Multicomponent Reactions

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Direct Synthesis of 2-(Aminomethyl)indoles through Copper(I)-Catalyzed Domino Three-Component Coupling and Cyclization Reactions**

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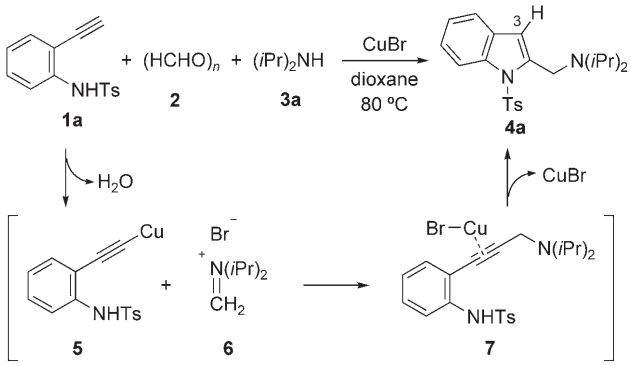
The indole nucleus is a prominent structural motif found in numerous natural products and synthetic compounds with important biological activities, and thus considerable attention has been directed toward general, flexible, and selective methods for the synthesis of highly functionalized indole derivatives.[1] Among the functionalized indoles, the 2-(aminomethyl)indole motif is a key structure that exists in several biologically active compounds,[2] including calindol.[3] Most of the synthetic routes to 2-(aminomethyl)indoles rely upon functionalized indoles such as indole-2-carboxylic acid or its derivatives as the starting materials,[2–4] which limit the structure of the target molecules that can be readily synthesized.

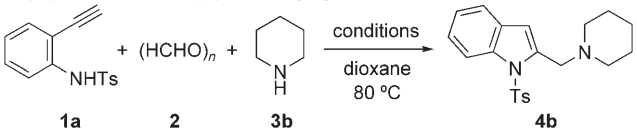
One current important area of modern synthetic chemistry is the development of efficient practical methods that minimize the requisite reagents, solvents, cost, time, and separation processes for the desired transformation and also minimize the formation of waste.[5] While the multicomponent reaction (MCR) approach is recognized as a powerful method toward this end, a catalytic domino reaction including a MCR would be more attractive to achieve this goal. During the course of our efforts directed toward the development of useful transformations of allenic compounds,[6,7] we found that treatment of N-protected ethynylaniline **1a** with paraformaldehyde (**2**) and diisopropylamine (**3a**) in the presence of copper(I) bromide (Crabbé conditions)[8] gave 2-(aminomethyl)indole derivative **4a** in 92% yield (Scheme 1) without formation of the expected [2-(*N*-tosylamino)phenyl]allene. This reaction would proceed presumably through a Mannich-type MCR followed by formation of the indole ring from the plausible intermediate **7**. This is the first example of the formation of an indole ring system by a three-component reaction without producing any salts as by-products, although the synthesis of indole derivatives by catalytic domino three-component reactions including Sonogashira-type cross-coupling of dihalobenzenes[9] and haloanilines[10] were recently reported.[11] Herein we present a copper(I)-catalyzed domino three-component coupling–cyclization reaction of ethynylaniline derivatives with high atom economy to produce 2-(aminomethyl)indoles, with water as the waste product. Construction of polycyclic indole derivatives through this domino reaction and palladium-catalyzed C–H functionalization is also presented.



Scheme 1. Domino three-component coupling-indole formation. Ts = toluene-4-sulfonyl.

