



An Efficient Synthesis of Functionalized 3-(α -amidobenzyl)-4-hydroxycoumarin Derivatives by ZnO Nanoparticles Promoted Condensation Reaction Between Aromatic Aldehyde, 4-hydroxycoumarin, and Amides

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ABSTRACT

An efficient and green protocol for the synthesis of 3-(α -amidobenzyl)-4-hydroxycoumarin derivatives by one pot, three component coupling reaction of aromatic aldehyde, 4-hydroxycoumarin, and amides has been developed using ZnO nanoparticles (NPs) as the catalyst. The procedure is formed in high yields, short reaction time and an environmentally friendly specificity.

Key words: 4-Hydroxycoumarin, ZnO nanoparticles (NPs), 3-(α -amidobenzyl)-4-hydroxycoumarins, aromatic aldehydes

INTRODUCTION

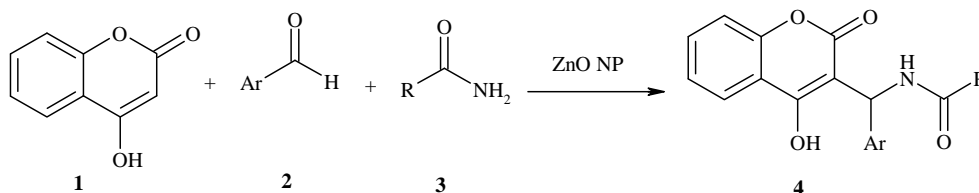
Multi-component reactions have been attracting much interest from synthetic chemists because they provide simple one-pot routes for the synthesis of complex molecules from simple and easily available starting materials. These processes are single-step and don't require separation and purification of intermediates and so save time, energy and raw materials¹. Recently, heterogeneous catalysts have attracted the

attention of researchers due to their economic and industrial significance and published reports indicate that they scored over homogeneous catalysts. Among these, nanoscale heterogeneous catalysts are highly preferred as they offer high surface area and low-coordinated sites, which are responsible for the higher catalytic activity²⁻⁴, having the advantage of easy product purification and reusability of the catalyst. The synthesis of coumarins and their derivatives has attracted considerable attention from organic and medicinal

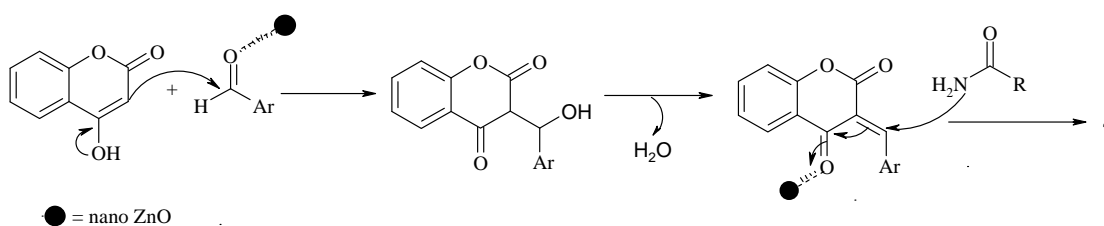
chemists for many years as a large number of natural products contain this heterocyclic nucleus. They are widely used as additives in food, perfumes, cosmetics, pharmaceuticals⁵ and optical brighteners⁶ and dispersed fluorescent and laser dyes⁷. Among the various substituted coumarins, 3-(benzyl)-substituted 4-hydroxycoumarins represents a significant class of compounds as biologically active compounds,^{8,9} (Fig. 1) and useful scaffolds, which can be used for the synthesis of 3,4-substituted compounds.¹⁰⁻¹³ The existing methods for the synthesis of 3-substituted 4-hydroxycoumarins include direct synthesis of the target compound¹⁴⁻¹⁷, or C3-alkylation/substitution of 4-hydroxycoumarin.¹⁸ Recently, we reported the reaction of 4-hydroxycoumarin, aromatic aldehydes, and acetonitrile in the presence of chlorosulfonic acid to produce 3-acetamido-alkyl-4-hydroxycoumarin derivatives.^{19,20} also we reported the reaction of 4-hydroxycoumarin, aromatic

aldehydes and amides in the presence *p*-toluene sulfonic acid in solvent-free conditions to produce 3-(α -amidobenzyl)-4-hydroxycoumarin derivatives²¹ but these methodologies have been associated with some shortcomings such as long reaction times, and difficulty in recovery and reusability of the catalysts. One of the best ways to overcome these difficulties is to employ heterogeneous catalysis, as it enables a convenient recovery and reuse of the catalyst from the reaction mixture through simple filtration or decantation.²²⁻²⁴

