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Cu_2O: a Simple and Efficient Reusable Catalyst for N-arylation of Nitrogen-containing Heterocycles with Aryl Halides

Yi-Zheng Huang · Hong Miao · Qiao-Hong Zhang · Chen Chen · Jie Xu

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Abstract Cu_2O was found to be a simple and efficient catalyst for the N-arylation of a variety of nitrogen-containing heterocycles with aryl and heteroaryl chlorides, bromides and iodides to give the products in excellent yields. The catalyst can be recovered simply and reused for several times without significant loss of activity.

Keywords Cu-catalyzed · N-arylation · Nitrogen-containing heterocycles · Aryl halides

1 Introduction

N-Arylheterocycles play important roles in medicinal [1], biological [2] and *N*-heterocyclic carbene chemistry [3]. Traditionally, they were prepared mostly by Ullmann-type coupling reactions. However, these reactions generally suffered from high temperatures (around 200 °C) and the use of stoichiometric amounts of copper reagents, which make their further applications limited [4]. To overcome these drawbacks, great progresses have been made on the modification of Ullmann-type coupling reactions [5–11]. A recent notable achievement has been made by Buchwald et al. who discovered, in the presence of appropriate copper compounds and ligands, the N-arylation of nitrogen-containing heterocycles with aryl halides could be achieved in good yields under mild conditions [6]. Following these pioneering works, a number of other groups have reported similar approaches for these reactions under mild conditions by using different kinds of copper compounds and ligands [7]. From an economic and environmental standpoint, however, it is more practical that reusable catalysts are developed. Recently, Choudary and Kantam et al. used different kinds of reusable heterogeneous copper catalysts for the N-arylation of nitrogen-containing heterocycles with aryl halides [8]. Subsequently, Punniyamurthy et al. used CuO nanoparticle as reusable catalyst for the N-arylation of amines with iodobenzene [9].

On the basis of the research works on Cu-catalyzed C–N bond formations in our laboratory [10], here we report our recent results on Cu-catalyzed N-arylation of a variety of nitrogen-containing heterocycles with aryl chlorides, bromides and iodides under mild conditions by using Cu_2O as a simple and efficient reusable catalyst.

2 Experimental

2.1 Materials and Methods

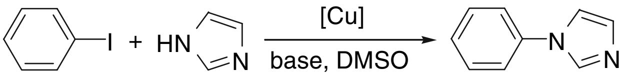
All solvents and reagents were used as purchased without further purification or modification. All the products are known and have been characterized by ^1H NMR, ^{13}C NMR, GC/MS (EI) and IR, and the melting points of the solid products have also been determined. ^1H NMR and ^{13}C NMR spectra were measured on a Bruker DRX-400 NMR spectrometer (400 MHz) with TMS as an internal standard. $CDCl_3$ was used as the solvent for all NMR spectra. GC/MS (EI) spectra were recorded on an Agilent 6890 N network GC system with an Agilent 5973 network mass selective detector (70 eV electron ionization). IR spectra were recorded on a Bruker Tensor 27 infrared spectrometer. Melting points were measured on a YAZAWA micro melting point apparatus (uncorrected).

Y.-Z. Huang · H. Miao · Q.-H. Zhang · C. Chen · J. Xu (✉)
State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Graduate School of the Chinese Academy of Sciences, Chinese Academy of Sciences, 457 Zhongshan Road,
Dalian 116023, P.R. China
e-mail: xujie@dicp.ac.cn

2.2 Typical Experimental Procedure

A mixture of aryl halide (1 mmol), nitrogen-containing heterocycle (1.5 mmol), Cu$_2$O (0.1 mmol), KOH (2 mmol) and DMSO (2 mL) was stirred at the temperature specified under Ar atmosphere until nearly complete conversion of aryl halide as monitored by GC or TLC, the cooled mixture was partitioned between ethyl acetate (10 mL) and water (3 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (5 mL). The combined organic layers were washed with brine (5 mL), dried over Na$_2$SO$_4$, and concentrated to give the crude product, which was purified by column chromatography on silica gel (200–300 mesh) using ethyl acetate/methanol as eluent to afford the desired product. Characterization data of two representative products are shown as follows: (a) 1-Phenyl-1*H*-imidazole (Table 1, entry 2), a light yellow liquid, ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.85$ (s, 1H), 7.49–7.45 (m, 2H), 7.39–7.34 (m, 3H), 7.28 (s, 1H), 7.21 (s, 1H) ppm; ^{13}C NMR (100.6 MHz, CDCl$_3$): $\delta = 137.4$, 135.7, 130.5, 130.0 (2C), 127.6, 121.5 (2C), 118.3 ppm; GC/MS (EI) *m*/*z* (%): 145 (11), 144 (100), 117 (47), 90 (36), 89 (12), 77 (28), 51 (16); IR (thin film, neat) cm^{-1}: 3118, 1598, 1509, 1304, 1252, 1110, 1059, 908, 760, 689, 661, 520. (b) 1-(3-Trifluoromethylphenyl)-1*H*-imidazole (Table 2, entry 6), a colorless liquid, ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.92$ (s, 1H), 7.66–7.61 (m, 4H), 7.34 (s, 1H), 7.25 (s, 1H) ppm; ^{13}C NMR (100.6 MHz, CDCl$_3$): $\delta = 137.9$, 135.6, 132.6 (q, $^2J_{CF} = 33.2$ Hz), 131.1, 130.8, 124.7, 124.3, 123.5 (q, $^1J_{CF} = 272.6$ Hz), 118.4, 118.2 ppm; GC/MS (EI) *m*/*z* (%): 213 (12), 212 (100), 193 (10), 185 (56), 166 (6), 158 (29), 145 (34), 135 (5), 125 (7), 116 (5), 95 (9), 75 (7); IR (thin film, neat) cm^{-1}: 3115, 1599, 1506, 1373, 1326, 1254, 1172, 1129, 1063, 896, 802, 699, 657.

