Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 631–634

$InBr_3$-catalyzed intramolecular cyclization of 2-alkynylanilines leading to polysubstituted indole and its application to one-pot synthesis of an amino acid precursor

Norio Sakai,* Kimiyoshi Annaka and Takeo Konakahara*

Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science (RIKADAI), Noda, Chiba 278-8510, Japan

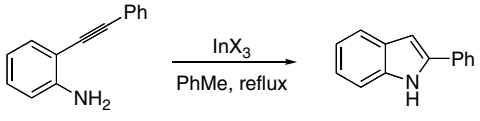
Received 2 November 2005; revised 18 November 2005; accepted 24 November 2005

Abstract—We describe $InBr_3$-catalyzed cyclization of 2-alkynylaniline derivatives having a variety of functional groups producing polysubstituted indoles. This methodology could be applied to the one-pot synthesis of an amino acid precursor by the addition of a catalytic amount of the indium salt, an imine, and TMSCl.

Practical syntheses of substituted indole derivatives have attracted considerable attention in organic, pharmaceutical, or medical chemistry, since this basic skeleton is broadening in natural products and biologically active substances.[1a,b] Among them, palladium,[2] copper,[3] other metal,[4] and base[5,6] mediated cyclization of 2-alkynylanilines is one of the most convenient methods for the preparation of polysubstituted indoles. Although a number of the examples have been reported in this community,[1c,d] there are still several disadvantages involving an introduction of a substituted group, such as an electron-withdrawing group on the nitrogen atom, a large amount of a loading catalyst, and limitation of a reaction substrate, which is sensitive to a strong base. On the other hand, we previously reported that $InBr_3$ effectively catalyzes Sonogashira-type coupling reaction to produce a variety of alkynes derivatives, and that the coordination of the indium to the alkyne π bond assists an intramolecular nucleophilic attack by the tethered amino group of *o*-alkynylaniline leading to 2-substituted indole.[4,7] In the previous work, we found that a catalytic activity of the indium was not lost by the unsubstituted amino group during the reaction. However, the cyclization reaction examined was only limited to one example. Hence, we became interested in the scope and limitation of the intramolecular cyclization of a 2-ethynylaniline derivative by the indium catalyst. We report herein the results of the indium-catalyzed cyclization of 2-ethynylaniline derivatives leading to the synthesis of polysubstituted indoles. We also disclose an efficiently one-pot synthesis of an amino acid precursor by sequential intramolecular cyclization of a tethered amino group, intermolecular addition of an imine.

Table 1 shows the results of the cyclization of 2-phenylethynylaniline (**1a**), which was prepared by the

Table 1. Examination of indium(III)-catalyzed intramolecular cyclization of **1a** leading to 2-phenylindole **2a**[a]



1a **2a**

Run	Cat (equiv)	Time (h)	Yield (%)[b]
1	$InBr_3$ (0.05)	1	95[c]
2	$InCl_3$ (0.05)	4	90
3	InI_3 (0.05)	3	6
4	$InBr_3$ (1)	0.2	98
5	—	24	18
6[d]	$InBr_3$ (0.05)	24	15

[a] Reaction was carried out using 2-phenylethynylaniline (0.5 mmol) and indium trihalide (0.05 equiv) in toluene (2 mL).
[b] NMR yield.
[c] Isolated yield.
[d] Reaction was carried out at room temperature.

Keywords: Indium bromide; Indole; Intramolecular cyclization; 2-Ethynylaniline.
* Corresponding authors. E-mail: sakachem@rs.noda.tus.ac.jp

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.11.121

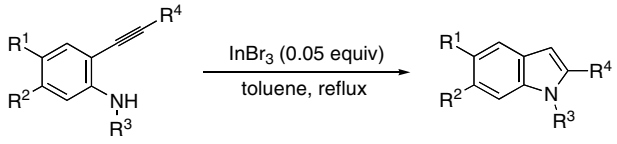
procedure previously reported,[8] under several conditions for optimized conditions.[9] On the basis of previous work, when the reaction using $InBr_3$ ran, the desired indole **2a** was obtained in nearly quantitative yield within 1 h (run 1). $InCl_3$ also showed a similar effect for the reaction, however, the reaction time slightly prolonged (run 2). In contrast, employment of InI_3 resulted in the formation of a complex mixture (run 3). The cyclization using a stoichiometric amount of indium bromide was completed faster than while using a catalytic amount of that (run 4). On the other hand, the reaction without an indium catalyst, or the reaction at room temperature did not afford the desired product in practical yield (runs 5 and 6). Consequently, we found that the toluene reflux conditions using 0.05 equiv of indium bromide from the viewpoints of reactivity and an economical cost showed the best result for the cyclization.[10,11]

