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Room temperature copper-catalyzed oxidative amidation of terminal alkynes for synthesis of α-ketoamides using O-benzoyl hydroxylamines as aminating reagent and oxidant

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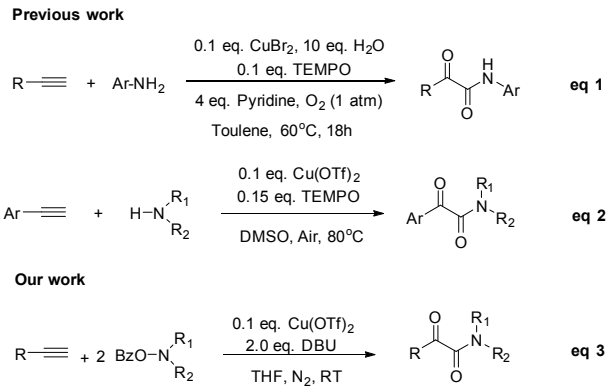
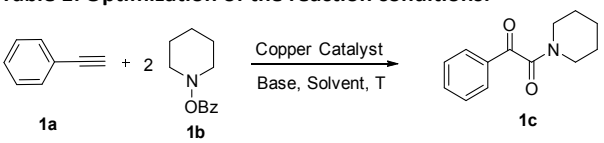
A novel and convenient copper-catalyzed oxidative amidation for synthesis of α-ketoamides has been successfully developed, which uses easily available *O*-benzoyl hydroxylamines as aminating reagent and oxidant. The reaction proceeds smoothly at room temperature and is compatible with a range of substrates to give the desired products in moderate to good yields.

α-Ketoamides are important functional scaffolds in many natural products, biological compounds, pharmaceuticals, and synthetic intermediates.[1] Significant efforts have been made toward the development of efficient methods for their preparation. Traditional approaches for accessing α-ketoamides mainly involve the condensation of their corresponding α-keto acids or α-keto acyl halides with amines.[2] Some alternative methods, such as double carbonylation reactions,[3] oxidative reactions[4] and other methods[5] have also been developed. Recently, the copper-catalyzed oxidative reaction for the synthesis of α-ketoamides have attracted much attention,[4a-4d] especially using commercially available terminal alkynes as coupling partners.[6] For example, Jiao etal. and Shah etal. have successfully developed copper-catalyzed methods for the preparation of α-ketoamides involving terminal alkynes as coupling partners with amines (Scheme 1, eq 1-2).[6a, 6b] While generally effective, the methods require external oxidants, additives and heating conditions. Therefore, developing new methods for the synthesis of α-ketoamides using easily available starting materials under mild conditions is still of promising interest. In the past decade, *O*-benzoyl hydroxylamines ($BzO\text{-}NR_1R_2$) have received great attention because of easy handling and preparation, and high reactivity in amination reactions as a convenient nitrogen source under mild conditions.[7] Herein, we present a novel and convenient copper-catalyzed oxidative amidation of terminal alkynes for the synthesis of α-ketoamides employing easily available *O*-benzoyl hydroxylamines ($BzO\text{-}NR_1R_2$) as dually a reactive aminating reagent and oxidant at room temperature (Scheme 1, eq 3).



Scheme 1. Synthesis of α-ketoamides.

Table 1. Optimization of the reaction conditions.[a]



1a 1b 1c

Entry	Catalyst	Base	Solvent	T(°C)	1c(%)[b]
1	CuI	DBU	THF	RT	52
2	CuBr	DBU	THF	RT	68
3	$CuCl_2$	DBU	THF	RT	62
4	$Cu(OTf)_2$	DBU	THF	RT	84
5	$Cu(OTf)_2$	DBU	THF	RT	82[c]
6	/	DBU	THF	RT	n.r.[d]
7	$Cu(OTf)_2$/BPO	DBU	THF	RT	38[e]
8	$Cu(OTf)_2/O_2$	DBU	THF	RT	46[f]
9	$Cu(OTf)_2$	Na_2CO_3	THF	RT	n.r.

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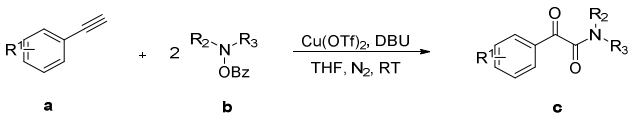
10	$Cu(OTf)_2$	K_2CO_3	THF	RT	n.r.
11	$Cu(OTf)_2$	*t*-BuOK	THF	RT	trace
12	$Cu(OTf)_2$	Et_3N	THF	RT	n.r.
13	$Cu(OTf)_2$	/	THF	RT	n.r.[g]
14	$Cu(OTf)_2$	DBU	toluene	RT	70
15	$Cu(OTf)_2$	DBU	dioxane	RT	trace
16	$Cu(OTf)_2$	DBU	H_2O	RT	n.r.
17	$Cu(OTf)_2$	DBU	THF	35	72
18	$Cu(OTf)_2$	DBU	THF	15	24

[a] General reaction conditions: copper catalyst (0.05 mmol, 10 mol%), phenylacetylene (2.0 mmol, 0.204g, 4.0 equiv.) and *N*-(benzoyloxy)piperidine (0.5 mmol, 0.103g, 1.0 equiv.), base (1.0 mmol, 2.0 equiv.), solvent (3.0 mL), N_2, 12 h.
[b] Isolated yield based on **1b**.
[c] $Cu(OTf)_2$ (0.1 mmol) was added as the catalyst.
[d] No copper catalyst was used, n.r.= no reaction.
[e] Benzoyl peroxide (BPO, 0.5 mmol) was added.
[f] The reaction was performed under oxygen balloon.
[g] No base was used.

