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Visible-Light-Promoted Cascade Radical Cyclization: Synthesis of 1,4-Diketones Containing Chroman-4-One Skeletons

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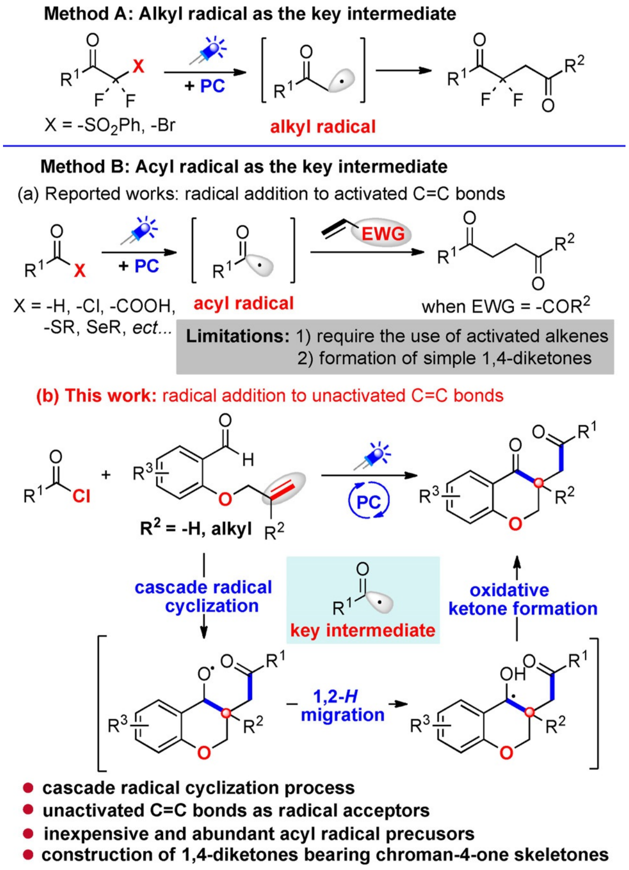
Abstract: A visible-light-induced cascade radical cyclization of aroyl chlorides with 2-(allyloxy)-benzaldehyde derivatives has been developed. The method takes advantages of unactivated C=C bonds as the acyl radical acceptors and offers a mild and green approach for the synthesis of 1,4-diketones bearing biologically important chroman-4-one skeletons with moderate to good yields.

The 1,4-diketones are versatile synthetic building blocks which have been wide used in the synthesis of important carbo- and heterocyclic ring structures, such as cyclopentenones, pyrroles, furans and thiophenes.[1] As the structural elements, they can be found in a wide range of pharmaceutical agents and natural isolates.[2] Consequently, there is no doubt that significant efforts have been devoted to the synthesis of this highly valuable synthon. Among the reactions developed, Michael addition-types of acyl radical to α,β-unsaturated carbonyl compounds is one of the most straightforward and powerful synthetic approach to access 1,4-diketones.[3] However, traditional methods for the generation of acyl radicals generally need the use of toxic organotin initiators, UV irradiation, high reaction temperature, or high CO pressure.[4] Thus, further explore of valuable process for the generation of acyl radicals and their application in the synthesis of important 1,4-diketones is still appealing, especially under green and mild reaction conditions.

In the past decade, chemical reactions initiated by visible light-induced photoredox catalysis has attracted considerable attentions because of its environmental compatibility and versatility in character.[5] A wide range of useful chemical structures can be easily accessed by using this benign methodology, including the synthesis of 1,4-diketones. Generally, visible-light promoted synthesis of 1,4-diketone derivatives can be divided into the following two categories. The first approach is the addition of photo-generated carbon-centered radical species to unsaturated carbon-carbon double bonds (Scheme 1, method A). In 2014, the group of Xiao reported a visible-light induced 1,4-diketone synthesis by using β-ketosulfones as the carbon-centered radical precursors.[6a] Very recently, Zhu et al. disclosed an elegant photoredox catalytic approach to fluoro-containing 1,4-diketones by using ethyl bromodifluoroacetate as the fluoroalkyl radical source.[6b] Another visible light photocatalytic method to the synthesis of 1,4-diketones are based on the conjugate addition of acyl radical to olefins (Scheme 1, method B).[7] In 2015, Shang, Fu et al. demonstrated a visible



Scheme 1. Visible Light-promoted synthesis of 1,4-diketones.

