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Synthesis of α-fluorinated phosphonoacetate derivatives using electrophilic fluorine reagents: Perchloryl fluoride versus 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor®)

Mong S. Marma, Leslie A. Khawli [1], Vahak Harutunian, Boris A. Kashemirov, Charles E. McKenna *

Department of Chemistry, University of Southern California, Los Angeles, CA 90089-0744, USA

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Abstract

Triethyl fluorophosphonoacetate and triethyl difluorophosphonoacetate are directly synthesized from triethyl phosphonoacetate by treatment with NaH and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor®). Contrary to a recent report [C.J. Hamilton, S.M. Roberts, J. Chem. Soc., Perkin Trans. 1 (1999) 1051–1056], the reaction proceeded in THF without the need for DMF as a co-solvent. This method is more selective and provides greater convenience and safety than fluorination of the same substrate by treatment with *t*-BuOK and perchloryl fluoride ($FClO_3$) in toluene while offering advantages over a number of previously described methods employing alternative electrophilic fluorinating reagents or other approaches. Either the monofluoro or the difluoro product can be obtained predominantly by adjusting the molar ratio of base and Selectfluor®. Triethyl 2-fluoro-2-phosphonopropionate (ethyl 2-(diethoxyphosphinyl)-2-fluoropropanoate) is also more conveniently made from triethyl 2-phosphonopropanoate using NaH/Selectfluor® in THF than with $FClO_3$/*t*-BuOK in toluene. Detailed procedures are given for obtaining the corresponding triacids in quantitative yield from the fluorinated triesters by *P,P*-silyldealkylation with bromotrimethylsilane followed by one-pot double hydrolysis with H_2O, and isolation as stable dicyclohexylammonium (DCHA) or pyridinium (Py) salts. Substitution of EtOH for H_2O in the latter procedure provides the CO-ester phosphonic diacids, isolated as DCHA salts, in one step. ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR data are given for the compounds prepared.

Keywords: Triethyl fluorophosphonoacetate; Triethyl difluorophosphonoacetate; Electrophilic fluorination; Selectfluor®; Perchloryl fluoride; Triethyl fluorophosphonopropionate; Fluorophosphonoacetic acid; Difluorophosphonoacetic acid

1. Introduction

α-Fluorinated derivatives of trialkyl phosphonoacetates (**1**) are useful precursors to the corresponding monofluoro- (**2e**) or difluoro- (**3e**) phosphonoacetic acids [1–3], which inhibit DNA polymerases [4], and in conjugation with carbocyclic nucleoside monophosphates form inhibitors of HIV reverse transcriptase [5].

When fluorine is substituted for one or both α-hydrogens in phosphonoacetic acid (**1e**), the resulting steric perturbation is relatively small, but the acid–base properties of the fluorinated derivatives are modified significantly [2], analogously to α-fluorinated methylenebisphosphonates [6–8]. Fluorine substitution also introduces a potentially useful ^{19}F NMR probe [9] into these molecules and, in monofluoro-substituted phosphonoacetates, creates a chiral center that has possible value in probing stereochemical interactions. In addition, triethyl fluorophosphonoacetate

* Corresponding author. Tel.: +1 213 740 7007; fax: +1 213 740 0930.
E-mail address: mckenna@usc.edu (C.E. McKenna).
[1] Current address: Department of Pathology, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089, USA.

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(**2a**) is a convenient starting point for preparation of cognate compounds, such as triethyl chlorofluoro- and bromofluorophosphonoacetate [10] and their corresponding acids [11], and has been used as a Wittig-Horner reaction partner for the synthesis of α-fluoro-α,β-unsaturated esters [12] and a fluorinated PGE1 analogue [13].

The monofluoro ester **2a** has been obtained previously by the reaction of ethyl bromofluoroacetate with triethyl phosphate [14], or of ethyl chlorofluoroacetate with sodium diethyl phosphate [15], and more recently, from metalation of $(EtO)_2P(O)CFHBr$ with Zn, followed by reaction of the resulting organozinc compound with ethyl chloroformate [16]. A similar route to **3a** via generation of an organozinc reagent from $(EtO)_2P(O)CF_2Br$ followed by CuBr-catalyzed reaction with ethyl chloroformate has been described [17]. *P,P*-diethyl difluorophosphonoacetic acid (**3d**) was prepared by CO_2-carboxylation of lithium diethyl difluoromethylphosphonate [5].

Some years ago, the senior author and independently Blackburn reported the synthesis of α-fluorinated tetraalkyl methylenebisphosphonates (formerly, methanediphosphonates) via fluorination of tetraalkyl methylenebisphosphonate carbanions with perchloryl fluoride [6,7]. α-Fluorinated methylenebisphosphonic acids are interesting analogues of pyrophosphoric acid and as such have led to the synthesis of related fluoromethylenebisphosphonate nucleotide analogues [18–24].

Our laboratory briefly communicated extension of this method to prepare **2a**, **3a**, and **5a** providing the corresponding acids and *C*-ethyl diacids [1]. However, subsequent commercial unavailability of $FClO_3$ and the hazards attending synthesis of this reagent have impeded use of this approach, and alternative methods have been sought (Fig. 1).

Recently, Hamilton [5] evaluated *N*-fluoro-*o*-benzenedisulfonamide (NFOBS), *N*-fluorobenzenesulfonamide (NFSI) and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor®) as possible ''electrophilic fluorine'' agents for preparation of **2a** directly from **1a**. Of these, Selectfluor® was found to fluorinate the sodio carbanion of triethyl phosphonoacetate in THF-DMF, but yields were low (17%). No product was

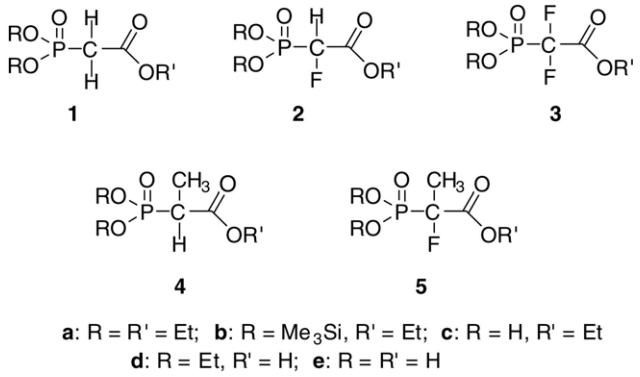


Fig. 1. Structures of phosphonoacetates and α-fluorinated derivatives.

observed (by TLC) in THF alone, and the added DMF was found to impair product recovery. Difluorination was not reported by these authors. The final triacid was prepared in several steps by sequential treatment of **2a** with NaOH (to de-esterify the $-CO_2Et$), BTMS and H_2O [5].

