ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 7634–7636

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COMMUNICATION

A CuBr-mediated aerobic reaction of 2-alkynylbenzaldehydes and primary amines: synthesis of 4-bromoisoquinolones†

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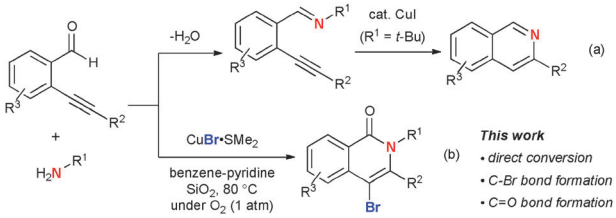
Received 11th May 2012, Accepted 9th June 2012
DOI: 10.1039/c2cc33426g

A method for synthesis of 4-bromoisoquinolones has been developed starting from 2-alkynylbenzaldehydes and primary amines mediated by CuBr under an O_2 atmosphere, where CuBr plays multiple roles to facilitate the present reactions.

Among nitrogen-containing heterocycles (azaheterocycles), isoquinolones and their derivatives are a common core component of some biologically active natural alkaloids as well as potent pharmaceutical drugs. The representative examples are kibdelones A–C (and their isomeric metabolites such as cervinomycin A_2 and SCH56036),[1] fredericamycin A,[2] alternarlactam,[3] and NSC314622.[4] Based on these backgrounds, diverse synthetic approaches to construct isoquinolone frameworks have been exploited,[5–8] while there remains a need for conceptually novel and versatile methodologies for chemical synthesis of isoquinolones from readily available building blocks with selective control of the substitution patterns.

Functionalization of alkynes with intramolecular nitrogen nucleophiles is one of the most fundamental and common strategies for azaheterocycle synthesis.[9] Especially, the reactions of 2-alkynyl benzaldimines could provide promising ways for preparation of substituted isoquinoline derivatives through electrophilic activation of alkynes under various types of reaction conditions (*e.g.* CuI-catalyzed isoquinoline formation, Scheme 1a).[10] These methods naturally require the preparation of aldimines by dehydrative condensation of benzaldehydes and primary amines, which often suffer from poor conversion and low chemical yield due to the instability of aldimines (especially when R^1 = alkyl groups). To complement such drawbacks, we became interested in direct conversion starting from 2-alkynylbenzaldehydes and primary amines. In this context, we were also encouraged by our recent interest in copper-mediated oxidative functionalization of carbon–carbon unsaturated bonds under aerobic conditions.[11,12] Herein, we report a CuBr-mediated aerobic reaction of 2-alkynylbenzaldehydes and primary amines in the presence of SiO_2 that leads to direct 4-bromoisoquinolone formation (Scheme 1b).



Scheme 1 Azaheterocycle synthesis by functionalization of alkynes.

We began our investigation with the copper-mediated aerobic reactions of 2-(phenylethynyl)benzaldehyde (**1a**) and benzylamine (**2a**) (Table 1). Interestingly, when a mixture of **1a** and **2a** (1.1 equiv.) was treated with 2.2 equiv. of $CuBr{\cdot}SMe_2$ and pyridine in toluene at 80 °C under an oxygen (O_2) atmosphere, *N*-benzyl-4-bromoisoquinolone **3aa** was isolated in 29% yield (entry 1). This unprecedented 4-bromoisoquinolone formation prompted us to optimize the reaction conditions further. The reaction could be accelerated by adding SiO_2 (entry 2),[13] and the yield of product **3aa** improved to 56% by using pyridine as a solvent with adding 1 equiv. of **2a** three times at every 1 h interval (in total 3 equiv. of **2a**)[14] (entry 3). It was found that the co-solvent system including pyridine proved to be optimal for this transformation (entries 4–6), and benzene–pyridine (5 : 1) solvent gave the best yield of **3aa** (77%, entry 6). Usage of 1.1 equiv. of $CuBr{\cdot}SMe_2$ rendered the reaction sluggish, giving **3aa** in 39% yield (entry 7). Moreover, catalytic use of $CuBr{\cdot}SMe_2$ with LiBr as an additional bromide source[15] did not promote the reaction (entry 8). The reaction with $CuBr_2$ (2.2 equiv.) worked to give **3aa**, although the yield dropped to 49% (entry 9). It is noted that the reactions with other amines such as triethylamine, DABCO, and 2,2′-bipyridine instead of pyridine did not give **3aa** at all. Furthermore, no 4-bromoisoquinolone formation was observed under a N_2 atmosphere. These results suggested that the presence of pyridine and molecular oxygen could play vital roles in this transformation.[16]