By modifying the original reaction conditions shown in Scheme 1 (CuBr, 1.0 equiv; (HCHO)$_n$, 2 equiv; and diisopropylamine, 3 equiv), we investigated the three-component formation of an indole ring under various reaction conditions (Table 1). To reduce the requisite amount of the amine

Table 1: Optimization of reaction conditions for the reaction with ethynylaniline **1a** and piperidine (**3b**).[a]



Entry	CuBr [mol%]	(HCHO)$_n$ [equiv]	Additive [equiv]	*t* [h]	Yield [%][b]
1	100	2.0	Et_3N [2.0]	0.25	71
2	10	2.0	Et_3N [2.0]	0.25	84
3	1	2.0	Et_3N [2.0]	0.25	92[c]
4	1	2.0	none	0.25	87
5	1	1.5	none	1	75
6	1	1.1	none	12	70

[a] Unless otherwise stated, reactions were carried out with **1** (0.18 mmol), (HCHO)$_n$ **2** (equivalents are shown in the Table), and piperidine (**3b**, 1.1 equiv) in 1,4-dioxane at 80 °C. [b] Yields of isolated products. [c] The reaction was conducted on a 1.25-mmol scale.

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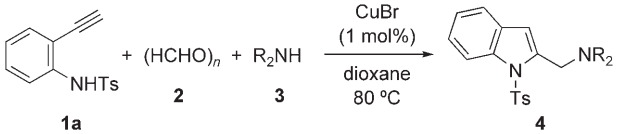
component **3**, the reaction was first examined in the presence of Et_3N (2 equiv) using 1.1 equivalents of piperidine **3b**, which gave the expected indole **4b** in 71% yield (Table 1, entry 1). A catalytic reaction using 10 or 1 mol% of CuBr is also possible, and gives rise to **4b** in better yields (84–92%, Table 1, entries 2 and 3). In contrast, the reaction in the absence of any copper salt led to recovery of the starting material. The addition of Et_3N is not essential (entry 4), although the yield of **4b** was slightly decreased (87%). This result can be rationalized by the plausible mechanism depicted in Scheme 1, in which the sulfonamide proton is efficiently transferred to the 3-position of the indole nucleus. A decreased loading of $(HCHO)_n$ (1.5 or 1.1 equivalents) is also tolerated in this transformation, and leads to **4b** in yields of 75 and 70%, respectively (Table 1, entries 5 and 6); however, a longer reaction time (1–12 h) was required.

Next, the reaction of **1a** with various amines **3a–e** under the optimized conditions (Table 1, entry 4) was investigated. The results are summarized in Table 2. The reaction with the bulky diisopropylamine (**3a**, 1.1 equiv) and a catalytic amount of CuBr (1 mol%) resulted in **4a** in 81% yield. As well as piperidine (**3b**; Table 2, entry 2), pyrrolidine (**3c**) was also a good amine component in this reaction (89%, Table 2, entry 3). When a volatile amine such as diethylamine (**3d**) was used, the reaction proceeded well (89%) if it was used in increased amount (2 equiv, Table 2, entry 4). Secondary amines with removable benzyl groups **3e** also afforded the desired 2-[(*N*,*N*-dibenzylamino)methyl]indole **4e** in good yield (78%; Table 2, entry 5).

Table 2: Reaction with various amines.[a]



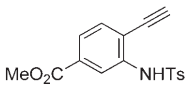
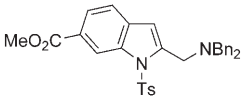
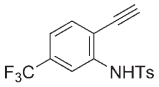
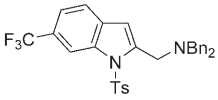
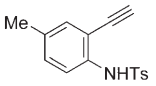
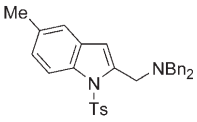
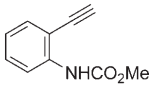
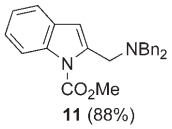
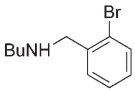
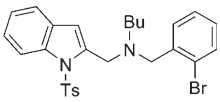
1a 4

Entry	Amine **3**	*t* [h]	Product	R	Yield [%][b]
1	iPr_2NH (**3a**)	0.25	**4a**	*i*Pr	81
2	piperidine (**3b**)	0.25	**4b**	$R_2=(CH_2)_5$	87
3	pyrrolidine (**3c**)	0.25	**4c**	$R_2=(CH_2)_4$	89
4	Et_2NH (**3d**)[c]	0.25	**4d**	Et	89
5	Bn_2NH (**3e**)	2	**4e**	Bn	78

[a] Unless otherwise stated, reactions were carried out with **1a** (0.18 mmol), $(HCHO)_n$ **2** (2.0 equiv), amine **3** (1.1 equiv), and CuBr (1 mol%) in 1,4-dioxane at 80°C. [b] Yields of isolated products. [c] 2 equivalents of amine **3d** were used because of its volatility.

