One-Pot Synthesis of 5-Arylpent-4-enoate Derivatives from Baylis-Hillman Acetates: Use of Phosphorous Ylide

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Basavaiah *et al*. have published some papers dealing with the Johnson-Claisen rearrangement of the Baylis-Hillman adducts in order to prepare 5-arylpent-4-enoates or 4-cyanoalk-4-enoates.[1] Shen *et al*. have also reported the synthesis of the latter compounds by using the sequential Michael reaction and Horner-Wadworth-Emmons (HWE) reaction of phosphonates.[2] Recently, we have also reported the synthesis of 5-arylpent-4-enoates from the Baylis-Hillman acetates.[3] The reaction was carried out *via* the tandem S_N2' reaction of diethyl malonate and subsequent decarbethoxylation process. However, the decarbethoxylation step required long reaction time (2-6 days) and high temperature (xylene, reflux).[3,4] Thus, mild reaction conditions were needed.

Recently Zaragoza reported one-step conversion of alcohols into nitriles with simultaneous two-carbon chain elongation by using (cyanomethyl)trimethylphosphonium iodide.[5] In the reaction, alcohols were converted into the corresponding iodides and react with the ylide to generate the corresponding alkylated phosphonium salts. Final hydrolysis with aqueous base furnished the desired products.[5] It is well known that phosphonium salt can be hydrolysed to the hydrocarbon analog.[6]

In this respect, we envisioned that if the reaction of the Baylis-Hillman acetate and appropriate phosphorous ylide would produce the corresponding phosphonium salt *via* the S_N2' type mechanism, we could prepare desired 5-arylpent-4-enoates. The reaction of the Baylis-Hillman acetate and phosphorous ylide has not been reported to the best of our knowledge.[7] Thus, we examined the possibility and report herein an efficient synthetic method for the synthesis of 5-arylpent-4-enoate derivatives.

As shown in Scheme 1, the reaction of the Baylis-Hillman acetate **1a** and (carbethoxymethylene)triphenylphosphorane (**2a**) in THF gave the phosphonium salt **3a**. We used the reaction mixture directly in the next hydrolysis step without further purification. Following hydrolysis of phosphonium salt **3a** was examined by using various conditions.[5,6] The use of aqueous KCN gave the best results (90% for **4a**). Instead, the use of aqueous $NaHCO_3$ (84%) or aqueous KI solution (64%) afforded **4a** in lower yields (Table 1). The structure of **4a** was exclusively *E*-form as in our previously paper.[7]

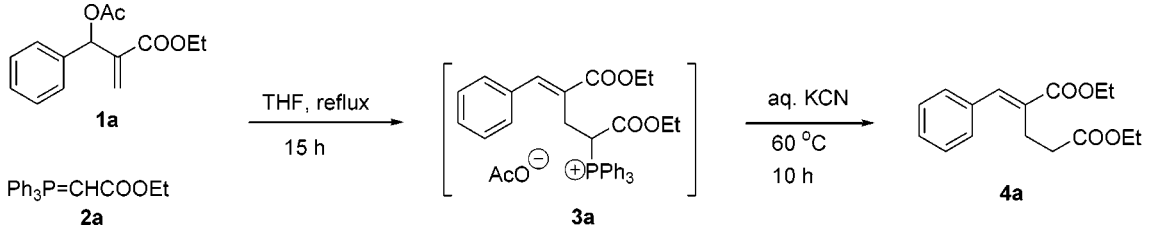
The representative results for the synthesis of 5-arylpent-4-enoates, **4a-g**, are summarized in Table 1. Baylis-Hillman acetates **1a-d** (derived from ethyl acrylate) and **1e-f** (derived from acrylonitrile) were used as substrates. In all cases we could obtain the desired products **4a-g** in 25-90% isolated yields. For the nitrile-substituted Baylis-Hillman acetates **1e** and **1f**, the obtained products **4f** and **4g** were the mixtures of *E* and *Z* isomers. Another ylide, 1-triphenylphosphoranylidene-2-propanone (**2b**), gave the corresponding product **4e**, albeite, in low yield. In this case we could not obtain the desired product by following the usual reaction sequence. The best result (25%) was obtained by simply mixing **1a** and **2b** in DMF and heating the reaction mixture for 25 h.

The reaction mechanism could be proposed as shown in Scheme 2. The reaction of **1a** and **2a** in THF gave the corresponding phosphonium salt **3a** (*vide supra*) *via* the addition-elimination process. Attack of cyanide ion to the phosphorous atom leaved ester enolate, which was protonated to give the product **4a**.

In conclusion we disclosed a facile synthetic method for the preparation of synthetically useful 5-arylpent-4-enoate derivatives. This procedure has some merits over the previous method[3] in the respects of (i) mild reaction conditions and (ii) one-pot reaction.

