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A ONE-POT SYNTHESIS OF TRIFLUOROMETHYLATED α,β-UNSATURATED ESTERS

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SUMMARY

Trifluoromethylated α,β-unsaturated esters were conveniently synthesized by reaction of organolithium compounds with a fluorinated biscarbonylphosphonium salt which was prepared in situ by acylation of the corresponding phosphorane with trifluoroacetic anhydride.

INTRODUCTION

Fluorinated α,β-unsaturated esters are important intermediates in synthetic organic chemistry, being essential components in the synthesis of some biologically active compounds [1]. Therefore reactions leading to the formation of them have attracted much attention. It is of much value to develop an effective method for the synthesis of the title compounds. Recently we have reported that fluorinated

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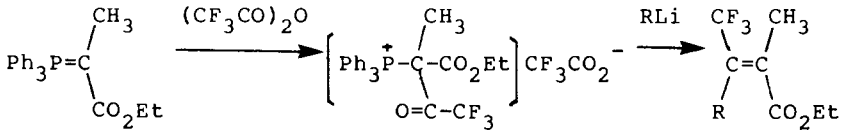
β-ketophosphonium salts reacted with nucleophiles to give fluoroalkenes [2] and fluoroenynes [3]. In our continuing investigation to exploit the synthetic utility of fluorinated β-ketophosphonium salts in organic synthesis, we now wish to report a facile synthesis of trifluoromethylated α,β-unsaturated esters by reaction of organolithium compounds with a fluorinated biscarbonylphosphonium salt.

RESULTS AND DISCUSSION

The fluorinated biscarbonylphosphonium salt **2** which was prepared from acylation of phosphorane **1** with trifluoroacetic anhydride has two reactive centres when it reacts with organolithium compounds. Because the trifluoroacetyl group is more reactive than carbethoxy group, the present reaction regioselectively gives only α,β-unsaturated esters. No unsaturated ketones are isolated.

The reaction sequence is as follows:



1 **2** **3**

a R=C_6H_5- d R=n-$C_8H_{17}C{\equiv}C$- g R=p-$CH_3OC_6H_4$-

b R=$C_6H_5C{\equiv}C$- e R=p-$CH_3C_6H_4$- h R=o-$CH_3OC_6H_4$-

c R=n-$C_4H_9C{\equiv}C$- f R=o-$CH_3C_6H_4$-

Elimination of triphenylphosphine oxide follows Cram's rule and gives the E-isomer highly stereoselectively. The results are shown in Table 1.

This facile one-pot synthesis of trifluoromethylated α,β-unsaturated esters is quite convenient with high stereoselectivity giving the E-isomer exclusively or predominately. It should be useful in the synthesis of trifluoromethylated biologically active compounds.

TABLE 1

Synthesis of Fluorinated α,β-Unsaturated Esters **3**

Compound	R	b.p.(°C/2mmHg)	Yield(%)[a]	E :Z[b]
3a	C_6H_5-	80	66	85:15
3b	$C_6H_5C{\equiv}C$-	88	41	77:23
3c	n-$C_4H_9C{\equiv}C$-	63	50	92:8
3d	n-$C_8H_{17}C{\equiv}C$-	74	46	100:0
3e	p-$CH_3C_6H_4$-	94	66	95:5
3f	o-$CH_3C_6H_4$-	88	59	86:14
3g	p-CH_3O-C_6H_4-	92	47	100:0
3h	0-CH_3O-C_6H_4-	90	40	100:0

[a] Isolated yields.

[b] The ratios of E- and Z-isomers are estimated on the basis of ^{19}F NMR data.

EXPERIMENTAL

All boiling points were uncorrected. Infrared spectra of liquid products were determined as films on a Shimadzu IR-440 Spectrometer. NMR spectra (chemical shifts in ppm from TMS for ^{1}H NMR and from external TFA for ^{19}F NMR, positive for upfield shifts) were obtained on a Varian EM-360 Spectrometer at 60 MHz. Mass spectra were recorded on a Finnigan GC-MC 4021 Mass Spectrometer.

General procedure for preparation of trifluoromethylated α,β-unsaturated esters 3

Trifluoroacetic anhydride (0.42g, 2 mmol) is added dropwise to the solution of carbethoxyethylidenetriphenylphosphorane (0.72g, 2 mmol) in absolute THF (15 ml) at -78°C under nitrogen. After stirring for 30 min at this temperature, phenyllithium (4mmol in absolute Et_2O) is slowly added for 30 min. The mixture is then warmed to room temperature and stirred for a further 3h. The product is isolated by column chromatography on silica gel eluting with petroleum ether (60-96 °C)/ ethyl acetate (10/1).

3a: 66% yield; b.p. 80°C/2mmHg; IR(film): 1740(s), 1670(m) cm^{-1}; ^{1}H NMR(CCl_4): δ 1.25(E+Z)(t,3H,J=6Hz), 1.72-1.80(E+Z)(m,3H), 4.20(E+Z)(q,2H,J=6Hz), 7.20-7.50(E+Z)(m,5H); ^{19}F NMR

(CCl_4): δ [-16.0(E) + (-17.2)(Z)](s,3F)ppm; MS m/e: 258(M^+, 69%), 213(M^+-OEt,100%), 185(M^+-CO_2Et,38%); Analysis: Calcd for $C_{13}H_{13}F_3O_2$: C,60.49; H,5.04; Found: C,60.34, H,5.01 %.

