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Dioxygen Activation under Ambient Conditions: Cu-Catalyzed Oxidative Amidation−Diketonization of Terminal Alkynes Leading to α-Ketoamides

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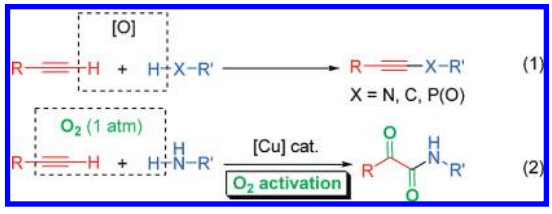
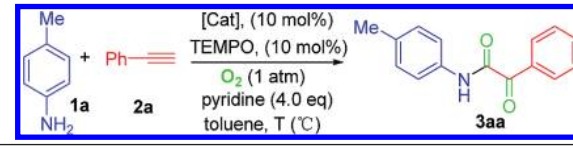
Dioxygen is an ideal oxidant and offers attractive academic and industrial prospects.[1] Significantly, dioxygen activation[2] for the functionalization of an organic molecule has been of long-standing interest to organic chemists because of its tremendous importance in chemistry as well as in biology.[3] In the past decades, alkynes have been extensively used in organic synthesis through transition-metal-catalyzed reactions. Recent breakthroughs involving the cross-dehydrogenative coupling (CDC)[4] reaction of terminal alkynes via C−H activation (eq 1) have been developed by the research groups of Stahl,[5a] Li,[5b] and Han.[5c] In these approaches, one new C−N, C−C, or C−P bond, respectively, is formed with retention of the triple C−C bond, facilitated by an oxidant such as O_2.[5a,c] However, this kind of coupling using molecular oxygen as the oxidant still remains a challenging research area, and the oxidation of alkynes with dioxygen has very rarely been investigated.[6] The combination of using dioxygen as the oxidant and as a reactant via dioxygen activation would substantially broaden the field of cross-coupling and offer more functionalized products. Herein, for the first time, we present a novel Cu-catalyzed oxidative amidation−diketonization reaction of terminal alkynes using O_2 as the oxidant and as a reactant via dioxygen activation (eq 2). This chemistry offers not only a new approach to α-ketoamides but also valuable mechanistic insights into this novel Cu catalysis.



During our investigation of indole synthesis via Pd-catalyzed reactions of anilines and alkynes using dioxygen as the oxidant,[7a] we discovered the rather surprising formation of 2-oxo-2-phenyl-*N*-*p*-toylacetamide (**3aa**) from 4-methylaniline (**1a**) and phenylacetylene (**2a**) when copper salts were used as catalyst precursors (Table 1, entry 1). To the best of our knowledge, the synthesis of α-ketoamides from alkynes via diketonization has not been reported to date. We envisioned that a radical process[7b,c] was possibly involved. The presence of 10 mol % 2,2,6,6-tetramethylpiperadine-1-oxyl (TEMPO)[8] promoted the yield of **3aa** to 25% (entries 1 and 2). However, this reaction did not work in the absence of Cu catalyst (entry 3). Gratifyingly, **3aa** was formed in 67% yield when catalyzed by $CuBr_2$ and TEMPO using O_2 at ambient pressure as the oxidant in toluene at 60 °C (entry 4). Attempts to use other metal catalysts such as Ag, Au, and Mn were not successful [see the Supporting Information (SI)]. After a great deal of screening of different parameters (see Table 1 and the SI), the highest yield (90%) was achieved when 10 equiv of **2a** was employed (entry 8).

Under these optimized conditions, the scope of aryl-substituted alkynes was investigated (Table 2). Notably, both electron-rich (para-, meta-, and ortho-substituted) and electron-deficient substrates

Table 1. Cu-Catalyzed Oxidative Amidation−Diketonization of **1a** with Alkyne **2a**[a]



