Preparation of α-Bromoacrylates: One-Pot Procedure for the Synthesis of Conjugated Acetylenic Carboxylates from Aldehydes with Ph_3P/Br_3CCO_2Et

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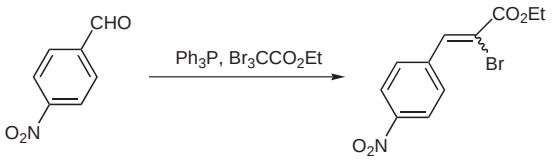
Abstract: We have established the optimal conditions for the Wittig reaction for synthesizing α-bromoacrylates with a high selectivity, and developed a simple and efficient one-pot procedure for preparing various conjugated acetylenic carboxylates in moderate to high yields.

Key words: α-bromoacrylate, conjugated acetylenic carboxylate, aldehyde, Wittig reaction

Conjugated acetylenic carboxylates are important intermediates that have been used for synthesizing a variety of cyclic compounds and pharmaceutical agents.[1] There are two approaches to preparing conjugated acetylenic carboxylates. One of them introduces substituents to triple bonds by the reaction of acetylides with electrophiles[2] and by metal-catalyzed cross-coupling reactions.[3] The other approach forms the triple bond itself by the reaction of appropriate substrates. It includes dehydrohalogenation of dihalo esters[4] and α-haloacrylates[5] and dehydration of β-keto esters.[6] However, they often suffer from unsatisfactory yields, expensive and toxic reagents, and lengthy procedures. Herein, we report on an efficient one-pot procedure for synthesizing the conjugated acetylenic carboxylates from aldehydes with Ph_3P and Br_3CCO_2Et via α-bromoacrylates.

α-Bromoacrylates are usually prepared by bromination–dehydrobromination sequence, but the method requires toxic reagents.[7] The Wittig reaction of aldehydes with bromophosphoranes is an attractive and convenient method for the synthesis of α-bromoacrylates.[8] However, the hazardous reagents such as molecular bromine are necessary for the preparation of bromophosphoranes. Burton et al. reported that the reaction of aldehydes with a mixture of Ph_3P and Br_3CCO_2Et produces α-bromoacrylates.[9] We attempted to prepare α-bromoacrylates under these reaction conditions. Treatment of *p*-nitrobenzaldehyde with Ph_3P/Br_3CCO_2Et in CH_2Cl_2 afforded the desired α-bromoacrylates in poor yield (Table 1, entry 1). This result prompted us to investigate the reaction to find out its optimal reaction conditions. The reaction was carried out in common organic solvents such as CH_2Cl_2, MeCN, benzene, DMF, and THF to examine the solvent effect. As presented in Table 1, the yields of the desired product depended significantly on the kind of solvents. The reaction afforded the α-bromoacrylate in high yield with high stereoselectivity when the reaction was carried out in THF (entries 5–7).

Table 1 Reaction of *p*-Nitrobenzaldehyde with a Mixture of Ph_3P and Br_3CCO_2Et under Various Conditions[a]



Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	CH_2Cl_2	r.t.	24	32
2	MeCN	r.t.	24	22
3	benzene	r.t.	24	0
4	DMF	r.t.	24	3
5	THF	r.t.	6	83 (96:4)[c]
6[d]	THF	r.t.	6	45 (94:6)[c]
7	THF	reflux	3	90 (96:4)[c]

[a] The reaction was carried out with Ph_3P (4 equiv) and Br_3CCO_2Et (2 equiv).
[b] Isolated yields based on the aldehyde.
[c] *Z*/*E* ratio was determined by ^1H NMR analysis.
[d] The reaction was carried out with Ph_3P (2 equiv) and Br_3CCO_2Et (1 equiv).

A number of aldehydes were subjected to our standard Ph_3P/Br_3CCO_2Et conditions. As shown in Table 2, the reaction of aromatic aldehydes with an electron-withdrawing group gave higher yields of the corresponding acetylenic carboxylates than the reaction of aldehydes with an electron-donating group (Table 2, entries 1–4). Heteroaromatic aldehydes such as 2-furaldehyde and 2-thiophenecarboxaldehyde afforded the corresponding conjugated acetylenic carboxylates in high yields (entries 5 and 6). Aliphatic aldehydes were less reactive than aromatic aldehydes, but the stereoselectivity still remained high (entries 7 and 8). Less reactive aldehydes such as aliphatic aldehydes required a prolonged reaction time. Ke-

