Acylation of Fluorocarbethoxy-Substituted Ylids: A Simple and General Route to α-Fluoro β-Keto Esters[1]

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Received January 18, 1990

(Fluorocarbethoxymethylene)tri-*n*-butylphosphorane (**3**) reacts with acid chlorides and anhydrides to form the corresponding carbon acylated phosphonium salts **4**, and hydrolysis of **4** under mild basic conditions provides RCOCFHCOOEt (**8**) in moderate yields. The reaction is applicable to primary, secondary, tertiary, cyclic, aromatic, and ester-substituted acid chlorides. Acylation with ethyl chloroformate and ethyl chlorothioformate leads to the diesters $CFH(COOEt)_2$ and EtSCOCFHCOOEt. Extension of this reaction sequence to perfluorinated and partially fluorinated acid chlorides did not proceed cleanly to give the expected phosphonium salts. However, the anion derived from $(EtO)_2P(O)CFHC(O)OEt$ reacts with R_FCOCl to form the corresponding C-acylated phosphonates **10**, and hydrolysis of **10** gives $R_FCOCFHCOOEt$.

Introduction

α-Fluoro β-keto esters have been used as precursors in the preparation of biologically active monofluorinated heterocycles[2] and fluorine-substituted isoprenyl derivatives.[3] The latter have found applications as hyperlipdemic drugs[4] and hormone substitutes[5] and in cancer chemotherapy.[6]

Preparation of title compounds by Claisen and crossed-Claisen condensation of fluoroacetates,[7] fluorination of reactive methylene moieties with $CFClO_3$[8] and $C_{19}XeF_6$,[9] acylation of the enol derived from fluoroacetates[2] and fluorine-substituted ketene silyl acetals,[10] and reaction of trifluoroethene with acid chlorides under Friedel–Crafts conditions[11] either require extreme reaction conditions or employ toxic and/or hazardous materials. Thus the search for a general and mild preparation of keto esters continues.

Acid halides, anhydrides, esters, thioesters, and *N*-acylimidazoles are known to acylate phosphonium ylids,[12] phosphonate and phosphine oxide anions,[13] and iminophosphoranes[14] to give the corresponding acyl-substituted compounds. The acylated derivatives are seldom isolated and usually are converted to a variety of products by hydrolysis, reduction, or olefination.

Herein, we describe a synthesis of α-fluoro β-keto esters via acylation followed by hydrolysis of $Bu_3P{=}CFCOOEt$ and $[(EtO)_2P(O)CFCOOEt]^-$.

Acylation of ylids such as $R_3P{=}CHR'$ requires 2 mol of ylid per mole of acid halide. The second mole is used to regenerate the acylated ylid from its conjugate acid, and the acid base reaction (transylidation) has been minimized by working at low temperatures[15] (0–20 °C) and using reagents with basic leaving groups such as $[OR^-]$ and $[SR^-]$.[16] Absence of hydrogen at the ylidic carbon in $Bu_3P{=}CFCOOEt$ and $[(EtO)_2P(O)CFCOOEt]^-M^+$ will also suppress the transylidation.

Results and Discussion

Reaction of ethyl bromofluoroacetate (**1**) with tri-*n*-butylphosphine to give the corresponding phosphonium salt **2** and the pregeneration of $[Bu_3P{=}CFCOOEt]$ (**3**) from **2** was recently reported.[17] Characterization of **3** via ^{19}F and $\{^1H\}^{31}P$ NMR spectroscopy indicated that the ylid exists as a mixture of two geometrical isomers in THF, where the negative charge is localized on oxygen. Acid

chlorides and anhydrides acylate $Bu_3P{=}CFCOOEt$ at carbon to form the corresponding phosphonium salts **4**, and hydrolysis of **4** with 5% aqueous $NaHCO_3$ produces the keto esters **8** in 38–70% isolated yields (Scheme I).

Scheme I

$$Bu_3P + \underset{\mathbf{1}}{CFHBrCOOEt} \xrightarrow[\text{rt, 40 h}]{\text{THF}} [Bu_3P^+CFHCOOEt]Br^- \underset{\mathbf{2}}{} \xrightarrow[-78\ ^\circ C]{n\text{-BuLi}} \underset{\mathbf{3}}{Bu_3P{=}CFCOOEt}$$

$$+ RC(O)X \xrightarrow[-78\ ^\circ C\ \text{to rt}]{} [Bu_3P^+CF(COR)COOEt]Br^- \xrightarrow[\text{rt}]{NaHCO_3(aq)} \underset{\mathbf{8}}{RC(O)CFHCOOEt} + Bu_3PO$$

X = Cl, OC(O)R

^{19}F and ^{31}P NMR analysis of the reaction mixture at room temperature indicated the absence of acylation at oxygen. The carbon acylated product **4** and oxygen acylated compound, $Bu_3P^+CF{=}C(OCOR)OEt$, **5**, are distinguishable from one another by virtue of the difference in

(1) (a) Presented in part at the 23rd Midwest Regional Meeting of the American Chemical Society, Iowa City, IA, November 1988, Abstract No. 157. Taken in part from the Ph.D. Thesis of A.T., University of Iowa, 1989. (b) A preliminary report of this work has appeared: Thenappan, A.; Burton, D. J. *Tetrahedron Lett.* **1989**, *30*, 6113.

