ORGANIC LETTERS

2008
Vol. 10, No. 16
3535−3538

Concise Synthesis of Indole-Fused 1,4-Diazepines through Copper(I)-Catalyzed Domino Three-Component Coupling−Cyclization−*N*-Arylation under Microwave Irradiation

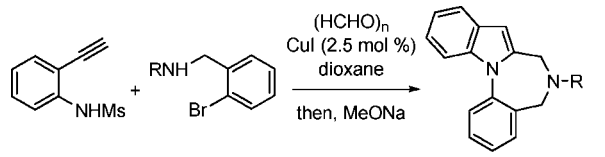
Yusuke Ohta, Hiroaki Chiba, Shinya Oishi, Nobutaka Fujii,* and Hiroaki Ohno*

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

hohno@pharm.kyoto-u.ac.jp; nfujii@pharm.kyoto-u.ac.jp

Received June 19, 2008

ABSTRACT



Indole-fused benzo-1,4-diazepines were synthesized by copper-catalyzed domino three-component coupling−indole formation−*N*-arylation under microwave irradiation from a simple *N*-mesyl-2-ethynylaniline. This method was also applicable to the formation of heterocycle-fused 1,4-diazepines.

New methods that produce complex, useful molecules from simpler materials in a single reaction vessel are important challenges in modern synthetic chemistry. Tandem catalysis,[1,2] which involves several catalytic cycles within the same medium to produce a desired product, is becoming increasingly important for the economic and environmental acceptability of the process. Copper salts are efficient catalysts in various transformations, including formation of carbon−

(1) For a recent review on concurrent tandem catalysis, see: (a) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001–1020. See also: (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186.

(2) For representative examples, see: (a) Burk, M. J.; Lee, J. R.; Martinez, J. P. *J. Am. Chem. Soc.* **1994**, *116*, 10847–10848. (b) Jeong, N.; Seo, S. D.; Shin, J. Y. *J. Am. Chem. Soc.* **2000**, *122*, 10220–10221. (c) Bielawski, C. W.; Louie, J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 12872–12873. (d) Son, S. U.; Park, K. H.; Seo, H.; Chung, Y. K.; Lee, S.-G. *Chem. Commun.* **2001**, 2440–2441. (e) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390–13391. (f) Komon, Z. J. A.; Diamond, G. M.; Leclerc, M. K.; Murphy, V.; Okazaki, M.; Bazan, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 15280–15285. (g) Dijk, E. W.; Panella, L.; Pinho, P.; Naasz, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2004**, *60*, 9687–9693. (h) van As, B. A. C.; van Buijtenen, J.; Heise, A.; Broxterman, Q. B.; Verzijl, G. K. M.; Palmans, A. R. A.; Meijer, E. W. *J. Am. Chem. Soc.* **2005**, *127*, 9964–9965.

(3) For reviews, see: (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221–3236. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449. (c) Chemler, S. R.; Fuller, P. H. *Chem. Soc. Rev.* **2007**, *36*, 1153–1160. (d) Carril, M.; SanMartin, R.; Domínguez, E. *Chem. Soc. Rev.* **2008**, *37*, 639–647.