Initially, the synthesis of *α*-ketoamides with phenylacetylene **1a** and *N*-(benzoyloxy)piperidine **1b** was investigated in the presence of copper catalyst to identify and optimize the reaction parameters (Table 1). To our delight, when the reaction was carried out with CuI (10 mol%) and DBU (2 eq) in THF (3.0 mL) at ambient temperature under nitrogen, the desired product could be detected (Table 1, entry 1). It was found that the copper catalysts such as $CuCl_2$, CuI, CuBr, $Cu(OTf)_2$ affected the reaction yield significantly (Table 1, entries 1-4). The best result was obtained in the presence of 10 mol% of $Cu(OTf)_2$ (0.05 mmol, 0.018g), phenylacetylene (2.0 mmol, 0.204g) and *N*-(benzoyloxy)piperidine (0.5 mmol, 0.103g), DBU (1.0 mmol, 0.152g) in THF (3.0 mL) at room temperature for 12 h, and 84% yield was got (Table 1, entry 4), while increasing the catalyst loading did not improve the product yield (Table 1, entry 5). No reaction occurred in the absence of copper catalyst (Table 1, entry 6). Notably, the copper-catalyzed oxidative amidation reaction did not have external oxygen source (Table 1, entries 1-5). Meanwhile, addition of other oxidants such as benzoyl peroxide (BPO, 1 eq) or oxygen into the catalytic system decreased the yield obviously (Table 1, entries 7 and 8). Therefore, we surmised that *N*-(benzoyloxy)piperidine could serve as dually aminating reagent and oxidant. During the study of bases, we noticed that the addition of DBU to the reaction showed the best efficiency (Table 1, entries 9-13). Then, the reaction was investigated in other solvents and THF was found to be the best choice (Table 1, entries 14-16). The reaction temperature was also screened and the reaction yields decreased obviously at lower or higher reaction temperatures (Table 1, entries 17 and 18). Thus, the optimized reaction conditions for the oxidative amidation of terminal alkynes involved using *O*-benzoyl hydroxylamines as dually aminating reagent and oxidant, $Cu(OTf)_2$ as the catalyst, DBU as the base, THF as the solvent and conducting the reaction at room temperature under nitrogen.

Table 2. Scope of copper-catalyzed oxidative amidation for the synthesis of *α*-ketoamides.[a]



a b c

Entry	a	b	c	Yield (%)[b]
1	**1a**	**1b**	**1c**	84
2	**2a**	**1b**	**2c**	82
3	**3a**	**1b**	**3c**	64
4	**4a**	**1b**	**4c**	72
5	**5a**	**1b**	**5c**	80
6	**6a**	**1b**	**6c**	78
7	**1a**	**2b**	**7c**	80
8	**1a**	**3b**	**8c**	72
9	**1a**	**4b**	**9c**	62
10	**1a**	**5b**	**10c**	68
11	**1a**	**6b**	**11c**	76
12	**1a**	**7b**	**12c**(isomer)	60
13	**2a**	**5b**	**13c**	65

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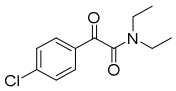
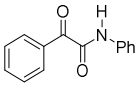
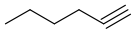
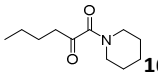
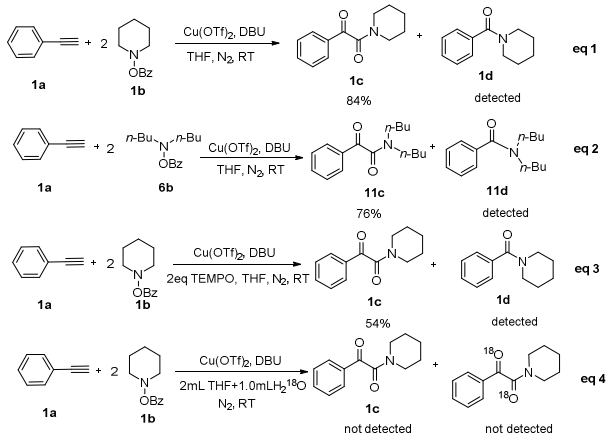
14	**6a**	**5b**	 **14c**	61
15	**1a**	 **8b**	 **15c**	0
16	 **7a**	**1b**	 **16c**	0

[a] Reaction conditions: copper(II) trifluoromethanesulfonate (0.05 mmol, 0.018g, 10 mol%), terminal alkyne **a** (2.0 mmol, 4.0 equiv.) and *O*-benzoyl hydroxylamine **b** (0.5 mmol, 1.0 equiv.), DBU (1.0 mmol, 0.152g, 2.0 equiv.), THF (3.0 mL), N_2, RT, 12 h.
[b] Isolated yield based on **b**.

