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CuO Nanoparticles: A Simple, Effective, Ligand Free, and Reusable Heterogeneous Catalyst for *N*-Arylation of Benzimidazole

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ABSTRACT: Copper(II) oxide (CuO) nanoparticles have been synthesized from copper acetate by simple precipitation method and were found to be an efficient and inexpensive catalyst for C−N cross-coupling reactions of benzimidazole with various aryl halides. The catalyst was characterized by scanning electron microscope, transmission electron microscope, Brunauer−Emmett−Teller—surface area, and X-ray diffraction analysis. Benzimidazole undergoes reaction with aryl bromides, aryl chlorides, or aryl fluorides in the presence of K_2CO_3 at moderate temperature. The yield of *N*-arylated benzimidazole is ranging from 55 to 92%. The effect of the particle size of the catalyst on *N*-arylation of benzimidazole with 4-chlorobenzonitrile was studied. Reusability of the CuO nanoparticles was also carried out, and the results were found to be good.

1. INTRODUCTION

C(ayrl)−N(heterocycle) bond formation is an important organic reaction since the resultant *N*-arylated heterocyclic product play an important role in a wide range of pharmaceuticals, natural products, and biologically active compounds[1−6] and have been exploited as precursors for versatile N-heterocyclic carbenes,[7−9] efficient ligands for transition metal catalysis,[10−12] or ionic liquids.[13,14] However, the standard protocol to prepare these moieties are either by aromatic nucleophilic substitution of benzimidazole with activated aryl halides,[15−17] or by traditional Ullmann type coupling[18,19] as well as the coupling of heterocycles with aryl lead, aryl bismuth, aryl borane, and aryl silane reagents.[20−23] However, these reactions suffered from several drawbacks such as harsh reaction condition (Ullmann reaction requires high-temperature and extended reaction time), stoichiometric amount of copper reagents, and low tolerance of functional groups, which limited their applications. A breakthrough has been made by Buchwald and coworkers who discovered that the Cu-catalyzed *N*-arylation of nitrogen-containing heterocycles with aryl halides could be achieved in good yields under mild conditions in the presence of bidentate N, N-ligand.[24−29] Recently, *N*-arylation is reported using copper salts in the absence of base in protic solvents.[30−32] Chiang et al. reported the heterogeneous protocol for C−N cross-coupling reactions with aryl boronic acids using a polymer supported copper catalyst.[33]

N-Arylation of benzimidazole is a vital organic transformation in the preparation of many drug molecules or its intermediates, to mention few, MRL-1237 (antiviral),[34] Telmisartan (angiotensin II receptor antagonist used in the management of hypertension), and TPBi (OLED) (Figure 1). Hence we have developed and report herein CuO nanoparticles as a ligand free catalyst for *N*-arylation of benzimidazole.

2. EXPERIMENTAL SECTION

2.1. General Remarks. All the reagents used were of chemically pure and analar grade. Commercial grade solvents were distilled according to standard procedures and dried over molecular sieves before use. All other chemicals were purchased from Aldrich and were used without further purification. X-ray diffraction (XRD) measurements were performed on a Rigaku Ultima III X-ray diffractometer using Cu Kα radiation. The morphology of the sample was observed on HITACHI S-3000H scanning electron microscope (SEM) and JEOL 21d00F transmission electron microscope (TEM). The surface area was analyzed on Gemini V surface area and pore size analyzer. NMR spectra were obtained on a 400 MHz BRUKER spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as a standard. The IR spectrum was recorded in Perkin-Elmer FT-IR spectrometer using KBr pellets. Thermogravimetric analysis was made with SII Nanotechnology Inc., EXSTAR6200 TG/DTA analyzer. Gas chromatogrph−mass spectrometer (GC-MS) analysis was carried out in a Thermoscientific GC-MS equipped with TR5MS (15 m × 0.25 mm i.d.) capillary column.

