DOI: 10.1002/adsc.201200296

Synthesis of Aryl Carbamates *via* Copper-Catalyzed Coupling of Aryl Halides with Potassium Cyanate

Xinye Yang,[a] Yihua Zhang,[a,*] and Dawei Ma[b,*]

[a] Center of Drug Discovery, China Pharmaceutical University, Nanjing 210009, People's Republic of China
E-mail: zyhtgd@sohu.com
[b] State Key Laboratory of Bioorganic & Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, People's Republic of China
Fax: (+86)-21-6416-6128; e-mail: madw@mail.sioc.ac.cn

Received: April 9, 2012; Revised: May 17, 2012; Published online: August 22, 2012

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200296.

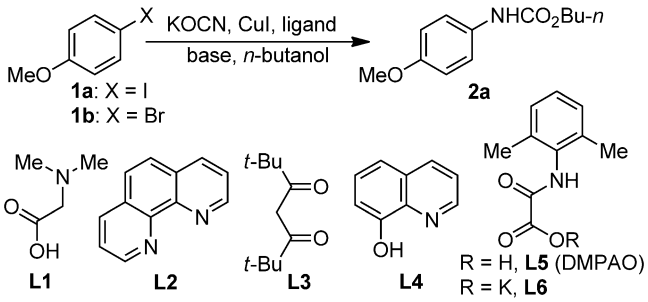
Abstract: Coupling of aryl halides with potassium cyanate takes place at 100–110 °C in alcohols under the catalysis of CuI (cuprous iodide) and 2-(2,6-dimethylphenylamino)-2-oxoacetic acid, affording the corresponding aryl carbamates with great diversity.

Keywords: aryl halides; carbamates; copper salts; coupling; ligands

The aryl carbamate moiety has been frequently found in pharmaceutically important molecules. Recent examples include anticancer agents,[1] antituberculosis agents,[2] mitogen-activated protein kinase 2 (MK2) inhibitors,[3] matrix metalloprotease 12 inhibitors[4] and HIV-1 protease inhibitors.[5] For a long time, these compounds have been predominantly prepared by condensation of anilines with phosgene derivatives.[6] Recently, two alternative approaches using metal catalysts have been reported.[7,8] One is the palladium-catalyzed reductive carbonylation of nitroarenes developed by Alper's group,[7] and the other is the copper-catalyzed coupling of arylboronic acids with potassium cyanate discovered by Baghersad and co-workers.[8]

Stimulated by Baghersad's result, we envisioned that aryl halides might go through a similar coupling reaction, and thereby giving a more economic approach for preparing aryl carbamates. With this idea in mind, we conducted a coupling of 4-iodoanisole with potassium cyanate. It was found that under the catalysis of 20 mol% CuI and 20 mol% *N*,*N*-dimethylglycine, the reaction took place in *n*-BuOH at 100 °C to afford the desired carbamate **2a** in 50% yield (Table 1, entry 1). Changing the ligand to 1,10-phenanthroline gave a decreased yield (entry 2), while little product was obtained in the cases of 2,2,6,6-tet-

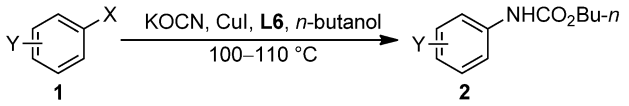
Table 1. Screening of reaction conditions for the copper-catalyzed coupling of potassium cyanate with 4-iodoanisole and 4-bromoanisole.[a]



Entry	X	[Cu]	Ligand	Base	Temp. [°C]	Yield [%][b]
1	I	CuI	**L1**	KOH	100	50
2	I	CuI	**L2**	–	100	30
3	I	CuI	**L3**	–	100	0
4	I	CuI	**L4**	–	100	<5
5	I	CuI	**L5**	KOH	100	80
6	I	CuI	**L6**	–	100	82
7	I	CuCl	**L6**	–	100	70
8	I	CuBr	**L6**	–	100	60
9	I	Cu_2O	**L6**	–	100	<5
10	Br	CuI	**L6**	–	100	45
11[c]	Br	CuI	**L6**	–	110	72
12[c,d]	Br	CuI	**L6**	–	110	85
13[e]	I	CuI	**L6**	–	100	20
14[f]	I	CuI	**L6**	–	100	10
15[g]	I	CuI	**L6**	–	100	50

