Iranian Journal of Catalysis 6(3), 2016, 237-243

IRANIAN JOURNAL OF CATALYSIS

Multi-component, one-pot, aqueous media preparation of dihydropyrano [3,2-c]chromene derivatives over MgO nanoplates as an efficient catalyst

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Received 28 June 2015; received in revised form 13 January 2016; accepted 22 February 2016

ABSTRACT

Red pine leaves were applied for the green method preparation of MgO nano-plates. The MgO nano-plates were used for the one-pot synthesis of 1 dihydropyrano [3,2-c] chromene derivatives. This procedure is very simple and affords excellent yields.

***Keywords**: MgO nano-plates, Dihydropyrano[3,2-c]chromenes, Red pine leaves, 4-Hydroxycoumarin.*

1. Introduction

The synthesis of dihydropyrano[3,2-c]chromene scaffolds through one-pot, multi-component reactions have emerged as an interesting area of research for organic chemists. This decision is due to the fact that chromenes are the main components of many naturally occurring products, and have useful biological and pharmacological aspects [1,2]. Some derivatives of chromenes are widely employed as pigments, cosmetics and potential agro-chemicals [1-6]. Fused chromenes exhibit a wide spectrum of pharmacological applications such as antitumor, cancer therapy, sex pheromones, antimicrobial and central nervous system activity [7-11].

The common route to the synthesis of chromenes scaffolds is the multicomponent condensation of aromatic aldehyde, malononitrile and activated phenols using basic and acidic catalyst including piperidine [12], ammonium salts [13,14], NaOH [15], K_2CO_3 [16], starch solution [17], $TiCl_4$ [18], $InCl_3$ [19], heteropolyacid [20], Et_3N [21], silica-bonded N-propylpiperazine sodium n-propionate (SBPPSP) [22], DBU [23], $Na_2CaP_2O_7$ (DIPH) [24] and CuO nano-structures [25].

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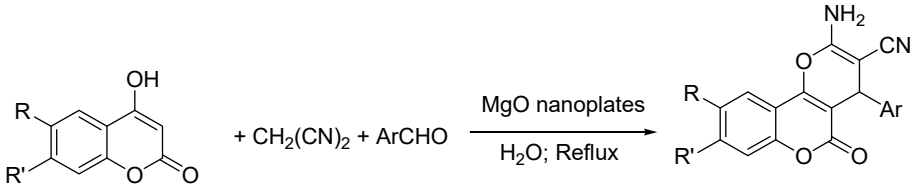
Although these methods are valuable as they provide an improvement in the synthesis of chromenes, some of them suffer from disadvantages such as being expensive catalysts and using toxic solvents and tedious work-up procedures. Thus, the development of a new procedure, including homogeneous catalysts as reusable solid catalysts to overcome these problems would be highly desirable.

The purpose of this study was to investigate the one-pot preparation of dihydropyrano[3,2-c]chromene derivatives using MgO-nano-plates as an efficient catalyst (Scheme 1).

2. Experimental

All reagents were purchased from Merck and Aldrich and used without further purification. The powder X-Ray diffraction patterns were measured with D_8, Advance, Bruker, axs, diffractometer using Cu-Kα irradiation. FE-SEM was taken by a Hitachi S-4160 photograph to examine the shape of the sample. NMR spectra were recorded on a Bruker Avance DPX 400 MHz instrument and measured in DMSO-d_6 relative to TMS. Elemental analysis was performed on a Heraeus CHN-O-Rapid analyzer. Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. TLC was performed on silica gel Polygram SIL G/UV 254 plates.



Scheme 1. Preparation of dihydropyrano[3,2-c]chromene derivatives using MgO nano-plates.

