JOC*Note*

Novel Synthesis of 2-Oxo-3-butynoates by Copper-Catalyzed Cross-Coupling Reaction of Terminal Alkynes and Monooxalyl Chloride

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Abstract: A general and efficient Cu(I)-catalyzed cross-coupling reaction of terminal alkynes and monooxalyl chloride for the synthesis of 2-oxo-3-butynoates and 2-oxo-3-butynoamides was developed. Readily available starting materials, the mild reaction conditions, wide functional group tolerance, and the obviation of stoichiometric organolithium or magnesium reagents combine to highlight this reaction.

2-Oxo-3-butynoic esters **1** constitute an important class of organic compounds due to their unique structure with multiple functional groups and potential use as irreversible inhibitors of brewer's yeast pyruvate decarboxylase.[1a] Several methods have been reported for the synthesis of 2-oxo-3-butynoates.[1] Of all of the reported methods, the direct coupling between acetylenic compounds and oxalic ester derivatives was most straightforward. However, due to the high reactivity of the oxalate substrate and the product in the presence of the acetylenic lithiums or Grignard reagents, neither acetylenic lithiums nor Grignard reagents can be used as nucleophile to react with readily available oxalic ester derivatives **2a**−**c**.[2] Activated oxalic ester derivatives, such as **2d**[1a] and **2e**,[1c] were used for a limited scope. However, they are expensive; they ultimately are derived from oxalate. We are interested in the synthesis of 2-oxo-3-butynoate using oxalate or oxalic acid chloride.

Cuprous iodide is a cheap and readily available but versatile transition metal reagent. Besides its role as cocatalyst in some palladium-catalyzed reactions, copper(I)-mediated reactions have also been explored in recent years.[3,4] The stoichiometric reaction of organocoppers and acyl chlorides has been reported as a general method for the construction of ketones.[5] The catalytic version of this reaction has also been realized in the acylation of terminal alkynes. However, the catalytic reaction has been sporadically studied and is highly substrate-dependent compared with the stoichiometric one.[6]

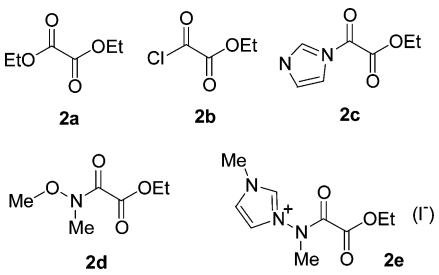
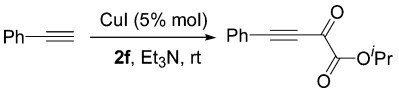


FIGURE 1. Possible intermediates for 2-oxo-3-butynoic esters.

TABLE 1. Cu(I)-Catalyzed Cross-Coupling Reaction of Phenylacetylene and Isopropyl Oxalyl Chloride[a]



entry	catalyst	solvent	ligand	yield (%)[b]
1	CuI	Et_3N	no	27
2	CuI	DMF	no	0
3	CuI	Toluene	no	30
4	CuI	CH_3CN	no	32
5	CuI	CH_2Cl_2	no	43
6	CuI	THF	no	77
7	CuOTf	THF	no	0
8	CuBr	THF	no	67
9	CuCl	THF	no	71
10	CuI	THF	dppe	53
11	CuI	THF	dppb	58
12	CuI	THF	bpy	69
13	CuI	THF	Phen[c]	57

[a] All of the reactions were carried out with phenylacetylene (1 mmol), isopropyl oxalyl chloride (1.2 mmol), Et_3N (2 mmol), and Cu(I) salt (5 mol %) in a specified solvent with or without ligand at room temperature for 12 h. [b] Isolated yield. [c] Phen = 1,10-phenanthroline.

(1) Chiu, C. C.; Jordan, F. *J. Org. Chem.* **1994**, *59*, 5763. (b) Katritzky, A. R.; Lang, H. *J. Org. Chem.* **1995**, *60*, 7612. (c) Heras, M. A.; Vaquero, J. J.; García-Navio, J. L.; Alvarez-Builla, J. *J. Org. Chem.* **1996**, *61*, 9009.

