

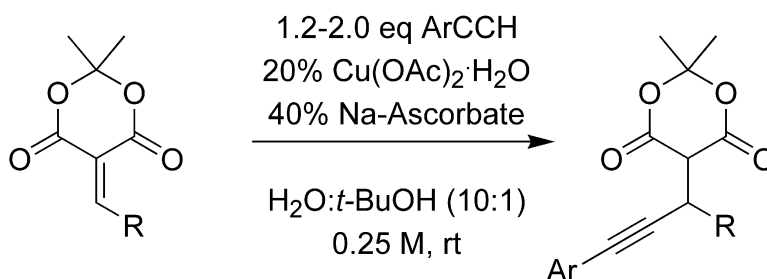
Communication

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 Catalytic in Copper: Conjugate Addition of Alkynes in Water**

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The First Conjugate Addition Reaction of Terminal Alkynes Catalytic in Copper: Conjugate Addition of Alkynes in Water

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The conjugate addition of carbanions to α,β -unsaturated carbonyls is a powerful strategy for C–C bond formation.¹ Of the various metal-based methods documented, those involving Cu(I) in catalytic or stoichiometric quantities have preeminence.² An important development in the history of organocopper chemistry was the observation that alkynyl-substituents on organocuprates do not undergo conjugate additions. This has led to their use as dummy ligands or placeholders on cuprates,³ permitting the selective transfer of alkyl or alkenyl groups in the course of conjugate addition reactions. Although this opened up possibilities for the effective use of organocuprates in complex molecule synthesis, it also has precluded the use of copper acetylides in conjugate additions. This is unfortunate, because such additions can provide access to γ,δ -alkynoates, which are versatile, useful building blocks for organic synthesis. Herein, we document that alkynyl copper reagents generated under aqueous conditions from terminal acetylenes, catalytic Cu(OAc)₂, and sodium ascorbate undergo additions to Meldrum's acid-derived Michael acceptors at room temperature (Scheme 1). The additions are not only novel, but also constitute the first example of the conjugate addition reaction of an acetylde catalytic in copper.

The addition of acetylides to unsaturated carbonyl acceptors is considerably underrepresented in the list of available methods for conjugate reactions. In this regard, the additions of aluminum,^{4–6} boron,^{5,7} and zinc alkynylides to unsaturated acceptors have been documented, with the last of these requiring the use of an activator such as *t*-BuMe₂SiOTf.⁸ Copper acetylides are observed to undergo conjugate addition to unsaturated ketones and aldehydes, albeit under forcing conditions in the presence of an excess (1.5 equiv) of both LiI and TMSI⁹ or *t*-BuMe₂SiOTf,¹⁰ under the typical conditions involving rigorous exclusion of oxygen and moisture. It is important to note that, in all of the cases cited above, acetylde is generated as a separate step, following deprotonation and transmetalation, thus requiring the use of stoichiometric quantities of at least one metal.^{11,12}

We have documented reaction methods for the in situ metalation of terminal acetylenes under mild conditions and their reaction with C=O and C=N electrophiles.^{13–15} In an effort to extend the useful reactions of such alkynes, we have been interested in studying their use in conjugate addition reactions. Of the various acceptors that could be employed in conjugate addition reactions, the condensation products of Meldrum's acid¹⁶ and aldehydes seemed particularly attractive as Michael acceptors for a number of reasons: (1) they are prepared from commercially available, inexpensive Meldrum's acid and aldehydes in water by simple heating;¹⁷ (2) after conjugate addition, the adducts may be converted to the corresponding β -alkynyl acids; and (3) the symmetry of these acceptors makes irrelevant the geometry of the olefin in the starting material.¹⁸ Although Meldrum's acid-derived alkylidenes have been used as Michael acceptors for Grignard additions,¹⁹ these involve the use

Scheme 1

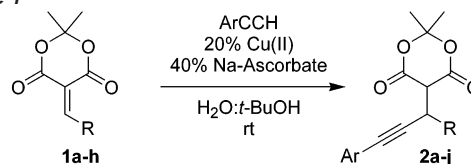


Table 1. Effect of the Counterions on the Cu-Catalyzed Conjugate Addition Reaction of PhC≡CH to **1a** (R = *i*-Pr)^a

entry	copper(II) source	yield
1	CuSO ₄ (H ₂ O) ₅	55%
2	CuCl ₂ (H ₂ O) ₂	31%
3	Cu(OAc)₂(H₂O)	78%
4	Cu ₂ (CO ₃)(OH) ₂	6%
5	Cu ₃ (PO ₄) ₂ (H ₂ O) ₂	4%
6	Cu(acac) ₂	45%

^a The addition reactions were conducted using 20 mol % Cu(II) salt, 1.2 equiv of PhC≡CH, and 40 mol % sodium ascorbate in 10:1 water/*t*-BuOH at 23 °C.

of stoichiometric quantities of an organometal, which is incompatible with aqueous reaction media.

It is known that in the presence of a base and Cu(I) salts, terminal acetylenes are converted to the corresponding alkynylides in water; however, if oxygen is not excluded, Cu(I)-acetylides participate in oxidative Glaser coupling.²⁰ In an effort to mitigate this side reaction, at the outset of our investigations, we decided to examine the generation and reaction chemistry of Cu(I)-alkynyl reagents prepared from Cu(II) salts in the presence of sodium ascorbate, a known reductant for Cu(II) to Cu(I).^{21,22} We anticipated that such a procedure would not only lead to a facile generation of Cu(I)-alkynylides avoiding the handling of sensitive Cu(I) salts, but also, significantly, serve prophylactically to preclude oxidative acetylde coupling. In preliminary experiments, in a 1:1 H₂O:*t*-BuOH mixture of 0.5 equiv of CuSO₄ pentahydrate and 2.5 equiv of sodium ascorbate, phenyl acetylene undergoes addition to acceptor **1a** (R = *i*-Pr) to give **2a** in 34% yield.

