A Stereoselective Synthesis of (Z)- and (E)-Trifluoromethylated α,β-Unsaturated Esters via Intramolecular Wittig Reaction

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Fluorinated dicarbonyl triphenylphosphoranes 1 reacted with a variety of Grignard reagents to give β-oxido ylides 2. Treatment of 2 with acetic acid or saturated aqueous methylamine hydrochloride, followed by elimination of triphenylphosphine oxide, gave trifluoromethylated α,β-unsaturated esters with the Z-isomers being the major products; while treatment of 2 with 5% aqueous hydrochloric acid under the same conditions afforded predominately E-isomers of the title compounds.

Introduction of trifluoromethyl group into organic molecules has become a most attractive subject because pharmaceutical and agricultural chemicals that contain trifluoromethyls group show unique biological activities.[1] Trifluoromethylated α,β-unsaturated esters are important intermediates in synthetic organic chemistry, particularly for the synthesis of biologically active compounds.[2] Usually they are prepared from trifluoromethyl ketones by Wittig condensation or Horner–Emmons reaction giving E-isomers predominately.[3] Reported methods for the preparation of the Z-isomer of trifluoromethylated α,β-unsaturated esters are rather cumbersome.[4] The Wittig condensation gives a mixture of E- and Z-isomers which is enriched in the Z-isomer by photosensitized isomerization of the double bond with benzophenone to give a photoequilibrium having an E:Z ratio of 57:43.[4] The Z ester was separated from its E-isomer by spinning band distillation.[4] Therefore a more efficient method would be valuable.

Results and Discussion

Recently we found that (E)-trifluoromethylated α,β-unsaturated esters could be conveniently synthesized by reaction of organolithium compounds with a fluorinated dicarbonyl phosphonium salt prepared in situ by acylation of the corresponding phosphorane with trifluoroacetic anhydride.[5] Alternatively, fluorinated (dicarbonylmethylene)triphenylphosphoranes could also be used to synthesize perfluoroalkylated α,β-unsaturated carbonyl compounds by reaction with various lithium reagents and protonation, giving E-isomers predominately.[6] As an extension of this study, we now report the reaction of Grignard reagents with fluorinated (dicarbonylmethylene)triphenylphosphoranes to give (Z)- and (E)-trifluoromethylated α,β-unsaturated esters depending upon the acid used to protonate the intermediate that is formed.

Fluorinated (dicarbonylmethylene)triphenylphosphoranes 1 are very stable because of the strong electron-withdrawing effect of the two carbonyl groups making them unreactive toward aldehydes or ketones. However, they did react with a variety of Grignard reagents afer protonation and elimination of triphenylphosphine oxide, giving trifluoromethylated α,β-unsaturated esters (Scheme I). The reaction is initiated by nucleophilic attack of Grignard reagents on the trifluoromethyl ketone carbonyl carbon of fluorinated phosphorane 1 to give β-oxido ylides 2. The trifluoromethyl ketone carbonyl carbon is more nucleophilic than the carboxy ester carbonyl due to the strong electron-withdrawing effect of the trifluoromethyl group, therefore the attack was chemospecific at the trifluoromethyl ketone carbonyl carbon. Treatment of 2 with acetic acid or saturated aqueous methylamine hydrochloride, followed by elimination of triphenylphosphine oxide, afforded trifluoromethylated α,β-unsaturated esters with Z-isomers as major products while treatment of 2 with 5% aqueous hydrochloric acid under the same conditions afforded predominately E-isomers of the title compounds.

On the basis of data reported in the literature,[3b,c,7] the chemical shift of the trifluoromethyl group in the Z-isomer appears at lower field than that of the corresponding E-isomer; hence the relative proportions of the Z- and E-isomers could be ascertained.

The results are summarized in Tables I–IV.

The following are noteworthy: (1) the stereoselectivity was reversed, when saturated aqueous methylamine hydrochloride or acetic acid was used in place of 5% aqueous hydrochloric acid for protonation. The former gave Z-selectivity and the latter gave E-selectivity. (2) In the case of β-oxido ylides generated from phenyl Grignard reagent, only E-selectivity was observed.

Experimental Section

General. Analytical samples were purified by Kugelrohr distillation with the oven temperature (ot) given. ^{19}F NMR spectra are reported as ppm upfield from TFA. MS were obtained using chemical ionization and are reported as m/e (relative intensity). Preparative TLC were performed with 20 × 20 cm² plates coated with silica gel GF (1000 μm).