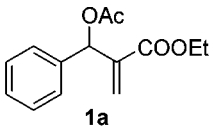
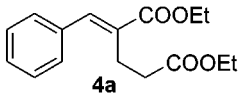
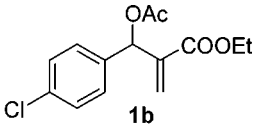
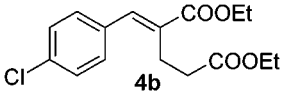
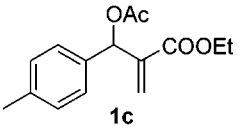
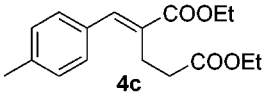
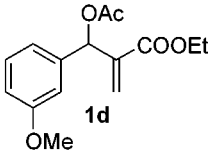
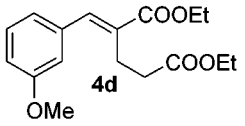
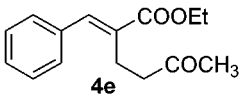
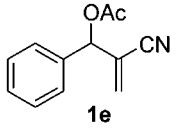
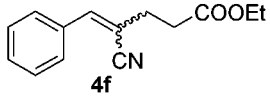
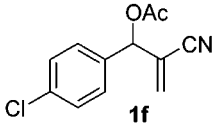
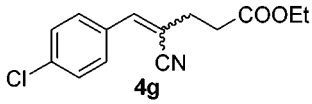
Experimental Section

All materials and solvents were of reagent grade as received from commercial sources. Baylis-Hillman adducts and their acetates were prepared as reported.[7]

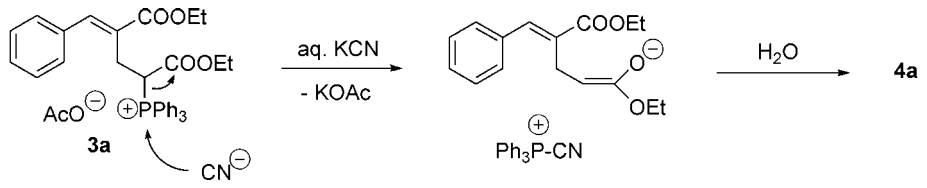


Scheme 1

Table 1. Synthesis of 5-arylpent-4-enoate derivatives **4a-g**

Entry	Substrate **1**	Conditions	Product **2**	Yield (%)
1	 **1a**	1. Ph_3P=CHCOOEt (**2a**, 1.0 equiv) THF, reflux, 15 h 2. aq. KCN (1.0 equiv) 60 °C, 10 h	 **4a**	90[a]
2	**1a**	1. same as in entry 1 2. aq. $NaHCO_3$ (2.0 equiv) 60 °C, 13 h	**4a**	84[a]
3	**1a**	1. same as in entry 1 2. aq. KI (3.0 equiv) 60 °C, 10 h	**4a**	64[a]
4	 **1b**	1. **2a** (1.0 equiv) THF, reflux, 24 h 2. aq. KCN (1.0 equiv) 60 °C, 18 h	 **4b**	60[a]
5	 **1c**	1. **2a** (1.0 equiv) THF, reflux, 24 h 2. aq. KCN (1.0 equiv) 60 °C, 18 h	 **4c**	64[a]
6	 **1d**	1. **2a** (1.0 equiv) THF, reflux, 24 h 2. aq. KCN (1.0 equiv) 60 °C, 18 h	 **4d**	74[a]
7	**1a**	Ph_3P=CHCOCH$_3$ (**2b**, 1.0 equiv) DMF, 110 °C, 25 h	 **4e**	25[a]
8	 **1e**	1. **2a** (1.0 equiv) THF, reflux, 24 h 2. aq. KCN (1.0 equiv) 60 °C, 24 h	 **4f**	84[b]
9	 **1f**	1. **2a** (1.0 equiv) THF, reflux, 24 h 2. aq. KCN (1.0 equiv) 60 °C, 22 h	 **4g**	76[b]

[a]Pure *E*-isomer. Trace amounts of *Z*-isomer was eliminated during column purification process. [b]*E*/*Z* = 1 : 3 mixtures.



Scheme 2

A typical procedure for the synthesis of 4a is as follows: To a stirred solution of **1a** (496 mg, 2.0 mmol) and (carbethoxymethylene)triphenylphosphorane (**2a**, 696 mg, 2.0 mmol) in THF (10 mL) was heated to reflux for 15 h. Aqueous solution of KCN (130 mg, 2.0 mmol in 5 mL of H_2O) was added and stirred at 60 °C for 10 h. After usual workup and column chromatographic purification (hexane/ether, 8 : 1) **4a** was obtained as clear oil, 498 mg (90%).

