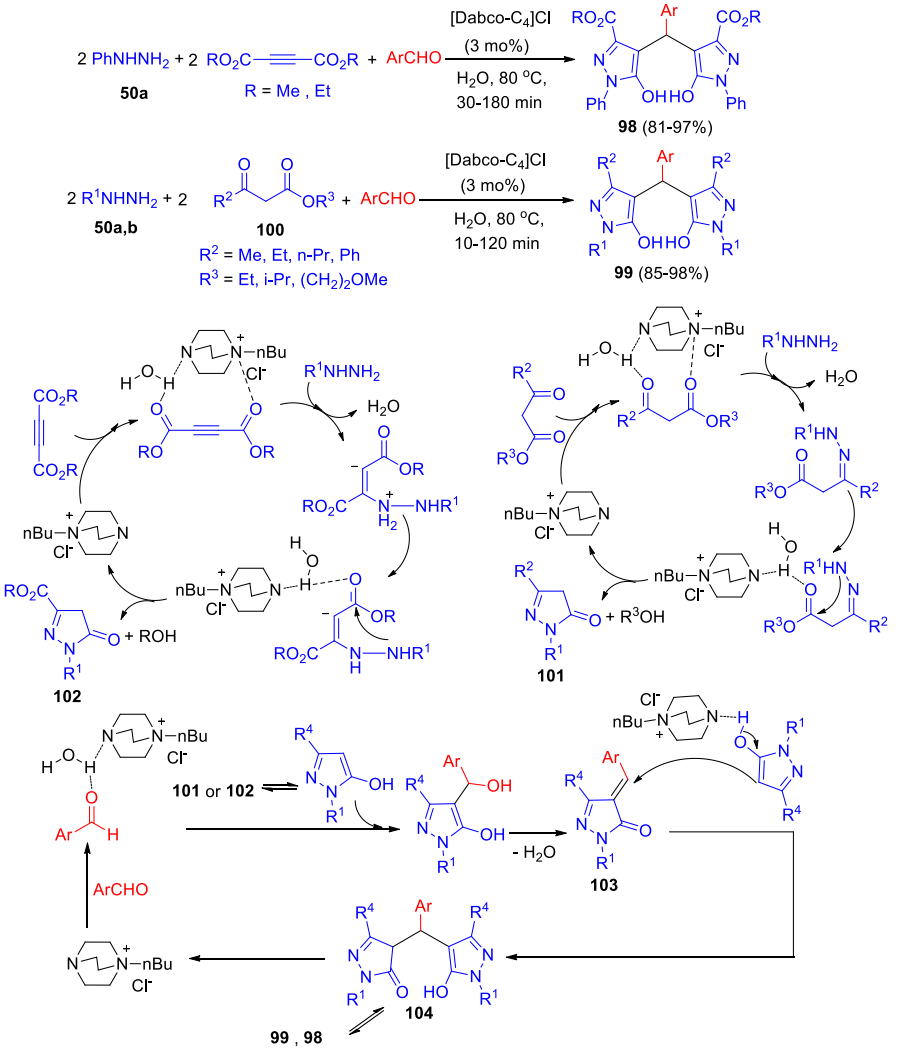


Scheme 25 Preparation of bispyrazoles **95** catalyzed by HC-SO_3H

A green, simple and efficient approach for the synthesis of bis(pyrazolyl)methanes **98** and **99** in 81–98% yields is described via condensation of hydrazines with dialkyl acetylenedicarboxylats/β-keto esters **100** and aromatic aldehydes in the presence of Dabco-base ionic liquid as a recyclable catalyst in H_2O at 80 °C for 10–180 min. A suggested mechanism for the preparation of the products is proposed in Scheme 26. The formation of products can be rationalized by the initial formation of intermediates **101** or **102** via condensation of hydrazines with dialkyl acetylenedicarboxylates or *β*-keto esters. Knoevenagel condensation of **101** or **102** with aldehyde and subsequent dehydration, led to the formation of **103**. Then, Michael addition of another intermediates **101** or **102** to **103** generated adducts **104** followed by tautomerization afforded the corresponding products **98** and **99** [121].

In 2018, Abed and co-workers obtained bis(pyrazolyl)methane derivatives in 85–96% yields from the condensation reaction of **50a** with **28** and different aryl/heteroaryl aldehydes using morpholinium glycolate as the homogeneous reusable catalyst under solvent-free conditions at 80 °C for 5–12 min. At the beginning of reaction, morpholinium glycolate activates **28,** and then **50a** attacks the carbonyl groups of **28** to give pyrazolone **2a**, which is further rearranged into tautomer **2b**. In a next step, Knoevenagel type of reaction takes place between activated aldehydes and **2b** followed by removing of H_2O to give arylidene intermediate. Then, Michael addition reaction between arylidene pyrazolone and **2b,** followed by tautomerization and aromatization affords the target products [122].

After that, an efficient synthesis of 4,4′-(phenylmethylene)bis(1*H*-pyrazol-5-ol)-3-carboxylates in 80–94% yields was achieved by the reaction of **50a**, dimethyl acetylenedicarboxylate (**78**) and aromatic aldehydes using nano-$NiZr_4(PO_4)_6$ as reusable catalyst in water at 60 °C within 15–28 min [123].



