RSC Advances

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Direct amination of azoles using $CuCl_2$ complexes of amines under mild conditions†

Cite this: *RSC Advances*, 2013, **3**, 9622

Received 6th February 2013,
Accepted 1st May 2013

DOI: 10.1039/c3ra41496e

www.rsc.org/advances

Juan Xu, Jiarong Li, Zhen Wei, Qi Zhang and Daxin Shi*

The efficient direct amination of azoles, including benzoxazole, benzothiazole and 1-methylbenzimidazole, was accomplished in moderate to good yields using $CuCl_2$ complexes of amines as a readily available and effective nitrogen source. The coupling reactions were performed under mild conditions: at 30–50 °C within 3–6 h, in air without oxidant, additive, ligand and anhydrous conditions.

Heteroarylamines have received much attention from synthetic chemists because of their ubiquity in pharmaceuticals and functional materials.[1] 2-Aminobenzoxazole derivatives are important compounds in medicinal chemistry, and significant targets in combinatorial approaches.[2] Some 2-aminobenzo-thiazole derivatives have protective effects against γ-irradiation *via* experiments on plasmid DNA.[3] The 1-methyl-2-amino-benzimidazoles are promising class of chemical compounds with different biological effects as immunotropic, diuretic or anti-histaminic.[4] The polyfunctionality of the aminoazole molecule has made it a building block for the synthesis of pharmacological interest.

Given the importance of the azole motif in biological medicinal chemistry and material chemistry, the transition-metal-catalyzed direct C–H functionalization of azole rings is of great interest[5] in organic synthesis because the reaction shows an advantage in atom efficiency compared to related cross-coupling with organometallic compounds.[6] Among the many types of C–H functionalization of azoles documented, the direct C–H amination of azoles pioneered by Mori,[7] Schreiber,[8] Chang,[9] Miura,[10] and others[11] provided a rapid and straightforward access to the heteroarylamines. However, all of the aforementioned methods inherently suffer from harsh conditions such as high temperature is required; the use of a stoichiometric amount of oxidant ($PhI(OAc)_2$, ICl, $Mn(OAc)_2$ or O_2) is inevitable. Additionally, the scope of aromatic amines is limited. Therefore, further development for direct C–H amination would be highly desired.

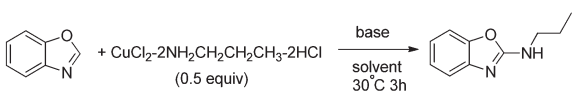
School of Chemical Engineering and Environment, Beijing Institute of Technology, Beijing 100081, China. E-mail: shidaxin@bit.edu.cn

† Electronic supplementary information (ESI) available: Detailed experimental procedures and spectroscopic data for the products. See DOI: 10.1039/c3ra41496e

In our recent research,[12] we found that metal complexes of diamines were easy to obtain from the reaction of amines/amides with relative metal halide in acidic ethanol solution.[13] This kind of complexes combines couple advantageous features: solid, stable in air, odorless smell, and excellent water-solubility.[14] Furthermore, it combines both the source of nitrogen and the catalytic center of metal ion. In view of these advantages, we envisaged whether this kind of complexes can be used in process of arylamination. Herein, we introduce $CuCl_2$ complexes of amines as a kind of readily available and effective nitrogen source for heteroaromatic C–H functionali-zation. All reactions are under open system and there is no need of oxidant, additive, ligand and anhydrous condition. Use of this type of reagent enables the formation of heteroarylamino linkages even at room temperature so as to provide a rapid and straight-forward access to the heteroarylamines of quite important in biological and medicinal chemistry.[15] To the best of our knowledge, there is no example for the preparation of heteroarylamines by coupling reactions of azoles with metal complexes of organic amines.

We began our optimization studies with benzoxazole and $CuCl_2$ complex of *n*-propylamine as model substrates (Table 1).

