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Synthesis of Pyrrolo[2,3-*b*]indole via Iodine(III)-Mediated Intramolecular Annulation

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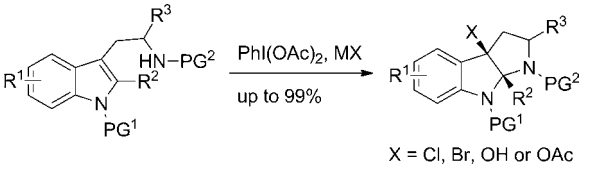
ABSTRACT



New synthetic procedures for the pyrrolo[2,3-*b*]indole skeleton have been developed via intramolecular annulation of indole derivatives under iodine(III). A series of indole derivatives with different protecting groups or substitutions were explored to facilitate the corresponding pyrrolo[2,3-*b*]indole compounds in excellent yields.

Among the nitrogen containing alkaloids, natural products with an indole heterocycle occupy a special place in organic chemistry. This is due to their interesting structures, significant bioactivities, and the historical importance they have played in the development of organic chemistry.[1] The pyrrolo[2,3-*b*]indole[2] skeleton is a key structural element in a wide selection of indole alkaloids which exhibit a diverse range of biological activities. This includes the potential inhibitor of lysine-specific histone methyltransferase (HMT) (+)-chaetocin,[3] the cholinesterase inhibitor (−)-physostigmine,[4] multidrug resistant (MDR) reversal agent (−)-ardeemin,[5] and the glycine receptor antagonist corymine (Figure 1).[6]

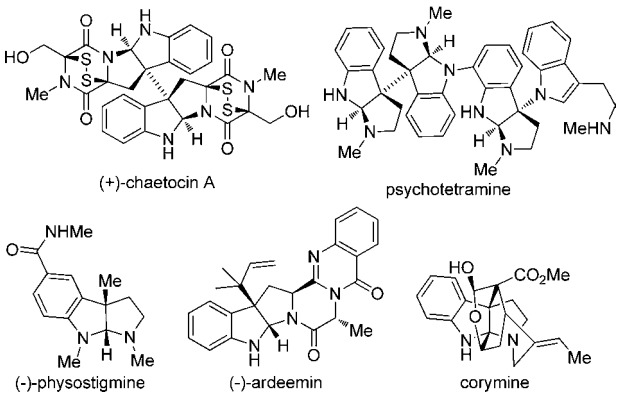


Figure 1. Representatives of the pyrrolo[2,3-*b*]indole containing natural alkaloids.

The significance of these pyrrolo[2,3-*b*]indole motifs has led to the demand for efficient synthetic methods. Numerous elegant methodologies have been developed for the

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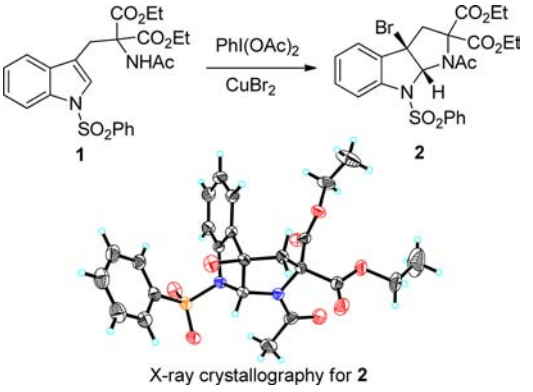
construction of this structural skeleton. A survey of the literature shows that these methods can be basically generalized into the following categories: Cyclopropanation/ring opening/iminium cyclization (CRI reaction);[7] bromination−cyclization;[8] copper-catalyzed cyclization of iodo-tryptophans;[9] selenocyclization reaction;[10] organocatalytic cascade addition−cyclization;[11] aza-Pauson−Khand cyclocarbonylation;[12] and organocatalyzed fluorocyclization.[13] During our efforts in the total syntheses of pyrrolo[2,3-*b*]indole containing natural products following known methods, we found that many side reactions occurred. These reactions resulted in lower product yields and increased difficulty of purification. The reported side reactions during the synthesis of pyrrolo[2,3-*b*]indole included aromatization, protecting group migration, oxidation, and some other reactions.[9,14] Furthermore, many of those reported methods normally required additional structural conversion to conduct the cyclization reaction. Therefore, an alternative methodology for efficiently preparing pyrrolo[2,3-*b*]indoles is required. Herein, we report the generation of the pyrrolo[2,3-*b*]indole skeleton through the reaction of the indole derivatives with phenyliodonium diacetate (PIDA) and metal halides.