We report here that treatment in THF with NaH followed by Selectfluor® can be used in place of *t*-BuOK/$FClO_3$ for direct fluorination of triethyl phosphonoacetate **1a** to produce predominantly either mono (**2a**) (40%, isolated) or difluorinated product (**3a**) (69%, isolated) by adjusting the molar ratio of NaH and Selectfluor®. Besides being a more practical, convenient and safer alternative to $FClO_3$, the new NaH/Selectfluor®-THF method is more selective, allowing preparation of **2a** or **3a** in single step. Similarly, **5a** was prepared in THF in excellent yield (85%, isolated) from triethyl phosphonopropionate **4a**. The corresponding triacids were obtained in one pot by conversion to the ethyl *P,P*-bis(TMS) esters with BTMS [25,26] and addition of water: the resulting phosphonic diacids lower the pH sufficiently to promote subsequent acid hydrolysis of the remaining carboxylate ester group on warming. Alternatively, the isolable, mixed alkyl silyl intermediate esters can be transformed into the CO–ethyl phosphonic diacids (e.g. **2c**, **3c**) by reaction with wet EtOH.

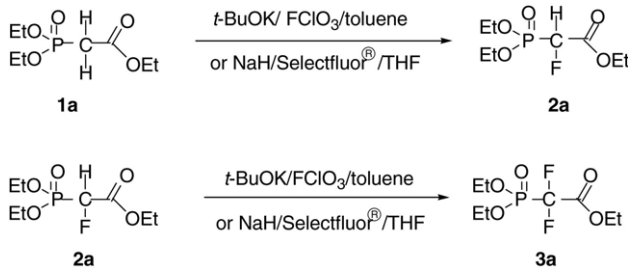
2. Results and discussion

Perchloryl fluoride reacts smoothly at 10–20 °C with triethyl phosphonoacetate **1a** potassium anion in toluene to give the monofluoro and difluoro esters **2a** and **3a**. The fluorination reaction proceeds as a titration of the anion with perchloryl fluoride and can be followed visually as the poorly soluble potassium salt of **1a** disappears. Completion of the reaction is easily detected by monitoring $FClO_3$ uptake using gas bubblers and is also signaled by a color change from yellow-orange to pale yellow. Appropriate safety procedures must be followed, notably, use of fluorocarbon grease and avoidance of contact between $FClO_3$ and combustible substances [6]. Results illustrating the influence of base source and ratio on product yields are summarized in Table 1. At varying ratios of *t*-BuOK (preferred over Na) to **1a** (1.0–1.7 eq.), mixtures of **2a**:**3a**

Table 1
Fluorination of **1a** with $FClO_3$[a]. Effect of base on product distribution

Base: **1a**		% Yield[b]	
Base	Ratio	**2a**	**3a**
Na	1:1	28	20 (12)[d]
t-BuOK	1:1	43	28 (4)[d]
t-BuOK	1.3:1	39	35 (10)[d]
t-BuOK	1.7:1	35[c]	45[c] (16)[d]

[a] Reaction conditions: vd. Experimental.
[b] ^{31}P NMR yield.
[c] Isolated yield.
[d] Side product derived from P–C cleavage of **3a**.



Scheme 1. Preparation of mono- and difluorophosphonoacetates.

were formed varying in composition from 4:3 to 7:8. If both **2a** and **3a** are desired, the synthesis then provides both together in ~80% total yield and approximately in equal proportion. Reaction at higher temperatures gave decreased yields due to excessive product breakdown (data not shown).

Increased conversion to **3a** at higher base:**1a** ratios was limited by more extensive formation of a side product with $\delta_P = 0.2$ ppm (s) (Table 1, **6**). This compound presumably arises from base-mediated cleavage of a C–P bond in **3a** as no ^{19}F-splitting of the ^{31}P NMR signal is observed. Cleavage of a CF_2–P bond, assumed to follow attack of base at phosphorus, occurs in tetraethyl difluoromethylenebisphosphonate under similar reaction conditions but in **3a**, where the ester carbonyl presents an alternative target to a basic nucleophile base, CF_2–P(O) bond breaking is evidently preferred over CF_2–C(O) bond breaking.

Fluorination of product **2a** competes with monofluorination of **1a**, owing to the base equilibria present, and some **3a** is always formed (Scheme 1). Where both compounds may be desired in comparable amount as has been the case in some of our work, this feature is advantageous. The extractive workup transfers residual chlorate salts to the aqueous phase for harmless disposal and also readily separates **2a** from **3a**. With the α-alkyl substituted substrate **5a**, the yield of desired product is higher, as no difluoro product is possible.

Several mechanisms have been proposed for fluorination of anions derived from acidic methylene compounds by $FClO_3$. One mechanism involves attack of the carbanion on fluorine [27–29]. Initial attack by enolate oxygen at chlorine giving a cyclic intermediate or a transition state that rearranges to make the new C–F bond has also been proposed [30]. Steric and other arguments have been opposed to this mechanism in specific cases [31].

