Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Cheap Cu(I)/Hexamethylenetetramine (HMTA) Catalytic System for C-N Coupling Reactions

Changsheng Cao [a], Zhongbo Lu [a], Zhengyuan Cai [a], Guangsheng Pang [b] & Yanhui Shi [a]

[a] College of Chemistry and Chemical Engineering and Key Laboratory of Biotechnology for Medical Plant, Xuzhou Normal University, Xuzhou, Jiangsu, China

[b] State Key Laboratory of Inorganic Synthesis and Preparative Chemistry, Jilin University, Changchun, Jilin, China

Accepted author version posted online: 18 Jul 2011.Published online: 14 Sep 2011.

To cite this article: Changsheng Cao , Zhongbo Lu , Zhengyuan Cai , Guangsheng Pang & Yanhui Shi (2012): Cheap Cu(I)/Hexamethylenetetramine (HMTA) Catalytic System for C-N Coupling Reactions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:2, 279-284

To link to this article: http://dx.doi.org/10.1080/00397911.2010.523857

Synthetic Communications®, 42: 279–284, 2012

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.523857

Taylor & Francis
Taylor & Francis Group

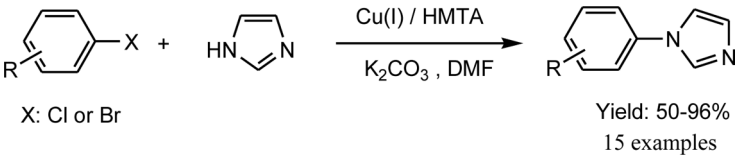
CHEAP Cu(I)/HEXAMETHYLENETETRAMINE (HMTA) CATALYTIC SYSTEM FOR C-N COUPLING REACTIONS

Changsheng Cao,[1] Zhongbo Lu,[1] Zhengyuan Cai,[1] Guangsheng Pang,[2] and Yanhui Shi[1]

[1]*College of Chemistry and Chemical Engineering and Key Laboratory of Biotechnology for Medical Plant, Xuzhou Normal University, Xuzhou, Jiangsu, China*

[2]*State Key Laboratory of Inorganic Synthesis and Preparative Chemistry, Jilin University, Changchun, Jilin, China*

GRAPHICAL ABSTRACT



Abstract *An efficient C-N coupling reaction of aryl chlorides or bromides with imidazole was successfully performed with cheap and commercially available catalytic system Cu(I)/HMTA. Both aryl bromides and aryl chlorides have been effectively catalyzed by Cu/HMTA, giving products in moderate to good yields. Moreover, aryl halides bearing either electron-withdrawing groups or electron-donating groups could be used in the reaction.*

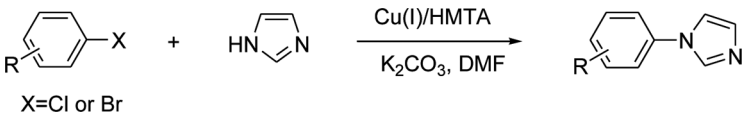
Keywords Aryl halides; C-N coupling; imidazole; N-arylimidazole

INTRODUCTION

N-Arylimidazole subunits are found in numerous natural products and in many biologically active pharmaceuticals.[1–3] Therefore, it is important to develop a useful method to synthesize these kinds of compounds. In recent years, mild transition metal-catalyzed cross-coupling of aryl halides with NH-containing heterocycles has been widely developed.[4–6] Despite some limitations of copper catalysts and the success of palladium-catalyzed reactions, copper-based protocols still attract great attention because copper is much cheaper, which make them the reactions of choice in large- and industrial-scale applications. Copper-based catalysts are often successful where palladium-based procedures have failed.[7] Since the initial report

Received May 1, 2010.

