JOC Article

Efficient Synthesis of Aminomethylated Pyrroloindoles and Dipyrrolopyridines via Controlled Copper-Catalyzed Domino Multicomponent Coupling and Bis-cyclization

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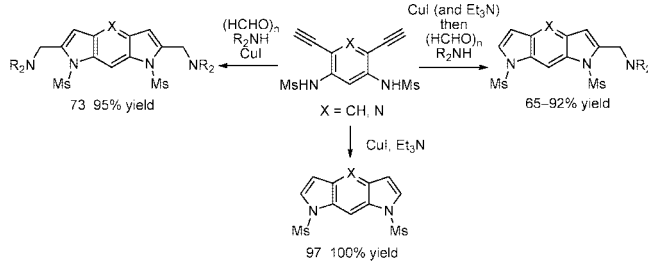

Efficient methods for the synthesis of pyrrole-fused indole derivatives via domino copper-catalyzed multicomponent coupling and bis-cyclization have been developed. The mono- or bis-aminomethylated pyrroloindoles and dipyrrolopyridines were selectively obtained in moderate to excellent yields by a controlled Mannich-type reaction−cyclization of 4,6-diethynyl-1,3-phenylenediamine or its pyridine congener with paraformaldehyde and a secondary amine. The high-yielding bis-cyclization of terminal alkynes without using Mannich-type reactions is also presented.

Introduction

Fused heterocyclic compounds containing pyridine and/or pyrrole rings are found in a large number of biologically active natural products including indole alkaloids[1,2] and, therefore, are considered as attractive templates for drug discovery.[3] Functionalized highly fused heterocycles are normally synthesized from monocyclic or acyclic substrates by stepwise construction of ring structures. Accordingly, for diversity-oriented synthesis of this class of compounds, time- and cost-consuming functional group modification and cyclization wasting reagents and solvents are often required. The simultaneous cyclization and functionalization via a multicomponent reaction (MCR) is an important strategy to overcome this problem, which makes it possible to efficiently prepare diverse derivatives bearing a variety of functionalities.[4,5] Multiple-ring construction including functionalization via a MCR would constitute a more powerful and direct approach to the diversity-oriented synthesis of fused heterocycles from a single precursor. Because this type of multicomponent tandem cyclization requires several reaction components having multiple reaction sites, an unregulated reaction readily forms a complex mixture of undesired products. To synthesize the desired compounds selectively, it is extremely important to

(1) For recent reviews, see: (a) Liu, J.-K. *Chem. Rev.* **2005**, *105*, 2723–2744. (b) Lewis, S. E. *Tetrahedron* **2006**, *62*, 8655–8681. (c) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264–287.

(2) For recent examples, see: (a) Ostrovidov, S.; Franck, P.; Joseph, D.; Martarello, L.; Kirsch, G.; Belleville, F.; Nabet, P.; Dousset, B. *J. Med. Chem.* **2000**, *43*, 1762–1769. (b) Takayama, H.; Ishikawa, H.; Kurihara, M.; Kitajima, M.; Aimi, N.; Ponglux, D.; Koyama, F.; Matsumoto, K.; Moriyama, T.; Yamamoto, L. T.; Watanabe, K.; Murayama, T.; Horie, S. *J. Med. Chem.* **2002**, *45*, 1949–1956. (c) Vzquez, M. J.; Roa, A. M.; Reyes, F.; Vega, A.; Rivera-Sagredo, A.; Thomas, D. R.; Dez, E.; Hueso-Rodrguez, J. A. *J. Med. Chem.* **2003**, *46*, 5117–5120. (d) Zhou, J.-L.; Lu, Y.-J.; Ou, T.-M.; Zhou, J.-M.; Huang, Z.-S.; Zhu, X.-F.; Du, C.-J.; Bu, X.-Z.; Ma, L.; Gu, L.-Q.; Li, Y.-M.; Chan, A. S.-C. *J. Med. Chem.* **2005**, *48*, 7315–7321. (e) Carr, G.; Chung, M. K. W.; Mauk, A. G.; Andersen, R. J. *J. Med. Chem.* **2008**, *51*, 2634–2637.

(3) For recent reviews, see: (a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748–8758. (b) Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Chem. Soc. Rev.* **2007**, *36*, 1120–1132. For recent examples, see: (c) Perzyna, A.; Marty, C.; Facompr, M.; Goossens, J.-F.; Pommery, N.; Colson, P.; Houssier, C.; Houssin, R.; Hnichart, J.-P.; Bailly, C. *J. Med. Chem.* **2002**, *45*, 5809–5812. (d) Trk, M.; Abid, M.; Mhadgut, S. C.; Trk, B. *Biochemistry* **2006**, *45*, 5377–5383. (e) Martino, G. D.; Edler, M. C.; Regina, G. L.; Coluccia, A.; Barbera, M. C.; Barrow, D.; Nicholson, R. I.; Chiosis, G.; Brancale, A.; Hamel, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2006**, *49*, 947–954. (f) Legentil, L.; Benel, L.; Bertrand, V.; Lesur, B.; Delfourne, E. *J. Med. Chem.* **2006**, *49*, 2979–2988. (g) Ueda, S.; Kato, M.; Inuki, S.; Ohno, H.; Evans, B.; Wang, Z.-X.; Peiper, S. C.; Izumi, K.; Kodama, E.; Matsuoka, M.; Nagasawa, H.; Oishi, S.; Fujii, N. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4124–4129.