Next, to extend the generality of this reaction, cyclization of various N-unsubstituted ethynylaniline prepared was carried out under optimized conditions, the results are displayed in Table 2. Cyclization of the ethynylaniline having not only an electron-donating group but also an electron-withdrawing group on a benzene unit was complete in a short time, producing the corresponding indole derivatives **2** in good to excellent yields (runs 1–6). In addition, when the reaction of substrates **1** containing an alkyl group, such as a hexyl and *tert*-butyl group next to a triple bond also underwent the reaction to produce the desired polysubstituted indole derivatives in good yields (runs 7–13). Moreover, attempts to cyclize N-substituted ethynylaniline having a benzyl or an acetyl group in the presence of the indium catalyst also were highly successful to produce N-substituted indoles **2n** and **2o** in good yields (runs 14 and 15).[12] These results strongly support the fact that the coordination of the indium to the alkyne π bond increases the electrophilicity of the triple bond facilitating the subsequent nucleophilic attack of the tethered amino group to form the desired indole.[13]

We then attempted to develop a simple method for a one-pot synthesis of an amino acid precursor involving an indolyl group via sequential intramolecular cyclization, intermolecular addition. After several examinations, we found a proper procedure for the desired reaction.[14] Thus, a catalytic amount of indium bromide initially undertook an intramolecular cyclization of ethynylaniline **1** producing in situ indole; the addition reaction of the indole with imine **3** in the presence of the further added indium salt and TMSCl occurred to produce indolyl amine derivative **4**.[15,16] Table 3 shows the results of one-pot synthesis using four types of ethynylaniline **1** and imine **3** having a trichloromethyl group,[17] the group of which is not only broadly found in a number of biologically active molecules, but also could be hydrolyzed by an alkaline solution to produce the ester.

In conclusion, we have reported that quite a small amount of $InBr_3$ efficiently catalyzes the cyclization of 2-alkynylaniline derivatives having a variety of functional groups to produce polysubstituted indoles in good to excellent yields. This simple catalytic system is remarkably tolerant to a variety of functional groups on the *o*-ethynylaniline and the unsubstituted amino group. We also succeeded in development for the one-pot synthesis of an amino acid precursor by the addition of a catalytic amount of the indium salt, the imine, and TMSCl. Further investigations toward the synthesis of

Table 2. Intramolecular cyclization of ethynylaniline **1** leading to 2-substituted indole **2**

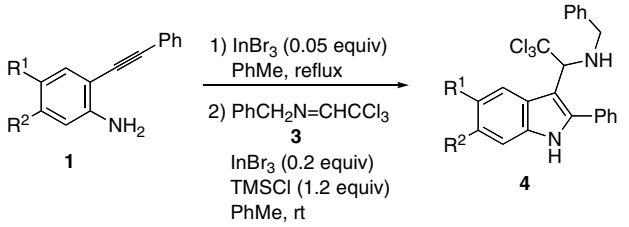


1 **2**

Run	Ethynylaniline **1**					Time (h)	Yield (%)[a]	
	R^1	R^2	R^3	R^4				
1	H	H	H	Ph	**1a**	1	**2a**	95
2	Me	H	H	Ph	**1b**	0.5	**2b**	98
3	Me	Me	H	Ph	**1c**	1	**2c**	90
4	NO_2	H	H	Ph	**1d**	2	**2d**	90
5	F	H	H	Ph	**1e**	2	**2e**	91
6	CN	H	H	Ph	**1f**	2	**2f**	98
7	Me	H	H	C_6H_{13}	**1g**	1.5	**2g**	62
8	Me	Me	H	C_6H_{13}	**1h**	1.5	**2h**	52
9	NO_2	H	H	C_6H_{13}	**1i**	8.5	**2i**	77
10	F	H	H	C_6H_{13}	**1j**	8.5	**2j**	86
11	CN	H	H	C_6H_{13}	**1k**	7	**2k**	89
12	Me	H	H	*t*-Bu	**1l**	4	**2l**	59
13	H	H	H	*t*-Bu	**1m**	4	**2m**	59
14	H	H	Bn	Ph	**1n**	0.5	**2n**	78
15	H	H	Ac	Ph	**1o**	2.5	**2o**	71

[a] Isolated yield.

