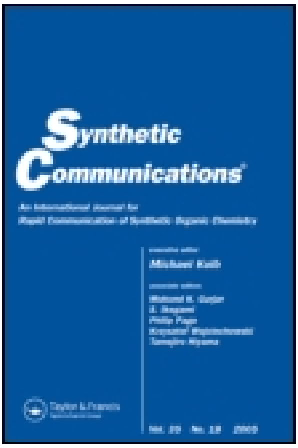

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On Water: A Practical and Efficient Synthesis of Benzoheterocycle Derivatives Catalyzed by Nanocrystalline Copper(II) Oxide

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ON WATER: A PRACTICAL AND EFFICIENT SYNTHESIS OF BENZOHETEROCYCLE DERIVATIVES CATALYZED BY NANOCRYSTALLINE COPPER(II) OXIDE

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Recyclable CuO nanoparticles provide an efficient, economic, and novel method for the synthesis of quinoxaline, benzoxazine, and benzothiazine. This method provides a wide range of substrate applicability, avoids the use of organic solvents, and gives benzoheterocycles in satisfactory yields.

Keywords: Benzothiazine; benzoxazine; CuO nanoparticles; quinoxaline; water

INTRODUCTION

1,4-Benzoxazin-3(4*H*)-one and 1,4-benzothiazin-3(4*H*)-one derivatives are an interesting group of compounds, both pharmacologically and agriculturally. The 1,4-benzoxazin-3(4*H*)-one moiety can be found in molecules that exhibit plant resistance factors against microbial diseases and insects and analgesic, antimicrobial and potassium-channel modulating properties, whereas 1,4-benzothiazin-3(4*H*)-ones, like semotiadil, are antihypertensive drugs, calcium antagonists, and highly potent inhibitors of low density lipoprotein (LDL) oxidation.[1]

Quinoxaline not only has application as dyes[2] and building blocks in the synthesis of organic semiconductors[3] but also serves as useful rigid subunits in macrocyclic receptors for molecular recognition[4] and chemically controllable switches.[5]

Nanocrystalline metal oxides find excellent applications as active adsorbents for gases and destruction of hazardous chemicals.[6] They are also gaining tremendous importance because of their distinct catalytic activities for various organic transformations. Recently, researchers have reported various[7–10] organic transformations using different nanocrystalline metal oxides. These high reactivities are

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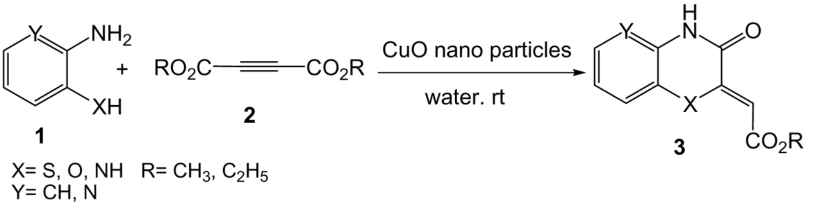
due to the high surface areas combined with unusually reactive morphologies. Copper oxide nanoparticles have been of considerable interest because of the role of CuO in catalyts, gas sensors, and semiconductors.[11,12] CuO nanoparticles were found to be effective catalysts for CO and NO oxidation as 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.

Among methods to prepare nanoparticles, supercritical hydrothermal synthesis is a unique technique to synthesize metal oxide and hydroxide nanocrystals from an aqueous solution of metal salts, in which the size, morphology, and crystal structure are controllable.[17] Supercritical water hydrothermal synthesis offers a relatively simple route that is inherently scalable and chemically much more benign than current technology. This method relies on the high reaction rate of hydrothermal synthesis above the critical temperature of water and lower solubility for the formed metal oxide,[18] which causes an extremely high degree of supersaturation of the metal oxide and thus allows nanoparticle formation.[19]

As a part of our ongoing research on the synthesis and catalytic applications of metal oxide nanoparticles, we first attempted synthesis of copper oxide nanoparticles by a batchwise supercritical hydrothermal method. Advantages of this method are shorter reaction time (<2 h) and possibility of performing it in a single step. After preparation of CuO nanoparticles and characterization by x-ray diffraction (XRD) and transition electron microscopy (TEM) techniques, the nanoparticles were employed as a recyclable catalyst for an efficient synthesis of benzoheterocycle (Scheme 1).

The XRD pattern of nano-sized 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 $Cu(OH)_3NO_3$. Average size of the obtained CuO particles shown in Fig. 2 is 5 nm. The mean value of surface area of CuO catalyst was 32.457 m^2/g from BET analysis.