[a] *Reaction conditions:* aryl halide (0.5 mmol), potassium cyanate (0.75 mmol), CuI (0.1 mmol), ligand (0.1 mmol), base (0.1 mmol), *n*-BuOH (1 mL), 24 h.
[b] Isolated yield.
[c] 1.0 mmol potassium cyanate was used.
[d] 0.2 mmol of **L6** was used.
[e] Using MeCN as solvent and adding 1 mmol of *n*-BuOH.
[e] Using dioxane as solvent and adding 1 mmol of *n*-BuOH.
[f] 0.05 mol of CuI and 0.1 mol of **L6** were used.

Table 2. Coupling of aryl halides with potassium cyanate in *n*-butanol.[a]



Entry	X	Y	Yield [%][b]
1	I	H	85
2	Br	H	90
3	I	4-Cl	78
4	Br	4-Cl	80
5	I	4-OMe	82
6	Br	4-OMe	85
7	I	4-Ac	80
8	Br	4-Ac	80
9	I	4-Ph	80
10	Br	4-Ph	82
11	I	4-NHAc	70
12	Br	4-NHAc	80
13	Br	4-NH_2	62[c]
14	I	3-F	71
15	Br	3-F	76
16	I	3-Me	85
17	Br	3-Me	87
18	I	3-Cl	75
19	Br	3-Cl	80
20	I	3-NO_2	70
21	Br	3-NO_2	76
22	I	2-Me	–[d]
23	I	2-Cl	–[d]

[a] *Reaction conditions:* aryl iodide (0.5 mmol), potassium cyanate (0.75 mmol), CuI (0.1 mmol), **L6** (0.1 mmol), *n*-BuOH (1 mL), 100 °C, 24 h; or aryl bromide (0.5 mmol), potassium cyanate (1.0 mmol), CuI (0.1 mmol), **L6** (0.2 mmol), *n*-BuOH (1 mL), 110 °C, 24 h.
[b] Isolated yield.
[c] Aryl bromide was recovered with about 15% yield.
[d] Reaction was carried out at 110–140 °C.

ramethylheptane-3,5-dione and quinolin-8-ol as the ligand (entries 3 and 4). The best result was obtained when 2-(2,6-dimethylphenylamino)-2-oxoacetic acid (DMPAO) was utilized (entry 5). Using its salt as the ligand, a similar result was observed in the absence of the base (entry 6). Switching the copper salt from CuI to CuCl, CuBr or Cu_2O decreased the yields slightly (entries 7–9). Under the same conditions, 4-bromoanisole gave a moderate yield (entry 10). Improved results could be obtained by adding more potassium cyanate (entry 11) and ligand (entry 12). We also tried to carry out the reaction in MeCN and dioxane, and reduce the catalytic loading, but failed to obtain satisfactory yields (entries 13–15).

Using *n*-BuOH as the solvent we next explored the reaction scope by varying the aryl halides. As summarized in Table 2, a number of *para*- and *meta*-substituted aryl halides, no matter whether they are electron-rich or electron-poor, were found to be applicable for this transformation. These results indicated that electronic nature of the substrates has little influence on the reaction course. However, steric hindrance was found to have a great impact on this coupling reaction, as evidenced by the fact that no coupling occurred even at 110–140 °C when two *ortho*-substituted aryl iodides were used (entries 22 and 23).

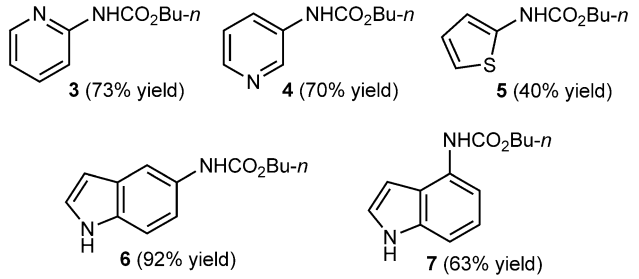


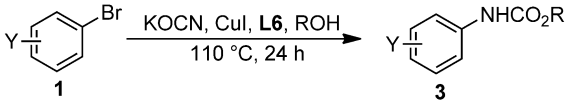
Figure 1. Structures of heteroaryl carbamates prepared *via* copper-catalyzed coupling.

