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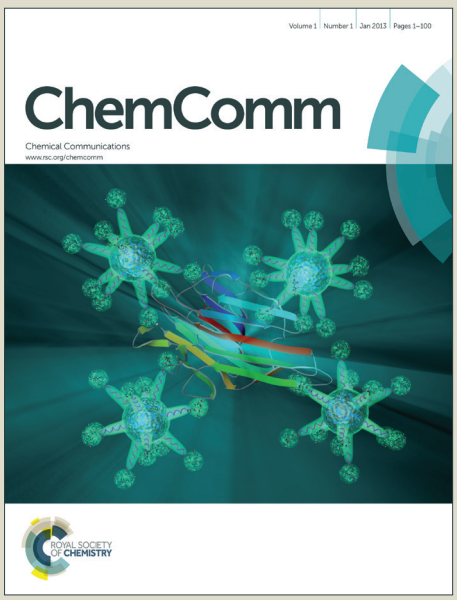




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EDGE ARTICLE

# Synthesis of Pyrroloindolines and Furoindolines via Cascade Dearomatization of Indole Derivatives with Carbenium Ion

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**A highly efficient intermolecular cascade dearomatization of substituted indoles with benzodithiolylium tetrafluoroborate has been developed. This reaction provides a novel strategy to construct C3 methyl-substituted pyrroloindolines and furoindolines under mild reaction conditions, the utility of which has been demonstrated by the synthesis of esermethol and physovenine in a highly concise manner.**

The pyrroloindolines and furoindolines are found as key structural elements in a large number of indole alkaloids[1] which exhibit attractive biological activities.[2] Within these families, many natural products bearing a C3 methyl group have been identified (Figure 1). As one of the array, analogues of (-)-physostigmine have received substantial interests because of their medicinal properties,[3] such as the treatment of myasthenia gravis, glaucoma, delayed gastric emptying and Alzheimer's disease. Therefore, much effort has been paid to developing efficient synthetic methods to construct these molecules.[4] Reported methods generally can be categorized into two groups, including the interrupted Fischer indolization reaction and initial synthesis of 3,3-disubstituted oxindoles followed by a subsequent elaboration. Despite these progresses being made, the direct synthesis of methyl-substituted pyrroloindolines and furoindolines from substituted indoles is still challenging.

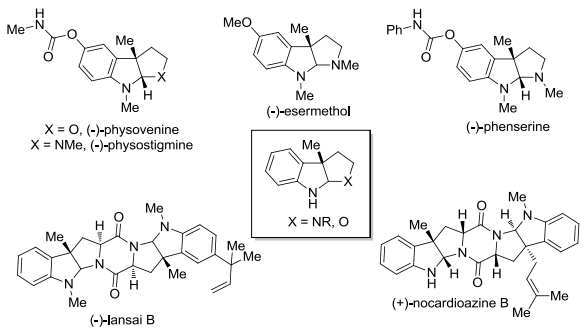
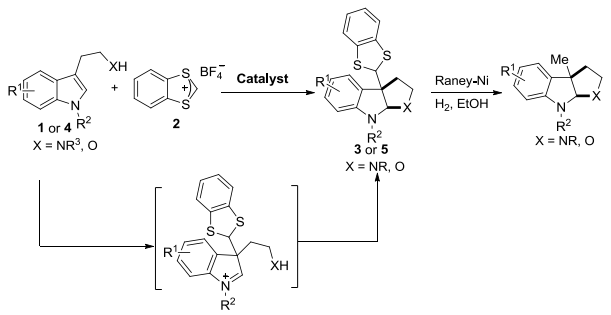



**Figure 1**. Representative indole alkaloids bearing C3 methyl group.

In recent years, cascade dearomatization reactions of indoles[5-7] have received considerable attention as they provide efficient and straightforward methods to construct [2,3]-fused indoline derivatives. As part of our ongoing research towards the development of dearomatization reactions,[8] we envisioned that the C3 methyl-substituted pyrroloindolines and furoindoines could be assembled through the reaction of tryptamines or tryptophols with electrophilic methylation reagents through a cascade electrophilic aromatic addition and iminium ion trapping (Scheme 1). To test this hypothesis, some commonly used methylation reagents (MeI, MeOTf, $Me_3OBF_4$ and $Me_2SO_4$) have been tested with *N*1-methyl-*N*10-carbomethoxytryptamine (**1a**) under various conditions, however, no desired product was observed. Then we turned our attention to benzodithiolylium tetrafluoroborate (**2**), which was employed in a formal α-methylation of aldehydes reported by Cozzi's group.[9] We found that tryptamines or tryptophols could react with commercially available **2** providing the C3 methyl-substituted pyrroloindolines or furoindoines after a further deprotection of 1,3-benzothiole (Scheme 1).[10] Herein, we report such a highly efficient cascade dearomatization of substituted indoles with benzodithiolylium tetrafluoroborate. Furthermore, the synthetic value of this method is well demonstrated by the synthesis of esermethol and physovenine.




