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Oxidative Coupling of Terminal Alkyne with α-Hydroxy Ketone: An Expedient Approach toward Ynediones

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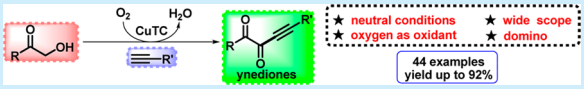
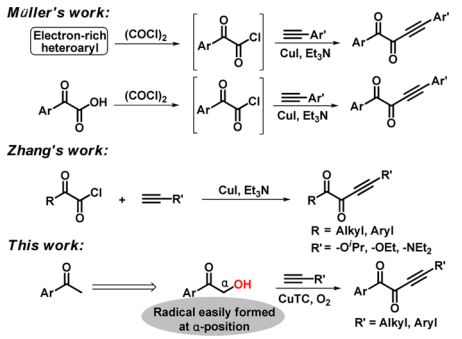
Supporting Information

ABSTRACT: An efficient and mild copper-catalyzed one-pot approach toward ynediones has been established. A variety of ynediones were constructed directly through oxidative coupling of alkyne with α-hydroxy ketone. Oxygen-oxidizing and neutral conditions in one-pot for a wide range of substrates including natural product derivatives make this transformation highly efficient and practical. On the basis of control experiments, *in situ* IR measurements, and isotopic labeling experiments, a plausible mechanism involving intermediate phenylglyoxal was drawn. Applications by synthesis of various heterocycles were also investigated.



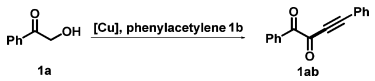
Ynediones are more densely functionalized electrophiles than ynones. Continuous two-carbonyl and alkynyl groups make ynedione a powerful synthetic precursor that could be easily transformed to a series of specific heterocycles.[1,2] However, because of a lack of ready and practical preparation, the application of ynediones remains rarely explored. To the best of our knowledge, most of the reported approaches toward ynediones employ Castro–Stephens coupling[3] involving glyoxylyl chlorides and terminal alkynes (Scheme 1).[4] Müller's group established a convenient method via *in situ* glyoxylation of electron-rich heteroaromatic nucleophiles and α-keto carboxylic acids with oxalyl chloride. The oxidative coupling[5] of α-hydroxy ketone and terminal alkyne[6,7] is supposed to be an efficient and direct method to ynedione, which is also a challenge. Terminal alkyne could barely avoid Glaser coupling[8] in the presence of oxidant and copper catalyst when coupled with ketones. Fortunately, we found a carbon–carbon cleavage system, showing that α-hydroxy ketone is a fantastic radical precursor at the α-position, which may oxidatively couple with terminal alkyne for the generation of ynediones.[9]

Scheme 1. Ynedione Synthesis



We commenced our study by investigating 2-hydroxy-1-phenylethanone **1a** coupling with phenylacetylene **1b**. The reaction was first performed in the presence of copper acetate and silver nitrate at 80 °C in dioxane under air, which generated the desired product **1ab** in 37% yield (Table 1, entry 1). Acetic acid was added to avoid Glaser coupling of **1b** (Table 1, entry 2). After a series of copper salts were tested, copper(I) thiophene-2-carboxylate was demonstrated to be the best choice (Table 1, entry 3). Considering solvents, toluene had an inhibiting effect on side products (Table 1, entries 4–6). Compound **1b** was

Table 1. Optimization for the Synthesis of Ynediones



entry	[Cu]	[Ag]	additive	solvent	note	yield[e] (%)
1	$Cu(OAc)_2$	$AgNO_3$	none	dioxane	*a*	37
2	$Cu(OAc)_2$	$AgNO_3$	AcOH	dioxane	*a*	53
3	CuTC	$AgNO_3$	AcOH	dioxane	*a*	63
4	CuTC	$AgNO_3$	AcOH	MeCN	*a*	trace
5	CuTC	$AgNO_3$	AcOH	THF	*a*	trace
6	CuTC	$AgNO_3$	AcOH	toluene	*a*	64
7	CuTC	none	none	toluene	*b*	77[c]
8	CuTC	none	none	toluene	*b*	82
9	CuTC	none	none	toluene	*b*	85[d]

[a]Reaction conditions: **1a** (0.2 mmol), **1b** (2.0 equiv), $AgNO_3$ (30 mol %), additive (1.0 equiv), and [Cu] (20 mol %) were stirred at 80 °C in solvent (2 mL) for 8 h under air. [b]Reaction conditions: **1a** (0.2 mmol) and CuTC (10 mol %) were stirred at 90 °C in solvent (2 mL) for 2 h under O_2, then **1b** (5.0 equiv) was added. The system was heated for another 4 h under O_2. [c]4.0 equiv of **1b** was added. [d]0.2 mmol of **1a** in 4 mL of toluene. [e]Isolated yields.

