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An approach to 6-trifluoromethyl-phenanthridines through visible-light-mediated intramolecular radical cyclization of trifluoroacetimidoyl chlorides[†]

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A mild and efficient visible light-mediated intramolecular radical cyclization of trifluoroacetimidoyl chlorides is developed for the synthesis of 6-(trifluoromethyl)phenanthridine derivatives. The reaction involves the generation of radical intermediates from $C(sp^2)$ -Cl bonds and a homolytic radical aromatic substitution (HAS) process.

Radical-mediated reactions have received considerable attention and become a powerful synthetic methodology in the past decades because of their high efficiency in forming new bonds and high functional-group compatibility.1 Among them, freeradical generation from organohalides is by far the most commonly utilized method to access carbon-centered radicals that have found numerous applications in chemical synthesis.² However, most of the reported such reactions often employ stoichiometric hazardous radical initiators. This drawback limits their utility and applications in organic synthesis as well as in the areas of pharmaceutical industry. Among the recent developments aimed at circumventing such drawbacks, the visible-light-induced radical reaction is an environmental alternative to traditional radical transformation by avoiding the use of hazardous radical initiators, and substantial achievements have been made.3 It was shown that the generation of radical intermediates from activated carbon-halogen bonds, such as α-halocarbonyl compounds,⁴ polyhalogenated alkanes,⁵ benzyl bromides bearing strong electron-withdrawing groups,6 and geminal halogenated sugars7 can be achieved with photocatalysis. In contrast, the in situ generation of radicals from organic halides possessing a $C(sp^2)$ -X bond by visible-light photoredox catalysis has been less explored, presumably owing to their high redox potentials.8 Recently, Stephenson et al. and Lee et al., independently, reported the reductive

transformations of unactivated alkyl, alkenyl and aryl iodides based on iridium(III) photocatalyst.^{8a,b} More recently, Zhou and co-workers have developed an efficient visible-light-promoted radical cyclization of trifluoroacetimidoyl chlorides with alkynes leading to the formation of 2-trifluoromethyl quinolines.⁹ Inspired by these results, we envisioned that the radical cyclization of trifluoroacetimidoyl chlorides in an intramolecular setting could be carried out to form trifluoromethylated phenanthridines.

Phenanthridine is an important scaffold found in many natural products, optoelectronic materials and synthetic compounds with various biological activities.10 In particular, trifluoromethylated phenanthridines are of significant interest because trifluoromethyl group can dramatically change the physical properties and biological activities of organic compounds.11 Major methods for the synthesis of this class of molecules include: (1) rhodium-catalyzed [2 + 2 + 2] cycloaddition reaction between diynes and alkynes (path a, Scheme 1);12 (2) palladium-catalyzed tandem Suzuki/C-H arylation reaction of N-aryltrifluoroacetimidoyl chlorides with arylboronic acids (path b);13 and (3) intermolecular radical addition/cyclization of 2-isocyanobiaryls with CF₃ radicals (path c).¹⁴ In connection with our interest radical cyclizations,15 we herein report an efficient catalytic protocol for the synthesis of 6-trifluoromethyl phenanthridines through photoredox-catalyzed intramolecular radical cyclization of trifluoroacetimidoyl chlorides.

The initial reaction of *N*-biaryltrifluoroacetimidoyl chloride (1a) was carried out in the presence of 3 mol% Ru(bpy)₃Cl₂·6H₂O as the catalyst, 2.0 equiv. of Et₃N as the base in CH₃CN under visible light irradiation (5 W blue LED). This set of conditions indeed afforded the desired phenanthridine 2a in 72% yield after 6 hours (Table 1, entry 1). Subsequently, we explored the effect of different bases and observed that the addition of organic base such as (iPr)₂NEt and (*n*Bu)₃N resulted in a clean reaction, affording better yields of 80% and 86%, respectively (entries 2–3). Inorganic bases, such as K₂CO₃, Cs₂CO₃ and NaOAc, almost completely shut down the radical cyclization (entry 4). The organic base was found to be essential



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Scheme 1 Synthesis of phenanthridines.

Table 1 Optimization of reaction conditions for 2a^a



Entry	Catalyst	Base	Solvent	Yield ^b (%)
1	Ru(bpy) ₂ Cl ₂ ·6H ₂ O	Et₂N	CH ₂ CN	72
2	$Ru(bpy)_3Cl_2 \cdot 6H_2O$	(ipr) ₂ NEt	CH ₃ CN	80
3	$Ru(bpy)_3Cl_2 \cdot 6H_2O$	$(nBu)_3N$	CH ₃ CN	86
4^c	$Ru(bpy)_3Cl_2 \cdot 6H_2O$	K ₂ CO ₃	CH ₃ CN	NR
5	$Ru(bpy)_3Cl_2 \cdot 6H_2O$	_ 0	CH ₃ CN	NR
6	$Ru(bpy)_{3}Cl_{2} \cdot 6H_{2}O$	(<i>n</i> Bu)₃N	DMF	75
7	$Ru(bpy)_3Cl_2 \cdot 6H_2O$	$(nBu)_3N$	NMP	70
8	$Ru(bpy)_{3}Cl_{2} \cdot 6H_{2}O$	$(nBu)_3N$	Toluene	36
9	$Ru(bpy)_3(PF_6)_2$	$(nBu)_3N$	CH ₃ CN	85
10	Eosin Y	$(nBu)_3N$	CH ₃ CN	52
11^d	_	$(nBu)_3N$	CH ₃ CN	NR
12^e	$Ru(bpy)_3Cl_2 \cdot 6H_2O$	$(nBu)_3N$	CH ₃ CN	53