Considering the above reports and in continuation of our research on multi-component reactions,^{25,26} Herein we have researched for three-component coupling of 4-hydroxycoumarin 1, aryl aldehydes 2, and amides 3, in the presence of ZnO nanoparticles as heterogeneous catalyst to the synthesis of 3-(α -amidobenzyl)-4-hydroxycoumarin derivatives 4 (Scheme 1).



Scheme 1:



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

RESULTS AND DISCUSSION

Firstly, in order to optimize the reaction conditions, the model reaction was carried out by using 4-hydroxycoumarin, 4-chlorobenzaldehyde, and acetamide under solvent-free conditions in the presence of different nanoparticle as catalysts and the results are listed in Table 1.

We examined this reaction in the presence of various nanoparticle catalysts in hand including

Fe₃O₄ nanoparticles, MgO nanoparticles, NiO nanoparticles, ZnO nanoparticles (Table 1). It was showed that ZnO nanoparticle was the most efficient catalyst for the reaction in Solvent-Free condition (Table 1, entry 6). However, only a trace amount of the product was formed in the absence of catalyst (Table 1, entry 1).

Afterward, optimization of catalyst amounts was carried out in the model study by using different amounts of the ZnO NPs. The higher yield was

obtained with increasing the amount of catalyst from 5 mol% to 15 mol%. However, further increase of the molar amount of the catalyst from 15 mol% to 25 mol% did not significantly increase the yield of the product (Figure 2). Hence, the optimum concentration of ZnO NPs was chosen 15 mol% in the model reaction.

To improve the yield of the target product, we carried out the test reaction in presence of various solvents and the results are presented in Table 2. As can be seen from this table, solvent-free conditions accelerated the rate of reaction and also high yields were obtained for all products.

To study the scope of the reaction, a series of aldehydes and amides were employed. The results are shown in Table 3. 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. It could also be concluded that the aldehydes bearing electron-withdrawing groups required shorter time and gave higher yields (Table 3). Compounds **4a-j** were known and their structures were deduced by comparison of melting points and spectral data with authentic samples.¹⁹⁻²¹

Although it is not clear how ZnO acts as a

Table 1. Optimization of the nanoparticles catalysed model reaction for synthesis of 3-acetamido-4-chlorophenyl-4-hydroxycoumarin under solvent-free condition^a

Entry	Catalyst	Catalyst (mol%)	Time(h)	Yield ^b (%)
1	Non	15	7	trace
2	NiO	15	5	30
3	Fe ₃ O ₄	15	5	40
4	MgO	15	5	45
5	ZnO bulk	15	5	50
6	ZnO	15	2	90

^a Reaction conditions: 4-hydroxy coumarin (1.0 mmol), acetamide (1.1 mmol), 4-chlorobenzaldehyde (1.0 mmol), neat 110 °C.

^b Isolated yield

Table 2. Solvent effect on the reaction between 4-hydroxycoumarin (1eq), 4-chlorobenzaldehyde (1 eq) and acetamide(1 eq) catalyzed by ZnO(15mol%)

Entry	Solvent	Temp(°C)	Time(h)	Yield(%)
1	Ethanol	Reflux	5	50
2	Dichloromethane	Reflux	5	52
3	1,2 Dichloroethane	Reflux	5	50
4	THF	Reflux	5	65
5	Toluene	Reflux	5	60
6	Solvent-free condition	110	2	90

Table 3. Three-component reaction of aromatic aldehydes, 4-hydroxycoumarin and amides catalyzed by ZnO NP