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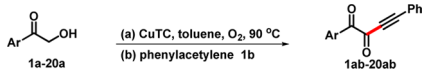
added after **1a** was oxygenated under oxygen atmosphere, and the yield was increased to 77% (Table 1, entry 7). The addition of silver nitrate or copper acetic acid, which probably helps to liberate Cu^+ from the formed alkynyl copper to oxidation of **1a**, produced no improvement in this reaction. Concentration of **1a** and **1b** was crucial as well (Table 1, entries 8 and 9). Finally, an 85% yield could be achieved under the conditions of 0.05 M **1a** in toluene.

With the optimized conditions identified, a series of α-hydroxy ketones were investigated (Table 2). It should be pointed out is

Table 2. Scope of α-Hydroxy Ketones[a]



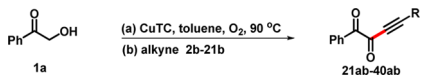
entry	Ar	isolated yield of ab (%)	entry	Ar	isolated yield of ab (%)
1	Ph	88[b] 62[c] (1ab)	11	*p*-Br-C_6H_4	63 (11ab)
2	*p*-MeO_2C-C_6H_4	61 (2ab)	12	*p*-I-C_6H_4	58 (12ab)
3	*p*-MeO-C_6H_4	67 (3ab)	13	1-naphthyl	76 (13ab)
4	*p*-NO_2-C_6H_4	56 (4ab)	14	2-naphthyl	65 (14ab)
5	4-biphenyl	86 (5ab)	15	2-furan	68 (15ab)
6	*o*-Me-C_6H_4	64 (6ab)	16	2-thiophene	76 (16ab)
7	*m*-Me-C_6H_4	71 (7ab)	17	3-thiophene	86 (17ab)
8	*p*-Me-C_6H_4	73 (8ab)	18	2-benzofuran	56 (18ab)
9	*p*-F-C_6H_4	81 (9ab)	19		63 (19ab)
10	*p*-Cl-C_6H_4	70 (10ab)	20	2-benzothiophene	62 (20ab)

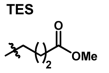
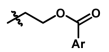
[a]Standard conditions: α-hydroxy ketone (0.2 mmol) and CuTC (10 mol %) were stirred at 90 °C in the solvent (4 mL) for 2 h under O_2, and then **1b** (5.0 equiv) was added. The system was heated for another 4 h under O_2. [b]2 mmol scale of **1a**. [c]10 mmol scale of **1a**.

that when **1a** was scaled up to 2 mmol (272 mg), the yield remained excellent. Even when the reaction performed on a 10 mmol (1.36 g) scale of **1a**, a 62% yield was obtained (Table 2, entry 1). α-Hydroxy ketones both with electron-donating and electron-withdrawing groups could be successfully converted to the corresponding ynediones in moderate-to-excellent yields (**2ab**−**5ab**). α-Hydroxy ketones with methyl-substituted at the *o*-, *m*-, and *p*-position on the aryl ring did not show strong steric effects (**6ab**−**8ab**). Not only inactive halogen substituted substrates bearing F and Cl but also copper-active substrates bearing Br and I could produce good yields (**9ab**−**12ab**). Further, this method could be applied to a variety of condensed rings and heterocycles, such as naphthalene (**13ab** and **14ab**), furan (**15ab**), thiophene (**16ab** and **17ab**), benzofuran (**18ab**), 2,3-dihydrobenzofuran (**19ab**), and benzothiophene (**20ab**).