^a Reaction conditions: 1a (0.3 mmol), catalyst (3 mol%) and base (2 equiv.) in solvent (3.0 mL) was irradiated by 5 W blue LED for 6 h.
 ^b Isolated yield. ^c Inorganic base: K₂CO₃, Cs₂CO₃, NaOAc were used.
 ^d Reaction was carried out without catalyst. ^e Reaction was carried out under ambient light.

to the reaction, since no desired product was detected in the absence of base (entry 5). Other solvents were found to be less effective for this reaction. Under the same reaction conditions, employment of the catalyst $Ru(bpy)_3(PF6)_2$ afforded a similar result. Photocatalytic active organic dye Eosin Y resulted in low yield. As expected, no reaction occurred in the absence of photocatalyst (entry 11). When the reaction was carried out

under ambient light, the reaction was much more sluggish with dramatically decreased yield (entry 12).

With the optimized reaction conditions in hand, we then explored the scope and limitations of the above reaction, and the results are summarized in Table 2. The effect of substituents on the arene (Ar_2) undergoing the cyclization reaction was first examined. This aromatic ring was found to be tolerant of both electron-rich groups such as methyl (2b) and methoxy (2e) and electron-deficient groups such as trifluoromethyl (2h) and phenyl (2i) on the *para*-position. The halogen-containing substrates (2f and 2j) were also compatible and gave the corresponding products in good yields, which allows further functionalization of the phenanthridines. The reaction was more



^{*a*} Reaction conditions: 1 (0.3 mmol), Ru(bpy)₃Cl₂·6H₂O (3 mol%) and (*n*Bu)₃N (0.6 mmol) in CH₃CN (3.0 mL) was irradiated by 5 W blue LED 6 h. ^{*b*} Isolated yield. ^{*c*} The ratio of regioisomers based on ¹⁹F NMR analysis. ^{*d*} Reacted for 12 h.

sensitive to the position of the substituents. For *ortho*substituted substrates, the corresponding phenanthridines (2j,k) were obtained in low yields due to the steric effect. The use of *meta*-substituted substrate **11** resulted in a mixture of the products **21** and **21'** with moderate regioselectivity (3:2). By contrast, the naphthyl substrate **1m** underwent this transformation to afford **2m** as the major regioisomer. In addition, this reaction was also sustainable with the thienyl group as substituent (**2n**). Next, the substituent effect at the arene moiety Ar_1 was evaluated. In all cases, substrates **10–s** proceeded smoothly to give the corresponding trifluoromethylated phenanthridines **20–s** in moderate to good yields. Likewise, the perfluoroalkylated substrate **1t** was also tested in this cyclization reaction, and the corresponding 6-perfluoroalkylated phenanthridine **2t** was formed smoothly.

To gain mechanistic insight into the photoredox-catalyzed intramolecular cyclization, the reaction was performed in presence of the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy). Under these conditions, the reaction was completely shut off, which could indicate that this reaction involves radical intermediates (Scheme 2).

According to the above experimental results and previous reports a plausible mechanism is proposed (Scheme 3). Initially, photoexcitation of $[Ru(bpy)_3]^{2+}$ by visible light generates excited $[Ru(bpy)_3]^{2+*}$, which is reductively quenched *via* single-electron-transfer (SET) by $(nBu)_3N$ to give $[Ru(bpy)_3]^+$ and the triethy-lammonium radical cation. The $[Ru(bpy)_3]^+$ then performs a single-electron reduction of the $C(sp^2)$ –Cl bond, forming a radical intermediate **A** and regenerating the catalyst $[Ru(bpy)_3]^{2+}$. Subsequently, radical **A** undergoes intramolecular cyclization to give the cyclohexadienyl radical intermediate **B**.



Scheme 2 Control experiment.



Scheme 3 Plausible mechanism.

Oxidation of the radical intermediate **B** followed by rearomatization provides the observed product **2**.

In summary, we have developed a mild and efficient method for the synthesis of 6-(trifluoromethyl)phenanthridines by means of visible-light-induced intramolecular radical cyclization of trifluoroacetimidoyl chlorides. This methodology represents a potential utility of photoredox catalysis for the generation of imidoyl radical by activation of $C(sp^2)$ –Cl bond.

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