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A rapid, easy, and efficient method for synthesis of 4,4'-(arylmethylene)-bis-(1H-pyrazol-5-ols), catalyzed by boehmite nanoparticles

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Abstract

An efficient and eco-friendly method is introduced for the synthesis of 4,4'-(arylmethylene)-bis-(1H-pyrazol-5-ols) by the condensation reaction of two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one with various aromatic aldehydes, catalyzed by the boehmite nanoparticles (BNPs). This heterogeneous catalyst was recycled and used in four runs for the reaction between benzaldehyde and 3-methyl-l-phenyl-5-pyrazolone without any loss of its catalytic activity.

Keywords: Heterogeneous catalyst , Aldehyde, One-pot reaction, 3-Methyl-l-phenyl-5-pyrazolone.

1. Introduction

Pyrazolones and bis-pyrazolones have been paid much attention for their various biological activities such as the selective COX-2 inhibitory [1], antitumor [2], and cytokine inhibitory ones [3].

2,4-Dihydro-3H-pyrazol-3-one derivatives including 4,4'-(arylmethylene)-bis-(3-methyl-1-phenyl-1H-pyrazol-5-ols) have a broad spectrum of approved biological activities, being used as the anti-inflammatory [4], gastric secretion stimulatory [5], anti-depressant [6], anti-bacterial [7], and anti-filarial agents [8].

Literature survey showed that the synthesis of 4,4'-(arylmethylene)-bis-(3-methyl-1-phenyl-1H-pyrazol-5-ols) can be accomplished by two methods: (i) Knoevenagel reaction of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one with aldehydes to form the corresponding arylidenepyrazolones followed by a base-promoted Michael reaction with a second equivalent of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one [9, 10]; (ii) one-pot tandem Knoevenagel–Michael reaction of aldehydes with two equivalents of 3-methyl-1-phenyl-1Hpyrazol-5(4H)-one under various reaction conditions [11]. The first method requires piperidine as a base catalyst, and the desired products are formed in poor (15–30%) yields [12]. The second method involves a non-catalyzed tandem Knoevenagel–Michael reaction under neutral conditions in either ethanol [13] or benzene [14].

Although the second method affords the corresponding 4,4'-(arylmethylene)-bis-(1H-pyrazol-5-ols) in reliable (70–90%) yields, the reaction requires an initial reflux

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of 3–12 h under the ambient temperature in order to go to completion.

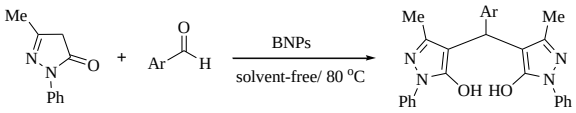
Perumal and co-workers [15] have reported the synthesis of 4,4'-(arylmethylene)-bis-(1H-pyrazol-5-ols) by the reaction of two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one with various aromatic aldehydes, catalyzed by ceric ammonium nitrate (CAN) as a homogenous catalyst in water. Karade and co-workers [16] have reported a similar reaction under reflux in water. Their protocol also involved the use of harsh reaction conditions with lowered yields.

Niknam and *et* al. have reported the synthesis of 4,4'-(arylmethylene)-bis-(1H-pyrazol-5-ols), catalyzed by silica-bonded S-sulfonic acid [17], sulfuric acid ([3-(3-silicapropyl)sulfanyl]propyl) ester [18], and N-(3-silicapropyl)-N-methylimidazolium hydrogen sulfate ([Sipmim]HSO4) [19] in refluxing ethanol. However, their method involved the use of a recyclable catalyst, and the reactions were carried out at long reaction times.

The development of heterogeneous catalysts for organic synthesis has become a major area of research. The potential advantages of these materials over homogeneous systems (simplified recovery, reusability, and the potential for incorporation in continuous reactors and micro-reactors) could lead to novel, environmentally benign chemical procedures for industry [20, 21].

Boehmite is an aluminum oxide hydroxide (γ-AlOOH) mineral, a component of aluminium ore bauxite containing extra hydroxyl groups on its surface. Recently, we have reported the preparation of BNPs, and used it as a catalyst for the synthesis of highly substituted imidazoles [22].

In continuation of our works to develop new catalysts for organic transformations [23-25], herein we report the use of the mild, rapid, efficient, and environmentally friendly BNPs catalyst for the preparation of 4,4'-(arylmethylene)-bis-(3-methyl-1-phenyl-1H-pyrazol-5-ols) from the solvent-free reaction of aromatic aldehydes with two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one in the presence of BNPs at 80 °C (Scheme 1).



