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Short Communication

Ultrasound-promoted greener synthesis of benzoheterocycle derivatives catalyzed by nanocrystalline copper(II) oxide

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ABSTRACT

CuO nanoparticles provide an efficient, economic, and novel method for the synthesis of quinoxaline, benzoxazine, and benzothiazine under ultrasonic irradiation. The protocol offers advantages in terms of higher yields, short reaction times, and mild reaction conditions, with reusability of the catalyst.

1. 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 which exhibit plant resistance factors against microbial diseases and insects, analgesic, antimicrobial and potassium channel modulating properties, whilst 1,4-benzothiazin-3(4*H*)-ones, like semotiadil, are antihypertensive drugs, calcium antagonists and highly potent inhibitors of LDL-oxidation [1].

Quinoxaline not only shows their applications 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. They are also gaining tremendous importance due to their distinct catalytic activities for various organic transformations. Recently, researchers have reported various [6–9] organic transformations using different nanocrystalline metal oxides. These high reactivities are due to the high surface areas combined with unusually reactive morphologies.

With increasing environmental consciousness in chemical research and industry, the challenge for a sustainable environment calls for clean procedures. Ultrasonic-assisted organic synthesis (UAOS) as a green synthetic approach is a powerful technique that is being used more and more to accelerate organic reactions. UAOS can be extremely efficient and it is applicable to a broad range of practical syntheses. The notable features of the ultrasound approach are enhanced reaction rates, formation of purer products in high yields, and easier manipulation. It is considered a processing aid in terms of energy conservation and waste management. When compared with traditional methods, this technique is more convenient taking green chemistry concepts into account [10]. However, the use of ultrasound in heterocyclic system is not fully explored. In order to expand the application of ultrasound in the synthesis of heterocyclic compounds, we wish to report a general, efficient and eco-friendly method for the synthesis of benzoheterocycle derivatives catalyzed by nanocrystalline copper(II) oxide (Scheme 1).

2. Experimental

2.1. Chemicals and apparatus

All the chemicals were obtained from Merck Company and used as received. CuO nanoparticles were prepared according to our previous work (average size of the obtained CuO particle was 5 nm and the mean value of surface area of the copper catalyst was 32.457 m^2/g from BET analysis) [11]. Melting points were measured using a Barnstead Electrothermal melting point apparatus. The ultrasound apparatus was cleaning bath Wiseclear 770 W

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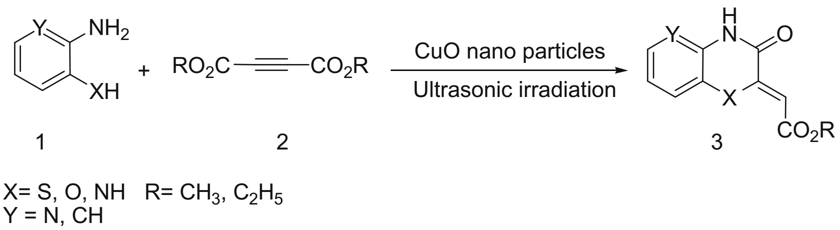


Scheme 1.

Table 1
Study of catalyst effect on reaction using **1**a and **2**a under ultrasound conditions at room temperature.

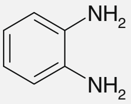
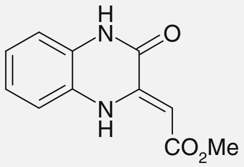
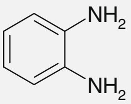
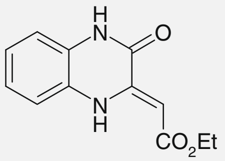
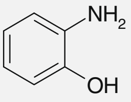
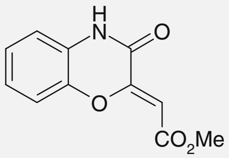
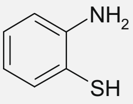
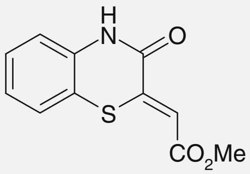
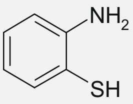
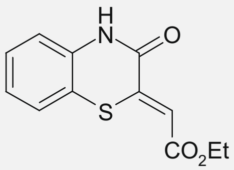
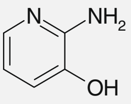
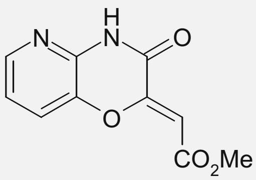
Entry	Catalyst	Time (min)	Yield (%)
1	No catalyst	15	17
2	CuO nanoparticles	15	94
3	Bulk CuO	15	61
4	Al_2O_3	15	53
5	Basic Al_2O_3	15	64
6	MgO	15	58

(Seoul, Korea). The operating frequency was 40 kHz and the output power was 200 W, estimated calorimetrically.

