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An efficient green synthesis of highly substituted imidazoles catalyzed by Al-MCM-41 nanoreactors

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Abstract

Al-MCM-41 nanoreactor is found to be a remarkable efficient catalyst for one-pot multicomponent cyclocondensation of benzil, aniline or ammonium acetate and aromatic aldehydes for the synthesis of polysubstituted imidazoles under solvent-free conditions. The reaction was efficiently promoted by nano-Al-MCM-41 and the heterogeneous catalyst was recycled for four runs in this reaction without losing its catalytic activity. The key advantages of this process are operational simplicity, reusable catalyst, shorter reaction time, convenient work-up procedures, avoiding the use of organic solvents and purification of products by non-chromatographic methods. By this advantage, several polysubstituted imidazoles, as pharmaceutical important molecules, can be prepared in high yield and high purity.

Keywords: Nano-Al-MCM-41; aromatic aldehyde; benzil; imidazole; aniline.

Introduction

Imidazoles are common scaffolds in highly significant biomolecules, including biotin, the essential amino acid histidine, histamine, the pilocarpine alkaloids [1] and other

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alkaloids, which have been shown to exhibit interesting biological activities such as antimicrobial, anticryptococcal, inhibition of nitric oxide synthase, and cytotoxic activities [2-5]. Imidazole derivatives have also been found to possess many pharmacological properties and are widely implicated in biochemical processes. The imidazole compounds were also used in photography as photosensitive compound [6]. They also serve as useful building blocks for the synthesis of other classes of compounds. Owing to the wide range of pharmacological and biological activities, the synthesis of imidazoles has become an important target in current years. Among them, tri- and tetrasubstituted imidazoles have received much attention recently [7].

A number of methods have been developed for the synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles. Generally, 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles are synthesized by three-component cyclocondensation of 1,2-diketone, α-hydroxyketone or α-ketomonoxime with an aldehyde, aniline and ammonium acetate, which comprise the use of ionic liquids [8] urea-functionalized Fe_3O_4/SiO_2 magnetic nanocatalyst [9] silica supported sulfuric acid [10] $InCl_3.3H_2O$ [11a] ceric ammonium nitrate (CAN) [11b] $NiCl_2.6H_2O/Al_2O_3$ [11c], SiO_2-Pr-SO_3H [12], nano-$SnCl_4.SiO_2$ [13], $BF_3.SiO_2$ [14], $FeCl_3.6H_2O$ [15], phosphomolybdic acid [16], $K_5CoW_{12}O_{40}.3H_2O$ [17] M/SAPO-34 nanocatalysts [18], *p*-TsOH [19], molecular iodine [20], L-proline [21], KSF supported 10-molybdo-2-vanadophosphoric acid [22], sulfated tin oxide [23], nano-Fe_3O_4 in ionic liquid [24], silica-bonded propylpiperazine-*N*-sulfamic acid (SBPPSA) [25], CH_3COOH [26], L-cysteine [27], clays, zeolite, nano-crystalline sulfated zirconia [28], glacial acetic acid [29] and clay supported titanium [30] under microwave-irradiation, solvent-free or classical conditions.

Considerable attention has been given to mesoporous materials such as MCM-41 family because of their unique properties [31-33]. They have high specific surface areas, high pore volumes, and tunable pore sizes with a narrow distribution. However, Si-based MCM-41 exhibits only mild acidity,

which is much weaker than that of the microporous zeolites.

In continuation of our ongoing research for the development of simple and efficient methods for the synthesis of various heterocyclic compounds by multicomponent reaction [34] herein we wish to report a simple, and efficient one-pot method for the synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles from benzil, aniline, ammonium acetate, aromatic aldehydes and using nano-Al-MCM-41 catalyst. The catalyst was prepared according to the procedure described in the literature [35].

Experimental

*General procedure for the synthesis of polysubstituted imidazoles (**5**, **6**)*

For the synthesis of compounds **5a-f**, Al-MCM-41 (10 mg) was added to a mixture of benzil (1 mmol), aniline (1 mmol), ammonium acetate (1 mmol) and aromatic aldehyde (1 mmol) and for the synthesis of compounds **6a-f**, Al-MCM-41 (10 mg) was added to a mixture of benzil (1 mmol), ammonium acetate (2 mmol) and aromatic aldehyde (1 mmol). The mixture was heated at 120 ^{o}C for the appropriate time as indicated in Tables 2 and 3. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion, ethanol (5 mL) was added and heated until the precipitate was dissolved. Then, the mixture was centrifuged (500 rpm). The catalyst was separated. The organic layer was decanted and concentrated under reduced pressure and then the product so obtained was recrystallized from ethanol to afford the pure product. The catalyst was then washed with ethanol to remove all the organic impurities and reused for evaluating the performance in the next reaction.