With the optimized reaction conditions in hand, we evaluated the scope of the copper-catalyzed oxidative amidation for the synthesis of α-ketoamides. As shown in Table 2, the reaction yields were slightly influenced by the electronic effect of substituents of terminal alkynes. Terminal alkynes with electron-donating methyl, tertiary butyl and pentyl groups (Table 2, entries 2-4) and electron-withdrawing fluoro and chloro groups (Table 2, entries 5-6) generated the desired products in moderate to good yields. Various *O*-benzoyl hydroxylamines with acyclic and cyclic *N*-alkyl substituents were explored by reacting with phenylacetylene (**1a)** under the optimum reaction conditions (Table 2, entries 7-12). The five-membered cyclic amines **2b** bearing a pyrrolidine moiety, the six-membered cyclic amines **1b** and **3b** bearing a piperidine and morpholine moiety, and the seven-membered cyclic amines **4b** bearing a azepane moiety are compatible to the reaction conditions (Table 2, entries 7-9). *O*-benzoyl hydroxylamines which were derived from *N,N*-diethyl **5b**, *N,N*-di-*n*- butyl **6b**, and *N*-*n*-butyl-*N*-ethyl **7b** amines were smoothly converted to α-ketoamides **10c–14c** in 60-76 % yields (Table 2, entries 10-14). An *O*-benzoyl-*N*-phenylhydroxylamine **8b**, which is prepared from primary phenylamine, could not be utilized in this protocol to furnish the desired compound **15c**, presumably because of the weak oxidative ability of **8b** (Table 2, entry 15). Aliphatic alkynes 1-hexyne **7a** also could not reacted with *N*-(benzoyloxy)piperidine **1b** under the optimized reaction condition (Table 2, entry 16).



Scheme 2. Control experiments.

To gain some understanding of the mechanism for this reaction, some control experiments were tentatively examined under the optimized reaction conditions (for mechanism details, see Supporting Information). We have concluded that oxygen source of the product **1c** come from *N*-(benzoyloxy)piperidine **1b** (Table 1, entries 1-8), and the detected phenyl(piperidin-1-yl)methanone **1d** also confirmed our speculation (Scheme 2, eq 1). We used *O*-benzoyl-*N,N*-dibutylhydroxylamine **6b** to repeat the reaction, *N,N*-dibutylbenzamide **11d** was also detected from the reaction (Scheme 2, eq 2). When the reaction was carried out with two equivalents of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), it could proceed smoothly and the reaction may not undergo a radical mechanism (Scheme 2, eq 3). When 2.0mL THF and 1.0mL $H_2{}^{18}O$ used as the solvent to repeat the reaction, no product was detected, and the Oxygen of the products did not come from the H_2O in THF (Scheme 2, eq 4).

In summary, we have developed a novel and convenient copper-catalyzed oxidative amidation of terminal alkynes for synthesis of α-ketoamides. This protocol displays attractive features including using easily available *O*-benzoyl hydroxylamines ($BzO\text{-}NR_1R_2$) as aminating reagent and oxidant, and conducting the reaction at room temperature. The reaction also exhibits some functional group tolerance and allows for the preparation of a number of α-ketoamides in moderate to good yields. The importance of the α-ketoamides scaffold would render this protocol attractive for both synthetic and medicinal chemistry.

Acknowledgements

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Room temperature copper-catalyzed oxidative amidation of terminal alkynes for synthesis of *α*-ketoamides using *O*-benzoyl hydroxylamines as aminating reagent and oxidant

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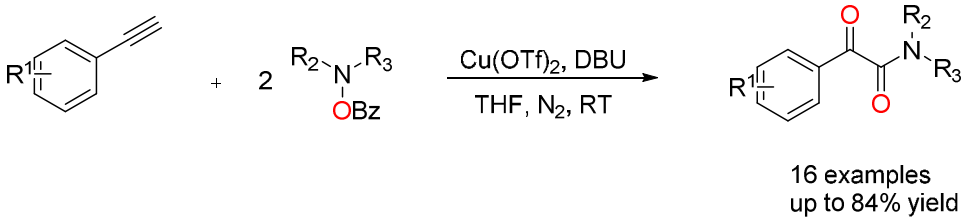
TOC Graphic



Abstract

A novel and convenient copper-catalyzed oxidative amidation for synthesis of *α*-ketoamides has been successfully developed, which uses easily available *O*-benzoyl hydroxylamines as aminating reagent and oxidant. The reaction proceeds smoothly at room temperature and is compatible with a range of substrates to give the desired products in moderate to good yields.