**Scheme 1** Proposed cascade dearomatization of indole derivatives.

In the initial study, *N*1-methyl-*N*10-carbomethoxytryptamine (**1a**)[11] and benzodithiolylium tetrafluoroborate (**2**) were selected as model substrates for the optimization of the reaction conditions.[12] In the presence of 10 mol% BINOL-derived phosphoric acid and 110 mol% $Na_2CO_3$, the reaction was performed in fluorobenzene at room temperature, and the desired product **3a** was obtained in only 20% yield, together with a significant amount of **3aa** by further alkylation at the C5-position of indole (entry1, Table 1). Then we tested the reaction at lower temperature to limit the further alkylation process (entries 2-6, Table 1). Gratifyingly, the yield of **3a** could be remarkably enhanced to 89% at -30 °C (entry 5, Table 1). The yield of **3a** was further improved to 94% by using toluene as the solvent (entry 7, Table 1). Several commonly used Brønsted acids were investigated (entry 8-10, Table 1) and it was found that the reaction with benzoic acid could provide similar yield (93% yield, entry 10, Table 1). Then benzoic acid was chosen for further screening of the reaction conditions. To our delight, increasing the loading of **1a** to 110 mol% resulted in an almost quantitative

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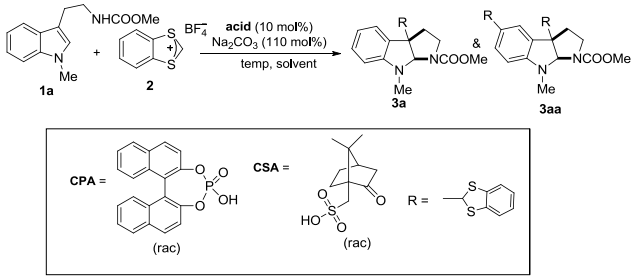
yield of **3a** (99% yield, entry 11, Table 1). It should be noted that only trace product could be detected in the absence of the base (entries 12-13, Table 1). Interestingly, **3a** was obtained in 88% yield without the addition of an acid (entry 14, Table 1). The corresponding salt of the acid likely acts as a phase transfer catalyst to promote the alkylation reaction.

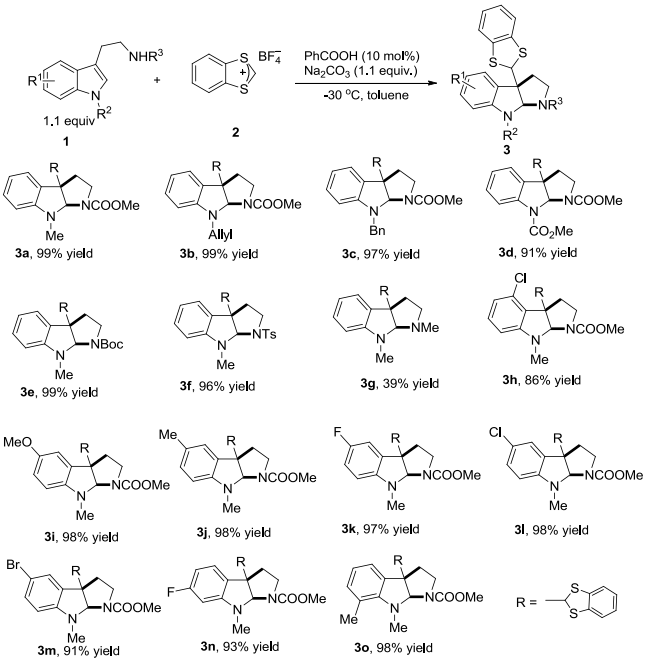
**Table 1** Optimization of the Reaction Conditions[a]