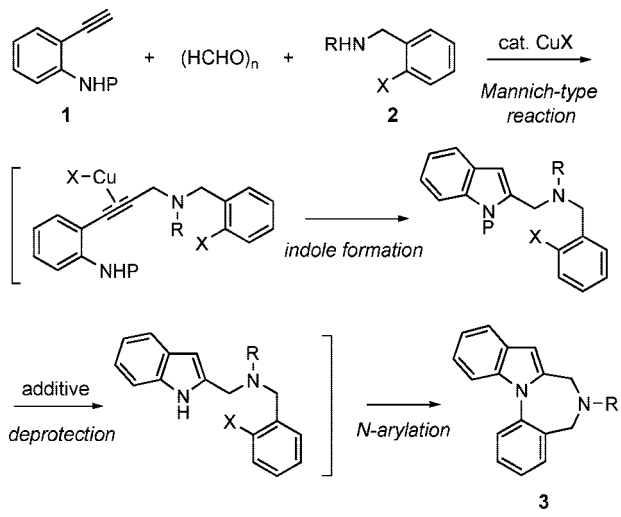
(4) For selected examples of tandem catalytic reaction using a copper salt including two catalytic cycles, see: (a) Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277–1280. (b) Kamijo, S.; Sasaki, Y.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 35–38. (c) Li, K.; Alexakis, A. *Tetrahedron Lett.* **2005**, *46*, 8019–8022. (d) Loones, K. T. J.; Maes, B. U. W.; Meyers, C.; Deruytter, J. *J. Org. Chem.* **2006**, *71*, 260–264. (e) Yuen, J.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 653–656. (f) Zhang, L.; Malinakova, H. C. *J. Org. Chem.* **2007**, *72*, 1484–1487. (g) Martin, R.; Laursen, C. H.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 3379–3382. (h) Français, A.; Urban, D.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8662–8665. (i) Kumaraswamy, G.; Ankamma, K.; Pitchaiah, A. *J. Org. Chem.* **2007**, *72*, 9822–9825.

10.1021/ol801383b CCC: $40.75
Published on Web 07/11/2008

carbon and carbon−nitrogen bonds.[3] We postulated they could play key parts in construction of complex nitrogen heterocycles with important biological activities through formation of multiple bonds.[4]

Indole and 1,4-benzodiazepine frameworks are useful templates for drug discovery. Indole-fused 1,4-diazepine,[5] found in various bioactive compounds, can also be an attractive drug template. We recently reported a novel copper(I)-catalyzed synthesis of 2-(aminomethyl)indoles via a three-component coupling−cyclization reaction.[6,7] This indole formation prompted us to develop a novel method for the synthesis of indole-fused tetracyclic compounds by three-component indole formation and simultaneous copper-catalyzed *N*-arylation (Scheme 1). We expected that a copper

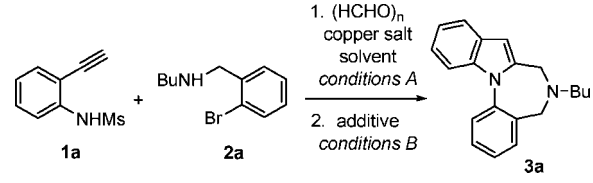
Scheme 1. Copper(I)-Catalyzed Domino Three-Component Coupling−Cyclization−*N*-Arylation Reaction



salt could catalyze multiple transformations, including Mannich-type coupling of ethynylaniline derivative **1** with formaldehyde and *N*-substituted *o*-halobenzylamine **2**, indole formation, and arylation of the indole nitrogen. In this paper, we report direct access to indole-fused tetracyclic compounds **3** containing the 1,4-diazepine framework by copper(I)-catalyzed domino reactions, which involve the formation of one carbon−carbon bond and three carbon−nitrogen bonds.

We chose *N*-mesyl-2-ethynylaniline **1a** as a model substrate because three-component indole formation requires *N*-substituted ethynylanilines.[6] Appropriate conditions were initially investigated for one-pot, three-component indole formation, deprotection of the mesyl group, and subsequent *N*-arylation. A mixture of **1a**, paraformaldehyde (2 equiv), and secondary amine **2a** (1.1 equiv) was treated with CuI (5 mol %) in toluene, and after indole formation was completed (monitored by TLC), an additive for cleavage of the *N*-mesyl group was introduced (Table 1).[8] Addition of MeOK and

