Sequential Transformation of Diethyl Phosphite. A Convenient Synthesis of Substituted (*E*)-3-Alkoxycarbonyl-β,γ-unsaturated Esters†

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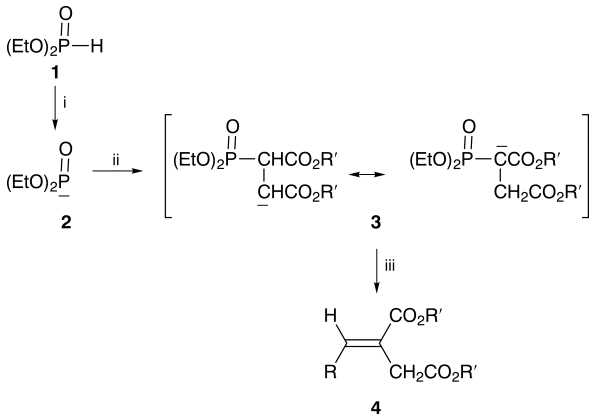
The sequential reaction of diethyl phosphite with sodium alkoxide, dimethyl maleate and aldehydes affords substituted (*E*)-3-alkoxycarbonyl-β,γ-unsaturated esters in 63–73% yields.

Recently, 3-alkoxycarbonyl-β,γ-unsaturated esters have attracted much attention since they are useful intermediates for the synthesis of substituted tetrahydrofurans which are essential components in many classes of naturally occurring bioactive compounds.[1,2] Examples are nucleosides, polyether antibiotics, insect pheromones, plant lignans and marine toxins.[2] The earlier method for the preparation of 3-alkoxycarbonyl-β,γ-unsaturated esters involves Stobbe condensation[3] which gives variable yields of the products contaminated with byproducts. The Wittig and Horner–Wadsworth–Emmons reactions were also applied to the synthesis of the title compounds[4,5] but their reagents require prior preparation. Very recently a one-pot three-component synthesis of the title compounds has been reported.[6] Therefore to develop an effective method for their preparation would be valuable.

Sequential transformations have attracted much interest in recent years because they provide a simple and efficient entry to complex compounds by including two or more transformations in a single operation to increase the complexity of substrate starting from commercially available, relatively simple precursors.[7] In our continuing investigation of the application of sequential transformation of phosphonates in organic synthesis[8] we report the sequential transformation of phosphite and its application to the synthesis of substituted (*E*)-3-alkoxycarbonyl-β,γ-unsaturated esters (Scheme 1).

Diethyl sodium phosphite, generated from diethyl phosphite and sodium alkoxide, reacted with dimethyl maleate to give the phosphoryl-stabilized carbanion **3**. Without isolation, **3** reacted with aldehydes giving 3-alkoxycarbonyl-β,γ-unsaturated esters **4** in good yields. The results are summarized in Table 1.



Scheme 1 *Reagents and conditions*: i, NaOR′ or NaH–R′OH, 20 °C, 0.5 h, R′ = Me, Et; ii, dimethyl maleate, 20 °C, 2 h; iii, RCHO, 20 °C, 3 h

Table 1 Preparation of substituted -3-alkoxycarbonyl-β,γ-unsaturated esters

Compound	R	R′	Yield (%)[a]
4a[b]	4-ClC_6H_4	Et	70
4b	4-FC_6H_4	Et	73
4c	4-$CH_3C_6H_4$	Et	71
4d	4-BrC_4H_6	Et	70
4e	4-$CF_3C_6H_4$	Et	65
4f	C_6H_5	Et	65
4g	Pr^n	Et	65
4h	2-Furyl	Et	64
4i	4-ClC_6H_4	Me	68
4j	4-FC_6H_4	Me	68
4k	4-$CH_3C_6H_4$	Me	66
4l	4-BrC_4H_6	Me	70
4m	4-$CF_3C_6H_4$	Me	63

[a]Isolated yields. [b]The NOESY spectrum of **4a** showed that the R group is *cis* with respect with the CH_2CO_2Et group.

The reaction is of wide scope since the R group may be alkyl, aryl and heterocyclic. it is noted that when sodium ethoxide was used as a base in ethyl alcohol, the diethyl diester was obtained exclusively since ester exchange had occurred.

