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Alkynoates as a Source of Reactive Alkylinides for Aldehyde Addition Reactions

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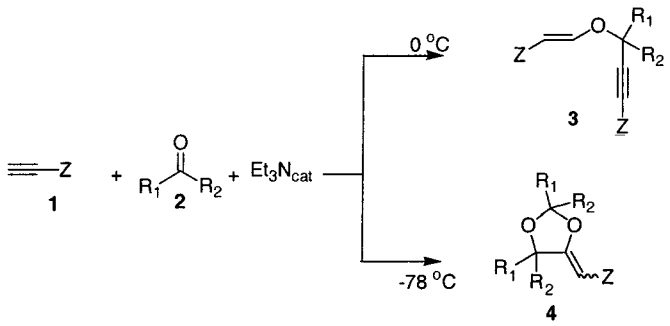
ABSTRACT



The reaction of activated alkynes with carbonyl compounds in the presence of a catalytic amount of a nucleophile leads to enol-protected functionalized propargyl alcohols and 1,3-dioxolane compounds by way of a mild carbon−carbon bond formation reaction.

The carbon−carbon bond-forming reaction using alkynes as a source of carbon nucleophiles is a useful method in organic synthesis.[1] Since alkynes possess a rich chemistry, the resulting coupled products are prone to undergo further transformations, making them versatile synthetic tools. However, most of the methods to form alkylinides employ the use of stoichiometric amounts of strong pyrophoric bases with terminal alkynes.[2] Because of their incompatibility with the electrophilic partner, alkylinides must be formed in a separate step.

Carreira[3a] has recently reported the catalytic activation of acetylene under mild conditions to form zinc acetylides

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Table 1. Results of the Reaction of Activated Alkyne Systems with Aldehydes in the Presence of a Catalytic Amount of Triethylamine[a]

			yield (%)				
			reaction conditions A[b] 0 °C	reaction conditions B[c] −78 °C			
entry	alkyne	carbonyl compound	**3**	**3**	**4**	**4Z** (*syn*:*anti*)[d]	**4E** (*syn*:*anti*)[d]
1	**1a**	**2a**	85	4	94	65 (5.3:1)	29 (4.6:1)
2	**1a**	**2b**	76	5	87	56 (5.2:1)	31 (3.1:1)
3	**1a**	**2c**	80	17 (6)[e]	70 (84)[e]	32 (2.3:1)	38 (1.6:1)
4	**1a**	**2d**	75	3	84	56 (5.5:1)	28 (3.0:1)
5	**1a**	**2d**	75[f]				
6	**1a**	**2e**	65	41 (28)[e]	13 (66)[e]	6 (21:1)	7 (5.1:1)
7	**1a**	**2f**	0	0	10[g]		
8	**1a**	**2g**	0[h]	0	90	90 (2.9:1)	
9	**1b**	**2a**	0[i]	0	82	19 (3.2:1)	63 (1.6:1)
10	**1b**	**2g**	0[j]	0	79[k]	79 (1.5:1)	
11	**1c**	**2a**	56[l]	0	93	93 (1.9:1)	
12	**1c**	**2g**	0	0	95	95 (3.0:1)	

