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A NOVEL ONE-POT SYNTHESIS OF TRIFLUOROMETHYLATED β,γ-UNSATURATED ESTERS AND NITRILES

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SUMMARY

Trifluoromethylated β,γ-unsaturated esters and nitriles can be synthesized by reaction of organozinc compounds with fluorinated β-ketophosphonium salts. This novel reaction without isolation of intermediates provides a convenient synthesis of the title compounds which may be useful intermediates for the preparation of fluorinated biologically active compounds.

INTRODUCTION

β,γ-Unsaturated esters and nitriles are useful intermediates in organic synthesis and esters have been noted as important functional groups in naturally occurring compounds [1]. The common method for the preparation of β,γ-unsaturated compounds is based on deprotonation and reprotonation of the corresponding α,β-unsaturated derivatives [2]. Tsuji et al. reported a palladium-catalyzed decarboxylation-carbonylation of allylic carbonates for the preparation of β,γ-unsaturated esters [3]. However, to the best of our knowledge, the trifluoromethylated β,γ-unsaturated esters and nitriles

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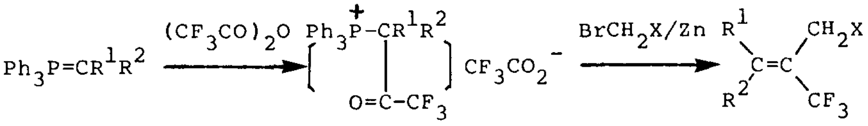
have not been reported previously. Therefore it is of much value to develop an effective method for the synthesis of trifluoromethylated β,γ-unsaturated esters and nitriles.

RESULTS AND DISCUSSION

Recently we found that carbon nucleophiles could attack fluorinated β-ketophosphonium salts leading to the formation of tetrasubstituted fluoroalkenes [4] and fluoroenynes [5]. In our continuing investigation to exploit the synthetic utility of fluorinated β-ketophosphonium salts in organic synthesis, we now wish to report a novel synthesis of trifluoromethylated β,γ-unsaturated esters and nitriles by reaction of organozinc compounds with fluorinated β-ketophosphonium salts.

The reaction sequence is shown as follows:



1 **2**

a $R^1=R^2=CH_3$; $X=CO_2CH_3$

b $R^1=R^2=CH_3$; $X=CO_2C_2H_5$

c $R^1,R^2=-(CH_2)_4-$; $X=CO_2CH_3$

d $R^1,R^2=-(CH_2)_4-$; $X=CO_2C_2H_5$

e $R^1,R^2=-(CH_2)_5-$; $X=CO_2CH_3$

f $R^1,R^2=-(CH_2)_5-$; $X=CO_2C_2H_5$

g $R^1=CH_3,R^2=CH_2Ph$; $X=CO_2CH_3$

h $R^1=C_2H_5;R^2=CH_2Ph$; $X=CO_2CH_3$

i $R^1,R^2=-(CH_2)_4-$; $X=CN$

j $R^1=CH_3,R^2=C_5H_{11}$; $X=CN$

The reaction of carbonyl compounds with haloesters in the presence of zinc is known as the Reformatsky reaction which creates a new carbon-carbon linkage to afford, after hydrolysis,β-hydroxy esters[6]. The present reaction is however different from the usual Reformatsky reaction. Organozinc compounds attack the β-ketophosphonium salt to produce betains followed by spontaneous elimination of triphenylphosphine oxide to give trifluoromethylated β,γ-unsaturated esters and nitriles. The eliminative Reformatsky reaction was carried out at room temperature, no reaction took place at -78 °C. The results are shown in Table 1.

This one-pot synthesis of trifluoromethylated β,γ-unsaturated esters and nitriles is quite convenient with high regioselectivity giving the β,γ-isomer exclusively. It should be useful in the synthesis of trifluoromethylated biologically active compounds.

TABLE 1

Preparation of Fluorinated Compounds 2

Compound	b.p(°C/mmHg)	Yield(%)[a]	E:Z[b]
2a	66/10	77	
2b	66/10	82	
2c	42/2	84	
2d	50/2	81	
2e	54/2	53	
2f	56/2	50	
2g	66/2	37	75:25
2h	70/2	26	78:22
2i	62/10	54	
2j	66/2	56	55:45

[a] Isolated yields based on trifluoroacetic anhydride.

