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The Reaction of Organozinc Reagents with Trifluoroacylated Phosphonates: Synthesis of Trifluoromethylated α,β-Unsaturated Esters with an Active Methylene Moiety

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ABSTRACT: *The consecutive reaction of phosphonates* **1** *with n-butyllithium, trifluoroacetic anhydride, and organozinc compounds gives trifluoromethylated α,β-unsaturated esters with an active methylene moiety and predominant Z-selectivity in 54–78% (3 steps) yields.* © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:289–292, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20018

INTRODUCTION

Much attention has been devoted to the synthesis of α,β-unsaturated acids and their esters, because such compounds have been noted as important structure feature in a number of naturally occurring compounds which show biological activities [1]. They are useful intermediates in synthesis of some bioactive compounds [2] and are able to undergo many useful synthetic transformations [3]. In the past several decades fluorinated α,β-unsaturated esters have attracted much interest, particularly for the synthesis of fluorine-containing bioactive compounds [4]. Recently, stereoselective synthesis of trisubstituted and tetrasubstituted α,β-unsaturated esters via copper-catalyzed coupling of enol triflates of β-ketoesters with Grignard-based zinc ate complexes was reported [5]. However, to the best of our knowledge, the synthesis of fluorinated tetrasubstituted α,β-unsaturated esters is still limited [6].

RESULTS AND DISCUSSION

As part of our continuing investigation of synthetic application of consecutive reaction of phosphorus compounds in organic synthesis [6b,7] herein we report the consecutive reaction of phosphonates **1** with *n*-butyllithium, trifluoroacetic anhydride, and organozinc compounds to give trifluoromethylated α,β-unsaturated esters with an active methylene moiety and predominant *Z*-selectivity. The reaction sequence is shown in Scheme 1.

Phosphonate **1** was treated with *n*-butyllithium in tetrahydrofuran (THF) at −78°C and the resulting carbanion **2** reacted with trifluoroacetic anhydride to form the intermediate **3** which was further reacted with organozinc compounds, followed by elimination of phosphate anion, giving substituted trifluoromethylated α,β-unsaturated esters with predominant *Z*-selectivity in 54–78% yields (3 steps). The results are summarized in Table 1.

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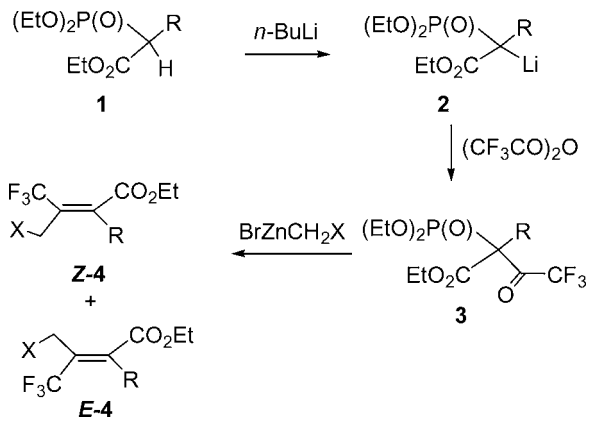
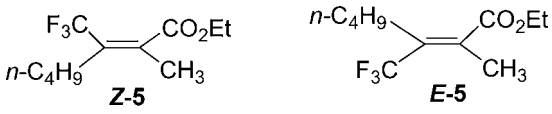


SCHEME 1

The ^{19}F NMR data of similar compounds ***Z*-5** and ***E*-5** have been reported [6b]:



$\delta = -17.7$ ppm $\qquad$ $\delta = -14.7$ ppm

If the trifluoromethyl group is cis with respect to the ester group, the chemical shifts of the trifluoromethyl group appear downfield (*Z*-**5**), while those trans with respect to the ester group are shifted upfield (*E*-**5**). In the cases of **4a–4e**, the chemical shifts of trifluoromethyl group are in the range of −17.0 to −18.1 ppm, hence the configurations of the **4a–4e** could be ascertained as *Z*-isomers. In addition, on the basis of coupling constant across the double bond reported in the literature [8], if the trifluoromethyl group was trans with respect to the F group, the $^4J_{\text{FFtrans}}$ ranged from 7 to 13 Hz, while for those cis with respect to the F group, the $^4J_{\text{Ffcis}}$ ranged from 21 to 31 Hz. Thus the configuration of **4f–4g** could be ascertained.

