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Accepted Article

Title: Visible-Light-Induced Trifluoromethylation of Isonitrile-Substituted Indole Derivatives: Access to 1-(Trifluoromethyl)-4,9-dihydro-3H-pyrido[3,4-b]indole and β-Carboline Derivatives

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Abstract: A visible-light-induced trifluoromethylation of isonitrile-substituted indole derivatives has been developed from the reaction of isonitrile-substituted indoles with Togni II reagent, affording 1-(trifluoromethyl)-4,9-dihydro-3*H*-pyrido[3,4-b]indoles in moderate to good yields. The further transformations to *β*-carboline derivatives and a *harmacine* derivative have been performed, demonstrating the potential synthetic utility of this method. A preliminary biological study indicated that the CF_3-containing *harmine* analogue significantly stimulated the secretion of glucagon-like peptide-1 (GLP-1), suggesting an improvement in treating diabetes

Keywords: visible-light catalyst; trifluoromethylation; *β*-carboline derivatives; Togni II reagent; biological study

Over the past decade, visible-light photoredox catalysis has been discovered by MacMillan,[1a] Yoon[1b] and Stephenson.[1c] Due to its efficient, mild, green characteristics, it has been intensively studied and broadly applied in organic synthesis with significant achievements.[2] Currently, it has become a powerful synthetic tool to construct complex molecules under mild conditions.[3] Organofluorine compounds have been extensively studied because of its unique physical and chemical properties.[4] Introducing fluorine or fluorine-containing group into organic compounds might display improved membrane permeability and increased bioavailability than those of non-fluorinated analogues as usual.[5] For this reason, trifluoromethyl group as an important building block has been widely used in drugs and drug candidates due to its special solubility and lipophilicity.[6] Thus far, the development of new strategies for introducing trifluoromethyl group into organic compounds has drawn a particular interest and many excellent works have been reported.[7] In this aspect, MacMillan's group has described a novel protocol for the asymmetric *α*-trifluoromethylation of aldehyde via cooperative photo- and organocatalysis in 2009.[8] Subsequently, the trifluoromethylation of olefins has also been achieved.[9] Moreover, the process of trifluoromethylation via synergistic photocatalysis and transition metal catalysis has been also reported by Sanford.[10]

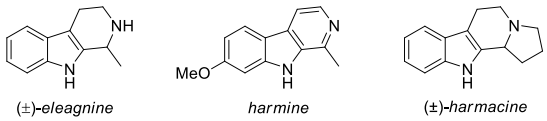
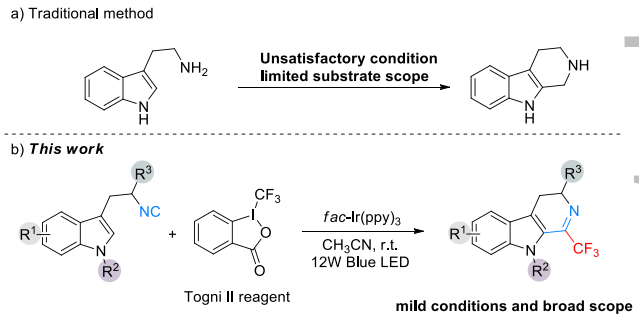


Figure 1. Structures of some *β*-carboline natural products.

In recently reported trifluoromethylation reactions, many commercially available reagents have been used as trifluoromethyl sources to participate in the photo-induced trifluoromethylation reactions such as Togni II reagent,[11] $TMSCF_3$,[12] Umemoto reagent,[13] CF_3SO_2Cl,[14] and Langlois reagent.[15]



Scheme 1. Previous work and this work on the synthesis of dihydro-*β*-carboline.

Isonitriles have a broad synthetic applications in multicomponent reactions.[16] In 2008, Studer and co-workers first reported the radical trifluoromethylation of isonitriles using Togni II reagent as the CF_3 source and Bu_4NI as an initiator, providing the trifluoromethylated phenanthridines in moderate to good yields.[17] After that, several related investigations on isonitriles have been also disclosed.[18] These intriguing findings inspired us to use isonitriles as accepters to realize trifluoromethylation under visible-light photoredox catalysis.

