Full paper

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CuO nanoparticle-catalyzed diaminations for synthesis of benzimidazole derivatives

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Copper oxide nanoparticles have been applied as an efficient catalyst for the formation of C–N bonds. They can catalyze diaminations for the regiospecific synthesis of 1,2-disubstituted benzimidazoles from 1,2-dihaloarenes and *N*-arylamidines. The best performance has been achieved using CuO nanoparticles with average diameter of 6.5 nm. In addition, the catalyst can be recycled and reused without any significant decrease in catalytic activity. Copyright © 2016 John Wiley & Sons, Ltd.

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Keywords: CuO nanoparticles; heterogeneous catalyst; benzimidazoles; amidine

Introduction

Benzimidazoles, an important class of nitrogen-containing heterocycles, show a wide range of biological activities such as antitumor, antiparasitic, antiviral and antimicrobial. In addition, this motif is the core structure of some marketed drugs such as esomeprazole, telmisartan, candesartan and bilastine.[1–4] Therefore, the design of a mild, original and sustainable method for the synthesis of the benzimidazole skeleton is of great importance in synthetic organic chemistry (Scheme 1). The classical synthesis methodology is the condensation of 1,2-diaminoarenes with either carboxylic acid derivatives or aldehydes.[5–8] Recently, transition-metal-catalyzed C–N cross-coupling reaction for the formation of benzimidazole derivatives has been developed.[9–17] For example, Evindar and Batey[18] reported an intramolecular aryl guanidinylation to give benzimidazoles with palladium or copper as catalyst. Ma and co-workers[19] and Buchwald and co-workers[20] demonstrated the synthesis of 1,2-disubstituted benzimidazoles via a palladium- or copper-catalyzed aryl amination/condensation process, respectively. Brasche and Buchwald also reported the $Cu(OAc)_2$-catalyzed synthesis of benzimidazoles from amidines in a process involving C–H functionalization/C–N bond formation.[21] Shortly afterwards, Shi and co-workers reported the formation of benzimidazoles through C–H activation catalyzed by palladium.[22] Later on, Deng and co-workers described the CuI/*N*,*N*′-dimethylethylenediamine (DMEDA)-catalyzed regiospecific reaction of 1,2-dihaloarenes with *N*-substituted amidines or guanidines.[23,24] You and co-workers also reported the regiospecific synthesis of 1,2-disubstituted (hetero)arylimidazoles.[25] However, the separation and recycling of the catalyst remains a problem in the aforementioned approaches. Considering the preference of modern green chemistry for more environmentally friendly methods, the development of an efficient reaction system with recyclable catalysts in the presence of mild inorganic base is highly desirable.

Nanoparticles have emerged as robust and high-surface-area heterogeneous catalysts, which serve as sustainable alternatives to conventional materials.[26–30] CuO nanoparticles have drawn attention due to their stability and availability.[31–34] For example, Punniyamurthy and co-workers reported the synthesis of substituted benzimidazoles via CuO nanoparticle-catalyzed intramolecular C–N coupling.[35] Previously we have reported the preparation of CuO nanoparticles with average diameter of 6.5 nm and their application as a highly efficient catalyst for arylations of heterocycle C–H bonds and oxidative coupling of amidines and benzyl alcohols.[36–38] As part of our ongoing research in developing CuO nanoparticle-catalyzed coupling reactions for the synthesis of heterocycles, we demonstrate herein an efficient, environmentally friendly and recyclable CuO nano-catalyst in the synthesis of benzimidazole derivatives via 1,2-dihaloarenes with *N*-substituted amidines.

Experimental

General

All reactions were carried out in flame-dried reaction vessels. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel. Commercially available chemicals were used without further purification. All the *N*-arylamidines[39,40] and CuO and Cu_2O nanoparticles[41–46] were prepared according to literature procedures.