| entry | acid | temp ($^{o}$C) | solvent | **3a**, yield (%)[b] | **3aa**, yield (%)[b] |
|---|---|---|---|---|---|
| 1 | CPA | rt | $C_6H_5F$ | 20 | 39 |
| 2 | CPA | 0 | $C_6H_5F$ | 35 | 37 |
| 3 | CPA | -10 | $C_6H_5F$ | 74 | 17 |
| 4 | CPA | -20 | $C_6H_5F$ | 87 | 11 |
| 5 | CPA | -30 | $C_6H_5F$ | 89 | 4 |
| 6 | CPA | -40 | $C_6H_5F$ | 68 | 18 |
| 7 | CPA | -30 | toluene | 94 | 0.5 |
| 8 | CSA | -30 | toluene | 90 | 6 |
| 9 | $TsOH{\cdot}H_2O$ | -30 | toluene | 77 | 12 |
| 10 | PhCOOH | -30 | toluene | 93 | 1.5 |
| **11**[c] | **PhCOOH** | **-30** | **toluene** | **99(99**[d]**)** | **<0.5** |
| 12[e] | PhCOOH | -30 | toluene | 3 | 5 |
| 13[f] | - | -30 | toluene | 3 | 7 |
| 14[g] | - | -30 | toluene | 88 | 5 |

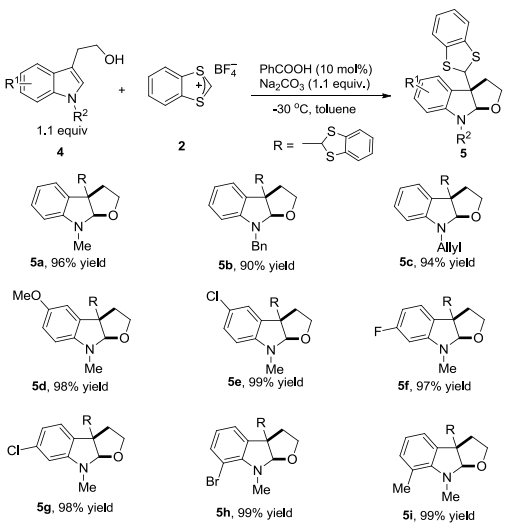
[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.11 mmol), $Na_2CO_3$ (0.11 mmol) in toluene (1.5 mL) at noted temperature. [b] Determined by HPLC analysis. [c] **1a** (0.22 mmol), **2** (0.2 mmol), $Na_2CO_3$ (0.22 mmol) in toluene (3.0 mL) at -30 $^{o}$C. [d] Isolated yield. [e] Without $Na_2CO_3$. [f] Without acid and $Na_2CO_3$. [g] Without acid.

Under the optimized reaction conditions (entry 11, Table 1), the scope of tryptamine derivatives was examined. The results are summarized in Scheme 2. Firstly, substrates with various *N*1-protected groups on the indole moiety were investigated and it was found that both electron-donating group (methyl, allyl, benzyl) and electron-withdrawing group ($CO_2Me$) were well tolerated, affording the corresponding dearomatized products in 91-99% yields (**3a** to **3d**). Secondly, different protecting groups (Boc, Ts, Me) on the amine of tryptamine were also explored. In the case of Boc and Ts, excellent yields (96-99%, **3e** and **3f**) were achieved for the desired pyrroloindoline products. However, for *N*-Me protected tryptamine, only moderate yield was obtained (39%, **3g**), due to the nucleophilicity of amine side chain. Next, varying the position and electronic property of the substituent (4-Cl, 5-OMe, 5-Me, 5-F, 5-Cl, 5-Br, 6-F, 6-Cl, 7-Me) on the indole core could all be tolerated. In all cases, the pyrroloindoline products were obtained in excellent yields (86-98%, **3h**–**3p**). The structure of products was determined by an X-ray crystallographic analysis of a single crystal of **3f**.[12]




**Scheme 2** Substrate scope for dearomatization of tryptamine derivatives.

To further broaden the substrate scope, we began to test tryptophols for this cascade dearomatization reaction with carbenium ion. When *N*-protected substituted tryptophols were subjected to the optimized conditions, excellent yields (90-96% yields, **5a** to **5c**) were obtained for the desired furoindoline products. Moreover, examination of the substituent patterns on the indole core revealed that this protocol was compatible with both electron-donating (5-OMe, 7-Me) and electron-withdrawing (5-Cl, 6-F, 6-Cl, 7-Br) group substituted tryptophols.