Another notable feature of the present coupling reaction is that a wide range of functional groups, such as chloro, methoxy, ketone, amide, amino, and nitro groups, were tolerated under these reaction conditions. We also attempted to use some heteroaryl bromides as the coupling partners, and were pleased to observe that 2-pyridinyl-, 3-pyridinyl-, 2-thiophenyl-, 5-indolyl- and 4-indolyl-substituted products **3–7** (Figure 1) could be synthesized in 40–92% yields. This advantage gives the flexibility for assembling functionalized aryl carbamates from substituted aryl and heteroaryl halides.

We next moved our attention to carrying out the coupling reaction of aryl bromides with potassium cyanate in different alcohols (Table 3). In a sealed tube, both methanol and ethanol worked well, affording methyl and ethyl carbamates in good yields (entries 1–9). The sterically bulky *i*-PrOH and functionalized allyl alcohol could also be employed, providing the corresponding aryl carbamates in 75–90% yield (entries 10–14). However, no desired product was isolated when *t*-BuOH was utilized (entry 15), indicating that tertiary alcohols are not favored in this transformation.

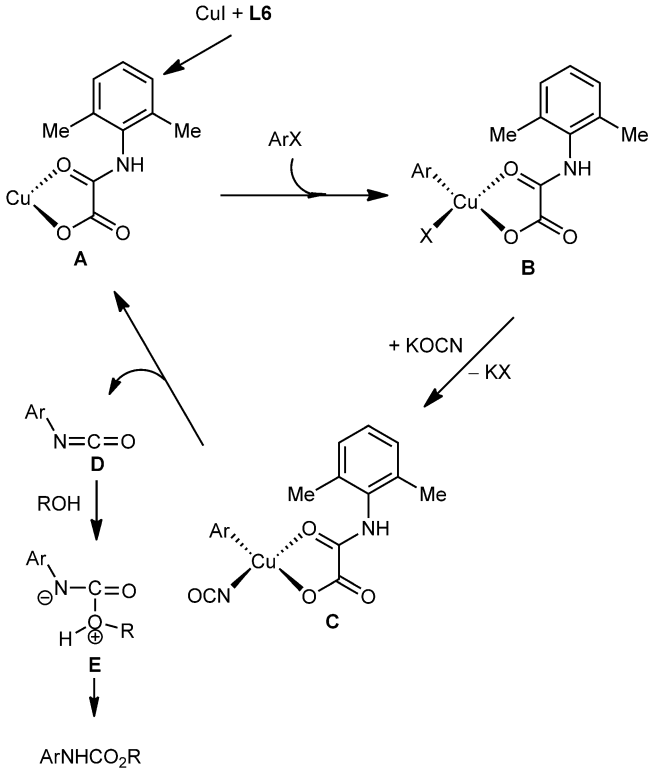
Although the detailed mechanism for the present transformation is not clear, we proposed that the coupling reaction might go through a typical oxidative addition/reductive elimination process as outlined in Scheme 1.[9] After formation of Cu(I) complex **A** from CuI and **L6**, oxidative addition with aryl halides might afford Cu(III) complex **B**.[10] Ligand exchange of **B** with potassium cyanate could deliver Cu(III) complex **C**, which would undergo reductive elimination to produce aryl isocyanide **D** and regenerate the complex **A**. Condensation of **D** with a suitable alcohol could provide the corresponding aryl carbamate.

Table 3. Coupling of aryl bromides with potassium cyanate in different alcohols.[a]



Entry	Y	R	Yield [%][b]
1	4-OMe	Me	75
2	4-Cl	Me	70
3	3-Me	Me	80
4	3-Cl	Me	81
5	3-Ac	Me	75
6	4-Ph	Me	72[c]
7	4-CO_2H	Me	70[c]
8	4-OMe	Et	79
9	4-Cl	Et	83
10	4-OMe	*i*-Pr	75
11	4-Cl	*i*-Pr	90
12	3-Cl	*i*-Pr	85
13	H	allyl	80
14	4-Cl	allyl	75
15	3-Cl	*t*-Bu	–

[a] *Reaction conditions:* aryl bromide (0.5 mmol), potassium cyanate (0.75 mmol), CuI (0.1 mmol), **L6** (0.2 mmol), solvent (1 mL), 110 °C, 24 h.
[b] Isolated yield.
[c] Aryl bromide was recovered in about 15% yield.



