Cu(I) Catalyst in DMF: An Efficient Catalytic System for the Synthesis of Furans from 2-(1-Alkynyl)-2-alken-1-ones

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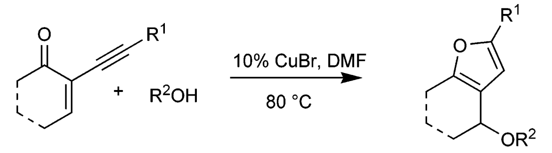
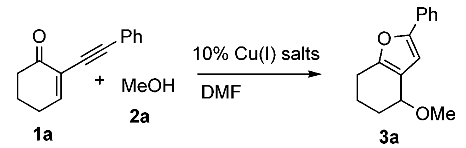


The cyclization of 2-(1-alkynyl)-2-alken-1-ones **1** proceeded very smoothly in the presence of alcohols **2** with a catalytic amount of Cu(I)Br in DMF at 80 °C, leading to the formation of highly substituted furans **3**. The catalytic system reported herein is easy to handle, compared to the previously known system wherein the reaction between **1** and **2** needed to use moisture sensitive gold(III) chloride.

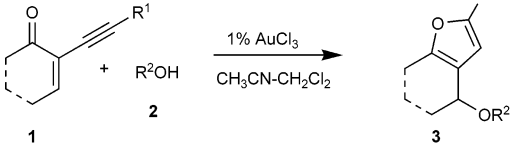
Furans are an important class of heterocyclic compounds which are extensively used as synthetic building blocks[1] and appear as a subunit in many natural products and substances of relevance for industry.[2] Considerable effort has been directed toward the development of new and efficient methodologies for the synthesis of furans.[3] One of the reliable approaches for the synthesis of this class of compounds is the cyclization of allenyl ketones and 3-alkyn-1-ones by use of transition metal catalysts.[4] Recently, an interesting $AuCl_3$-catalyzed cyclization of 2-(1-alkynyl)-2-alken-1-ones leading to substituted furans has been described (eq 1).[5] We believe that the reaction proceeds via the formation of an oxonium ion that is trapped by various nucleophiles to afford the corresponding products. Although this method is general, it employs a highly air-sensitive catalyst that requires special handling.

TABLE 1. Effect of Various Cu(I) Salts on the Formation of Furans[a]



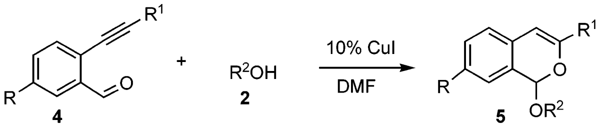
entry	catalyst (10%)	time (h)	NMR yield (%)[b]
1	none	12	0[c]
2	CuI	2	32
3	CuBr	2	85 (91)[c]
4	CuCl	2	42
5	$CuCl(PPh_3)$	2	trace
6	CuCN	2	11

[a] Methanol (0.3 mmol) was added to a solution of **1** (0.2 mmol) and catalyst (0.02 mmol) in DMF (0.2 mL) and the mixture was heated at 80 °C for the specified time. [b] Yields were determined by ^1H NMR spectroscopy with dibromomethane as an internal standard. [c] Isolated yields are shown in parentheses.

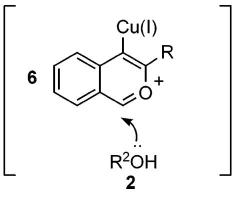


(1)

Previous work in our laboratories has shown that CuI in DMF is a highly effective catalytic system for the synthesis of cyclic alkenyl ethers **5** from acetylenic aldehydes **4**.[6] The proposed mechanism is that the resonance-stabilized oxonium ion **6**, formed by the nucleophilic attack of the aldehydic oxygen to the copper coordinated alkynes, is being trapped by alcohols to give the desired products (eq 2).



(2)



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[2] Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: New York, 1984; Vol. 4, pp 657−712.

[3] (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795−819. (b) Gilchrist, T. L. *Contemp. Org. Synth.* **1994**, *1*, 205−217. (c) Gilchrist, T. L. *Contemp. Org. Synth.* **1995**, *2*, 337−356. (d) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 615−628. (e) Hou, X. L.; Cheung, H. Y.; Hong, T. Y.; Kwan, P. L.; Lo, T.-H.; Tong, S.-Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955−2020. (f) Tae, J.; Kim, K.-O *Tetrahedron Lett.* **2003**, *44*, 2125−2128. (g) Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, *64*, 7687−7692. (h) Gabriele, B.; Salerno, G.; Pascali, F. D.; Costa, M.; Chiusoli, G. P. *J. Org. Chem.* **1999**, *64*, 7693−7699.