Thus, the sequential transformation of diethyl phosphite provides a convenient synthesis of the title compounds under mild conditions to give the *E*-isomer.

Experimental

All boiling points are uncorrected with the oven temperature (ot) given. The IR spectra of products were obtained as films on a Perkin-Elmer 983 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer (δ values in ppm from tetramethylsilane, in $CDCl_3$, *J* values are given in Hz). Mass spectra were measured on a Finnigan GC–MS-4021 mass spectrometer.

General Procedure for the Synthesis of 3-*alkoxy-*β,γ*-unsaturated* **4**.—Sodium alkoxide or NaH (2 mmol) was added with stirring to a solution of diethyl phosphite (2 mmol) in absolute alcohol (10 ml) at 20 °C under nitrogen. The reaction mixture was stirred for 0.5 h at 20 °C and dimethyl maleate (0.29 g, 2 mmol) was slowly added. The mixture was stirred for 2 h and the aldehyde (2 mmol) was added. After addition the mixture was stirred for further 3 h and saturated aqueous NH_4Cl solution (2 ml) was added. The reaction mixture was extracted with diethyl ether (3 × 20 ml). The combined organic layer was washed with brine (20 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue which was purified by flash chromatography on silica gel eluting with light petroleum (bp 60–90 °C)–ethyl acetate (20:1) to give the product **4**.

Ethyl (*E*)-4-(4-*chlorophenyl*)-3-*ethoxycarbonylbut*-3-*enoate* **4a**.—Yield, 70%. Bp 182 °C at 1 mmHg; (lit.,[5] bp 135–138 °C at 0.2 Torr); ν_{max}/cm^{-1}; 2980, 1730, 1640, 1450, 1280, 1180, 1030; δ_H 1.26 (t, 3H, *J* 7.1), 1.33 (t, 3H, *J* 7.1), 3.48 (s, 2H), 4.17 (q, 2H, *J* 7.1), 4.29 (q, 2H, *J* 7.1), 7.26–7.38 (m, 4H), 7.82 (s, 1H); *m*/*z* 296 (M^+, 65%), 251 (93), 223 (48), 151 (80), 149 (58), 15 (100).

Ethyl (*E*)-4-(4-*fluorophenyl*)-3-*ethoxycarbonyl*-3-*enoate* **4b**.—Yield, 73%. Oil; ν_{max}/cm^{-1}; 2980, 1740, 1640, 1480, 1270, 1210, 1030; δ_H 1.20 (t, 3H, *J* 7.1), 1.26 (t, 3H, *J* 7.1), 3.42 (s, 2H), 4.11 (q, 2H,

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J 7.1), 4.22 (q, 2H, *J* 7.1), 6.95–7.05 (m, 2H), 7.20–7.37 (m, 2H), 7.73 (s, 1H); *m*/*z* 281 (M^++1, 13%), 280 (M^+, 49), 235 (89), 234 (51), 206 (35), 134 (64), 133 (100), 115 (15). (Found: C, 63.94; H, 6.25. $C_{15}H_{17}FO_4$ requires C, 64.28; H, 6.11%).

Ethyl (*E*)-4-(4-*methylphenyl*)-3-*ethoxycarbonylbut*-3-*enoate* **4c**.—Yield, 71%. Bp 161 °C at 1 mmHg (lit.,[5] bp 135–138 °C at 0.4 Torr); ν_{max}/cm^{-1}; 2980, 1740, 1640, 1450, 1270, 1130, 1030; δ_H 1.26 (t, 3H, *J* 7.1), 1.33 (t, 3H, *J* 7.1), 2.36 (s, 3H), 3.53 (s, 2H), 4.20 (q, 2H, *J* 7.1), 4.22 (q, 2H, *J* 7.1), 7.11–7.35 (m, 4H), 7.87 (s, 1H); *m*/*z* 276 (M^+, 72%), 231 (44), 230 (68), 202 (52), 131 (98), 129 (100), 115 (38), 99 (26).

