



# Copper-catalyzed aerobic oxidative coupling of terminal alkynes with $\alpha$ -carbonyl aldehydes: An expedient approach toward ynediones

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## ABSTRACT

An efficient and mild one-pot approach for copper-catalyzed aerobic oxidative coupling of  $\alpha$ -carbonyl aldehydes with terminal alkynes toward ynediones has been developed. Moreover, a variety of ynediones were constructed under the optimized reaction conditions, and a plausible mechanism was presented based on a series of control experiments.

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## Introduction

Heteroaryl 1,2-diketone, a class of versatile and powerful structure units in organic synthesis, are an ideal choice to prepare heterocyclic compounds with pharmacological properties including hydantoin, imidazoles, oxadiazoles and thiopheno-diones [1]. Ynediones contain a continuous two-carbonyl and are more densely functionalized electrophiles, which could be easily converted to a series of specific heterocycles [2,3]. Despite their excellent organic potential, ynediones have remained rarely explored because of a lack of ready and practical preparation [4]. Therefore, a directly expedient and efficient access to this class of compounds would be much meaningful.

In the past few years, reports about the synthesis of ynediones were extremely rare. To our knowledge, the most of the reported strategies for synthesis of ynediones employed Castro-Stephens coupling with glyoxylyl chlorides and terminal alkynes (Scheme 1, Eq. 1) [5,6]. Müller's group developed a method through *in situ* glyoxylation of electron-rich heteroaromatic nucleophiles and  $\alpha$ -keto carboxylic acids with oxalyl chloride (Scheme 1, Eq. 2). In addition, Zhang and co-workers established a copper-catalyzed oxidative coupling approach toward ynediones from  $\alpha$ -hydroxy ketone and terminal alkyne (Scheme 1, Eq. 3) [7]. Nevertheless, the advances

mentioned before suffered from some drawbacks: (1) starting materials were not easily available and reaction cost was expensive, which might limit their application; (2) conversion of target products was not very high owing to Glaser coupling of terminal alkynes [8]. Therefore, it is highly eager to establish a simple and effective method to prepare ynediones under low-cost reaction system. Herein, we presented an expedient and efficient method for copper-catalyzed aerobic oxidative coupling of  $\alpha$ -carbonyl aldehydes with terminal alkynes toward ynediones, which has a low-cost reaction system and high conversion (Scheme 1, Eq. 4).

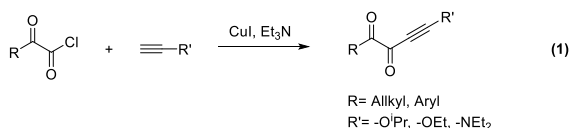
## Results and discussion

Initially, the reaction of phenylglyoxal monohydrate **1a** with phenylacetylene **2a** was chosen as the model reaction to identify optimal reaction conditions through screening a range of reaction factors. All reactions were conducted under an O<sub>2</sub> environment and the results were showed in Table 1. The model reaction was carried out in the presence of various copper catalysts in 4 mL Toluene at 90 °C for 4 h (Table 1, entry 1–4). Among these copper catalysts, Cu(OAc)<sub>2</sub> performed the best catalytic effect, affording the target product **3aa** in 34% yield (Table 1, entry 1). With the view of further improving its catalytic capacity, additives were screened (Table 1, entry 5–7). To our delight, acetic acid was added to inhibit Glaser coupling of **2a** and the yield of **3aa** increased to 64% (Table 1, entry 6). Then, the reaction temperature was also screened (Table 1,

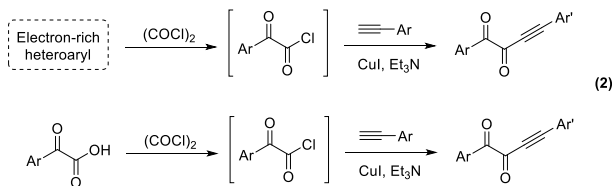
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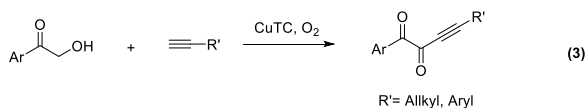
## Zhang's work



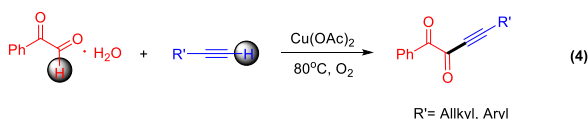
## Müller's work



## Zhang's work

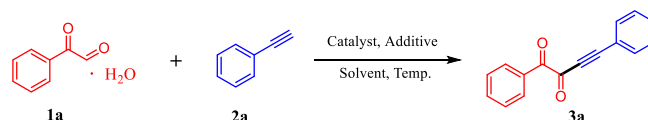


## This work



**Scheme 1.** Copper-catalyzed aerobic oxidative coupling of  $\alpha$ -carbonyl aldehydes with terminal alkynes to ynediones.