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Table I. Preparation of RC(O)CFHCOOEt

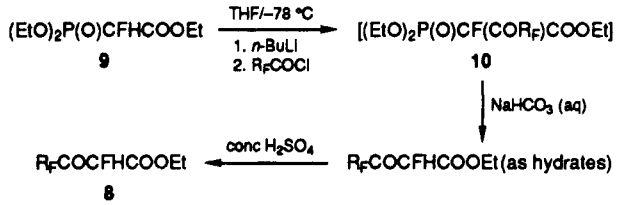
$$Bu_3P{=}CFCOOEt \xrightarrow[2.\ NaHCO_3(aq)]{1.\ RC(O)Cl} RC(O)CFHCOOEt \text{ (method A)}$$

$$(EtO)_2P(O)FHC(O)OEt \xrightarrow[2.\ R_fC(O)Cl\ 3.\ NaHCO_3(aq)]{1.\ n\text{-}BuLi} R_fC(O)CFHCOOEt \text{ (method B)}$$

					^{19}F NMR	
no.	R	method	isolated[a] yield, %	bp, °C/mmHg	ppm	coupling constant, Hz
8a	CH_3[b]	A	60	60–62/4.0	−193.7 (dq)	49 and 4
8b	CH_3CH_2	A	50	48–52/2.2	−195.8 (dt)	49 and 2
8c	$(CH_3)_2CH$	A	58	62–63/2.5	−196.3 (d)	49
8d	$(CH_3)_3C$	A	56	56–61/2.0	−191.1 (d)	49
8e	C_6H_{11}	A	68	76–84/0.5	−196.2 (d)	49
8f	EtO	A	50	72–74/3.5	−195.6 (d)	49
8g	C_6H_5	A	70	112–114/0.4	−191.4 (d)	49
8h	$CH_3OCOCH_2CH_2$	A	38	92–97/0.45	−195.9 (d)	49
8i	EtS	B	57	74–77/0.5	−192.2 (d)	49
8j	$n\text{-}C_3F_7$[c]	B	77	45–47/5.0	−199.7 (dt)	46 and 8
8k	CF_3[d]	B	60	42–43/43	−199.5 (dq)	47 and 11
8l	CF_2Cl[e]	B	67	60–65/38	−198.6 (dt)	48 and 15

[a] Isolated yields are based on acid chloride. [b] Acylation using acetic anhydride. [c] $CF_3CF_2CF_2$ −80.8 (t, $^4J_{F,F}$ = 9 Hz); $CF_3CF_2CF_2$ −127.1 (s, broad); and CF_3CF_2CFF' −118.4 (dq) and −119.4 (dq). [d] CF_3 −82.2 (d, $^4J_{F,F}$ = 11 Hz). [e] CF_2Cl −64.2 (d, $^4J_{F,F}$ = 15 Hz).

Scheme II



their chemical shifts and coupling constants ($^2J_{PCF}$) in ^{19}F and ^{31}P NMR spectra.

A variety of acid chlorides can be employed in the acylation reaction as shown in Table I. Primary, secondary, tertiary, cyclic, and aromatic acid chlorides will all react with **3** to afford the corresponding phosphonium salts **4** in good yields. Reaction of **3** with ethyl chloroformate and ethyl chlorothioformate leads to the diesters, $CFH(COOEt)_2$ and EtSCOCFHCOOEt. Preparation of $CH_3OCOCH_2CH_2COCFHCOOEt$ from **3** and 3-carbomethoxypropionyl chloride indicated that the ester functionality is stable under the reaction conditions. Anhydrides are also effective in carrying out the acylation as illustrated by the synthesis of $CH_3COCFHCOOEt$ from **3** and acetic anhydride.

Acylation of **3** with perfluorinated and partially fluorinated acid chlorides such as CF_3COCl, $n\text{-}C_3F_7COCl$, and $CF_2ClCOCl$ did not proceed cleanly to give good yields of the expected phosphonium salts. ^{19}F NMR analysis of the reaction mixture indicated the presence of mono- and diacylated products. For example, treatment of CF_3COCl with **3** in THF leads to the formation of a mixture of $[Bu_3P^+CF(COCF_3)COOEt]Cl^-$, and $(CF_3CO)_2CFCOOEt$. The double acylation was circumvented by acylation of the anion derived from $(EtO)_2P(O)CFHC(O)OEt$, **9**. Treatment of $[(EtO)_2P(O)CFCOOEt]^-Li^+$ with fluorine substituted acid chlorides gives the corresponding C-acylated phosphonates **10** in good yields (Scheme II). Hydrolysis of **10** with 5% aqueous $NaHCO_3$ results in the formation of keto esters as hydrates. Distillation of these hydrates from concentrated H_2SO_4 yields $R_FCOCFHCOOEt$ **8** as anhydrous liquids.

The anion derived from **9** reacts with other acid halides such as benzoyl chloride, acetyl chloride, and ethyl chloroformate to produce the respective C-acylated phosphonates **11** in 71–97% ^{19}F NMR yields (vs C_6F_6 as an internal standard) (eq 1). The outcome is independent of the

$$(EtO)_2P(O)CFHCOOEt \xrightarrow[2.\ RCOCl]{THF/-78\ °C,\ 1.\ n\text{-}BuLi} [(EtO)_2P(O)CF(COR)COOEt] \quad (1)$$
9 **11**

R = Ph, CH_3, EtO

metal ion used for anion generation. For example, formation of the anion either by NaH or *n*-BuLi and subsequent acylation with ethyl chloroformate gives only $[(EtO)_2P(O)CF(COOEt)_2]$.

