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Visible light mediated C–H trifluoromethylation of (hetero)arenes†

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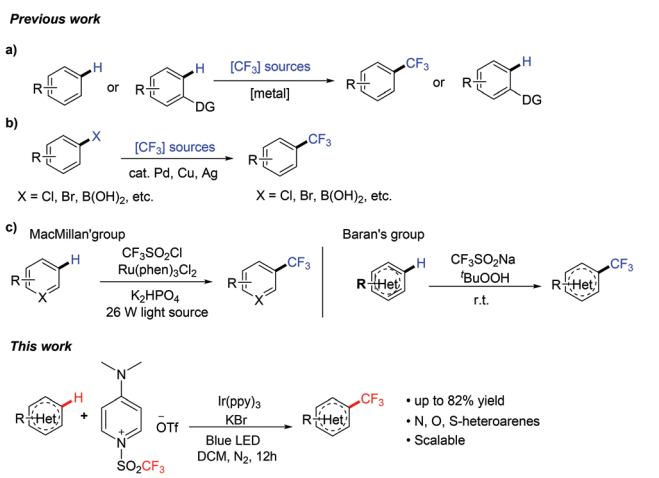
A protocol for visible light mediated C–H trifluoromethylation of unactivated (hetero)arenes under blue LED irradiation has been developed. The reaction enables the rapid construction of a range of CF_3-containing (hetero)arenes in moderate to high yields from the readily accessible trifluoromethylsulfonyl-pyridinium salt (TFSP). This protocol is also suitable for nitrogen-containing aromatic heterocycles, which are potentially useful in medicinal chemistry.

Introduction

Due to its strong electron-withdrawing effects and high lipophilicity, the trifluoromethyl group (CF_3) has been of increasing importance in pharmaceuticals, agrochemicals, and materials sciences.[1] During the past decades, a variety of CF_3-containing pharmaceuticals and agrochemicals, such as celecoxib, efavirenz, penthiopyrad, and beflubutamid, have been developed.[2] Since these bioactive molecules always possess aromatic heterocyclic skeletons, significant efforts have been devoted to developing efficient methods for the incorporation of a CF_3 group into these skeletons,[3] and various trifluoromethylation reagents have been applied, including CF_3SO_2Na,[4] CF_3I,[5] Togni reagent,[6] $TMSCF_3$,[7] $FSO_2CF_2CO_2Me$[8] and Umemoto reagent.[9] While these methods usually require stoichiometric metal salts or prefunctionalized substrates (Scheme 1(a) & (b)),[10] the development of efficient methods for introduction of CF_3 into heteroarenes is in high demand.

Direct C–H trifluoromethylation is an efficient approach for accessing CF_3-containing heteroarenes.[11] In the last few decades, many protocols have been developed, including transition metal-mediated/catalyzed cross-coupling C–H trifluoromethylation and radical trifluoromethylation[12] of arenes. In spite of these tremendous advances, most of them are limited due to stoichiometric amounts of metal salts and substrates with electron-rich or directing groups, which significantly restrict their synthetic application. Recently, significant progress has been made by MacMillan[12a] and Baran[12b] independently (Scheme 1(c)), efficiently achieving radical C–H trifluoromethylation of arenes and heteroarenes with broad substrate scopes under mild conditions, albeit with low regioselectivity. While aromatic heterocycles are essential pharmacophores in drugs, there is considerable interest in rapid introduction of CF_3 into these kinds of compounds with complexity from readily available starting materials through a visible light mediated C–H trifluoromethylation approach.



Scheme 1 Direct trifluoromethylation of arenes and heteroarenes.

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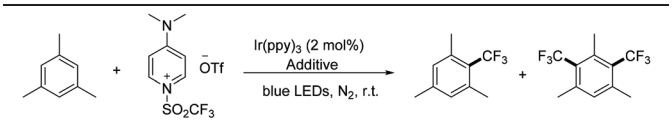
We have been interested in the development of easily accessible trifluoromethylation reagents with low cost. Previously, we have described that the trifluoromethylsulfonyl-pyridinium salt TFSP, a white solid synthesized from Tf_2O, is air-stable and convenient to use.[13] We have also realized an efficient azido or cyano-trifluoromethylation of alkenes employing TFSP as a facile CF_3 source.[14] Herein, we reported the visible light mediated C–H trifluoromethylation of unactivated (hetero) arenes in the presence of Ir(ppy)$_3$ under blue LED irradiation.