(2) Hauptmann, H.; Mader, M. *Synthesis* **1978**, 307.

(3) Copper-catalyzed coupling reaction of aryl halides: (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (b) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803. (c) Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269. (d) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (e) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973. (f) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (g) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459. (h) Jeffery, T. *Tetrahedron Lett.* **1989**, *30*, 2225. (i) Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1992**, *33*, 5363. (j) Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716.

(4) A stoichiometric amount of copper used in the arylations of terminal alkynes has been reported and is known as the Castro reaction: (a) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 2163. (b) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313. (c) Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071. (d) Ogawa, T.; Kusume, K.; Tanaka, M.; Hayami, K.; Suzuki, H. *Synth. Commun.* **1989**, *19*, 2199. (e) Castro, C. E.; Havlin, R.; Honwad, V. K.; Malte, A.; Mojé, S. *J. Am. Chem. Soc.* **1969**, *91*, 6464.

(5) Miller, M. J.; Lyttle, M. H.; Streitwieser, A., Jr. *J. Org. Chem.* **1981**, *46*, 1977. (b) Robin. R. *C. R. Hebd. Seances Acad. Sci. Ser. C* **1976**, *282*, 281; *Chem. Abstr.* **1976**, *85*, 32378a. (c) Normant, J.-F.; Bourgain, M. *Tetrahedron Lett.* **1970**, 2659. (d) Kraus, G. A.; Frazier, K. *Tetrahedron Lett.* **1978**, 3195. (e) Coutrot, P.; Grison, C.; Lachgar, M.; Ghribi, A. *Bull. Soc. Chim. Fr.* **1995**, 925. (f) Normant, J.-F.; Piechucki, C. *Bull. Chim. Soc. Fr.* **1972**, 2402. (g) Normant, J.-F.; Bourgain, M. *Bull. Chim. Soc. Fr.* **1973**, 2137.

(6) Chowdhury, C.; Kundu, N. G. *Tetrahedron Lett.* **1996**, *37*, 7323. (b) Chowdhury, C.; Kundu, N. G. *Tetrahedron* **1999**, *55*, 7011. (c) Wang, J.-X.; Wei, B.; Hu, Y.; Liu, Z.; Fu, Y. *Synth. Commun.* **2001**, *31*, 3527. (d) Zanina, A. S.; Shergina, S. I.; Sokolov, I. E.; Kotlyarevskii, I. L. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1990**, 2551. (e) Shergina, S. I.; Sokolov, I. E.; Zanina, A. S. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1992**, 158.

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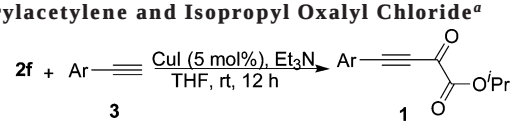
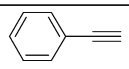
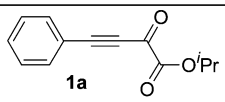
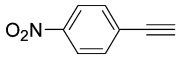
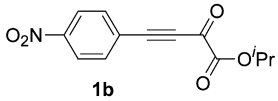
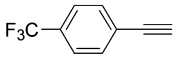
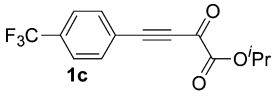
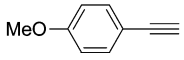
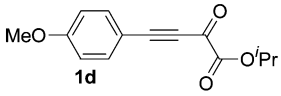
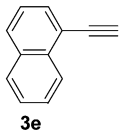
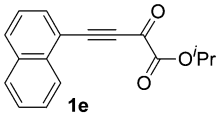
TABLE 2. Cu(I)-Catalyzed Cross-Coupling Reaction of Arylacetylene and Isopropyl Oxalyl Chloride[a]



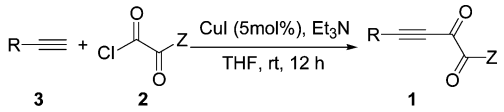
entry	alkyne (**3**)	product (**1**)	yield %[b]
1	 **3a**	 **1a**	77
2	 **3b**	 **1b**	43
3	 **3c**	 **1c**	45
4	 **3d**	 **1d**	85
5	 **3e**	 **1e**	91