Materials. THF was purified by distillation from sodium benzophenone ketyl. Trifluoroacetylated phosphoranes 1 were prepared according to the known procedures.[8] Grignard reagents

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Scheme I

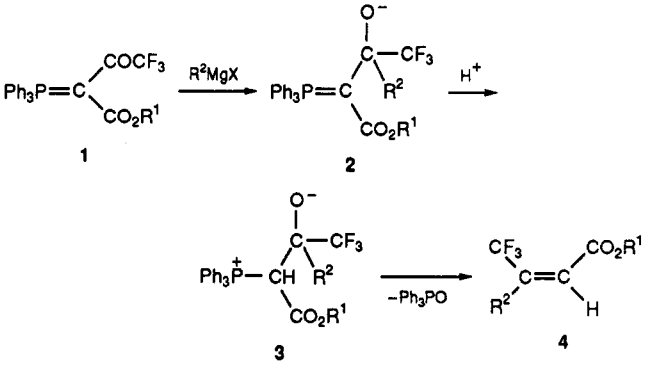

Table I. Protonation of β-Oxido Ylides 2 with 5% Hydrochloric Acid

compd	R^1	R^2	X	reactn temp (°C)	yield[a] (%)	Z:E[b]
4a	t-Bu	n-C_6H_{13}	Br	rt	94	0:100
4b	t-Bu	$PhCH_2$	Cl	rt	86	3:97
4c	t-Bu	n-Bu	Br	0	95	4:96
4d	t-Bu	Et	I	0	84	8:92
4e	t-Bu	Me	I	0	89	10:90
4f	t-Bu	PhC≡C	I	rt	88	12:88
4g	Et	Me	I	0	72	25:75
4h	Et	PhC≡C	I	rt	91	25:75

[a] Isolated yields. [b] The ratio of Z- and E-isomers was estimated on the basis of NMR spectra.

Table II. Protonation of β-Oxido Ylides 2 with Acetic Acid

compd	R^1	R^2	X	reactn temp (°C)	yield[a] (%)	Z:E[b]
4d	t-Bu	Et	I	0	81	93:7
4e	t-Bu	Me	I	0	90	92:8
4f	t-Bu	PhC≡C	I	rt	85	77:23
4h	Et	PhC≡C	I	rt	87	73:27
4a	t-Bu	n-C_6H_{13}	Br	rt	95	71:29
4g	Et	Me	I	0	75	70:30
4c	t-Bu	n-Bu	Br	0	92	68:32
4b	t-Bu	$PhCH_2$	Cl	rt	84	40:60

[a] Isolated yields. [b] The ratio of Z- and E-isomers was estimated on the basis of NMR spectra.

Table III. Protonation of β-Oxido Ylides 2 with Saturated Aqueous Methylamine Hydrochloride

compd	R^1	R^2	X	reactn temp (°C)	yield[a] (%)	Z:E[b]
4a	t-Bu	n-C_6H_{13}	Br	rt	94	94:6
4b	t-Bu	$PhCH_2$	Cl	rt	85	91:9
4c	t-Bu	n-Bu	Br	0	92	90:10

[a] Isolated yields. [b] The ratio of Z- and E-isomers was estimated on the basis of NMR spectra.

were prepared by adding halides to magnesium turning under nitrogen in diethyl ether with gentle boiling. PhC≡CMgI was prepared in situ from equal equivalents of phenylacetylene and MeMgI in THF at 0 °C for 1 h.

Typical Procedure for the Preparation of Trifluoromethylated α,β-Unsaturated Esters 4. Grignard reagent (5 mmol) was added dropwise to a solution of trifluoromethylated phosphorane 1 (4 mmol) in THF (20 ml) under N_2, the mixture was stirred at 0 °C or 20 °C for 1 h, and the proton donor (1 mL of 5% HCl, 1 mL of HOAc, or 1 mL of saturated aqueous CH_3NH_2HCl) was added. The mixture was warmed to 20 °C, and stirred for 2 h, and diethyl ether (20 mL) was added. The organic layer was washed repeatedly with water to neutral pH and dried (Na_2SO_4). Evaporation of the solvents gave the residue which was purified by preparative TLC on silica gel eluting with petroleum ether (60–90 °C)/ethyl acetate (95:5), affording the product 4. The component in front was identified as E-isomer, while the one behind was the Z-isomer.

