ORGANIC LETTERS

2008
Vol. 10, No. 6
1163−1166

A New Route to Indolines by the Cu-Catalyzed Cyclization Reaction of 2-Ethynylanilines with Sulfonyl Azides

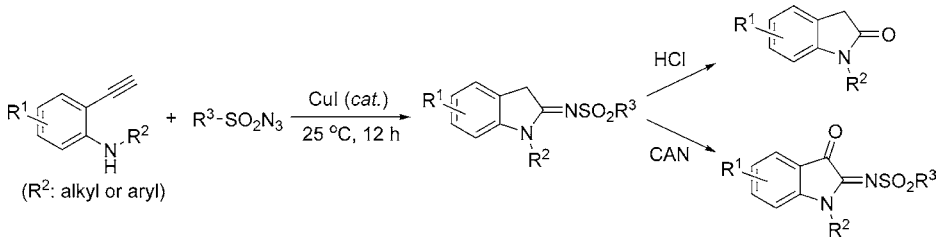
Eun Jeong Yoo and Sukbok Chang*

Center for Molecular Design and Synthesis (CMDS), Department of Chemistry and School of Molecular Science (BK21), Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, Republic of Korea

sbchang@kaist.ac.kr

Received January 9, 2008

ABSTRACT



It is revealed that 2-sulfonyliminoindolines can be efficiently synthesized by the Cu-catalyzed cyclization reaction of *N*-alkyl- or aryl-substituted 2-ethynylanilines with sulfonyl azides. This new route to the indoline derivatives is characterized by mild reaction conditions, facile introduction of functional groups at the 2-position of the indoline ring, and the wide substrate scope. Selective transformation of indoline to oxindole and isatin analogs is also demonstrated.

Indolines and their oxidized derivatives including indoles and oxindoles are highly important pharmacophores that appear in numerous biologically active natural products.[1] Because of the ubiquitous presence of the bicyclic heterocycles in both natural and synthetic bioactive compounds,[2] development of new synthetic methods to the core skeleton is of great interest. As a result, a range of transition metal-mediated procedures using Pd, Ni, or Rh species have been documented.[3] Despite this advance, there is still a great need to develop more convenient and diversity-oriented catalytic systems that can accommodate such attractive features as easily accessible starting materials, mild reaction conditions, and nontoxic side products.

Although some examples of tandem reactions are known to afford heterocyclic compounds with a high degree of molecular complexity,[4] most of these approaches do not fulfill all of the desired features mentioned above. Additionally, to the best of our knowledge, no synthetic routes aimed at preparing indoline derivatives have been reported using tandem processes with the concomitant introduction of 2-functional groups.

1,*n*-Aminoalkynes are regarded as versatile reactants for the generation of cyclic amino compounds, mainly through the catalytic hydroamination pathway.[5] Along this line, we recently reported a novel catalytic approach to cyclic amidines upon the reaction of 1,3- or 1,4- aminoalkynes with electron-deficient azides under mild conditions (Scheme 1, eq 1).[6] It was proposed that the reaction proceeded via a tandem manner; metal-mediated intramolecular hydroamination followed by [3+2] cycloaddition of the resulting cyclic

(1) Southon, I. W.; Buchingham, D. J. In *Dictionary of Alkaoids*; Cordell, G. A., Saxton, J. E., Shmma, M., Eds.; Chapman and Hall: New York, 1989.

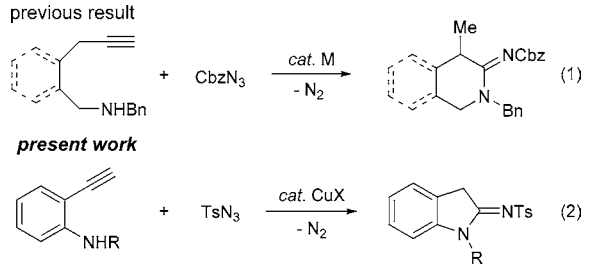
(2) Chang, J.; Heieh, H.; Chang, C.; Hsu, K.; Chiang, Y.; Chen, C.; Kuo, C.; Liou, J. *J. Med. Chem.* **2006**, *49*, 6656−6659.

(3) For selected recent example, see (a) Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.* **2003**, *5*, 2311−2314. (b) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35−37. (c) Shintani, R.; Yamagami, T.; Hayashi, T. *Org. Lett.* **2006**, *8*, 4799−4801. (d) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906−13907.