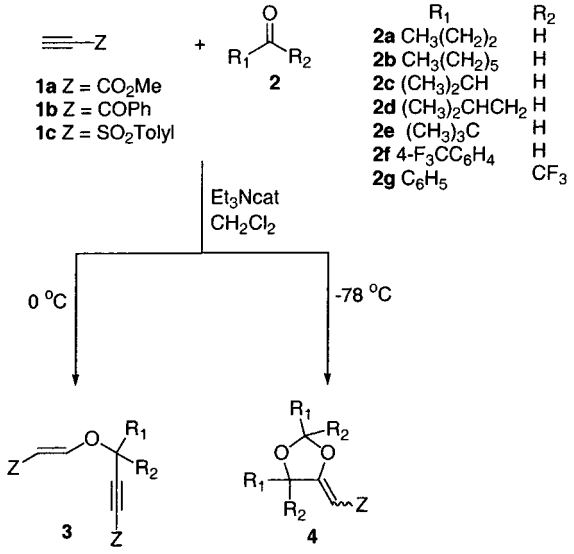
[a] See ref 6 for experimental procedure. Yield based on alkyne system. [b] 0.6 equiv of aldehyde. [c] 2 equiv of aldehyde. [d] Isomer ratios determined by integration of nonoverlapping signals in the ^{1}H NMR spectra. [e] 4.0 equiv of aldehyde. [f] 2.0 equiv of aldehyde. 5% mixture of 1,3-dioxolane compounds. [g] Product detected by ^{1}H NMR and partially purified by column chromatography. [h] 29% of 1,3-dioxolane compounds. [i] 23% of 1,3-dioxolane compounds. [j] 27% of 1,3-dioxolane compounds. [k] Allowed to warm to −30 °C, 6 h. [l] 4% of 1,3-dioxolane compounds. [m] 29% of 1,3-dioxolane compounds.

which in turn have been shown to add to nitrones, imines, and aldehydes, with the last products giving propargylic alcohols in a high enantiomeric ratio when chiral amino alcohols are employed. Knochel has independently reported on the activation of acetylenes with CsOH/DMSO, a process which proceeds in analogy to that reported with KOH/DMSO.[3b]

An alternative way to activate the terminal C−H bond could be the use of α,β-unsaturated alkyne systems. On the basis of this idea, we wish to report our results when these systems are reacted with carbonyl compounds in the presence of a catalytic amount of a nucleophile. The addition of heteronucleophiles to α,β-unsaturated alkynones or alkynoates is well documented in the literature,[4] but there are no reports of the reaction in a catalytic fashion. Recently, Kataoka[5] has reported the catalytic Lewis acid promoted heteronucleophile addition to α,β-unsaturated alkynones or alkynoates in the presence of aldehydes to produce Baylis−Hillman adducts in good yields.

We have found that, depending on the reaction temperature, the reaction of methyl propiolate **1** with aldehydes **2** in the presence of a catalytic amount of triethylamine as the nucleophile produces either enol-protected functionalized propargyl alcohols **3** or 1,3-dioxolane compounds **4** (Scheme 1), in good yields (Table 1). The 1,3-dioxolane compounds

Scheme 1



are formed as racemic mixtures of four diastereoisomers: **Z**-*syn*, **Z**-*anti*, **E**-*syn*, and **E**-*anti*. The stereochemical assignment of the 1,3-dioxolane diastereoisomers was made by ^{1}H and ^{13}C NMR correlation experiments and fully confirmed by X-ray diffraction studies of the acid derivative of ***Z***-*syn* 1,3-dioxolane **4**, Z = CO_2Me, R_1 = $CH_3(CH_2)_5$, R_2 = H.

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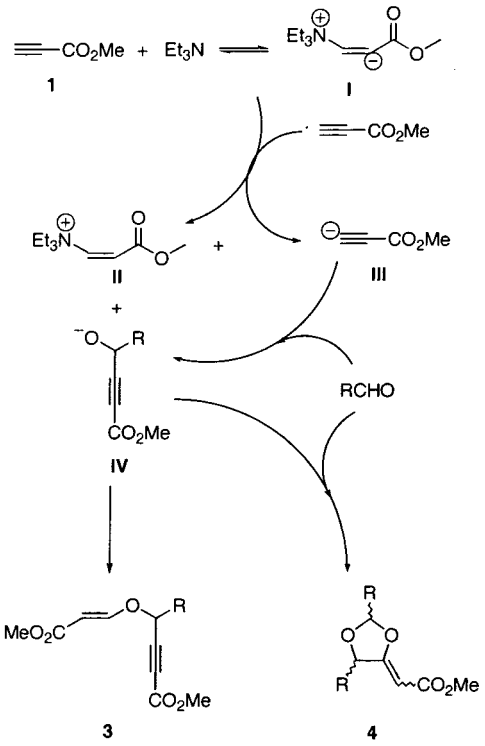
Scheme 2. Proposed Mechanism for the Formation of **3** and **4**