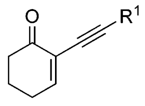
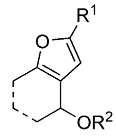
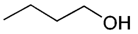
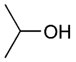
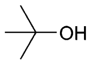
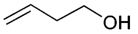
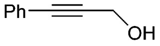
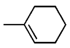
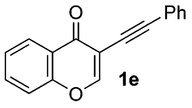
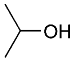
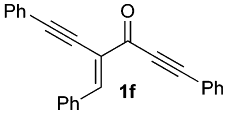
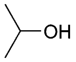
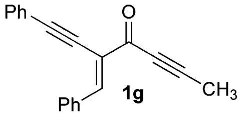
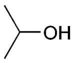
[4] (a) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285−2288. (b) Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1994**, *59*, 7169−7171. (c) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1991**, *56*, 960−969. (d) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816−5819. (e) Kel'in, A. V.; Gevorgyan, V. *J. Org. Chem.* **2002**, *67*, 95−98. (f) Hou, X. L.; Yang, Z.; Wong, H. N. C. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon Press: Oxford, UK, 2002; Vol. 14, pp 139−179. (g) Cacchi, S. *J. Organomet. Chem.* **1999**, *576*, 42−64.

[5] Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164−11165.

[6] Patil, N. T.;Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 5139−5142. For other reports on synthesis of the cyclic alkenyl ethers, see: (a) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028−9029. (b) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764−765. (c) Mondal, S.; Asao, N.; Nogami, T.; Yamamoto, Y. *J. Org. Chem.* **2003**, *68*, 9496−9498. (d) Yue, D.; Ca, N. D.; Larock, R. C. *Org. Lett.*, **2004**, 6, 1581−1584. (e) Wei, L.-L.; Wei, L.-M.; Pan, W.-B.; Wu, M.-J. *Synlett* **2004**, 1497−1502.

10.1021/jo050191u CCC: $30.25

TABLE 2. CuBr-Catalyzed Cyclization Reaction of 2-(1-Alkynyl)-2-alken-1-ones[a]

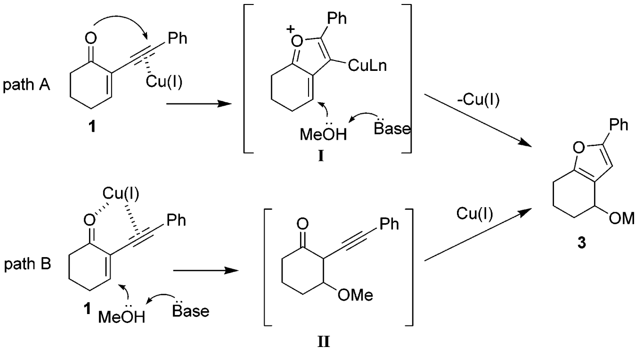
entry	substrate(**1**)	R^2OH (**2**)	product (**3**)	yield (%)[b]
		R^2OH		
1	**1a** R^1 = Ph	 **2b**	**3b**	66
2	**1a** R^1 = Ph	 **2c**	**3c**	62
3	**1a** R^1 = Ph	 **2d**	**3d**	complex mixture
4	**1a** R^1 = Ph	 **2e**	**3e**	66
5	**1a** R^1 = Ph	 **2f**	**3f**	43
6	**1b** $R^1 = C_6H_4$-*p*-CF_3	MeOH **2a**	**3g**	73
7	**1c** $R^1 = C_6H_4$-*p*-CH_3	MeOH **2a**	**3h**	76
8	**1d** R^1 = 	MeOH **2a**	**3i**	72
9	 **1e**	MeOH **2a**	**3j**	71
10	**1e**	 **2c**	**3k**	78
11	 **1f**	MeOH **2a**	**3l**	89
12	**1f**	 **2c**	**3m**	79
13	 **1g**	MeOH **2a**	**3n**	74
14	**1g**	 **2c**	**3o**	66

[a] The reactions of 2-(1-alkynl)-2-alken-1-ones **1** (0.2 mmol) with alcohols **2** (0.3 mmol) in the presence of CuBr (10 mol %) were carried out at 80 °C in DMF (0.2 mL). [b] Isolated yields.