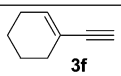
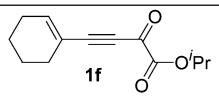
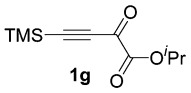
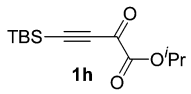
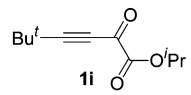
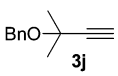
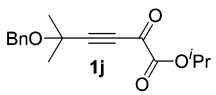
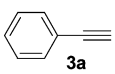
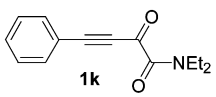
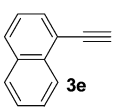
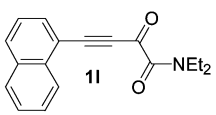
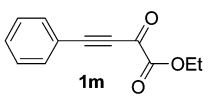
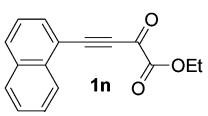
[a] All of the reactions were carried out with aryl acetylene (1 mmol), isopropyl oxalyl chloride (1.2 mmol), CuI (5 mol %), and Et_3N (2 mmol) in THF at room temperature for 12 h. [b] Isolated yield.

Within our recently initiated program on asymmetric transfer hydrogenation, 2-oxo-3-butynoate and its derivatives are needed as substrates. There is no report of transition metal-catalyzed coupling reaction to synthesize this type of compound in the literature. Initially, we applied the literature reaction conditions for the coupling of alkyne and acyl chloride[6] to the reaction between phenyl acetylene and isopropyl oxalyl chloride **2f** in the presence of 5 mol % of CuI in Et_3N; the desired product, 2-oxo-4-phenyl-3-butynoic acid isopropyl ester (**1a**), was isolated in 27% yield (entry 1, Table 1). This enlightening result prompted us to optimize the reaction conditions for this coupling reaction. Herein, we report our preliminary results on this copper-mediated coupling reaction.

For the coupling of alkyne and acyl chloride[6] reported in the literature, triethylamine is required as reaction solvent to obtain the best results; this limits the practical use of this reaction. To reduce the use of triethylamine, a variety of solvents were screened, and THF was found to be the best solvent as shown in Table 1. In the presence of 2 equiv of triethylamine, the reaction proceeded smoothly in THF at room temperature to give the desired product in 77% yield (entry 6, Table 1). To further improve the reaction efficiency, several ligands were used in the copper-catalyzed reaction; however, when 1 or 2 equiv of ligands (relative to Cu) was employed, no improvement was found under these conditions (entries 10−13, Table 1). Different copper(I) sources have also been examined; CuCl, CuBr, and CuI showed similar reactivity, while CuOTf was totally inert. Therefore, the optimized condition for the coupling reaction between terminal alkynes (1 mmol) and isopropyl oxalyl chloride (1.2 mmol) is using 5 mol % of CuI as catalyst in THF in the presence of 200 mol % of Et_3N.

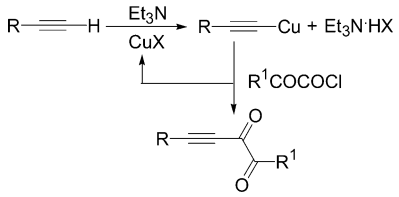
TABLE 3. Cu(I)-Catalyzed Cross-Coupling Reaction of Terminal Alkynes and Isopropyl Oxalyl Chloride or Diethylaminooxalyl Chloride[a]



entry	alkyne (**3**)	product (**1**)	yield %[b]
1	 **3f**	 **1f**	70
2	 **3g**	 **1g**	50
3	 **3h**	 **1h**	65
4	 **3i**	 **1i**	66
5	 **3j**	 **1j**	84
6	 **3a**	 **1k**	50
7	 **3e**	 **1l**	95
8	**3a**	 **1m**	67
9	**3e**	 **1n**	89

[a] All of the reactions were carried out with terminal alkynes (1 mmol), isopropyl oxalyl chloride, diethylaminooxalyl chloride, or ethyl oxalyl chloride (1.2 mmol), CuI (5 mol %), and Et_3N (2 mmol) in THF at room temperature for 12 h. [b] Isolated yield.