TABLE 1 Substituted Trifluoromethylated α,β-Unsaturated Esters Prepared

Compound	*R*	*X*	*Yield (%)*[a]	*Ratio (Z:E)*[b]
4a	CH_3	CO_2Me	66	100:0
4b	CH_3	CO_2Et	62	100:0
4c	CH_3	CO_2Pr^i	54	100:0
4d	CH_3	CO_2Bu^t	62	100:0
4e	CH_3	CH_2=CH	57	100:0
4f	F	CO_2Et	74	5:95[c]
4g	F	CO_2Bu^t	78	34:66[c]
4h	F	CH_2=CH	66	14:86[c]

[a]Isolated yields.
[b]The ratios of *E*- and *Z*-isomers are estimated on the basis of NMR data.
[c]According to the sequence rules, in **4f–4h** (fluorine group instead of methyl group), when the fluorine group is trans with respect to the trifluoromethyl group, the stereoisomer is assigned as the *E*-isomer and, conversely in **4a–4e** they are assigned as the *Z*-isomer.

It is noteworthy that the title compounds with an active methylene moiety are able to deprotonate by a base forming a carbanion, which would be a potential useful fluorine-containing building block in organic synthesis.

When the organozinc reagent with double bond moiety ($BrZnCH_2CH$=CH_2) (**4e** and **4h**) is used as starting material, the trifluoromethylated dienyl carboxylates were obtained.

In summary this methodology provides a convenient synthesis of the title compounds, which would be useful intermediates in the synthesis of fluorine-containing biological active compounds.

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). ^{19}F NMR spectra were taken on a Varian EM-360 (60 MHz) spectrometer with CF_3CO_2H as external standard, positive for upfield shifts. Mass spectra were measured on a Finnigan GC-MS-4021 mass spectrometer. HRMS data were obtained on a Finnigan-Mat 8430 high resolution mass spectrometer.

Diethyl (1-ethoxycarbonyl-1-fluoromethyl)-phosphonate

It was prepared according to the known method [9].

General Procedure for the Preparation of Substituted Trifluoromethylated α,β-Unsaturated Esters

Treatment of phosphonate (**1**) (3 mmol) with *n*-butyllithium (3 mmol) in absolute THF (15 ml) at −78°C under nitrogen gave the phosphoryl-stabilized carbanion **2**, which was stirred at −78°C for 0.5 h under nitrogen. Trifluoroacetic anhydride (0.63 g, 3 mmol) was added to it in one portion. After stirring at −78°C for 0.5 h, the reaction mixture was allowed to warm to 20°C and the organozinc reagent [9 mmol, prepared from 9 mmol of bromoacetic ester and 9 mmol (0.59 g) of zinc powder] [10] was added to the mixture, which was stirred for another 4 h. The reaction mixture was poured into 0.5 N HCl solution (15 ml) and the water layer was

extracted with ethyl ether (3 × 20 ml). The combined organic layer was washed with water (3 × 15 ml) and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography eluting with petroleum ether (60–90°C)-ethyl acetate (99:2) to give the product **4**.

*Z-Ethyl 4-methoxycarbonyl-3-trifluoromethyl-2-methylbut-2-enoate (***Z-4a***)*

Yield: 66%; bp. 78°C/2 mm Hg. $Z{:}E = 100{:}0$. IR (neat): υ = 2990, 1750, 1730, 1660, 1440, 1270, 1130 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 4.24$ (q, $J = 7.1$ Hz, 2H), 3.70 (s, 3H), 3.48 (s, 2H), 2.14 (q, $J = 1.8$ Hz, 3H), 1.30 (t, $J = 7.1$ Hz, 3H). ^{19}F NMR ($CDCl_3$/TFA): $\delta = -17.2$ (s, 3F). MS: m/z (%) = 255 ($M^+ + 1$, 18), 223 (87), 209 (100), 208 (50), 195 (30), 181 (86), 180 (66), 167 (38). Anal Calc. for $C_{10}H_{13}F_3O_4$ (254.20): C, 47.25; H, 5.15. Found: C, 46.85; H, 4.99.

