Organic LETTERS

Visible-Light-Promoted Dual C−C Bond Formations of Alkynoates via a Domino Radical Addition/Cyclization Reaction: A Synthesis of Coumarins

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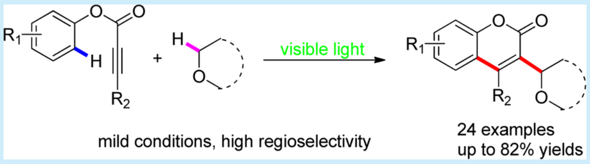
Supporting Information

ABSTRACT: A visible-light-promoted, mild, and direct difunctionalization of alkynoates has been accomplished. This procedure provides a new strategy toward synthesis of the coumarin core structure by photoredox-mediated oxidation to generate the α-oxo radical, which supervenes a domino radical addition/cyclization reaction in moderate to good yields with high regioselectivity at ambient temperature.



mild conditions, high regioselectivity

24 examples
up to 82% yields

Direct functionalization of C−H bonds has drawn great attention during the past decade owing to its step- and atom-economy with environmental sustainability to construct C−C and C−heteroatom bonds.[1] Unlike the C(sp^2)−H bonds,[2] direct functionalization of C(sp^3)−H bonds in a predictable and efficient manner has become a central challenge in modern organic chemistry for their relatively strong bond dissociation energy (BDE) and the low polarity.[3] Recently, transition-metal-catalyzed C(sp^3)−H functionalization reactions with copper,[4] palladium,[5] nickel,[6] and so on[7] have been reported. However, these methods require high reaction temperatures and the use of coordinating directing groups to achieve the key C(sp^3)−H activation step, which extremely limits their applications in complex molecule synthesis.

Visible light photoredox catalysis for the activation of organic molecules has received much attention in recent years.[8] For its intrinsic characteristics of sustainability and green chemistry, the direct functionalization of C−H bonds via photoredox catalysis has become a hot topic.[9] On the other hand, the difunctionalization of alkynes has emerged as a fascinating and powerful tool for the construction of various valuable organic compounds due to its high efficiency in the cascade formation of carbon−carbon and carbon−heteroatom bonds.[10] In this field, the difunctionalization of readily available alkynoates via a cascade radical cyclization has been proved to be an efficient strategy in the construction of 3-functionalized coumarins,[11,12] which have been widely found in the structures of natural products, pharmaceuticals and biologically active molecules with anticoagulant,[13] antitumor,[14] antimalarial,[15] anti-HIV,[16] and antimicrobial properties.[17] Nevertheless, to date, only a few methods for the difunctionalization of alkynoates with a C(sp^3)−H bond adjacent to an oxygen atom (ethers) was reported. In 2014, Li's group developed a Cu-catalyzed synthesis of 3-etherified aza- or oxaspiro[4.5]trienones from *N*-arylpropiolamides or phenyl alkynoates and ethers through oxidative C(sp^3)−H functionalization, ipso-carbocyclization, and dearomatization cascade.[18] Two years later, the group of Zhu used a similar strategy to access trisubstituted olefins through radical addition, aryl migration, and decarboxylation processes.[19] However, both of the reported reactions needed high reaction temperatures (110 or 120 °C) to generate the active radical species. Inspired and encouraged by these excellent works and considering the high pharmacological activities of coumarins, herein we report a photoredox-catalyzed C(sp^3)−H bond activation of ether derivatives which subsequently undergo a domino radical addition/cyclization reaction with alkynoates to deliver a variety of 3-functionalized coumarins in moderate to good yields with high regioselectivity at ambient temperature (Scheme 1).