Displacement of the phosphonate moiety from **11** either by hydrolysis under basic conditions or by reduction was unsuccessful. Treatment of **11** with 5% aqueous NaOH at room temperature produced $[(EtO)_2P(O)CFHC(O)OEt]$ as the major product, and RCOCFHCOOEt was present only in trace quantities (<10%). Similar results were also observed with less basic carbonate and bicarbonate solutions. It appears that the site of cleavage in **11** during hydrolysis is dictated by the electron-withdrawing ability of the acyl group at the carbon α to phosphorus. With strong electron-withdrawing groups such as $CF_3C(O)$, $C_3F_7C(O)$, and $CF_2ClC(O)$, the phosphorus carbon bond of **11** cleaves to produce $R_FCFHCOOEt$. On the other hand, with RC(O) groups, where R = nonfluorinated, the carbon bond cleaves to depart with the anion $[(EtO)_2P(O)CFCOOEt]^-$ as the leaving group.

Selective cleavage can be achieved by use of fluoride ion. Treatment of **11** (R = Ph) with potassium fluoride in triglyme at 40–50 °C for 24 h produced PhCOCFHCOOEt along with an equimolar quantity of $[(EtO)_2P(O)F]$. The regioselective cleavage may best be explained by the formation of a strong P–F bond in the byproduct. Since the keto esters **8** (R = nonfluorinated) can be conveniently prepared via an acylation–hydrolysis sequence of the phosphorane **3**, the above methodology was not extended to other acylated phosphonates, and, furthermore, the byproduct $(EtO)_2P(O)F$[18] is toxic.

Removal of the phosphonate moiety from **11** by reductive cleavage with zinc and acetic acid, metallic sodium,

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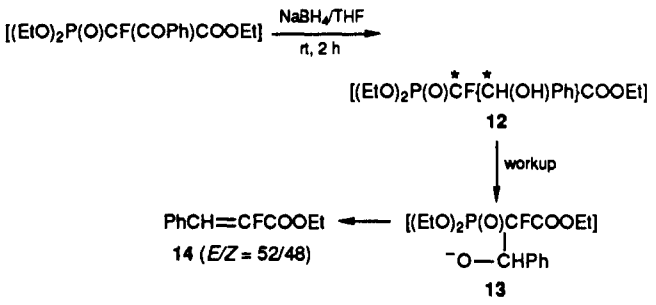
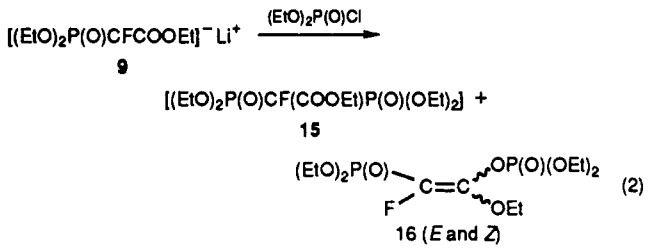
Scheme III



or lithium at room temperature was also unsuccessful. In the presence of reducing agents, the acylated phosphonate **11** reverted to $(EtO)_2P(O)CFHC(O)OEt$, and ^{19}F NMR analysis of the reaction mixture indicated the absence of RCOCFHCOOEt. However, the use of sodium borohydride as a reducing agent leads to a mixture of two geometrical isomers of α,β-unsaturated ester **14** after workup (Scheme III).

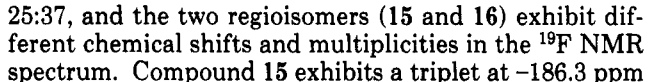
The initial step of this reaction sequence is the reduction of the ketone carbonyl moiety to form the secondary alcohol **12**. Under the reaction conditions, this alcohol gets deprotonated to form a betaine-type intermediate **13**, which collapses intramolecularly to form **14** and $[(EtO)_2P(O)O]^-Na^+$. Evidence for the formation of **12** was confirmed via ^{19}F NMR analysis of the reaction mixture. Compound **12** exhibits two sets of dd in the ^{19}F NMR spectrum, and the doublet of doublets are due to two sets of diastereoisomers which arise as a result of two adjacent chiral carbons. In a related study, Durant[20] and co-workers have shown that the anion derived from $(EtO)_2P(O)CH_2COOEt$ can be acylated at carbon to form the corresponding acylated phosphonates, which can then be transformed to RCH=CHCOOEt by reduction and subsequent base treatment.

In addition to carboxylic acid chlorides, phosphoric acid chlorides will also acylate the anion, $[(EtO)_2P(O)CFCOOEt]^-Li^+$ to form the respective acylated phosphonates. Treatment of the anion obtained from **9** with $(EtO)_2P(O)Cl$ leads to a mixture of C and O acylated products (eq 2). The ratio of C/O-acylated products is



25:37, and the two regioisomers (**15** and **16**) exhibit different chemical shifts and multiplicities in the ^{19}F NMR spectrum. Compound **15** exhibits a triplet at −186.3 ppm ($^2J_{FCP}$ = 70 Hz), whereas the resonance due to **16** is observed as two sets of dd at −179.9 and −186.8 ppm, respectively. The two dd's are due to two geometrical isomers (E/Z = 1/1) of the O-acylated phosphonate **16**.

