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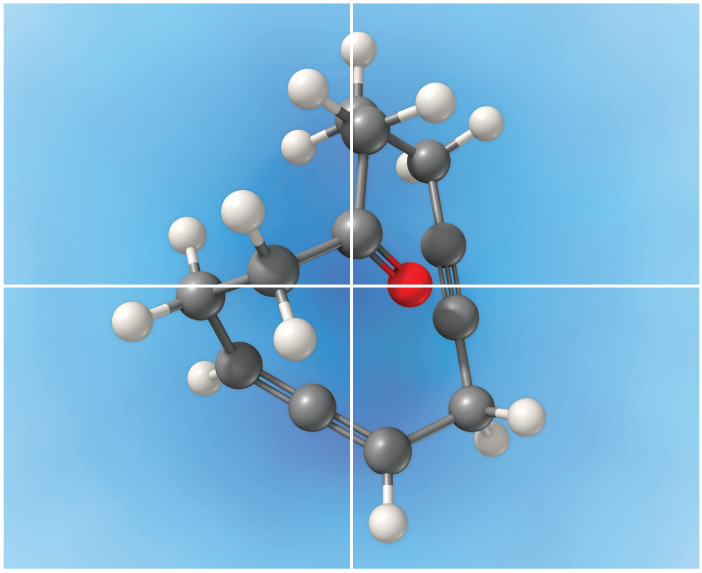

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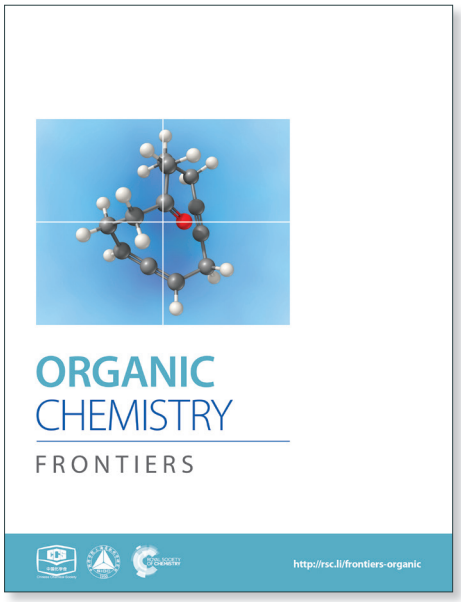

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ARTICLE TYPE

Radical decarboxylative annunlations of alkynoates with 2-oxoacetic acids: Synthesis of 3-acylcoumarins via 5-*exo* cyclization and ester Migration

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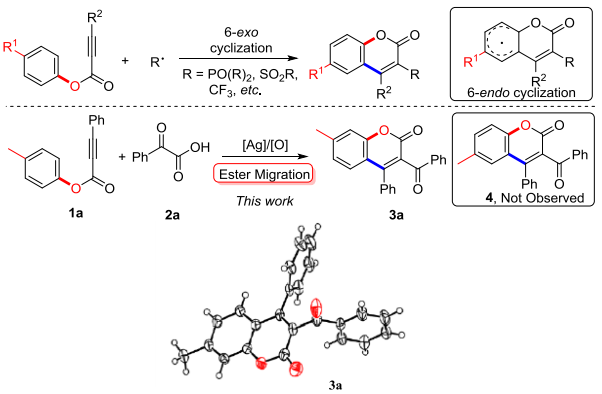
A silver-promoted decarboxylative annulations of alkynoates with 2-oxoacetic acids is reported, leading to the formation of 3-acyl4-arylcoumarins. In the process, radical decarboxylative acylation, 5-*exo* cyclization, and ester migration are mainly involved.

