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Nanosized magnesium oxide as catalyst for the rapid and green synthesis of substituted 2-amino-2-chromenes

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Abstract—A nanosized magnesium oxide catalyzed three-component condensation reaction of aldehyde, malononitrile, and α-naphthol proceeded rapidly in water–PEG to afford corresponding 2-amino-2-chromenes in high yields at room temperature. The greener protocol was found to be fairly general and the catalyst was reused in subsequent reactions with consistent activity.

1. Introduction

Organic transformations involving benign reaction media are of considerable interest in synthesis; especially multi-component condensation (MCC) reactions in which two or more steps are completed without isolation of any intermediate.[1] The use of many toxic and volatile organic solvents, particularly chlorinated hydrocarbons, as reaction media contributes pollution to the environment, and it is highly desirable to develop environmentally benign processes that can be conducted in green solvents. The low cost of water and polyethylene glycol (PEG), along with their non-toxic nature, renders them as attractive media for chemical synthesis and transformations. Moreover, in many cases these solvents can be recycled and reused to alleviate the problem of solvent disposal. In general, PEG is non-toxic, being used in cosmetics and food products, is potentially recyclable and is water-miscible, which facilitates its removal from reaction products.[2] Reactions in aqueous media offer many advantages such as simple operation and high efficiency in many organic reactions that involve water soluble substrates and reagents.[1] Further, the potential for cost savings is tremendous from the point of raw material, energy, cost, and time, by using MCC approach. These advantages become even more attractive if such reactions can be conducted using heterogeneous recyclable catalysts.

Heterogeneous catalysts are advantageous over conventional homogeneous catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be reused after activation, thereby making the process economically viable. Among the heterogeneous basic catalysts, magnesium oxide is a versatile material used as catalyst for several base-catalyzed organic transformations,[3] toxic waste remediation, and as additive in refractory, paint, and superconductor products.[4–6]

The 2-amino-chromenes are widely employed as pigments, cosmetics, potential agrochemicals, and represent an important class of chemical entities being the main constituents of many natural products.[7–9] Thus the synthesis of 2-amino-chromenes is of much importance to organic chemists. The most straightforward synthesis of this heterocyclic nucleus involves the MCC of aldehyde, malononitrile, and an activated phenol in the presence of piperidine using acetonitrile or ethanol as a reaction solvent.[10] Recently, relatively benign reagents such as cetyltrimethylammonium chloride and basic alumina in water have also been used.[11] However, most of the reported methods require prolonged reaction time, reagents in stoichiometric amount, toxic solvents, and generate moderate yields of the product. In continuation of our interests to develop environmentally benign protocols via MCC approach,[12] we report herein our results with nanosized magnesium oxide that efficiently catalyzed

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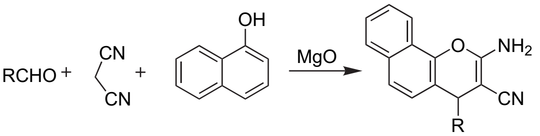
three-component condensation of aldehyde, malononitrile, and α-naphthol in methanol, water, or PEG–water as reaction medium (Scheme 1).



Scheme 1.

2. Results and discussion

In this paper, we describe a simple and high yielding protocol for the synthesis of 2-amino-2-chromenes involving the three-component, one-pot condensation of aldehyde, malononitrile, and α-naphthol using nanosized magnesium oxide as a novel and eco-friendly heterogeneous catalyst. The MgO catalyst is generally prepared by the decomposition of various magnesium salts or magnesium hydroxide [$Mg(OH)_2$, brucite]. However, the MgO formed by this method usually exhibits relatively large grain sizes, inhomogeneous morphologies, and small surface areas. These structural and textural features limit its application as a catalyst. Several novel methods such as controlled precipitation, sol–gel route, sol–gel followed by hypercritical drying, amorphous citrate method, and preparation under hydrothermal conditions, have been reported in literature for preparation of nanosized MgO particles.[4–6] These methods are highly advantageous in terms of the crystallite size and shape, surface area, and surface basic characteristics of the synthesized MgO particles. The particle size and surface morphology of synthesized MgO by wet chemical procedure depend upon several factors such as the rate of hydrolysis of magnesium salts, temperature, type of base, concentration of the salt, and drying and calcination steps. Proper choice of these parameters can lead to particles of uniform morphology and size. In this study, we have prepared nanosized MgO catalyst and used it successfully in the synthesis of 2-amino-chromenes. The XRD pattern of the synthesized MgO particles in the 2θ range of 30–65° is shown in Figure 1. Broad and intense peaks were observed at 2θ values of 36.8, 42.7 and 62.1°, corresponding to the d values of 2.43, 2.11, and 1.49 Å, respectively. These peaks indicate the presence of face centered cubic structure of the synthesized MgO particles.