Selected data for **4a**:[3] oil; IR (KBr) 1734, 1707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 2.45-2.51 (m, 2H), 2.77-2.83 (m, 2H), 4.03 (q, J = 7.2 Hz, 2H), 4.20 (q, J = 7.2 Hz, 2H), 7.27-7.32 (m, 5H), 7.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.07, 14.19, 22.99, 33.44, 60.32, 60.81, 128.47, 128.49, 129.05, 131.38, 135.21, 140.01, 167.69, 172.61.

Spectroscopic data of other compounds are as follows. **4b** (*E*): oil; IR (KBr) 2981, 1732, 1709, 1250, 1092 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 2.54 (t, J = 8.0 Hz, 2H), 2.84 (t, J = 8.0 Hz, 2H), 4.11 (q, J = 7.2 Hz, 2H), 4.28 (q, J = 7.2 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.15, 14.24, 23.00, 33.35, 60.48, 61.01, 128.82, 130.41, 132.05, 133.68, 134.49, 138.69, 167.51, 172.56; Mass (70 eV) *m/z* (rel. intensity) 129 (61), 163 (100), 236 (99), 264 (69), 310 (M^+, 21), 312 (M^++2, 70). **4c** (*E*): oil; IR (KBr) 1739, 1705, 1254 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 2.53-2.58 (m, 2H), 2.86-2.92 (m, 2H), 4.14 (q, J = 7.2 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.70 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.15, 14.28, 21.28, 23.08, 33.49, 60.39, 60.83, 129.24, 129.30, 130.52, 132.37, 138.74, 140.09, 167.94, 172.79; Mass (70 eV) *m/z* (rel. intensity) 115 (25), 129 (43), 143 (100), 188 (47), 216 (46), 244 (40), 290 (M^+, 16). **4d** (*E*): oil; IR (KBr) 2981, 1732, 1709, 1238 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 2.45-2.50 (m, 2H), 2.77-2.82 (m, 2H), 3.73 (s, 3H), 4.02 (q, J = 7.2 Hz, 2H), 4.19 (q, J = 7.2 Hz, 2H), 6.78-6.88 (m, 3H), 7.22 (t, J = 7.8 Hz, 1H), 7.61 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.13, 14.26, 23.16, 33.54, 55.21, 60.41, 60.91, 114.29, 114.36, 121.52, 129.57, 131.66, 136.58, 139.99, 159.58, 167.74, 172.69; Mass (70 eV) *m/z* (rel. intensity) 115 (20), 159 (100), 215 (27), 260 (25), 306 (M^+, 16). **4e** (*E*): oil; IR (KBr) 2970, 1701, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, J = 7.2 Hz, 3H), 2.15 (s, 3H), 2.65-2.72 (m, 2H), 2.78-2.84 (m, 2H), 4.28 (q, J = 7.2 Hz, 2H), 7.32-7.41 (m, 4H), 7.72 (s, 1H); Mass (70 eV) *m/z* (rel. intensity) 43 (64), 115 (50), 129 (100), 157 (90), 200 (75), 246 (M^+, 10). **4f** (*E*+*Z*): oil; IR (KBr) 2981, 2210, 1736, 1227 cm^{-1}; *E*-form: ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3H), 2.64-2.85 (m, 4H), 4.14 (q, J = 7.2 Hz, 2H), 7.27-7.73 (m, 6H). *Z*-form: ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 2.64-2.85 (m, 4H), 4.15 (q, J = 7.2 Hz, 2H), 7.03 (s, 1H), 7.27-7.73 (m, 5H), 7.70-7.73 (m, 2H); Mass (70 eV) *m/z* (rel. intensity) 115 (37), 155 (100), 184 (16), 229 (M^+, 30). **4g** (*E*+*Z*): oil; IR (KBr) 2981, 2210, 1732, 1184 cm^{-1}; *E*-form: ^1H NMR ($CDCl_3$) δ 1.18 (t, J = 7.2 Hz, 3H), 2.59-2.62 (m, 2H), 2.69-2.72 (m, 2H), 4.08 (q, J = 7.2 Hz, 2H), 7.14 (s, 1H), 7.21 (d, J = 8.6 Hz, 2H), 7.33 (d, J = 8.6 Hz, 2H). Z-form: ^1H NMR ($CDCl_3$) δ 1.18 (t, J = 7.2 Hz, 3H), 2.56-2.66 (m, 4H), 4.08 (q, J = 7.2 Hz, 2H), 6.91 (s, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H); Mass (70 eV) *m/z* (rel. intensity) 127 (27), 140 (29), 154 (100), 176 (31), 189 (75), 263 (M^+, 28), 265 (M^++2, 9).

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