ELSEVIER

Journal of Fluorine Chemistry 77 (1996) 45–50

JOURNAL OF FLUORINE CHEMISTRY

Preparation of α-fluoro-β-per(poly)fluoroalkyl-substituted enol ethers

Alagappan Thenappan [1], Donald J. Burton *

Department of Chemistry, University of Iowa, Iowa City, IA 52242, USA

Received 15 July 1995; accepted 25 November 1995

Abstract

Fluorocarboethoxymethylene tri-n-butylphosphorane, $Bu_3P{=}CFCOOEt$ (**3**), reacts with per- and poly-fluoroalkyl-substituted carboxylic acid esters, ethyl formate and γ-butyrolactone to give the corresponding enol ethers, $R_FC(OEt){=}CFCOOEt$ (**4**), in good yield. Non-activated esters failed to react with **3**. With the anion derived from ethyl diethylphosphonofluoroacetate, $(EtO)_2P(O)CFHCOOEt$ (**5**), a mixture of **4** and β-ketoesters, $R_FC(O)CFHCOOEt$ (**7**), is formed.

Keywords: Preparation; Fluoro-per(poly)fluoroalkyl-substituted enol ethers; NMR spectroscopy; IR spectroscopy; Mass spectrometry

1. Introduction

Enol ethers constitute an important class of compounds in organic synthesis and many of them have been widely used as intermediates in the preparation of biologically-active compounds [1]. Fluorine-containing vinylic ethers display alkylating properties with both organic and inorganic nucleophiles [2]. Perfluoroalkenyl ethers of bile alcohols are known to reduce the interfacial tension between perfluorooctyl bromide and the emulsifying agent Pluronic F-68 [3]. Preparation of enol ethers utilizing Wittig reagents are known [4] and recently Begue et al. [5] have reported the parameters which influence the product distribution and yield of the Wittig reaction of alkylidenephosphoranes with perfluoroalkyl acid derivatives. This report prompted us to disclose our own results of the reaction of perfluoroalkyl esters with fluorine-substituted phosphoranes and phosphonate carbanions. In our continuing research to develop methods of preparation of α-fluoroesters [6], we have investigated the Wittig reaction of tri-n-butyl(fluorocarboethoxymethyl)-phosphonium bromide (**2**) and the Horner–Wadsworth–Emmons reaction of ethyl diethylphosphonofluoroacetate (**5**) with substituted esters and lactones, including fluoro compounds.

2. Results and discussion

Recently, we have reported the reaction of ethyl bromofluoroacetate (**1**) with tri-n-butylphosphine to give the corresponding phosphonium salt **2**, and the pre-generation of $Bu_3P{=}CFCOOEt$ (**3**) from **2** and n-butyllithium [6a]. Addition of fluorinated ethyl esters (R_FCOOEt, $R_F = CF_3$, C_2F_5, C_3F_7, CF_2Cl, CF_2Br) to a THF solution of **3** gave an *E* and *Z* mixture of enol ethers **4** in 54%–70% isolated yield (Scheme 1). The *E*/*Z* ratios of **4a–f** (Table 1) were determined by integration of the vinylic fluorine resonances in the ^{19}F NMR spectra, which appear between −130 to −143 ppm upfield from $CFCl_3$. In each case, the downfield chemical shift was assigned to the vinylic fluorine of the *E*-isomer, whereas the upfield signal was assigned to the *Z*-isomer. Confirmation of these assignments by nuclear Overhauser effect (NOE) experiments was reported previously [6d]. Coupling of the vinylic fluorines with those of CF_2, CF_3 moieties attached to the vicinal carbon was observed and the *cis* $J_{FC=CCF}$ value (22–29 Hz) was usually larger than the *trans* $J_{FC=CCF}$ value (5–10 Hz). *E*-Isomers predominated in the mixtures and the *E*/*Z* ratios varied from 3:1 to 8:1.

$$Bu_3P + CFHBrCOOEt \xrightarrow[\text{RT, 40 h}]{\text{THF}} [Bu_3P^+CFHCOOEt]Br^- \xrightarrow[-78\ ^\circ C]{^nBuLi}$$
(1) (2)

$$Bu_3P{=}CFCOOEt + R_FCOOEt \xrightarrow[6\ h]{-78\ ^\circ C \rightarrow RT}$$
(3)

$$R_FC(OEt){=}CFCOOEt + Bu_3P{=}O$$
(4)

($R_F = CF_3$, C_2F_5, C_3F_7, CF_2Cl, CF_2Br)

Scheme 1.

The enol ethers were stable during work-up (steam distillation) and hydrolysis of $CF_2BrC(OEt){=}CFCOOEt$ (**4e**) to its corresponding β-ketoester required strongly acidic con-

[1] Current address: AlliedSignal Inc., Buffalo Research Laboratory, 20 Peabody Str., Buffalo, NY 14210, USA.

* Corresponding author.