Ethyl (*E*)-4-(4-*bromophenyl*)-3-*ethoxycarbonyl*-3-*enoate* **4d**.—Yield, 70%. Oil; ν_{max}/cm^{-1}; 2980, 1740, 1640, 1450, 1280, 1180, 1030; δ_H 1.26 (t, 3H, *J* 7.1), 1.32 (t, 3H, *J* 7.1), 3.47 (s, 2H), 4.17 (q, 2H, *J* 7.1), 4.28 (q, 2H, *J* 7.1), 7.21 (dd, 2H, *J* 1.7, 5.0 Hz), 7.50 (dd, 2H, *J* 1.8, 5.0 Hz), 7.80 (s, 1H); *m*/*z* 342 (M^++1, 68%), 341 (M^+, 26), 340 ($M^+ - 1$, 65), 297 (100), 295 (96), 188 (50), 160 (13), 129 (27), 115 (93) (Found: C, 52.80; H, 5.11. $C_{15}H_{17}BrO_4$ requires C, 52.80; H, 5.02%).

Ethyl (*E*)-4-(4-*trifluoromethylphenyl*)-3-*ethoxycarbonylbut*-3-*enoate* **4e**.—Yield, 65%. Oil; ν_{max}/cm^{-1}; 2950, 1720, 1620, 1500, 1330, 1170, 1020; δ_H 1.27 (t, 3H, *J* 7.1), 1.34 (t, 3H, *J* 7.1), 3.47 (s, 2H), 4.18 (q, 2H, *J* 7.1), 4.30 (q, 2H, *J* 7.1), 7.45 (d, 2H, *J* 8.2), 7.64 (d, 2H, *J* 8.2), 7.89 (s, 1H); *m*/*z* 331 (M^++1, 33%), 286 (20), 285 (100), 165 (8), 115 (8) (Found: C, 58.03; H, 5.24. $C_{16}H_{17}F_3O_4$ requires C, 58.18; H, 5.19%).

Ethyl (*E*)-4-*phenyl*-3-*ethoxycarbonylbut*-3-*enoate* **4f**.—Yield, 65%. Bp 158 °C at 1 mmHg (lit.,[5] bp 132–134 °C at 0.4 Torr); ν_{max}/cm^{-1}; 2980, 1740, 1640, 1450, 1270, 1130; δ_H 1.27 (t, 3H, *J* 7.1), 1.33 (t, 3H, *J* 7.1), 3.52 (s, 2H), 4.17 (q, 2H, *J* 7.1), 4.27 (q, 2H, *J* 7.1), 7.30–7.42 (m, 5H), 7.89 (s, 1H), *m*/*z* 263 (M^++1, 33%), 262 (M^+, 100), 231 (83), 216 (28), 130 (39), 129 (70).

Ethyl (*E*)-3-*ethoxycarbonylhept*-3-*enoate* **4g**.—Yield, 65%. Oil; ν_{max}/cm^{-1}; 2980, 1730, 1650, 1450, 1330, 1240, 1040; δ_H 0.92 (t, 3H, *J* 7.4), 1.22 (t, 3H, *J* 7.1), 1.24 (t, 3H, *J* 7.1), 1.40–1.53 (m, 2H), 2.15 (m, 2H), 3.31 (s, 2H), 4.11 (q, 2H, *J* 7.1), 4.17 (q, 2H, *J* 7.1), 6.94 (d, 1H, *J* 7.6); *m*/*z* 229 (M^++1, 40%), 184 (17), 183 (100), 182 (27), 155 (15), 154 (13) (Found: C, 63.05; H, 9.04. $C_{12}H_{20}O_4$ requires C, 63.14; H, 8.83%).

Ethyl (*E*)-4-(2-*furyl*)-3-*ethoxycarbonylbut*-3-*enoate* **4h**.—Yield, 64%. Bp 137 °C at 1 mmHg (lit.,[5] bp 120–121 °C at 0.5 Torr); ν_{max}/cm^{-1}; 3130, 2980, 1730, 1700, 1480, 1210, 1100; δ_H 1.21 (t, 3H, *J* 7.2), 1.31 (t, 3H, *J* 7.2), 3.84 (s, 2H), 4.14 (q, 2H, *J* 7.1), 4.27 (q, 2H, *J* 7.1), 6.47 (dd, 1H, *J* 1.7, 3.4), 6.64 (d, 1H, *J* 3.4), 7.51 (d, 1H, *J* 1.7), 7.53 (s, H); *m*/*z* 252 (M^+, 87%), 207 (61), 179 (100), 151 (46), 106 (34), 79 (44).