Scheme 26 [Dabco-C_4]Cl catalyzed synthesis of bispyrazoles **98** and **99**

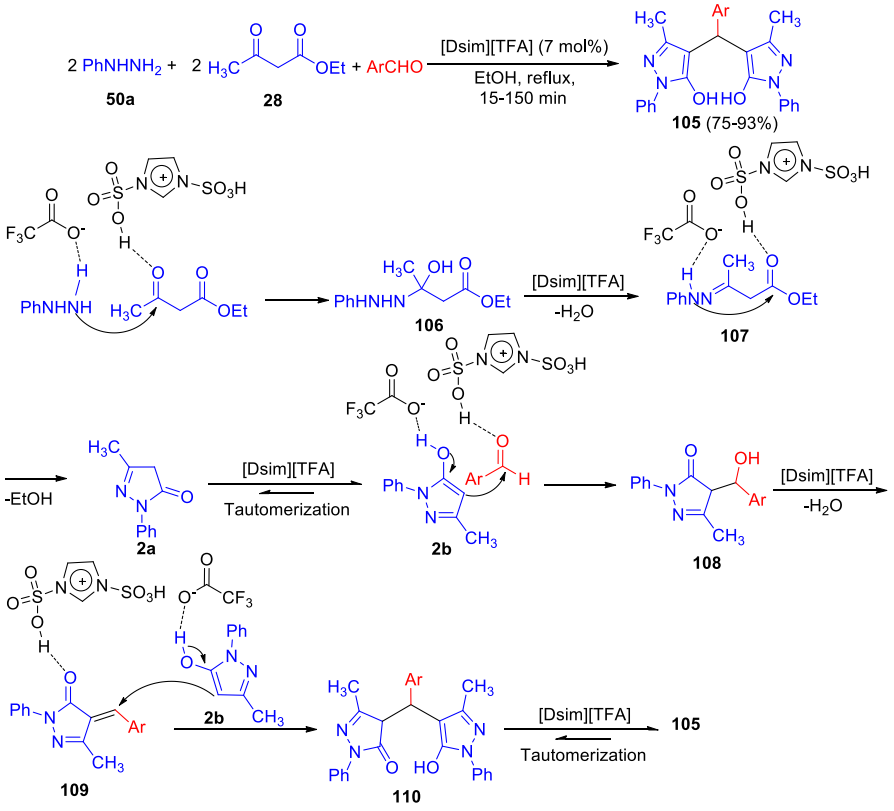
Zare and Abshirini noted that treatment of **50a**, **28** and aromatic aldehydes using *N*,*N*,*N*′,*N*′-tetramethylethylenediaminium-*N*,*N*′-disulfonic acid hydrogen sulfate ([TMEDSA][HSO_4]$_2$) as a Brønsted-acidic ionic liquid catalyst in EtOH at 70 °C for 20–50 min afforded bis(pyrazolyl)methanes in 81–93% yields [124].

Potassium arylmethylene-4-(1*H*-pyrazol-5-ol)-4′-(1*H*-pyrazol-5-olate) derivatives have been synthesized in 68–88% yields by the condensation reaction of dimethyl acetylenedicarboxylate or diethyl acetylenedicarboxylate, **50a**, aryl aldehydes and K_2CO_3 without any catalyst in EtOH under refluxing for 5 h [125].

Moreover, ionic liquid 1,3-disulfonic acid imidazolium trifluoroacetate ([Dsim][TFA]) is employed as a highly efficient catalyst for the condensation reaction

between **50a**, **28** and aryl aldehydes in refluxing EtOH. In this reaction, bis(pyrazolyl) methanes **105** have been synthesized in 75–93% yields within 15–150 min. A suggested mechanism is illustrated in Scheme 27. Firstly, trifluoroacetate anion of the catalyst assists **50a** for nucleophilic addition to the activated carbonyl group of **28** (by acidic hydrogen of [Dsim][TFA]) to give **106**, which is converted into **107** by dehydration. Intermediate **107** undergoes intramolecular cyclization to yield **2a**. **2a** is converted to its tautomer **2b**, and this tautomer is added to the carbonyl group of aldehyde to give intermediate **108**, which is then afforded Michael acceptor **109** by dehydration. Afterwards, Michael addition reaction of another molecule **2b** to **109** provides **110**. Tautomerization of **110** leads to the desired products **105**. The high catalytic effectuality of [Dsim][TFA] can be attributed to helping both acidic and basic moieties of it (cation and anion) for progressing all steps of the reaction; *i.e.* dual-functionality [126].

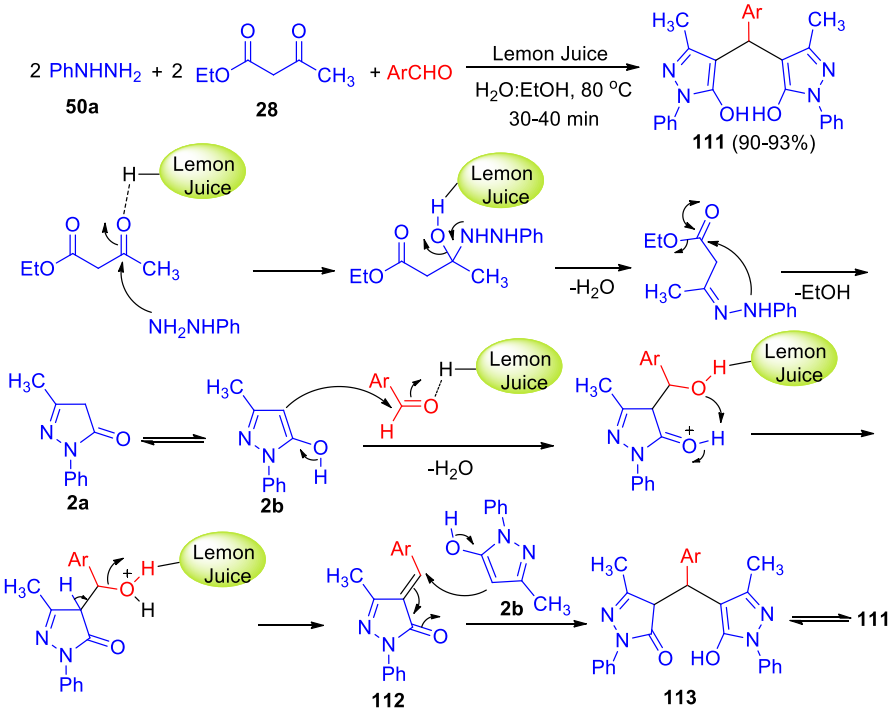
Silica bonded *n*-propyl-4-aza-1-azoniabicyclo[*2.2.2*]octane hydrogen sulfate ((SB-DABCO)HSO_4) is synthesized as a dual-catalyst and used for the preparation of bispyrazoles in 81–89% yields by the condensation reaction of hydrazine derivatives ($RNHNH_2$: $R = C_6H_5$, 4–Me–C_6H_4, 4–OMe–C_6H_4), *β*-keto esters



