



# Visible-light-mediated cascade difunctionalization/cyclization of alkynoates with acyl chlorides for synthesis of 3-acylcoumarins

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## ABSTRACT

A new visible-light-mediated radical cyclization of alkynoates with acyl chlorides is described for the one-pot construction of diverse 3-acylcoumarins with high efficiency and selectivity. This method is successful by sequential difunctionalization of an alkynes C–C triple bond with the C–Cl bonds of acyl chloride and aromatic C(sp<sup>2</sup>)–H bonds. The cyclization is proposed to simultaneously form two new carbon–carbon bonds, and involves radical acylation, 5-*exo-trig* cyclization, and ester migration.

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## Introduction

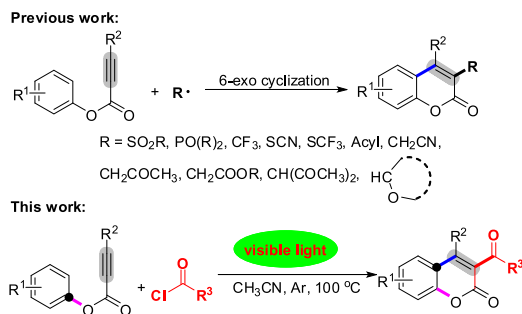
Coumarin skeletons rank among the most important heterocycles in many natural products,<sup>1</sup> pharmaceutically active molecules,<sup>2,3</sup> and dyes,<sup>4</sup> and they are also widely applied in materials field.<sup>5</sup> More importantly, coumarin derivatives are also widely used as anticancer, anticoagulant, anti-inflammatory, antibacterial, anti-HIV, enzymatic inhibitors, and anti-psoriasis in medicinal chemistry,<sup>6</sup> or as illumination light source material sciences and fluorescent probes.<sup>7</sup> Thus, development of new and efficient strategies for construction of these compounds under mild condition will be significant for the screening of novel biologically active molecules. Recently, the cascade functionalization and cyclization of aryl alkynoate esters has been developed as a powerful method to synthesize 3-functionalized coumarins (Scheme 1).<sup>8</sup> For instance, a variety of 3-substituted coumarins have been obtained via radical alkyne sulfonation,<sup>8a,b</sup> phosphorylation,<sup>8c</sup> trifluoromethylation,<sup>8d</sup> thiocyanation,<sup>8e</sup> trifluoromethylthiolation,<sup>8e</sup> difluoroacetylation,<sup>8f</sup> cyanomethylation,<sup>8g</sup> 3-acetylation,<sup>8h,i</sup> alkylation<sup>8j</sup>/cyclization pathways under oxidative or redox-neutral reaction conditions. Additionally, it was described that 3-acylcoumarins could be

prepared by the functionalization of aryl alkynoate esters with aldehydes<sup>8k,8l</sup> or 2-oxoacetic acids<sup>8m–o</sup> following a radical addition and cyclization mechanisms. Although such oxidative radical-mediated strategy was extended to introduce acyl radicals into coumarins, the harshness of the not freely available precursors and strong oxidative conditions would limit their applications in medicine and chemical industry. Thus, it is highly eager to develop more convenient and efficient methods under mild and environmental benign conditions to generate acyl radical and employ them for constructing 3-acylcoumarins.

Recently, the visible light photocatalysis strategy has proven to be a particularly powerful and straightforward tool for synthetic conversions in organic synthesis, due to its attractive properties such as environmentally friendly, excellent functional group tolerance, availability, and safety.<sup>9</sup> Recently, Xu group<sup>10a,b</sup> and our group<sup>10c</sup> applied acyl radicals produced from abundant and commercially available acyl chlorides into cascade annulations transformations under visible-light photocatalysis. Inspired by these development of visible-light photocatalysis reactions,<sup>9–11</sup> we present a new difunctionalizing acylation of activated alkynes for the synthesis of valuable 3-acylcoumarins under visible-light-mediated photocatalysis (Scheme 1). This strategy was achieved by sequential acylation, 5-*exo-trig* cyclization, and ester migration to form two new carbon–carbon bonds simultaneously, provided a new and convenient route for affording 3-acylcoumarins under mild conditions.

