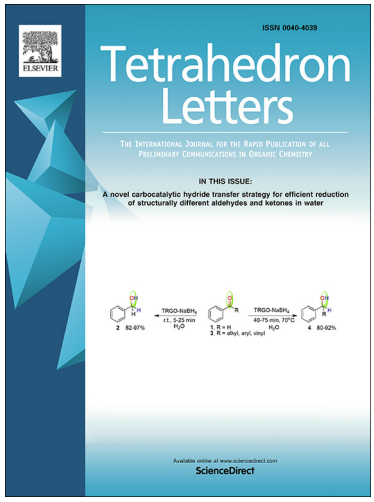

Transition-Metal-Free, Visible-Light-Mediated Regioselective C–H Trifluoromethylation of Imidazo[1,2-a]pyridines

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Transition-Metal-Free, Visible-Light-Mediated Regioselective C–H Trifluoromethylation of Imidazo[1,2-a]pyridines

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ABSTRACT

A transition-metal-free, visible-light-induced trifluoromethylation of imidazo[1,2-a]pyridines has been developed at mild conditions by employing cheap and commercially available anthraquinone-2-carboxylic acid (AQN-2-CO_2H) as the photo-organocatalyst, and Langlois reagent as the trifluoromethylating reagent. A series of 3-(trifluoromethyl)imidazo[1,2-a]pyridine derivatives with broad functionalities could be conveniently and efficiently obtained by direct regioselective functionalization.

Introduction

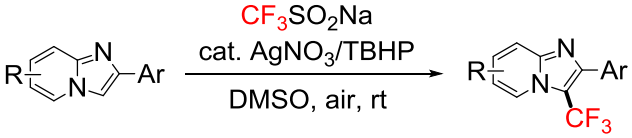
Fluorine-containing organic molecules have gained increasing attentions [1]. Fluorine can alter the physicochemical properties of organic molecules [2], and wide applications in medicinal chemistry, agrichemicals, and materials science [3]. Recently, impressive achievements have been covered about the trifluoromethylation of organic molecules [4], using electrophilic [5], nucleophilic [6], and radical [7] trifluoromethylating reagents. Among the developed methods of radical trifluoromethylation, photoredox-catalyzed radical trifluoromethylations have attracted significant notice [8].

Visible light is an abundant, eco-friendly and accessible energy source [9]. Over the past decade, visible-light photoredox-catalyzed organic synthesis has achieved great progress [10]. Since 2008, when MacMillan and coworkers reported visible light photoredox catalysis for organic synthesis by $Ru(bpy)_3Cl_2$ [11], numerous photocatalysts have entered this field, such as noble metal polypyridine and phenylpyridyl complexes [12], organic dyes [13]. In recent years, many photo-organocatalysts as inexpensive and nontoxic substitution have gained more favor [14]. In 2013, Itoh reported the direct trifluoromethylation of arenes and heteroarenes under visible light irradiation by using CF_3SO_2Na as the source of trifluoromethyl group and anthraquinone-2-carboxylic acid (AQN-2-CO_2H) as photoredox-catalyst [15].

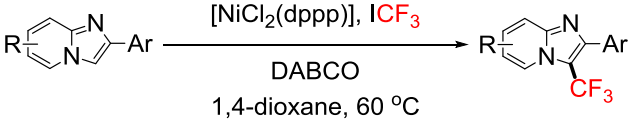
Imidazoheterocycles as an important nitrogen-containing compound, are the core of many drug molecules, such as Alpidem, Zolimidine, Saripidem, Zolpidem, and Minodronic Acid, etc [16]. Thus, substantial methods for the synthesis and modification of imidazoheterocycles have been extensively reported [17]. In the midst of them, there are a few reports about

a) Previous work

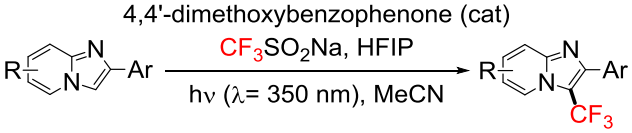
Hajra, 2015 (ref. 18):