[b] The ratios of E- and Z-isomers were estimated on the basis of NMR spectra.

EXPERIMENTAL

All boiling points were uncorrected. Infrared spectra of products were obtained as films on a Shimadzu IR-440 Spectrometer. NMR spectra (chemical shifts in ppm from TMS for ^{1}H NMR and from 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 Mass Spectrometer.

General procedure for preparation of trifluoromethylated β,γ-unsaturated esters and nitriles 2

A solution of phosphorane **1** generated from the corresponding phosphonium salt (3 mmol) and phenyllithium (3 mmol) in THF (30 ml) is cooled to -78°C and trifluoroacetic anhydride (ca. 2 mmol) is slowly added with stirring until the characteristic ylidic colour disappeared. After stirring at -78 °C for 15 min the reaction mixture is allowed to warm to room temperature and a solution of organozinc compounds prepared from bromoacetic esters (2 mmol) and zinc powder (0.2g,3 mmol) is added. (In case of 2i and 2j bromoacetic nitrile 3 mmol and zinc powder 4 mmol are added directly into the reaction mixture). The mixture is stirred at room temperature for a further 3 h. The product is isolated by column chromatography eluting with petroleum (b.p. 30-60 °C)/ethyl acetate (10:1).

2a: 77% yield; b.p. 66 °C/10mmHg; IR(film): 1740(s), 1664(m) cm^{-1}; ^{1}H NMR(CCl_4): 3.64(s,3H), 3.13(s,2H), 1.97(q,3H,J=2.0 Hz), 1.82(q,3H,J=2.0Hz); ^{19}F NMR(CCl_4): -17.2(s,3F)ppm; MS m/e: 197(M^++1,12%), 177(M^+-F,100%), 165(M^+-OCH_3,4%), 137(M^+-CO_2CH_3,31%); Analysis: Calcd for $C_8H_{11}F_3O_2$: C,49.00, H,5.61; Found: C,49.31, H,5.66%.

2b: 82% yield; b.p. 66°C/10mmHg; IR(film): 1742(s), 1672(m) cm^{-1}; ^1H NMR(CCl_4): 4.01(q,2H, J=6.0Hz), 3.05(s.2H), 1.90 (q,3H,J=2.0Hz), 1.75(q,3H,J=2.0Hz), 1.12(t,3H,J=6.0Hz); ^{19}F NMR(CCl_4): -19.0(s,3F)ppm; MS m/e: 211(M^++1,22%), 191(M^+-F, 100%),165(M^+-OC_2H_5,2%), 137(M^+-$CO_2C_2H_5$,22%); Analysis: Calcd for $C_9H_{13}F_3O_2$: C,51.45, H,6.19; Found: C,51.10, H,6.06%.

2c: 84% yield; b.p. 42°C/2mmHg; IR(film): 1740(s),1680(m) cm^{-1}; ^1H NMR(CCl_4): 3.57(s,3H), 3.00(s,2H),2.00-3.00(m,4H), 1.30-2.00(m,4H); ^{19}F NMR(CCl_4); -15.0(s.3F)ppm; MS m/e: 223 (M^++1,9%), 222(M^+,4%), 203(M^+-F,94%),191(M^+-OCH_3,7%),163(M^+-CO_2CH_3,38%);Analysis: Calcd for $C_{10}H_{13}F_3O_2$: C,54.08, H:5.85; Found: C,53.63, H,5.94%.

2d: 81% yield; b.p. 50°C/2mmHg; IR(film): 1732(s),1680(m) cm^{-1}; ^1H NMR(CCl_4): 4.00(q,2H,J=6.0Hz), 3,00(s,2H), 2,05-2.75(m, 4H), 1.40-1.85(m, 4H), 1,15(t, 3H, J=6.0Hz); ^{19}F NMR (CCl_4): -15.8(s,3F)ppm; MS m/e: 237(M^++1,25%), 217(M^+-F, 100%), 163(M^+-$CO_2C_2H_5$,37%); Analysis: Calcd for $C_{11}H_{15}F_3O_2$: C,55.95, H,6.35, Found: C,55.79, H,6.40%.

