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Silver-Catalyzed Synthesis of 3-Phosphorated Coumarins via Radical Cyclization of Alkynoates and Dialkyl *H*-Phosphonates

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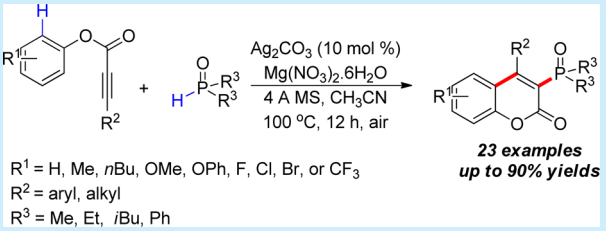
Supporting Information

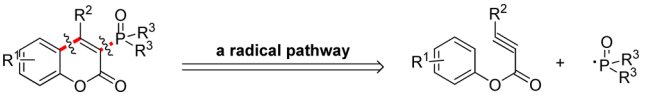
ABSTRACT: Ag_2CO_3-catalyzed difunctionalization of alkynes via a radical phosphonation and C−H functionalization tandem process was developed to synthesize various 3-phosphonated coumarins in moderate to high yields with high regioselectivity. A catalytic amount of cheap and nontoxic silver salt was employed in the domino C−P and C−C formation of alkynoates for the first time. Mechanistic studies indicate that the reaction pathway might proceed via the generation and cyclization of a phosphonated vinyl radical intermediate.



Aromatic organophosphorus compounds could be found in many natural products, pharmaceuticals, materials science, and synthetic intermediates.[1] In light of their importance, the development of C−P bond construction has been a research focus up to now. Several extensively utilized methods of C−P bond construction have been established and developed, for example, the traditional reaction of an electrophilic phosphorus reagent with a carbon nucleophile[2] and transition-metal-catalyzed cross-coupling reactions.[3] After approximately two decades of relative neglect, the addition of P-centered radicals to unsaturated systems is once again being actively investigated and has become a reliable procedure for the synthesis of organophosphorus compounds.[4] Recently, the intermolecular addition of P-centered radicals to alkynes has attracted great attention.[4a] Generally, the synthetic value of radical additions to alkynes is due to the highly reactive vinyl radicals formed by this step which can be trapped by fast cyclization or addition onto other π-systems. To the best of our knowledge, only very few cascade reactions initiated by the addition of P-centered radicals to alkynes have been reported.[5] Thus, the development of efficient P-radical tandem procedures is highly in demand and a promising alternative for the construction of highly complex organophosphorus frameworks.

Generally, P-centered radicals are generated from radical initiators such as peroxides,[6] azo compounds,[7] R_3B/O_2,[8] Ag/$K_2S_2O_8$,[9] etc. Since the seminal contribution by Ishii, manganese salts have been generally used in the phosphorus radical chemical field.[5d,e,10] Very recently, several groups have successively reported that silver salts could work with $Ph_2(O)PH$ to form the active phosphinoyl radicals [$Ph_2P(O)^•$] which have been applied to the addition of unsaturated systems.[11] With our interest in phosphonated coumarins,[3j] we hypothesize that the silver might catalyze the addition of P-radical to alkynoates and conduct the direct cyclization to afford the corresponding phosphonated coumarins as potential pharmaceutical agents[12] (Scheme 1). Herein, we describe a domino preparation of 3-phosphonated coumarins through a silver-catalyzed sequential radical C−P/C−C process between aryl alkynoates and dialkyl *H*-phosphonates.

Scheme 1. Silver-Catalyzed Tandem Coupling Reaction



At the onset of our studies, the tandem radical phosphonation−cyclization of readily prepared phenyl alkynoate (**1a**) with diethyl *H*-phosphonate (**2a**) was investigated in the presence of 1 equiv of $AgNO_3$ in CH_3CN at 100 °C for 12 h. To our delight, the target product **3a** was detected in 23% yield (Table 1, entry 1). The structure of **3a** was unambiguously confirmed by X-ray analysis (Figure 1). Motivated by this result, we further optimized the reaction conditions of this radical cascade process. When the loading of $AgNO_3$ was reduced to 10 mol %, only a trace amount of **3a** was observed (Table 1, entry 2). Interestingly, introducing $Mg(NO_3)_2$ as an additive, the yield increased to 47% and was improved further to 67% with the addition of 4 Å MS (Table 1, entries 3−5). Using $Mg(NO_3)_2$ and 4 Å MS as additives, the different silver and copper salts were evaluated. The results revealed that Ag_2CO_3 gave the highest yield (Table 1, entries 6−12). Other nitrate additives such as $Cd(NO_3)_2·4H_2O$, $Ni(NO_3)_2·6H_2O$, $Co(NO_3)_2·6H_2O$, and $NaNO_3$ also performed in this reaction (Table 1, entries 13−16). Decreasing the reaction temperature led to the yield