SSDI 0022-1139(95)03382-3

Table 1
Preparation of RC(OEt)=CFCOOEt

$$[Bu_3P^+CFHCOOEt]Br^- \xrightarrow[(2)\ RCOOEt]{(1)\ ^nBuLi/THF} RC(OEt)=CFCOOEt \quad \text{(Method A)}$$
(2) (4)

$$(EtO)_2P(O)CFHCOOEt \xrightarrow[(2)\ RCOOEt]{(1)\ ^nBuLi/THF} RC(OEt)=CFCOOEt \quad \text{(Method B)}$$
(5) (4)

Entry No.	R	Method	Yield [a] (%)	B.p. (°C/mmHg)	E/Z [b]
4a	CF_3	A	70	75–77/40	5.6:1
4b	CF_3CF_2	A	67	65–68/12	3:1
4c	$CF_3CF_2CF_2$	A	54	55–61/4.5	8:1
4d	CF_2Cl	A	68	81–85/10	6:1
4e	CF_2Br	A	56	86–92/6	8:1
4f [c]	H	B	48	–	15:1
4f [d]	H	A	63 [e]	–	4:1
4a	CF_3	B [b]	–	–	2:1

[a] Isolated yields based on RCOOEt.
[b] E/Z Ratios determined by integration of vinylic fluorine signals in the ^{19}F NMR spectrum.
[c] In addition to **4f**, 19% of HC(O)CFHCOOEt (**12**) was also isolated.
[d] In addition to **4f**, 17% HC(O)CFHCOOEt (**12**) was also formed.
[e] ^{19}F NMR yield (vs. C_6F_6 as internal standard).

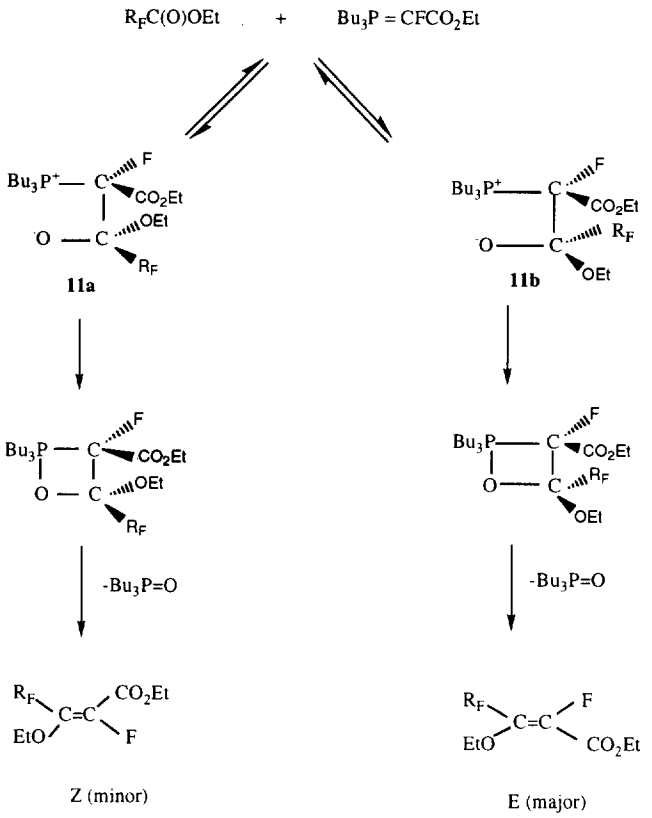
ditions (Eq. (1)). Treatment of a solution of **4e** in n-hexane with an equimolar quantity of concentrated sulfuric acid at 50 °C for 24 h gave **6** in 42% conversion, and about 50% **4e** was left unreacted. The ketoester **6** was identified by comparison of its ^{19}F NMR spectrum with that of an authentic sample [6c].

$$CF_2BrC(OEt)=CFCOOEt \xrightarrow[50\ ^\circ C,\ 24\ h]{conc.\ H_2SO_4} CF_2BrC(O)CFHCOOEt \quad (1)$$
(**4e**, *E* & *Z*) (**6**)

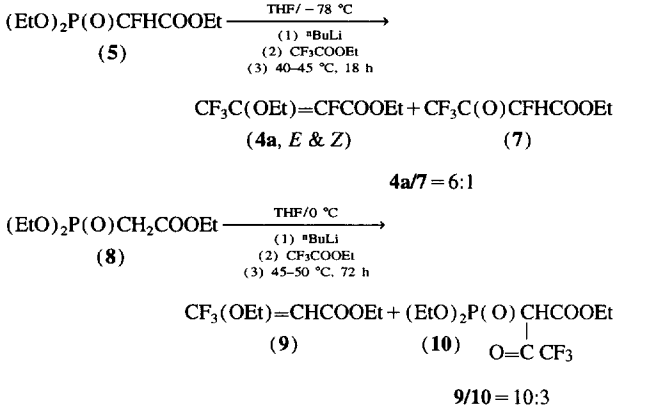
Begue and coworkers have reported that, in the presence of lithium salts, perfluoroalkyl esters react with $Ph_3P=CHR$ {R = $PhCH_2CH_2$, $PhCH_2CH_2CH_2$, 4-$(OMe)C_6H_4CH_2CH_2$, 3,4-$(OMe)_2C_6H_3CH_2CH_2$, c-C_6H_{11}, c-$C_6H_{11}CH_2$, n-C_5H_{11} and n-C_6H_{13}} to give, after basic hydrolysis, perfluoroalkyl ketones as the major product [5]. Under the same reaction conditions, semi-stabilized and disubstituted phosphoranes {$Ph_3P=CRR'$, R = Ph, 3-$(CF_3)C_6H_4$, 4-$(OMe)C_6H_4$ and R' = H, c-C_6H_{11}} give enol ethers exclusively, and the stabilized phosphorene, $Ph_3P=CHCOOEt$, failed to react. In contrast, the fluorinated analog, $Bu_3P=CFCOOEt$ (**3**), reacts with perfluoroalkyl esters at room temperature to form the corresponding enol ethers in good yields. ^{19}F NMR analysis of the reaction mixture before isolation did not show any acylated phosphoranes or ketones.

