

Synthesis of *N*-Azolylinroles by Copper-Catalyzed C–H/N–H Coupling–Annulation Sequence of *o*-Alkynylanilines

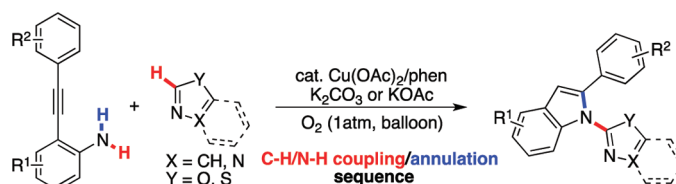
Yoshiro Oda, Koji Hirano,* Tetsuya Satoh, and Masahiro Miura*

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita,
Osaka 565-0871, Japan

k_hirano@chem.eng.osaka-u.ac.jp; miura@chem.eng.osaka-u.ac.jp

Received December 19, 2011

ABSTRACT



A wide range of *o*-alkynylanilines undergo a copper-catalyzed direct C–H/N–H coupling with azoles followed by benzannulation to form the corresponding *N*-azolylinroles in good yields. The domino reaction proceeds effectively with molecular oxygen as the sole oxidant and provides a new dehydrogenative access to the titled compounds of interest in pharmaceutical and material sciences.

In this letter, we report a copper-catalyzed C–H/N–H coupling–annulation sequence of *o*-alkynylanilines for the synthesis of *N*-azolylinroles.

The indole nucleus is found in many pharmaceuticals and functional materials. In particular, *N*-heteroaryl derivatives have received much attention due to their unique biological and physical properties.¹ The most common approach to the target motifs is the palladium-² and copper-catalyzed³ C–N bond forming reaction of *N*-H indoles with heteroaryl halides.

Meanwhile, recent developments in the metal-promoted direct C–H functionalization chemistry enabled an oxidative direct C–H/N–H coupling of some heteroarenes with alkylamines, anilines, and amides.⁴ Our group also succeeded in the copper-mediated direct amination of azoles.⁵ In the course of this study, we attempted the direct coupling of azoles with *N*-H indoles leading to the *N*-azolylinroles (Scheme 1, route a). However, our preliminary experiments with 2-phenyl-1,3,4-oxadiazole (**1a**) and some *N*-H indoles by using copper catalysts completely failed: the reported successful systems containing Cu(OAc)₂/PPh₃/NaOAc^{4l} and Cu(OAc)₂/pyridine/Na₂CO₃^{4m} or our original conditions, Cu(OAc)₂/1,10-phenanthroline (phen)/K₂CO₃, resulted in no formation of the desired products. Thus, we envisioned a new working scenario with *o*-alkynylanilines, in which the first copper-catalyzed intermolecular direct C–N formation would furnish the corresponding *N*-azolylinrole intermediates, and the subsequent benzannulation under the same copper catalysis⁶ could produce the *N*-azolylinroles in one synthetic operation (route b).

On the basis of the above hypothesis, treatment of 2-(phenylethynyl)aniline (**2a**) with **1a** in the presence of an excess of Cu(OAc)₂ and K₂CO₃ under O₂ (1 atm, balloon) in refluxing toluene furnished the desired *N*-azolylinrole **3aa** in 71% yield (Table 1, entry 1). While

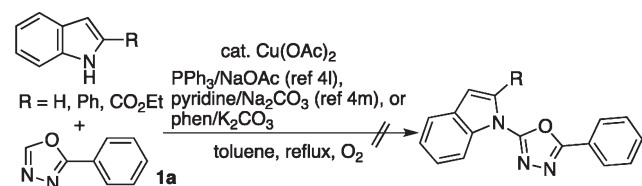
(1) Reviews: (a) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, 27, 1113. (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, 105, 2873. (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, 106, 2857. Selected examples: (e) Hall, A.; Billinton, A.; Brown, S. H.; Chowdhury, A.; Giblin, G. M. P.; Goldsmith, P.; Hurst, D. N.; Naylor, A.; Patel, S.; Scoccitti, T.; Theobald, P. J. *Bioorg. Med. Chem. Lett.* **2008**, 18, 2684. (f) Lahser, F. C.; Gu, Z. *PCT Int. Appl.* 2010, WO 2010117939, A120101014. (g) Kim, C. S.; Cho, Y. J.; Kwon, H. J.; Kim, B. O.; Kim, S. M.; Yoon, S. S. *Int. Appl.* 2010, WO 2010107244, A2 20100923.