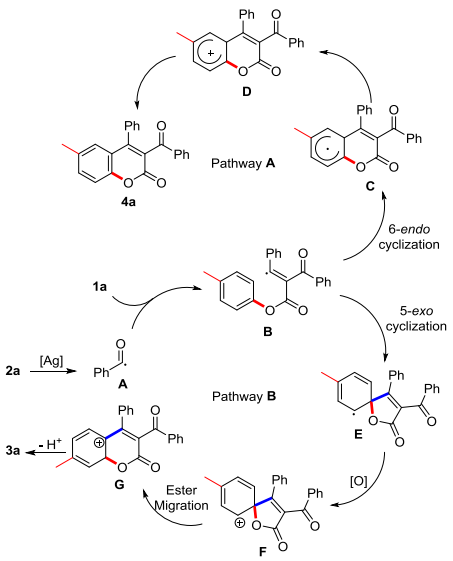
Coumarin scaffold, which is always found in many bioactive natural products and pharmaceuticals, is generally accepted as one of the important class of heterocyclic compounds. [1] Consequently, much attention has been paid to methodology development for facile, mild, and efficient synthesis of coumarin derivatives.[2] Presently, one of notable achievements has been defined as alkynoates-based radical 6-*endo* cyclization, and has already installed many functional groups such as phosphonate and arylsulfonyl groups into coumarin skeleton with high efficiency and broad substrate scope (Scheme 1).[3] Very recently, we developed a novel radical pathway to introduce trifluoromethyl group into the coumarin core at 3-position, where alkynoates with Togni's reagent were employed as starting materials, and an array of 3-trifluoromethylcoumarins was



Scheme 1 Proposed route for the synthesis of 3-acylcoumarins

produced efficiently under mild conditions.[3c] In this process, radical trifluoromethylation of alkynoates and *6-endo* cyclization produced the desired 3-trifluoromethylcoumarins. As our continuous interest in the methodology development for the synthesis of privileged heterocycles,[4] we would like to introduce other versatile building blocks into coumarins structure with a wish to synthesize various 3-funtionalized coumarins in a radical fashion. We thus riveted our attention on 3-acylcoumarin architectures, which is one type of coumarins with bioactivities of antioxidant, antitumor, and antiimflammatory *etc*.[5] Traditional accesses to 3-acylcoumarins were intensively focused on substrate-based condensation.[6] Understandably, to develop its new synthetic methodology is highly desirable.

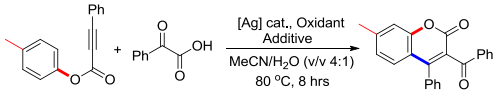
On the other hand, it is well-known that carbonyl radical could often be generated from aldehydes.[7] Possibly, due to aldehydes readily being oxidized, excess of aldehydes was always indispensable in the reactions. As an elegant alternative source, 2-oxoacetic acids could offer acyl radical through silver-catalyzed decarboxylation.[8] Therefore, we anticipated that 3-acylcoumarins could be afforded through radical silver-promoted decarboxylative annulation of alkynoates with 2-oxoacetic acids.



Scheme 2 Proposed mechanism for the synthesis of 3-acylcoumarins

In our preliminary trials, we are pleased to find that the model reaction of alkynoate **1a** with 2-phenyl-2-oxoacetic acid **2a** resulted in a product in 38% yield in the presence of 20 mol % Ag_2CO_3, 2.0 equiv $K_2S_2O_8$ in DMF at 80 °C. To our surprise, structure identification by NMR and X-ray diffraction suggested that the product was not our anticipated product **4a** but an unexpected compound **3a** (Scheme 1). Structural comparison of

Table 1 Initial studies for the silver-prompted reaction of alkynoate **1a** with 2-oxoacetic acid **2a**.[a]



1a 2a 3a

Entry	Catalyst	Oxidant	additive	Solvent	Yield (%)[b]
1	Ag_2CO_3	$K_2S_2O_8$	-	DMF	38
2	Ag_2CO_3	$K_2S_2O_8$	-	MeCN	21
3	Ag_2CO_3	$K_2S_2O_8$	-	DMF/H_2O	16
4	Ag_2CO_3	$K_2S_2O_8$	-	MeCN/H_2O	45
5	$AgNO_3$	$K_2S_2O_8$	-	MeCN/H_2O	38
6	Ag_2CO_3	$(NH_4)_2S_2O_8$	-	MeCN/H_2O	40
7	Ag_2CO_3	Oxone	-	MeCN/H_2O	NR
8	Ag_2CO_3	$PhI(OAc)_2$	-	MeCN/H_2O	NR
9	Ag_2CO_3	TBHP	-	MeCN/H_2O	NR
10	Ag_2CO_3	$K_2S_2O_8$	Na_2CO_3	MeCN/H_2O	52
11	***Ag_2CO_3***	***$K_2S_2O_8$***	***NaOAc***	***MeCN/H_2O***	***74***
12	Ag_2CO_3	$K_2S_2O_8$	$KHCO_3$	MeCN/H_2O	68
13	Ag_2CO_3	$K_2S_2O_8$	KOH	MeCN/H_2O	71
14[c]	Ag_2CO_3	$K_2S_2O_8$	NaOAc	MeCN/H_2O	62
15	-	$K_2S_2O_8$	NaOAc	MeCN/H_2O	NR
16[d]	Ag_2CO_3	$K_2S_2O_8$	NaOAc	MeCN/H_2O	8