After the great tolerance of α-hydroxy ketones was demonstrated, different functionalized terminal alkynes also performed well. In fact, not only arynes but also alkyl acetylenes, which show the mismatchment in other methodologies, worked well in the transformation. Aryne with methyl and methoxyl groups offered moderate to excellent yields (**21ab** and **22ab**). Long-chain alkyl-substituted alkynes, such as 1-hexyne (**23ab**) and 1-octyne (**24ab**), could also afford a moderate yield after *p*-benzoquinone was added to promote the oxidative process.[10] Cycloalkane-substituted alkynes, such as cyclopropyl (**25ab**) and cyclohexyl (**26ab**) acetylenes, could be transformed to the desired products in 69% and 50% yield, respectively. Terminal alkyl acetylenes bearing various hydroxyl protection groups, including TBS, TBDPS, Bn, THP, and allyl (**27**−**31ab**), were all compatible in this reaction to afford the desired products, which showed great application potential in organic synthesis. Phenyl, phthalimide, chlorine, TES, and ester groups (**32ab**−**36ab**) were tolerated in the present reaction system as well. Only one alkynyl was transformed to the ynedione when disubstituted terminal-alkyne substrate was applied (**37ab**). Alkyl acetylenes containing phenyl or heterocycle using ester as a linkage produced the products as well (**38ab**−**40ab**).

Table 3. Scope of Alkynes[a]

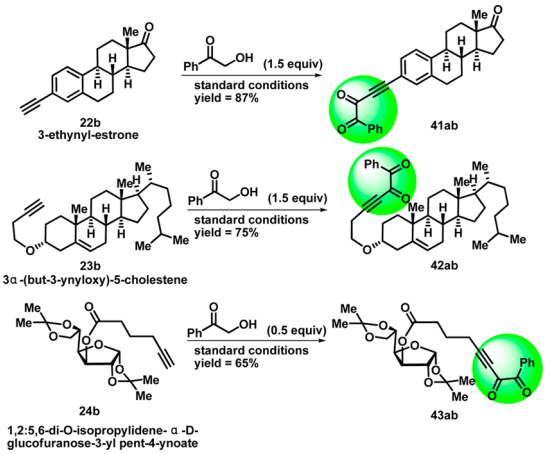


entry	R	isolated yield of ab (%)	entry	R	isolated yield of ab (%)
1	*p*-Me-C_6H_4	92 (21ab)	14		60 (34ab)
2	*p*-MeO-C_6H_4	58 (22ab)	15	TES	53 (35ab)
3	*n*-butyl[b]	59 (23ab)	16		67 (36ab)
4	*n*-hexyl[b]	54 (24ab)			
5	cyclopropyl	69 (25ab)			
6	cyclohexyl[c]	50 (26ab)			
7			17		57 (37ab)
	R' = OTBS	66 (27ab)			
8	R' = OTBDPS	77 (28ab)			
9	R' = OBn	53 (29ab)	18		
10	R' = OTHP	52 (30ab)			
11	R' = OAllyl	60 (31ab)		Ar = Ph	66 (38ab)
12	R' = Ph	73 (32ab)	19	Ar = 2-furan	52 (39ab)
13	R' = N(phth)	53 (33ab)	20	Ar = 2-thiophene	55 (40ab)

[a]Standard conditions: **1a** (0.2 mmol) and CuTC (10 mol %) were stirred at 90 °C in solvent (4 mL) for 2 h under O_2, and then terminal alkyne (5.0 equiv) was added. The system was heated for another 4 h under O_2. [b]2.0 equiv of benzoquinone was added. [c]50 mol % of CuTC was added.

The late-stage modification of a bioactive molecule is highly important for medical chemistry studies. Notably, 3-ethynylestrone **22b** containing carbonyl group and four continuous chiral centers resulted in the desired product in 87% yield by this method. 3α-(But-3-ynyloxy)-5-cholestene **23b** with an alkenyl group and eight chiral centers produced a 75% yield of the desired product. Moreover, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose-3-yl pent-4-ynoate **24b** with sensitive sugar acetal and acetone-protecting groups was also tolerated and produced the corresponding products in 65% yield, which showed great potential for drug late-stage modification (Scheme 2).[11]

Scheme 2. Late-Stage Modification



To gain mechanistic insight into this one-pot synthesis of ynediones, several control experiments were conducted. When **1a** was subjected to standard conditions, we observed that an intermediate formed before **1b** was added (Scheme 3, eq 1). Through crude ^1H NMR, it presented a mixture of phenylglyoxal **1d**, phenylglyoxal monohydrate **1c**, and other side products, which indicated that the intermediate was not stable. When the copper catalyst was removed, or oxygen was changed to nitrogen