We began our study of the reaction shown in Scheme 1 by optimizing the reaction conditions for the preparation of **3a**; the reaction was carried out in water at rt for 30 min. To our delight, at rt the reaction proceeded smoothly, and the product was furnished in 94% yield after workup and simple isolation from water. A



Scheme 1. An efficient synthesis of benzoheterocycles.

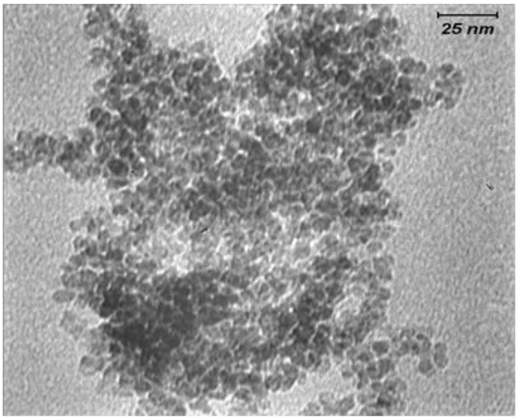


Figure 1. Transmission electron micrographs of CuO nanoparticles.

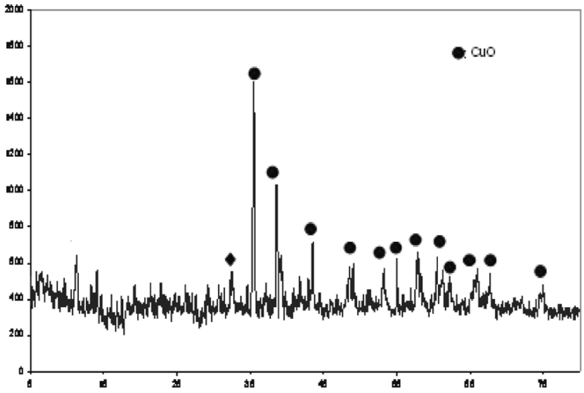


Figure 2. XRD pattern of CuO nanoparticles.

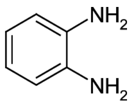
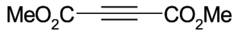
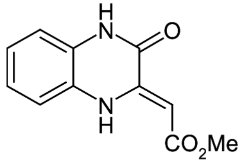
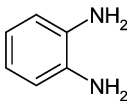
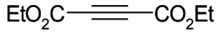
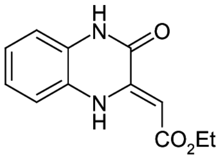
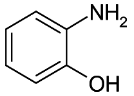
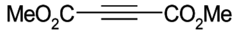
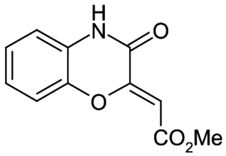
summary of the optimization experiment is provided in Table 1. In addition to MeCN, CH_2Cl_2, and EtOH were also tested as the reaction solvents. In these cases, product **3**a was formed in slightly lower yield (Table 1).

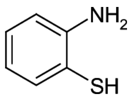
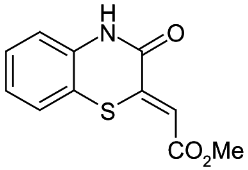
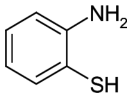
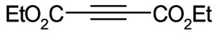
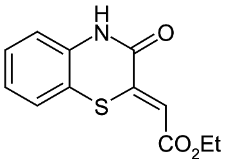
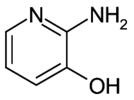
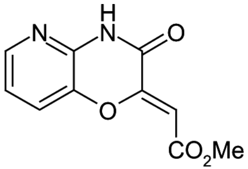
Table 1. Synthesis of **3**a with CuO nanoparticles at different reaction conditions

Entry	T (°C)	Solvent	Yield (%)
1	RT	Water	94
	Reflux	Water	94
2	Reflux	CH_2Cl_2	81
3	Reflux	EtOH	86
4	Reflux	MeCN	79

^{a}Reaction condition: aromatic amine **1a** (1 mmol), dialkyl acetylenedicarboxylate **2a** (1 mmol), and catalyst (0.003 mmol).

Table 2. Reactions of 2-aminothiophenol, 2-aminophenol, and *o*-phenylenediamines with DMAD or DEAD

						Mp (°C)	
Entry	**1**	**2**	**3**	Time (min)	Yield (%)	Found	Ref.
a				35	94	226–227	227
b				35	91	218	218
c				40	89	150	150

d				30	98	263–264	264
e				30	96	221	221
f				40	90	117	117–118

[a]Reaction condition: aromatic amine **1** (1 mmol), dialkyl acetylenedicarboxylate **2** (1 mmol), catalyst (0.003 mmol), water, rt.