2.2. General procedure

A mixture of aromatic amine (1 mmol), dialkyl acetylenedicarboxylate (1 mmol) and CuO nanoparticles (0.03 mmol) in 10 mL EtOH was irradiated by ultrasound at room temperature for the required reaction time. The progress of the reaction was monitored by TLC using *n*-hexane:ethylacetate (4:1) as developer. The ultrasonic apparatus used showed the temperature automatically so

Table 2
The reactions of 2-aminothiophenol, 2-aminophenol and *o*-phenylenediamines with DMAD or DEAD under ultrasonic condition at room temperature.

Entry	**1**	**2**	**3**	Time (min)	Yield (%)	Mp (°C)	Ref. Mp (°C) [2]
a		$MeO_2C-{\equiv}-CO_2Me$		15	94	226–227	227
b		$EtO_2C-{\equiv}-CO_2Et$		15	91	218	218
c		$MeO_2C-{\equiv}-CO_2Me$		20	89	150	150
d		$MeO_2C-{\equiv}-CO_2Me$		10	98	264	263–264
e		$EtO_2C-{\equiv}-CO_2Et$		10	96	221	221
f		$MeO_2C-{\equiv}-CO_2Me$		20	90	117	117–118

the temperature was controlled and fixed at room temperature by pouring cold water in the bath in the case of any elevation of temperature. After completion of the reaction, the catalyst was separated by simple centrifugation. After evaporating the solvent, the crude product was obtained. The product was recrystallized from ethanol.

All products are known compounds and were identified by comparison of their physical and spectroscopic data with those reported for authentic samples [2].

2.3. Recycling of the catalyst

After completing the model reaction, the catalyst was separated by simple centrifugation and washed three times with 10 ml portions of dichloromethane and dried at 150 °C overnight and subjected to a second run of the reaction process with the same substrate.

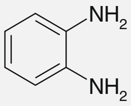
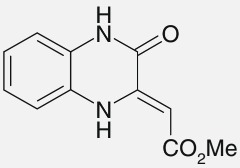
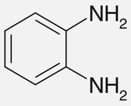
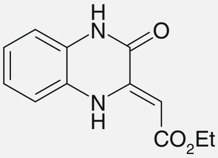
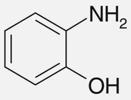
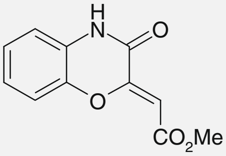
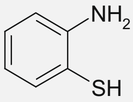
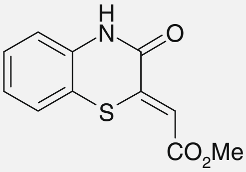
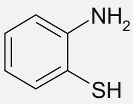
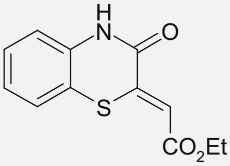
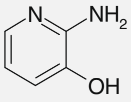
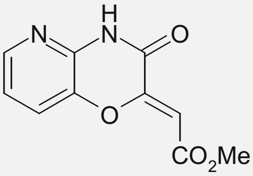
3. Result and discussion

In order to determine the most appropriate reaction conditions and evaluate the catalytic efficiency of CuO nanoparticles, the synthesis of **3**a (the reaction of *o*-phenylenediamine and dimeyhyl acetylenedicarboxylate (DMAD)) as a model reaction was carried out in various conditions. Attempts for the synthesis of **3**a under ultrasound irradiation were examined using MgO as catalyst and the desired product was obtained in 58% yield. A variety of catalysts were examined. By using basic Al_2O_3 and Al_2O_3 provided **3**a in 64% and 53% yield, respectively. Moreover, low yields were obtained in the absence of a catalyst. The CuO nanoparticles showed the best activity, and the product **3**a was obtained in 94% yield (Table 1).

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 (1 h, 68%).

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 [12].

Table 3
The reactions of 2-aminothiophenol, 2-aminophenol and *o*-phenylenediamines with DMAD or DEAD at room temperature.

