J|A|C|S COMMUNICATIONS

Published on Web 12/10/2009

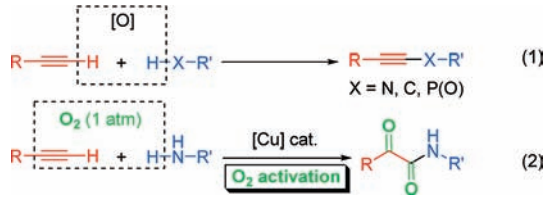
Dioxygen Activation under Ambient Conditions: Cu-Catalyzed Oxidative Amidation−Diketonization of Terminal Alkynes Leading to α-Ketoamides

Chun Zhang[†] and Ning Jiao*[,†,‡]

State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Xue Yuan Road 38, Beijing 100191, China, and State Key Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Received October 19, 2009; E-mail: jiaoning@bjmu.edu.cn

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]

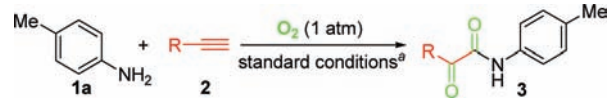
entry	catalyst	additive (equiv)	*T* (°C)	% yield of **3aa**[b]
1[c]	$CuCl_2 \cdot 2H_2O$	none	110	15
2	$CuCl_2 \cdot 2H_2O$	none	110	25
3	none	none	110	0
4	$CuBr_2$	none	60	67
5[d]	$CuBr_2$	none	60	50
6[c,d]	$CuBr_2$	none	60	trace
7	**$CuBr_2$**	**H_2O (10)**	**60**	**77**
8[e]	**$CuBr_2$**	**H_2O (10)**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



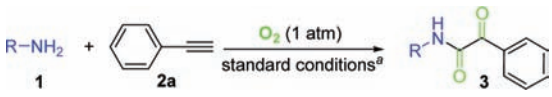
entry	R (**2**)	% yield[b] (**3**)
1	Ph (**2a**)	77 (**3aa**)
2	4-Me-C_6H_4 (**2b**)	67 (**3ab**)
3	3-Me-C_6H_4 (**2c**)	51 (**3ac**)
4	2-Me-C_6H_4 (**2d**)	62 (**3ad**)
5	4-F-C_6H_4 (**2e**)	71 (**3ae**)
6	4-Br-C_6H_4 (**2f**)	56 (**3af**)
7	2,4-F_2-C_6H_4 (**2g**)	57 (**3ag**)
8	3,5-F_2-C_6H_4 (**2h**)	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.

[†] Peking University.
[‡] Chinese Academy of Sciences.

10.1021/ja908911n

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

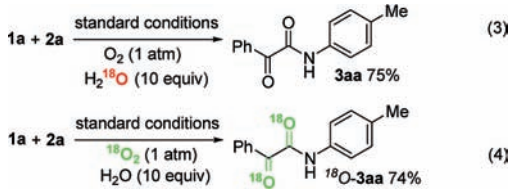


entry	R (**1**)	% yield[b] (**3**)
1	4-Me-C_6H_4 (**1a**)	77 (**3aa**)
2	3-Me-C_6H_4 (**1b**)	50 (**3ba**)
3	2-Me-C_6H_4 (**1c**)	40 (**3ca**)
4	4-CF_3O-C_6H_4 (**1d**)	36 (**3da**)
5	Ph (**1e**)	47 (**3ea**)
6	2-naphthyl (**1f**)	51 (**3fa**)
7	4-MeO-C_6H_4 (**1g**)	77 (**3ga**)
8	4-F-C_6H_4 (**1h**)	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_H^β (13.3 G), and α_H^γ (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**.

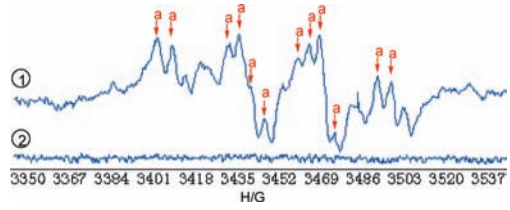
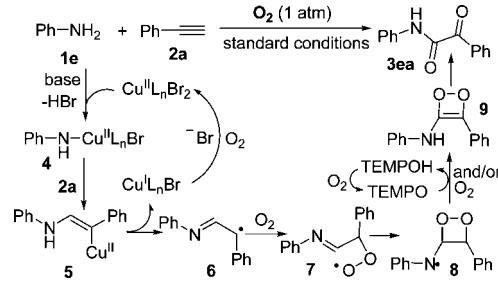


Figure 1. EPR spectra (X band, 9.7 GHz, room temperature) for reaction mixtures in the presence of (1) the radical trap DMPO (2.5×10^{-2} M) and (2) SOD (2.5×10^{-3} M) and DMPO (1.25×10^{-2} M).