Under reaction conditions A, at 0 °C, methyl propiolate combines with the aldehyde in a 2:1 stoichiometric ratio, furnishing the enol-protected functionalized propargyl alcohols **3**. On the other hand, under reaction conditions B, at −78 °C, the methyl propiolate and the aldehyde react in a 1:2 stoichiometric ratio, affording the 1,3-dioxolane compounds **4**. It seems that there is no significant dependence on the amount of aldehyde used when the reaction is carried out at 0 °C. When an excess of 2 equiv of aldehyde is used at 0 °C, only 5% of the cyclized compound **4** is observed (Table 1, entry 5). However, for more hindered aldehydes, an excess of electrophiles is required in order to improve the yield in 1,3-dioxolane compounds at −78 °C (Table 1, entries 3 and 6). Intriguingly, the activated aromatic aldehydes do not react at 0 °C and only 10% of 1,3-dioxolane compounds are observed at −78 °C (Table 1, entry 7), and with the activated ketone trifluoroacetophenone **2g** cyclized compounds are formed either at 0 °C or at −78 °C (Table 1, entry 8).

The use of other unsaturated alkyne systems such as alkynone **1b** and alkyne sulfone **1c** gave some unexpected results (Table 1, entries 9−12) which seem to support that the idea of a subtle mechanism operating in this process. At 0 °C only **1c** produced the enol-protected propargyl alcohol in moderate yield when reacted with butyraldehyde **2a**. However, at −78 °C both **1b** and **1c** react either with the aldehyde **2a** or the activated ketone **2g** to form the 1,3-dioxolane compounds **4** in good to excellent yield.

At present, the reaction mechanism is not clear. One of the tentatively proposed mechanisms is depicted in Scheme 2. The nucleophile triggers the reaction by Michael type nucleophilic addition at the triple bond. Next the vinylammonium carbanion **I** formed reacts in an acid−base sense with another molecule of methyl propiolate producing the vinylammonium **II** and the acetylide **III** which adds to the aldehyde. The evolution of the intermediate **IV** strongly depends on the reaction temperature: at 0 °C **IV** reacts with the vinylammonium intermediate **II** to afford the enol-protected propargyl alcohol **3** while at −78 °C it combines with a molecule of aldehyde and, after a Michael type cyclization step, the 1,3-dioxolane compound forms.

In summary, a novel reactivity pattern allows the putative formation of an acetylide species, under mild controlled experimental conditions, which can be diverted to two distinctly and highly functionalized compounds at will. The reaction provides highly functionalized compounds that prove to be of great significance in generating diversity in combinatorial libraries[7] and the development of multicomponent transformations.[8]

Applications and scope of this reaction are being studied in our laboratory. Preliminary results show that the 1,3-dioxolane compounds **4** are easily transformed into γ-butyrolactones[9] by way of a stereoconvergent hydrolysis reaction