The prepared nanometric catalyst was characterized using powder X-ray diffraction with graphite-monochromatized Cu Kα radiation (λ = 0.154060 nm) in the 2θ range from 10° to 80°. Field-emission scanning electron microscopy (FESEM) images were obtained using an S-4800 instrument with an accelerating voltage of 5 kV. Transmission electron microscopy (TEM) images were recorded with a FEI Tecnai G^2 20 high-resolution microscope at an acceleration voltage of 200 kV. All new compounds were fully

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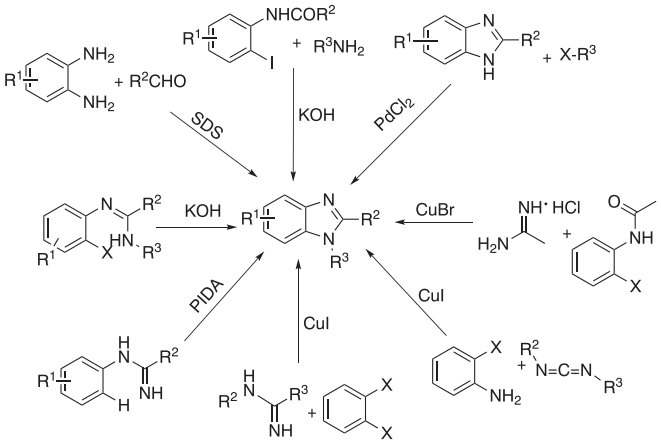

Scheme 1. Efficient syntheses of benzimidazoles.

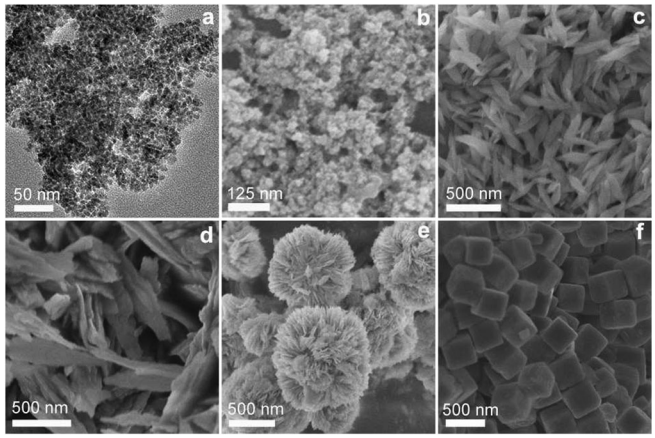

Figure 1. (a) TEM image of CuO nanoparticles. FESEM images of (b) CuO nanoparticles, (c) CuO nanospindles, (d) CuO nanoplates, (e) CuO nanoflowers and (f) Cu_2O nanocubes.

characterized. Melting points were determined with melting point apparatus in open capillaries and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with 300 MHz NMR spectrometers using $CDCl_3$ as solvent and tetramethylsilane as an internal standard. High-resolution mass spectral data were obtained with ionization mode of ESI using an Agilent 6200 LC/MS TOF.

General procedures for 1,2-Disubstituted Benzimidazoles

The reactions were typically carried out using 1,2-diiodobenzene (0.50 mmol), amidine (0.60 mmol), CuO (0.050 mmol), base (2.0 mmol) and ligand (0.050 mmol) in diglyme (2 ml) under reflux in argon for 24 h. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate (3 × 5 ml). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The crude products were purified by column chromatography on silica gel (300–400 mesh) with petroleum ether–ethyl acetate as eluent.

Recycling of the catalysts

The separated precipitates in the procedure described above were washed sufficiently with deionized water and ethanol three times each and then dried under vacuum at 50 °C for 8 h. The CuO nanoparticles were then recovered.

