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Thionium-Based One-Pot Construction of Homo-/Heterodimeric Pyrroloindoline from Tryptamine

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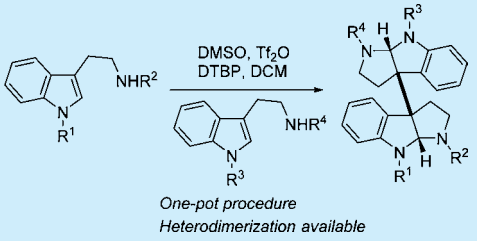
Supporting Information

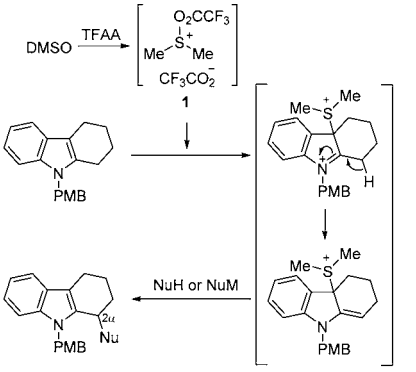
ABSTRACT: We report a one-pot procedure for forming a dimeric pyrroloindoline framework with a thionium reagent. The cyclization of tryptamine with DMSO and Tf_2O, followed by substitution with indole derivatives, produced racemic 3a-indolylpyrroloindolines. The method enables rapid access to heterodimeric pyrroloindolines as well as to homodimeric pyrroloindolines.



The dimeric pyrroloindoline framework is a key structural element in pyrroloindoline alkaloids, an important class of natural products possessing diverse biological activities.[1] Although the synthetic research of the framework has received considerable attention, the most challenging aspect of the synthesis is the construction of vicinal quaternary carbons. The framework has been synthesized from oxindole via a double Heck cyclization,[2] dialkylations,[3] and oxidative coupling reactions.[4] A more biosynthetic approach, starting from tryptamine and tryptophan using the coupling reactions via 3a-phenylselenylpyrroloindoline,[5] 3a-bromopyrroloindoline,[6] or 1-hydroxyindole,[7] has also been reported. To access the framework rapidly, some examples of the oxidative coupling[8] of tryptamine and tryptophan have been demonstrated. These methods were applied to the synthesis of homodimeric alkaloids. In nature, there are many heterodimeric alkaloids, which show various bioactivities. Although a heterodimerization method has been developed recently,[9] a concise approach to heterodimeric pyrroloindolines has not been reported because the cross-coupling of tryptamine is challenging theme. We have previously developed an aliphatic C−H functionalization at the indole 2α-position mediated by reactive thionium species **1**,[10] which is generated from DMSO and TFAA (Scheme 1).[11] As an extension of this work, we envisioned that 3a-thionium intermediate **3** was generated during the thionium **1**-mediated cyclization of tryptamine **2**. Substitution with the second tryptamine **2** molecule followed by intramolecular cyclization of the pendant aminoethyl group of **4** should produce a dimeric pyrroloindoline, such as folicanthine (**5**)[12−14] or chimonanthine (**6**)[15−17] (Scheme 2). Herein, we report the synthesis of dimeric pyrroloindolines using our thionium chemistry, and we demonstrate the efficiency of this method through the concise syntheses of the alkaloids (±)-folicanthine (**5**), (±)-calycanthidine (**7**),[18,19] and (±)-chimonanthidine (**8**).[20]

To demonstrate feasibility of thionium **1**-mediated dimerization, we initially explored the reaction of tryptamine and the thionium reagent with *N*-methylindole as an external nucleophile (Table 1). Treatment of readily available tryptamine **2a** with DMSO and Tf_2O[21] at −78 °C for 10 min followed by the reaction with 2,6-di-*tert*-butylpyridine (DTBP) and *N*-methylindole at the same temperature for 10 min afforded the desired 3a-(3-indolyl)pyrroloindoline **9a** (65%) (entry 1). After *N*-methylindole was added, warming the mixture to 0 °C increased the yield to 73% (entry 2). Reducing the amount of *N*-methylindole provided a practical procedure for preparing **9a** without loss of yield (entry 3). The cascade reaction of N^a-methyl tryptamine **2b** afforded product **9b** in a yield similar to that of N^a-allyltryptamine **2a** (entries 3 vs 4). In the case of N^b-methoxycarbonyl derivative **2c**, the cyclization proceeded more smoothly than that of N^b-Boc derivative **2b** and gave **9c** in high yield (entry 5). When indole was used as a nucleophile, a similar reaction afforded **9d** regioselectively in 94% yield (entry 6). Our method provides a concise and preferential route to 3a-(3-indolyl)pyrroloindolines under very mild conditions. The Friedel−Crafts type coupling reaction