The indole structure widely exists in biomolecules and drugs due to its unique biocompatibility and bioactivities.[19] As a branch of indole derivatives, *β*-carboline derivatives such as (±)-*eleagnine*, *harmine* and (±)-*harmacine* have a wide bioactivities in antitumor, receptor inhibition and antidiabetic (Figure 1).[20] However, the limited substrate scope for the synthesis of *β*-carboline derivatives has impaired their potential applications. In the meantime, some of the synthetic methods were also carried

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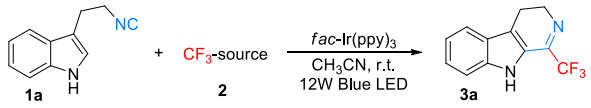
out under harsh conditions (Scheme 1a).[21] On the basis of these circumstances, we envisaged to develop a new method to synthesize trifluoromethylated dihydro-*β*-carboline in the presence of Togni II reagent upon visible-light photoredox catalysis. Herein, we wish to report a trifluoromethylation reaction of isonitrile-substituted indole derivatives[22] via visible-light photoredox catalysis to produce a series of trifluoromethylated dihydro-*β*-carboline derivatives, which exhibit the potential usefulness in pharmaceutical chemistry (Scheme 1b).

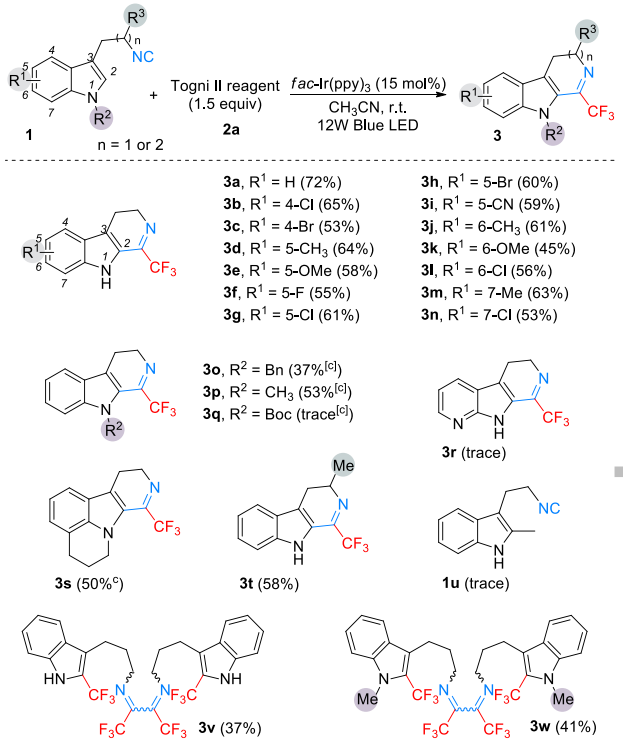
Table 1. Optimization of the reaction conditions for the synthesis of **3a**



entry	catalyst	CF_3-source	solvent	yield (%)
1	MB & TMEDA (1.5 eq)	Togni II reagtent (**2a**)	CH_3CN	50
2	MB	Togni II reagtent	CH_3CN	25
3[b]	TMEDA	Togni II reagtent	CH_3CN	31
4	$Ir(ppy)_2(dppe)PF_6$	Togni II reagtent	CH_3CN	47
5	$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	Togni II reagtent	CH_3CN	19
6	$Ru(Phen)_3Cl_2$	Togni II reagtent	CH_3CN	48
7	*fac*-Ir(ppy)$_3$	Togni II reagtent	CH_3CN	54
8[c]	*fac*-Ir(ppy)$_3$	Togni II reagtent	CH_3CN	83 (72[d])
9[c]	*fac*-Ir(ppy)$_3$	Togni I reagtent (**2b**)	CH_3CN	28
10[c]	*fac*-Ir(ppy)$_3$	Umemoto reagent (**2c**)	CH_3CN	n.d.
11[c]	*fac*-Ir(ppy)$_3$	CF_3SO_2Cl (**2d**)	CH_3CN	n.d.
12[c]	*fac*-Ir(ppy)$_3$	Togni II reagtent	DCE	22
13[c]	*fac*-Ir(ppy)$_3$	Togni II reagtent	DCM	15
14[e]	*fac*-Ir(ppy)$_3$	Togni II reagtent	CH_3CN	67
15[f]	*fac*-Ir(ppy)$_3$	Togni II reagtent	CH_3CN	69
16[b]	*fac*-Ir(ppy)$_3$	Togni II reagtent	CH_3CN	n.r.
17	-	Togni II reagtent	CH_3CN	n.r.