Table 1. Screening of Reaction Conditions Using Ethynylaniline **1a** and Secondary Amine **2a**[a]



entry	catalyst (mol %)	solvent	conditions A[b]	additive (equiv)	conditions B[b]	yield[c] (%)
1	CuI (5)	toluene	reflux 6 h	MeOK (6)	reflux 1 h	43
2	CuI (5)	toluene	reflux 6 h	*t*-BuOK (6)	reflux 0.5 h	38
3	CuI (5)	toluene	reflux 6 h	MeONa (6)	reflux 3 h	51
4	CuI (5)	toluene	reflux 6 h	MeONa (6) ligand (0.1)[d]	80 °C 4 h	34
5	CuBr (5)	toluene	reflux 6 h	MeONa (6)	reflux 3 h	49
6	CuI (5)	toluene	MW, 170 °C 20 min	MeONa (6)	MW, 170 °C 20 min	64
7	CuI (5)	dioxane	MW, 170 °C 20 min	MeONa (6)	MW, 170 °C 20 min	81
8	CuI (1)	dioxane	MW, 170 °C 20 min	MeONa (6)	MW, 170 °C 20 min	77
9	CuI (2.5)	dioxane	MW, 170 °C 20 min	MeONa (6)	MW, 170 °C 20 min	88

[a] After the reaction with 2-ethynylaniline **1a**, paraformaldehyde (2 equiv), and secondary amine **2a** (1.1 equiv) was completed on TLC, additives were introduced. [b] MW = microwave irradiation. [c] Isolated yields. [d] Ligand = (±)-*trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine.

heating of the reaction mixture under reflux for 1 h promoted the desired arylation of the indole nitrogen to afford the expected tetracyclic compound **3a**[9] in ca. 43% yield (entry 1). *t*-BuOK was less effective, leading to ca. 38% yield of **3a** (entry 2). These runs furnished tetracyclic compound **3a** containing some impurities that were not easily removed, but the reaction with MeONa under reflux for 3 h gave pure **3a** in 51% yield after column chromatography (entry 3).

(5) (a) Maryanoff, B. E.; Nortey, S. O.; Gardocki, J. F. *J. Med. Chem.* **1984**, *27*, 1067–1071. (b) Ho, C. Y.; Hageman, W. E.; Persico, F. J. *J. Med. Chem.* **1986**, *29*, 1118–1121. (c) Suzuki, H.; Shinpo, K.; Yamazaki, T.; Niwa, S.; Yokoyama, Y.; Murakami, Y. *Heterocycles* **1996**, *42*, 83–86. (d) Sasaki, S.; Ehara, T.; Sakata, I.; Fujino, Y.; Harada, N.; Kimura, J.; Nakamura, H.; Maeda, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 583–585. (e) Kau, T. R.; Schroeder, F.; Ramaswamy, S.; Wojciechowski, C. L.; Zhao, J. J.; Roberts, T. M.; Clardy, J.; Sellers, W. R.; Silver, P. A. *Cancer Cell* **2003**, *4*, 463–476. (f) Ennis, M. D.; Hoffman, R. L.; Ghazal, N. B.; Olson, R. M.; Knauer, C. S.; Chio, C. L.; Hyslop, D. K.; Campbell, J. E.; Fitzgerald, L. W.; Nichols, N. F.; Svensson, K. A.; McCall, R. B.; Haber, C. L.; Kagey, M. L.; Dinh, D. M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2369–2372. (g) Ducker, C. E.; Griffel, L. K.; Smith, R. A.; Keller, S. N.; Zhuang, Y.; Xia, Z.; Diller, J. D.; Smith, C. D. *Mol. Cancer Ther.* **2006**, *5*, 1647–1659. (h) Yang, S.-M.; Malaviya, R.; Wilson, L. J.; Argentieri, R.; Chen, X.; Yang, C.; Wang, B.; Cavender, D.; Murray, W. V. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 326–331.

