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Journal Name

COMMUNICATION

Synthesis of Functionalized Pyrroloindolines via Visible-Light-Induced Radical Cascade Reaction: Rapid Synthesis of (±)-Flustraminol B

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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The development of visible-light-induced synthesis of functionalized pyrroloindolines via a radical cascade reaction is reported. The reaction shows a broad substrate scope and highlights a mild nature of the reaction condition. A range of substitutions on indole aromatic rings and N-centers are well tolerated, including a free allylic alcohol. Relying on the strategy, a rapid synthesis of (±)-flustaminol B was achieved.

The hexahydropyrrolo[2,3-b]indole, commonly referred as the pyrroloindoline, is a key heterocyclic motif in a wide selection of alkaloids,[1] exhibiting a broad range of biological properties, such as antibacterial activities,[2] cytotoxic activities,[3,4] and the inhibition of cholinesterase[5]. Since many pyrroloindoline natural products bear C3a quaternary centers, the structures may be categorized by the different atomic attachments on the C3a position, which could be a carbon (as in flustramine B[6] (**1**) or asperazine[7] (**2**)), a nitrogen (as in psychotriasine[8] (**3**) and pestalazine B[9] (**4**)) or an oxygen (as in brevianamide E[10] (**5**) and flustaminol B[11] (**6**))(Figure 1). Since the early studies of Pikl[12] and Robinson[13] on this class of heterocyclic structures, their synthetic challenge combined with promising pharmaceutical values has drawn dramatic attentions in synthetic organic communities, resulting in a variety of creative ways to prepare such heterocyclic core structures.[14,15] Recently, visible-light photoredox catalysis has been leading efficient access to heterocycles and related natural products.[16] More specifically, Stephenson reported a visible-light-mediated total synthesis of pyrroloindoline alkaloid gliocladin C via a single-electron reductive dehalogenation/intermolecular radical coupling strategy, where the photocatalytic procedure was used on a C3a-bromopyrroloindoline substrate.[17] Interested in developing a photocatalytic radical cascade avenue to pyrroloindoline core structure, we herein report a visible-light-induced synthesis of pyrroloindolines via an amidyl radical cyclization/carbon radical functionalization cascade.

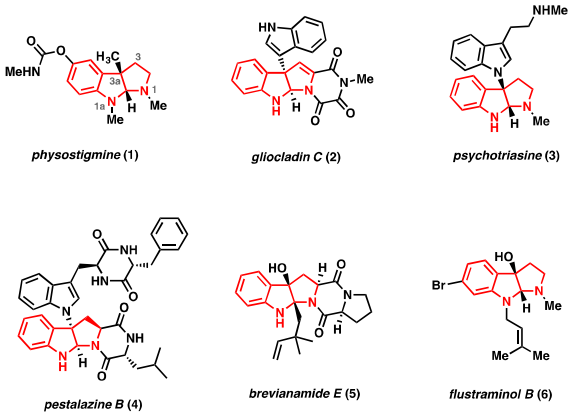

Figure 1. Representative pyrroloindoline natural products.

In addition to a clear basis of interest in pyrroloindolines at both synthetic and biological levels, we considered it as a compelling target structure to exploit the reactivity of amidyl radicals. Amidyl radicals represent a valuable class of reactive species with potentially broad applications in the formation of C-N and synthesis of N-heterocycles.[18-20] Based on Ingold's pioneering studies, amidyl radicals exhibited remarkably high electrophilic character, which offered them an umpolung reactivity that complemented the nucleophilic character of the N-species in classic polar reaction modes.[21] However, their usefulness in organic synthesis was limited by the harsh condition of generation, where hazardous radical initiators, elevated temperature, or high-energy UV irradiation was required. Recently, the generation of amidyl radicals via visible-light photoredox catalysis and their application organic synthesis were described by several groups.[22] Particularly, Leonori reported an elegant transition-metal-free generation of amidyl radical through a photocatalytic fragmentation of electron-poor aryloxy amides (**7**), and its application on intramolecular hydroamination and intermolecular N-Arylation

