Indian Journal of Fundamental and Applied Life Sciences ISSN: 2231– 6345 (Online)
An Open Access, Online International Journal Available at www.cibtech.org/sp.ed/jls/2015/01/jls.htm
2015 Vol.5 (S1), pp. 5288-5293/Dehghan and Shams
Review Article

MgO NANOPARTICLES CATALYZED SIMPLE AND EFFICIENT SYNTHESIS OF BENZYLAMINO COUMARINE DERIVATIVES UNDER IN AQUEOUS MEDIA

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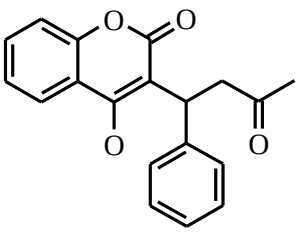
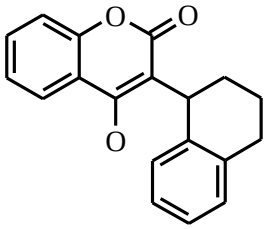
ABSTRACT
An efficient one-pot synthesis of benzylamino coumarin derivatives via a three-component condensation of 4-hydroxycoumarin, cyclic secondary amine, and aromatic aldehyde in the presence of magnesium oxide nanoparticles as a heterogeneous catalyst in water as a green solvent at room temperature.

Keywords: *One-pot Synthesis, Benzylamino Coumarin Derivatives, MgO Nanoparticles, Green Synthesis*

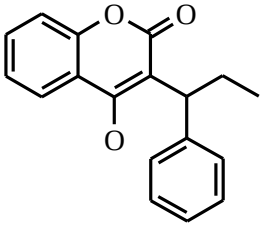
INTRODUCTION
Modern synthetic design demands high efficiency in terms of minimization of synthetic steps together with maximization of complexity (Trost, 1991). One of the ways to fulfill these goals is the development and use of multicomponent reactions which consist of several simultaneous bond-forming reactions and allow the high efficient synthesis of complex molecules starting from simple substrates in a one-pot manner (Bienayme *et al.,* 2000). The synthesis of coumarins and their derivatives has attracted considerable attention from organic and medicinal chemists for many years as a large number of natural products contain this heterocyclic nucleus. They are widely used as additives in food, perfumes, cosmetics, pharmaceuticals (O'Kennedy and Thornes, 1997) and optical brighteners (Zabradnik, 1992) and dispersed fluorescent and laser dyes (Murray *et al.,* 1982). Among the various substituted coumarins, 3-(benzyl)-substituted 4-hydroxycoumarins represents a significant class of compounds as biologically active compounds (Figure 1), (Raj *et al.,* 1994; Hadler and Shadbolt, 1975) and useful scaffolds, which can be used for the synthesis of 3,4-substituted compounds (Estevez-Braun and Gonzalez, 1997; Clerici and Porta, 1993; Mizuno *et al.,* 1988; Wang *et al.,* 1996). The existing methods for the synthesis of 3-substituted 4-hydroxycoumarins include direct synthesis of the target compound (Dittmer, 2005; Kalinin and Snieckus, 1998; Kalinin *et al.,* 1998; *Davis et al.,* 1997) or C3-alkylation/substitution of 4-hydroxycoumarin (Reddy *et al.,* 2008).



Warfarin



Coumatetralyl

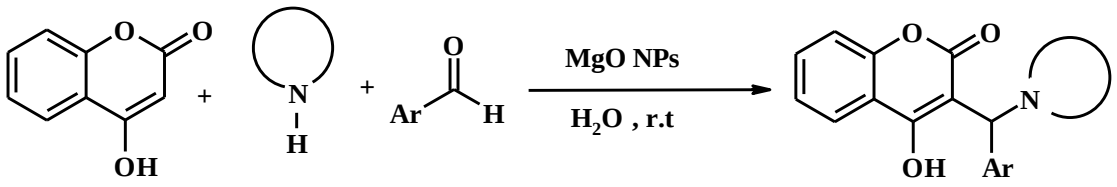


Phenprocoumon

Figure 1

Recently, development of nano catalysts has emerged as a fertile field for research and innovation. In particular, nanocrystalline oxides have proven useful to chemists in the laboratory and industry due to the efficient activation of the adsorbed compounds and reaction rate enhancement, selectivity, easier work-up and recyclability of the supported catalysts and the eco-friendly green reaction conditions

