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Original Research Article

Synthesis of bis(4-hydroxycoumarin)methanes using nano-CuO/CeO_2 as recyclable catalyst

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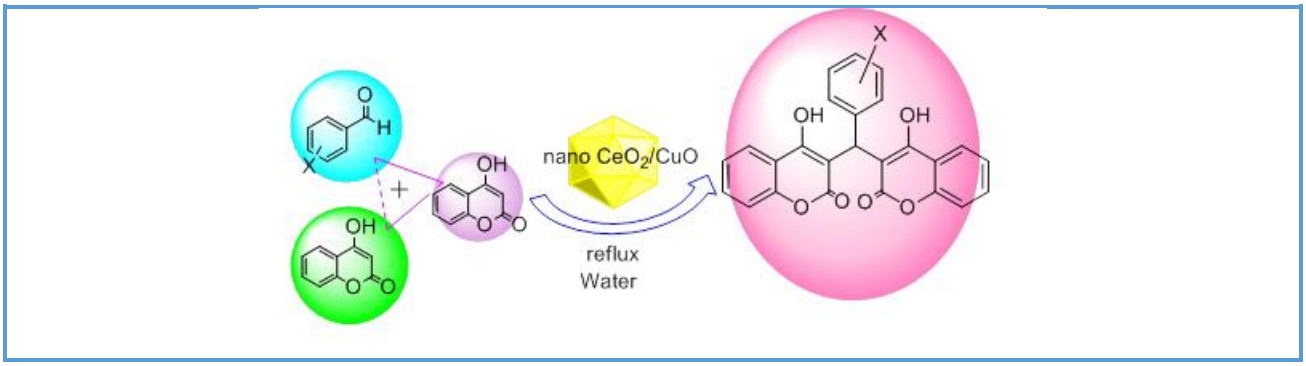
ABSTRACT

Coumarin derivatives have been widely utilized as agrochemicals, cosmetics, and pigments, demonstrating broad spectrum biological and pharmacological activities. In this research study, we reported an efficient and environmentally benign one-pot multi–component reaction for the synthesis of bis(4-hydroxylcoumarin) methanes derivatives from the reaction of 4-hydroxycoumarin and aromatic aldehydes in the presence of a catalytic amount of nano- CuO/CeO_2. The advantages of this method are including, good yields (92-97%), short reaction times, simple work-up and reusable catalyst. The catalyst could be recycled and reused for five times without much loss in its activity. As is evident from this research study, the best efficiency for the synthesis of bis(4-hydroxylcoumarin) methanes is achieved with the nano-CuO/CeO_2 catalyst in the shortest time.

