

Granulated copper oxide nano-catalyst: a novel and efficient catalyst for C–N cross-coupling of amines with iodobenzene

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Abstract Nano-structured CuO granules catalyze the C–N cross-coupling of amines with iodobenzene in excellent yields. The reaction is simple, efficient, and operates in air under ligand-free conditions.

Keywords Iodobenzene · CuO nanoparticles · Alginate · Nano-structured CuO granules · Ligand-free conditions

Introduction

The synthesis of *N*-arylamines and *N*-arylheterocycles is an active area in organic synthesis because of the occurrence of these moieties in biologically important natural products, pharmaceuticals, and their applications in materials research. Among the various strategies developed to date, the copper-catalyzed Ullmann reaction has proven to be the most convenient synthetic route for installing an *N*-aryl functionality [1].

However, the synthetic scope of this reaction is strongly limited by the insolubility of copper(I) salts in organic solvents, the high reaction temperatures required (~200 °C), and the sensitivity of the substituted aryl halide to the harsh reaction conditions applied. Another major drawback of this

protocol is the use of stoichiometric amounts of copper or copper salts, which results in the production of large quantities of waste, making this method environmentally unfriendly [2]. To overcome these limitations, much attention has recently focused on developing catalytic systems to reduce the environmental impact of the processes [3–6]. Copper complexes containing electron-rich ligands have been studied considerably for the cross-coupling of nitrogen nucleophiles with aryl halides [7–10]. Most of the systems involve a homogeneous process, and the ligand chelated with the metal plays a crucial role in the catalysis.

Very recently, the employment of nanocrystalline metal oxides as catalysts in organic synthesis has attracted much attention [11]. CuO nanoparticles have been studied for C–N, C–O, and C–S bond formations via cross-coupling reactions of nitrogen, oxygen, and sulfur nucleophiles with aryl halides [12, 13].

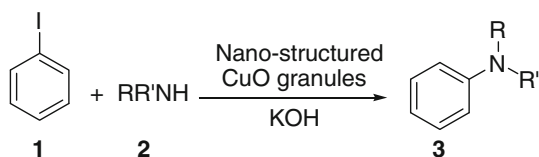
Despite their great chemical reactivity, nano-catalysts in general and nano metal oxides in particular suffer from having an inappropriate physical form that makes their practical applications often unfeasible or at least formidable. Industrial processes, especially fixed bed operations, often require casting of nano powder catalysts into a granulated structure. In order to shape green bodies from powders, many methods can be used, such as pressing, slip casting, tape casting, injection molding, and gel casting. Gel casting has been widely studied for the last decade [14–16].

Alginate is a type of gelling polysaccharide, which can be dissolved in water at room temperature (RT) and then gelled after casting by cross-linking with divalent metal ions [17]. Several reports have demonstrated the gel casting of micron and submicron powders by using sodium alginate [18–20].

We herein describe a method for the preparation of spherical granules of CuO nano-catalyst that preserve a

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Scheme 1

great portion of their initial specific surface area by using sodium alginate. The separation of nano-structure catalysts is often very difficult; in particular, when the particles are too fine, they should pass through any filter available. However, after algination, nanoparticles were fixed into a granulated structure so we could separate them very easily by filtration. The prepared catalysts were then used in the Ullmann cross-coupling of amines with iodobenzene under ligand-free conditions (Scheme 1).

Result and discussion

Catalyst preparation

Granulated copper oxide nano-catalyst was prepared via a three-step procedure. First, copper oxide nanoparticles were synthesized by hydrothermal decomposition of copper nitrate under supercritical water conditions. Second, the nanoparticles were immobilized in the polymeric matrix of sodium alginate. Third, high temperature calcination under an airstream entirely removed the carbonaceous materials and resulted in a pebble-type catalyst of high porosity.

The X-ray diffraction (XRD) patterns of nano-sized and bulk CuO are shown in Fig. 1. All the XRD peaks are indexed to the monoclinic crystal system of CuO. The average size of the obtained CuO particles 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 surface area of the CuO catalyst was 32.5 m²/g from Brunauer–Emmett–Teller (BET) analysis.