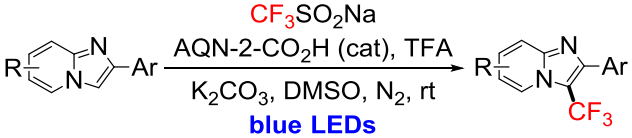
Wang, 2016 (ref. 19):



Rueping, 2016 (ref. 20):



b) This work: trifluoromethylation with visible light



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

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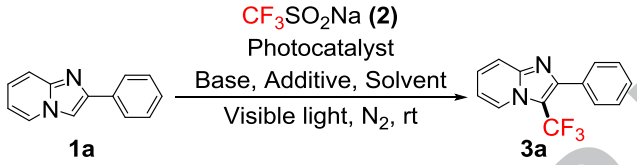
the introduction of trifluoromethyl groups into imidazoheterocycles that are very valuable means of modification. In 2015, Hajra reported silver-catalyzed regioselective oxidative trifluoromethylation of imidazoheterocycles with Langlois' reagent as trifluoromethylating reagent [18]. In 2016, Wang reported nickel-catalyzed C-H trifluorometylation of imidazoheterocycles with trifluoromethyl iodide (ICF_3) as trifluoromethylating reagent [19]. In 2016, Rueping reported photo-organocatalysed trifluoromethylation of imidazoheterocycles in batch and continuous flow with UV light [20]. For all we know, there is no method of transition-metal-free direct C-H trifluoromethylation of imidazoheterocycles using photo-organocatalyst in visible light. Herein, we report a direct method for the trifluoromethylation of imidazo[1,2-a]pyridines using anthraquinone-2-carboxylic acid (AQN-2-CO_2H) as photo-organocatalyst in visible light.

Results and discussion

Initially, we chose 2-phenylimidazo[1,2-a]pyridine (**1a**) and CF_3SO_2Na (Langlois reagent) as the model substrates to optimize the reaction conditions (Table 1). It is gratifying that the desired product was obtained in 74% yield (entry 1) when the reaction was conducted in photo-organocatalyst AQN-2-CO_2H (2 mol%), CF_3SO_2Na (4.0 equiv.), K_2CO_3 (0.5 equiv.) and TFA (trifluoroacetic acid, 0.06 equiv.) in DMSO solvent at room temperature under N_2 balloon atmosphere with 3 W blue LED irradiation. When the photo-organocatalyst AQN-2-CO_2H was replaced with AQN-2-CH_3, a remarkable decline in the yield of **3a** was recorded (54%, entry 2). Similarly, when the reaction was carried out by employing AQN-2-Cl (entry 3), Na Eosin Y (entry 4) or $Ru(bpy)_3Cl_2$•$6H_2O$ (entry 5) instead of AQN-2-CO_2H, the yield of **3a** has no improvement. Control experiments demonstrated that the yield was reduced when AQN-2-CO_2H was absent from the reaction mixture (entry 6) and no desired product was observed without light (entry 7). The yield of **3a** was also decreased without TFA or K_2CO_3 (entry 8 and 9). Furthermore, various solvents, including DMF, MeCN, THF and MeOH, were also investigated (entries 10-13). However, no higher yield was gained by altering the solvent. In addition, a series of bases, Cs_2CO_3, $(i\text{-}Pr)_2NEt$ and DBU (entries 14-16), were screened, but all led to lower product yields. Fortunately, a modicum of improvement of the yield was observed, with double the amount of K_2CO_3 (entry 17). Lastly, the oxygen was adverse to the reaction (entry 18).

