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One-Pot Reaction of Carboxylic Acids, Ynol Ethers, and *m*-CPBA for Synthesis of α-Carbonyloxy Esters

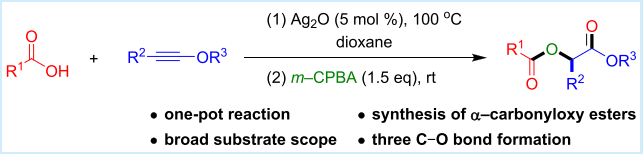
Linwei Zeng,[†] Hironao Sajiki,*[,‡] and Sunliang Cui*[,†]

[†]Institute of Drug Discovery and Design, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China

[‡]Laboratory of Organic Chemistry, Gifu Pharmaceutical University, Gifu 501-1196, Japan

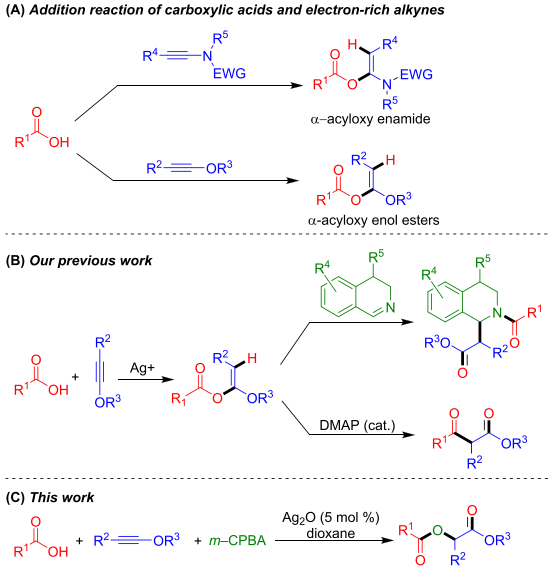
Supporting Information

ABSTRACT: A novel one-pot reaction of carboxylic acids, ynol ethers, and *m*-CPBA for the synthesis of α-carbonyloxy esters in the presence of Ag_2O is described. This process provides a direct approach to α-carbonyloxy esters with the achievement of formation of three C−O bonds. The protocol is featured with readily available starting materials and broad substrate scope. Control reactions and isotope-labeling reactions were conducted to elucidate a plausible mechanism.



Ynamides and ynol ethers are electron-rich alkynes which exhibit versatile properties in organic synthesis.[1] Typically, these alkynes would show dual electronic and nucleophilic reactivities. Typically, the addition reaction of electron-rich alkynes and carboxylic acids has been investigated for divergent transformation in organic synthesis.[2,3] For example, Lam and co-workers reported an efficient and regioselective addition between carboxylic acids and ynamides under the promotion of $Pd(OAc)_2$.[4] Bi established a catalyst-free addition between ynamides and carboxylic acids for accessing α-acyloxy enamides (Scheme 1A),[5] while Zhao developed a racemization-free synthesis of amides and peptides in which an in situ generated α-acyloxy enamide intermediate from ynamides and carboxylic acids was involved in the process.[6] Meanwhile, Zhu and co-workers established a Ag_2O-catalyzed regio- and stereoselective addition of carboxylic acids to ynol ethers toward formation of α-acyloxy enol esters (Scheme 1A).[7]

Scheme 1. Reactions of Carboxylic Acids and Ynol Ethers



Interestingly, the α-acyloxy enol esters could serve as versatile synthons in organic synthesis. For example, Wharton reported that α-acyloxy enol esters could react with carboxylic acids and amines to deliver anhydrides and amides, respectively.[8] Moreover, Kita revealed that ynol ethers could serve as coupling reagents for ester and lactone synthesis from hydroxyl compounds and carboxylic acids.[9] In addition, Kita also reported a Semmer−Wolff aromatization between cyclohexanone oxime and α-acyloxy enol esters.[10]

Despite these advances, the development of ynol ethers in multicomponent reactions remains continuously interesting and important because multicomponent reactions could achieve the construction of molecules with remarkable structural diversity and brevity.[11] Previously, our group established a three-component synthesis of tetrahydroisoquinolines (THIQs) from ynol ethers, carboxylic acids, and dihydroisoquinolines (DHIQs) (Scheme 1B).[12] In addition, we developed a one-pot synthesis of β-keto esters via a DMAP-promoted intramolecular rearrangement of in situ generated α-acyloxy enol esters from ynol ethers and carboxylic acids.[13] Encouraged by these results,[8c,d,14] we hypothesized that the in situ generated α-alkoxy enol intramolecular Baeyer−Villiger reaction cascade would deliver α-carbonyloxy esters directly. Herein, we wish to report a one-pot reaction of carboxylic acids, ynol ethers, and *m*-CPBA for synthesis of α-carbonyloxy esters (Scheme 1C).

