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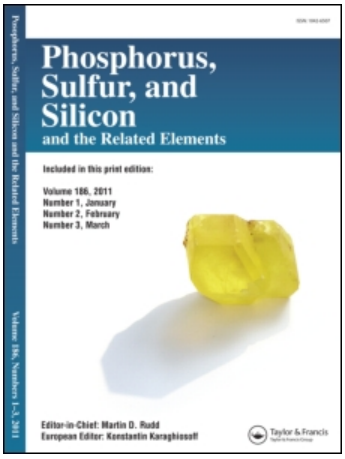

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APPLICATION OF FLUOROCARBETHOXY-SUBSTITUTED PHOSPHONATE: A FACILE ENTRY TO SUBSTITUTED 2-FLUORO-3-OXOESTERS

Hou-Jen Tsai[a]
[a] Department of Applied Chemistry, Chung Cheng Institute of Technology, Tao-Yuan, Taiwan

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APPLICATION OF FLUOROCARBETHOXY-SUBSTITUTED PHOSPHONATE: A FACILE ENTRY TO SUBSTITUTED 2-FLUORO-3-OXOESTERS

HOU-JEN TSAI

Department of Applied Chemistry, Chung Cheng Institute of Technology, Ta-Hsi, Tao-Yuan, Taiwan

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Diethyl(fluorocarbethoxymethyl)phosphonate **1a** or diisopropyl(fluorocarbethoxymethyl)phosphonate **1b,** prepared from triethyl phosphite or triisopropyl phosphite with ethyl bromofluoroacetate, react with n-butyllithium in THF to give the corresponding phosphonate carbanions $[(RO)_2P(O)CFCO_2Et]^-Li^+$ **2a** (R = Et) and **2b** (R = i-Pr). Addition of trimethylsilyltrifluoroacetate $CF_3C(O)OSiMe_3$ to a THF solution of phosphonate carbanions formed the enolate of ethyl trifluoroacetylfluoroacetate $[CF_3C(O)CFCO_2Et]^-Li^+$ **3.** Subsequent protonation, alkylation or allylation of the enolate afforded substituted 2,4,4,4-tetrafluoro-3-oxoesters $CF_3C(O)CFR_1CO_2Et$ **10**

Keywords: fluorophosphonate; Michaelis-Arbuzov reaction; enolate; alkylation; allylation; 3-oxoesters

INTRODUCTION

α-Fluoro-β-keto esters are reagents of considerable interest in synthetic organofluorine chemistry, and a number of them have been successfully employed as intermediates in the synthesis of biologically active monofluorinated heterocycles[1,2] and fluorine-substituted isoprenyl derivatives.[3] The latter have found applications as hyperlipidaemic drugs,[4] hormone substitutes[5] and in cancer chemotherapy.[6] The main synthetic methods currently available for the preparation of α-Fluoro-β-keto esters are based on the acylation of fluorinated ketene silyl acetals with acid chlorides to produce 2-fluoro-3-oxoesters esters $RC(O)CFHCO_2Et$ ($R = CF_2Cl$, C_3F_7, C_2H_5).[7] The crossed-condensation reaction between trifluoroacetate and ethylfluoroacetate in the presence of sodium hydride gives the 2,4,4,4-tetrafluoro-3-oxoesters $CF_3C(O)CFHCO_2Et$.[8] The

anion derived from $(EtO)_2P(O)CFHCO_2Et$ reacts with R_fCOCl to form the corresponding C-acylated phosphonates $[(EtO)_2P(O)CF(COR_f)CO_2Et]$, followed by subsequent hydrolysis of the acylated phosphonates gives $R_fCOCFHCO_2Et$ ($R_f = CF_2Cl$, n-C_3F_7, CF_3).[9,10] Herein, we demonstrate the synthesis of substituted 2,4,4,4-tetrafluoro-3-oxoesters via the reaction of phosphonate carbanions $[(RO)_2P(O)CFCO_2Et]^-Li^+$ with trimethylsilyltrifluoroacetate to form the enolate of ethyl trifluoroacetylfluoroacetate, followed by subsequent alkylation or allylation of the enolate to give the titled compounds.