Table 1 Optimization studies of benzoxazole with $CuCl_2$ complex of *n*-propylamine



Entry	Base	Solvent	Yield (%)
1	K_2CO_3	CH_3CN	89
2	Na_2CO_3	CH_3CN	82
3	$NaHCO_3$	CH_3CN	80
4	Et_3N	CH_3CN	74
5	Pyridine	CH_3CN	72
6	No	CH_3CN	0
7	K_2CO_3	CH_2Cl_2	70
8	K_2CO_3	1,4-Dioxane	65
9	K_2CO_3	MeOH	71

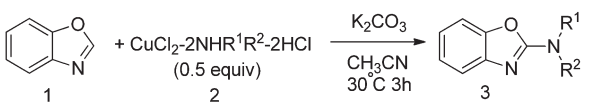
After the extensive screening of various solvents and bases, we found that the amination of benzoxazole and $CuCl_2$ complex of *n*-propylamine afforded *N*-propylbenzoxazol-2-amine in 89% yield with K_2CO_3 as base and CH_3CN as solvent (Table 1, entry 1). The use of other organic or inorganic bases, including Na_2CO_3, $NaHCO_3$, NEt_3 and pyridine, could promote the reaction, although the yield was inferior to that using K_2CO_3 (Table 1, entries 2–6). Solvents such as CH_3CN, CH_2Cl_2, 1,4-dioxane and MeOH were investigated. CH_3CN was more favored. With CH_2Cl_2, 1,4-dioxane and MeOH, yields were comparatively low. Notably, the amination reaction could even be carried out within 3 h at room temperature. All solvents were analytical grade without pre-treatment, which indicated the coupling process was fairly insensitive to water and no special precautions was required to exclude moisture from this reaction.

With the optimized conditions for direct C–H amination in hand, a variety of amines were chose to form $CuCl_2$ complexes and were examined for the direct amination of benzoxazole (Table 2).

As summarized in Table 2, a wide range of $CuCl_2$ complexes of amines could undergo the amination. The reactions with acyclic and cyclic alkylamines proceeded without any difficulties to afford the corresponding amination products. Acyclic amines such as *n*-propylamine (**3a**), dimethylamine (**3b**) and ethane-1,2-diamine (**3c**) were smoothly reacted to give the product. Cyclic amines were readily employed for this reaction. For instance, benzoxazoles bearing cyclic amino groups such as pyrrolidinyl (**3d**) and morpholinyl (**3e**), as well as *N*-methylpiperazinyl (**3f**) could be isolated in good yields. To our delight, we found that the amination was also efficiency in aromatic amines. Both electron-withdrawing and electron-donating functional groups were tolerated well on the aryl ring of the amines. 2-Aminobenzoxazole derivatives substituted with phenyl (**3g**), 4-nitrophenyl (**3h**), and *p*-tolyl (**3i**) groups were easily obtained.

The synthesis of 2-aminobenzoxazole or 1-methyl-2-amino-benzimidazoles requires multiple-step sequences which makes it difficult to lend themselves to the syntheses of many structural analogues.[16] To overcome this obstacle, we expand the direct C–H functionalization to benzothiazole and 1-methylbenzo-imidazole with $CuCl_2$ complexes of amines (Table 3). These transformations offer successful examples of challenging intermolecular C–N bond formation using aromatic C–H and $CuCl_2$ complexes of amines.

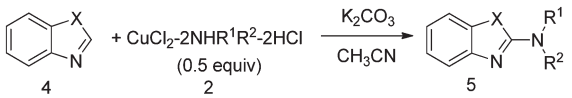
Table 2 Reaction scopes of the direct amination of benzoxazole



1 2 3

Entry	R^1	R^2	Product	Yield (%)
1	$CH_2CH_2CH_3$	H	**3a**	89
2	CH_3	CH_3	**3b**	92
3	$NH_2CH_2CH_2$	H	**3c**	79
4	$(CH_2)_4$		**3d**	90
5	$(CH_2)_2O(CH_2)_2$		**3e**	91
6	$(CH_2)_2N(CH_3)(CH_2)_2$		**3f**	82
7	Ph	H	**3g**	76
8	4-NO_2Ph	H	**3h**	72
9	4-CH_3Ph	H	**3i**	81

