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Nanocrystalline Copper(II) Oxide-Catalyzed One-Pot Synthesis of Imidazo[1,2-a]quinoline and Quinolino[1,2-a]quinazoline Derivatives via a Three-Component Condensation

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NANOCRYSTALLINE COPPER(II) OXIDE-CATALYZED ONE-POT SYNTHESIS OF IMIDAZO[1,2-*a*]QUINOLINE AND QUINOLINO[1,2-*a*]QUINAZOLINE DERIVATIVES VIA A THREE-COMPONENT CONDENSATION

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A simple, efficient, and practical procedure for the synthesis of imidazo[1,2-a]quinoline and quinolino[1,2-a]quinazoline derivatives using CuO nanoparticles as a novel catalyst in excellent yields is described. The catalyst can be recovered conveniently and reused at least four times without any loss of activity.

Keywords: CuO nanoparticles; imidazo[1,2-a]quinoline; quinolino[1,2-a]quinoline

INTRODUCTION

Heterocyclic chemistry has always been one of the most valuable sources of novel compounds with diverse biological activity, mainly because of the unique ability of the compounds to mimic the structure of peptides and to bind reversibly to proteins. To medicinal chemists, the true utility of heterocyclic structures is the ability to synthesize one library based on one core scaffold and screen it against a variety of different receptors, yielding several active compounds.

Almost unlimited combinations of fused heterocyclic structures can be designed, resulting in novel polycyclic frameworks with the most diverse physical, chemical, and biological properties.

The fusion of several rings leads to geometrically well-defined rigid polycyclic structures and thus holds the promise of a high functional specialization, resulting from the ability to orient substituents in three-dimensional spaces. Therefore, efficient methodologies resulting in polycyclic structures from biologically active heterocyclic templates are always of interest to both organic and medicinal chemists.^[1]

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Heterogeneous catalysis is an economically and ecologically important field in catalysis research because these catalysts have many advantages: They are noncorrosive, environmentally benign, and present few disposal problems. They are also much easier to separate from liquid products and they can be designed to give higher activity, better selectivity, and longer catalyst lifetimes.^[2–4] Because of these advantages, research on chemical reactions using solid bases as catalysts has increased over the past decade.^[5] Many types of heterogeneous catalysts, such as alkaline earth metal oxides, anion exchange resins, and various alkali metal compounds supported on alumina or zeolite can catalyze many types of chemical reactions, such as isomerization, aldol condensation, Knoevenagel condensation, Michael condensation, oxidation, and transesterification.^[6–11]

Copper oxide nanoparticles have been of considerable interest because of the role of CuO in catalysis, gas sensors, and semiconductors.^[12] CuO nanoparticles were found to be effective catalysts for CO and NO oxidation as well as for the oxidation of volatile organic chemicals such as methanol.^[13] Very recently, Kantam et al. reported the asymmetric hydrosilylation reaction of prochiral ketones with excellent enantioselectivity,^[14] synthesis of propargylamines via three-component coupling of aldehydes, amines, and alkynes,^[15] and direct asymmetric aldol reactions^[16] catalyzed by nanocrystalline copper oxide. CuO nanoparticles also find excellent applications as catalysts for coupling of diaryl diselenide with aryl halides,^[17] alkyne–azide cycloadditions,^[18] and C-N cross coupling of amines with iodobenzene.^[19]

As a consequence of our interest in aqueous media organic syntheses and in an effort to design a solid base catalyst for the synthesis of fused heterocyclic structures, we have determined that CuO nanoparticles efficiently catalyze the one-pot synthesis of imidazo[1,2-a]quinoline and quinolino[1,2-a]quinazoline (Scheme 1).

In past decades, many methods have been developed to synthesize different shapes of CuO nanostructures, such as the metal organic deposition technique,^[20] microwave irradiation,^[21] sol-gel-like dip technique,^[22] hydrothermal method,^[23]



Scheme 1. One-pot synthesis of imidazo[1,2-a]quinoline and quinolino[1,2-a]quinazoline.

reverse micelle-assisted rout,^[24] chemical method,^[25] and simple template-free solution rout.^[26]

Supercritical water hydrothermal synthesis (SCWHS) is among the most active fields of green chemistry. It is a relatively simple and environmentally benign process.

We attempted the synthesis of copper oxide nanoparticles by batchwise supercritical hydrothermal method. Advantages of this method over previous synthetic approaches are shorter reaction time and possibility of performing a single-step process.

The x-ray diffusion (XRD) pattern of nanosized particles is shown in Fig. 1. All diffraction peaks of x-rays are indexed to the monoclinic crystal system of CuO. No characteristic peaks are observed for other possible impurities, such as $Cu(OH)_2$, Cu_2O , or $Cu(OH)_3NO_3$. The average size of the obtained CuO particle shown in Fig. 2 is 5 nm. The crystallite size was also calculated by x-ray line-broadening analysis using the Scherrer equation; we found that the average CuO crystallite size was 8 nm. The mean value of surface area of CuO catalyst was 19.59 m²/g from Brunauer–Emmet–Teller (BET) analysis.

