Tetrahedron Letters 48 (2007) 4207–4210

Tetrahedron Letters

# Benzotriazole: an excellent ligand for Cu-catalyzed N-arylation of imidazoles with aryl and heteroaryl halides

Akhilesh Kumar Verma,* Jaspal Singh, V. Kasi Sankar,
Ritu Chaudhary and Ramesh Chandra

*Synthetic Organic Chemistry Research Laboratory, Dr. B.R. Ambedkar Center for Biomedical Research, University of Delhi, Delhi 110007, India*

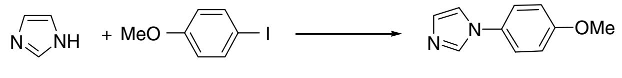
Received 18 January 2007; revised 12 April 2007; accepted 16 April 2007
Available online 20 April 2007

**Abstract**—Benzotriazole (BtH) is an efficient ligand for the Cu-catalyzed N-arylation of imidazoles with aryl and heteroaryl halides. A combination of CuI/BtH was found to be an efficient and inexpensive catalyst system to carry out the N-arylation of imidazoles affording the corresponding products in good to excellent yields.

*N*-Arylimidazoles are structural motifs found in many biologically active compounds and natural products.[1] The development of mild and highly efficient methods for their synthesis has recently gained considerable attention in synthetic chemistry, and accordingly, many procedures have been reported for their synthesis.[2–6] Traditionally, this moiety is prepared by nucleophilic aromatic substitution of an activated aryl halide and by copper mediated coupling of heterocycles with aryl halides. In both cases, the reactions were limited to those of aryl halides bearing strong electron withdrawing substituents and required harsh conditions (Ullmann reaction requiring high temperature, extended periods of time using stoichiometric copper).[2] Despite the recent development of Pd catalyzed C–N bond forming reactions,[3] copper catalyzed N-arylation of imidazoles and other nitrogen heterocycles with aryl halides promoted by ligands has attracted much attention due to its economy and efficiency.[2,4,5] These highly efficient ligands include diazabutadiene,[4a] 2-aminopyrimidine-4,6-diol,[4b] 1,10-phenanthroline derivatives,[4c–f] diamines,[4g–i] aminoarenethiols,[4j] amino acid derivatives,[4k–m] 8-hydroxyquinoline,[4n] pyrrolidine-2-phosphates,[4o] oxime–phosphine oxides[4p] and phosphoramidite.[4q] A more practical ligand promoted Cu-catalyzed chemistry is being developed and these new methods are yet to become general for the N-arylation of imidazoles.

Our group has been utilizing benzotriazole as a catalyst for various transformations due to its some interesting properties.[7] As a part of our research, we noticed that this air and moisture stable compound has excellent coordination capability, which would be favourable for stabilizing catalytic species and assisting catalytic cycles. Herein we report our preliminary investigations on the use of BtH as a ligand for the Cu-catalyzed N-arylation of imidazoles.

**Table 1.** Screening the reaction conditions for the copper-catalyzed N-arylation of imidazole **1a** with 1-iodo-4-methoxybenzene **2a**[a]



**1a** **2a** **3a**

| Entry | [Cu]/mol % | BtH (mol %) | Base | solvent | Yield (%) |
|---|---|---|---|---|---|
| 1 | CuI/10 | — | $Cs_2CO_3$ | DMF | Trace |
| 2 | CuI/10 | 20 | $Cs_2CO_3$ | DMF | 90 |
| 3 | CuI/10 | 10 | $Cs_2CO_3$ | DMF | 80 |
| 4 | CuI/10 | 20 | $Cs_2CO_3$ | $CH_3CN$ | 68 |
| 5 | CuI/10 | 20 | $Cs_2CO_3$ | DMSO | 90 |
| 6 | CuI/10 | 20 | $Cs_2CO_3$ | Toluene | 65 |
| 7 | CuI/10 | 20 | $Et_3N$ | DMSO | <30 |
| 8 | CuI/10 | 20 | KO*t*-Bu | DMSO | 96 |
| 9 | CuI/5 | 10 | KO*t*-Bu | DMSO | 96 |
| 10 | $Cu_2O$/10 | 20 | KO*t*-Bu | DMSO | <40 |
| 11 | CuCl/10 | 20 | KO*t*-Bu | DMSO | <30 |

[a] Reaction conditions: all reactions were performed with 1 mmol of imidazole, 1 mmol of ArX, 1.4 mmol of base, in 1 ml of solvent at 110 °C.