We commenced our study by investigating the silver oxide catalyzed reaction between benzoic acid **1a** and ynol ether **2a**. Initially, we carried out the reaction by mixing **1a**, **2a**, and 5 mol % of Ag_2O in dioxane at 100 °C to deliver α-alkoxy enol ester intermediate **4a** and then added 3-chloroperoxybenzoic

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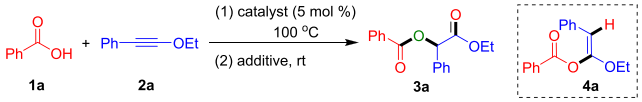
acid (*m*-CPBA) to test the rearrangement at ambient temperature. To our delight, a desired α-carbonyloxy ester **3a** was indeed formed and isolated in 83% yield (Table 1, entry

Table 1. Reaction Optimization[a]



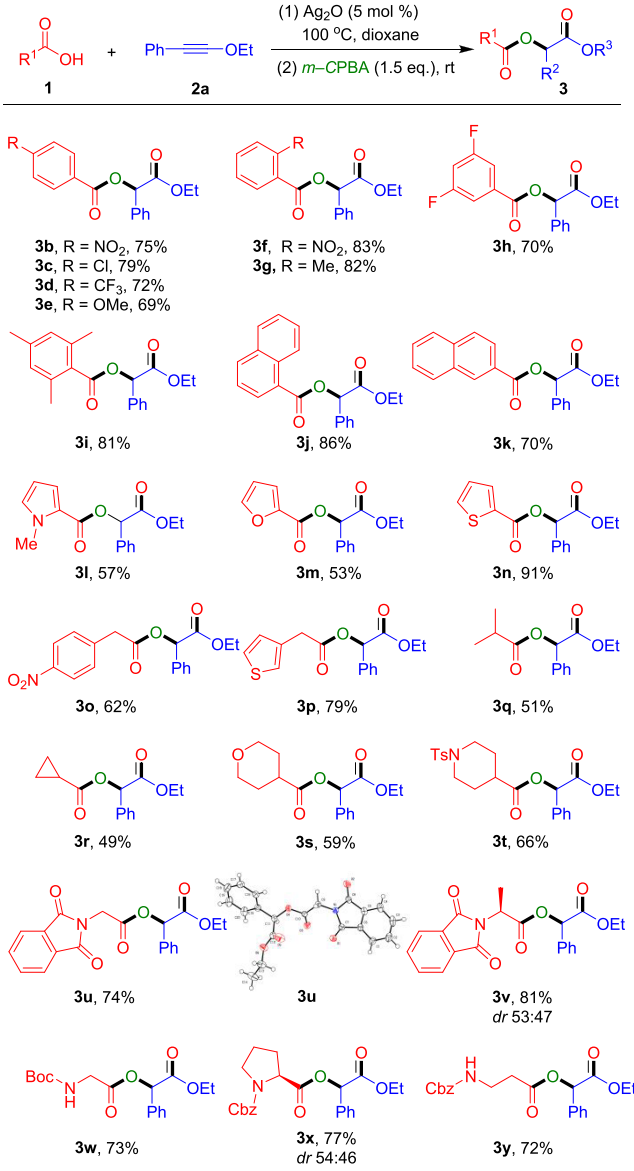
entry	catalyst	additive	solvent	yield[b] (%)
1	Ag_2O	*m*-CPBA	dioxane	83
2	Ag_2O	H_2O_2	dioxane	0
3	AgOTf	*m*-CPBA	dioxane	53
4	Ag_2CO_3	*m*-CPBA	dioxane	77
5	$AgBF_4$	*m*-CPBA	dioxane	73
6	$Cu(OAc)_2$	*m*-CPBA	dioxane	trace
7	$Cu(OTf)_2$	*m*-CPBA	dioxane	trace
8	$Zn(OTf)_2$	*m*-CPBA	dioxane	trace
9	none	*m*-CPBA	dioxane	0
10	Ag_2O	*m*-CPBA	DCE	59
11	Ag_2O	*m*-CPBA	toluene	53
12	Ag_2O	*m*-CPBA	THF	47
13	Ag_2O	*m*-CPBA	DMF	trace
14[c]	Ag_2O	*m*-CPBA	dioxane	82