*Z-Ethyl 4-ethoxycarbonyl-3-trifluoromethyl-2-methylbut-2-enoate (***Z-4b***)*

Yield: 62%; bp. 89°C/2 mm Hg. $Z{:}E = 100{:}0$. IR (neat): υ = 2990, 1750, 1730, 1660, 1270, 1200, 1130, 1040 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 4.24$ (q, $J =$ 7.1 Hz, 2H), 4.16 (q, $J = 7.1$ Hz, 2H), 3.46 (s, 2H), 2.34 (q, $J = 2.1$ Hz, 3H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.25 (t, $J = 7.1$ Hz, 3H). ^{19}F NMR ($CDCl_3$/TFA): $\delta = -17.0$ (s, 3F). MS: m/z (%) = 269 ($M^+ + 1$, 8), 223 (100), 222 (38), 195 (82), 194 (31), 167 (83), 166 (38), 148 (36), 128 (34). Anal Calc. for $C_{11}H_{15}F_3O_4$ (268.23): C, 49.26; H, 5.64. Found: C, 48.92; H, 5.67.

*Z-Ethyl 4-i-propoxycarbonyl-3-trifluoromethyl-2-methylbut-2-enoate (***Z-4c***)*

Yield: 54%; bp. 90°C/2 mm Hg. $Z{:}E = 100{:}0$. IR (neat): υ = 2990, 1740, 1660, 1270, 1200, 1130, 1040 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 5.01$ (sept, $J =$ 6.3 Hz, 1H), 4.24 (q, $J = 7.1$ Hz, 2H), 3.43 (s, 2H), 2.13 (q, $J = 1.9$ Hz, 3H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.22 (d, $J = 6.3$ Hz, 6H). ^{19}F NMR ($CDCl_3$/TFA): $\delta = -17.3$ (s, 3F). MS: m/z (%) = 283 ($M^+ + 1$, 23), 241 (46), 223 (100), 196 (9), 195 (38), 167 (14), 43 (25). Anal Calc for $C_{12}H_{17}F_3O_4$ (282.25): C, 51.06; H, 6.07. Found: C, 50.86; H, 5.91.

*Z-Ethyl 4-t-butoxycarbonyl-3-trifluoromethyl-2-methylbut-2-enoate (***Z-4d***)*

Yield: 62%; bp. 96°C/2 mm Hg. $Z{:}E = 100{:}0$. IR (neat): υ = 2990, 1740, 1660, 1370, 1130, 1040 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 4.24$ (q, $J = 7.1$ Hz, 2H), 3.36 (s, 2H), 2.12 (q, $J = 2.2$ Hz, 3H), 1.40 (s, 9H), 1.30 (t, $J = 7.1$ Hz, 3H). ^{19}F NMR ($CDCl_3$/TFA): $\delta =$ −17.5 (s, 3F). MS: m/z (%) = 297 ($M^+ + 1$, 12), 242 (13), 241 (100), 224 (5), 223 (45), 195 (7), 175 (5).

HRMS: m/z Calc. for $C_{13}H_{19}F_3O_4$: 296.1235, Found 296.1237.

*Z-Ethyl 3-trifluoromethyl-2-methylhexa-2,5-dienoate (***Z-4e***)*

Yield: 57%; bp. 85°C/10 mm Hg. $Z{:}E = 100{:}0$. IR (neat): υ = 2990, 1730, 1730, 1670, 1270, 1190, 1130 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 5.88$–5.72 (m, 1H), 5.16–5.09 (m, 2H), 4.26 (q, $J = 7.1$ Hz, 2H), 3.06 (d, $J = 6.0$ Hz, 2H), 2.09 (q, $J = 2.4$ Hz, 3H), 1.32(t, $J = 7.1$ Hz, 3H). ^{19}F NMR ($CDCl_3$/TFA): $\delta = -18.1$ (s, 3F). MS: m/z (%) = 220 ($M^+ - 2$, 3), 179 (31), 177 (44), 149 (56), 130 (53), 129 (100), 109 (31), 79 (53). Anal Calc. for $C_{10}H_{13}F_3O_2$ (222.20): C, 54.05; H, 5.90. Found: C, 53.76; H, 5.89.