Table 3 Reaction scopes of the direct amination of Benzothiazole and 1-methylbenzimidazole[a]



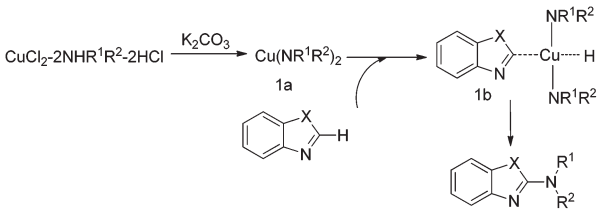
4 2 5

Entry	X	R^1	R^2	Product	Yield (%)
1	S	$CH_2CH_2CH_3$	H	**5a**	83
2		CH_3	CH_3	**5b**	78
3		$(CH_2)_4$		**5c**	81
4		$(CH_2)_5$		**5d**	79
5		$(CH_2)_2O(CH_2)_2$		**5e**	80
6		$(CH_2)_2N(CH_3)(CH_2)_2$		**5f**	75
7		4-CH_3Ph	H	**5g**	69
8	NCH_3	CH_2CH_3	CH_2CH_3	**5h**	66
9		$(CH_2)_5$		**5i**	68
10		$(CH_2)_2O(CH_2)_2$		**5j**	62
11		4-NO_2Ph	H	**5k**	60

[a] Benzothiazole: 30 °C for 5 h; 1-methylbenzimidazole: 50 °C for 6 h.

By using the modified protocol, various types of $CuCl_2$ complexes of amines could take place the amination reaction and afford products. 2-aminobenzothiazole derivatives substituted with dimethyl (**5a**), *n*-propyl (**5b**), pyrrolidinyl(**5c**), piperidinyl (**5d**), morpholinyl (**5e**), and *N*-methyl-piperazinyl (**5f**) as well as *p*-tolyl groups (**5g**) were easily obtained, thus offering an additional opportunity for further manipulation of the products. Meanwhile, when 1-methyl-benzimidazole was treated with $CuCl_2$ complexes of amines, the corresponding product were obtained in moderate yield (**5h**, **5i**, **5j**, **5k**). Although a higher reaction temperature (50 °C) was required to achieve satisfactory product yields, the $CuCl_2$ complexes system was efficient enough to include various types of amines reactants.

Although comprehensive studies are required to elucidate the mechanistic details of the present reactions, a tentative proposal is presented in Scheme 1. As shown in Scheme 1, we thought organocopper **1a** and **1b** would be the key intermediates.[8] Then C–N reductive elimination at the 2-position to give the amination product. Ligandless "$CuNPh_2$" arose from any form of copper (metal, Cu^+ or Cu^{2+}) was proposed by Paine[17] in 1987 to be an intermediate in Ullmann reactions. From then on, there has been



Scheme 1 A proposed mechanism for the direct amination of azoles.

great progress in the mechanisms and models for copper mediated nucleophilic aromatic substitution.[18]

In summary, we have developed a new catalytic system for the direct amination of azoles by using $CuCl_2$ complexes of amines as nitrogen source with K_2CO_3 in CH_3CN. The reaction is highly attractive from the synthetic point of view in that optimal reaction conditions are mild, and substrate scope is broad. In addition, a mechanistic proposal is made on the basis of the results. The present reaction, therefore, is anticipated to be a powerful tool for the synthesis of 2-aminoazoles which are important pharmacophores of high biological activity. Ongoing work seeks to uncover the detailed mechanism and expand the reaction scope with $CuCl_2$ complexes of amines of high potential in direct C–H amination chemistry.

