

Carbon Dioxide Triggered and Copper-Catalyzed Domino Reaction: Efficient Construction of Highly Substituted 3(2*H*)-Furanones from Nitriles and Propargylic Alcohols

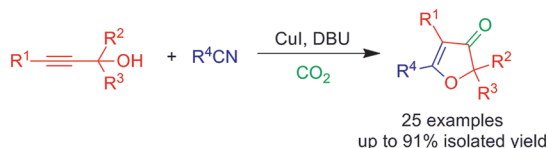
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ABSTRACT



A novel carbon dioxide triggered and copper-catalyzed domino reaction for the efficient synthesis of highly substituted 3(2*H*)-furanones from readily available nitriles and propargylic alcohols has been developed. Carbon dioxide is a prerequisite for achieving the present catalytic transformation, and one of the oxygen atoms of carbon dioxide is incorporated into the 3(2*H*)-furanones. Nitriles not only act as the reaction solvent but also as the reactant; copper salts play dual roles of activating both the propargylic alcohols and nitriles.

During the past several decades, the reactions of propargylic alcohols and carbon dioxide have received much attention, as they can yield cyclic carbonates,¹ oxazolidinones,²

or carbamates³ under different reaction conditions and use carbon dioxide as a cheap and safe C1 feedstock. Herein, we present the first carbon dioxide triggered and copper-catalyzed domino reaction for the efficient synthesis of highly substituted 3(2*H*)-furanones from readily available nitriles⁴ and propargylic alcohols (Scheme 1).

(1) (a) Inoue, Y.; Ishikawa, J.; Taniguchi, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1204. (b) Uemura, K.; Kawaguchi, T.; Takayama, H.; Inoue, Y. *J. Mol. Catal. A: Chem.* **1999**, *139*, 1. (c) Fournier, J.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron Lett.* **1989**, *30*, 3981. (d) Kayaki, Y.; Yamamoto, M.; Ikariya, T. *J. Org. Chem.* **2007**, *72*, 647. (e) Gu, Y.; Shi, F.; Deng, Y. *J. Org. Chem.* **2004**, *69*, 391. (f) Yamada, W.; Sugawara, Y.; Cheng, H. M.; Ikeno, T.; Yamada, T. *Eur. J. Org. Chem.* **2007**, 2604. (g) Jiang, H.-F.; Wang, A.-Z.; Liu, H.-L.; Qi, C.-R. *Eur. J. Org. Chem.* **2008**, 2309. (h) Yoshida, S.; Fukui, K.; Kikuchi, S.; Yamada, T. *J. Am. Soc. Chem.* **2010**, *132*, 4072.

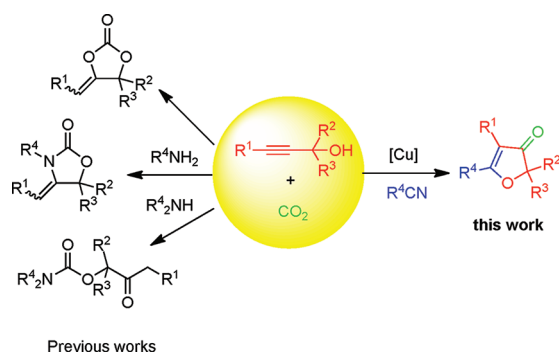
(2) (a) Fournier, J.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron Lett.* **1990**, *31*, 1721. (b) Gu, Y.; Zhang, Q.; Duan, Z.; Zhang, J.; Zhang, S.; Deng, Y. *J. Org. Chem.* **2005**, *70*, 7376. (c) Jiang, H.; Zhao, J.; Wang, A. *Synthesis* **2008**, 763. (d) Jiang, H.-F.; Zhao, J.-W. *Tetrahedron Lett.* **2009**, *50*, 60.