Characterization data for 2-(2-hydroxy-3-methoxyphenyl)-1,4,5-triphenyl-*1H*-imidazole (5f)

White powder; IR (KBr) (υmax, cm^{-1}): 3283, 3057, 2957, 1597, 1495, 1441, 1373, 1325, 1231, 1145; ^{1}H NMR (400 MHz, DMSO-d$_6$); 3.79 (s, 3H, OCH$_3$), 6.26 (d, 1H, $^{3}J_{HH}$ = 8.4 Hz, Ar-H), 6.50 (t, 1H, $^{3}J_{HH}$ = 8.4 Hz, Ar-H), 6.91 (d, 1H, $^{3}J_{HH}$ = 8.4 Hz, Ar-H), 7.21-7.46 (m, 15H, Ar-H), 12.60 (s, 1H, OH) ppm; ^{13}C NMR (100 MHz, DMSO-d$_6$); 56.18, 113.09, 114.29, 118.11, 118.95, 126.56, 127.43, 128.94, 128.99, 129.16, 129.21, 129.75, 129.82, 130.09, 131.21, 131.77, 133.60, 134.67, 137.06, 145.00, 147.93, 148.88 ppm; MS (EI): *m/z* (%) 418 (M^{+}, 100), 417 (87), 400 (10), 389

(25), 376 (25), 268 (8), 193 (7), 165 (30), 77 (27); Anal. calcd. For $C_{28}H_{22}N_2O_2$: C, 80.38; H, 5.26; N, 6.70. Found: C, 80.34; H, 5.30; N, 6.76.

Results and discussion

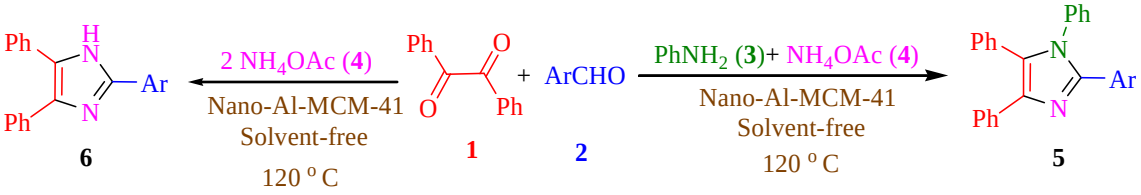
Initially, a model reaction was conducted by taking benzil (1.0 mmol), benzaldehyde (1.0 mmol) and ammonium acetate (2.0 mmol) in the presence of 10 mg catalyst at a temperature of 80-150 ^{o}C under solvent-free conditions. We were pleased to find that the reaction proceeded smoothly and almost complete conversion of reactants was observed at 120 ^{o}C to afford the desired product (**6a**) in 91% yield within 45 min (Table 3, Entry 1). To optimize the amount of the catalyst, the reaction was carried out with different amounts of Al-MCM-41 (2, 5, 7, 15 and 20 mg) under solvent-free condition and it was found that 10 mg gives the best results (Table 1, Entry 3). As indicated in Table 1, a further increasing of catalyst loading does not affect the yield, but slightly slow down the reaction. After optimising the experimental conditions, to explore the synthetic scope and the generality of the present protocol, various reactions were performed with a wide variety of aromatic aldehydes with benzil, aniline, ammonium acetate for the syntheses of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles (Scheme 1). The reaction time and percentage yield of the products (**5a-f** and **6a-e**) are shown in Table 2 and Table 3, respectively.