[a] Reactions were carried out using **1a** (0.2 mmol), **2** (0.3 mmol), catalyst (5 mol%) in N_2-purged dry solvents (2.0 mL) at ambient temperature, using 12W blue light irradiation for 3 hours. Yields were determined by ^{19}F NMR spectroscopic data of crude reaction mixture using 4-bromobenzotrifluoride as an internal standard. [b] In the dark conditions. [c] 15 mol% catalyst loading. [d] Isolated yield. [e] 15 mol% catalyst loading, 1.0 equivlent of **2a** loading. [f] 15 mol% catalyst loading, 2.0 equivlent of **2a** loading.
n.r.: no reaction; n.d.: not detected

Initially, we investigated the reaction outcome of **1a** with 1.5 eq of Togni II reagent **2a** in the presence of TMEDA using 5 mol% of methylene blue (MB) as the photosensitizer in MeCN (Table 1, entry 1). We found that the desired product **3a** was obtained in 50% yield. However, MB itself could also catalyze the reaction, giving **3a** in 25% yield (Table 1, entry 2). Moreover, we also realized that TMEDA itself could catalyze this reaction independently even without irradiation of blue LED (Table 1, entry 3). Therefore, we optimized the reaction conditions by using metal complexes as the photosensitizers and found that the use of *fac*-Ir(ppy)$_3$ (5 mol%) gave **3a** in 54% yield (Table 1, entries 4-7). Using 15 mol% of *fac*-Ir(ppy)$_3$ produced **3a** in 83% NMR yield (72% isolated yield) (Table 1, entry 8). Others CF_3-sources such as Togni I reagent **2b**, Umemoto reagent **2c**, and CF_3SO_2Cl **2d** did not perform as well as that of **2a** (Table 1, entries 9-11). The examination of solvent effect revealed that MeCN is the best choice (Table 1, entries 12 and 13). Increasing and reducing the employed amounts of **2a** did not further improve the yield of **3a** (Table 1, entries 14 and 15). The control experiments indicated that no reaction occurred in the dark conditions (Table 1, entry 16) and the photocatalyst of *fac*-Ir(ppy)$_3$ was essential to the formation of **3a** (Table 1, entry 17). A scale up of this reaction has been indicated on page S19 in the Supporting Information.



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), catalyst (15 mol%) in N_2-purged dry solvent (2.0 mL) were added to an oven-dried Schlenk tube at ambient temperature, using 12W bule light irradiation for 3 hours. [b] Isolated yields of **3**. [c] Using 12 W bule light irradiation for 10 hours.

Scheme 2. Substrates scope of the synthesis of **3**.[a,b]

With the optimized reaction conditions in hand, the substrate scope and functional group tolerance were next examined. As shown in Scheme 2, various substituted indoles regardless of whether they have electron-poor or -rich substituents on the aromatic rings were all compatible, affording the corresponding products **3a-3n** in moderate to good yields. When *N*-substituted indoles were used in this reaction, the desired products **3o** and **3p** were obtained in 37-53% yields after a prolonged reaction time. For *N*-Boc-protected substrate, only trace of the desired product **3q** was produced due to the electronic effect, suggesting that the substituent on nitrogen atom caused a significant impact on the nucleophilicity of *C*-2 position in indole **1**. The use of 7-aza-indole derivative also afforded trace of **3r** presumably due to the same reason. In the case of cyclic alkyl group substituted substrate, the desired product **3s** could be given in 50% yield. Alkyl carbon chain substituted substrate was also tolerated, furnishing the desired product **3t** in 58% yield. When 2-methyl-substituted indole derivative **1u** was used as substrate, only trace of unknown product was formed and most of starting materials were recovered. Surprisingly, when the carbon chain of isonitrile was extended from two carbon atoms to three carbon atoms, the corresponding products **3v** and **3w** were formed via a radical-initiated dimerization in 37% and 41% yields, respectively, rather than the desired cyclization products. These two products may have isomers around the C=N double bond. On the basis of ^{19}F NMR spectroscopy, they should have a symmetrical structure. Due to the lack of enough H atoms around the C=N double bond, we can not identify their real conformation at the present stage.

We recognized that product **3** could be further transformed to *β*-carboline derivatives that have a wide range

of biological activities upon oxidation. Thus, several products **3** were converted into *β*-carboline derivatives **4** upon treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The reactions proceeded smoothly, giving the desired products **4a**-**4e** in good yields, ranging from 59% to 80% (Scheme 3). The structure of **4a** has been unambiguously confirmed by X-ray diffraction. The corresponding ORTEP drawing is shown in Figure 2 and its CIF data are presented in the Supporting Information. It should be noted that *β*-carboline derivative **4d** has a similar structure as that of the natural product *harmine*.