(3) (a) Bruneau, C.; Dixneuf, P. H. *Tetrahedron Lett.* **1987**, *28*, 2005. (b) Sasaki, Y.; Dixneuf, P. H. *J. Org. Chem.* **1987**, *52*, 4389. (c) Kim, T. J.; Kwon, K. H.; Kwon, S. C.; Baeg, J. O.; Shim, S. C.; Lee, D. H. *J. Organomet. Chem.* **1990**, *389*, 205. (d) Shim, S. C.; Baeg, J. O.; Doh, C. H.; Youn, Y. Z.; Kim, T. J. *Bull. Korean Chem. Soc.* **1990**, *11*, 467. (e) Kim, H. S.; Kim, J. W.; Kwon, S. C.; Shim, S. C.; Kim, T. J. *J. Organomet. Chem.* **1997**, *545–546*, 337. (f) Kwon, S. C.; Cho, C. S.; Shim, S. C.; Kim, T. J. *Bull. Korean Chem. Soc.* **1999**, *20*, 103. (g) Qi, C.-R.; Jiang, H.-F. *Green Chem.* **2007**, *9*, 1284. (h) Qi, C.; Huang, L.; Jiang, H. *Synthesis* **2010**, 1433.

(4) For recent reports involving nitriles as low-cost starting material, see: (a) Ueda, S.; Nagasawa, H. *J. Am. Soc. Chem.* **2009**, *131*, 15080. (b) Lindh, J.; Sjöberg, P. J. R.; Larhed, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 7733. (c) Neumann, J. J.; Suri, M.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 7790. (d) He, W.; Li, C.; Zhang, L. *J. Am. Soc. Chem.* **2011**, *133*, 8482.

(5) (a) Smith, A. B., III; Guaciaro, M. A.; Schow, S. R.; Wovkulich, P. M.; Todu, B. H.; Hall, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 219. (b) Jerris, P. J.; Smith, A. B., III. *J. Org. Chem.* **1981**, *46*, 577. (c) Smith, A. B., III; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M., Jr.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501. (d) Manfredini, S.; Baraldi, P. G.; Bazzanini, R. B.; Guarneri, M.; Simoni, D.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1994**, *37*, 2401. (e) Goss, R. J. M.; Fuchser, J.; O'Hagan, D. *Chem. Commun.* **1999**, 2255. (f) Steel, P. G. *Chem. Commun.* **1999**, 2257. (g) Chimichi, S.; Boccalini, M.; Cosimelli, B.; Viola, G.; Vedaldi, D.; Dall'Acqua, F. *Tetrahedron Lett.* **2002**, *43*, 7473. (h) Li, Y.; Hale, K. J. *Org. Lett.* **2007**, *9*, 1267. (i) Stierle, A. A.; Stierle, D. B.; Patacini, B. *J. Nat. Prod.* **2008**, *71*, 856. (j) Ishikawa, M.; Ninomiya, T.; Akabane, H.; Kushida, N.; Tsujiuchi, G.; Ohyama, M.; Gomi, S.; Shito, K.; Murata, T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1457.

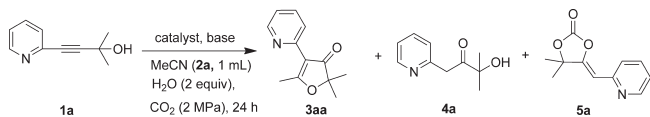
Scheme 1. Reactions Involving Propargylic Alcohols and Carbon Dioxide



The 3(2*H*)-furanones have attracted tremendous interest in biologically active natural product research and synthetic chemistry.⁵ A classical approach to substituted 3(2*H*)-furanones involved acid-catalyzed cyclization/dehydration of 1-hydroxy-2,4-diketones.^{5b,c} To improve the synthetic efficiency, many alternative strategies have been developed, including metal-free processes^{5d,g,6} as well as transition-metal-catalyzed cyclizations.⁷ However, challenges still remain because (a) most of the current approaches suffer from limited substrate scope or the lack of readily available precursors and (b) the synthetic procedures are usually tedious. Therefore, the development of general routes that allow the facile assembly of substituted 3(2*H*)-furanones from readily available and simple starting materials remains an important objective.