The mechanism of formation of the CuO nanoparticle is this: When water is heated up to its critical point ($T_c = 374 \,^{\circ}$ C, $P_c = 22.1$ MPa), it changes from a polar liquid to a fluid with a low dielectric constant. At the same time, the dissociation constant of water (K_w) remarkably increases, giving rise to correspondingly increased concentrations of H⁺ and OH⁻. From this point, the key role is played by OH⁻ ions whose enhanced concentration according to Adschiri et al. leads to a rigorous hydrolysis of the metal salts that is immediately followed by a dehydration step (Scheme 2).

Adschiri et al. also pointed out that dielectric constant of water, the most significant factor that controls the solvent power of water, declines at supercritical



Figure 1. XRD patterns of CuO particles prepared at supercritical condition and calcination of copper nitrate trihydrate.



Figure 2. Transmission electron micrographs of CuO nanoparticles.

 $Hydrolysis: Cu(NO_3)_2 + 2OH^- \rightarrow Cu(OH)_2 + 2NO_3^-$

Dehydration: $Cu(OH)_2 \rightarrow CuO + H_2O$

Scheme 2. The mechanism of formation of the CuO nanoparticle.

condition, and hence the formed metal oxide can no longer stay in the aqueous phase and must precipitate. As a result, at high temperature, supersaturation for precipitation of metal oxide becomes greater, which consequently leads to creation of more nucleation centers and thus formation of smaller particles (i.e., nanoparticles).^[27]

First, the mixture of benzaldehyde, malononitrile, and enaminone **1a** was chosen as the model reaction to detect whether the use of CuO nanoparticle was efficient. The reaction was carried out simply by mixing benzaldehyde, malononitrile, and enaminone **1a** in water as solvent in the presence of a catalytic amount of CuO nanoparticles (10 mmol%). The mixture was heated at 50 °C for 35 min, and the imidazo[1,2-*a*]quinoline **4a** was obtained in 78% yield.

Encouraged by the result, we studied different reaction parameters, and the results are summarized in Table 1. Only a trace amount of the target product was

Entry	Catalyst	Catalyst (mmol%)	Time (min)	Yield (%)	
1	None	_	180	Trace	
2	CuO nanoparticles	30	35	96	
3	Bulk CuO	50	60	73	
4	MgO	50	60	78	
5	Al_2O_3	50	50	81	
6	ZnO	50	65	69	

Table 1. Formation of 4a with different basic catalyst^{*a*}

^{*a*}Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), and enaminone **1a** (1 mmol), x mmol% catalyst; water; 50 °C.

observed when the mixture of benzaldehyde, malononitrile, and enaminone **1a** was heated under similar conditions in the absence of CuO nanoparticles even after heating for 3 h, thus highlighting the role of CuO nanoparticles as a promoter. We have changed the amount of the CuO nanoparticles from 10 to 50 mmol%, finding that the yield of product **4a** was improved as the amount of CuO nanoparticles increased from 10 to 30 mmol%. The yield did not improve when the amount of the catalyst was further increased from 30 to 50 mmol%. Therefore, 30 mmol% of CuO nanoparticles was considered to be most suitable.

The CuO nanoparticle catalyst was studied along with other known solid base catalysts using the model reaction for the synthesis of the corresponding imidazo[1,2-*a*] quinoline **4a**. The results are summarized in Table 1. The results show that the three-component reactions catalyzed by Al_2O_3 , ZnO, and MgO proceed in longer reaction times and afforded moderate product yields.

Afterward, the catalytic activity of the bulk CuO and CuO nanoparticle was tested in the preparation of **4a**. The obtained results are shown in Table 1. When the model reaction was conducted with bulk CuO, a poor yield of the product was obtained, while nano-CuO afforded excellent yields (Table 1).

The increased catalytic activity of nano-CuO over bulk CuO may be attributed to the higher surface area of nano-CuO than bulk CuO as well as the higher surface concentration of the reactive sites. As seen with other metal oxides, once they are made into nanoparticles, their reactivity is greatly enhanced. This is thought to be due to the morphological differences. Whereas larger crystallites have only a small percentage of the reactive sites on the surface, smaller crystallites will possess a much higher surface concentration of such sites.^[28]

The formation of **4** is likely to proceed via initial condensation of aldehydes **2** with malononitrile **3** to afford 2-arylidenemalononitrile **5**. The addition compound **5**



Scheme 3. The reaction mechanism.

Entry	Enaminone	R_1		Product (4)	Mp (°C)	Ref. mp (°C) ^[29]	Time (min)	Yield (%)
1	1a	C ₆ H ₅	4a	O C N NH O O O NH	299	299–300	35	96
2	1a	4-MeOC ₆ H ₄	4b	OCH3 OCH3 CN NH	294	294–296	40	93
3	1a	4-BrC ₆ H ₄	4c	Br CN NH	298	298–299	30	89
4	1b	C ₆ H ₅	4d		298	298–299	35	91
5	1b	4-ClC ₆ H ₄	4 e		241	240–242	35	93
6	1b	4-MeC ₆ H ₄	4f		298	298–300	45	89

 Table 2. Synthesis of imidazo[1,2-a]quinoline and quinolino[1,2-a]quinazoline derivatives

to enaminones 1 then furnished the intermediate product 8, which upon intermolecular cyclization and dehydration gave rise to 4 (Scheme 3).