Initially, the reaction between phenyl 3-phenylpropiolate **1a** and tetrahydrofuran **2a** was carried out by using a 34 W blue LED strip as the visible light source, with the assistance of Ru(bpy)$_3$Cl$_2$ (0.05 equiv) and *t*-BuOOH (4.00 equiv, 5.5 M in decane) under argon atmosphere. The desired 3-etherified coumarin **3a** was produced in 40% yield (Table 1, entry 1) in a mixed solvent of MeCN and tetrahydrofuran (1:1 volume ratio) at ambient temperature for 40 h. Changing photoredox catalysts from Ru(bpy)$_3$(PF$_6$)$_2$ to eosin Y could not increase the yield of the desired product (Table 1, entries 2 and 3). Other oxidants such as DCP (dicumyl peroxide), BPO (benzoyl peroxide), DTBP (di-*tert*-butyl peroxide), and LPO (lauroyl peroxide) led to very low yields of **3a** (Table 1, entries 4−7). Furthermore, the solvent effect was shown to be

Received: June 26, 2016

DOI: 10.1021/acs.orglett.6b01857
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Difunctionalization of Alkynoates with an α-Csp^3–H Bond in Ether Derivatives

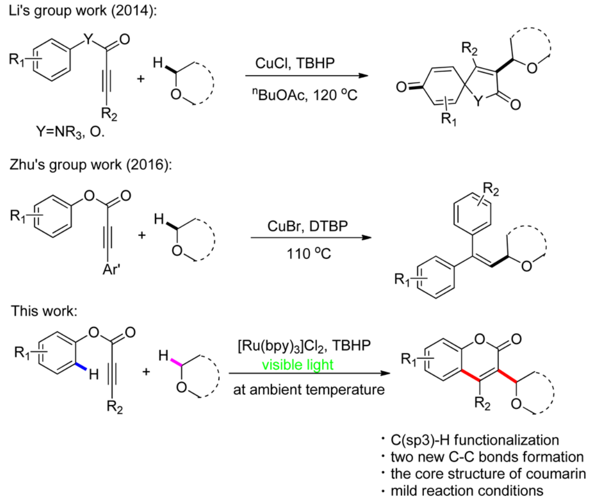
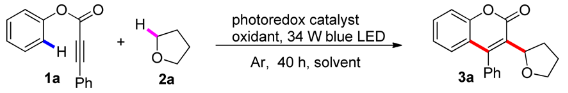


Table 1. Optimization of the Reaction Conditions[a]



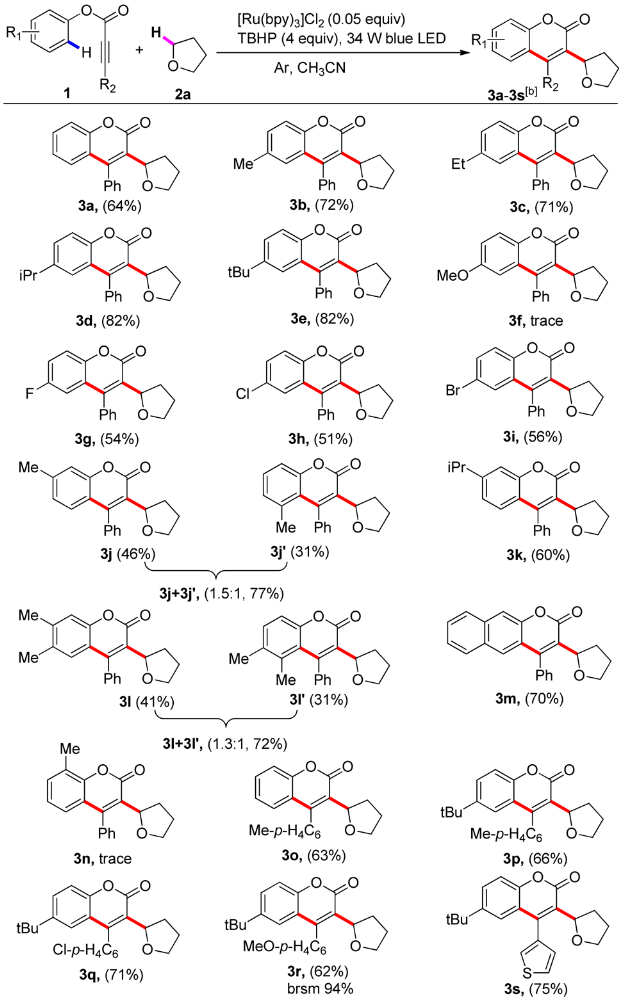
entry	photoredox catalyst	oxidant	solvent	yield[b] (%)
1	$[Ru(bpy)_3]Cl_2$	TBHP[c]	CH_3CN	40
2	$Ru(bpy)_3(PF_6)_2$	TBHP	CH_3CN	35
3	eosin Y	TBHP	CH_3CN	0
4	$[Ru(bpy)_3]Cl_2$	DCP	CH_3CN	trace
5	$[Ru(bpy)_3]Cl_2$	BPO	CH_3CN	trace
6	$[Ru(bpy)_3]Cl_2$	DTBP	CH_3CN	0
7	$[Ru(bpy)_3]Cl_2$	LPO	CH_3CN	trace.
8	$[Ru(bpy)_3]Cl_2$	TBHP	THF	20
9	$[Ru(bpy)_3]Cl_2$	TBHP	MeOH	15
10	$[Ru(bpy)_3]Cl_2$	TBHP	CH_2Cl_2	25
11	$[Ru(bpy)_3]Cl_2$	TBHP	DCE	12
12[d]	$[Ru(bpy)_3]Cl_2$	TBHP	CH_3CN	34
13[e]	$[Ru(bpy)_3]Cl_2$	TBHP	CH_3CN	22
14[f]	**$[Ru(bpy)_3]Cl_2$**	**TBHP**	**CH_3CN**	**64**
15[f,g]	$[Ru(bpy)_3]Cl_2$	TBHP	CH_3CN	24
16[h]	$[Ru(bpy)_3]Cl_2$	TBHP	CH_3CN	trace

