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Copper-Catalyzed Domino Rearrangement/Dehydrogenation Oxidation/Carbene Oxidation for One-Pot Regiospecific Synthesis of Highly Functionalized Polysubstituted Furans

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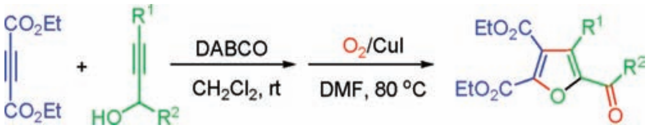
ABSTRACT



A novel and efficient method for the regiospecific synthesis of polysubstituted furan aldehydes/ketones has been developed via a copper(I)-catalyzed rearrangement/dehydrogenation oxidation/carbene oxidation sequence of 1,5-enynes in situ formed from alkynols and diethyl but-2-ynedioate under atmospheric pressure. The domino reaction proceeds smoothly under mild conditions with commercially available catalysts and affords highly functionalized furans in moderate to good yields.

The development of new domino processes that construct highly functionalized polysubstituted organic compounds from easily available starting materials is an important goal of synthetic chemistry and also represents a continuing challenge.[1] Recently, transition-metal-catalyzed domino processes have been widely examined for the synthesis of polysubstituted furans,[2] which have appeared as key structural units in many important pharmaceuticals[3] and bioactive natural products.[4] To achieve this goal, we are particularly attracted to the possibilities of combining fundamental reaction strategies to access highly functionalized polysubstituted furans[5] that are difficult to be accessed by other protocols. In this context, we wish to report a new type of domino process—copper(I)-catalyzed rearrangement/dehydrogenation oxidation/carbene oxidation[6] sequence of 1,5-enynes which are formed in situ from alkynols and diethyl but-2-ynedioate.

We began by treating 1,5-enyne (**3a**), the adduct of **1a** with **2a** in the presence of a catalytic amount of DABCO

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(1) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Taylor, R. J. K.; Reid, M.; Foot, J.; Raw, S. A. *Acc. Chem. Res.* **2005**, *38*, 851. (c) Ikeda, S. *Acc. Chem. Res.* **2000**, *33*, 511. (d) Tietze, L. F.; Kinzel, T.; Brazel, C. C. *Acc. Chem. Res.* **2009**, *42*, 367. (e) Kim, B. G.; Snapper, M. L. *J. Am. Chem. Soc.* **2006**, *128*, 52. (f) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (g) Mallagaray, I.; Domínguez, G.; Gradillas, A.; Castells, J. P. *Org. Lett.* **2008**, *10*, 597. (h) Bertrand, M. B.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 4661.

(2) (a) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 5195. (b) Ma, S.; Li, L. *Org. Lett.* **2000**, *2*, 941. (c) Pearlman, B. A.; McNamara, J. M.; Hasan, I.; Sekizaki, H.; Kishi, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4248. (d) Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925. (e) Yao, T. L.; Zhang, X. X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (f) Hu, Y. H.; Zhang, Y.; Yang, Z.; Fathi, R. *J. Org. Chem.* **2002**, *67*, 2365.

(3) (a) Cacchi, S. *J. Organomet. Chem.* **1999**, *576*, 42. (b) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955.

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(5) (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (b) Zinsmeister, H. D.; Becker, H.; Eicher, T. *Angew. Chem., Int. Ed.* **1991**, *30*, 130. (c) Miki, K.; Yokoi, T.; Nishino, F.; Ohe, K.; Uemura, S. *J. Organomet. Chem.* **2002**, *645*, 228. (d) Miki, K.; Yokoi, T.; Nishino, F.; Kato, Y.; Washitake, Y.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 1557.

10.1021/ol900364y CCC: $40.75

(10 mol %),[7] with 2.5 mol % of $AgBF_4$[8] or CuI in DMF at 80 °C. It is unexpected that different polysubstituted furan rings, **3aa** and **4aa**, were obtained highly regiospecifically (Scheme 1). Since rare general procedures are available for the synthesis of α-carbonyl polysubstituted furans, our attention was piqued by the potential of this novel transformation, which would make possible an expedient synthetic route for furan aldehydes/ketones. Hence, we decided to optimize the reaction conditions for the formation of formylfuran with **1a** and **2a** as substrates (Table 1).