Scheme 1

2. Experimental

All chemicals were purchased from Merck or Fluka Chemical Companies. All known compounds were identified by comparison of their melting points and ^{1}H NMR data with those reported in the literature. Powder X-ray diffraction (XRD) patterns were collected with a Philips PW-1800 or STOE diffractometer with Cu Kα radiation. Electron microscopy was performed with a JEOL JSM-6360LV transmission electron microscope.

2. 1. Catalyst preparation

The boehmite nanoparticles (BNPs) catalyst was prepared according to a previously published procedure [24]. Aluminum-2-butoxide (10 mL, 2 M) in 2-butanol was placed in a 300-mL-stainless steel autoclave, which contained 50 ml of deionized water. The autoclave was then heated for 5 h at 100 ºC in an oven. After cooling the autoclave, the powder produced was filtered off, and dried at 100 ºC overnight to give the BNPs catalyst.

2. 2. Typical procedure for synthesis of 4, 4'-(arylmethylene)-bis-(3-methyl-1-phenyl-1H-pyrazol-5-ols) 3

A mixture of an aromatic aldehyde (1.0 mmol), 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2.0 mmol), and BNPs (10 mg) was stirred at 80 °C under solvent-free conditions for an appropriate time (Table 2). The reaction progress was monitored by TLC. After completion of the reaction, the mixture was cooled down to room temperature. Ethanol was then added to the mixture, which was subsequently filtered to remove the catalyst. After evaporation of the solvent, the residue was crystallized from ethanol. 4, 4'-(arylmethylene)-bis-(3-methyl-1-phenyl-1H-pyrazol-5-ol) derivatives structures were confirmed by using IR,

and ^{1}HNMR spectra data. The physical data IR, NMR of known compounds were found to be identical with those reported in the literature [16, 17, 18, 19]

3. Results and discussion

Among the different methods used for the preparation of boehmite nanoparticles (BNPs), hydrothermal-assisted sol-gel technique has some advantages such as preparation in a one-pot process and processing at low temperatures. The most promising property of the hydrothermal-processed BNPs is the formation of a highly crystalline single-phase product with no organic residues [26, 27]. This was confirmed by the IR spectrum, XRD pattern, and Transmission electron microscopy (TEM).

The acidic sites of boehmite are shown in Fig. 1. The bridged and terminal surface hydroxyl groups of boehmite give two different stretching vibrations at 3413 and 3321 cm^{-1} in the IR spectrum (Fig. 2). Also, a sharp absorption band appeared for the BNPs at 1639. cm^{-1}, which is due to the adsorbed water molecules. In addition, a high intensity band can be observed in 1072 cm^{-1}, which was assigned to the bending vibration of the AlO-H group. Moreover, a high intensity bands could be observed at 752, and 489 cm^{-1}, which was due to the stretching, and bending vibration of the Al–OH groups.

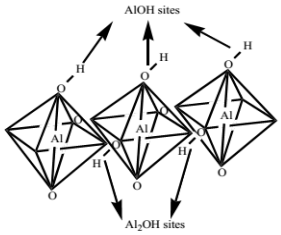


Fig. 1. Bridged and terminal hydroxyl groups of BNPs

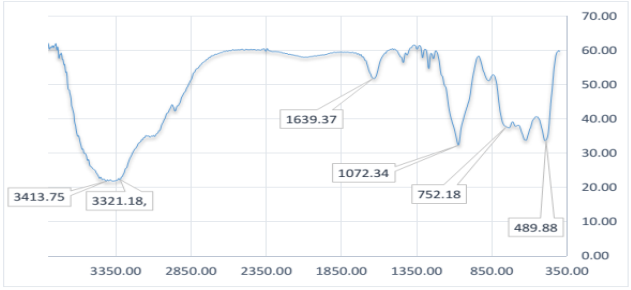


Fig. 2. FT-IR spectra of BNPs

The calculation of particle size from the XRD pattern according to the Scherer equation shows 10 nm particles for BNPs (Fig. 3). This is confirmed by the transmission electron microscopy image of BNPs (Fig. 4). In this image, needle-shaped BNPs are seen over 50 nm long and up to 10 nm in width. Effective surface area of the BNPs is 326 m^2 g^{-1} according to BET experiments.