2.2. Synthesis of Catalyst. CuO nanoparticles were synthesized according to the literature method.[35] A 300 mL aliquot of 0.02 M copper acetate aqueous solution was mixed with 1 mL of glacial acetic acid in a round-bottomed flask equipped with refluxing device. The solution was heated to 100 °C with vigorous stirring; then about 0.8 g of sodium hydroxide solid was rapidly added into the above boiling solution until the value of the mixture reached pH 6−7, where a large amount of black precipitate was simultaneously produced. After being cooled to room temperature, the precipitate was centrifuged, washed once with distilled water and three times with absolute ethanol, respectively, and dried in air at room temperature (Scheme 1).

2.3. Procedure for *N*-Arylation of Benzimidazole. In a typical *N*-arylation procedure, nanocrystalline CuO (31 mg, 10 mol %) was added to a mixture of 4-chlorobenzonitrile (138 mg, 1 mmol), benzimidazole (142 mg, 1.2 mmol), and K_2CO_3 (276 mg, 2 mmol) in *N*,*N*-dimethylacetamide (DMAc; 4 mL) and stirred at 120 °C. After completion of the reaction (as monitored by thin-layer

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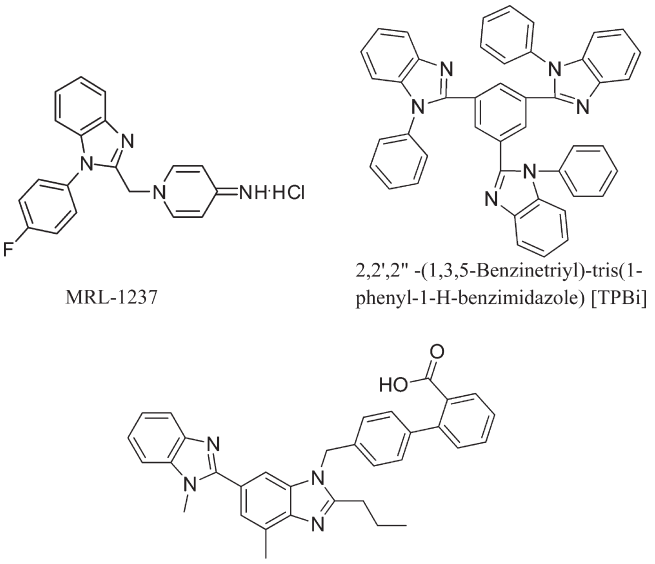


Figure 1. Examples for pharmaceutically and industrially important *N*-arylated benzimidazole derivatives.

Scheme 1. Synthesis of CuO Nanoparticles

$Cu(CH_3COO)_2$ (aq) —(glacial AcOH, NaOH; 100 ^{0}C, pH 6-7)→ CuO Nanoparticles

chromatography (TLC)), the reaction mixture was centrifuged to separate the catalyst and washed several times with ethyl acetate. The filtrate was quenched with aqueous sodium hydrogen carbonate and the product was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 70/30) to afford pure 4-(1*H*- benzo[*d*]imidazol-1-yl)benzonitrile; mp, 130−132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.16 (s, 1H, −CH=N), 7.39−7.88 (m, 8H, aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): 111.57 (−C≡N), 134.22 (−CH=N), 124.46 (C−N). FT-IR (KBr): ν(C−N) 1289, ν(C=N) 1665, ν(C≡N) 2224 cm^{-1}. MS (GC): m/z 219.06 (M+).

3. RESULTS AND DISCUSSION

3.1. Preparation and Characterization of Catalyst. CuO nanoparticles have been synthesized from aqueous copper(II) acetate solution by precipitation method. This procedure is cost-effective whereas commercially available CuO nanoparticles are relatively expensive.[36]

The crystallinity of the nano-CuO was examined by powder X-ray diffraction. The powder XRD peaks shown in Figure 2 could be indexed to the monoclinic crystal system in good agreement with the reported data. The broadness of peaks indicates the nanocrystalline nature of CuO. The particle size of the nano-CuO powder was estimated using Scherrer's formula.

