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Synthesis of Hydrazide-Containing Chroman-2-ones and Dihydroquinolin-2-ones via Photocatalytic Radical Cascade Reaction of Aroylhydrozones

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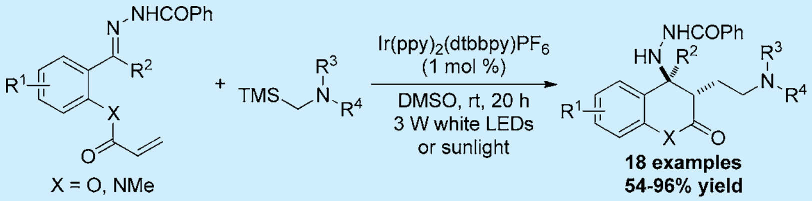
Supporting Information



ABSTRACT: A general and efficient visible light photocatalytic α-amino carbon radical-based cascade reaction of aroylhydrazones has been described. This protocol tolerates a wide array of α-silylamines and aroylhydrazones to afford the corresponding diversely functionalized hydrazide-containing chroman-2-ones and dihydroquinolin-2-ones in generally good yields with excellent diastereoselectivities.

Synthetic chemists continuously seek new efficient, selective, and high yielding chemical transformations that proceed under mild and operationally simple conditions.[1] With the develoment of various methods for the generation of reactive radicals in a controllable and selective fashion, radical-based tandem reactions have been established as a potential access to such ideal reactions.[2,3] However, many radical cascade reactions typically require stoichiometric radical initiators or harsh conditions. In recent years, visible light photocatalysis has emerged as a powerfully enabling strategy for the development of new catalytic radical cascade reactions due to its unique ability in formation of various reactive radicals and radical ions under mild and sustainable conditions.[4] Using this protocol, a wide range of photogenerated carbon radicals and heteroatom radicals mediated cascade reactions have been developed for the synthesis of various structurally diverse carbocycles and heterocycles from simple and readily available materials.[5,6] Despite these advances, further exploration of other types of radicals to enrich the scope of this category of photocatalytic radical cascade reactions is still highly desirable.

Chroman-2-ones and dihydroquinolin-2-ones constitute a large proportion of oxygen- and nitrogen-containing heterocycles and are omnipresent components of numerous biologically active natural products and potent pharmaceutical drugs (Figure 1).[7] Hydrazide is also a significant structural motif that is prevalent in many biologically relavent molecules and natural products.[8] As a result, numerous efforts have been directed toward the synthesis of the above-mentioned fameworks. Owing to their fascinating biological profiles, the development of new photocatalytic radical cascade reactions enabling assembly of diversified and densely functionalized heterocyclic molecules bearing these pharmacophores would be useful for identifying novel biological candiates for drug discovery. Moreover, the N−N bond in the hydrazide moieties would allow for further functional group elaboration.[9]

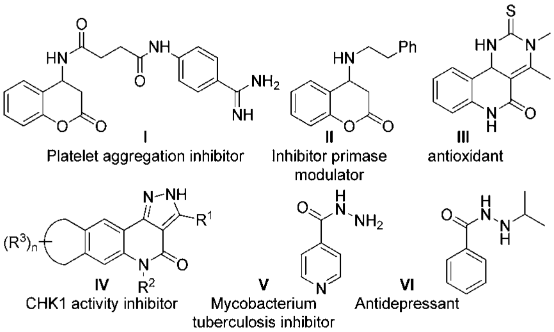


Figure 1. Biologically importance of chroman-2-one, dihydroquinolin-2-one, and hydrazide-based scaffolds.

Pioneered by the works of Pandey, Reiser, and Nishibayashi in the visible light photoredox-catalyzed radical addition reactions of α-amino radicals (Scheme 1a and 1b),[10] synthetic utilization of these reactive species has recently been extensively explored to construct various nitrogen-containing compounds.[11] However, further extension of their application to the radical cascade reaction remains largely unexplored. Herein, as part of our ongoing research programs toward the photocatalytic synthesis of heterocycles,[12] we wish to report a new