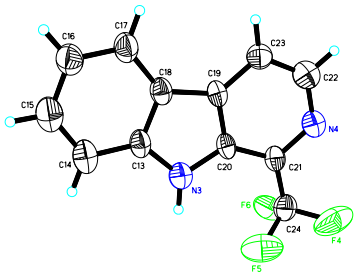
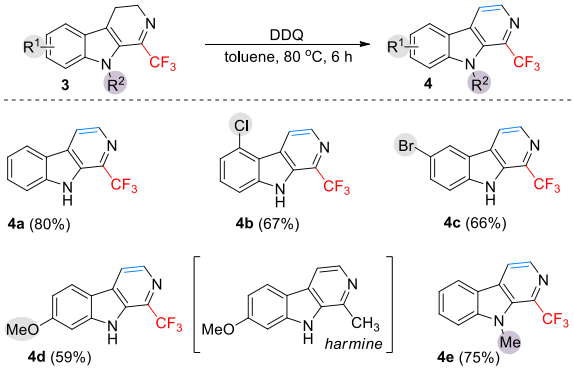


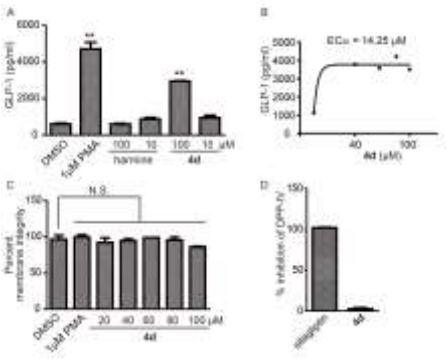
Figure 2. X-ray crystal structure of **4a**.



[a] To a Schlenk tube was added DDQ (1.5 eq), then **3** (1.0 eq) dissolved in toluene was added to the Schlenk tube. The mixture was stirred at 80 °C for 6 h. Isolated yields of **4**.

Since *harmine* has various types of pharmacological activities, such as antitumor,[23] antidepression[24] and antidiabetic,[20b,25] we were intrigued by the potential biological activities of **4d**. Therefore, we subsequently examined its effect on an in vitro model for diabetes in the secretion of glucagon-like peptide-1 (GLP-1), which plays an important role in limiting postprandial glucose level. Although harmine had no significant effect on the secretion of GLP-1, intriguingly, **4d** effectively stimulated GLP-1 release in mouse intestinal cell line STC-1 with an EC_{50} of 14.25 μM (Figures 2A & 2B). Furthermore, **4d** did not exhibit significant cytotoxicity in STC-1 cells (Figure 2C). We also conducted a preliminary exploration on the mechanism of **4d**-stimulated GLP-1 release. As shown in Figure 2D, **4d** barely inhibited the activity of DPP-IV, which is an enzyme that degrades GLP-1 rapidly. Further investigations of its antidiabetic activities and mechanisms are under way.

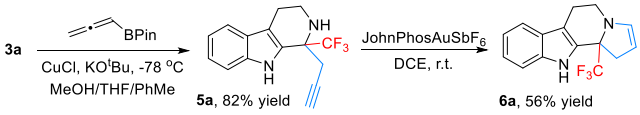
The effect of **4d** on diabetes was also evaluated by using another *in vitro* model-glucose consumption. Neither *harmine* nor **4d** promoted glucose consumption in L6 skeletal muscle cells (Figure S1A). We also evaluated its cytotoxicity in human lung cancer cell line A549. As shown in Figure S1B, **4d** moderately inhibited the proliferation of lung cancer cells with half maximal inhibitory concentration (IC_{50}) of 29.83 μM, which was less potent than that of *harmine* (IC_{50} = 10.22 μM).



(A) STC-1 cells were treated with solvent control (DMSO), positive control (1.0 μM PMA) and compound (100 and 10 μM *harmine* or **4d**) for 2 hours. Then the concentration of GLP-1 in the culture medium was measured. (B) STC-1 cells were treated with 20, 40, 60, 80, 100 μM **4d**, respectively. The culture media were collected and measured of the release of GLP-1. (C) The release of lactate dehydrogenase (LDH) was measured, which indicates the integrity of cell membrane. (D) The effect of **4d** on the activity of DPP-IV was evaluated by Cayman's DPP-IV Inhibitor Screening Assay. 100 μM sitagliptin was included as a positive control. The data are represented as mean ± SD. Statistical significance was calculated using Student's t-test. **P<0.01; N.S., not significant.