$$\text{crystalline size} = \frac{K\lambda}{\beta \cos \theta}$$

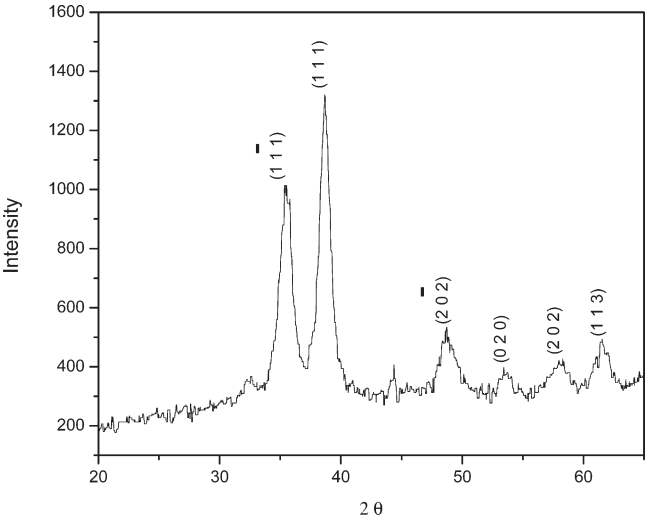


Figure 2. Powder XRD pattern of CuO nanoparticles.

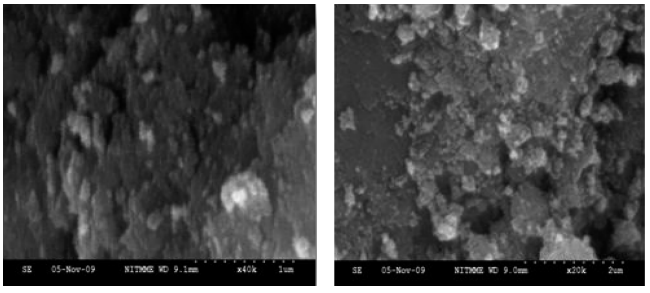


Figure 3. Scanning electron microscopic images of nano-CuO particles.

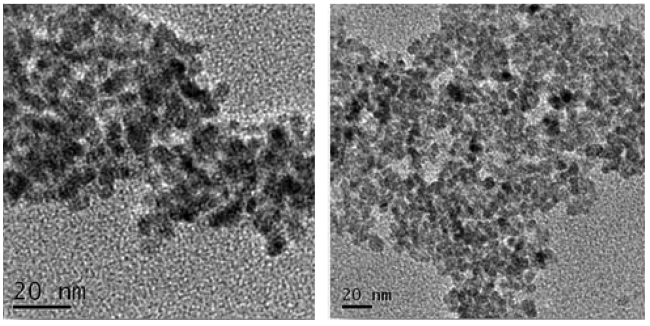
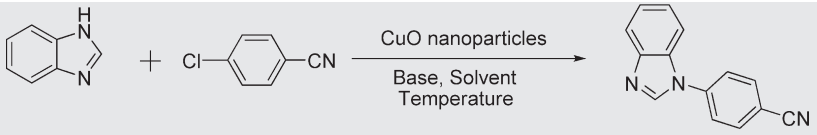


Figure 4. Transmission electron microscopic images of nano-CuO particles.

where K is the shape factor (0.9), λ is the wavelength of X-rays (1.541 Å), and β is the full width at half-maximum. The particle size of the formed CuO nanoparticles is found to be 6−8 nm. From the SEM analysis (Figure 3), the shape of formed CuO nanoparticles was found to be spherical. Similarly, from the TEM images (Figure 4), the particle size was confirmed to be less than 10 nm which is in good agreement with the calculation made by Scherrer's equation. The Brunauer−Emmett−Teller (BET) surface area of CuO nanoparticle was found to be 81 m^2/g. This value matches with the already reported literature value.[35] Thermal stability of the catalyst was found with thermogravimetric analysis, which reveals that the prepared CuO nanoparticles can be stable up to 927 °C.