Entry	R	Ar	Time(min)	Yield(%)	mp (°C) ²⁴
4a	CH ₃	4-Cl-C ₆ H ₄	120	90	177-179(175-177) ¹⁵⁻²⁰
4b	CH ₃	2-Cl-C ₆ H ₄	120	90	209(208-210) ¹⁵⁻²⁰
4c	CH ₃	4-Br-C ₆ H ₄	125	89	174(172-174) ¹⁵⁻²⁰
4d	CH ₃	C ₆ H ₅	130	85	183(184-186) ¹⁵⁻²⁰
4e	CH ₃	4-NO ₂ -C ₆ H ₄	125	90	179-183(179-182) ¹⁵⁻²⁰
4f	CH ₃	3-NO ₂ -C ₆ H ₄	125	86	193-195(195-196) ¹⁵⁻²⁰
4g	CH ₃	3-CH ₃ O-C ₆ H ₄	135	80	202-204(203-206) ¹⁵⁻²⁰
4h	CH ₃	2-CH ₃ O-C ₆ H ₄	135	76	192(190-191) ¹⁵⁻²⁰
4i	CH ₃	2-HO-C ₆ H ₄	120	85	146-147(146-148) ¹⁵⁻²⁰
4j	C ₂ H ₅	C ₆ H ₅	120	80	185(184-186) ²¹

catalyst for the reaction, on the basis of the surface of metal oxides exhibit both Lewis acid and Lewis base character²⁷ and according to the literature survey,²⁸⁻³⁰ the suggested mechanism for the formation of the products is shown in Scheme 2. The reaction of 4-hydroxycoumarin with aromatic aldehydes in the presence of ZnO NPs catalyst is proposed to give 3-benzylidene-chroman-2,4-diones. These 3-benzylidene-chroman-2,4-diones, generated in situ, react with amide to form the 3-acetamido -alkyl-4-hydroxycoumarin products (Scheme 2).

The reusability of the catalyst was tested in the synthesis of 3-(α -amidobenzyl)-4-hydroxycoumarin, as shown in Figure 2. The catalyst was recovered after each run, washed with ethanol,

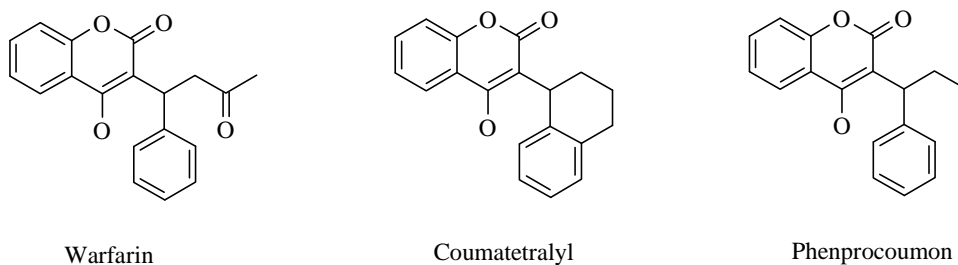
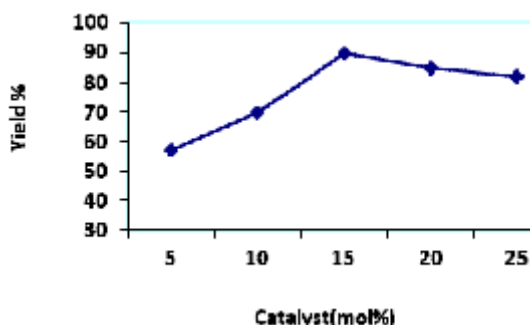
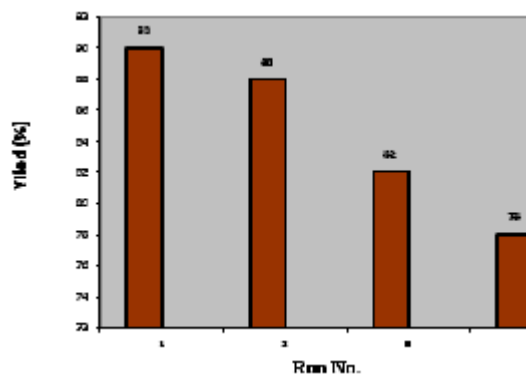


Fig. 1.

**Fig. 2: Influence of the amount of the catalyst on the model reaction**

dried in an oven at 100 °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 3). (Figure 3)

**Fig. 3: 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. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^1H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at in $\text{DMSO-}d_6$ solution using TMS as internal standard. The chemicals used in this work purchased from fluka (Buchs, Switzerland) and were used without further purification.