We hypothesized that cyclization of 2-(1-alkynyl)-2-alken-1-ones **1** might also proceed under our previously developed catalytic system, i.e., Cu(I) in DMF. Indeed, our hypothesis proved correct and we report herein a detailed study on the Cu(I)-catalyzed cyclization of 2-(1-alkynyl)-2-alken-1-ones to substituted furans.

The results of varying the Cu(I) salts are summarized in Table 1. The reaction of **1a** with methanol **2a** at 80 °C in the absence of any catalyst did not yield any desired product, the starting material being decomposed (Table 1, entry 1). As anticipated, the use of a copper(I) catalyst such as CuI gave the desired product **3a**, albeit in 32% yield (entry 2). Surprisingly, when CuBr was employed as a catalyst, the desired product **3a** was isolated in 81% yield (entry 3). The use of other copper(I) catalysts such as CuCl, CuCl(PPh_3), and CuCN, however, was not satisfactory as judged by the ^1H NMR spectra of the crude reaction mixture (entries 4–6). The reason for the vary-

SCHEME 1. A Proposed Mechanism for the Cyclization of 2-(1-Alkynyl)-2-alken-1-ones



ing efficiencies by different Cu(I) salts is not clear at present.

The optimum reaction stoichiometry was found to be **1a**:**2a**:CuBr = 1:1.5:0.1 for the formation of **3a**. Next we investigated the annulation reaction of various 2-(1-alkynyl)-2-alken-1-ones **1**. The results are summarized in Table 2. Treatment of **1a** with *n*-butanol **2b** under the standard conditions gave the desired product **3b** in 66% yield (entry 1). The reaction of the secondary alcohol *i*-PrOH with **1a** proceeded smoothly to afford product **3c** in 62% yield (entry 2). However, in the case of *tert*-butyl alcohol **2d** a complex mixture of unidentified products was obtained indicating that tertiary alcohols are not suitable nucleophiles in this reaction (entry 3). Upon treatment with homoallyl alcohol **2e** and 3-phenyl-2-propyn-1-ol **2f**, the substrate **1a** underwent smooth annulation reactions giving rise to the corresponding furans **3e** and **3f** in 66% and 43% yields, respectively (entries 4 and 5). The substituent on the aromatic ring of R^1 does not affect the efficiency of the reaction. Thus when substrates **1b**, **1c**, and **1d** were treated with methanol under the standard conditions, the corresponding furans **3g**, **3h,** and **3i** were obtained in good yields (entires 6−8). Upon treatment with MeOH and *i*-PrOH, the substrate **1e** gave the products **3j** and **3k**, respectively, in high yields (entries 9−10). Employing 2-(1-alkynyl)-2-alken-1-ones **1f** as a substrate, the annulation proceeded well with methanol and *i*-PrOH to give the products **3*l*** and **3m** in 89% and 79% yield, respectively (entries 11 and 12). As mentioned in entries 13 and 14, the acyclic substrate **1g** underwent smooth annulation reactions with MeOH and *i*-PrOH to produce furans **3n** and **3o** in 74% and 66% yield, respectively.

A proposed mechanism is shown in Scheme 1. There are two conceivable pathways: (i) The nucleophilic attack of carbonyl oxygen to the copper coordinated alkynes[7] might result in the formation of the resonance stabilized oxonium ion **I** (path A),[8] which upon subsequent trapping with alcohols followed by protonation with regeneration of the Cu(I) catalyst produces the furans. (ii) The activation of carbonyl group occurs through the coordination of Cu(I) to carbonyl oxygen and the π-bond of the alkyne,[9] which increases the electrophilicity at the β-position thereby facilitating the addition of methanol in Michael addition fashion (path B) to form intermediate **II**. The alkynyl ketone intermediate **II** formed in this way might undergo in situ cyclization in the presence of Cu(I) salts to produce furans.[10] It should be noted that the reaction did not proceed in other organic solvents such as benzene, toluene, CH_2Cl_2, THF, 1,4-dioxane, etc. The use of DMF is essential for this reaction. This observation indicates that DMF may act as a Lewis base that deprotonates a proton from methanol thereby facilitating the nucleophilic addition of methanol. Although it is very difficult to determine the precise reaction pathway, we believe the former mechanism since the metal-catalyzed formation of oxonium ion is well-known in the literature[8] for these types of substrates.