(4) For recent reviews, see: (a) Dmling, A. *Chem. Rev.* **2006**, *106*, 17–89. (b) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463–472.

(5) For recent examples, see: (a) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 9625–9631. (b) Siamaki, A. R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2006**, *128*, 6050–6051. (c) Mihovilovic, M. D.; Stanetty, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 3612–3615. (d) Barluenga, J.; Mendoza, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 1644–1647.

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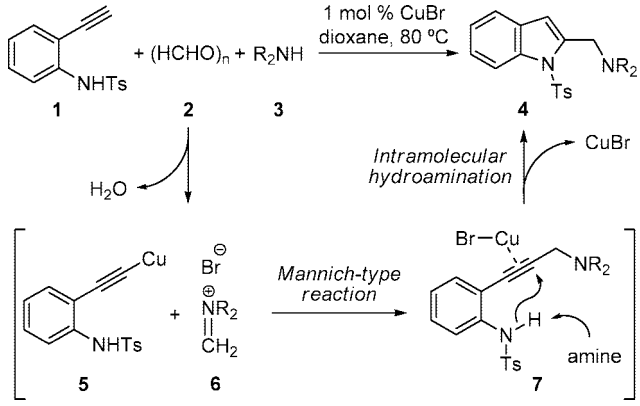
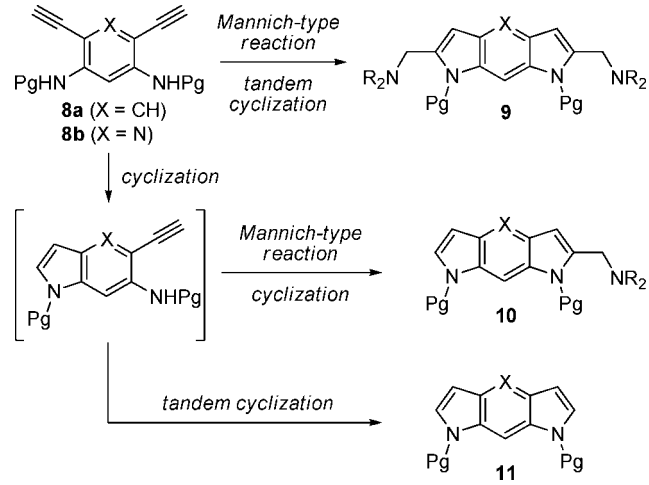
SCHEME 1. Copper-Catalyzed Domino Three-Component Coupling and Cyclization



control the reactions by appropriate choice of the reaction conditions as well as functionality of the substrates.

In recent years, we reported a direct synthesis of 2-(aminomethyl)indoles **4** via copper-catalyzed domino three-component coupling and cyclization reactions of ethynylaniline **1** (Scheme 1).[6,7] This reaction would proceed through a Mannich-type three-component reaction of **1** with paraformaldehyde **2** and a secondary amine **3** through formation of copper acetylide **5** from a terminal alkyne, followed by the copper-catalyzed intramolecular hydroamination[8] of the internal alkyne. Based on this reaction, we designed a multicomponent tandem cyclization reaction of 1,3-phenylenediamine bearing two terminal alkynes or its pyridine congener (**8**) with 1 or 2 equiv of formaldehyde and a secondary amine (Scheme 2). Three types of tricyclic compounds **9**−**11** can be selectively synthesized from the common substrates **8**: (1) successive Mannich-type reactions of **8** at both alkynes followed by tandem cyclization would give bis-aminomethylated tricyclic compounds **9**, (2) monocyclization of **8** followed by a Mannich-type reaction and the second cyclization would afford monoaminomethylated tricyclic compounds **10**, and (3) tandem cyclization of **8** without using a Mannich-type reaction would yield 2,6-unsubstituted tricyclic compounds **11**. Herein, we report the copper-catalyzed selective synthesis of pyrroloindole derivatives[9] and dipyrrolopyridine derivatives[10] **9**−**11** (X = CH and X = N, respectively) by a controlled Mannich-type reaction−cyclization.