Table 1. Optimization of reaction conditions [a]



1a **3a**

Entry	Photocatalyst	Base	Solvent	Yield (%) [b]
1	AQN-2-CO_2H	K_2CO_3	DMSO	74
2	AQN-2-CH_3	K_2CO_3	DMSO	54
3	AQN-2-Cl	K_2CO_3	DMSO	55
4	Na Eosin Y	K_2CO_3	DMSO	26
5	$Ru(bpy)_3Cl_2$•$6H_2O$	K_2CO_3	DMSO	41
6	—	K_2CO_3	DMSO	29
7 [c]	AQN-2-CO_2H	K_2CO_3	DMSO	0
8 [d]	AQN-2-CO_2H	K_2CO_3	DMSO	55
9	AQN-2-CO_2H	—	DMSO	30
10	AQN-2-CO_2H	K_2CO_3	DMF	65
11	AQN-2-CO_2H	K_2CO_3	CH3CN	40
12	AQN-2-CO_2H	K_2CO_3	THF	8
13	AQN-2-CO_2H	K_2CO_3	MeOH	46
14	AQN-2-CO_2H	Cs_2CO_3	DMSO	41
15	AQN-2-CO_2H	$(i\text{-}Pr)_2NEt$	DMSO	24
16	AQN-2-CO_2H	DBU	DMSO	26
17 [e]	AQN-2-CO_2H	K_2CO_3	DMSO	81
18 [f]	AQN-2-CO_2H	K_2CO_3	DMSO	39

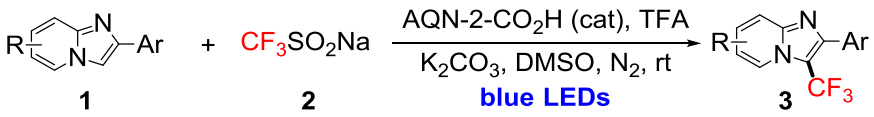
[a] Reaction conditions: **1a** (0.2 mmol), **2** (4.0 equiv.), photocatalyst (2 mol%), base (0.5 equiv.), TFA (0.06 equiv.) and solvent (2.5 mL), irradiation with 3 W blue LEDs for 24 h, N_2 balloon, rt.
[b] Isolated yield, based on **1a**.
[c] In the dark.
[d] TFA (0 equiv.) was added.
[e] Base (1 equiv.) was added.
[f] In oxygen balloon.

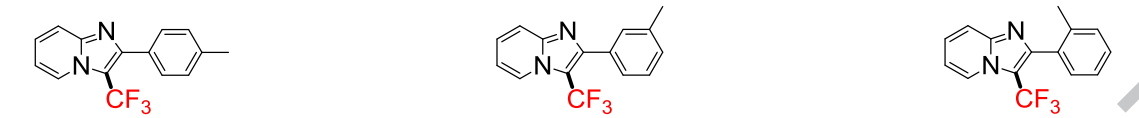
With the optimal reaction conditions in hand, we then investigated the scope of substrates, and the results are shown in Table 2. A wide range of substituted imidazo[1,2-a]pyridines reacted with CF_3SO_2Na to generate desired products with satisfactory yields. Imidazopyridines substituted with a methyl group at different positions gave moderate yields (**3b-d**). Imidazopyridine with another electron-donating group was also successfully trifluoromethylated (**3e**). The polyphenyl-substituted substrates also performed well under the optimal conditions, and the corresponding trifluoroethylated products (**3f-g**) were obtained in reasonable yields. Electron-withdrawing groups, such as fluoro, chloro, bromo, trifluoromethyl, on the phenyl ring at different position of imidazopyridines were well tolerated in this reaction system, 2-(4-bromophenyl)imidazo[1,2-a]pyridine especially gave a good yield (81%). The antiulcer drug Zolimidine was also smoothly trifluoromethylated with moderate yield (**3o**). Substrates with methyl or halogen atom on the pyridine ring were compatible under the standard conditions, as well. 2-thienylimidazo[1,2-a]pyridine also reacted well to afford corresponding product (**3s**). It is delightful that alkenyl, methyl or no group containing imidazopyridines also afforded the desired products in standard conditions.

To further expand the substrate scope of this methodology, other imidazoheterocycles like imidazo[2,1-b]thiazole and benzo[d]imidazo[2,1-b]thiazole were explored, and the results are shown in Table 3. The corresponding trifluoroethylated products (**5a-b**) were nevertheless afforded in moderate to good yields under the developed conditions.