RESULTS AND DISCUSSION

The Michaelis-Arbuzov reaction[11] of triethyl phosphite or triisopropyl phosphite with ethyl bromofluoroacetate, prepared from the hydrolysis of 1-ethoxy-1,2,2-trifluoro-2-bromoethane $C_2H_5OCF_2CFHBr$ with concentrated sulfuric acid, gives diethyl(fluorocarbethoxymethyl)phosphonate **1a** and diisopropyl(fluorocarbethoxymethyl)phosphonate **1b** in 75 % and 71 % isolated yields, repectively (Equation (1)).

$$F_2C=CFBr \xrightarrow[RT]{C_2H_5ONa/C_2H_5OH} C_2H_5OCF_2CFHBr \xrightarrow[0°C]{H_3O^+} CFHBrCO_2Et$$

$$(RO)_3P + CFHBrCO_2Et \xrightarrow{140\text{–}150°C} \underset{\mathbf{1}}{(RO)_2P(O)CFHCO_2Et} + EtBr \qquad (1)$$

1a: R = Et 75%
1b: R = i-Pr 71%

The anions $[(EtO)_2P(O)CFCO_2Et]^-Li^+$ **2a** and $[(i\text{-}PrO)_2P(O)CFCO_2Et]^-Li^+$ **2b** generated from dialkyl(fluorocarbethoxymethyl)phosphonate $(RO)_2P(O)CFHCO_2Et$ **1a** and **1b** react with trimethylsilyltrifluoroacetate to afford enolate $[CF_3C(O)CFCO_2Et]^-Li^+$ **3.** Subsequent alkylation or allylation of **3** gives the substituted 2,4,4,4-tetrafluoro-3-oxoesters (Equation (2)).

$$\underset{\mathbf{1}}{(RO)_2P(O)CFHCO_2Et} \xrightarrow[2)\ CF_3C(O)OSiMe_3\ \ 3)\ R_1X]{1)\ n\text{-}BuLi/THF,\text{-}78C} \underset{\mathbf{10}}{CF_3C(O)CFR_1CO_2Et} \qquad (2)$$

R = Et, i-Pr
R_1 = H, CH_3, $CH_2\text{-}CH=CH_2$
X = Cl, Br, I

The most likely mechanism for the preparation of substituted 2,4,4,4-tetrafluoro-3-oxoesters is shown in Scheme I.

Deprotonation of **1** with n-butyllithium at -78°C gives carbanion $[(RO)_2P(O)CFCO_2Et]^-Li^+$ **2.** Nucleophilic addition of trimethylsilyltrifluoroac-

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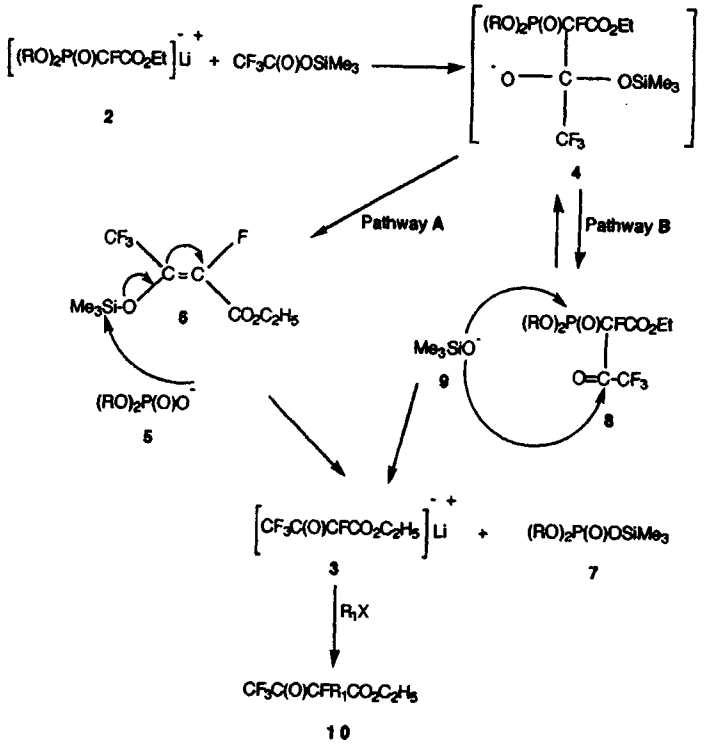

