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Direct Synthesis of Polysubstituted Quinoline Derivatives by $InBr_3$-Promoted Dimerization of 2-Ethynylaniline Derivatives

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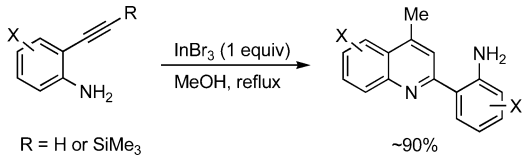
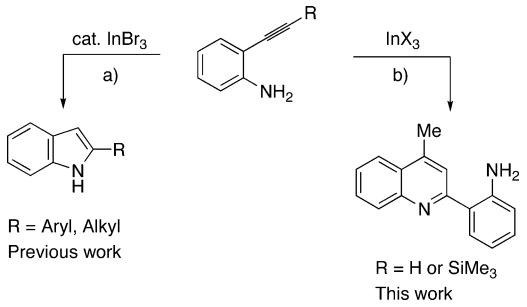


$InBr_3$ promotes the dimerization of 2-ethynylaniline derivatives containing an unsubstituted terminal carbon leading to the production of polysubstituted quinoline derivatives in good yield.

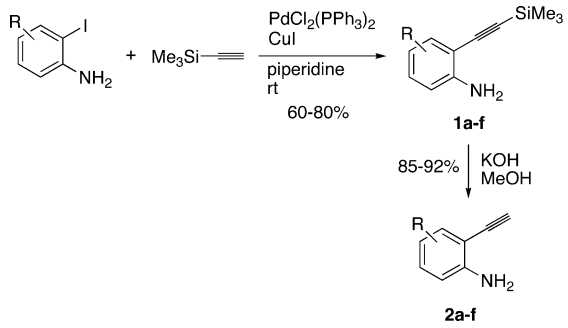
In a previous study,[1] we reported on the $InBr_3$-catalyzed intramolecular cyclization of a variety of 2-ethynylanilines leading to the preparation of 2-substituted indole derivatives (path a in Scheme 1). However, when the reaction was carried out using a substrate with a trimethylsilyl group or with no substituent group on the terminal carbon under optimal conditions, the desired indole product was not produced. Instead, a small amount of an unidentified product was isolated. To determine its structure, the crystalline product was subjected to an X-ray crystallographic analysis. The X-ray analysis of the crystalline product indicated the quinoline skeleton, formed by the dimerization of the ethynylaniline derivative (see Figure 1 in Supporting Information).[2] Herein, we report on a further study of this reaction, which led to the development of a facile synthesis of quinoline derivatives from this type of ethynylaniline derivative via the use of an indium salt (path b in Scheme 1).[3] The synthesis of polysubstituted quinolines is of considerable interest in the fields of organic and pharmaceutical chemistry.[4]

Initially, 2-ethynylaniline derivatives, **2a**−**f**, as reaction substrates were prepared via a Sonogashira-coupling reaction between 2-iodoaniline derivatives and trimethylsilylacetylene and a subsequent deprotection of the TMS group from the anilines, **1a**−**f**, obtained (Scheme 2). We then investigated the dimerization of 2-ethynylaniline (**2a**) in the presence of indium(III) halide as a model reaction. Table 1 shows the results of the search for optimized conditions. In a preliminary investigation,[5] methanol was found to be the best solvent for this reaction. When the reaction was conducted using a catalytic amount of indium bromide in 1 M methanol solution, the yield of the desired product, **3a**, was moderate (entries 1 and 2). However, when a stoichiometric amount of $InBr_3$ was used, the reaction proceeded cleanly without any byproducts being produced, and the yield was further improved to 90% (entry 3). On the other hand, changing the In catalyst to either $InCl_3$, InI_3, or $In(OTf)_3$ resulted in slightly lower yields (entries 4−6). Needless to say, in the absence of the indium salt, no cyclization occurred (entry 7). Consequently, we found that refluxing methanol in the presence of a stoichiometric amount of $InBr_3$ gave the best results for the mutual cyclization. In this context, when the reaction was performed with a substrate having a trimethylsilyl group at a terminal alkyne carbon in the presence of the indium salt, the same product **3a** was produced in 50% yield.[6]

SCHEME 1



SCHEME 2



(1) Sakai, N.; Annaka, K.; Konakahara, T. *Tetrahedron Lett.* **2006**, *47*, 631.

