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

Alagappan Thenappan¹, Donald J. Burton *

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

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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 cor-



Scheme 1.

responding phosphonium salt 2, and the pre-generation of Bu₃P=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 ¹⁹F NMR spectra, which appear between -130 to -143ppm upfield from CFCl₃. 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 CF₂, CF₃ moieties attached to the vicinal carbon was observed and the cis $J_{\text{FC}=\text{CCF}}$ 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.

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.

Table 1 Preparation of RO	C(OEt)=CFCOOEt				
[Bu ₃ P ⁺ CFHCOO (2)	$(1) \stackrel{\text{OBuLi/THF}}{(2) \text{ RCOOEt}} RC($	OEt)=CFCOOEt (Method (4)	I A)		
$(EtO)_{2}P(O)CFHCOOEt \xrightarrow{(1) \text{ "BuLi/THF}} RC(OEt) = CFCOOEt (Method B)$ (5) (4)					
Entry No.	R	Method	Yield ^a (%)	B.p. (°C/mmHg)	
4a 4b 4c 4d 4e 4f ^c 4f ^d	CF ₃ CF ₃ CF ₂ CF ₃ CF ₂ CF ₂ CF ₂ CI CF ₂ Br H H	A A A A B A	70 67 54 68 56 48 63 °	75-77/40 65-68/12 55-61/4.5 81-85/10 86-92/6 -	
4a	CF ₃	Вь	-	_	

^a Isolated yields based on RCOOEt.

^b E/Z Ratios determined by integration of vinylic fluorine signals in the ¹⁹F 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 ¹⁹F 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 ¹⁹F NMR spectrum with that of an authentic sample [6c].

$$CF_{2}BrC(OEt) = CFCOOEt \xrightarrow{\text{conc. } H_{2}SO_{4}} (4e, E \& Z)$$

$$CF_{2}BrC(O)CFHCOOEt \quad (1)$$

$$(6)$$

Begue and coworkers have reported that, in the presence of lithium salts, perfluoroalkyl esters react with $Ph_3P=CHR$ {R = PhCH₂CH₂, PhCH₂CH₂CH₂, 4-(OMe)C₆H₄CH₂CH₂, 3,4-(OMe)₂C₆H₃CH₂CH₂, c-C₆H₁₁, c-C₆H₁₁CH₂, n-C₅H₁₁ and n-C₆H₁₃} to give, after basic hydrolysis, perfluoroalkyl ketones as the major product [5]. Under the same reaction conditions, semi-stabilized and disubstituted phosphoranes {Ph₃P=CRR', R = Ph, 3-(CF₃)C₆H₄, 4-(OMe)C₆H₄ and R' = H, c-C₆H₁₁} give enol ethers exclusively, and the stabilized phosphorene, Ph₃P=CHCOOEt, failed to react. In contrast, the fluorinated analog, Bu₃P=CFCOOEt (**3**), reacts with perfluoroalkyl esters at room temperature to form the corresponding enol ethers in good yields. ¹⁹F 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 Bu₃P=CHCOOEt was not reacted with the activated esters to compare its reactivity directly with Bu₃P=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.

 E/Z^{b}

5.6:1 3:1 8:1 6:1 8:1 15:1 4:1 2:1

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

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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 CF₃COOEt 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 CF₃COOEt 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 Ph₃P=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 CFCl₃ as internal standard) in the ¹⁹F NMR spectrum, and GC-MS analysis indicated a molecular ion of 174. The ringopened acylated phosphonate 14, present as a minor component in the mixture, exhibited a singlet at -223.9 ppm.