Address correspondence to Yanhui Shi, College of Chemistry and Chemical Engineering and Key Laboratory of Biotechnology for Medical Plant, Xuzhou Normal University, Xuzhou, Jiangsu, 221116, China. E-mail: yhshi_2000@126.com



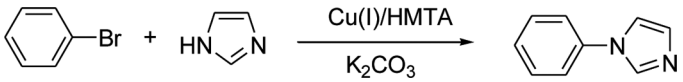
Scheme 1. Synthesis of N-arylimidazole compounds.

by Kiyomori et al.[8] various types of ligands and catalytic systems have been developed.[9–11] However, most of the studies reported employed either iodo- or bromoarenes as substrates. The coupling of N-H heterocycles with cheaper and less reactive aryl chloride substrates still remains a challenging problem. In addition, some of the very efficient nitrogen ligands are rather expensive and may require multiple steps for their syntheses. Therefore, it is very important to develop a cost-effective and efficient ligand/catalyst system that facilitates direct C-N cross-coupling reactions. Herein, we report our studies in using catalytic amounts of Cu(I) with commercially available and cheap hexamethylenetetramine (HMTA) as ligand in C-N coupling reactions of aryl halides with imidazole (Scheme 1).

RESULTS AND DISCUSSION

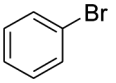
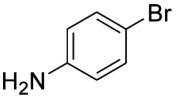
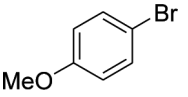
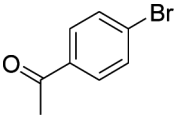
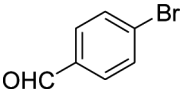
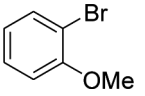
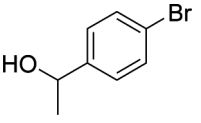
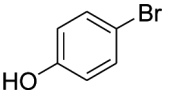
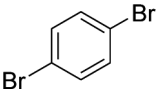
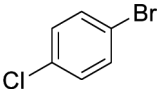
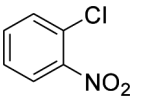
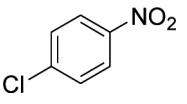
In our search for a cheap and readily available ligand in the C-N coupling, we started by investigating the C-N coupling reactions of bromobenzene with imidazole with different cheap available ligands (Table 1, entries 1–3). In Comparison with the widely used N-donor ligand N,N,N′,N′-tetramethyl-1,2-ethylenediamine (TMEDA), the HMTA ligand gave a better result under the same conditions. The yield with glucose was good as well, but the purification of the desired product was difficult because of some by-products due to the messy reaction. To determine the most suitable reaction conditions for the N-phenylation of imidazole, the catalytic activities of Cu(I)/HMTA were examined under different conditions (Table 1, entries 4–11). The

Table 1. Effect of reaction conditions on C-N coupling of imidazole with bromobenzene



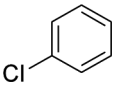
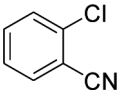
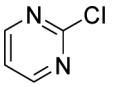
Entry	Cat. (5%)	Ligand (5%)	Temp. (°C)	Solvent	Time (h)	GC yield (%)
1	CuI	HMTA	130	DMF	20	95
2	CuI	TMEDA	130	DMF	20	36
3	CuI	Glucose	130	DMF	20	80% (messy)
4	CuI	HMTA	110	DMF	20	62
5	CuI	HMTA	120	DMF	20	78
6	CuI	HMTA	130	DMF	20	96
7	CuI	HMTA	140	DMF	20	96
8	CuI	HMTA	130	DMSO	20	92
9	CuI	HMTA	130	Tol.	20	90
10	CuCl	HMTA	130	DMF	20	95
11	Cu_2O	HMTA	130	DMF	20	95

Table 2. Synthesis of N-arylimidazoles

Entry	Aryl halide	Isolated yield (%)
1		93
2		50
3		72
4		80
5[a]		76
6[a]		84
7[a]		88
8[a]		60
9[a]		71
10[a]		52
11		96
12		95

(*Continued*)

Table 2. Continued

Entry	Aryl halide	Isolated yield (%)
13		50
14		50
15		96

[a]CuI was used instead of CuCl.