Then, we selected the optimized reaction condition to examine the universality of this catalyst's application. A series of aromatic aldehydes was selected to undergo



Figure 3. IR spectra of CuO: (a) newly prepared and (b) used four times.

the condensation in the presence of a catalytic amount of CuO nanoparticles (30 mmol%) in water at 50 °C (Table 2). The results in Table 2 indicate that the aromatic aldehydes bearing different functional groups such as chloro, bromo, methyl, or methoxy were able to undergo the condensation reaction.

The insolubility of the catalyst CuO in different organic solvents and water provided an easy method for its separation from the product. Recycling experiments were performed using the CuO nanoparticle catalyst for the synthesis of imidazo [1,2-a]quinoline **4a**. These recycling experiments show that the CuO nanoparticle catalyzes the reaction with consistent activity even after four cycles. IR spectra of the resulting solids indicate that the catalyst can be recovered without structural degradation (Fig. 3).

In conclusion, we have reported herein several noteworthy features of a new catalyst for the synthesis of imidazo[1,2-a]quinoline and quinolino[1,2-a]quinazoline through the three-component condensation of benzaldehyde, malononitrile, and enaminones **1a** or **1b** using CuO nanoparticles. This protocol offers many attractive features such as greater yields and economic viability of the catalyst. The reaction proceeds in water, and isolation of the catalyst is easily achieved. The catalyst is recoverable and can be used in several runs without loss of catalytic activity. This makes the method economic, benign, simple, and convenient for the synthesis of imidazo[1,2-*a*]quinoline and quinolino[1,2-*a*]quinazoline, which are of biological and medicinal importance.

EXPERIMENTAL

Preparation of the Ordinary Copper Oxide

To study physicochemical properties of the obtained CuO nanoparticles, the bulk of CuO powder (nonnanometric) as comparison reference was prepared by a two-step calcination procedure. At first, crystalline copper nitrate trihydrate was charged into a porcelain crucible and gently heated on a hot plate until most of the hydration water was removed. Then, the crucible was transferred into a muffle furnace and heated up to $400 \,^{\circ}$ C for 22 h, and at the end, the produced CuO product was gently crushed and screened.

Preparation of the CuO-Nanoparticles Catalyst

Copper(II) nitrate trihydrate (Merck A G for synthesis) was used as the precursor for synthesis of nano-CuO. Preparation of CuO took place in a stainless steel (316 L) autoclave that was able to endure working temperature and pressure of 550 °C and 610 atm, respectively. Concentration of Cu(NO₃)₂ was $0.05 \text{ mol} \cdot \text{dm}^{-3}$, and the heating period was about 2 h. Synthesis was carried out at 500 °C to accelerate the hydrolysis reactions and thus shorten the fabrication period. To maintain the safety margin, the 200-cm³ stainless steel autoclave was loaded with only 60–80 cm³ of the solution.

After removing it from the furnace, the autoclave was quenched by cold water and CuO nanoparticles were recovered from the discharged solution by high-speed centrifugation at 14,000 rpm for about 60 min. The produced nanoparticles were then washed three times in the same centrifuge with ultrapure water and dried at ambient temperature. Nanoparticles were characterized by XRD (Philips PW 1800) and transmission electron microscope (TEM) (LEO 912AB) tests.

General Procedure for the Synthesis of Enaminones 1a and b

A mixture of 5,5-dimethyl-1,3-cyclohexanedione (1 mmol), amine (1 mmol), and CuO nanoparticles (30 mmol%) was refluxed in 5 mL water for 45 min. Upon completion, as monitored by thin-layer chromatography (TLC), the reaction mixture was cooled to room temperature. The solid products were filtered and diluted with chloroform, and the catalyst was removed by simple centrifugation. After evaporation of solvent, the resulting solid was recrystallized from EtOH to give the pure products (**1a and b**).

General Procedure for the Synthesis of Compound 4

A mixture of aldehyde 2 (1 mmol), malononitrile 3 (1 mmol), enaminones 1a or 1b (1 mmol), and CuO nanoparticles (30 mmol%) in H₂O (5 mL) was heated at 50 °C for 30–45 min (the progress of the reaction being monitored by TLC using *n*-hexane/ ethyl acetate as an eluent, 2:3). Upon completion of the reaction, the reaction mixture was filtered to isolate the solid product. Then solid product was diluted with chloroform, and the catalyst was removed by simple centrifugation (the catalyst is not soluble in chloroform). After evaporation of solvent, more purification was obtained by recrystallization from ethanol.

Spectral data of the products described in this article are the same as those reported in a previously published paper.^[29]

Catalyst Recovery and Recycling

After completing the model reaction, the catalyst was separated, washed three times with 10-ml portions of chloroform, dried at $150 \,^{\circ}$ C for 1 h, and subjected to a second run of the reaction process with the same substrate.

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