In contrast, the reaction between $(EtO)_2PCl$ and the anion generated from $[(RO)_2P(O)CFHCOOEt]$ leads to C-acylated phosphonate **17** exclusively (eq 3). The regioselectivity may best be explained by HSAB principle.[21]



The P(III) acid chloride is softer than its P(V) analogue and prefers to bond to carbon, which is softer than oxygen. On the other hand, with the hard acid $(EtO)_2P(O)Cl$, the major product is the O-acylated phosphonate.

In the ^{19}F NMR spectra, compounds **17a** and **17b** exhibit resonances at −192.5 ppm ($^2J_{FCP(V)}$ = 73 Hz and $^2J_{FCP(III)}$ = 66 Hz) and −192.6 ppm ($^2J_{FCP(V)}$ = 75 Hz and $^2J_{FCP(III)}$ = 61 Hz), respectively. The higher coupling constant was assigned to the phosphorus(V) terminus, and the assignment was made on the basis of the difference in magnitude of coupling constants between fluorine and phosphorus with different oxidation states in compounds such as $(RO)_2PCF_3$ [$^2J_{FCP(III)}$ = 60–90 Hz] and $(RO)_2P(O)CF_3$ [$^2J_{FCP(V)}$ = 110 Hz].[22]

Oxidation of the P(III) center in **17a** and **17b** to P(V) using 90% *tert*-butyl peroxide solution and dry air converts **17a** to $(EtO)_2P(O)CFHC(O)OEt$ and **17b** to $(i\text{-PrO})_2P(O)CFHCOOEt$, respectively.

In summary, we have shown that acylation of fluorocarbethoxy-substituted ylids such as $Bu_3P{=}CFCOOEt$ and $[(EtO)_2P(O)CFCOOEt]^-M^+$ provide a direct entry to potentially useful α-fluoro β-keto esters. By choosing the appropriate ylid, the desired oxoesters RCOCFHCOOEt or $R_FCOCFHCOOEt$ can be obtained in moderate to good yields. Acylation with several acid chlorides and anhydrides demonstrates the scope of our methodology. Since the acylated phosphonates and phosphonium salts are hydrolyzed in situ to form the title compounds, our method provides the convenience of carrying out all the transformations in one pot under mild reaction conditions.

Experimental Section

General. All the reactions were performed in an oven-dried apparatus that consisted of a two- or three-necked round-bottomed flask equipped with a septum port, a Teflon-coated magnetic stirbar, and a reflux condenser connected to a nitrogen source and mineral oil bubbler. The extra necks of the flask were fitted with glass stoppers.

All boiling points are uncorrected. ^{19}F, ^1H, and $\{^1H\}^{31}P$ NMR spectra were recorded on a 90-MHz multinuclear spectrometer, and $\{^1H\}^{13}C$ NMR spectra were recorded on a 360-MHz spectrometer. All chemical shifts are reported in parts per million downfield (positive) of the standard. The purity of all title compounds was judged to be 95% by ^{19}F and ^1H NMR spectral determinations. ^{19}F NMR spectra are referenced against internal $CFCl_3$, ^1H and ^{13}C NMR spectra against internal $(CH_3)_4Si$, and ^{31}P NMR spectra against an external 85% H_3PO_4 capillary. FT-IR spectra were recorded as CCl_4 solutions. All the mass spectral analyses were performed at 70 eV in the electron-impact mode. GLPC analyses were performed on a 5% OV-101 column with a thermal conductivity detector.

Materials. Ethyl bromofluoroacetate (**1**) was prepared by a method similar to the preparation of ethyl chlorofluoroacetate given in ref 23. Tetrahydrofuran was obtained from Fisher and was purified by distillation from sodium benzophenone ketyl. Tri-*n*-butylphosphine was obtained from M&T and was purified by Blackburn's method.[24] Triethyl and triisopropyl phosphites were obtained from Aldrich Chemical Co. and were distilled from sodium metal at reduced pressure. *n*-Butyllithium (2.5 M *n*-

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(22) Emsley, J.; Hall, D. *The Chemistry of Phosphorus*; Harper & Row: London, 1976; p 87.

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(24) Blackburn, G. M.; Parratt, M. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1417.

hexane solution) was obtained from Aldrich Chemical Co., and its concentration was determined using Duhamel's procedure (method B).[25] Perfluorinated and partially fluorinated acid chlorides were prepared by a literature method[26] from benzoyl chloride and the corresponding fluorinated acids. They were purified by treatment with quinoline (10% v/v) prior to use. All the other acid chlorides were obtained from Aldrich Chemical Co. and were distilled over calcium hydride prior to use.

