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Iodine-mediated regioselective C2-amination of indoles and a concise total synthesis of (±)-folicanthine†

Ying-Xiu Li, Hai-Xi Wang, Shaukat Ali, Xiao-Feng Xia and Yong-Min Liang*

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Highly substituted 2-aminated indoles can be prepared in moderate to excellent yields by regioselective C2-amination of indoles promoted by iodine. As a key step in a concise synthesis of (±)-folicanthine, its core structure was easily obtained by one step cyclization–dimerization of substituted tryptophan in high yield on a gram scale.

Indole is a privileged structural motif found in many clinically used therapeutic drugs[1] and natural products.[2,3] Hence, there is a continuing interest in reactions that allow for direct indole functionalization. Among them, the direct formation of C–C bonds of indole derivatives has been extensively studied.[4] However, the direct formation of C–N bonds of indoles has not been well studied up to now. Recently, our group developed a Pd/Cu-catalyzed method[5] for direct formation of C–N bonds at the C2-position of indoles.

Over the past decades, many reactions have been reported using iodine as a promoter or a catalyst.[6] We have previously reported the C–N bonds formation of *N*-protected indole derivatives to prepare 2,3′-biindoles and 4-(1*H*-indol-2-yl)-morpholines.[7] However, due to the structural restriction of morpholines, 4-(1*H*-indol-2-yl)morpholines are difficult to convert into more useful derivatives of indoles. To further extend the scope and applicability of our reaction, we wished to develop a more useful amination reaction at the C2-position of indoles. Herein, we report a successful example of iodine-induced regioselective C–N bonds formation of *N*-protected indole derivatives with *N*-tosylbenzenamines affording 1-methyl-*N*-phenyl-*N*-tosyl-1*H*-indol-2-amines.

Hexahydropyrroloindole alkaloids are a major class of natural products that are formally derived from tryptophan. The alluring structure of these indole alkaloids (Fig. 1)[8] combined with their biological activities has stimulated a significant interest of synthetic chemists in their total syntheses.[9] Polymeric tryptamine-based alkaloids belong to a structurally and biologically fascinating class of natural products.[10] The vast majority of these molecules are linked through C–C bonds

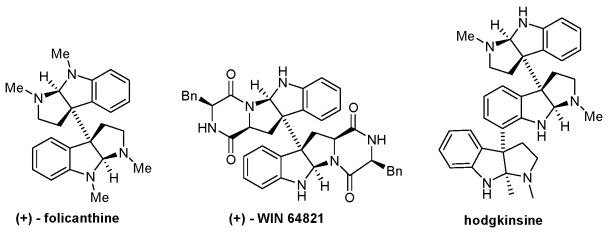

Fig. 1 Some indole natural products with diverse pharmacological properties.

to give oligomeric structures. One widely explored strategy for the synthesis of these natural products from tryptophan derivatives is to utilize the intramolecular ring closure. Previously, Movassaghi's group reported a protocol for synthesis of (+)-folicanthine from hexahydropyrroloindole. The procedure involves cyclization of the *N*-methoxycarbonyl-tryptophan methyl ester to generate the tricyclic hexahydropyrroloindole and dimerization as the key steps.[11] However, the cyclization and dimerization were done in two distinct steps and require a stoichiometric amount of metal complex to allow dimerization in good yield.

As part of our ongoing investigations on application of our reaction, we envisioned that (±)-folicanthine could be constructed starting from two molecules of 2-(1-methyl-1*H*-indol-3-yl)-*N*-tosylethaneamine **4** by applying the intramolecular version of our reaction (Scheme 2). Herein we describe a three step synthesis of (±)-folicanthine with an improved 50% overall yield.

We started our study by examining whether the indole **1a** could be converted into the corresponding indole derivative **3a**. To our delight, when K_2CO_3 was used as a base in acetonitrile, we found that 4-methyl-*N*-(1-methyl-1*H*-indol-2-yl)-*N*-(*p*-tolyl)-benzenesulfonamide **3a** could be isolated in 70% yield after 3 h (Table 1, entry 1). In order to improve the reaction efficiency, optimization studies were then performed by changing the nature of solvents (entries 8–14), bases (entries 1–7) and iodine loadings (entries 15 and 16). With a series of detailed investigations, the reaction conditions were eventually optimized as: 0.5 mmol of **1a** and 1 mmol of **2a**, 2.0 equiv. of I_2, 2.0 equiv. of Cs_2CO_3 as base in acetonitrile as solvent at room temperature (entry 3).