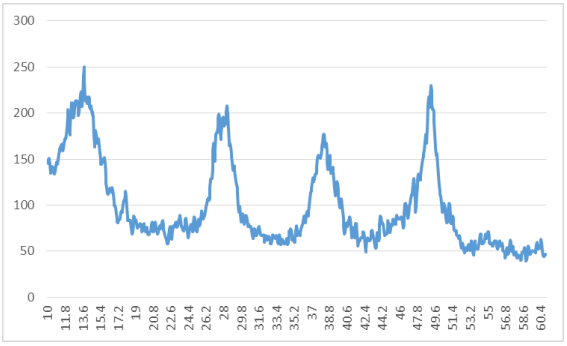


Fig. 3. XRD patterns of BNPs

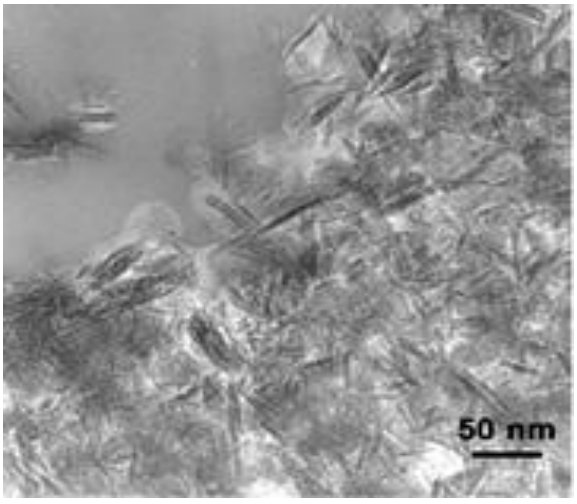


Fig. 4. Transmission electron microscopy image of BNPs.

Table 1: Optimization of reaction conditions

Entry	Ar	Product	Time (min)	Yield[b] (%)	m.p. / lit. m.p. (^{0}C) [ref.]
1	C_6H_5-	**3a**	10	90	168-170/171-173 [16]
2	4-Me-C_6H_4-	**3b**	25	89	200-202/198-200 [16]
3	4-MeO-C_6H_4-	**3c**	27	87	174-176/173-175 [16]
4	2-MeO-C_6H_4-	**3d**	30	88	209-211/210-212 [29]
5	2-OH-C_6H_4-	**3e**	15	96	226-228/227-229 [18]
6	4-Br-C_6H_4-	**3f**	12	92	181-183/183-185 [16]
7	4-Cl-C_6H_4-	**3g**	10	95	200-202/199-201 [16]
8	2-Cl-C_6H_4-	**3h**	20	90	232-234/235-237 [18]
9	2,4-Cl_2-C_6H_3-	**3i**	20	92	226-228/227-229 [17]
10	4-F-C_6H_4-	**3j**	8	92	181-183/181-183 [18]
11	4-NO_2-C_6H_4-	**3k**	25	95	225-227/225-227 [18]
12	3-NO_2-C_6H_4-	**3l**	30	97	145-147/146-147 [16]
13	2-Furfuryl	**3m**	20	96	188-189/189-191 [18]
14	2-Thienyl	**3n**	35	95	181-183/181-183 [19]
15	2-Pyridinyl	**3o**	35	93	

[a]Isolated yield

In order to study the effect of the catalyst loading on the condensation reaction of aromatic aldehydes with 1-phenyl-3-methyl-5-pyrazolone, the reaction of benzaldehyde with two equivalents of 1-phenyl-3-methyl-5-pyrazolone was chosen as a model reaction (Table 1).

Firstly, several solvents were screened for the reaction in the presence of a catalytic amount of the BNPs. The results obtained showed that the efficiency and yield of the reaction under solvent-free conditions at 80 ºC were higher than those obtained in solvents like H_2O, EtOH, CH_3CN, THF, DMF, and 1,4-dioxane (Table 1, entry 1-8). When the reaction was carried out in the absence of a catalyst, the target product was not formed even after 3 h under the above-mentioned conditions (Table 1, entry 9).

Increasing the temperature did not improve the yield (Table 1, entry 10), whereas the yield was reduced by increasing and decreasing the amount of BNPs (Table 1, entries 11 and 12). The results obtained for this condensation reaction in the presence of solid acids such as *p*-toluene sulfuric acid, and zeolite-HY are shown in Table 1.

Therefore, we employed the optimized condition (10 mg BNPs) for the condensation reaction of various aryl aldehydes with 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one into the corresponding 4,4'-(arylmethylene)-bis-(3-methyl-1-phenyl-1H-pyrazol-5-ols) (Table 2).