Scheme 27 Synthesis of bispyrazoles **105** using [Dsim][TFA]

($R'COCH_2CO_2Et$: R' = Me, Pr, Ph) and aryl and heteroaryl aldehydes in refluxing EtOH for 35–480 min. The proposed mechanism for this reaction involves formation of pyrazolone intermediate of hydrazines and β-keto esters. After this, the tandem Knoevenagel–Michael reaction of pyrazolone intermediate with aldehydes leads to the formation of the target products. They suggested that ((SB-DABCO)HSO_4) serves two catalytic functions: first, to electrophilically activate the aldehydes and carbonyl group of β-keto esters through the interaction between positively charged hydrogen of HSO_4^- and the carbonyl oxygen, and second, to enhance the nucleophilicity of the hydrazines and β-keto esters through the interaction between C_α–H with nitrogen of DABCO-like part of the catalyst [127].

Farooqui et al. succeeded in the formation of bispyrazoles **111** in 90–93% yields by the condensation of **50a**, **28** and aromatic aldehydes using lemon juice as an efficient and eco-friendly catalyst in EtOH/H_2O at 80 °C for 30–40 min. In a reasonable mechanism that is outlined in Scheme 28, at first, **2a** convert to **2b** after tautomerisation. Next, **2b** attacks to the carbonyl group of aldehyde that is activated by the lemon juice via hydrogen bonds and results to intermediate **112** as a Michael acceptor after dehydration. Then, another molecule of **2b** attacks to **112** to afford Intermediate **113**, which is converted into the target products **111** after tautomerisation and aromatization. All the synthesized compounds showed good to moderate antibacterial, antifungal and antioxidant activities [128].

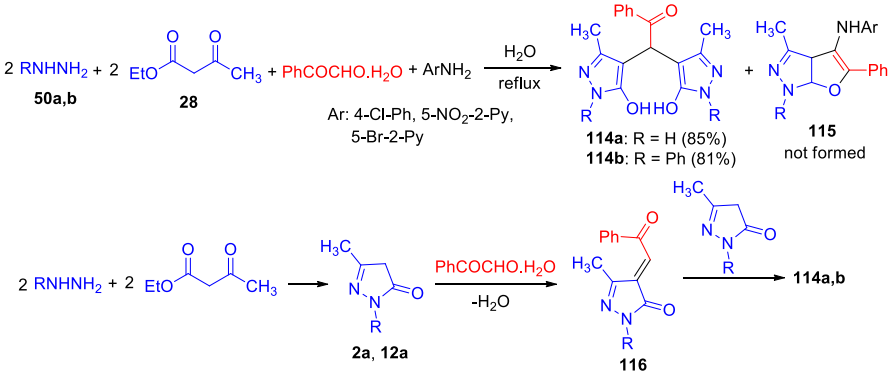


Scheme 28 Lemon juice catalyzed synthesis of bispyrazole derivatives **111**

In 2019, Olyaei and co-workers developed the preparation of 2,2′-bis(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-1-phenylethanone **114a** in 85% yield through the condensation of **28**, **50b** and phenylglyoxal monohydrate using heteroarylamines containing electron-withdrawing group in water under reflux conditions within 55 min. Also, condensation of **28** and **50a** by using guanidine hydrochloride (10 mol%) as catalyst in H_2O under refluxing after 90 min gave 3-methyl-1-phenyl-1*H*-pyrazol-5-ol. Then, by the addition of phenylglyoxal monohydrate and heteroarylamines containing electron-withdrawing group to the reaction mixture under reflux conditions afforded 2,2-bis(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1-phenylethanone (**114b**) in 81% after 60 min. In these reactions, bis-pyrazolylmethanes were obtained as only products instead of the expected 1*H*-furo[2,3-c]pyrazole-4-amine derivatives **115**. As a proposed mechanism depicted in Scheme 29, the reaction occurred via initial formation of intermediate **116** from the reaction of **2a** or **12a** and phenylglyoxal monohydrate followed by Michael addition of pyrazols instead of amines to **116** resulted products **114a,b** because of the higher nucleophilicity of pyrazol than amines bearing strong electron-withdrawing group [129].

Later, cage like $CuFe_2O_4$ hollow nanostructure is synthesized and used as a reusable catalyst for the preparation of bis(pyrazolyl)methanes in 89–98% yields by the one pot condensation reactions of hydrazines **50a,b**, **28** and different aromatic aldehydes at 80 °C within 2–25 min under the solvent-free condition. The high activity of the catalyst could be described by the presence of open cavities in this structure. It allows the reaction to be carried out into the interior spaces of catalyst structure due to the ability of the reactants for diffusion [130].

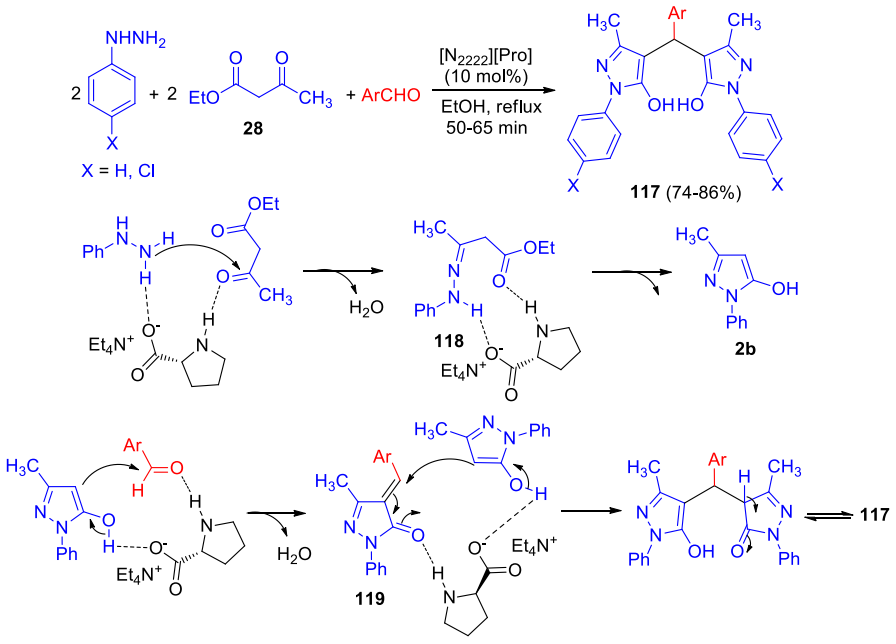
Alpha-Casein as a recyclable and non-toxic catalyst was applied for the preparation of bis(pyrazolyl)methanes in 79–94% yields via the condensation reaction of **28**, **50b** and aromatic aldehyde in EtOH:H_2O (2:1) at 60 °C for 15–40 min. In the proposed mechanism, **12a** is formed from the reaction between **28** and **50b**. Then, arylidene intermediate is produced via Knoevenagel condensation of **12a** with the activated carbonyl group of the aromatic aldehyde. Finally, desirable products are obtained by Michael addition of another **12a** to arylidene intermediate [131].