With the standard reaction conditions in hand, we then explored the scope of the method. These conditions were found to be compatible with a wide range of indoles and *N*-tosylbenzenamines as illustrated in Table 2. The substituents on the *N*-tosylbenzenamines had little effect on the reaction

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China. E-mail: liangym@lzu.edu.cn; Fax: 0086-931-8912582; Tel: 0086-931-8912582
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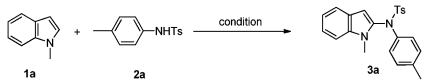
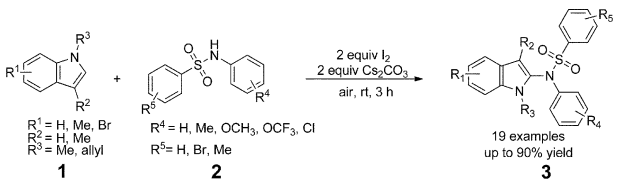
Table 1 Optimization of reaction conditions[a]

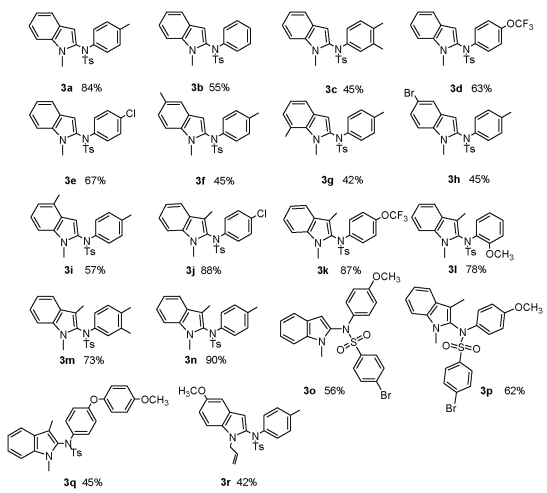


Entry	Base	Solvent	*t*/h	I_2 [equiv.]	Yield[b] [%]
1	K_2CO_3	CH_3CN	3	2	70
2	$NaHCO_3$	CH_3CN	3	2	Trace
3	**Cs_2CO_3**	**CH_3CN**	**3**	**2**	**84**
4	NaOH	CH_3CN	3	2	72
5	$(CH_3)_3COK$	CH_3CN	3	2	68
6	NaOAc	CH_3CN	3	2	20
7	$LiOH·H_2O$	CH_3CN	3	2	80
8	Cs_2CO_3	CH_2Cl_2	3	2	55
9	Cs_2CO_3	THF	3	2	50
10	Cs_2CO_3	Dioxane	3	2	46
11	Cs_2CO_3	DMF	3	2	41
12	Cs_2CO_3	Toluene	3	2	50
13	Cs_2CO_3	DCE	3	2	51
14	Cs_2CO_3	CH_3NO_2	3	2	NR
15	Cs_2CO_3	CH_3CN	8	0.1	8
16	Cs_2CO_3	CH_3CN	3	1	76

[a] Conditions: 0.5 mmol **1a**, 1.0 mmol **2a**, 1.0 mmol I_2 and 1.0 mmol of base in acetonitrile (2.0 mL) at room temperature. [b] Isolated yield.

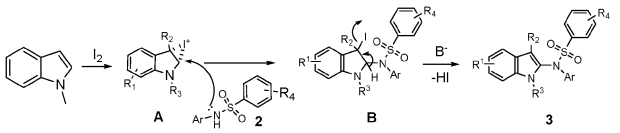
Table 2 Scope of metal-free C2-amination of indoles[a,b]





[a] Conditions: 0.5 mmol **1a**, 1.0 mmol **2a** with 1.0 mmol I_2, 1.0 mmol Cs_2CO_3 in acetonitrile 2.5 mL at room temperature. [b] Isolated yield.

