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Synthesis of Fused Pyran Derivatives via Visible-Light-Induced Cascade Cyclization of 1,7-Enynes with Acyl Chlorides

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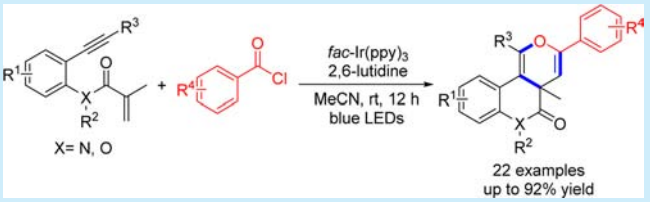
Supporting Information

ABSTRACT: A photocatalytic cascade cyclization of 1,7-enynes with acyl chlorides has been established. This method offers an operationally simple access to diverse fused pyran derivatives with a broad substrate scope in high yields from simple acyl chlorides via an acyl radical intermediate.

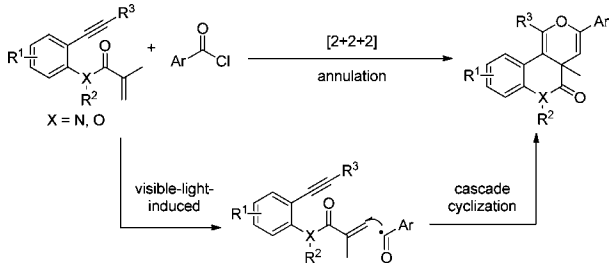


Fused pyran derivatives and their structural analogues are important heterocyclic motifs[1] that are prevalent in natural products exhibiting a wide of bioactivities. These valuable skeletons have also been widely applied to organic synthesis, drug discovery, and material science.[2] Therefore, many chemists have been interested in developing novel and efficient methods to synthesize these compounds.[3] However, the established methods of constructing pyran skeletons still requires several synthetic steps with rather low overall yields.[4] Thus, the development of new atom- and step-economic reactions to construct those valuable heterocyclic motifs will make an important contribution to this research field.

Acyl radicals are valuable radical intermediates with a long history, but the application of these radicals in organic synthesis has largely lagged behind that of simple alkyl and even vinyl radicals due to their nucleophilicity and the strict conditions required for their generation.[5] Recently, many chemists focused on the generation and development of acyl radicals via various strategies.[6] Wallentin's group[7] and Wang's group[8] reported that acyl radicals derived from aromatic carboxylic acids and α-oxocarboxylic acids, respectively, have been used to initiate cyclization cascades to generate heterocyclic compounds. Notably, Li and co-workers[9d] applied acyl radicals derived from simple aldehydes into the iron-catalyzed radical cascade cyclization[9,10] of 1,*n*-enynes, which provided the most rapid and atom-economic protocol to build fused polycyclic hydrocarbons. For all this, it is highly desired to develop more efficient methods under environmentally benign and mild conditions to produce various acyl radicals and apply these important intermediates to construct complex molecular scaffolds.

In recent years, the increasingly rapid development of visible-light photoredox catalysis has offered a powerful and straightforward tool to generate a variety of radical intermediates via unique one-electron-transfer pathways, which promoted the inventions of many valuable new chemical reactions.[11] Inspired by the radical cascade cyclization[12] and based on our work on the development of visible-light photoredox catalysis reactions,[13] we envisioned that it would be possible to generate acyl radicals from commercially available and abundant acyl chlorides and then use them in valuable cascade annulation reactions. More specifically, an acyl radical would be generated from a simple acyl chloride under visible-light-mediated photoredox catalysis and then used as a nucleophilic radical to start the cascade cyclization of 1,7-enynes (Scheme 1).

Scheme 1. Visible-Light-Induced Cascade Cyclization



A detailed description of our proposed mechanism for the radical cascade cyclization of a 1,7-enyne with acyl chloride is outlined in Scheme 2. At the beginning, irradiation of [*fac*-^{III}Ir(ppy)$_3$] (in which ppy = 2-phenylpyridine) will generate the long-lived *[*fac*-^{III}Ir(ppy)$_3$] at the excited state (τ = 1.9 μs).[14] Since *[*fac*-^{III}Ir(ppy)$_3$] can function as either a reductant or an oxidant, this excited state may undergo a single-electron transfer event even with a scarce amount of benzoyl chloride **2a** to initiate the catalytic cycle and provide the oxidizing [*fac*-^{IV}Ir(ppy)$_3$]. The nucleophilic acyl radical **4** is generated at this time and starts the radical cyclization process via attacking the carbon−carbon double bond of 1,7-enyne **1a**. Then, the vinyl radical intermediate **6** is formed by a radical cyclization with the C−C triple bond and oxidized by