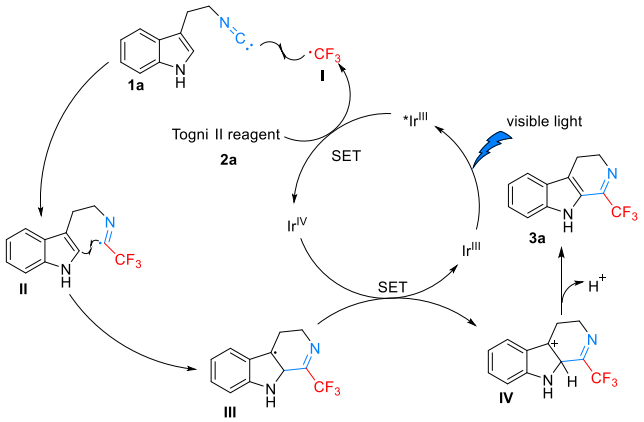
Figure 3 4d stimulates the release of GLP-1 in STC-1 cells

Furthermore, to evaluate the synthetic utility of the obtained product **3**, we further investigated the synthesis of **6a** from **3a** as a short total synthesis of *harmacine* derivative since a variety of natural product shares a characteristic 6-5-6-5-cyclic core structure (Scheme 4). Firstly, to a THF solution of CuCl was added a THF solution of KO*t*Bu, and the resulting mixture was stirred for 0.5 hour at room temperature, and then was added 0.5 mL toluene followed by cooling to -78 °C. Allenylboronic acid pinacol ester was added to the mixture followed by addition of a MeOH/THF solution of **3a**. The reaction mixture was stirred at -78 °C for four hours. Then, it was warmed to -40 °C and was further stirred for 36 hours. After isolation and purification, the desired product **5a** was acquired in 82% yield. A gold(I)-catalyzed cyclization of **5a** in DCE successfully produced the desired product **6a** in 56% yield.



Scheme 4. Transformation: two step synthesis of *harmacine* derivative.

On the basis of the previous reports, a plausible reaction mechanism is proposed in Scheme 5. Initially, the photosensitizer Ir^{III} was excited to $^{*}Ir^{III}$ upon visible light irradiation, which was oxidized by Togni II reagent **2a** to give CF_3 radical **I** and Ir^{IV} species via a single-electron-transfer (SET) process. Subsequently, the addition of CF_3 radical to the isonitrile group in **1a** generated the imidoyl radical **II**. This radical intermediate underwent an intramolecular cyclization at the *C*-2 position of indole to afford intermediate **III**, which produced the cationic intermediate **IV** along with regeneration of Ir^{III} species through another SET process. Deprotonation of intermediate **IV** furnished the desired trifluoromethylation product **3a**.



Scheme 5. A plausible mechanism for the formation of **3**.

In summary, we have developed a novel visible-light-induced trifluoromethylation of isonitrile-substituted indole derivatives, giving a variety of 1-(trifluoromethyl)-4,9-dihydro-3*H*-pyrido[3,4-b]indole derivatives in moderate to good yields. This strategy provided a direct process for the construction of a single C-CF_3 bond. The further transformations to *β*-carboline derivatives and a CF_3-containing *harmacine* derivative exhibited the potential synthetic and biological utilities of this method. Interestingly, the biological activity study also demonstrated that the obtained CF_3-containing product **4d** might possess a better therapeutic effect of treating diabetes. Further investigations on the application of this methodology to synthesize more interesting and biologically active compounds are underway in our laboratory.

Experimental Section

General Procedure for Synthesis of 3

Isocyanid (0.2 mmol, 1.0 equiv.), Togni's II reagent (0.3 mmol, 1.5 equiv.), *fac*-Ir(ppy)$_3$ (0.03 mmol, 0.15 equiv.) were placed in a oven-dried Schlenk tube. Then 2.0 mL anhydrous acetonitrile (degassed by nitrogen for 30 minutes to remove oxygen in solvent) was added. The Schlenk tube was sealed and exposed to blue LED strips (12 W LED strips was 5 cm away from the tube) at room temperature and then the reaction mixture was stirred for 3 hours. The reaction mixture was concentrated and the residue was purified directly by a column chromatography to afford the desired products.

Detailed descriptions of experimental procedures and their spectroscopic data as well as the crystal structures are presented in the Supporting Information. CCDC 1541586 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

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Updates

Visible-Light-Induced Trifluoromethylation of Isonitrile-Substituted Indole Derivatives: Access to 1-(Trifluoromethyl)-4,9-dihydro-3*H*-pyrido[3,4-b]indole and *β*-Carboline Derivatives

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