During the course of our continuing investigations on the reaction between propargylic alcohols and carbon dioxide,^{1g,2c,d,3g,h} we observed that 2,2,5-trimethyl-4-(pyridin-2-yl)furan-3(2*H*)-one (**3aa**) formed as a byproduct together with 3-hydroxy-3-methyl-1-(pyridin-2-yl)butan-2-one (**4a**) and (*Z*)-4,4-dimethyl-5-((pyridin-2-yl)methylene)-1,

Table 1. Optimization of Reaction Conditions^a



entry	catalyst	base	<i>t</i> (°C)	conversion of alcohol (%)	yield (%) ^b 3aa (4a/5a)
1	CuI	DBU	rt	>99	8 (9/77)
2	CuI	DBU	50	>99	64 (19/—)
3	CuI	DBU	70	>99	82 (—/—)
4	CuI	DBU	90	>99	78 (—/—)
5 ^c	CuI	DBU	70	0	n. r. ^d
6	Cu(OTf) ₂	DBU	70	>99	42 (—/—)
7	CuSO ₄	DBU	70	>99	76 (—/—)
8	Cu(OAc) ₂	DBU	70	>99	48 (—/—)
9	CuCl ₂	DBU	70	>99	43 (—/—)
10	CuBr ₂	DBU	70	>99	80 (—/—)
11	CuCl	DBU	70	>99	36 (trace/—)
12	CuBr	DBU	70	>99	61(—/—)
13 ^e	CuI	DBU	70	73	36 (31/—)
14 ^f	CuI	DBU	70	>99	65 (23/—)
15	AgOAc	DBU	70	>99	trace (76/—)
16	PdCl ₂	DBU	70	>99	unidentified mixture
17	FeCl ₂	DBU	70	>99	unidentified mixture
18	CuI	Et ₃ N	70	>99	40(—/—)
19	CuI	DMAP	70	0	n. r. ^d
20	CuI	DABCO	70	0	n. r. ^d
21	CuI	Pyridine	70	77	trace (—/59)

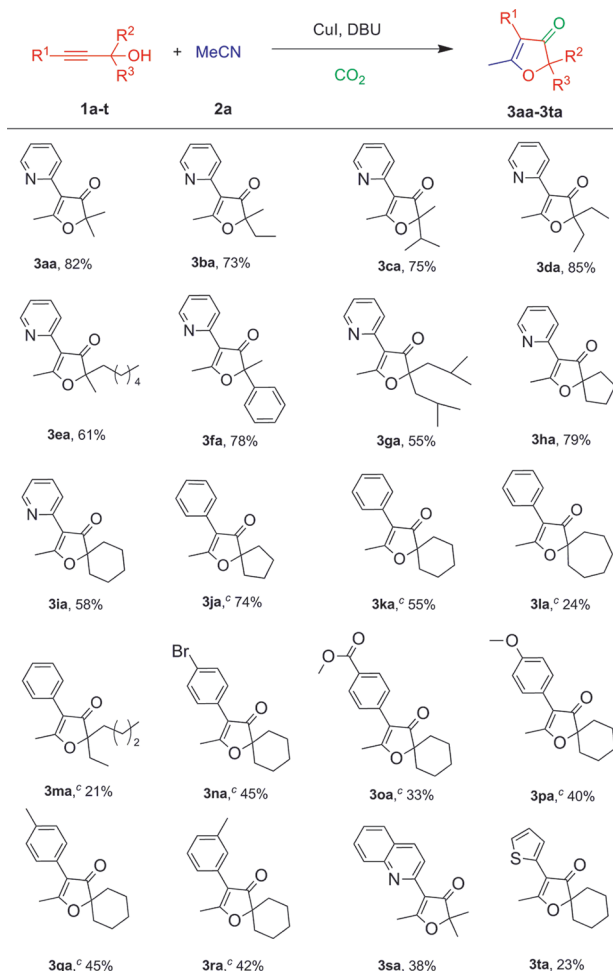
^a Reaction conditions: **1a** (0.5 mmol), MeCN (**2a**, 1 mL), H₂O (1 mmol), catalyst (0.1 mmol), base (0.25 mmol), CO₂ (2 MPa), 24 h. ^b Isolated yields. ^c The reaction was carried out under a nitrogen pressure of 2 MPa in the absence of CO₂. ^d No reaction. ^e 0.05 mmol of CuI was added. ^f 0.125 mmol of DBU was added.

3-dioxolan-2-one (**5a**) when 2-methyl-4-(pyridin-2-yl)but-3-yn-2-ol (**1a**) was treated with 20 mol % of CuI in wet acetonitrile under 2 MPa of CO₂ at room temperature in the presence of 0.5 equiv of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (Table 1, entry 1). The formation of the 3(2*H*)-furanone **3aa** was very unexpected and interesting. It seems that acetonitrile in the reaction acts not only as a solvent but also as a reactant for the new C—C/C—O bond formation. This surprising finding encouraged us to carefully adjust reaction parameters for the selective generation of **3aa** with **1a** and acetonitrile (**2a**) as well as to elucidate the mechanism of the transformation.