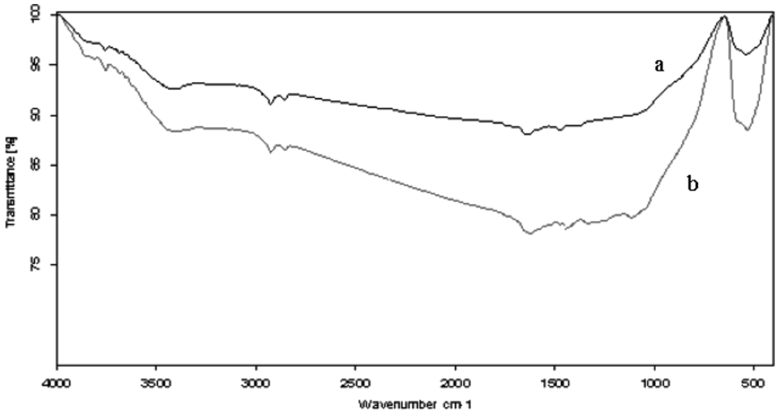


Figure 3. IR spectra of CuO: (a) newly prepared and (b) used three times.

To demonstrate the efficiency and the applicability of the present method, we performed the reaction with dimeyhyl acetylenedicarboxylate (DMAD) or diethyl acetylenedicarboxylate (DEAD) with 2-amino-phenol and 2-amino-benzenethiol in water at 50°C and in the presence of CuO nanoparticles.

All the reactions proceeded to completion at the time indicated in Table 2, and the yield data are for the isolated products. As shown in Table 2, we can see a series of **1** reacted with **2** to give the corresponding products **3** in good yields.

The efficiency of bulk CuO catalyst was also studied for this reaction, but the model reaction did not go to completion in the presence of this catalyst even after long reaction times (2 h).

The increased catalytic activity of nano-CuO over commercially available 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.[19]

The nano-CuO catalyst could be reused for four cycles without loss of activity and selectivity. Infrared (IR) spectra of fresh and used nano-CuO catalyst confirmed the fact that the structure and morphology of the catalyst remained the same during the course of the reaction (Fig. 3).

In summary, there is no doubt that CuO nanoparticles are an effective catalyst and provide a new and useful method to synthesize benzoheterocycle derivatives. The catalysts show environmentally friendly character and can be easily prepared, stored, and recycled without obvious loss of activity. Because of water-resistant and oil-resistant character of CuO nanoparticles, the catalysts can also be reused more conveniently. Therefore, a simple workup procedure, mild reaction conditions, and good yields make our methodology a valid contribution to the existing processes in the field of benzoheterocycle derivatives.

EXPERIMENTAL

Preparation of the CuO-Nanoparticle Catalyst

Copper(II) nitrate trihydrate (Merck A. G.) was used as the precursor for synthesis of copper oxide nanoparticles. Preparation of CuO was implemented in a stainless steel (316 Lit) autoclave that is able to endure working temperature and pressure of 550°C and 610 atm, respectively. Hydrothermal synthesis of 0.05 $\mathrm{mol\,dm^{-3}}$ $Cu(NO_3)_2$ during 2 h was carried out at 500°C to accelerate the hydrolysis reactions and thus shorten the fabrication period. To maintain the safety margin, the 200-cm^3 stainless steel autoclave was loaded with only 60–80 cm^3 of the solution. After removing it from the furnace, the autoclave was quenched by cold water, and CuO nanoparticles were recovered from discharged solution by high-speed centrifugation at 14,000 rpm for 60 min. Purification of the produced nanoparticles was performed by conducting centrifugation and decantation of washed samples with water three times and then drying at ambient temperature.

Physical Measurements

Size and morphology of the obtained nanoparticles were observed by TEM (LEO 912AB) (Fig. 2). Crystal structure of the prepared CuO nanoparticles and final microspheres was analyzed by using Cu Kα radiation (Philips PW 1800) (Fig. 1). The surface area of the CuO nanoparticles were determined by the nitrogen adsorption BET method (Quantachrome Instruments, Nova 2000e).

Catalytic Reactions

The substituted aromatic amine (1 mmol) was dissolved in water (5 mL), and dialkyl acetylenedicarboxylate (1 mmol) and catalyst (0.003 mmol) were added. The reaction mixture was stirred at room temperature and monitored by thin-layer chromatography (TLC).

Upon completion of the reaction, the reaction mixture was allowed to cool to room temperature, and the solution was filtered to isolate the solid product. The solid product was diluted with chloroform, and the catalyst was removed by simple filtration (the catalyst is not soluble in chloroform). After evaporation of solvent, more purification was obtained by column chromatography (eluted with 2:3 EtOAc–petroleum ether).

All the products obtained were characterized by spectroscopic methods such as IR and ^1H NMR, for unknown compounds (^{13}C NMR and analytical data), and also by comparison with the reported spectral data and melting point.[2]

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