Lapsed commercial availability (e.g. in North America) of perchloryl fluoride, and its synthetic inaccessibility have led to efforts to find an alternative ''electrophilic fluorine'' reagent by replacement of the ClO_3 moiety of perchloryl fluoride by a more docile leaving group. Thus, α-fluorocarbonyl compounds have been made from enolates reacting with CF_3OF [32], F_2/CF_3CO_2Na in Freon® at −75 °C [33] or XeF_6-graphite [34]. None of these methods have yet been applied to β-diphosphonates or β-phosphonocarboxylate esters to our knowledge. The use of nucleophilic fluorination, as illustrated in conversion of α-hydroxybenzyl phosphonate esters into α-fluoro esters by diethylamino sulfur trifluoride (DAST) [35] depends upon availability of the α-hydroxy phosphonoacetate. Fluorination of trialkyl bromo- or chlorophosphonoacetate with CaF_2-supported KF [36,37] is a further possibility, provided the monohalosubstrate proves sufficiently reactive. However, since the initial finding that perfluoro-*N*-fluoropiperidine can convert the sodium salt of 2-nitropropane and diethyl malonate to 2-fluoro-2-nitropropane and diethyl difluoromalonate, respectively, there has been an increasing focus on N–F fluorinating agents [38–40]. Among them, notable are *N*-fluoropyridine-2 (1H)-one [41], *N*-fluoro-*N*-alkylsulfonamides [42], *N*-fluoropyridinium salts [43], and finally 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2] octane bis(tetrafluoroborate) (Selectfluor®) [44–46].

It was previously reported [5] that treatment of the sodium salt of **1a** in THF with Selectfluor® gave no detectable **2a** in THF. We find that the anion of triethyl phosphonoacetate, produced via deprotonation by NaH in anhydrous, ice-cold THF, readily reacts with Selectfluor® to give **2a**, and also **3a**. Either **2a** or **3a** can be the predominant product depending on the equivalents of NaH used and the excess of Selectfluor® (Table 2). This method, therefore, can be adjusted to obtain one of the products predominantly in a single step. When one equivalent of NaH and 1.0–1.5 eq. Selectfluor® were used, triethyl fluorophosphonoacetate **2a** (40–50%) was cleanly formed, only a trace of triethyl difluorophosphonoacetate **3a** being detected (^{31}P NMR) in the reaction mixture. No side product derived from P–C bond cleavage was observed (Table 2), and refluorination of recovered **1a** could potentially increase the yield to >70%. On the other hand, with 2.5 eq. NaH and 3.0 eq. Selectfluor®, triethyl difluorophosphonoacetate **3a** was the only fluorinated product (78%, by ^{31}P NMR), the remainder being the presumed phosphate compound **6** ($\delta_P = 0.2$ ppm, ~22%) derived from P–C cleavage as observed with the $FClO_3$/*t*-BuOK method. Pure triethyl fluorophosphonoacetate **2a** and triethyl difluorophosphonoacetate **3a** were obtained by adapting the isolation procedures used in the $FClO_3$ method.

As the Selectfluor® molecule has two positive charges and retains a single charge after fluorine atom transfer, both unreacted Selectfluor® and its byproduct are fairly soluble

Table 2
Fluorination of **1a** with Selectfluor®. Effect of **1a**:base:Selectfluor® ratio on product distribution[a]

NaH (eq.)	Selectfluor (eq.)	%Conversion	**2a** (%)	**3a** (%)
1.0	1.0	46	46	Trace
1.0	1.5	51	51 (40)[b]	Trace
1.3	1.5	56	38	12 (6)[c]
2.2	3.0	100	11	77 (12)[c]
2.5	3.0	100	0	78 (69)[b](22)[c]

[a] Based on ^{31}P NMR.
[b] Isolated yield.
[c] Side product **6** derived from P–C cleavage of **3a**.

Table 3
Fluorination of **4a** with Selectfluor®. Effect of **4a**:NaH:Selectfluor® ratio on product yield

4a (eq.)	NaH (eq.)	Selectfluor (eq.)	%Yield[a]
1.0	1.1	1.5	90
1.0	1.3	1.5	97 (85)[b]

[a] ^{31}P NMR yield.
[b] Isolated yield.

in water; they can be readily removed by partitioning the reaction mixture between water and CH_2Cl_2 or EtOAc. The monofluorinated product (**2a**) is partially soluble in water, so to minimize product loss during aqueous workup, a minimum of water and excess organic solvent should be used. When an excess of NaH is used to produce difluorinated product **3a**, undesired P–C bond cleavage is reduced by running the reaction at lower temperature (0 °C). In fluorination of **4a**, the desired product **5a** can be formed very cleanly (97% conversion by ^{31}P NMR) with no P–C bond cleavage observed, and the product is readily purified by distillation or chromatography. For this reaction, a slight excess of NaH (1.3 eq.) and about 1.5 eq. Selectfluor® were required for complete fluorination (Table 3).

Treatment of esters **2a**, **3a** and **5a** with BTMS at 50 °C gave the expected [25,26] ethyl *P*,*P*-bis(trimethylsilyl) esters **2b**, **3b** and **5b** in quantitative yield, conveniently monitored by the resulting upfield ^{31}P NMR shift of about 19 ppm (Table 5), or by observing the disappearance of the $POCH_2CH_3$ proton resonances, as noted in other silyl-dealkylations [6,25,26]. In agreement with a similar finding for tetraalkyl mono- and difluoromethylenebisphosphonates [6], the electron deficient **2a** and **3a** display somewhat attenuated reactivity in silyldealkylation by BTMS, consistent with a phosphonium-like transition state in this reaction. In our hands, the moderate increase in temperature and recoverable excess of BTMS needed to facilitate silyldealkylation of these electron-deficient phosphonate esters resulted in a satisfactorily clean, quantitative reaction. We showed previously [25,26] that similar silyl esters can be isolated and fully characterized, as is demonstrated here for **1b**, but in preparing the other α-fluoroacids described here these intermediates were used without purification.