The first step in the synthesis of the nano-structured CuO granules was the preparation of the aqueous CuO nanoparticle suspension. Fabrication of the granules (MSs) was then effected by mixing of the CuO suspension with sodium alginate solution, and dropwise injection of the obtained sol into BaCl₂ solution through a 0.50-mm medical needle to gelify and form granules (Fig. 3). The size of the droplets and thus granules was adjusted by mean of a pneumatic cutting system which blew an airstream around the injecting needle. Particles obtained by the dripping method were calcined at different temperature [600 °C (MS₁), 700 °C (MS₂), 800 °C (MS₃)]. With respect to particle morphology, the calcination temperature played an

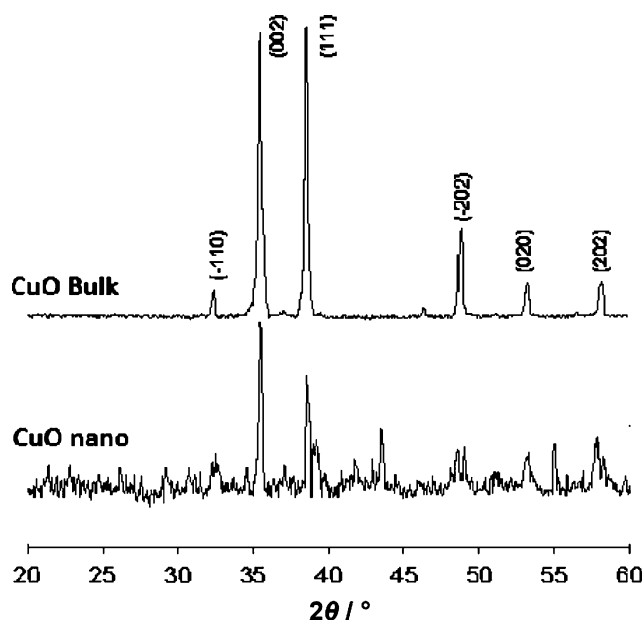


Fig. 1 XRD patterns of CuO particles prepared under supercritical conditions and bulk CuO

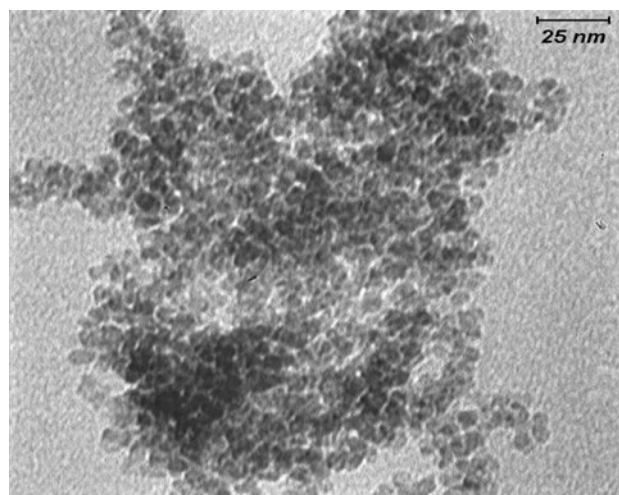


Fig. 2 Transmission electron micrographs of the CuO nanoparticles

important role in determining the surface characteristics of the granules.

Table 1 summarizes the results of BET analysis of the final granulated products. The maximum surface area was presented by MS₁, which was calcined at the lowest temperature. The XRD patterns of the nano-structured CuO granules are shown in Fig. 4. All the XRD peaks are indexed to the monoclinic crystal system of CuO. The XRD pattern of the copper oxide granules formed at 800 °C shows relatively sharp peaks with the highest intensity as shown in Fig. 4. This is mainly due to the growth of crystallite size. Figure 5 shows the shape, size, and morphology of different microspheres that have

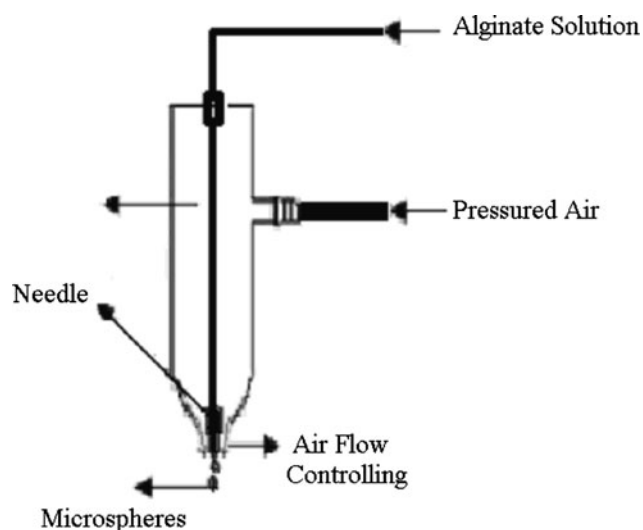


Fig. 3 Schematic diagram of the apparatus used for preparation of the nano-structured CuO granules