To gain insight into the mechanism of this reaction, a few controlled experiments were carried out. No trifluoroethylated product was observed when the radical scavenger TEMPO was added into the system, and the desired product was detected by GC-MS (see the Supporting information for details), which indicated that a free radical process would be involved. From the experiments and literature reports [15, 18], the probable mechanism of the reaction is described in Scheme 2. At first, the CF_3 radical is generated from the photoredox-catalyzed cyclization. The ground and excited redox states of AQN are important for this process. In the cyclization, $CF_3SO_2^-$ would transfer electron to the excited state of AQN (AQN*) to generate $CF_3SO_2^{\bullet}$ and $AQN^{\bullet-}$ radical based on their redox potentials. $AQN^{\bullet-}$would be facile oxidized by SO_2 produced by cleavage of $CF_3SO_2^{\bullet}$ to regenerated AQN. Subsequently, the CF_3 radical reacted with imidazopyridines to form the radical intermediate **A**. The intermediate **A** was oxidized by the CF_3 radical to give the carbocation intermediate **B**. Finally, the intermediate **B** afforded the product by eliminating H^+.

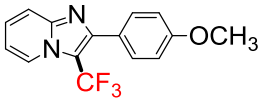
Table 2. Substrate Scope of Imidazopyridines [a]

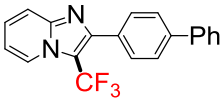


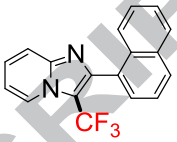

3b, 54%

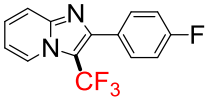
3c, 50%

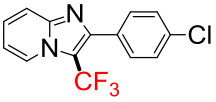
3d, 49%

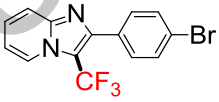

3e, 66%

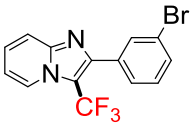

3f, 63%

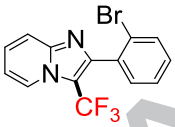

3g, 56%

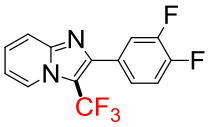

3h, 54%

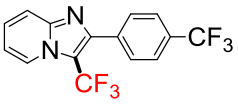

3i, 65%

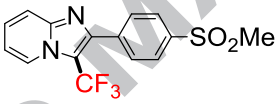

3j, 81%

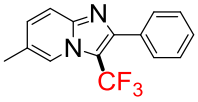

3k, 73%

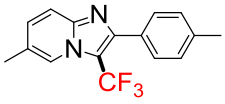

3l, 67%

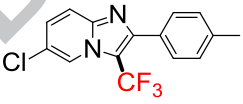

3m, 50%

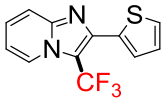

3n, 77%

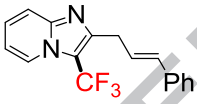

3o, 55%

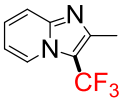

3p, 67%

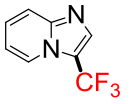

3q, 47%


3r, 45%


3s, 71%

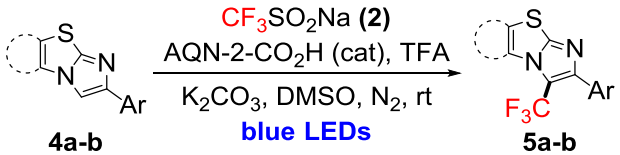

3t, 29%

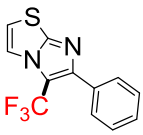

3u, 50%

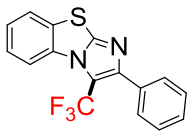

3v, 11%

[a] Reaction conditions: 1 (0.2 mmol), 2 (4.0 equiv.), AQN-2-CO_2H (2 mol%), K_2CO_3 (1.0 equiv.), TFA (0.06 equiv.) and DMSO (2.5 mL), irradiation with 3 W blue LEDs, N_2 balloon, rt.