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.

Acknowledgment. Financial support from Peking University, the National Natural Science Foundation of China (20702002, 20872003), and the National Basic Research Program of China (973 Program 2009CB825300) is greatly appreciated. We thank Prof. Chaozhong Li, Jingfen Lu, Yufei Song, and Li-Zhu Wu for helpful discussions. We thank Riyuan Lin in this group for reproducing the results for **3ab**, **3aj**, **3ga**, and **3ia**.

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

References

(1) Dioxygen has been used as an ideal oxidant. For some reviews, see: (a) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329. (b) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400.
(2) For some reviews, see: (a) Special issue on dioxygen activation by metalloenzymes and models: *Acc. Chem. Res.* **2007**, *40*, 465−634. (b) Limberg, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5932.
(3) (a) Klinman, J. P. *J. Biol. Inorg. Chem.* **2001**, *6*, 1. (b) Bollinger, J. M., Jr.; Krebs, C. *Curr. Opin. Chem. Biol.* **2007**, *11*, 151.
(4) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335, and references therein.
(5) (a) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (b) Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075. (c) Gao, Y.; Wang, G.; Chen, L.; Xu, P.; Zhao, Y.; Zhou, Y.; Han, L.-B. *J. Am. Chem. Soc.* **2009**, *131*, 7956.
(6) For the Pd-catalyzed cleavage reaction of alkynes with molecular dioxygen, see: (a) Wang, A.; Jiang, H. *J. Am. Chem. Soc.* **2008**, *130*, 5030. For Pd-catalyzed diketonization of alkynes with H_2O, see: (b) Ren, W.; Xia, Y.; Ji, S.-J.; Zhang, Y.; Wan, X.; Zhao, J. *Org. Lett.* **2009**, *11*, 1841.
(7) (a) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572. For our recent work on radical reactions, see: (b) Zhou, W.; Zhang, L.; Jiao, N. *Tetrahedron* **2009**, *65*, 1982. (c) Zhou, W.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7094.
(8) For some reviews of the application of TEMPO in synthesis, see: (a) Vogler, T.; Studer, A. *Synthesis* **2008**, 1979. (b) De Souza, M. V. N. *Mini-Rev. Org. Chem.* **2006**, *3*, 155. (c) Bragd, P. L.; van Bekkum, H.; Besemer, A. C. *Top. Catal.* **2004**, *27*, 49. (d) Geisslmeir, D.; Jary, W. G.; Falk, H. *Monatsh. Chem.* **2005**, *136*, 1591. (e) Sheldon, R. A.; Arends, I. W. C. E.; ten Brink, G.-J.; Dijksman, A. *Acc. Chem. Res.* **2002**, *35*, 774.
(9) (a) Yamakoshi, Y.; Sueyoshi, S.; Fukuhara, K.; Miyata, N.; Masumizu, T.; Kohno, M. *J. Am. Chem. Soc.* **1998**, *120*, 12363. (b) Finkelstein, E.; Rosen, G. M.; Rauckman, E. J. *J. Am. Chem. Soc.* **1980**, *102*, 4994. (c) Samuni, A.; Murali Krishna, C.; Riesz, P.; Finkelstein, E.; Russo, A. *Free Radical Biol. Med.* **1989**, *6*, 141. (d) Izzet, G.; Zeitouny, J.; Akdas-Killig, H.; Frapart, Y.; Ménage, S.; Douziech, B.; Jabin, I.; Mest, Y. L.; Reinaud, O. *J. Am. Chem. Soc.* **2008**, *130*, 9514. (e) Zhao, H.; Joseph, J.; Zhang, H.; Karoui, H.; Kalyanaraman, B. *Free Radical Biol. Med.* **2001**, *31*, 599. (f) Ou, Z.-Z.; Chen, J.-R.; Wang, X.-S.; Zhang, B.-W.; Cao, Y. *New J. Chem.* **2002**, *26*, 1130.
(10) (a) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (b) Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1. (c) Stella, L. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, p 407. (d) Guindon, Y.; Guerin, B.; Landry, S. R. *Org. Lett.* **2001**, *3*, 2293. (e) Liu, F.; Liu, K.; Yuan, X.; Li, C. *J. Org. Chem.* **2007**, *72*, 10231.
(11) (a) Chen, Y.-X.; Qian, L.-F.; Zhang, W.; Han, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 9330. (b) Speier, G.; Párkányi, L. *J. Org. Chem.* **1986**, *51*, 218.
(12) (a) Simándi, L.; Simándi, T. M.; May, Z.; Besenyei, G. *Coord. Chem. Rev.* **2003**, *245*, 85. (b) Schank, K.; Beck, H.; Werner, F. *Helv. Chim. Acta* **2000**, *83*, 1611.

JA908911N