Table 1 Surface area of granules at different condition

Entry	Temperature (°C)	Time (h)	BET ($\text{m}^2 \text{g}^{-1}$)
MS ₁	600	6	18.74
MS ₂	700	6	9.16
MS ₃	800	6	5.65

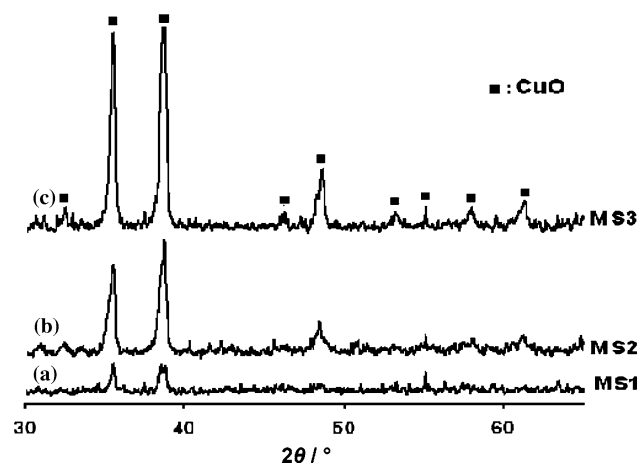


Fig. 4 XRD patterns of nano-structured CuO granules a MS₁, b MS₂, c MS₃

undergone different thermal treatments. The size of all microspheres is in the range of 300–500 μm .

Catalytic reactions

The cross-coupling reaction of aniline with iodobenzene was chosen as a model reaction to study the catalytic

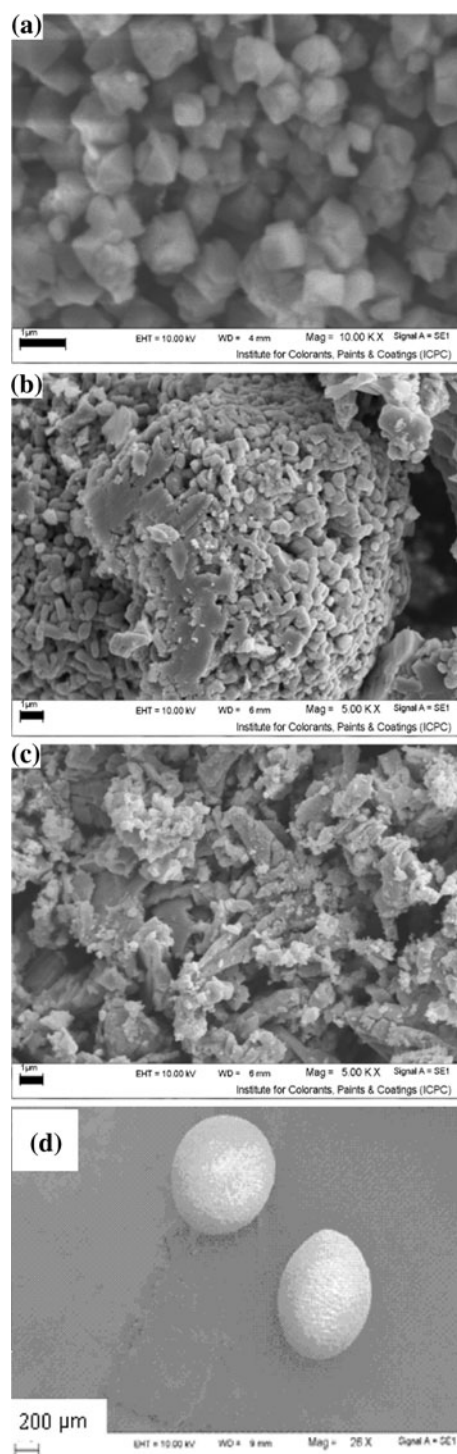


Fig. 5 SEM images of a MS₁, b MS₂, c MS₃ (scale size 1 μm), d shape of the nano-structured CuO granules (scale size 200 μm)

activity of the nano-structured CuO granules. We attempted various reaction conditions including different copper sources, bases, and solvents to optimize the Ullmann coupling.

Several readily available copper(II) salts such as $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ were screened for the

Ullmann coupling reaction of iodobenzene with aniline at 110 °C using 1.26 mol% of copper salt as the catalyst and 1 equiv of KOH in dimethyl sulfoxide (DMSO) under air. The experiments showed that commercially available copper sources catalyze this reaction to afford the corresponding product **3a** in low yields of 33–48% (Table 2, entries 1, 2). The size of CuO plays an important role in terms of yields and reaction times. When the reaction was conducted with bulk CuO, a poor yield of the product was obtained (Table 2, entry 3).