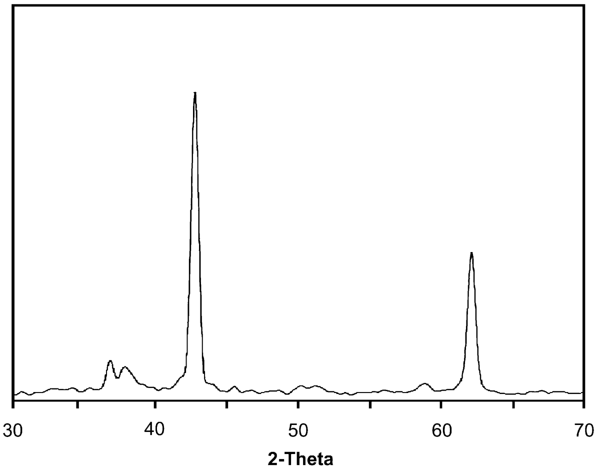


Figure 1. X-ray diffraction pattern of the synthesized MgO samples.

The scanning electron micrograph (SEM) of the synthesized MgO particles is shown in Figure 2a. Small agglomerated particles of disordered surface morphology are observed in the SEM picture of the MgO samples. The transmission electron micrograph (TEM) of the MgO particles is shown in Figure 2b. The particle size of the MgO sample is typically in the range of 100–200 nm. The small crystallites are irregular in shape and are attached to each other along the grain boundaries. Similar particle sizes have been reported earlier for MgO particles prepared by hydrolysis of $Mg(NO_3)_2 \cdot 6H_2O$ using aqueous ammonia solution under hydrothermal conditions.[4] However, unlike in the earlier case, lamellar structure was not observed for the particles synthesized by this method. This is probably due to the difference in the calcination procedure used for the preparation of these materials. Ding et al. have used stepwise calcination with special precautions to retain the lamellar structure of the intervening brucite phase.[4] In the present study, the temperature was linearly raised to 500 °C and maintained at that temperature for 3 h. Under the prevailing condition, it is likely that the lamellar structure of the intervening brucite phase was destroyed as it is being transformed to MgO phase.

The treatment of benzaldehyde, malononitrile, and α-naphthol in presence of magnesium oxide in methanol under refluxing conditions resulted in the formation of 2-amino-2-chromene in 96% yield (Table 1, entry 1). Under similar reaction condition, various substituted 2-amino-2-chromenes were obtained (Table 1, entries 2–6). The catalytic activity of the synthesized nanosized MgO particles was compared with the commercially available MgO catalyst. The reactions were carried out in methanol for both the catalysts for 1 h at 40 °C. The products were collected periodically at a time interval of 5 min and analyzed by gas chromatography. Figure 3 shows the variation of the percentage conversion of benzaldehyde to the product in the reaction mixture with time. It was observed that the initial activity of the nanosized MgO was much faster as compared to the commercial MgO catalyst. After 30 min of the reaction, the nanosized MgO shows 55% conversion of the benzaldehyde to the product as compared to the 35% observed in case of commercial MgO catalyst.

