Conjugate Addition

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Cu$^{\text{I}}$-Catalyzed Conjugate Addition of Ethyl Propiolate**

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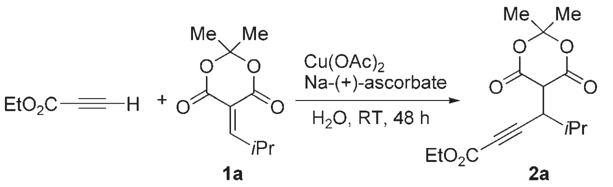
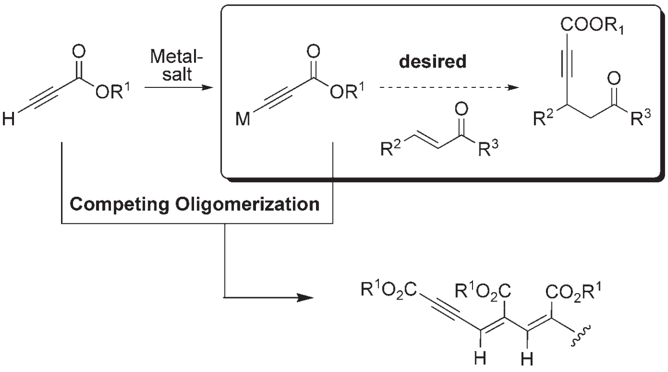
Conjugate addition of carbon nucleophiles to acceptors constitutes an important strategy for the construction of C–C bonds in chemical synthesis.[1] This can be appreciated in the significant strides that the field has recently witnessed for alkyl, alkenyl, and aryl nucleophiles. However, conjugate additions involving acetylides by contrast remain relatively underexplored, especially as it concerns functionalized alkynes. Herein we document a remarkably selective process in which ethyl propiolate is employed as a nucleophile in conjugate addition reactions to Meldrum's acid derived acceptors [Eq. (1)]. The reaction is noteworthy because it documents for the first time the selective activation of propiolates using substoichiometric quantities of a Cu salt and, significantly, it involves the use of copper propiolates in catalytic, chemoselective additions to Michael acceptors in the presence of propiolate and the product alkynoate, both of which are excellent electrophiles.



(1)

There are only limited number of examples for the conjugate additions of metal alkynylides.[2] In this regard, the conjugate additions of copper alkynylides have presented a particular challenge,[3] because of the known property of alkynilides to bind to copper as nontransferable ligands.[4] Recently, we have disclosed copper(I)-catalyzed conjugate additions of acetylenes to Meldrum's acid derived acceptors under very mild conditions.[5] In addition, the reaction could be rendered enantioselective in the presence of a new P,N ligand, albeit the process was reported to be limited to aryl acetylenes.[5b]

We have been interested in expanding the versatility of this process with respect to the nature of the acetylide component.[6] The ability to carry out C–C bond formation with acetylenes possessing useful functionality would not only expand the scope of the reaction but also facilitate the synthetic elaborations that can be carried out on the products. In this regard, particularly attractive terminal alkynes to consider are the esters derived from propiolic acid, itself prepared from CO$_2$ and acetylene, or welding gas. Although nucleophilic addition reactions of lithiated propiolates to carbonyl compounds have been the subject of recent intense study by Crimmins et al.,[7] the conjugate addition of propiolates has not, to the best of our knowledge, been reported to date. In recent studies, Koide and co-workers have elegantly demonstrated the generation and use of silver acetylides in C=O addition reactions.[7c] In their pioneering work, the reaction of $Ag\text{-}C{\equiv}CCO_2Et$ with cinnamaldehyde in the presence of [Cp$_2$ZrCl$_2$] provided only the 1,2-addition product. It stands to reason that the conjugate addition reaction of metalated propiolates to acceptors would present a unique set of obstacles (Scheme 1). The first of these is that although the metal propiolates may be generated in analogy to the silver acetylides, the carbanionic species are sufficiently unreactive that additional activation (e.g. [Cp$_2$ZrCl$_2$]) would be necessary for subsequent conjugate addition. Of greater concern, however, is the fact that the reactant (propiolate) and alkynoate products of the reaction include an alkynoate acceptor. Indeed, it is known that propiolates are themselves excellent acceptors for conjugate additions of various nucleophiles.[8,7c] Moreover, the starting metal acetylide can participate in self-addition reactions to form oligomeric products.[8a] Finally, potential pitfalls aside, as part of our program on the chemistry of metal acetylides, the generation of metallated propiolates and their reaction in a catalytic process was of fundamental interest.



Scheme 1. Reaction pathways available to metalated propiolates.