$$(EtO)_{2}P(O)CFHCOOEt \xrightarrow{(1) \ ^{n}Bu}_{(2) \ HCOOEt} \xrightarrow{(2) \ HCOOEt}_{5} \xrightarrow{(2) \ HCOOEt}_{-78 \ ^{\circ}C} \xrightarrow{\text{THF}}_{RT}$$

$$HC(OEt)=CFCOOEt + HC(O)CFHCOOEt \xrightarrow{4f(12 = 4:1 \ \text{and } E/Z = 15:1}_{2} \xrightarrow{4f/12 = 4:1 \ \text{and } E/Z = 15:1}$$

$$Bu_{3}P=CFCOOEt + HCOOEt \xrightarrow{\text{THF}}_{-78 \ ^{\circ}C} \xrightarrow{-\rightarrow RT}_{3}$$

$$HC(OEt)=CFCOOEt + HC(O)CFHCOOEt \xrightarrow{4f(12 = 4:1 \ \text{and } E/Z = 4:1}_{2} \xrightarrow{4f/12 = 4:1 \ \text{and } E/Z = 4:1}$$

$$(EtO)_{2}P(O)CFHCOOEt \xrightarrow{\text{THF}/-78 \ ^{\circ}C}_{(1) \ ^{\alpha}Bu}$$

$$(2) \ \gamma \text{-butyrolactone}$$

$$\int_{0}^{C}C=CFCOOEt + (EtO)_{2}P(O)CFCOOEt \atop{13 \ (major)} \xrightarrow{O=C(CH_{2})_{3}OLi} \xrightarrow{14 \ (minor)}$$

$$Scheme 4.$$

In conclusion, the Wittig reaction of fluorocarboethoxysubstituted 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. ¹⁹F and ¹H NMR spectra were recorded on a JEOL FX90Q (83.81 MHz) spectrometer and {¹H} ¹³C NMR spectra were recorded on a Bruker 360 MHz spectrometer.¹⁹FNMR spectra were referenced against internal CFCl₃, ¹H and ¹³C spectra against internal (CH₃)₄Si. ¹⁹F NMR chemical shifts are reported in parts per million upfield (negative) of the standard, ¹H and ¹³C 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]. CF2BrCOOEt 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, N₂ 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 ¹⁹F 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 nbutyllithium 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 CF₃COOEt 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 $(2 \times 25 \text{ ml})$ 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 $(2 \times 25 \text{ ml})$. The combined material was dried (MgSO₄), 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**: ¹⁹F NMR (CDCl₃) &: 66.7 (d, 3F); 142.7 (q, 1F, ⁴*J*_{F,Fcis} = 25 Hz) ppm. ¹H NMR (CDCl₃) &: 1.4 (t); 4.1 (q); 4.4 (t); 1.4 (t, ³*J*_{H,H}=7 Hz) ppm. ¹³C NMR (CDCl₃) &: 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: ¹⁹F NMR δ : 65.2 (d, 3F, ⁴J_{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 C₂F₅COOEt 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: ¹⁹F 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. ¹H NMR (CDCl₃) δ : 1.4 (t); 4.1 (q); 4.4 (q); 1.4 (t,

 ${}^{3}J_{\text{H,H}} = 7$ Hz) ppm. 13 C NMR (CDCl₃) δ : 115.2 (tm, ${}^{1}J_{\text{C,F}} = 287$ Hz); 140 (tq, ${}^{2}J_{\text{C,F}} = 26$ Hz); 73.9 (s); 15.1 (s); 147.9 (d, ${}^{1}J_{\text{C,F}} = 272$ Hz); 158.7 (d, ${}^{2}J_{\text{C,F}} = 31$ Hz); 62.6 (s); 13.9 (s) ppm.