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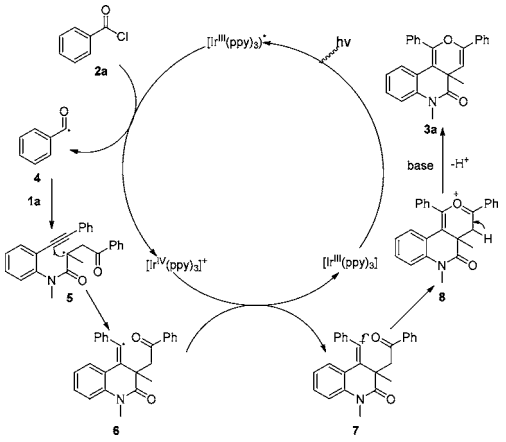
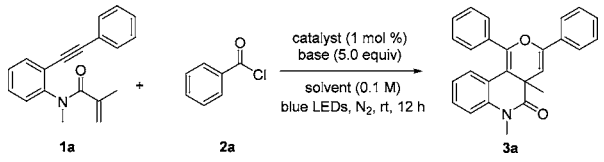
Scheme 2. Possible Mechanism



[*fac*-^{IV}Ir(ppy)$_3$] to afford intermediate **7**. Finally, the intermediate **7** is cyclized to give oxonium cation **8**, which is converted to the desired product **3a** by deprotonation.

To test our hypothesis, benzene-linked 1,7-enyne **1a** and benzoyl chloride **2a** were chosen as the model substrates for the reaction. Surprisingly, the desired annulation product **3a** was afforded in a yield of 47% when the reaction was treated with *fac*-Ir(ppy)$_3$ (1 mol %) and 2,6-lutidine (5.0 equiv) in degassed MeCN under irradiation by a 5 W blue LED for 12 h at room temperature (Table 1, entry 1). However, when the catalyst was

Table 1. Optimization of the Reaction Conditions[a]



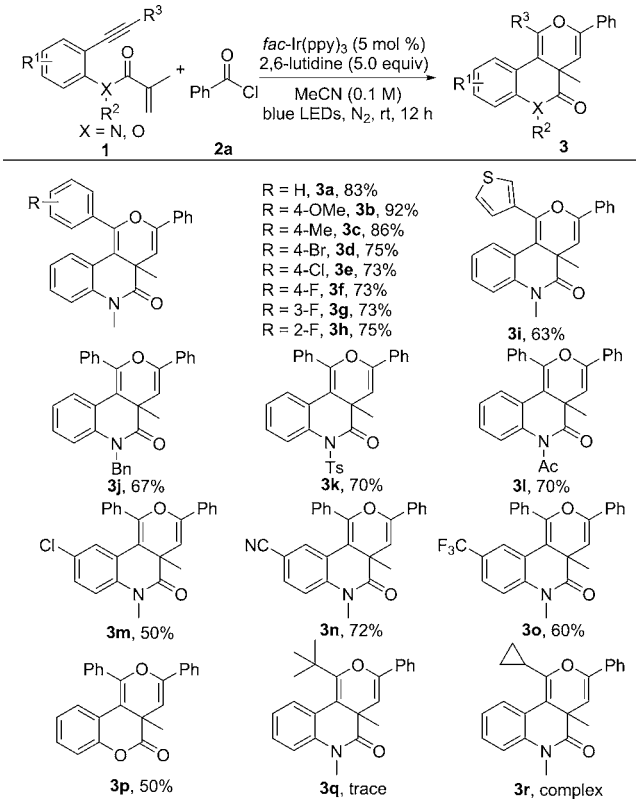
entry	catalyst	solvent	base	yield[b] (%)
1	*fac*-Ir(ppy)$_3$	MeCN	2,6-lutidine	47
2	Ru(bpy)$_3$Cl$_2$	MeCN	2,6-lutidine	0
3	Eosin Y	MeCN	2,6-lutidine	0
4	*fac*-Ir(ppy)$_3$	THF	2,6-lutidine	45
5	*fac*-Ir(ppy)$_3$	CH_2Cl_2	2,6-lutidine	39
6	*fac*-Ir(ppy)$_3$	DMA	2,6-lutidine	0
7	*fac*-Ir(ppy)$_3$	toluene	2,6-lutidine	34
8	*fac*-Ir(ppy)$_3$	MeCN	K_2CO_3	26
9	*fac*-Ir(ppy)$_3$	MeCN	Et_3N	0
10	*fac*-Ir(ppy)$_3$	MeCN	iPr_2Net	0
11[c]	*fac*-Ir(ppy)$_3$	MeCN	2,6-lutidine	60
12[d]	*fac*-Ir(ppy)$_3$	MeCN	2,6-lutidine	80
13[e]	*fac*-Ir(ppy)$_3$	MeCN	2,6-lutidine	0
14	none	MeCN	2,6-lutidine	0