To our delight, when the reaction temperature was increased from room temperature to 70 °C, the yield of the 3(2*H*)-furanone **3aa** was dramatically increased from 8% to 82% although a small amount of unidentified product was also formed (entry 3), but a further increase in the temperature above 70 °C resulted in a slight decrease in the yield of the product (entry 4). It is noteworthy that when the procedure was performed under a nitrogen pressure of 2 MPa in the absence of CO₂, no reaction

(6) (a) Felman, S. W.; Jirkovsky, I.; Memoli, K. A.; Borella, L.; Wells, C.; Russell, J.; Ward, J. *J. Med. Chem.* **1992**, *35*, 1183. (b) Chimichi, S.; Boccalini, M.; Cosimelli, B.; Dall'Acqua, F.; Viola, G. *Tetrahedron* **2003**, *59*, 5215. (c) Saxena, R.; Singh, V.; Batra, S. *Tetrahedron* **2004**, *60*, 10311. (d) Langer, P.; Krummel, T. *Chem. Commun.* **2000**, 967. (e) Langer, P.; Krummel, T. *Chem.—Eur. J.* **2001**, *7*, 1720. (f) Winkler, J. D.; Oh, K.; Asselin, S. M. *Org. Lett.* **2005**, *7*, 387. (g) Villemain, D.; Jaffrès, P.-A.; Hachémi, M. *Tetrahedron Lett.* **1997**, *38*, 537. (h) Kato, K.; Nouchi, H.; Ishikura, K.; Takaishi, S.; Motodate, S.; Tanaka, H.; Okudaira, K.; Mochida, T.; Nishigaki, R.; Shigenobu, K.; Akita, H. *Tetrahedron* **2006**, *62*, 2545. (i) Trofimov, B. A.; Shemyakina, O. A.; Mal'kina, A. G.; Ushakov, I. A.; Kazheva, O. N.; Alexandrov, G. G.; Dyachenko, O. A. *Org. Lett.* **2010**, *12*, 3200. (j) Poonoth, M.; Krause, N. *J. Org. Chem.* **2011**, *76*, 1934.

(7) (a) Liu, Y.; Liu, M.; Guo, S.; Tu, H.; Zhou, Y.; Gao, H. *Org. Lett.* **2006**, *8*, 3445. (b) Kirsch, S. F.; Binder, J. T.; Liébert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 5878. (c) Binder, J. T.; Crone, B.; Kirsch, S. F.; Liébert, C.; Menz, H. *Eur. J. Org. Chem.* **2007**, 1636. (d) Crone, B.; Kirsch, S. F. *J. Org. Chem.* **2007**, *72*, 5435. (e) Bunnelle, E. M.; Smith, C. R.; Lee, S. K.; Singaram, S. W.; Rhodes, A. J.; Sarpong, R. *Tetrahedron* **2008**, *64*, 7008. (f) Reiter, M.; Turner, H.; Mills-Webb, R.; Gouverneur, V. *J. Org. Chem.* **2005**, *70*, 8478. (g) Silva, F.; Reiter, M.; Mills-Webb, R.; Sawicki, M.; Klär, D.; Bensch, N.; Wagner, A.; Gouverneur, V. *J. Org. Chem.* **2006**, *71*, 8390. (h) Marson, C. M.; Edaa, E.; Morrell, J. M.; Coles, S. J.; Hursthouse, M. B.; Davies, D. T. *Chem. Commun.* **2007**, 2494. (i) Egi, M.; Azechi, K.; Saneto, M.; Shimizu, K.; Akai, S. *J. Org. Chem.* **2010**, *75*, 2123.