2.1. Preparation of MgO nano-plates

At first 50 g of ground red pine leaves was inserted in a 250 balloon flask containing 100 mL of de-ionized water and refluxed for 2h. Afterwards, the extract was filtered to cut off the red pine leaf bodies. The extract was combined with 15 mL of aqueous ammonia (37%). Next, the prepared solution was pureed drop-wise to an aqueous solution of Mg(II) (prepared by dissolving of magnesium chloride (20 mmol) in 50 mL of water) under vigorous magnetic stirring. Next, the resulting mixture was aged for 5h until a gel was formed. Finally, the gel was filtered washed with water for three times, dried and calcinated at 500°C for 2h.

2.2. General procedure

To a mixture of 4-hydroxycoumarin (1.0 mmol), aromatic aldehyde (1 mmol) and malononitrile (1 mmol) in water (5 mL), MgO nano-plate (0.5 mmol) was added as the catalyst, and the mixture was stirred for an appropriate time at reflux condition. After the reaction was completed, the solid compound obtained was filtered off and the crude products were purified by recrystallization from EtOH.

Selected spectral data

*2-amino-4,5-dihydro-9-methyl-5-oxo-4-phenylpyrano [3,2-c]chromene-3-carbonitrile (**Table 2, Entry 14**):*

^{1}HNMR (400 MHz, DMSO-d_6): δ = 2.45 (s, 3H, CH_3), 4.45 (s, 1H, CH), 7.20-7.34 (m, 7H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.73 (s, 1H) ppm. ^{13}CNMR (100 MHz, DMSO-d_6): δ = 21.2, 37.3, 57.7, 103.9, 113.4, 116.6, 119.8, 122.9, 124.7, 127.4, 127.7, 128.6, 129.3, 133.6, 144.7, 153.4, 154.2, 158.9, 160.3 ppm. Found: C, 72.94; H, 4.55; N, 8.66% $C_{20}H_{14}N_2O_3$, requires: C, 72.72; H, 4.27; N, 8.48%.

*2- amino-4,5- dihydro-8,9- dimethyl-5- oxo-4- phenyl pyrano[3,2-c]chromene-3-carbonitrile (**Table 2, Entry 15**):*

^{1}HNMR (400 MHz, DMSO-d_6): δ = 2.36 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.44 (s, 1H, CH), 7.19-7.33 (m, 7H), 7.46 (s, 1H), 7.71 (s, 1H) ppm. ^{13}CNMR (100 MHz, DMSO-d_6): δ = 18.6, 20.9, 37.4, 57.5, 103.4, 112.9, 117.3, 118.1, 127.1, 127.4, 127.8, 128.5, 129.4, 135.2, 135.6, 151.4, 154.7, 159.3, 160.2 ppm. Found: C, 73.54; H, 4.97; N, 8.36% $C_{21}H_{16}N_2O_3$, requires: C, 73.24; H, 4.68; N, 8.13%.

*2- amino-4,5- dihydro-8,9- dimethyl-5- oxo-4- p- tolyl pyrano[3,2-c]chromene-3-carbonitrile (**Table 2, Entry 16**):*

^{1}HNMR (400 MHz, DMSO-d_6): δ = 2.22 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.44 (s, 3H,CH_3), 4.42 (s, 1H, CH), 7.05 (d, *J* = 7.9 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 7.36 (s, 2H, NH_2), 7.45 (s, 1H), 7.70 (s, 1H) ppm. ^{13}CNMR (100 MHz, DMSO-d_6): δ = 18.7, 21.1, 21.9, 37.3, 58.0, 103.5, 113.0, 117.3, 118.2, 122.5, 124.7, 127.1, 129.4, 132.9, 135.2, 135.5, 151.3, 154.7, 159.2, 160.1 ppm. Found: C, 74.03; H, 5.23; N, 8.05% $C_{22}H_{18}N_2O_3$, requires: C, 73.73; H, 5.06; N, 7.82%.