(Yin, 2004; Drexler and Amiridis, 2002; Mehrabi and Kazemi-Mireki, 2011) The surface of metal oxides, such as TiO_2, Al_2O_3, ZnO, CuO and MgO, exhibits both Lewis acid and Lewis base character (Tanabe, 1970). They are excellent adsorbents for a wide variety of organic compounds and increase the reactivity of the reactants. In any metal oxide, surface atoms make a distinct contribution to its catalyst activity. In powder particles, the number of surface atoms is a large fraction of the total. The high surface area to volume ratio of metal oxide nanoparticles is mainly responsible for their catalytic properties (Bell, 2003). High yield, selectivity and recycla- bility have been reported for a variety of nanocatalyst-based organic reactions (Satyanarayana *et al.,* 2012). Nano magnesium oxide is certainly one of the most interesting metal oxides, because it has surface properties, which suggest that a very rich organic chemistry may occur there (Kabashima *et al.*, 1997). Herein we wish to uncover another significant catalytic activity of MgO nanoparticles (NPs), for the one pot three-component reaction between of 4-hydroxycoumarin **1**, secondary amine **2** and aromatic aldehyde **3** in aqueous media (Scheme1).



1 **2** **3** **4**

(Scheme 1)

Table 1: Optimization of the reaction conditions for the synthesis of 4a

Entry	(Catalyst)(mol %)	Solvent	Temp(^{0}C)	Time (mins)	Yield[b](%)
1	Non	H_2O	RT	360	trace
2	Al_2O_3 NPs (10)	H_2O	RT	240	36
3	NiO NPs (10)	H_2O	RT	240	34
4	ZrO_2 NPs (10)	H_2O	RT	240	36
5	Bulk MgO (15)	H_2O	Reflux	180	58
6	MgO NPs (5)	H_2O	RT	120	70
7	MgO NPs (10)	H_2O	RT	120	82
8	MgO NPs (15)	H_2O	RT	120	92
9	MgO NPs (20)	H_2O	RT	120	90
10	MgO NPs (15)	H_2O	Reflux	120	92
11	MgO NPs (15)	EtOH	RT	120	85
12	MgO NPs (15)	THF	RT	120	80

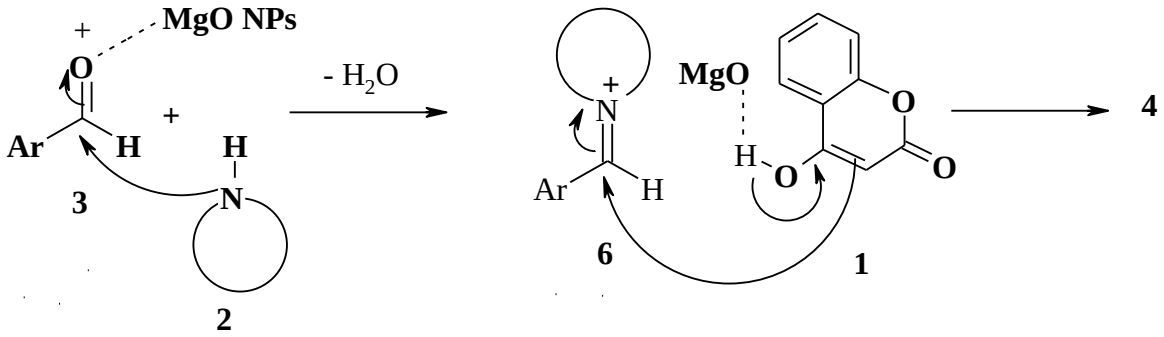
[a] Reaction conditions: 4-hydroxy coumarin (1.0 mmol), Piperidine (1 mmol) ,4-bromo benzaldehyde (1.0 mmol).
[b] Isolated yield