Table 1 Screening reaction conditions for copper-catalyzed N-arylation of imidazole with iodobenzene[a]



Entry	[Cu]	Base	Temp (°C)	Yield (%)[b]
1	Cu$_2$O	KOH	90	49
2	Cu$_2$O	KOH	110	99 (90)
3[c]	Cu$_2$O	KOH	110	97
4	–	KOH	110	0
5	Cu$_2$O	Cs$_2$CO$_3$	110	76
6	Cu$_2$O	K$_3$PO$_4$	110	61
7	Cu$_2$O	K$_2$CO$_3$	110	25
8	CuI	KOH	110	100 (91)
9	Cu	KOH	110	70
10	CuO	KOH	110	24
11[d]	Cu$_2$O	KOH	110	4
12[e]	Cu$_2$O	KOH	110	99 (90)

[a] Iodobenzene (1 mmol), imidazole (1.5 mmol), [Cu] (0.1 mmol), base (2 mmol) and DMSO (2 mL) under Ar atmosphere for 24 h

[b] GC yield, and yield in parentheses refer to isolated yield

[c] 0.05 mmol Cu$_2$O was used

[d] With toluene as solvent instead of DMSO

[e] DMSO (2 mL) and H$_2$O (0.1 mL) was used as solvent

3 Results and Discussion

3.1 Screening Reaction Conditions for Copper-catalyzed N-arylation of Imidazole with Iodobenzene

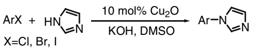
In our initial experiment, iodobenzene (1 equiv) was treated with imidazole (1.5 equiv) in DMSO at 90 °C for 24 h in the presence of Cu$_2$O (0.1 equiv) and KOH (2 equiv), only moderate yield of 1-phenylimidazole was obtained. To our delight, the yield of 1-phenylimidazole was increased dramatically to 99% when the reaction proceeded at 110 °C (Table 1, entries 1 and 2). Halving the amount of Cu$_2$O could also result in excellent yield, while no desired product was obtained in the absence of it (Table 1, entries 3 and 4). As shown in Table 1, bases influenced the progress of the reaction greatly. Other bases such as Cs$_2$CO$_3$, K$_3$PO$_4$ and K$_2$CO$_3$ were also evaluated but proved inferior to KOH (Table 1, entries 5–7). The influence of copper compounds was also investigated. 1-phenylimidazole was formed in quantitative yield when CuI was used, while Cu powder and CuO resulted in inferior yields (Table 1, entries 8–10). Solvent played an important role in this reaction. When toluene, a less polar solvent, was used instead of DMSO, only a trace amount of desired product was obtained (Table 1, entry 11). The presence of a trace amount of water in the reaction system did not affect the reactivity of the substrates, which showed it was not necessary to perform the reaction in dry solvent (Table 1, entry 12).

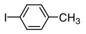
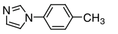
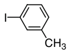
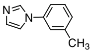
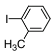
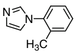
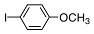
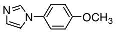
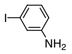
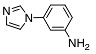
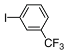
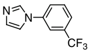
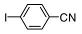
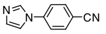
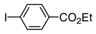
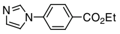
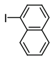
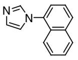
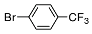
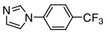
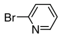
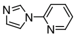
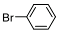
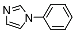
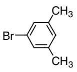
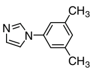
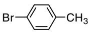
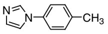
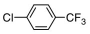
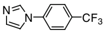
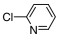
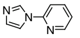
3.2 Cu$_2$O Catalyzed N-arylation of Imidazole with Various Aryl Halides

Although a slightly higher yield was obtained when CuI was used (compare Table 1, entries 8 with 2), Cu$_2$O was chosen in this study due to the following two reasons. Firstly, it is much cheaper than CuI. Secondly, on the contrary to CuI, it is very difficult for Cu$_2$O to be dissolved in DMSO, which makes it possible to be reused.

