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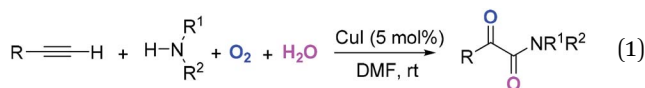
Copper-catalyzed synthesis of α -ketoamides using water and dioxygen as the oxygen source†

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The reaction employing H_2O and O_2 as the co-oxygen source in the catalytic synthesis of α -ketoamides is described. This copper-catalyzed reaction is carried out in a tandem manner constituted by the hydroamination of alkyne, hydration of vinyl–Cu complex and subsequent oxidation. Isotope labeling and radical capture experiments reveal that the oxygen atom of α -ketone at α -ketoamides derives from O_2 and the oxygen atom of amide group originates from H_2O .

Introduction

The introduction of oxygen atoms into organic molecules to construct oxygenated compounds is one of the most fundamental subjects in organic chemistry. From a “green and sustainable chemistry” perspective, water and dioxygen are the most environmentally benign and cost-effective oxygen-containing reagents.¹ Consequently, employing them as oxygen sources offers appealing access to oxygen-containing organic compounds.^{2,3} Herein, the example of direct utilization of H_2O and O_2 as the co-oxygen source to assemble α -ketoamides is reported. Isotope labeling and radical capture experiments demonstrate that the oxygen atom of α -ketone at α -ketoamide derives from dioxygen and the oxygen atom of amide group originates from water (eqn (1)).



α -Ketoamides have attracted increasingly synthetic pursuit of chemists, as key structural motifs of many biologically active compounds and versatile building blocks.⁴ Various synthetic methods for the preparation of α -ketoamides have been developed over the past decades, such as amidation of α -ketoacids,⁵ oxidation of enamines,⁶ ynamines,⁷ arylacetamides⁸ and α -cyanoamides,⁹ Pd-catalyzed double carbonylative amination of aryl halides,¹⁰ and the oxidation of acyl cyanophosphoranes followed by amidation of the resulting α,β -diketone nitriles.¹¹ Most of these well established approaches toward α -ketoamides often

require toxic, expensive or preformed oxygen sources, such as SeO_2 , $\text{K}_2\text{Cr}_2\text{O}_7$, CO, TBHP, and O_3 . Thus, the development of direct incorporation oxygen atoms from clean and cheap oxygen sources into organic frameworks to construct α -ketoamides is highly desirable.¹² In 2010, Zhu reported the transformation of aldehydes with isocyanides to α -ketoamides using water as the oxygen source.¹³ Recently, various metal-catalyzed or metal-free methods for the oxidative synthesis of α -ketoamides from terminal alkynes,¹⁴ aryl acetaldehydes,¹⁵ ketones,¹⁶ 1-arylethanol,¹⁷ phenethyl alcohol derivatives,¹⁸ and ethylarenes¹⁹ have also been developed by using dioxygen as oxygen source. In 2019, Wei and co-workers reported the transformation of α -ketoacids with isocyanides to α -ketoamides using water as the oxygen source.²⁰

Multicomponent reaction has emerged as a powerful protocol to construct complex organic compounds.²¹ The present multicomponent reaction of copper-catalyzed direct oxidative transformation of alkynes and secondary amines to α -ketoamides is realized at room temperature without any ligand or additive, in which H_2O and O_2 were employed as the co-oxygen source (eqn (1)). Preliminary mechanistic studies suggest that this multicomponent reaction is performed in a tandem manner constituted by the hydroamination of alkyne, hydration of vinyl–Cu complex and subsequent oxidation with dioxygen. This methodology not only provides an interesting and attractive approach to α -ketoamides, but also allows an avenue to simultaneously introduce oxygen atoms from H_2O and O_2 into organic frameworks to access multi-oxygen containing compounds.

Results and discussion

During the course of investigation on transition-metal-catalyzed oxidative transformation of alkynes and secondary amines to α -ketoamides, we found CuBr can catalyze the reaction of phenylacetylene **1a** with piperidine **2a** to give the product **3aa** in presence of H_2O (2 equiv.) under O_2 without ligand or additive (Table 1, entry 1). Preliminary exploration showed that no **3aa** was detected when the reaction was performed in the absence of

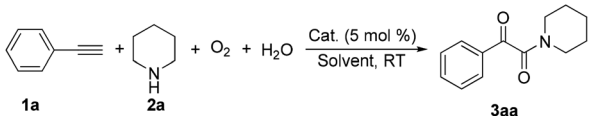
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Table 1 Optimization of reaction conditions^a

			
Entry	Catalyst (mol%)	Solvent	3aa ^b (%)
1	CuBr	THF	21
2	CuBr	THF	0 ^c
3	CuBr	THF	0 ^d
4	CuBr ₂	THF	18
5	CuCl ₂	THF	15
6	CuCl	THF	14
7	Cu(OTf) ₂	THF	16
8	(CH ₃ CN) ₄ CuPF ₆	THF	21
9	CuI	THF	43
10	AgOTf	THF	0
11	RhCl ₃	THF	0
12	InCl ₃	THF	0
13	AlF ₃	THF	0
14	AuBr ₃	THF	Trace
15	—	THF	0
16	CuI	1,4-Dioxane	25
17	CuI	MeOH	0
18	CuI	EtOH	0
19	CuI	DME	45
20	CuI	DCE	32
21	CuI	Toluene	23
22	CuI	DMSO	34
23	CuI	DMF	71
24	CuI	DMF	46 ^e

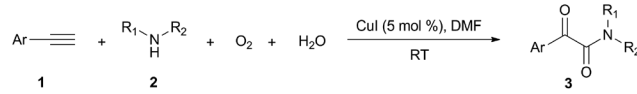
^a Reaction conditions: **1a** (2 mmol), **2a** (0.5 mmol), catalyst (5 mol%), H₂O (2 equiv.), O₂ (balloon), solvent (0.5 mL), at room temperature, 12 h. ^b Isolated yields based on **2a**. ^c Under N₂. ^d Dry THF was used and 4 Å molecular sieve was added. ^e Under air.