[a] Reaction conditions: phenyl 3-phenylpropiolate (**1a**, 0.15 mmol), THF (**2a**, 1 mL), photocatalyst (5.0 mol %), oxidant (4 equiv), CH_3CN(1 mL) at ambient temperature under argon for 40 h. [b] isolated yield. [c] tBuOOH 5.5 M in decane. [d] 2 mL **2a**. [e] 0.5 mL **2a**. [f] 3 mL **2a**. [g] 2 equiv K_2CO_3 was added. [h] Without visible light irradiation.

comparatively significant during this reaction. When THF, MeOH, CH_2Cl_2, or 1,2-dichloroethane (DCE) was used in place of MeCN in the mixed solvent, poor yields of **3a** were obtained under otherwise self-same reaction conditions (12–25%, Table 1, entries 8–11). We then considered whether the yield of **3a** could be improved when the amount of **2a** was increased (Table 1, entries 12–14). When MeCN/THF (1:3, volume ratio) was used as a reactant and solvent system, the yield was readily increased to 64% (Table 1, entry 14), and K_2CO_3 as an additive was later proven to be ineffective in augmenting the yield of **3a** further (Table 1, entry 15). Finally, control experiments conducted under the absence of visible light unambiguously pointed to complete inhibition of the reactivity (Table 1, entry 16). It is noteworthy that the present optimal conditions include performing the reactions under an insert atmosphere, for we found that the raw material was consumed faster under inert gas protection than in air, and the former gave a better overall yield than the latter.

With the optimized reaction conditions in hand, we then examined the substrate scope and limitations of our domino radical cyclization reaction. First, various alkynoates were subjected to the optimized reaction conditions (Scheme 2).

Scheme 2. Reaction Scope of Phenyl 3-Arylpropiolates[a]

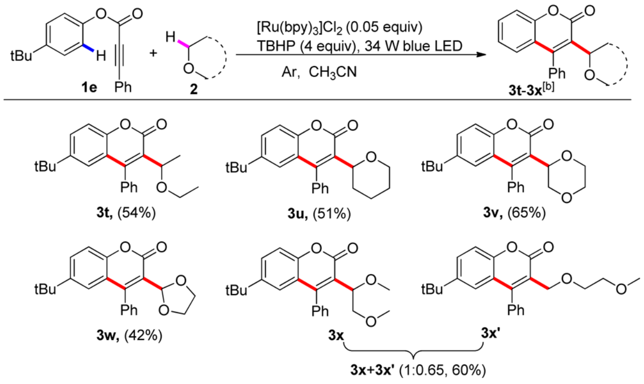


[a] Reaction conditions: **1** (0.15 mmol), **2a** (3 mL), $Ru(bpy)_3Cl_2$ (5 mol %), TBHP (4 equiv), CH_3CN (1 mL), 34 W blue LED strip, at ambient temperature under argon for 40–48 h. [b] Isolated yields.