Table 3. Substrate Scope of Imidazoheterocycles [a]



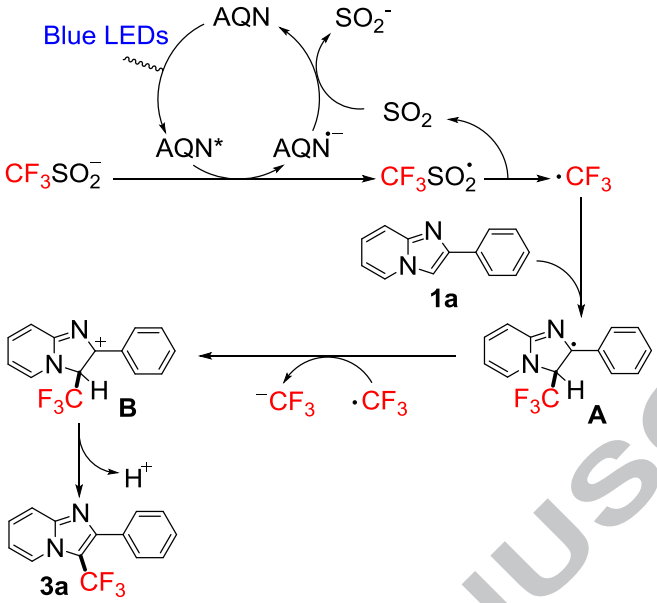

5a, 51%


5b, 70%

[a] Reaction conditions: 4 (0.2 mmol), 2 (4.0 equiv.), AQN-2-CO_2H (2 mol%), K_2CO_3 (1.0 equiv.), TFA (0.06 equiv.) and DMSO (2.5 mL), irradiation with 3 W blue LEDs, N_2 balloon, rt.

Conclusions

In conclusion, we have developed an efficient and mild method for trifluoromethylation of imidazopyridines by employing Langlois reagent as the source of trifluoromethyl group in visible light. This method is a transition-metal-free, dir-



Scheme 2. Plausible reaction mechanism.

ect trifluoromethylation by employing cheap trifluoromethyl-ating agent under visible light irradiation. A series of 3-(trifluoromethyl)imidazo[1,2-a]pyridine derivatives with broad functionalities could be conveniently and efficiently obtained in moderate to good yields. Other imidazoheterocycles like imidazo[2,1-b]thiazole and benzo[d]imidazo-[2,1-b]thiazole were also well tolerated to this protocol. We believe this method is of great value in introducing trifluoromethyl group into imizazopyridine derivatives to strengthen their physiochemical properties.

Acknowledgments

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Supplementary Material

Supplementary data to this article can be found online at …

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Transition-Metal-Free, Visible-Light-Mediated Regioselective C–H Trifluoromethylation of Imidazo[1,2-a]pyridines

Qiguang Zhou, Song Xu and Ronghua Zhang

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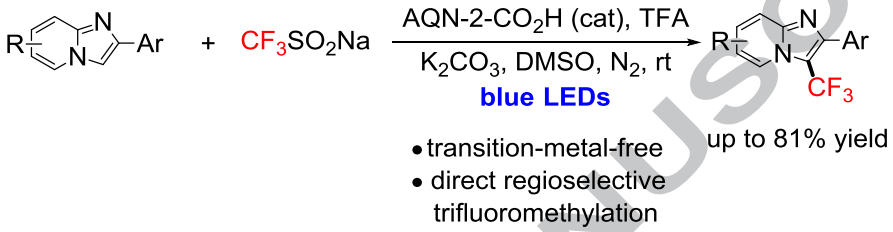

Highlights

Transition-metal-free visible-light-induced trifluoromethylation of imidazopyridines.

Anthraquinone-2-carboxylic acid as the photo-organocatalyst.

Photoredox catalyzed cyclization generate trifluoromethyl radical.