2e: 52% yield; b.p. 54°C/2mmHg; IR(film): 1750(s), 1660(m) cm^{-1}; ^1H NMR(CCl_4): 3.61(s,3H), 3.11(s.2H),1.93-2.53(m,4H), 1.43-1.83(m,6H) ^{19}F NMR(CCl_4): -20.5(s,3F)ppm; MS m/e: 237 (M^++1,100%),217(M^+-F,81%); Analysis: Calcd for $C_{11}H_{15}F_3O_2$: C,55.95, H,6.35; Found: C,55.74, H,6.31%.

2f: 50% yield; b.p. 56 °C/2mmHg; IR(film): 1750(s), 1668(m) cm^{-1}; ^{1}H NMR(CCl_4): 4.10(q,2H,J=6.0Hz), 3.16(s,2H), 2.05-2.58(m, 4H), 1.48-1.88(m, 6H), 1.26(t, 3H ,J=6.0Hz); ^{19}F NMR (CCl_4): -20.3(s,3F)ppm; MS m/e: 251(M^++1,96%), 231(M^+-F, 100%), 177(M^+-$CO_2C_2H_5$,28%); Analysis: Calcd for $C_{12}H_{17}F_3O_2$: C,57.62, H,6.80; Found: C,57.16, H,6.77%.

2g: 37% yield; b.p. 66 °C/2mmHg; IR(film): 1745(s),1660(m) cm^{-1}; ^{1}H NMR(CCl_4): 7.10(E)+7.06(Z)(s,5H), 3.55(E+Z)(s,3H), 3.20(E)+3.38(Z)(s,2H),1.95(E+Z)(s,2H), (1.70-1.90)(E)+(1.50-1.70)(Z)(m,3H); ^{19}F NMR(CCl_4): [-19.0(E)+(-20.3)(Z)](t,3F, J=36Hz)ppm; MS m/e: 273(M^++1,8%), 272(M^+,6%), 253(M^+-F,11%), 241(M^+-OCH_3, 6%), 213(M^+-CO_2CH_3, 11%); Analysis: Calcd for $C_{14}H_{15}F_3O_2$: C,61.79, H,5.51; Found: C,62.22, H,5.58%.

2h: 26% yield; b.p. 70 °C/2mmHg; IR(film): 1745(s), 1660(m) cm^{-1}; ^{1}H NMR(CCl_4): 7.09(E)+ 7.05(Z)(s,5H), 3.55(E)+3.60 (Z)(s,3H), 3.15(E)+3.43(Z)(s,2H), 2.00(E+Z)(s,4H); 1.00(E)+ 1.36(Z)(t,3H,J=8.0Hz); ^{19}F NMR(CCl_4): [-19.5(E)+(-20.5)(Z)] (s,3F)ppm; MS m/e: 287(M^++1,39%), 286(M^+,31%),267(M^+-F,34%), 255(M^+-OCH_3, 10%), 227(M^+-CO_2CH_3, 7%); Analysis: Calcd for $C_{15}H_{17}F_3O_2$: C,62.93, H,5.94; Found: C,63.47, H,6.06%.

2i: 54% yield; b.p. 62 °C/10mmHg; IR(film): 2230(w),1678(m) cm^{-1}; ^{1}H NMR(CCl_4): 3.06(s,2H), 2.30-2.70(m,4H),1.60(m,4H); ^{19}F NMR(CCl_4): -15.6(s,3F)ppm; MS m/e: 190(M^++1,100%), 189 (M^+, 14%), 170(M^+-F, 38%); Analysis: Calcd for $C_9H_{10}F_3N$: C,57.17, H,5.29, N,7.41; Found: C,56.65, H,5.32, N.7.25%.

2j: 56% yield; b.p. 66°C/2mmHg; IR(film): 2230(w), 1660(m) cm^{-1}; ^1H NMR(CCl_4): 3.00(E+Z)(s,2H); 1.60-2.30(E+Z)(m,5H), 0.60-1.60(m,9H); ^{19}F NMR(CCl_4): [-19.1(E)+(-19.5)(Z)](s,3F) ppm; MS m/e: 220(M^++1,76%),219(M^+,5%),200(M^+-F.6%);Analysis: Calcd for $C_{11}H_{16}F_3N$: C,60.29, H,7.30, N,6.39;Found: C,59.94, H,7.33, N,6.84%,

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