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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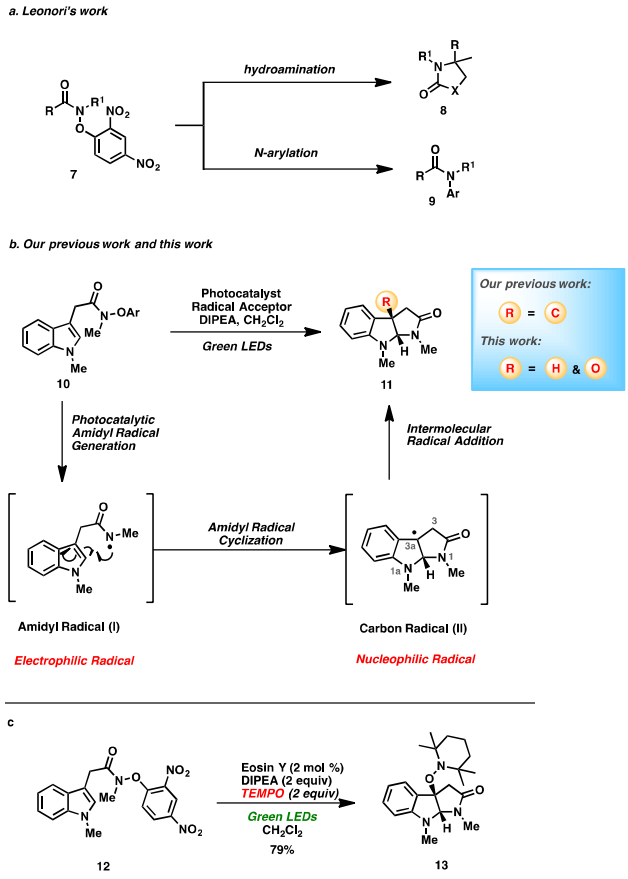
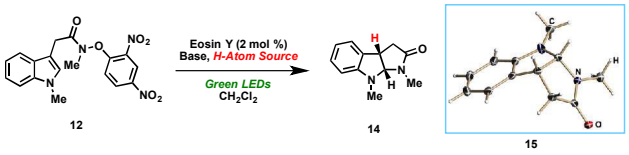
reactions (Scheme 1a).[22e] In this article, we envision that the indole acetic acid derived amidyl radical (**I**) would first react with the indole domain via a fast 5-membered ring cyclization. The resulting nucleophilic C3a radical (**II**) could then couple with a radical acceptor to provide the pyrroloindoline core structure (Scheme 1b). The proposed radical process was confirmed by trapping the C3a radical (**II**) by TEMPO reagent (Scheme 1c). Previously, we have demonstrated that the benzylic carbon radical (**II**) could react with an electron-deficient alkene system, introducing a carbon substituent at C3a position.[23] In this report, we investigated the potential C-H and C-O functionalization of the C3a carbon radical (**II**) (Scheme 1b).



Scheme 1. Visible-Light-Mediated Construction of Pyrroloindoline

We started our studies by examining the cascade reaction between indole derivative **12** and different H-atom sources (Table 1). According to Leonori's report,[22e] organic photocatalyst eosin Y and green light-emitting diode (LED) irradiation were employed in the reaction condition optimization. We started the process according to Leonori's hydroamination procedure, using K_2CO_3 as base, 1,4-cyclohexadiene (1,4-CHD) as H-atom source, and acetone as solvent (Table 1, entry 1). Unfortunately, no desired cyclization product **14** was detected. Switching to the optimal base/solvent combination in our previous reports, 1,4-CHD still is not a suitable H-atom source for this type of cyclization. A survey of various H-atom sources demonstrated that *t*-BuSH was optimal, generating **14** in 78% yield after 10 hours at room temperature (Table 1, entries 3-7). Happily, an X-ray structure was obtained, which confirmed the cyclic structure of the product **14**. Other organic bases (Et_3N, TMEDA, and DMAP) were also able to serve as additives in this transformation, delivering the pyrroloindoline **14** in 45%, 44% and 37% yield respectively (Table 1, entries 8-10).

Table 1. Reaction condition optimization[a]



Entry	Base	H-atom source	Yield[b] (%)
1[c]	K_2CO_3	1,4-cyclohexadiene	0
2	DIPEA	1,4-cyclohexadiene	0
3	DIPEA	PhSH	0
4	DIPEA	BnSh	55
5	DIPEA	L-cysteine	25
6	DIPEA	cyclohexanethiol	70
7	DIPEA	*t*-BuSH	78
8	Et_3N	*t*-BuSH	45
9	TMEDA	*t*-BuSH	44
10	DMAP	*t*-BuSH	37

[a]Reactions irradiated with two 6 W, 520 nm light-emitting diode (LED) flood lamps for 10 h. [b]Isolated yield.[c]Reaction conducted in acetone.

Encouraged by these results, we then focused on attention on exploring the scope of the photocatalytic hydroamination. Table 2 summarizes experiments probing various substitution of indole backbone. We were pleased to find that indole derivatives bearing both electron-withdrawing group and election-donating group cyclized smoothly, providing the corresponding pyrroloindoles in good yields (Table 2, entries 2 and 3). In addition, the procedure well accommodated C2a-substituted indoles, affording corresponding cyclized products in good yields (Table 2, entries 4-6).