Scheme 2. Scope of Propargylic Alcohols^{a,b}

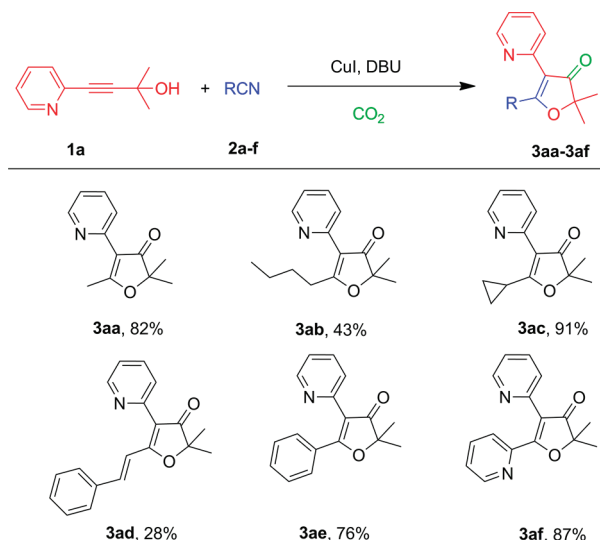
^a Reaction conditions: **1** (0.5 mmol), CuI (0.1 mmol), DBU (0.25 mmol), MeCN (1 mL), H₂O (1 mmol), CO₂ (2 MPa), 70 °C, 24 h. ^b Isolated yields. ^c CO₂ (6 MPa), 100 °C.

occurred, indicating that CO₂ is a prerequisite for the transformation (entry 5). Screening of Cu sources showed that, besides CuI, CuSO₄ and CuBr₂ are also good catalysts for the reaction (entries 6–12). The loading of the catalyst CuI and DBU has a significant effect on the reaction. Reducing the amount of CuI (from 0.2 to 0.1 equiv) or DBU (from 0.5 to 0.25 equiv) resulted in a decrease in the yield of **3aa** together with **4a** as the major byproduct (entries 13 and 14). We also investigated the catalytic activities of several other metal salts and found that silver acetate, which has been reported as an efficient catalyst for the addition of carbon dioxide to propargylic alcohols to give the corresponding cyclic carbonates,^{1f} produced **4a** in 76% yield under our conditions (entry 15). Palladium(II) chloride and iron(II) chloride resulted in the formation of a complex mixture of products (entries 16 and 17). The results in Table 1 also show that the nature of the organic base has a profound impact on the reaction. Replacement of DBU with triethylamine led to a marked reduction of the yield of **3aa** (entry 18), while with (*N,N*-dimethylamino)pyridine (DMAP) or 1,4-diazabicyclo[2.2.2]octane

(DABCO) as organic bases the reaction could not proceed and the starting material was recovered quantitatively (entries 19 and 20). Pyridine gave **5a** as the major product with a 59% yield (entry 21). Moreover, acetonitrile itself was found to be the best solvent for the reaction since other solvents investigated gave poor yields of the product **3aa** (see Supporting Information).

The scope of the reaction was then explored with various propargylic alcohols, and the results are summarized in Scheme 2. A variety of internal tertiary propargylic alcohols with a 2-pyridyl substituent at the acetylenic terminus were able to undergo the reaction and generated the corresponding 3(2H)-furanones in moderate to high yields (**3aa–3ia**). Substrates with an aryl moiety at the acetylenic position showed less reactivity and usually required a higher temperature and CO₂ pressure. The sterically more bulky **1l** and **1m** afforded the desired products in low yields but with decomposition as a side reaction. The major byproduct ketones were isolated and determined by GC-MS. Noteworthy is the functional group compatibility, as both electron-withdrawing and -donating groups on the phenyl ring were tolerated. Even 2-quinolinyl and 2-thiophenyl substituted propargylic alcohols can undergo this conversion to generate **3sa** and **3ta** in relatively lower yields (38% and 23%, respectively). Unfortunately, propargylic alcohols with a proton or an alkyl group at the acetylenic terminus could not undergo the reaction and led predominantly to decomposition.

Furthermore, various nitriles were employed to probe the scope of the reaction substrates (Scheme 3). To our delight, besides acetonitrile, other nitriles such as cyclopropanecarbonitrile (**2c**), benzonitrile (**2e**), and 2-cyanopyridine (**2f**) could undergo the reaction smoothly and gave the corresponding 3(2H)-furanones in good to high yields. Valeronitrile (**3b**) and cinnamonitrile (**3d**) showed lower

Scheme 3. Scope of Nitriles^{a,b}

^a Reaction conditions: **1a** (0.5 mmol), CuI (0.1 mmol), DBU (0.25 mmol), RCN (1 mL), H₂O (1 mmol), CO₂ (2 MPa), 70 °C, 24 h. ^b Isolated yields.

