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Rapid, efficient and eco-friendly synthesis of coumarin derivatives using MgO nanoparticles in [bmim]BF_4

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Abstract: In this study, coumarin derivatives were synthesized through one-pot reaction using MgO nanoparticles as a highly efficient reusable heterogeneous base catalyst in ionic liquid [bmim]BF_4. The advantages of this method include high yields, short reaction times, solvent-free and mild reaction condition, one-pot procedure, operational simplicity and use of inexpensive and non-toxic catalyst.

Keywords: Coumarin, MgO nanoparticles, Ionic liquid, Heterogeneous catalyst, Solvent-free, One-pot.

Introduction

Coumarin and its derivatives are widespread in nature and are very important organic compounds. These compounds have attracted much attention due to their wide range of biological and pharmacological activities [1]. Some biological properties such as molluscacidal, anthelmintic, and hypnotic activities and anticoagulant agent were reported for them. Coumarin derivatives also find applications in fragrance, agrochemical industries [2,3], food, cosmetics , optical brighteners, dispersed fluorescent and laser dyes [4]. So, the synthesis of coumarins and their derivatives is of increasing interest. Several routes have been reported for the synthesis of coumarins such as Pechmann [5], Perkin [6], Knoevenagel [7], Reformatsky [8] and Wittig [9] reactions.

Recently, metal oxides have been used as efficient heterogeneous catalysts in various organic reactions because of their stability in a variety of reaction conditions and non-toxicity [10, 11]. The efficiency of these heterogeneous catalysts can be improved by the use of nano-sized metal oxides because of their high surface area to volume ratio [12]. Magnesium oxide (MgO) is a low cost, easily available, and non-toxic material which has been widely used as a highly efficient heterogeneous catalyst in various organic transformations in ionic liquid [13]. Ionic Liquids (ILs) have been used as alternative green solvents in organic synthesis due to their ionic characteristic, different structure and unique properties which lead to specific effects [14,15]. In continuation of our interest in using ILs, water or solvent-free systems as green reaction media [16,17], we wish to report one-pot synthesis of coumarin derivatives in high to excellent yields in the presence of MgO nanoparticles as an efficient catalyst in [bmim]BF_4 as a green medium (Scheme **1**).

Results and discussion

The reaction between salicylaldeyde and diethylmalonate was chosen as a pilot reaction for the synthesis of coumarin **3f**. For this purpose salicylaldehyde (1 mmol) and diethylmalonate (1 mmol) was added to 3 cm^3 [bmim]BF_4 and mixed

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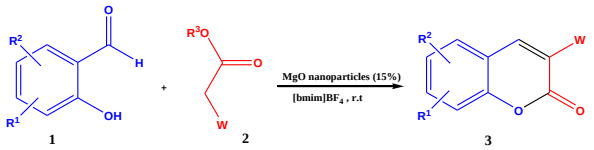
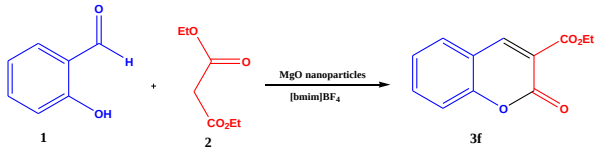
thoroughly at room temperature in the absence of catalyst for 2h. The reaction conditions were very mild and carried out in solvent-free system. The progress of the reaction was monitored by TLC. The work-up of the reaction mixture afforded the product **3f** in 15% yield (Table **1**, entry 1). Study of the procedure at higher temperatures showed that no significant changes were observed in the relative yield (Table **1**, entries 2). The result indicated that the catalyst should be absolutely necessary for the Knoevenagel reaction. In continuation of this work, the catalytic activity of MgO nanoparticles was examined. MgO nanoparticles were prepared according to the literature [18]. The reaction was complete in a shorter time and the yield was increased with the addition of catalyst MgO nanoparticles (Table **1**, entry 3). With the encouraging initial result, optimization of the reaction conditions was studied using various combinations of the reactants, MgO nanoparticles and ionic liquid. It was found that the best yield of the product was obtained using 1/1 molar ratios of salicylaldehyde/diethylmalonate in the presence of MgO nanoparticles (15 mol%). The recyclability and stability of catalyst were investigated under the optimized reaction condition. The results showed that the recovered catalyst could be satisfactorily used for the fifth run without the remarkable loss of catalytic activity (Table **2**). Furthermore, the scope of this methodology was extended by reaction of various salycilaldehydes **1** with active methylene compounds **2** under optimal conditions in this procedure (Table **3**).