The reactivity of alkylidene phosphoranes such as $R_3P=CR_1R_2$, is usually determined by the substituents attached to the carbon and phosphorus atoms [7]. $Ph_3P=CHCOOEt$ is more stable and less reactive than its corresponding trialkyl analog, $Bu_3P=CHCOOEt$, and the higher stability is due to an increased positive charge on the phosphorus by electron-withdrawing phenyl groups. Although $Bu_3P=CHCOOEt$ was not reacted with the activated esters to compare its reactivity directly with $Bu_3P=CFCOOEt$ (**3**), the effect of the α-fluorine substituent on the stability of **3** can vary from modest stabilization to strong destabilization [8], depending on the geometry of the carbon. Destabilization is greater with planar carbanions [8c] and the carbon in **3** will have a more planar character from delocalizing its negative charge through conjugation with the adjacent carbonyl group. The less stable and more reactive phosphorane **3** reacted with activated esters to give the enol ethers exclusively. Selective formation of enol ethers from the Wittig reaction of **3** with perfluoroalkyl esters indicates that the intermediate adduct prefers to eliminate tri-n-butylphosphine oxide than ethoxide and this selectivity was attributed [9] to substituent stabilization of the incipient double bond of the vinyl ether.

In the presence of lithium salts, a high degree of *E*-stereoselectivity was observed in the reaction of **3** with esters (Table 1). The formation of the intermediate betaine **11** from **3** and esters is reversible [6b], and that intermediate can exist in two diastereoisomeric forms **11a** and **11b** (Scheme 2). Steric hindrance between the ester and R_F groups will be greater in **11a** than **11b** and irreversible decomposition of kinetic (**11a**) and thermodynamic (**11b**) isomers will give a specific ester. The relative rates of formation and decomposition of the intermediate will determine the E/Z ratio. Tetrahedral alkoxy anions are stabilized by R_F groups [10] and stable betaines are known to decompose slowly [11]. Slow decomposition will lead to more reversibility of the initial



Scheme 2.



Scheme 3.

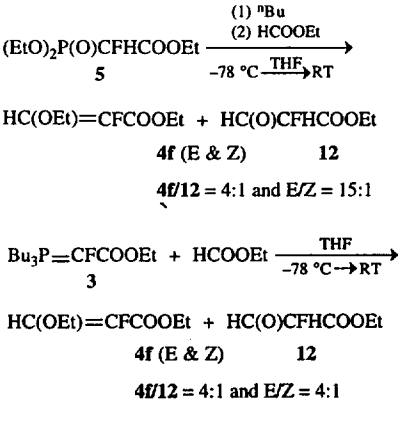
step to form the thermodynamic isomer (*E*-isomer) as the major product.

Reactions of **3** with esters were all carried out with lithium bases and the effects of metal ions and solvents on the *E*/*Z* ratio have not been determined. Although the complexation of soluble lithium salts with the intermediate **11** will retard its reversibility between kinetic and thermodynamic isomers, reactions under salt-free conditions should favor more *E*-isomer.

Unlike the butylphosphorane **3**, the anion derived from $(EtO)_2P(O)CFHCOOEt$ (**5**) did not undergo the Horner–Wadsworth–Emmons reaction with CF_3COOEt at room temperature. However, when the reaction mixture was warmed to 40–45 °C for 18 h, a 6:1 mixture of enol ethers **4a** and β-ketoester **7** was formed (Scheme 3). The conversion of CF_3COOEt to the two products together, as determined by NMR analysis, was 66% and there was no unreacted phosphonate anion in the reaction mixture.

The *E*/*Z* ratio of enol ethers produced by this route was 2:1 and **7** was identified by comparison with an authentic sample [6c]. Similarly, when the anion generated from $(EtO)_2P(O)CH_2COOEt$ (**8**) was reacted with CF_3COOEt at 50 °C for 24 h, a 10:3 mixture of enol ethers **9** and acylated phosphonate **10** was formed in 64% NMR yield (Scheme 3). A similar product distribution obtained from both phosphonates **5** and **8** indicates that substitution at the carbanionic center has little effect on the reaction outcome.

With the non-activated esters, only ethyl formate reacted with both the phosphorane **3** and the phosphonate anion from **5** to give a 4:1 mixture of enol ethers **4f** and β-ketoester **12** in 70% yield (Scheme 4). The Wittig reaction of $Ph_3P{=}CHR$ (R = COOEt, Ph) with ethyl formate to give the corresponding vinyl ethers in excess of 90% yield is reported [12]. Other non-activated esters such as ethyl acetate failed to react with both **3** and **5**. However, when the phosphonate anion derived from **5** was reacted with a cyclic ester such as γ-butyrolactone, both the enol ether **13** and the ring-opened acylated phosphonate **14** were formed in 56% NMR yield (Scheme 4). Both γ-butyrolactone and δ-valerolactone are known to react with the sodium enolate of diethyl cyanomethylphosphonate to give the corresponding vinylic products in 40% and 75% yield, respectively [13]. The vinylic fluorine signal of **13** appeared as a singlet (− 162.7 ppm upfield from $CFCl_3$ as internal standard) in the ^{19}F NMR spectrum, and GC–MS analysis indicated a molecular ion of 174. The ring-opened acylated phosphonate **14**, present as a minor component in the mixture, exhibited a singlet at − 223.9 ppm.