In this study, the initial activity clearly indicates that the particle size in nanoregime helps to expedite the reaction. This is in agreement with a recent report where an increase in the initial activity was observed in case of nanoparticles as compared to the bulk catalyst.[13] In order to examine the solvent effect and in our quest for the deployment of a benign reaction medium, the three-component condensation was explored in water. The nanosized magnesium oxide catalyzed condensation of three-component reaction proceeded smoothly in water under refluxing condition while affording substituted 2-amino-2-chromenes in moderate yield (Table 1, entries 1–6). The three-component condensation in water required relatively longer reaction time and afforded moderate yields of the product, probably because of the poor

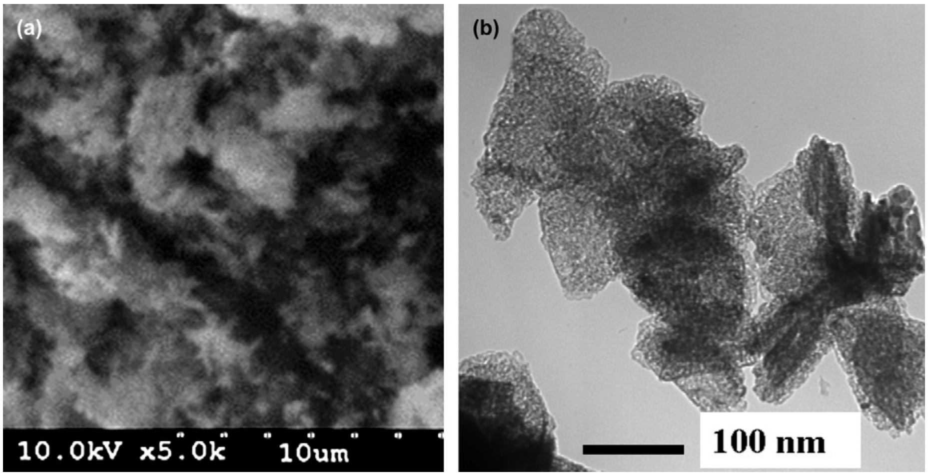


Figure 2. (a) Scanning electron micrograph and (b) transmission electron micrograph of the synthesized MgO.

Table 1. Synthesis of 2-amino-2-chromenes in methanol and water

Entry[a]	R	Yield (%)[b]		Mp (°C)
		Methanol	Water	
1	C_6H_5	96	86	178–180
2	4-OMeC_6H_4	95	85	176–179
3	3-$NO_2C_6H_4$	96	92	208–211
4	4-$NO_2C_6H_4$	97	93	231–234
5	4-ClC_6H_4	89	86	230–232
6	2-Furyl	87	84	169–172

[a] All the products were characterized by IR and NMR (^{1}H and ^{13}C NMR).
[b] Yield refers to the pure isolated products.

solubility of the reactants in comparison with methanol. After the completion of reaction in water, the magnesium oxide was recovered by extraction of the organic compounds followed by filtration of the aqueous mixture.

The initial formation of benzylidenemalononitrile by the Knoevenagel addition of malononitrile to the aldehyde has been reported without catalysis in polar protic solvent.[14] In view of the importance of polar protic solvent in the formation of benzylidenemalononitrile and substrate solubility, the reaction was conducted in PEG 400. We noticed that the MgO catalyzed condensation of benzaldehyde, malononitrile, and α-naphthol in PEG also required the same reaction time without any appreciable improvement in reaction yield. Because of the poor solubility of aldehyde, malononitrile, and α-naphthol in water at room temperature, we decided to explore three-component condensation in a mixture of PEG and water. Surprisingly, the reaction in 1:1 mixture of PEG and water was completed within 15 min at ambient temperature. Different combinations of PEG and water led us to conclude that equal amounts of both solvents are ideal for the efficient and rapid condensation of benzaldehyde, malononitrile, and α-naphthol. To study the generality of this protocol, syntheses of various substituted 2-amino-2-chromenes were accomplished (Table 2). Aromatic aldehydes with electron-withdrawing or donating groups were employed to afford the corresponding 2-amino-2-chromenes in good to excellent yields. In the case of aldehyde bearing electron donating group, condensation was found to be relatively slow (Table 2, entry 2). Reaction in PEG–water mixture generated almost similar yields of the products; however, three-component condensation was rapid and occurred at room temperature. The role of MgO was found to be crucial in the success of reaction as no product was detected in absence of the catalyst.