Graphical Abstract



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Introduction

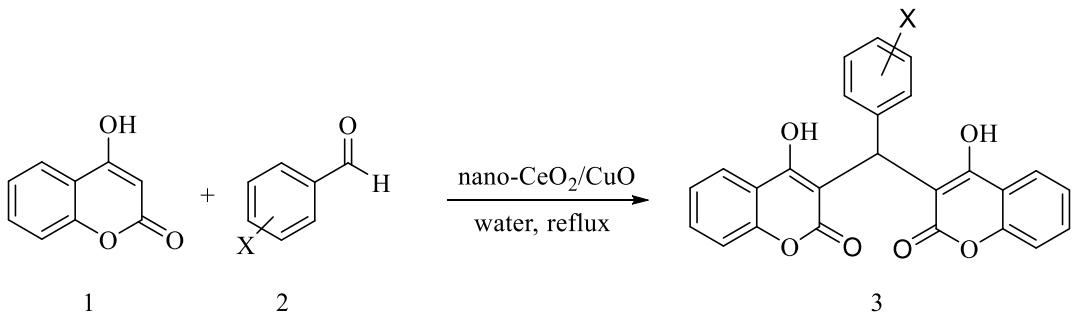
Coumarins are oxygenated heterocycles that play a critical role in many natural products and have numerous biological activities and therapeutic applications, including anticoagulant activity, antiviral activity, use as an antibiotic, spasmolytic activity, antimicrobial activity, anticancer activity, and antioxidant activity. They also have antifungal, anti-insect, and anti-inflammatory properties and are employed to prevent disease and regulate growth. They are also used as food additives and cosmetics [1]. Coumarin derivatives have many biological activities and therapeutic applications including, anticoagulant activity [3], antiviral activity [2], use as an antibiotic (novobiocin and analogues) [4], spasmolytic activity [5], antimicrobial activity, anticancer activity, and antioxidant activity [6]. They also have anti-helminthic, anti-fungal, anti-insect, and anti-inflammatory properties and are applied to prevent disease and regulate growth [6]. Coumarins are involved in the inhibition of HIV by acting on integrase and reverse transcriptase, which has an essential role in HIV replication [8, 9]. Several studies have attempted to prevent the growth of bacteria using natural coumarins such as herniarin, umbelliferone, and scopoletin [10, 11]. In addition to aforementioned biological activities, coumarin derivatives have a role in inhibiting platelet aggregation and have anti-psoriasis properties [12–14]. These beneficial heterocycles are involved in the function of plant growth hormones and growth regulators, respiratory control, photosynthesis, and defense against various infections [15]. They are also used as food additives and cosmetics [16]. One of the other applications of coumarins is the construction of coumarin-based chromogenic sensors for cations and anions since anions play a major role in our daily lives and are very important for physiological function and industrial processes, and the possibility of their identification is important [17]. Due to the critical applications of coumarin derivatives, the synthesis of these compounds is of great importance. Studies indicate that there are various new techniques with the help of the microwave, ionic liquids, solvent-free techniques, and using homogeneous and heterogeneous catalysts, methane sulfonic acid, tetrabutyl, and heteropolyacids (HPAs). Although all of these approaches are valuable, many methods have disadvantages of low efficiency, long reaction time, non-recyclable catalysts, expensive reagents, severe reaction conditions, and harmful solvents. Therefore, the development of a simple, efficient, and environmentally friendly method that covers the concept of "green chemistry" is of great importance. Subsequently, we will examine the different methods that have suitable conditions. Due to their characteristics, such as surface-active sites, high stability, and specific surface area, nanocatalysts have attracted much attention [18–28]. These properties exhibit excellent catalytic performance, such as high and selective activity required in industrial production [29].

The most important achievement of nanotechnology in catalyst science is the unification of the size and distribution of active catalytic pores. This is because if we can have the same distribution of size and properties of active centers, we will not face different reactions. This means that we will not have by-products, and we will not have to spend a lot of money on separation. Moreover, environmental pollution will be reduced without byproducts. Nanocatalysts accelerate the reaction speed compared to catalysts, and the efficiency of the products is higher than other catalysts [30].

Nano-CuO/CeO_2 catalyst is an important rare oxide from the earth that attracts more

attention due to its diversity. This oxide has been used in fuel cells, oxygen gas sensors, polishing materials, oxygen permeation membrane systems, and as a catalyst in various technological processes [31].

Heterocyclic compounds have attracted a great deal of attention due to their wide range of biological and pharmaceutical properties and it is used in various industries [32–34]. As a part of our work on multicomponent reactions (MCRs) and developing new selective and environmentally friendly methodologies for the synthesis of various heterocyclic compounds, and in continuation of our research on the use of water as solvent, we are going to introduce nano-CuO/CeO_2 as a mild and highly efficient catalyst for the synthesis of bis(4-hydroxylcoumarin) methanes at ambient conditions (Scheme 1).



Scheme 1. Synthesis of bis(4-hydroxylcoumarin) methanes

Experimental

Material and methods

Chemicals were supplied from the Merck (Darmstadt, Germany) and Sigma-Aldrich chemical Co. All products were characterized by spectra and physical data. Characterizations were carried out using the Melting points (Electrothermal 9100), ^{1}H-NMR (Bruker 500 MHz), TEM (HRTEM, TF 20 Tecnai G2 200 kV FEI), Fourier transform infrared (model Nexus-870, Nicolet Instrument), Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel.