Scheme 4.

In conclusion, the Wittig reaction of fluorocarboethoxy-substituted phosphoranes and phosphonate anions with perfluoroalkyl, formate and cyclic esters provides a direct entry to α-fluoro-β-perfluoroalkyl-substituted enol ethers with the ester functionality at the α position. The ready availability of esters and suitable precursors, mild reaction conditions and simplicity of the experimental procedure make this approach a convenient method for the preparation of enol ethers.

3. Experimental details

3.1. General

All reactions were performed in oven-dried glassware and boiling points were determined during distillation and are reported uncorrected. ^{19}F and ^{1}H NMR spectra were recorded on a JEOL FX90Q (83.81 MHz) spectrometer and $\{^{1}H\}$ ^{13}C NMR spectra were recorded on a Bruker 360 MHz spectrometer. ^{19}F NMR spectra were referenced against internal $CFCl_3$, ^{1}H and ^{13}C spectra against internal $(CH_3)_4Si$. ^{19}F NMR chemical shifts are reported in parts per million upfield (negative) of the standard, ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million downfield (positive) of the standard. Coupling constants are reported in Hertz. IR spectra were recorded on a Mattson Cygnus 100 FT-IR spectrometer as neat liquids using a solution cell with a 0.1-cm path length. GC–MS spectra were obtained at 70 eV in the electron impact mode. GLPC analyses were performed on a 5% OV-101 column with a thermal conductivity detector.

3.2. Materials

Ethyl bromofluoroacetate (**1**) was prepared by a method similar to the *Organic Syntheses* preparation of ethyl chlorofluoroacetate [14]. Tetrahydrofuran, obtained from Fisher, was purified by distillation from sodium benzophenone ketyl. Tri-n-butylphosphine, obtained from M & T was purified by the method of Blackburn and Parratt [15]. Triethyl phosphite, n-butyllithium (2.5 M n-hexane solution) and ethyl formate were obtained from Aldrich Chemical Co. Triethyl phosphite was distilled from sodium metal at reduced pressure. Ethyl formate was distilled prior to use. The concentration of n-butyllithium was determined using the method of Duhamel and Plaquevent (Method B) [16]. Fluorinated esters {R_FCOOEt, $R_F = CF_3$, n-C_2F_5, n-C_3F_7 and CF_2Cl} were prepared by literature procedures [17]. $CF_2BrCOOEt$ was prepared by a modified literature procedure [18] from bromine, ethanol, chlorotrifluoroethylene, concentrated sulfuric acid and oleum (65%). Preparations of $[Bu_3P^+CFHCOOEt]Br^-$ (**2**), $[Bu_3P{=}CFCOOEt]$ (**3**) and $(EtO)_2P(O)CFHCOOEt$ (**5**) have been reported previously [6a].

3.3. General procedure for the preparation of an E and Z mixture of RC(OEt)=CFCOOEt (4)

3.3.1. Method A: Preparation of $CF_3C(OEt)$=CFCOOEt (4a)

A 250 ml two-necked round-bottomed flask, equipped with a septum port, Teflon-coated magnetic stir bar, N_2 tee and a reflux water condenser, was charged sequentially with 50 ml of THF, 5.1 g (25 mmol) of tri-n-butylphosphine and 4.6 g (25 mmol) of ethyl bromofluoroacetate. The resultant homogeneous solution was stirred at room temperature for 40 h and ^{19}F NMR analysis of the reaction mixture indicated that 86% of CFHBrCOOEt was converted to the corresponding phosphonium salt **2**. The salt solution was cooled to −78 °C and 8.6 ml (21.5 mmol) of a 2.5 M n-hexane solution of n-butyllithium was added dropwise via a syringe. The resultant bright yellow solution of ylid **3** was stirred at −78 °C for 20 min and then 2.4 g (17 mmol) of CF_3COOEt was added via a syringe in one portion. The reaction mixture was stirred at −78 °C for 1 h, warmed to room temperature over 6 h and then diluted with 200 ml of cold water. The organic layer was washed with brine solution (25 ml), the aqueous layer extracted with diethyl ether (2×25 ml) and the combined organic material subjected to steam distillation. The organic layer of the steam distillate was separated and the aqueous layer of the distillate extracted with diethyl ether (2×25 ml). The combined material was dried ($MgSO_4$), filtered and concentrated via atmospheric distillation. Reduced pressure distillation through a 6 in. Vigreaux column gave 2.75 g (70%) of product, b.p. 75–77 °C/40 mmHg; GLPC purity 96.6% and *E*/*Z* ratio = 5.6:1.