Encouraged by this lead result, we undertook a thorough investigation of the reaction conditions. We were pleased to find that the use of lower loadings of Cu(II) and sodium ascorbate as well as changing the solvent ratio led to improved yields. Examination of various copper salts was also undertaken (Table 1). The counterion associated with Cu(II) proved to have a significant influence on the reaction yield. Optimal results for the addition of PhC≡CH (1.2 equiv) to **1a** were obtained when 20 mol % Cu(OAc)₂ monohydrate in 10:1 water/*t*-BuOH was used, furnishing **2a** in 78% yield.

Under optimized conditions, a number of substrates have been investigated (Table 2). A variety of substituents, aromatic and heteroaromatic (entries 2–8), branched (entry 1) and unbranched (entry 10) aliphatic, as well as alkenes, can be tolerated on the acceptor. Importantly, in the case of $\alpha,\beta,\gamma,\delta$ -diene acceptors, only

Scheme 2

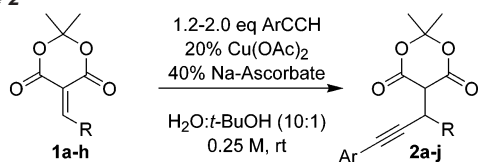


Table 2. Conjugate Addition of Terminal Alkynes to Meldrum's Acid-Derived Acceptors^a

entry	acceptor/R	adduct/Ar	time (h)	yield ^d
1	1a <i>i</i> -Pr	2a Ph	8.5	78%
2	1b Ph	2b Ph	3	85%
3	1b Ph	2c 2-furyl	4	70%
4	1b Ph	2d <i>p</i> -Br-C ₆ H ₄	4	72%
5	1c <i>p</i> -MeO-C ₆ H ₄	2e Ph	26	96%
6	1d <i>p</i> -NO ₂ -C ₆ H ₄	2f Ph	22	55%
7	1e <i>p</i> -Cl-C ₆ H ₄	2g Ph	22	88%
8	1f 2-furyl	2h Ph	31	85%
9	1g (<i>E</i>)-PhCH=CH	2i Ph	42	98%
10	1h Et	2j Ph	9	65%

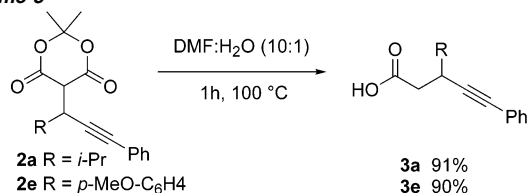
^a For all entries, the conditions outlined in Scheme 2 were utilized; for entries 1–4, 1.2 equiv of alkyne was employed; for entries 5–10, 2.0 equiv of alkyne was used.

1,4-addition is observed (entry 9). Both electron-rich and -poor aromatic groups are tolerated on the alkyne including heteroaromatics (entries 3, 4).²³

A number of observations are worth highlighting, as they underscore the unusual reactivity aspects of the system. In this respect, the reaction does not proceed in the absence of either ascorbate or Cu(II) salts (or both). Under conditions where oxygen is rigorously excluded, Cu(I)-alkynyls generated (terminal alkyne + CuOAc) in degassed water fail to undergo conjugate addition to **1b**.²⁴ As such, the ascorbate may play an important role that goes beyond reducing Cu(II). Moreover, the use of water as solvent is critical for the success of the reaction. Thus, the conjugate addition is not just a process that works in organic solvents and can coincidentally be carried out in water; indeed, as the water content is diminished by the addition of organic cosolvents, the reactivity of the system falls off.

An attractive feature of the adducts isolated is their ready conversion to β -alkynyl carboxylic acids. Thus, as is typified by the reactions of **2a** and **2e**, simple heating in a DMF/water solution furnishes alkynyl acids **3a** and **3e** in 91% and 90% yield, respectively (Scheme 3).

Scheme 3



In summary, we have documented the first conjugate addition of alkynes that is catalytic in copper. Importantly, the reaction proceeds with derivatives of Meldrum's acid (<\$0.5/g) under aqueous conditions in the presence of Cu(OAc)₂ (<\$20/kg) and sodium ascorbate (<\$40/kg).²⁵ The convenience with which the starting materials are accessed (Meldrum's acid + aldehydes in H₂O with heating) as well as the simplicity of the reaction conditions (room temperature, H₂O/*t*-BuOH) provide access to a class of compounds that can serve as useful building blocks for synthesis, but have otherwise been difficult to access. Moreover, the reaction is fundamentally new, opening up opportunities for a class of

carbanionic reagents that had been previously relegated as unreactive, or "dummy ligands".

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Supporting Information Available: Experimental procedures and spectral data for all products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (23) At the current level of development, aliphatic substituted alkynes afford 5–10% yield adduct with **1b**, and enynes such as 2-methyl-1-buten-3-yne furnish 20% yield of the corresponding adduct.
- (24) In our current working model, we believe that a Cu-acetylide is the key reactive intermediate. Preliminary observations involving the effect on the reaction of adding known ligands for copper are consistent with such a species.
- (25) Prices quoted are those for bulk quantities of material.

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