Table 1. Optimization of Reaction Conditions for the CuO Nanoparticles-Catalyzed *N*-Arylation of Benzimidazole (1a) with 4-Chlorobenzonitrile (1b) To Form *N*-Arylated Benzimidazole (1c)[a]



1a 1b 1c

Entry	Solvent[b]	Base	Amount of Base (mmol)	Amount of Catalyst (mol %)	Temperature (°C)	Time (h)	Yield[c] (%)
1	DMF	K_2CO_3	2	10	120	24	22
2	**DMAc**	**K_2CO_3**	**2**	**10**	**120**	**24**	**86**
3	THF	K_2CO_3	2	10	120	24	6
4	DMSO	K_2CO_3	2	10	120	24	63
5	DMAc	KOH	2	10	120	24	27
6	DMAc	K_3PO_4	2	10	120	24	Trace
7	DMAc	$(CH_3)_3COK$	2	10	120	24	6
8	DMAc	K_2CO_3	1	10	120	24	49
9	DMAc	K_2CO_3	3	10	120	24	39
10	DMAc	K_2CO_3	4	10	120	24	26
11	DMAc	K_2CO_3	2	0	120	24	No reaction
12	DMAc	K_2CO_3	2	5	120	24	20
13	DMAc	K_2CO_3	2	15	120	24	19
14	DMAc	K_2CO_3	2	10	80	24	10
15	DMAc	K_2CO_3	2	10	100	24	11
16	DMAc	K_2CO_3	2	10	140	24	2
17	DMAc	K_2CO_3	2	10	120	12	29
18	DMAc	K_2CO_3	2	10	120	36	88
19	DMAc	K_2CO_3	2	10	120	48	90

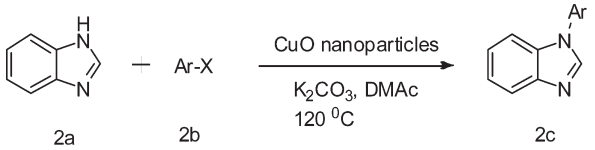
[a] All the reactions were performed with 1.2 mmol (142 mg) of benzimidazole and 1 mmol (138 mg) of 4-chlorobenzonitrile. [b] A 4 mL aliquot of solvent was used in all the reactions. [c] Isolated yield.

3.2. Optimization of Reaction Conditions. Initially, the reaction conditions such as solvent, base, amount of base, amount of catalyst, temperature, and reaction time were optimized. To screen the reaction conditions, the reaction between benzimidazole and 4-chlorobenzonitrile was carried out at different reaction conditions. The data are listed in Table 1.