Next, we tested the reaction by trapping the C3a radical with a molecule of oxygen. Pleasingly, C3a-hydroxypyrroloindoline **21** was afforded in 75% yield by employing the standard reaction procedure (Eosin Y, DIPEA, O_2, Green LEDs). We then evaluated the scope of this transformation (Scheme 2). A series of indole derivatives were prepared and subjected to the reaction conditions. In all cases, the reaction proceeded smoothly to furnish the corresponding C3a-hydroxypyrroloindolines in good yields (65%-84%). These examples (**22**-**36**) demonstrated that the catalytic system was tolerant of alkyl substitution, halogen substitution, and alkoxy substitution at C4, C5, C6, and C7 positions. Moreover, different substitutions on both nitrogen centers (**37**-**43**) were also compatible with the reaction condition. An X-ray structure of compound **39** was obtained, confirming the hydroxypyrroloindolines structure. More excitingly, a free

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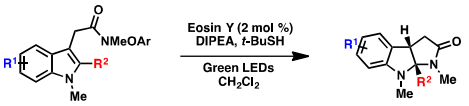
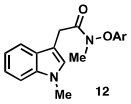
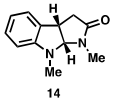
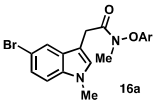
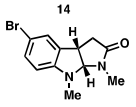
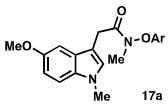
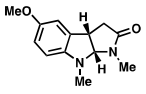
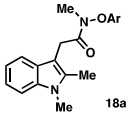
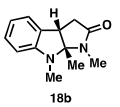
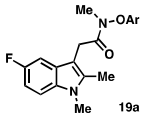
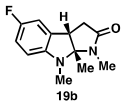
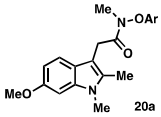
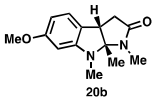
allylic alcohol motif was well tolerated in the reaction condition, highlighting the mild nature of the reaction system. In addition, the reaction condition could also be applied to C2a substituted indole derivatives, providing corresponding products (**44**-**47**) in good yields, 76%, 71%, 77%, and 69% respectively.

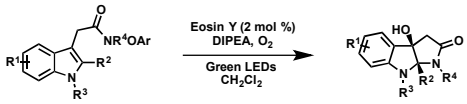
Table 2. Hydroamination of indoles[a,b]

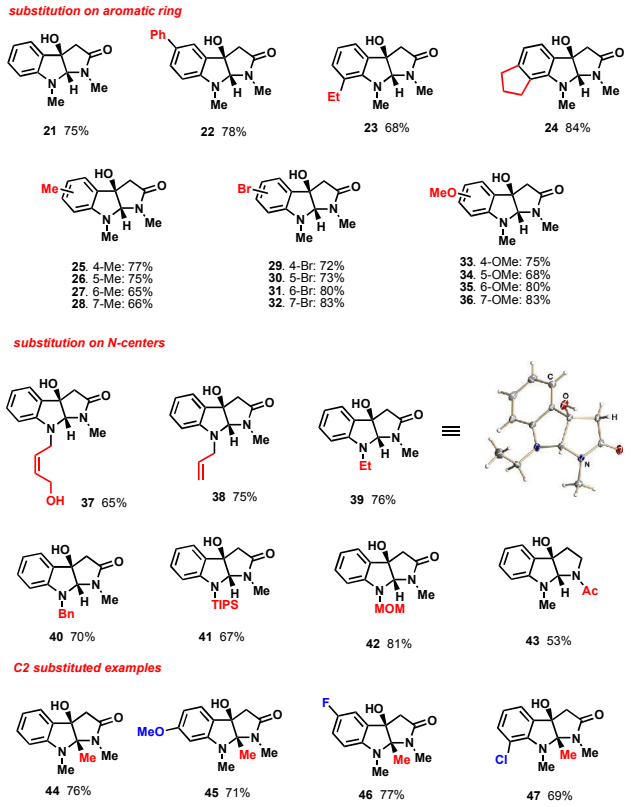


Entry	Indole	Pyrroloindoline	Yield[c] (%)
1	 12	 14	78
2	 16a	 16b	68
3	 17a	 17b	79
4	 18a	 18b	82
5	 19a	 19b	78
6	 20a	 20b	75