O₂ or H₂O (Table 1, entries 2 and 3). These results suggested that H₂O might be served as the oxygen source of **3aa** and O₂ as the oxidant or both of them were used as the co-oxygen source. This interesting phenomenon prompted us to optimize the reaction conditions and disclose the accurate origination of the oxygen atoms of α -ketoamides.

Initially, the reaction of phenylacetylene **1a** with piperidine **2a** was performed to examine the catalytic activity of various transition metal complexes including Au, Ag, Cu, Rh, Ni, Pd, Al, Bi, and In salts in the presence of H₂O (2 equiv.) under the oxygen atmosphere. As shown in Table 1, among those metal catalysts examined (entries 4–14), CuI was found to be the best catalyst to catalyze the formation of α -ketoamide **3aa**. No conversion was observed in the absence of catalyst (entry 15). The screening of solvents indicated that DMF was the optimal reaction medium (entries 16–23). This reaction could also proceed smoothly under the air atmosphere (entry 24).

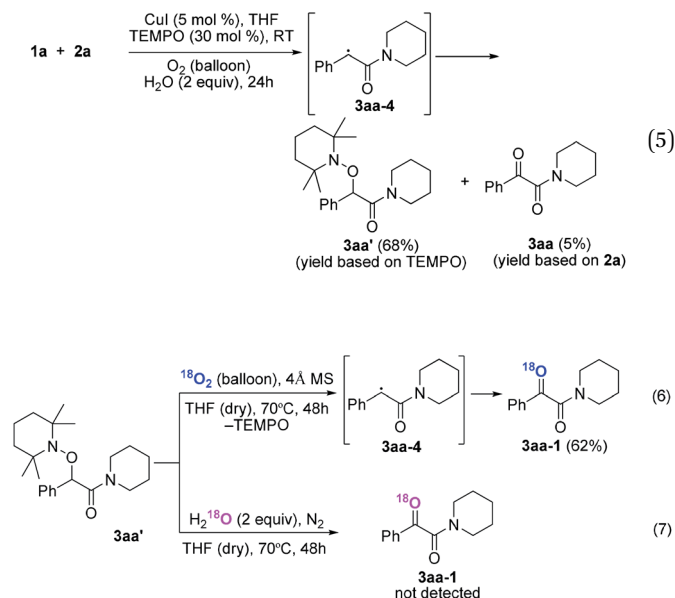
With the optimized conditions in hand, the scope of this new reaction was investigated (Table 2). Generally, the reaction tolerated electron-donating (*para*-, *meta*-, and *ortho*-substituted) and electron-withdrawing groups at the aromatic ring of alkynes (Table 2, entries 1–5). It was found that the reaction

Table 2 Copper-catalyzed synthesis of α -ketoamides^a

				
Entry	Alkyne (1)	Amine (2)	Product (3)	Yield ^b (%)
1	1a	2a	3aa	71
2	1b	2a	3ba	72
3	1c	2a	3ca	61
4	1d	2a	3da	60
5	1e	2a	3ea	56
6	1f	2a	3fa	64
7	1g	2a	3ga	57
8	1a	2b	3ab	65
9	1a	2c	3ac	56
10	1a	2d	3ad	64
11	1b	2c	3bc	65
12	1b	2d	3bd	62
13	1c	2c	3cc	63
14	1c	2d	3cd	60
15	1d	2c	3dc	61



of **3aa'** to singly ^{18}O -labeled α -ketoamide and TEMPO was observed in the presence of $^{18}\text{O}_2$ at 70 °C (**3aa-1**, eqn (6)). Meanwhile, no conversion of **3aa'** to **3aa-1** was detected in the presence of H_2^{18}O under N_2 (eqn (7)). These results suggested that the carbonyl oxygen atom of α -ketone at α -ketoamide **3aa** derived from molecular oxygen *via* a radical oxidation process.



Based on the above experiments and previous reports,^{26–28} we proposed a postulated reaction pathway for this transformation as outlined in Scheme 1. Firstly, the complex **4** was formed by the reaction of the Cu species with alkyne **1** and amine **2**. Then, the migration of amine to the triple bond led to the formation of the vinyl-Cu intermediate **5**. Next, **5** underwent hydration to give **6**. Subsequently, **7** was formed through the oxidation of **6** with dioxygen. Finally, the reductive elimination of the copper species of **7**²⁷ followed by double oxidation with dioxygen would deliver the desired product **3**.^{2,28}

Conclusions

In summary, we have successfully developed a tandem copper catalyzed approach to α -ketoamides from terminal alkynes, secondary amines, dioxygen, and water at room temperature without ligand or additive, in which O_2 and H_2O were used as the co-oxygen source of α -ketoamides. The present method opens a new window to construct complicated oxygen-containing compounds. Further studies of the detailed mechanism of this process and its application are underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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