[a]Unless otherwise noted, the reaction was carried out with **1a** (0.1 mmol), **2a** (0.5 mmol), base (0.5 mmol), and catalyst (0.001 mmol) in solvent (anhydrous, 1 mL) at room temperature. [b]Isolated yield. [c]*fac*-Ir(ppy)$_3$ (0.002 mmol). [d]*fac*-Ir(ppy)$_3$ (0.005 mmol). [e]In the dark.

changed to Ru(bpy)$_3$Cl$_2$ or Eosin Y, the product **3a** was not formed (entries 2, 3). In an attempt to improve the reaction efficiency, a number of solvents were tested, and the results showed that THF gave a similar yield (45%) (entry 4), while others such as CH_2Cl_2, DMA, and toluene gave poor reaction yields (entries 5–7). Furthermore, other additives had a negative effect on the yields, and therefore, 2,6-lutidine was the optimal additive (entries 8–10). Increasing the photocatalyst loading could lead to higher yields (entries 11 and 12). Further control experiments revealed that both light and *fac*-Ir(ppy)$_3$ were essential for the reaction (entries 13 and 14).

With the reaction conditions optimized, the substrate scope of this transformation was then evaluated, and the results are listed in Scheme 3. A wide variety of benzene-linked 1,7-enynes

Scheme 3. Scope of 1,*n*-Enynes



reacted smoothly to give the corresponding pyrano[4,3-*c*]quinoline derivatives with good yields. For example, the electron-donating substitutions on the aromatic ring at the terminal alkyne containing the methoxyl and methyl groups were well tolerated (**3b** and **3c**, 92 and 86% yield, respectively). Moreover, this cyclization strategy was also suitable for electron-deficient substrates (**3d–h**, 73–75% yield). With respect to heteroaromatic systems, thienyl alkyne **3i** was also suitable for this transformation in a yield of 63%. Differently N-substituted 1,7-enyne substrates were also effective in the reaction, including those bearing benzyl (Bn), tosyl (Ts), and acetyl (Ac) groups (**3j–l**, 70–75% yield). Furthermore, substrates with a substituent such as Cl, CN, or CF_3 on the aromatic ring of the aniline moiety also performed well under the standard conditions (**3m–o**, 50–72% yield). The phenol-linked 1,7-enyne worked as well in the reaction (**3p**, 50% yield). However, the alkylalkynes such as *tert*-butylalkyne **3q** or cyclopropylalkyne **3r** were inert and did not afford the desired product.

We next explored the scope of the aroyl chloride with **1a** as the substrate (Scheme 4). It was found that aroyl chlorides with electron-rich substituents, such as *p*-toluoyl chloride and *p*-anisoyl chloride, afforded the corresponding products in excellent yields (**3s** and **3t**, 82 and 90% yield). The aroyl chlorides with halogen atom substituents reacted smoothly to