First, to find optimal conditions, the reaction of 4-Bromobenzaldehyde (1 mmol), 4-hydroxycoumarin (1 mmol) and piperidine (1 mmol) in the presence of the MgO nanoparticles as the catalyst was selected. The model reaction was carried out under various reaction conditions, and the results are summarized in Table 1. According to the obtained data, using the MgO nanoparticles (NPs), in solvent H_2O at room temperature is the best condition for the benzylamino coumarin formation.
When MgO NPs was used, the reaction was completed after 2 h (the reaction progress was monitored by TLC) and 3-((4-bromophenyl)(piperidin-1-yl)methyl)-4-hydroxy-2H-chromen-2-one (**4a**) was obtained in 92% yield (Table 1, entry 8). Moreover, we found that the yields were obviously affected by the loading of MgO NPs. When 5 mol %, 10 mol %, 15mol %, and 20 mol % of MgO NPs were used, the yields were 70%, 82%, 92%, and 90%, respectively (Table 1, entries 6–9). Therefore, 15 mol % of MgO NPs was sufficient and a larger excess of catalyst did not increase the yields significantly (Table 1, entry 8). In addition, no product was detected in the absence of the catalyst.
Furthermore, it was found that refluxing all the components in presence of 15 mol% of MgO NPs in water not improve the yields. The effect of the solvent was also studied. It was observed that using water as the reaction solvent, the reaction time becomes shorter and the yield higher.
To study the scope of the reaction, a series of aldehydes and amides were employed. The results are shown in Table 2. In all cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in good yields (Table 2). Compounds **4a-b** was new and their structures were deduced by elemental and spectral analysis. But compounds **4a-i** was known and their structures were deduced by comparison of melting points and spectral data with authentic sample (Rao *et al.*, 2012; Kumar *et al.*, 2011).

Table 2: Three-component reaction of aromatic aldehydes, 4-hydroxycoumarin and secondary amine catalyzed by MgO NPs

Entry	Ar	Amine	Time(min)	Yield %	mp (°C)[lit]
4a	4-Br-C_6H_4	Piperidine	120	92	184-186
4b	4-CH_3O-C_6H_4	Piperidine	135	89	145
4c	4-NO_2-C_6H_4	Piperidine	125	88	183(180-182)[24]
4d	4-Cl-C_6H_4	Piperidine	120	90	188(188-190)[25]
4e	C_6H_5	Piperidine	120	86	182(182-184)[25]
4f	4-ClC_6H_5	Pyrolidine	120	90	179(176-178)[24,25]
4g	2-$O_2NC_6H_4$	Pyrolidine	125	89	184(182-185)[24,25]
4h	C_6H_5	Pyrolidine	120	82	172(172-174)[24,25]
4i	4-CH_3O-C_6H_4	Pyrolidine	125	88	142(140)[25]
4j	4-CH_3-C_6H_4	Pyrolidine	125	86	185(180-182)[24]
4k	3-O_2N-C_6H_4	Pyrolidine	125	87	189(188-190)[25]

According to both Lewis acid and Lewis base character of MgO. Reasonable possibility mechanism of the reaction is represented in Scheme 2. In which imine intermediate **6** formed by the reaction of aldehyde and secondary amine. Subsequent nucleophilic addition of 4-hydroxy coumarin **1** to this intermediate **6** afford the formation of product **4**.



Scheme 2: Suggested pathway for the formation of compounds 4a-j

The reusability of the catalyst was tested in the synthesis of 3-((4-bromophenyl)(piperidin-1-yl)methyl)-4-hydroxy-2H-chromen-2-one, as shown in Figure 2. The catalyst was recovered after each run, washed with ethanol, dried in an oven at 100 ^{o}C for 15 min prior to use and tested for its activity in the subsequent run. The catalyst was tested for 4 runs. It was seen that the catalyst displayed very good reusability (Figure 2).