**Table 1**  
Screening of optimal conditions.<sup>a</sup>



Entry	Cat.	Add. <sup>d</sup>	Sol.	Temp.	Yield <sup>b</sup> (%)
1	Cu(OAc) <sub>2</sub>	–	Toluene	90 °C	34
2	CuTC	–	Toluene	90 °C	16
3	CuBr	–	Toluene	90 °C	0
4	CuI	–	Toluene	90 °C	0
5	Cu(OAc) <sub>2</sub>	Pyridine AcOH	Toluene	90 °C	Trace
6	Cu(OAc) <sub>2</sub>	AcOH	Toluene	90 °C	64
7	Cu(OAc) <sub>2</sub>	Pyridine	Toluene	90 °C	0
8	Cu(OAc) <sub>2</sub>	AcOH	Toluene	50 °C	0
9	Cu(OAc) <sub>2</sub>	AcOH	Toluene	80 °C	85
10	Cu(OAc) <sub>2</sub>	AcOH	Toluene	110 °C	51
11	Cu(OAc) <sub>2</sub>	AcOH	Toluene	120 °C	43
12	Cu(OAc) <sub>2</sub>	TFA	Toluene	80 °C	Trace
13	Cu(OAc) <sub>2</sub>	TfOH	Toluene	80 °C	41
14	Cu(OAc) <sub>2</sub>	2-Picolinic acid	Toluene	80 °C	0
15	Cu(OAc) <sub>2</sub>	2-TCA	Toluene	80 °C	54
16	Cu(OAc) <sub>2</sub>	AcOH	DMSO	80 °C	0
17	Cu(OAc) <sub>2</sub>	AcOH	DMF	80 °C	0
18	Cu(OAc) <sub>2</sub>	AcOH	1,4-Dioxane	80 °C	0
19	Cu(OAc) <sub>2</sub>	AcOH	H <sub>2</sub> O	80 °C	0
20 <sup>c</sup>	Cu(OAc) <sub>2</sub>	AcOH	Toluene	80 °C	92

<sup>a</sup> Reaction conditions: 1a (0.2 mmol), 2a (4 equiv.), catalyst (10 mol%) and additive (20 mol%) dissolved in solvent (4 mL) and stirred at 80 °C for 4 h in a sealed tube equipped with an O<sub>2</sub> balloon, unless otherwise noted.

<sup>b</sup> Isolated yields.