Scheme 1. Ag- or Cu-Catalyzed One-Pot Synthesis of Furan Derivatives

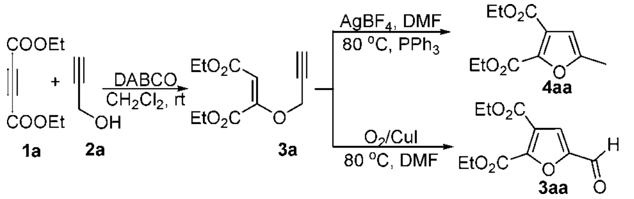
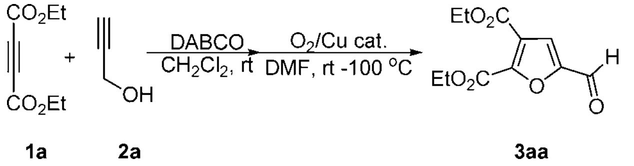


Table 1. Optimization of Reaction Conditions

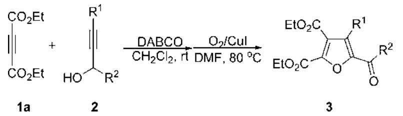


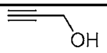
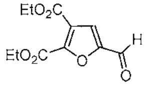
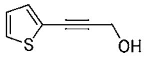
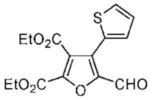
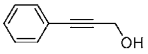
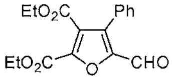
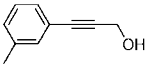
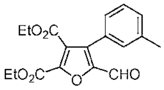
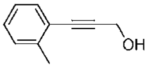
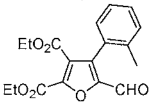
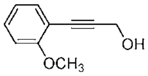
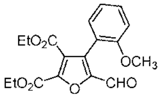
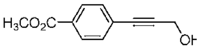
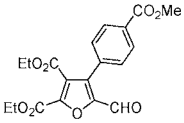
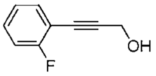
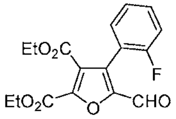
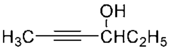
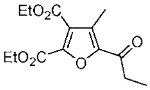
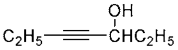
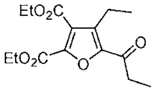
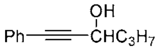
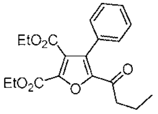
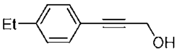
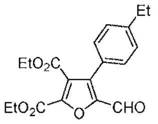
entry	Cu cat.	solvent	T (°C)	yield[a] (%)
1	CuCl	DMF	50	53
2	CuI	DMF	50	71
3	CuBr	DMF	50	62
4	CuO	DMF	50	19
5	Cu_2O	DMF	50	59
6	$CuBr_2$	DMF	50	23
7	CuI	CH_2Cl_2	50	45
8	CuI	toluene	50	44
9	CuI	THF	50	19
10	CuI	1,4-dioxane	50	27
11	CuI	DMF	rt	8
12	CuI	DMF	80	78
13	CuI	DMF	30	31
14	CuI	DMF	100	74

[a] Isolated yields.

Various copper catalysts were initially examined for the desired process to screen the optimal reaction conditions. In a typical procedure, **1a** (0.5 mmol), **2a** (0.5 mmol), and

Table 2. Cu(I)-Catalyzed One-Pot Synthesis of Furan



entry	alkynoates	alkynol	product (yield %)[a]
1	**1a**	 **2a**	 **3aa** (78)
2	**1a**	 **2b**	 **3ab** (68)
3	**1a**	 **2c**	 **3ac** (71)
4	**1a**	 **2d**	 **3ad** (67)
5	**1a**	 **2e**	 **3ae** (52)
6	**1a**	 **2f**	 **3af** (45)
7	**1a**	 **2g**	 **3ag** (69)
8	**1a**	 **2h**	 **3ah** (61)
9	**1a**	 $H_3C-\!\!\equiv\!\!-\overset{OH}{CH}C_2H_5$ **2i**	 **3ai** (57)
10	**1a**	 $C_2H_5-\!\!\equiv\!\!-\overset{OH}{CH}C_2H_5$ 2j	 **3aj** (54)
11	**1a**	 $Ph-\!\!\equiv\!\!-\overset{OH}{CH}C_3H_7$ **2k**	 **3ak** (59)
12	**1a**	 **2l**	 **3al** (64)

[a] Isolated yields.

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(6) For reveiws, see: (a) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (b) Raper, E. S. *Coord. Chem. Rev.* **1994**, *129*, 91. (c) Raper, E. S. *Coord. Chem. Rev.* **1985**, *61*, 115. For copper carbene complexes, see:(d) Kirmse, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 1088. For copper carbene oxidation, see: (e) Barluenga, J.; Riesgo, L.; Vicente, R.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2008**, *130*, 13528.

(7) Fan, M. J.; Lian, G. Q.; Liang, Y. M. *Tetrahedron* **2006**, *62*, 6782.

