

# Sequential Transformation of Diethyl Phosphite. A Convenient Synthesis of Substituted (*E*)-3-Alkoxy carbonyl- $\beta,\gamma$ -unsaturated Esters†

*J. Chem. Research (S)*,  
1998, 642–643†

Yanchang Shen\* and Zenghong Zhang

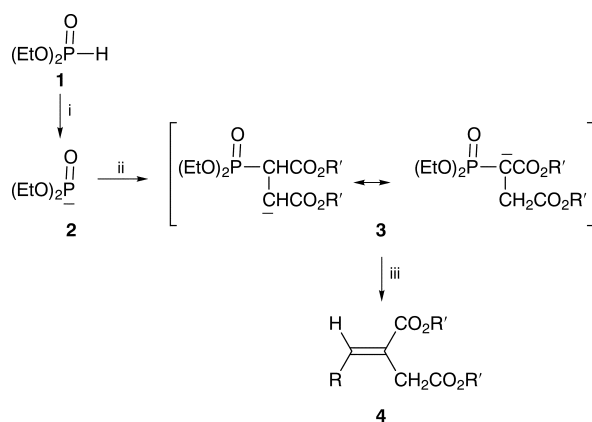
Shanghai Institute of Organic Chemistry, Academia Sinica, 354 Fenglin Lu, Shanghai 200032, China

The sequential reaction of diethyl phosphite with sodium alkoxide, dimethyl maleate and aldehydes affords substituted (*E*)-3-alkoxy carbonyl- $\beta,\gamma$ -unsaturated esters in 63–73% yields.

Recently, 3-alkoxy carbonyl- $\beta,\gamma$ -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.<sup>1,2</sup> Examples are nucleosides, polyether antibiotics, insect pheromones, plant lignans and marine toxins.<sup>2</sup> The earlier method for the preparation of 3-alkoxy carbonyl- $\beta,\gamma$ -unsaturated esters involves Stobbe condensation<sup>3</sup> 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<sup>4,5</sup> but their reagents require prior preparation. Very recently a one-pot three-component synthesis of the title compounds has been reported.<sup>6</sup> 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.<sup>7</sup> In our continuing investigation of the application of sequential transformation of phosphonates in organic synthesis<sup>8</sup> we report the sequential transformation of phosphite and its application to the synthesis of substituted (*E*)-3-alkoxy carbonyl- $\beta,\gamma$ -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-alkoxy carbonyl-



**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

\*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

**Table 1** Preparation of substituted -3-alkoxy carbonyl- $\beta,\gamma$ -unsaturated esters

Compound	R	R'	Yield (%) <sup>a</sup>
<b>4a</b> <sup>b</sup>	4-ClC <sub>6</sub> H <sub>4</sub>	Et	70
<b>4b</b>	4-FC <sub>6</sub> H <sub>4</sub>	Et	73
<b>4c</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Et	71
<b>4d</b>	4-BrC <sub>6</sub> H <sub>4</sub>	Et	70
<b>4e</b>	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Et	65
<b>4f</b>	C <sub>6</sub> H <sub>5</sub>	Et	65
<b>4g</b>	Pr <sup>n</sup>	Et	65
<b>4h</b>	2-Furyl	Et	64
<b>4i</b>	4-ClC <sub>6</sub> H <sub>4</sub>	Me	68
<b>4j</b>	4-FC <sub>6</sub> H <sub>4</sub>	Me	68
<b>4k</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Me	66
<b>4l</b>	4-BrC <sub>6</sub> H <sub>4</sub>	Me	70
<b>4m</b>	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Me	63

<sup>a</sup>Isolated yields. <sup>b</sup>The NOESY spectrum of **4a** showed that the R group is *cis* with respect with the CH<sub>2</sub>CO<sub>2</sub>Et group.

$\beta,\gamma$ -unsaturated esters **4** in good yields. The results are summarized in Table 1.