We discovered that when the indole derivative **1** was treated with 1.2 equiv of PIDA and $CuBr_2$ in anhydrous dichloromethane under argon, the racemic pyrrolo[2,3-*b*]-indole compound **2** was afforded in 92% yield within 5 h (Table 1). The bromo group, which originated from $CuBr_2$, was installed on the C3 position. The presence of the bromo group on the C3 position promises that this skeleton can be further converted in this position for alkylation, amination, dimerization, and other reactions to synthesize related natural products. It was also observed that the newly generated pyrrolo ring connected with the indole motif in a cis-manner. This structural characterization was confirmed by X-ray crystallography (Table 1).

To optimize the reaction conditions, we screened the common solvents with $CuBr_2$ as the source of halide. The results indicated that both acetonitrile and THF gave almost quantitive yields, whereas dichloromethane, 1,2-dichloroethane, and methanol gave acceptable yields,

Table 1. Invention and Optimization of PIDA-Mediated Annulation of Tryptamine Derivative **1** under $CuBr_2$



entry	solvent	time (h)[a]	yield (%)[b]
1	CH_2Cl_2	5	92
2	MeCN	3	99
3	THF	5	98
4	$ClCH_2CH_2Cl$	5	89
5	MeOH	5	88
6	Et_2O	48	53
7	CCl_4	48	50
8	DMF	48	36
9	dioxane	48	21
10	toluene	48	20

[a] Uncompleted conversion of starting materials for those 48 h reactions. [b] Isolated yields.

ranging from 88% to 92% (Table 1). It was also observed that for other solvents, such as ether, tetrachloromethane, dioxane, DMF, and toluene, the yields were very low even when the reaction time was elongated to 48 h. The amount of PIDA was also explored by using 2.5, 2.0, 1.2, and 1.1 equiv, and the experimental results showed that 1.2 equiv of PIDA was enough for the complete conversion of starting material **1** to pyrrolo[2,3-*b*]indole **2**.

Besides using $CuBr_2$ as the source of halide, we found that $CuCl_2$ could also generate the corresponding pyrrolo-[2,3-*b*]indole chloride **3** in good yield (Table 2, entry 8). Different metal halides were then utilized to conduct the reaction in acetonitrile. As depicted in Table 2, both the metal bromides and chlorides could afford the related pyrrolo[2,3-*b*]indole products. It was noticed that most of the yields of bromides were higher than those of chlorides except for magnesium halides and zinc halides (Table 2, entries 5 and 13, entries 8 and 15, and entries 9 and 16). Conversely, the metal iodides did not give the iodo-product (Table 2, entry 20). It was also observed that alkali halides could not serve as halide sources (Table 2, entries 10, 11, 18, and 19). Moreover, it was noteworthy that if the metal had different valences, then the higher valence metal halides would afford products in a higher yields than the lower valence metal halides (Table 2, entries 1 and 2, entries 8 and 9, and entries 15 and 16). From the above results, we found that using acetonitrile as the solvent and cupric bromide as the halide source would be the best reaction