In conclusion, we have applied our newly developed catalytic system, Cu(I) salts in DMF, for the efficient cyclization of 2-(1-alkynyl)-2-alken-1-ones, which leads to the formation of highly functionalized furans. Although relatively high temperature (80 °C) was needed for the complete reaction, the availability of inexpensive Cu(I) salts and avoidance of drybox use compares favorably with the previously reported gold-catalyzed reaction. Further applications of this catalytic system are being investigated in our laboratory.

Experimental Section

^1H and ^{13}C spectra were operated at 400 and 100 MHz, respectively, all referenced to internal tetramethylsilane (TMS) at 0.0 ppm. Reactions were monitored by thin-layer chromatography (Merck 60 F_{254}). Column chromatography was performed on neutral silica gel (60N, 100−210 μm) and elution with a hexane/AcOEt, 99:1, solvent system. All substrates **1a**−**g** were prepared by the known literature procedures from readily available alkenones and alkynes.[5] MeOH, *i*-PrOH, and DMF were purchased from "Wako Pure Chemical Industries Ltd" and used as such without further drying. Cu(I)Br was purchased from Aldrich. The catalyst was weighed and added to the reaction in the air.

The preparation of **3a** is representative. To a mixture of 2-(1-alkynyl)-2-alken-1-one **1a** (0.040 g, 0.2 mmol), MeOH (0.010 g, 0.3 mmol), and Cu(I)Br (0.003 g, 0.02 mmol) was added DMF (0.2 mL) and the resulting solution was stirred until the disappearance of starting material on TLC at 80 °C. Water (10 mL) was added and the product was extracted with ethyl acetate. The extracts were washed with water and dried over anhydrous

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[7] The complexation between alkyne and Cu(I) salts is known, see: (a) Macomber, D. W.; Rausch, M. D. *J. Am. Chem. Soc.* **1983**, *105*, 5325−5329. More recently such complexation has been applied to the synthesis of alkynylcopper, see: (b) Ito, H.; Arimoto, K.; Sensui, H.-O.; Hosomi, A. *Tetrahedron Lett.* **1997**, *38*, 3977−3980. (c) Ikegashita, K.; Nishihara, Y.; Hirabayashi, K.; Mori, A.; Hiyama, T. *Chem. Commun.* **1997**, 1039−1040. (d) Nishihara, Y.; Ikegashita, K.; Mori, A.; Hiyama, T. *Chem. Lett.* **1997**, 1233−1234. (e) Nishihara, Y.; Ikegashita, K.; Mori, A.; Hiyama, T. *Tetrahedron Lett*. **1998**, *39*, 4075−4078. (f) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.-I.; Mori, A.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 1780−1787. (g) Nishihara, Y.; Takemura, M.; Mori, A.; Osakada, K. *J. Organomet. Chem.* **2001**, *620*, 282−286.

[8] Such type of transition metal catalyzed oxonium ion formation is known in the case of the compound containing alkynes tethered with carbonyl groups, see: (a) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto. Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650−12651. (b) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc*. **2004**, 126, 7458−7459. (c) Sato, K.; Yudha, S. S., Asao, N.; Yamamoto, Y. *Synthesis* **2004**, *9*, 1409−1412. (d) Asao, N.; Nogami, T.; Lee, S.; Yamamoto Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921−10925. (e) Kusama, H.; Funami, H.; Shido, M.; Hara, Y.; Takaya, J.; Iwasawa N. *J. Am. Chem. Soc.* **2005**, *127*, 2709−2716. (f) Zhu, J.; Germain, A. R.; Porco, J. A., Jr. *Angew. Chem.*, *Int. Ed.* **2004**, *43*, 1239−1239.

[9] The simultaneous coordination of copper(I) salts to the π-bond of alkynes and heteroatoms is known, see: Kamijo, S.; Yamamoto, Y. *J. Org. Chem.* **2003**, *68*, 4764−4771.

[10] (a) Kelin, A. V.; Gevorgyan, V. *J. Org. Chem.* **2002,** *67*, 95−98. (b) Reference 5.

sodium sulfate. The solvent was removed, and the residue was then filtered through a short silica gel column with hexane/AcOEt, 99:1, as eluent to give pure product **3a** (0.037 g, 81%).

Acknowledgment. N.T.P. thanks the Japan Society for the Promotion of Science (JSPS) for a postdoctoral research fellowship.

Supporting Information Available: Experimental details, characterization data of compounds **3b**, **3c**, **3e**, **3g**, **3h**, **3k**, **3m**, and **3o** and ^{1}H NMR of spectra of all compounds **3a**–**o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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