Scheme 1. Possible mechanism for the formation of aryl carbamates *via* CuI/**L6**-catalyzed coupling of aryl halides and potassium cyanate.

In summary, we have demonstrated that coupling of aryl halides with potassium cyanate could occur under the catalysis of CuI and a bidentate ligand. This result provides another example to demonstrate the potential for extending copper-catalyzed arylation processes by using unusual nucleophiles.[11] This method is very reliable for preparing aryl carbamates as a number of functionalized aryl halides could be employed as the coupling partners. Thus, it may find good applications in organic synthesis.

Experimental Section

Typical Experimental Procedure

A Schlenk tube was charged with 4-iodoanisole (0.5 mmol), potassium cyanate (0.75 mmol), CuI (0.1 mmol), ligand (0.1 mmol), and 1 mL of *n*-BuOH, evacuated and backfilled with argon. The reaction mixture was stirred at 100 °C for 24 h. The cooled reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water, brine, and dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel using 1:5 ethyl acetate and hexanes as eluent to provide butyl 4-methoxyphenylcarbamate.

Acknowledgements

The authors are grateful to the Ministry of Science and Technology (grant 2009ZX09501-00), Chinese Academy of Sciences and National Natural Science Foundation of China (grants 20632050 & 20921091) for their financial support.

References

[1] a) V. K. Sharma, K-C. Lee, E. Venkateswararao, C. Joo, M.-S. Kim, N. Sharma, S. H. Jung, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6829; b) A. Gopalsamy, H. Yang, J. W. Ellingboe, H-R. Tsou, N. Zhang, E. Honores, D. Powell, M. Miranda, J. P. McGinnis, S. K. Rabindran, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1591; c) M. Kelly, Y. Lee, B. Liu, T. Fujimoto, J. Freundlich, B. Dorsey, G. A. Flynn, A. Husain, W. R. J. Moore, *PCT Int. Jan.* WO 2008008059 A1, **2008**; d) R. S. Shetty, Y. Lee, B. Liu, A. Husain, R. W. Joseph, Y. X. Lu, D. Nelson, J. Mihelcic, W. Chao, K. K. Moffett, A. Schumacher, D. Flubacher, A. Stojanovic, M. Bukhtiyarova, K. Williams, K-J. Lee, A. R. Ochman, M. S. Saporito, W. R. Moore, G. A. Flynn, B. D. Dorsey, E. B. Springman, T. Fujimoto, M. J. Kelly, *J. Med. Chem.* **2011**, *54*, 179; e) B. Q. Gong, F. Hong, C. Kohm, L. Bonham, P. Klein, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1455; f) H. Y. Li, Y. Wang, L. Yan, R. M. Campbell, B. D. Anderson, J. R. Wagner, J. M. Yingling, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3585; g) J. C. Verheijen, D. J. Richard, K. Curran, J. Kaplan, M. Lefever, P. Nowak, D. J. Malwitz, N. Brooijmans, L. Toral-Barza, W. G. Zhang, J. Lucas, I. Hol-

lander, S. Ayral-Kaloustian, T. S. Mansour, K. Yu, A. Zask, *J. Med. Chem.* **2009**, *52*, 8010; h) D. J. Burkhart, B. L. Barthel, G. C. Post, B. T. Kalet, J. W. Nafie, R. K. Shoemaker, T. H. Koch, *J. Med. Chem.* **2006**, *49*, 7002.

[2] K. Kumar, D. Awasthi, S-Y. Lee, I. Zanardi, B. Ruzsicska, S. Knudson, P. J. Tonge, R. A. Slayden, I. Ojima, *J. Med. Chem.* **2011**, *54*, 374.

[3] S. Lin, M. Lombardo, S. Malkani, J. J. Hale, S. G. Mills, K. Chapman, J. E. Thompson, W. X. Zhang, R. Wang, R. M. Cubbon, E. A. O'Neill, S. Luell, E. Carballo-Jane, L. Yang, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3238.

[4] W. Li, J. C. Li, Y. C. Wu, J. J. Wu, R. Hotchandani, K. Cunningham, I. McFadyen, J. Bard, P. Morgan, F. Schlerman, X. Xu, S. Tam, S. J. Goldman, C. Williams, J. Sypek, T. S. Mansour, *J. Med. Chem.* **2009**, *52*, 1799.