References

1 (*a*) R. Hili and A. K. Yudin, *Nat. Chem. Biol.*, 2006, **2**, 284; (*b*) P. S. Taylor, P. Ghalsasi and P. M. Lahti, *Tetrahedron Lett.*, 2004, **45**, 6295; (*c*) S. Guo, B. Qian, Y. Xie, C. Xia and H. Huang, *Org. Lett.*, 2011, **13**, 522; (*d*) N. Matsuda, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2011, **13**, 2860; (*e*) J. Y. Kim, S. H. Cho, J. Joseph and S. Chang, *Angew. Chem., Int. Ed.*, 2010, **49**, 9899.

2 (*a*) S. R. Hoertner, T. Ritschel, B. Stengl, C. Kramer, W. B. Schweizer, B. Wagner, M. Kansy, G. Klebe and F. Diederich, *Angew. Chem., Int. Ed.*, 2007, **46**, 8266; (*b*) P. C. Kohler, T. Ritschel, W. B. Schweizer, G. Klebe and F. Diederich, *Chem.–Eur. J.*, 2009, **15**, 10809.

3 C. Prouillac, P. Vicendo, J. C. Garrigues, R. Poteau and G. Rima, *Free Radical Biol. Med.*, 2009, **46**, 1139.

4 A. T. Mavrova, P. Denkova, Y. A. Tsenov, K. K. Anichinaa and D. I. Vutchevc, *Bioorg. Med. Chem.*, 2007, **15**, 6291.

5 (*a*) H. Q. Do and O. Daugulis, *J. Am. Chem. Soc.*, 2007, **129**, 12404; (*b*) H. Q. Do, R. M. K. Khan and O. Daugulis, *J. Am. Chem. Soc.*, 2008, **130**, 15185; (*c*) L. Ackermann, A. Althammer and S. Fenner, *Angew. Chem., Int. Ed.*, 2009, **48**, 201; (*d*) D. Zhao, W. Wang, F. Yang, J. Lan, L. Yang, G. Gao and J. You, *Angew. Chem., Int. Ed.*, 2009, **48**, 3296; (*e*) J. Canivet, J. Yamaguchi, I. Ban and K. Itami, *Org. Lett.*, 2009, **11**, 1733; (*f*) N. Matsuyama, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2009, **11**, 4156; (*g*) J. Huang, J. Chan, Y. Chen, C. Broths, J. K. D. Baucom, R. D. Larsen and M. M. Faul, *J. Am. Chem. Soc.*, 2010, **132**, 3674; (*h*) H. Hachiya, K. Hirano, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.*, 2010, **49**, 2202; (*i*) Y. Nakao, N. Kashihara, K. S. Kanyiva and T. Hiyama, *Angew. Chem., Int. Ed.*, 2010, **49**, 4451; (*j*) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.*, 2011, **40**, 5068.

6 G. Dyker, *Angew. Chem., Int. Ed.*, 1999, **38**, 1698.

7 (*a*) D. Monguchi, T. Fujiwara, H. Furukawa and A. Mori, *Org. Lett.*, 2009, **11**, 1607; (*b*) D. Monguchi, A. Yamamura, T. Fujiwara, T. Somete and A. Mori, *Tetrahedron Lett.*, 2010, **51**, 850; (*c*) T. Kawano, N. Matsuyama, K. Hirano, T. Satoh and M. Miura, *J. Am. Chem. Soc.*, 2010, **132**, 6900.

8 Q. Wang and S. L. Schreiber, *Org. Lett.*, 2009, **11**, 5178.

9 (*a*) S. H. Cho, J. Y. Kim, S. Y. Lee and S. Chang, *Angew. Chem., Int. Ed.*, 2009, **48**, 9127; (*b*) J. Joseph, J. Y. Kim and S. Chang, *Chem.–Eur. J.*, 2011, **17**, 8294.

10 (*a*) M. Miyasaka, K. Hirano, T. Satoh, R. Kowalczyk, C. Bolm and M. Miura, *Org. Lett.*, 2011, **13**, 359; (*b*) N. Matsuda, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2011, **13**, 2860.