Results and discussion

To establish the optimal conditions, we initiated our investigation with mesitylene (**2a**) as a model substrate under blue LED irradiation by screening numerous variants, including photocatalysts, additives, and solvents (Table 1). Among the solvents tested, DCM was the best choice (entries 1–5). Among the photocatalysts examined, Ir(ppy)$_3$ showed the best catalytic activity (entries 6–9). After screening additives, KBr was selected (entries 10–12). Increasing the amount of TFSP to 2.5 equiv. and the volume of the solvent to 3 mL resulted in increases of both conversion and yield. Control experiments demonstrated that both the photocatalyst and visible light were necessary for the reaction (entries 15 and 16). Finally, treatment of **2a** with 2.5 equiv. of TFSP and 1.0 equiv. of KBr in the presence of Ir(ppy)$_3$ in 3 mL of DCM under blue LED irradiation gave the desired products **3a**-mono/**3a-bis** in 83/14 yields.

With the optimized reaction conditions in hand, we then investigated the substrate scope of the visible light mediated C–H trifluoromethylation (Table 2). Various (hetero)arenes underwent this transformation to give the desired products in moderate to high yields (**3a–x**). Arenes with electron-donating or neutral substituents were compatible with the reaction conditions (**3a–e**), whereas arenes with electron-withdrawing substituents exhibited little conversion. Heteroarenes with a wide range of functional groups could be tolerated, such as alkyl, halogen (–Cl and –Br), nitrile, acetyl, ester, *tert*-butoxycarbonyl, tosyl and trifluoromethyl (**3f–t**), except the nitro group. Interestingly, the carboxyl group, which tended to react with bases, remained intact in this C–H trifluoromethylation (**3k**). Although regioselectivities are always present for unsymmetrical heteroarenes with more than one reactive site, our protocol could lead to a major product with high regioselectivity and a desirable yield in most cases. For example, the trifluoromethylations of pyrroles (**3g–i**), furans (**3j and k**) and thiophenes (**3l and m**) were prone to occur at the C2 position with excellent regioselectivities and yields, synergistically governed by both the electron-rich effect and the steric effect. Moreover, this protocol was further applied in the late-stage functionalization of biologically active molecules and their derivatives. Naturally occurring motifs, such as pentoxifylline (**3u**), theophylline derivatives (**3v**) and coumarin derivatives (**3x**), were successfully transformed, thereby demonstrating the practicality of this protocol. It is worth noting that a gram-scale synthesis of

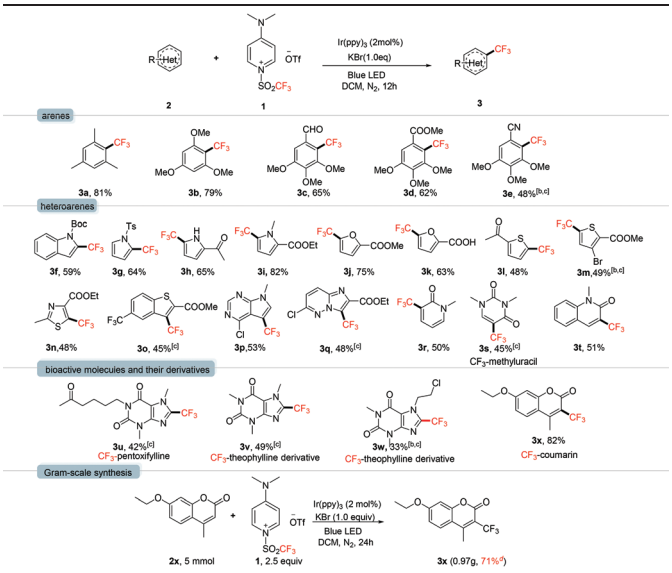
Table 1 Optimization of the reaction conditions[a]



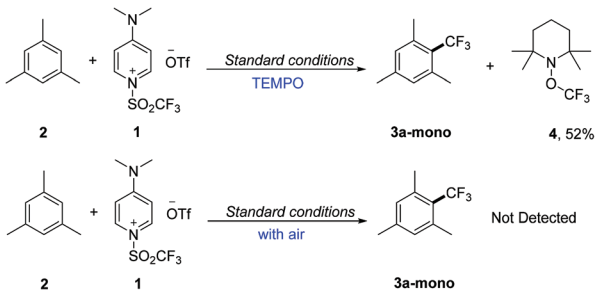
Entry	Photocatalyst	Solvent	Additive	Yield[b] (%)
1	Ir(ppy)$_3$	CH_3CN	—	44/1
2	Ir(ppy)$_3$	DMF	—	15/0
3	Ir(ppy)$_3$	DCM	—	65/11
4	Ir(ppy)$_3$	THF	—	6/0
5	Ir(ppy)$_3$	EA	—	47/1
6	Eosin Y	DCM	—	n.d.
7	Rhodamine B	DCM	—	n.d.
8	Ru(bpy)$_3$Cl$_2$	DCM	—	n.d.
9	Ir[dF(CF$_3$)ppy]$_2$(dtbpy)PF$_6$	DCM	—	7/0
10	Ir(ppy)$_3$	DCM	KBr	70/10
11	Ir(ppy)$_3$	DCM	NaBr	66/9
12	Ir(ppy)$_3$	DCM	$ZnBr_2$	n.d.
13[c]	Ir(ppy)$_3$	DCM	KBr	77/10
14[c,d]	**Ir(ppy)$_3$**	**DCM**	**KBr**	**83/14**
15[e]	Ir(ppy)$_3$	DCM	KBr	n.d.
16[f]	Ir(ppy)$_3$	DCM	KBr	7/0