The efficacy of Cu_2O for general N-arylation of imidazole with various aryl halides was further evaluated. As shown in Table 2, aryl iodides, bromides and chlorides could all react with imidazole in excellent yields. The reactivity order of the aryl halides is iodides > bromides > chlorides (compare Table 1, entry 2, Table 2, entries 1, 10, 11 with Table 2, entries 12, 14, 15, 16, respectively). As far as aryl iodides and bromides were concerned, electron-withdrawing and -donating groups were all tolerated. Electron-withdrawing groups on the aryl halides usually promoted the reactions (compare Table 2, entries 6–8, 10 with Table 1, entry 2, Table 2, entry 12, respectively), while electron-donating groups on the aryl iodides usually depressed the reactions to a certain extent (compare Table 2, entries 1–5 with Table 1, entry 2). *Ortho* (Table 2, entry 3), *meta* (Table 2, entries 2, 5–6 and 13) and *para* (Table 2, entries 1, 4, 7, 8, 10 and 14, 15) substitutions on the aryl halides were all tolerated under these reaction conditions. Furthermore, imidazole can be selectively arylated in the presence of a free $-NH_2$ group (Table 2, entry 5). 4-Iodobenzonitrile, an aryl iodide with nitrile group, was also tolerated the reaction condition when 4 Å molecular sieves were added or Cs_2CO_3 was used as base instead of KOH. The reaction of ethyl 4-iodobenzoate with imidazole was inefficient when KOH was used as base even in the presence of 4 Å molecular sieves because of the partial hydrolysis of the ester to benzoic acid. However, an excellent yield of the ester-N-arylated product was obtained when Cs_2CO_3 was used as base instead of KOH and in the presence of 4 Å molecular sieves (Table 2, entries 7, 8). This system was also successfully applied to N-arylation of imidazole with heteroaryl halides such as 2-bromopyridine and 2-chloropyridine (Table 2, entries 11 and 16). The coupling of aryl chloride such as 4-chlorobenzotrifluoride with imidazole was also accomplished (Table 2, entry 15).

Table 2 Cu_2O catalyzed N-arylation of imidazole with various aryl halides[a]



Entry	Aryl Halide	Product	Temp (°C)	Time (h)	Yield (%)[b]
1			125	24	91
2			125	24	90
3			125	24	88
4			125	24	90
5			125	24	85
6			110	16	92
7			100	24	88[c], 86[d]
8			100	24	85[c, d]
9			110	24	90
10			110	24	90
11			110	24	91
12			130	24	91[e]
13			130	24	90[e]
14			130	24	88[e]
15			130	24	88
16			130	24	89

[a] Aryl halide (1 mmol), imidazole (1.5 mmol), Cu_2O (0.1 mmol), KOH (2 mmol) and DMSO (2 mL) under Ar atmosphere

[b] Isolated yields

[c] 200 mg 4 Å molecular sieves were added

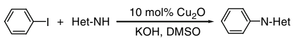
[d] Cs_2CO_3 was used as base instead of KOH

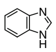
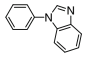
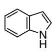
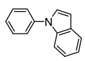
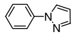
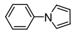
[e] 0.2 mmol Cu_2O was used

3.3 Cu_2O Catalyzed N-arylation of Various Nitrogen-containing Heterocycles with Iodobenzene

In order to expand the scope of this method, a variety of other nitrogen-containing heterocycles such as benzimidazole, indole, pyrazole and pyrrole were successfully coupled with iodobenzene to give the corresponding N-arylated products in excellent yields (Table 3, entries 1–4).

Table 3 Cu_2O catalyzed N-arylation of various nitrogen-containing heterocycles with iodobenzene[a]



Entry	Het-NH	Product	Yield (%)[b]
1			88
2			90
3			92
4			91

[a] Iodobevnzene (1 mmol), Het-NH (1.5 mmol), Cu_2O (0.1 mmol), KOH (2 mmol) and DMSO (2 mL) under Ar atmosphere at 120 °C for 24 h

[b] Isolated yields

Table 4 Recycle studies of Cu_2O for N-arylation of imidazole and pyrrole with iodobenzene[a]

Run	Yield (%)[b]	Run	Yield (%)[b]
1	90	1	91
2	90	2	91
3	89	3	90
4	88	4	89

[a] Iodobenzene (1 mmol), imidazole or pyrrole (1.5 mmol), Cu_2O (0.1 mmol), KOH (2 mmol) and DMSO (2 mL) under Ar atmosphere at 120 °C for 24 h

[b] Isolated yields

3.4 Recycle Studies of Cu_2O for N-arylation of Imidazole and Pyrrole with Iodobenzene

Catalyst recycle experiments were also carried out and the results are presented in Table 4. The catalyst was recovered by simple filtration and reused for several cycles without significant loss of activity.

4 Conclusion

In conclusion, cheap air stable Cu_2O was found to be a simple and efficient catalyst for N-arylation of a variety of nitrogen-containing heterocycles with aryl and heteroaryl chlorides, bromides and iodides. The catalyst can be recovered simply and reused for several cycles without significant loss of activity. Further studies to expand the applications of the catalytic system are currently underway in our laboratory.

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