results showed that the higher reaction temperature led to better yields (entries 4–7), and it was found that the copper sources and solvents are not sensitive to the C-N coupling reaction. Even though the use of dimethyl formamide (DMF) gave the best results among the solvents that were tested, dimethyl sulfoxide (DMSO) and toluene are suitable solvents for CuI/HMTA-catalyzed N-arylation of imidazole (entries 9 and 10) as well. Replacing CuI with CuCl or Cu_2O did not reduce the catalytic activity very much (entries 10 and 11). To further expand the reaction scope of this Cu/HMTA-catalyzed C-N coupling reaction, a wide variety of bromo- or chlorobenzenes were selected to react with imidazole using 5% CuCl and 5% HMTA with K_2CO_3 as base in DMF at 130°C. The results are summarized in Table 2. CuCl was chosen over CuI because of the relatively low cost of CuCl, and CuCl is rarely reported in literature as a Cu source in the C-N coupling reaction. However, CuI has been used in some reactions to obtain better yields (Table 2, entries 5–10). It is apparent from Table 2 that both aryl bromides and aryl chlorides have been effectively catalyzed by Cu/HMTA, giving products in good yields. Furthermore, the desired product could be obtained with aryl halides bearing either electron-withdrawing groups or electron-donating groups. In most cases, the reactions were completed within 24 h in good yields. It is worth mentioning that steric hindrance does not play a big role in the reaction (Table 2, entries 3 and 6; entries 11 and 12).

In conclusion, we have developed an efficient and cheap catalyst system for C-N cross coupling of imidazole with aryl halides using HMTA as ligand, which is a very cheap and commercially available N-donor compound. The studies indicate that the Cu(I)/HMTA system has catalyzed N-arylation of imidazole effectively. In addition, Cu(I)/HMTA can catalyze the coupling reaction with both aryl chlorides and bromides. In some reactions, CuI can be replaced by low-cost CuCl. The experimental procedure is also very simple and convenient.

EXPERIMENTAL

Melting points were determined on a XT-5B microscopic melting-point spectrometer and were uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ or

DMSO-d_6 with Me_4Si as internal standard using a Bruker-400 spectrometer. Electron impact–mass spectrometry (EI-MS) spectra were obtained with an Agilent 6890A-5973 N gas chromatography–mass spectrometer (GC-MS). The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported procedures.

General Procedure for the Synthesis of N-Arylimidazole Derivatives

Under an inert atmosphere, a 4-mL reaction vial was charged with K_2CO_3 (1 mmol), CuI or CuCl (2.5–5% mmol), HMTA (2.5–5% mmol), imidazole (0.6 mmol), and aryl halide (0.5 mmol). After it was sealed with a cap containing a polytetrafluoroethylene (PTFE) septum, 1 mL of dry DMF was injected by syringe. The reaction mixture was heated to 130–140 °C for 20–40 h. The reaction was monitored by GC. After the starting material was completely consumed, the reaction was stopped and the mixture was cooled to room temperature. The reaction mixture was passed through a plug of celite and rinsed with 10 mL of ethyl acetate. The filtrate was washed by 15 mL of H_2O. After the organic layer was concentrated, the residue was purified by column chromatography on silica gel to give the desired product.

Selected Data for Products

1-(4-Methoxyphenyl)-1*H*-imidazole (3). White solid, mp 64–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.77 (s, 1H, NC*H*N), 7.32–7.18 (m, 4H, Ar*H*), 7.00 (d, 2H, NC*H*, $J = 8.8$ Hz), 3.85 (s, 3H, OCH_3); EI-MS: 174.

4-Imidazol-1-yl-benzaldehyde (5). White solid, mp 150–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 10.01 (s, 1H, C*H*O), 8.03 (d, 2H, Ar*H*), 8.00 (s, 1H, NC*H*N), 7.59 (d, 2H, Ar*H*), 7.40 (s, 1H, NC*H*), 7.28 (s, 1H, NC*H*); EI-MS: 172.

1,4-*Bis*(imidazole-1-yl)-benzene (9). White solid, mp 215–217 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.89 (s, 2H, 2NC*H*N), 7.53 (s, 4H, Ar*H*), 7.32 (s, 2H, NC*H*), 7.26 (s, 2H, NC*H*); EI-MS: 210.

1-(4-Nitro-phenyl)-1*H*-imidazole (12). Orange solid, mp 190–192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 8.39 (d, 2H, Ar*H*), 7.98 (s, 1H, NC*H*N), 7.59 (d, 2H, Ar*H*), 7.38 (s, 1H, NC*H*), 7.29 (s, 1H, NC*H*); EI-MS: 189.

2-Imidazol-1-yl-benzonitrile (14). White solid, mp 146–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.79 (s, 1H, NC*H*N), 7.78–7.39 (m, 4H, Ar*H*), 7.30 (s, 1H, NC*H*), 7.21 (s, 1H, NC*H*); EI-MS: 169.