SCHEME I

etate $CF_3C(O)OSiMe_3$ to the THF solution of **2** affords betaine **4.** There are two possible pathways to form enolate $[CF_3C(O)CFCO_2Et]^-Li^+$ **3** from betaine **4.** Intramolecular elimination of **4** gives phosphonate salt $(RO)_2P(O)O^-Li^+$ **5** and olefin **6** (pathway **A**). Nucleophilic attack of **5** on the silicon of **6** leads to the formation of enolate intermediate $[CF_3C(O)CFCO_2Et]^-Li^+$ **3** and $(RO)_2P(O)OSiMe_3$ **7.** On the other hand, betaine **4** may also undergo elimination to give the α-fluoro-β-keto phosphonate $(RO)_2P(O)CF(C(O)CF_3)CO_2Et$ **8** and trimethylsilanoate ion $Me_3SiO^-Li^+$ **9** (pathway **B**). Attack of trimethylsilanoate ion **9** on the carbonyl group of **8** goes back to betaine **4**. However, nucleophilic attack of trimethylsilanoate ion **9** on the phosphorus of **8** leads to the same result as pathway **A** to form enolate $[CF_3C(O)CFCO_2Et]^-Li^+$ **3** and $(RO)_2P(O)OSiMe_3$ **7.** Alkylation or allylation of **3** affords substituted 2,4,4,4-tetrafluoro-3-oxoesters.

Evidences consistent with the proposed mechanism were obtained from the following experiments. Deprotonation of the isolated product 2,4,4,4-tetrafluoro-3-oxoester $CF_3C(O)CFHCO_2Et$ **10a** with n-butyllithium gave enolate $[CF_3C(O)CFCO_2Et]^-Li^+$ **3**, which exhibited the same ^{19}F NMR spectrum

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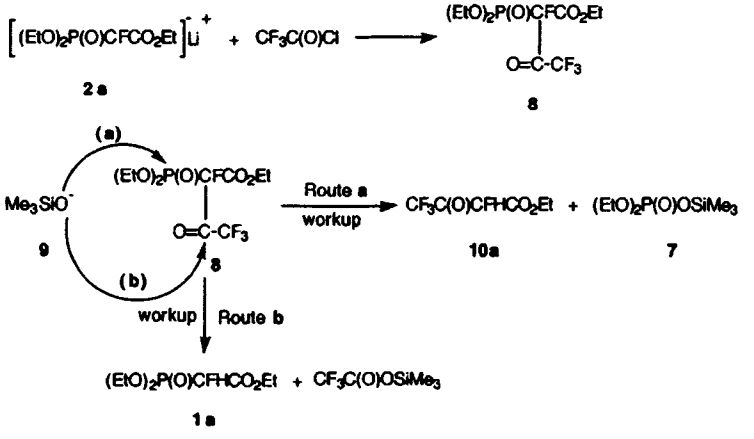
signals with the product from the reaction between $(EtO)_2P(O)CFHCO_2Et$ **1a** and trimethylsilyl trifluoroacetate. The ^{19}F NMR spectrum showed a doublet at -71.3 ppm (J = 18 Hz) and a quartet at -193.0 ppm (J = 18 Hz) for $[CF_3C(O)CFCO_2Et]^-Li^+$ **3.** Meanwhile, addition of trimethylsilyl trifluoroacetate to a THF solution of $[(EtO)_2P(O)CFCO_2Et]^-Li^+$ **2a** exhibited a signal at -9.0 ppm in the ^{31}P NMR which was confirmed as the resonance of the compound $(EtO)_2P(O)OSiMe_3$ **7.**[12] The above evidences are consistent with the mechanism proposed in Scheme I. That the pathway **B** is another possible route in Scheme I to form enolate $[CF_3C(O)CFCO_2Et]^-Li^+$ **3** has been confirmed by the following experiment (Scheme II).



