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Access to the Pyrroloindoline Core via [3 + 2] Annulation as well as the Application in the Synthetic Approach to (±)-Minfiensine

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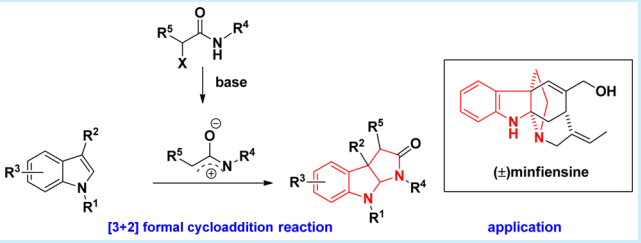
Supporting Information

ABSTRACT: A [3 + 2] formal cycloaddition reaction using aza-oxyallyl cation as a synthetic synthon was developed to construct the pyrroloindololine core. With this novel method, a variety of C3-substituted indoles were readily converted into the corresponding pyrroloindoline analogues at room temperature in the mixed solvents. To further demonstrate the utility of this method, a synthetic approach to the total synthesis of (±)-minfiensine was developed in quite concise fashion.



Indole alkaloids containing a pyrroloindoline motif are present in a variety of natural products (Figure 1).[1] Their

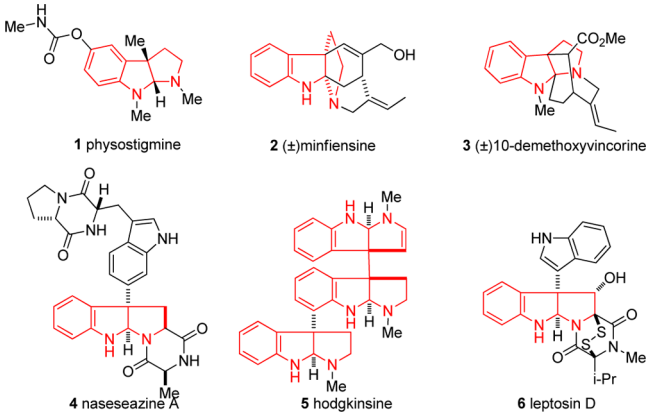


Figure 1. Some natural products containing hexahydropyrrolo[2,3-*b*]indole core.

unique structural features and versatile biological activities make them very special synthetic targets for organic chemists. Consequently, lots of new methods for the construction of pyrroloindoline scaffold were developed during the past decade. In particular, the methods using tryptamine or its derivatives as the starting materials were intensively explored.[2] However, the direct utilization of indole or C3-substituted indoles to construct pyrroloindoline scaffold remains to be extensively investigated.[3] Recently, the Reisman group reported a highly enantioselective [3 + 2]-cycloaddition reaction employing C3-substitued indoles and 2-aminoacrylate to construct pyrroloindoline analogues.[4] Later on, the Davis group developed a rhodium(II) catalyzed [3 + 2]-cycloaddition reaction to prepare enantioenriched pyrroloindolines.[5] More recently, the Wang group reported a method to construct pyrroloindolines with excellent enantioselectivities by using *meso*-aziridine and C3-alkylindoles as the reaction partners.[6] Soon after this report, the Chai and Wang groups disclosed a kinetic resolution approach to pyrroloindoline cores by copper(I) catalyzed asymmetric [3 + 2] annulations of indoles with racemic 2-arylaziridines.[7] Along with this approach, we decided to develop another 1,3-dipolar synthon coupled with C3-substitued indoles to furnish [3 + 2] annulations.

Due to their unique chemical features of aza-oxyallyl cations, this chemistry immediately drew our attention when we started our investigations. In 1960s, the aza-oxyallyl cation was suggested as the reaction intermediate when Sheehan studied α-lactam chemistry.[8] In 1993, the Sakamoto group showed the most convincing evidence for aza-oxyally cation intermediates.[9] However, only until 2011, Jeffrey group reported the first example involving aza-oxyally cations in his pioneering work on [4 + 3]-cycloaddition reaction.[10] Inspired by his elegant and original studies, we embarked on the exploration of the possibilities regarding [3 + 2] annulation involving aza-oxyally cations with C3-substituted indoles to construct pyrroloindolines while applying this reaction in the synthesis of related indole alkaloids. Unsurprisingly, the Jeffrey group and Wu group very recently realized a similar strategy to construct pyrroloindoline scaffolds.[11]