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), and Ag_2O (5 mol %) were added to solvent (2 mL) and heated at 100 °C for 5 h, and then the additive (1.5 equiv) was added at ambient temperature and kept at the same temperature. [b]Yield refers to isolated product. [c]*m*-CPBA (1.25 mmol) was used.

1). The product was identified by ^1H NMR, ^{13}C NMR, and MS analysis. Replacing *m*-CPBA with hydrogen peroxide would completely suppress the cascade reaction, while only **4a** was isolated (entry 2). Meanwhile, the utilization of other silver salts, such as AgOTf, $AgBF_4$, and Ag_2CO_3, was less effective, and the products could be formed in slightly lower yields (entries 3−5). When $Cu(OAc)_2$, $Cu(OTf)_2$, and $Zn(OTf)_2$ were used as catalysts, no products were observed (entries 6−8). The next survey of solvents revealed that DCE, toluene, THF, and DMF were not optimal and the yields would decrease (entries 10−13). In addition, when the amount of *m*-CPBA was increased to 5 equiv, the yield was not improved significantly (entry 14).

With the optimized reaction conditions in hand, we next tested the substrate scope. As shown in Scheme 2, a variety of substituted benzoic acids could proceed well in this one-pot reaction to deliver products in moderate to good yields, and valuable groups such as nitro, methoxy, chloro, trifluoromethyl, and fluoro were tolerated (**3b**−**3i**). Meanwhile, the naphthyl carboxylic acids and heterocyclic carboxylic acids including pyrrole, furan, and thiophene could participate in this process to produce the corresponding α-carbonyloxy esters (**3j**−**3n**). Aliphatic carboxylic acids, including 4-nitrophenylacetic acid, 3-thiopheneaectic acid, isopropyl acid, cyclopropyl carboxylic acid, tetrahydro-2*H*-pyran-4-carboxylic acid, and piperidine-4-carboxylic acid, were also applicable in this one-pot reaction (**3o**−**3t**). Notably, when *N*-protected amino acids including glycine, L-alanine, L-proline, and β-alanine were subjected to this process, the products could be formed in good yields (**3u**−**3y**). In addition, the products generated from L-alanine (**3v**) and L-proline (**3x**) showed dr values of 53:47 and 54:46,

Scheme 2. Scope of Carboxylic Acids[a]



[a]Reaction conditions: **1** (0.25 mmol), **2a** (0.25 mmol) and Ag_2O (5 mol %) were added to dioxane (2 mL) and heated at 100 °C for 5 h, then *m*-CPBA (1.5 equiv) was added and the solution was stirred at ambient temperature for another 12 h. Yields refer to isolated products.

respectively. Furthermore, the structure of **3u** was unambiguously confirmed by X-ray analysis.

On the other hand, the scope of ynol ethers was also tested. As shown in Scheme 3, a series of aryl-substituted ynol ethers were subjected to this one-pot reaction to react with carboxylic acids, and various products were obtained in moderate to good yields. The substituted groups in the benzene ring including *p*-methyl, *p*-methoxy, *p*-fluoro, *p*-chloro, *o*-chloro, and *m*-methyl were all amenable (**3z**−**3k′**). Interestingly, 2-naphthyl- and thiophene-2-yl-substituted ynol ethers were also compatible to deliver the desired **3l′** and **3m′** in 80% and 69% yields, respectively. In addition, the methoxy ynol ether was also applicable in this one-pot reaction to furnish **3n′** in 79% yield. Meanwhile, the aliphatic and terminal ynol ether could engage in this process to deliver the products **3o′** and **3p′**, albeit in