(4) For selected recent examples, see: (a) Poondra, R. R.; Tumer, N. J. *Org. Lett.* **2005**, *7*, 863−866. (b) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906−13907. (c) Michael, D. G.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777−4779.

10.1021/ol800049b CCC: $40.75
Published on Web 02/21/2008

Scheme 1



enamines with azides, and then subsequent rearrangement of the triazoline intermediates upon release of nitrogen or diazomethane molecule.

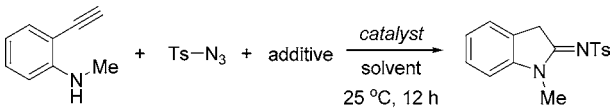
During our studies, we were wondering whether the reaction of 2-ethynylanilines with azides might follow a different initial step rather than hydroamination. This surmise was based on our previous work on the Cu-catalyzed three-component additions between 1-alkynes, sulfonyl- or phosphoryl azides, and amines, alcohols, or water.[7] Herein, we report results on the three-functional group coupling reaction, from which indoline derivatives can be readily obtained under mild conditions (Scheme 1, eq 2).

At the outset of our studies, we examined various reaction conditions using 2-ethynyl-*N*-methylaniline (**1a**) and *p*-toluenesulfonyl azide (**2a**) as representative reacting partners (Table 1). No conversion was observed in the presence of Pd or Ru catalysts in THF (entries 1−2), strongly suggesting that the hydroamination-initated process does not operate in this case.[6]

In a sharp contrast, the reaction was catalyzed by CuI species to afford 1-methyl-2-(*p*-toluenesulfonyl)imino-indoline (**3a**) although with a moderate yield (entry 3). It turned out that reaction efficiency was significantly dependent on the reaction conditions employed. For example, base additives (entries 4−6), reaction media (entries 6−8), the source of the copper catalysts (entries 8−11), the amounts of catalysts (entries 8 and 12), and substrate concentrations all affected the reaction outcome (entries 12 and 13). When phosphoryl- or acyl azides were allowed to react with **1a**, only poor conversion into corresponding indoline (<5%) was observed under various reaction conditions.

The optimized reaction conditions for the formation of **3a** were subsequently applied to a wide range of 2-ethynylanilines and sulfonyl azides, and the results are summarized in Table 2. It turns out that variation of *N*-substituents in the 2-ethynylanilines does not alter efficiency of the reactions. For example, substrates bearing *N*-methyl or *N*-phenyl groups react smoothly with similar efficiency (entries 1−2). Notably, removable *N*-substituents such as *N*-benzyl, *N*-(*p*-methoxy)benzyl, or *N*-allyl group were readily employed resulting in comparable product yields (entries 3−5). Some functional groups such as cyano or ester moieties were also tolerated under the conditions (entries 6−7).

Table 1. Cascade Reaction for Indoline Derivative in Various Reaction Conditions[a]



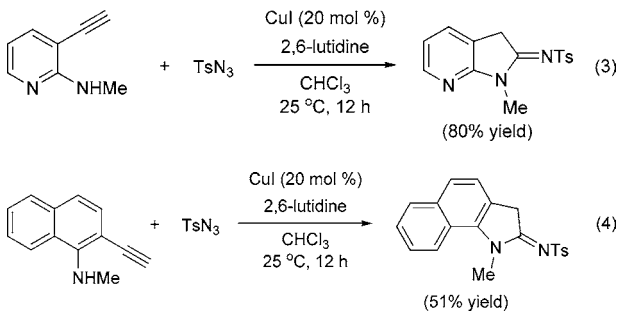
1a 2a 3a

entry	catalyst (mol %)	additive	solvent	yield (%)[b]
1	$PdCl_2$ (10)	–	THF	<1[c]
2	$Ru_3(CO)_{12}$ (10)	–	THF	<1[c]
3	CuI (10)	–	THF	46
4	CuI (10)	Et_3N	THF	<1
5	CuI (10)	K_2CO_3	THF	<1[c]
6	CuI (10)	2,6-lutidine	THF	76
7	CuI (10)	2,6-lutidine	1,4-dioxane	67
8	CuI (10)	2,6-lutidine	$CHCl_3$	81
9	CuCl (10)	2,6-lutidine	$CHCl_3$	68
10	CuOAc (10)	2,6-lutidine	$CHCl_3$	11
11	$Cu(OAc)_2$ (10)	2,6-lutidine	$CHCl_3$	41
12	CuI (20)	2,6-lutidine	$CHCl_3$	91
13[d]	CuI (20)	2,6-lutidine	$CHCl_3$	64

[a] 2-Aminoalkyne (0.5 mmol), tosyl azide (1.2 equiv), additive (1.2 equiv), and catalyst were stirred in the indicated solvent (1.0 mL) at 25 °C for 12 h. [b] ^1H NMR yield (internal standard: 1,1,2,2-tetrachloroethane). [c] No conversion. [d] $CHCl_3$ (2.0 mL) was used.

