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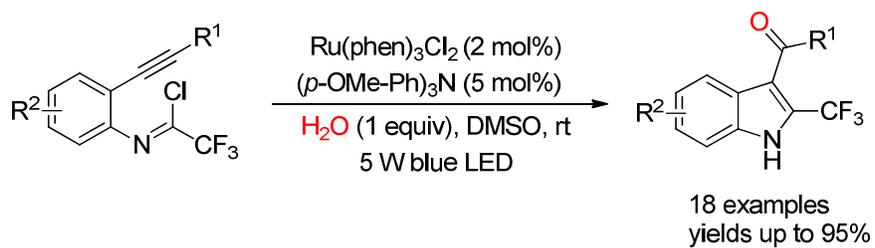


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A visible-light induced intramolecular radical cyclization of N-[2-(alkynyl)phenyl]trifluoroacetimidoyl chlorides is described. The reaction allows the rapid construction of diverse 2-trifluoromethyl-3-acylindoles in a sequential C-C and C-O bonds formation process under mild conditions.



Journal Name

COMMUNICATION

Synthesis of 2-Trifluoromethyl Indoles via Visible-Light Induced Intramolecular Radical Cyclization

Received 00th January 20xx,
Accepted 00th January 20xx

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DOI: 10.1039/x0xx00000x

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A visible-light induced intramolecular radical cyclization of N-[2-(alkynyl)phenyl]trifluoroacetimidoyl chlorides is described. The reaction allows the rapid construction of diverse 2-trifluoromethyl-3-acylindoles in a sequential C-C and C-O bonds formation process under mild conditions.

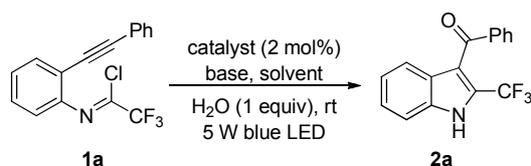
Organofluorine compounds are playing more and more important roles in medicinal chemistry, agriculture chemistry and material science.¹ Screening of fluorinated derivatives by means of fragment based drug discovery (FBDD) has become a widely used method to discover novel therapeutics.² Owing to the high prevalence of indole scaffolds in nature products,³ the development of pharmaceutically important molecules based on 2-trifluoromethylated indoles core structures has been frequently employed over the last decades.⁴ Consequently, it is of importance to develop novel and efficient approaches to access this compound class.⁵⁻¹² Transition-metal catalyzed radical⁵ or electrophilic trifluoromethylation⁶ are straight approaches to introduce a CF₃ group into indoles. However, these methods revealed some drawbacks such as the use of expensive trifluoromethylated reagents, poor regioselectivity, or extra steps for N-protection and deprotection. Another commonly used strategy is the assembly of 2-(trifluoromethyl)indoles starting from easily available trifluoromethylated building blocks.⁷⁻¹² Several methods such as Cu-catalyzed coupling of 2-halotrifluoroacetanilides with β-keto esters,⁸ Pd-catalyzed intramolecular cyclization of N-(*o*-haloaryl)-alkynylimines,⁹ titanium-catalyzed carbonyl coupling of 2-acyltrifluoroacetanilides,¹⁰ Pd-catalyzed annulation of fluoroalkylated alkynes with *o*-iodoaniline,¹¹ and radical trifluoromethylation of isonitriles¹² have been reported. Despite great achievements in this area, there is still room for innovation, especially from the viewpoints of green and environmentally friendly organic synthesis.

Recently, visible-light photoredox catalyst has emerged as a powerful tool to develop sustainable chemical processes.¹³ In this context, we reported a visible-light-promoted intermolecular radical cyclization of trifluoroacetimidoyl chlorides with alkynes leading to the formation of 2-trifluoromethyl quinolines.¹⁴ Fu and co-worker developed an intramolecular radical cyclization of trifluoroacetimidoyl chlorides for the synthesis of 6-(trifluoromethyl)phenanthridine derivatives based on the activation of C(sp²)-Cl bond under visible-light irradiation.¹⁵ As a continuation of our interest in visible-light photoredox radical chemistry,¹⁶ we envisioned that this protocol could facilitate the intramolecular radical cyclization of N-(*o*-alkylaryl) trifluoroacetimidoyl chlorides **1** to give 2-trifluoromethyl-3-acylindole derivatives. Although Uneyama reported a similar radical process in 1993, the reaction required the irradiation of iodide or telluride of **1** under a 438W high-pressure mercury lamp for 3-4 days, which restricted its practical application in the synthesis.¹⁷