Having optimized the reaction conditions (Table 1, entry 6), we examined the generality of this 4-bromoisoquinolone formation. By varying substituents R^1 of primary amines **2** (Table 2), it was shown that several benzyl amines **2b–d** including methoxy, methyl, and fluoro groups on the benzene

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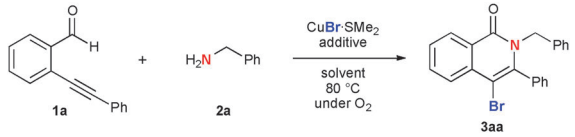
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data of products, and copies of ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c2cc33426g

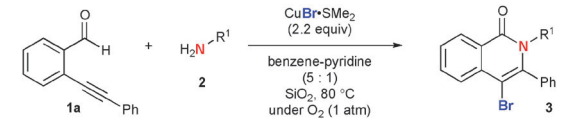
Table 1 Optimization of the reaction conditions[a]

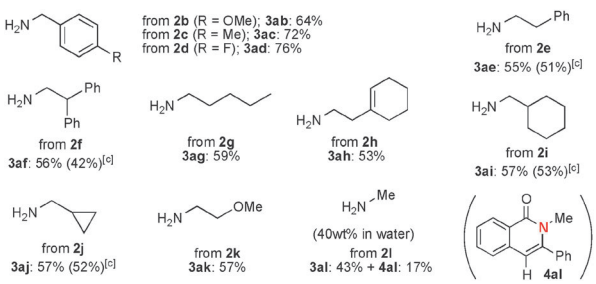


Entry	CuBr·SMe$_2$ (equiv.)	Additive	Solvent	Time (h)	Yield[b] (%)
1[c,d]	1.1	—	Toluene	22	29 (31)[e]
2[c,d]	1.1	SiO_2	Toluene	1	34
3	2.2	SiO_2	Pyridine	4	56
4	2.2	SiO_2	Toluene–pyridine (5 : 1)	6	64
5	2.2	SiO_2	DCE–pyridine (5 : 1)	3.5	72
6	2.2	SiO_2	Benzene–pyridine (5 : 1)	4	77 (80)[f]
7	1.1	SiO_2	Benzene–pyridine (5 : 1)	4	39[g]
8	0.2[h]	SiO_2	Pyridine	7	2
9[i]	2.2	SiO_2	Benzene–pyridine (5 : 1)	4	49[g] (0)[j]

[a] Unless otherwise noted, the reactions were conducted using 0.3 mmol of **1a** and 0.9 mmol of **2a** (3 equiv.) in solvent (3 mL, 0.1 M) in the presence of 0.3 g of SiO_2 at 80 °C under an O_2 atmosphere, where 0.3 mmol of **2a** was added at every 1 h interval. [b] Isolated yields. [c] 2.2 equiv. of pyridine was added. [d] 1.1 equiv. of **2a** was used. [e] Recovery yield of **1a**. [f] The yield of **3aa** using 0.5 mmol of **1a** and 1.5 mmol of **2a** with 0.3 g of SiO_2. [g] ^{1}H NMR yield. [h] LiBr (2 equiv.) was added. [i] $CuBr_2$ was used instead of CuBr·SMe$_2$. [j] The yield under a N_2 atmosphere. DCE = 1,2-dichloroethane.

Table 2 Scope of primary amines **2**[a,b]



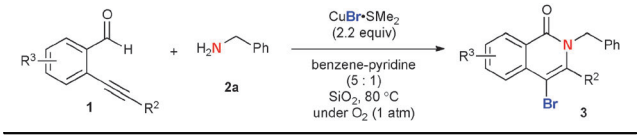


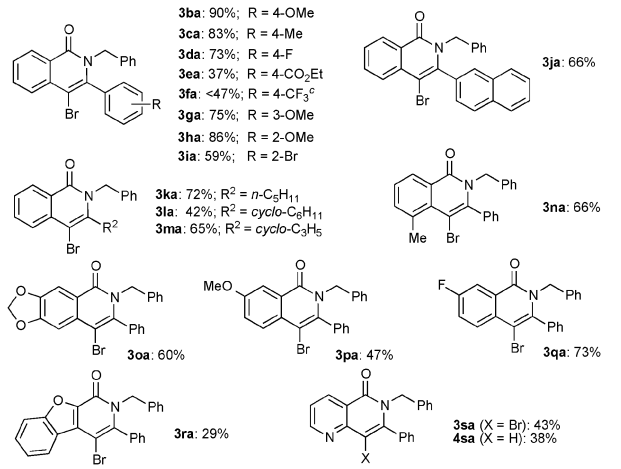
[a] Unless otherwise noted, the reactions were conducted using 0.5 mmol of **1a** and 1.5 mmol of **2** (3 equiv.) in solvent (5 mL, 0.1 M) at 80 °C under an O_2 atmosphere, where 0.5 mmol of **2a** was added at every 1 h interval. [b] Isolated yields were recorded above. [c] The yields of **3** from the reactions with 1.2 equiv. of amines **2**.