The scope of sulfonyl azides that could be used was also broad, and a wide range of derivatives readily afforded the corresponding 2-sulfonyliminoindolines in good to excellent yields. In fact, reaction efficiency was not significantly affected by the electronic variation of the arenesulfonyl azides (entries 8−11). Not only aryl- but also alkylsulfonyl azides reacted smoothly with 2-aminoalkynes (entries 12−13).

3-Alkynyl-2-aminopyridines also participated in the reaction with tosyl azide leading to 2-sulfonylimino-1*H*-pyrrolopyridine in good yield (eq 3). A fused tricyclic benzoindoline derivative was obtained in a moderate yield when 1-amino-2-ethynylnaphthalene was allowed to react with sulfonyl azides (eq 4).[8]

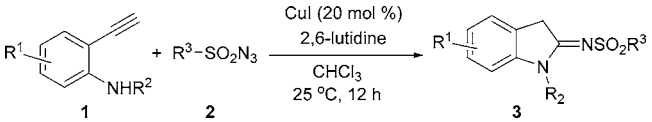


Interestingly, we found that the progress of the present tandem reactions could be controlled by the nature of the

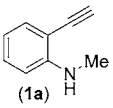
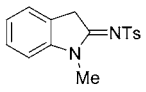
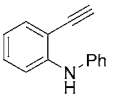
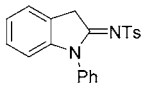
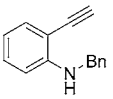
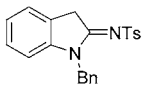
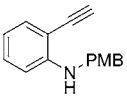
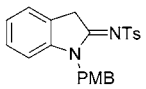
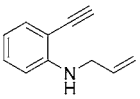
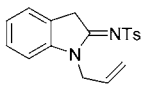
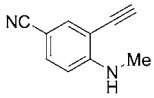
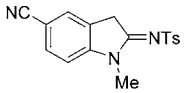
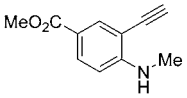
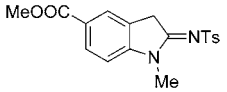
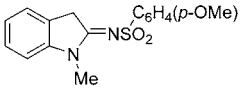
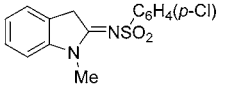
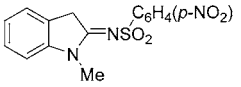
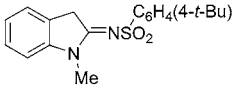
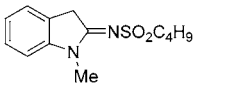
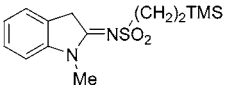
(5) (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873−2920. (b) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126−1136. (c) Ezquerra, J.; Pedregal, C.; Lamas, C.; Barluenga, J.; Perez, M.; Garcia-Martin, M. A.; Gonzalez, J. M. *J. Org. Chem.* **1996**, *61*, 5804−5812. (d) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843−3846.

(6) Chang, S.; Lee, M. J.; Jung, D. Y.; Yoo, E. J.; Cho, S. H.; Han, S. K. *J. Am. Soc. Chem.* **2006**, *128*, 12366−12367.

Table 2. Cu-Catalyzed Synthesis of Indoline Derivatives[a]



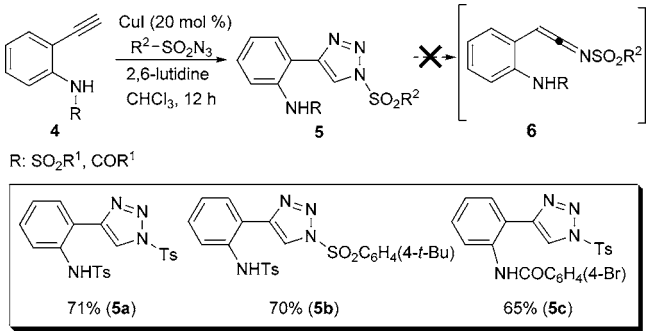
1 2 3

entry	aminoalkyne	R^3	product (**3**)	yield (%)[b]
1	 (**1a**)	4-MeC_6H_4 (**2a**)		91
2		**2a**		84
3		**2a**		80
4[c]		**2a**		88
5		**2a**		85
6		**2a**		70
7		**2a**		64
8	**1a**	4-$OMeC_6H_4$		86
9	**1a**	4-ClC_6H_4		90
10	**1a**	4-$NO_2C_6H_4$		76
11	**1a**	(4-*t*-Bu)C_6H_4		72
12	**1a**	C_4H_9		88
13	**1a**	$TMS(CH_2)_2$		61