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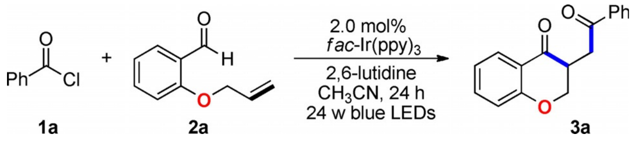
light photoredox-catalyzed decarboxylative 1,4-addition reaction, in which α-oxocarboxylic acids were employed to generate acyl radicals.[8a] Shortly after this elegant discovery, other types of acyl radical precursors, including carboxylic anhydrides,[9] aldehydes,[10] 2-*S*-pyridyl thioesters,[11] aroyl chlorides,[12] 4-acyl-1,4-dihydropyridines[13] and oxime esters[14] were sequentially investigated to conduct such valuable radical addition reactions. Although encouraging improvements have been achieved in this field, the above photo-generated acyl radicals are all limited addition to electron-deficient alkenes. It is still great appealing to explore the potential reactivity of acyl radicals, especially in the reaction with unactivated C=C bonds and the construction of molecular complexity under visible light photoredox catalytic conditions.

Within the frame of our ongoing research interests devoted to the synthesis of valuable heterocyclic compounds,[15] we describe herein a visible light-promoted cascade radical cyclization of aroyl chlorides with *o*-(allyloxy)arylaldehydes (Scheme 1). It is worth noting that the photo-generated acyl radical can be efficiently trapped by un-activated C=C bond in this process. The reaction proceeds through a radical cyclization/1,2-*H* migration/oxidative ketone formation cascade which enables the one-step, efficient synthesis of various 1,4-diketones bearing biologically important chroman-4-one skeletons.[16]

At the outset, benzoyl chloride **1a** and 2-(allyloxy)-benzaldehyde **2a** was selected as model substrates to identify the reaction efficiency. As revealed in Table 1, the desired annulation product **3a** could be isolated in 61% yield when the reaction was performed in the presence of 2.0 mol% *fac*-Ir(ppy)$_3$ as photoredox catalyst, 2.0 equiv 2,6-lutidine as base, in degassed CH_3CN under irradiation with 24 W blue LED for 24 h at room temperature (entry 1). Solvent screening revealed that DMF also gave a comparable yield (entry 2, 57%), while other tested reaction medias such as DCM, DCE, EtOAc, THF, and 1,4-dioxane were all inferior in terms of reaction yields (entries 3–7). It was found that the base had a significant effect on the reaction efficiency. Only 35% yield of **3a** was obtained when 2,6-lutidine was replaced by Et_3N (entry 8). And no desired annulation product was observed by using inorganic base, such as K_2CO_3 and Cs_2CO_3 (entries 9 and 10). To our delight, the reaction yield of **3a** could be further improved to 65% when the ratio of **1a** to **2a** was improved from 2:1 to 1:2 (entry 11). Finally, control experiments indicated that the photoredox catalyst, blue LED irradiation, and 2,6-lutidine are all crucial to this cascade radical cyclization process (entries 12–14).

Table 1. Reaction optimization between **1a** and **2a.**[a]