Preparation of catalyst nano-CuO/CeO_2

The mixture of $Ce(NO_3)_3.6H_2O$ and $Cu(NO_3)_2.3H_2O$ were dissolved in distilled water at equal molar ratios. Then, two times molar citric acid was added to the stirred mixture solution containing cerium and copper nitrate. The solution is heated in a water bath to obtain a viscous gel. In the process, the color of the mixture changed from blue to green. The resulting gel is placed at 110 °C overnight. It is then calcined at 600 °C for 4 h [35]. X-ray diffraction (XRD, X-Pert Pro MPD, Cu-Ká: λ=1.54 Å), scanning electron microscope (SEM, SU-70, Hitachi), and transmission electron microscope (TEM, TF 20 Tecnai G2 200 kV FEI) images of the catalyst are demonstrated in Figure 1-3. The dimensions of utilized CuO/CeO_2 nanoparticles were determined with TEM (Figure 2). The CuO/CeO_2 nanoparticles utilized in the following investigation were between 20 nm and 50 nm in diameter.

Typical procedure for Preparation of bis(4-hydroxylcoumarin) methanes derivatives

The procedure is in a way that the desired aromatic aldehyde (1 mmol), 4-hydroxy coumarin (2 mmol), nano-CuO/CeO_2 catalyst (0.05 g), and water (5 mL) as a solvent were mixed in a 50 mL balloon.