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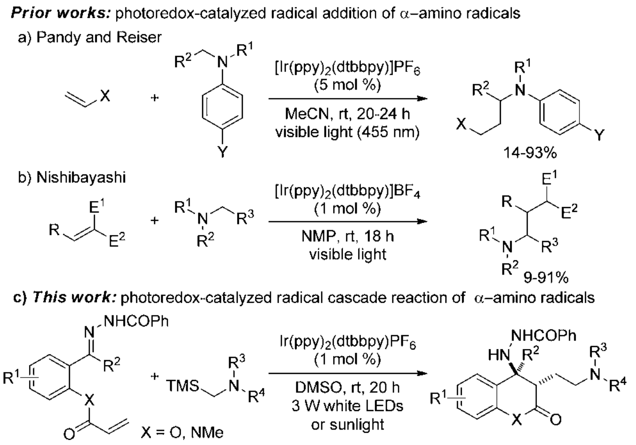
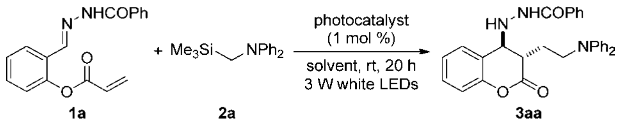
Scheme 1. Reaction Design of Photocatalytically Generated α-Amino Radicals



type of radical cascade reaction between photogenerated α-amino radicals and acryloyl ester- and acrylamide-tethered aroylhydrazones (Scheme 1c).

Reaction optimization was initiated with acryloyl ester-tethered aroylhydrazone **1a** and α-silylamine **2a** using the commonly used photocatalysts at 1 mol % catalyst loading. Pleasingly, the expected radical cascade reaction did indeed proceed smoothly with the use of $Ir(ppy)_2(dtbbpy)PF_6$ as the photocatalyst under 3 W white LED irradiation in DMF, giving the cyclic product **3aa** in 63% yield as a single diastereomer (Table 1, entry 1).

Table 1. Condition Optimization[a]

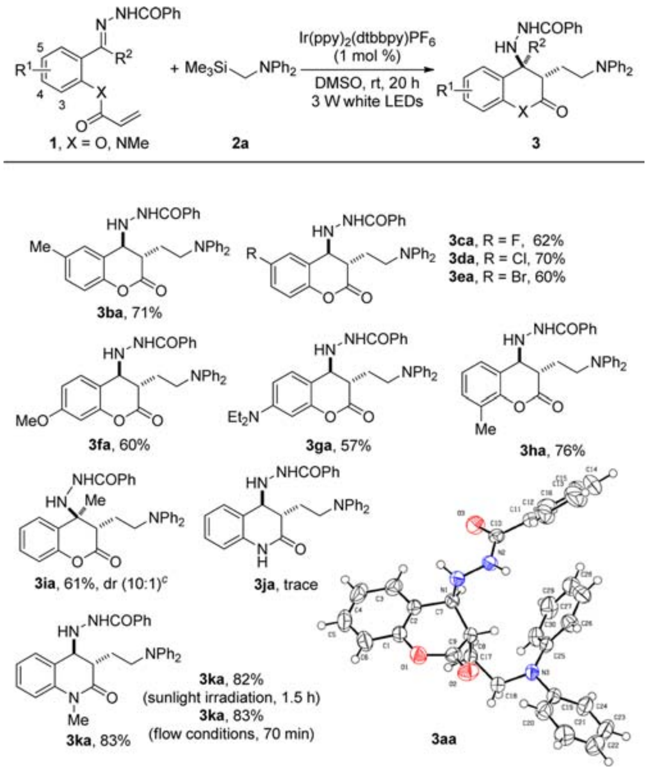


entry	photocatalyst	1a/2a	solvent	yield[b](%)
1	$Ir(ppy)_2(dtbbpy)PF_6$	1/1.2	DMF	63
2	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	1/1.2	DMF	58
3	*fac*-$Ir(ppy)_3$	1/1.2	DMF	0
4	$Ir(ppy)_2(dtbbpy)PF_6$	1/1.5	DMF	72
5	$Ir(ppy)_2(dtbbpy)PF_6$	1/1.5	DMSO	76
6	$Ir(ppy)_2(dtbbpy)PF_6$	1/1.5	MeCN	40
7	$Ir(ppy)_2(dtbbpy)PF_6$	1/1.5	DMA	68
8	$Ir(ppy)_2(dtbbpy)PF_6$	1/1.5	THF	44
9	$Ir(ppy)_2(dtbbpy)PF_6$	1/1.5	CH_2Cl_2	13
10[c]	$Ir(ppy)_2(dtbbpy)PF_6$	1/1.5	DMSO	67
11[d]	–	1/1.5	DMSO	0
12[e]	$Ir(ppy)_2(dtbbpy)PF_6$	1/1.5	DMSO	0

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.24 or 0.30 mmol), photocatalyst (1 mol %), 2.0 mL of solvent, 20 h, 3 W white LEDs, and rt. [b]Isolated yield. [c]10 equiv of H_2O were added. [d]Without photocatalyst. [e]Without visible light irradiation.