In a preliminary screening for reactivity, we were delighted to find that adduct **2a** can be obtained under mild conditions involving the combination of a Cu$^{\text{II}}$ salt and

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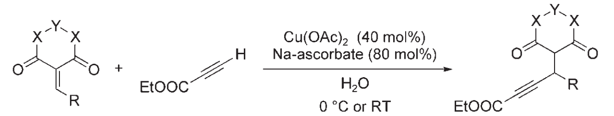
sodium ascorbate in water. These conditions are similar to those that we have employed previously for aryl acetylides and those that have been used in the cycloaddition reaction of terminal acetylenes and azides.[9] Following optimization of the reaction conditions, differently substituted acceptors were allowed to react with ethyl propiolate (Table 1). For substrates **1b** and **1d**–**g**, the reactions were carried out at 5 °C, because these substrates slowly undergo hydrolysis at room temperature (entries 2 and 4–7, Table 1). Acceptors with linear, branched, and cyclic alkyl substituents provided moderate to good yields of the addition products. The reactions with **1f** and **1g** went to completion to afford the addition product **2f** and **2g**, respectively (entries 6 and 7, Table 1). However, the chromatographic purification of these adducts led to substantial decomposition. Therefore, these adducts were subjected to alkyne reduction to give the saturated products **5f** and **5g**, which were stable [Eq. (2)].

Table 1: Conjugate addition to achiral acceptors.[a]

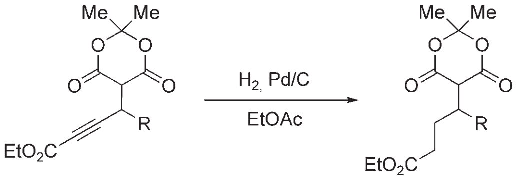


1a-g (X = O, Y = CMe$_2$)
3a (X = NMe, Y = CO)

2a-g (X = O, Y = CMe$_2$)
4a (X = NMe, Y = CO)

Entry	Substr.	R	Product	Yield [%]
1	**1a**	*i*Pr	**2a**	92
2[b]	**1b**	*c*-Hex	**2b**	84
3	**1c**	*c*-Pr	**2c**	65
4[b]	**1d**	Et	**2d**	54
5[b]	**1e**	*i*Bu	**2e**	90
6[b]	**1f**	$(CH_2)_2Ph$	**2f**	61[c]
7[b]	**1g**	*n*-pentyl	**2g**	74[c]
8	**3a**	*i*Pr	**4a**	75

[a] Reaction conditions: 40 mol% of Cu(OAc)$_2$, 80 mol% of ascorbate, and 10 equiv of ethyl propiolate for 48 h at RT. [b] Reactions conducted at 5 °C. [c] Yield of the saturated products **5** [see Eq. (2)].



2f (R = (CH$_2$)$_2$Ph)
2g (R = *n*-Pentyl)

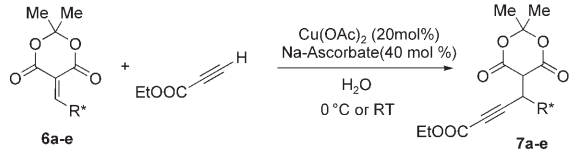
5f (61% from **1f**)
5g (74% from **1g**)

(2)

Interestingly, aryl- and alkenyl-substituted acceptors were unreactive under these conditions, and only the starting materials were recovered; thus they represent a limitation of the method at hand.[10] Barbituric acid derived acceptor **3a** can also be used as a substrate, and the adduct **4a** was isolated in good yield (entry 8, Table 1). To the best of our knowledge, this represents the first instance of the use of barbiturate-derived acceptors in conjugate addition reactions.

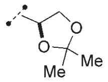
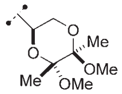
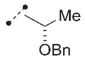
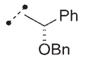
We examined next diastereoselective conjugate additions to Meldrum's acid acceptors (Table 2). The substrates were conveniently prepared from chiral aldehydes and Meldrum's acid by Knoevenagel condensation using a catalytic amount of piperidine.[11] With these acceptors in hand, we attempted the addition of propiolate under conditions similar to those described above. The reactions with substrates bearing γ-oxygen substituents were considerably faster than those in Table 1. Owing to the higher reactivity of these acceptors, the reaction time and Cu loading could be reduced. For example, the reaction with glyceraldehydes-derived acceptor **6a** reached completion within 4 h at 0 °C (entry 1, Table 2). More importantly, for the reactions with **6a**–**d**, the products **7a**–**d** were obtained as single diastereomers.[12]

Table 2: Conjugate additions to chiral acceptors.



6a-e

7a-e

Entry	Substr.	R*	Cond.	Prod.	Yield [%]	d.r.[a]
1	**6a**		0 °C, 4 h	**7a**	82	> 19:1
2	**6b**		RT, 2 h	**7b**	79	> 19:1
3	**6c**		0 °C, 24 h	**7c**	63	> 19:1
4	**6d**		0 °C, 24 h	**7d**	84	> 19:1

[a] Determined by H NMR spectroscopy.