SCHEME 2. Multicomponent Tandem Cyclization Reactions of 8



Results and Discussion

Synthesis of 2,6-Bis(aminomethyl)pyrroloindole Derivatives. In our previous study on the three-component indole formation, the intramolecular hydroamination required *N*-substituted ethynylanilines.[6] Therefore, we first investigated the pyrroloindole formation from 4,6-diethynyl-1,3-phenylenediamines **12**−**14** having acetyl, tosyl, or mesyl groups on both of the nitrogen atoms (Table 1).[11] We found that this reaction is strongly dependent on the substituents on the nitrogen atoms. When using diacetamide **12**, a Mannich adduct **18a** was obtained without producing the desired intramolecular hydroamination product (entry 1). On the other hand, the reaction of ditosylamide **13** gave the desired product **16a** in 34% yield along with a monoaminomethylated pyrroloindole derivative **19a** in 14% yield (entry 2). Among the three substrates tested, dimesylamide **14** showed the most promising result to afford the desired product **17a** in 69% yield (entry 3). We then optimized the reaction conditions using the dimesylamide **14**. Lowering the reaction temperature to 60 or 40 °C slightly decreased the yields of **17a** (entries 4 and 5). According to the previous report,[8d,f] the counteranion of copper catalysts considerably affects the reactivity of the alkyne toward intramolecular hydroamination. Among the copper salts investigated [CuI, CuBr, CuCl, $CuBr_2$ and $Cu(OAc)_2$, entries 3 and 6−9], CuI afforded the highest yield of **17a** (entry 3). When using $Cu(OAc)_2$, 25% yield of monoaminomethylated pyrroloindole **20a** was obtained (entry 9). These results suggest that $Cu(OAc)_2$ more strongly activates the alkyne toward the intramolecular hydroamination than the copper halides. Finally, the best result was obtained when a mixed solvent of toluene and dioxane (1:1) was used in the reaction (85%, entry 10).

Using the optimized reaction conditions (Table 1, entry 10), we next investigated the scope of this reaction using several secondary amines (Table 2). The reactions using piperidine **3b** proceeded faster than diethylamine **3a** to give **17b** in excellent yield (95%, entry 1). The presence of the removable allyl groups did not affect the yield, although a prolonged reaction time was

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

(7) For related reactions, see: (a) Ohta, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2008**, 835–837. (b) Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 3535–3538.

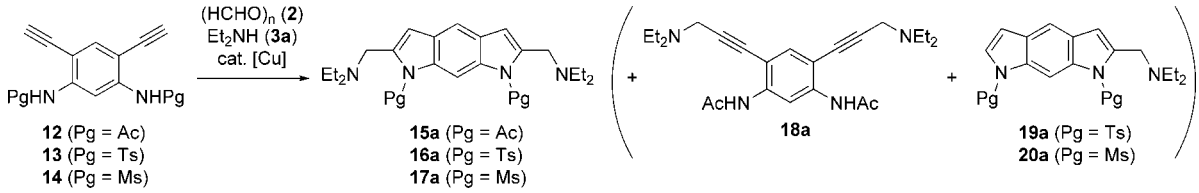
(8) For representative examples, see: (a) Fujiwara, J.; Fukutani, Y.; Sano, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 7177–7179. (b) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Nagano, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1305–1308. (c) Ma, C.; Yu, S.; He, X.; Liu, X.; Cook, J. M. *Tetrahedron Lett.* **2000**, *41*, 2781–2785. (d) Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277–1280. (e) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843–3846. (f) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126–1136. (g) Kamijo, S.; Sasaki, Y.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 35–38. (h) Nishikawa, T.; Koide, Y.; Kajii, S.; Wada, K.; Ishikawa, M.; Isobe, M. *Org. Biomol. Chem.* **2005**, *3*, 687–700. (i) Majumdar, K. C.; Mondal, S. *Tetrahedron Lett.* **2008**, *49*, 2418–2420.

(9) For examples of synthesis of pyrroloindole derivatives, see: (a) Ezquerra, J.; Pedregal, C.; Lamas, C.; Barluenga, J.; Prez, M.; Garca-Martin, G. A.; Gonzlez, J. M. *J. Org. Chem.* **1996**, *61*, 5804–5812. (b) Burling, S.; Field, L. D.; Li, H. L.; Messerle, B. A.; Shasha, A. *Aust. J. Chem.* **2004**, *57*, 677–680. (c) Schenck, L. W.; Sippel, A.; Kuna, K.; Frank, W.; Albert, A.; Kucklaender, U. *Tetrahedron* **2005**, *61*, 9129–9139.

(10) For examples of the synthesis of dipyrrolo[2,3-*b*:3′,2′-*e*]pyridine derivatives, see: (a) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488–2490. (b) Karadin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571–1587.

(11) For synthesis of the requisite substrates, see the Supporting Information.

TABLE 1. Optimization of Reaction Conditions for Cu-Catalyzed Three-Component Coupling and Tandem Cyclization[a]



12 (Pg = Ac)
13 (Pg = Ts)
14 (Pg = Ms)

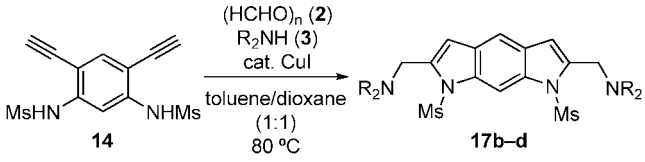
15a (Pg = Ac)
16a (Pg = Ts)
17a (Pg = Ms)

19a (Pg = Ts)
20a (Pg = Ms)

entry	substrate	T (°C)	[Cu]	solvent	time (h)	products (% yield)[b]
1	**12**	80	CuI	dioxane	12	**15a** (0), **18a** (68)
2	**13**	80	CuI	dioxane	0.5	**16a** (34), **19a** (14)
3	**14**	80	CuI	dioxane	2	**17a** (69), **20a** (8)
4	**14**	60	CuI	dioxane	2	**17a** (67), **20a** (13)
5	**14**	40	CuI	dioxane	5	**17a** (56), **20a** (5)
6	**14**	80	CuBr	dioxane	1	**17a** (25)
7	**14**	80	CuCl	dioxane	0.5	**17a** (38)
8	**14**	80	$CuBr_2$	dioxane	1	**17a** (50)
9	**14**	80	$Cu(OAc)_2$	dioxane	0.5	**17a** (21), **20a** (25)
10	**14**	80	CuI	toluene/dioxane (1:1)	2.5	**17a** (85), **20a** (trace)

[a] All of the reactions were carried out with the substrate (0.1 mmol), $(HCHO)_n$ **2** (4.0 equiv as HCHO), Et_2NH **3a** (2.2 equiv), and a copper salt (3 mol %). [b] Isolated yields.