And, the anti relative configuration was also determined by X-ray crystallographic analysis (Scheme 2).[13] It was found that the photocatalyst $Ru(bpy)_3Cl_2{\cdot}6H_2O$ also proved to be effective for the reaction, although resulting in a slight decrease of yield (entry 2). However, the use of *fac*-$Ir(ppy)_3$ as the photocatalyst in the present reaction resulted in no formation of any product, probably due to the lower oxidizing potential of its photoexcited state (entry 3). Using the photocatalyst $Ir(ppy)_2(dtbbpy)PF_6$, the yield was further improved to 72% with the ratio of **1a** to **2a** being changed to 1/1.5 (entry 4). Then, a brief survey of the reaction media demonstrated that DMSO gave rise to superior results over other solvents, with **3a** being obtained in 76% yield (entries 4−9). Notably, the reaction could still work well even in the presence of 10 equiv of H_2O to give rise to comparable results (entry 10). In the control experiments, no desired product **3aa** was detected without photocatalyst or light irradiation, confirming that the present reaction is a photocatalytic process (entries 11−12).

Scheme 2. Photocatalytic Radical Cascade Reaction of Aroylhydrazones 1 with α-Silylamine 2a[a,b]

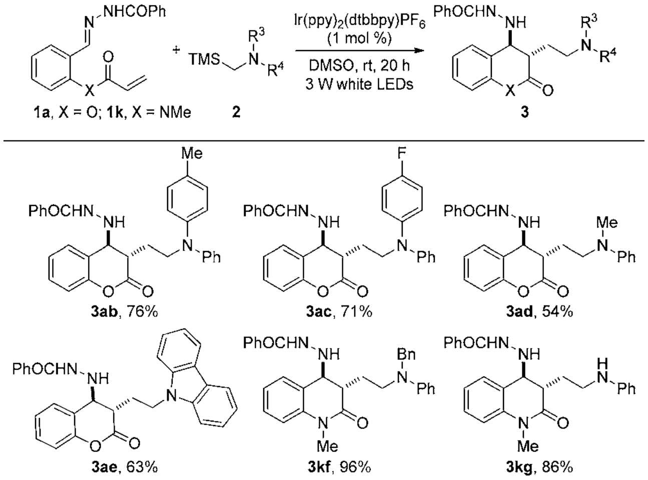


[a]Reactions were performed with **1** (0.20 mmol), **2a** (0.30 mmol), and $Ir(ppy)_2(dtbbpy)PF_6$ (1 mol %) in DMSO (2.0 mL) at rt under irradiation by 3 W white LEDs for 20 h. [b]Isolated yield. [c]Diastereomeric ratio was determined by ^1H NMR analysis.

With the optimized reaction conditions in hand, we first examined a range of other aroylhydrazones to explore the substrate scope and generality (Scheme 2). It was found that a range of aroylhydrazones with variations in the electronic and steric properties of the substituents on the phenyl ring can be well tolerated. For instance, the substrates **1b−h** with various electron-donating (e.g., methyl) or electron-withdrawing (e.g., fluoro, chloro, bromo) functional groups at the C5-position of benzene ring reacted smoothly with α-silylamine **2a**, affording the corresponding products **3ba−ea** in 60−71% yield. Moreover, 3- and 4-substituted substrates with methoxyl, diethyl amine, or methyl groups also proved to be suitable for the reaction to produce **3fa−ha** in a range of 57−76% yields. Importantly, the reaction with sterically demanding acetophenone-derived aroylhydrazone **1i** also worked well to afford **3ia** in 61% yield with high diastereoselectivity. While the N-free acrylamide-tethered acroylhydrazone **1j** was ineffective under the standard conditions, *N*-methyl protected substrate **1k** participated in the radical cascade reaction successfully to furnish the expected product **3ka** in 83% yield. Notably, when the reaction of **1k** was excuted under natural sunlight irradiation or flow conditions, the reaction time could be significantly shortened and give comparable yields of **3ka**.[14] Remarkably, in most of the cases, the chroman-2-one and dihydroquinolin-2-one products were obtained as a single diastereomer.