(*E*)-**4a**: ^{19}F NMR ($CDCl_3$) δ: 66.7 (d, 3F); 142.7 (q, 1F, $^{4}J_{F,Fcis} = 25$ Hz) ppm. ^{1}H NMR ($CDCl_3$) δ: 1.4 (t); 4.1 (q); 4.4 (t); 1.4 (t, $^{3}J_{H,H} = 7$ Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 120.8 (qd, $^{1}J_{CF} = 279$, $^{3}J_{C,F} = 4$ Hz); 140.2 (qd, $^{2}J_{C,F} = 35$, $^{2}J_{C,F} = 30$ Hz); 73.1 (s); 15.2 (s); 146.3 (dq, $^{1}J_{C,F} = 268$, $^{3}J_{C,F} = 3$ Hz); 159.1 (d, $^{2}J_{C,F} = 31$ Hz); 62.6 (s); 14.1 (s) ppm.

(*Z*)-**4a**: ^{19}F NMR δ: 65.2 (d, 3F, $^{4}J_{F,Ftrans} = 10$ Hz); 137.5 (q, 1F) ppm. FT-IR (cm^{-1}): 3060 (s); 2990 (s); 1780 (s); 1700 (m); 1150–1350 (s, broad); 1065 (s). GC–MS *m*/*z*, % abundance: 230 (1.0); 202 (16.3); 174 (100.0); 157 (33.0); 156 (57.4); 105 (35.0); 87 (25.5); 29 (20.2).

3.3.2. Preparation of $C_2F_5C(OEt)$=CFCOOEt (4b)

Similarly, compound **4b** was prepared by method A from 7.1 g (35 mmol) of tri-n-butylphosphine, 6.5 g (35 mmol) of ethyl bromofluoroacetate, 50 ml of THF, 13.2 ml (33 mmol) of a 2.5 M n-hexane solution of n-butyllithium and 5.2 g (27 mmol) of C_2F_5COOEt at room temperature for 6 h. The purified product, 4.8 g (67%), was isolated by distillation, b.p. 65–68 °C/12 mmHg; GLPC purity 100% and *E*/*Z* ratio = 3:1.

(*E*)-**4b**: ^{19}F NMR (acetone-d_6) δ: 83.6 (dt, 3F, $^{3}J_{F,F} = 2$, $^{5}J_{F,Fcis} = 10$ Hz); 117.9 (dq, 2F, $^{4}J_{F,Fcis} = 28$ Hz); 139.7 (t,q) ppm. ^{1}H NMR ($CDCl_3$) δ: 1.4 (t); 4.1 (q); 4.4 (q); 1.4 (t,

$^3J_{H,H}$=7 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 115.2 (tm, $^1J_{C,F}$=287 Hz); 140 (tq, $^2J_{C,F}$=26 Hz); 73.9 (s); 15.1 (s); 147.9 (d, $^1J_{C,F}$=272 Hz); 158.7 (d, $^2J_{C,F}$=31 Hz); 62.6 (s); 13.9 (s) ppm.

(*Z*)-**4b**: ^{19}F NMR δ: 81 (t, 3F); 114.5 (dq, 2F, $^4J_{F,Ftrans}$=5 Hz); 130.6 (t, 1F) ppm. FT-IR (cm^{-1}): 3020 (s); 2970 (s); 1770 (s); 1685 (m); 1480 (m); 1360–1150 (s, broad); 1140–1080 (m, broad); 945 (m). GC–MS *m/z*, % abundance: 281 (0.1); 280 (0.9); 252 (24.4); 224 (100.0); 207 (30.4); 206 (52.0); 105 (63.1); 87 (45.0); 29 (23.8).

3.3.3. Preparation of $C_3F_7C(OEt)$=CFCOOEt (4c)

Similarly, compound **4c** was prepared by method A from 7.1 g (35 mmol) of tri-n-butylphosphine, 6.5 g (35 mmol) of ethyl bromofluoroacetate, 50 ml of THF, 13.2 (33 mmol) of a 2.5 M n-hexane solution of n-butyllithium and 6.5 g (27 mmol) of C_3F_7COOEt at room temperature for 6 h. The purified product, 4.8 g (54%), was isolated by distillation, b.p. 55–61 °C/4.5 mmHg; GLPC purity 100% and *E/Z* ratio=8:1.

(*E*)-**4c**: ^{19}F NMR ($CDCl_3$) δ: 81.2 (t, 3F, $^4J_{F,F}$=10 Hz); 127.6 (d, 2F, $^5J_{F,Fcis}$=15 Hz); 116.5 (dq, 2F, $^4J_{F,Fcis}$=28 Hz); 139.9 (m, 1F) ppm. ^{1}H NMR ($CDCl_3$) δ: 1.4 (t); 4.1 (q); 4.4. (q); 1.4 (t, $^3J_{H,H}$=7 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 117.8 (m, $^1J_{C,F}$=288 Hz); 141.4 (tq, $^2J_{C,F}$=27 Hz); 73.8 (s); 15 (s); 147.9 (d, $^1J_{C,F}$=273 Hz); 158.5 (d, $^2J_{C,F}$=31 Hz); 62.5 (s); 13.9 (s) ppm.