Preparation of $[Bu_3P^+CFHC(O)OEt]Br^-$ (2), $[Bu_3P{=}CFCOOEt]$ (3), and $(EtO)_2P(O)CFHC(O)OEt$ (9) was reported recently.[17]

Representative Procedure for the Preparation of RC(O)CFHCOOEt (8). Method A: Preparation of $CH_3CH_2C(O)CFHCOOEt$ (8b). To a cooled (−78 °C) solution of the ylid **3**, generated from 7.1 g (35 mmol) of tri-*n*-butylphosphine, 6.5 g (35 mmol) of ethyl bromofluoroacetate, and 14 mL (35 mmol) of *n*-butyllithium in 50 mL of THF in a 300-mL two-necked flask equipped with the standard assembly, was added 3.2 g of freshly distilled propranoyl chloride (35 mL) in 50 mL of THF dropwise via syringe. The resultant mixture was allowed to warm to room temperature over a period of 5 h and stirred at that temperature overnight. The reaction mixture was then hydrolyzed by addition of 50 mL of a 5% aqueous $NaHCO_3$ solution, and the resulting mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with 100 mL of cold water, and the organic layer was separated, washed successively with brine (25 mL) and water (25 mL), and subjected to steam distillation. The aqueous layer of the steam distillate was extracted with Et_2O (2 × 25 mL), and the combined organic materials were dried ($MgSO_4$) and concentrated on a rotary evaporator to yield a pale yellow residue. Distillation of the residue through a 6-in. Vigreaux column at 48–52 °C (2.2 mmHg) (lit.[10] bp 54 °C (1.0 mmHg)) gave 2.8 g (50%) of **8b**, 100% pure by GLPC analysis. ^{19}F NMR: see Table I. ^1H NMR: 5.3 (d, $^2J_{H,F_{gem}}$ = 49 Hz), 4.3 (q, $^3J_{H,H}$ = 7 Hz), 2.7 (qd, $^4J_{H,F}$ = 2 Hz), 1.3 (t) and 1.1 (t, $^3J_{H,H}$ = 7 Hz). ^{13}C NMR: 201.8 (d, $^2J_{C,F}$ = 22 Hz), 164.4 (d, $^2J_{C,F}$ = 24 Hz), 91.4 (d, $^1J_{C,F}$ = 197 Hz), 62.7 (s), 32.1 (s), 14.1 (s), and 6.8 (s). IR: 2985 (m), 1762 (s), 1738 (s), 1240 (m), and 1199 (m). Mass spectrum: *m/e* 163 (0.1), 162 (0.2, M^+), 78 (9.3), 60 (9.3), and 57 (100.0).

Preparation of $CH_3C(O)CFHCOOEt$ (8a) Using Acetic Anhydride (Method A). Yield: 3.1 g (60%). Bp: 60–62 °C (4 mmHg) (lit.[2] bp 83–85 °C (19 mmHg)). GLPC purity 100%. ^{19}F NMR: see Table I. ^1H NMR: 5.2 (d, $^2J_{F,H_{gem}}$ = 49 Hz), 4.3 (q, $^3J_{H,H}$ = 7 Hz), 2.4 (d, $^4J_{H,F}$ = 4 Hz), and 1.3 (t). ^{13}C NMR: 199.0 (d, $^2J_{C,F}$ = 23 Hz), 164.2 (d, $^2J_{C,F}$ = 24 Hz), 91.6 (d, $^1J_{C,F}$ = 197 Hz), 62.7 (s), 26.1 (s), and 14.0 (s). IR: 2993 (m), 1766 (s), 1743 (s), 1207 (s), and 1099 (s). Mass spectrum: *m/e* 149 (0.5), 148 (5.5, M^+), 106 (48.1), 103 (47.0), 78 (100.0), 76 (16.4), and 60 (40.2).

Preparation of $(CH_3)_2CHC(O)CFHCOOEt$ (8c) (Method A). Yield: 3.4 g (58%). Bp: 62–63 °C (2.5 mmHg). GLPC purity 100%. ^{19}F NMR: see Table I. ^1H NMR: 1.2 (d, $^3J_{H,H}$ = 7 Hz), 1.3 (t), 3.2 (m, $^4J_{H,F}$ = 3 Hz), 4.3 (q, $^3J_{H,H}$ = 7 Hz), and 5.3 (d, $^2J_{H,F_{gem}}$ = 49 Hz). ^{13}C NMR: 204.8 (d, $^2J_{C,F}$ = 22 Hz), 164.4 (d, $^2J_{C,F}$ = 24 Hz), 90.7 (d, $^1J_{C,F}$ = 198 Hz), 62.6 (s), 37.0 (s), 17.9 (s), 17.4 (s), and 14.1 (s). IR: 2980 (m), 1764 (s), 1734 (s), 1268 (s), 1206 (s). Mass spectrum: *m/e* 177 (0.1), 176 (0.5, M^+), 106 (5.6), 78 (53.2), 71 (100.0), 60 (16.4), and 55 (4.5).

Preparation of $(CH_3)_3CC(O)CFHCOOEt$ (8d) (Method A). Yield: 3.5 g (56%). Bp: 56–61 °C (2.0 mmHg). GLPC purity 100%. ^{19}F NMR: see Table I. ^1H NMR: 5.5 (d, $^2J_{H,F_{gem}}$ = 49 Hz), 4.3 (q, $^3J_{H,H}$ = 7 Hz), 1.3 (t), and 1.25 (s). ^{13}C NMR: 204.9 (d, $^2J_{C,F}$ = 18 Hz), 165.0 (d, $^2J_{C,F}$ = 24 Hz), 89.0 (d, $^1J_{C,F}$ = 197 Hz), 62.4 (s), 27.0 (s), 25.8 (s), and 14.0 (s). IR: 2975 (m), 1763 (s), 1718 (s), 1204 (m), and 1018 (w). Mass spectrum: *m/e* 190 (0.2, M^+), 106 (17.3), 85 (20.3), 78 (19.7), and 57 (100.0).