Scheme 1: MgO nanoparticles catalyzed solvent-free synthesis of coumarins.

Table 1: Optimization of reaction conditions for the synthesis of **3a**.



Entry	**1**	**2**	Catalyst (mol%)	Temperature (°C)	Time (min)	Yield[a] (%)
1	1	1	-	27	120	15
2	1	1	-	70	120	15
3	1	1	10	27	60	80
4	1	1	10	70	60	85
5	1	1	15	27	25	92
6	1	1	20	27	25	92
7	1.5	1	15	27	25	92
8	1	1.5	15	27	25	90
9	1	1	15	70	25	90

[a]Isolated yields.

Table 2: The recyclability of the MgO nanoparticles catalyst for the synthesis of **3a** and **3i**.

Run	Product **3a** Yield[a] (%)	Productc **3i** Yield[a] (%)
1	90	80
2	90	80
3	88	79
4	87	75
5	85	77

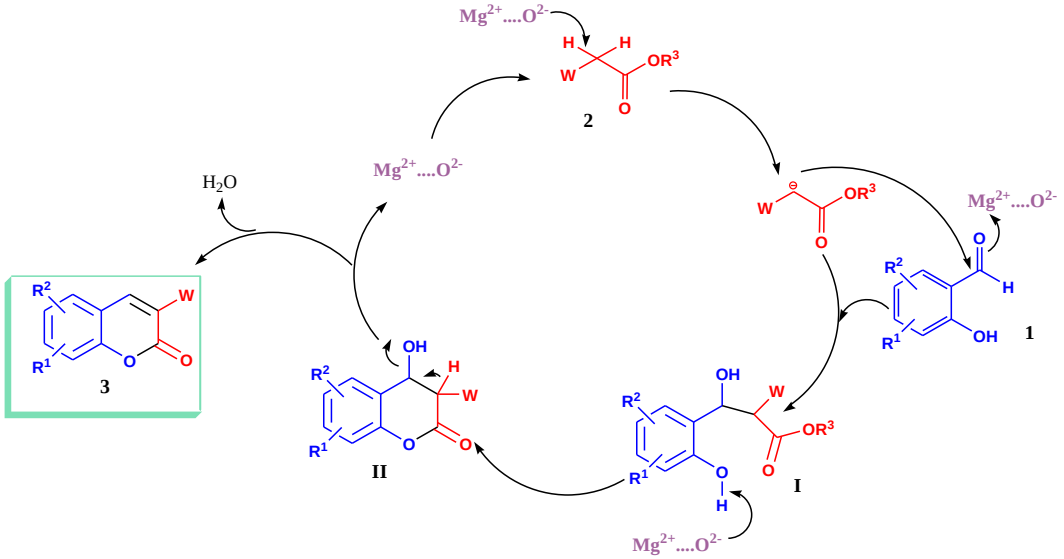
[a]Isolated yields.

Table 3: Facile synthesis of coumarins by the Knoevenagel condensation catalyzed by the MgO nanoparticles.

