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Highly active nano-MgO catalyzed, mild, and efficient synthesis of amidines via electrophilic activation of amides

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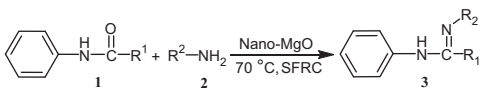
ABSTRACT

Nano-MgO catalyzed synthesis of amidine derivatives is developed under solvent-free reaction condition at 70 °C. Reusability of the catalyst and shorter reaction time as well as high yields are the advantages of this procedure.

More recently, nano magnesium oxide (MgO) has been utilized extensively because of its potential applications as catalyst.[1] In the domain of catalysis, MgO has a potent basic property which is exploited in various organic transformations[2] and also allows the high-yield synthesis of the significant molecules.[3] Synchronizing with the theme of green chemistry,[4] syntheses of *N*-bonded compounds under solvent-free conditions have received much attention.[5]

Amidines are significant intermediates in the synthesis of many biologically active compounds[6] and there are many strategies reported in the literature for their synthesis.[7] They also serve as important synthons for the preparation of azacyclic compounds.[8] Thus, the synthesis of amidines is still a topic of immense scope. Here we disclose a practical, convenient, and greener procedure for the synthesis of amidines under solvent-free conditions at 70 °C catalyzed by nano-MgO (Scheme 1). Ogata et al.[9] reported the synthesis of amidines in the presence of polyphosphoric acid trimethylsilyl ester by treating amine and amide in equimolar ratio at 160 °C under nitrogen atmosphere. But lower yield of the products, high reaction temperature, application of corrosive reagent and its non reusability, and tiresome reaction condition made the methodology less advantageous. To the best of our knowledge, there is no report on nano-MgO catalyzed synthesis of amidines.

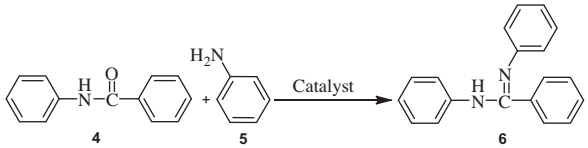
The study was initiated by the model reaction (Scheme 2) between **4** (5 mmol, 680 mg) and **5** (5 mmol, 0.45 mL) to give **6** without using any catalyst/solvent at 120 °C (Table 1). Under this condition, a mixture of unknown compounds was detected (Table 1, entry 1). Utilizing 5 mL of solvents (Table 1, entries 2–7) and conducting the reaction at lower temperature did not lead to product formation. As indicated in Table 1, when pyridine (10 mol %) was used as catalyst at 70 °C for this transformation then **6** was isolated in 7% yield (Table 1, entry 8). This observation prompted us to opt for the best base catalyst for the synthesis of **6**. Several base catalysts were tested under the current condition but the reaction could not be improved both in terms of yields and time (Table 1, entries 9–14). When fully characterized nano-MgO[9] was used under the present conditions, it increased the yield to a reasonable extent (Table 1, entry 15). To obtain better yield of **6**, the catalyst loading was optimized (Table 1, entry 15–18) and it was found that nano-MgO worked efficiently at 5 mol % (Table 1,



1 2 3

R^1 = Aryl, methyl, cyclohexyl and R^2 = Aryl, cyclohexyl

Scheme 1. Synthesis of amidine.



4 5 6

Scheme 2. Model reaction.

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Table 1
Optimization of reaction condition[a]

Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	None	None	120	20	[c]
2	None	EtOH	70	23	NR[d]
3	None	MeOH	70	18	NR[d]
4	None	CH_3CN	80	20	NR[d]
5	None	THF	70	22	NR[d]
6	None	H_2O	80	24	NR[d]
7	None	DMSO	100	16	NR[d]
8[e]	Pyridine	SFRC	70	12	7
9[e]	K_2CO_3	SFRC	70	15	5
10[e]	NaOH	SFRC	70	19	15
11[e]	KOH	SFRC	70	24	10
12[e]	Et_3N	SFRC	70	13	Trace
13[e]	PPh_3	SFRC	70	17	[c]
14[e]	Imidazole	SFRC	70	17	[c]
15[e]	Nano-MgO[i]	SFRC	70	7	80
16[f]	Nano-MgO[i]	SFRC	70	5	85
17[g]	Nano-MgO[i]	SFRC	70	3	94
18[h]	Nano-MgO[i]	SFRC	70	9	80
19[g]	Bulk MgO	SFRC	70	12	68
20[g]	Nano-Al_2O_3[j]	SFRC	70	7	70

[a] Reaction condition: **4** (5 mmol, 680 mg) and **5** (5 mmol, 0.45 mL), SFRC or solvent (5 mL), stirring.
[b] Isolated yields.
[c] Mixture of unknown compounds.
[d] No reaction.
[e] 10 mol % catalyst was used.
[f] 7 mol % catalyst was used.
[g] 5 mol % catalyst was used.
[h] 3 mol % catalyst was used.
[i] Particles size (17.4–16.4 nm).
[j] Particle size (37.4–39.7 nm).