Results and discussion

The synthesized CuO and Cu_2O were characterized using TEM and FESEM (Fig. 1). Our initial investigations were focused on CuO nanoparticle-catalyzed diamination for the synthesis of benzimidazoles. When *N*-phenylbenzimidamide (**1a**) derived from the addition of aniline to benzonitrile was refluxed with 1,2-diiodobenzene (**2a**) in diglyme in the presence of 10 mol% of CuO nanoparticles and 10 mol% of 1,10-phenanthroline (phen), benzimidazole (**3a**) was obtained in 66% yield (Table 1, entry 1). Among the various copper sources employed (entries 2–8), it is observed that nanoparticles are better catalysts than non-nanoparticles. Low yields are obtained for two conventional catalysts, $Cu(OAc)_2{\cdot}H_2O$ (25%) and commercial CuO powder (about 200 mesh, 30%), while nano-catalysts such as CuO nanospindles, CuO nanoplates, CuO nanoflowers and Cu_2O nanocubes give the desired products in higher yields, among which CuO nanoparticles with average diameter of 6.5 nm were found to be the most effective catalyst. No product is formed in the absence of any catalyst, and all starting materials are recovered from the reaction system. Solvent effect studies show that diglyme is the best (entries 9–12). A series of bases were also investigated to reveal that $K_3PO_4{\cdot}3H_2O$ gives the highest yield (entries 13–17). It is observed that the product yield is decreased to 43% on decreasing the catalyst loading from 10 to 5 mol%, whereas no significant increase is observed when using 20 mol% of catalyst (entries 18 and 19). Other factors such as ligand, temperature and reaction time with preset optimized reaction conditions were screened for the reaction. It is interesting to find that the reaction does not proceed well without ligand, and phen is the best ligand (entries 20–24). The temperature also has a significant effect on this reaction: the yield is dramatically increased from 35% at 120 °C to 64% at 130 °C and 82% yield is achieved at 150 °C (entries 25–27). Lower yield is obtained when the reaction time is changed from 24 to 12 h; however, no significant increase in yield is observed when the reaction time is extended to 48 h (entries 28 and 29). Based on all the results discussed above, the optimized reaction conditions are: 10 mol% CuO nanoparticles in the presence of 4 equiv. of $K_3PO_4{\cdot}3H_2O$ in refluxing diglyme for 24 h. Under the optimized conditions, the desired benzimidazole product is obtained in 90% yield.

With the optimized reaction conditions in hand, we then turned our attention to the scope of the reaction. The results are shown in Scheme 2. It is found that moderate to good yields are achieved for amidines with both electron-withdrawing and electron-donating substituents on the arene ring. The influence of the electronic variation of amidines on the yield is negligible. Then, we discovered that the steric hindrance has an important effect on the reaction, amidine with bulky substituents affording lower yields. For example, only 51% yield is obtained when amidine with *n*-dodecyl substituent is used and no product is detected when 2,6-diisopropyl-substituted benzimidamide is employed as substrate. Also various substituents on *o*-dihalobenzenes were studied: CH_3, CF_3 and Cl could be tolerated. It is found that *o*-dihalobenzenes with electron-donating substituents can lead to higher yields than those with electron-withdrawing substituents. When *o*-diiodobenzene is changed to *o*-bromoiodobenzene, almost identical results are obtained. However, *o*-dibromobenzene and *o*-dichlorobenzene under the same conditions lead to only 51 and 30% yield of products, respectively.

The reusability of the CuO nanoparticles was investigated. As evident from Table 2, no significant decrease in the catalytic