Entry	R^1	R^2	R^3	W	Product	Time (min)	Yield[a] (%)	Melting Point (°C)	
								Found	Reported [ref.]
1	H	H	Me	CN	**3a**	15	90	180-182	182-184 [21]
2	H	8-OMe	Me	CN	**3b**	18	87	226-227	224-225 [21]
3	H	6-Br	Me	CN	**3c**	20	83	199-201	200-201 [21]
4	7-OH	H	Me	CO_2Me	**3d**	25	85	265-267	265-267 [19]
5	7-OMe	H	Me	CO_2Me	**3e**	22	86	122-124	123-124 [20]
6	H	H	Et	CO_2Et	**3f**	25	92	95-96	94-97 [19]
7	8-OMe	H	Et	CO_2Et	**3g**	20	83	90-91	88-90 [21]
8	7-OMe	H	Et	CO_2Et	**3h**	20	87	133-135	132-133 [20]
9	7-OMe	8-Br	Et	CO_2Et	**3i**	30	80	190-193	189-190 [20]
10	7-NEt_2	H	Et	CO_2Et	**3j**	25	89	75-76	77-78 [21]

[a]Isolated yields.

A plausible mechanism for the formation of product **3** in the presence of MgO nanoparticles in ionic liquid is shown in Scheme **2**. At first, the methylene group of **2** is activated by MgO nanoparticles to nucleophilic attack on carbonyl group of salicylaldehyde. On the other hand, coordination of the carbonyl group of salicylaldehyde facilitates this attack that results intermediate **I**. Subsequently, intermediate **II** is formed by intramolecular cyclization. Following this, intermediate **II** is converted to product **3** by dehydration.



Scheme 2: Plausible mechanism for the synthesis of coumarins in the presence of MgO nanoparticles.

Conclusion

In conclusion, we have demonstrated that MgO nanoparticle is an effective catalyst for the Knoevenagel condensation for the synthesis of coumarin derivatives in green and mild reaction condition. The catalyst is easily available, non-toxic and low cost. Moreover, this methodology offers several advantages including high yields, operational simplicity, solvent-free and mild reaction conditions which make this method a useful and attractive process for the synthesis of these compounds.

Experimental

General Information:

All reagents were purchased from Merck and used without further purification. Infrared spectra were recorded in KBr and were determined on a Perkin Elmer FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance AC-400 MHz using $CDCl_3$ or DMSO-d_6 as the deuterated solvents and TMS as internal standard. All melting points are uncorrected and measured in open glass-capillaries using Stuart melting point apparatus.

General Procedure for Coumarins ***(3a-3j):***

Salicylaldehyde derivatives (2 mmol), active methylene compounds (2 mmol) and MgO nanoparticles (15 mol%) were added to [bmim]BF_4 (3 ml) and mixed thoroughly and stirred for the time as shown in Table **3**, at room temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/n-hexane: 1/3), the mixture was extracted with ethylacetate. Ethyl acetate was evaporated using a rotary evaporator and the crude mixture was purified by silica gel (Merck 230-240 mesh) column chromatography using (ethylacetate/n-hexane:1/5) as eluent to give pure coumarins (**3a-3j**).

2-Oxo-2H-chromene-3-carbonitrile (**3a**):

IR (KBr) (ν_{max}/cm^{-1}): 2231, 1713, 1647; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.34 (m, 2H), 7.55 (dd, *J* = 7.46, 1.62 Hz, 1H), 7.73 (dd, *J*= 7.54, 1.45 Hz, 1H), 8.31 (s, 1H);^{13}C-NMR (100MHz, DMSO-d_6) δ 103.5, 112.0, 117.5, 117.3, 128.1,128.5, 135.5, 152.1, 155.2, 156.8.

8-Hydroxy-2-oxo-2H-chromene-3-carbonitrile (**3b**):

IR (KBr) (ν_{max}/cm^{-1}): 3386 (broad), 2260, 1755, 1643; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.23–7.40 (m, 3H), 8.76 (s, 1H), 8.89 (s, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 105.5, 114.4, 115.3, 119.0, 128.1, 131.4, 136.9, 153.2, 157.1, 160.3.

6-Bromo-2-oxo-2H-chromene-3-carbonitrile (**3c**):

IR (KBr) (ν_{max}/cm^{-1}): 2323, 1752, 1648; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.18 (d, *J*= 7.36 Hz, 1H), 7.35 (dd, *J*= 7.36,1.96 Hz, 1H), 7.44 (d, *J*= 1.96 Hz,1H), 8.82 (s, 1H); ^{13}CNMR (100 MHz, DMSO-d_6) δ 105.5, 114.3, 116.0, 120.0, 128.6, 131.1, 138.7, 152.5, 157.9, 160.3.