(*Z*)-**4c**: ^{19}F NMR δ: 81.2 (t, 3F, $^4J_{F,F}$=10 Hz); 125.4 (s, 2F); 113.5 (q, 2F); 130.8 (broad s, 1F) ppm. FT-IR (cm^{-1}): 2980–2955 (s); 1745 (s); 1465 (m); 1350–1100 (s, broad); 900 (m); 750 (m). GC–MS *m/z*, % abundance: 330 (0.4); 302 (12.7); 274 (47.2); 256 (26.0); 105 (100.0); 87 (80.5); 69 (13.1); 45 (15.5); 29 (94.7); 28 (49.6); 27 (24.1).

3.3.4. Preparation of $CF_2ClC(OEt)$=CFCOOEt (4d)

Similarly, compound **4d** was prepared by method A from 7.1 g (35 mmol) of tri-n-butylphosphine, 6.5 g (35 mmol) of ethyl bromofluoroacetate, 50 ml of THF, 12.8 ml (32 mmol) of a 2.5 M n-hexane solution of n-butyllithium and 4.3 g (27 mmol) of CF_2ClCOOEt at room temperature for 6 h. The purified product, 4.0 g (63%), was isolated by distillation, b.p. 81–85 °C/10 mmHg; GLPC purity 95% and *E/Z* ratio=6:1.

(*E*)-**4d**: ^{19}F NMR (acetone-d_6) δ: 54.5 (d, 2F, $^4J_{F,Fcis}$=28 Hz); 139.7 (t, 1F) ppm. ^{1}H NMR ($CDCl_3$) δ: 1.4 (t); 4.1 (q); 4.3 (q); 1.4 (t, $^3J_{H,H}$=7 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 122.5 (td, $^1J_{C,F}$=296, $^3J_{C,F}$=5 Hz); 144.5 (tq, $^2J_{C,F}$=29 Hz); 73.5 (s); 15.2 (s); 144.2 (d, $^1J_{C,F}$=269 Hz); 158.9 (d, $^2J_{C,F}$=31 Hz); 62.4 (s); 14.2 (s) ppm.

(*Z*)-**4d**: ^{19}F NMR δ: 53.7 (d, 2F, $^4J_{F,Ftrans}$=6 Hz); 136.6 (t, 1F) ppm. FT-IR (cm^{-1}): 2990 (w); 2945 (w); 1750 (s); 1255 (s); 1225 (s); 1040 (m); 980 (m); 880 (w). GC–MS *m/z*, % abundance: 248 (0.2); 246 (0.6); 211 (12.9); 192 (13.0); 190 (41.1); 105 (83.9); 87 (40.7); 32 (15.5); 29 (100.0); 28 (57.5); 27 (39.8).

3.3.5. Preparation of $CF_2BrC(OEt)$=CFCOOEt (4e)

Similarly, compound **4e** was prepared by method A from 7.1 g (35 mmol) of tri-n-butylphosphine, 6.5 g (35 mmol) of ethyl bromofluoroacetate, 50 ml of THF, 12.4 ml (31 mmol) of a 2.5 M n-hexane solution of n-butyllithium and 5.3 g (26 mmol) of CF_2BrCOOEt at room temperature for 6 h. The purified product, 4.2 g (56%), was isolated by distillation, b.p. 86–92 °C/6 mmHg; GLPC purity 96% and *E/Z* ratio=8:1.

(*E*)-**4e**: ^{19}F NMR (acetone-d_6) δ: 50.9 (d, 2F, $^4J_{F,Fcis}$=29 Hz); 138.8 (t, 1F) ppm. ^{1}H NMR (acetone-d_6) δ: 1.4 (t); 4.2 (q); 4.4 (q); 1.4 (t, $^3J_{H,H}$=7 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 113.5 (td, $^1J_{C,F}$=310, $^3J_{C,F}$=5 Hz); 145.5 (td, $^2J_{C,F}$=28 Hz); 73.6 (s); 15.3 (s); 143.2 (d, $^1J_{C,F}$=268 Hz); 159 (d, $^2J_{C,F}$=30 Hz); 62.4 (s); 14.1 (s) ppm.

(*Z*)-**4e**: ^{19}F NMR δ: 50.3 (d, 2F, $^4J_{F,Ftrans}$=5 Hz); 137.1 (t, 1F) ppm. FT-IR (cm^{-1}): 2980 (m); 2940 (m); 1735 (s); 1340 (m); 1335 (m); 1240–1200 (s, broad); 1150 (m); 1020 (s); 960 (m); 840 (m). GC–MS *m/z*, % abundance: 292 (0.7); 290 (0.7); 264 (10.2); 236 (22.1); 234 (22.7); 211 (24.6); 155 (100.0); 105 (40.0); 87 (35.9); 29 (27.6).

3.4. General procedure for the preparation of an E and Z mixture of RC(OEt)=CFCOOEt (4)

3.4.1. Method B: Preparation of HC(OEt)=CFCOOEt (4f)

Into a 200 ml, two-necked flask, equipped with a septum port, Teflon-coated magnetic stir bar, N_2 tee and reflux condenser, was charged 75 ml of THF and 9.4 g (38.7 mmol) of $(EtO)_2P(O)CFHCOOEt$ (**5**). The resultant homogeneous solution was stirred vigorously and cooled to −78 °C, and then 15.5 ml (38.8 mmol) of "BuLi was added dropwise via a syringe. After stirring the resultant yellow ylid solution at −78 °C for 20 min, 7.2 g (96.7 mmol) of ethyl formate was added via a syringe in one portion. The reaction mixture was stirred at −78 °C for 1 h, warmed to room temperature over 4 h and stirred at room temperature for an additional 16 h. Isolation and purification of the product as described in method A gave 3.0 g (48%) of compound **4f** and 1.0 g (19%) of compound **12** as a mixture, b.p. of that mixture 96–99 °C/10 mmHg; GLPC purity of three products together 95% and *E/Z* ratio of **4f**=15:1.