[a] Reaction conditions: Substrate **2a** (0.2 mmol), **1** (2 equiv.), Ir(ppy)$_3$ (2 mol%) and the additive (1 equiv.) in the solvent (2 mL) were irradiated with 11.5 W blue LEDs at room temperature under a N_2 atmosphere for 12 h. [b] The yields represent the ratio of **3a**-mono/**3a-bis** and were determined by ^{19}F NMR spectroscopy with PhF as the internal standard. [c] **1** (2.5 equiv.). [d] DCM (3 mL). [e] Without blue LEDs. [f] Without Ir(ppy)$_3$.

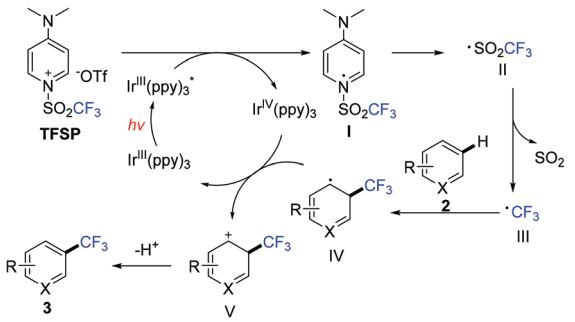
Table 2 Substrate scope of the trifluoromethylation[a,b,c,d]



[a] Reaction conditions: Substrates **2** (0.5 mmol), **1** (1.25 mmol), Ir(ppy)$_3$ (2 mol%) and KBr (0.5 mmol) in DCM (6 mL) were irradiated with blue LEDs under a N_2 atmosphere for 12 h. Yields of isolated products. [b] The reaction time was 48 h. [c] Some of the starting material remained. [d] 71% yield was obtained for a 5 mmol-scale reaction (5 mmol of **2x**).



Scheme 2 Preliminary mechanistic experiments.



Scheme 3 Proposed reaction mechanism.

CF_3-containing coumarin derivatives could proceed well with 71% yield.

To get an insight into the possible mechanism, the radical inhibitor 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added in the reaction system and the yield decreased dramatically. A TEMPO adduct, TEMPO-CF_3, was detected in 52% yield (determined by ^{19}F NMR spectroscopy) (Scheme 2, top). Moreover, the reaction was inhibited completely in the presence of oxygen (Scheme 2, bottom). All these indicate that the process involves a trifluoromethyl radical. Stern–Volmer measurements (see the ESI†) indicated that TFSP could effectively quench the excited state of the Ir-catalyst, reflecting that this process proceeded through a single electron transfer (SET) between TFSP and the excited state IrIII(ppy)$_3$*. Based on the above results, a plausible reaction mechanism is proposed as shown in Scheme 3. Firstly, $Ir^{III}(ppy)_3$ was irradiated with blue LEDs to generate the excited state $Ir^{III}(ppy)_3$*; the latter could reduce **TFSP** to generate radical **I**. Homolysis of radical **I** leads to trifluoromethanesulfonyl radical **II** which undergoes the loss of SO_2 to give trifluoromethyl radical **III**.[15] The latter reacts with (hetero)arenes **2** to give radical **IV** which is subsequently oxidized by $Ir^{IV}(ppy)_3$ to give carbocation intermediate **V** with the regeneration of $Ir^{III}(ppy)_3$. The carbocation intermediate **V** undergoes deprotonation to give the target product **3**.

Conclusions

In summary, we have developed an efficient method for the synthesis of CF_3-containing (hetero)arenes *via* a visible light mediated C–H trifluoromethylation. With the readily accessible trifluoromethylsulfonyl-pyridinium salt (TFSP), a variety of aromatic (hetero)cycles undergo catalytic C–H trifluoromethylation to give (hetero)arenes in moderate to high yields. This visible light mediated C–H trifluoromethylation provides a rapid access to various CF_3-containing (hetero)arenes, especially nitrogen-containing aromatic heterocycles, which are potentially useful in medicinal chemistry.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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