---

*Keywords*: Benzotriazole; CuI; N-arylation; Imidazoles.

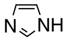
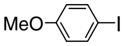
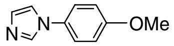
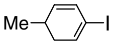
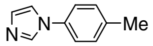
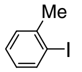
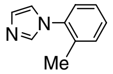
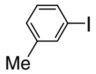
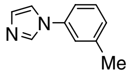
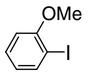
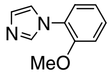
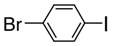
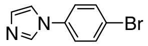
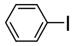
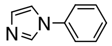
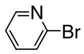
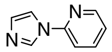
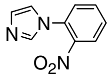
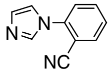
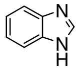
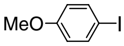
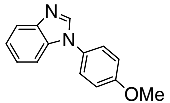
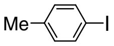
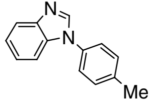
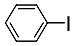
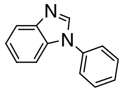
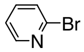
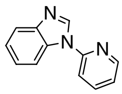
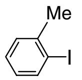
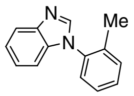
* Corresponding author. Tel.: +91 11 27666272x231; fax: +91 11 27666248; e-mail: akhilesh682000@yahoo.com

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.04.061

With BtH as ligand, a set of experiments was carried out to optimize the reaction conditions. The N-arylation of imidazole **1a** with 1-iodo-4-methoxybenzene **2a** was studied to identify a suitable catalyst/ligand/base system in different solvents. As shown in Table 1, without the aid of a ligand, treatment of substrate **1a** with **2a**, CuI and $Cs_2CO_3$ in DMF afforded only a trace amount of the corresponding product **3a** after 24 h (entry 1), whereas the yield of **3a** was enhanced sharply to 90% in 12 h when 20 mol % of BtH was added (entry 2, Table 1). Further, the study showed that almost the same yield of product was obtained with 10 mol % of BtH. Other solvents and bases were also investigated and we observed a maximum yield of 96% using KO*t*-Bu in DMSO (entry 8).[8] Other copper compounds (CuCl and $Cu_2O$) were also evaluated but proved inferior to CuI (entries 10 and 11, Table 1).

The efficacy of the CuI/BtH/KO*t*-Bu system for general N-arylation of imidazoles with aryl halides and hetero-

**Table 2.** CuI catalyzed N-arylation of imidazole and benzimidazole with various aryl halides[a]

| Entry | Imidazole | Arx | Product | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  **1a** |  **2a** |  **3a** | 95 (97) |
| 2 | |  **2b** |  **3b** | 96 (98) |
| 3 | |  **2c** |  **3c** | 92 (96) |
| 4 | |  **2d** |  **3d** | 98 (100) |
| 5 | |  **2e** |  **3e** | 93 (95) |
| 6 | |  **2f** |  **3f** | 96 (98) |
| 7 | |  **2g** |  **3g** | 97 (100) |
| 8 | |  **2h** |  **3h** | 98 (98) |
| 9 | |  **2i** |  **3i** | 100 |
| 10 | |  **2j** |  **3j** | 100 |
| 11 |  **1b** |  **2a** |  **3k** | 94 (97) |
| 12 | |  **2b** |  **3l** | 95 (96) |
| 13 | |  **2g** |  **3m** | 98 (98) |
| 14 | |  **2h** |  **3n** | 98 (98) |
| 15 | |  **2c** |  **3o** | 95 (98) |