ring were tolerated to give the corresponding *N*-benzylisoquinolones **3** in good yields. The reactions also proceeded smoothly with other types of alkyl amines **2e–2k**, which could possess normal alkyl groups as well as alkenyl (for **2h**), cyclopropyl (for **2j**), and methoxy (for **2k**) groups. In the case of methyl amine **2l**, the corresponding 4-bromoisoquinoline **3al** was formed in 43% yield along with 17% yield of protonated isoquinolone **4al**.[17]

Next, the effect of substituents on 2-alkynylbenzaldehydes **1** was examined using benzylamine (**2a**) (Table 3). The substituents R^2 on the alkyne could include not only various aryl groups (for **3ba–3ja**) but also several normal- and cyclo-alkyl

Table 3 Scope of 2-alkynylbenzaldehydes **1**[a,b]

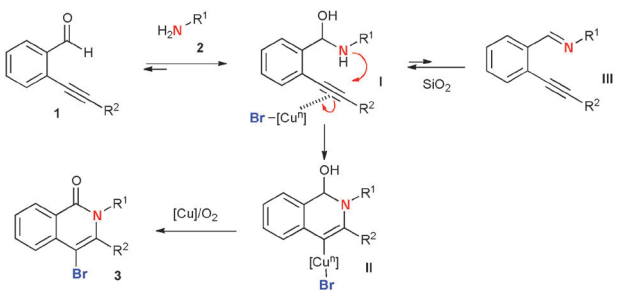




[a] Unless otherwise noted, the reactions were conducted using 0.5 mmol of **1** and 1.5 mmol of **2a** (3 equiv.) in solvent (5 mL, 0.1 M) at 80 °C under an O_2 atmosphere, where 0.5 mmol of **2a** was added at every 1 h interval. [b] Isolated yields were recorded above. [c] The purity of **3fa** is about 90%.

groups (for **3ka–3ma**), giving the corresponding isoquinolones **3** in good yields except for the cases of electron-deficient aryl groups (for **3ea** and **3fa**). On the benzene ring, several electron-donating groups (for **3na–3pa**) as well as a fluorine atom (for **3qa**) could be introduced as R^3. This method could allow for incorporating heteroaryl motifs such as benzofuran (for **3ra**) and pyridine (for **3sa**), although the yields were moderate, and protonated isoquinolone **4sa** was isolated along with 4-bromoisoquinoline **3sa** from the reaction of pyridyl derivative **1s**.

Based on these results and the several control experiments conducted (see ESI† for details), a proposed reaction pathway is outlined in Scheme 2. The reaction of aldehyde **1** and amine **2** gives hemiaminal **I**, which undergoes 6-*endo* cyclization onto electrophilically activated alkyne with [Cu^n]Br[18] to give vinyl copper species **II** (path a). Alternatively, formation of aldimine **III** followed by its cyclization might be proposed, which is unlikely because of the lower yield of 4-bromoisoquinolone starting from isolated aldimine **III** under the present aerobic reaction conditions (see ESI†, Scheme S3a). The possible role



Scheme 2 A proposed reaction mechanism.

of SiO_2 might be to drive the equilibrium between hemiaminal **I** and aldimine **III** to the **I** side. From putative intermediate **II**, further C–Br reductive elimination[19] and oxidation of the C–O bond by the Cu/O_2 system[20] deliver 4-bromoisoquinolone **3**. Nonetheless, CuBr plays multiple roles as the promoter of N–C bond forming cyclization, the bromine carrier, and the oxidant for the formation of the C=O bond under the present aerobic conditions.[21]

In summary, a method for synthesis of 4-bromoisoquinolones has been developed using 2-alkynylbenzaldehydes and primary amines mediated by CuBr under an O_2 atmosphere, where CuBr plays multiple roles to facilitate the present reactions. Further investigation of the scope and the reaction mechanism as well as application of this strategy for synthesis of biologically active molecules is currently underway.

This work was supported by funding from Nanyang Technological University and Singapore Ministry of Education.

Notes and references

1 (*a*) R. Ratnayake, E. Lacey, S. Tennant, J. H. Gill and R. J. Capon, *Chem.–Eur. J.*, 2007, **13**, 1610; (*b*) R. Ratnayake, E. Lacey, S. Tennant, J. H. Gill and R. J. Capon, *Org. Lett.*, 2006, **8**, 5267, and references therein.