2-Imidazol-1-yl-pyrimidine (15). Orange solid, mp 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 8.70 (d, 2H, 2NC*H*, $J = 4.8$ Hz), 8.63 (s, 1H, NC*H*N), 7.90 (s, 1H, C*H*), 7.21 (t, 1H, NC*H*), 7.18 (s, 1H, NC*H*); EI-MS: 146.

ACKNOWLEDGMENTS

We are grateful to SPF for ROCS, SEM, PAPD; the State Key Laboratory of Inorganic Synthesis and Preparative Chemistry (2009-06) at Jilin University; the

Qing Lan Project (08QLT001 and 08QLD006) of the Jiangsu Education Committee; and the National Science Foundation of China (NSFC) 21071121 for financial support.

REFERENCES

1. Quan, M. L.; Lam, P. Y. S.; Han, Q.; Pinto, D. J. P.; He, M. Y.; Li, R.; Ellis, C. D.; Clark, C. G.; Teleha, C. A.; Sun, J.-H.; Alexander, R. S.; Bai, S.; Luettgen, J. M.; Knabb, R. M.; Wong, P. C.; Wexler, R. R. Discovery of 1-(3′-aminobenzisoxazol-5′-yl)-3-trifluoromethyl-N-[2-fluoro-4-[(2′-dimethylaminomethyl)imidazol-1-yl]phenyl]-1H-pyrazole-5-carboxyamide hydrochloride (razaxaban), a highly potent, selective, and orally bioavailable factor Xa inhibitor. *J. Med. Chem.* **2005**, *48*, 1729–1744.
2. Smallheer, J. M.; Alexander, R. S.; Wang, J.; Wang, S.; Nakajima, S.; Rossi, K. A.; Smallwood, A.; Barbera, F.; Burdick, D.; Luettgen, J. M.; Knabb, R. M.; Wexler, R. R.; Jadhav, P. K. SAR and factor IXa crystal structure of a dual inhibitor of factors IXa and Xa. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5263–5267.
3. Qiao, J. X.; Cheng, X.; Modi, D. P.; Rossi, K. A.; Luettgen, J. M.; Knabb, R. M.; Jadhav, P. K.; Wexler, R. R. 5-Amidinobenzo[b]thiophenes as dual inhibitors of factors IXa and Xa. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 29–35.
4. Altman, R. A.; Buchwald, S. L. 4,7-Dimethoxy-1,10-phenanthroline: An excellent ligand for the Cu-catalyzed N-arylation of imidazoles. *Org. Lett.* **2006**, *8*, 2779–2782.
5. Chow, W. S.; Chan, T. H. Microwave-assisted solvent-free N-arylation of imidazole and pyrazole. *Tetrahedron Lett.* **2009**, *50*, 1286–1289.
6. Xia, N.; Taillefer, M. A very simple copper-catalyzed synthesis of anilines by employing aqueous ammonia. *Angew. Chem. Int. Ed.* **2009**, *48*, 337–339.
7. Choudary, B. M.; Sridhar, C.; Kantam, M. L.; Venkanna, G. T.; Sreedhar, B. Design and evolution of copper apatite catalysts for N-arylation of heterocycles with chloro- and fluoroarenes. *J. Am. Chem. Soc.* **2005**, *127*, 9948–9949.
8. Kiyomori, A.; Marcoux, J.; Buchwald, S. L. An efficient copper-catalyzed coupling of aryl halides with imidazoles. *Tetrahedron Lett.* **1999**, *40*, 2657–2660.
9. Huang, Y. Z.; Gao, J.; Ma, H.; Miao, H.; Xu, J. Ninhydrin: An efficient ligand for the Cu-catalyzed N-arylation of nitrogen-containing heterocycles with aryl halides. *Tetrahedron Lett.* **2008**, *49*, 948–951.
10. Kantam, M. L.; Venkanna, G. T.; Sridhar, C.; Sreedhar, B.; Choudary, B. M. An efficient base-free N-arylation of imidazoles and amines with arylboronic acids using copper-exchanged fluorapatite. *J. Org. Chem.* **2006**, *71*, 9522–9524.
11. Suresh, P.; Pitchumani, K. Per-6-amino-β-cyclodextrin as an efficient supramolecular ligand and host for Cu(I)-catalyzed N-arylation of imidazole with aryl bromides. *J. Org. Chem.* **2008**, *73*, 9121–9124.