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Ninhydrin: an efficient ligand for the Cu-catalyzed N-arylation of nitrogen-containing heterocycles with aryl halides

Yi-Zheng Huang, Jin Gao, Hong Ma, Hong Miao, Jie 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, PR China

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Abstract

Cu_2O/ninhydrin was found to be an efficient catalyst system for the N-arylation of nitrogen-containing heterocycles with aryl and heteroaryl iodides, bromides and even unactivated chlorides to give the products in moderate to excellent yields.

Keywords: Ninhydrin; Cu-catalyzed; N-Arylation; Nitrogen-containing heterocycles

N-Arylheterocycles play important roles in medicinal,[1] biological[2] and *N*-heterocyclic carbene chemistry.[3] Traditionally, these compounds were prepared mostly by Ullmann-type coupling reactions. However, these reactions usually proceeded at high temperatures (around 200 °C) and often required using 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.[5–9] A recent notable achievement has been made by Buchwald and co-workers who discovered that in the presence of bidentate N,N-ligands, the Cu-catalyzed 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, with different kinds of copper compounds and appropriate bidentate N,N-, N,O- or O,O-ligands.[7] However, the coupling partners of nitrogen-containing heterocycles were generally confined to aryl iodides and bromides. There are only a few reports where aryl chlorides were used as coupling partners,[7c–g,8b,9g–l] and the examples of unactivated aryl chlorides used as coupling partners have remained sparse.

On the basis of the research efforts on Cu-catalyzed C–N bond formations in our laboratory,[8] we report our recent results on Cu-catalyzed N-arylation of nitrogen-containing heterocycles with aryl iodides, bromides and even unactivated chlorides under mild conditions by using ninhydrin as ligand.

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_2O (0.1 equiv) and KOH (2 equiv); only moderate yield of 1-phenylimidazole was obtained. Prolonging the reaction time to 72 h led to only a slight increase of yield (Table 1, entry 1). To our delight, 1-phenylimidazole was formed in quantitative yield when 20 mol % of ninhydrin was added (Table 1, entry 3). More than 90% yields of 1-phenylimidazole were also obtained when some other O,O-ligands (Fig. 1) were added (Table 1, entries 4–7). Solvents played an important role in this reaction. When toluene, a less polar solvent, was used instead of DMSO, only a trace amount of the desired product was obtained (Table 1, entry 9). Bases influenced the progress of the reaction greatly. Moderate yields were obtained when K_2CO_3, Cs_2CO_3 and K_3PO_4 were used, while only a low yield of 1-phenylimidazole was obtained

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* Corresponding author. Tel./fax: +86 411 84379245.
E-mail address: xujie@dicp.ac.cn (J. Xu).

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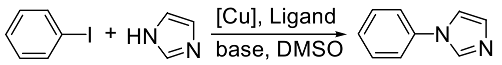
Table 1
Screening reaction conditions for copper-catalyzed N-arylation of imidazole with iodobenzene[a]



Entry	[Cu]	Ligand	Base	Yield[b] (%)
1	Cu_2O	—	KOH	49, 63[c]
2	—	—	KOH	0
3	Cu_2O	L1	KOH	100 (92)
4	Cu_2O	L2	KOH	94
5	Cu_2O	L3	KOH	91
6	Cu_2O	L4	KOH	92
7	Cu_2O	L5	KOH	94
8	Cu_2O	L6	KOH	49
9[d]	Cu_2O	L1	KOH	4
10	Cu_2O	L1	K_2CO_3	83
11	Cu_2O	L1	Cs_2CO_3	74
12	Cu_2O	L1	K_3PO_4	70
13	Cu_2O	L1	$(n\text{-Pr})_3N$	24
14	CuI	L1	KOH	87
15	CuBr	L1	KOH	70
16	CuCl	L1	KOH	54
17	CuO	L1	KOH	44
18	Cu	L1	KOH	82

[a] Reaction conditions: iodobenzene (1 mmol), imidazole (1.5 mmol), [Cu] (0.1 mmol), ligand (0.2 mmol), base (2 mmol) and DMSO (2 ml) under Ar atmosphere at 90 °C for 24 h.