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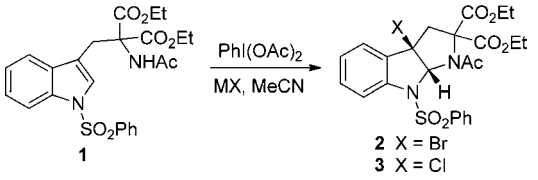
Table 2. Synthesis of Pyrrolo[2,3-*b*]indole Derivatives by Using Different Metal Halides



entry	metal halide	time (h)[a]	yield (%)[b]
1	$FeCl_3$	48	83
2	$FeCl_2$	48	68
3	$ZnCl_2$	3	83
4	$MgCl_2$	48	61
5	$MnCl_2$	48	61
6	$CaCl_2$	36	79
7	$CoCl_2$	48	73
8	$CuCl_2$	20	87
9	CuCl	48	37
10	KCl	48	0
11	NaCl	48	0
12	$MgBr_2$	5	41
13	$MnBr_2$	48	86
14	$ZnBr_2$	3	79
15	$CuBr_2$	3	99
16	CuBr	48	63
17	$NiBr_2$	48	69
18	KBr	48	0
19	NaBr	48	0
20	CuI	48	0

[a] Uncompleted conversion of starting materials for those 48 h reactions. [b] Isolated yields.

conditions, which generated the product in almost quantitive isolated yield (Table 2, entry 15).

The application scope of the reaction was further investigated with various indole derivatives under the optimized conditions. The results are summarized in Figure 2. The *N*-protecting groups on indole, such as benzylsulfonyl and acetyl, did not affect the reaction except for the Boc which slightly lowered the yield (Figure 2, compounds **6**, **9**, and **12**). Likewise, this reaction was also sustainable by changing protecting groups on the pyrrolo nitrogen from acetyl to formyl groups. However, when both of the *N*-protecting groups were bulky (such as Boc), none of the product was isolated. This might be due to the presence of two big groups near the reaction site resulting in sluggish cyclization.[9] It was also shown that the substitutions on the aryl ring did not affect the reactions. When nitro, chloro, or methoxyl carbonate groups were introduced on the aryl ring, high yield products were obtained. Tryptamine and 2-methyl-tryptamine also showed excellent results (compounds **15** and **16**). When chiral substrate L-tryptophan was subjected to reaction, exoproduct **17** was obtained in 89% yield along with a trace amount of

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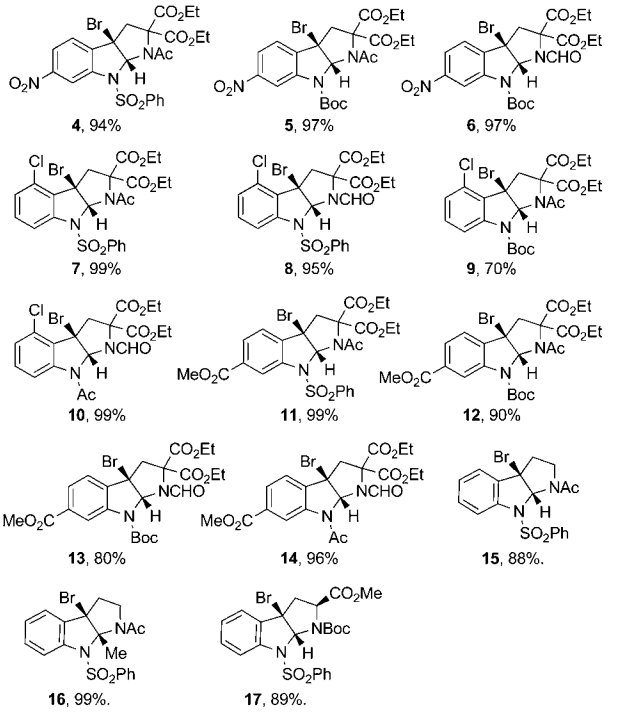
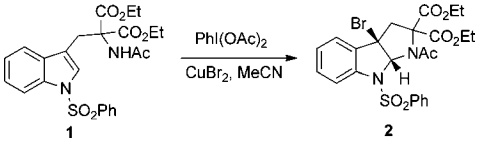


Figure 2. Exploration the scope of preparation pyrrolo[2,3-*b*] indoles via intramolecular annulation mediated by PIDA.