Entry	1	2	3	Time (min)	Yield (%)
a		$\mathrm{MeO_2C{-}{\equiv}{-}CO_2Me}$		45	81
b		$\mathrm{EtO_2C{-}{\equiv}{-}CO_2Et}$		45	84
c		$\mathrm{MeO_2C{-}{\equiv}{-}CO_2Me}$		50	76
d		$\mathrm{MeO_2C{-}{\equiv}{-}CO_2Me}$		40	88
e		$\mathrm{EtO_2C{-}{\equiv}{-}CO_2Et}$		40	87
f		$\mathrm{MeO_2C{-}{\equiv}{-}CO_2Me}$		50	83

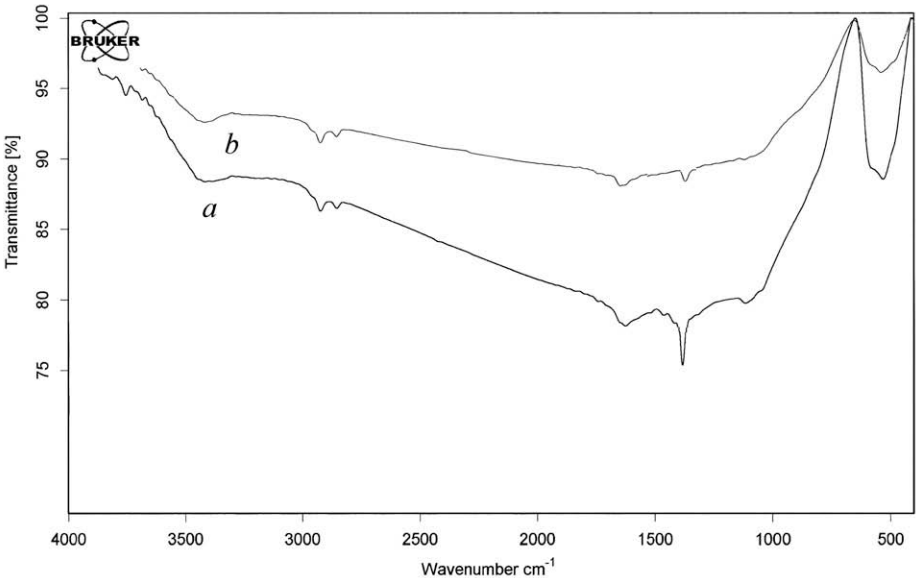


Fig. 1. IR spectra of CuO: (a) newly prepared; (b) used 3 times.

In order to demonstrate the efficiency and the applicability of the present method, we performed the reaction of a variety of dimeyhyl acetylenedicarboxylate (DMAD) or diethyl acetylenedicarboxylate (DEAD) with *o*-phenylenediamine, 2-amino-phenol and 2-amino-benzenethiol in ethanol at room temperature and in the presence of CuO nanoparticles under ultrasonic irradiation.

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

To investigate the role of ultrasonic irradiation in this method, the reactions were carried out in the presence of the same amount of CuO nanoparticles under stirring condition in EtOH at room temperature. The results are summarized in Table 3. It is clear that, under the same reaction conditions, reactions under ultrasonic irradiation led to relatively higher yields and shorter reaction times.

It is presumed that the efficiency using ultrasound irradiation is due to the cavitation phenomena. An ultrasonic wave is a pressure wave with alternate compressions and rarefactions which is able to break the intermolecular forces maintaining the cohesion of the liquid and produces a cavity in the rarefaction section of the wave. The chemical and physical effects of ultrasound derive primarily from acoustic cavitation which includes formation, growth and collapse of the cavity [13–15]. Bubble collapse in liquids results in an enormous concentration of energy from the conversion of kinetic energy of liquid motion into heating of the contents of the bubble. The high local temperatures and pressures produced by cavitation lead to a diverse set of applications of ultrasound such as accelerating the rate of the reaction, changing the reaction pathway, enhancing chemical reactivity and important uses in synthetic organic compounds. [16]. Catalyst regeneration is essential for industrial production. The recycled catalyst could not be used directly because some organic matter was adsorbed on the catalyst. The recycled catalyst was first washed with dichloromethane to get rid of most organic adsorbents and dried at 150 °C overnight. IR spectra of the resulting solids indicate that the catalyst can be recovered without structural degradation (Fig. 1).

The nano-CuO catalyst could be reused for three cycles with only a gradual decrease in its activity. For example, the reaction of *o*-phenylenediamine and dimeyhyl acetylenedicarboxylate (DMAD) afforded corresponding quinoxaline **3**a in 94, 91, and 89 % yields over three successive runs.

4. Conclusion

This work demonstrates a novel and highly efficient methodology for the synthesis of benzoheterocycle derivatives in presence of CuO nanoparticles under ultrasound irradiation. In addition of efficiency and simplicity, this protocol provides a very fast and low cast procedure for the synthesis of these products.

Acknowledgements

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