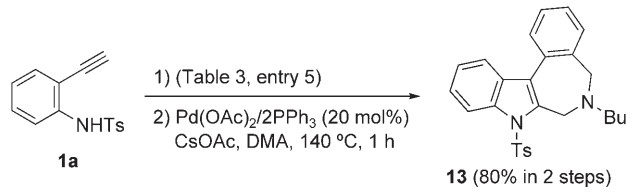
The reaction of various substituted components was then investigated. Anilines **1b** and **1c** bearing an electron-withdrawing methoxycarbonyl or trifluoromethyl group at the 3-position were allowed to react with dibenzylamine in the presence of a copper catalyst (1 mol%) to afford indoles **8** (79% yield) and **9** (61% yield), respectively (Table 3, entries 1 and 2). The reaction of **1d**, which has an electron-donating methyl group, also showed sufficient reactivity and gave indole **10** in 78% yield (Table 3, entry 3). This three-component cyclization is also applicable to the synthesis of 2-(aminomethyl)indoles having nitrogen-protecting groups other than the tosyl group: for example, *N*-(methoxycarbonyl)indole derivative **11** was prepared in 88% yield starting from ethynylaniline **1e** (Table 3, entry 4). The reaction is also possible with unsymmetrical secondary amines with functional groups: amine **3f** yielded indole **12** with a bromine atom on the benzene ring in 80% yield (Table 3, entry 5) without causing any undesired side reactions.

Table 3: Reaction of variously substituted components.[a]

Entry	Ethynylaniline	Amine	conditions	Product (yield)[b]
1	 **1b**	Bn_2NH, **3e**	80°C, 5 h	 **8** (79%)
2	 **1c**	Bn_2NH, **3e**	80°C, 3 h	 **9** (61%)
3	 **1d**	Bn_2NH, **3e**	80°C, 5 h then reflux, 1 h	 **10** (78%)
4	 **1e**	 **3b**	80°C, 15 min	 **11** (88%)
5	**1a**	 **3f**	80°C, 3 h then reflux, 1 h	 **12** (80%)

[a] All reactions were carried out with **1** (0.18 mmol), $(HCHO)_n$ **2** (2.0 equiv), amine **3** (1.1 equiv), and CuBr (1 mol%) in 1,4-dioxane. [b] Yields of isolated products.

The polycyclic indole is an important core framework for biologically active compounds.[12] Therefore, the development of an efficient method for the construction of this framework is strongly required.[13] We expected that the newly developed three-component reaction for the formation of an indole ring would serve as an extremely useful synthetic route to this class of compounds. We thus investigated the construction of polycyclic indole skeletons by a sequential three-component reaction leading to the formation of an indole ring followed by a palladium-catalyzed functionalization of a C–H bond. As shown in Scheme 2, the formation of an indole ring system



Scheme 2. Construction of a polycyclic indole structure by a three-component reaction and palladium-catalyzed cyclization. DMA = dimethylacetamide.

from N-protected ethynylaniline **1a** (Table 3, entry 5) and, after purification, subsequent palladium-catalyzed cyclization of the resulting 2-(aminomethyl)indole **12** gave the desired dihydrobenzoazepine-fused indole **13** in 80% yield over the two steps.

In conclusion, we have developed a novel domino three-component coupling reaction for the synthesis of 2-(aminomethyl)indoles and polycyclic indole derivatives. This study has resulted in the first catalytic multicomponent construction of an indole ring that produces water as the only theoretical by-product. This domino reaction, in which two carbon–nitrogen bonds and one carbon–carbon bond are formed, is synthetically useful since functionalized 2-(aminomethyl)indoles and their polycyclic derivatives can be obtained directly from readily available N-protected ethynylanilines.