(2) Selected publications: (a) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. J. *J. Am. Chem. Soc.* **1998**, 120, 827. (b) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, 2, 1403. (c) Watanabe, M.; Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **2000**, 41, 481. (d) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, 66, 7729.

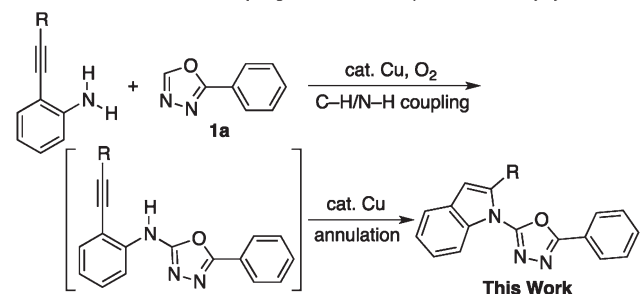
(3) (a) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, 124, 11684. Relevant Chan–Lam coupling: (b) Mederski, W. W. K. R.; Lefort, M.; Germann, M.; Kux, D. *Tetrahedron* **1999**, 55, 12757. (c) Yu, S.; Saenz, J.; Srirangam Jayaram, K. *J. Org. Chem.* **2002**, 67, 1699. (d) Bekolo, H. *Can. J. Chem.* **2007**, 85, 42.

Scheme 1. Dehydrogenative Approaches to *N*-Azolyllindoles

route a: direct C–H/N–H coupling of azoles with *N*-H indoles



route b: direct C–H/N–H coupling–annulation sequence of *o*-alkynylanilines



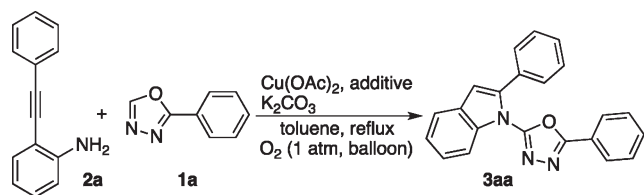
stoichiometric in copper, our postulated process would be operative. We then turned our attention to the catalytic variant. Not surprisingly, a decrease in the amount of $\text{Cu}(\text{OAc})_2$ to 20 mol % resulted in a lower yield of **3aa**

(4) With palladium, see: (a) Tsang, W. C. P.; Zheng, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (c) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (d) Jordan-Hore, A. A.; Johansson, C. C. C.; Gullias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (e) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (f) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466. (g) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694. (h) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996. (i) Yoon, S. W.; Bihn, J. H.; Kim, B. S. *Org. Lett.* **2011**, *13*, 3738. With copper, see: (j) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (k) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842. (l) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607. (m) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (n) Shuai, Q.; Deng, G.; Chua, Z.; Bohle, D. S.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 632. (o) Zhao, H.; Wang, M.; Su, W.; Hong, M. *Adv. Synth. Catal.* **2010**, *352*, 1301. (p) John, A.; Nicholas, K. M. *J. Org. Chem.* **2011**, *76*, 4158. With silver, see: (q) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127. With cobalt and manganese, see: (r) Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899. Metal-free processes: (s) Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 8605. (t) Froehr, T.; Sindlinger, C. P.; Kloeckner, U.; Finkbeiner, P.; Nachtsheim, B. J. *Org. Lett.* **2011**, *13*, 3754. (u) Laman, M.; Prabhu, K. R. *J. Org. Chem.* **2011**, *76*, 7938. (v) Kim, H. J.; Kim, J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 16382. (w) Wertz, S.; Kodama, S.; Studer, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 11511. (x) Kantak, A. A.; Potavathi, S.; Barham, R. A.; Romano, K. M.; DeBoef, B. *J. Am. Chem. Soc.* **2011**, *133*, 19960. Also see: (y) Armstrong, A.; Collins, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2282. (z) Zhang, M. *Synthesis* **2011**, 3408.