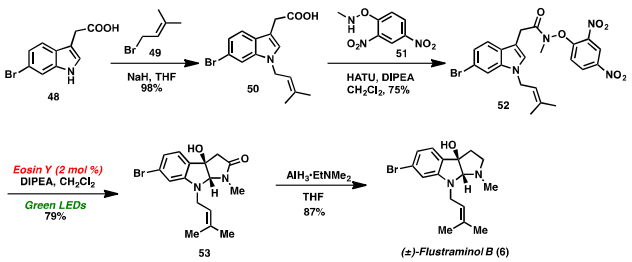
[a]Reactions irradiated with two 6 W, 520 nm light-emitting diode (LED) flood lamps for 10 h. [b]Ar=2,4-$(NO_2)_2$-C_6H_3. [c]Isolated yield.

Having established the feasibility of the visible-light mediated radical cascade strategy, we turn to the synthesis of marine alkoid flustraminol B.[11] The flustramines, flustramides, and flustraminols are a small family of marine alkaloids isolated from the Bryozoa Flusta foliacea.[6,11,24] Structurally, they are a unique subgroup of the pyrroloindoline natural products because of the incorporation of a (C6)-bromine substituent on the indoline ring system. Early biological studies have shown both flustramines A and B could block voltage-activated potassium channels and exhibit skeletal and smooth muscle relaxant properties.[25] However, the whole alkaloid family has not been well studied on broad biological investigations. Given that the pyrroloindoline skeleton might represent a valuable template for pharmaceutical studies, we were prompted to pursue a rapid access to this class of natural products.[26] The synthesis of (±)-flustraminol B commenced with N-prenylation of commercial available 6-bromoindole acetic acid, delivering **50** in 98% yield. Amide coupling of **50** and **51** provided the desired aryloxy amide **52** in 75% yield. Photocatalytic amidyl radical generation, intramolecular cyclization, followed by trapping the C3a radical with molecule of oxygen furnished the skeleton of the natural product in good yield (79%, **53**). Reduction of the amide **53** gave the natural product (±)-flustraminol B (**6**) in a total of 4 steps (Scheme 3).





Scheme 2. Hydroxyamination of Indoles



Scheme 3. Rapid synthesis of (±)-flustraminol B

A plausible mechanism for the reaction is outlined in Scheme 4a. Although it is known that DIPEA could reductively quench excited eosin Y (**EY***), the Stern-Volmer emission quenching experiments suggested that aryloxy-amide **12** quench **EY*** at a significantly higher rate (Scheme 4b). Consequently, we propose that the **EY*** reduced the aryl unit

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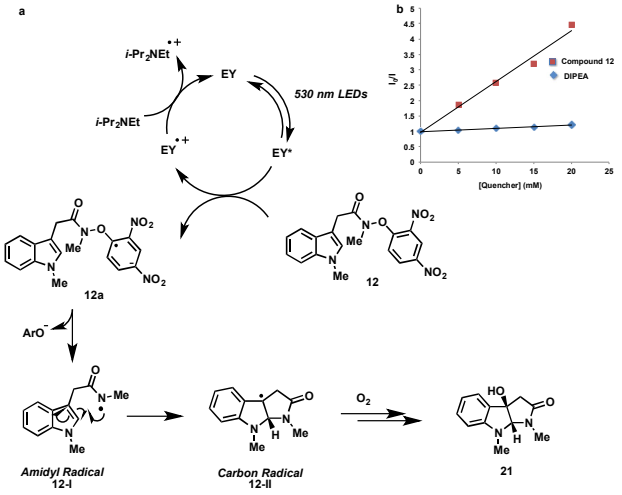
to generate **12a**, which then afforded the amidyl radical **12-I** through a fragmentation. The resulting amidyl radical (**12-I**) went through an intramolecular cyclization, affording C3a radical (**12-II**). The C3a radical was then trapped by O_2, delivering the C3a-hydroxypyrroloindoline product (**21**). The photoactive catalyst (**EY**) was expected to be regenerated by oxidizing DIPEA. Light On-Off experiments showed the light irradiation was necessary for the reaction to reach completion (Supporting Information).



Scheme 4. Proposed Mechanism

In summary, we have developed a visible-light-mediated synthesis of functionalized pyrroloindolines by radical cascade process A range of functional groups are tolerated on the indole backbone to prepare C3a-hydroxypyrroloindolines. A variety of substitutions on both N-centers could be accommodated, including a free allylic alcohol, in these mild reaction conditions. Based on this strategy, a 4-step synthesis of (±)-flustraminol B was achieved.

Conflicts of interest

There are no conflicts to declare.

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