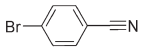
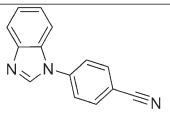
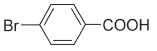
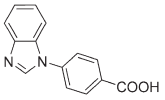
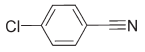
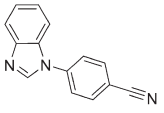
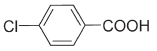
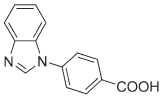
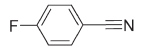
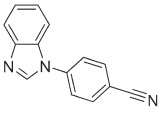
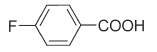
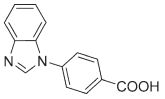
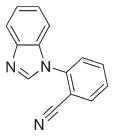
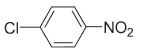
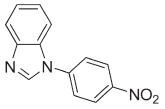
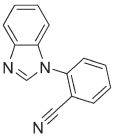
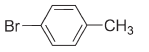
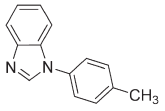
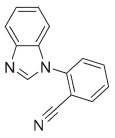
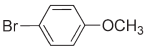
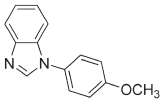
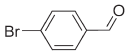
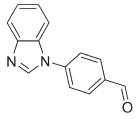
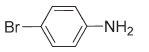
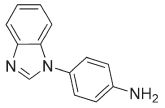
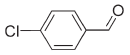
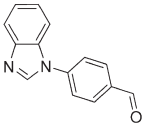
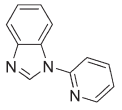
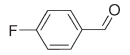
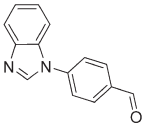
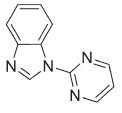
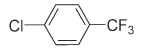
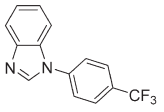
From the data given in Table 1, it is concluded that among the four different solvents such as *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMAc), tetrahydrofuran (THF), and dimethyl sulfoxide (DMSO), the solvent *N*,*N*-dimethylacetamide is found to be a better one (Table 1, entries 1−4). Similarly among the four bases such as potassium hydroxide (KOH), potassium carbonate (K_2CO_3), potassium phosphate (K_3PO_4), and potassium *tert*-butoxide ($(CH_3)_3COK$), the base potassium carbonate (2 mmol) is an efficient one (Table 1, entries 2, 5−10). A 10 mol % amount of CuO nanoparticles is found to be the optimum amount of catalyst (Table 1, entries 2, 12 and 13). Excess or less than 10 mol % CuO decreases the yield of product. In the absence of catalyst no reaction takes place (Table 1, entry 11). It is noted that temperature has significant effect on the efficiency of present catalytic system. Product was obtained in good yield only at 120 °C (Table 1, entries 2, 14−16). Higher or lower temperature makes the reaction slower. The *N*-arylated benzimidazole product was obtained in 86% yield after stirring at 120 °C in DMAc for 24 h (Table 1, entry 2). The yield is not increased significantly after 24 h (Table 1, entries 18, 19). Finally the conditions mentioned in entry 2 (Table 1) were chosen as the optimum condition for the *N*-arylation of benzimidazole with 4-chlorobenzonitrile.

3.3. Extension of Scope. The scope of the present catalytic system was extended by the reaction of benzimidazole with various aryl halides (Table 2). The yield is reasonably high (55−92%). The ortho-substituted aryl halides (Table 2, entries 4−6) gave poor yield compared to the para-substituted aryl halides (Table 2, entries 1−3). This may be due to the steric effect of cyano group at the ortho position. The yield is comparable with already reported catalytic systems for *N*-arylation of heterocycles.[37,38] The bromo group is one of the better leaving groups as compared to the chloro and fluoro groups (the leaving group ability of halogens is in the order of I > Br > Cl > F). Hence, the aryl bromides react faster as compared to the aryl chlorides and fluorides (Table 2, entries 12−14). Usually C−F bond activation is not so easy because of the poor leaving group ability of the fluorine. But the aryl fluorides containing ortho or para electron withdrawing groups are also coupled with benzimidazole to afford the corresponding *N*-arylated products in excellent yields (Table 2, entries 3, 6, 9, and 14). This clearly shows the efficiency of the present catalytic system. As the electron withdrawing effect of the substituent at the phenyl ring increases, the reactivity towards *N*-arylation also increases. Since the nitro group is one of the strongest electron withdrawing

Table 2. CuO Nanoparticles-Catalyzed *N*-Arylation of Benzimidazole with Various Aryl Halides[a]



2a 2b 2c

Entry	Ar-X (2b)	Product (2c)	Time (h)	Yield (%)[b]	Entry	Ar-X (2b)	Product (2c)	Time (h)	Yield (%)[b]
1			22	80	12			26	80
2			24	86	13			26	78
3			24	70	14			26	75
4			32	61	15			20	92
5			24	60	16			28	71
6			28	55	17			28	65
7			24	80	18			28	63
8			24	77	19			22	88
9			28	67	20			18	93
10			24	84	21			24	85
11			22	81					

[a] All the reactions were performed with 1 mmol of ArX, 1.2 mmol (142 mg) of benzimidazole, and 2 mmol (276 mg) of K_2CO_3 in 4 mL of DMAc at 120 °C. [b] Isolated yield.