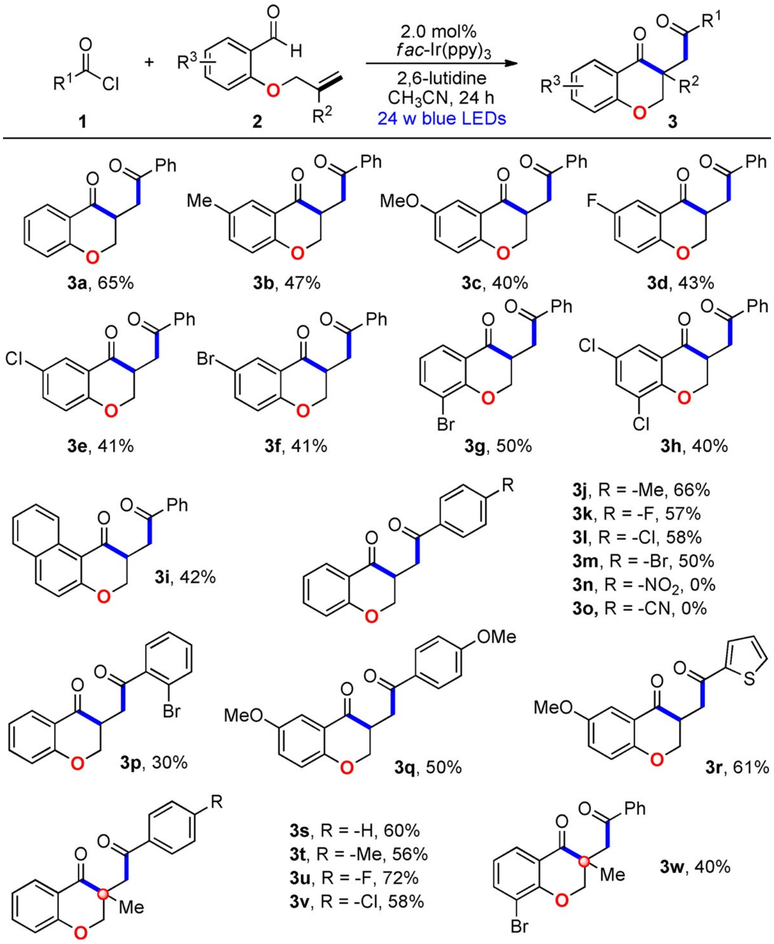
Entry	Deviation from standard conditions	Yield [%][b]
1	None	61
2	DMF instead of CH_3CN	57
3	DCM instead of CH_3CN	52
4	DCE instead of CH_3CN	45
5	EA instead of CH_3CN	48
6	THF instead of CH_3CN	43
7	1,4-dioxane instead of CH_3CN	51
8	Et_3N instead of 2,6-lutidine	35
9	K_2CO_3 instead of 2,6-lutidine	trace
10	Cs_2CO_3 instead of 2,6-lutidine	trace
11	**1a**:**2a** = 1:2	65
12	Without *fac*-Ir(ppy)$_3$	n.r.
13	In the dark	n.r.
14	Without 2,6-lutidine	n.r.

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), 2,6-lutidine (0.4 mmol), *fac*-Ir(ppy)$_3$ (0.004 mmol) in the indicated solvent (2.0 mL), irradiation by 24 W blue LEDs at room temperature for 24 h under argon atmosphere. [b] Isolated yield.

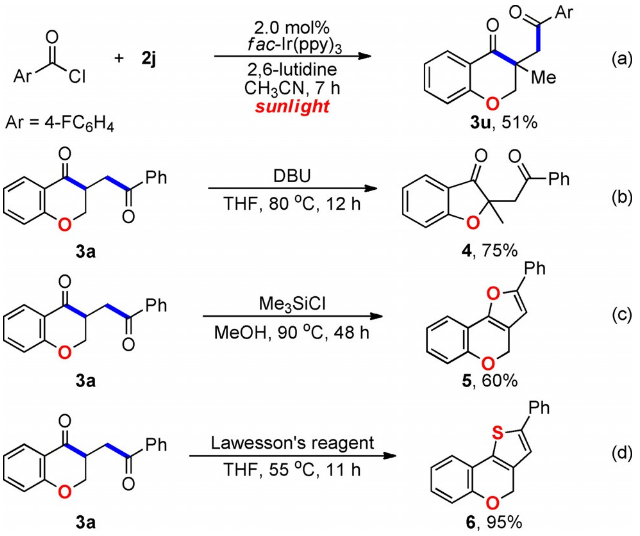
With the optimal reaction conditions in hand, we next set out to investigate the substrate scope for the reaction (Scheme 2). It was found that this photocatalytic cascade radical cyclization reaction can tolerate a wide range of substituents on the benzene ring of 2-(allyloxy)-benzaldehyde derivatives. Both electron-donating (e.g., methyl, methoxy) and electron-withdrawing (e.g., fluoro, chloro, bromo) groups could be successfully introduced at different positions on the aryl ring of **2**, affording the corresponding chroman-4-ones **3b–g** in moderate to good yields. Moreover, the disubstituted and naphthalene derived substrates worked well to provide **3h** and **3i** in 40% and 42% isolated yields, respectively.