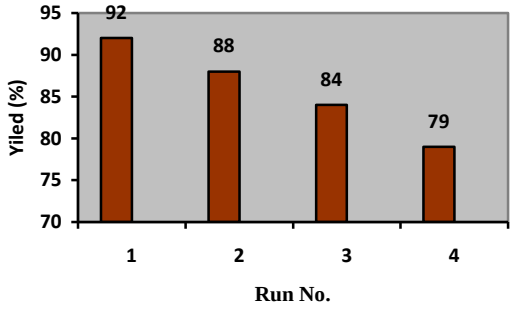


Figure 2: Reusability of the catalyst

Experimental

Melting points were determined with an electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-400 Avance spectrometer at solution in $CDCl_3$ or d_6-DMSO using TMS as internal standard. The chemicals used in this work purchased from fluka (Buchs, Switzerland) and were used without further purification.

General Experimental Procedure

A mixture of aromatic aldehyde (1.0 mmol), secondary amine (1.0 mmol), and nano- MgO (15 mol %) in water (15ml) was added 4-hydroxy coumarin (1.0 mmol) and the reaction mixture was vigorously stirred at room temperature for 120-135 min, after completion of the reaction as indicated by TLC, the reaction mixture was extracted with ethyl acetate (3*10ml). The extract was then centrifuged to separate the nanocatalyst. Upon concentrating the extract under reduced pressure, crude product was obtained which was finally purified by recrystallisation from ethanol.

*3-((4-bromophenyl)(piperidin-1-yl)methyl)-4-hydroxy-2H-chromen-2-one***(4a):**

white powder, Yield: 92%; mp 184-186°C, IR (KBr) (ν_{max}, cm^{-1}): 3010(OH), 1667(C=O). Analyses: Calcd. for $C_{21}H_{20}BrNO_3$: C, 60.88; H, 4.87; N, 3.38; Found: C, 60.25; H, 4.78; N, 3.19%. ^{1}H NMR (400 MH_Z, $CDCl_3$): δ = 1.70-1.88 (m, 6H, $3CH_2$) , 3.27 (br, 4H, $2CH_2$), 6.08 (s, 1H,CH), 7.14-8.68 (m, 8H of aromatic) ppm; ^{13}C NMR (100 MH_Z, $CDCl_3$): δ = 22.31, 22.87,45.37 ($3CH_2$), 73.15 (CH), 103.01, 115.69, 119.47, 120.16, 123.71, 125.44, 128.58, 131.26, 131.57, 152.73, 168.15(aromatic carbons), 171.67(C=O) ppm.

*4-Hydroxy-3-[(4-methoxy-phenyl)-piperidin-1-yl-methyl]-chromen-2-one***(4b):**
white powder, Yield: 89%; mp 145°C, IR (KBr) (ν_{max}, cm^{-1}): 3035(O-H), 1691(C=O). Analyses: Calcd. for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83; Found: C, 72.22; H, 6.51; N, 3.79%. ^1H NMR (400 MH_Z, $CDCl_3$): δ = 1.60-1.78(m, 6H,$3CH_2$) , 3.22-3.26(m, 4H,$2CH_2$), 3.76-3.79 (br, 3H,OCH_3) 6.17(s, 1H,CH), 6.77-8.11(m, 8H of aromatic) ppm; ^{13}C NMR (100 MH_Z, $CDCl_3$): δ = 22.22, 22.62, 36.12, 45.33 ($3CH_2$,OCH_3), 70.32 (CH), 103.66, 113.67, 115.58, 120.35, 123.57, 125.32, 127.65, 131.30, 132.17, 152.73, 157.60, 168.14(aromatic carbons), 171.23(C=O) ppm.

CONCLUSION

In conclusion, we have proposed an efficient one-pot procedure for the synthesis of benzylamino coumarin derivatives by the three-component coupling of 4-hydroxycoumarin, cyclic secondary amine, and aromatic aldehyde over MgO nanoparticle catalyst in water as a green reaction medium. The attractive features of this protocol are simple procedure, cleaner reaction, use of reusable, nontoxic and inexpensive heterogeneous nano catalyst.

ACKNOWLEDGEMENT

We gratefully acknowledge financial support from the Research Council of the Islamic Azad University of Yazd

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