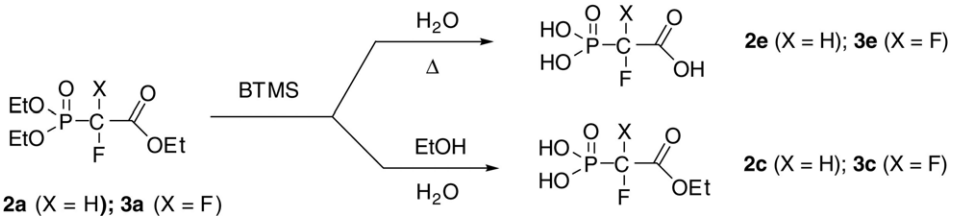
In contact with H_2O at room temperature, the silyl esters spontaneously hydrolyze to the corresponding phosphonic acids, which on gentle warming of the solution (50 °C, 6 h) cleanly undergo further hydrolysis of their remaining CO–ethyl ester function, allowing one-pot preparation of the triacids **2e**, **3e**, and **5e** in good yields. Thus, inclusion of an additional silylation step using iodotrimethylsilane to convert the ethyl *P*,*P*-bis(trimethylsilyl) esters [2,17] into tris(trimethylsilyl) esters or preliminary basic hydrolysis of the C–O ester can be avoided [5]. The acids are hygroscopic but are easily converted to stable (>1 year), crystalline bis(dicyclohexylammonium) or pyridinium salts. A curious property of the acid **3e** is its tendency to turn black on prolonged storage at room temperature. This behavior was not observed with **2e** under the same storage conditions, and remains unexplained [47].

The second hydrolysis step can be averted by replacing the H_2O with ethanol or acetone containing a small amount of H_2O (Scheme 2). Under these conditions, the partial ethyl esters **2c** and **3c** can be isolated in good yield. Compounds **2c** and **3c** are readily handled as dicyclohexylammonium salts (mono-salts are obtained, confirming that pK_2 involves the carboxylic acid group in the corresponding triacids **2e** and **3e**, which form di-salts).

In principle, the complementary carboxylic acid-phosphonate diesters should be available by careful alkaline hydrolysis of the triesters, as demonstrated in the conversion of **1a** to **1d** in 0.01 M NaOH (see experimental for detail). However, the difluorinated triester showed a tendency to decompose under these conditions.

NMR data used in characterizing the compounds are presented in Tables 4 and 5. The ^{1}H NMR spectrum of **2a** (Table 4) manifests diastereotopic splitting of the CH_3CH_2[PO] resonances, as expected. A generally similar ^{1}H NMR spectral pattern is seen for **5a**. The difluoro ester **3a**, lacking a chiral center, has only a single **CH_3**CH_2[PO] methyl resonance.

Turning next to the ^{13}C NMR data (Table 4), several aspects can be noted. Firstly, the ^{13}C δ values for the α-carbons in **2a** and **3a** show expected large downfield shifts with increasing fluorine substitution, and the chemical shift of the CH_2[CO] carbons is a few ppm upfield of the CH_2[PO] carbons in both compounds. A small long-range ^{13}C–^{31}P coupling (6 Hz) is observed for the –OCH_2**CH_3**[PO] and –**OCH_2**CH_3[PO] carbon nuclei. The larger *J* value (193 Hz) in the pair of doublets for CHFP in **2a** is identified as J_{CF} rather than J_{CP} (157 Hz) on the basis of comparison to the ^{13}C NMR spectrum of **3a**, where the different multiplicity (CF_2 versus CP) makes the assignment unambiguous. This reverses the assignment of J_{CP} = 191 Hz made for CHFP in a related phosphonoacetate [48].



Scheme 2. Dealkylation pathways of triethyl fluorophosphonoacetates.

Table 4
α-Fluorophosphonoacetates: ^{1}H and ^{13}C NMR data

Compound	δ ^{1}H ($CDCl_3$; J in Hz)	δ ^{13}C ($CDCl_3$; J in Hz)
Et_3FPAA (**2a**)	1.27 (t, $^{3}J_{HH}$ = 7.1, CH_3[CO]) 1.30, 1.31 (2td, $^{3}J_{HH}$ = 7, $^{4}J_{PH}$ = 0.6, $2CH_3$) 4.18 (m, $2CH_2$ [PO]) 4.27 (2q, $^{3}J_{HH}$ = 7.1, CH_2[CO]) 5.10 (dd, $^{2}J_{FH}$ = 47, $^{2}J_{HP}$ = 12, CHF)	14.1 (q, $^{1}J_{CH}$ = 127, CH_3[CO]) 16.1 (qd, $^{1}J_{CH}$ = 128, $^{3}J_{CP}$ = 6, $2CH_3$[PO]) 62.3 (t, $^{1}J_{CH}$ = 147, CH_2[CO]) 64.2, 64.2 (td, $^{3}J_{CH}$ = 149, $^{2}J_{CP}$ = 6,$2CH_2$[PO]) 85.7 (ddd, $^{1}J_{CH}$ = 313, $^{1}J_{CF}$ = 195, $^{1}J_{CP}$ = 157, CHF) 165.0 (dd, $^{2}J_{CF}$ = 22, $^{2}J_{CP}$ = 5, C═O)
Et_3F_2PAA (**3a**)	1.34 (t, $^{3}J_{HH}$ = 7.1, CH_3[CO]) 1.36 (td, $^{3}J_{HH}$ = 7.1, $^{4}J_{HP}$ = 0.8, $2CH_3$[PO]) 4.16 (m, $2CH_2$[PO]) 4.25 (q, $^{3}J_{HH}$ = 7.15, CH_2[CO])	14.4 (q, $^{1}J_{CH}$ = 127, CH_3[CO]) 16.8 (qd, $^{1}J_{CH}$ = 126, $^{2}J_{CP}$ = 6, $2CH_3$[PO]) 64.6 (t, $^{1}J_{CH}$ = 151, CH_2[CO]) 66.2 (td, $^{1}J_{CH}$ = 150, $^{2}J_{CP}$ = 6, $2CH_2$[PO]) 112.5 (td, $^{1}J_{CF}$ = 271, $^{1}J_{CP}$ = 202, CF_2) 162.7 (td. $^{2}J_{CF}$ = 27, $^{2}J_{CP}$ = 18, CO)
Et_3FPPA (**5a**)	1.12 (t, $^{3}J_{HH}$ = 7.1, CH_3[CO]) 1.14, 1.15 (2td, $^{3}J_{HH}$ = 7.1, $^{4}J_{HP}$ = 0.6, 1.72 (dd, $^{3}J_{HF}$ = 23, $^{3}J_{HP}$ = 15, $FCCH_3$) 4.03 (m, $2CH_2$[PO]) 4.10 (q, $^{3}J_{HH}$ = 7.1, CH_2[CO])	13.9 (q, $^{1}J_{CH}$ = 127, CH_3[CO]) 16.3 (qd, $^{1}J_{CH}$ = 128, $^{3}J_{CP}$ = 6, $2CH_3$[PO]) 20.1 (qd, $^{1}J_{CH}$ = 132, $^{2}J_{CF}$ = 22, $FCCH_3$) 62.1 (t, $^{1}J_{CH}$ = 148, CH_2[CO]) 64.0 (td, $^{1}J_{CH}$ = 149, $^{2}J_{CP}$ = 16.7, $2CH_2$[PO]) 92.9 (dd, $^{1}J_{CF}$ = 194, $^{1}J_{CP}$ = 168, $FCCH_3$) 167.7 (dd. $^{2}J_{CF}$ = 23, $^{2}J_{CP}$ = 5, CO)