Table IV. Protonation of β-Oxido Ylides 2 Generated from Phenyl Grignard Reagent (PhMgBr)

compd	R^1	reactn temp (°C)	proton donor	yield[a] (%)	Z:E[b]
4i	t-Bu	0	HCl	86	8:92
4j	Et	−10	HCl	85	8:92
4i	t-Bu	0	HOAc	81	8:92
4j	Et	−10	HOAc	82	8:92
4i	t-Bu	0	CH_3NH_2HCl	81	8:92

[a] Isolated yields. [b] The ratio of Z- and E-isomers was estimated on the basis of NMR spectra.

***tert*-Butyl (*Z*)-3-(trifluoromethyl)-2-decenoate (*Z*-4a):** bp 192 °C; IR (neat) 1670 (C=C), 1740 (C=O) cm^{-1}; ^{19}F NMR −15.1; ^1H NMR 0.87 (t, J = 7.2 Hz, 3H, CH_3), 1.12–1.72 (m, 8H), 1.48 (s, 9H, t-Bu), 2.19 (t, J = 7.2 Hz, 2H, CH_2), 5.92 (m, 1H, CH=C); MS 281 (3, M + 1), 280 (3, M^+), 223 (14), 207 (100, M − OBu). Anal. Calcd for $C_{14}H_{23}F_3O_2$: C, 59.98; H, 8.27. Found: C, 59.99; H, 8.27.

***tert*-Butyl (*E*)-3-(trifluoromethyl)-2-decenoate (*E*-4a):** bp 176 °C; IR (neat) 1670 (C=C), 1730 (C=O) cm^{-1}; ^{19}F NMR δ −8.8; ^1H NMR δ 0.87 (t, J = 7.2 Hz, 3H, CH_3), 1.12–1.72 (m, 8H), 1.50 (s, 9H, t-Bu), 2.58 (t, J = 7.2 Hz, 2H, CH_2), 6.18 (q, J = 0.9 Hz, 1H, CH=C); MS 281 (4, M + 1), 280 (3, M^+), 224 (78), 207 (100, M − OBu). Anal. Calcd for $C_{14}H_{23}F_3O_2$: C, 59.98; H, 8.27. Found: C, 60.15; H, 8.35.

***tert*-Butyl (*Z*)-4,4,4-trifluoro-3-benzyl-2-butenoate (*Z*-4b):** bp 189 °C; IR (neat) 1670 (C=C), 1730 (C=O) cm^{-1}; ^{19}F NMR δ −14.9; ^1H NMR δ 1.47 (s, 9 H, t-Bu), 3.51 (d, J = 1.6 Hz, 2H, CH_2), 5.66 (t, J = 1.6 Hz, 1H, CH=C), 7.04–7.43 (m, 5H, Ph); MS 285 (2, M − 1), 209 (24, M − Ph), 181 (20), 153 (100). Anal. Calcd for $C_{15}H_{17}F_3O_2$: C, 62.92; H, 5.99. Found: C, 62.83; H, 6.09.

***tert*-Butyl (*E*)-4,4,4-trifluoro-3-benzyl-2-butenoate (*E*-4b):** bp 178 °C; IR (neat) 1670 (C=C), 1730 (C=O) cm^{-1}; ^{19}F NMR δ −10.5; ^1H NMR δ 1.45 (s, 9H, t-Bu), 4.02 (s, 2H, CH_2), 6.38 (m, 1H, CH=C), 7.08–7.28 (m, 5H, Ph); MS 287 (89, M + 1), 286 (9, M^+), 231 (100), 213 (20, M − OBu). Anal. Calcd for $C_{15}H_{17}F_3O_2$: C, 62.92; H, 5.99. Found: C, 62.95; H, 5.83.

***tert*-Butyl (*Z*)-3-(trifluoromethyl)-2-heptenoate (*Z*-4c):** bp 179 °C; IR (neat) 1660 (C=C), 1740 (C=O) cm^{-1}; ^{19}F NMR δ −14.3; ^1H NMR δ 0.91 (t, J = 7.2 Hz, 3H, CH_3), 1.28–1.72 (m, 4H), 1.49 (s, 9H, t-Bu), 2.21 (t, J = 7.2 Hz, 2H, CH_2), 5.93 (s, 1H, CH=C); MS 252 (1, M^+), 225 (29), 183 (13, CF_3), 179 (100, M − OBu). Anal. Calcd for $C_{12}H_{19}F_3O_2$: C, 57.13; H, 7.59. Found: C, 56.89; H, 7.62.