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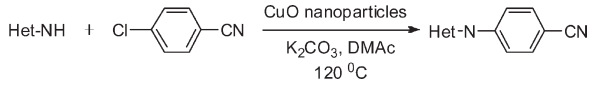
groups, it gives better yield (92%, Table 2, entry 15) as compared to other substrates. When *N*-arylation of benzimidazole was carried out with aryl halides having electron releasing substituent (Table 2, entries 16−18), products were obtained in lower yield compared to the aryl halides having electron withdrawing substituent. This catalytic system gave good results with the heterocyclic aryl halides (Table 2, entries 19−21). Especially, 2-bromopyrimidine gave a good yield of 93% with the reaction time of 18 h (Table 2, entry 20). The scope of this catalytic system was extended to various nitrogen containing heterocycles such as imidazole, carbazole, pyrrole, and indole. All the heterocyclic systems gave good yield ranging from 73 to 88% (Table 3, entries 1−4).

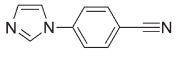
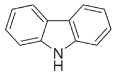
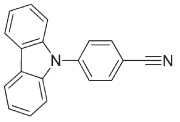
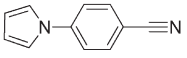
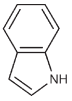
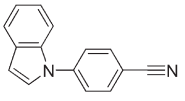
3.4. Comparison with Bulk CuO. Surface area and particle size play a vital role in the field of catalysis. The effect of surface area and particle size of the copper(II) oxide catalyst over *N*-arylation of benzimidazole with 4-chlorobenzonitrile was studied and given in Table 4. As the particle size of the catalyst increases, the surface area to volume ratio decreases. As the surface area to volume ratio decreases, the number of active sites per unit area decreases. Hence, it is observed that the bulk CuO which possesses low surface area and large particle size gave poor yield (Table 4, entry 2), whereas the CuO nanoparticle with comparatively high surface area gave good yield (Table 4, entry 1). This clearly indicates the significance of CuO nanoparticle on *N*-arylation of benzimidazole.

3.5. Reusability. The recycling ability of the catalyst is very important for industrial applications. After washing with ethyl acetate, we could reuse CuO nanoparticles for *N*-arylation of benzimidazole with 4-chlorobenzonitrile, and results are shown in Figure 5. The catalyst can be used for four times with almost consistent activity. Even at the fourth run, the yield of *N*-arylated product is 90%, indicating an excellent reusability and chemical stability of the catalyst.

3.6. Proposed Mechanism. On the basis of observation, a typical mechanism proposed for CuO nanoparticles-catalyzed *N*-aylation of benzimidazole with aryl halide is given in Figure 6. In the first step the aryl halides adsorbed on the surface of the CuO nanoparticles. The excess charge generated due to this adsorption could be shared among the CuO nanoparticles. Then

Table 3. CuO Nanoparticles-Catalyzed *N*-Arylation of Various Heterocycles with 4-Chlorobenzonitrile[a]



Entry	Het-NH	Product	Time (h)	Yield (%)[b]
1			15	88
2			24	73
3			24	80
4			24	82

[a] All of the reactions were performed with 1.2 mmol of heterocycles, 1 mmol (138 mg) of 4-chlorobenzonitrile, and 4 mL of DMAc at 120 °C. [b] Isolated yield.

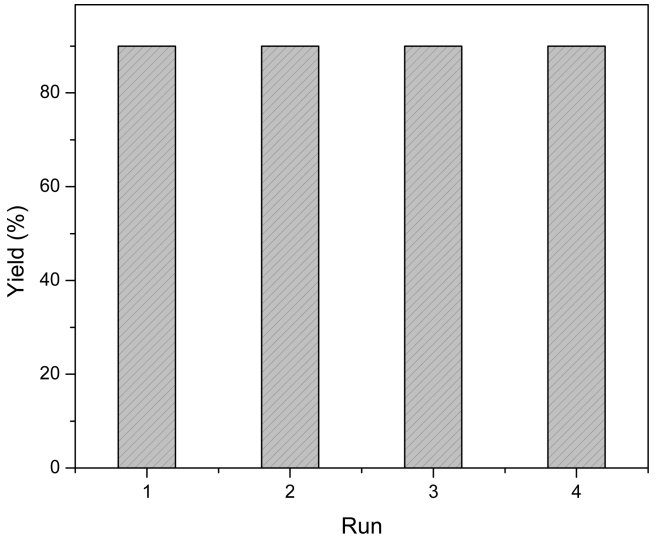
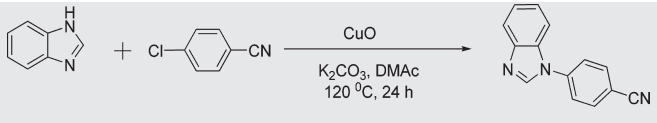