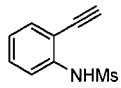
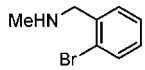
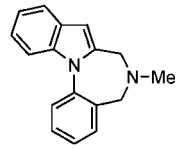
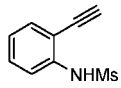
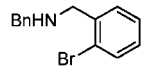
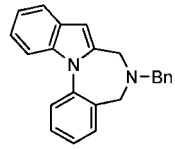
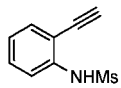
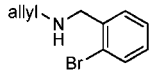
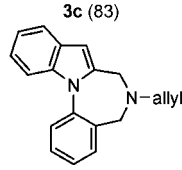
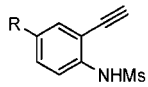
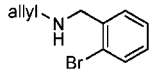
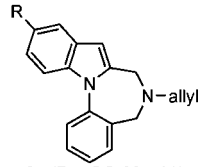
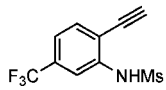
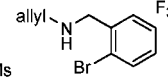
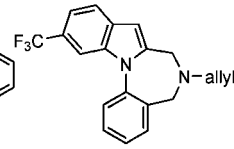
(6) Ohno, H.; Ohta, Y.; Oishi, S.; Fujii, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2295–2298.

(7) For a related isoquinoline formation, see: (a) Ohta, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2008**, 835–837.

(8) One portion addition of all the reactants including the alkoxide at the beginning of the reaction caused decomposition of the starting material.

(9) For patent information including a related tetracyclic compound, see: Ivashchenko, A. V.; Ilyin, A. P.; Kysil, V. M.; Trifilenkov, A. S.; Tsirulnikov, S. A.; Shkirando, A. M.; Churakova, M. V.; Lomakina, I. O.; Potapov, V. V.; Zamaletdinova, A. I.; Tkachenko, S. Y.; Kravchenko, D. V.; Khvat, A. V.; Okun, I. M.; Kyselev, A. S. *PCT Int. Appl.* **2007**, WO2007117180.

Table 2. Construction of Tetracyclic Compounds Using Substituted Ethynylanilines and *o*-Bromobenzylamines[a]

Entry	Ethynylaniline	Secondary Amine	Product (%)[b]
1			
	1a	**2b**	**3b** (51)
2			
	1a	**2c**	**3c** (83)
3			
	1a	**2d**	**3d** (81)
			
4	**1b**: R = CO_2Me	**2d**	**3e** (R = CO_2Me, 23)
5	**1c**: R = CF_3	**2d**	**3f** (R = CF_3, 81)
6	**1d**: R = Me	**2d**	**3g** (R = Me, 85)
7			
	1e	**2d**	**3h** (53)

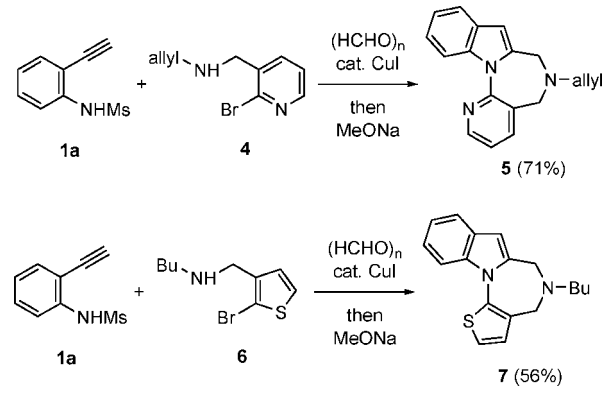
[a] All reactions were conducted with ethynylaniline **1**, paraformaldehyde (2 equiv), and secondary amine **2** (1.1 equiv) in the presence of CuI (2.5 mol %) in 1,4-dioxane at 170 °C for 20−40 min under microwave irradiation. After the indole formation was completed on TLC, MeONa (6 equiv) was added and the mixture was heated at 170 °C for 20 min under microwave irradiation. [b] Isolated yields.