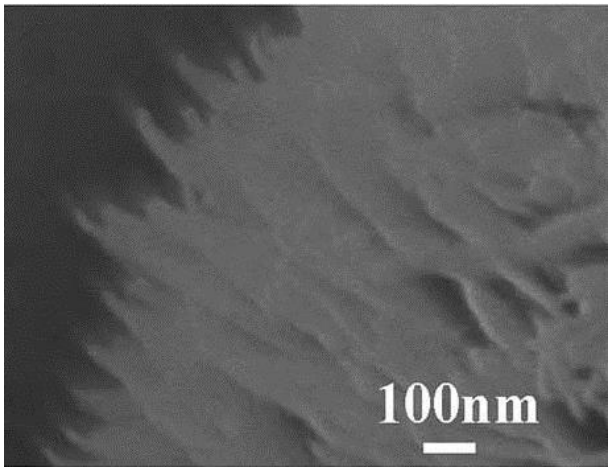


Figure 1. SEM image of nano-CuO/CeO_2

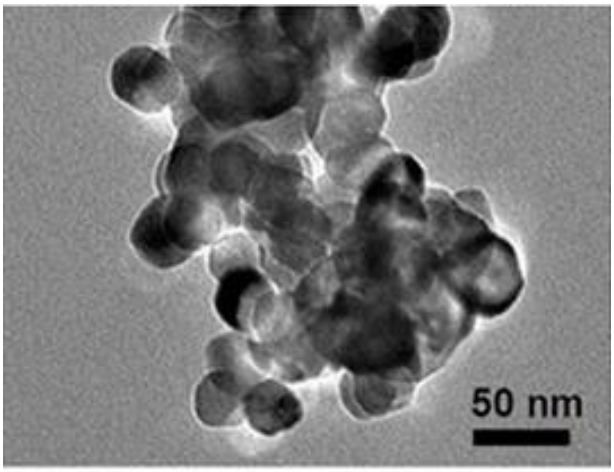


Figure 2. TEM image of nano-CuO/CeO_2

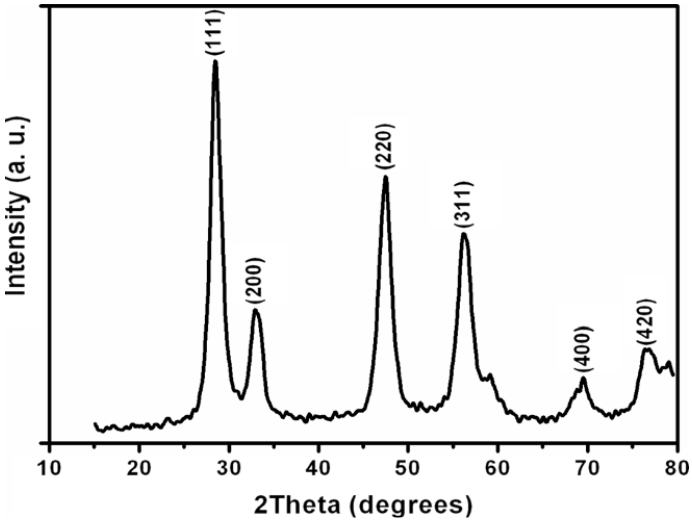


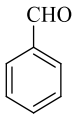
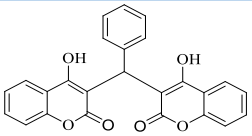
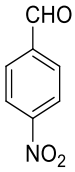
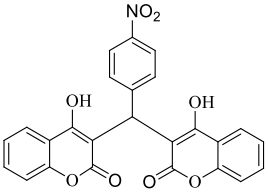
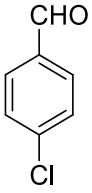
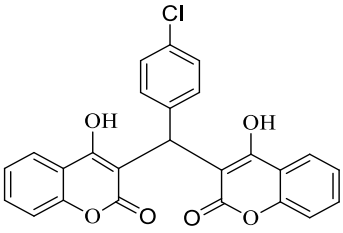
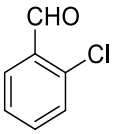
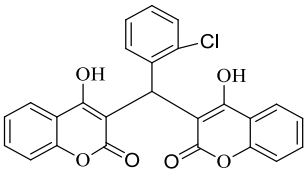
Figure 3. XRD pattern of nano-CuO/CeO_2

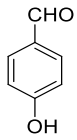
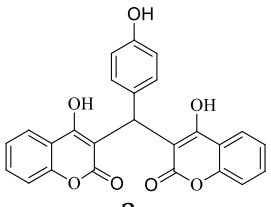
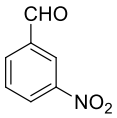
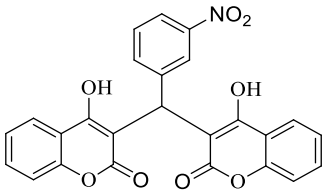
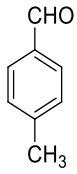
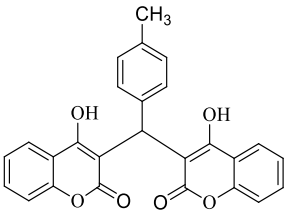
The mixture was stirred with heat under reflux conditions using a magnetic stirrer. The reaction progress rate was monitored using TLC in a mixture of ethyl acetate and *n*-hexane in a ratio of 2:1. After completion of the reaction, the mixture was cooled to room temperature. The solid is separated and smoothed by filter paper, and after dissolving the solid in hot ethanol, the insoluble catalyst was removed by filtration, and the filtered solution was excluded for the formation of crystals. By evaporation of the solvent, the desired product crystals were obtained with high purity and yield. The melting points and IR and H NMR spectra of the obtained crystals were taken and compared with references.

(**3a**): IR (KBr) (ν_{max}, cm^{-1}): 3378, 3073, 2928, 1696, 1653, 1619 and 1569. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.91 (s, 2H), 7.95 (dd, 2H, J1 = 7.8, J2 = 2.8 Hz), 7.65–7.56 (m, 2H), 7.47 (d, 2H, J = 7.2 Hz), 7.38–7.36 (m, 7H), 6.33 (s, 1H).

(**3b**): IR (KBr) (ν_{max}, cm^{-1}): 3388, 3067, 2888, 1719, 1656, 1617, 1568, 1538 and 1349. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 10.91 (s,2H), 7.95 (dd, 2H, J1=7.8 Hz, J2=2.8 Hz), 7.69–7.61 (m, 2H), 7.49 (d, 2H, J = 7.2 Hz), 7.42–7.39 (m, 7H), 6.42 (s, 1H).

Table 1. Synthesis of substituted bis(4-hydroxylcoumarin) methanes catalyzed by nano-CuO/CeO_2

Entry	Aldehyde	product	Time (h)	Yield (%)	Experimental Melting Point	Theory Melting Point [36]
1		 3a	3	94	234-236	234-235
2		 3b	3	96	237-238	236-237
3		 3c	3	96	260-261	258-260
4		 3d	3	95	267-269	266-268

5		 3e	3	93	225-227	224-226
6		 3f	3	97	236-238	235-237
7		 3g	3	92	268-269	268-270

Results and Discussion

Based on previous studies on developing new and heterogeneous catalyst systems for fine chemical preparation, we have established a one-pot reaction of various aldehydes with 4-hydroxy coumarin in water in the presence of nano-CuO/CeO_2 as available and green catalyst in good yields. The reaction is multicomponent and ideal, and no intermediate isolation is required in this reaction. As a result, a small percentage of the product is lost during separation. The catalyst used does not dissolve in any solvent, so its isolation is very easy. The reaction time is low, and the reaction efficiency is high (Table 2).