Next, the scope of the reaction with respect to aryl aroyl chlorides **1** was examined (Scheme 2). It was observed that electronic modification of aroyl chlorides **1** had some effects on the reaction efficiency. Aroyl chlorides bearing electron-donating (-Me, -OMe) and weak electron-withdrawing (-F, -Cl, -Br) groups could smoothly react with 2-(allyloxy)-benzaldehyde **2a** under the optimized conditions, giving the resulting 1,4-diketones **3j–m**, **3q** in generally good yields. However, 4-nitrobenzoyl chloride and 4-cyanobenzoyl chloride did not react at all which might because of the strong electron-withdrawing group reduce the addition susceptibility of acyl radical to C=C bonds (**3n** and **3o**).[16b] In addition, a relatively low yield of the desired product was obtained when 2-bromobenzoyl chloride was involved which could be attributed to steric effects (**3p**, 30%). Apart from benzoyl chloride derivatives, thiophene-2-carbonyl chloride also proved to be a reliable substrate, affording **3r** in 61% yield. It is worth noting that heterocycles 3s-w bearing an important quaternary carbon center, could be unambiguously produced by using this developed method.

To demonstrate the preparative utility of this method, the follow-up chemistry was investigated as shown in Scheme 3. First, Moderate yield of **3u** was obtained when the reaction was performed by direct sunlight irradiation (Scheme 3a). More significantly, the chromanone product **3a** could be efficiently transfer to benzofuranone **4** in 75% yield through a base-catalyzed rearrangement process (Scheme 3b).[17a] It is well known that 1,4-diketones are indispensable building blocks for the synthesis of structurally specific heterocyclic ring structures.[1] For instance, treatment of **3a** with Me_3SiCl in MeOH at 90 °C provided polyheterocycle **5** in good yield (Scheme 3c).[17b] The 2-phenyl-4*H*-thieno[3,2-*c*]chromene **6** could



Scheme 2. Reaction scopes.[a,b] [a] **1** (0.1 mmol), **2** (0.2 mmol), 2,6-lutidine (0.2 mmol), *fac*-Ir(ppy)$_3$ (0.002 mmol) in CH$_3$CN (1.0 mL), irradiation by 24w blue LEDs at room temperature for 24 h under argon atmosphere. [b] Isolated yield.



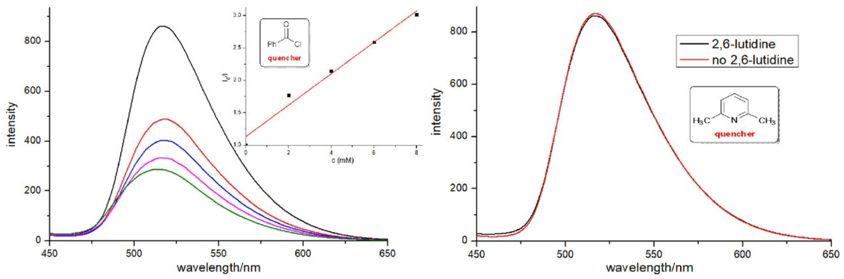
Scheme 3. Sun-light irradiation reaction and synthetic transformations of **3a**.

also be easily prepared in high yield by the reaction of **3a** with Lawesson's reagent (Scheme 3d).[6]