Preparation of $C_6H_{11}C(O)CFHCOOEt$ (8e) (Method A). Yield: 4.8 g (68%). Bp: 76–84 °C (0.5 mmHg). GLPC purity 100%. ^{19}F NMR: see Table I. ^1H NMR: 5.3 (d, $^2J_{H,F_{gem}}$ = 49 Hz), 4.3 (dd, $^4J_{H,F}$ = 2.0 Hz), 2.2–2.9 (s, broad), 1.8 (s, broad), and 1.3 (t, $^3J_{H,H}$ = 7 Hz). ^{13}C NMR: 203.7 (d, $^2J_{C,F}$ = 22 Hz), 164.5 (d, $^2J_{C,F}$ = 24 Hz), 90.7 (d, $^1J_{C,F}$ = 198 Hz), 62.5 (s), 46.6 (s), 28.2 (s), 27.7 (s), 25.8 (s), 25.6 (s), 25.3 (s), and 14.1 (s). IR: 2946 (s), 2932 (s), 1764 (s), 1730 (s), 1272 (m), 1107 (s), and 1027 (m). Mass spectrum: 216 (0.3, M^+), 111 (35.3), 84 (8.0), 83 (100.0), 78 (9.5), and 55 (30.3).

Preparation of $CFH(COOEt)_2$ (8f) (Method A). Yield: 2.9 g (50%). Bp: 72–74 °C (3.5 mmHg) (lit.[11] bp 110–111 °C (22 mmHg)). GLPC purity 98%. ^{19}F NMR: see Table I. ^1H NMR: 5.5 (d, $^2J_{F,H_{gem}}$ = 48 Hz), 4.3 (q, $^3J_{H,H}$ = 7 Hz), and 1.3 (t); ^{13}C NMR: 164.0 (d, $^2J_{C,F}$ = 24 Hz), 85.9 (d, $^1J_{C,F}$ = 196 Hz), 62.7 (s), and 14.0 (s). IR: 2985 (m), 1776 (s), 1264 (s), 1168 (s), and 1032 (m). Mass spectrum: *m/e* 178 (0.2, M^+), 177 (0.1), 133 (20.8), 106 (19.6), 105 (26.7), 78 (100.0), and 60 (23.6).

Preparation of $PhC(O)CFHCOOEt$ (8g) (Method A). The product was purified by flash chromatography on a silica gel (200–425-mesh, Fisher Scientific) column with 8:2 *n*-hexane/ethyl acetate as eluent. Yields: 5.1 g (70%). Bp: 112–114 °C (0.4 mmHg) (lit.[11] 125–128 °C) (4.0 mmHg)). GLPC purity 100%. ^{19}F NMR: see Table I. ^1H NMR: 7.4–8.1 (m), 6.0 (d, $^2J_{F,H_{gem}}$ = 49 Hz), 4.3 (q, $^3J_{H,H}$ = 7 Hz), and 1.2 (t). ^{13}C NMR: 189.7 (d, $^2J_{C,F}$ = 19 Hz), 164.9 (d, $^2J_{C,F}$ = 24 Hz), 134.6 (s), 133.6 (s), 129.5 (s), 128.9 (s), 89.7 (d, $^1J_{C,F}$ = 196 Hz), 62.4 (s), and 13.9 (s). IR: 3072 (w), 1764 (s), 1696 (s), 1283 (s), 1213 (s), and 1109 (s). Mass spectrum: *m/e* 165 (0.1), 109 (27.7), 105 (56.3), 77 (100.0), 76 (9.3), 75 (7.5), 74 (9.8), 60 (34.4), 51 (66.4), and 50 (34.6).

Preparation of $CH_3OC(O)CH_2CH_2C(O)CFHCOOEt$ (8h) (Method A). The product was purified by flash chromatography on a silica gel column with 8:2 *n*-hexane/ethyl acetate as eluent. Yield: 2.5 g (38% yield). Bp: 92–97 °C (0.45 mmHg). GLPC purity 93%. ^{19}F NMR: see Table I. ^1H NMR: 5.3 (d, $^2J_{H,F_{gem}}$ = 51 Hz), 4.3 (q, $^3J_{H,H}$ = 7 Hz), 3.7 (s), 2.9 (m), 2.7 (t, $^3J_{H,H}$ = 6 Hz), and 1.3 (t). ^{13}C NMR: 200.0 (d, $^2J_{C,F}$ = 21 Hz), 173.0 (s), 164.8 (d, $^2J_{C,F}$ = 24 Hz), 92.1 (d, $^1J_{C,F}$ = 195 Hz), 62.9 (s), 51.9 (s), 34.0 (s), 27.6 (s), and 14.2 (s). IR: 1764 (s), 1741 (s), 1227 (m), and 1208 (m). Mass spectrum: *m/e* 221 (0.2), 220 (0.1, M^+), 161 (18.0), 143 (9.9), 115 (100.0), 87 (25.0), 60 (30.8), 59 (36.4), and 55 (37.2).