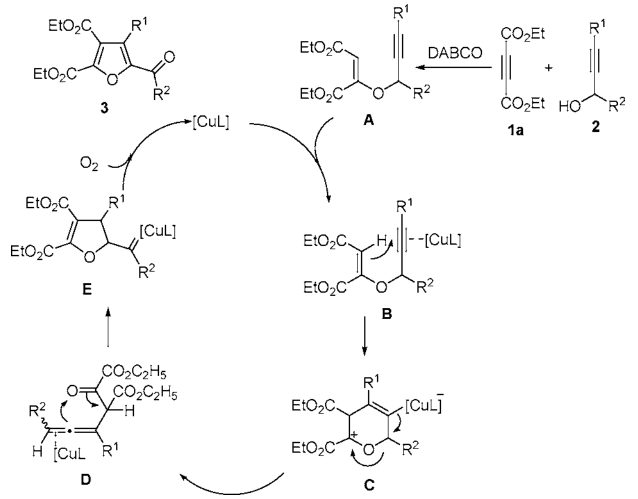
DABCO in CH_2Cl_2 were stirred for 10 min at room temperature, and then the solution was evaporated to dryness under reduced pressure. Subsequently, 2.5 mol % of CuCl and DMF were added at 50 °C. After completion of the reaction (monitored by TLC), **3aa** was isolated in 53% yield (entry 1). When CuI and CuBr were used as the catalyst, the reaction gave **3aa** in 71% and 62% yields, respectively (entries 2 and 3). Other catalysts were employed in the reaction but only led to moderate yields (entries 4−6). Different solvents and temperatures were also examined (entries 7−14), and the best result was obtained by using DMF at 80 °C (entry 12).

With the optimal reaction conditions in hand, that is, CuI as the suitable catalyst and DMF as the solvent, we next explored the scope of a one-pot regiospecific synthesis of polysubstituted furan aldehydes/ketones (Table 2). All of the substrates provided similar isolated yields for the formation of furan aldehydes/ketones. The reaction was found to tolerate a broad substitution range for R^1 and R^2 (including alkyl, aryl). We found that substituents presented on the para and meta positions of the aromatic group of an alkynol such as **2d**, **2g**, or **2l** have no negative effects on the reaction. However, if more sterically hindered ortho substitutents on an aromatic group such as **2e** or **2f** were employed, the corresponding products were obtained in lower yields. When other alkynoates, such as ethyl propiolate or ethyl but-2-ynoate, were used, no desired products were detected.

As Table 2 illustrated, susceptible aldehyde products were formed without further oxidation to acid, which indicated a direct carbene-oxidation process. Interestingly, the desired products were only detected with copper salt as a catalyst in anhydrous DMF under atmospheric pressure, which revealed that the oxygen atom of α-carbonyl furans originated from molecular oxygen.

On the basis of these experimental results, a tentative mechanistic interpretation of the preceding observations is proposed in Scheme 2. DABCO-promoted nucleoaddition of propargyl alcohol to electron-deficient alkynoates formed enyne adduct **A**.[7] A 6-*endo-dig* addition of the enol ether onto copper(I)−alkyne complex **B** resulted in the formation of intermediate **C**, which collapsed into the *β*-allenic ketone **D**.[9] Then, a rearrangement took place in which *β*-allenic ketone **D** was converted to carbene complex **E**[10] in the presence of a copper catalyst and air. Subsequently, carbene complex **E** underwent sequential dehydrogenation oxidation and carbene oxidation[11] with an oxygen metathesis to give **3** as the desired product.

Scheme 2. Plausible Reaction Mechanism



In summary, we have developed a new type of copper(I)-catalyzed domino process which proceeds through a rearrangement/dehydrogenation oxidation/carbene oxidation sequence of 1,5-enynes, which is formed in situ from alkynols and **1a** under atmospheric pressure. This domino process provides an efficient method for the regiospecific synthesis of furan aldehydes/ketones which are useful synthetic intermediates for bioactive compounds. Further studies into the scope and synthetic applications of this reaction are being carried out in our laboratory.

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Supporting Information Available: Experimental procedure and characterization of compounds **3aa**−**3al**. This material is available free of charge via the Internet at http://pubs.acs.org

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(8) It was also found that when $AgBF_4$ was used as a catalyst, normal furan product was produced; a similar result has been reported before:Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925.

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(11) (a) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **1999**, *121*, 11680. (b) Perdicchia, D.; Licandro, E.; Maiorana, S.; Vandoni, B.; Baldoli, C. *Org. Lett.* **2002**, *4*, 827. (c) Barluenga, J.; Andina, F.; Fernández-Rodríguez, M. A.; García-García, P.; Merino, I.; Aguilar, E. *J. Org. Chem.* **2004**, *69*, 7352. (d) Witham, C. A.; Mauleón, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838.