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A Convenient Synthesis of Substituted 3-Alkoxycarbonyl-β,γ-unsaturated Esters with Predominant Z-Selectivity

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ABSTRACT: *The consecutive reaction of bis[2,2,2-trifluoroethyl]phosphite with sodium hydride, dimethyl maleate, and aldehydes gives 3-alkoxycarbonyl-β,γ-unsaturated esters with predominant* Z*-selectivity in 62–94% yields (*Z/E *= 85–60:15–40). The* Z- *and* E*-isomer can be separated conveniently by column chromatography.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:276–279, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10142

INTRODUCTION

In the past few decades the use of the Horner–Wadsworth–Emmons (HWE) reaction in organic synthesis has increased significantly [1] and it was employed in a variety of versatile synthetic routes, enabling the synthesis of many functionalized compounds, particularly of naturally occurring products [2]. However, the usual HWE reagents with alkylphosphono groups produce thermodynamically favored *E*-olefins [le]. For the purpose of preparing *Z*-olefins, several attempts have been made by changing of reaction conditions or phosphonate reagents, but the success was still limited [3]. Among them, the methods of Still [3a] and Ando [3c–f] have been shown to be the most versatile and selective. The former used methyl [bis(trifluoroethyl)phosphono]acetate in the HWE reaction, while the latter employed ethyl (diarylphosphono)acetates as reagents.

RESULTS AND DISCUSSION

In recent years, 3-alkoxycarbonyl-β,γ-unsaturated esters have attracted much interest because they are useful intermediates for the synthesis of substituted tetrahydrofurans, which are essential components in a variety of naturally occurring bioactive compounds [4]. As part of our continuing investigation of synthetic application of consecutive reaction of phosphorus compounds in organic synthesis [5], herein we report a convenient synthesis of substituted 3-alkoxycarbonyl-β,γ-unsaturated esters with predominant Z-selectivity by using bis[2,2,2-trifluoroethyl]phosphite as a starting material via sequential transformations. The reaction sequence is shown in Scheme 1.

Bis[2,2,2-trifluoroethyl]phosphite (**1**) was treated with sodium hydride in tetrahydrofuran (THF) at 25°C and the resulting carbanion **2** reacted with dimethyl maleate **3** to form the intermediate **4**, which was further reacted with aldehydes, followed by elimination of phosphonate anion, giving substituted 3-alkoxycarbonyl-β,γ-unsaturated esters (**6**) with predominant Z-selectivity in 62–94% yields (Z/E = 85–60:15–40). The Z- and E-isomer can be

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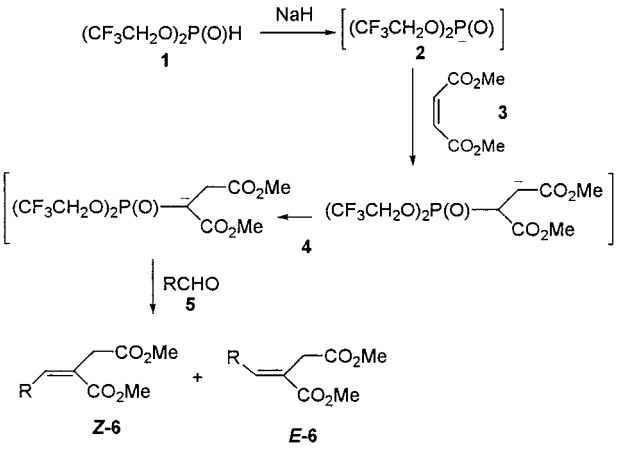

SCHEME 1

separated conveniently by column chromatography. The results are summarized in Table 1.

The chemical shift of vinyl proton in E-isomer of substituted 3-alkoxycarbonyl-β,γ-unsaturated esters has been reported in the range of $\delta = 7.83$–8.00 ppm [6]. Thus, we assigned the chemical shift of vinyl proton in the range of $\delta = 7.82$–7.91 as E-isomer, while that in the range of $\delta = 6.73$–6.89 as Z-isomer. For the further confirmation of the configuration of the products we performed the NOESY spectrum of the major product of **6b**. It showed that the vinyl proton is cis with respect to the CH_2CO_2Me group (Z-isomer).

EXPERIMENTAL

All boiling points are uncorrected. The IR spectra of liquid products were determined as films on a Digilab FTS-20E spectrometer. ^{1}H NMR spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer (values in ppm from $SiMe_4$, in $CDCl_3$; *J* values are given in Hz). Mass spectra were measured on a Finnigan GC-MS-4021 mass spectrometer.