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**Scheme 1.** Oxidative radical difunctionalization of alkyne leading to coumarins.

## Results and discussion

We initiated our studies by combining phenyl 3-phenylpropiolate (**1a**) with benzoyl chloride (**2a**) using  $\text{Ir}(\text{ppy})_3$  (2 mol %) as the photocatalyst for the tandem cyclization reaction (Table 1). To our delight, the desired 3-benzoyl-4-phenyl-2H-chromen-2-one **3aa** was obtained in 81% yield in the presence of 2 equiv 2,6-lutidine (0.4 mmol) as additive, and acetonitrile ( $\text{CH}_3\text{CN}$ , 2 mL) as solvent at 100 °C by irradiation with a 5 W blue LED light for 24 h (Table 1, entry 1). Next, we focused on optimizing the reaction conditions (Table 1). However, no 3-acylcoumarin **3aa** was detected when using  $\text{Ru}(\text{bpy})_2\text{Cl}_2$  and Eosin Y instead of  $\text{Ir}(\text{ppy})_3$  (entries 2–3). Further experiments demonstrated that either  $\text{Ir}(\text{ppy})_3$  or light was indispensable for this tandem reaction (Table 1, entries 4–5).

The amount of  $\text{Ir}(\text{ppy})_3$  was found to affect the reaction, and 2 mol %  $\text{Ir}(\text{ppy})_3$  was preferred (entry 1 versus entry 6). However, the yield of **3aa** decreased to 68% when using 36 W compact fluorescent light instead of 5 W blue LED light (entry 7). Extensive screening of the effect of bases revealed that other base such as  $\text{Na}_2\text{CO}_3$ ,  $\text{NaHCO}_3$ , and pyridine lead to lower yields (entries 8–10). In an attempt to get the best reaction conditions, a series of solvents

**Table 1**  
Optimization of the reaction conditions.<sup>a</sup>

Entry	Variation from the standard conditions	Yield %
1	None	81
2 <sup>b</sup>	$\text{Ru}(\text{bpy})_3\text{Cl}_2$ instead of $\text{Ir}(\text{ppy})_3$	0
3 <sup>b</sup>	Eosin Y instead of $\text{Ir}(\text{ppy})_3$	0
4 <sup>b</sup>	Without $\text{Ir}(\text{ppy})_3$	0
5 <sup>b</sup>	Without additional light	0
6	$\text{Ir}(\text{ppy})_3$ (5 mol %)	80
7 <sup>c</sup>	None	68
8	$\text{Na}_2\text{CO}_3$ instead of 2,6-lutidine	41
9	$\text{NaHCO}_3$ instead of 2,6-lutidine	37
10	Pyridine instead of 2,6-lutidine	61
11	Toluene instead of $\text{CH}_3\text{CN}$	36
12	Dioxane instead of $\text{CH}_3\text{CN}$	45
13	THF instead of $\text{CH}_3\text{CN}$	37
14 <sup>b</sup>	DMF instead of $\text{CH}_3\text{CN}$	0
15	At 110 °C	78
16	At 90 °C	69
17 <sup>d</sup>	None	72

<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol, 2 equiv),  $\text{Ir}(\text{ppy})_3$  (2 mol %), 2,6-lutidine (2 equiv),  $\text{CH}_3\text{CN}$  (2 mL) at 100 °C under an argon atmosphere and 5 W blue LED light for 24 h.

<sup>b</sup> Most of starting material **1a** was recovered, and the rest was decomposed.

<sup>c</sup> 36 W compact fluorescent light instead of 5 W blue LED light.