To validate our hypothesis, trifluoroacetimidoyl chloride **1a**, which could be easily prepared from CF₃CO₂H, CCl₄, and *o*-alkynylaniline,¹⁸ was chosen as the model substrate for the optimization. Initially, **1a** was irradiated with a 5 W blue LED in the presence of Ru(bpy)₃Cl₂ (2 mol%), ⁿBu₃N (2 equiv.) and H₂O (1 equiv.) in 0.5 mL of MeCN at room temperature for 12 hours. To our disappointment, **1a** was completely hydrolyzed to give trifluoroacetamide (Table 1, entry 1). The use of the mixture of ⁿBu₃N (0.25 equiv.) and K₂CO₃ (2 equiv.), which is a good option in our previous intermolecular reaction,¹⁴ also led to the full hydrolysis of **1a** (Table 1, entry 2). We speculated this outcome was caused by two reasons: 1) the direct hydrolysis is favored by the strong bases; 2) The electron donation ability of tributylamine is not competent enough to initiate a fast radical reaction. To circumvent these problems, four weak bases including Ph₃N (E_{red} = +0.92 V vs SCE), (*p*-OMe-Ph)Ph₂N (E_{red} = +0.76 V vs SCE), (*p*-OMe-Ph)₂PhN (E_{red} = +0.63 V vs SCE) and (*p*-OMe-Ph)₃N (E_{red} = +0.55 V vs SCE) were examined (Table 1 entries 3-6).¹⁹ We were delight to find that the desired 2-CF₃ indole **2a** was obtained in the yield of 26% when 30 mol% of (*p*-OMe-Ph)Ph₂N was used. (*p*-OMe-Ph)Ph₂N has similar electron donation ability as ⁿBu₃N (E_{red} = +0.78 V vs SCE),²⁰ but is a weaker

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Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x0xx00000x

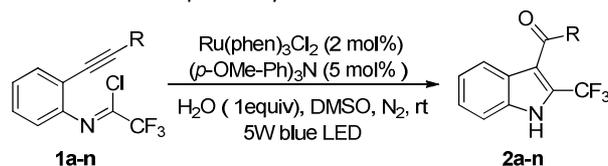
Table 1 Optimization of Reaction Conditions.^a

Entry	Catalyst	Base (mol%)	Solvent	Yield (%) ^b
1	Ru(bpy) ₃ Cl ₂	<i>n</i> Bu ₃ N (200)	MeCN	ND ^c
2 ^d	Ru(bpy) ₃ Cl ₂	<i>n</i> Bu ₃ N (30)	MeCN	ND
3	Ru(bpy) ₃ Cl ₂	Ph ₃ N (30)	MeCN	ND
4	Ru(bpy) ₃ Cl ₂	(<i>p</i> -OMe-Ph) ₂ PhN (30)	MeCN	26
5	Ru(bpy) ₃ Cl ₂	(<i>p</i> -OMe-Ph) ₂ PhN (30)	MeCN	43
6	Ru(bpy) ₃ Cl ₂	(<i>p</i> -OMe-Ph) ₃ N (30)	MeCN	55
7	Ir(ppy) ₃	(<i>p</i> -OMe-Ph) ₃ N (30)	MeCN	55
8	[Ir(ppy) ₂ (dtbbpy)]PF ₆	(<i>p</i> -OMe-Ph) ₃ N (30)	MeCN	28
9	Eosin Y	(<i>p</i> -OMe-Ph) ₃ N (30)	MeCN	ND
10	Rose Begals	(<i>p</i> -OMe-Ph) ₃ N (30)	MeCN	ND
11	Ru(phen) ₃ Cl ₂	(<i>p</i> -OMe-Ph) ₃ N (30)	MeCN	71
12	Ru(phen) ₃ Cl ₂	(<i>p</i> -OMe-Ph) ₃ N (30)	DMSO	89
13	Ru(phen)₃Cl₂	(<i>p</i>-OMe-Ph)₃N (5)	DMSO	96
14	—	(<i>p</i> -OMe-Ph) ₃ N (5)	DMSO	ND
15 ^e	Ru(phen) ₃ Cl ₂	(<i>p</i> -OMe-Ph) ₃ N (5)	DMSO	ND

^aReaction conditions: **1a** (0.2 mmol), catalyst (2 mol%), H₂O (1 equiv.), solvent (0.5 mL), rt, N₂, 5 W blue LED. ^bYields were determined by ¹H NMR. ^cNot detected. ^d2 equiv. of K₂CO₃ was added. ^eNo light.