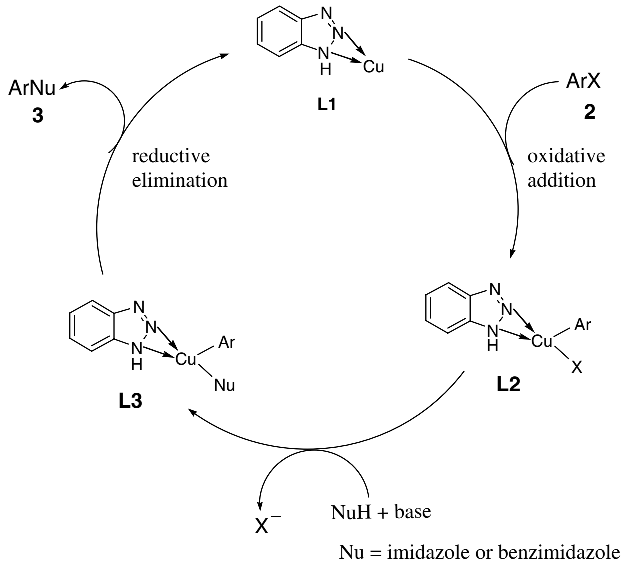
[a] Reaction conditions: all reactions were performed with 1 mmol of imidazole, 1 mmol of ArX, 1.4 mmol of KO*t*-Bu, 5 mol % of CuI and 10 mol % of BtH in 1 ml of DMSO at 110 °C.

[b] Isolated yields, values in parentheses are the yields determined by the GC analysis.

aryl bromide **2h** was evaluated and the results are summarized in Table 2. In the presence of CuI (5 mol %), BtH (10 mol %) and KO*t*-Bu (1.4 equiv), the N-arylation of **1a** with **2a** and **2h** occurred smoothly to afford the corresponding products in 95% and 98% yields, respectively. Encouraged by these results, a variety of aryl halides **2b**–**j** were treated with **1a** or **1b** under the standard reaction conditions. The results obtained indicated that all the aryl iodides with electron releasing substituents underwent N-arylation smoothly in 3–8 h. These N-arylations of deactivated haloarenes using KO*t*-Bu as base were quite impressive over unreactive systems using other bases (Table 1). The catalyst system developed was also successfully amenable to the N-arylation of imidazoles with fluoroarenes (Table 2, entries 9 and 10). As illustrated in Table 2, 1-fluoro-2-nitrobenzene **2i** and 2-fluorobenzonitrile **2j** gave the desired products in short reaction times (30 min), in 100% yields.

As described in Scheme 1 we have formulated a possible mechanism for the copper catalyzed N-arylation of imidazoles based on the previously reported mechanism.[2,4,9] Chelation of Cu(I) with BtH occurs to form the Cu(I) species **L1**, which is more reactive towards oxidative addition than stabilized intermediate **L2**[9] generated by the oxidative addition of **L1** to the aryl halide. In the presence of base, imidazole reacted with intermediate **L2** readily to afford intermediate **L3**, which undergoes reductive elimination to provide the desired product and regenerate the active Cu(I) species. Further study on the mechanism is in progress.

In conclusion, we have reported that BtH is an excellent, inexpensive and simple ligand for the N-arylation of imidazoles with a diverse range of aryl halides providing excellent yields of products. Efforts are being made to extend the application of the CuI/BtH/base system to the formation of other C–N bonds.



**Scheme 1.**

## Acknowledgements

We thank the Department of Science and Technology, New Delhi, for financial support. J.S. is thankful to the CSIR for SRF.