Methyl 7-Hydroxy-2-oxo-2H-chromene-3-carboxylate (**3d**):

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.86 (s, 3H), 6.60 (d, *J*=1.8 Hz, 1H), 6.83 (dd, *J*= 8.11, 1.8 Hz, 1H), 7.55 (d, *J*= 8.11 Hz, 1H), 8.51 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 53.6, 110.1, 110.5, 112.1, 131.2, 134.8, 150.2, 150.5,154.7, 164.5, 166.9.

Methyl 7-Methoxy-2-oxo-2H-chromene-3-carboxylate (**3e**):

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.82 (s, 3H), 6.69 (d, *J*= 2.4 Hz,1H), 6.97 (dd, *J*= 8.5, 2.4 Hz, 1H), 7.50 (d, *J*= 8.5 Hz, 1H), 8.36 (s, 1H);^{13}CNMR (100 MHz, $CDCl_3$) δ 16.3, 62.7, 104.1, 115.5, 116.2, 116.8, 131.6, 148.8, 159.8, 161.4, 164.1, 164.9.

Ethyl 2-Oxo-2H-chromene-3-carboxylate (**3f**):

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (t, *J*= 7.22 Hz, 3H), 4.31 (q, *J*= 7.22 Hz, 2H), 6.80–7.50 (m, 4H), 8.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.19, 56.24, 104.2, 117.5, 118.1, 119.1, 133.6, 151.12, 152.0, 162.3, 163.3, 168.0.

Ethyl 8-Methoxy-2-oxo-2H-chromene-3-carboxylate (**3g**):

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, *J*= 7.15 Hz, 3H), 3.80 (s, 3H), 4.32 (q, *J*= 7.15 Hz, 2H), 7.22–7.33 (m, 2H), 7.29–7.39 (m, 1H), 8.32 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 56.3, 65.2, 106.1, 115.9, 116.0, 116.9, 134.2, 150.1, 158.9, 161.5, 164.4, 167.1.

Ethyl 7-Methoxy-2-oxo-2H-chromene-3-carboxylate (**3h**):

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, *J*= 7.25 Hz, 3H), 3.81 (s, 3H), 4.43 (q, *J*= 7.25 Hz, 2H), 6.81 (d, *J*= 2.5 Hz, 1H), 6.93 (dd, *J*= 8.7, 2.5 Hz, 1H),7.56 (d, *J*= 8.7 Hz, 1H), 8.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 55.5, 62.4, 103.0, 115.4, 116.5, 117.9, 133.7, 149.9, 160.5, 160.9, 164.5, 166.6.

Ethyl 8-bromo-7-hydroxy-2-oxo-2H-chromene-3-carboxylate (**3i**):

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34 (t, J= 7.35 Hz, 3H), 4.23 (q, *J*= 7.35 Hz, 2H), 6.75 (d, *J*= 8.27 Hz, 1H), 7.72 (d, *J*= 8.27 Hz, 1H), 8.62 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 17.7, 63.7, 110.9, 111.5, 112.5, 131.8, 132.3, 149.9, 151.9, 156.9, 164.4, 165.8.

Ethyl 7-Diethylamino-2-oxo-2H-chromene-3-carboxylate (**3j**):

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, *J*= 7.32 Hz, 3H), 3.83 (s, 3H), 4.32 (q, *J*= 7.32 Hz, 2H), 6.81 (d, *J*= 2.2 Hz, 1H), 6.88 (dd, *J*= 8.1, 2.2 Hz, 1H),7.50 (d, *J*= 8.1 Hz, 1H), 8.51 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 19.0, 52.1, 61.0, 102.6, 115.2, 116.1, 118.5, 134.0, 148.0, 159.1, 169.0, 165.5, 166.8.

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