Table 5
α-Fluorophosphonoacetates: ^{31}P and ^{19}F NMR data (cf. refs. [2,3])

Compound	Solvent δ	^{31}P (J in Hz)	δ ^{19}F (J in Hz)
Et_3FPAA (**2a**)	$CDCl_3$	10.7 (ddp, $^{2}J_{PF}$ = 71.5, $^{2}J_{PH}$ = 12, $^{3}J_{PH}$ = 8)	−214.7 (dd, $^{2}J_{PF}$ = 72, $^{2}J_{FH}$ = 47)
Et_3F_2PAA (**3a**)	$CDCl_3$	3.9 (tp, $^{2}J_{PF}$ = 96.4, $^{3}J_{PH}$ = 8)	−116.6 (d, $^{2}J_{PF}$ = 96.4)
Et_3FPPA (**5a**)	$CDCl_3$	13.8 (dqp, $^{2}J_{PF}$ = 84, $^{3}J_{PH}$ = 15,$^{3}J_{PH}$ = 8)	−176.1 (dq, $^{2}J_{PF}$ = 84, $^{3}J_{FH}$ = 23
$(TMS)_2EtFPAA$ (**2b**)	$CDCl_3$	−7.5 (dd, $^{2}J_{PF}$ = 73, $^{2}J_{PH}$ = 12)	–
$EtFPAA$ (**2c**)[a]	$CDCl_3$	5.5 (dd, $^{2}J_{PF}$ = 63, $^{2}J_{PH}$ = 12)	−214.5 (dd, $^{2}J_{PF}$ = 64, $^{2}J_{FH}$ = 18)
EtF_2PAA (**3c**)[a]	$CDCl_3$	0.86 (t, $^{2}J_{PF}$ = 79)	−122.5 (d, $^{2}J_{PF}$ = 79.5)
FPAA (**2e**)[a]	D_2O	8.4 (dd, $^{2}J_{PF}$ = 69, $^{2}J_{PH}$ = 12)	−206.8 (dd, $^{2}J_{PF}$ = 68, $^{2}J_{FH}$ = 14)
FPAA (**2e**)[b]	D_2O	8.6 (dd, $^{2}J_{PF}$ = 69, $^{2}J_{PH}$ = 14)	−207.1 (dd, $^{2}J_{PF}$ = 68, $^{2}J_{FH}$ = 15)
$Et(TMS)_2F_2PAA$ (**3b**)	$CDCl_3$	−14.5 (t, $^{2}J_{PF}$ = 100)	–
F_2PAA (**3e**)[a]	D_2O	4.1 (t, $^{2}J_{PF}$ = 91)	−116.3 (d, $^{2}J_{PF}$ = 90)
F_2PAA (**3e**)[b]	D_2O	3.6 (t, $^{2}J_{PF}$ = 88)	−118.4 (d, $^{2}J_{PF}$ = 90)
FPPA (**5e**)[a]	D_2O	14.6 (dq, $^{2}J_{PF}$ = 82, $^{3}J_{PH}$ = 14.5)	–

[a] DCHA salt.
[b] Pyridinium salt.

The ^{31}P NMR data (Table 5) for the product esters indicate that the second fluorine substituent gives an upfield shift (ca. 7 ppm). This shielding effect is also seen in tetraethyl fluoromethylenebisphosphonates [6]. The ^{31}P chemical shift values for the product acid salts are pH sensitive and thus are less exactly compared here, since the sample pH was not adjusted.

The ^{19}F NMR data (Table 5) for **2a** and **3a** may be correlated with the data for the corresponding tetraethyl α-fluorinated methylenebisphosphonates [6]. In both sets of compounds, inclusion of the second fluorine atom causes a downfield shift of ca. 100 ppm, while $^{2}J_{FP}$ increases by about 23 Hz.

In conclusion, compared to $FClO_3$/*t*-BuOK or /Na in toluene, direct fluorination of **1a** in THF and NaH with Selectfluor®, using the procedures detailed here, possesses important advantages of safety, selectivity and simplicity for a practical one-step preparation of either **2a** or **3a**. Similar fluorination of **4a** provides a facile route to **5a**. The new procedure affords ready access to the α-fluoro phosphonoacetic triacid derivatives **2e**, **3e**, **5e** and the CO–Et monoesters **2c** and **3c**. Details of convenient one-pot preparations of the latter are provided, leading directly to their stable pyridinium or DCHA salts.