[a] 2-Ethynylaniline (0.5 mmol), sulfonyl azide (1.2 equiv), 2,6-lutidine (1.2 equiv), and CuI (20 mol %) in chloroform (1.0 mL) at 25 °C for 12 h. [b] Isolated yield. [c] PMB: *p*-methoxybenzyl.

N-substituents on the 2-ethynylaniline substrates.[9] Unlike *N*-alkyl- and aryl reactants, *N*-sulfonyl- or *N*-acyl substituted 2-ethynylanilines did not convert completely to indolines. Rather, we isolated, with moderate to high yields, 1-(*N*-sulfonyl)-1,2,3-triazole compounds **(5a**−**c**) when *N*-sulfonyl- or *N*-acylaminoalkynes (**4**) were applied to the same reaction conditions (Scheme 2). This result is readily explained by

Scheme 2



the previously proposed pathways in the Cu-catalyzed three-component coupling reactions,[10] in which triazole initially forms upon the [3+2] cycloaddition of azide and Cu-acetylide. The ring-opening of the *N*-sulfonyl triazolyl intermediate followed by release of N_2 might be subsequently carried out leading to another key intermediate, ketenimine (**6**). It is reasonable to assume that the low nucleophilicity of amide in the substrates (**4**) does not drive the succeeding process to ketenimine intermediate into which the tethered secondary amino group adds to afford 2-sulfonyliminoindoline.

The present catalytic route to indolines was successfully applied to a large scale reaction. For instance, the reaction of 1.0 g of 2-ethynyl-*N*-phenylaniline with *p*-toluenesulfonyl azide provided the desired indoline product in 72% yield (Scheme 3). The indoline compounds obtained in this study were found to be quantitatively oxidized to the corresponding isatin analogs (e.g., **7**) upon treatment of 2-sulfonyliminoindolines with cerium(IV) ammonium nitrate (CAN).[11] It

(7) (a) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038−2039. (b) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347−1350. (c) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046−16047. (d) Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1897−1900. (e) Kim, S. H.; Jung, D. Y.; Chang, S. *J. Org. Chem.* **2007**, *72*, 9769−9771. (f) Cho, S. H.; Hwang, S. J.; Chang, S. *Org. Synth.* **2008**, *85*, 131−137.

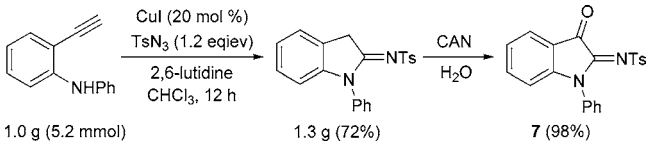
(8) When 4-(*N*-benzylamino)-1-butyne was employed as a substrrate, the reaction did not proceed and we could not observe desired product. In addition, the reaction of *N*-methyl-2-[(trimethylsilyl)ethynyl]aniline, as one representative internal alkynyl substrate, did not take place.

(9) Whereas reactions of 1,3- or 1,4-aminoalkynes were postulated to proceed through the catalytic hydroamination route (Ref 6), those of 2-ethynylanilines are proposed here to form triazoles first followed by ring-opening process.

(10) (a) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154−3157. (b) Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I. H.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1730−1733.

(11) Escolano, C.; Vallverdú, L.; Jones, K. *Tetrahedron* **2002**, *58*, 9541−9545.