Table 3. Proton-Trapping Study on the Intramolecular Annulation of Indole with $CuBr_2$



entry	H-sponge	time (h)	yield (%)[a]
1	5 mol %	3	99
2	50 mol %	24	0
3	100 mol %	24	0

[a] Isolated yields.

endoproduct. The stereoselectivity was considered to arise from the kinetically favored exoproduct.[15]

To investigate the reaction mechanism, we conducted the annulation reaction by a proton-trapping study with different amounts of proton sponge (*N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine). As shown in Table 3, the annulation reaction was effectively inhibited by 0.5 equiv of proton sponge. These results indicated that the reaction underwent an ionic intermediate.[16]

On the basis of the above experimental results, a plausible mechanism is proposed in Scheme 1. PIDA is activated by a catalytic amount of acid to generate

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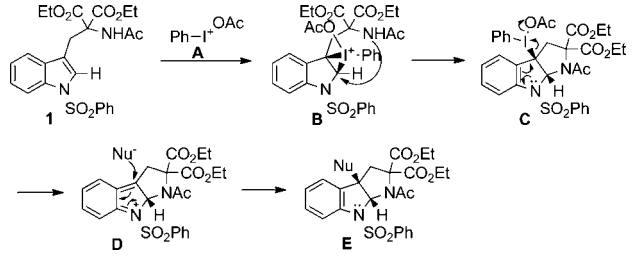
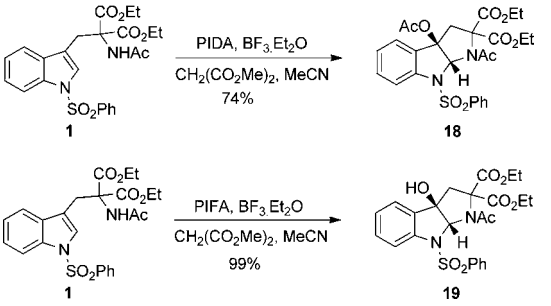
Scheme 1. Proposed Mechanism of Iodine(III) Mediate Annulation



Scheme 2. Generation of Acetate or Hydroxyl Pyrrolo[2,3-*b*]-indole Derivatives



electrophilic species **A**,[17] which was added to a 2,3-double bond of indole **1** to give intermediate **B**. An intramolecular nucleophilic displacement with amide occurred followed by elimination of one molecule of PhI and acetate to give intermediate **D**. Nucleophilic addition to the intermediate **D** afforded pyrrolo[2,3-*b*]indole product. This mechanism also explained the reason why $CuBr_2$ could react while KBr could not, since $CuBr_2$ is a Lewis acid and would generate a trace amount of acid in situ to activate the reaction.

The proposed mechanism was further confirmed when, in the absence of halides, the intermediate **D** was trapped by acetate or the trifluoroacetate anion of PIDA or phenyliodonium bis(trifluoroacetate) (PIFA). As shown in Scheme 2, acetate pyrrolo[2,3-*b*]indole derivative **18** was obtained when PIDA was used or hydroxyl pyrrolo-[2,3-b]indole derivative **19** for PIFA. The hydroxyl **19** was generated by hydrolysis of trifluoroacetate during workup.

In conclusion, we have developed an efficient method to construct pyrrolo[2,3-*b*]indoles from indole derivatives with iodine(III). Experiments indicated that many metal halides could be used as the source of halides and that $CuBr_2$ was discovered to afford the product in almost quantitive yield. On the basis of the experimental data, an iodonium mechanism was proposed for the iodine(III)-mediated annulation. In consideration of its excellent reaction efficiency, wide substrate scope, mild reaction conditions, and stereoselectivity, the present intramolecular annulation will be an attractive route to the practical synthesis of pyrrolo[2,3-*b*]indoles and other related nitrogen-containing heterocycles.

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Supporting Information Available. General experimental procedures and characterization of new compounds, including ^1H and ^{13}C NMR spectra, and X-ray structure of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.