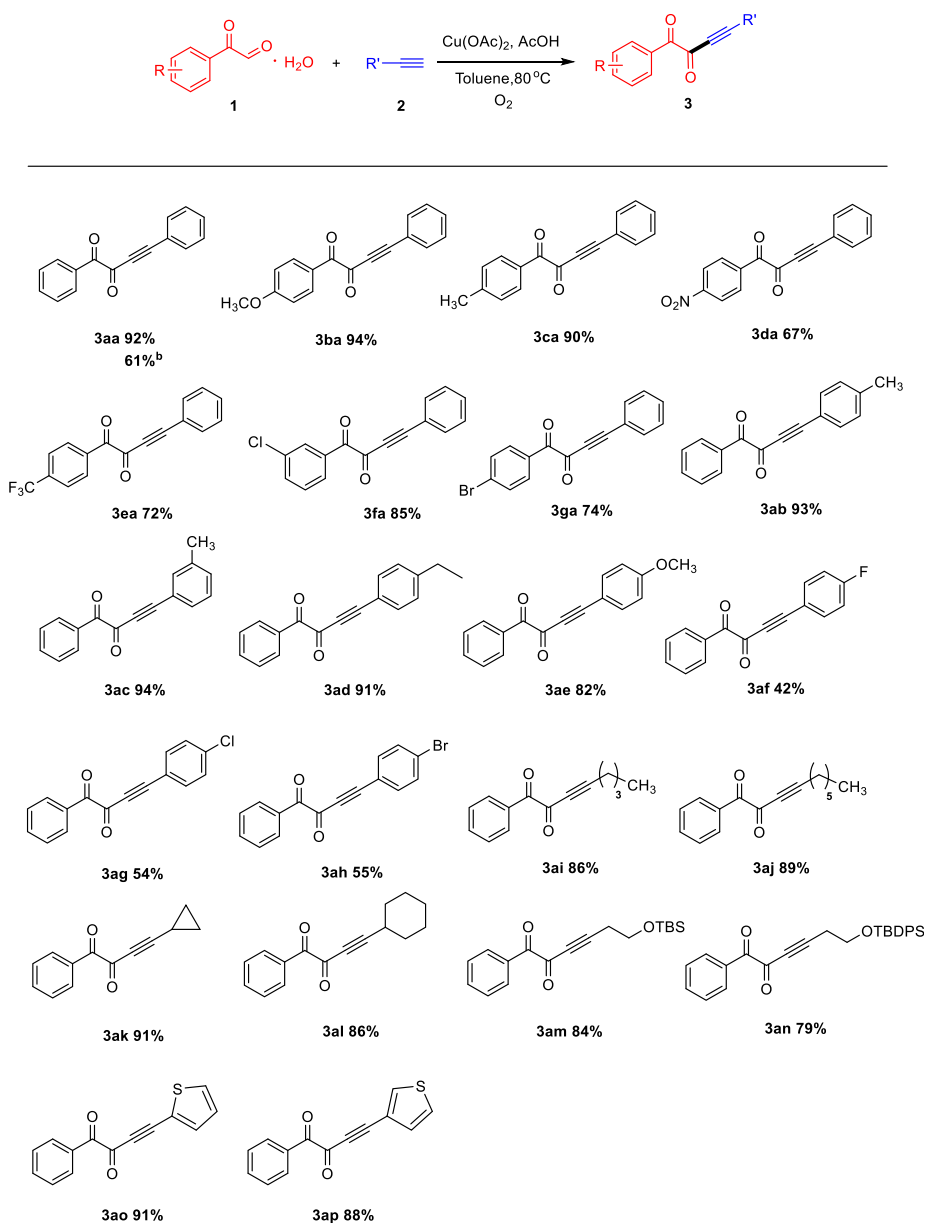
<sup>c</sup> 1 equiv. of 2a was added.

<sup>d</sup> TFA = trifluoroacetic acid; TfOH = trifluoromethanesulfonic acid; 2-TCA = 2-thiophenezoic acid.

entry 8–11). When the reaction temperature was decreased to 80 °C, 85% yield of **3aa** was obtained (Table 1, entry 9). However, when the reaction temperature was too high, yield of **3aa** decreased probably owing to decomposition of **1a** under high temperature atmosphere. Subsequently, the reaction proceeded in other different acid, and results showed that acetic acid is the ideal additive (Table 1, entry 12–15). And, a series of solvents were examined, such as DMSO, DMF, H<sub>2</sub>O and 1, 4-Dioxane, which presented that Toluene is the best solvent in this reaction (Table 1, entry 16–19). Next, different concentrations of **2a** were also tested for the reason that atomic economy is one of the significant contents of green chemistry. Gratifyingly, only 1 equiv. of **2a** was added to this reaction affording the highest yield 92% of **3aa** (Table 1, entry 20), the optimized reaction conditions were finally determined: 0.2 mmol phenylglyoxal monohydrate **1a**, 0.2 mmol phenylacetylene **2a**, 10 mol% Cu(OAc)<sub>2</sub> and 20 mol% AcOH dissolved in 4 mL Toluene and stirred at 80 °C for 4 h in a sealed tube under an O<sub>2</sub> environment.

With the optimized conditions identified, both  $\alpha$ -carbonyl aldehydes and terminal alkynes were explored (Table 2). It should be mentioned that when **1a** was scaled up to 10 mmol (1.34 g), the yield of **3aa** remained excellent (Supporting information). As is shown in Table 2,  $\alpha$ -carbonyl aldehydes both with electron-donating and electron-withdrawing groups could react smoothly to afford the corresponding ynediones in moderate to excellent yields (**3ba–3ea**). Notably, electron-donating groups were more reactive than electron-withdrawing groups. Furthermore, the inactive halogen substituted substrates including Cl and Br could also produce good yields (**3fa** and **3ga**).

