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Visible-Light-Promoted Metal-Free C-H Trifluoromethylation of Imidazopyridines

Xia Mi,[a] Yuanfang Kong,[a] Huaixia Yang,[a] Jingyu Zhang,*[a] Chao Pi,[b] Xiuling Cui*[b]

Abstract: A metal-free photo redox C-H trifluorometlylation of imidazopyridines is described. The reaction is operationally simple and the easy-handling CF_3SO_2Na serves as an effective fluoroalkyl radical precursor. Various functional groups were tolerated under blue LED light to access the desired products in satisfied yields at room temperature.

The trifluoromethyl group plays an important role in pharmaceuticals, agrochemicals, and functional materials.[1] Hence, the research of selective introduction of a trifluoromethyl group into organic molecules has become a hot topic in modern organic chemistry.[2] Trifluoromethylation,[3] especially via photo redox catalysis, represents an attractive alternative for a mild and efficient method to produce active CF_3 radical.[4] In this strategy, a variety of CF_3 radical precursors, such as CF_3I,[4c] CF_3SO_2Cl,[4e,4i] $TMSCF_3$,[4k] Togni reagent,[4g] Umemoto reagent,[4h] Langlois reagent (CF_3SO_2Na),[4f] and Baran's reagent,[4d] have been used for the incorporation of a CF_3 group into diverse skeletons. Trifluoromethylation starting from commercially available, low cost, and easy-handling Langlois reagent is more appealing. The redox potential of the Langlois reagent is 1.05 V (vs. SCE).[5] Generally, it requires transition metal iridium complexes or stoichiometry oxidant, such as $K_2S_2O_8$, TBHP, $PhI(OAc)_2$, to oxidize the Langlois reagent, which is not compatible with sensitive functional groups. Several organic dyes such as rose bengal, methylene blue, and Nile red have proven to be efficient in visible-light-promoted trifluoromethylation and show the advantages of efficiency, cheapness and non-toxicity.[6] Mesitylacridinium species have known as the photo redox catalyst to realize hydrotrifluromethylation,[5] vicinal difunctionalization of alkenes[7] and cascade radical triflurometlylation of isocyanides.[8] However, there is no report on the trifluorometlylation of (hetero)-arenes using the acridinium / CF_3SO_2Na system. We proposed that a high oxidizing mesitylacridinium ($E^{red}_{1/2}$ > 1.8 V vs. SCE) [9] would be an effective photo oxidant to generate reactive CF_3 radicals from the Langlois reagent to achieve C-H trifluorometlylation of imidazopyridines with visible-light irradiation.

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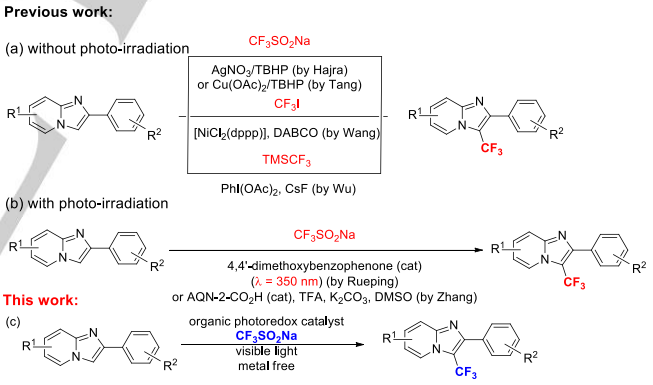
As a privileged heterocyclic scaffold, imidazopyridine is found in diverse bioactive natural products and pharmaceuticals.[10] Numerous methods have been developed for the synthesis and medication of this core.[11] Some methods have been reported for the trifluoromethylation of imidazo[1,2-a]pyridine and its derivatives (Scheme 1a).[12] However, only a few reports involved visible-light-induced trifluoromethylation of imidazopyridines.[13] In 2015, Rueping's group first showed the trifluoromethylation of imidazopyridine using benzophenone derivative as photo redox catalyst under near-UV irradiation (λ = 350 nm), however only one example was involved and afforded moderate yield. Recently, Zhang and coworkers reported trifluoromethylation of imidazo[1,2-a]pyridines by employing anthraquinone-2-carboxylic acid as the photo-organo catalyst with the addition of base and acid (Scheme 1b). Herein we present a mild and photo redox protocol for trifluoromethylation of imidazo[1,2-a]pyridine derivatives with mesityl acridinium as photo redox catalyst and CF_3SO_2Na as a CF_3 radical source under transition-metal-free condition at room temperature (Scheme 1c).