(*E*)-**4f**: ^{19}F NMR ($CDCl_3$) δ: 159.3 (d, $^3J_{F,H}$=20 Hz) ppm. ^{1}H NMR ($CDCl_3$) δ: 6.9 (dt, 1H, $^3J_{H,F}$=19, $^4J_{H,H}$=2 Hz); 1.3 (t); 4.2 (q); 4.3 (q); 1.4 (t, $^3J_{H,H}$=7 Hz) ppm.

(*Z*)-**4f**: ^{19}F NMR δ: 175 (d) ppm. Compound **12**: ^{19}F NMR ($CDCl_3$) δ: 202.6 (dd, $^2J_{F,H}$=49, $^3J_{F,H}$=15 Hz) ppm. GC–MS *m/z*, % abundance: **4f**: 162 (8.1); 106 (100.0); 89 (47.6); 88 (79.2); 60 (13.0); 45 (16.3); 32 (23.8); 29 (70.7); 28 (73.2); 27 (41.4). Compound **12**: 135 (5.8); 134 (0.3); 107 (10.9); 103 (23.7); 75 (22.6); 62 (13.2); 47 (59.9); 32 (29.9); 29 (58.8); 28 (100.0); 27 (21.1).

Similarly, treatment of the phosphonium salt **2** generated from 0.6 g (3 mmol) of tri-n-butylphosphine and 0.6 g (3 mmol) of ethyl bromofluoroacetate in 5 ml of THF with 1.2 ml (3 mmol) of n-butyllithium and 0.2 g (3 mmol) of

HCOOEt at room temperature for 14 h by method A produced a reaction mixture consisting of (*E*)-HC(OEt)=CFCOOEt, (*Z*)-HC(OEt)=CFCOOEt (**4f**) and HC(O)CFHCOOEt (**12**) in a 63:16:21 ratio. The total ^{19}F NMR yield (vs. C_6F_6 as internal standard) of the three products based on ethyl formate was 80% and the *E*/*Z* ratio of enol ethers was 4:1.

3.5. Hydrolysis of $CF_2BrC(OEt)$=CFCOOEt (4e, E & Z) with concentrated sulfuric acid

A 20 ml, two-necked flask, equipped with a septum port, a magnetic stir bar and a condenser, was charged with 1.5 g (5 mmol) of $CF_2BrC(OEt)$=CFCOOEt (**4e**, *E* & *Z*), 5 ml of n-hexane and 0.16 ml (5 mmol) of concentrated sulfuric acid. The resultant mixture was initially stirred at room temperature for 16 h and then heated to 50 °C and stirred at that temperature for an additional 24 h. ^{19}F NMR analysis of the reaction mixture indicated that 42% of the vinyl ether had hydrolyzed to form $CF_2BrC(O)CFHCOOEt$ (**6**). ^{19}F NMR (n-hexane) δ: 197.5 (dt, J_{FCH} = 46 and J_{FCCCF} = 9 Hz) ppm. Further heating of the reaction mixture at 50 °C for 48 h did not improve the conversion and unreacted vinyl ethers were present in the reaction mixture.

3.6. Reaction of the anion derived from $(EtO)_2P(O)CH_2COOEt$ (8) with CF_3COOEt

A 20 ml, two-necked flask, equipped with a septum port, a magnetic stir bar and a condenser, was charged with 10 ml of THF and 1.06 g (4.7 mmol) of phosphonate **8**. The resultant solution was stirred vigorously and cooled to 0 °C and then 1.9 ml (4.7 mmol) of ^{n}BuLi was added dropwise via a syringe. After stirring the resultant yellow ylid solution at 0 °C for 20 min, 0.57 g (4 mmol) of ethyl trifluoroacetate was added via a syringe in one portion. The reaction mixture was stirred at 0 °C for 1 h, warmed to room temperature over 2 h, heated to 50 °C and stirred at that temperature for an additional 72 h. ^{19}F NMR analysis of the reaction mixture indicated the presence of (*Z*)-$CF_3C(OEt)$=CHCOOEt (**9**), CF_3COOEt and $(EtO)_2P(O)CH(COCF_3)COOEt$ (**10**) in a 20:15:6 ratio. (*Z*)-**9**: ^{19}F NMR (THF) δ: 70.4 (d, $^4J_{F,H}$ = 2 Hz) ppm. Compound **10**: 78.0 (s) ppm. CF_3COOEt: 75.8 (s) ppm. ^{19}F NMR yield (vs. $C_6H_5CF_3$) of **9** and **10** together based on ethyl trifluoroacetate was 64%.