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. <sup>1</sup>H NMR spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer ( $\delta$  values in ppm from tetramethylsilane, in CDCl<sub>3</sub>, *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- $\beta,\gamma$ -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<sub>4</sub>Cl 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<sub>2</sub>SO<sub>4</sub>. 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.<sup>5</sup> bp 135–138 °C at 0.2 Torr);  $\nu_{\max}/\text{cm}^{-1}$ : 2980, 1730, 1640, 1450, 1280, 1180, 1030;  $\delta_{\text{H}}$  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*<sup>+</sup>, 65%), 251 (93), 223 (48), 151 (80), 149 (58), 15 (100).

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

*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.,<sup>5</sup> bp 135–138 °C at 0.4 Torr);  $\nu_{\max}/\text{cm}^{-1}$ : 2980, 1740, 1640, 1450, 1270, 1130, 1030;  $\delta_H$  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-ethoxycarbonylbut-3-enoate 4d.**—Yield, 70%. Oil;  $\nu_{\max}/\text{cm}^{-1}$ : 2980, 1740, 1640, 1450, 1280, 1180, 1030;  $\delta_H$  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;  $\nu_{\max}/\text{cm}^{-1}$ : 2950, 1720, 1620, 1500, 1330, 1170, 1020;  $\delta_H$  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.,<sup>5</sup> bp 132–134 °C at 0.4 Torr);  $\nu_{\max}/\text{cm}^{-1}$ : 2980, 1740, 1640, 1450, 1270, 1130;  $\delta_H$  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;  $\nu_{\max}/\text{cm}^{-1}$ : 2980, 1730, 1650, 1450, 1330, 1240, 1040;  $\delta_H$  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.,<sup>5</sup> bp 120–121 °C at 0.5 Torr);  $\nu_{\max}/\text{cm}^{-1}$ : 3130, 2980, 1730, 1700, 1480, 1210, 1100;  $\delta_H$  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.,<sup>5</sup> bp 133–134 °C at 0.3 Torr);  $\nu_{\max}/\text{cm}^{-1}$ : 2960, 1740, 1640, 1440, 1260, 1040;  $\delta_H$  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;  $\nu_{\max}/\text{cm}^{-1}$ : 2950, 1710, 1640, 1440, 1370, 1270, 1020;  $\delta_H$  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.,<sup>5</sup> bp 138 °C at Torr);  $\nu_{\max}/\text{cm}^{-1}$ : 2950, 1740, 1640, 1440, 1280, 1020;  $\delta_H$  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;  $\nu_{\max}/\text{cm}^{-1}$ : 2950, 1720, 1640, 1490, 1280, 1210, 1050;  $\delta_H$  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;  $\nu_{\max}/\text{cm}^{-1}$ : 2950, 1720, 1620, 1440, 1330, 1170, 1050;  $\delta_H$  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%).

We thank the National Science Foundation of China and Academia Sinica for financial support.

Received, 11th March 1998; Accepted, 9th June 1998  
Paper E/8/03769H

## References

- M. Gordaliza, J. M. M. del Corral, M. A. Castro, M. A. Salinero, A. San Feliciano, J. M. Dorado and F. Valle, *Synlett*, 1996, 1201 and references cited therein.
- F. Perron and K. F. Abizati, *Chem. Rev.*, 1989, **89**, 1617.
- W. S. Johnson and G. H. Daub, *Organic React.*, 1951, **6**, 1.
- A. F. Cameron, F. D. Duncanson, A. A. Freer, V. W. Armstrong and R. Ramage, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1030.
- S. Linke, J. Kurz, D. Lipinski and W. Gau, *Liebigs Ann. Chem.*, 1980, 542.
- S. W. McCombie and C. A. Luchaco, *Tetrahedron Lett.*, 1997, **38**, 5775.
- L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131; A. Padwa, E. A. Curtis and V. P. Sandanayaka, *J. Org. Chem.*, 1996, **61**, 73; L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; P. J. Parsons, C. S. Penkett and A. J. Shell, *Chem. Rev.*, 1996, **96**, 195.
- Y. Shen and J. Ni, *J. Org. Chem.*, 1997, **62**, 7260; Y. Shen and J. Ni, *J. Chem. Res. (S)*, 1997, 358.