Synthesis of nano-ZnO

Zinc oxide nanoparticles was prepared as previously described in the literature ³¹. In a typical procedure, zinc acetate (9.10 g, 0.05 mol) and oxalic acid (5.4 g, 0.06 mol) were combined by grinding in an agate mortar for 1 h at room temperature. Afterwards, the formed $\text{ZnC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$ nanoparticles were calcinated at 450 °C for 30 min to produce ZnO nanoparticles under thermal decomposition conditions. The morphology, structure and size of the samples were investigated by Scanning Electron Microscopy (SEM). Fig. 4 indicates that the original morphology of the particle was approximately spherical with the diameter varying between 20 and 35 nm.

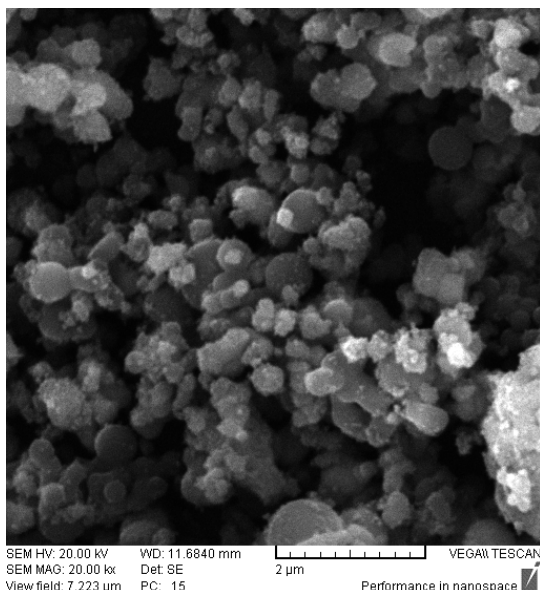


Fig. 4: SEM image of synthesized ZnO nanoparticles

General procedure

A mixture of 4-hydroxycoumarin (1.0 mmol), aromatic aldehyde (1.0 mmol), amide (1.0 mmol), and nano-ZnO (15 mol %) was heated at 110 °C for 120-135 min. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature. The solid residue was dissolved in hot ethanol and centrifuged to separate the catalyst. By recrystallization from ethanol, pure products were obtained.

N-[(4-Hydroxy-2-oxo-2H-chromen-3-yl)phenylmethyl propionamide (**4j**). white powder, m.p. 184 - 186°C, IR (KBr) (ν_{max} cm^{-1}): 3320 (NH), 1674, 1629 (2 C=O). Analyses: Calcd. for $\text{C}_{19}\text{H}_{17}\text{NO}_4$: C, 70.58; H, 5.30; N, 4.33%. Found: C, 70.71; H, 5.22; N, 4.35%. MS (m/z, %): 323 (10). ^1H NMR (500 MHz, d_6 -DMSO): δ = 0.91 (t, J_{HH} = 7.6 H_z , 3 H, CH_3), 2.27 (q, J_{HH} = 7.6 H_z , 2 H, CH_2), 6.58 (1 H, d, J_{HH} = 8.8 Hz, CH), 7.20 (1 H, t, J_{HH} = 7 Hz, CH of C_6H_5), 7.26-7.31 (4 H, m, 4 CH of C_6H_5), 7.36-7.41 (2 H, m, 2 CH of coumarin moiety), 7.65 (1 H, t, J_{HH} = 8 Hz, CH of coumarin moiety), 8.05 (1 H, d, J_{HH} = 8 Hz, CH of coumarin moiety), 8.38 (1 H, d, J_{HH} = 8.8 Hz, NH), 10.15 (1 H, broad, OH). ^{13}C NMR (125.8 MHz, d_6 -DMSO): δ = 10.16 (CH_3), 28.69 (CH_2), 47.39 (CH), 106.69, 116.62, 116.77, 124.29, 124.50, 126.98, 152.82, 161.99, and 162.30 (carbons of coumarin moiety), 126.49, 128.17, 132.87 and 141.07 (carbons of C_6H_5), 174.21 (NC=O).

CONCLUSION

In summary, we have described a simple, efficient, and environmentally benign one-pot procedure for the synthesis of 3-(α -amidobenzyl)-4-hydroxycoumarin derivatives by using catalytic amount of ZnO-NPs under solvent-free conditions. The advantages of the reported method are inexpensive and easily available starting materials, simple reaction conditions, low loading of catalyst, safety and reusability of catalyst, high yields, single-product reaction and simple workup procedure.

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