3.7. Reaction of the anion derived from $(EtO)_2P(O)CHFCOOEt$ (5) with γ-butyrolactone

A 25 ml, two-necked flask, equipped with a septum port, a magnetic stir bar and a condenser, was charged with 5 ml of THF and 0.52 g (2.2 mmol) of phosphonate **5**. The resultant solution was stirred vigorously and cooled to −78 °C and then 0.9 ml (2.2 mmol) of ^{n}BuLi was added dropwise via a syringe. After stirring the resultant yellow ylid solution at −78 °C for 20 min, 0.19 g (2.2. mmol) of γ-butyrolactone was added via a syringe in one portion. The reaction mixture was stirred at −78 °C for 1 h, warmed to room temperature over 4 h and stirred at that temperature for an additional 16 h. ^{19}F NMR analysis of the reaction mixture indicated the presence of enol ether **13** as the major product, and acylated phosphonate **14** and CFH_2COOEt as minor products. ^{19}F NMR yields (vs. C_6F_6) of the enol ether **13** and acylated phosphonate **14** were 56% and 5%, respectively. Compound **13**: ^{19}F NMR (THF) δ: 162.7 (s) ppm. Compound **14**: 223.9 (s) ppm. CFH_2COOEt: 231 (t, $^2J_{F,H}$ = 48 Hz) ppm. The reaction mixture was flash-distilled under reduced pressure and the flash-distillate was analyzed by GC–MS methods. GC–MS *m*/*z*, % abundance: 174 (M^+, 5.1); 143 (70.2); 87 (30.1); 69 (60.3); 57 (40.1); 55 (38.6); 43 (66.9); 41 (100).

Acknowledgement

We thank the National Science Foundation for financial support of this work.

References

[1] (a) S. Denmark, C.B.W. Senanayake and G.D. Ho, *Tetrahedron, 46* (1990) 4857; (b) C. Huang, V.S. Venturella, A.I. Cholli, F.M. Venutolo, A.T. Siberman and G.G. Vernice, *J. Fluorine Chem., 45* (1989) 239; (c) J.M. Percy, *Tetrahedron Lett., 31* (1990) 3931.

[2] V.F. Snegirev, K.N. Makarov and I.L. Knunyants, *J. Fluorine Chem., 17* (1981) 441.

[3] (a) A.A. Malik and C.M. Sharts, *J. Fluorine Chem., 41* (1988) 393; (b) A.A. Malik and C.M. Sharts, *J. Fluorine Chem., 34* (1987) 395.

[4] J.B. Ousset and C. Mioskowski, *Tetrahedron Lett., 25* (1984) 5903.

[5] J.P. Begue, D.B. Delpon, D. Mesureur, G. Nee and S.W. Wu, *J. Org. Chem., 57* (1992) 3807.

[6] (a) A. Thenappan and D.J. Burton, *J. Org. Chem., 55* (1990) 2311; (b) A. Thenappan and D.J. Burton, *J. Org. Chem., 55* (1990) 4639; (c) A. Thenappan and D.J. Burton, *J. Org. Chem., 56* (1991) 273; (d) H.J. Tsai, A. Thenappan and D.J. Burton, *J. Org. Chem., 59* (1994) 7085.

[7] J. March, *Advanced Organic Chemistry*, 3rd edn., Wiley, New York, 1985.

[8] (a) R.D. Chambers, *Fluorine in Organic Chemistry*, Wiley, New York, 1973; (b) R.E. Banks, B.E. Smart and J.C. Tatlow, *Organofluorine Chemistry, Principles and Applications*, Plenum Press, New York, 1994; (c) R.E. Banks, D.W.A. Sharp and J.C. Tatlow, *Fluorine – The First Hundred Years*, Elsevier Sequoia, New York, 1986.

[9] P.J. Murphy and J. Brennan, *Chem. Soc. Rev., 17* (1988) 1.

[10] (a) D. Seebach, *Angew. Chem., Int. Ed. Engl., 29* (1990) 1320; R.L. Salvador and M. Saucier, *Tetrahedron, 27* (1971) 1221; (c) J.P. Guthrie, *Can. J. Chem., 53* (1975) 898.

[11] (a) F. Ramirez, C.P. Smith and J.F. Pilot, *J. Am. Chem. Soc., 90* (1968) 6726; (b) F. Campa, R. Canela, J. Coll, A. Messeguer and A. Roca, *Tetrahedron, 34* (1978) 2179; (c) F. Campa, F.J. Sanchez and A. Messeguer, *Synthesis*, (1988) 823.

[12] V. Subramanyan, E.H. Silver and A.H. Soloway, *J. Org. Chem., 41* (1976) 1272.

[13] A.J. Duggan, M.A. Adams, P.J. Brynes and J. Meinwald, *Tetrahedron Lett.*, (1978) 4323.

[14] B. Englund, *Org. Synth., Collect. Vol. IV*, (1963) 423.

[15] G.M. Blackburn and M.J. Parratt, *J. Chem. Soc., Perkin Trans. 1*, (1986) 1417.

[16] L. Duhamel and J. Plaquevent, *J. Org. Chem., 44* (1979) 3404.

[17] W. Koppes, *Ph.D. Thesis*, University of Iowa, 1972; A. Moffat and H. Hunt, *J. Am. Chem. Soc., 79* (1957) 54.

[18] O. Paleta, F. Liska and A. Posta, *Collect. Czech. Chem. Commun., 35* (1970) 1302.