base than *n*Bu₃N. The yields were further increased to 43% and then 55% when (*p*-OMe-Ph)₂PhN and (*p*-OMe-Ph)₃N were used as the electron donors respectively. It is worth noting that the red solution of **1a**, Ru(bpy)₃Cl₂ and (*p*-OMe-Ph)₃N in MeCN turns into deep blue immediately upon stirring under visible light irradiation. This dramatic color change indicates the formation of triarylamine radical cation, which has been confirmed by Gopidas and Flowers in their kinetic investigation of the electron-transfer reaction.^{19b} When Ru(bpy)₃Cl₂ was replaced with Ir(ppy)₃ catalyst, the yield was almost identical (Table 1, entry 7), while [Ir(ppy)₂(dtbbpy)]PF₆ afforded the indole **2a** only in 28% yield (Table 1, entry 8). We also examined the reactions using organic dyes such as eosin Y and Rose Begals as the catalysts, but none of desired product was detected (Table 1, entries 9 and 10). Gratifyingly, the reaction gave the 2-CF₃ indole **2a** in 71% yield when Ru(phen)₃Cl₂ was employed (Table 1, entry 11). By applying this catalyst system with dry DMSO as the solvent, **2a** was formed in 89% yield (Table 1, entry 12). Reducing the loading of (*p*-OMe-Ph)₃N to 5 mol% led to an almost quantitative 96% yield (Table 1, entry 13). The reaction did not take place in the absence of photocatalyst, or without the irradiation of blue LED (Table 1, entries 14 and 15). Notably, as a sharp contrast to time consuming method developed by Uneyama, the present reaction could be completed in 1 hour.

With the optimized reaction conditions in hand, we explored the versatility and functional group tolerance of this photoreaction. First, the different alkynes connected to the *ortho*-position of *N*-phenyl trifluoroacetimidoyl chlorides were varied. As summarized in table 2, the reaction was not significantly affected by the

Table 2 Substrate scope of alkyne motif.^a

Entry	Substrate	R	Product	Yield% ^b
1	1a	Ph	2a	90
2	1b		2b	73
3	1c		2c	68
4	1d		2d	82
5	1e		2e	75
6	1f		2f	75
7	1g		2g	77
8	1h		2h	78
9	1i		2i	79
10	1j		2j	76
11	1k	<i>n</i> -C ₄ H ₉	2k	43
12	1l		2l	28
13	1m	H	2m	50
14	1n	TMS	2n	36

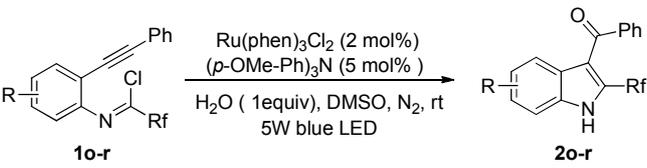
^a All the reaction were carried out by using trifluoroacetimidoyl chlorides **1** (0.2 mmol), Ru(phen)₃Cl₂ (2 mol%), (*p*-OMe-Ph)₃N (5 mol%), H₂O (1 equiv.) in 0.5ml dry DMSO under the irradiation of 5 W blue LED at room temperature. ^b Isolated yield.

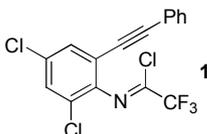
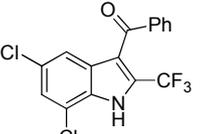
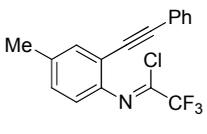
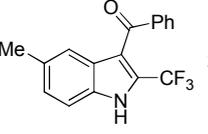
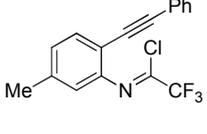
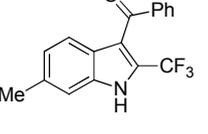
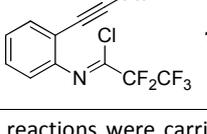
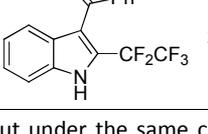
substituents on the phenyl ring of the alkyne moiety, both electron-donating groups such as Me, OMe and electron-withdrawing groups including halogen (F, Cl, Br) and cyano group could be well-tolerated. Substrates with the other aromatics and heteroaromatic ring were also examined, and they also worked efficiently and gave good yields of the desired products such as **2i** and **2j**. Hexynyl substituted trifluoroacetimidoyl chloride **1k** was successfully assembled to form 2-trifluoromethyl indole **2k** in the yield of 43%. Substrate **1l** bearing a cyclopropane motif generated the desired product **2l** in diminished yield, but no ring open product was detected in this case. It is worth noting that terminal alkyne **1n** was suitable substrate for the reaction, affording 2-trifluoromethyl-3-formyl indole **2m** in 50% yield. Owing to the prosperous chemical

transformation of formyl group, this compound has been used as the key intermediate for the preparation of various 2-trifluoromethylindole based drug candidates. Finally, trimethylsilane group, which is easily removed in visible-light reactions, also tolerate the reaction conditions.