The configuration at the newly created stereogenic center in the major diastereomer of **7b** was unambiguously established by X-ray crystallographic analysis (Figure 1).[13] Formation of the observed *syn* configuration may be explained by using the stereochemical model proposed by Yamamoto et al.[14] According to this model, the nucleophile would approach from the same face of the electrophile as the γ-oxygen in the reactive conformation wherein nonbonding 1,3-

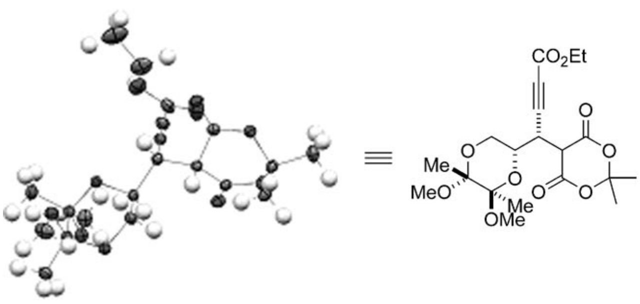
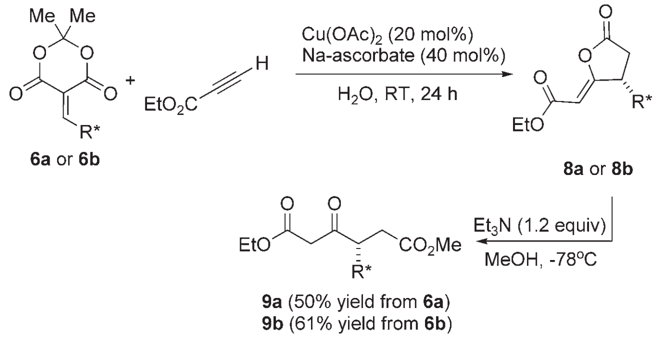


Figure 1. X-ray crystal structure of *syn*-**7b**.

allylic strain is minimized. This model has been used to explain the high *syn* selectivity observed in conjugate additions of various organocopper nucleophiles to acceptors.[15]

Additional observations made in the course of optimization studies are worth noting. Thus, when these reactions are carried out at room temperature and over extended periods, the conjugate adduct undergoes decarboxylation (Scheme 2).[16] In this regard, subjection of **6a** and **6b** to the copper-catalyzed addition reaction at room temperature leads to the quantitative formation of lactones **8a** and **8b**, respectively, after 24 h as single diastereomers. Treatment of these with triethylamine at low temperature affords keto diesters **9a** and **9b**. These alternative products will be useful building blocks for syntheses of biologically active molecules.



Scheme 2. Preparation of keto diesters **9a**,**b**.

In conclusion, a convenient method for copper-mediated conjugate addition of ethyl propiolate to Meldrum's acid derived acceptors has been developed. When the acceptor bears a γ-oxygen functionality, the reaction was significantly accelerated and these chiral acceptors underwent highly diastereoselective conjugate additions. The study expands the scope of conjugate addition reactions to include propiolates, giving products with functionality that can be further elaborated. Significantly and without precedence, we report for the first time the metalation of a propiolate ester using substoichiometric amounts of Cu^I, and use of the copper propiolate in reaction chemistry. The future extension of this work involves exploration of chiral ligands for this process and other types of acceptors. Finally, from a broader perspective, the ability to metalate propiolates under catalytic conditions may find applications in other synthetically important C−C bond-forming reactions.

Experimental Section

Representative procedure: A test tube (100 × 12 mm) equipped with a stir bar was charged with $Cu(OAc)_2$ (20 mg, 0.10 mmol, 0.4 equiv) and deionized water (0.4 mL). Sodium (+)-ascorbate (40 mg, 0.20 mmol, 0.8 equiv) was added to the stirring solution. The reaction mixture was stirred for 5 min, and during this time the solution turned brown initially and then orange. Ethyl propiolate (253 μL, 2.50 mmol, 10 equiv) was added to the reaction mixture, which was stirred for 10 min. During this time the color changed from orange to yellow. Then compound **1a** (48 mg, 0.25 mmol) was added, and the reaction mixture was stirred vigorously at room temperature for 48 h. The reaction mixture was diluted with saturated aqueous ammonium chloride (1 mL) and extracted with dichloromethane (10 mL × 3). The combined organic solutions were dried over Na_2SO_4, passed through a pad of Celite (40 mm × 1 cm), and concentrated. The residue was purified by chromatography (20 mm × 7 cm SiO_2, 3:1—1:1 hexane/EtOAc) to afford **2a** (68 mg, 92%) as a white solid.

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[12] For the reaction using the *tert*-butyldimethylsilyl(TBS)-protected analogue of **6c**, the reaction was very sluggish and the product was isolated as single diastereomer in only 15% yield. The result indicates that the approach of the nucleophile is hindered by the steric bulk of the substrate or the TBS group is preventing the possible coordination of copper propiolate to the γ-oxygen.

[13] See the Supporting Information. CCDC 635258 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[15] Coordination of the copper propiolate to the γ-oxygen of the acceptor may also be possible. Although the coordinating ability of organocopper reagents is considered insignificant compared to that of organolithium or -magnesium species, there is a striking reactivity difference in this reaction when the γ-oxygen is protected as TBS ether (see Ref. [12]).

[16] Decarboxylation may be facilitated by trace amount of Cu^{II} salt. A similar Au^{I}-catalyzed cyclization has been reported: A. Buzas, F. Gagosz, *Org. Lett.* **2006**, *8*, 515 – 518.