TABLE 2. Synthesis of 2,6-Disubstituted Pyrroloindoles 17 with Various Secondary Amines[a]



14

17b–d

entry	R_2NH	time (h)	product (% yield)[b]
1	piperidine (**3b**)	0.5	**17b** (95)
2	$(allyl)_2NH$ (**3c**)	18	**17c** (89)
3	$(i\text{-Pr})_2NH$ (**3d**)	18	**17d** (6)
4[c]	$(i\text{-Pr})_2NH$ (**3d**)	0.5	**17d** (84)

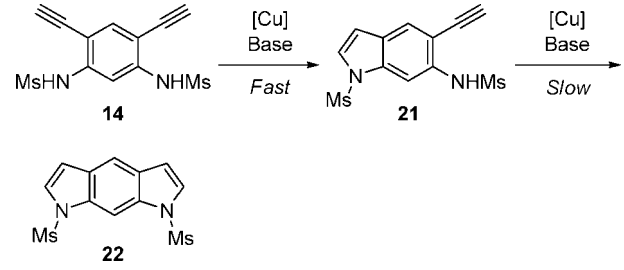
[a] Unless otherwise stated, reactions were carried out with **14** (0.1 mmol), $(HCHO)_n$ **2** (4.0 equiv as HCHO), R_2NH **3** (2.2 equiv), and CuI (3 mol %) in toluene/1,4-dioxane (1:1). [b] Isolated yields. [c] 30 mol % of CuI was used.

required (89% yield, entry 2). On the other hand, use of bulky diisopropylamine **3d** considerably decreased the yield of **17d** to only 6% (entry 3). This limitation can be overcome by use of an increased amount of CuI (30 mol %) to afford **17d** in 84% yield (entry 4).

Synthesis of 2-(Aminomethyl)pyrroloindole Derivatives and 2,6-Unsubstituted Pyrroloindole. For selective synthesis of monoaminomethylated pyrroloindoles through introduction of a single aminomethyl group and bis-cyclization, two strategies can be employed: a controlled Mannich-type reaction of one of the alkynes followed by tandem cyclization and a controlled monohydroamination at the single alkyne followed by a Mannich-type reaction and hydroamination of the other. We chose the latter strategy expecting that the second cyclization of the indole derivative **21** would be slower than the first cyclization of benzene derivative **14** because of the lower acidity of the mesylamide proton of **21** on a more electron-rich indole ring than the proton of **14** which was on a benzene ring, thus contributing to the successful monocyclization of **14** (Scheme 3).

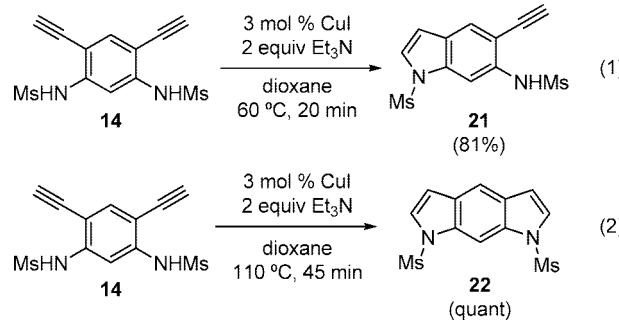
Based on this hypothesis, we tested the selective mono- and bis-cyclization using **14**. Fortunately, we succeeded to selectively obtain indole **21** in high yield (81%) when **14** was treated with 3 mol % of CuI and 2 equiv of Et_3N in dioxane at 60 °C

SCHEME 3. Expected Stepwise Cyclization of the Dimesylamide 14



14 **21** **22**

SCHEME 4. Intramolecular Hydroamination of 14

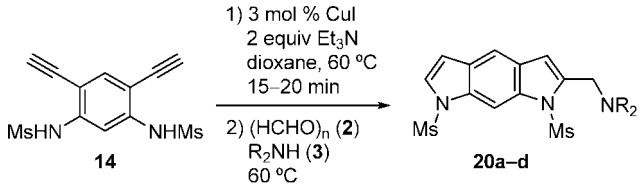


14 **21** (81%) (1)

14 **22** (quant) (2)

(Scheme 4, eq 1). The elevated reaction temperature (110 °C) easily formed pyrroloindole **22** in quantitative yield (Scheme 4, eq 2). Inspired by these results, we attempted to selectively synthesize 2-(aminomethyl)pyrroloindole **20** through the indole intermediate **21** in a one-pot fashion. The phenylenediamine **14** was treated with CuI (3 mol %) and Et_3N (2 equiv) in dioxane. After completion of the monocyclization (monitored by TLC), paraformaldehyde **2** and diethylamine **3a** were added to the reaction mixture to give the desired product **20a** in 78% yield (Table 3, entry 1). The reaction using other amines such as piperidine **3b**, diallylamine **3c**, and diisopropylamine **3d** also gave satisfactory results (entries 2−4). Remarkably, bulky isopropyl groups did not interfere in this reaction (entry 4), while the synthesis of bis(aminomethyl)pyrroloindole using diisopropylamine **3d** required increased loading of the catalyst (Table 2, entry 4).

