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An Efficient Synthesis of Benzylamino Coumarin Derivatives via Three-component Coupling of 4-hydroxycoumarin, Aromatic Aldehyde and Cyclic Secondary Amine Catalyzed by CuO Nanoparticles

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Abstract

A green and efficient one-pot synthesis of benzylamino coumarin derivatives was conducted by a three-component condensation of 4-hydroxycoumarin, cyclic secondary amine, and aromatic aldehyde in the presence of CuO nanoparticles (NPs) as a heterogeneous catalyst in water at room temperature.

Keywords: *multicomponent reaction, 3-benzyl substituted coumarin derivative, CuO nanoparticles (NPs), green synthesis.*

Introduction

Multicomponent reactions (MCRs) typically involve more than two reactants to combine in a sequential manner giving highly selective products while retaining majority of the atoms in the starting material. MCRs have received a considerable attention because of their wide range of applications in pharmaceutical chemistry for the creation of structural diversity and combinatorial libraries for drug discovery [1-3]. Coumarin and its derivatives are an important class of heterocyclic compounds, which constitute the key core of various natural products [4,5]. They exhibit a wide range of biological activities such as anti-HIV, antimalarial, insecticidal, and antioxidant properties [6, 7]. Most significant are 3-substituted-4-hydroxy coumarin derivatives which have important clinical applications [8-10] (Scheme 1).

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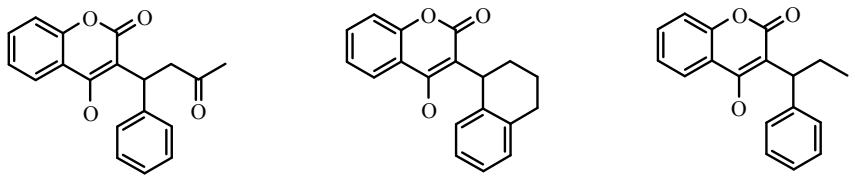


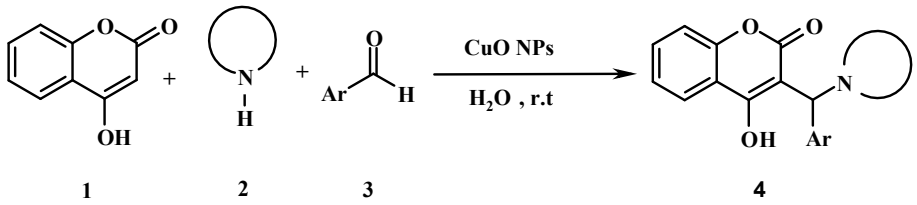
Warfarin Coumatetralyl Phenprocoumon

Scheme 1. 3-substituted-4-hydroxy coumarin derivatives

Recently, the application of nanoparticles (NPs) as catalysts has attracted worldwide attention because of their high catalytic activity and improved selectivity [11]. The surface of metal oxides, such as TiO_2, Al_2O_3, ZnO, CuO and MgO, exhibits both Lewis acid and Lewis base character [12]. 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 [13]. High yield, selectivity and recycla- bility have been reported for a variety of nanocatalyst-based organic reactions [14]. Nano copper oxide certainly one of the most interesting metal oxides, because it has surface properties, which suggest that a very rich organic chemistry may occur there [15-17]. Herein we wish to uncover another significant catalytic activity of CuO nanoparticles (NPs), for the one pot three-component coupling reaction of 4-hydroxycoumarin with an aromatic aldehyde and a secondary amine (Scheme 2) in aqueous media.

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 13C NMR spectra were recorded on Bruker DRX-400 Avance spectrometer at solution in CDCl3using TMS as internal standard. The chemicals used in this work purchased from fluka (Buchs, Switzerland) and were used without further purification.



Scheme 2. Synthesis of benzylamino coumarin derivatives catalysed by CuO nanoparticles (NPs) at room temperature.

Initially, in order to optimize the reaction conditions, the model reaction was carried out by using 4-Bromobenzaldehyde, 4-hydroxycoumarin, and piperidine in solvent H_2O at room temperature in the presence of different nanoparticle as catalysts and the results are listed in Table 1 (Scheme 2).

