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Tandem metal-free oxidative radical 5-*exo* dearomative spirocyclization and ester migration: generation of 3-functionalized coumarins from alkynoates

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ABSTRACT

A tandem metal-free oxidative radical cyclization of alkynoates is described to synthesize 3-acetonylcoumarins. In the process, a distinctive mechanism, which involves radical addition of 2,4-diones to alkynoates, oxidative 5-*exo* dearomative spirocyclization and ester migration, is proposed in this paper.

1. Introduction

Acceptably, coumarin is considered to be a ‘privileged’ motif in medicinal chemistry and ubiquitously found in many natural products, bioactive molecules and pharmaceuticals.[1] Given their utilisation potential, tremendous efforts were devoted to their synthetic methodology development,[2] with a wish to prepare coumarin derivatives from readily available substrates under mild conditions. As is well known, Pechmann condensation was recognized as one of most attractive methods.[3] With the development of palladium chemistry, palladium catalysis was used to construct coumarin motifs.[4]

Recently, a particular emphasis was put on alkynoates-based chemistry, probably due to its versatility in heterocycle-producing transformations.[5–9] Reported by Fujiwara, He, Song, Tunge, and other groups, transitional metal catalysis (especially, palladium catalysis and gold catalysis) enabled the synthesis of coumarin derivatives through a formal hydroarylation of alkynoates in a manner of 6-*endo* cylization (Scheme 1a).[6] Starting from methoxyl-substituted alkynoates, Larock and co-workers in 2005 developed a dearomative spirocyclization, which was also defined as electrophilic *ipso*-cyclization, to synthesize spiro[4,5]trienones with high efficiency.[7d] In these reactions, electrophilic iodination reagents such as ICl and NIS improved electrophilicity of triple bonds, thus facilitating intramolecular spirocyclization (Scheme 1b).[7] According to recent findings reported by Kita's group, the in situ generated hypervalent iodide (I^{III+}) could trigger the electrophilic *ipso*-cyclization as well.[8] Assisted by external nucleophiles, Li and co-workers highlighted that the alkynoates without methoxyl group also went through electrophilic *ipso*-cyclization to form spiro[4,5]trienyl acetates.[9a] Actually, this electrophilic *ipso*-cyclization was a process involving a formal electrophilic 5-*exo* dearomative spirocyclization. Encouraged by the above information and considering the importance of coumarins as well as our continuous interests in developing novel synthetic methodologies to construct heterocyclic architectures,[10] we would like to develop a radical 5-*exo* dearomative spirocyclization of alkynoates combined with other reactions to synthesize 3-functionalized coumarin scaffolds. As shown in Scheme 1c, we hypothesized the intermediate **A**, which was generated from radical addition of alkynoates, occurred to undergo oxidative radical 5-*exo* dearomative spirocyclization to afford a spirocyclic cation **C**. Followed by ester migration and re-aromatization, this tandem reaction delivered 3-functionalized coumarin motif (Scheme 1c). To the best of our knowledge,

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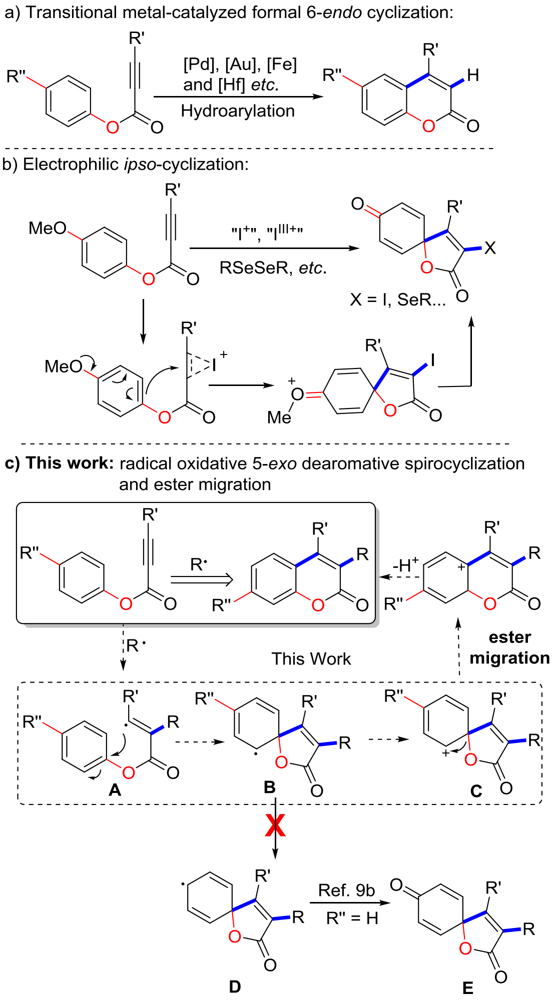


Scheme 1. Proposed route for the synthesis of 3-acetonylcoumarins via tandem radical 5-*exo* cyclization and ester migration of alkynoates.

oxidative radical 5-*exo* dearomative spirocyclization of alkynoates to 3-etherified azaspiro[4.5]trienones has been witnessed by Li and co-workers.[9b] In this transformation, the intermediate **B** was rearranged to the intermediate D, which was trapped by hydroxyl group and then oxidized to provide the desired 3-etherified azaspiro[4.5]trienones. Rather than radical rearrangement to intermediate **D**, our group found that the intermediate **B** can be oxidized into the intermediate **C** in the presence of $K_2S_2O_8$ as oxidant. Spirocyclic cation **C** was prone to undergo 1,2-carbon cation rearrangement to form 3-substituted coumarins. To date, acyl groups were successfully smuggled by our group into 3-position of coumarins through tandem radical 5-*exo* cyclization and ester migration of alkynoates. In the reactions, the R″ group in coumarins was formally migrated from *para* to *meta* position of ester. Considering its efficiency and potential utilization of coumarins, we would like to introduce more versatile building blocks into C3 position of coumarins via the above methodology.

