Coupling Reactions

A Straightforward and Mild Synthesis of Functionalized 3-Alkynoates**

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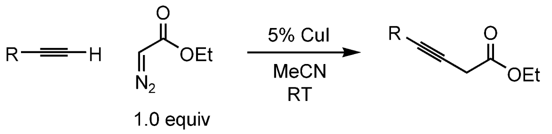
The methods that have been described to date for the synthesis of 3-alkynoates generally require multiple steps and/or highly basic reaction conditions.[1] One very attractive route to 3-alkynoates would be by the coupling of readily available terminal alkynes with diazoesters. Unfortunately, in the absence of a catalyst, treatment of alkynes with diazo compounds preferentially generates cyclopropenes and C_{alkyl}–H insertion products.[2] With respect to metal-catalyzed processes,[3] in the presence of rhodium complexes, reactions of terminal alkynes with diazo compounds lead not to insertion into the $C_{alkynyl}$–H bond, but typically to cyclopropenation.[4] In the case of copper, the only synthetically useful couplings that have been reported are also methods for cyclopropenation;[5] a few groups have observed the formation of a 3-alkynoate, but none of the procedures is general, elevated temperatures are employed, and the yields are modest (0–45 %).[6]

In this communication we describe the development of a versatile method for coupling alkynes with diazocarbonyl compounds to produce 3-alkynoates [Eq. (1)]. Some noteworthy attributes of the system include its efficiency (1:1 ratio of reactants), mildness (room temperature), simplicity (no additional ligand), and functional-group tolerance (e.g., alkenes, heteroatoms, and hydroxy groups).



(1)

In an initial study, we explored the reaction of phenylacetylene with ethyl diazoacetate. In the presence of copper complexes such as CuCl, CuOTf, CuCN, CuSCN, Cu_2O, and CuOAc, we obtain essentially none of the target 3-alkynoate

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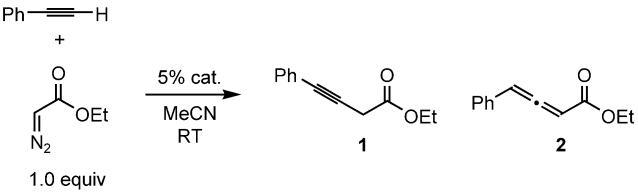
(Table 1, entry 1). In contrast, CuBr and CuI are effective catalysts for the desired transformation (entries 2 and 3). The choice of solvent is critical: use of *i*PrOH, THF, dioxane, acetone, or $CHCl_3$ leads to a significantly lower yield (< 10 %).[7]

Table 1: Catalysts tested for the synthesis of 3-alkynoates **1** from alkynes and diazoesters.



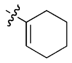
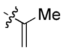
Entry	Catalyst	**1** [%][a]	**2** [%][a]
1	CuCl, CuOTf, CuCN, CuSCN, Cu_2O, CuOAc	< 5	< 5
2	CuBr	70	5
3	CuI	90	8

[a] Yields were determined by NMR spectroscopy vs. an internal standard (average of two runs).

Interestingly, cyclopropenation of the alkyne is not a detectable side reaction for the CuBr- or CuI-catalyzed processes (< 5 %). Furthermore, the formation of fumarate and maleate side products, a complication that plagues many copper-catalyzed reactions of diazoesters, is minimal (< 5 %), thereby allowing the use of a 1:1 mixture of alkyne:diazoester, without slow addition of the diazoacetate.[8] We do, however, observe a small quantity of the allene isomer (**2**) of the 3-alkynoate.[9]

We have determined that CuI-catalyzed coupling of terminal alkynes with diazoesters provides a general route to 3-alkynoates (Table 2).[10] Thus, aryl- (entry 1), alkyl- (entry 2), hindered alkyl- (entry 3), functionalized alkyl- (entry 4), and silyl-substituted (entry 5) alkynes are all suitable substrates. Formation of the desired 3-alkynoate proceeds in preference not only to cyclopropenation of an alkyne, but also to cyclopropanation of an alkene (entries 6 and 7). Furthermore, neither Lewis-basic groups such as sulfides and ethers, which could react with a copper carbene to form ylides (entries 8–10),[11] nor hydroxy groups, which could undergo O–H insertion (entry 11),[12] interfere with the reaction.

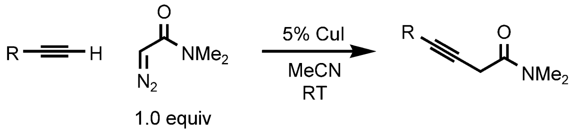
Table 2: Copper-catalyzed couplings of alkynes with a diazoester [Eq. (1)].