(Z)-**4b**: ¹⁹F 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: ¹⁹F NMR (CDCl₃) 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. ¹H NMR (CDCl₃) δ : 1.4 (t); 4.1 (q); 4.4. (q); 1.4 (t, ³J_{H,H}=7 Hz) ppm. ¹³C NMR (CDCl₃) 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: ¹⁹F NMR δ : 81.2 (t, 3F, ⁴*J*_{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 CF₂ClCOOEt 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**: ¹⁹F NMR (acetone-*d*₆) δ : 54.5 (d, 2F, ⁴*J*_{F,F,cis} = 28 Hz); 139.7 (t, 1F) ppm. ¹H NMR (CDCl₃) δ : 1.4 (t); 4.1 (q); 4.3 (q); 1.4 (t, ³*J*_{H,H}=7 Hz) ppm. ¹³C NMR (CDCl₃) δ : 122.5 (td, ¹*J*_{C,F}=296, ³*J*_{C,F}=5 Hz); 144.5 (tq, ²*J*_{C,F}=29 Hz); 73.5 (s); 15.2 (s); 144.2 (d, ¹*J*_{C,F}=269 Hz); 158.9 (d, ²*J*_{C,F}=31 Hz); 62.4 (s); 142.2 (s) ppm.

(Z)-4d: ¹⁹F 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 CF₂BrCOOEt 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: ¹⁹F NMR (acetone- d_6) δ : 50.9 (d, 2F, ⁴ $J_{F,Fcis}$ = 29 Hz); 138.8 (t, 1F) ppm. ¹H NMR (acetone- d_6) δ : 1.4 (t); 4.2 (q); 4.4 (q); 1.4 (t, ³ $J_{H,H}$ =7 Hz) ppm. ¹³C NMR (CDCl₃) δ : 113.5 (td, ¹ $J_{C,F}$ =310, ³ $J_{C,F}$ =5 Hz); 145.5 (td, ² $J_{C,F}$ =28 Hz); 73.6 (s); 15.3 (s); 143.2 (d, ¹ $J_{C,F}$ =268 Hz); 159 (d, ² $J_{C,F}$ =30 Hz); 62.4 (s); 14.1 (s) ppm.

(*Z*)-4e: ¹⁹F NMR δ : 50.3 (d, 2F, ⁴*J*_{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, N₂ tee and reflux condenser, was charged 75 ml of THF and 9.4 g (38.7 mmol) of $(EtO)_2 P(O) CFHCOOEt$ (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: ¹⁹F NMR (CDCl₃) δ : 159.3 (d, ³ $J_{F,H}$ =20 Hz) ppm. ¹H NMR (CDCl₃) δ : 6.9 (dt, 1H, ³ $J_{H,F}$ =19, ⁴ $J_{H,H}$ =2 Hz); 1.3 (t); 4.2 (q); 4.3 (q); 1.4 (t, ³ $J_{H,H}$ =7 Hz) ppm.

(*Z*)-**4f**: ¹⁹F NMR δ : 175 (d) ppm. Compound **12**: ¹⁹F NMR (CDCl₃) δ : 202.6 (dd, ²*J*_{F,H}=49, ³*J*_{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 ¹⁹F NMR yield (vs. C₆F₆ 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 CF₂BrC(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. ¹⁹F NMR analysis of the reaction mixture indicated that 42% of the vinyl ether had hydrolyzed to form CF₂BrC(O)CFHCOOEt (6). ¹⁹F 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)CH₂COOEt (8) with CF₃COOEt

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 "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. ¹⁹F NMR analysis of the reaction mixture indicated the presence of (Z)-CF₃C(OEt)=CHCOOEt (9), CF₃COOEt and (EtO)₂P(O)CH(COCF₃)COOEt (10) in a 20:15:6 ratio. (Z)-9: ¹⁹F NMR (THF) δ : 70.4 (d, ⁴J_{F, H}=2 Hz) ppm. Compound 10: 78.0 (s) ppm. CF₃COOEt: 75.8 (s) ppm. ¹⁹F 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 "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. ¹⁹F NMR analysis of the reaction mixture indicated the presence of enol ether **13** as the major product, and acylated phosphonate **14** and CFH₂COOEt as minor products. ¹⁹F NMR yields (vs. C₆F₆) of the enol ether **13** and acylated phosphonate **14** were 56% and 5%, respectively. Compound **13**: ¹⁹F NMR (THF) δ : 162.7 (s) ppm. Compound **14**: 223.9 (s) ppm. CFH₂COOEt: 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).

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