## References and notes

1. For selected recent examples, see: (a) Zhong, C.; He, J.; Xue, C.; Li, Y. *Bioorg. Med. Chem.* **2004**, *12*, 4009; (b) Dyck, B.; Goodfellow, V. S.; Phillips, T.; Grey, J.; Haddach, M.; Rowbottom, M.; Naeve, G. S.; Brown, B.; Saunders, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1151; (c) Smallheer, J. M.; Alexander, R. S.; Wang, J.; Wang, S.; Nakajima, S.; Rossi, K. A.; Smallwod, A.; Barbera, F.; Burdick, D.; Luettgen, J. M.; Knabb, R. M.; Wexler, R. R.; Jadhav, P. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5263; (d) Qiao, J. X.; Cheng, X.; Modi, D. P.; Rossi, K. A.; Luettgen, J. M.; Knabb, R. M.; Jadhav, P. K.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 29; (e) Mano, T.; Okumura, Y.; Sakakibara, M.; Okumura, T.; Tamura, T.; Miyamoto, K.; Stevens, R. W. *J. Med. Chem.* **2004**, *47*, 720; (f) Roppe, J.; Smith, N. D.; Huang, D.; Tehrani, L.; Wang, B.; Anderson, J.; Brodkin, J.; Chung, J.; Jiang, X.; King, C.; Munoz, B.; Varney, M. A.; Prasit, P.; Cosford, N. D. P. *J. Med. Chem.* **2004**, *47*, 4645; (g) Venkatesan, A. M.; Gu, Y.; Santos, O. D.; Abe, T.; Agarwal, A.; Yang, Y.; Petersen, P. J.; Weiss, W. J.; Mansour, T. S.; Nukaga, M.; Hujer, A. M.; Bonomo, R. A.; Knox, J. R. *J. Med. Chem.* **2004**, *47*, 6556; (h) Lange, J. H. M.; van Stuivenberg, H. H.; Coolen, H. K. A. C.; Adolfs, T. J. P.; McCreary, A. C.; Keizer, H. G.; Wals, H. C.; Veerman, W.; Borst, A. J. M.; de Looff, W.; Verveer, P. C.; Kruse, C. G. *J. Med. Chem.* **2005**, *48*, 1823; (i) 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. *J. Med. Chem.* **2005**, *48*, 1729; (j) Barchéchath, S. D.; Tawatao, R. I.; Corr, M.; Carson, D. A.; Cottam, H. B. *J. Med. Chem.* **2005**, *48*, 6409; (k) Voets, M.; Antes, I.; Scherer, C.; Müller-Vieira, U.; Biemel, K.; Barassin, C.; Marchais-Oberwinkler, S.; Hartmann, R. W. *J. Med. Chem.* **2005**, *48*, 6632; (l) Wiglenda, T.; Ott, I.; Kircher, B.; Schumacher, P.; Schuster, D.; Langer, T.; Gust, R. *J. Med. Chem.* **2005**, *48*, 6516; (m) Jiang, W.; Guan, J.; Macielag, M. J.; Zhang, S.; Qiu, Y.; Kraft, P.; Bhattacharjee, S.; John, T. M.; Haynes-Johnson, D.; Lundeen, S.; Sui, Z. *J. Med. Chem.* **2005**, *48*, 2126.
2. (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337; (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400; (c) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.
3. Jiang, L.; Buchwald, S. L. Palladium-Catalyzed Aromatic Carbon–Nitrogen bond Formation. In *Metal-catalyzed Cross-Coupling Reactions*; 2nd ed., de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; pp 699–760.
4. For papers on copper-catalyzed N-arylations of imidazoles with aryl halides, see: (a) Liu, Y.-H.; Chen, C.; Yang, L.-M. *Tetrahedron Lett.* **2006**, *47*, 9275–9278; (b) Xie, Y.-X.; Pi, S.-F.; Wang, J.; Yin, D.-L.; Li, J.-H. *J. Org. Chem.* **2006**, *71*, 8324–8327; (c) Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657; (d) Kuil, M.; Bekedam, E. K.; Visser, G. M.; van den Hoogenband, A.; Terpstra, J. W.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Van Strijdonck, G. P. F. *Tetrahedron Lett.* **2005**, *46*, 2405; (e) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779; (f) Kuil, M.; Bekedam, E. K.; Visser, G. M.; van den Hoogenband, A.; Terpstra, J. W.; Kamer, P. C.; van