Scheme 29 Synthesis of bispyrazoles **114a,b**

Guanidine hydrochloride as an organocatalyst was applied for the synthesis of bispyrazoles in 82–92% yields by the reaction of **50, 28** and various aromatic aldehydes in water under reflux conditions within 30–60 min. It should be noted that synthesis of **2a** was carried out via the reaction of **50a** with **28** by using catalyst in refluxing water for 90 min. In this reaction, the condensation reaction of **50** with **28** catalyzed by guanidinium chloride afford adducts **2a** and **12a**, which are tautomerize to **2b** and **12b**, respectively. Then, arylidene intermediate is likely formed by the condensation of aromatic aldehyde with **2b** and **12b**. Subsequently, Michael addition of another intermediate **2b** and **12b** to arylidene intermediates, followed by tautomerization give the corresponding products [132].

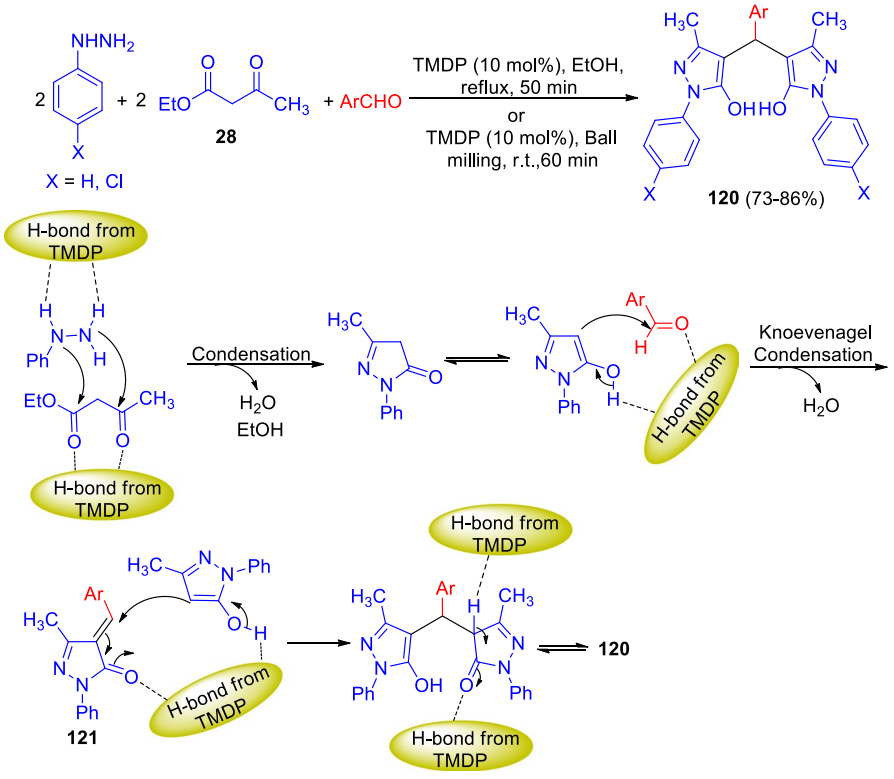
In 2020, Ghaffari Khaligh and co-workers obtained bis(pyrazolyl)methane derivatives **117** in 74–86% yields by the reaction of phenylhydrazine or 4-chlorophenylhydrazine with **28** and aromatic aldehydes using etraethylammonium L-prolinate as reusable catalyst in refluxing EtOH for 50–65 min. A possible reaction mechanism is presented in Scheme 30. The L-prolinate can act simultaneously as a hydrogen bond donor and a Lewis base through the secondary amine and carboxylate groups, respectively, to activate the phenylhydrazines and **28**. Intermediate **118** is formed by nucleophilic attack of phenylhydrazine to the activated **28** followed by dehydration. Intramolecular cyclization of **118** affords adduct **2a**, which is tautomerize to **2b**. Nucleophilic addition of **2b** to the activated carbonyl group of aldehyde followed by dehydration gives intermediate **119**. Finally, the second molecule of **2b** is added to **119** to yield bispyrazoles **117** [133].



Scheme 30 Tetraethylammonium L-prolinate catalyzed synthesis of bis(pyrazolyl)methanes **117**

4,4'-Trimethylenedipiperidine) TMDP) was as an organocatalyst employed for the synthesis of bis(pyrazolyl)methanes **120** in 73–86% yields by condensation of phenylhydrazines with **28** and aryl/heteroaryl aldehydes. The reaction was performed by conventional and nonconventional processes: (a) in EtOH under refluxing in the presence of catalyst (b) at ambient temperature using organocatalyst in a planetary ball mill (rotational frequency (10 Hz)) under solvent-free conditions. Also, the organocatalyst could be recycled and reused for ten runs. A probable reaction mechanism is illustrated in Scheme 31. The TMDP can act simultaneously as a hydrogen bond donor and a Lewis base through the nitrogen atom of second piperidine moiety to promote the condensation reaction of phenylhydrazine with **28** which affords 3-methyl-l-phenyl-5-pyrazolone. The catalyst also activates the carbonyl group of aldehyde for the Knoevenagel condensation, which gives the intermediate **121**. Finally, Michael addition of the second molecule of 3-methyl-l-phenyl-5-pyrazolone to **121** affords bispyrazoles **120** [134].