3b: 41% yield; b.p. 88°C/2mmHg; IR(film): 2220(w), 1740(s), 1640(m)cm^{-1}; ^{1}H NMR(CCl_4): δ 1.35(E+Z)(t, 3H, J=6Hz), 2.05-2.45(E+Z)(m,3H), 4.20(E+Z)(q,2H,J=6Hz), 7.42(E+Z)(s,5H); ^{19}F NMR(CCl_4): δ [-15.3(E)+(-17.1)(Z)](s,3F)ppm; MS m/e: 282(M^+, 100%), 237(M^+-OEt,60%), 209(M^+-CO_2Et, 16%). Analysis: Calcd for $C_{15}H_{13}F_3O_2$: C,63.85, H,4.61; Found: C,63.98, H, 4.83 %.

3c: 50% yield; b.p. 63°C/2mmHg; IR(film): 2220(w), 1740(s), 1640(m)cm^{-1}; ^{1}H NMR(CCl_4): δ 0.64-1.64(E+Z)(m, 9H), 2.00-2.15 (E+Z)(m,3H), 2.39(E+Z)(t,3H.,J=6Hz), 4.20(E+Z)(q, 2H,J=6Hz); ^{19}F NMR(CCl_4): δ [-15.4(E)+(-17.4)(Z)](s,3F)ppm; MS m/e: 263 (M^++1,100%), 262(M^+,9%), 217(M^+-OEt,62%), 189(M^+-CO_2Et,12%). Analysis: Calcd for $C_{13}H_{17}F_3O_2$: C,59.56, H, 6.49; Found: C, 59.66, H,6.60 %.

3d: 46% yield; b.p. 74°C/2mmHg; IR(film): 2230(w), 1740(s), 1640(m)cm^{-1}; ^{1}H NMR(CCl_4): δ 0.70-1.50 (m,17H), 2.00-2.17(m, 3H), 2.36(t, 3H, J=6Hz), 4.15(q, 2H, J=6Hz); ^{19}F NMR(CCl_4):δ -17.4(s,3F)ppm; MS m/e: 319(M^++1,100%), 318(M^+,10%), 273(M^+ -OEt,94%),245(M^+-CO_2Et,9%); Analysis: Calcd for $C_{17}H_{25}F_3O_2$: C,64.17, H,7.86; Found: C,64.16, H,7.73 %

3e: 66% yield; b.p. 94°C/2mmHg; IR(film): 1740(s), 1670(m) cm^{-1}; ^{1}H NMR(CCl_4):δ1.31(E+Z)(t, 3H, J=6Hz), 1.70-1.84(E+Z)(m,3H), 2.34(E+Z)(s,3H), 4.21(E+Z)(q,2H,J=6Hz), 7.14(E+Z)(s, 4H); ^{19}F NMR(CCl_4):δ[-15.6(E)+(-16.4)(Z)](s,3F)ppm; MS m/e: 272(M^+,100%), 227(M^+-OEt,71%), 199(M^+-CO_2Et,15%); Analysis: Calcd for $C_{14}H_{15}F_3O_2$: C,61.79, H,5.51; Found: C,62.25, H,5.52 %.

3f: 59% yield; b.p. 88°C/2mmHg; IR(film): 1740(s), 1670(m) cm^{-1}; ^{1}H NMR(CCl_4):δ1.34(E+Z)(t,3H,J=6Hz), 1.52-1.77(m, 3H), 2.25(E+Z)(s,3H), 4.27(E+Z)(q, 2H, J=6Hz), 7.02(E+Z)(m, 4H); ^{19}F NMR(CCl_4): δ[-15.4(E)+(-16.7(Z)](s, 3F)ppm; MS m/e: 273(M^++1,15%), 272(M^+,7%), 227(M^+-OEt,66%), 199(M^+-CO_2Et, 24%); Analysis: Calcd for $C_{14}H_{15}F_3O_2$: C,61.79, H,5.51; Found: C, 62.03, H,5.65 %.

3g: 47% yield; b.p. 92°C/2mmHg; IR(film): 1740(s), 1660(m) cm^{-1}; ^{1}H NMR(CCl_4): δ1.20(t, 3H, J=6Hz), 1.40-1.75(m, 3H), 3.64(s, 3H), 4.08(q, 2H, J=6Hz), 6.62-7.08(m, 4H); ^{19}F NMR (CCl_4): δ-15.3(s,3F)ppm; MS m/e: 288(M^+, 100%), 243(M^+-OEt, 71%), 215(M^+-CO_2Et,16%); Analysis: Calcd for $C_{14}H_{15}F_3O_3$: C,58.36, H,5.20; Found: C,58.23, H,5.31 %.

3h: 40% yield; b.p. 90°C/2mmHg; IR(film): 1740(s), 1670(m) cm^{-1}; ^{1}H NMR(CCl_4): δ1.23(t, 3H, J=6Hz), 1.45-1.75(m, 3H), 3.70(s, 3H), 4.13(q, 2H, J=6Hz), 6.70-7.20(m, 4H); ^{19}F NMR (CCl_4): δ-15.7(s,3F)ppm; MS m/e: 288(M^+, 95%), 243(M^+-OEt, 100%), 215(M^+-CO_2Et,5%); Analysis: Calcd for $C_{14}H_{15}F_3O_3$: C,58.36, H,5.20; Found: C,58.25, H,5.19 %.

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