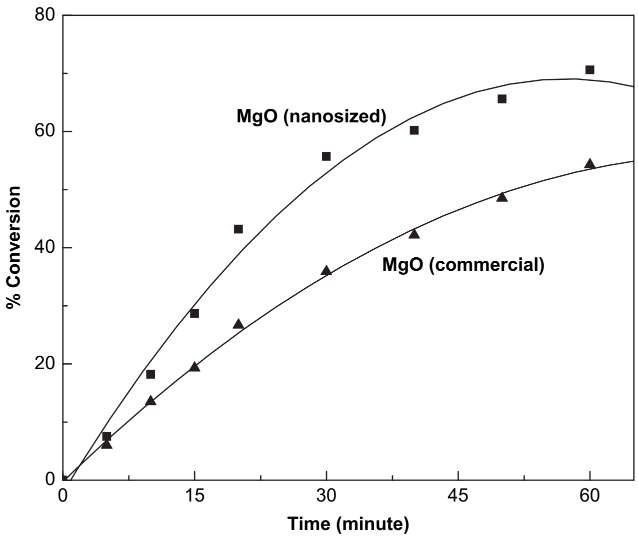


Figure 3. Comparison of the catalytic activity of synthesized MgO nanoparticle with commercial MgO catalyst.

After conducting the reaction with varying amounts of MgO, it was concluded that for 2 mmol of the substrates, 50 mg of the catalyst was sufficient for formation of the products. Further increasing the amount of the catalyst did not improve the results significantly. After completion of the reaction,

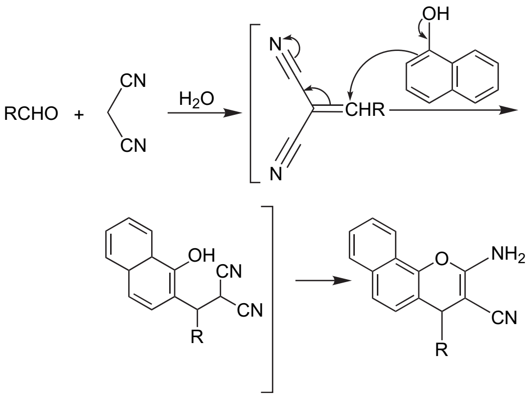
Table 2. Synthesis of 2-amino-2-chromenes in PEG–water (1:1)

Entry[a]	R	Yield (%)[b], PEG–water (1:1)	Time (min)
1	C_6H_4	96	15
2	4-OMeC_6H_4	82	90
3	3-$NO_2C_6H_4$	84	15
4	4-$NO_2C_6H_4$	70	15
5	4-ClC_6H_4	98	20
6	2-Furyl	95	15

[a] All the products were characterized by IR and NMR (^{1}H and ^{13}C NMR).
[b] Yield refers to the pure isolated products.

the catalysts were regenerated using two procedures. In the first case, the catalyst was washed three times with 10 ml portions of methanol and dried at 150 °C overnight. The other method employed for regeneration was simply heat treatment at 450 °C in air for 2 h. Both the methods were effective to regenerate the catalytic activity of the MgO sample. The reactivated catalyst was reused for second and third consecutive cycles without any significant loss in catalytic activity.

Mechanistically, the reaction occurs via initial formation of benzylidenemalononitrile in quantitative yield by the Knoevenagel addition of malononitrile to the aldehyde and followed by loss of water molecules. Subsequently, *ortho* C-alkylation of α-naphthol and nucleophilic addition of hydroxyl moiety to the nitrile produce 2-amino-chromenes (Scheme 2).



Scheme 2. Mechanistic pathway for the formation of chromenes.