We explored the model reaction using *N*-benzyl-3-methylindole and N−H or substituted α-haloamides as the reaction substrates. Initially, the model reaction was attempted under the Föhlisch conditions.[12] However, when both starting materials were subjected to the standard conditions using TFE (trifluoroethanol) as the single solvent, we encountered a problem related to the solubilities. Thus, we quickly switched to use the mixed solvents (TFE/DCM, 10/1) to run the model reaction. To our delight, the desired product was obtained in 38% yield in the mixed solvents and with Et_3N as base (Table 1,

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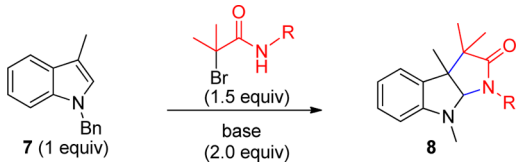
Table 1. Optimization of Reaction Conditions[a]



entry	R	base	solvent	yield (%)[b]
1	OBn	Et_3N	CF_3CH_2OH/DCM (10/1)	38
2	OBn	Et_3N	HFIP/DCM (10/1)	76
3	OBn	K_2CO_3	HFIP/DCM (10/1)	96
4	OBn	Et_3N	DCM	0
5	OBn	Et_3N	THF	0
6	OBn	Et_3N	dioxane	0
7	OBn	Et_3N	toluene	0
8	OBn	Et_3N	DMF	0
9	OBn	Et_3N	CH_3CN	0
10	H	K_2CO_3	HFIP/DCM (10/1)	0
11	Bn	K_2CO_3	HFIP/DCM (10/1)	0

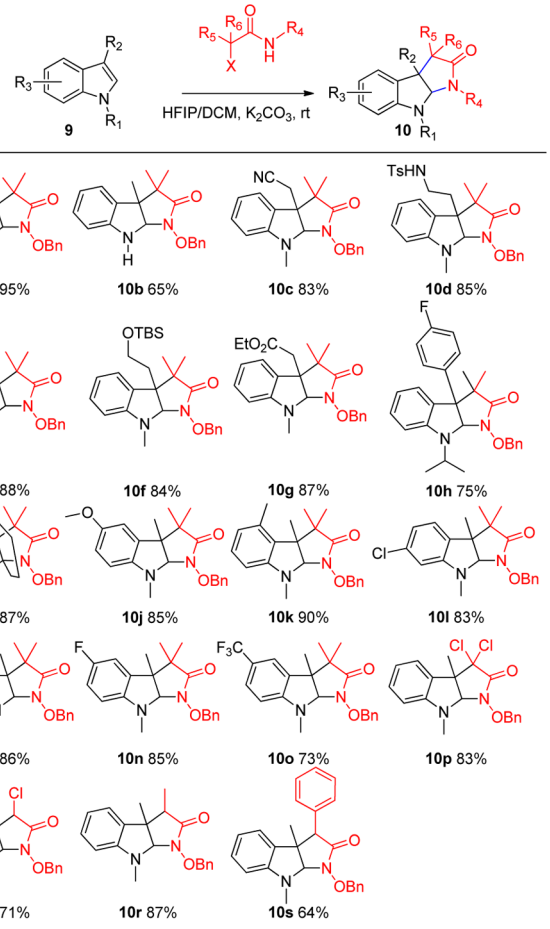
[a]Conditions: **7** (1.0 equiv), α-haloamides (1.5 equiv), base (2.0 equiv), and solvent (1.0 M) at room temperature. [b]Isolated yield.

entry 1). Changing the solvent from TFE to HFIP (hexafluoroisopropanol) further improved the yield to 76% (Table 1, entry 2). When we replaced organic base Et_3N with inorganic base K_2CO_3, excellent yield was achieved in the mixed solvents (Table 1, entry 3). As anticipated, when R was a hydrogen or benzyl group, the corresponding product could not be obtained (Table 1, entry 10 or 11). In addition, the reaction was attempted in different solvents, no desired product was observed (Table 1, entry 4−9).

With the optimized conditions in hand, we began to explore the scope of this cycloaddition reaction (Scheme 1). Different 3-substituted *N*-methylindoles were first investigated. The different functional groups including ester, nitrile, ether, olefin, protected amine, and fluorophenyl are all tolerated in the reaction conditions. Good to high yields were obtained (Scheme 1, **10a** and **10c−g**). When R1 was a hydrogen or isopropyl group, the reaction proceeded smoothly to afford the corresponding product in good yield (Scheme 1, **10b** or **10h**). When 2,3-substituted *N*-methylindole was used as a substrate, the desired product was formed in 87% yield (Scheme 1, **10i**). This result inspired us to apply this method later on in the total synthesis of the complex natural products. When indole ring contains an electron-donating or electron-withdrawing group, the reaction with 2-bromo-2-methyl-*N*-(phenylmethoxy)-propanamide occurred in good yield (Scheme 1, **10j−o**). When *N*-(benzyloxy)-2,2,2-trichloroacetamide was used as a precursor of the aza-oxyallyl cation, the reaction still occurred in 83% yield (Scheme 1, **10p**). Then when *N*-(benzyloxy)-2,2-dichloroacetamide was subjected to the reaction conditions, the reaction also occurred in good yield to provide a 1:1 diastereomeric ratio of the mixed compounds (Scheme 1, **10q**). As anticipated, when other monomethyl substituted α-haloamides were utilized as starting materials, the mixture of diastereomers with 1:1 ratio was obtained in moderate to good yield (Scheme 1, **10r** and **10s**). Notably, product **10s** was obtained just in moderate yield because the reaction occurred to afford a small amount of oxindole byproducts via an intramolecular pathway except the desired product.