Entry	R	Yield [%][a]
1	Ph	76
2	CH_2Ph	74
3[b,c]	*t*Bu	98[e]
4	$CH_2CH_2CO_2Et$	87[e]
5[b]	TMS	84
6		71
7		58
8	CH_2SPh	56
9	CH_2SEt	63
10	CH_2OTHP[d]	87[e]
11	CH_2OH	75[f]

[a] Yields of isolated products (average of two runs), unless otherwise noted. [b] 10 % CuI was used. [c] 1.2 equiv of alkyne was used. [d] THP = tetrahydropyranyl. [e] Contains 3–5 % of the allene isomer. [f] Yield was determined by NMR spectroscopy vs. an internal standard.

In certain instances, we have experienced difficulty removing the allene side product from the target 3-alkynoate (e.g., Table 2, entries 3, 4, 10, and 11). To address this purification issue, as well as to explore the scope of the coupling with respect to other diazo compounds, we examined the reaction of alkynes with a diazoamide ($N_2CHCONMe_2$). We were pleased to observe that CuI is also an effective catalyst for these couplings (Table 3);[13] as for reactions of diazoesters, a small amount of the allene is produced, but this is readily removed by flash chromatography.

Table 3: Copper-catalyzed couplings of alkynes with a diazoamide.



Entry	R	Yield [%][a]
1[b]	*t*Bu	70
2	$CH_2CH_2CO_2Et$	71
3	CH_2OMe	57
4	CH_2OTHP	81
5	CH_2OH	54

[a] Yields of isolated products (average of two runs). [b] 1.1 equiv of alkyne was used.

In conclusion, a general, metal-catalyzed intermolecular coupling of terminal alkynes with diazo compounds has been developed, providing ready access to 3-alkynoates. It is noteworthy that this carbon–carbon bond-forming reaction proceeds efficiently under nonbasic conditions at room temperature with a simple and inexpensive catalyst, and that an array of potentially reactive functional groups are tolerated.

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Keywords: alkynes · copper · diazo compounds · homogeneous catalysis

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[1] For some examples, see: a) S.-i. Usugi, H. Yorimitsu, H. Shinokubo, K. Oshima, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2687–2690; b) R. M. Williams, D. J. Aldous, S. C. Aldous, *J. Org. Chem.* **1990**, *55*, 4657–4663; c) J. Hooz, R. B. Layton, *Can. J. Chem.* **1972**, *50*, 1105–1107.
[2] For a discussion, see: O. M. Nefedov, E. A. Shapiro, A. B. Dyatkin in *Supplement B: The Chemistry of Acid Derivatives, Vol. 2* (Ed.: S. Patai) Wiley, New York, **1992**, pp. 1527–1528.

[3] M. P. Doyle, M. A. McKervey, T. Ye in *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, **1998**.

[4] For leading references, see: a) reference [3], Chapter 4.11; b) M. N. Protopopova, E. A. Shapiro, *Russ. Chem. Rev.* **1989**, *58*, 667 – 681.

[5] For a discussion and leading references, see: M. M. Díaz-Requejo, M. A. Mairena, T. R. Belderrain, M. C. Nicasio, S. Trofimenko, P. J. Pérez, *Chem. Commun.* **2001**, 1804 – 1805.

[6] a) V. E. Baikov, L. P. Danilkina, K. A. Ogloblin, *Russ. J. Gen. Chem.* **1983**, *53*, 2172 – 2173; b) E. A. Shapiro, I. E. Dolgii, O. M. Nefedov, *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1980**, *29*, 1493 – 1499; c) I. E. Dolgii, E. A. Shapiro, O. M. Nefedov, *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1974**, *23*, 929; d) M. Vidal, M. Vincens, P. Arnaud, *Bull. Soc. Chim. Fr.* **1972**, 657 – 665; e) V. K. Jones, A. J. Deutschman Jr. , *J. Org. Chem.* **1965**, *30*, 3978 – 3980.

[7] The observed solvent effects may be due in part to the relative solubility of CuI.

[8] For a discussion of this problem, see p. 6 of: T. Rovis, D. A. Evans, *Prog. Inorg. Chem.* **2001**, *50*, 1 – 150. The typical remedy is to use a large excess of the substrate (e.g., as the solvent) and to employ slow addition of the diazo compound.

[9] The 3-alkynoate:allene ratio does not change as the reaction progresses, which suggests that the 3-alkynoate is not an intermediate in the formation of the allene.

[10] The isomeric allene is the only identifiable side product.

[11] For an early example, see: G. Pourcelot, L. Veniard, P. Cadiot, *Bull. Soc. Chim. Fr.* **1975**, 1281 – 1283. See also reference [3], Chapter 7.

[12] This result is particularly noteworthy in light of a recent report of selective O–H insertion upon reacting propargyl alcohol with ethyl diazoacetate in the presence of a CuTp catalyst (Tp = a homoscorpionate ligand): M. E. Morilla, M. J. Molina, M. M. Díaz-Requejo, T. R. Belderrain, M. C. Nicasio, S. Trofimenko, P. J. Pérez, *Organometallics* **2003**, *22*, 2914 – 2918.

[13] We have not optimized the reaction conditions for the reactions in Table 3; they are the same as those used for the reactions in Table 2.