Some representative R^1-substituted phenyl alkynoates were evaluated under the standard reaction conditions, including electron-donating groups, electron-withdrawing groups, and halogens. The alkynoates containing electron-donating groups, such as Me, Et, *i*-Pr, and *t*-Bu on the *para*-position of phenyl rings reacted smoothly with tetrahydrofuran (**2a**), generating the corresponding coumarins (**3a–e**) in moderate to good yields (64–82%). It should be noted that substrate **1f** with a strong electron-donating substituent (MeO) on the phenyl ring proved to be unsuitable for the present reaction conditions, providing a trace amount of the desired product **3f**. Moreover, halogens (F, Cl, and Br) attached on the substrate **1** could be well tolerated, giving the desired products (**3g–i**) in 51–56% yields. The reaction of substrates **1j** and **1l** with a methyl group on the *meta*-position of the phenyl ring reacted well with **2a**, successfully converting into the corresponding products in good yields (72–77%), whereas **3j**, **3j′** and **3l**, **3l′** were formed in a ratio of two regioisomers (1.5:1 and 1.3:1, respectively). Using the substrate **1k** with an isopropyl instead of methyl groups on the *meta*-position of the phenyl ring, **3k** was obtained in 60% yield with good regioselectivity, which could be attributed to the hindrance effect caused by the isopropyl group. However, a significant steric effect was observed during the reaction between **1n** with a methyl group on the *ortho*-position of the phenyl ring and **2a**, and a trace amount of **3n** was found. On the other hand, alkynoates with different R^2 functional groups were evaluated as well. All of the tested substrates (**3o**–**s**) underwent the desired reaction smoothly and gave the corresponding products with good yields (62%–75%) regardless of electron-donating or -withdrawing groups. In particular, when R^2 is a 3-thienyl group, the corresponding substrate **1s** was also found to be suitable for the reaction with an excellent yield (**3s**, 75%). Moreover, the alkynoate with a cyclopropane group at the alkyne site was also tested under the standard conditions. Unfortunately, it gave a complex mixture in which we could not identify any main product together with some recovered raw material.

Owing to the diversity of ether compounds, we next investigated the applicability of various simple ether derivatives in this transformation (Scheme 3). To our delight, common simple ethers such as diethyl ether, tetrahydropyran, 1,4-dioxane, and 1,3-dioxolane all reacted smoothly with **1e** to generate the corresponding coumarins (**3t**–**w**) in moderate to good yields (42–65%), and their reactions all proceeded with high regioselectivities. When 1,2-dimethoxyethane was used to test this transformation, a mixture of two regioisomers **3x** and **3x′** was obtained in 60% total yield with a ratio of 1:0.65, respectively. Additionally, the cyclohexane, cyclopentane, and *N*-methylmorpholine were tested under the standard reaction conditions instead of ether. However, none of them gave the desired substituted coumarin product, and most of the raw starting materials were recovered.