Simultaneous addition of racemic *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine, an efficient ligand for CuI-catalyzed intermolecular *N*-arylation of indoles,[10] was not effective for the present formation of 1,4-diazepine (34%, entry 4). Replacement of CuI by CuBr slightly decreased the yield of **3a** (49%, entry 5). Microwave-assisted conditions at 170 °C for the formation of indole and diazepine improved the overall yield to 64% (entry 6). Investigation of the reaction solvent and loading of the catalyst (entries 6−9) revealed that 2.5 mol % of CuI in dioxane most effectively produced **3a** in 88% yield within 40 min (entry 9).

Having established optimal conditions (Table 1, entry 9), we examined the scope of this indole-fused benzodiazepine formation using several 2-ethynylanilines **1a**−**d** and secondary amines **2b**−**d** (Table 2). Whereas the reaction of 2-ethynylaniline **1a**, paraformaldehyde, and 2-bromobenzylamine **2b** bearing a smaller *N*-substituent under standard conditions gave the corresponding indole-fused benzodiazepine **3b** in relatively low yield (51%, entry 1), the reaction using **2c** or **2d**, carrying a removable nitrogen substituent such as benzyl and allyl groups, proceeded smoothly to give **3c** and **3d** in 83% and 81% yields, respectively (entries 2 and 3). Ethynylaniline **1b** bearing a methoxycarbonyl group at the para-position of the amino group, gave a poor result to afford **3e** (23% yield), along with a complex mixture of unidentified products (entry 4).[11] Anilines **1c** and **1d** with a *p*-trifluoromethyl or methyl group, respectively, were good substrates for this copper-catalyzed reaction sequence (entries 5 and 6). The reaction with ethynylaniline **1e** containing a trifluoromethyl group at the meta position gave a moderate yield of **3h** (53% yield, entry 7). Thus, the copper-catalyzed synthesis of indole-fused benzodiazepine was applicable to various *N*-substituted *o*-bromobenzylamines and 2-ethynylanilines with an electron-donating or electron-withdrawing group.

Synthesis of tetracyclic compounds containing a heterocycle-fused 1,4-diazepine was investigated (Scheme 2). By employing the secondary amines **4** and **6** involving a pyridine and thiophene moiety, respectively, the reaction directly delivered the desired pyridine- and thiophene-fused tetracyclic compounds **5** and **7** in 71% and 56% yields, respectively. From these observations, this copper-catalyzed formation of tetracyclic compounds allows the synthesis of indole-fused 1,4-diazepines containing another heterocyclic ring system.

Scheme 2. Direct Synthesis of Pyridine- or Thiophene-Fused Tetracyclic Compounds



In conclusion, we developed a novel method for the preparation of fused indoles by copper-catalyzed domino three-component coupling−indole formation−*N*-arylation. Starting from simple 2-ethynylanilines and *o*-bromobenzylamines, complex indole-fused tetracyclic compounds were

(10) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684–11688.

(11) Since the formation 2-(aminomethyl)indole using **1b** and **2d** proceeded efficiently (quantitative yield), deprotection conditions using MeONa caused undesired side reactions.

easily and directly synthesized in a single reaction vessel. This is the first example of copper-catalyzed one-pot reaction including three catalytic cycles and formation of four bonds. Further studies for construction of other heterocyclic ring systems as well as development of novel drug templates using this method are underway.

Acknowledgment. This work was supported by a Grant-in-Aid for Encouragement of Young Scientists (A) (H.O.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and Targeted Proteins Research Program. Y.O. is grateful to Research Fellowships of the Japan Society for the Promotion of Science (JSPS) for Young Scientists. Appreciation is expressed to Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation (NIBIO).

Supporting Information Available: A General experimental procedure and ^{1}H and ^{13}C NMR spectra for all indole-fused 1,4-diazepines (**3a**−**h**, **5**, and **7**). This material is available free of charge via the Internet at http://pubs.acs.org.

OL801383B