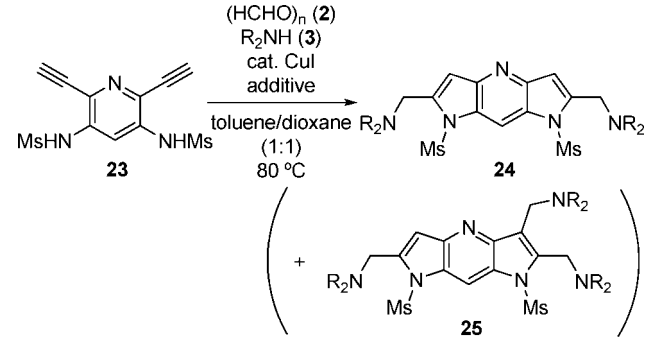
TABLE 3. One-Pot Synthesis of 20 with Various Secondary Amines[a]



entry	R_2NH	time (h)	product (% yield)[b]
1	Et_2NH (**3a**)	2.5	**20a** (78)
2	piperidine (**3b**)	0.75	**20b** (85)
3	$(allyl)_2NH$ (**3c**)	12	**20c** (90)
4	$(i\text{-}Pr_2)NH$ (**3d**)	1.5	**20d** (92)

[a] All the reactions were carried out with **14** (0.1 mmol), $(HCHO)_n$ **2** (2.0 equiv as HCHO), R_2NH **3** (1.1 equiv), and CuI (3 mol %) in 1,4-dioxane. [b] Isolated yields.

TABLE 4. Synthesis of 2,6-Bis(aminomethyl)dipyrrolopyridine 24[a]



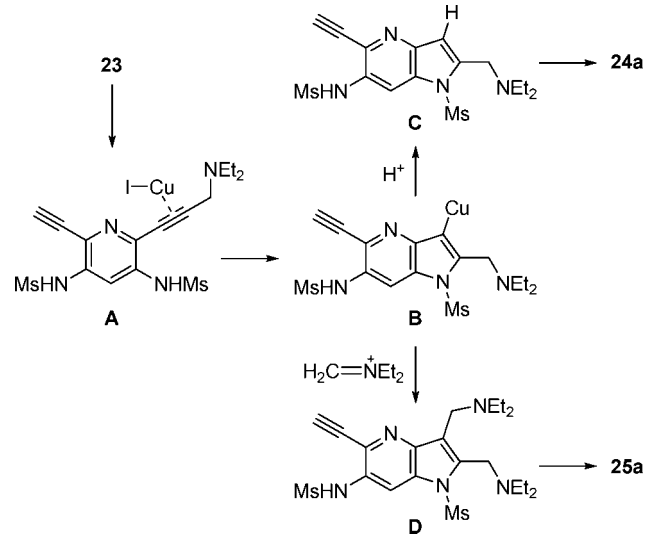
entry	additive (equiv)	R_2NH	time (h)	products (% yield)[b]
1	none	Et_2NH (**3a**)	0.5	**24a** (72), **25a** (ca. 16)
2	MeOH (1)	Et_2NH (**3a**)	0.5	**24a** (81), **25a** (ca. 9)
3	MeOH (2)	Et_2NH (**3a**)	0.5	**24a** (72), **25a** (ca. 10)
4	CF_3CH_2OH (1)	Et_2NH (**3a**)	0.5	**24a** (68), **25a** (ca. 16)
5	MeOH (1)	piperidine (**3b**)	0.25	**24b** (75)
6	MeOH (1)	$(allyl)_2NH$ (**3c**)	0.5	**24c** (73)
7[c]	MeOH (1)	$(i\text{-}Pr)_2NH$ (**3d**)	0.5	**24d** (76)

[a] Unless otherwise stated, reactions were carried out with **23** (0.1 mmol), $(HCHO)_n$ **2** (4.0 equiv as HCHO), R_2NH **3** (2.2 equiv), and CuI (3 mol %) in toluene/1,4-dioxane (1:1). [b] Isolated yields. [c] 30 mol % of CuI was used.