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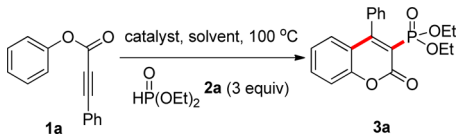
Table 1. Optimization of the Reaction Conditions[a]



entry	cat. (mol %)	additive (equiv)	yield[b] (%)
1[c]	$AgNO_3$ (100)	–	23
2[c]	$AgNO_3$ (10)	–	trace
3[c]	$AgNO_3$ (10)	$Mg(NO_3)_2$ (0.3)	47
4	$AgNO_3$ (10)	$Mg(NO_3)_2$ (0.3)	67
5	$AgNO_3$(10)	$Mg(NO_3)_2$ (0.5)	53
6	AgOAc (10)	$Mg(NO_3)_2$ (0.3)	55
7	Ag_2O (10)	$Mg(NO_3)_2$ (0.3)	56
8	AgOTf (10)	$Mg(NO_3)_2$ (0.3)	57
9	$AgBF_4$ (10)	$Mg(NO_3)_2$ (0.3)	50
10	Ag_2CO_3 (10)	$Mg(NO_3)_2$ (0.3)	80
11	CuCl (10)	$Mg(NO_3)_2$ (0.3)	trace
12	$Cu(OAc)_2$(10)	$Mg(NO_3)_2$ (0.3)	39
13	Ag_2CO_3 (10)	$Cd(NO_3)_2$ (0.3)	45
14	Ag_2CO_3 (10)	$Ni(NO_3)_2$(0.3)	50
15	Ag_2CO_3 (10)	$Co(NO_3)_2$ (0.3)	40
16	Ag_2CO_3 (10)	$NaNO_3$ (0.3)	40
17[d]	Ag_2CO_3 (10)	$Mg(NO_3)_2$ (0.3)	71
18[e]	Ag_2CO_3 (10)	$Mg(NO_3)_2$ (0.3)	79
19	–	$Mg(NO_3)_2$ (0.3)	nr

[a]Reaction condition: **1a** (0.25 mmol), **2a** (3 equiv), catalyst, additive, 4 Å MS (50 mg), CH_3CN (1 mL), 100 °C (oil bath) for 12 h. [b]Isolated yield. [c]Without 4 Å MS. [d]90 °C (oil bath). [e]18 h.

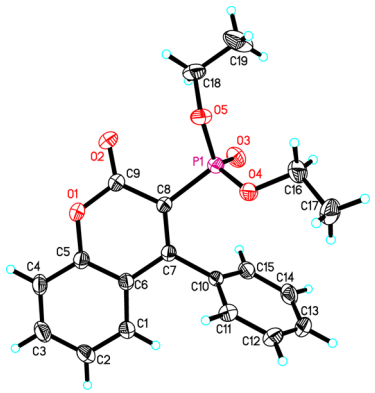
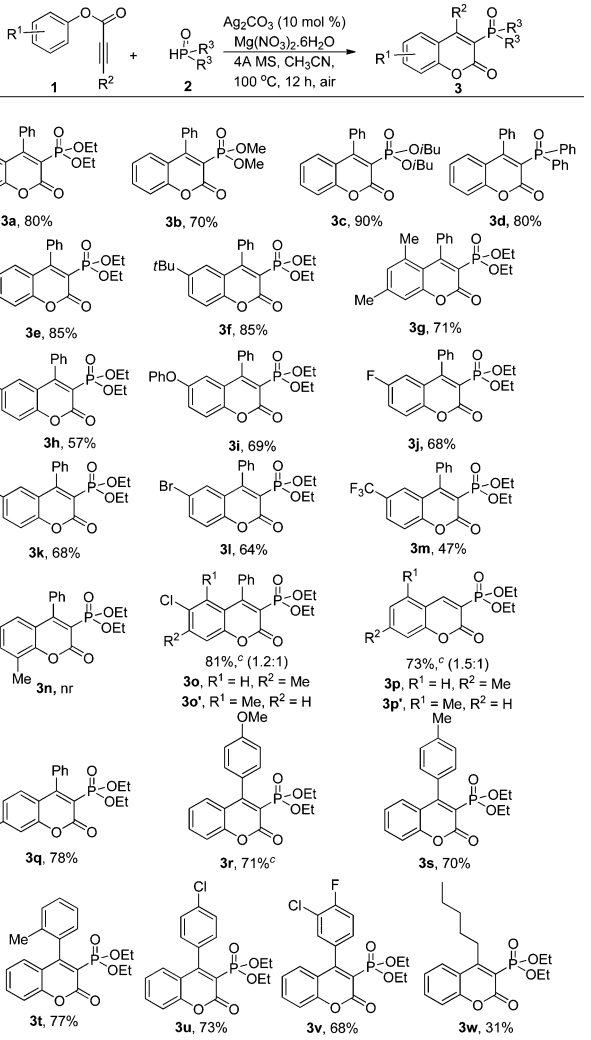


