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Facile Synthesis of 1,2,3,4-Tetrahydro-β-carbolines by One-Pot Domino Three-Component Indole Formation and Nucleophilic Cyclization

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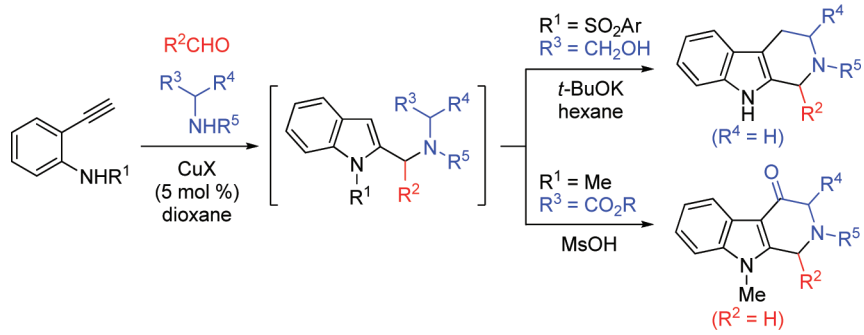
ABSTRACT



Two direct synthetic methods of 1,2,3,4-tetrahydro-β-carboline derivatives have been developed. After initial indole formation by copper-catalyzed domino three-component coupling−cyclization using an appropriate ethynylaniline, aldehyde, and a secondary amine, treatment with *t*-BuOK/hexane or MsOH afforded the desired tetrahydro-β-carboline derivatives in moderate to good yields.

Intense interest in modern organic chemistry has been directed toward the development of simple methods which produce structurally complex compounds in high yields under mild and environmentally friendly conditions. In particular, cascade[1] or one-pot reactions which include a multicomponent reaction[2] using simple starting materials provide an efficient and powerful tool for atom-economical synthesis.

A 1,2,3,4-tetrahydro-β-carboline, which consists of a tricyclic indole, is an attractive drug template due to its potential antioxidative activity.[3] Carboline derivatives are also useful as intermediates for natural product synthesis.[4,5] Because construction of tetrahydro-β-carbolines is mostly dependent on the Pictet−Spengler[4] and related reactions,[5] development of alternative synthetic methodolo-

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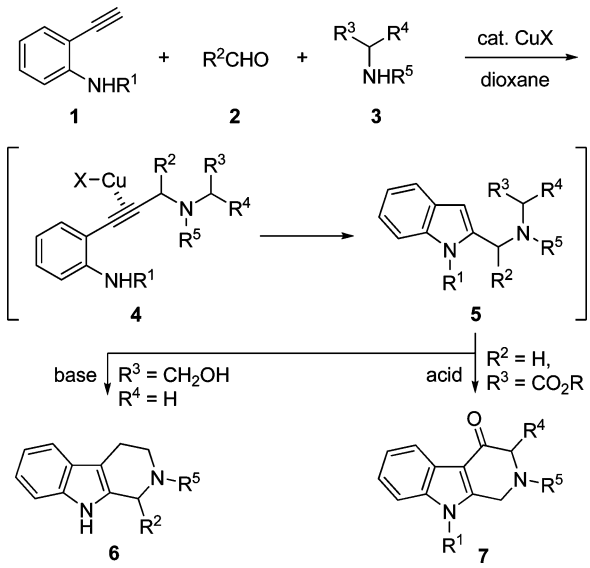
gies is extremely important to ensure diversity-oriented synthesis.[6]

We recently reported the copper-catalyzed synthesis of 2-(aminomethyl)indoles via a domino three-component coupling−cyclization reaction of a 2-ethynylaniline, paraformaldehyde, and a secondary amine.[7,8] Bosch and co-workers previously reported that treatment of a 2-[*N*-(benzenesulfonyl)indol-2-yl]piperidin-4-one derivative having an *N*-hydroxylethyl group with *t*-BuOK brought about the formation of the corresponding indolo[2,3-*a*]quinolizine, although this was an isolated example.[9] On the other hand, it is well established that cyclization at the 3-position of *N*-alkylindoles containing an ester group is efficiently promoted by a strong acid to afford 4-oxotetrahydro-β-carbolines.[10] Based on this chemistry, we expected that 2-(aminomethyl)indole **5**, generated by copper-catalyzed indole formation using ethynylanilines **1**, aldehydes **2**, and secondary amines **3** bearing an appropriate functionality ($R^3 = CH_2OH$ or CO_2R), could be converted into β-carboline derivatives **6** or **7** by a second cyclization at the C-3 position (Scheme 1). This sequential