2.1. Experimental

Triethyl phosphonoacetate and triethyl 2-phosphonopropionate were purchased from Aldrich and distilled before use. Potassium *t*-butoxide (*t*-BuOK) from the same vendor was used immediately from a freshly opened bottle and handled under N_2. BTMS and Selectfluor® (Aldrich) were used as received. Dicyclohexylamine (Aldrich) was distilled before use. Perchloryl fluoride was purchased from Ozark-Mahoning Co., currently Ozark Fluorine Specialties (carries

the reagent in its catalog, but no longer supplies it). Perchloryl fluoride is a powerful oxidant and it is essential to follow exactly safe procedures in using it: for general precautions, see previously cited references [6]. Apparatus in contact with $FClO_3$ was connected with Tygon tubing. Ground-glass joints were lubricated with "Series 2s-25" halocarbon grease, and "KF-3" halocarbon oil was used in gas bubblers; both materials were obtained from Halocarbon Products Corp., Hackensack, NJ. Tetrahydrofuran (EMD) was purified by distillation from Na. Other solvents were also of analytical reagent grade and were used directly. Glassware used in the fluorinations was dried overnight at 150 °C. Melting points were determined on a Mel-Temp or Thomas-Hoover apparatus in capillary tubes and are uncorrected. Proton (^{1}H), carbon (^{13}C), phosphorus (^{31}P) and fluorine (^{19}F) NMR spectra were measured on a Bruker AM-360 MHz or AC-250 MHz spectrometer. Chemical shifts are reported relative to external TMS (^{1}H), internal $CDCl_3$ [$\delta = 77.0$] (^{13}C), external 85% H_3PO_4 (^{31}P) or external $CFCl_3$ (^{19}F). All chemical shifts upfield of the reference are given as negative values. NMR data for products described below are collected in Tables 4 (H,C) and 5 (P,F). Elemental analyses were performed by Galbraith Laboratories. Note: until the toxicity of the α-fluoro compounds described in this paper has been established, they should be handled appropriately in view of the known toxicity of fluoroacetic acid.

2.2. Fluorination of triethyl phosphonoacetate carbanion by perchloryl fluoride

A 2 L three-necked round-bottomed flask equipped with an inlet gas bubbler attached to a subsurface gas addition tube, a condenser connected to an outlet gas bubbler, and an addition funnel was charged under N_2 with 8.40 g (74.8 mmol) *t*-BuOK in 400 mL toluene. The magnetically stirred suspension was cooled to 5 °C (ice bath) and a solution of 10.0 g (44.6 mmol) triethyl phosphonoacetate in 200 mL dry toluene was added dropwise. As addition proceeded, the mixture thickened into a slurry. It was allowed to warm to 10 °C and stirred vigorously while the inlet gas was changed from N_2 to perchloryl fluoride, using a 3-way stopcock. The brown reaction mixture became yellow and gradually clarified as perchloryl fluoride was passed in at the maximal rate consistent with total absorption, as determined by comparing inlet and outlet gas bubblers, while the temperature was maintained between 10 and 20 °C by occasional cooling with an ice bath. When the outlet gas bubbler again became active after approximately 50 min, flow was reduced three-fold and then stopped when inlet and outlet bubbling rates were equivalent. After flushing the apparatus with N_2, the clear, pale yellow reaction mixture was extracted with 2 × 50 mL portions of H_2O. The toluene phase was dried ($MgSO_4$) and the solvent removed by rotary evaporation at reduced pressure and 50 °C. ^{31}P NMR analysis of the residue (11 g) showed that **2a** ($\delta_P = 11.8$ ppm) and **3a** ($\delta_P = 4.0$ ppm) constituted at least 80% of the phosphorus-containing products; the remaining 20% was **1a** ($\delta_P = 21$ ppm) and a side product (**6**) with $\delta_P = 0.2$ ppm (s) was observed by ^{31}P NMR.

2.3. Triethyl difluorophosphonoacetate *3a*

The residue described above was partitioned between hexane (200 mL) and 0.1 M $NaHCO_3$ (5 × 50 mL) and the hexane extracts were dried ($MgSO_4$). Removal of the solvent by rotary evaporation at reduced pressure left 5.4 g pure triethyl difluorophosphonoacetate (45%) which was vacuum distilled to give a colorless oil, bp 66–67 °C (0.02 mm); TLC (EtOAc:benzene, 2:1) R_f 0.46; NMR: H, C, P, F (Tables 4 and 5). Anal: found: C, 37.23; H, 5.97%. $C_8H_{15}O_5F_2P$ requires C, 36.93; H, 5.81%.

2.4. Triethyl fluorophosphonoacetate *2a*

The bicarbonate fractions were combined and re-extracted with chloroform (5 × 50 mL). The chloroform extracts were dried ($MgSO_4$), and the solvent removed in vacuo. ^{31}P NMR of the residue showed a mixture (7.2 g) of triethyl fluorophosphonoacetate ($\delta_P = 11.8$ ppm) and triethyl phosphonoacetate ($\delta_P = 21$ ppm). The two compounds could not be easily separated by fractional distillation due to their similar boiling points. They were obtained by flash chromatography on a 63 mm × 457 mm column of Kieselgel 60, 230–400 mesh, eluted with ethyl acetate/benzene (2:1) (4 L) to yield twenty fractions. Fractions 15–20 (1 g) contained starting material **1a**; TLC (EtOAc/benzene, 2:1) R_f 0.22. Fractions 5–13 were combined to provide 3.9 g pure triethyl fluorophosphonoacetate (36%), which was vacuum distilled to give a colorless oil: bp 78–80 °C (0.01 mm); TLC (EtOAc/benzene, 2:1) R_f 0.37; NMR: H, C, P, F. (Tables 4 and 5); Anal: found: C, 39.79; H, 6.68%. $C_8H_{16}O_5FP$ requires C, 39.68; H, 6.66%.