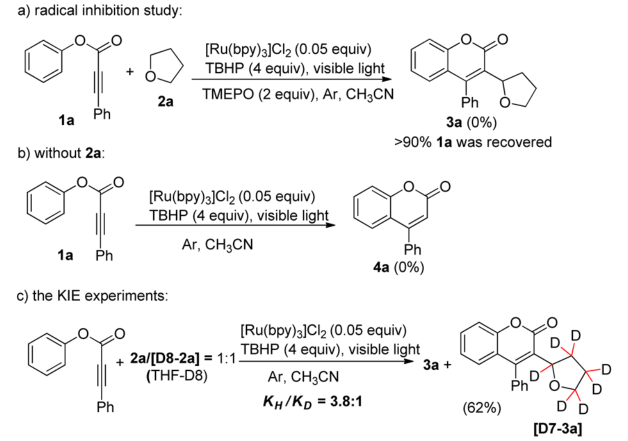
Scheme 3. Reaction Scope of Ethers[a]



[a]Reaction conditions: **1e** (0.15 mmol), **2** (3 mL), Ru(bpy)$_3$Cl$_2$ (5 mol %), TBHP (4 equiv), CH$_3$CN (1 mL), 34 W blue LED strip, at ambient temperature under argon for 40–48 h. [b]Isolated yields.

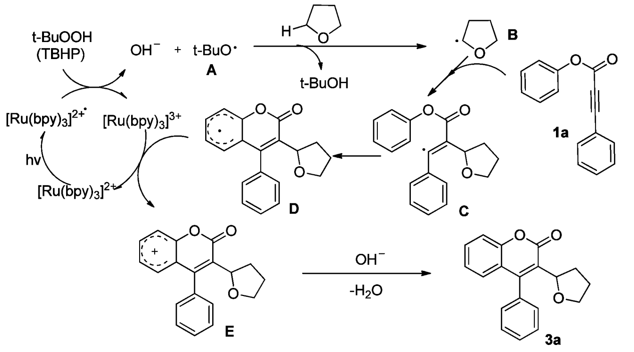
To obtain a detailed mechanistic insight for this transformation, some control experiments were performed as shown in Scheme 4. When the well-known radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added under the standard conditions, the reaction was obviously inhibited (Scheme 4a). This outcome was consistent with our hypothesis that the reaction proceeds via a radical pathway. When **1a** was treated under the standard conditions in the absence of **2a**, C–H functionalization did not occur, and the cyclization product **4a** was not detected (Scheme 4b). This result indicated coumarin **4a** might not be the key intermediate in the present reaction system. A large kinetic isotope effect was discovered using a mixture of THF **2a** and THF-d_8 **[D8]-2a** (k_H/k_D = 3.8), indicating that the cleavage of the C(sp^3)–H bond adjacent to the oxygen atom of THF constitutes a rate-limiting step.[18,20]

Scheme 4. Control Experiments



On the basis of the above results and previous literature,[11,12] a plausible reaction mechanism via a free-radical-type process is depicted in Scheme 5.[21] The sequence would be initiated through irradiation by the blue LED, and the photocatalyst undergoes a metal-to-ligand charge transfer and subsequent intersystem crossing to generate a relatively long-lived ruthenium(II) species in an excited state.[22] This reductant readily undergoes single electron transfer with *tert*-butyl hydroperoxide (TBHP) to give a *tert*-butoxyl radical **A**, which abstracts a hydrogen atom from tetrahydrofuran to give the new α-oxo radical **B** and *t*-BuOH. Selective addition of the radical **B** to the α-position of the C═O bond in alkynoate **1a** generates the vinyl radical **C**. The intermediate **C** then cyclizes to the aryl ring to form the radical intermediate **D**. Subsequently, oxidation of intermediate **D** with the ruthenium(III) species gives the carbocation intermediate **E**. Finally, species **E** is deprotonated, regenerating the aromatic system and affording the desired 3-etherified coumarin product **3a**.

Scheme 5. Possible Reaction Mechanism



In summary, we have conceived and demonstrated an efficient, visible-light-mediated, direct difunctionalization of alkynoates, during which two new C−C bonds were formed in one step, toward the synthesis of the biologically attractive coumarin core structure in moderate to good yields. This procedure avoids limitations commonly associated with transition-metal-mediated C−H activation, including requirements for high reaction temperatures and chelating directing groups. Further applications of this protocol in organic synthesis are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01857.

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Science Foundation of China (21472079 and 21572088), PCSIRT (IRT_15R28), and the Fundamental Research Funds for the Central Universities (lzujbky-2015-50, lzujbky-2016-ct02).

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