Representative Procedure for the Preparation of RC(O)CFHCOOEt (8). Method B: Preparation of $EtSC(O)CFHCOOEt$ (8i). Into a 250-mL, two-necked flask equipped with the standard assembly was charged 50 mL of THF and 6.9 g (28.5 mmol) of $(EtO)_2P(O)CFHC(O)OEt$. The resultant homogeneous solution was stirred and cooled to −78 °C, and then 11.5 mL of (28.5 mmol) *n*-BuLi was added dropwise via syringe. After the resultant ylid solution was stirred at −78 °C for 20 min, 3.5 g (28 mmol) of ethyl chlorothioformate dissolved in 10 mL of THF was added slowly via syringe. The resulting mixture was stirred at −78 °C for 1 h and then allowed to warm to room temperature over 5 h. Isolation and purification of the reaction mixture as described in method A gave 3.1 g (57%) of **8i** (bp 74–77 °C (0.5 mmHg)), 91% pure by GLPC analysis. ^{19}F NMR: see Table I. ^1H NMR: 5.3 (d, $^2J_{H,F_{gem}}$ = 49 Hz), 4.3 (q, $^3J_{H,H}$ = 7 Hz), 3.0 (q, $^3J_{H,H}$ = 7 Hz), 1.34 (t), and 1.30 (t). ^{13}C NMR: 192.3 (d, $^2J_{C,F}$ = 28 Hz), 163.4 (d, $^2J_{C,F}$ = 25 Hz), 90.7 (d, $^1J_{C,F}$ = 201 Hz), 62.9 (s), 23.2 (s), 14.2 (s), and 14.0 (s). IR: 1773 (s), 1699 (s), 1266 (m), 1197 (m), and 1122 (m). Mass spectrum: *m/e* 196 (0.4), 195 (0.6), 194 (6.7, M^+), 106 (12.2), 105 (11.1), 89 (100.0), 78 (53.5), 77 (12.5), 61 (12.8), and 60 (22.9).

Preparation of $C_3F_7C(O)CFHCOOEt$ (8j) (Method B). Yield: 6.9 g (77%). Bp: 45–47 °C (5 mmHg) (lit.[10] bp 52–54 °C (6 mmHg)). GLPC purity 100%. ^{19}F NMR: see Table I. ^1H NMR: 6.2 (d, $^2J_{F,H_{gem}}$ = 46 Hz), 4.4 (q, $^3J_{H,H}$ = 7 Hz), and 1.3 (t). ^{13}C NMR: 186.3 (td), 163.0 (d, $^2J_{C,F}$ = 24 Hz), 89.4 (d, $^1J_{C,F}$ = 197 Hz), 64.2 (s), and 14.2 (s). IR: 3424 (w), 2985 (w), 1735 (m), 1723 (m), 1255 (m), 1199 (s), 1113 (m), and 1023 (m). Mass spectrum: *m/e* 302 (2.0, M^+), 257 (45.0), 169 (20.0), 133 (43.7), 131 (13.0), 119 (20.6), 113 (13.2), 111 (54.5), 109 (11.2), 105 (75.7), 100 (21.7), 87 (24.3), 79 (48.3), 77 (28.8), 69 (100.0), 60 (64.1), and 51 (32.5).

Preparation of $CF_3C(O)CFHCOOEt$ (8k) (Method B). Yield: 4.3 g (60%). Bp: 42–43 °C (43 mmHg) (lit.[7] bp 138–139 °C). GLPC purity 96%. ^{19}F NMR: see Table I. ^1H NMR: 5.1 (d, $^2J_{F,H_{gem}}$ = 47 Hz), 4.3 (q, $^3J_{H,H}$ = 7 Hz), and 1.3 (t); ^{13}C NMR: 167.8 (d, $^2J_{C,F}$ = 22 Hz), 121.9 (q, $^1J_{C,F}$ = 287 Hz), 86.2 (d, $^1J_{C,F}$ = 199 Hz), 63.7 (s), and 13.8 (s). IR: 2985 (w), 1736 (s), 1724 (s), 1261 (s), 1220 (s), 1199 (s), 1072 (s), 1006 (s), and 981 (m). Mass spectrum: *m/e* 157 (6.3), 130 (2.4), 129 (2.5), 78 (3.4), 69 (100.0),

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60 (24.8), 51 (5.5), and 50 (17.7).

Preparation of $CF_2ClC(O)CFHCOOEt$ (8l) (Method B). Yield: 2.8 g (67%). Bp: 60–65 °C (38 mmHg) (lit.[10] bp 162–164 °C (atm pressure)). GLPC purity 96%. ^{19}F NMR: see Table I. ^1H NMR: 5.6 (d, $^2J_{F,H_{gem}}$ = 48 Hz), 4.3 (q, $^3J_{H,H}$ = 7 Hz), and 1.4 (t). ^{13}C NMR: 206 (s), 166.3 (d, $^2J_{C,F}$ = 25 Hz), 128.1 (t, $^1J_{C,F}$ = 306 Hz), 88.2 (d, $^1J_{C,F}$ = 198 Hz), 62.2 (s), and 14.3 (s). IR: 2909 (w), 1763 (s), 1741 (s), 1200 (s), and 1028 (s). Mass spectrum: *m/e* 220 (2.8, $C_6H_6F_3O_3{}^{37}Cl$), 218 (11.5, $C_6H_6F_3O_3{}^{35}Cl$), 211 (13.3), 192 (11.8), 190 (35.5), 173 (10.6), 172 (14.4), 105 (100.0), 87 (40.8), 44 (10.4), and 40 (66.2).