Ansari et al. described green synthesis of 4,4′-((4-methoxyphenyl)methylene) bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) and 4,4′-((4-nitrophenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) by the condensation reaction of **50a**, **28** and 4-methoxybenzaldehyde or 4-nitrobenzaldehyde under ultrasonic irradiation in



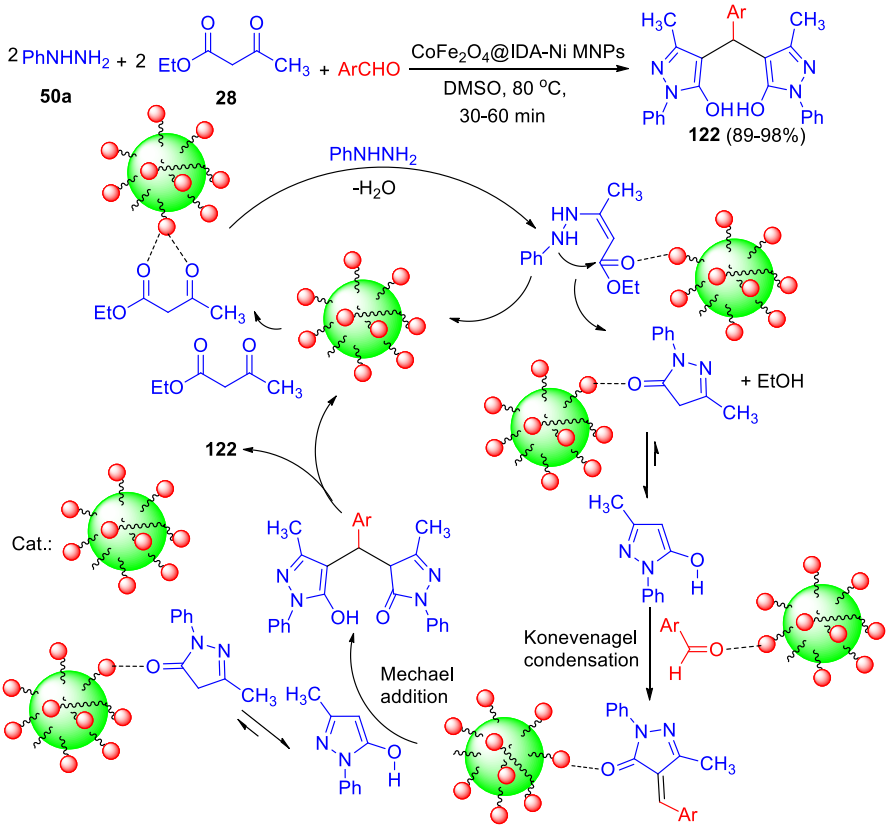
Scheme 31 TMDP catalyzed synthesis of bispyrazoles **120**

EtOH/H_2O for 15–20 min and its potential application was investigated for N80 steel corrosion mitigation in 15% HCl. The results indicated that the good inhibitive action of bis(pyrazol-5-ols) in the acidic solution, which is due to the formation of inhibitor film [135].

After that, a highly efficient and environmentally benign method designed for the solvent-free preparation of bispyrazole derivatives from the condensation of substituted aromatic aldehyde, **50a** and **28**. Ionic liquid (NMPYT) was used as an ecofriendly catalyst under microwave irradiation for 13–20 min and resulted the corresponding products in 85–94% yields [136].

Furthermore, Tamoradi and co-workers noted that treatment of **50a** with **28** and aromatic aldehydes using Ni complex supported on $CoFe_2O_4$ NPs as a recyclable catalyst in DMSO at 80 °C for 30–60 min afforded bis(pyrazolyl)methane derivatives **122** in 89–98% yields. Proposed mechanism for the preparation of bispyrazoles **122** in the presence of $CoFe_2O_4$@IDA-Ni MNPs is outlined in Scheme 32 [137].

Jonnalagadda et al. have demonstrated an efficient method for the preparation of bis(pyrazolyl)methane derivatives in 92–99% yields under ultrasound irradiation