*2-amino-4-(4-chlorophenyl)-4,5-dihydro-8,9-dimethyl-5-oxopyrano[3,2-c]chromene-3-carbonitrile (**Table 2, Entry 17**):*

^{1}HNMR (400 MHz, DMSO-d_6): δ = 2.37 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.48 (s, 1H, CH), 7.24 (d, *J* = 8.1 Hz, 2H), 7.39 (s, 2H, NH_2), 7.43-7.47 (m, 3H), 7.71 (s, 1H) ppm. ^{13}CNMR (100 MHz, DMSO-d_6): δ = 18.7, 20.9, 37.8, 58.7, 103.5, 113.1, 117.2, 118.2, 127.1, 129.7, 133.1, 131.9, 135.2, 135.5, 142.6, 151.3, 154.6, 159.3, 160.2 ppm. Found: C, 66.73; H, 4.23; N, 7.63% $C_{21}H_{15}ClN_2O_3$, requires: C, 66.58; H, 3.99; N, 7.40%.

*2-amino-4-(3-chlorophenyl)-4,5-dihydro-8,9-dimethyl-5-oxopyrano[3,2-c]chromene-3-carbonitrile (**Table 2, Entry 18**):*

^{1}HNMR (400 MHz, DMSO-d_6): δ = 2.36 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.47 (s, 1H, CH), 7.24-7.56 (m, 7H), 7.71 (s, 1H) ppm. ^{13}CNMR (100 MHz, DMSO-d_6): δ = 18.7, 20.9, 37.6, 58.5, 103.5, 113.0, 117.2, 118.1 127.2, 127.8, 128.6, 129.4, 130.7, 132.1, 135.2, 135.4, 143.3, 151.3, 154.7, 159.3, 160.1 ppm. Found: C, 66.71; H, 4.27; N, 7.65% $C_{21}H_{15}ClN_2O_3$, requires: C, 66.58; H, 3.99; N, 7.40%.

2-amino-4,5-dihydro-4-(3,4-dimethoxyphenyl)-8,9-dimethyl-5-oxopyrano[3,2-c]chromene-3-carbonitrile (***Table 2, Entry 19***):

^{1}HNMR (400 MHz, DMSO-d_6): δ = 2.37 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4.41 (s, 1H, CH), 6.75 (d, *J* = 8.1 Hz, 1H), 6.86 (s, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 7.35 (s, 2H, NH_2), 7.47 (s, 1H), 7.70 (s, 1H) ppm. ^{13}CNMR (100 MHz, DMSO-d_6): δ = 18.7, 21.0, 36.6, 55.4, 55.6, 58.3, 103.7, 113.1, 117.1, 118.2, 120.1, 123.3, 125.6, 127.1, 133.0, 135.2, 135.4, 148.0, 148.6, 151.5, 154.7, 159.4, 160.3 ppm. Found: C, 68.53; H, 5.36; N, 7.14% $C_{23}H_{20}ClN_2O_5$, requires: C, 68.31; H, 4.98; N, 6.93%.

3. Results and Discussion

MgO nanoplates were synthesized *via* a simple precipitation method through using an extract solution of red pine leaves. The XRD pattern of the as-prepared product, as shown in Fig. 1, reveals that all diffraction peaks can be perfectly indexed to a cubic MgO with calculated lattice constants a = b = c = 4.217A°, in agreement with the reported data (reference code: 01-071-1176). No impurity peaks were detected in the XRD pattern. The average crystalline size of the sample was determined by Scherrer equation is 63 nm.

Field emission scanning electronic microscopy (FE-SEM) was used to study the morphology of the surface of the MgO nano-plates (Fig. 2). The analysis of the obtained picture shows clearly that the surface of the as-prepared MgO nano-plates has a homogeneous microstructure made up of layers of various sizes and forms. The plates shaped irregular grains with a lateral size of 40-110 nm. This means that the extract solution of red pine leaves has an obvious influence on the morphology and particle size of the adsorbent. The nano-plate structure of the MgO can play an important role in its catalytic activity.

In order to examine the catalytic activity of MgO nano-plates a mixture of 4-hydroxycoumarin (1 mmol), benzaldehyde (1 mmol) and malononitrile (1 mmol) was stirred in water at room temperature over MgO nano-plates (0.25 mmol) catalyst. No other additive was necessary to promote the reaction.