SCHEME 1. Possible Mechanism for the Coupling Reaction



A series of aryl acetylenes were subjected to the optimized reaction conditions to react with isopropyl oxalyl chloride, and the results are summarized in Table 2. Moderate to good yields were achieved with a variety of alkyne substrates. Electron-rich substrates (entries 4, 5, Table 2) gave better yields than those of electron-deficient ones (entries 2, 3, Table 2). It is noteworthy that substrate with a nitro group, which is intolerable to organolithium or organomagnesium reagents, is also compatible under these conditions to give a moderate yield.

Besides terminal aryl alkynes, this coupling reaction could also be successfully applied to many other types of alkynes (entries 1−5, Table 3), and good yields were achieved in most cases. However, 1-hexyne, methyl propargyl ether, and ethyl propiolate did not undergo this reaction under the same conditions. When diethylaminooxalyl chloride (**2g**) was used instead of isopropyl oxalyl chloride, alkynyl α-keto amides were obtained in good yields.[7] Therefore, this reaction is an efficient synthetic method for the synthesis of 2-oxo-3-butynoamides, which are difficult to make from the corresponding esters by transfer amidation or from the acids and amines due to the competitive Michael addition reaction.

A possible mechanism for this reaction is described in Scheme 1. The terminal alkyne reacts with cuprous iodide to give the alkynyl copper, which further reacts with isopropyl oxalyl chloride to give the 2-oxo-3-butynoic ester and regenerate the catalyst: cuprous chloride.

In conclusion, we have developed a general and efficient Cu(I)-catalyzed cross-coupling reaction of terminal alkynes and monooxalyl chlorides for the synthesis of 2-oxo-3-butynoates and 2-oxo-3-butynoamides. This is the first report employing a transition metal catalyst to make this type of compound. The readily available, cheap starting materials, mild reaction conditions, good substrate generality, wide functional group tolerance, and the obviation of stoichiometric lithium or magnesium reagents combine to make this method a most competitive alternative.

(7) Only two reports have been published about its synthesis: Chauvelier, J. *Bull. Soc. Chim. Fr.* **1966**, 1721, and ref 1b.

Experimental Section

General Procedure for the Cross-Coupling Reaction. An oven-dried Schlenk reaction tube equipped with a magnetic stirrer bar and a Teflon stopcock was evacuated while hot and allowed to cool under argon. The tube was charged in sequence with CuI (10.1 mg, 0.05 mmol), triethylamine (0.28 mL, 2 mmol), and THF (5 mL). Once a colorless clear solution formed, the alkyne (1 mmol) and monooxalyl chloride (2 mmol) were added and the reaction was allowed to proceed at room temperature. When the reaction was completed, saturated aqueous $NaHCO_3$ (5 mL) and diethyl ether (20 mL) were added. The reaction system was allowed to partition, and the organic phase was dried with Na_2SO_4, filtered, and concentrated on a rotary evaporator. The residue was purified by silica gel chromatography to give the cross-coupling product.

1a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 6.3 Hz, 2 H), 7.53 (t, J = 7.5 Hz, 1 H), 7.42 (t, J = 7.5 Hz, 2 H), 5.21 (hept, J = 6.3 Hz, 1 H), 1.41 (d, J = 6.3 Hz, 6 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.9, 158.7, 133.7, 131.7, 128.7, 119.0, 97.7, 87.1, 71.6, 21.4; MS m/z 216 (M^+), 130 (13), 129 (100), 101 (8), 75 (16); IR (neat) 2202, 1753, 1737 cm^{-1}; HRMS calcd for $C_{13}H_{12}O_3$ 216.0786, found 216.0778.

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Supporting Information Available: Experimental details and analytical data for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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