TABLE 1 Substituted 3-Alkoxycarbonyl-β,γ-unsaturated Esters Prepared

	R	*Yield (%)*[a]	*Ratio (Z/E)*[b]
6a	4-$(CH_3)_2NC_6H_4$	90	85:15
6b	4-$CH_3C_6H_4$	94	82:18
6c	4-ClC_6H_4	76	81:19
6d	C_6H_5	80	78:22
6e	E-$CH_3CH{=}CH$	93	71:29
6f	E-$C_6H_4CH{=}CH$	86	68:32
6g	2,4-$Cl_2C_6H_3$	62	60:40

[a]Isolated yields.
[b]Isolated ratios.

*Bis(2,2,2-trifluoroethyl)phosphite (**1**)* was prepared according to the known method [7].

*General Procedure for the Synthesis of 3-Alkoxy-β,γ-unsaturated Esters (**6**)*

Bis(2,2,2-trifluoroethyl)phosphite (2.5 mmol) was added slowly with stirring to a suspension of sodium hydride [NaH, 0.1 g (60%), 2.5 mmol] in THF (20 ml) at 20°C under nitrogen. The reaction mixture was stirred for 0.5 h at 20°C and dimethyl maleate (0.34 g, 2.5 mmol) was slowly added. The mixture was further stirred for 0.5 h and the aldehyde (2 mmol) was added. After addition, the mixture was stirred further for 3 h and HCl solution (2 M, 30 ml) was added. The reaction mixture was extracted with ethyl acetate (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 ether (bp 60–90°C)/ethyl acetate (10:1) to give the product **6**. The component in front was identified as E-isomer (minor product), while the one behind was the Z-isomer (major product). In the cases of **6e** and **6f**, the reverse is true.

*Z-Methyl 4-(4-Dimethylaminophenyl)-3-methoxycarbonylbut-3-enoate (**Z-6a**).* Yield: 77%; oil. IR (neat): $\nu = 2950, 1740, 1710, 1610, 1530, 1440, 1360, 1220, 1190, 1170, 810$ cm^{-1}. ^{1}H NMR ($CDCl_3$/TMS): $\delta = 7.32$ (d, $J = 8.2$ Hz, 2H), 6.73 (s, 1H), 6.62 (d, $J = 8.2$ Hz, 2H), 3.71 (s, 3H), 3.69 (s, 3H), 3.42 (s, 2H), 2.96 (s, 6H). MS: *m/z* (%) = 278 ($M^+ + 1$, 20), 277 (M^+, 100), 218 (56), 159 (32), 158 (94). Anal. Calc. for $C_{15}H_{19}NO_4$ (277.32): C, 64.97; H, 6.91; N, 5.05. Found: C, 64.74; H, 6.90; N, 4.83.

*E-Methyl 4-(4-Dimethylaminophenyl)-3-methoxycarbonylbut-3-enoate (**E-6a**).* Yield: 13%; oil. IR (neat): $\nu = 2960, 1740, 1720, 1700, 1610, 1530, 1440, 1240, 1200, 1170, 1080, 810$ cm^{-1}. ^{1}H NMR ($CDCl_3$/TMS): $\delta = 7.82$ (s, 1H), 7.31 (d, $J = 8.9$ Hz, 2H), 6.69 (d, $J = 8.9$ Hz, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.63 (S, 2H), 3.00 (s, 6H). MS: *m/z* (%) = 278 ($M^+ + 1$, 17), 277 (M^+, 93), 218 (56), 159 (35), 158 (100). Anal. Calc. for $C_{15}H_{19}NO_4$ (277.32): C, 64.97; H, 6.91; N, 5.05. Found: C, 64.62; H, 7.00; N, 5.00.

*Z-Methyl 4-(4-Methylphenyl)-3-Methoxycarbonylbut-3-enoate (**Z-6b**).* Yield: 77%; bp 120°C/0.5 mm Hg. IR (neat): $\nu = 2950, 1740, 1710, 1440, 1240, 1210, 1170, 1130$ cm^{-1}. ^{1}H NMR ($CDCl_3$/TMS): $\delta = 7.19$ (d, $J = 8.2$ Hz, 2H), 7.11 (d, $J = 8.2$ Hz, 2H), 6.83 (s, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 3.46

(d, $J = 0.7$ Hz, 2H), 2.33 (s, 3H). MS: *m/z* (%) = 248 (M^+, 49), 216 (45), 188 (30), 129 (100), 115 (28), 59 (18). Anal. Calc. for $C_{14}H_{16}O_4$ (248.27): C, 67.73; H, 6.50. Found: C, 67.62; H, 6.50.