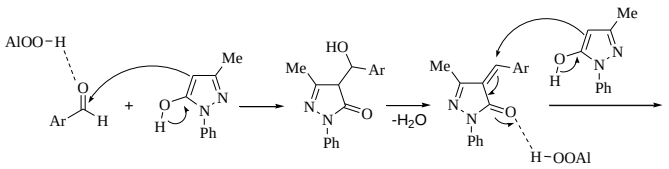
Table 2 Preparation of compound 3 catalyzed by BNPs under solvent-free conditions[a]

Entry	Catalyst	Catalyst loading (mg)	Solvent	Temp (°C)	Time (min)	Yeild[a] (%)
1	BNPs	10	H_2O	Reflux	180	20
2	BNPs	10	EtOH	Reflux	180	75
3	BNPs	10	CH_3CN	Reflux	180	65
4	BNPs	10	DCM	Reflux	180	25
5	BNPs	10	THF	Reflux	180	15
6	BNPs	10	DMF	100	180	trace
7	BNPs	10	1,4-Dioxane	100	180	45
8	BNPs	10	neat	80	15	90
9	-----	------	neat	80	180	trace
10	BNPs	10	neat	120	10	90
11	BNPs	20	neat	80	15	80
12	BNPs	5	neat	80	60	60
13	P-TSA	10	neat	80	15	50
14	Zeolite-HY	10	neat	80	15	65

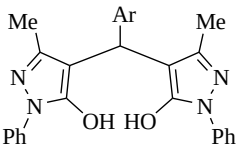
[a]Reaction conditions: aromatic aldehyde (1.0 mmol), compound **1** (2.0 mmol), BNPs (0.01 g), 80 ºC.
[b]Isolated yield.

As shown in Table 2, variation in the electronic properties and the position of functional groups on the aromatic ring of the aldehyde did not show an obvious impact on the yield of the reaction. Furthermore, the steric effects of the substituents at the ortho-position of the aromatic aldehyde did not have an obvious impact on the yield of the reaction. On the other hand, benzaldehydes with electron-donating (Table 2, entries 2-5) or electron-withdrawing groups (entries 10-12) were condensed into the corresponding 4,4'-(arylmethylene)-bis-(3-methyl-1-phenyl-1H-pyrazol-5-ols) in high yields. Notably, BNPs efficiently catalyzed the reaction when hetero-aromatic aldehydes were applied (Table 2, entries 13-15).

A plausible mechanism for the synthesis of products 3 in the presence of BNPs can be given as shown in Scheme 2. The reaction is thought to proceed in a stepwise manner. In the first step, BNPs formulate electrophilic activation of the aldehyde to increase the rate of formation of the knoevenagel product [A]. In the second step, it accelerates the rate of the Michael addition of a second equivalent of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one on the arylidenepyrazolones **[A]** for the formation of compounds **3**.



[A]



Scheme 2. Proposed mechanism

The possibility of recycling the catalyst was examined using the reaction of benzaldehyde and 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one under the optimized conditions. In order to recover the catalyst, the separated catalyst was washed with ethanol twice and reused after drying. The recycled catalyst could be reused for four times (Table 3).

Table 3. Synthesis of product **3a** catalyzed by the recycled catalyst

Entry	Number of cycle	Yield (%)
1	1	90
2	2	87
3	3	85

using the reaction of benzaldehyde and 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one under the

A comparative study of the reaction conditions for the synthesis of 4,4'-(phenylmethylene)-bis-(3-methyl-1-phenyl-1H-pyrazol-5-ol) **3a** using the methods given in Table 4 and reported in the present letter demonstrate that the present protocol is indeed superior to several other ones. Most of the listed methodologies suffer from some limitations such as the prolonged reaction times, and elevated temperatures. This new procedure is environmentally friendly, clean, and more efficient than the reported methods.

4. Conclusion

In conclusion, we have demonstrated an environmentally benign three-component condensation reaction of aldehydes with two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one using BNPs as a heterogeneous green catalyst under solvent-free conditions. This method offers several advantages like milder reaction condition, shorter reaction time, cleaner reaction, green and reusability of the catalyst, high yield, and simple experimental and isolation procedures, making it a useful route to the synthesis of 4,4'-(arylmethylene)-bis-(3-methyl-1-phenyl-1H-pyrazol-5-ols).

Table 4. Comparison of our results with previously reported methods for synthesis of product **3a**

Entry	Catalyst	Reaction conditions	Time (min)	Yield (%) [Ref.]
1	Silica-bonded S-sulfonic acid (0.1 g)	EtOH, Reflux	120	80 [17]
2	Sulfuric Acid ([3-(3-Silicapropyl) sulfanyl]propyl ester (0.1 g)	EtOH, Reflux	180	90 [18]
3	Catalyst-free	H_2O, reflux	8 h	76 [16]
4	Silica-bonded Ionic Liquid (0.15 g)	EtOH, Reflux	120	89 [19]
5	BNPs (0.01 g) This work	Solvent-free	10	90

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