(2) See details in Supporting Information. Crystal data for **3a**: $C_{16}H_{14}N_2$, MW = 234.29, orthorhombic, a = 9.7558(9) Å, b = 9.0365(9) Å, c = 26.814(3) Å, U = 2363.8(4) Å^3, T = 273 K, space group $Pbca$, Z = 8, μ(Mo−Kα) = 0.069 mm^{-1}, 12 610 reflections measured, 2763 independent reflections (R_{int} = 0.0300), R_1 = 0.0539, wR_2 = 0.2075.

(3) For selected reviews and papers on reactions mediated by indium, see: (a) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1995**, *60*, 1920. (b) Yasuda, M.; Miyai, T.; Shibata, I.; Baba, A.; Nomura, R.; Matsuda, H. *Tetrahedron Lett.* **1995**, *36*, 9497. (c) Loh, T.-P.; Wei, L.-L. *Tetrahedron Lett.* **1998**, *39*, 323. (d) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015. (e) Ranu, B. C. *Eur. J. Org. Chem.* **2000**, 2347. (f) Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem.* **2001**, *66*, 7741. (g) Bandini, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Synthesis* **2002**, 1110. (h) Yadav, J. S.; Reddy, B. V. S.; Raju, A. K.; Rao, C. V. *Tetrahedron Lett.* **2002**, *43*, 5437. (i) Sakai, N.; Hirasawa, M.; Konakahara, T. *Tetrahedron Lett.* **2003**, *44*, 4171. (j) Sakai, N.; Hirasawa, M.; Konakahara, T. *Tetrahedron Lett.* **2005**, *46*, 6407. (k) Sakai, N.; Kanada, R.; Hirasawa, M.; Konakahara, T. *Tetrahedron* **2005**, *61*, 9298.

(4) (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science, Ltd.: Oxford, 2000; pp 121−150. (b) Balasubramanian, M.; Keay, J. G. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 5, pp 245−300. (c) Erian, A. W. *Chem. Rev.* **1993**, *93*, 1991.

(5) When the reaction ran with other solvents in the presence of 5 mol % of $InBr_3$ for 24 h, the quinoline was produced in 28 (PhMe), 2 (Et_2O), 45 (1,4-dioxane), and 50% (MeOH) yields.

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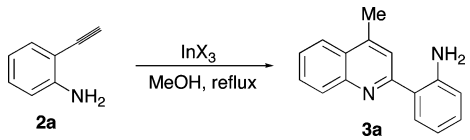
TABLE 1. Optimization of the Dimerization of 2a Using an Indium Catalyst[a]

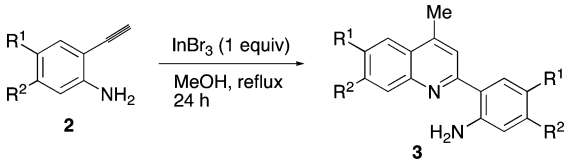


2a 3a

entry	InX_3 (equiv)	time (h)	yield[b] (%)
1	$InBr_3$ (0.05)	36	70
2	$InBr_3$ (0.2)	48	62
3	$InBr_3$ (1)	24	90
4	$InCl_3$ (1)	24	76
5	InI_3 (1)	24	69
6	$In(OTf)_3$ (1)	24	71
7		24	0[c]

[a] The reaction was carried out in MeOH (0.6 mL) using 2-ethynylaniline (**2a**, 0.6 mmol). [b] NMR yield. [c] Recovery (78%) of **2a**.

TABLE 2. $InBr_3$-Promoted Cyclization of Ethynylaniline Derivative 2 Leading to Quinoline 3



2 3

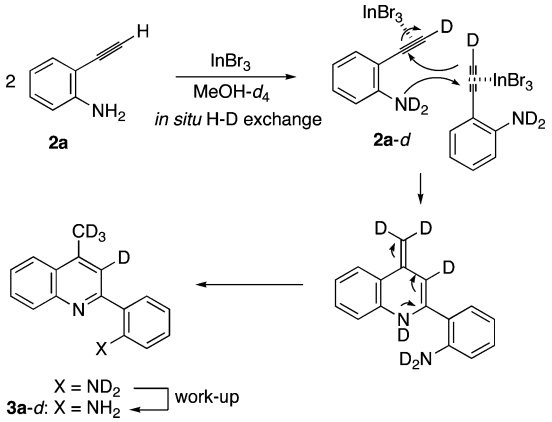
entry	R^1	R^2			yield (%) of **3**[a]
1	H	H	**2a**	**3a**	89
2	Me	H	**2b**	**3b**	79
3	Me	Me	**2c**	**3c**	84
4	F	H	**2d**	**3d**	56
5	CN	H	**2e**	**3e**	81
6	NO_2	H	**2f**	**3f**	80

[a] Isolated yield.