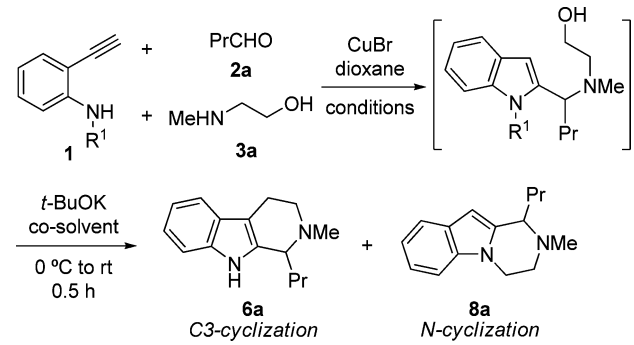
Scheme 1. Two Direct Routes to 1,2,3,4-Tetrahydro-β-carboline Derivatives



reaction is challenging in that various reactive components exist in the reaction mixture, including unprotected amine(s), an aldehyde, and an ester/alcohol, especially when *N*-alkylanilines are employed. Herein we report two direct routes to 1,2,3,4-tetrahydro-β-carboline derivatives by a copper-catalyzed three-component coupling−indole formation−nucleophilic cyclization at the 3-position. To the best of our knowledge, there is no precedent for multicomponent synthesis of tetrahydro-β-carbolines, except for those using the Pictet−Spengler-type reaction.[2a,11]

The initial attempt was carried out with *N*-tosyl-2-ethynylaniline **1a**, butanal **2a** (2 equiv), and 2-(*N*-methylamino)ethanol **3a** (1.1 equiv) in the presence of 5 mol % of CuBr (Table 1). After the three-component indole formation

Table 1. One-Pot, Three-Component Synthesis of Tetrahydro-β-carbolines Using *t*-BuOK[a]



entry	R^1	conditions	cosolvent	yield[b] (%) **6a**	**8a**
1	Ts (**1a**)	80 °C, 1 h		31	69
2	Ts (**1a**)	80 °C, 1 h	Et_2O	23	20
3	Ts (**1a**)	80 °C, 1 h	hexane	53	33
4	Ms (**1b**)	80 °C, 2 h	hexane	29	35
5	Mts (**1c**)	80 °C, 2 h	hexane	19	43
6	SO_2Ph (**1d**)	80 °C, 1.5 h	hexane	63	25
7	$SO_2C_6H_4$(4-Br) (**1e**)	80 °C, 0.5 h	hexane	58	14
8	$SO_2C_6H_4$(4-Cl) (**1f**)	80 °C, 0.5 h	hexane	65	18
9	$SO_2C_6H_4$(4-F) (**1g**)	80 °C, 0.5 h	hexane	48	20
10	$SO_2C_6H_4$(4-NO_2) (**1h**)	80 °C, 0.5 h	hexane	23	10
11	$SO_2C_6H_4$(4-Cl) (**1f**)	50 °C, 1.5 h	hexane	75	25

[a] Ethynylaniline **1** (0.18 mmol), *n*-PrCHO **2a** (2 equiv), and 2-(*N*-methylamino)ethanol **3a** (1.1 equiv) in dioxane (2 mL) were treated with CuBr (5 mol %) under the conditions shown. After the indole formation was complete (monitored by TLC), cosolvent (2 mL) and *t*-BuOK (3 equiv) were added at 0 °C and the reaction mixture was stirred at 0 °C for 5 min and rt for an additional 30 min. [b] Isolated yields.

in dioxane was complete as monitored by TLC (1 h at 80 °C), *t*-BuOK (3 equiv) was added to the reaction mixture. Although the desired bis-cyclization product 1,2,3,4-tetrahydro-β-carboline derivative **6a** was obtained in 31% yield, the *N*-cyclization product **8a** was formed as the major product (69% yield, entry 1).[12] To improve the selectivity of the second cyclization, we optimized the reaction conditions for deprotection−cyclization as well as the nitrogen protecting group.[13] Addition of Et_2O as the cosolvent slightly improved