Scheme 1. Trifluoromethylation of imidazo[1,2-a]pyridines.

Our investigation was commenced with imidazo[1,2-a]pyridine (**1a**) and CF_3SO_2Na (**2**) as starting materials under the irradiation of a 3 W blue LED (Table 1). No desired product was obtained using $Ir(ppy)_3$, $Ru(bpy)_3Cl_2$, Eosin Y as the catalyst (entries 1-3). A high oxidation potential acridinium **A** showed good reactivity and the desired C-H triflurometlylated product **3a** was afforded in 42% yield (entry 4). The effect of solvent was explored with acridinium **A** as catalyst. The result revealed that 1,2-dichloroethane (DCE) was a suitable medium compared to other solvents, such as tetrahydrofuran (THF), MeCN, and $CHCl_3$ (entries 5-8). To further improve yield of target product, other acridiniums with counter anions or substitutions were tested (entries 9-10). The desired product **3a** could be formed in 53% yield when acridinium **C** was employed as a catalyst (entry 10).

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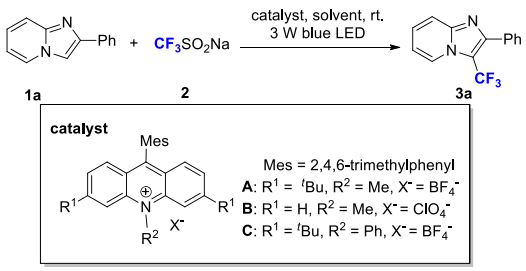
Working at lower concentration (from 1.0 mL to 2.0 mL DCE) gave 63% yield. However, when 3.0 mL of solvent was loaded, the reaction decreased its efficiency (entries 11-12). Increased the loading of **1a** afforded a yield of 74% (entry 14), while the product yield was decreased with higher loading of CF_3SO_2Na (entry 13). A similar yield of 75% was achieved after irradiation for 36 hours (entry 15). Inferior results were obtained when the loading of acridinium **C** was decreased (entry 16). Trace amount of product was provided in absence of photo catalyst or in the dark (entries 17-18).

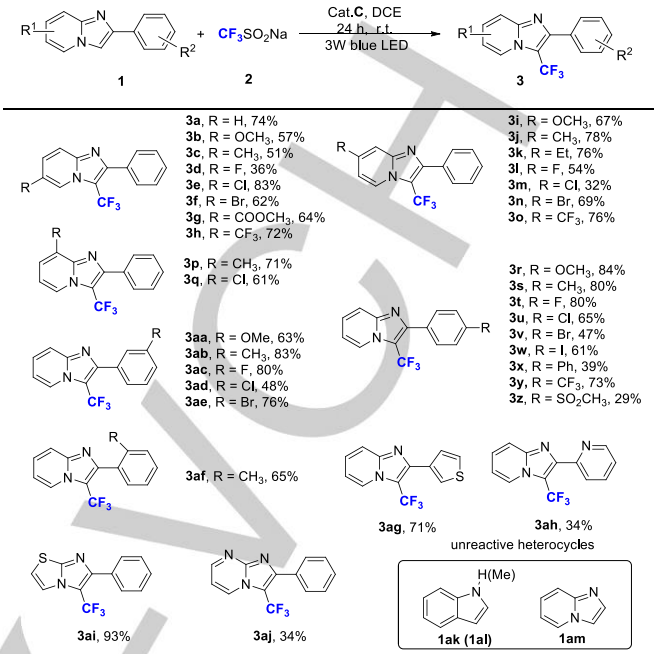
Table 1. Screening the reaction conditions.[a]