We compared the catalytic activity of CuO nanoparticles with that of the nano-structured CuO granules (MS₁, MS₂, MS₃). The highest yield was obtained with CuO nanoparticles and surprisingly CuO granules (MS₁) gave comparable yields to CuO nanoparticles (Table 2). The high surface area of the copper oxides is supposed to be important for the catalytic performance. Although the granulation of nanoparticles by the immobilization–calcination method reduces their specific surface area from 32.5 to 18.74 m²/g, the surface area is still much larger than that of bulk CuO (0.49 m²/g).

Although it is possible to slightly increase the yield of the reaction by using CuO nanoparticles, the nano-structured CuO granule-catalyzed reaction has the advantages of easy product purification, efficient recycling of the catalyst, and minimization of metal oxide traces in the product. Thus, we chose CuO granules (MS₁) as the catalyst for this reaction.

To study the effect of the solvent on the yield of this reaction, the model reaction was carried out in various solvents and under solvent-free conditions by using 1.26 mol% of CuO granules (MS₁) as the catalyst. As shown in Table 3 the best results in terms of yield and time were achieved under solvent-free conditions.

The same reaction was carried out at temperatures ranging from 90 to 120 °C, with an increment of 10 °C each time. The yield of product **3a** was increased, and the reaction time was shortened when the temperature was increased from 90 to 110 °C. Temperatures above 110 °C had no obvious influence on this reaction. Therefore, a temperature of 110 °C was chosen for all further reactions. Virtually no product was detected when a mixture of iodobenzene and aniline was stirred at room temperature. A temperature of at least 90 °C is required for appreciable conversion to product.

We also investigated the coupling of iodobenzene with aniline using different bases (Table 4). Among the bases we selected, KOH gave the best result, and K₂CO₃ was less efficient. The application of NEt₃ and pyridine as base failed to yield the desired product.

The scope of the copper-catalyzed aryl amination reaction was explored by using CuO granules (MS₁) as the copper source and 1 equiv of KOH as the base under

Table 2 C–N cross-coupling of aniline with iodobenzene in the presence of copper(II) compounds

Entry	Catalyst	Time (h)	Yield (%)
1	CuSO ₄ ·5H ₂ O	10	48
2	Cu(OAc) ₂ ·H ₂ O	10	33
3	CuO bulk	10	55
4	Nano-CuO	2	96
5	MS ₁	2	93
6	MS ₂	5	78

Catalyst (1.26 mol%), aniline (1.2 mmol), iodobenzene (1 mmol), KOH (1 mmol), and DMSO (1 cm³) were stirred at 110 °C

Table 3 C–N cross-coupling of aniline with iodobenzene in different solvents and temperatures

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	DMSO	110	2	93
2	Toluene	110	8	56
3	DMF	110	10	35
4	Solvent free	110	2	95
5	Solvent free	120	2	95
6	Solvent free	90	8	21
7	Solvent free	RT	10	–

CuO granules (1.26 mol%), aniline (1.2 mmol), iodobenzene (1 mmol), KOH (1 mmol), and solvent (1 cm³)

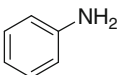
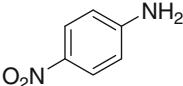
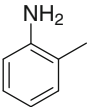
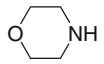
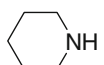
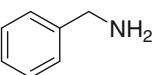
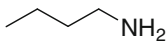
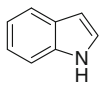
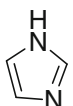
Table 4 C–N cross-coupling of aniline with iodobenzene in the presence of different bases

Entry	Base	Time (h)	Yield (%)
1	KOH	2	95
2	K ₂ CO ₃	5	45
3	NEt ₃	10	–
4	Pyridine	10	–

CuO granules (1.26 mol%), aniline (1.2 mmol), iodobenzene (1 mmol), and base (1 mmol) were stirred at 110 °C under solvent-free conditions

solvent-free conditions. The coupling reaction of iodobenzene with various amines was carried out using this catalyst system, and the desired amination products were obtained in good to high yields. As shown in Table 5, anilines having electron-donating groups showed greater reactivity than those with electron-withdrawing groups. These reaction conditions were also suitable for the cross-coupling of alkyl amines and *N*-heterocyclic compounds with iodobenzene. As nano-structured CuO granules are a heterogeneous catalyst, the recyclability of the catalyst in this coupling reaction was examined. The coupling of aniline with iodobenzene was chosen as a model reaction. After each cycle, the catalyst was recovered by simple