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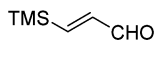
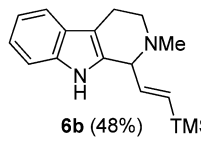
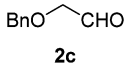
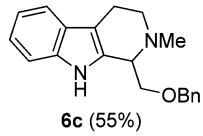
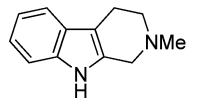
the selectivity but decreased the combined yield to 43% (entry 2). In contrast, use of hexane led to the formation of **6a** as the major product (53% yield, entry 3). These results are in good agreement with Bosch's observation, in which carrying out the reaction in a less polar solvent improved the selectivity of the C-3 cyclization over the *N*-cyclization.[9] The *N*-protecting groups of 2-ethynylaniline, mesyl, and mesitylenesulfonyl (Mts) groups were less effective for selective formation of **6a** (entries 4 and 5). The reaction of **1d** bearing an *N*-benzenesulfonyl group gave a better result (entry 6) than that of the *N*-tosyl derivative **1a** (entry 2). This result promoted us to utilize more electron-deficient benzenesulfonamides **1e**−**h** bearing an electron-withdrawing atom on the benzene ring (entries 7−10). The results indicated that the 4-chlorophenylsulfonyl group was the best protecting group of the aniline nitrogen of **1** (entry 8). In this case, the 2,3-unsubstituted *N*-arylsulfonylindole, formed by intramolecular hydroamination of **1** without resulting in a Mannich-type reaction, was observed as a byproduct. We also tested the reaction at a lower temperature (50 °C) for the three-component indole formation and obtained **6a** in 75% yield (entry 11).[14]

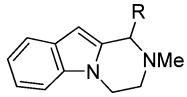
Under the optimized conditions (Table 1, entry 11), the scope of this one-pot tetrahydro-β-carboline synthesis was explored using ethynylaniline derivative **1f** and several aldehydes (Table 2). Reaction with aldehyde **2b** or **2c** containing a (trimethylsilyl)vinyl or benzyloxymethyl group afforded **6b** and **6c** in moderate yields (entries 1 and 2, 48% and 55%, respectively), accompanied by the byproduct **8b** and **8c**, respectively. In these reactions, a prolonged reaction time and elevated temperature were necessary for completion of the initial indole formation, presumably because of the steric bulkiness of the functional groups. The reaction with paraformaldehyde **2d** gave **6d** in 45% yield (entry 3).[15]

We next investigated the acid-induced direct construction of a 4-oxotetrahydro-β-carboline scaffold using amino esters **3b**−**j** (Table 3). In this reaction, use of anilines without an electron-

Table 2. Synthesis of Tetrahydro-β-carbolines Using Several Aldehydes[a]

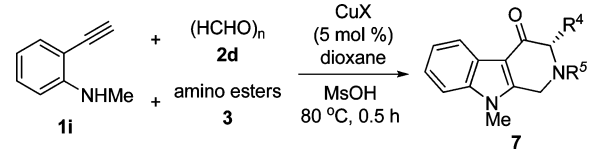
entry	aldehyde	conditions[b]	product (yield)[c,d]
1	 **2b**	50 °C, 2 h then 100 °C, 0.5 h	 **6b** (48%) **8b** (8%)
2	 **2c**	50 °C, 2 h then 100 °C, 0.5 h	 **6c** (55%) **8c** (16%)
3	$(HCHO)_n$ **2d**	50 °C, 0.5 h	 **6d** (45%) **8d** (0%)[e]

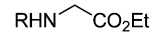
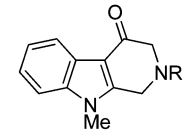
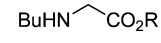
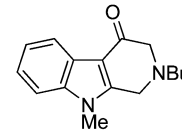
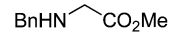
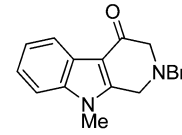
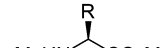
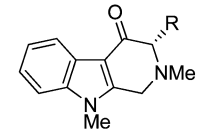
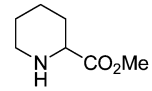
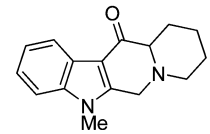
[a] Ethynylaniline **1f** (0.18 mmol), aldehyde **2** (2 equiv), and 2-(*N*-methylamino)ethanol **3a** in dioxane were treated with CuBr (5 mol %) under the conditions shown. Hexane (2 mL) and *t*-BuOK were then added at 0 °C, and the reaction mixture was stirred at 0 °C for 5 min and rt for an additional 30 min. [b] Conditions for the initial indole formation. [c] Isolated yields. [d] Structures of **8b**−**d** are shown below. [e] Not isolated.