**Scheme 3** Substrate scope for dearomatization of tryptophol derivatives.

In addition, a chiral substrate was tested to examine the stereoselective transformation. Tryptophan derivative **6** could be utilized in this cascade dearomatization reaction, providing compound **7** in 97% yield with excellent diastereoselectivity (dr = 94/6, Scheme 4). Further examining the asymmetric version of the current cascade dearomatization reaction only gave the

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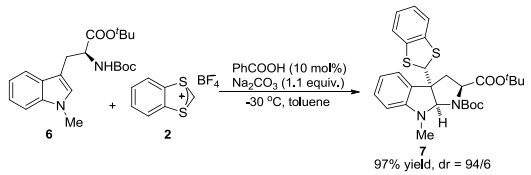
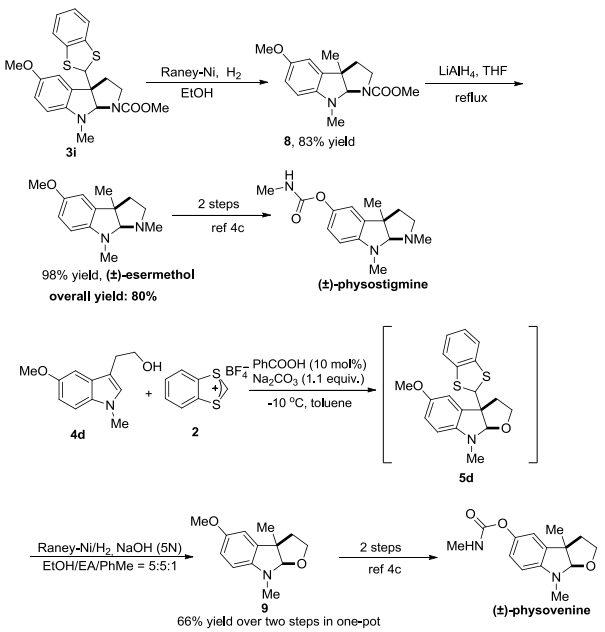
product with a relatively low enantioselectivity (up to 10% ee).[10] The low ee is probably due to the strong background reaction.



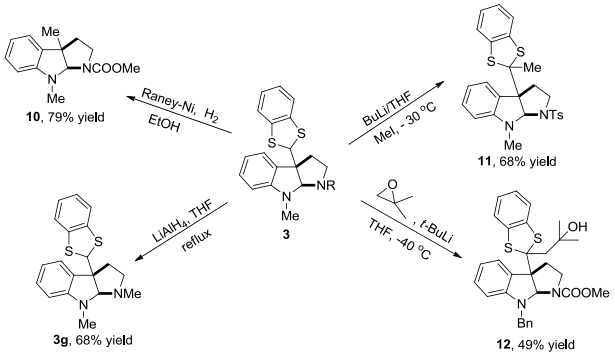

**Scheme 4** Synthesis Dearomatization reaction of tryptophan derivative.

To demonstrate the synthetic value of the current methodology, we applied this method in the synthesis of esermethol and physovenine. As depicted in Scheme 5, under the Raney Ni/$H_2$ conditions, deprotection of the 1,3-benzothiole group in **3i** easily took place to afford compound **8** in 83% yield. Further reduction of the methylcarbamate moiety with $LiAlH_4$ afforded (±) esermthol in 98% yield. Notably, esermethol is a synthetic precursor of physostigmine and phenserine,[4c] which are known as acetylcholinesterase inhibitors. In addition, dearomatization of **4d** and subsequent one-pot deprotection of the 1,3-benzothiole group provided compound **9** in 66% yield over two steps. Compound **9** is an intermediate for the synthesis of physovenine.[4c]




**Scheme 5** Synthesis of esermethol and physovenine.

To further demonstrate the utility of the dearomatized products, several transformations have been performed. Product **3a** was easily converted into the corresponding methyl substituted compound **10** after deprotection of 1,3-benzothiole group. The reduction of **3a** with $LiAlH_4$ provided **3g** in 68% yield. In addition, methylation product **11** could be obtained by the treatment of **3a** with MeI after lithiation by *n*-BuLi at -30 °C. Furthermore, compound **3c** could be converted to **12** in 49% yield after lithiation and subsequent reaction with isobutylene oxide.




**Scheme 6** Transformations of product **3**.

In summary, we have developed an efficient method to construct pyrroloindoline and furoindoline skeletons by an intermolecular cascade dearomatization of indole derivatives with carbenium ion. The current reaction features readily available starting materials, wide substrate scope, excellent yields, and mild reaction conditions. The products obtained from this method could undergo diverse transformations including the total synthesis of esermethol and physovenine in a highly concise manner.

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† Electronic Supplementary Information (ESI) available: Experimental procedures and analysis data for new compounds. See DOI: 10.1039/b000000x/

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12 For details, see the Supporting Information.