SCHEME II

The anion **2a** derived from diethyl(fluorocarbethoxymethyl)phosphonate **1a** undergoes acylation with trifluoroacetyl chloride $CF_3C(O)Cl$ to give the α-fluoro-β-keto phosphonate $(EtO)_2P(O)CF(C(O)CF_3)CO_2Et$ **8**. Addition of potassium trimethyl silanolate $KOSiMe_3$ to the α-fluoro-β-keto phosphonate **8** affords both the phosphorus attacked products $CF_3C(O)CFHCO_2Et$ **10a,** $(EtO)_2P(O)OSiMe_3$ **7** (Route **a**) and the carbonyl attacked products $(EtO)_2P(O)CFHCO_2Et$ **1a**, $CF_3C(O)OSiMe_3$ (Route **b**). The product $CF_3C(O)CFHCO_2Et$ **10a** (from route **a**) showed signals at -83.3 ppm (d, J = 9.8 Hz) and -200.7 ppm (d,q, J = 40, J = 9.8 H_z) in ^{19}F NMR spectrum. The products $(EtO)_2P(O)CFHCO_2Et$ **1a** and $CF_3C(O)OSiMe_3$ (from route **b**) showed signals at -211.0 ppm (d,d, J = 73, J = 46 Hz) and -75.8 ppm (s), respectively.

The results of protonation, alkylation and allylation of enolate **3** in the preparation of substituted 2,4,4,4-tetrafluoro-3-oxoesters are reported in Table I.

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TABLE I Preparation of $CF_3C(O)CFR_1CO_2Et$

$[(RO)_2P(O)CFCO_2Et]^-Li^+$ (**2a, 2b**) —1) $CF_3C(O)OSiMe_3$, 2) R_1X, Reflux→ $CF_3C(O)CFR_1CO_6C_2H_5$ (**10**)

No.	R	R_1	X	Yields (%)[a]
10a	C_2H_5	H	Cl	58
10b	i-C_3H_7	H	Cl	56
10c	C_2H_5	CH_3	I	46
10d	i-C_3H_7	CH_3	I	49
10e	C_2H_5	CH_2=CH-CH_2	Br	52
10f	i-C_3H_7	CH_2=CH-CH_2	Br	50
10g	C_2H_5	H	Cl	55[b]

[a] Isolated yields are based on $(RO)_2P(O)CFHCO_2Et$.
[b] $(EtO)_2P(O)CH_2CO_2Et$ as starting material to get $CF_3C(O)CH_2CO_2Et$.

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Hydrolysis of the enolate **3** with a 3N HCl solution results in the formation of keto ester as hydrate. Distillation of the hydrate from an equal volume concentrated sulfuric acid as a dehydrating agent[10] affords $CF_3C(O)CFHCO_2Et$ (**10a, 10b**) as anhydrous liquid. Similarly, alkylation or allylation of enolate **3** with iodomethane or allyl bromide give the corresponding products $CF_3C(O)CF(CH_3)CO_2Et$ (**10c,10d**) and $CF_3C(O)CF(CH_2 - CH{=}CH_2)CO_2Et$ (**10e, 10f**) in moderate yields. Addition of trimethylsilyltrifluoroacetate $CF_3C(O)OSiMe_3$ to a THF solution of triethyl phosphonoacetate carbanion $[(EtO)_2P(O)CHCO_2Et)]^-Li^+$ also achieved the product of ethyl trifluoroacetylfluoroacetate $CF_3C(O)CH_2CO_2Et$ **10g.** However, no 2-fluoro-3-oxoester $CH_3C(O)CFR_1CO_2Et$ was observed when phosphonate carbanion $[(EtO)_2P(O)CFCO_2Et]^-Li^+$ **2a** reacted with trimethylsilyl acetate $CH_3C(O)OSiMe_3$. The most likely explanation for this observation is that carbonyl group in trimethylsilylacetate was not active enough to be attacked by the anion of diethyl(fluorocarbethoxymethyl) phosphonate $[(EtO)_2P(O)CFCO_2Et]^-Li^+$ **2a** to form enolate ethyl acetylfluoroacetate $[CH_3C(O)CFCO_2Et]^-Li^+$.