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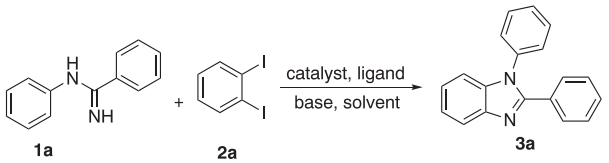
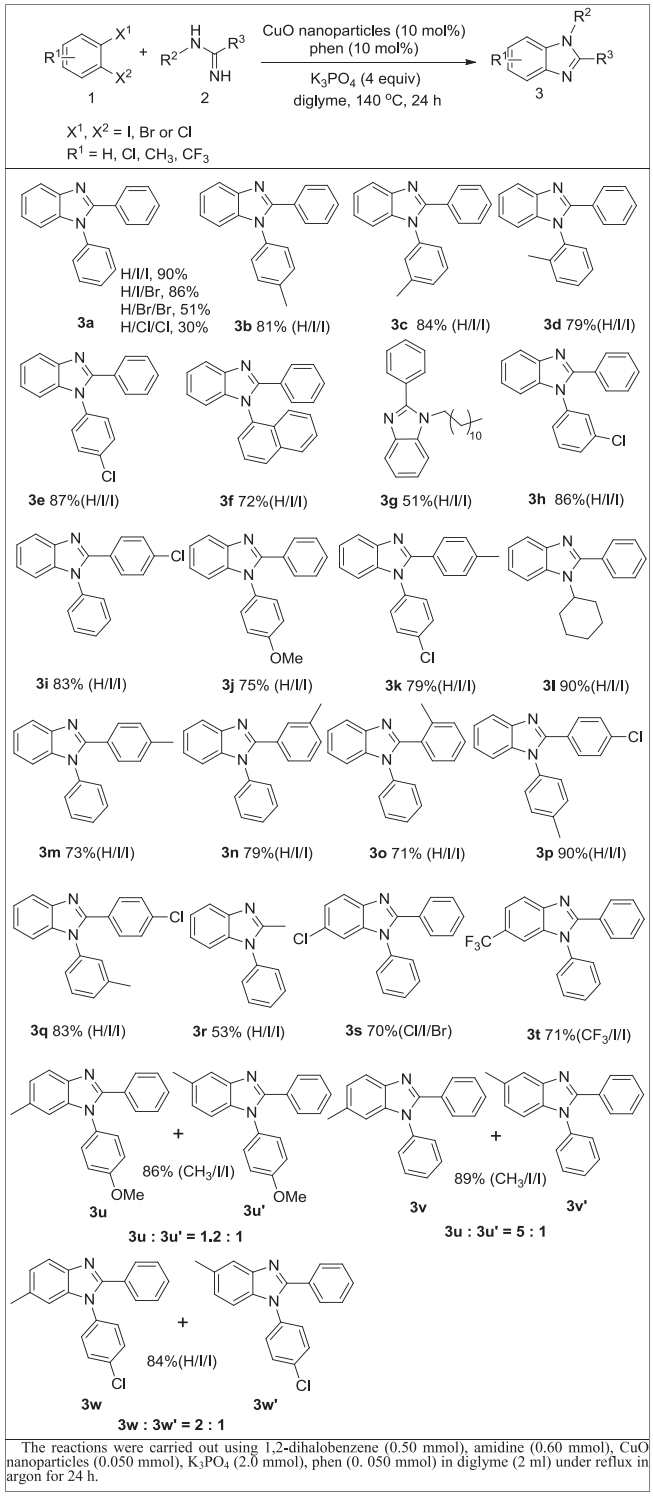
Table 1. Optimization of nano-CuO-catalyzed cascade reaction of *N*-phenylbenzimidamide[a]