Optimization was done with a variation of the reaction medium. The results have been summarized in Table 1.

The difference in the results indicated the influence of solvent on reaction mechanism. No yield was obtained in non-polar solvents. Polar organic solvents like CH_3CN, EtOH, EtOAc, MeOH afforded low yields. The highest yield of product (80%) was achieved in aqueous condition. The next reaction was done using various amounts of catalyst loading.

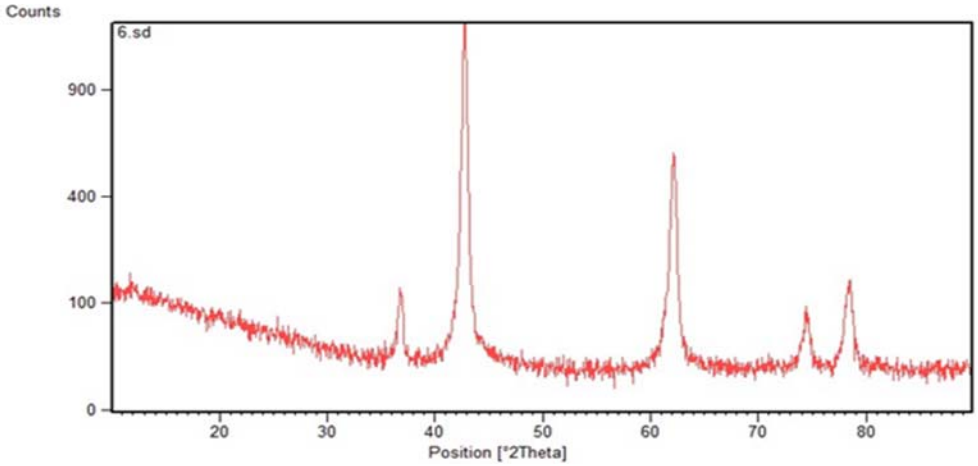


Fig. 1. XRD pattern of MgO nano-plates.

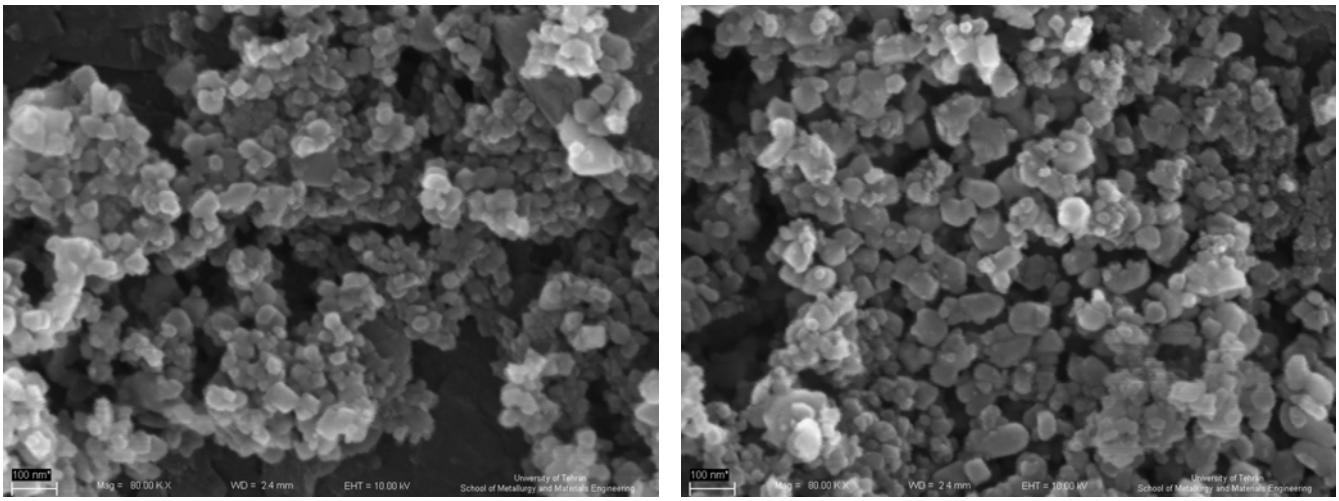


Fig. 2. FE-SEM micrographs of MgO nano-plates.