2 R. C. Pandey, M. W. Toussaint, R. M. Stroshane, C. C. Kalita, A. A. Aszalos, A. L. Garretson, T. T. Wei, K. M. Byrne, R. F. Geoghegan Jr. and R. J. White, *J. Antibiot.*, 1981, **34**, 1389.

3 A. H. Zhang, N. Jiang, W. Gu, J. Ma, Y. R. Wang, Y. C. Song and R. X. Tan, *Chem.–Eur. J.*, 2010, **16**, 14479.

4 G. Kohlhagen, K. Paull, M. Cushman, P. Nagafuji and Y. Pommier, *Mol. Pharmacol.*, 1998, **54**, 50.

5 For reports on isoquinolone synthesis by metal-catalyzed intramolecular cyclization of 2-alkynylbenzamides or 2-alkynylbenzoylazide, see: (*a*) C.-C. Liu, K. Parthasarathy and C.-H. Cheng, *Org. Lett.*, 2010, **12**, 3518; (*b*) V. R. Batchu, D. K. Barange, D. Kumar, B. R. Sreekanth, K. Vyas, E. A. Reddy and M. Pal, *Chem. Commun.*, 2007, 1966; (*c*) H. Sashidam and A. Kawamukai, *Synthesis*, 1999, 1145.

6 For reports on isoquinolone synthesis using benzamides and alkynes *via ortho*-metallation, see: (*a*) M. I. Antczak and J. M. Ready, *Chem. Sci.*, 2012, **3**, 1450; (*b*) L. Ackermann, A. V. Lygin and N. Hofmann, *Angew. Chem., Int. Ed.*, 2011, **50**, 6379; (*c*) H. Shiota, Y. Ano, Y. Aihara, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2011, **133**, 14952; (*d*) N. Guimond, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2011, **133**, 6449; (*e*) S. Mochida, N. Umeda, K. Hirano, T. Satoh and M. Miura, *Chem. Lett.*, 2010, 744; (*f*) G. Song, D. Chen, C.-L. Pan, R. H. Crabtree and X. Li, *J. Org. Chem.*, 2010, **75**, 7487; (*g*) T. K. Hyster and T. Rovis, *J. Am. Chem. Soc.*, 2010, **132**, 10565.

7 For reports on isoquinolone synthesis by Ni(0)-catalyzed denitrogenative or decarbonylative coupling with alkynes, see: (*a*) Y. Kajita, S. Matsubara and T. Kurahashi, *J. Am. Chem. Soc.*, 2008, **130**, 6058; (*b*) T. Miura, M. Yamauchi and M. Murakami, *Org. Lett.*, 2008, **10**, 3058.

8 For other types of isoquinolone synthesis, see: (*a*) C. S. Yeung, T. H. H. Hsieh and V. M. Dong, *Chem. Sci.*, 2011, **2**, 544; (*b*) E. R. Walker, S. Y. Leung and A. G. M. Barrett, *Tetrahedron Lett.*, 2005, **46**, 6537; (*c*) R. Grigg, V. Sridharan and L.-H. Xu, *J. Chem. Soc., Chem. Commun.*, 1995, 1903; (*d*) J. A. Wendt, P. J. Gauvreau and R. D. Bach, *J. Am. Chem. Soc.*, 1994, **116**, 9921; (*e*) G. Mehta, S. R. Shah and Y. Venkateswarlu, *Tetrahedron*, 1994, **50**, 11729.

9 For reviews, see: (*a*) N. T. Patil and Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395; (*b*) Y. Yamamoto, *J. Org. Chem.*, 2007, **72**, 7817; (*c*) G. Zeni and R. C. Larock, *Chem. Rev.*, 2004, **104**, 2285; (*d*) I. Nakamura and Y. Yamamoto, *Chem. Rev.*, 2004, **104**, 2127.

10 For selected reports, see: (*a*) N. Asao, Y. S. Salprima, T. Nogami and Y. Yamamoto, *Heterocycles*, 2008, **76**, 471; (*b*) S. Obika, H. Kono, Y. Yasui, R. Yanada and Y. Takemoto, *J. Org. Chem.*, 2007, **72**, 4462; (*c*) Q. Ding and J. Wu, *Org. Lett.*, 2007, **9**, 4959; (*d*) N. Asao, S. Yudha, T. Nagomi and Y. Yamamoto, *Angew. Chem., Int. Ed.*, 2005, **44**, 5526; (*e*) G. Dai and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 920; (*f*) G. Dai and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 7042; (*g*) Q. Huang, J. A. Hunter and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 3437; (*h*) K. R. Roesch and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 86; (*i*) Q. Huang and R. C. Larock, *Tetrahedron Lett.*, 2002, **43**, 3557; (*j*) G. Dai and R. C. Larock, *Org. Lett.*, 2001, **3**, 4035; (*k*) Q. Huang, J. A. Hunter and R. C. Larock, *Org. Lett.*, 2001, **3**, 2973.