*Ethyl 4-ethoxycarbonyl-3-trifluoromethyl-2-fluorobut-2-enoate (***4f***)*

Yield: 74%; bp. 86°C/2 mm Hg. $Z : E = 5 : 95$. IR (neat): υ = 2990, 1750, 1660, 1320, 1200, 1160, 1090, 1020 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 4.36$ (q, $J =$ 7.1 Hz, 2H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.72 (d, $J = 1.6$ Hz, 0.05 × 2H), 3.40 (d, $J = 3.8$ Hz, 0.95 × 2H), 1.35 (t, $J = 7.1$ Hz, 3H), 1.26 (t, $J = 7.1$ Hz, 3H). ^{19}F NMR ($CDCl_3$/TFA): $\delta = -17.5$ (d, $J = 10$ Hz, 0.95 × 3F), −14.5 (d, $J = 24$ Hz, 0.05 × 3F), 28.8 (m, 1F). MS: m/z (%) = 273($M^+ + 1$, 9), 253 (13), 227 (26), 199 (43), 172 (86), 171 (100), 152 (60), 132 (68). Anal Calc. for $C_{10}H_{12}F_4O_4$ (272.19): C, 44.13; H, 4.44. Found: C, 43.91; H, 4.48.

*Ethyl 4-tert-butoxycarbonyl-3-trifluoromethyl-2-fluorobut-2-enoate (***4g***)*

Yield: 78%; bp. 88°C/2 mm Hg. $Z : E = 34 : 66$. IR (neat): υ = 2990, 1740, 1660, 1380, 1330, 1280, 1160, 1020 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 4.42$–4.34 (m, 2H), 3.66(d, $J = 1.7$ Hz, 0.34 × 2H), 3.34 (d, $J =$ 3.8 Hz, 0.66 × 2H), 1.47 (s, 9H), 1.37 (t, $J = 7.2$ Hz, 3H). ^{19}F NMR ($CDCl_3$/TFA): $\delta = -17.8$ (d, $J = 10$ Hz, 0.66 × 3F), −14.0 (d, $J = 24$ Hz, 0.34 × 3F), 29.8 (m, 0.66 × 1F), 32.4 (m, 0.34 × 1F). MS: m/z (%) = 301 ($M^+ + 1$, 16), 245 (100), 227 (28), 57 (54). HRMS: m/z Calc. for $C_{12}H_{16}F_4O_4$: 300.0985, Found 300.0953.

*Ethyl 3-trifluoromethyl-2-fluorohexa-2,5-dienoate (***4h***)*

Yield: 66%; bp. 82°C/10 mm Hg. $Z : E = 14 : 86$. IR (neat): υ = 2990, 1740, 1670, 1640, 1270, 1190, 1380,

1350, 1280, 1220, 1140 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): $\delta = 5.90–5.72$ (m, 1H), 5.25–5.10 (m, 2H), 4.35 (q, $J = 7.1$ Hz, 2H), 3.40 (d, $J = 6.1$ Hz, $0.86 \times 2H$), 3.10 (dd, $J = 6.1$, 3.6 Hz, $0.14 \times 2H$), 1.37 (t, $J = 7.2$ Hz, 3H). ^{19}F NMR ($CDCl_3$/TFA): $\delta = -17.6$ (d, $J = 10$ Hz, $0.14 \times 3F$), -15.6 (d, $J = 24$ Hz, $0.86 \times 3F$), 32.5–34.8 (m, 1F). MS: m/z (%) = 227 ($M^+ + 1$, 28), 199 (34), 172 (47), 171 (73), 152 (38), 132 (37), 57 (100). HRMS: m/z Calc. for $C_9H_{10}F_4O_2$: 226.0617, Found 226.0604.

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