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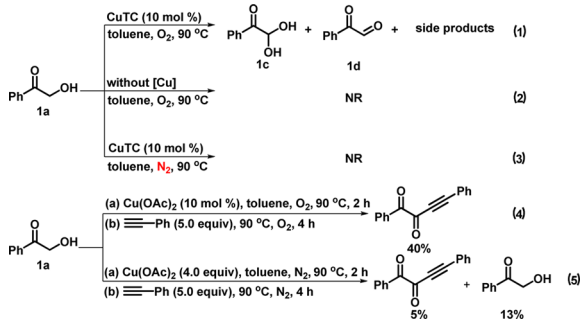
Scheme 3. Control Experiments for Intermediate Formation



under standard conditions, the reaction would not proceed (Scheme 3, eqs 2 and 3), which illustrates that **1a** was oxidized with the cooperation of copper and oxygen.[12] Furthermore, this reaction was respectively oxidized by catalytic copper(II) (10 mol %) under oxygen atmosphere and stoichiometric copper(II) (4.0 equiv) under nitrogen atmosphere (Scheme 3, eqs 4 and 5), which showed that the former provided a much better result (40% and 5%). This comparison indicated that oxygen played multiple roles in the reaction process rather than only oxidizing copper from low to high valence.

To further confirm the unstable intermediate, *in situ* IR measurements were attempted to observe the whole process of this reaction (Figure 1). Phenylglyoxal intermediate with two

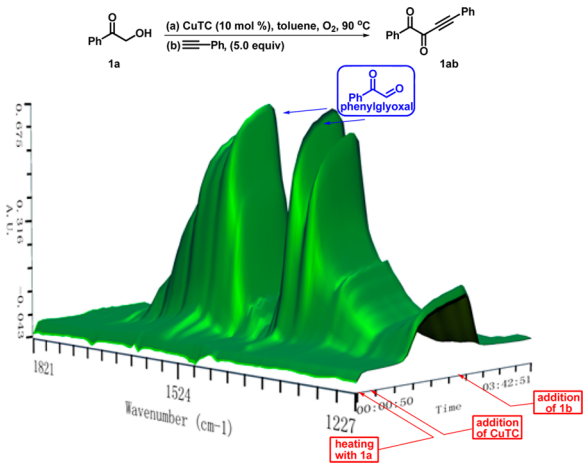
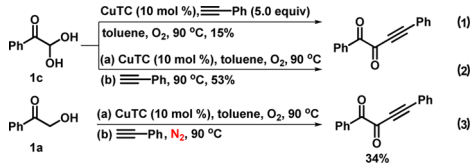


Figure 1. *In situ* IR measurements.

clear peaks (characteristic stretch at ν = 1552 and 1429 cm^{-1}) formed gradually after copper(I) thiophene-2-carboxylate was added to a solution of **1a** in toluene, and after the addition of **1b**, the intermediate disappeared immediately. During further investigations, a 15% desired product was obtained when the stable phenylglyoxal monohydrate **1c** directly reacted with **1b** (Scheme 4, eq 1). When **1b** was added after **1c** was heated for 2 h, a 53% yield was achieved (Scheme 4, eq 2). *In situ* IR

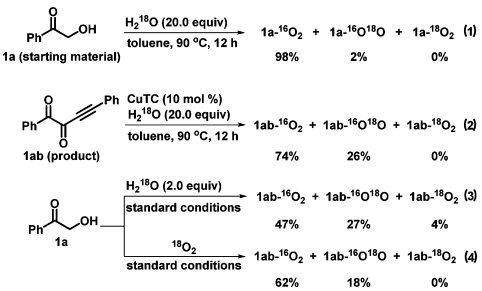
Scheme 4. Control Experiments from Proposed Intermediates



measurements were conducted again to observe the transformation from **1c** to **1ab** (Supporting Information). Both the control experiments and *in situ* IR measurements demonstrated the active intermediate is phenylglyoxal **1d**. If the reaction was conducted under nitrogen after the oxidation of **1a**, it resulted in a 34% yield of the desired product **1ab** without other intermediates being observed (Scheme 4, eq 3).