***tert*-Butyl (*E*)-3-(trifluoromethyl)-2-heptenoate (*E*-4c):** bp 162 °C; IR (neat) 1670 (C=C), 1730 (C=O) cm^{-1}; ^{19}F NMR δ −8.7; ^1H NMR δ 0.92 (t, J = 7.2 Hz, 3H, CH_3), 1.30–1.64 (m, 4H), 1.50 (s, 9H, t-Bu), 2.60 (t, J = 7.2 Hz, 2 H, CH_2), 6.22 (q, J = 1.6 Hz, 1H, CH=C); MS 253 (12, M + 1), 197 (10), 179 (20, M − OBu), 57 (100). Anal. Calcd for $C_{12}H_{19}F_3O_2$: C, 57.13; H, 7.59. Found: C, 56.88; H, 7.43.

***tert*-Butyl (*Z*)-(trifluoromethyl)-2-pentenoate (*Z*-4d):** bp 160 °C; IR (neat) 1670 (C=C), 1730 (C=O) cm^{-1}; ^{19}F NMR δ −14.5; ^1H NMR δ 1.10 (t, J = 7.7 Hz, 3H, CH_3), 1.49 (s, 9H, t-Bu), 2.25 (dq, J = 0.9, 7.7 Hz, 2H, CH_2), 5.92 (t, J = 0.9 Hz, 1H, CH=C); MS 225 (21, M + 1), 169 (27), 151 (58, M − OBu), 57 (100). Anal. Calcd for $C_{10}H_{15}F_3O_2$: C, 53.56; H, 6.74. Found: C, 53.49; H, 6.56.

***tert*-Butyl (*E*)-(trifluoromethyl)-2-pentenoate (*E*-4d):** bp 149 °C; IR (neat) 1670 (C=C), 1740 (C=O) cm^{-1}; ^{19}F NMR δ −8.6; ^1H NMR δ 1.16 (t, J = 7.7 Hz, 3H, CH_3), 1.51 (s, 9H, t-Bu), 2.63 (q, J = 7.7 Hz, 2H, CH_2), 6.18 (q, J = 1.2 Hz, 1H, CH=C); MS 225 (24, M + 1), 169 (42), 152 (60), 57 (100). Anal. Calcd for $C_{10}H_{15}F_3O_2$: C, 53.56; H, 6.74. Found: C, 53.41; H, 6.85.

***tert*-Butyl (*Z*)-4,4,4-trifluoro-3-methyl-2-butenoate (*Z*-4e):** bp 144 °C; IR (neat) 1680 (C=C), 1730 (C=O) cm^{-1}; ^{19}F NMR δ −13.2; ^1H NMR δ 1.48 (s, 9H, t-Bu), 1.96 (d, J = 1.6 Hz, 3H, CH_3), 5.96 (q, J = 1.6 Hz, 1H, CH=C); MS 211 (7, M + 1), 138 (59), 58 (100). Anal. Calcd for $C_9H_{13}F_3O_2$: C, 51.42; H, 6.23. Found: C, 51.28; H, 6.10.

***tert*-Butyl (*E*)-4,4,4-trifluoro-3-methyl-2-butenoate (*E*-4e):** bp 128 °C; IR (neat) 1680 (C=C), 1730 (C=O) cm^{-1}; ^{19}F NMR δ −6.4; ^1H NMR δ 1.49 (s, 9 H, t-Bu), 2.18 (d, J = 1.6 Hz,

3H, CH_3), 6.20 (m, 1H, CH=C); MS 211 (1, M + 1), 137 (54, M - OBu), 109 (15, M - CO_2Bu), 57 (100). Anal. Calcd for $C_9H_{13}F_3O_2$: C, 51.42; H, 6.23. Found: C, 51.50; H, 5.94.

***tert*-Butyl 3-(trifluoromethyl)-5-phenylpent-2-en-4-ynoate (4f)**: obtained as a mixture of *Z*- and *E*-isomers; ot 84 °C/1 mmHg; IR (neat) 1650 (C=C), 1730 (C=O), 2190 (C≡C) cm^{-1}; ^{19}F NMR δ -10.7 (*E*-isomer) and -16.3 (*Z*-isomer); ^1H NMR δ 1.53 (s, 9H, *t*-Bu), 6.42 (s, *Z*-isomer) and 6.51 (q, J = 1.0 Hz, *E*-isomer) (1H, CH=C), 7.20-7.62 (m, 5H, Ph); MS 297 (7, M + 1), 296 (6, M^+), 241 (100), 223 (20, M - OBu). Anal. Calcd for $C_{16}H_{15}F_{32}$: C, 64.85; H, 5.10. Found: C, 65.10; H, 4.97.