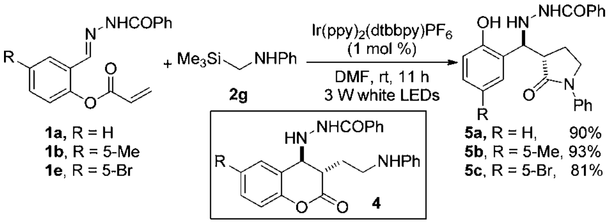
Next, we further investigated the scope of the reaction by reacting aroylhydrazone substrates **1a** and **1k** with an array of α-silylamines **2** (Scheme 3). Under the standard conditions, the reaction with *N*,*N*-diaryl α-silylamines **2b** and **2c** bearing a substituent on one of the aromatic rings (i.e., methyl, fluoro) reacted well with **1a** to give **3ab** and **3ac** with 76% and 71% yields, respectively. α-Amino radical precursors **2d** and **2e** were also applicable to the reaction system, delivering the corresponding products **3ad** and **3ae** in 54–63% yield. Once again, aroylhydrazone **1k** reacted smoothly with tertiary aniline **2f** and secondary amine **2g** to give the desired products **3kf** and **3 kg** with 96% and 86% yields.

Scheme 3. Photocatalytic Radical Cascade Reaction of Aroylhydrazones 1a with α-Silylamine 2[a,b]



[a]Reactions were carried out with **1** (0.20 mmol), **2** (0.3 mmol), and Ir(ppy)$_2$(dtbbpy)PF$_6$ (1 mol %) in DMSO (2.0 mL) at rt under irradiation by 3 W white LEDs for 20 h. [b]Isolated yield. [c]45 h reaction time.

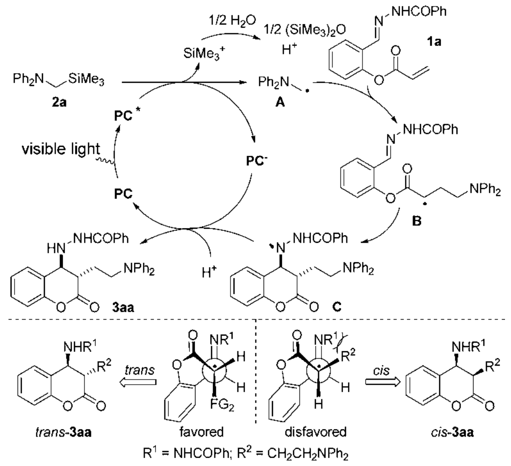
Interestingly, as for the reactions of hydrazones **1a–b**, **1e** and silylaniline **2g**, it was found that a new class of biologically and synthetically important γ-lactams **5a–c** were obtained instead with 81–90% yields without addition of any stiochiometric bases (eq 1). Based on Nishibayashi's work,[10d] we reasoned that the γ-lactam products **5** should be formed through a ring opening of the initially formed products **4** by nucleophilic attack of the secondary amine moiety.[14]



(1)

In the presence of radical quencher TEMPO, the model reaction of **1a** and **2a** was completely suppressed, which is indicative of a radical process.[14] On the basis of the previous literature,[10] we proposed a plausible mechanism for the present radical cascade reaction (Scheme 4). First, upon visible light irradiation, the photoexcited catalyst (**PC***) oxidizes the α-silylamine **2a** by a single electron transfer (SET) process to give the key intermediate, α-amino radical **A**, together with a trimethylsilyl cation after subsequent desilylation.[15] Then, the α-amino radical species **A** undergoes an intermolecular radical addition to the C=C bond to give α-carbonyl radical **B**, which further added to the C=N bond of the hydrazone moiety in a *trans*-selective manner mainly owing to the steric hindrance. A SET-based reduction of the intermediate **C** by the reduced photocatalyst (**PC**$^-$) completes the catalytic cycle, resulting in the regeneration of the ground state photocatalyst (**PC**) and forming the nitrogen anion intermediate. A subsequent protonation of the nitrogen anion furnishes the final product **3aa**. A 0.002 quantum yield of the model reaction suggests that the chain propagation is not a main mechanistic pathway.[14]

Scheme 4. Proposed Mechanism



In conclusion, we have developed a new and efficient α-amino carbon radical-based radical addition/cyclization cascade of aroylhydrazones by visible light photocatalysis. This protocol provides a new approach for the synthesis of a range of densely functionalized heterocycles in good yields. Further application of this methodology to access other biologically important heterocycles is currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03174.

Experimental procedures and full spectroscopic data for all new compounds (PDF)
X-ray crystallographic data for **3aa** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) CCDC 1510963 (**3aa**) Crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/daa_request/cif.

(14) See the Supporting Information for details.

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