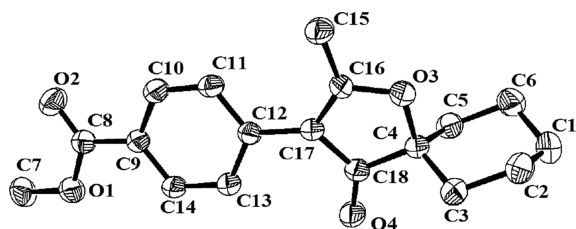
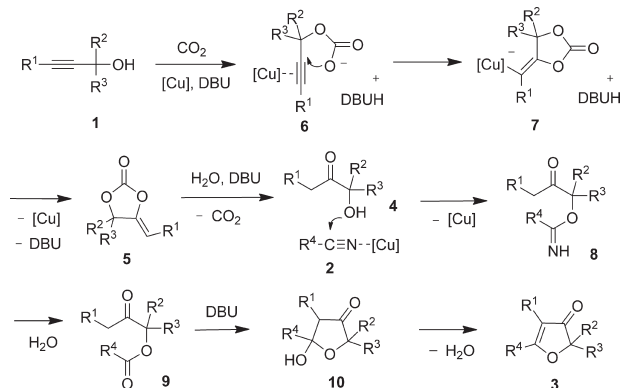


Figure 1. X-ray structure of 3(2H)-furanone **30a**.

reactivity and produced the corresponding products in low yields.

A single crystal of product **30a** was obtained by slow crystallization from a mixture of petroleum ether and ethyl acetate, and its structure was established by single-crystal X-ray analysis (Figure 1).

Scheme 4. Plausible Reaction Mechanism

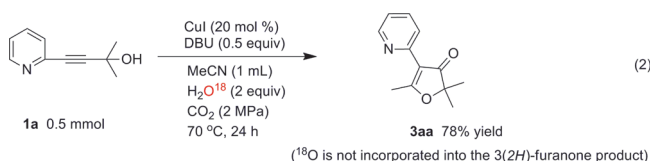
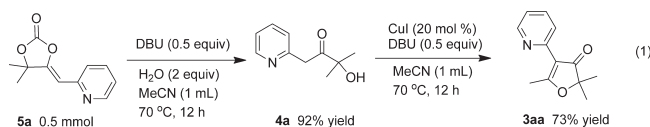


On the basis of previous reports and our experimental results, a domino process is proposed in Scheme 4. First, the reaction is triggered by cycloaddition of CO_2 to the propargylic alcohol **1** in the presence of the copper salt and DBU, affording the *Z*-alkylidene cyclic carbonate **5** via **6** and **7**.^{1f,g,2c,d,3g,h} Hydrolysis of **5** then occurs to yield the intermediate **4**. Next, copper promotes nucleophilic attack of **4** on the nitrile **2** to form the intermediate **8**,⁸ which can be converted to the ester **9** in the presence of

(8) Kukushkin, V. Y.; Pombeiro, A. J. L. *Chem. Rev.* **2002**, *102*, 1771.

water. Subsequent intramolecular Claisen condensation of **9** provides **10** which eventually affords the product **3** via dehydration.^{6h,i}

The steps from **5** to **4** and from **4** to **3** were confirmed by the control experiments (eq 1). Moreover, when the transformation was performed in the presence of H_2O^{18} , the ^{18}O -labeled product was not detected (eq 2), indicating that the oxygen atom of the carbonyl group of the product **3** originated from carbon dioxide.



In conclusion, we have demonstrated, for the first time, a carbon dioxide triggered and Cu-catalyzed domino process for the synthesis of highly substituted 3(2H)-furanones from propargylic alcohols and nitriles. This current approach shows certain advantages due to its low cost, the readily available catalyst and starting materials, and its simple experimental procedure. Work to improve the catalyst efficiency and expand the substrate range, as well as further experiments to investigate the mechanism of this reaction, is now in progress in our laboratory.

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Supporting Information Available. Experimental procedures and characterization of compounds **3aa–3af**. This material is available free of charge via the Internet at <http://pubs.acs.org>.