After the tolerance of  $\alpha$ -carbonyl aldehydes was demonstrated, various functionalized terminal alkynes also performed well. Actually, not only aryl acetylenes but also alkyl acetylenes show good

**Table 2**  
Substrates scope.<sup>a</sup>

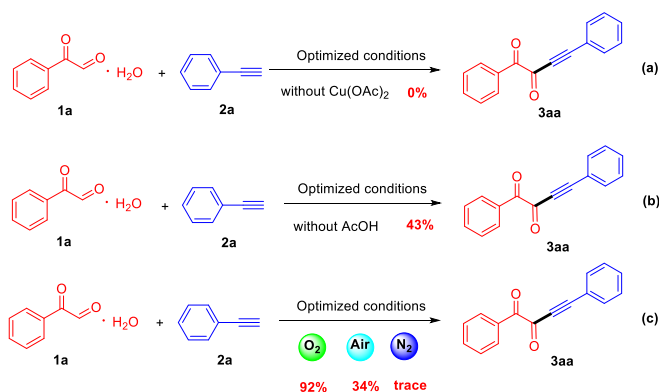
<sup>a</sup>Reaction conditions: **1** (0.2 mmol), **2** (4 equiv.),  $\text{Cu}(\text{OAc})_2$  (10 mol%) and AcOH (20 mol%) dissolved in solvent (4 mL) and stirred at  $80^\circ\text{C}$  for 4 h in a sealed tube equipped with an  $\text{O}_2$  balloon.

<sup>b</sup>10 mmol of **1a**.

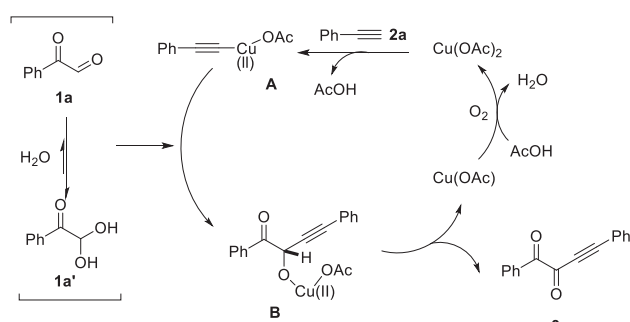
reactivity in this transformation. Aryl acetylenes with electron-donating groups gave excellent yields, such as methyl, methoxy and ethyl (**3ab-3ae**). Halogen substituted substrates could also afford a moderate yield (**3af-3ah**). Long-chain alkyl-substituted alkynes containing 1-hexyne and 1-octyne could be subjected to the reaction (**3ai** and **3aj**). Cycloalkane-substituted alkynes, such as cyclopropyl and cyclohexyl acetylenes, could be converted to the desired products in 91% and 86% yield, respectively (**3ak** and **3al**). Terminal alkyl acetylenes bearing hydroxyl protection groups including TBS and TBDPS were compatible in this transformation to provide the desired products, which presented great application potential in organic synthesis (**3am** and **3an**). Alkyl acetylenes containing heterocycle employing ester as a linkage afforded target products as well (**3ao** and **3ap**).

Then, we carried out some control experiments in order to explore the mechanism of this transformation (Scheme 2). No target product **3aa** was formed when the reaction was preceded in the absence of  $\text{Cu}(\text{OAc})_2$  (Scheme 3, Eq.1). The reaction also proceeded and provided the desired product in 43% yield under the modified conditions without AcOH (Scheme 3, Eq.2). These experiments show that  $\text{Cu}(\text{OAc})_2$  is essential for the reaction and AcOH is as an additive to inhibit side reaction and improve the yield. Moreover, we investigated the role of  $\text{O}_2$  in the reaction system (Scheme 3, Eq.3). The results indicate that  $\text{O}_2$  is the significant oxidant in the reaction.

On the basis of results above and previous literature reports [9], a plausible reaction mechanism for copper-catalyzed aerobic oxidative coupling of  $\alpha$ -carbonyl aldehydes with terminal alkynes



Scheme 2. Control experiments.



Scheme 3. Plausible reaction mechanism.

was described in Scheme 3. Initially, there is an equilibrium between **1a** and its monohydrate **1a'** in the system. Then, phenylacetylene **2a** reacts with  $Cu(OAc)_2$  to provide alkynyl copper **A**, which attacks **1a** resulting in the formation of the intermediate **B**. Eventually, the intermediate **B** undergoes self-oxidation and reduction to produce target product **3aa** with elimination of  $Cu(I)$ , which undergoes  $O_2$ -assisted regeneration to  $Cu(II)$  that re-enters the reaction system (Scheme 3).

## Conclusion

In conclusion, we established a protocol for copper-catalyzed aerobic oxidative coupling of  $\alpha$ -carbonyl aldehydes with terminal

alkynes toward ynediones under mild conditions. These transformations afforded various ynediones in high yields with a broad substrate scope under an easy reaction system, and a plausible mechanism was presented based on some control experiments. Further investigations of their applications are underway in our laboratory.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tetlet.2019.07.005>.

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