Table 1: Optimization of the reaction conditions in the synthesis of 2-amino-4,5-dihydro-5-oxo-4-phenylpyrano [3,2-c]chromene-3-carbonitrile.

Entry	Catalyst (mmol)	Temp. (°C)	Solvent (5 mL)	Yield (%)[a]
1	0.25	Reflux	*n*-Hexane	-
2	0.25	Reflux	CH_2Cl_2	-
3	0.25	Reflux	Et_2O	-
4	0.25	Reflux	EtOAc	10
5	0.25	Reflux	EtOH	25
6	0.25	Reflux	MeOH	30
7	0.25	Reflux	CH_3CN	15
8	0.25	80	-	10
9	0.1	Reflux	H_2O	65
10	0.5	Reflux	H_2O	85
11	0.75	Reflux	H_2O	86
12	1	Reflux	H_2O	84
13	0.25	Reflux	H_2O	80

[a]Isolated Yields, reaction time: 2 h

The optimal catalyst amount was found to be 0.5 mmol. The use of lesser amounts of the MgO afforded inferior product yield (Table 1). On the other hand, the use of higher quantities of the MgO did not provide any significant advantage in the increasing of the reaction yield (Table 1).

The effect of the reaction temperature is presented in Fig. 3, in which the activation temperature of the reaction was changed in a range of 25-100°C. Practically no catalytic activity for the synthesis of 2- amino-5- oxo-4- phenyl-4,5- dihydropyrano[3,2-c] chromene-3-carbonitrile was observed at room temperature. The catalytic activity for the MgO nanoplates developed above 50°C and increased with increasing temperature.

To study the scope and limitations of this procedure, a series of experiments was carried out using a variety of aromatic aldehydes. The results are shown in Table 2.

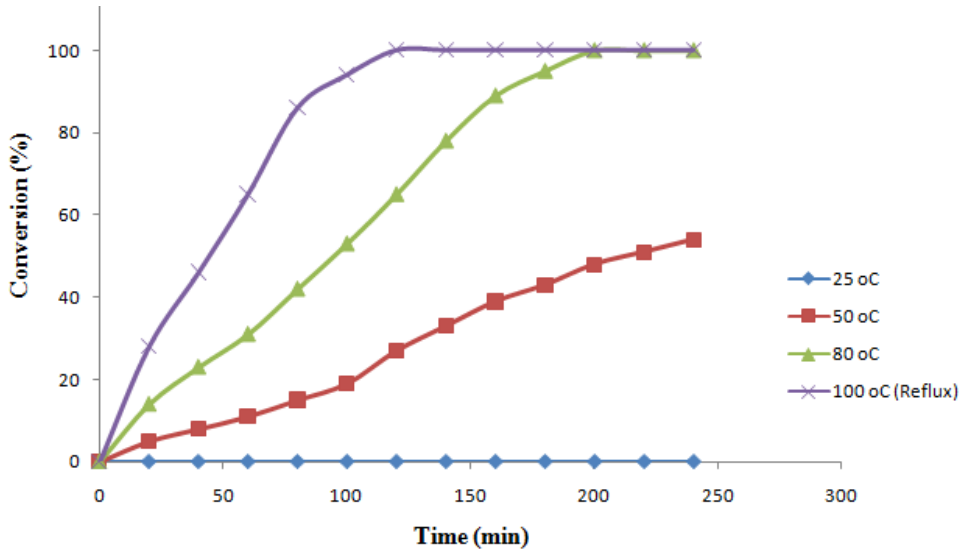


Fig. 3. Temperature effect on the synthesis of 2-amino-4,5-dihydro-5-oxo-4-phenylpyrano[3,2-c]chromene-3-carbonitrile.