Table 2
Nano-MgO catalyzed synthesis[11] of amidine derivatives [a] *vide* Scheme 1

Entry	R^1	R^2	Time (h)	Yield[b,c] (%)	Melting point (°C)[16]
1	C_6H_5	C_6H_5	3	94	142.8–144.8
2	C_6H_5	4-$OCH_3C_6H_4$	3	94	108.1–109.6
3	C_6H_5	4-$CH_3C_6H_4$	3	93	130.8–131.2
4	C_6H_5	4-$NO_2C_6H_4$	5	90	182.7–183.5
5	C_6H_5	4-ClC_6H_4	6	91	140.1–141.3
6	C_6H_5	C_6H_{11}	5	85	142.0–142.8
7	CH_3	C_6H_5	5	92	126.3–127.8
8	C_6H_{11}	C_6H_5	6	88	110.0–111.7
9	4-$NO_2C_6H_4$	C_6H_5	5	89	150.6–153.4
10	4-ClC_6H_4	C_6H_5	5	88	149.1–149.3

[a] Reaction condition: **1** (1 mmol) and **2** (1 mmol), Nano-MgO (5 mol %), SFRC, stirring.
[b] Yields refer to the isolated pure products.
[c] Products were characterized by IR and NMR (^1H and ^{13}C) spectroscopy, MS and also by comparing their melting points with the authentic ones.

entry 17). When the catalyst was changed to nano-Al_2O_3 and bulk MgO at 5 mol % loading under the similar conditions, low yields were recorded and were found to be inferior to nano-MgO (Table 1, entries 19–20). Bulk MgO having larger particles with smaller surface area was found to be less reactive than nano-MgO under the present reaction conditions. Overall, the reaction with nano-MgO was found to be very clean and no side product/by product (s) was formed.

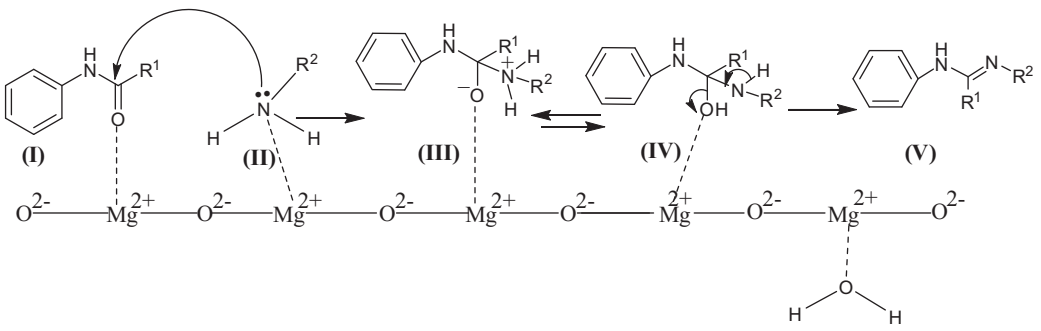
With this efficient system in hand, we next extended the scope of the substrate to various alkyl/aryl amines (Table 2). We found that the reaction was applicable to a broad range of derivatives. However, a careful analysis of the results from Table 2 indicates that amines with electron donating moiety reacted smoothly requiring less time (Table 2, entries 1–3), but amines substituted with electron-withdrawing functionality required more time to react (Table 2, entries 4 and 5) providing comparable yields. However, under the present conditions, in comparison to aryl amines, cyclohexylamine furnished the desired amidine in good yield (Table 2, entry 6). In our studies, aniline was used to accomplish the corresponding amidine derivatives when treated with *N*-phenylacetamide and cyclohexanecarboxylic acid phenylamide under the current reaction conditions (Table 2, entries 7 and 8). When electron withdrawing groups were present in the amide structure, the reaction took longer time for the formation of product (Table 2, entries 9 and 10). This might be due to the steric hindrance provided by the substituted phenyl groups in amide to the incoming nucleophile. When the reaction was performed involving both R^1 and R^2 as a methyl group, it furnished very poor yield (7%).

A tentative mechanism has been proposed for the synthesis of amidine derivatives (Scheme 3). It is hypothesized that the non-bonded pair of electron on oxygen atom of carbonyl moiety in amide possibly co-ordinates to the vacant *3p* orbital of Mg^{2+} of nano-MgO facilitating the electrophilic activation of amide (I). Now (II) can attack as a nucleophile to form an intermediate (III). Finally the elimination of water from (IV) gave rise to the formation of amidine (V). The activation of the substrate by nano-MgO has been reported previously.[10]

Table 3
Recyclability[a] of nano-MgO

Entry	Catalyst recovery (%)	Time (h)	Yield[b] (%)
1st run[c]	99	3	94
2nd run[c]	96	4	94
3rd run[c]	90	6	91
4th run[c]	84	7	88

[a] Reaction condition: Nano-MgO (5 mol %), **4** (5 mmol, 680 mg), **5** (5 mmol, 0.45 mL), SFRC.
[b] Yields refer to the isolated **6**.
[c] The recovered catalyst was used under identical reaction conditions to those for the 1st run.



Scheme 3. Tentative mechanism for the synthesis of amidine.