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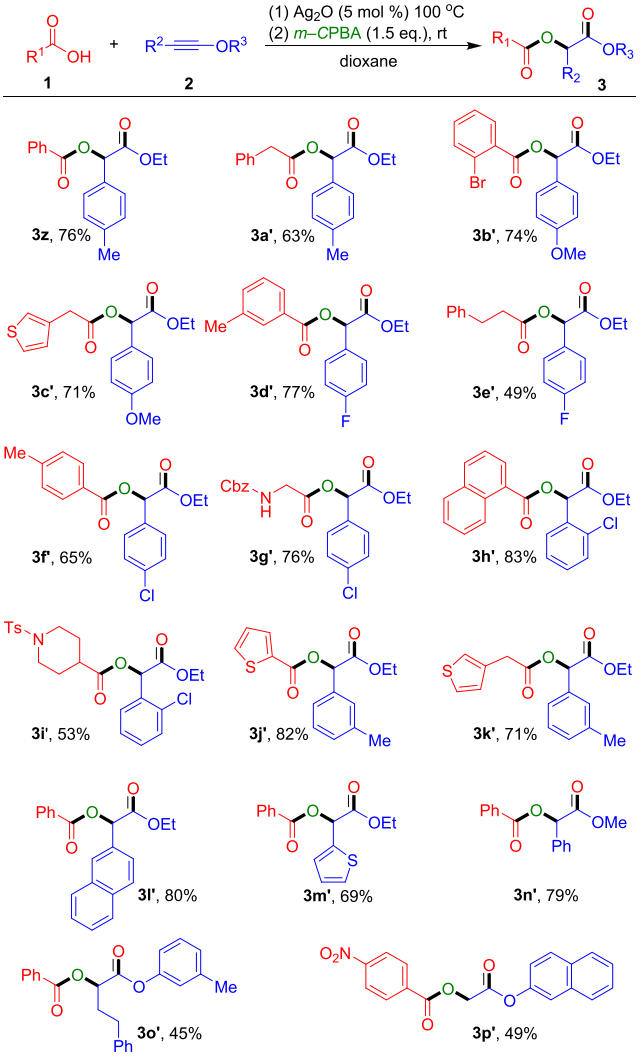
Scheme 3. Scope of Ynol Ethers[a]



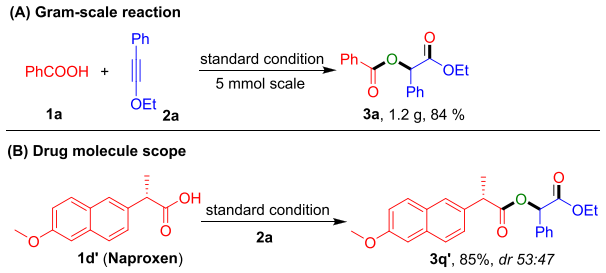
[a]Reaction conditions: **1** (0.25 mmol), **2** (0.25 mmol) and Ag_2O (5 mol %) were added to dioxane (2 mL) and heated at 100 °C for 5 h, then *m*-CPBA (1.5 equiv) was added and the solution was stirred at ambient temperature for another 12 h. Yields refer to isolated products.

slightly lower yields. Therefore, this one-pot reaction offers an efficient and direct approach to α-carbonyloxy esters.[15]

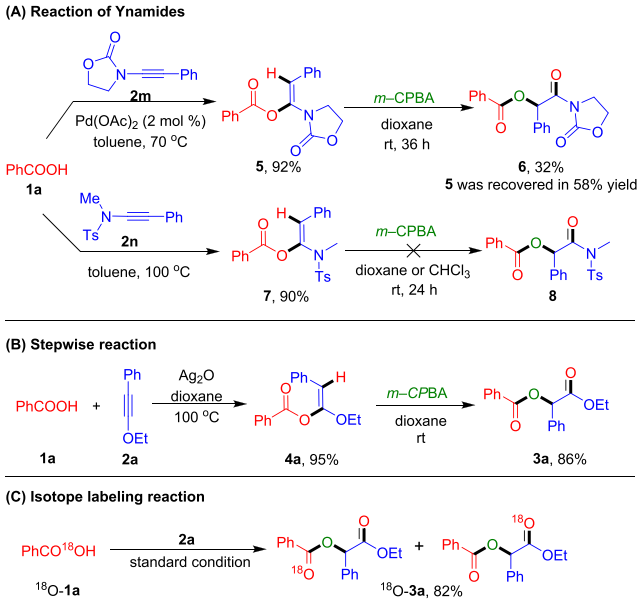
To test the synthetic utility of this one-pot reaction, a gram-scale reaction of benzoic acid **1a** and ynol ether **2a** was conducted. Gratifyingly, the reaction proceeded well, and 1.2 g of α-carbonyloxy ester **3a** was formed in 84% yield (Scheme 4A). Furthermore, the anti-inflammatory drug naproxen was subjected to reaction with ynol ether **2a** under standard conditions (Scheme 4B), and the desired product **3q′** was generated in 85% yield (dr 53:47). Thus, this protocol provides a convenient method for the late-stage functionalization of biological interesting molecules.