8b: R = (*E*)-CH=CHTMS
8c: R = CH_2OBn
8d: R = H

Table 3. Preparation of 4-Oxotetrahydro-β-carboline by Domino Three-Component Coupling−Indole Formation and Successive MsOH-Induced Cyclization[a]



entry	amino esters	conditions[b]	product (yield)[c]
		A	
1	**3b**: R = Me		**7a** (72%)
2	**3c**: R = allyl		**7b** (77%)
			
3	**3d**: R = Et	A	**7c** (70%)
4	**3e**: R = Me	A	**7c** (68%)
			
5	**3f**	A	**7d** (32%)
6	**3f**	B	**7d** (57%)
			
7	**3g**: R = Me	C	**7e**: R = Me (63%)
8	**3h**: R = *i*-Bu	C	**7f**: R = *i*-Bu (37%)
9	**3i**: R = Bn	C	**7g**: R = Bn (46%)
10	 **3j**	C	 **7h** (29%)

[a] The mixture of ethynylaniline **1g** (0.19 mmol), paraformaldehyde **2d** (2 equiv), and amino ester **3** (1.2 equiv) in dioxane was stirred with CuX (5 mol %) under microwave irradiation (300 W). After indole formation was complete on TLC, the reaction mixture was treated with MsOH at 80 °C for 30 min. [b] Conditions A: CuI, 170 °C, 1 h. Conditions B: CuBr, 120 °C, 15 min, then 140 °C, 15 min. Conditions C: CuBr, 120 °C, 15 min. [c] Isolated yields.

withdrawing group on the nitrogen atom is essential to secure the nucleophilicity of the intermediate indoles of type **5** (Scheme 1). A mixture of *N*-methyl-2-ethynylaniline **1i**, paraformaldehyde **2d**, and *N*-methylglycine ethyl ester **3b** was treated with 5 mol % of CuBr in dioxane at 170 °C under microwave irradiation (conditions A) followed by the reaction with MsOH[16] to give the desired 4-oxo-1,2,3,4-tetrahydro-β-carboline **7a** in 72% yield (entry 1). The *N*-allyl- or *N*-butylglycine derivatives **3c** and **3d** showed clean conversion to **7b** and **7c**, respectively (entries 2 and 3). Methyl ester **3e** was also a good component for this one-pot reaction (entry 4). Whereas **3f** having an *N*-benzyl group resulted in sluggish conversion in the indole formation step using conditions A (entry 5), use of CuBr, a more reactive catalyst for the initial three-component indole formation than CuI, led to 57% of **7d** after treatment with MsOH (conditions B, entry 6). This one-pot construction of β-carboline derivatives also tolerated such chiral amino acid derivatives as **3g**−**i** (entries 7−9).[17] The tetracyclic compound **7h** can be easily obtained from racemic pipecolinate **3j**, although in relatively low yield (29%, entry 10).[18]

In conclusion, we have developed two direct synthetic routes to 1,2,3,4-tetrahydro-β-carboline derivatives by copper-catalyzed three-component indole formation followed by successive cyclization at the 3-position of indole. When an aminoethanol was used as the amine component, the 4-chlorophenylsulfonyl group is the protecting/activating group of choice for the second cyclization induced by *t*-BuOK. On the other hand, *N*-methyl-2-ethynylaniline and α-amino esters were good components for MsOH-induced cyclization at C-3 to produce various 4-oxo-1,2,3,4-tetrahydro-β-carbolines, including optically active ones. These two methodologies using three-component coupling of readily available substrates should contribute to diversity-oriented synthesis of tetrahydro-β-carbolines as a druglike scaffold.

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Supporting Information Available: General experimental procedure and ^{1}H and ^{13}C NMR spectra for all of the synthesized tetrahydro-β-carbolines (**6a**−**d** and **7a**−**h**) as well as *N*-cyclization products (**8a**−**c**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Recently, we reported a selective *N*-cyclization with an aryl bromide moiety; see ref 8b.

(13) Bosch proposed that the arylsulfonyl group on the indole nitrogen would be transferred to the primary hydroxy group by the action of in situ generated *t*-BuOTs, and nucleophilic attack of the C-3 position of the resulting NH-indole furnishes the corresponding cyclization product; see ref 9.

(14) When NaH was used instead of *t*-BuOK, the desired product **6a** was not obtained. This suggests that the C-3 cyclization proceeds through rearrangement of the arylsulfonyl group from the nitrogen atom of the indole to the hydroxyl group, as proposed by Bosch et al.

(15) The high polarity of **6d** considerably lowered the chemical yield during purification with column chromatography over silica gel. Use of alumina column partly improved the yield of **6d** (45%).

(16) Other acids were less effective. For example, after indole formation with **1g**, **2d**, and **3d** was completed, the reaction mixture was treated with polyphosphoric acid (PPA) to give **7c** in only 19% yield.

(17) The product **7e** was obtained in 95% ee [Chiralcel OD-H, with a linear gradient of *i*-PrOH (20−40% over 45 min) in hexane in the presence of 0.1% Et_2NH]. HPLC charts (**7e** and an enantiomeric mixture **7e**/*ent*-**7e**) were given in the Suppoting Information.

(18) It should be noted that the indole formation of Mannich adducts derived from **1g** did not proceed when using aldehydes other than paraformaldehyde and amino esters.