Optimization of the amount of catalyst in the synthesis of bis-coumarin

To determine the appropriate amount of catalyst, the synthesis reaction of **3a** was intended as the model reaction, and different values of catalyst were evaluated. The catalyst has a low reaction efficiency in small amounts, and the amount of efficiency is constant and cost-effective by increasing it that less amount with better efficiency was selected (Table 3).

Optimization of the temperature in the synthesis of bis-coumarin

To reach the appropriate temperature conditions, the model reaction was performed at different temperatures and reflux. As indicated, the highest efficiency was observed in reflux conditions (Table 4).

Optimization of the solvent in the synthesis of Bis-coumarin

To optimize the solvent, the model reaction was performed in water, ethanol and water/ethanol, acetonitrile and chloroform, where the water had the best efficiency under reflux conditions (Table 5).

Reusability of CuO/CeO_2 catalyst

After completion of the model reaction, 10 mL of ethyl acetate was added to the contents on filter paper containing catalyst.

Table 2. Comparison of various catalysts for the synthesis of bis(4-hydroxylcoumarin) methanes

Entry	Catalyst	Time(h)	Yield(%)
1	SiO_2Cl	3.5	85
2	$NaHSO_4/SiO_2$	4	85
3	$H_{14}[NaP_5W_{30}O_{110}]$	5	88
4	$RuCl_3$	3	88
5	Nano CuO/CeO_2	3	94

Table 3. Comparison of amount of catalysts for the synthesis of **3a**

Entry	Amount of catalysts (g)	Yield (%)[a]
1	0.02g	66
2	0.03g	80
3	0.05g	94
4	0.08g	94
5	0.1g	94

[a] Yields were analyzed by GC

Table 4. Comparison of different temperature for the synthesis of **3a**

Entry	Time (h)	Temperature (°C)	Yield (%)
1	3	25	66
2	3	50	75
3	3	reflux	94

The mixture was stirred using a magnetic stirrer at room temperature for 5 min. The reaction mixture was smoothed. As the catalyst was insoluble in ethyl acetate, it remained on the filter. Then, in order to reuse the catalyst, the substances on the filter were washed several times with acetone. After drying, the reaction with it was repeated to evaluate the potency of the catalyst (Table 6).

Proposed mechanism

Initially, nano CuO/CeO_2 activates 4-hydroxy coumarin (1) and benzaldehyde (2), and a condensation reaction takes place between them, and a double bond is formed with the exit of water. In the next part, with a Michael addition, bis-coumarin (4) is formed. In the reaction pathway, the nanocatalyst performs the compounds' activation so that the reaction takes place in a short time with the best efficiency and high selectivity (Scheme 2).

Conclusions

In this work, we have found a simple, convenient, straightforward and practical procedure for the synthesis of coumarin derivatives with high efficiency and short time reaction. All starting materials are readily available from commercial sources. Nano-CuO/CeO_2 catalysts are recyclable, heterogeneous, environmentally benign solid catalysts possessing desirable properties such as high thermal and hydrothermal stability. The target nano CuO/CeO_2 is prerequisite in green chemistry. There are some remarkable properties which are playing noticeable roles,