*E-Methyl 4-(4-Methylphenyl)-3-methoxycarbonylbut-3-enoate (***E-6b***) [8].* Yield: 17%; oil. IR (neat): $\nu = 3030$, 2950, 1740, 1710, 1640, 1610, 1510, 1440, 1270, 1200, 1170, 1000 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 7.87$ (s, 1H), 7.25 (d, $J = 8.3$ Hz, 2H), 7.19 (d, $J = 8.3$ Hz, 2H), 3.82 (s, 3H), 3.72 (s, 3H), 3.56 (s, 2H), 2.36 (s, 3H). MS: *m/z* (%) = 248 (M^+, 70), 216 (46), 216 (50), 129 (100), 115 (28), 59 (16).

*Z-Methyl 4-(4-Chlorophenyl)-3-methoxycarbonylbut-3-enoate (***Z-6c***).* Yield: 58%; bp 128°C/0.5 mm Hg. IR (neat): $\nu = 2950$, 1740, 1720, 1590, 1490, 1440, 1240, 1210, 1170, 1020 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 7.28$ (d, $J = 8.6$ Hz, 2H), 7.21 (d, $J = 8.6$ Hz, 2H), 6.81 (s, 1H), 3.70 (s, 3H), 3.64 (s, 3H), 3.45 (s, 2H). MS: *m/z* (%) = 270 ($M^+ + 2$, 25), 268 (M^+, 70), 236 (81), 151 (49), 149 (91), 130 (38), 115 (100), 59 (57). Anal. Calc. for $C_{13}H_{13}ClO_4$ (268.69): C, 58.11; H, 4.88. Found: C, 58.10; H, 4.94.

*E-Methyl 4-(4-Chlorophenyl)-3-methoxycarbonylbut-3-enoate (***E-6c***) [8].* Yield: 15%; oil. IR (neat): $\nu = 3000$, 2950, 1740, 1720, 1640, 1590, 1490, 1440, 1330, 1280, 1200, 1170, 1090, 1010 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 7.84$ (s, 1H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.27 (d, $J = 8.4$ Hz, 2H), 3.82 (s, 3H), 3.73 (s, 3H), 3.50 (s, 2H). MS: *m/z* (%) = 270 ($M^+ + 2$, 35), 268 (M^+, 97), 237 (62), 236 (91), 208 (62), 151 (46), 149 (95), 130 (37), 115 (100), 59 (46).

*Z-Methyl 4-(Phenyl)-3-methoxycarbonylbut-3-enoate (***Z-6d***) [9].* Yield: 62%; oil. IR (neat): $\nu = 3030$, 2950, 1740, 1720, 1440, 1245, 1210, 1170, 1130, 700 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 7.25$–7.50 (m, 5H), 6.87 (s, 1H), 3.70 (s, 3H), 3.63 (s, 3H), 3.47 (s, 2H). MS: *m/z* (%) = 234 (M^+, 76), 203 (63), 202 (64), 174 (24), 116 (39), 115 (100), 91 (19).

*E-Methyl 4-(Phenyl)-3-methoxycarbonylbut-3-enoate (***E-6d***) [8].* Yield: 18%; oil. IR (neat): $\nu = 3060$, 2950, 1740, 1710, 1640, 1490, 1450, 1440, 1330, 1270, 1220, 1200, 1170, 1100 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 7.91$ (s, 1H), 7.26–7.40 (m, 5H), 3.84 (s, 3H), 3.74 (s, 3H), 3.55 (s, 2H). MS: *m/z* (%) = 234 (M^+, 49), 203 (41), 202 (57), 174 (28), 116 (39), 115 (100), 91 (19), 59 (15).