(products **3b–3e**), although a slightly lower yield was obtained with disubstituted *N*-tosylbenzenamines (product **3c**). When the substituents on the benzene ring of *N*-methyl indole were changed, moderate yields of the corresponding products were afforded (products **3f–3i**). Interestingly, the yields of 1,3-dimethyl-1*H*-indole substrates (products **3j–3n**) were higher than those of 1-methyl-1*H*-indoles and 1-allyl-1*H*-indoles (products **3a–3i** and **3r**). It may be due to the fact that when hydrogen at C3 of indoles



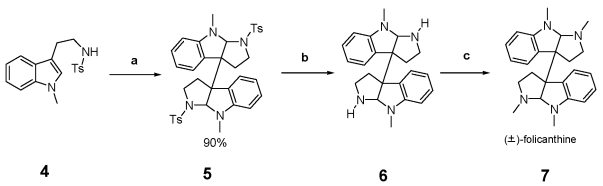
Scheme 1 Proposed mechanism for C2-amination of indoles.[7]

is replaced by a methyl group, HI is more easily eliminated (see the mechanism in Scheme 1). The yields of **3o** and **3p** were similar to the yields of 1,3-dimethyl-1*H*-indole and 1-methyl-1*H*-indole substrates. After this we examined the effect of substituents on the indolic *N*-atom. We found that methyl and allyl groups were well tolerated (Table 2, products **3a–3q** and **3r**) but with tosyl, benzyl groups and free *N–H* no reaction was observed. Furthermore, simple tosylamide or other free amides as substrates were also investigated. However, for the C2-amination reaction of indoles with simple tosylamide or other free amides, no desired product **3** was observed under the standard reaction conditions. To our disappointment, when benzofuran was subjected to the reaction conditions, no reaction was observed.

The proposed reaction mechanism[5d] is shown in Scheme 1 which involves the cyclic iodonium ion **A** formed by coordination of the indole double bond to an iodine cation. Anti attack by the tosylated amino group on **B** and subsequent elimination of a HI molecule in the presence of base give 2-aminated indole **3**.

Encouraged by the successful intermolecular 2-amination of *N*-protected indoles, the intramolecular 2-amination of *N*-protected indoles was next examined. A surprising and interesting transformation of compound **4** to skeleton **5** was observed in one step and in excellent 90% yield. When the similar reaction conditions were applied to *N*-methyl tosylated tryptophan methyl ester, the expected dimerization product was not obtained but only the cyclization product was recovered in good yield. Detosylation[12] and subsequent methylation[13] of compound **5** afforded (±)-folicanthine in 50% overall yield over three steps. To our excitement, step a of our reaction (Scheme 2) can be enlarged to a gram scale without affecting the reaction yield. In addition, in the structure of both compound **5** and natural product (±)-folicanthine was unambiguously confirmed through X-ray crystallography analysis.

In order to have more insight into the mechanism of step a in Scheme 2, TEMPO was added to the reaction mixture as a radical scavenger. It was found that the yield of **5** was decreased dramatically. When the amount of TEMPO was increased to 10 equiv., the desired product was not afforded.



Scheme 2 Total synthesis of (±)-folicanthine: (a) 10 mmol **4**, 20 mmol I_2, 20 mmol Cs_2CO_3 in 25 mL acetonitrile at room temperature, 1 h, 90% yield. (b) Sodium-naphthalenide (0.5 M), (freshly prepared sodium-naphthalenide solution was used), **5** (122 mg, 0.19 mmol) in THF (5 mL) at −78 °C, 56% yield. (c) Formalin (37%, 5.5 μL, 0.0734 mmol, 5.2 equiv.) sodium triacetoxyborohydride (15.6 mg, 0.0734 mmol, 5.2 equiv.), **6** (5.0 mg, 0.0145 mmol, 1 equiv.) in acetonitrile (700 μL) at 23 °C and placed under an argon atmosphere, 99% yield.

This shows that step a most probably involves a free radical mechanism. The experimental and theoretical study of the exact mechanism for the transformation is in progress.

In conclusion, we have developed a highly efficient, atom-economical, environmentally friendly and metal-free methodology for direct C2 amination of indoles with *N*-tosylbenzenamines at ambient temperature. The mild conditions permit a broad set of functionalities both in the indoles and in the *N*-tosylbenzenamines and a variety of compounds can be prepared in moderate to excellent yields. As a key step in a concise synthesis of (±)-folicanthine, its core structure was easily obtained by one step cyclization–dimerization of substituted tryptophan in high yield on a gram scale.

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