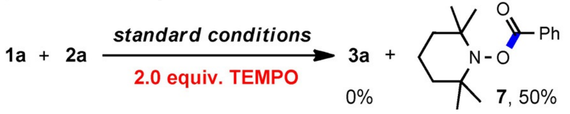
Some control experiments were subsequently conducted to deepen our understanding of the reaction mechanism. Stern–Volmer fluorescence quenching experiments by using benzoyl chloride and 2,6-lutidine as the quencher indicated that benzoyl chloride could efficiently quench the photo-excited *fac*-Ir(ppy)$_3$, where it presumably engaged in a SET process (Scheme 4a). Moreover, the model reaction was completed inhibited when 2.0 equiv TEMPO was added to the reaction mixture (Scheme 4b). Instead, the radical trapping product **7** was isolated in 50% yield, indicating the formation of benzoyl radical.

Based on the experimental evidence in combination with previous literature reports, a plausible reaction mechanism was proposed in Scheme 5. Initially, *fac*-Ir(ppy)$_3$ transferred to its photo-excited state under the irradiation with visible light. Then, single-electron reduction of benzoyl chloride with Ir^{III*} provided the key benzoyl radical **A** with the formation of Ir^{IV} species.[18] Radical addition of **A** to C=C bond of 2-(allyloxy)-benzaldehyde afforded radical **B**, which subsequently underwent an intramolecular radical addition to give oxygen-centered radical **C**. 1,2-hydrogen migration of **C** delivered radical **D**,[19] which could serve as reductant to reduce Ir^{IV} to Ir^{III} to complete the photocatalytic cycle and yield the carbon cation intermediate **E**. Finally, base-promoted deprotonation of **E** provided the final chroman-4-one product.

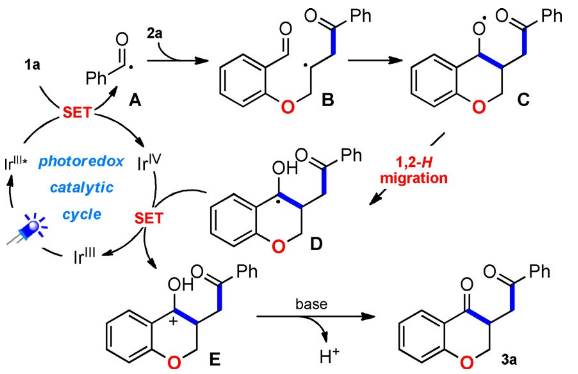
(a) fluorescence quenching experiment



(b) radical trapping experiment



Scheme 4. Mechanistic studies.



Scheme 5. Proposed reaction mechanism.

In summary, we have developed a visible-light-promoted cascade radical cyclization of aroyl chlorides with 2-(allyloxy)-benzaldehyde derivatives. The reaction proceeded through a radical cyclization/1,2-H migration/oxidative ketone formation cascade which provided an efficient route to various 1,4-diketones bearing biologically important chroman-4-one skeletons in moderate to good yield. Comparing with the well-developed activated alkenes as radical acceptors, the photo-generated acyl radical was efficiently trapped by the unactivated C=C bond in this process. Moreover, the sun-light irradiation reaction and the synthetic transformation of the formed 1,4-diketones to other important polyheterocycles further rendered this approach attractive and valuable.

Experimental Section

General procedure: A flame-dried Schlenk-tube equipped with a magnetic stir bar was charged with **1 a** (1.0 equiv, 0.1 mmol), *fac*-Ir(ppy)$_3$ (0.02 equiv, 0.002 mmol) in 1.0 mL CH_3CN was added **2 a** (2.0 equiv, 0.2 mmol) and 2,6-lutidine (2.0 equiv, 0.2 mmol) under a nitrogen atmosphere. The reaction mixture was then stirred under the irradiation with 24 W blue LEDs for 24 h. The solvent was then removed under reduced pressure with the aid of a rotary evaporator. The crude residue was purified by silica gel column chromatography to afford pure product **3 a** as a yellow solid in 65 % yield.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,4-Diketones · Acyl radical · Photoredox catalysis · Radical cyclization · Visible light

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