Table 2. Synthesis of dihydropyrano[3,2-c]chromene deriviatives using MgO nano-plates as catalyst (Scheme 1)

Entry	Aldehyde	R	R'	Time (h)	Yield (%)[a]	m.p.(°C)		Ref.
						Found	Reported	
1	Benzaldehyde	H	H	2	85	255-257	256-258	[22]
2	4-Methylbenzaldehyde	H	H	3	77	255-257	259–260	[22]
3	4-Methoxybenzaldehyde	H	H	3	71	248-250	248-250	[23]
4	4-Chlorobenzaldehyde	H	H	2	84	259-261	252–255	[22]
5	2-Chlorobenzaldehyde	H	H	3	70	274-276	275-277	[17]
6	3-Nitrobenzaldehyde	H	H	1.5	86	262–264	262–264	[22]
7	4-Nitrobenzaldehyde	H	H	1.5	84	261-263	258–260	[22]
8	4-Hydroxybenzaldehyde	H	H	4	68	265-267	260–263	[22]
9	4-Bromobenzaldehyde	H	H	2	88	249-251	247–249	[22]
10	4-*N*,*N'*-Dimethyl amino benzaldehyde	H	H	4	72	225-227	224-225	[23]
11	furan-2-carbaldehyde	H	H	3	65	251-253	250-252	[23]
12	2,4-Dichlorobenzaldehyde	H	H	3	86	260-262	258-259	[23]
13	4-Fluorobenzaldehyde	H	H	2	80	261-263	262-263	[23]
14	Benzaldehyde	CH_3	H	3	85	249-251	-	-
15	Benzaldehyde	CH_3	CH_3	3	84	251-253	-	-
16	4-Methylbenzaldehyde	CH_3	CH_3	3	89	255-257	-	-
17	4-Chlorobenzaldehyde	CH_3	CH_3	2	94	271-273	-	-
18	3-Chlorobenzaldehyde	CH_3	CH_3	2	93	269-271	-	-
19	3,4-diMethoxybenzaldehyde	CH_3	CH_3	3.5	79	233-235	-	-

[a]Isolated yields. All known products have been reported previously in the literature and were characterized by comparison of NMR spectra with authentic samples [15-24].

The reactions worked well with almost all the aldehydes. However, aromatic aldehydes bearing electron withdrawing groups showed better reactivity and the reactions were completed in shorter time. As it is revealed from the literature [12-24], the condensation of aldehydes and malononitrile leads to the formation of benzylidenemalononitrile intermediate. Substitution of electron withdrawing groups on the aromatic ring decreases the activation energy for the subsequent Michel addition of 4-hydroxycoumarin to the benzylidenemalononitrile intermediate. No product was achieved when acetaldehyde as an aliphatic aldehyde was used.

Fig. 4 shows the conversion of 4-methylbenzaldehyde *versus* of the reaction time under the optimized conditions (catalyst: 0.5 mmol, H_2O, reflux). The condensation reaction of 4-hydroxycoumarin, 4-methylbenzaldehyde and malononitrile was followed by gas chromatography based on the disappearance of starting materials (4-methylbenzaldehyde). The products were collected periodically at a time interval of 20 min and analyzed by gas chromatography. The concentration of 4-methylbenzaldehyde decreases with time linearly (up to 80%) during the first reaction period of 1.5h. Then, the conversion slows down and approaches a plateau after a period of 1.5h.