Figure 1. X-ray structure of compound **3a**.

reduction (Table 1, entry 17), and the yield could not be increased further with a longer reaction time (Table 1, entry 18). In addition, a control experiment showed that, without the catalyst, $Mg(NO_3)_2$ alone could not promote this reaction (Table 1, entry 19).

With optimized reaction conditions in hand, the radical phosphonation−cyclization method was applied for various substrates (Scheme 2). The reaction could proceed well by using diverse dialkyl *H*-phosphonates to afford the corresponding products in good yields (**3a−c**). Expectedly, diphenylphosphine oxide is also a suitable P-radical precursor for this transformation, and the desired product **3d** was isolated in 80% yield. Subsequently, various alkynoates were subjected to the optimized reaction conditions (**3e−w**). A variety of aryl 3-phenylpropiolates with *para* and *meta* substituents on the phenoxy ring were smoothly cyclized to obtain the corresponding coumarins in moderate to good yields (**3e−l**). With a strong electron-withdrawing substituent (CF_3) on the phenoxy ring, the corresponding product **3m** was only obtained in 47% yield. The steric hindrance was very distinct. With a methyl group on the *ortho*-position of the phenoxy ring, no desired product **3n** was observed under optimal reaction conditions. To investigate the regioselectivity of the discovered cascade reaction, aryl alkynoates bearing a *meta*-substituted phenoxy ring (**2o−q**) were prepared and successfully converted into the corresponding products in good yields. Whereas **3o**, **3o′** and **3p**, **3p′** were formed in a ratio of two isomers (1.2:1 and 1.5:1 respectively), product **3q** was obtained in high yield with complete regiocontrol. These results indicated that cyclization preferably occurred at the position distal to the *meta* substituent. On the other hand, we also evaluated functional groups linked with the alkynyl. Different substituted aryl groups underwent the reaction smoothly and converted into the corresponding products with good yields regardless of electron-donating or -withdrawing groups (**3r−w**). In particular, phenyl

Scheme 2. Silver-Catalyzed Phosphorus Carbocyclization of Alkynoates[a,b]



[a]Reaction condition: **1** (0.25 mmol), **2** (3 equiv), Ag_2CO_3 (10 mol %), $Mg(NO_3)_2$ (0.3 equiv), 4 Å MS (50 mg), solvent (1 mL), 100 °C (oil bath) under air for 12 h. [b] Isolated yields. [c] A total yield of two isomers is shown.

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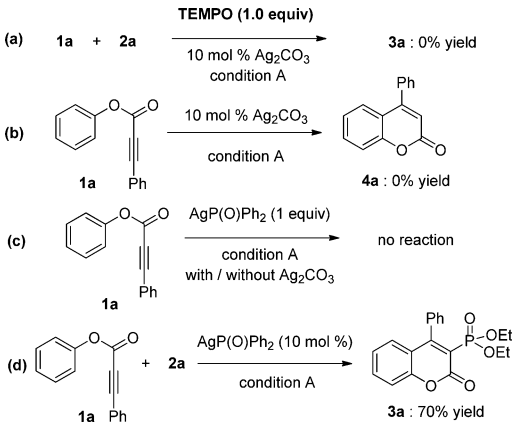
2-octynoate was also found to be suitable for the reaction with a moderate yield (**3w**).