To further demonstrate the utility of this novel method, we decided to apply this [3 + 2] formal cycloaddition reaction in

Scheme 1. Substrate Scope of the [3 + 2] Annulation with C3-Substituted Indoles[a]



[a]Conditions: **9** (0.20 mmol), α-haloamides (0.30 mmol), K_2CO_3 (0.40 mmol) in HFIP/DCM (2.0 mL/0.20 mL) at room temperature.

the synthesis of complex indole alkaloids. An indole alkaloid, minfiensine, has received lots of attention from the synthetic community due to its unique structural features.[13] Different synthetic pathways were applied in the total synthesis of minfiensine.[14] Herein, we reported our synthetic approach to minfiensine based on this novel [3 + 2]-cycloaddition reaction (Scheme 2). Our synthesis began with this [3 + 2] annulation between *N*-(benzyloxy)-2,2,2-trichloroacetamide and compound **11**, which is commercially available. The reaction occurred in 72% yield to afford compound **12**. To reductively cleave both C−Cl and N−OBn bonds, different reaction conditions were attempted. SmI_2 was initially found to cleave both C−Cl and N−OBn bonds to afford the desired product **13**. Although SmI_2 in THF solution is commercially available, it is quite expensive. This stopped us from large scale of preparation of amide **13**. Fortunately, we found the mixture of $RuCl_3$ with Zn−Cu couple also could reductively cleave both C−Cl and N−OBn bonds in excellent yield but with much less cost. Then amide **13** was treated with $LiAlH_4$ to afford amine **14** in moderate yield. Amine **14** was readily converted into aniline **16** through the alkylation and hydrolysis process in very good yield. Undoubtedly, the advanced intermediate, aniline **16** could be rather easily manipulated in three steps by following the similar reported reactions to afford (±)-minfiensine.[14b,e,f] The whole synthetic strategy could potentially complete the

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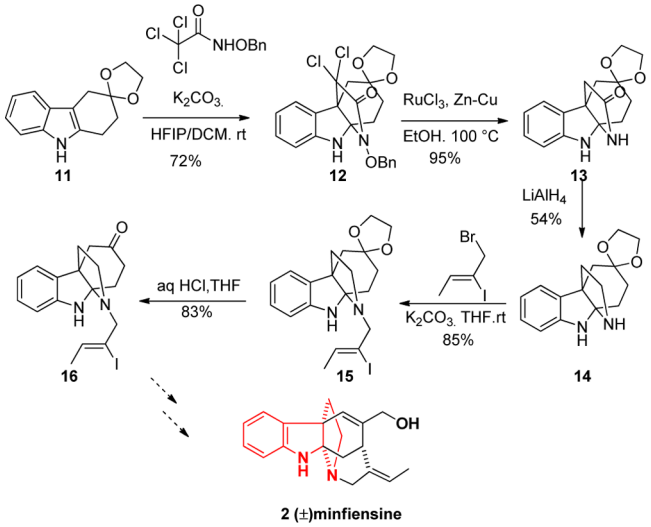
Scheme 2. Application of [3 + 2] Formal Cycloaddition Reaction in the Synthetic Approach to (±)-Minfiensine



total synthesis of (±)-minfiensine in eight steps from the commercially available compound **11**.

In conclusion, we reported a [3 + 2] formal cycloaddition reaction using aza-oxyallyl cation as a synthetic synthon to construct the pyrroloindololine core. Different functional groups are well-tolerated in such reaction conditions. With this novel method, a variety of C3-substituted indoles were readily converted into the corresponding pyrroloindoline analogues at room temperature in the mixed solvents. To further demonstrate the application of this method, a synthetic approach to (±)-minfiensine was developed in very concise fashion. This reaction provides a rapid synthetic approach to the related indole alkaloids. The investigations of asymmetric version of this [3 + 2] annulation are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03421.

Detailed experimental procedures, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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