Scheme 1. C−H Functionalization at the Indole 2α-Position in Our Previous Work



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Scheme 2. Synthetic Strategy for the One-Pot Construction of Dimeric Pyrroloindoline by Thionium Species 1

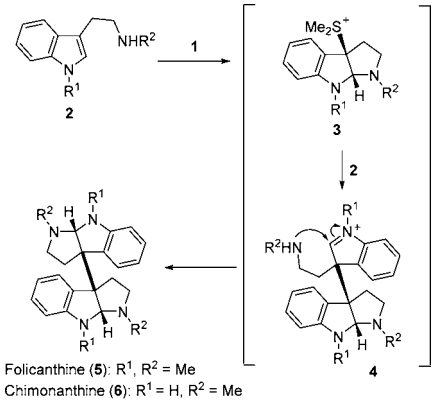
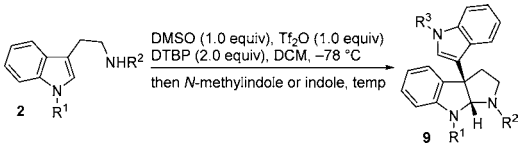


Table 1. One-Pot Synthesis of 9 and Optimization of the Reaction Conditions



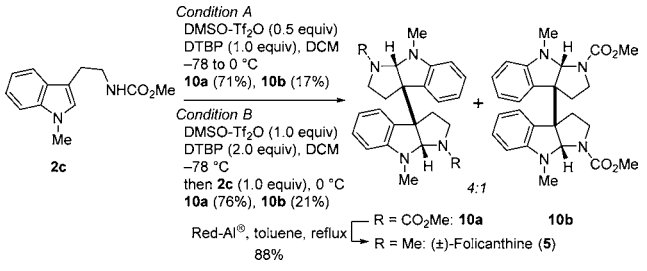
entry		R^1	R^2	R^3	temp (°C)	indole (equiv)	yield[a] (%)
1	**2a**	allyl	Boc	Me	−78	5.0	**9a** 65[b]
2	**2a**	allyl	Boc	Me	0	5.0	**9a** 73[b]
3	**2a**	allyl	Boc	Me	0	1.0	**9a** 72[b]
4	**2b**	Me	Boc	Me	0	1.0	**9b** 71[b]
5	**2c**	Me	CO_2Me	Me	0	1.0	**9c** 95
6	**2c**	Me	CO_2Me	H	0	1.0	**9d** 94

[a]Isolated yield. [b]Unidentified product was also obtained.

between indole and 3a-bromopyrroloindoline[22] forms 3a-(3-indolyl)pyrroloindoline and its regioisomer.[23] This may indicate the possibility that our thionium-mediated reaction is mechanistically different from the Friedel–Crafts-type reaction.[24]

With the above-optimized conditions in hand, we then attempted to synthesize dimeric pyrroloindolines in a one-pot procedure (Scheme 3). Using 0.5 equiv of DMSO–Tf_2O and