Acknowledgment. We thank the National Science Foundation and the Air Force Office of Scientific Research for financial support of this work.

Registry No. 1, 401-55-8; 8a, 1522-41-4; 8b, 759-67-1; 8c, 127224-01-5; 8d, 118460-47-2; 8e, 118460-46-1; 8f, 685-88-1; 8g, 1479-22-7; 8h, 127224-04-8; 8i, 127224-02-6; 8j, 127224-03-7; 8k, 685-69-8; 8l, 87405-76-3; 9, 2356-16-3; EtCOCl, 79-03-8; $(CH_3)_2CHCOCl$, 79-30-1; $(CH_3)_3CCOCl$, 3282-30-2; $C_6H_{11}COCl$, 2719-27-9; EtOCOCl, 541-41-3; PhCOCl, 98-88-4; $MeOCO(CH_2)_2COCl$, 1490-25-1; EtSCOCl, 2941-64-2; $F_3C(CF_2)_2COCl$, 375-16-6; F_3CCOCl, 354-32-5; $ClCF_2COCl$, 354-24-5; Bu_3P, 998-40-3; acetic anhydride, 108-24-7.

Supplementary Material Available: ^1H and ^{19}F NMR spectra for 8a–l (34 pages). Ordering information is given on any current masthead page.

Synthesis and Chemistry of a New, Functionalized Polycyclic Azoalkane. A Novel Entry into the Homopentaprismane Ring System

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Received May 10, 1990

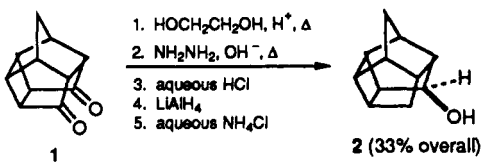
Reaction of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione, **1**) with (*p*-tolylsulfonyl)hydrazine (1 equiv) followed by in situ reduction of the product thereby obtained with sodium borohydride afforded two products, i.e., hexacyclic azoalkane **3** (34%) and *exo*-3-(*p*-tolylsulfonyl)tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undecan-*endo*-6-ol (**4**, 19%). The structure of **3** was established via X-ray crystallographic analysis of its corresponding *O*-benzoyl derivative **5a**. Reaction of **4** with acetic anhydride–pyridine gave the corresponding *O*-acetyl derivative **6**, whose structure was established by X-ray crystallographic methods. The corresponding reaction of **1** with (*p*-tolylsulfonyl)hydrazine alone afforded **3** as the exclusive reaction product in 66% yield. Subsequent reduction of **3** with sodium borohydride afforded **4** (84%). The results of mechanistic studies revealed that the conversion of **3** to **4** proceeds stepwise, i.e., with loss of nitrogen from **3** to form 3-(*p*-tolylsulfonyl)tetracylo[6.3.0.0^{4,11}.0^{5,9}]undec-2-en-6-one (**7**), which is subsequently reduced in situ by sodium borohydride. Irradiation of a benzene solution of **3** (Pyrex filter) afforded *exo*-(*p*-tolylsulfonyl)-PCUD-8-one (**9**, 48%). Similar irradiation of **5a** produced the corresponding substituted homopentaprismane (**11a**, 71%), whereas irradiation of **5c** (i.e., the *O*-acetyl derivative of **3**) gave a mixture of two products, i.e., homopentaprismane **11b** (52%) and the corresponding homohypostrophene **12** (14%), along with recovered **5c** (15%). The results of a control study revealed that **12** is not an intermediate in the formation of **11b** from **5c**. Structures of **9** and of **11a** were determined by X-ray crystallographic methods.

Introduction

As part of a general program that is concerned with the synthesis and chemistry of novel, substituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes (PCUDs),[1] we have recently undertaken the synthesis of some unusual cage amines via (i) reductive amination of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane-8,11-dione (PCUD-8,11-dione, **1**)[2] and (ii) sodium borohydride and sodium cyanoborohydride reduction of PCUD-8,11-dione monobenzylimine.[3] Roughly spherical cage amines of this type are of interest as analogues of 1-aminoadamantane, whose activity as an antiviral and anti-Parkinsonism agent is well established.[4]

In this connection, it was of interest to prepare PCUD-*endo*-8-ol (**2**) in quantity as starting material for the synthesis of amino-substituted PCUDs. In the past, this compound has been prepared from **1** in four steps (Scheme I).[5] In the present study, a shorter alternative route was investigated wherein **2** might be synthsized in a one-pot, two-step process via (i) reaction of **1** with (*p*-tolylsulfonyl)hydrazine followed by (ii) in situ reduction of the corresponding PCUD-8,11-dione monotosylhydrazone thereby obtained with sodium borohydride.[6] However, in our hands, application of this reaction sequence starting with **1** failed to afford any of the desired product **2**. Instead, two other products, **3** and **4**, were obtained in 19% and 34% yield, respectively (Scheme II).

Scheme I



1 **2 (33% overall)**

Product Characterization. Structure characterization of **3** and **4** was accomplished in part via analysis of their

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