entry	catalyst	solvent/v (mL)	yield (%)[b]
1	$Ir(ppy)_3$	DCE/1	ND
2	$Ru(bpy)_3Cl_2$	DCE/1	ND
3	Eosin Y	DCE/1	ND
4	**A**	DCE/1	42
5	**A**	DMSO/1	11
6	**A**	THF/1	18
7	**A**	MeCN/1	22
8	**A**	$CHCl_3$/1	36
9	**B**	DCE/1	11
10	**C**	DCE/1	53
11	**C**	DCE/2	63
12	**C**	DCE/3	59
13 [c]	**C**	DCE/2	39
14 [d]	**C**	DCE/2	74
15 [d], [e]	**C**	DCE/2	75
16 [d], [f]	**C**	DCE/2	66
17 [d]	**C**	DCE/2	trace
18 [d], [g]	**C**	DCE/2	trace

[a] **1a** (0.2 mmol), **2** (0.3 mmol), photocatalyst (5 mol %), solvent (1.0 mL), 3 W blue LED. [b] Isolated yields. [c] **2** (0.4 mmol) [d] **1a** (0.3 mmol), **2** (0.2 mmol). [e] 36 h. [f] catalyst **C** (2 mol %). [g] Dark. [h] ND = not detected.

Table 2. Scope of imidazopyridines.[a]



[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.2 mmol), **C** (5 mol %), DCE (2.0 mL), 3 W blue LED for 24 h. Isolated yields.

With the optimized reaction conditions in hand (Table 1, entry 14), we next explored the scope of this C-H trifluoromethylation of imidazopyridines. As shown in Table 2, imidazo[1,2-a]pyridines bearing -Me, -OMe or halogen substituents on pyridine ring at different position efficiently reacted with CF_3SO_2Na to afford the desired products with moderate to good yields (**3b**-**3q**). Imidazo[1,2-a]pyridines with methyl ester at C-6 was tolerated and resulted in 64% yield (**3g**). Then we examined the effect of substituents in C-2 position of imidazo[1,2-a]pyridines (**3r**-**3af**). Imidazopyridine moiety with electron-donating groups, such as -CH_3 and -OCH_3 on the phenyl ring, afforded the desired products with good yields (**3r**, **3s**, **3aa**, **3ab** and **3af**). The crystal structure of **3s** was confirmed by X-ray single crystal diffraction, as shown in supporting information. Halogens were also well tolerated (**3t**-**3w** and **3ac**-**3ae**). Strong electron-withdrawing groups, for example -CF_3 in a phenyl ring, successfully afforded the desired products **3y**. To our delight, thiophene- and pyridine-substituted imidazo[1,2-a]pyridines also furnished the products with 71% and 34% yields, respectively (**3ag**, **3ah**). In addition, imidazo[2,1-b]thiazole and phenylimidazo[1,2-a]pyrimidine were found to be effective for this reaction (**3ai**, **3aj**). However, unsubstituted imidazopyridine and indoles did not work in this catalytic system.

To probe the mechanism of this transformation, we attempted to perform the reaction in the presence of radical scavenger TEMPO (2,2,6,6-tetramethylpiperidinooxyl) under standard reaction conditions (Scheme 2). The formation of trifluoromethylated imidazopyridine was totally suppressed and TEMPO-CF_3 adduct **4** was detected in 14% yield by ^{19}F NMR spectroscopy.[5] This result suggested that CF_3 radical was involved in this reaction.