3. Conclusions

The nanosized magnesium oxide has been employed for the first time as a novel and efficient catalyst for the benign synthesis of various substituted 2-amino-2-chromenes in a three-component condensation approach. The attractive features of this protocol are: simple experimentation procedure, use of benign reaction solvents, cost effectiveness, the recyclability of catalysts, and its adaptability for the synthesis of a diverse set of 2-amino-2-chromenes.

4. Experimental

4.1. General

Melting points were measured on a Micro Scientific Works apparatus and are uncorrected. IR spectra were recorded on a JASCO IR spectrophotometer using KBr pallets. ^{1}H and ^{13}C NMR spectra were recorded with Bruker NMR spectrometer at 400 MHz using TMS as internal standard. Reactions were monitored by thin layer chromatography (TLC) on 0.2 mm silica gel F_{254} plates. All the products are known compounds and are characterized by comparing their IR, ^{1}H NMR, and melting points with those reported in literature. The XRD pattern of the MgO sample was recorded in the 2θ range of 30–700° using a Shimadzu XD-D1 diffractometer employing Cu Kα radiation (λ= 1.5418 Å). Scanning electron micrograph pictures were taken using Jeol JSM-5300 microscope (acceleration voltage10 kV). The sample powder was deposited on a carbon tape before mounting on a sample holder. In order to reduce the charge developed on the sample, gold sputtering was done for 3 min. The transmission electron micrographs (TEM) were obtained with a Jeol-1200EX microscope. The MgO sample for TEM was prepared by dispersing the powdered sample in ethanol by sonication and then drop drying on a copper grid (400 mesh) coated with carbon film.

4.2. Synthesis of nanosized MgO

The MgO nanoparticles were synthesized by precipitation of the magnesium hydroxide gels in aqueous solution using $Mg(NO_3)_2$ as salt and liquid ammonia as the precipitating agent. Initially, the pH of 200 ml of distilled water was adjusted to 10.5 by addition of liquid ammonia. To this solution, 0.1 M magnesium nitrate solution was added dropwise with continuous stirring. The rate of addition of the salt solution was kept at 20 ml/h. During the addition, the pH of the mixture decreased due to hydrolysis of the salt. The pH was maintained at 10.5 by controlled addition of liquid ammonia solution. After completion of the precipitation procedure, the mixture was stirred at room temperature for 12 h, filtered, repeatedly washed with distilled water, dried at 120 °C, and calcined at 500 °C for 2 h. The calcinations step was carried out in a temperature programmable Muffle furnace in flowing air. The temperature of the furnace was linearly raised from room temperature to 500 °C with an increment of 10 °C/min. At 500 °C, the temperature was maintained for 2 h to yield the final material.

4.3. Synthesis of 2-amino-2-chromenes in methanol

A mixture of benzaldehyde (2 mmol), malononitrile (2 mmol), α-naphthol (2 mmol), and MgO (50 mg) in methanol (15 ml) was refluxed for 1 h. After completion of the reaction, as indicated by TLC, MgO was removed by filtration and excess methanol was distilled off. The crude product so obtained was recrystallized from methanol to afford the pure product in 96% yield (Table 1, entry 1); IR (KBr) 3400–3270, 2180, 1660, 1400, 1100 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (1H, s, H-4), 6.90 (1H, d, J=8.0 Hz, H-5), 7.08–7.22 (5H, m, Ar-H), 7.43–7.53 (3H, m, Ar-H), 7.22 (1H, d, J=8.0 Hz, H-7), 8.09 (1H, d, J=8.0 Hz, H-10); ^{13}C NMR (400 MHz, $CDCl_3$) δ 40.92, 61.06, 108.50, 116.66, 120.75, 123.20, 124.81, 125.95, 126.80, 126.92, 127.79, 129.04, 129.46, 133.27, 133.38, 142.90, 143.31, 158.98.