*Z-Methyl 3-Methoxycarbonylhepta-3,5-dienoate (***Z-6e***).* Yield: 67%; oil. IR (neat): $\nu = 2950$, 1740, 1720, 1640, 1440, 1230, 1200, 1180, 980 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 7.14$ (ddq, $J = 14.9$, 11.1, 1.5 Hz, 1H), 6.42 (d, $J = 11.1$ Hz, 1H), 5.90–6.10 (m, 1H), 3.71 (s, 3H), 3.64 (s, 3H), 3.24 (s, 2H), 1.82 (dd, $J = 6.9$, 1.5 Hz, 3H). MS: *m/z* (%) = 199 ($M^+ + 1$, 19), 198 (M^+, 55), 183 (23), 167 (100), 139 (18), 79 (15). Anal. Calc. for $C_{10}H_{14}O_4$ (198.21): C, 60.59; H, 7.12. Found: C, 60.44; H, 7.17.

*E-Methyl 3-Methoxycarbonylhepta-3,5-dienoate (***E-6e***).* Yield: 26%; oil. IR (neat): $\nu = 2960$, 1740, 1710, 1650, 1440, 1300, 1250, 1200, 1170, 1090, 780 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 7.30$ (d, $J = 10.5$ Hz, 1H), 7.10–7.35 (m, 2H), 3.73 (s, 3H), 3.67 (s, 3H), 3.41 (s, 2H), 1.86 (d, $J = 6.2$ Hz, 3H). MS: *m/z* (%) = 199 ($M^+ + 1$, 24), 198 (M^+, 46), 183 (21), 167 (100), 139 (16). Anal. Calc. for $C_{10}H_{14}O_4$ (198.21): C, 60.59; H, 7.12. Found: C, 60.29; H, 7.26.

*Z-Methyl 5-Phenyl-3-methoxycarbonylhexa-3,5-dienoate (***Z-6f***).* Yield: 58%; oil. IR (neat): $\nu = 3020$, 1740, 1700, 1630, 1440, 1290, 1210, 980, 800, 750, 690 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 7.97$ (dd, $J = 15.6$, 11.2 Hz, 1H), 7.45–7.60 (m, 2H), 7.20–7.45 (m, 3H), 6.78 (d, $J = 15.6$ Hz, 1H), 6.66 (d, $J = 11.2$ Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.37 (s, 2H). MS: *m/z* (%) = 260 (M^+, 30), 200 (36), 187 (10), 169 (30), 155 (14), 141 (100), 115 (26). Anal. Calc. for $C_{15}H_{16}O_4$ (260.28): C, 69.22; H, 6.20. Found: C, 69.26; H, 5.97.

*E-Methyl 5-Phenyl-3-methoxycarbonylhexa-3,5-dienoate (***E-6f***).* Yield: 28%; oil. IR (neat): $\nu = 2950$, 1740, 1710, 1630, 1440, 1290, 1240, 1200, 1170, 1080, 980, 750 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta =$ 7.45–7.65 (m, 3H), 7.25–7.45 (m, 3H), 6.90–7.00 (m, 2H), 3.80 (s, 3H), 3.71 (s, 3H), 3.57 (s, 2H). MS: *m/z* (%) = 260 (M^+, 31), 200(39), 169(30), 141(100), 115 (26). Anal. Calc. for $C_{15}H_{16}O_4$ (260.28): C, 69.22; H, 6.20: Found: C, 69.41; H, 6.26.

*Z-Methyl 4-(2,4-Dichlorophenyl)-3-methoxycarbonylbut-3-enoate (***Z-6g***).* Yield: 37%; oil. IR (neat): $\nu = 2950$, 1740, 1720, 1590, 1470, 1440, 1220, 1180 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 7.38$ (s, 1H), 7.10–7.30 (m, 2H), 6.89 (s, 1H), 3.69 (s, 3H), 3.59 (s, 3H), 3.49 (s, 2H). MS: *m/z* (%) = 302 (M^+, 3), 269 (36), 267 (100), 149 (12). Anal. Calc. for $C_{13}H_{12}Cl_2O_4$ (303.14): C, 51.50; H, 3.99. Found: C, 51.48; H, 3.61.

*E-Methyl 4-(2,4-Dichlorophenyl)-3-methoxycarbonylbut-3-enoate (***E-6g***) [10].* Yield: 25%; oil. IR (neat): $\nu = 3090$, 2960, 1740, 1720, 1590, 1470, 1440, 1290, 1210, 1180, 1100 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 7.83$ (s, 1H), 7.40 (d, $J = 1.7$ Hz, 1H), 7.15–7.25

(m, 2H), 3.80 (s, 3H), 3.69 (s, 3H), 3.35 (s, 2H). MS: *m/z* (%) = 302 (M^+, 1), 269 (35), 267 (100), 149 (24).

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