In conclusion, the reaction of dialkyl(fluorocarbethoxymethyl)phosphonate anions $[(RO)_2P(O)CFCO_2Et]^-Li^+$ **2a** and **2b** with trimethylsilyltrifluoroacetate $CF_3C(O)OSiMe_3$, followed by subsequent protonation, alkylation or allylation of the the prepared enolate ethyl trifluoroacetyl fluoroacetate $[CF_3C(O)CFCO_2Et]^-Li^+$

3 provides a general, one-pot synthesis of substituted 2,4,4,4-tetrafluoro-3-oxoesters $CF_3C(O)CFR_1CO_2Et$ **10.**

EXPERIMENTAL

^1H and ^{19}F NMR spectra were recorded on a Bruker WM360X spectrometer and are referenced against internal $(CH_3)_4Si$ and $CFCl_3$. ^{31}P NMR spectrum were recorded on a 90-MHz multinuclear spectrometer and are referenced against external 85 % H_3PO_4. FTIR spectra were recorded on a Mattson Cygnus 100 FTIR spectrophotometer. All the mass spectral analyses were performed at 70 eV in the electron-impact mode on a single quadrapole instrument interfaced to a gas chromatograph fitted with a OV-101 column. Ethyl bromofluoroacetate ($CFHBrCO_2Et$) was prepared similar to the reported preparation of ethyl chlorofluoroacetate.[13] Tetrahydrofuran was distilled from sodium benzophenone ketyl at atmospheric pressure prior to use. Normality of the reagent n-Butyllithium was determined by the method of the Duhamel and Plaquevent procedure.[14] Triethyl phosphonoacetate ($(EtO)_2P(O)CH_2CO_2Et$), trifluoroacetyl chloride ($CF_3C(O)Cl$), trimethylsilyltrifluoroacetate ($CF_3C(O)OSiMe_3$), potassium trimethylsilanolate ($KOSiMe_3$) and trimethylsilylacetate ($CH_3C(O)OSiMe_3$) were used without further purification. Triethyl phosphite ($(EtO)_3P$) and triisopropyl phosphite ($(i\text{-}PrO)_3P$) were distilled from sodium metal at reduced pressure. Methyl iodide (CH_3I) and allyl bromide ($CH_2{=}CHCH_2Br$) were distilled prior to use.

Preparation of ethyl bromofluoroacetate $CFHBrCO_2Et$

1-ethoxy-1,1,2-trifluoro-2-bromoethane (1.20 mols, 248 g) was charged into a 1000 mL three-necked flask equipped with a teflon-coated magnetic stirbar, a constant pressure addition funnel and a gas outlet tube leading to the back of the hood. The contents of the flask were cooled to 0°C *via* an ice-water bath and concentrated sulfuric acid (1.95 mols, 105 mL) was slowly added from the addition funnel for a period of one hour. After the acid was added, the reaction mixture was stirred at 0°C for two hours and then poured into 500 g ice water. (CAUTION : gloves must be worn to give protection from highly corrosive hydrofluoric acid in the reaction mixture). The lower organic layer was separated and washed with saturated sodium bicarbonate solution (3 × 120 mL) until the washings were neutral to litmus paper. The organic layer was then washed successively with saturated sodium chloride solution (2 × 80 mL), and water (2 × 80

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mL), dried over anhydrous $MgSO_4$ and filtered. Distillation of the filterate at 63-65°C and 35 mmHg gave 133 g (60 %) of the titled compound; GLPC purity: 99 %; ^{19}F NMR: -151.2 (d, J_{FCH} = 51); ^{1}H NMR: 6.58 (d, 1H, J_{HCF} = 51), 4.35 (q, 2H, J = 7), 1.35 (t, 3H, J = 7); ^{13}C NMR: 164.7 (d, J_{CCF} = 26), 80.9 (d, J_{CF} = 263), 63.2, 13.9.