Scheme 3. Cerium(IV) Ammonium Nitrate (CAN)-mediated Conversion of Indolines to Isatin Analog

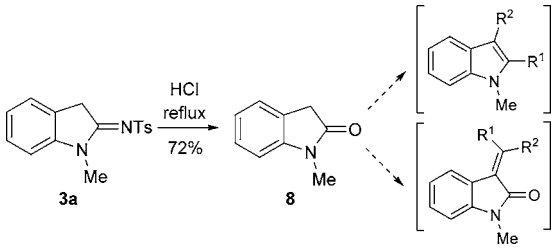


should be noted that the isatin skeleton has been known to have highly interesting bioactivities.[12]

The synthetic utility of 2-sulfonyliminoindolines was additionally demonstrated in the conversion of these molecules to oxindole derivatives. When indoline **3a** was hydrolyzed in acidic conditions, 1-methyloxindole (**8**) was produced in good yield (Scheme 4). The oxindole species are considered to be important building blocks in both organic synthesis[13] and medicinal chemistry.[14] In fact, it is known that oxindoles are readily derivatized into 2,3-disubstituted indoles[14] or 3-alkylideneoxindoles,[15] which are interesting metabolic intermediates.[16]

In summary, we have developed a new synthetic route to 2-sulfonyliminoindolines using the reaction of 2-ethynylanilines with sulfonyl azides in the presence of CuI catalyst. Significantly, it offers important pharmacophores in good yields with a wide substrate scope under mild reaction conditions.

Scheme 4. Hydrolysis of 2-Iminoindoline to Oxindole



Acknowledgment. This research was supported by the KOSEF grant (No. R01-2007-000-10618-0) and CMDS at KAIST. We acknowledge the Korea Basic Science Institute (KBSI) for the mass analysis.

Supporting Information Available: Experimental details and ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800049B

(12) (a) Hyatt, J. L.; Moak, T.; Hatfield, M. J.; Tsurkan, L.; Edwards, C. C.; Wierdl, M.; Danks, M. K.; Wadkins, R. M.; Potter, P. M. *J. Med. Chem.* **2007**, *50*, 1876−1885. (b) Chu, W.; Rothfuss, J.; d'Avignon, A.; Zeng, C.; Zhou, D.; Hotchkiss, R. S.; Mach, R. H. *J. Med. Chem.* **2007**, *50*, 3751−3755. (c) Vine, K. L.; Locke, J. M.; Ranson, M.; Pyne, S. G.; Bremner, J. B. *J. Med. Chem.* **2007**, *50*, 5109−5117.

(13) (a) Inoue, M.; Furuyama, H.; Sakazaki, H.; Hirama, M. *Org. Lett.* **2001**, *3*, 2863−2865. (b) Kaiser, M.; Groll, M.; Renner, C.; Huber, R.; Moroder, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 780−783. (c) Albrecht, B. K.; Williams, R. M. *Org. Lett.* **2003**, *5*, 197−200. (d) Lin, S.; Yang, Z-Q. *J. Am. Chem. Soc.* **2004**, *126*, 6347−6355. (e) Miura, T.; Takshashi, Y.; Murakami, M. *Org. Lett.* **2007**, *9*, 5075−5077.

(14) (a) Mohanmmadi, M.; McMahon, G.; Sun, L.; Tang, C.; Hirth, P.; Yeh, B. K.; Hubbard, S. R.; Schlessinger, J. *Science* **1997**, *276*, 955−960. (b) Noble, M. E. M.; Endicott, J. A.; Johnson, L. N. *Science* **2004**, *303*, 1800−1805. (c) Yanada, R.; Obika, S.; Kobayashi, Y.; Inokuma, T.; Oyama, M.; Yanada, K.; Takemoto, Y. *Adv. Synth. Catal.* **2005**, *347*, 1632−1642.

(15) (a) Deberly, A.; Abenhaim, D.; Bourdais, J. *J. Heterocycl. Chem.* **1975**, *12*, 1087−1090. (b) Bergman, J.; Carlsson, R.; Sjoberg, B. *J. Heterocycl. Chem.* **1977**, *14*, 1123−1134.

(16) (a) Daisley, Roy W.; Walker, J. *Eur. J. Med. Chem.* **1979**, 47−52. (b) Bruni, P.; Cardellini, L.; Cardillo, B.; Tosi, G. *J. Heterocycl. Chem.* **1982**, *19*, 211−213. (c) Suresh, J. R.; Syam Kumar, U. K.; Ila, H.; Junjappa, H. *Tetrahedron* **2001**, *57*, 781−790.

(17) (a) Tokunaga, T.; Hume, W. E.; Umezome, T.; Okazaki, K,; Ueki, Y.; Kumagai, K.; Hourai, S.; Nagamine, J.; Seki, H.; Taiji, M.; Noguchi, H.; Nagata, R. *J. Med. Chem.* **2001**, *44*, 4641−4649. (b) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Med. Chem.* **2006**, *49*, 3432−3435. (c) Bindra, J.S. Oxindole Alkaloids. In *Alkaloid Chemistry and Physiology*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. 14, pp 83−121.