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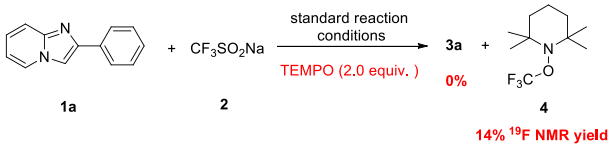
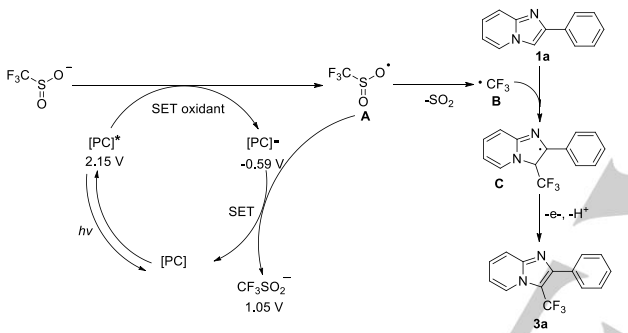


Scheme 2. Radical capture experiment in the presence of TEMPO.

A plausible mechanism for the C-H trifluoromethylation of imidazo[1,2-a]pyridines is shown in Scheme 3. Under the photocatalytic conditions, electron transfer from CF_3SO_2- to the excited-state acridinium [PC]* is expected to efficiently generate CF_3SO_2 and [PC]*- radicals. The cleavage of CF_3SO_2 radical products CF_3 radical and SO_2. Subsequently, the CF_3 radical reacted with imidazo[1,2-a]pyridine **1a** to produce the intermediate **C**. Then, intermediate **C** was oxidized and dehydrogenated to generate compound **3a**. [PC]*- was oxidized by CF_3SO_2 radical to generate [PC] on the basis of their redox potentials to finish the photocatalytic cycle.[4f]



Scheme 3. Proposed reaction mechanism

In conclusion, we have developed an efficient and photoredox-based protocol for the C-H trifluoromethylation of imidazo[1,2-a]pyridines using acridinium as the photo redox catalyst and CF_3SO_2Na as CF_3 source. A series of the desired products were afforded in satisfied yields under the transition-metal-free condition, which displays potential for further application in medicinal and agrochemical research.

Experimental Details.

Under N_2 atmosphere, a reaction tube (25 mL) equipped with a magnetic stirrer bar was charged with imidazo[1,2-a]pyridine (**1**, 0.3 mmol), CF_3SO_2Na (**2**, 0.2 mmol), acridinium (0.01 mmol, 5 mol %) and 1,2-DCE (2.0 mL). The reaction mixture was stirred with a 3 W blue LED irradiation at room temperature for 24 h, filtered through a pad of celite and then washed with CH_2Cl_2 (10 mL×3). The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (elute: EA/PE) to give the desired product **3**.

Acknowledgements

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Keywords: C-H trifluorometlylation • photochemistry • organocatalysis • imidazopyridines • radical reaction • metal-free

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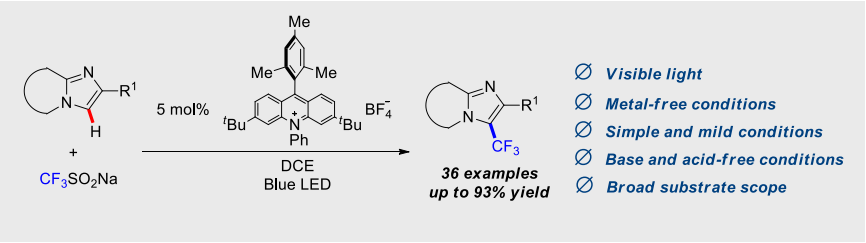

C-H Trifluoromethylation: An efficient, mild and photo redox-based protocol for the C-H trifluoromethylation of imidazo[1,2-a]pyridines has been developed using acridinium as photo redox catalyst and the easy-handling CF_3SO_2Na as CF_3 source. A series of desired products were afforded in satisfied yields under transition-metal-free condition, which displays potential for further application in synthetic research.

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