(5) (a) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900. (b) Miyasaka, M.; Hirano, K.; Satoh, T.; Kowalczyk, R.; Bolm, C.; Miura, M. *Org. Lett.* **2011**, *13*, 359. (c) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860.

(6) Reviews: (a) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (b) Vicente, R. *Org. Biomol. Chem.* **2011**, *9*, 6469. Copper-based systems: (c) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126. (d) Swamy, N. K.; Yazici, A.; Pyne, S. G. *J. Org. Chem.* **2010**, *75*, 3412. (e) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2012**, *77*, 617.

Table 1. Optimization Studies for Copper-Catalyzed C–H/N–H Coupling–Annulation Sequence of 2-(Phenylethynyl)-aniline (**2a**) with 2-Phenyl-1,3,4-oxadiazole (**1a**) for the Synthesis of **3aa**^a



entry	$\text{Cu}(\text{OAc})_2$ (mol %)	additive (mol %)	3aa , % yield ^b
1	200	none	(71)
2	20	none	46
3	20	pyridine (100)	65
4	20	bpy ^c (20)	53
5	20	phen ^d (20)	85 (79)
6	20	bathophen ^e (20)	75
7 ^f	200	none	19
8 ^f	20	phen (20)	2

^a Reaction conditions: $\text{Cu}(\text{OAc})_2$, additive, K_2CO_3 (0.60 mmol), **1a** (0.60 mmol), **2a** (0.30 mmol), toluene (2.0 mL), reflux, 3–10 h, O_2 (1 atm, balloon). ^b The yields are determined by ^1H NMR. Yield of isolated product is in parentheses. ^c 2,2'-Bipyridine. ^d 1,10-Phenanthroline. ^e 4,7-Diphenyl-1,10-phenanthroline. ^f Under N_2 .

(entry 2). Thus, we subsequently tested the addition of some additives to support the copper center. Nitrogen-based ligands generally improved the reaction efficiency (entries 3–6), with phen proving to be optimal (entry 5). Other reaction systems using CuCl_2 , $\text{Cu}(\text{OTf})_2$, Na_2CO_3 , Cs_2CO_3 , DMF, or DMSO gave no positive effect on yield (data not shown). In the absence of molecular oxygen, the yield largely dropped under either stoichiometric or catalytic conditions (entries 7 and 8).

With catalytic conditions employed for entry 5 in Table 1, we performed the domino reaction of **2a** with a range of 1,3,4-oxadiazoles **1**. The representative *N*-azolyllindole products are illustrated in Table 2. Oxadiazoles **1** containing electron-donating methoxy as well as electron-withdrawing chloro and trifluoromethyl groups underwent the reaction very smoothly to afford the corresponding indoles **3ba–da** in good yields. A bulky naphthalene motif could be employed without any difficulties (**3ea**). While the alkyl-substituted oxadiazole showed somewhat lower reactivity, the satisfactory yield was obtained under stoichiometric conditions (**3fa**). The generality of *o*-alkynylanilines was also good. At the alkyne terminus, electronically and sterically diverse functions such as methyl, methoxy, chloro, trifluoromethyl, and 1-naphthyl groups were equally tolerated (**3ab–af** and **3cb–cd**). The thienyl-substituted aniline was transformed to the indole–thiophene conjugation **3ag** in a comparable yield. Moreover, the copper catalysis could accommodate primary, secondary, and tertiary alkyl substituents (**3ah–aj**). The C5-substituted indoles **3ak** and **3al** were also readily accessible under standard conditions.