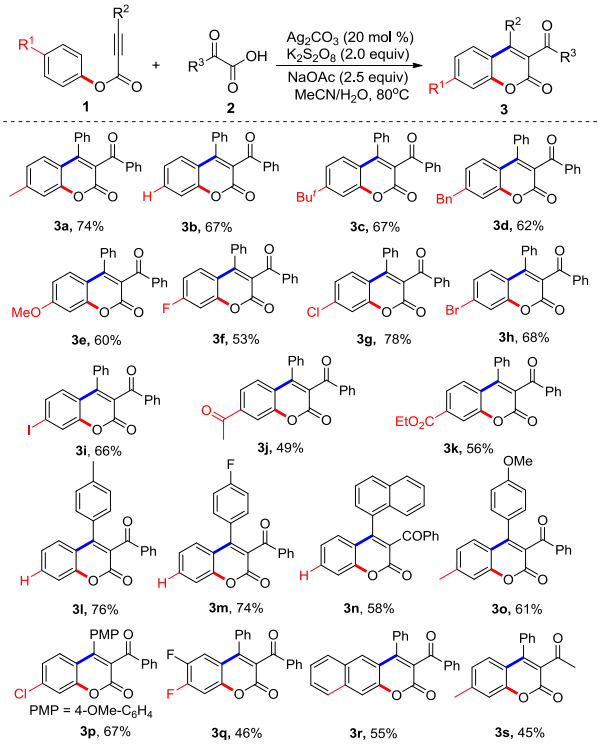
[a] Reaction conditions: alkynoates **1a** (1.0 equiv), 2-oxoacetic acid **2a** (1.2 equiv), silver carbonate (20 mol %), $K_2S_2O_8$ (2.0 equiv), NaOAc (2.5 equiv), MeCN/H_2O (v/v 4:1), 80 °C, 8 hrs. [b] Isolated yield based on alkynoates **1a**. [c] In the presence of 10 mol % of Ag_2CO_3; [d] 2.0 equiv TEMPO was added.

compound **3a** with **4a** revealed that ester migration probably took place in **3a**-producing reaction.

However, the very recent Wu's findings indicated that acyl radicals, which were derived from aldehydes, reacted with alkynoates to form the product **4a**. [9] In the process, radical acylation and 6-*endo*-cyclization were involved (Pathway **A**, Scheme 2). From these results, it is convinced that our transformation goes through another pathway which is distinctive from Wu's. In light of these previous achievements obtained by other groups and us, a tandem process combining radical acylation, 5-*exo* annulation,[10] with ester migration was proposed to explain the formation of the unexpected product **3a** (Pathway **B**, Scheme 2). As illustrated in Scheme 2, acyl radical species **A**, which was generated from silver-catalyzed decarboxylation of 2-phenyl-2-oxoacetic acid **2a**, would occur to undergo a radical acylation of alkynoates **1a**, leading to intermediate **B**. The following 5-*exo* cyclization provided a spirocyclic species **E**, which readily converted into intermediate **F** in the presence of oxidant. Ester migration and de-protonation then released the desired 3-acylcoumarins **3a**. Compared with Wu's results, it is believed that the discrepancy probably attributed to relatively slow rate of producing acyl radical through silver-catalyzed decarboxylation. Thanks to slow rate of producing acyl radical, concentration of intermediate **B** was always low in our method, and thus occurred to go through 5-*exo* cyclization with the formation of intermediate **E** specifically.