Experimental Section

General procedure for three-component formation of an indole: Piperidine (**3b**; 20.0 μL, 0.20 mmol) was added at room temperature under Ar to a stirred suspension of N-tosylated ethynylaniline **1a** (50 mg, 0.18 mmol), paraformaldehyde (**2**; 11.1 mg, 0.37 mmol), and CuBr (0.26 mg, 0.0018 mmol) in dioxane. After stirring the mixture for 15 min at 80 °C, it was concentrated under reduced pressure and purified by column chromatography over silica gel with hexane/EtOAc (5:1) as the eluent to afford the desired product **4b** (59.2 mg, 87%) as a colorless oil: IR: $\tilde{\nu}$ = 1367 (NSO_2), 1173 cm^{-1} (NSO_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.42–1.49 (m, 2H, CH_2), 1.50–1.58 (m, 4H, 2 × CH_2), 2.33 (s, 3H, Ph*Me*), 2.44-2.54 (m, 4H, 2 × NCH_2), 3.84 (s, 2H, 1′-CH_2), 6.54 (s, 1H, 3-H), 7.18 (d, J = 8.4 Hz, 2H, Ar), 7.25 (ddd, J = 7.4, 7.4, 1.1 Hz, 1H, Ar), 7.17–7.20 (m, 1H, Ar), 7.44 (d, J = 7.4 Hz, 1H, Ar), 8.03 (d, J = 8.4 Hz, 2H, Ar), 8.07 ppm (d, J = 8.3 Hz, 1H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 24.3, 25.9 (2C), 54.6, 56.1 (2C), 111.2, 114.5, 120.4, 123.2, 124.0, 127.2 (2C), 129.0, 129.4 (2C), 136.5, 137.0, 138.4, 144.4 ppm; MS (FAB) m/z (%): 369 (100); HRMS (FAB) calcd for $C_{21}H_{25}N_2O_2S$ [M+H$^+$]: 369.1637; found: 369.1632.

Synthesis of polycyclic indole **13** by palladium-catalyzed functionalization of the C–H bond: $Pd(OAc)_2$ (4.3 mg, 0.019 mmol), PPh_3 (10 mg, 0.038 mmol), and CsOAc (36 mg, 0.19 mmol) were added to a stirred solution of **12** (50 mg, 0.095 mmol) at room temperature under Ar. After stirring the mixture for 1 h at 140 °C, it was concentrated under reduced pressure and purified by column chromatography over silica gel with hexane/AcOEt (4:1) as the eluent to afford the desired product **13** (42 mg, quant.) as a colorless oil: IR: $\tilde{\nu}$ = 1374 (NSO_2), 1174 cm^{-1} (NSO_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, J = 7.2 Hz, 3H, CH_3), 1.39–1.49 (m, 2H, CH_3CH_2), 1.61–1.68 (m, 2H, $CH_2CH_2CH_2$), 2.30 (s, 3H, Ph*Me*), 2.67 (t, J = 7.2 Hz, 2H, NCH_2CH_2), 3.42 (s, 2H, NCH_2), 4.05 (s, 2H, NCH_2), 7.16 (d, J = 8.8 Hz, 2H, Ar), 7.23–7.45 (m, 5H, Ar), 7.67 (d, J = 6.1 Hz, 1H, Ar), 7.73 (d, J = 7.6 Hz, 1H, Ar), 7.83 (d, J = 8.4 Hz, 2H, Ar), 8.57 ppm (d, J = 8.4 Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 20.6, 21.5, 30.1, 47.9, 55.8, 56.2, 115.6, 119.3, 123.8, 124.0, 124.8, 126.7 (2C), 127.2, 127.4, 127.5, 128.0, 129.7 (2C), 130.6, 134.4, 135.4 (2C), 137.0, 137.0, 144.7 ppm; MS (FAB) m/z (%): 445 (100); HRMS (FAB) calcd for $C_{27}H_{29}N_2O_2S$ [MH$^+$]: 445.1950; found: 445.1952.

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