Preparation of diethyl(carboethoxyfluoromethyl)phosphonate $(EtO)_2P(O)CFHCO_2Et$ (1a)

A 300 mL three-necked flask equipped with a thermometer, a teflon-coated magnetic stirbar and an air condenser (15 cm) topped with a nitrogen tee tube leading to a source of nitrogen was charged with 0.96 mols (125 g, 129 mL) of freshly distilled triethyl phosphite and 0.54 mols (100 g, 63 mL) of ethyl bromofluoroacetate. The contents of the flask were heated to 148°C for 11 hours. Distillation of the reaction mixture at 109-112°C and 1.1 mmHg (lit.[15] bp 111-114°C/1.2 mmHg) gave 97 g (75 %) of the titled phosphonate; GLPC purity: 99%; ^{19}F NMR: -211.0 (d,d, J_{FCP} = 73.0, J_{FCH} = 46.0); ^{31}P NMR : 10.6 (J_{PCF} = 71.8, J_{PCH} = 9.5, J_{POCH} = 6.2); ^{1}H NMR: 5.24 (d, d, 1H, J_{HCF} = 46.0, J_{HCP} = 9.5), 4.37-4.21 (m, 6H), 1.31-1.25 (m, 9H); ^{13}C NMR: 164.8 (d, J_{CCF} = 21.8), 84.6 (d,d, J_{CF} = 196.1, J_{CP} = 158.4), 64.3, 64.2, 64.1, 16.4, 16.3, 14.1; GC-MS m/z (relative intensity): 243 (M^+ + 1, 0.31), 242 (M^+, 0.38), 214 (M^+-CH_2 = CH_2, 11.84), 197 (M^+-OEt, 38.78), 187 (30.20), 186 (M^+-2CH_2 = CH_2, 44.49), 169 (M^+-CO_2Et, 18.67), 159(100.00), 155 (42.04), 137 (M^+-$CFHCO_2Et$, 26.94), 131(40.82), 130(31.43), 127 (38.37), 114 (64.08), 109 (93.06), 105 (M^+-$(EtO)_2P(O)$, 4.26), 99 (54.69), 93 (53.88), 81 (88.16), 78 (74.76), 65 (83.27). FTIR spectrum (CCl_4 solution, cm^{-1}): 2984 (m, C-H), 2939 (w), 2932 (w), 1764 (s, C=O), 1444 (m), 1370 (m), 1325 (s, C-F), 1275 (m, P=O), 1272 (s), 1232 (m, C-O-C), 1094 (m), 1053 (m), 1025 (m), 1029 (m, P-O-C), 979 (m).

Preparation of diisopropyl(carboethoxyfluoromethyl)phosphonate $(i\text{-}PrO)_2P(O)CFHCO_2Et$ (1b)

B.p. = 101-104°C/0.5 mmHg; GLPC purity: 99 %; ^{19}F NMR: -209.6 (d,d, J_{FCP} = 72.0, J_{FCH} = 48.0); ^{31}P NMR: 8.5 (J_{PCF} = 72.0)· ^{1}H NMR: 5.40 (d, d, 1H, J_{HCF} = 44, J_{HCP} = 12), 4.80 (m, 2H), 4.30 (q, 2H, J = 7.3), 1.4 - 1.3 (m, 15H); ^{13}C NMR: 164.9 (d, J_{CCF} = 21.8), 84.6 (d,d, J_{CF} = 195, J_{CP} = 195), 62.3, 24.1, 23.7, 14.1; GC-MS m/z (relative intensity): 272 (M^++ 2, 8.0), 271 (M^+ + 1, 77.0), 269 (M^+- 1, 2.0), 263 (0.80), 253 (0.40), 243 (100), 229 (11.0), FTIR spectrum (CCl_4 solution, cm^{-1}): 2985 (m, C-H), 2933 (m), 1760 (s, C=O), 1279 (m, P=O), 1272 (s), 1221 (m, C-O-C), 1032 (m, P-O-C).