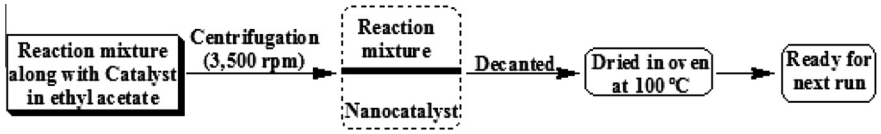


Figure 1. Flow sheet representation of catalyst isolation.

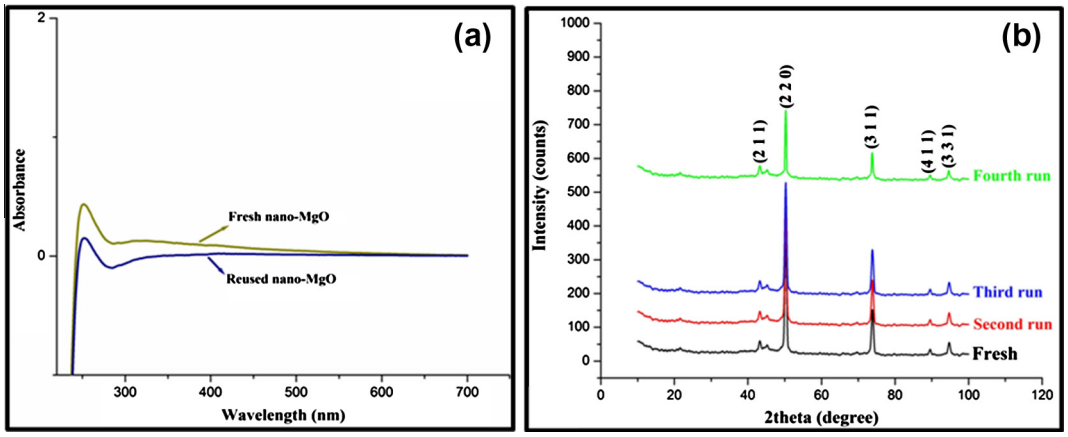


Figure 2. (a) UV-Visible spectra and (b) Powder XRD pattern of fresh and reused nano-MgO.

In this heterogeneous process, the catalyst was recyclable with a slight loss in its activity (Table 3). After completion of the reaction (Scheme 2), the catalyst was recovered from the reaction mixture by adding ethyl acetate (10 mL) under centrifugation (3500 rpm). The extracted catalyst in this way was decanted and finally dried in an oven at 100 °C for 7 h. It was then reused for the fresh reaction (Fig. 1). A slight decrease in catalytic activity was observed with recyclization (Table 3).

In addition, the powder X-ray diffraction analysis exhibited identical peaks for both the fresh and recovered nano-MgO (Fig. 2(b)). However, the intensity of the peaks (220), (311), (411), and (331) diminished slightly which might be due to loss during centrifugation and subsequent removal of the supernatant liquid. The loss of 15.4% of the catalyst[9] (Fig. 2(a)) was determined by UV visible spectroscopy. This might be the reason for a slight decrease in catalytic activity of the catalyst.

In conclusion, we have demonstrated that nano-MgO is highly active in catalyzing the mild and efficient synthesis of amidine derivatives under solvent-free conditions at 70 °C. The method offers several advantages including excellent yields of the products, safe handling, experimental simplicity, catalyst recyclability, and cost effectiveness which make it useful.

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11. To a two-necked round bottomed flask (50 mL), nano-MgO (5.0 mol %, 2.0 mg) was added along with the addition of *N*-phenylbenzamide (1.0 mmol, 197 mg) and stirred (30 min) on a preset oil bath at 70 °C. After that aniline (1 mmol, 0.91 mL) was added, stirring was continued till the required time (the progress of the reaction was judged by TLC). The reaction mixture was brought to room temperature and ethyl acetate (3 × 10 mL) was added and centrifuged at 3500 rpm to pellet out the nanocatalyst. It was then washed with hot ethanol (5 × 10 mL) to remove all the organic impurities. Finally, it was decanted and dried in an oven at 100 °C for 7 h. Then the catalyst was reused in the next run in the reaction. Having done this, the reaction mixture (in ethyl acetate) was washed with water and brine, dried over anhydrous Na_2SO_4, concentrated in a rotary evaporator, and finally the crude product was purified by column chromatography (30% ethyl acetate: hexane as the eluent). All the products listed in Table 2 are known compounds and have been characterized by comparing with those reported.[10]
N,N′-Diphenyl-benzamidine (Table 2, entry 1): A off white solid (256.8 mg, 94%); R_f = 0.35 (30% AcOEt: hexane); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.45 (br, 1H, N-H), 7.46–7.52 (m, 15H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 163.7, 153.4, 146.1, 132.5, 131.8, 130.2, 129.3, 128.1, 127.3, 125.0, 122.3, 118.4, 115.7; IR (KBr pellets) ν_{max}: 3356 cm^{-1} (N–H), 1618 cm^{-1} (C=N); *m*/*z* (GC–MS) 272.13 [M$^+$]; Anal. Calcd (%) for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92; N, 10.29%. Found: C, 83.73, H, 5.87, N, 10.26%.