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

[c] At 90 °C for 72 h.

[d] With toluene as solvent instead of DMSO.

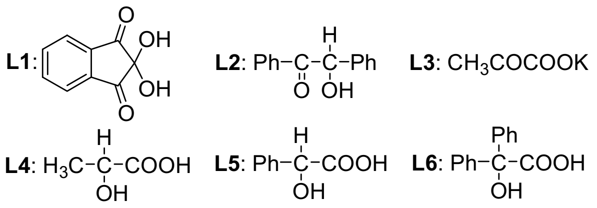
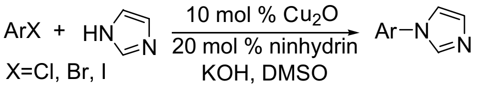


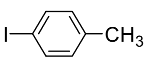
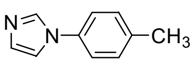
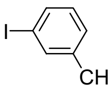
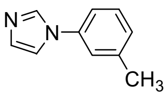
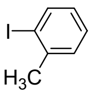
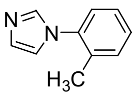
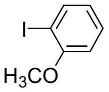
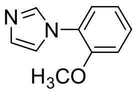
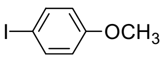
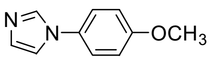
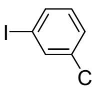
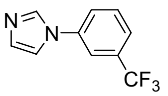
Fig. 1. Ligands for copper-catalyzed N-arylation of imidazole.

when tripropylamine, an organic base, was used (Table 1, entries 10–13). Other copper compounds (CuI, CuBr, CuCl, CuO and Cu powders) were also evaluated but proved inferior to Cu_2O (Table 1, entries 14–18).

The efficacy of the Cu_2O/ninhydrin system for general N-arylation of imidazole with various aryl halides was further evaluated, and the results are summarized in Table 2. The results indicate that the reactivity order of the aryl halides is iodides > bromides > chlorides (compare Table 1, entry 3 and Table 2, entries 1, 8–11 and 13–16). Electron-withdrawing and -donating groups on the aryl halides were all tolerated. Electron-withdrawing groups on the aryl halides usually promoted the reactions (compare Table 2, entries 6, 8 and 13 with Table 1, entry 3, Table 2, entries 10 and 15, respectively). Compared with iodobenzene, aryl iodides with electron-donating groups needed a slightly higher temperature to couple with imidazole in about 90% of isolated yields in 24 h (compare Table 2, entries

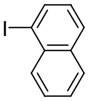
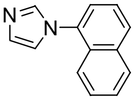
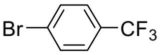
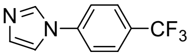
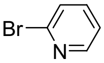
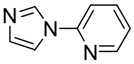
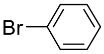
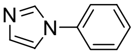
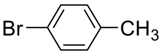
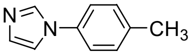
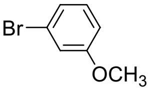
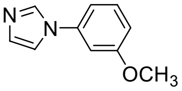
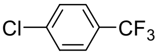
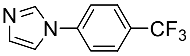
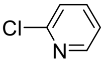
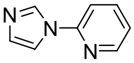
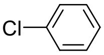
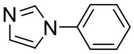
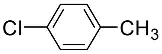
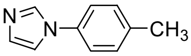
Table 2
Cu_2O/ninhydrin-catalyzed N-arylation of imidazole with various aryl halides[a]



Entry	Aryl halide	Product	Temp (°C)	Time (h)	Yield[b] (%)
1			110	24	91
2			110	24	90
3			110	24	89
4			110	24	90
5			110	24	89
6			90	16	92

(continued on next page)

Table 2 (*continued*)

Entry	Aryl halide	Product	Temp (°C)	Time (h)	Yield[b] (%)
7			100	24	90
8			110	24	91
9			110	24	92
10			110	48	80, 91[c]
11			110	48	76, 87[c]
12			110	48	78, 90[c]
13			130	24	90
14			130	24	91
15[d]			150	48	49
16[d]			150	48	46

[a] Reaction conditions: aryl halide (1 mmol), imidazole (1.5 mmol), Cu_2O (0.1 mmol), ninhydrin (0.2 mmol), KOH (2 mmol) and DMSO (2 ml) under Ar atmosphere.