Cyclization reactions of several ethynylanilines were similarly run under the above optimal conditions, and the results are shown in Table 2. For example, the use of a substrate containing an electron-rich group afforded the desired product **3b** in 79% yield (entry 2). The use of **2c** gave the 2,4,6,7-tetrasubstituted quinoline **3c** in good yield (entry 3). With the exception of the 4-fluoro-substituted aniline **2d**, the use of an ethynylaniline derivative containing an electron-withdrawing group also gave the corresponding product (entries 5 and 6). In any case, all entries successfully underwent the desired dimerization, producing the corresponding quinoline derivatives in good to excellent yields.

To better understand the reaction pathway for the cyclization, a deuterium-labeling experiment was conducted. When the reaction with 2-ethynylaniline (**2a**) was carried out in MeOH-d_4 at 65 °C, quinoline **3a**-*d* with a deuterated 4-methyl group and a deuterated 3-position was obtained, after purification. During the reaction, NMR showed a rapid in situ H−D exchange on the terminal carbon of **2a**. On the basis of the deuterium-labeling results, a plausible mechanism for the dimerization is shown in Scheme 3. A reaction using ethynylaniline with no substituent group at the terminal carbon would enable the approach of two molecules of the aniline **2a**-*d*, activated by $InBr_3$, to lead to the dimerization. In contrast, in the case of aniline derivatives having an aliphatic/aromatic group,[1] a steric repulsion at the terminal carbon would retard the approach between two molecules, preferring the intramolecular cyclization to the dimerization. Moreover, indium bromide seems to be activated at the alkyne π-bond, leading to the facile intermolecular cyclization of **2a**-*d*.[7]

SCHEME 3. Plausible Reaction Path for the Dimerization



2a 2a-*d*

The findings show that $InBr_3$ promotes the dimerization of substituted 2-ethynylanilines, without a substituent group on the terminal carbon, to produce polysubstitued quinolines, in contrast to our previous report. To our knowledge, this is the first direct synthesis of a quinoline skeleton via a dimerization of identical molecules.

Experimental Section

General Procedure for the Dimerization of 2. To a 10 mL reaction flask under argon, containing freshly distilled methanol (0.6 mL), 2-(ethynyl)aniline **2** (140 mg, 0.600 mmol) and $InBr_3$ (212 mg, 0.600 mmol) were added. The resulting mixture was refluxed and monitored by TLC until the starting material had been consumed. After the usual workup, the crude product was purified by silica gel column chromatography (hexane/AcOEt = 7:3) to afford the polysubstituted quinoline **3** (yields are collected in Table 2).

General Procedure for the Dimerization of 2a in MeOH-d_4. To an NMR tube equipped with a screw cap containing methanol-d_4 (0.75 mL) under argon, 2-ethynylaniline (**2a**, 87.8 mg, 0.750 mmol) and $InBr_3$ (265 mg, 0.750 mmol) were added. The resulting mixture was refluxed and monitored by NMR until the starting material had been consumed. After the usual workup, the crude product was purified by silica gel column chromatography (hexane/AcOEt = 7:3) to afford **3a**-*d* in 63% (55 mg) yield.

Acknowledgment. This work was partially supported by a fund for "High-Tech Research Center" Project for Private Universities: a matching fund subsidy from MEXT, 2000−2004 and 2005−2007.

(6) A copper(II)-promoted reaction of a similar ethynylaniline derivative resulted in the formation of an indole derivative, see: (a) Ezquerra, J.; Pedregal, C.; Lamas, C.; Barluenga, J.; Pérez, M.; García-Martín, M. A.; González, J. M. *J. Org. Chem.* **1996**, *61*, 5804. (b) Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277. (c) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126.

(7) For examples of indium salts activating alkyne π electrons, see: (a) Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2000**, 1573. (b) Tsuchimoto, T.; Hatanaka, K.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2003**, 2454. (c) Sakai, N.; Annaka, K.; Konakahara, T. *Org. Lett.* **2004**, *6*, 1527. (d) Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 1363.

Supporting Information Available: Detailed Procedures and spectroscopic data for compounds **1**, **2**, and **3**, copies of ^{1}H NMR spectra for **1a**−**f**, **2a**−**f**, and **3a**-*d*, ORTEP of **3a**, and X-ray data for **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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