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General Procedure for Preparation of $CF_3C(O)CFRCO_2Et$ as Described for Preparation of ethyl 2,4,4,4-tetrafluoro-3-oxo butanoate **10a** *from $(EtO)_2P(O)CFHCO_2Et$* **(1a)**

A solution of 16.0 mmol (3.87 g) of $(EtO)_2P(O)CFHCO_2Et$ and 30 mL of dry THF were cooled to -78°C via a dry ice/i-PrOH slush bath under nitrogen. To the cooled solution, 16.0 mmols (6.4 mL) of a 2.5 M n-butyllithium was added dropwise via syringe. The resultant bright yellow solution was stirred at -78°C for 20 minutes and then 16.0 mmols (2.97 g, 2.7 mL) of trimethylsilyl trifluoroacetate was added dropwise via syringe. The resultant mixture was stirred at -78°C for one hour and then allowed to warm to room temperature and stirred at room temperature for 5 hours until the complete consumption of the ylide was observed by ^{19}F NMR spectrum. Analysis of the reaction mixture indicated the presence of two compounds with the following signals: -75.8 ppm (s), -71.3 ppm (d, J = 18 Hz) and -193.0 ppm (q, J = 18 Hz). The signal at -75.8 ppm corresponds to unreactive trimethylsilyl trifluoroacetate, and the signals at -71.3 ppm and -193.0 ppm corresponds to the enolate. Treatment of the reaction mixture with 2.5 mL of a 6 N HCl solution, stirring at room temperature overnight, drying over $MgSO_4$ and concentration on a rotary evaporator yielded a yellow residue. Distillation of the residue in the presence of an equal volume of concentrated H_2SO_4 at 40-45°C and 35 mmHg (lit.[8]bp 138-139°C, lit.[10] bp 42-43°C/43 mmHg) gave 1.81 g (58 %) of the titled compound. ^{19}F NMR: -83.3 (d, $^4J_{F,F}$ = 9.8), -200.7 (d, q, $^2J_{F,H}$ = 40, $^2J_{F,F}$ = 9.8); ^1H NMR: 5.05 (d, 1H, $^1J_{H,F}$ = 47.7), 4.38 (q, 2H, $^3J_{H,H}$ = 7.1), 1.43 (t, 3H). MS m/z: 174(M^+-CH_2 = CH_2), 157(M^+- OEt), 133(M^+-CF_3), 129(M^+-CO_2Et), 105(M^+-$CF_3C(O)$), 45(100.00). FTIR spectrum (CCl_4 solution): 3418(broad), 2973(s), 2971(s), 2930(s), 2908(m), 2882(m), 1743(s), 1735(s), 1466(m), 1299(s), 1254(s), 1187(m), 1162(m).

Preparation of ethyl 2,4,4,4-tetrafluoro-2-methyl-3-oxo-butanoate **(10c, 10d)**

B.p. = 53-63°C/60mmHg. ^{19}F NMR: -80.0 (d, $^4J_{F,F}$ = 12), -166.7 (q, q, $^3J_{F,H}$ = 22); ^1H NMR: 4.40 (q, 2H, $^3J_{H,H}$ = 7.1),1.76 (d, 3H, $^3J_{H,F}$ = 18.4), 1.37 (t, 3H). MS m/z: 218(M^++2), 217(M^++1), 215(M^+-1), 201(M^+-CH_2), 187(M^+-C_2H_5), 171(M^+-OEt), 147(M^+-CF_3), 143(M^+-CO_2Et), 119(M^+-$CF_3C(O)$), 97($CF_3C(O)$), 74(100.00), 69(CF_3).

Preparation of ethyl 2-fluoro-2-trifluoroacetyl-pent-4-enoate **(10e, 10f)**

B.p.=39-48°C/15mmHg. ^{19}F NMR : -74.3 (d, $^4J_{F,F}$ = 15), -172.3 (t, q, $^3J_{F,H}$ = 27); ^1H NMR: 5.76 (m, 1H), 5.28 (m, 2H), 4.34 (q, 2H), 2.90 (m, 2H), 1.30 (t, 3H).