3-acetonylcoumarins were important intermediates in organic synthesis. Many biological molecules and fluorescences were derived from this key intermediate.[11] However, methodology for the synthesis of 3-acetonylcoumarins remains rare. Traditional accesses resorted to condensation reactions of salicylal,[12] Friedel–-Crafts of coumarin acyl chloride,[13] and hydrolysis of 3-alkynylcoumarins.[14] Inspired by what mentioned above, we envisioned that 1,3-dicarbonyls can be introduced into coumarins to provide 3-acetonylcoumarins by the above strategy involving oxidative radical 5-*exo* dearomative spirocyclization and ester migration of alkynoates.

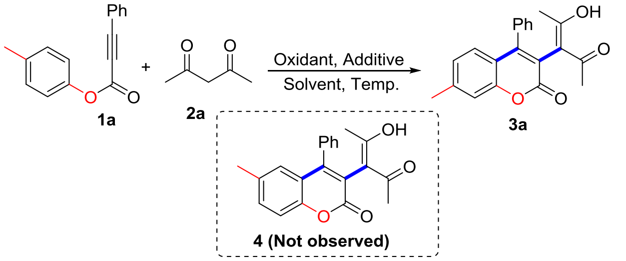
2. Results and discussion

To verify possibility of the transformation, the reaction of tolyl alkynoate **1a** with acetylacetone **2a** was selected as model reaction. As we know, treatment of acetylacetone **2a** with manganese(III) acetate ($Mn(OAc)_3$) readily produced methene radical.[15] The reaction in the presence of 2 equiv $Mn(OAc)_3$ was thus ran firstly (entry 1, Table 1). Other oxidants such as DDQ and CAN did not improve the efficiency (data not shown in Table 1). The negative results pushed us to examine other methene radical-producing protocols. To our delight, the combination of $K_2S_2O_8$ with TBAB made this tandem reaction successfully, leading to the desired coumarin **3a** in 35% isolated yield (entry3, Table 1). The exact structure of coumarin **3a** was identified by NMR, HRMS and X-ray diffraction (see Scheme 2).[16] Therefore, our proposed pathway involving 5-*exo* dearomative spirocyclization and ester migration seems reliable to account for the preparation of coumarin **3a** from phenyl alkynoate **1a**.

To the best of our knowledge, many literature witnessed radical oxidative cyclization of aryl alkynoates for the synthesis of 3-functionalized coumarins.[17] To date, a variety of building blocks including trifluoromethyl, carbonyl and phosphite was installed into coumarin core. A generally-accepted pathway, which was constituted by radical addition, oxidative 6-*endo* cyclization and

Table 1

Initial studies for tandem 5-*exo* cyclization and ester migration of alkynoate **1a** and 1,3-carbonyl **2a**[a]



Entry	Oxidant	Additive	Solvent	Yield (%)[b]
1	$Mn(OAc)_3$	—	DCE	NR
2	TBHP	TBAB	DCE	NR
3	$K_2S_2O_8$	TBAB	DCE	35
4	$(NH_4)_2S_2O_8$	TBAB	DCE	31
5	$K_2S_2O_8$	TBAC	DCE	21
6	$K_2S_2O_8$	TBAI	DCE	Trace
7	$K_2S_2O_8$	TBAB	MeCN	33
8	$K_2S_2O_8$	TBAB	Toluene	15
9	$K_2S_2O_8$	TBAB	Dioxane	Trace
10	$K_2S_2O_8$	TBAB	DMF	Complex
11[c]	$K_2S_2O_8$	TBAB	DCE/H_2O	51
12[c]	$K_2S_2O_8$	TBAB	DCE/MeOH	48
13[c]	$K_2S_2O_8$	TBAB	$MeCN/H_2O$	30
14[c]	$K_2S_2O_8$	TBAB	$Toluene/H_2O$	28
15[c]	$K_2S_2O_8$	TBAB	$Dioxane/H_2O$	19
16[c,d]	$K_2S_2O_8$	TBAB	DCE/H_2O	50
17[c,e]	$K_2S_2O_8$	TBAB	DCE/H_2O	NR
18[c,f]	$K_2S_2O_8$	TBAB	DCE/H_2O	NR

[a] Reaction conditions: **1a** (1.0 equiv), **2a** (3.0 equiv), additive (2.0 equiv), oxidant (2.0 equiv), 70 °C, overnight.

[b] Isolated yield based on 2-alkynoate **1a**.

[c] Co-solvent (*v*/*v*=1:1).

[d] 90 °C.

[e] 20 mol % TBAB was used.

[f] 2 equiv TEMPO was added. TBAB=*Tetra*-*n*-butyl ammonium bromide; TBAC=*Tetra*-*n*-butyl ammonium chloride; TBAI=*Tetra*-*n*-butyl ammonium iodide; NR=no reaction.

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