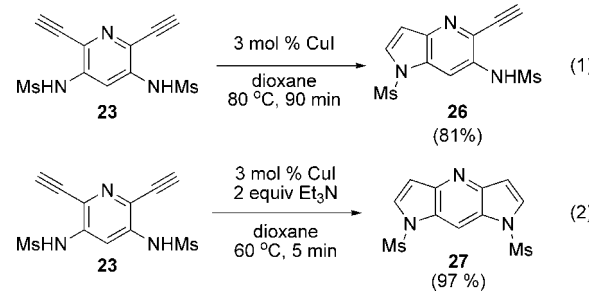
Synthesis of 2,6-Bis(aminomethyl)dipyrrolopyridine Derivatives. As an application of the developed methodologies to the construction of a novel druglike scaffold, we next investigated the reaction of the pyridine analogue **23**. Initially, we applied diaminopyridine derivative **23** to the reaction conditions for synthesis of bis-aminomethylated tricycles (Table 4). The reaction of **23** with paraformaldehyde **2**, diethylamine **3a**, and 3 mol % of CuI in toluene/dioxane (1:1) afforded the desired 2,6-bis(aminomethyl)dipyrrolopyridine **24a** in 72% yield accompanied by formation of undesired 2,3,6-tris(aminomethyl)dipyrrolopyridine **25a** in ca. 16% yield (entry 1). This byproduct **25a** would be generated via a Mannich-type reaction of the alkenyl copper intermediate **B** (Scheme 5)[12] because treatment of the isolated **24a** under the reaction conditions did not promote further aminomethylation at the 3-position. Then, we examined the effect of alcohol as an additive, expecting that

(12) Hiroya et al. reported the C-3 functionalization reaction of indole through the alkenyl copper intermediate.[8f]

SCHEME 5. Plausible Reaction Mechanism for Formation of 25a



SCHEME 6. Intramolecular Hydroamination of 23

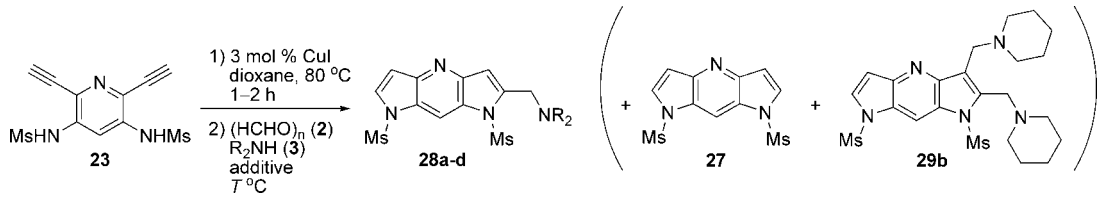


protonation of the intermediate **B** would accelerate formation of the desired product **24a** (Table 4, entries 2−4). As we expected, addition of MeOH (1 equiv) slightly increased the yield of **24a** (81%, entry 2). However, increased loading of MeOH (2 equiv) and use of the more acidic CF_3CH_2OH (1 equiv) were less effective (entries 3 and 4). We next investigated the scope of this reaction using several secondary amines (entries 5−7) and obtained the corresponding products **24b−d** in good yields (73−76%).

Synthesis of 2-(Aminomethyl)dipyrrolopyridine Derivatives and 2,6-Unsubstituted Dipyrrolopyridine. Finally, selective synthesis of monoaminomethylated dipyrrolopyridines as well as a 2,6-unsubstituted derivative was investigated (Scheme 6). In sharp contrast to the reaction of the benzene derivative **14** (Scheme 4), tandem cyclization proceeded completely under the same reaction conditions used for synthesis of indole **21** to give the dipyrrolopyridine **27** in 97% yield (Scheme 4, eq 2). Interestingly, the azaindole **26** was synthesized in 81% yield under these conditions without using Et_3N (Scheme 4, eq 1). This is presumably due to the electron-deficient nature of the pyridine ring as well as the basicity of the pyridine moiety.

Next we tested the selective formation of 2-(aminomethyl)-dipyrrolopyridine derivative **28** by base-free monocyclization followed by a Mannich-type reaction−cyclization in a one-pot manner (Table 5). After completion of the monocyclization of **23** with 3 mol % of CuI in dioxane (monitored by TLC), paraformaldehyde **2** (2 equiv) and piperidine **3b** (1.1 equiv) were added to the reaction mixture to give the desired compound **28b** as a major product (58% yield, entry 1). However, a

TABLE 5. One-Pot Synthesis of 2-(Aminomethyl)dipyrrolopyridine 28[a]



entry	T (°C)	additive (equiv)	R_2NH	time (h)	products (% yield)[b]
1	80	none	piperidine (**3b**)	0.25	**28b** (58%), **27** (35%)
2	rt	none	piperidine (**3b**)	12	**28b** (37%), **27** (61%)
3	100	none	piperidine (**3b**)	0.08	**28b** (58%), **27** (19%)
4[c]	80	none	piperidine (**3b**)	0.08	**28b** (58%), **27** (26%)
5	80	PPTS[d] (2)	piperidine (**3b**)	6	**28b** (49%), **27** (50%)
6[e]	80	none	piperidine (**3b**)	0.25	**28b** (68%), **27** (10%), **29b** (trace)
7[e,f]	80	MeOH (1)	piperidine (**3b**)	0.25	**28b** (73%), **27** (13%), **29b** (trace)
8[e,f]	80	MeOH (1)	Et_2NH (**3a**)	0.25	**28a** (65%)
9[e,f]	80	MeOH (1)	$(allyl)_2NH$ (**3c**)	0.5	**28c** (66%)
10[e,f]	80	MeOH (1)	$(i\text{-}Pr)_2NH$ (**3d**)	0.5	**28d** (33%)
11[e,f,g]	80	MeOH (1)	$(i\text{-}Pr)_2NH$ (**3d**)	0.5	**28d** (66%)