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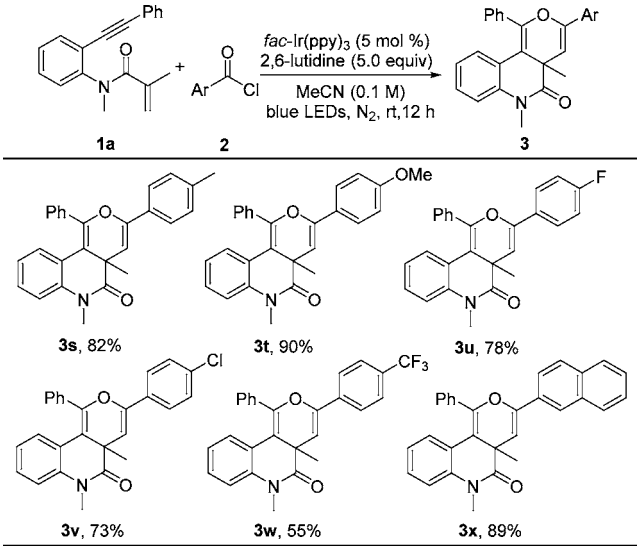
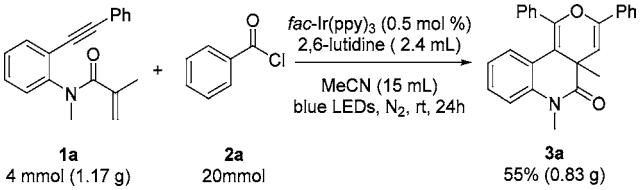
Scheme 4. Scope of Acyl Chlorides



afford the corresponding products in good yields (**3u** and **3v**, 78 and 80% yield). 4-(Trifluoromethyl)benzoyl chloride, which has a strong electron-withdrawing group on the aromatic ring, afforded the fused pyran **3w** in 55% yield even with the reaction time extended to 18 h. In addition, 2-naphthoyl chloride was well tolerated under the optimal conditions to obtain the desired product **3x** in a yield of 87%.

To demonstrate the synthetic value of this photoredox-catalyzed [2 + 2 + 2] annulation further, a gram-scale reaction was performed successfully. A 1.17 g portion of 1,7-enyne **1a** yielded 0.83 g (55% yield) of the fused pyran product with a slight decrease in the yield relative to the small-scale reaction (Scheme 5).

Scheme 5. Scalable Synthesis



We also studied the mechanism of acyl radical formation using fluorescence quenching techniques (Figure 1a, left) and an electrochemical method (see the Supporting Information). The Stern–Volmer analysis revealed that the photoluminescence of *fac*-Ir(ppy)$_3$ was quenched by benzoyl chloride **2a** in acetonitrile at 25 °C (Figure 1a, right). In contrast, 2,6-lutidine itself does not quench the excited state of *fac*-Ir(ppy)$_3$ in the same solution, since there was no difference in the performance between benzoyl chloride and 2,6-lutidine solution and benzoyl chloride solution (see the Supporting Information). Because the energy transfer from the excited *fac*-Ir(ppy)$_3$ to **2a** is negligible, the fluorescence quenching should be attributed to the electron transfer from the excited *fac*-Ir(ppy)$_3$ to **2a**. A radical-trapping experiment showed that adding TEMPO abolished this reaction (Figure 1b), while 2,2,6,6-tetramethylpiperidin-1-yl benzoate was obtained in high yield in the presence of TEMPO. Collectively, these results demonstrated

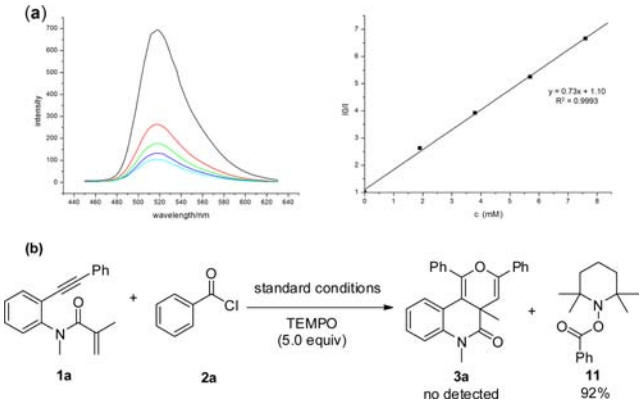


Figure 1. (a) (Left) Fluorescence quenching of *fac*-Ir(ppy)$_3$ (1.00×10^{-4} M) with progressive addition of **2a** in acetonitrile. (Right) Stern–Volmer plot of *fac*-Ir(ppy)$_3$ and variable benzoyl chloride. (b) Radical-trapping experiment.

that this radical reaction was initiated by the acyl radical from benzoyl chloride.

In summary, we have developed a novel visible-light induced cascade cyclization between benzene-linked 1,7-enynes and benzoyl chlorides to synthesize a wide range of fused pyran compounds. This method provides a new approach for producing acyl radicals from benzoyl chlorides and also an efficient synthesis of fused pyran molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03684.

Detailed experimental procedures and full spectroscopic data for all new compounds (PDF)

X-ray data for **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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