<sup>d</sup> **1a** (1.0 g, 4.50 mmol) and solvent (10 mL) for 72 h.

were tested, and other solvents such as toluene, dioxane, THF, and DMF gave poor reaction yields (entries 11–14). Different reaction temperature experiments turned out that a yield achieved at 110 °C was similar to that at 100 °C (entry 15), but the yield decreased 69% at 90 °C (entry 16). We were delighted to find that a reaction on a 1 g (4.50 mmol) scale of alkyne **1a** was successful in performing a good yield (entry 17).

Having established the standard reaction conditions, we first searched the scope of aryl 3-phenylpropiolates (**1**) with respect to benzoyl chloride (**2a**) for this new radical cyclization process (Table 2). Initially, a variety of aryl 3-phenylpropiolates (**1**) in reactions with benzoyl chloride (**2a**) were examined, indicating a broad tolerance of substituted groups on the aromatic rings of substrates **1**. Aryl 3-phenylpropiolates with an electron-donating group, such as Me, OMe, or Ph on the *para*-position of the phenoxy rings reacted with **2a** to afford the corresponding products in 78–84% yields (**3ba–da**). Meanwhile, aryl 3-phenylpropiolates bearing an electron-withdrawing group including F, Cl, Br,  $\text{CF}_3$ , or Ac on the *para*-position of the phenoxy rings underwent the reaction to afford the anticipated products in 68–78% yields (**3ea–ia**). According to these results, the alkyneates with electron-withdrawing groups shown lower reactivity than that with electron-donating groups in terms of the reaction yields (**3ba–ia**). Interestingly, when *meta*-methyl alkyneate **1j** was utilized, the reaction afforded a mixture of products **3ja** and **3ja'** and the ratio was about 3:2. To our surprise, these two compounds could be isolated by column chromatography. Furthermore, *ortho*-substituted system was not suitable for the reaction (**3ka**). In addition, different substituted aryl groups linked with the alkynyl of alkyneates **1** could also be suitable for constructing the 3-acyl-4-aryl coumarin derivatives in moderate to good yields (**3la–ra**). Nevertheless, the steric factor also affected the radical cyclization process according to the yields of products **3la**, **3na**, and **3oa**. Unfortunately, alkylpropiolates such as *n*-pentylpropiolate **1s** could not go through the transformation and most of starting material was recovered (**3sa**).

We next investigated the scope of acyl chlorides **2** in the presence of phenyl 3-phenylpropiolate (**1a**),  $\text{Ir}(\text{ppy})_3$ , 2,6-lutidine, and  $\text{CH}_3\text{CN}$ . As shown in Table 3, we were pleased to discover this process could be applied to radical cyclization with a wide range of aryl chlorides **2b–2n**, including a variety of substituted benzoyl chlorides and heterocyclic acyl chlorides. The results showed that

**Table 2**  
Visible-light-mediated cyclization of alkyneates (**1**) with benzoyl chloride (**2a**).<sup>a</sup>

<b>3aa</b> , 81% <b>3ba</b> , 84% <b>3ca</b> , 80% <b>3da</b> , 78% <b>3ea</b> , 75% <b>3fa</b> , 78% <b>3ga</b> , 72% <b>3ha</b> , 70% <b>3ia</b> , 68%	<b>3ja:3ja'</b> = 3:2, 74% <b>3ka</b> , 0% <b>3la</b> , 70% <b>3ma</b> , 68% <b>3na</b> , 77% <b>3oa</b> , 83% <b>3pa</b> , 79% <b>3qa</b> , 73% <b>3ra</b> , 65% <b>3sa</b> , trace
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<sup>a</sup> Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol, 2 equiv),  $\text{Ir}(\text{ppy})_3$  (2 mol %), 2,6-lutidine (2 equiv),  $\text{CH}_3\text{CN}$  (2 mL) at 100 °C under an argon atmosphere and 5 W blue LED light for 24 h.

<sup>b</sup> Isolated yield.

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