Table 2. Copper-Catalyzed C–H/N–H Coupling–Annulation Sequence for the Synthesis of Various *N*-Azolyllindoles **3**^a

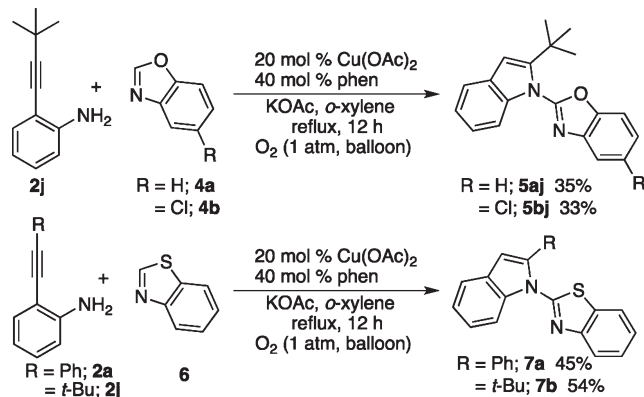
entry	R ¹ , R ² 2	R ³ 1	3 , % yield ^b
1	R ¹ = H, R ² = Ph (2a)	R ³ = 4-MeOC ₆ H ₄ (1b)	3ba , 79
2	2a	R ³ = 4-ClC ₆ H ₄ (1c)	3ca , 85
3	2a	R ³ = 4-CF ₃ C ₆ H ₄ (1d)	3da , 89
4	2a	R ³ = 1-naphthyl (1e)	3ea , 81
5 ^c	2a	R ³ = 2-phenethyl (1f)	3fa , 72
6	R ¹ = H, R ² = 4-MeC ₆ H ₄ (2b)	R ³ = Ph (1a)	3ab , 84
7	2b	1c	3cb , 83
8	R ¹ = H, R ² = 4-MeOC ₆ H ₄ (2c)	1a	3ac , 78
9	2c	1c	3cc , 87
10	R ¹ = H, R ² = 4-ClC ₆ H ₄ (2d)	1a	3ad , 76
11	2d	1c	3cd , 81
12	R ¹ = H, R ² = 4-CF ₃ C ₆ H ₄ (2e)	1a	3ae , 69
13	R ¹ = H, R ² = 1-naphthyl (2f)	1a	3af , 83
14	R ¹ = H, R ² = 3-thienyl (2g)	1a	3ag , 83
15	R ¹ = H, R ² = Bu (2h)	1a	3ah , 83
16	R ¹ = H, R ² = cyclohexyl (2i)	1a	3ai , 84
17	R ¹ = H, R ² = <i>t</i> -Bu (2j)	1a	3aj , 90
18	R ¹ = 4-Me, R ² = Bu (2k)	1a	3ak , 90
19	R ¹ = 4-Cl, R ² = Bu (2l)	1a	3al , 83

^a Reaction conditions: Cu(OAc)₂ (0.060 mmol), phen (0.060 mmol), K₂CO₃ (0.60 mmol), **1a** (0.60 mmol), **2a** (0.30 mmol), toluene (2.0 mL), reflux, 10 h, O₂ (1 atm, balloon). ^b Isolated yield of products is shown. ^c With 0.30 mmol of Cu(OAc)₂ and without phen.

We next turned our attention to some 1,3-azoles other than 1,3,4-oxadiazoles (Scheme 2). Under modified conditions with KOAc and *o*-xylene as a base and a solvent, respectively, benzoxazoles **4** and benzothiazole (**6**) took part in the reaction to form the desired *N*-azolyllindoles **5** and **7** albeit with moderate efficiencies. Attempts to apply benzimidazole and polyfluoroarenes remained unsuccessful at this stage.

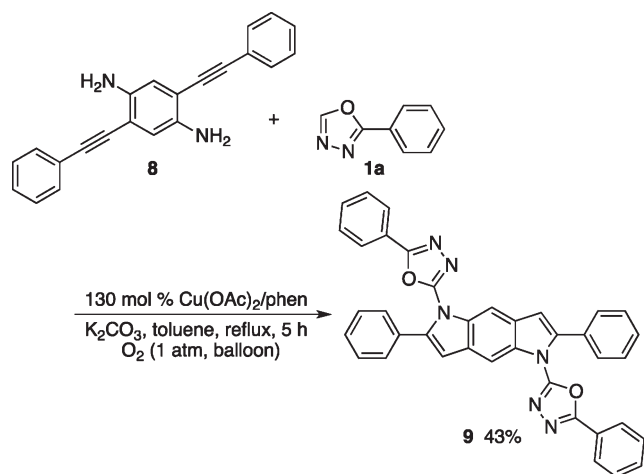
Finally, we applied the domino C–H/N–H coupling–annulation to the reaction of 2,5-dialkynylphenylenediamine **8** for the synthesis of the benzodipyrrole skeleton⁷ that bears the azole group on nitrogen (Scheme 3). Synthetic utilities of this double cyclization approach have been demonstrated by