Table 1. Optimization of the nanoparticles catalysed model reaction for synthesis of benzylamino coumarin derivatives in aqueous media.[a]

Entry	Catalyst	Catalyst (mol%)	Time(h)	Yield[b] (%)
1	Non	15	5	trace
2	NiO	15	5	30
3	Fe_3O_4	15	5	40
4	MgO	15	5	45
5	ZnO bulk	15	5	50
6	ZnO	15	4	92

[a] Reaction conditions: 4-hydroxy coumarin (1.0 mmol), 4-Bromobenzaldeyde (1.0 mmol), piperidine (1.0 mmol), room temperature
[b] Isolated yield

We examined this reaction in the presence of various nanoparticle catalysts in hand including Fe_3O_4 nanoparticles, MgO nanoparticles, NiO nanoparticles, CuO nanoparticles (Table 1). It was showed that CuO nanoparticle was the most efficient catalyst for the reaction in aqueous media (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 CUO NPs. The higher yield was obtained with increasing the amount of catalyst from 5 mol% to 20 mol%. However, further increase of the molar amount of the catalyst from 20 mol% to 30 mol% did not significantly increase the yield of the product (Figure 1). Hence, the optimum concentration of CuO NPs was chosen 20 mol% in the model reaction.

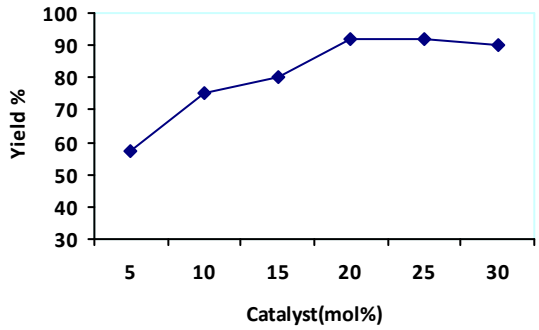


Figure 1. Influence of the amount of the catalyst on the model reaction.

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, using water as the reaction solvent, the reaction time becomes shorter and the yield higher. Furthermore, it was found that refluxing all the components in presence of 20 mol% of CuO NPs in water not improve the yields.

Table 2. Solvent effect on the reaction between 4-hydroxycoumarin (1eq), 4-Bromobenzaldehyde (1 eq) and piperidine (1 eq) catalyzed by CuO (20mol%).

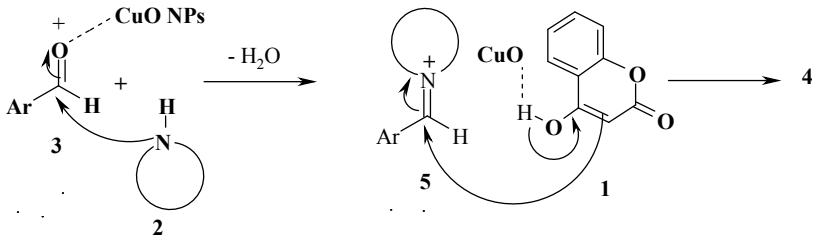
Entry	Solvent	Temp(^{0}C)	Time(h)	Yield(%)
1	Ethanol	room temp	5	65
2	Methanol	room temp	5	60
3	THF	room temp	5	55
4	Toluene	room temp	5	50
5	H_2O	room temp	4	92
6	Solvent- free	110	3	45

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 (Table 3). Compounds **4a-b** were new and their structures were deduced by elemental and spectral analysis. but compounds **4a-i** were known and their structures were deduced by comparison of melting points and spectral data with authentic samples [18,19].

Table 3. Synthesis of benzylamino coumarins over of CuO NPs catalyst.

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)[18]
4d	4-Cl-C_6H_4	Piperidine	120	90	188(188-190)[19]
4e	C_6H_5	Piperidine	120	86	182(182-184)[19]
4f	4-ClC_6H_5	Pyrolidine	120	90	179(176-178)[18,19]
4g	2-$O_2NC_6H_4$	Pyrolidine	125	89	184(182-185)[18,19]
4h	C_6H_5	Pyrolidine	120	82	172(172-174)[18,19]
4i	4-CH_3O-C_6H_4	Pyrolidine	125	88	142(140)[19]
4j	4-CH_3-C_6H_4	Pyrolidine	125	86	185(180-182)[18]
4k	3-O_2N-C_6H_4	Pyrolidine	125	87	189(188-190)[19]

According to both Lewis acid and Lewis base character of CuO. Reasonable possibility mechanism of the reaction is represented in Scheme **3** in which imine intermediate **5** formed by the reaction of aldehyde and secondary amine. Subsequent nucleophilic addition of 4-hydroxy coumarin **1** to this intermediate **5** affords the formation of product **4**.