Table 1. Optimization for the synthesis of **6a**

Entry	Catalyst (mg)	Time (min)	Temperature (^{o}C)	Yield (%) 6a
1	10	45	80	65
2	10	45	100	78
3	10	45	120	91
4	10	45	150	80
5	2	45	120	42
6	5	45	120	64
7	7	45	120	82
8	15	45	120	89
9	20	45	120	89

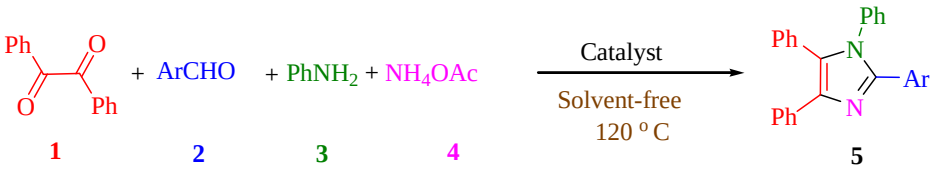
It is interesting to note that the pure products of all these reactions can be obtained just by recrystallization of the crude materials from ethanol by avoiding tedious work-up and column-chromatographic separation. As shown in Tables 2 and 3, it was clear that a variety of aromatic aldehydes with electron-withdrawing or electron-donating groups were employed as substrates and the reactions afforded the corresponding products in high to excellent yields.

In order to demonstrate the merites of present method in comparisions with other reported methods in the synthesis of highly substituted imidazoles, we have tabulated some of the results in Table 4. The results show the promising feature of this method in terms of reaction rate and the yield of the product with those reported in the literature.



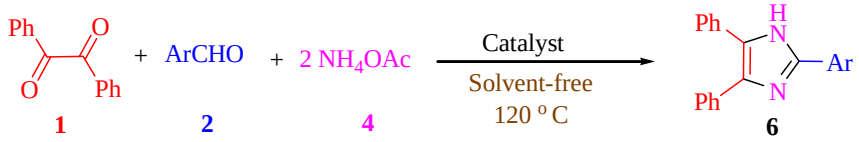
Scheme 1. Synthesis of polysubstituted imidazoles

Table 2. Synthesis of 1,2,4,5-tetrasubstituted imidazoles **5**



Entry	Aromatic	Product	Time (min)	Yield (%)	M.P. (°C)	
					Found	Reported [Ref.]
1	4-Cl C_6H_4	**5a**	50	92	165-167	160-163 [24]
2	4-Br C_6H_4	**5b**	60	87	156-157	152-154 [28]
3	4-Me C_6H_4	**5c**	45	91	184-186	186-188 [24]
4	2-OH C_6H_4	**5d**	45	88	250-252	252-254 [24]
5	4-F C_6H_4	**5e**	40	90	233-234	236 [36]
6	2-OH-3-MeO C_6H_3	**5f**	30	85	196-198	-

Table 3. Synthesis of 2,4,5-tetrasubstituted imidazoles **6**



1 **2** **4** **6**

Entry	Aromatic	Product	Time (min)	Yield (%)	M.P. (°C) Found	M.P. (°C) Reported [Ref.]
1	C_6H_5	**6a**	45	91	273-275	274-276 [28]
2	2-Cl C_6H_4	**6b**	50	93	192-193	190-191 [21]
3	4-Cl C_6H_4	**6c**	50	90	262-264	260-262 [28]
4	4-Me C_6H_4	**6d**	45	89	224-226	232-234 [28]
5	2-OH C_6H_4	**6e**	45	86	211-212	202-205 [21]

Table 4. Studynig efficiency of the presence method over some reported catalysts

Entry	Catalyst	Product	Conditions	Time (min)	Yield (%)	Ref.
1	SBA-15/TFE	**5a**	90 °C	210	92	[38]
2	Montmorilonite K10	**5a**	EtOH/ reflux	100	80	[28]
3	$[(CH_2)_4SO_3HMIM][HSO_4]$	**5a**	Neat/140 °C	120	87	[39]
4	Nano- Al-MCM-41	**5a**	Neat/120 °C	50	92	Present work
5	Montmorilonite K10	**6c**	EtOH/ reflux	95	75	[28]
6	L-Proline	**6c**	MeOH/ 60 °C	540	88	[21]
7	Glacial acetic acid	**6c**	Reflux	300	83	[29]
8	Nano- Al-MCM-41	**6c**	Neat/120 °C	50	90	Present work