4.4. Synthesis of 2-amino-2-chromenes in water

A mixture of benzaldehyde (2 mmol), malononitrile (2 mmol), α-naphthol (2 mmol), and MgO (50 mg) in water (15 ml) was refluxed for 1 h. After completion of the reaction, as indicated by TLC, the mixture was extracted with ethyl acetate (3×5 ml). The organic phase was dried, filtered, and excess ethyl acetate was distilled off (filtration of both organic and aqueous phases led to the recovery of solid magnesium oxide). The residue was recrystallized from methanol to afford the pure product in 86% yield (Table 1, entry 1).

4.5. Synthesis of 2-amino-2-chromenes in PEG–water mixture

A mixture of benzaldehyde (2 mmol), malononitrile (2 mmol), α-naphthol (2 mmol), and MgO (50 mg) in PEG–water (1 ml; 1:1) was stirred at room temperature for 15 min. On completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water and the solid product was removed by filtration. The product was separated from catalyst by dissolving into hot methanol followed by simple filtration. The filtrate was concentrated to afford the pure product in 96% yield (Table 2, entry 1).

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References and notes

1. (a) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095; (b) Grieco, P. A. *Organic Synthesis in Water*; Blackie: London, 1998; (c) Wei, W.; Keh, C. C. K.; Li, C. J.; Varma, R. S. *Clean Tech. Environ. Policy* **2005**, *7*, 62; (d) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275.
2. Chen, J.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. *Green Chem.* **2005**, *7*, 64.
3. Hattori, H. *Chem. Rev.* **1995**, *95*, 537.
4. Ding, Y.; Zhang, G.; Wu, H.; Hai, B.; Wang, L.; Qian, Y. *Chem. Mater.* **2001**, *13*, 435.
5. Wang, J. A.; Novaro, O.; Bokhimi, X.; Lopez, T.; Gomez, R.; Navarrete, J.; Llanos, M. E.; Lopez-Salinas, E. *J. Phys. Chem. B* **1997**, *101*, 7448.
6. Koper, O. B.; Lagadic, I.; Volodin, A.; Klabunde, K. *J. Chem. Mater.* **1997**, *9*, 2468.
7. Ellis, G. P. The Chemistry of Heterocyclic Compounds. In *Chromenes, Chromanes, and Chromones*; Weissberger, A., Taylor, E. C., Eds.; John Wiley: New York, NY, 1977; Chapter II, p 13.
8. (a) Hafez, E. A.; Elnagdi, M. H.; Elagamey, A. A.; El-Taweel, F. A. M. *Heterocycles* **1987**, *26*, 903; (b) Sofan, M. A.; El-Taweel, F. M. A.; Elnagdi, M. H. *Liebigs Ann. Chem.* **1989**, 935; (c) Abdel Galil, F. M.; Riad, B. Y.; Sherif, S. M.; Elnagdi, M. H. *Chem. Lett.* **1982**, 1123.
9. Varma, R. S.; Dahiya, R. *J. Org. Chem.* **1998**, *63*, 8038.
10. (a) Bloxham, J.; Dell, C. P.; Smith, C. W. *Heterocycles* **1994**, *38*, 399; (b) Elagamey, A. G. A.; El-Taweel, F. M. A. A. *Indian J. Chem.* **1990**, *29B*, 885; (c) Elagamey, A. G. A.; El-Taweel, F. M. A. A.; Khodeir, M. N. M.; Elnagdi, M. H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 464.
11. Ballini, R.; Bosica, G.; Conforti, M. L.; Maggi, R.; Mazzacani, A.; Righi, P.; Sartori, G. *Tetrahedron* **2001**, *57*, 1395.
12. (a) Varma, R. S.; Kumar, D. *Tetrahedron Lett.* **1999**, *40*, 7665; (b) Kappe, C. O.; Kumar, D.; Varma, R. S. *Synthesis* **1999**, 1799.
13. Valdés-Solís, T.; Marbán, G.; Fuertes, A. B. *Catal. Today* **2006**, *116*, 354.
14. Bigi, F.; Conforti, M. L.; Maggi, R.; Piccinno, A.; Sartori, G. *Green Chem.* **2000**, *2*, 101.