11 (*a*) S. Ohta, N. Tsuno, S. Nakamura, N. Taguchi, M. K. Yamashita and M. Fujieda, *Heterocycles*, 2000, **53**, 1939; (*b*) A. Balkis, B. Haider, M. A. El-Apasery and M. H. Einagdi, *J. Chem. Res.*, 2004, **8**, 575; (*c*) P. Zanirato and S. Cerini, *Org. Biomol. Chem.*, 2005, **3**, 1508; (*d*) I. Titova, T. Vakul'skaya, L. Larina, M. Mizandrontsev, V. Volkov, G. Dolgushin and V. Lopyrev, *Russ. J. Org. Chem.*, 2005, **41**, 1306; (*e*) V. Amo, S. R. Dubbaka, A. Krasovskiy and P. Knochel, *Angew. Chem., Int. Ed.*, 2006, **45**, 7838; (*f*) G. Piersanti, L. Giorgi, F. Bartoccini, G. Tarzia, P. Minetti, G. Gallo, F. Giorgi, M. Castorina, O. Ghirardi and P. Carminati, *Org. Biomol. Chem.*, 2007, **5**, 2567; (*g*) M. Kienle, C. Dunst and P. Knochel, *Org. Lett.*, 2009, **11**, 5158; (*h*) A. Sankaranarayanan, G. Raman, C. Busch, T. Schultz, P. I. Zimin, J. Hoyer, R. Köhler and H. Wulff, *Mol. Pharmacol.*, 2009, **75**, 281; (*i*) H. Zhao, M. Wang, W. Su and M. Hong, *Adv. Synth. Catal.*, 2010, **352**, 1301; (*j*) S. Guo, B. Qian, Y. Xie, C. Xia and H. Huang, *Org. Lett.*, 2011, **13**, 522; (*k*) T. Froehr, C. P. Sindlinger, U. Kloeckner, P. Finkbeiner and B. J. Nachtsheim, *Org. Lett.*, 2011, **13**, 3754; (*l*) Y. Li, Y. Xie, R. Zhang, K. Jin, X. Wang and C. Duan, *J. Org. Chem.*, 2011, **76**, 5444; (*m*) J. Wang, J. Hou, J. Wen, J. Zhang and X. Yu, *Chem. Commun.*, 2011, **47**, 3652.

12 J. R. Li, X. Chen, D. X. Shi, S. L. Ma, Q. Li, Q. Zhang and J. H. Tang, *Org. Lett.*, 2009, **11**, 1193.

13 J. Xu, D. X. Shi, Z. Wei, Y. F. Wei, Q. Zhang and J. R. Li, *Chin. J. Org. Chem.*, 2012, **32**, 776.

14 J. Xu and J. R. Li, *J. Chem. Res.*, 2012, **36**, 381.

15 S. R. Whitefield and M. S. Sanford, *J. Am. Chem. Soc.*, 2007, **129**, 15142.

16 (*a*) J. J. Perkins, A. E. Zartman and R. S. Meissner, *Tetrahedron Lett.*, 1999, **40**, 1103; (*b*) P. P. Seth, D. E. Robinson, E. A. Jefferson and E. E. Swayze, *Tetrahedron Lett.*, 2002, **43**, 7303; (*c*) R. D. Carpenter, P. B. DeBerdt, K. S. Lam and M. J. Kurth, *J. Comb. Chem.*, 2006, **8**, 907.

17 A. J. Paine, *J. Am. Chem. Soc.*, 1987, **109**, 1496.

18 (*a*) R. J. Mills, N. J. Taylor and V. Snieckus, *J. Org. Chem.*, 1989, **54**, 4372; (*b*) E. D. Blue, A. Davis, D. Conner, T. B. Gunnoe, P. D. Boyle and P. S. White, *J. Am. Chem. Soc.*, 2003, **125**, 9435; (*c*) J. W. Tye, Z. Q. Weng, A. M. Johns, C. D. Incarvito and J. F. Hartwig, *J. Am. Chem. Soc.*, 2008, **130**, 9971; (*d*) R. Giri and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 15860.