(6) **Experimental procedure.** Reaction conditions A: To a solution under nitrogen atmosphere of methyl propiolate (3.90 mmol) and butyraldehyde (2.34 mmol) in dry DCM (10 mL) cooled to 0 °C was added triethylamine (fractionally distilled) (1.95 mmol). The reaction mixture was stirred for 2 h and then quenched with 1 M HCl (5 mL). After extracting with DCM (3 × 10 mL), the organic layers were dried over anhydrous sodium sulfate. After removing the solvent at reduced pressure, the products were purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 90/10) to yield **3**. Selected spectroscopic data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93 (t, 3H, J = 7.4 Hz), 1.44−1.52 (m, 2H), 1.81−1.88 (m, 2H), 3.67 (s, 3H), 3.75 (s, 3H), 4.61 (t, 1H, J = 6.6 Hz), 5.34 (d, 1H, J = 12.5 Hz), 7.51 (d, 1H, J = 12.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.30, 159.74, 152.89, 98.89, 82.85, 78.35, 70.08, 52.67, 50.95, 36.27, 17.90, 13.24. IR ($CHCl_3$, cm^{-1}) 2242.3, 1716.0, 1646.1, 1625.8. Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.11; H, 6.57. MS, *m*/*z* (relative intensities) 240 (M+, 5.2), 181 (22), 139 (100), 107 (24), 79(22). 397 mg (85%). Reaction conditions B: To a solution under nitrogen atmosphere of methyl propiolate (2.58 mmol) and butyraldehyde (5.17 mmol) in dry DCM (10 mL) cooled to −78 °C was added triethylamine (fractionally distilled) (1.29 mmol). The reaction mixture was stirred for 2 h and then quenched with 1 M HCl (5 mL). After extracting with DCM (3 × 10 mL), the organic layers were dried over anhydrous sodium sulfate. After removing the solvent at reduced pressure, the products were purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 90/10) to yield **4** in 94% yield as a mixture of diastereoisomers: **4*Z*** 65% (5.3:1, *syn*:*anti*) and **4*E*** 29% (4.6:1, *syn*:*anti*). The geometric ***E*** isomers were an inseparable mixture. Selected spectroscopic data: ^{1}H NMR ($CDCl_3$, 500 MHz): **E**-*syn* δ 0.93 (t, 3H, J = 7.6 Hz), 0.95 (t, 3H, J = 7.5 Hz), 1.39−1.51 (m, 4H), 1.59−1.68 (m, 1H), 1.68−1.74 (m, 2H), 2.02−2.09 (m, 1H), 3.64 (s, 3H), 5.10 (dt, 1H, J = 8.3, 2.1 Hz), 5.29 (t, 1H, J = 7.8 Hz), 5.32 (d, 1H, J = 1.8 Hz). Characteristic of **E**-*anti* δ 5.23 (d, 1H, J = 1.2 Hz), 5.35 (dm, 1H, J = 9.6 Hz), 5.42 (t, 1H, J = 4.7 Hz). **Z**-*syn* δ 0.93 (t, 3H, J = 7.6 Hz), 0.94 (t, 3H, J = 7.6 Hz), 1.41−1.55 (m, 4H), 1.56−1.63 (m, 1H), 1.64−1.74 (m, 1H), 1.74−1.88 (m, 2 H), 3.66 (s, 3H), 4.51 (dd, 1H, J = 7.7, 3.4 Hz), 4.75 (d, 1H, J = 1.4 Hz), 5.36 (t, 1H, J = 4.7 Hz). Characteristic of **Z**-*anti* δ 4.69 (dd, 1H, J = 8.5, 4.0 Hz), 4.77 (s, 1H), 5.60 (t, 1H, J = 4.9 Hz). **Z**-*syn* δ 167.24, 165.97, 108.31, 85.60, 79.99, 50.82, 35.15, 34.16, 18.11, 16.51, 13.70. IR ($CHCl_3$, cm^{-1}) 1709.8, 1667.9. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.17; H, 8.86. MS, *m*/*z* (relative intensities) 228 (M$^+$, 30), 186 (55), 185 (30), 157 (27), 127(37), 114 (100), 101 (65), 84 (25), 69 (68), 55 (24).

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of all diastereoisomers. Nonetheless, the stereoselective version of the reaction is being addressed and the results as well as mechanistic studies will be published in due course.

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Supporting Information Available: Experimental procedure and analytical and spectroscopic data for compounds **3** and **4**. X-ray data for the acid derivative of **4** ***Z-syn*** $Z = CO_2Me$, $R_1 = CH_3(CH_2)_5$, $R_2 = H$. This material is available free of charge via the Internet at http://pubs.acs.org.

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