[b] Isolated yields.

[c] 130 °C for 24 h.

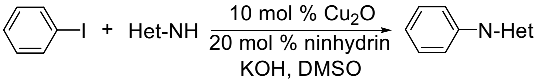
[d] Cu_2O (0.2 mmol), ninhydrin (0.3 mmol).

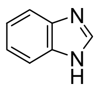
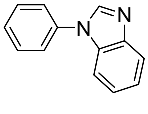
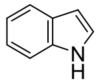
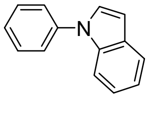
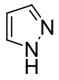
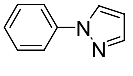
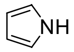
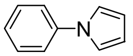
1–5 with Table 1, entry 3). Furthermore, excellent yields of *N*-aryl imidazole were obtained when hindered aryl halides such as 2-methyliodobenzene and 2-methoxyiodobenzene were used (Table 2, entries 3 and 4). This system was also successfully applied to N-arylation of imidazole with heteroaryl halides such as 2-bromopyridine and 2-chloropyridine (Table 2, entries 9 and 14). Remarkably, aryl chlorides could be used as the coupling partners of imidazole. An excellent yield was obtained when 4-chlorobenzotrifluoride, an activated aryl chloride, was used (Table 2, entry 13). Moderate yields were still achieved even in the N-arylation of imidazole with chlorobenzene and electron-donating aryl chloride such as 4-methylchlorobenzene (Table 2, entries 15 and 16).

The efficacy of the Cu_2O/ninhydrin system for general N-arylation of various nitrogen-containing heterocycles such as benzimidazole, indole, pyrazole and pyrrole with iodobenzene was further evaluated, and the results are summarized in Table 3. All the tested nitrogen-containing heterocycles resulted in excellent yields (Table 3, entries 1–4).

In conclusion, ninhydrin was found to be an efficient ligand for the Cu_2O-catalyzed N-arylation of nitrogen-containing heterocycles with aryl and heteroaryl iodides, bromides and even unactivated chlorides.[10] The mechanism of the reactions and further studies to expand the applications of the catalytic system are currently underway in our laboratory.

Table 3
Cu_2O/ninhydrin-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] Reaction conditions: iodobenzene (1 mmol), Het-NH (1.5 mmol), Cu_2O (0.1 mmol), ninhydrin (0.2 mmol), KOH (2 mmol) and DMSO (2 ml) under Ar atmosphere at 110 °C for 24 h.

[b] Isolated yields.

Acknowledgements

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1. For selected examples, see: (a) Craig, P. N. In *Comprehensive Medicinal Chemistry*; Drayton, C. J., Ed.; Pergamon Press: New York, 1991; Vol. 8; (b) Wiglenda, T.; Gust, R. *J. Med. Chem.* **2007**, *50*, 1475; (c) Leopoldo, M.; Lacivita, E.; Giorgio, P. D.; Colabufo, N. A.; Niso, M.; Berardi, F.; Perrone, R. *J. Med. Chem.* **2006**, *49*, 358; (d) Barchechath, S. D.; Tawatao, R. I.; Corr, M.; Carson, D. A.; Cottam, H. B. *J. Med. Chem.* **2005**, *48*, 6409.
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3. For reviews, see: (a) Nair, V.; Bindu, S.; Sreekumar, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 5130; (b) Hermann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290.
4. (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382; (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.
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10. *Typical experimental procedure*: a mixture of aryl halide (1 mmol), nitrogen-containing heterocycle (1.5 mmol), Cu_2O (0.1 mmol), ninhydrin (0.2 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_2SO_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. All the products are known and have been characterized by ^1H NMR, ^{13}C NMR, GC/MS (EI), and the melting points of the solid products have also been determined.