11 (*a*) Y.-F. Wang, X. Zhu and S. Chiba, *J. Am. Chem. Soc.*, 2012, **134**, 3679; (*b*) K. K. Toh, Y.-F. Wang, E. P. J. Ng and S. Chiba, *J. Am. Chem. Soc.*, 2011, **133**, 13942; (*c*) L. Zhang, J.-Y. Lee, N. Yamazaki and S. Chiba, *Synlett*, 2011, 2167; (*d*) L. Zhang, G. Y. Ang and S. Chiba, *Org. Lett.*, 2011, **13**, 1622; (*e*) L. Zhang, G. Y. Ang and S. Chiba, *Org. Lett.*, 2010, **12**, 3682; (*f*) S. Chiba, L. Zhang and J.-Y. Lee, *J. Am. Chem. Soc.*, 2010, **132**, 7266.

12 For recent reviews on copper-catalyzed aerobic oxidative transformation, see: (*a*) C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.*, 2012, **41**, 3464; (*b*) Z. Shi, C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.*, 2012, **41**, 3381; (*c*) A. E. Wendlandt, A. M. Suess and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2011, **50**, 11062.

13 Anderson *et al.* recently reported the effect of SiO_2 as an additive for aerobic oxidative transformation of alkynes, see: S. Z. Tasker, B. M. Brandsen, K. A. Ryu, G. S. Snapper, R. J. Staples, R. L. DeKock and C. E. Anderson, *Org. Lett.*, 2011, **13**, 6244.

14 Oxidative dimerization of benzylamine (**2a**) to *N*-benzylbenzaldimine was observed as a side reaction under the present reaction conditions. To minimize this dimerization, 1 equiv. of benzylamine (**2a**) was added three times at every 1 h interval. For a prior report of oxidative dimerization of benzylamines, see: S. S. Kim, S. S. Thakur, J. Y. Song and K.-H. Lee, *Bull. Korean Chem. Soc.*, 2005, **26**, 499, and references therein.

15 L. Yang, Z. Lu and S. S. Stahl, *Chem. Commun.*, 2009, 6460.

16 It was found that CuCl and CuI also showed reactivity under the present reaction conditions but gave 4-chloro- and 4-iodoisoquinolones, respectively, while the yields were lower (23 and 39%), see ESI† for more details.

17 The reactions with β-alanine ethyl ester and 3-phenylprop-2-yn-1-amine were also examined, see ESI† for more details. The reaction of β-alanine ethyl ester (**2m**) (as a hydrochloride salt) with **1a** under the standard reaction conditions provided the corresponding 4-bromoisoquinoline **5** and protonated isoquinoline **6** in 42% and 28% yields, respectively, with certain C–N bond cleavage, and the desired 4-bromoisoquinolone was not formed at all (see ESI† for more details). Similarly, 3-phenylprop-2-yn-1-amine (**2n**) also delivered the corresponding 4-bromoisoquinoline **5** without forming the desired 4-bromoisoquinolone **3**. It is noted that aromatic amines (anilines) did not work at all to provide any cyclized product under the present reaction conditions.

18 In the present aerobic conditions, $Cu^{I}Br$ might be oxidized by molecular oxygen to $Cu^{II}Br$ species, which might facilitate the isoquinolone formation. For recent reviews on copper–dioxygen systems, see: (*a*) M. Rolff and F. Tuczek, *Angew. Chem., Int. Ed.*, 2008, **47**, 2344; (*b*) E. A. Lewis and W. B. Tolman, *Chem. Rev.*, 2004, **104**, 1047; (*c*) P. Gamez, P. G. Aubel, W. L. Driessen and J. Reedijk, *Chem. Soc. Rev.*, 2001, **30**, 376; (*d*) M. Fontecave and J.-L. Pierre, *Coord. Chem. Rev.*, 1998, **170**, 125.

19 (*a*) A. Vigalok, *Chem.–Eur. J.*, 2008, **14**, 5102; (*b*) A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 14844.

20 W. Xu, Y. Jiang and H. Fu, *Synlett*, 2012, 801.

21 Pyridine might play the roles of base and ligand on the copper species in the present 4-bromoisoquinoline formation.