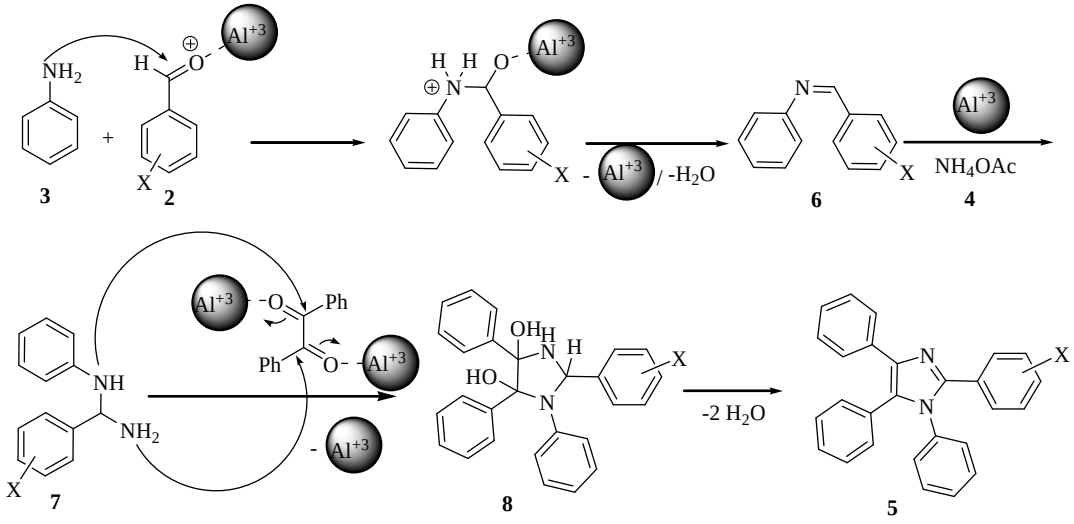
Additionally, the present catalyst seems to be more beneficial from the economical and accessibility point of view (Table 4, Entries 4 and 8).

One of the most important advantages of heterogeneous catalysis over the homogeneous counterpart is the possibility of reusing the catalyst by simple filtration, without loss of activity. Finally, we investigated the reusability of the catalyst in the model reaction. At the end of the reaction, the catalyst was recovered and reused for the similar reaction. This process was carried out over three runs without appreciable reduction in the catalytic activity of the catalyst. The results of these observations for the model reaction are shown in Table 5. A probable mechanism for the synthesis of tetrasubstituted imidazoles may be postulated as shown below (Scheme 2).

Table 5. Recyclability of the catalyst for the synthesis of imidazoles

No of Cycles[a]	**Fresh**	**Run 1**	**Run 2**	**Run 3**
Yields[b]	91	91	89	88
Time (min)	60	60	60	60

[a]Reaction conditions: benzil (1.0 mmol), ammonium acetate (2.0 mmol), benzaldehyde (1.0 mmol): catalyst (0.01 g), temperature: 120 ^{o}C
[b]Isolated yields



Scheme 2. Plausible mechanism for the formation of 1,2,4,5-tetrasubstituted imidazoles in the presence of nano-Al-MCM-41 catalyst

As can be seen in Scheme 2, nano-Al-MCM-41 is a Lewis acid and so it can activate the carbonyl group of aldehyde **2** to decrease the energy of transition state. Then the nucleophilic attack of aniline **3** on the activated carbonyl of aldehyde resulted in the formation of imine **6**, and it was followed by nucleophilic attack of the *in situ* generated ammonia from **4** on the imine, giving the intermediate **7**. The last one reacts with the activated benzil leading to the formation of intermediate **8**, followed by loss of two water molecules, to form final product **5**. Moreover, the probable mechanism for the synthesis of trisubstituted imidazoles is the same as that for tetrasubstituted imidazoles but in this case ammonium acetate was handled instead of aniline.

The products **5a-e** and **6a-f** were known compounds; their authenticity was established by ^{1}H and ^{13}C NMR, FT-IR and their melting points compared with that reported in literature. The product **5f** is a new compound and established by their ^{1}H and ^{13}C NMR, FT-IR, MS and elemental analysis.

Conclusion

In conclusion, we have developed a simple and efficient one-pot multicomponent methodology for the synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles catalyzed by 10 mg nano-Al-MCM-41 catalyst. Simplicity of operation, high yields, novel and reusable catalyst, easy work-up and purification of compounds by non-chromatographic method (crystallization only) are the key advantages of this method.

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