Scheme 3. Possible reaction mechanismfor the formation of benzyl amino coumarin.

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 3. The catalyst was recovered after each run, washed with ethanol, dried in an oven at 100 oC for 15 min prior to use and tested for its activity in the subsequent run. The catalyst was tested for 3 runs. It was seen that the catalyst displayed very good reusability (Figure 2).

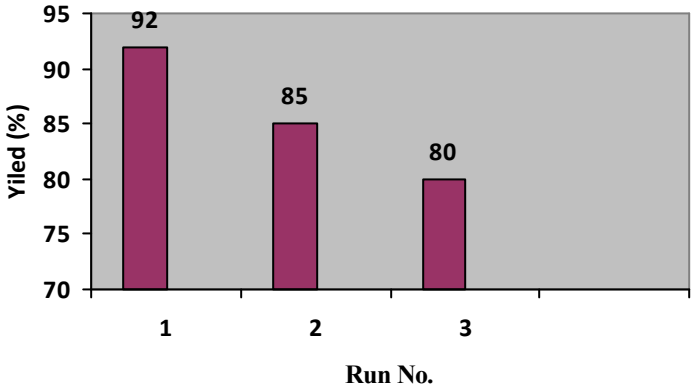


Figure 2. Reusability of the catalyst.

Synthesis of nano-CuO

Copper oxide nanoparticles was prepared as previously described in the literature [16, 20]. In a typical procedure Solution of NaOH (100 mL, 0.1 mol/L) was added to solution of $Cu(CH_3COO)_2$-$2H_2O$ (0.1 mol/L) in ethanol/ water. The obtained mixtures were sonicated for 30 min with 30 W ultrasound powers. To investigate the role of surfactants on the size and morphology of nanoparticles, we used 1 g of polyvinyl alcohol (PVA) in the reaction. The morphology, structure and size of the samples were investigated by Scanning Electron Microscopy (SEM). Figure 3 indicates that the original morphology of the particle was approximately spherical with the diameter varying between 35 and 103 nm.

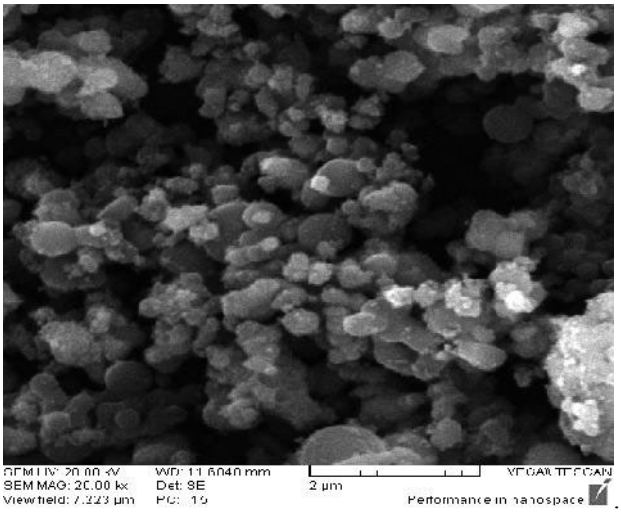


Figure 3. SEM image of synthesized CuO nanoparticles.

General experimental procedure

To a solution of aldehyde (1 mmol), 4-hydroxy coumarin (1 mmol), and CuO NPs (0.2 mmol) (0.1 mmol) in water (15ml), secondary amine (1 mmol) was added and the reaction mixture was vigorously stirred at room temperature for

120-135 min. After completion of the reaction (TLC), the reaction mixture was extracted with ethyl acetate (3 * 10ml). The extract was then filtered to separate the nano catalyst. 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 MHZ, $CDCl_3$): 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 MHZ, $CDCl_3$): δ = 22.31, 22.87,45.37 (3CH2), 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 MHZ, $CDCl_3$): 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 MHZ, $CDCl_3$): 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.

Conclusions

In conclusion, we have developed a convenient methodology for the synthesis of *α*-benzylamino coumarin derivatives by the three-component coupling of 4-hydroxycoumarin, cyclic secondary amine, and aromatic aldehyde by using CuO NPs as 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.

Acknowledgements

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