Methyl (*E*)-4-(4-*chlorophenyl*)-3-*methoxycarbonylbut*-3-*enoate* **4i**.—Yield, 68%. Bp 165 °C at 1 mmHg (lit.,[5] bp, 133–134 °C at 0.3 Torr); ν_{max}/cm^{-1}; 2960, 1740, 1640, 1440, 1260, 1040; δ_H 3.49 (s, 2H), 3.72 (s, 3H), 3.82 (s, 3H), 7.29 (d, 2H, *J* 8.5), 7.34 (d, 2H, *J* 8.5), 7.83 (s, 1H); *m*/*z* 269 (M^++1, 37%), 268 (M^+, 100), 239 (36), 237 (95), 236 (44), 150 (8), 149 (23), 115 (23).

Methyl (*E*)-4-(4-*fluorophenyl*)-3-*methoxycarbonylbut*-3-*enoate* **4j**.—Yield, 68%, Oil; ν_{max}/cm^{-1}; 2950, 1710, 1640, 1440, 1370, 1270, 1020; δ_H 3.52 (s, 2H), 3.74 (s, 3H), 3.83 (s, 3H), 7.06–7.12 (m, 2H), 7.26–7.37 (m, 2H), 7.86 (s, 1H); *m*/*z* 252 (M^+, 75%), 221 (87), 220 (66), 192 (25), 149 (21), 133 (100). (Found: C, 61.97; H, 5.43. $C_{13}H_{13}FO_4$ requires C, 61.90; H, 5.19%).

Methyl (*E*)-4-(4-*methylphenyl*)-3-*methoxycarbonylbut*-3-*enoate* **4k**.—Yield, 66%. Bp 142 °C at 1 mmHg (lit.,[5] bp 138 °C at Torr); ν_{max}/cm^{-1}; 2950, 1740, 1640, 1440, 1280, 1020; δ_H 2.37 (s, 3H), 3.56 (s, 2H), 3.73 (s, 3H), 3.82 (s, 3H), 7.19–7.26 (m, 4H), 7.88 (s, 1H); *m*/*z* 249 (M^++1, 35%), 248 (M^+, 100), 217 (98), 188 (11), 129 (36), 115 (9).

Methyl (*E*)-4-(4-*bromophenyl*)-3-*methoxycarbonylbut*-3-*enoate* **4l**.—Yield, 70%; Oil; ν_{max}/cm^{-1}; 2950, 1720, 1640, 1490, 1280, 1210, 1050; δ_H 3.49 (s, 2H), 3.73 (s, 3H), 3.82 (s, 3H), 7.23 (d, 2H, *J* 8.4), 7.51 (d, 2H, *J* 8.4), 7.81 (s, 1H); *m*/*z* 314 (M^++1, 100%), 313 (M^+, 28), 312 (95), 283 (63), 281 (63), 201 (41), 174 (54), 115 (88) (Found: C, 49.86; H, 4.17. $C_{13}H_{13}BrO_4$ requires C, 49.86; H, 4.18%).

Methyl (*E*)-4-(4-*trifluoromethylphenyl*)-3-*methoxycarbonylbut*-3-*enoate* **4m**.—Yield, 63%. Oil; ν_{max}/cm^{-1}; 2950, 1720, 1620, 1440, 1330, 1170, 1050; δ_H 3.49 (s, 2H), 3.74 (s, 3H), 3.84 (s, 3H), 7.47 (d, 2H, *J* 8.2), 7.64 (d, 2H, *J* 8.2), 7.91 (s, 1H); *m*/*z* 303 (M^++1, 12%), 302 (M^+, 44), 283 (24), 270 (100), 242 (45), 183 (58), 164 (19), 115 (44) (Found: C, 55.49; H, 4.33. $C_{14}H_{13}F_3O_4$ requires C, 55.63; H, 4.34%).

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