2.5. Triethyl 2-fluoro-2-phosphonopropionate *5a* from perchloryl fluoride method

Triethyl 2-phosphonopropionate (8.50 g, 35.7 mmol) in toluene (150 mL) was added under N_2 to a well-stirred solution of *t*-BuOK (4.4 g, 39 mmol) in toluene (300 mL) at ice-bath temperature. The clear, brownish mixture was allowed to warm to 10 °C and perchloryl fluoride was passed in rapidly at 10–20 °C until the end point was evident as described above (30 min). The resulting solution was flushed with N_2 and then extracted with H_2O (3 × 15 mL). The toluene extracts were dried ($MgSO_4$) and the solvent removed in vacuo. ^{31}P NMR analysis of the residue showed that the desired product **5a** ($\delta_P = 13.8$ ppm) made up 85% of the phosphorus-containing products; the remaining 15% was accounted for by a side product ($\delta_P = 0.2$ ppm). The two compounds were easily isolated by vacuum distillation. Triethyl 2-fluoro-2-phosphonopropionate (7.13 g, 78% yield) was obtained as a colorless oil, bp

77–79 °C (0.01 mm). NMR: H, C, P, F. (Tables 4 and 5). Anal: found: C, 42.41; H, 7.25%. $C_9H_{18}O_5FP$ requires C, 42.19; H, 7.08%.

2.6. Preparation of triethyl fluorophosphonate **2a** using Selectfluor®

To 185 mg NaH (4.6 mmol; 60% in oil) dispersed in 6 mL anhydrous THF under N_2, 1.0 g triethyl phosphonoacetate (4.5 mmol) was added dropwise at 0 °C. The reaction mixture was stirred 30 min at the same temperature and an additional hour at room temperature. The reaction was recooled to 0 °C and Selectfluor® (2.37 g, 6.75 mmoles) was added at once. The reaction mixture was stirred for 1 h with continued cooling followed by 4 h at room temperature. ^{31}P NMR showed that triethyl α-fluorophosphonoacetate **2a** (δ_P = 10.7 ppm, d, $^2J_{PF}$ = 71.5 Hz, P–H decoupled) was the main product (with a trace of difluorinated product **3a**, δ_P = 3.5 ppm, t, $^2J_{PF}$ = 95.1 Hz, P–H decoupled) in the reaction mixture; the remainder was starting material (δ_P = 20.5 ppm, s, P–H decoupled). The reaction mixture was then treated with 25 mL aq. NH_4Cl (5%) and extracted with EtOAc (3 × 100 mL). The EtOAc fractions were combined and dried over $MgSO_4$, concentrated under vacuum, and the residual product was purified by silica gel column chromatography (EtOAc: toluene/5:1, R_f 0.53). The product obtained by chromatography contained a trace of difluoro derivative **3a**, which was removed by the following procedure: the sample was dissolved in hexane (25 mL) and extracted with 0.1 M $NaHCO_3$ solution (3 × 100 mL), leaving the **3a** in the hexane phase. The aqueous phase was then extracted with CH_2Cl_2 (5 × 100 mL). After drying ($MgSO_4$) and evaporation of solution, pure **2a** was obtained as a colorless oil (0.42 g, 40% yield). The product was characterized by ^1H, ^{13}C and ^{31}P NMR (Tables 4 and 5).

2.7. Preparation of triethyl difluorophosphonoacetate **3a** using Selectfluor®

To 223.0 mg NaH (60% in oil, 5.6 mmol) dispersed in 5 mL dry THF under N_2, freshly distilled triethyl phosphonoacetate (0.5 g, 2.2 mmol) was added dropwise at 0 °C and stirred for 1 h, followed by 1 h at room temperature. The reaction mixture was recooled to 0 °C and Selectfluor® (2.37 g, 6.69 mmol) was added in two portions. After stirring for 1 h at 0 °C and then 3 h at room temperature, the ^{31}P NMR of the reaction mixture showed complete conversion of the starting material **1a** to triethyl difluorophosphonoacetate **3a** (δ_P = 3.4 ppm, t, J = 96.4 Hz, P-H decoupled, 78%) and a side product **6** (22%). The reaction mixture was quenched by the addition of 0.1 M $NaHCO_3$ (100 mL) and difluorinated product **3a** was then extracted by hexane (3 × 100 mL). After drying on $MgSO_4$, the solvent was evaporated under vacuo to obtain **3a** as clear oil (398 mg, 69% yield), NMR as in Tables 4 and 5.

2.8. 2-Fluoro-2-phosphonoproprionate **5a** using Selectfluor®

To 214 mg NaH (60% in oil, 5.35 mmol) in 6 mL dry THF under N_2, freshly distilled triethyl 2-phosphonopropionate **4a** (1.0 g, 4.19 mmol) was added dropwise (0 °C) and the mixture stirred for 1 h, then for 1 h at room temperature. Selectfluor® (2.23 g, 6.29 mmol) was added at once at 0 °C. After stirring for 1 h, the mixture was brought to room temperature and stirring continued overnight. ^{31}P NMR showed clean conversion to the fluorinated product **5a** (97%) with no P–C bond cleavage evident. The reaction was quenched by addition of 25 mL aq. NH_4Cl (5%). After extraction with CH_2Cl_2 (3 × 100 mL), the combined organic phases were dried ($MgSO_4$), concentrated and chromatographed on silica gel (EtOAc: CH_2Cl_2/9:1), R_f 0.52) giving **5a** (0.91 g, 85% yield) as a colorless oil, characterized by ^1H, ^{13}C and ^{31}P NMR (Tables 4 and 5).

2.9. Ethyl P,P-bis(trimethylsilyl) phosphonoacetate **1b**

Bromotrimethylsilane (2.26 g, 14.8 mmol) was added dropwise with stirring under N_2 to triethyl phosphonoacetate (1.23 g, 5.48 mmol). The reaction progress was readily followed by ^{31}P or ^1H NMR. After 6 h at 50 °C, ethyl bromide and excess silylating reagent was removed in vacuo to leave the product (100% by ^{31}P NMR), which was vacuum distilled to give a colorless oil, bp 70–71 °C (0.02 mm); ^{31}P NMR ($CDCl_3$) δ = 1.2 ppm (*t*, $^2J_{PH}$ = 22.5 Hz). HR-MS: required for $C_{10}H_{25}O_5PSi_2$: 312.099; found (molecular ion, m/z): 312.098.