[a] Unless otherwise stated, reactions were carried out with **23** (0.1 mmol), $(HCHO)_n$ **2** (2.0 equiv as HCHO), and piperidine **3a** (1.1 equiv). [b] Isolated yields. [c] $(HCHO)_n$ **2** (5.0 equiv as HCHO) and piperidine **3a** (5.0 equiv) were used. [d] Pyridinium *p*-toluenesulfonate. [e] A solution of $(HCHO)_n$ **2** (4.0 equiv as HCHO) and R_2NH **3** (2.0 equiv) in toluene (heated at 80 °C for 5 min) was added to the reaction mixture. [f] MeOH was added before addition of $(HCHO)_n$ **2** and R_2NH **3**. [g] 30 mol % of CuI was used.

considerable amount of 2,6-unsubstituted dipyrrolopyridine **27** was also obtained (35% yield). Neither lowering nor raising the reaction temperature improved the yield of **28b** (entries 2 and 3). Use of an excess amount of both paraformaldehyde **2** and piperidine **3b** (5 equiv, respectively) was also ineffective (entry 4). We expected that the undesired cyclization at the terminal alkyne of the intermediate **26** can be hampered under less basic conditions as in Scheme 6. However, addition of a weak acid, pyridinium *p*-toluenesulfonate (PPTS), decreased the yield of **28b** with a prolonged reaction time (entry 5). As already described, use of a mixed solvent of toluene and dioxane suppressed the undesired second cyclization of **14** before the Mannich-type reaction (Table 1, entries 3 and 10). Accordingly, we examined addition of toluene along with paraformaldehyde **2** and piperidine **3b** to obtain an improved yield of **28b** (68% yield) and 10% yield of **27** (entry 6). In this case, a trace of bis-aminomethylated product **29b** was detected. The second cyclization in the presence of MeOH (1 equiv) was conducted to afford **28b** in an improved yield (73%, entry 7). While the reaction with diethylamine **3a** and diallylamine **3c** afforded **28a** and **28c**, respectively, in moderate yields (entries 8 and 9), the reaction using diisopropylmine **3d** resulted in only 33% yield (entry 10). Similar to the reaction of **14** (Table 2, entry 4), the yield of **28d** was moderately improved by use of 30 mol % of CuI (entry 11).

Conclusion

We have developed efficient methodologies for synthesis of aminomethylated pyrroloindoles and dipyrrolopyridines. Starting from arenes with two terminal alkynes and two amino groups as the common substrates, three types of pyrroloindoles and dipyrrolopyridines were synthesized directly in moderate to excellent yields by simply changing the reaction conditions. These synthetic methodologies will provide a powerful tool for divergent preparation of pyrroloindole and dipyrrolopyridine derivatives. Further studies for development of biologically active compounds utilizing these druglike templates are now in progress.

Experimental Section

General Procedure for Synthesis of 2,6-Bis(aminomethyl)pyrroloindoles 17a−d. Synthesis of 2,6-Bis[(*N*,*N*-diethylamino)methyl]-1,7-bis(methylsulfonyl)pyrrolo[3,2-*f*]indole (17a) (Table 1, Entry 10). Diethylamine **3a** (23 μL, 0.22 mmol) was added to a mixture of paraformaldehyde **2** (12 mg, 0.40 mmol) and CuI (0.6 mg, 0.003 mmol) in toluene/1,4-dioxane (1:1, 1.0 mL) under Ar. The mixture was stirred at 80 °C for 5 min and then cooled to room temperature. To the mixture was added **14** (31 mg, 0.10 mmol) at room temperature, and the mixture was stirred at 80 °C for 2.5 h. The solvent was removed under reduced pressure, and the residue was chromatographed on alumina (hexane/EtOAc = 4/1) to afford **17a** (41 mg, 85%) as a white solid: mp 154−155 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (t, J = 7.2 Hz, 12H, 4 × CH_2CH_3), 2.63 (q, J = 7.2 Hz, 8H, 4 × CH_2CH_3), 3.49 (s, 6H, 2 × SO_2CH_3), 3.90 (s, 4H, 2 × NCH_2Ar), 6.56 (s, 2H, Ar), 7.55 (s, 1H, Ar), 8.83 (s, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.8 (4C), 41.2 (2C), 45.6 (4C), 51.6 (2C), 99.8, 110.4 (2C), 110.6, 125.6 (2C), 135.5 (2C), 139.5 (2C). Anal. Calcd for $C_{22}H_{34}N_4O_4S_2$: C, 54.75; H, 7.10; N, 11.61. Found: C, 54.49; H, 7.10; N, 11.53.