Leeuwen, P. W. N. M.; van Strijdonck, G. P. F. *Tetrahedron Lett.* **2005**, *46*, 2405; (g) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727; (h) Alcalde, E.; Dinarès, I.; Rodríyguez, S.; Garcia de Miguel, C. *Eur. J. Org. Chem.* **2005**, 1637; (i) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578; (j) Jerphagnon, T.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *Org. Lett.* **2005**, *7*, 5241; (k) Ma, D.; Cai, Q. *Synlett* **2004**; (l) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164; (m) Lv, X.; Wang, Z.; Bao, W. *Tetrahedron* **2006**, *62*, 4756; (n) Liu, L.; Frohn, M.; Xi, N.; Dominguez, C.; Hungate, R.; Reider, P. J. *J. Org. Chem.* **2005**, *70*, 10135; (o) Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2005**, *70*, 8107; (p) Xu, L.; Zhu, D.; Wu, F.; Wang, R.; Wan, B. *Tetrahedron* **2005**, *61*, 6553; (q) Zhang, Z.; Mao, J.; Zhu, D.; Wu, F.; Chen, H.; Wan, B. *Tetrahedron* **2006**, *62*, 4435; (r) Choudary, B. M.; Sridhar, C.; Kantam, M. L.; Venkanna, G. T.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 9948; (s) Son, S. U.; Park, I. K.; Park, J.; Hyeon, T. *Chem. Commun.* **2004**, 778.

5. For selected representative papers on copper-catalyzed N-arylations of imidazoles with other reagents, see: (a) Lopez-Alvarado, P.; Avendaño, C.; Menéndez, J. C. *J. Org. Chem.* **1995**, *60*, 5678; (b) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233; (c) Collman, J. P.; Zhong, M.; Zeng, L.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 1528; (d) Collman, J. P.; Zhong, M.; Zhang, C.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 7892; (e) Lan, J.-B.; Chen, L.; Yu, X.-Q.; You, J.-S.; Xie, R.-G. *Chem. Commun.* **2004**, 188; (f) Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600; (g) Fedorov, A. Y.; Finet, J.-P. *Tetrahedron Lett.* **1999**, *40*, 2747; (h) Kang, S.-K.; Lee, S.-H.; Lee, D. *Synlett* **2000**, 1022; (i) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, 674.
6. For selected recent papers on the synthesis of N-aryl imidazoles via other transformations, see (a) Lee, S.-H.; Yoshida, K.; Matsushita, H.; Clapham, B.; Koch, G.; Zimmermann, J.; Janda, K. D. *J. Org. Chem.* **2004**, *69*, 8829; (b) Li, W.; Lam, Y. *J. Comb. Chem.* **2005**, *7*, 644; (c) Gracias, V.; Gasiecki, A. F.; Djuric, S. W. *Org. Lett.* **2005**, *7*, 3183; (d) Szczepankiewicz, B. G.; Rohde, J. J.; Kurukulasuriya, R. *Org. Lett.* **2005**, *7*, 1833; (e) Siamaki, A. R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2006**, *128*, 6050.
7. (a) Katritzky, A. R.; Verma, A. K.; He, H.; Chandra, R. *J. Org. Chem.* **2003**, *68*, 4938; (b) Tiwari, R. K.; Singh, J.; Singh, D.; Verma, A. K.; Chandra, R. *Tetrahedron* **2005**, *61*, 9513; (c) Tiwari, R. K.; Singh, D.; Singh, J.; Chhillar, A.; Chandra, R.; Verma, A. K. *Eur. J. Med. Chem.* **2006**, *41*, 40; (d) Tiwari, R. K.; Singh, D.; Singh, J.; Yadav, V.; Phatak, A. K.; Dabur, R.; Chhillar, A.; Singh, R.; Sharma, G. L.; Chandra, R.; Verma, A. K. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 413–416; (e) Chaudhary, P.; Kumar, R.; Verma, A. K.; Singh, D.; Yadav, V.; Chhillar, A.; Sharma, G. L.; Chandra, R. *Bioorg. Med. Chem.* **2006**, *14*, 1819; For a review on the use of benzotrizole see: (f) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409.
8. *Typical experimental procedure*: To a round-bottomed flask containing CuI (5 mol %) and benzotriazole (10 mol %) in 1 ml of DMSO, 1 mmol of aryl halide was added followed by 1 mmol of imidazole and 1.4 equiv KO*t*-Bu. The reaction mixture was stirred vigorously for 3–8 h at 110 °C. After the reaction was complete, ethyl acetate was added to the mixture, which was then washed with water, dried over $Na_2SO_4$ and evaporated under vacuum. The residue was purified by column chromatography (hexanes) to afford the desired product. All the products are known and have been characterized by $^1H$ NMR and LCMS.[2]
9. Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312.