MS m/z: 244(M^++2), 243(M^++1), 242(M^+), 214(M^+-CH_2 = CH_2), 197(M^+-OEt), 169(M^+- CO_2Et), 145(M^+-$CF_3C(O)$), 117(M^+-CH_2 = CH_2-$CF_3C(O)$, 100), 69(CF_3).

Preparation of ethyl 4,4,4-trifluoro-3-oxo butanoate 10g from $(EtO)_2P(O)CH_2CO_2Et$

^{19}F NMR: -77.2 (s); ^1H NMR: 5.68 (s, 2H), 4.34 (q, 2H), 1.30 (t, 3H). MS m/z: 184(M^+, 0.10), 156(M^+-CH_2=CH_2, 0.04), 139(M^+-OEt, 1.24), 115(M^+-CF_3, 1.36), 111(M^+ -CO_2Et, 0.05), 87(M^+-$CF_3C(O)$). FTIR spectrum (CCl_4 solution): 3442(broad), 2931(s), 2962(s), 2931(s), 2871(m), 1741(s), 1701(m), 1261(m), 1215(s), 1212(s), 1167(s), 1162(m).

Reaction of $(EtO)_2P(O)CF(COCF_3)CO_2Et$ 8 with $KOSiMe_3$

A solution of 5.0 mmols (1.21 g) of $(EtO)_2P(O)CFHCO_2Et$ and 8 mL of dry THF were cooled to -78°C via a dry ice/i-PrOH slush bath under nitrogen. To the cooled solution, 5.0 mmols (2.0 mL) of a 2.5 M n-butyllithium was added dropwise via syringe. The resultant bright yellow solution was stirred at -78°C for 20 minutes followed by dropwise addition of 1.29 g (10.0 mmols) of trifluoroacetyl chloride. The resultant clear yellow solution was stirred at -78°C for one hour and then allowed to warm to room temperature over 5 hours. To the reaction mixture, 5.0 mmols (0.62 g) of potassium trimethylsilanoate was added and the resultant mixture was stirred at room temperature for 10 hours. The reaction mixture was poured into water (60 mL) and the water layer was extracted with ether (3 × 50 mL). The combined of the organics were washed with dilute sodium bicarbonate until the washings were neutral to litmus paper. The resulting solution was washed successively with brine (30 mL) and water (30 mL), dried over $MgSO_4$ and concentrated on a rotary evaporator to give $CF_3C(O)CFHCO_2Et$, $(EtO)_2P(O)CFHCO_2Et$ and $CF_3C(O)OSiMe_3$. $CF_3C(O)CFHCO_2Et$ showed signals at -83.3 ppm (d, J = 9.8 Hz) and -200.7 ppm (d, q, J = 40, J = 9.8 Hz) in ^{19}F NMR spectrum, and signals at -75.8 ppm (s) and -211.0 ppm (d, d, J = 73, J = 46 Hz) were assigned to $CF_3C(O)OSiMe_3$ and $(EtO)_2P(O)CFHCO_2Et$, respectively.

Deprotonation of ethyl 2,4,4,4-tetrafluoro-3-oxo butanoate **10a** *to $CF_3C(O)CFCO_2Et]^-Li^+$*

0.45 mL THF and 4 mL of $CF_3C(O)CFHCO_2Et$ **10a** were charged into a NMR tube. ^{19}F NMR analysis of the mixture showed signals at -83.3 ppm (d, J = 9.8 Hz) and -200.7 ppm (d, q, J = 40, J = 9.8 Hz), which were assigned to

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$CF_3C(O)CFHCO_2Et$. To the mixture in the NMR tube, a few drops of 2.5 M n-hexane solution of n-butyllithium was added and the resultant solution was mixed thoroughly. ^{19}F NMR analysis of the resultant mixture gave the following signals: -71.3 ppm (d, J = 18 Hz) and -193.0 ppm (m), which were assigned to $[CF_3C(O)CFCO_2Et]^-Li^+$ **3.**

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