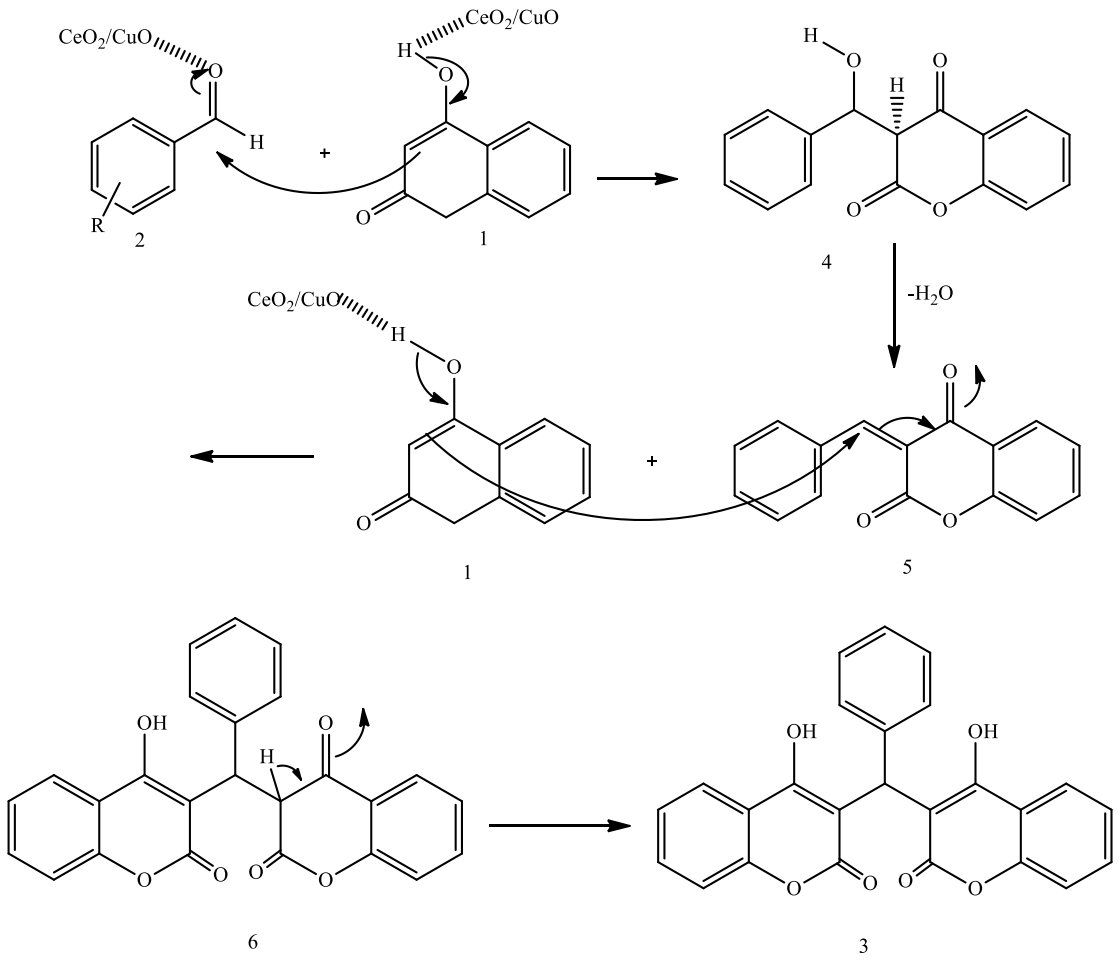
Table 5. Synthesis of **3a** in the presence of different solvents using nano-CuO/CeO_2 as a catalyst

Entry	Solvent	Yield (%)[a]
1	THF	68
2	C_2H_5OH	91
3	CH_3CN	85
4	$CHCl_3$	71
5	water	94
6	Solvent-free	91

[a] Yields were analyzed by GC

Table 6. Reuse of the nano CuO/CeO_2 for the synthesis of **3a**

Entry	Run	Yield(%)[a]
1	First	94
2	Second	92
3	Third	90
4	Fourth	88
5	Fifth	85



Scheme 2. A plausible mechanism for the one-pot synthesis of bis(4-hydroxylcoumarin) methanes

such as: mildness of the conversion, simple experimental part, and also ability of compatible with various functional groups, impressive and efficient yields, short reaction times, and the easy workup procedure. Finally, these features make target procedure more attractive to synthesize a variety of these derivatives. Some advantages of this procedure are: 1) the experimental simplicity and the easy work-up procedure, 2) the compatibility with various functional groups, 3) use of the green, easy to handle and reusable catalyst, and 4) high yields of the products. The procedure is very simple and can be used as an alternative to the existing procedures.

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