Table 5 C–N cross-coupling of amines with iodobenzene

Entry	Amine	Time (h)	Yield (%)
a		2	95
b		10	76
c		2	92
d		6	91
e		7	89
f		4	90
g		10	91
h		3	93
i		20	87

CuO granules (MS₁, 1.26 mol%), amine (1.2 mmol), iodobenzene (1 mmol), and KOH (1 mmol) were stirred at 110 °C under solvent-free conditions

filtration, washing with deionized water and ethanol, and then drying in vacuo. The recovered CuO granules were used directly in the next cycle. The recycling results are listed in Table 6 and show that the catalyst was still highly efficient after the fifth cycle.

In conclusion, we have developed a new method of granulation of CuO nanoparticles that preserves a great

Table 6 Recycling of CuO granules

Run	1	2	3	4	5
Time (h)	2	2	3	3	3
Yield (%)	95	93	89	86	84

portion of their initial specific surface area. The resulting granules were used as a catalyst for the efficient C–N cross-coupling reaction of amines with iodobenzene. The scope of the reaction using our catalyst is quite broad; various aryl, alkyl, and *N*-heterocyclic amines react with iodobenzene. Furthermore, nano-structured CuO granules can be recovered and recycled by simple filtration of the reaction solution and reused for at least five consecutive trials without a decrease in their activity.

Experimental

Batchwise supercritical hydrothermal synthesis of CuO nanoparticles

Copper(II) nitrate trihydrate (Merck AG, for synthesis) was used as the precursor for synthesis of nano copper oxide. Preparation of CuO took place in a stainless steel (316 dm³) autoclave that was able to endure a working temperature and pressure of 550 °C and 610 bar, respectively. The concentration of Cu(NO₃)₂ was 0.05 mol dm⁻³, and the heating period was about 2 h. The synthesis was carried out at 500 °C to accelerate the hydrolysis reactions and thus shorten the fabrication period. To maintain a suitable safety margin, the 200-cm³ stainless steel autoclave was loaded with only 60–80 cm³ of the solution. The autoclave was removed from the furnace, quenched with cold water, and the 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 then dried at ambient temperature.

Preparation of nano-structured CuO granules

CuO nanoparticles (2 g) were dispersed in 5 cm³ deionized water and the mixture was stirred to form an aqueous CuO suspension, and the reaction mixture was exposed to ultrasonic irradiation for 30 min. Afterwards 14 cm³ of gelatin aqueous solution (sodium alginate, 3.6 wt%) was added, and the mixture was stirred mechanically for 2 h. The resulting alginate–CuO nanoparticle solution was sprayed through a thin inner nozzle ($\varnothing = 0.5$ mm) into a 0.1 mol dm⁻³ barium chloride solution with pressurized air blown from an outer space of the nozzle (Fig. 3). The

resultant beads were allowed to stand in the solution for 3 h at room temperature on a magnetic stirrer, and then they were washed three times with pure water and eventually dried at 400 °C for 10 h. The dried granules were transferred into a muffle furnace and calcined at 600 °C (MS₁), 700 °C (MS₂), and 800 °C (MS₃) for 6 h to decompose and burn all of the organic materials.

Characterization

The crystal structures of the prepared CuO nanoparticles and final granules were analyzed by using Cu K α radiation (Philips PW 1800). The particle size and morphology of the nanocrystalline particles were examined using a transmission electron microscope (TEM, LEO 912AB). In the case of granules, a scanning electron microscope (SEM, LEO1455VP) was used for the same purpose. The surface areas of the CuO nanoparticles and the nano-structured CuO granules were determined by the nitrogen adsorption BET method (Quantachrome Instruments, Nova 2000e).

Catalytic reactions

CuO granules (MS₁, 1.26 mol%) were added to a stirred solution of amine (1.2 mmol), iodobenzene (1 mmol), and KOH (1 mmol). The reaction mixture was heated at 110 °C for the appropriate time (Table 5) and then allowed to cool to room temperature. Diethyl ether (2 cm³) and 2 cm³ water were then added to the reaction mixture and the catalyst was removed by high speed centrifugation (for CuO nano-catalyst) or simple filtration (for CuO granules). The reaction mixture was further extracted with diethyl ether (3 \times 5 cm³). The combined organic phases were washed with brine and dried over sodium sulfate. The solvent was removed by rotary evaporation to give a residue which was purified on silica gel column chromatography using ethyl acetate and hexane as eluent.

All products were known and characterized by comparison of their physical and spectra data with those already reported [13, 21–24].

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