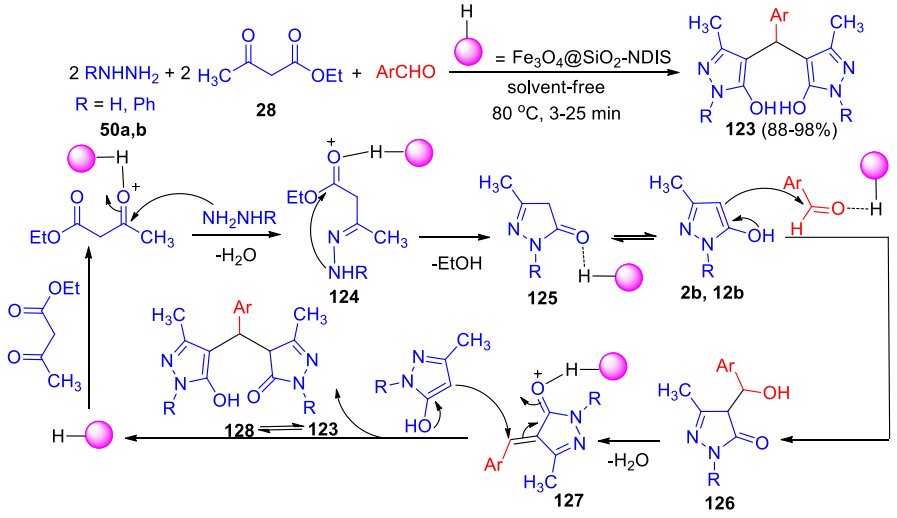


Scheme 32 $CoFe_2O_4$@IDA-Ni MNPs catalyzed synthesis of bispyrazoles **122**

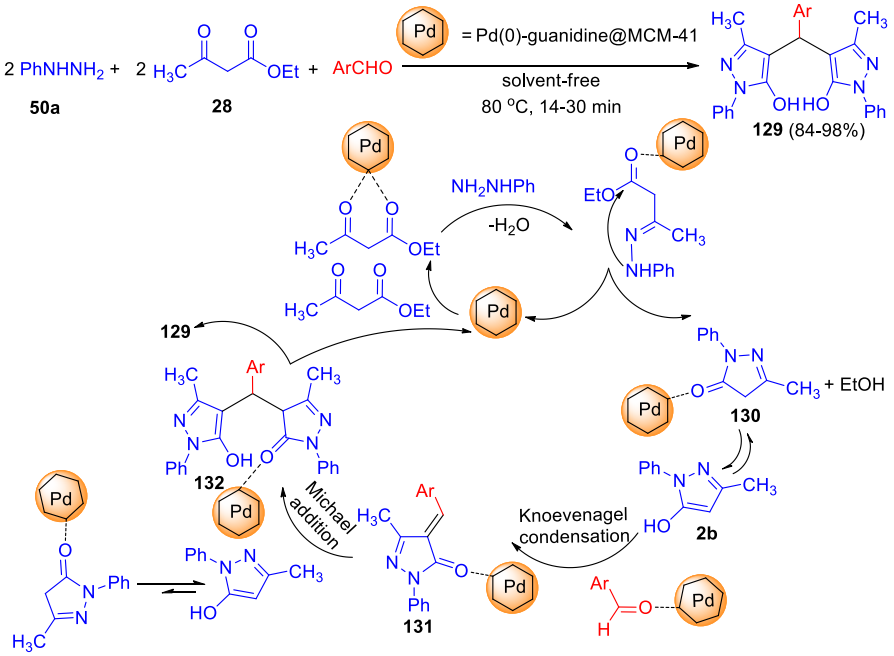
using **28**, **50a** and aromatic aldehydes as reactants in EtOH:H_2O at ambient temperature for 5–8 min. Treatment of **50a** with **28** produces the pyrazolone intermediate **2a**, which then tautomerizes to give the intermediate **2b**. Next, condensation of aryl aldehyde with **2b** affords Knoevenagel arylidene intermediate. In the next step, Michael addition of **2b** to arylidene intermediate, followed by tautomerization leading to the formation of the target products [138].

Brønsted acidic dicationic ionic liquid immobilized on Fe_3O_4@SiO_2NPs as a magnetically separable catalyst was applied for the preparation of bis(pyrazolyl) methanes **123** in 88–98% yields by condensation of **50a,b** with **28** and aromatic aldehydes at 80 °C under solvent-free conditions for 3–25 min. A plausible mechanism is represented in Scheme 33. Initially, nucleophilic addition of **50** to the activated carbonyl group **28** affords **124**, which undergoes intramolecular cyclization, followed by removal of EtOH leading to the formation of pyrazolone **125**. In the next step, pyrazolones **125** rearranged into tautomers **2b** and **12b** and underwent Knoevenagel condensation to activated aldehydes to give intermediate **126**. Michael acceptor **127** is formed by dehydration of **126** and treated with second molecule of pyrazolone to yield intermediate **128**, which undergo tautomerization and aromatization to yield the target products **123** [139].

A rapid, green and efficient procedure for the preparation of bispyrazole derivatives **129** in 84–98% yields is reported via condensation of **50a** with **28** and aromatic aldehydes using Pd(0)-guanidine@MCM-41 as a recyclable catalyst at 80 °C under solvent-free conditions for 14–30 min. The reasonable mechanism for synthesis of **129** is illustrated in Scheme 34. In the first step, palladium nanocatalyst activates carbonyl groups in the ethyl acetoacetate, and then **50a** attacks the carbonyl groups to give pyrazolone **130**, which is further rearranged into tautomer **2b**. Next, a Knoevenagel-type of reaction takes place between activated aldehyde and **2b** followed by dehydration to yield adduct **131**. Subsequently, Michael addition reaction



Scheme 33 Synthesis of bispyrazoles **123** using Fe_3O_4@SiO_2-NDIS

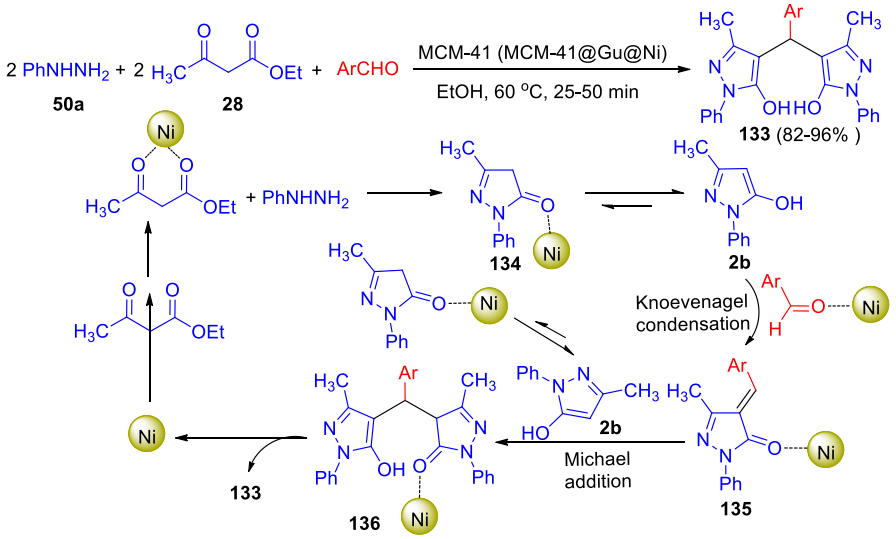


Scheme 34 MCM-41@guanidine-Pd(0) catalyzed synthesis of bis(pyrazolyl)methanes **129**

between **131** and **2b** is facilitated to generate intermediate **132**, which undergoes tautomerization and aromatization leads to the formation of the desired products **129** [140].