Entry	Catalyst (10 mol%)	Base	Ligand	Solvent	Yield (%)[b]
1	CuO nanoparticles	K_2CO_3	Phen	Diglyme	66
2	CuO (200 mesh)	K_2CO_3	Phen	Diglyme	30
3	CuO nanospindles	K_2CO_3	Phen	Diglyme	46
4	CuO nanoplates	K_2CO_3	Phen	Diglyme	50
5	CuO nanoflowers	K_2CO_3	Phen	Diglyme	58
6	Cu_2O nanocubes	K_2CO_3	Phen	Diglyme	20
7	$Cu(OAc)_2{\cdot}H_2O$	K_2CO_3	Phen	Diglyme	25
8	—	K_2CO_3	Phen	Diglyme	—
9	CuO nanoparticles	K_2CO_3	Phen	Toluene	20
10	CuO nanoparticles	K_2CO_3	Phen	DMSO	—
11	CuO nanoparticles	K_2CO_3	Phen	DMF	Trace
12	CuO nanoparticles	K_2CO_3	Phen	Xylene	—
13	CuO nanoparticles	Cs_2CO_3	Phen	Diglyme	56
14	CuO nanoparticles	NEt_3	Phen	Diglyme	45
15	CuO nanoparticles	K_3PO_4	Phen	Diglyme	90
16	CuO nanoparticles	Na_2CO_3	Phen	Diglyme	51
17	CuO nanoparticles	NaOAc	Phen	Diglyme	33
18	CuO nanoparticles	K_3PO_4	Phen	Diglyme	43[c]
19	CuO nanoparticles	K_3PO_4	Phen	Diglyme	91[d]
20	CuO nanoparticles	K_3PO_4	DMEDA	Diglyme	33
21	CuO nanoparticles	K_3PO_4	L-Proline	Diglyme	51
22	CuO nanoparticles	K_3PO_4	dppm	Diglyme	46
23	CuO nanoparticles	K_3PO_4	—	Diglyme	—
24	CuO nanoparticles	K_3PO_4	H_2acac	Diglyme	Trace
25	CuO nanoparticles	K_3PO_4	Phen	Diglyme	35[e]
26	CuO nanoparticles	K_3PO_4	Phen	Diglyme	64[f]
27	CuO nanoparticles	K_3PO_4	Phen	Diglyme	82[g]
28	CuO nanoparticles	K_3PO_4	Phen	Diglyme	51[h]
29	CuO nanoparticles	K_3PO_4	Phen	Diglyme	93[i]

[a]Reaction conditions: 1,2-diiodobenzene (0.50 mmol), *N*-phenylbenzimidamide (1.2 equiv.), base (4 equiv.), catalyst (10 mol %), ligand (10 mol%), solvent (2 ml), under reflux in argon for 24
[b]Isolated yields
[c]CuO (5 mol%)
[d]CuO (20 mol%)
[e]120°C
[f]130°C
[g]150°C
[h]12 h.
[i]48 h

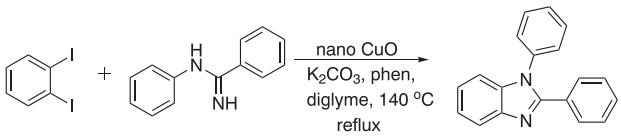


The reactions were carried out using 1,2-dihalobenzene (0.50 mmol), amidine (0.60 mmol), CuO nanoparticles (0.050 mmol), K_3PO_4 (2.0 mmol), phen (0. 050 mmol) in diglyme (2 ml) under reflux in argon for 24 h.

Scheme 2. Synthesis of benzimidazole derivatives catalyzed by CuO nanoparticles.

activity for the diamination of 1,2-diiodobenzene with *N*-phenylbenzimidamide is observed when recovered CuO nanoparticles are used. To examine whether the observed catalysis was derived from CuO nanoparticles or leached copper species, the diamination of 1,2-diiodobenzene was carried out under the optimized conditions and the catalyst was removed from the mixture by centrifugation after 6 h. The leaching of copper from the CuO nanoparticles during the reaction was examined using atomic absorption spectroscopic analysis, and a slight leaching (< 1 ppm) is observed. However, no further progress of reaction is observed for the 'catalyst-free' solution under the same conditions even after 18 h. We thus believe that the reaction may proceed through an oxidative addition, anion substitution,[47] then by a reductive elimination process on the surface of the CuO nanoparticles which are stabilized by phen via a heterogeneous process.[36]

Table 2. Successive reactions using recycled CuO nanoparticles[a]



Test	Yield (%)
1	90
2	86
3	83

[a]Reaction conditions: 1,2-diiodobenzene (0.50 mmol), *N*-phenylbenzimidamide (1.2 equiv.), CuO nanoparticles (10 mol%), phen (10 mol%), K_3PO_4 (4 equiv.), diglyme (2 ml), under reflux in argon for 24 h

Conclusions

We have developed a practical and efficient CuO nanoparticle-catalyzed synthesis of benzimidazoles via tandem amination reaction in good to excellent yields. The CuO nano-catalyst can be recycled and reused without any significant decrease in the catalytic activity.

Acknowledgments

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