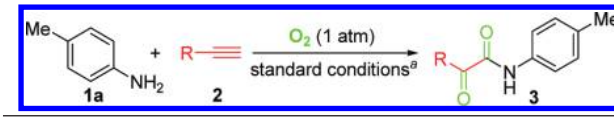
entry	catalyst	additive (equiv)	*T* (°C)	% yield of **3aa**[b]
1[c]	$CuCl_2 \cdot 2H_2O$	none	110	15
2	$CuCl_2 \cdot 2H_2O$	none	110	25
3	none	none	110	0
4	$CuBr_2$	none	60	67
5[d]	$CuBr_2$	none	60	50
6[c,d]	$CuBr_2$	none	60	trace
7	**$CuBr_2$**	**H_2O (10)**	**60**	**77**
8[e]	**$CuBr_2$**	**H_2O (10)**	**60**	**90**

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (1.25 mmol), cat. (0.025 mmol), TEMPO (0.025 mmol), pyridine (1.0 mmol), H_2O (2.5 mmol), toluene (3 mL), O_2 (1 atm), 18 h. [b] Isolated yields. [c] The reaction was carried out in the absence of TEMPO. [d] The reaction was carried out under air. [e] A 90% yield was obtained when 10 equiv of **2a** was used.

in our cases could be transformed into the desired products. In addition, a heteroaryl-substituted alkyne, 3-thienylacetylene (**2i**), provided **3ai** in 64% yield (Table 2, entry 9). It is noteworthy that alkenyl-substituted alkynes such as **2l** and **2m** survived well, leading to **3al** (65%) and **3am** (24%), respectively (entries 12 and 13).

The scope of the Cu-catalyzed oxidative amidation−diketonization reaction was further expanded to a variety of substituted anilines **1** (Table 3). These results indicate that anilines with electron-donating groups proceeded more efficiently than anilines containing electron-withdrawing groups. It is noteworthy that halo-substituted anilines

Table 2. Cu-Catalyzed Oxidative Amidation−Diketonization of **1a** with Alkynes **2**[a]



entry	R (**2**)	% yield[b] (**3**)
1	Ph (**2a**)	77 (**3aa**)
2	4-Me-C_6H_4 (**2b**)	67 (**3ab**)
3	3-Me-C_6H_4 (**2c**)	51 (**3ac**)
4	2-Me-C_6H_4 (**2d**)	62 (**3ad**)
5	4-F-C_6H_4 (**2e**)	71 (**3ae**)
6	4-Br-C_6H_4 (**2f**)	56 (**3af**)
7	2,4-F_2-C_6H_4 (**2g**)	57 (**3ag**)
8	3,5-F_2-C_6H_4 (**2h**)	55 (**3ah**)
9	3-thienyl (**2i**)	64 (**3ai**)
10	4-MeO-C_6H_4 (**2j**)	63 (**3aj**)
11	4-Et-C_6H_4 (**2k**)	70 (**3ak**)
12	styrenyl (**2l**)	65 (**3al**)
13	1-cyclohexenyl (**2m**)	24 (**3am**)
14	*n*-octyl (**2n**)	0 (**3an**)

[a] Standard reaction conditions: **1a** (0.25 mmol), **2** (1.25 mmol), $CuBr_2$ (0.025 mmol), TEMPO (0.025 mmol), pyridine (1.0 mmol), H_2O (2.5 mmol), toluene (3 mL), 60 °C, O_2 (1 atm), 18 h. [b] Isolated yields.

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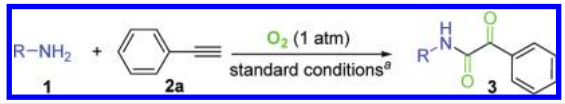
Table 3. Cu-Catalyzed Oxidative Amidation−Diketonization of **1** with **2a**[a]

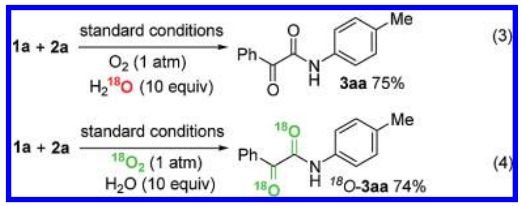


entry	R (**1**)	% yield[b] (**3**)
1	4-Me-C_6H_4 (**1a**)	77 (**3aa**)
2	3-Me-C_6H_4 (**1b**)	50 (**3ba**)
3	2-Me-C_6H_4 (**1c**)	40 (**3ca**)
4	4-CF_3O-C_6H_4 (**1d**)	36 (**3da**)
5	Ph (**1e**)	47 (**3ea**)
6	2-naphthyl (**1f**)	51 (**3fa**)
7	4-MeO-C_6H_4 (**1g**)	77 (**3ga**)
8	4-F-C_6H_4 (**1h**)	47 (**3ha**)
9	4-Cl-C_6H_4 (**1i**)	41 (**3ia**)
10	4-Br-C_6H_4 (**1j**)	32 (**3ja**)
11	4-COOEt-C_6H_4 (**1k**)	22 (**3ka**)
12	*n*-butyl (**1l**)	0 (**3la**)