Table 3. A one-pot procedure for amino acid precursor **4**[a]



Run	Ethynylaniline **1**			Time (h)[b]		Yield (%)[c]
	R^1	R^2				
1	H	H	**1a**	2.5	**4a**	89
2	Me	H	**1b**	1	**4b**	75
3	Me	Me	**1c**	0.5	**4c**	88
4	F	H	**1e**	7.5	**4e**	84

[a] Cyclization of ethynylaniline **1** (0.5 mmol) and subsequent addition of imine **3** (1 mmol) was carried out in toluene (4 mL).
[b] For a reaction time in the first step, see Table 2.
[c] Isolated yield based on 2-phenylethynylaniline derivative **1**.

biologically active substances by using the present method are currently in progress.

Acknowledgments

This work was partially supported by a grant from the Japan Private School Promotion Foundation and a fund for 'High-Tech Research Center' Project for Private Universities: a matching fund subsidy from MEXT, 2000–2004, and 2005–2007.

References and notes

1. (a) Glasby, J. S. *Encyclopedia of the Alkaloids*; Plenum Press: New York, 1975; (b) Sundberg, R. J. *Indoles*; Academic Press: San Diego, 1996; (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873, and references cited therein; (d) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.
2. (a) Taylor, E. C.; Katz, A. H.; Salgado-Zamora, H.; McKillop, A. *Tetrahedron Lett.* **1985**, *26*, 5963; (b) Iritani, K.; Matsubara, S.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799; (c) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581; (d) Rudisillt, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856; (e) Cacchi, S.; Carnicelli, V.; Marinelli, F. *J. Organomet. Chem.* **1994**, *475*, 289; (f) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, *50*, 11803; (g) Saulnier, M. G.; Frennesson, D. B.; Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1995**, *36*, 7841; (h) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001; (i) Zhang, H.-C.; Ye, H.; White, K. B.; Maryanoff, B. E. *Tetrahedron Lett.* **2001**, *42*, 4751; (j) Dai, W.-M.; Guo, D.-S.; Sun, L.-P. *Tetrahedron Lett.* **2001**, *42*, 5275.
3. (a) Ezquerra, J.; Pedregal, C.; Lamas, C.; Barluenga, J.; Pêrez, M.; Garcîa-Martîn, M. A.; Gonzâlez, 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) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843; (d) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126; (e) Hiroya, K.; Itoh, S.; Sakamoto, T. *Tetrahedron* **2005**, *61*, 10958.
4. Sakai, N.; Annaka, K.; Konakahara, T. *Org. Lett.* **2004**, *6*, 1527.
5. (a) Yasuhara, A.; Kanamori, Y.; Kaneko, M.; Numata, A.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 529; (b) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488; (c) Dai, W.-M.; Sun, L.-P.; Guo, D.-S. *Tetrahedron Lett.* **2002**, *43*, 7699; (d) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571; (e) Sun, L.-P.; Huang, X.-H.; Dai, W.-M. *Tetrahedron* **2004**, *60*, 10983.
6. For cyclization of an ethynyl aniline via an iodination process, see: Barluenga, J.; Trincado, M.; Rubio, E.; Gonzâlez, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406.
7. For selected reviews and papers for indium promotes or catalyzes reaction, see; (a) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015; (b) Ranu, B. C. *Eur. J. Org. Chem.* **2000**, 2347; (c) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633; (d) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1995**, *60*, 1920; (e) Yasuda, M.; Miyai, T.; Shibata, I.; Baba, A.; Nomura, R.; Matsuda, H. *Tetrahedron Lett.* **1995**, *36*, 9497; (f) Loh, T.-P.; Wei, L.-L. *Tetrahedron Lett.* **1998**, *39*, 323; (g) Babu, G.; Perumal, P. T. *Tetrahedron Lett.* **1998**, *39*, 3225; (h) Miyai, T.; Onishi, Y.; Baba, A. *Tetrahedron Lett.* **1998**, *39*, 6291; (i) Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem.* **2001**, *66*, 7741; (j) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Eur. J. Org. Chem.* **2002**, 1578; (k) Bandini, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Synthesis* **2002**, 1110; (l) Yadav, J. S.; Reddy, B. V. S.; Raju, A. K.; Rao, C. V. *Tetrahedron Lett.* **2002**, *43*, 5437; (m) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Tetrahedron* **2002**, *58*, 8227; (n) Bandini, M.; Fagioli, M.; Melloni, A.; Umani-Ronchi, A. *Synthesis* **2003**, 397; (o) Yadav, J. S.; Reddy, B. V. S.; Swamy, T. *Synthesis* **2004**, 106; (p) Hayashi, N.; Shibata, I.; Baba, A. *Org. Lett.* **2004**, *6*, 4981; (q) Shibata, I.; Kato, H.; Ishida, T.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 711; (r) Sakai, N.; Kanada, R.; Hirasawa, M.; Konakahara, T. *Tetrahedron* **2005**, *61*, 9298; (s) Sakai, N.; Hirasawa, M.; Konakahara, T. *Tetrahedron Lett.* **2005**, *46*, 6407.
8. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.
9. General procedure for the intramolecular cyclization of **1**. To a 10 mL reaction flask containing a freshly distilled toluene (2 mL) under argon was added 2-ethynylaniline **1a** (96 mg, 0.50 mmol) and $InBr_3$ (0.025 mmol). The resulting mixture was refluxed and monitored by GC or TLC until the starting material was consumed. After the usual work-up, the crude product was purified by silica gel column chromatography to afford the 2-substituted indole **2a** (91 mg, 95%) as a pale yellow solid.
10. Other polar solvents, such as $CHCl_3$, THF, and CH_3CN were not effective for the reaction.
11. When the cyclization of **1a** ran with other Lewis acids (5 mol %), such as $BF_3{\cdot}OEt_2$, $AlCl_3$, and $B(C_6F_5)_3$ in toluene at 110 °C for 12 h, the desired product **2a** was obtained in lower yield ($BF_3{\cdot}OEt_2$: 22%, $AlCl_3$: 31%, $B(C_6F_5)_3$: 29%). Another group investigated a similar cyclization of an ethynylaniline derivative, see Ref. 3b.
12. In case of 2-ethynylaniline (R^1, R^2, R^3, and $R^4 = H$), the corresponding indole product was not obtained under the present conditions.
13. For examples of indium salt activates 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) Nakamura, M.; Endo, K.;

Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 13002; (d) Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 1363; (e) See Ref. 4.

14. General procedure for the one-pot synthesis of **4**. To 2 mL of toluene was added $InBr_3$ (11.3 mg, 0.025 mmol), 2-ethynylaniline **1a** (96.5 mg, 0.50 mmol), and the mixture was refluxed for the corresponding times shown in Table 1. A toluene solution (2 mL) of $InBr_3$ (45 mg, 0.10 mmol), imine **3** (1.0 mmol, 236 mg), and TMSCl (0.60 mmol, 65 mg) was also stirred at room temperature for 1 h. The latter solution was added to the former solution via a cannula. The resulting mixture was stirred at room temperature until the starting materials were consumed. After usual work-up, the crude product was purified by silica gel column chromatography to afford the corresponding product **4a** as a gray solid (191 mg, 89%). mp (dec) 133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.81 (br s, 1H), 3.83 (d, 1H, $J = 13$ Hz), 4.05 (d, 1H, $J = 13$ Hz), 4.87 (s, 1H), 7.07–7.37 (m, 13H), 8.24 (br s, 1H), 8.26 (d, 1H, $J = 8.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.7, 71.0, 105.4, 107.0, 110.9, 120.2, 122.3, 123.0, 126.6, 127.1, 128.1, 128.3, 128.5, 128.8, 129.0, 132.9, 135.7, 139.6, 140.3; MS (FAB): *m*/*z* 429, 311; Anal. Calcd for $C_{23}H_{19}N_2Cl_3$: C, 64.28; H, 4.46; N, 6.52. Found: C, 64.28; H, 4.41; N, 6.43.
15. Although the role of TMSCl is not clear at this stage, it is known that a coexistence of Lewis acid and TMSCl promotes reactivity of an addition reaction, see: (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015; (b) Yamanaka, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 159; (c) Huang, T.; Li, C.-J. *Tetrahedron Lett.* **2000**, *41*, 6715; (d) Lee, P. H.; Lee, K.; Sung, S.-Y.; Chang, S. *J. Org. Chem.* **2001**, *66*, 8646; (e) Sakai, N.; Hamajima, T.; Konakahara, T. *Tetrahedron Lett.* **2002**, *43*, 4821; (f) Tsuji, R.; Yamanaka, M.; Nishida, A.; Nakagawa, M. *Chem. Lett.* **2002**, 428; (g) Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* **2003**, *44*, 6767; (h) Sakai, N.; Hirasawa, M.; Hamajima, T.; Konakahara, T. *J. Org. Chem.* **2003**, *68*, 483; (i) Yamanaka, M.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* **2003**, *68*, 3112.
16. When the reaction ran with 0.2 equiv of $InBr_3$ in the first step without an extra load of $InBr_3$ for the second step, the desired amino acid precursor **4a** was produced in 57% yield.
17. Selected papers for Lewis acid-promoted reaction of indole with imines, see: (a) Gong, Y.; Kato, K.; Kimoto, H. *Synlett* **2000**, 1058; (b) Gong, Y.; Kato, K. *Tetrahedron: Asymmetry* **2001**, *12*, 2121; (c) Gong, Y.; Kato, K.; Kimoto, H. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2121.