General Procedure for Synthesis of 2-(Aminomethyl)pyrroloindoles 20a−d. Synthesis of 2-[(*N*,*N*-Diethylamino)methyl]-1,7-bis(methylsulfonyl)pyrrolo[3,2-*f*]indole (20a) (Table 3, Entry 1). Et_3N (29 μL, 0.20 mmol) was added to a mixture of **14** (31 mg, 0.10 mmol) and CuI (0.6 mg, 0.003 mmol) in 1,4-dioxane (1.0 mL) under Ar. The mixture was stirred at 60 °C for 15−20 min (completion of formation of **21** was monitored by TLC) and then cooled to room temperature. To the mixture were added paraformaldehyde **2** (6 mg, 0.20 mmol) and diethylamine **3a** (12 μL, 0.11 mmol), and then the mixture was stirred at 60 °C for 2.5 h. The solvent was removed under reduced pressure, and the residue was chromatographed on alumina (hexane/EtOAc = 4/1) to afford **20a** (31 mg, 78%) as a white solid: mp 114−115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (t, J = 7.2 Hz, 6H, 2 × CH_2CH_3), 2.64 (q, J = 7.2 Hz, 4H, 2 × CH_2CH_3), 3.13 (s, 3H, SO_2CH_3), 3.53 (s, 3H, SO_2CH_3), 3.91 (s, 2H, NCH_2Ar), 6.60 (s, 1H, Ar), 6.74 (d, J = 3.7 Hz, 1H, Ar), 7.47 (d, J = 3.7 Hz, 1H, Ar), 7.68 (s, 1H, Ar), 8.65 (s, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.7 (2C), 40.2, 41.4, 45.6 (2C), 51.6, 98.8, 108.5, 110.4, 112.0, 126.0, 126.8, 127.7, 133.1, 135.8, 139.7. Anal. Calcd for $C_{17}H_{23}N_3O_4S_2$: C, 51.36; H, 5.83; N, 10.57. Found: C, 51.39; H, 5.64; N, 10.65.

General Procedure for Synthesis of 2,6-Bis(aminomethyl)dipyrrolopyridines 24a−d. Synthesis of 2,6-Bis[(*N*,*N*-diethylamino)-methyl]-1,7-bis(methylsulfonyl)dipyrrolo[3,2-*b*:2′,3′-*e*]pyridine (24a) (Table 4, Entry 2). Diethylamine **3a** (23 μL, 0.22 mmol) was added to a mixture of paraformaldehyde **2** (12 mg, 0.40 mmol) and CuI (0.6 mg, 0.003 mmol) in toluene/1,4-dioxane (1:1, 1.0 mL) under Ar. The mixture was stirred at 80 °C for 5 min and then cooled to room temperature. To the mixture were added MeOH (4 μL, 0.10 mmol) and **23** (31 mg, 0.10 mmol) at room temperature, and the mixture was stirred at 80 °C for 30 min. The solvent was removed under reduced pressure, and the residue was chromatographed on alumina (hexane/EtOAc = 4/1) to afford **24a** (39 mg, 81%) as a white solid: mp 158−159 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (t, J = 7.0 Hz, 12H, 4 × CH_2CH_3), 2.65 (q, J = 7.0 Hz, 8H, 4 × CH_2CH_3), 3.57 (s, 6H, 2 × SO_2CH_3), 3.97 (s, 4H, 2 × NCH_2Ar), 6.73 (s, 2H, Ar), 9.03 (s, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.7 (4C), 41.9 (2C), 45.6 (4C), 51.5 (2C), 107.4, 111.2 (2C), 128.7 (2C), 143.2 (2C), 144.7 (2C). Anal. Calcd for $C_{21}H_{33}N_5O_4S_2$: C, 52.15; H, 6.88; N, 14.48. Found: C, 52.05; H, 6.73; N, 14.18.

General Procedure for Synthesis of 2-(Aminomethyl)dipyrrolopyridines 28a−d. Synthesis of 2-[(*N*,*N*-Diethylamino)methyl]-1,7-bis(methylsulfonyl)dipyrrolo[3,2-*b*:2′,3′-*e*]pyridine (28a) (Table 5, Entry 8). The mixture of **23** (31 mg, 0.10 mmol) and CuI (0.6 mg, 0.003 mmol) in 1,4-dioxane (0.5 mL) was stirred under Ar at 80 °C for 1−2 h (completion of formation of **26** was monitored by TLC) and then cooled to room temperature. To the mixture were added MeOH (4 μL, 0.10 mmol) and a preheated solution at 80 °C for 5 min of paraformaldehyde **2** (12 mg, 0.40 mmol) and diethylamine **3a** (21 μL, 0.20 mmol) in toluene (0.5 mL), and then the mixture was stirred at 80 °C for 15 min. The solvent was removed under reduced pressure, and the residue was chromatographed on alumina (hexane/EtOAc = 2/3) to afford **28a** (26 mg, 65%) as a white solid: mp 165−166 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (t, J = 7.0 Hz, 6H, 2 × CH_2CH_3), 2.66 (q, J = 7.0 Hz, 4H, 2 × CH_2CH_3), 3.17 (s, 3H, SO_2CH_3), 3.60 (s, 3H, SO_2CH_3), 3.99 (s, 2H, NCH_2Ar), 6.77 (s, 1H, Ar), 6.93 (d, J = 4.0 Hz, 1H, Ar), 7.73 (d, J = 4.0 Hz, 1H, Ar), 8.87 (s, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.6 (2C), 41.0, 42.0, 45.6 (2C), 51.4, 106.4, 109.4, 111.2, 126.1, 128.7, 130.0, 143.7, 145.2, 146.6. Anal. Calcd for $C_{16}H_{22}N_4O_4S_2$: C, 48.22; H, 5.56; N, 14.06. Found: C, 47.97; H, 5.41; N, 13.85.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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