[a] The standard reaction conditions are given in Table 2, footnote a. [b] Isolated yields.

survived well, leading to halo-substituted α-ketoamides (Table 3, entries 8−10), which could be used for further transformations.

The transformation of **1a** and **2a** was tested in the presence of $H_2{}^{18}O$ (10 equiv). However, the ^{18}O-labeled product ***18O*-3aa** was not detected (eq 3). Further investigation under an $^{18}O_2$ atmosphere [using mass spectrometry (MS) and high-resolution MS; see the SI] proved the dioxygen activation, indicating that both oxygen atoms of the α-ketoamide originated from molecular dioxygen (eq 4).



In the electron paramagnetic resonance (EPR) spectra monitored with the addition of the radical trap 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO), the signal corresponding to DMPO−OO(H) was identified[9] [see the "a" peaks in trace 1 of Figure 1; they are 12 classical peaks, and the calculated hyperfine splittings are g_0 (2.006), α_N (14.4 G), α^{β}_H (13.3 G), and α^{γ}_H (2.4 G)]. Furthermore, the above signal disappeared with the addition of superoxide dismutase (SOD) (trace 2 in Figure 1). The EPR results (for more details, see the SI) indicate that the superoxide radical **7** (Scheme 1) is a key intermediate involved in this kind of transformation.

A hypothesized mechanism of this transformation is shown in Scheme 1. The proposed initiated complex **4** would insert alkyne **2a** to give Cu^{II} intermediate **5**. Next, imine radical **6** would potentially be generated, and this would be followed by the formation of the key intermediate, superoxide radical **7**. Further intramolecular cycloaddition to the imine would form the corresponding aminyl radical **8**.[10] Intermediate **8** would then undergo the second hydrogen abstraction facilitated by TEMPO or oxygen, resulting in intermediate **9**,[11] and the subsequent fragmentation[6a,12] of **9** would produce the desired α-ketoamide **3ea**.

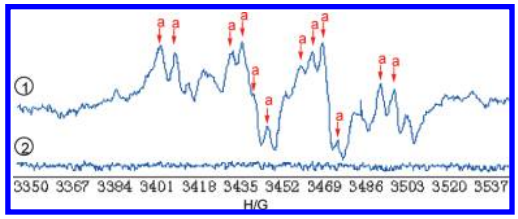
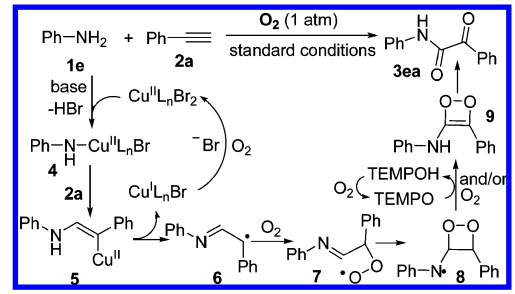


Figure 1. EPR spectra (X band, 9.7 GHz, room temperature) for reaction mixtures in the presence of (1) the radical trap DMPO (2.5×10^{-2} M) and (2) SOD (2.5×10^{-3} M) and DMPO (1.25×10^{-2} M).

Scheme 1. Proposed Mechanism for the Direct Transformation



In conclusion, we have demonstrated the first Cu-catalyzed oxidative amidation−diketonization reaction of terminal alkynes leading to α-ketoamides. O_2 not only participates as the ideal oxidant but also undergoes dioxygen activation under ambient conditions via a radical process. This chemistry also offers a valuable mechanistic insight into this novel Cu catalysis. Further studies to clearly understand the reaction mechanism and the synthetic applications are ongoing in our laboratory.

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Supporting Information Available: Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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