To probe the reaction mechanism, control reactions were conducted. Two typical ynamides **2m** and **2n** were prepared and subjected to the reaction with benzoic acid **1a** to furnish the corresponding α-acyloxy enamides **5** and **7**,[4,5] which were next treated with *m*-CPBA (Scheme 5A). With respect to **5**, the desired product **6** was formed in only 32% yield, while the reaction of **7** did not deliver any product. Meanwhile, a

Scheme 4. Gram-Scale Reaction and Application



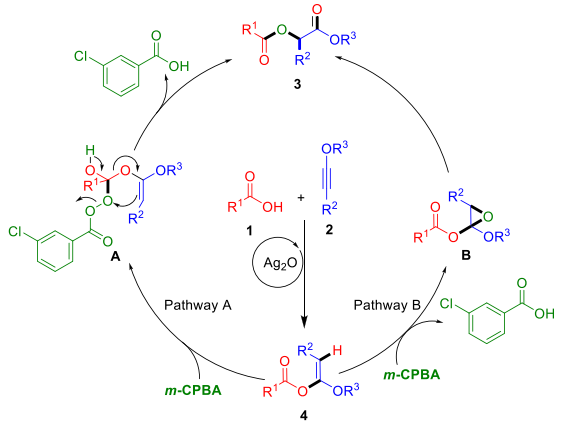
Scheme 5. Control Reaction



stepwise reaction was also conducted (Scheme 5B). The intermediate **4a** could be isolated in excellent yield (95%), which was subjected to reaction with *m*-CPBA to deliver **3a** in 85% yield. Furthermore, an isotope-labeling reaction was performed (Scheme 5C). An ^{18}O-labeled benzoic acid ^{18}O-**1a** was prepared and subjected to reaction with **2a**. The ^{18}O-labeled **3a** was generated in 82% yield, in which the labeled oxygen atom was incorporated in both carbonyl groups.

On the basis of these results and the literature,[4,8,9,16] the plausible reaction mechanism was proposed in Scheme 6.

Scheme 6. Proposed Reaction Mechanism



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Initially, the α-alkoxy enol ester **4** was formed from carboxylic acid **1** and ynol ether **2** under the promotion of catalytic Ag_2O. Subsequently, there are two plausible reaction pathways. For pathway **A**, the carbonyl group of α-alkoxy enol ester **4** is added by *m*-CPBA to deliver intermediate **A**, which transforms to α-carbonyloxy ester **3** via a Baeyer−Villiger type reaction and fragment cascade. With respect to pathway B, the alkenyl C−C double bond of α-alkoxy enol ester **4** was epoxidized by *m*-CPBA to give intermediate **B**, which rapidly rearranged to give the final product **3**.

In summary, a novel one-pot reaction of carboxylic acids, ynol ethers, and *m*-CPBA for synthesis of α-carbonyloxy esters has been developed. The protocol features readily available starting materials, a broad substrate scope, and a simple experimental procedure and is also synthetically useful in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02323.

Full experimental procedures, characterization data, and NMR spectral data (PDF)

Accession Codes

CCDC 1916376 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: sajiki@gifu-pu.ac.jp.
*E-mail: slcui@zju.edu.cn.

ORCID

Hironao Sajiki: 0000-0003-2792-6826
Sunliang Cui: 0000-0001-9407-5190

Notes

The authors declare no competing financial interest.

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