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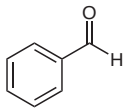
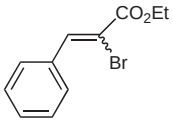
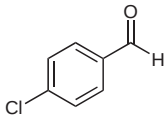
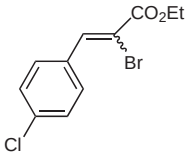
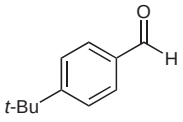
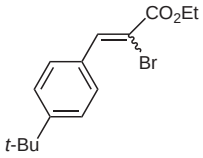
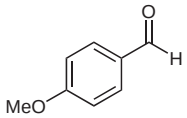
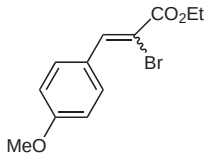
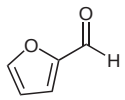
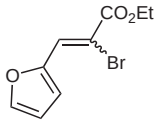
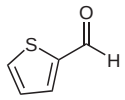
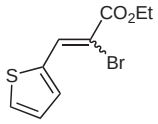
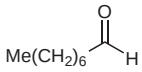
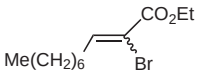
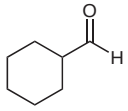
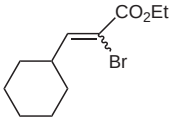
Table 2 Synthesis of α-Bromoacrylates[a]

Entry	Aldehyde	Product	Time (h)	Yield (%)[b] (*Z*/*E*)[c]
1			3	83 (95:5)
2			3	90 (98:2)
3			3	80 (92:8)
4			12	68 (92:8)
5			12	71 (90:10)
6			12	74 (92:8)
7			12	69 (88:12)
8			12	74 (89:11)

[a] The reaction was carried out with Ph_3P (4 equiv) and Br_3CCO_2Et (2 equiv) in boiling THF.
[b] Isolated yields based on aldehydes.
[c] *Z*/*E* ratio was determined by ^1H NMR analysis.

tone was not a good substrate under these reaction conditions.

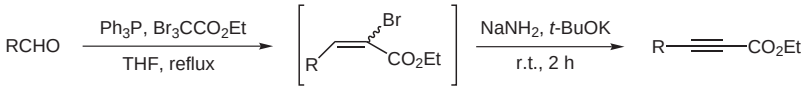
The *Z*/*E* ratio was determined by ^1H NMR on the basis of the chemical shifts of vinyl protons of the crude mixtures. The vinyl protons of *Z*-isomers are deshielded owing to the CO_2Et group.[10] The reaction with various aldehydes showed a high selectivity for *Z*-isomers.

The proposed method may find a wide range of applications because α-bromoacrylates have been used as versatile precursors for forming carbon–carbon bonds by metal-catalyzed cross-couplings such as Still couplings,[11] Suzuki couplings,[12] Sonogashira couplings,[13] and copper-catalyzed trifluoromethylations.[14]

With a reliable method for preparing α-bromoacrylates in our hands, we tried to develop a one-pot procedure for preparing acetylenic carboxylates. It has been known that dehydrohalogenation of vinyl halides can be accomplished only with strong bases.[5] We performed dehydrobromination of 2-bromo-3-(4-nitrophenyl)acrylate with strong bases such as *t*-BuLi and *t*-BuOK. 2-Bromo-3-(4-nitrophenyl)acrylate was generated in situ from the reaction of *p*-nitrobenzaldehyde with Ph_3P and Br_3CCO_2Et was treated with *t*-BuLi, affording a poor yield (5%) of acetylenic carboxylates (Table 3, entry 1). With an excess of *t*-BuOK, the yield of acetylenic carboxylates somewhat increased, but it was not satisfactory (entry 2). It was reported that a 1:1 mixture of $NaNH_2$ and *t*-BuOK is very effective as a base for elimination reactions.[15] When a 1:1 mixture of $NaNH_2$ and *t*-BuOK was used as a base, the yield of the acetylenic carboxylate drastically improved to 82% (entry 3). A wide range of aldehydes were treated un-

der these reaction conditions, giving moderate to high yields of the corresponding conjugated acetylenic carboxylates. Aromatic aldehydes that had an electron-withdrawing substituent were good substrates for the reaction (entries 5–8). A substituent at the *ortho*-position of aromatic aldehyde did not diminish the reactivity (entries 7 and 8). Aromatic aldehydes that had an electron-donating group and heteroaromatic aldehydes afforded the corresponding acetylenic carboxylates in moderate yields (entries 9–13). Aliphatic aldehydes gave moderate yields of acetylenic carboxylates (entries 14 and 15). The reaction with a conjugated aldehyde proceeded efficiently affording a high yield of the conjugated acetylenic carboxylate (entry 16).