Subsequently, substrates scope with respects to substitutes on the phenyl group attached to nitrogen were investigated (Table 3). The reaction of the *o,p*-Cl₂ substituted imidoyl chloride **1o** gave the 93% yield of **2o** and no dehalogenated product observed. Good yields were obtained when placing a methyl-substituent at the *para*- or *meta*-position of the aromatic ring. An analogous substrate bearing a perfluoroethyl substituent on acetimidoyl chloride **1r** afforded an excellent yield of **2r** as well.

Table 3 Substrate scope.^a

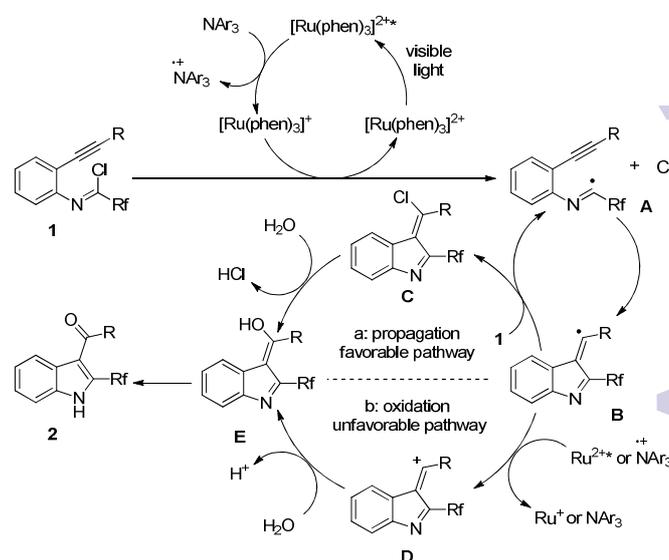


Entry	Substrate	Product	Yield% ^b
1			93
2			75
3			76
4			95

^a All the reactions were carried out under the same conditions as described in Table 2. ^b Isolated yield.

A plausible mechanism for this visible-light induced intramolecular radical cyclization is proposed in Scheme 1.^{13,14} Initially, photoexcitation of Ru(phen)₃²⁺ generates excited [Ru(phen)₃²⁺]*. Single-electron transfer from electron donor tris(4-anisyl)amine to excited [Ru(phen)₃²⁺]* gives rise to Ru(phen)₃⁺ and NAr₃ radical cation *via* a reductive quenching process. Reductive cleavage of the sp² C-Cl bond of trifluoroacetimidoyl chloride **1** by the Ru(phen)₃⁺ gives imidoyl radical **A** with concomitant regeneration of Ru(phen)₃²⁺ catalyst. Subsequently, intramolecular radical addition of **A** to alkyne provide vinyl radical **B**, which might deliver 2-CF₃ indole **2** through two different pathways: path a is the

propagation between vinyl radical **B** and **1**, affording vinyl chloride **C** and imidoyl radical **A**. The 3-acyl moiety would be derived by hydrolysis of vinyl chloride **C**;¹⁷ path b involves single-electron oxidation of **A** by excited [Ru(phen)₃²⁺]* or by the tris(4-anisyl)amine radical cation **B** to give vinyl cation **D**, which was trapped by H₂O and then enol isomerization. To understand the mechanism of the reaction, a "light/dark" experiment was performed. Initially, the reaction was irradiated with visible-light for 5 minutes, ¹H-NMR analysis revealed only 26% of **1a** was consumed. Then the light source was removed and the reaction was stirred in the dark for additional 1 hour, the desired indole **2a** was finally obtained in the yield of 79%. This experiment demonstrated that continuous irradiation of visible light was not necessary for this transformation. Moreover, the oxidant of a vinyl radical to a vinyl cation has been proved to be a thermodynamically unfavored process in Stephenson's report on visible-light mediated atom transfer radical addition of organic halides to alkynes.²¹ As a result, an alternative mechanism which the formation of vinyl cation is less likely in this transformation.



Scheme 1 Plausible reaction mechanism

Conclusions

In conclusion, we have developed an efficient method for the synthesis of 2-trifluoromethyl indoles via intramolecular radical cyclization of trifluoroacetimidoyl chlorides. Moreover, this approach allows the installation of various acyl groups formyl group onto the 3-position of indoles under mild conditions. A wide range of functional groups were found that are able to tolerate the reaction conditions. Mechanistically, this photoreaction was initiated by visible-light photoredox catalyst, followed by a radical chain propagation process. Further application of this method is currently under investigation in our laboratory.

Notes and references

‡ We are grateful to the funds from the National Natural Science Foundation of China (21472249 and 21202207), the Pearl River S&T Nova Program of Guangzhou (2013J2200017), and the Fundamental Research Funds for the Central Universities (14lgzd05).

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