We thus optimized the reaction conditions. All result-affecting factors including silver source, oxidant, additive, solvent, and temperature were evaluated in the reactions. The results were presented in table 1. From the results of solvent screening, it seemed that moisture was critical in the reaction, and the co-solvent of acetonitrile and water (v/v = 4:1) was the best choice,

Table 2 Synthesis of subtituted 3-acylcoumarins via a silver-prompted decarboxylic annulation of alkynoates and 2-oxoacetic acids.[a]



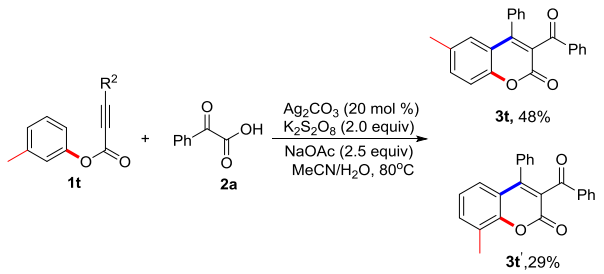
[a] Isolated yield based on alkynoates **1**.

providing the desired product **3a** in 45% yield (Entry 4, table 1). Which probably owing to the fact water could improve the solubility of silver salt and oxidant in solvent. Changing catalyst to other silver salt (silver nitrate) with better solubility in water did not bring about a better result (Entry 5, table 1). Other oxidants including $(NH_4)_2S_2O_8$, Oxone, $PhI(OAc)_2$, and TBHP were also explored, but no improved outcomes were observed (Entries 6-9, table 1). The evaluation of additive revealed that a proper base could drastically improve the reaction efficiency. When sodium acetate was used as the additive, the reaction afforded **3a** in 74% yield (Entry 11, table 1). Reducing the loading of silver carbonate to 10 mol % gave an inferior yield in the reaction (Entry 14, table 1). Temperature and reaction time only slightly affected the reaction results (data not shown in table 1). No reaction was observed in absence of silver carbonate (Entry 15, table 1). The reaction almost failed when 2.0 equiv TEMPO was added (Entry 16, table 1), with the production of the desired molecule **3a** in only 8% yield.

With the optimized conditions in hand (20 mol % Ag_2CO_3, 2.0 equiv $K_2S_2O_8$, 2.5 equiv NaOAc in MeCN/H_2O at 80 °C), we then examined the scope and generality of radical decaboxylative annulation of alkynoates **1** and 2-oxoacetic acids **2**. The corresponding results were illustrated in Table 2. From the results shown in Table 2, a series of substituted 3-acylcoumarins **3** were achieved as expected. The electron effect exerted minimal impact on the yields of the reactions. In the reactions, the substituent R^1 could be replaced by both electron-rich groups and electron-deficient groups. For examples, the reactions produced the corresponding products **3c**-**3e** in good yields when R^1 was *tert*-

butyl, benzyl, and methoxyl, respectively. Additionally, substrates with Electron-withdrawing groups such as halide, acetyl and ester groups were proved to be excellent reaction partners, affording corresponding products **3f-3k** in 49-78% yields. Surprisingly, the substituent R^2 was limited by aryl groups. When a compound with an alkyl group at R^2 position was used as the substrate, the reaction did not deliver the target molecule (data not shown in Table 2). When R^2 was an aryl group, the electron effect of the substituent on aryl group did not have great impact on the results, and all these reactions could provide corresponding products in moderate to good yields. Double

Table 3 a silver-prompted decarboxylic annulation of *m*-methyl alkynoates **1t** and 2-oxoacetic acids **2a**.[a]



[a] Isolated yield based on alkynoates **1t**.

fluoro substituted substrate **1q** and Naphtalenyl alkynoate **1r** were compatible for the reaction with the formation of the expected 3-acylcoumarin **3q** and **3r** in 46% and 55% yield, respectively. Methyl group substituted 2-oxoacetic acid was also an efficient source of acyl group, which was introduced into the expected molecule **3s** in 45% yield.

Interestingly, when *m*-methyl alkynoate **1t** was employed as the substrate, the reaction afforded a mixed product **3t** and **3t'**. The ratio of these two compounds was about 5:3. To our delight, these two compounds could be isolated and purified through chromatographic column.

In conclusion, we developed a novel silver-promoted decarboxylative annulation for the synthesis of 3-acylcoumarins with high efficiency and good tolerance of functional groups. In this process, it is believed that a radical acylation, 5-*exo* cyclization and ester migration are involved. This protocol represented the first examples that coumarin derivatives were prepared from alkynoates via radical 5-*exo* annulation and ester migration. Its application into the synthesis of other 3-substituted coumarins is ongoing in our lab. The results will be published in due course.

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Notes and references

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*†Electronic Supplementary Information (ESI) available: [Experimental procedure, characterization data, ^1H and ^{13}C NMR spectra of compounds **3** and CCDC reference number 1043097(compound **3a**).]. See DOI: 10.1039/b000000x/*

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