Figure 5. Reusability of CuO nanoparticles for *N*-arylation of benzimidazole with 4-chlorobenzonitrile (reaction conditions: 1.2 mmol (142 mg) of benzimidazole, 1 mmol (138 mg) of 4-chlorobenzonitrile, 2 mmol (276 mg) of K_2CO_3, and 10 mol % (31 mg) of CuO nanoparticles in 4 mL of DMAc at 120 °C).

Table 4. Comparison of Nano-CuO and Bulk CuO Catalyst on *N*-Arylation of Benzimidazole with 4-Chlorobenzonitrile[a]



Entry	Catalyst	Particle Size (nm)	Surface area (m^2/g)	Yield[b] (%)
1	CuO [c]	8	81	86
2	CuO [d]	314	18	52

[a] All the reactions were performed with 1.2 mmol (142 mg) of benzimidazole, 1 mmol (138 mg) of 4-chlorobenzonitrile, 2 mmol (276 mg) of K_2CO_3, and 10 mol % of CuO catalyst in 4 mL of DMAc at 120 °C. [b] Isolated yield. [c] Prepared as per procedure given in section 2.2. [d] Prepared by using the procedure given in section 2.2 but at 25 °C.

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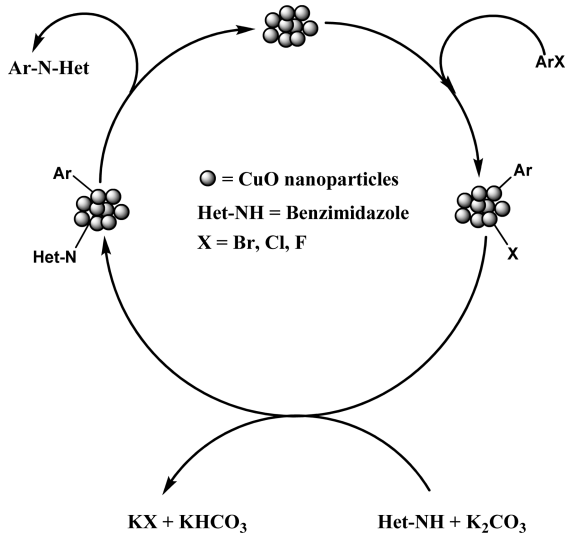

Figure 6. Proposed mechanism for CuO nanoparticles-catalyzed *N*-arylation of benzimidazole with aryl halides.

it undergoes reaction with benzimidazole and base. Finally, the catalytic cycle is completed by the elimination of *N*-arylated benzimidazole. Excess or less than 10 mol % CuO decreases the yield of product (Table 1, entries 2, 12, and 13); this observation also supports the proposed mechanism. While the catalyst amount is increased, aryl and benzimidazole ions might not be adsorbed close enough to interact effectively. Similarly while the catalyst amount is decreased, there may not be sufficient number of active sites for the adsorption of substrates.

4. CONCLUSIONS

In conclusion, CuO nanoparticles were found to be a cheap, air-stable, and efficient catalyst for *N*-arylation of benzimidazole with a variety of aryl halides. The procedure is simple, general, ligand-free, and efficient to afford the cross-coupled products in high yield. Since nanocrystalline CuO is a heterogeneous catalyst, it can be easily separated from the reaction mixture as well.

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