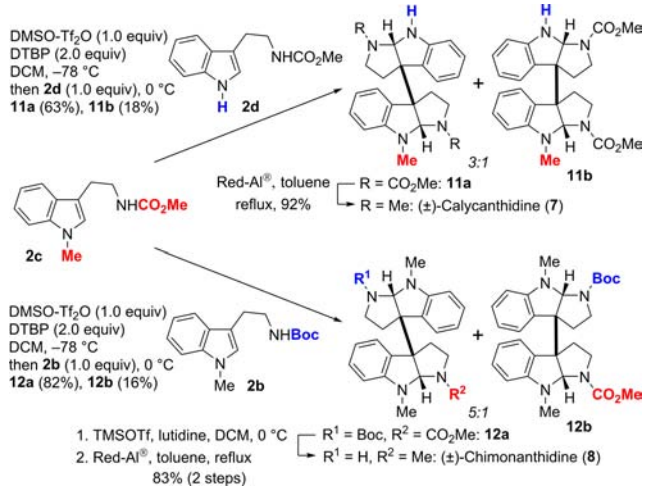
Scheme 3. Syntheses of Homodimeric Pyrroloindolines



1.0 equiv of tryptamine **2c** resulted in regioselective dimerization to afford racemic bispyrroloindoline **10a** (71%) and meso bispyrroloindoline **10b** (17%) as a mixture of stereoisomers (conditions A).[25,26] When 1.0 equiv of DMSO–Tf_2O was used, tryptamine **2c** was consumed completely and **10a** and **10b** were not formed within 10 min at −78 °C. However, the continuous injection of the second tryptamine **2c** allowed the one-pot cascade reaction to proceed smoothly at 0 °C (conditions B) and **10a** (76%) and **10b** (21%) were formed in similar yields to conditions A. The methoxycarbonyl groups of **10a** were reduced with Red-Al to produce (±)-folicanthine (**5**). The NMR, IR, and HRMS data for synthetic (±)-**5** matched those of the natural product.[12,14]

Inspired by this success, we focused on developing the one-pot heterodimerization of tryptamine (Scheme 4). In a manner

Scheme 4. Direct Heterodimeric Pyrroloindoline Syntheses



similar to homodimerization (conditions B), the successive cyclization of **2c** and substitution with the second tryptamine **2d** afforded both heterodimeric product **11a** (63%) and its diastereomer **11b** (18%) via the one-pot procedure.[27] The Red-Al reduction of **11a** gave (±)-calycanthidine (**7**). When **2b** was used as the external nucleophile, the coupling reaction gave **12a** (82%) and **12b** (16%). Removal of the Boc group in **12a** followed by Red-Al reduction of the methoxycarbonyl group afforded (±)-chimonanthidine (**8**). The NMR, IR, and HRMS data for synthetic (±)-**7** and (±)-**8** were identical to those reported for the natural products.[18,20] The synthesis of heterodimerized pyrroloindolines has only been reported via the fragmentation of unsymmetrical pyrroloindolyl diazenes by Movassaghi and co-workers.[9]

In conclusion, we have developed a one-pot thionium-mediated synthetic approach to dimeric pyrroloindoline frameworks. The combination of DMSO and Tf_2O activates effectively the indole nucleus in tryptamine to form pyrroloindoline and dimeric compounds are formed by substitution with external tryptamines. This reaction enables the efficient synthesis of heterodimeric pyrroloindolines, which has not been accomplished before. We confirmed the versatility of this method by synthesizing several biologically active alkaloids. We are currently developing an enantioselective version of the method and using it to synthesize various 3a-substituted pyrroloindolines.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analysis data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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DEDICATION

This work is dedicated to Dr. Masanori Sakamoto, Professor Emeritus of Meiji Pharmaceutical University, on the occasion of his 77th birthday (KIJU).

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(20) Chimonanthidine: isolation, structure, and racemic synthesis: 14b.

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(24) The detail of the reaction mechanism is now under investigation.

(25) The represented stereocontrolled syntheses of the racemic- and meso-forms were reported in refs 2, 3, 9, and 13a.

(26) Overman and Movassaghi reported highly stereocontrolled methods, but our method was not regarded as stereocontrolled for the generation of diastereomers in a 3:1−5:1 ratio. The ratio could be due to facial selectivity in the attack of **2** on intermediate **3** affected by the steric hindrance of **3**. The diastereomers **10a/b**, **11a/b**, and **12a/b** were easily separated by silica gel column chromatography. The details of the reaction mechanism and improvement of diastereoselectivity were under investigation.

(27) The reaction of tryptamine **2c** and active thionium species might be too fast (within 10 min at −78 °C) to produce homodimeric product before the addition of nucleophile.