A rapid and very efficient approach for the preparation of bispyrazoles **133** in 82–96% yields has been reported using nickel-guanidine complex immobilized on MCM-41 (MCM-41@Gu@Ni) as a recyclable nanocatalyst (5 times) by the reaction of aromatic aldehydes, **50a** and **28** in EtOH at 60 °C for 25–50 min. The plausible mechanism for the synthesis of **133** is represented in Scheme 35. Firstly, the carbonyl group **28** is activated by the nanocatalyst nickel for attack of lone pair of nitrogen form **50a** to yield pyrazolone **134**. Subsequently, the activated aromatic aldehyde undergoes a tandem reaction with intermediate **2b** (which is the tautomer of intermediate **134**) leads to intermediate **135** after dehydration. The next step is a Michael addition of another intermediate **2b** to **135** to afford intermediate **136**, which is then tautomerize to the expected products **133** [141].

In 2021, a tetradentate acidic catalyst based on pentaerythritol tetrabromide and methylimidazole is synthesized and used for the solvent-free synthesis of bispyrazoles **137** in 88–97% yields from **50a**, **28** and aryl aldehydes. The reaction proceeds at 100 °C within 4–14 min. The reasonable mechanism for the formation of **137** is depicted in Scheme 36. Initially, condensation reaction between **50** and **28** affords intermediate **138**, which is converted into the product **139** by dehydration. In the next step, pyrazolone **2a** is produced by cyclization of product **139** and removal of EtOH, which is in equilibrium with its tautomeric form **2b**. Subsequently, intermediate **140**



Scheme 35 MCM-41@Gu@Ni catalyzed synthesis of bispyrazoles **133**

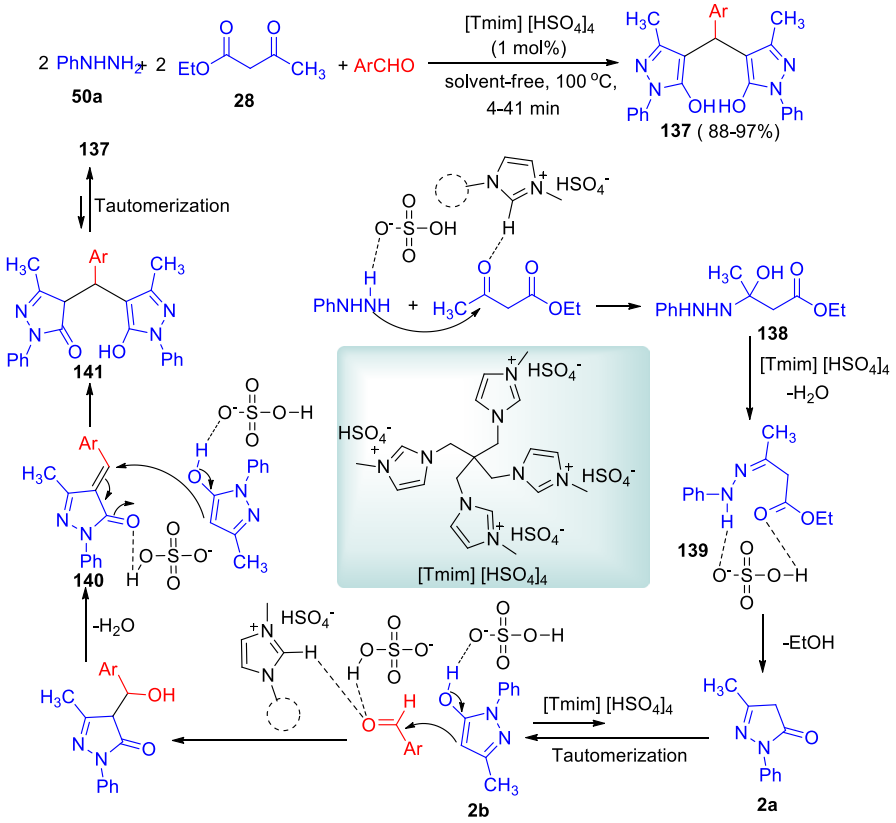
is obtained via condensation of **2b** with the activated carbonyl group of aromatic aldehyde. Then, Michael addition reaction between **140** and another intermediate **2b** affords the adduct **141**. In the last step, after tautomerization and aromatization, the corresponding products **137** are formed [142].

After that, an efficient strategy for the synthesis of (Fe_3O_4@THAM-Pd) as a recoverable organometallic nanocatalyst has been designed and used for the preparation of bispyrazoles **142** in 60–92% yields by coupling of **28**, **50b** and aromatic aldehydes at 70 °C for 35–60 min in EtOH:H_2O (1:1). A possible mechanistic pathway is illustrated in Scheme 37. Firstly, pyrazolone produced from the reaction between **28** and **50b**. Then, the addition of pyrazolone to the carbonyl group of the aldehydes activated by the catalyst affords Knoevenagel adduct **143**. Finally, Michael addition of another pyrazolone to **143** leads to the desirable products **142** [143].

Recently, Patil and co-workers synthesized a series of bispyrazoles **144** in 84–94% yields by the condensation reaction of **28**, **50b** and aromatic aldehydes using a naturally sourced bio-surfactant, chickpea leaf exudates (CLE), as a recyclable Brønsted acid-type catalyst in *iso*-PrOH at 60 °C within 15–30 min (Scheme 38). Also, *iso*-PrOH provides dual performance (co-surfactant and co-solvent) in this reaction [144].