Isotopic-labeling experiments showed that the starting material α-hydroxy ketone **1a** barely underwent oxygen atom exchange with water (Scheme 5, eq 1), while 26% of the product

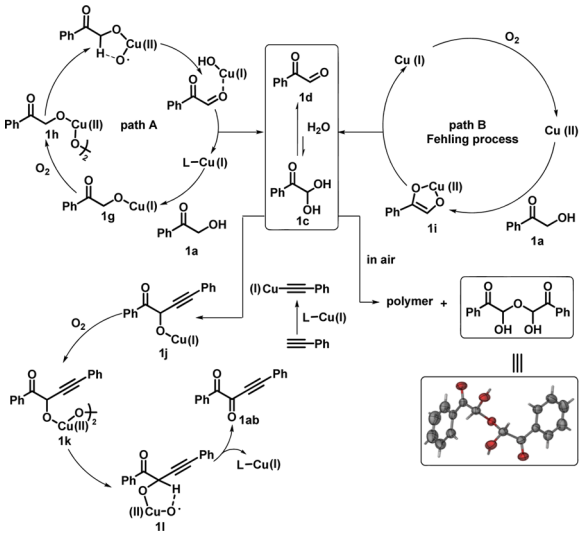
Scheme 5. Isotopic Labeling Experiments



ynedione **1ab** had been exchanged by ^{18}O from $H_2{}^{18}O$ (Scheme 5, eq 2). Furthermore, two isotopic labeling experiments comparing $H_2{}^{18}O$ (2.0 equiv) and $^{18}O_2$ were also performed. When the reaction was launched in the presence of $H_2{}^{18}O$ (2.0 equiv), **1ab-$^{16}O_2$** (47%), **1ab-$^{18}O^{16}O$** (27%), and **1ab-$^{18}O_2$** (4%) were detected (Scheme 5, eq 3). When the reaction was conducted under $^{18}O_2$ atmosphere, **1ab-$^{16}O_2$** (62%) and **1ab-$^{18}O^{16}O$** (18%) were detected (Scheme 5, eq 4). It indicated that the oxygen atom of the ynediones originated from α-hydroxy ketones and water, not from oxygen gas.

On the basis of the above results, a plausible mechanism was drawn (Scheme 6). The oxidation of hydroxyl underwent in two probable paths. In path A, copper alkoxide **1g** produced binuclear copper(II) peroxide **1h** with the help of oxygen. Homolytic cleavage followed by hydrogen atom abstraction afforded **1d** and the hydroxy copper(I) species. After rapid exchange between the hydroxy ligand and alcohol **1a**, along with the loss of a water molecule, the copper alkoxide **1g** was regenerated.[13] In path B, **1a**

Scheme 6. Plausible Mechanism



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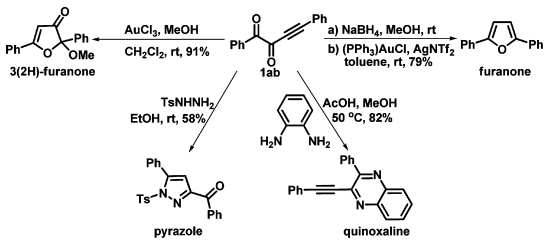
tautomerized into an enediol ligand **1i** coordinating to copper(II). After direct electron transfer, **1d** and copper(I) formed. The oxygen oxidized copper from (I) to (II) valence. Stoichiometric control experiments (Scheme 3, eq 4 ahd 5) indicated path A should be dominant. In addition, there was an equilibrium between **1d** and its monohydrate **1c** in the system, which was in favor of **1d**. After **1b** was added, alkynyl copper formed. **1j** would be generated by the addition of alkynyl copper to phenylglyoxal. Subsequently, it was oxidized by copper(I) thiophene-2-carboxylate and oxygen again to produce 1,4-diphenylbut-3-yne-1,2-dione. Moreover, the dimer's presence in the mixture of intermediate was confirmed by X-ray crystallography.[14]

With plenty of ynedione **1ab** resulting from a gram-scale reaction (Table 2, **1ab**), further synthetic applications were conducted to furnish various products including 3(2*H*)-furanone, pyrazole, quinoxaline, and furanone in good-to-excellent yields (Scheme 7). These diverse structures illustrate the versatility of ynedione as synthetic building block.

Scheme 7. Synthetic Applications



In conclusion, an efficient copper-catalyzed one-pot synthesis of ynediones has been developed. The mild conditions showed great compatibility of various functional groups, offering a straightforward means to achieve late stage modification of complex natural product analogues. According to the control experiments, *in situ* IR measurements, and isotopic labeling experiments, a distinct mechanism was proven. Further synthetic application of ynediones is currently under way in our group, which will be reported in the future.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, NMR spectra, X-ray data (CIF), and analytical data. 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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■ DEDICATION

Dedicated to Professor Lixin Dai on the occasion of his 90th birthday.

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(14) CCDC-1002199 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.