Scheme 2. Copper-Catalyzed C–H/N–H Coupling–Annulation Sequence of *o*-Alkynylanilines **2** with Benzoxazoles **4** and Benzothiazole (**6**)



Tsuji and Nakamura,⁸ and Field.⁹ Pleasingly, when oxadiazole **1a** and **8** were subjected to substoichiometric conditions

Scheme 3. A Double Cyclization Approach to *N*-Azolyllbenzodipyrrole



(130 mol % Cu(OAc)₂/phen to **8**), the desired benzodipyrrole core **9** was obtained in 43% yield.

Although the exact reaction mechanism still remains unclear at the present stage, a Cu(II)/O₂-catalyzed oxidative C–N coupling of azole **1** with aniline **2** could initially occur through a (heteroaryl)(ArNH)Cu species,¹⁰ forming the *N*-azolyllaniline intermediate.¹¹ Given the necessity of molecular oxygen (Table 1, entries 7 and 8), an O₂-promoted oxidation process of Cu(II) to Cu(III) might

(7) For unique lower ionization potential and electron affinities of benzodipyrroles, see: Salzner, U.; Lagowski, J. B.; Pickup, P. G.; Poirier, R. A. *Synth. Met.* **1998**, *96*, 177.

(8) (a) Tsuji, H.; Yokoi, Y.; Mitsui, C.; Ilies, L.; Sato, Y.; Nakamura, E. *Chem.—Asian J.* **2009**, *4*, 655. Also see: (b) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 944. (c) Tsuji, H.; Mitsui, C.; Ilies, L.; Sato, Y.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 11902.

(9) Clentsmith, G. K. B.; Field, L. D.; Messerle, B. A.; Shasha, A.; Turner, P. *Tetrahedron Lett.* **2009**, *50*, 1469.

(10) Relevant reaction mechanism: (a) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (b) Kitahara, M.; Hirano, K.; Tsurugi, H.; Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 1772. (c) Wei, Y.; Zhao, H.; Kan, J.; Su, W.; Hong, M. *J. Am. Chem. Soc.* **2010**, *132*, 2522 and ref 4l, m, and o.

be involved prior to the C–N bond formation.¹² Subsequent annulation of this intermediate proceeds via an electrophilic activation of the alkynyl moiety by the π -acidic nature of a Cu(II) salt to afford the product **3**.

In conclusion, we have developed a copper-catalyzed oxidative C–H/N–H coupling–annulation sequence

(11) A copper-catalyzed oxidative C–H/N–H coupling of primary anilines is not trivial. The reported successful examples are limited to special anilines that bear electron-deficient groups such as NO₂; see ref 4o and 4p. Thus, we speculate that the *o*-alkynyl group can act as a directing group for the efficient intermolecular C–N coupling. For a related directing effect of alkynyl groups, see: Asao, N.; Asano, T.; Ohishi, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4817.

(12) (a) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196. (b) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044. (c) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068.

between azoles and *o*-alkynylanilines. This domino reaction provides a new dehydrogenative approach to *N*-azoly-lindoles of biological and physical interest. Moreover, this protocol can be applied to the synthesis of the π -extended *N*-azolybenzodipyrrole structure.

Acknowledgment. This work was partly supported by Grants-in-Aid from MEXT and JSPS, Japan. K.H. acknowledges Kansai Research Foundation for the Promotion of Science.

Supporting Information Available. Detailed experimental procedures and characterization data of compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.