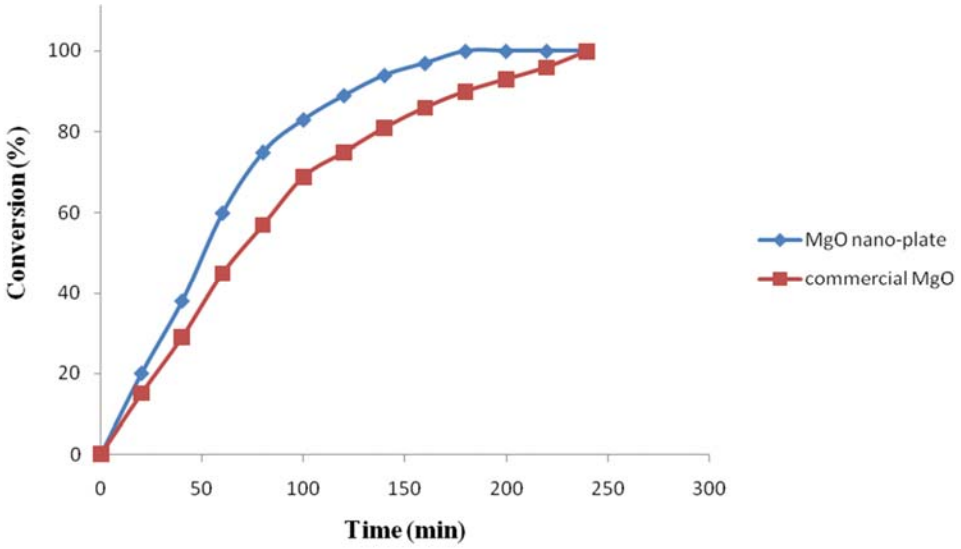


Fig. 4. Comparison of the catalytic activity of MgO nanoplate with commercial MgO.

In comparison the catalytic activity of MgO nano-plate (80% conversion after 1.5h) is higher than commercial MgO (69% conversion after 1.5h).

In order to show the efficacy of MgO nanoplates, a comparison was done with some Lewis acid catalysts for the synthesis of 2-amino-5-oxo-4-phenyl-4,5- dihydropyrano [3,2-c] chromene- 3- carbonitrile (Table 3). The reactions were done in the same condition as well as the optimized condition for MgO nanoplates. As Table 3 shows, MgO nanoplates uniquely enhanced the synthesis of the desired product in different terms (reaction time and isolated yield).

To investigate reusability of MgO nanoplates, it was separated easily from the reaction mixture and washed with EtOAc, dried in the air and then was activated in an oven at 80°C for 30 min. Finally, the recycled catalyst was reused for a further condensation reaction of 4-hydroxycoumarin, benzaldehyde and malononitrile. The results revealed that the catalyst could be reused for at least five runs (The yields were 85, 83, 84, 82 and 80%) without a significant loss of its catalytic activity.

In summary, a high yielding one-pot condensation reaction of 4-hydroxycoumarin, aromatic aldehydes and malononitrile for the synthesis of dihydropyrano[3,2-c]chromene deriviatives was developed. MgO nano-plates prepared *via* a green method have been used in catalytic quantities. Various aromatic aldehydes afforded the corresponding products in high yields. MgO can be recovered and reused for sequential batches of reactions without significant loss of the catalytic activity.

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Table 3. Comparison of the results of MgO nanoplates in the synthesis of 2-amino-4,5-dihydro-5-oxo-4-phenylpyrano [3,2-c]chromene-3-carbonitrile with some other Lewis acid catalysts.

Entry	Catalyst	Time (h)	Yield (%)[a]
1	MgO nanoplates	2	85
2	MgO commercial	2	79
3	ZnO	2	80
4	CaO	3	74
5	BaO	3	54
6	Fe_2O_3	4	49
7	Al_2O_3	4	68
8	Bi_2O_3	4	75
9	CeO_2	3	73
10	NiO	2.5	83
11	TiO_2	4	55
12	SnO	4	64
13	V_2O_5	4	45
14	SiO_2	4	20
15	PbO	4	35
16	CuO	3	78
17	ZrO_2	3	68

[a]Isolated Yields, reaction condition: catalyst (0.5 mmol), H_2O reflux.

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