[5] A. Ali, G. S. K. K. Reddy, M. N. L. Nalam, S. G. Anjum, H. Cao, C. A. Schiffer, T. M. Rana, *J. Med. Chem.* **2010**, *53*, 7699.

[6] a) T. W. Green, P. G. M. Wuts, in: *Protecting Groups in Organic Synthesis*, 2nd edn., Wiley, New York, **1999**; b) J. S. Yadav, G. S. Reddy, M. M. Reddy, H. M. Meshram, *Tetrahedron Lett.* **1998**, *39*, 3259; c) E. Angeles, A. Santillan, I. Martinez, A. Ramirez, E. Moreno, M. Salmon, R. Martinez, *Synth. Commun.* **1994**, *24*, 2441.

[7] Q. Yang, A. Robertson, H. Alper, *Org. Lett.* **2008**, *10*, 5079.

[8] E. Kianmehr, M. H. Baghersad, *Adv. Synth. Catal.* **2011**, *353*, 2599.

[9] For a discussion on the mechanism of ligand-promoted Ullmann-type coupling reactions, see: a) D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450; b) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054; c) F. Monnier, M. Taillefer, *Angew. Chem.* **2009**, *121*, 7088; *Angew. Chem. Int. Ed.* **2009**, *48*, 6954; d) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2010**, 13; e) E. Sperotto, G. P. M. Klink, G. Koten, J. G. Vries, *Dalton Trans.* **2010**, *39*, 10338; f) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.

[10] a) A. Casitas, A. E. King, T. Parella, M. Costas, S. S. Stahl, X. Ribas, *Chem. Sci.* **2010**, *1*, 326; b) L. M. Huffman, A. Casitas, M. Font, M. Canta, M. Costas, X. Ribas, S. S. Stahl, *Chem. Eur. J.* **2011**, *17*, 10643.

[11] For recent examples on copper-catalyzed arylation with unusual nucleophiles, see: a) J. Kim, S. Chang, *Chem. Commun.* **2008**, 3052; b) M. S. Lam, H. W. Lee, A. S. C. Chan, F. Y. Kwong, *Tetrahedron Lett.* **2008**, *49*, 6192; c) K. L. Jones, A. Porzelle, A. Hall, M. D. Woodrow, N. C. O. Tomkinson, *Org. Lett.* **2008**, *10*, 797; d) H. Kaddouri, V. Vicente, A. Ouali, F. Ouazzani, M. Taillefer, *Angew. Chem.* **2009**, *121*, 339; *Angew. Chem. Int. Ed.* **2009**, *48*, 333; e) L. Jiang, X. Lu, H. Zhang, Y. Jiang, D. Ma, *J. Org. Chem.* **2009**, *74*, 4542; f) D. Wang, Q. Cai, K. Ding, *Adv. Synth. Catal.* **2009**, *351*, 1722; g) D. Ma, S. Xie, P. Xue, X. Zhang, J. Dong, Y. Jiang, *Angew. Chem.* **2009**, *121*, 4286; *Angew. Chem. Int. Ed.* **2009**, *48*, 4222; h) X. Liu, H. Fu, Y. Jiang, Y. Zhao, *Angew. Chem.* **2009**, *121*, 354; *Angew. Chem. Int. Ed.* **2009**, *48*, 348; i) Y. Jiang, Y. Qin, S. Xie, X. Zhang, D. Ma, *Org. Lett.* **2009**, *11*, 5250; j) M. Cortes-Salva, B.-L. Nguyen, J. Cuevas, K. R. Pennypacker, J. C. Antilla, *Org. Lett.* **2010**, *12*, 1316; k) K. G. Thakur, D. Ganapathy, G. Sekar, *Chem. Commun.* **2011**, *47*, 5076; l) E. Racine, F. Monnier, J. Vors, M. Taillefer, *Org. Lett.* **2011**, *13*, 2818; m) D. Ma, X. Lu, L. Shi, H. Zhang, Y. Jiang, X. Liu, *Angew. Chem.* **2011**, *123*, 1150; *Angew. Chem. Int. Ed.* **2011**, *50*, 1118; n) H. Hammoud, M. Schmitt, F. Bihel, C. Antheaume, J.-J. Bourguignon, *J. Org. Chem.* **2012**, *77*, 417.