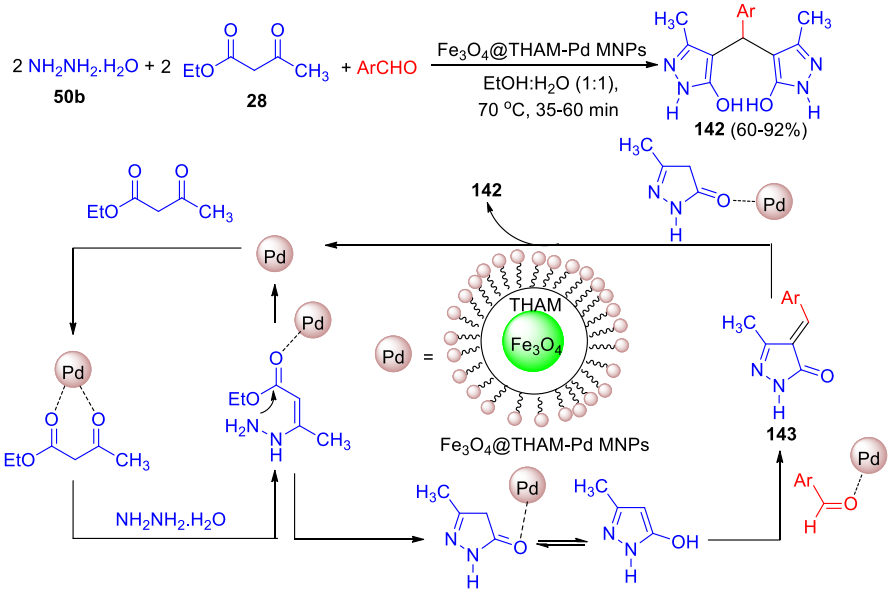
Conclusions

Pyrazole and its derivatives such as 4,4′-(arylmethylene)-bis-(1*H*-pyrazol-5-ols) have attracted interest because they exhibit a wide range of biological activities such as antibacterial, antioxidant, antifungal, anti-malarial, anti-inflammatory, anti-nociceptive, antipyretic, antivirals, antidepressant, antitumor, anti-filarial agents and as

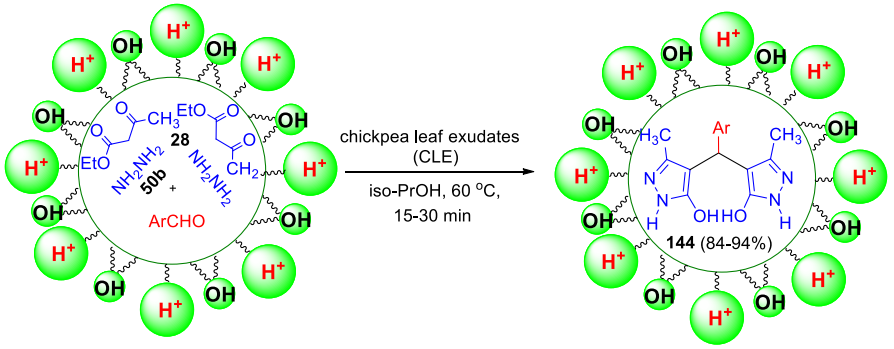


Scheme 36 [Tmim] $[HSO_4]_4$ catalyzed synthesis of bis(pyrazolyl)methanes **137**

the chelating and extracting reagents for different metal ions. The present work contributes the different classical strategies for the synthesis of bispyrazole derivatives via one-pot pseudo three-component reactions and one-pot pseudo five-component reactions and reporting their applications for the period of 2014 to early 2021 in the presence of various homogeneous and heterogeneous catalysts such as nano-$SiO_2/HClO_4$, ZnO NPs, Ph_3CCl, $NH_4(OAc)$, biosurfactant, Mohr's salt, 2-carbamoylhydrazine-1-sulfonic acid, CsF, $H_3PW_{12}O_{40}$, nanomagnetite-Fe_3O_4, $SbCl_5/SiO_2$ NPs, Cu-isatin Schiff base supported on γ-Fe_2O_3, MNPs@$VO(OH)_2$, alum, [Amb] L-prolinate, $Ce(SO_4)_2.4H_2O$, 4-H_3SPA, caffeine-H_3PO_4, TMBSED][Cl]$_2$, {Fe_3O_4@SiO_2@$(CH_2)_3$-thiourea dioxide-SO_3H/HCl}, γ-AlOOH, silica vanadic acid, GO/Fe_3O_4/L-proline, Ni-guanidine@MCM-41NPs, GO@PyH-CH_3SO_3, chitosan-SO_3H, La-guanine@SBA-15, Zr-guanine-MCM-41, 2-hydroxy ethylammonium propionate, $ZnAl_2O_4$ nanoparticles, $Ce(SO_4)_2.4H_2O$, HAP@$AEPH_2$-SO_3H, $CuCr_2O_4$, Na^+-MMT-[pmim]HSO_4, [Et_3NH][HSO_4], ([MIm]ClO_4, CeO_2 NPs, 1-(carboxymethyl)pyridinium chloride {[cmpy]Cl}, 4-(succinimido)-1-butane sulfonic acid, Ag/TiO_2, aspirin, L-proline, La$(OTf)_2$-grafted-GO, sulfonated honeycomb



Scheme 37 Fe_3O_4@THAM-Pd MNPs catalyzed synthesis of bispyrazoles **142**



Scheme 38 Synthesis of bispyrazoles **144** by using chickpea leaf exudates (CLE)

coral, $[Mn\text{-}4CSMP]Cl_2$, Dabco-base, morpholinium glycolate, nano-$NiZr_4(PO_4)_6$, $[TMEDSA][HSO_4]_2$, [Dsim][TFA], $(SB\text{-}DABCO)HSO_4$, lemon juice, $CuFe_2O_4$, alpha-Casein, guanidine hydrochloride, etraethylammonium L-prolinate, 4,4'-trimethylenedipiperidine, $CoFe_2O_4$@IDA-Ni MNPs, Fe_3O_4@SiO_2NPs, Pd(0)-guanidine@MCM-41, MCM-41@Gu@Ni, [Tmim] $[HSO_4]_4$, Fe_3O_4@THAM-Pd, chickpea leaf exudates, Bronsted acids or catalyst-free conditions under green approach, ultrasound and microwave-mediated and solvent-free conditions. The advantages of the above methodologies include: environmentally friendly and operational simplicity, green conditions, extremely short times, high efficiency, simple work-up procedures, easily recyclable, reusable and excellent activity of the catalysts, the use

of a nontoxic, biocompatible, biodegradable and metal-free ionic liquids and high to excellent yields of the some new products. In addition, this review article will help not only to the synthetic chemists but also to the medicinal and pharmaceutical chemists to update information on recent developments in this field.

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