Table 3 One-Pot Synthesis of Conjugated Acetylenic Carboxylates[a]



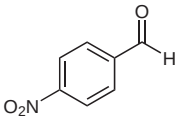
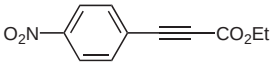
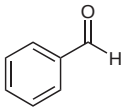
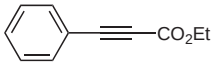
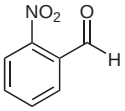
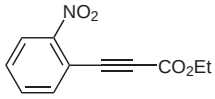
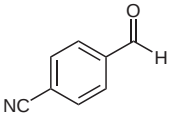
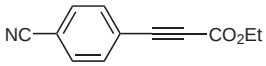
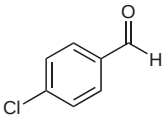
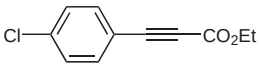
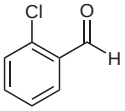
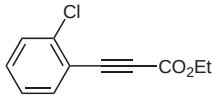
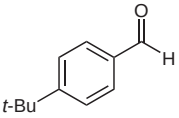
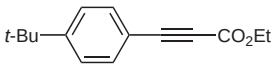
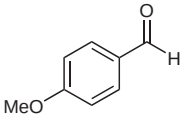
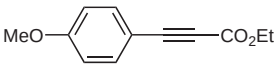
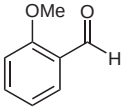
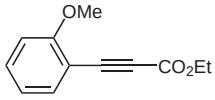
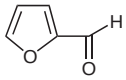
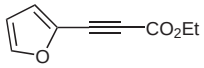
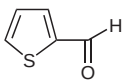
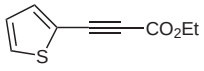
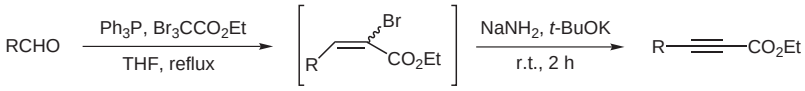
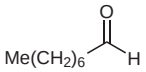
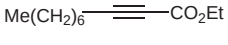
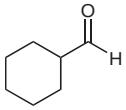
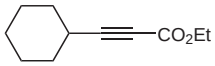
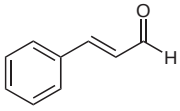
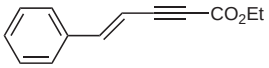
Entry	Aldehyde	Product	Time (h)[b]	Isolated yield (%)
1			3	5[c]
2			3	34[d]
3			3	82
4			3	76
5			3	83
6			3	80
7			3	80
8			3	81
9			3	70
10			12	60
11			12	58
12			12	61
13			12	62

Table 3 One-Pot Synthesis of Conjugated Acetylenic Carboxylates[a] (continued)



Entry	Aldehyde	Product	Time (h)[b]	Isolated yield (%)
14			12	57
15			12	59
16			3	85

[a] See the typical experimental procedure for the reaction conditions.[16]
[,b] Reaction time for the first step.
[c] The reaction was carried out with *t*-BuLi (3.0 equiv).
[d] The reaction was carried out with *t*-BuOK (3.0 equiv).

In conclusion, we have established the optimal conditions for the Wittig reaction for synthesizing α-bromoacrylates, and developed a simple and efficient one-pot procedure for preparing conjugated acetylenic carboxylates from aldehydes. The availability of a wide variety of aldehydes may make the present reaction an important tool for preparing the conjugated acetylenic carboxylates.

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(16) **Typical Procedure**: To a mixture of Ph_3P (1.31 g, 5 mmol) and Br_3CCO_2Et (0.81 g, 2.5 mmol) in THF (6 mL) under argon was added a solution of *p*-nitrobenzaldehyde (0.19 g, 1.25 mmol). After heating at reflux for 3 h, the reaction mixture was cooled to r.t. A mixture of $NaNH_2$ (0.78 g, 1.88 mmol) and *t*-BuOK (0.21 g, 1.88 mmol) in THF (3 mL) was added to the reaction mixture. After stirring at r.t. for 2 h, the mixture was diluted with Et_2O, washed with brine, and dried over anhyd $MgSO_4$. After evaporation of the solvent, the residue was separated by column chromatography on silica gel (hexane–EtOAc, 9:1) affording the product in 82% yield; mp 122–123 °C (lit.[3d] 120–121 °C). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 9.0 Hz, 2 H), 7.78 (d, *J* = 9.0 Hz, 2 H), 4.37 (q, *J* = 7.0 Hz, 2 H), 1.38 (t, *J* = 7.0 Hz, 3 H).