Ethyl (*Z*)-4,4,4-trifluoro-3-methyl-2-butenoate (*Z*-4g): bp 135 °C (lit.[4] bp 126 °C/650 mmHg); IR (neat) 1680 (C=C), 1740 (C=O) cm^{-1}; ^{19}F NMR δ -12.3; ^1H NMR δ 1.31 (t, J = 7.2 H, 3H, CH_3), 1.99 (d, J = 1.6 Hz, 3H, CH_3), 4.22 (q, J = 7.2 Hz, 2H, CH_2), 6.05 (q, J = 1.6 Hz, 1H, CH=C).

Ethyl (*E*)-4,4,4-trifluoro-3-methyl-2-butenoate (*E*-4g): bp 121 °C (lit.[4] bp 116-118 °C/650 mmHg); IR (neat) 1685 (C=C), 1750, (C=O) cm^{-1}; ^{19}F NMR δ -6.6; ^1H NMR δ 1.30 (t, J = 7.2 Hz, 3H, CH_3), 2.24 (d, J = 1.6 Hz, 3H, CH_3), 4.21 (q, J = 7.2 Hz, 2H, CH_2), 6.26 (m, 1H, CH=C).

Ethyl 3-(trifluoromethyl)-5-phenylpent-2-en-4-ynoate (4h): obtained as a mixture of *Z*- and *E*-isomers; ot 100 °C/1 mmHg; IR (neat) 1630 (C=C), 1730 (C=O), 2190 (C≡C) cm^{-1}; ^{19}F NMR δ -10.5 (*E*-isomer) and -16.0 (*Z*-isomer); ^1H NMR δ 1.22 (t, J = 7.2 Hz, 3H, CH_3), 4.18 (q, J = 7.2 Hz, 2H, CH_2), 6.41 (s, *Z*-isomer) and 6.50 (q, J = 1.2 Hz, *E*-isomer) (1 H, CH=C), 7.10-7.53 (m, 5 H, Ph); MS 269 (43, M + 1), 268 (100, M^+), 223 (87, M - OEt), 195 (48, M - CO_2Et). Anal. Calcd for $C_{14}H_{11}F_3O_2$: C, 62.68; H, 4.13. Found: C, 62.42; H, 4.13.

***tert*-Butyl 4,4,4-trifluoro-3-phenyl-2-butenoate (4i)**: obtained as a mixture of *Z*- and *E*-isomers; ot 60 °C/1 mmHg; IR (neat) 1660 (C=C), 1730 (C=O) cm^{-1}; ^{19}F NMR δ -10.5 (*E*-isomer) and -17.3 (*Z*-isomer); ^1H NMR δ 1.20 (s, 9H, *t*-Bu), 6.22 (s, *Z*-isomer) and 6.49 (q, J = 1.3 Hz, *E*-isomer) (1H, CH=C), 7.20-7.44 (m, 5H, Ph); MS 273 (44, M + 1), 272 (1, M^+), 217 (90), 199 (100, M - OBu). Anal. Calcd for $C_{14}H_{15}F_3O_2$: C, 61.76; H, 5.55. Found: C, 61.87; H, 5.35.

Ethyl 4,4,4-trifluoro-3-phenyl-2-butenoate (4j): obtained as a mixture of *Z*- and *E*-isomers; ot 75 °C/2 mm Hg (lit.[3a] *E*-isomer: bp 220 °C/747 mmHg); IR (neat) 1670 (C=C), 1740 (C=O) cm^{-1}; ^{19}F NMR δ -10.0 (*E*-isomer) and -17.3 (*Z*-isomer); ^1H NMR 1.07 and 1.38 (t, J = 7.2 Hz, 3H, CH_3), 3.97 and 4.34 (q, J = 7.2 Hz, 2H, CH_2), 6.36 (s, *Z*-isomer) and 6.63 (q, J = 1.3 Hz, *E*-isomer) (1H, CH=C), 7.38-7.70 (m, 5H, Ph).

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