To gain insight into the mechanism of this transformation, a series of control experiments were carried out (Scheme 3). The

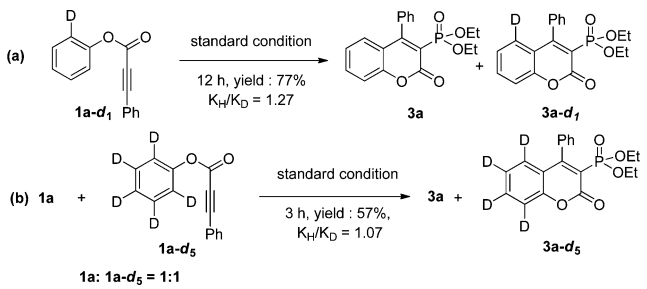
Scheme 3. Control Experiments



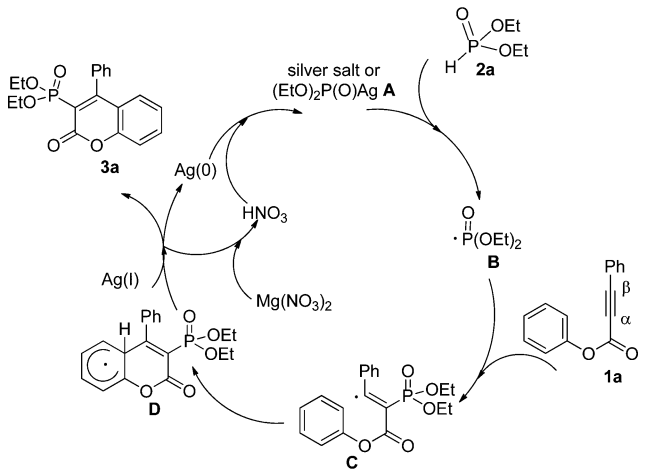
reaction was completely suppressed in the presence of 1.0 equiv of TEMPO as a radical scavenger (Scheme 3a). It was consistent with our hypothesis that the reaction proceeds via a radical pathway. When **1a** was performed under the standard conditions without **2a**, C−H functionalization did not occur, and the cyclization product **4a** was not detected (Scheme 3b). Thus, we conclude that the first step is the phosphonation with Ag_2CO_3.[11c] When the [$Ph_2P(O)Ag$] complex was used in a stoichiometric fashion, no conversion of **1a** was observed with or without Ag_2CO_3. In contrast to previously reported examples,[11b,c] our results indicated that (1) $Ph_2(O)PAg$ could not add to **1a** to form the silver species and (2) P-radicals are active intermediates in this process.[11e] However, in the presence of a catalytic amount of [$Ph_2P(O)Ag$], the reaction of **1a** and **2a** could proceed smoothly to give **3a** in 70% yield, thus suggesting that P-radicals are generated from dialkyl *H*-phosphonates oxidized by Ag_2CO_3 or [$R_2P(O)Ag$] (Scheme 3c, d). To further understand the catalytic cycle of the carbon phosphorylation, the intra- and intermolecular kinetic isotope effects (KIE) were investigated (the intramolecular K_H/K_D = 1.27 and intermolecular K_H/K_D = 1.07) (Scheme 4), which indicate that C−H bond cleavage on the phenoxy ring is not involved in the rate-determining step.

With these results in hand, a plausible mechanism involving a radical-type catalytic cycle is depicted in Scheme 5. First, a phosphorus radical **B** is generated from diethyl *H*-phosphonate **2a** by Ag_2CO_3[11e] or the intermediate **A**. Selectivity addition of the P-radical to the α-position of the C═O bond in **1a** then

Scheme 4. Deuterium Labelling Experiments



Scheme 5. Possible Mechanism



gives the vinyl radical **C** stabilized by the phenyl group. The resulting vinyl radical **C** undergoes cyclization to generate the intermediate **D**. Subsequently, a single-electron transfer (SET) from **D** to silver(I) would release the product **2a** along with HNO_3 and silver(0). In the presence of HNO_3, the silver(0) was oxidized to silver(I).

In summary, we have demonstrated a novel approach to the synthesis of 3-phosphonated coumarins starting with readily prepared alkynoates and the commercially available *H*-phosphonates as a P-radical precursor. Various 3-phosphonated coumarins were prepared with high regioselectivity in moderate to high yields. The cheap and nontoxic silver salt was employed in catalyzing the carbon phosphonation of alkynoate for the first time. A plausible mechanism was proposed involving phosphonation via the addition of P-radicals, and radical cyclization. Further mechanistic studies and extension of the current method to other substrates are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data and copies of NMR spectra for all new compounds and X-ray crystallographic data for compound **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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