2.10. Ethyl P,P-bis(trimethylsilyl) fluorophosphonoacetate **2b**

In a similar reaction, bromotrimethylsilane (1.26 g, 8.2 mmol) was added dropwise with stirring under N_2 to triethyl fluorophosphonoacetate (0.50 g, 2.1 mmol). At 50 °C after 6 h, rotary evaporation at reduced pressure gave 0.68 g product (100% by ^{31}P NMR). NMR: P, F (Table 5). The compound was further characterized by conversion to the acid **2c** (see below).

2.11. Ethyl fluorophosphonoacetate **2c** (dicyclohexylammonium salt)

To 0.34 g (1.0 mmol) of **2b** under N_2 was added with stirring 10 mL of ethanol containing 20 μL (1.1 mmol) H_2O. After 3 h at room temperature, the reaction mixture was evaporated at reduced pressure to give the diacid (100% by ^{31}P NMR) which was isolated as its dicyclohexylammonium salt. For this purpose, the reaction product was dissolved in ethanol and excess dicyclohexylamine added. The precipitated salt (0.12 g, 33%) was recrystallized successively from ethanol/acetone and ethanol: mp >225 °C, NMR: P, F (Table 5). Anal:

found: C, 51.63; H, 8.34; N, 3.71%. $C_{16}H_{31}O_5FNP.1/4\ H_2O$ requires C, 51.67; H, 8.54; N, 3.77%.

2.12. Fluorophosphonoacetic acid **2e** (bis(dicyclohexylammonium) and pyridinium salts)

The silyl ester **2b** (0.34 g, 1.0 mmol) was stirred with 10 mL of H_2O. After 6 h at 50 °C, the reaction mixture was evaporated to dryness at reduced pressure to give the triacid (100% by ^{31}P NMR) which was characterized as the bis(dicyclohexylammonium) salt, prepared as described above and recrystallized successively from ethanol/acetone and absolute ethanol: mp 183–185 °C (softens at 168 °C). NMR: P, F (Table 5). Anal: found: C, 59.74; H, 9.93; N, 5.11%. $C_{26}H_{50}O_5FN_2P$ requires C, 59.98; H, 9.68; N, 5.38%.

Alternatively, ester **2a** (100 mg, 0.413 mmol) was refluxed overnight in conc. HCl; the syrupy residue left after evaporation in vacuo was treated with 2–3 times excess dry pyridine and the resultant salt recrystallized from methanol and dried 12 h at 60 °C: 93.3 mg (96%), mp 179–180 °C. NMR: P, F (Table 5). Anal: found: C, 35.39; H, 3.71; N, 5.99%. $C_7H_8O_5FNP$ requires C 35.61; H 3.41; N 5.93%.

2.13. Ethyl P,P-bis(trimethylsilyl) difluorophosphonoacetate **3b**

Bromotrimethylsilane (1.17 g, 7.64 mmol) was added dropwise under N_2 with stirring to triethyl difluorophosphonoacetate (0.25 g, 0.96 mmol). After 6 h at 50 °C, evaporation under reduced pressure left the product (0.32 g, 100% by ^{31}P NMR). NMR: P, F (Table 5). Further characterization was carried out by conversion to the corresponding acid (described below).

2.14. Ethyl difluorophosphonoacetate **3c** (dicyclohexylammonium salt)

To 0.16 g (0.46 mmol) of **3b** under N_2 was added with stirring 10 mL of ethanol containing 10 μL (0.55 mmol) H_2O. After 3 h at room temperature, the reaction mixture was evaporated to dryness at reduced pressure to give the diacid (100% by ^{31}P NMR). The dicyclohexylammonium salt was prepared and recrystallized as described above: 0.2 g, mp >225 °C. NMR: P, F (Table 5). Anal: found: C, 50.16; H, 7.73; N, 3.53%. $C_{16}H_{30}O_5F_2NP$ requires C, 49.87; H, 7.85; N, 3.63%.

2.15. Difluorophosphonoacetic acid **3e** (bis(dicyclohexylammonium) and pyridinium salts)

The silyl ester (**3b**) (0.16 g, 0.46 mmol) was stirred in 10 mL of H_2O at 50 °C for 6 h. Evaporation under reduced pressure gave the triacid (100%). The bis(dicyclohexylammonium) salt was prepared and recrystallized as described above: mp 224–226 °C. NMR: P, F. Anal: found: C, 58.22; H, 8.96; N, 5.36%. $C_{26}H_{49}O_5F_2N_2P$ requires C, 57.98; H, 9.17; N, 5.20%. Pyridinium salt, prepared from **3a** as described above, mp: 117–119 °C (sintered). NMR: P, F (Table 5). Anal: found: C, 33.23; H, 3.25; N, 5.66%. $C_7H_8O_5F_2NP$ requires C, 32.96; H, 3.16; N, 5.49%.

2.16. 2-Fluoro-2-phosphonopropionic acid **5e** (bis(dicyclohexylammonium salt))

Treatment of **5a** with excess bromotrimethylsilane followed by aqueous work up as described above gave the desired product (90%), characterized as the bis(dicyclohexylammonium) salt, mp 198–199 °C. NMR: P (Table 5). Anal: found: C, 58.50; H, 10.01; N, 4.95%. $C_{27}H_{52}O_5FN_2P.H_2O$ requires C, 58.67; H, 9.85; N, 5.07%.

2.17. P,P-Diethyl phosphonoacetic acid **1d**

Triethyl phosphonoacetate (1.0 g, 4.5 mmol) was added to a solution of 0.01 M sodium hydroxide (20 mL). Reaction progress was followed by ^1H NMR. After 8 h at 50 °C, the solution was passed into a column of Dowex 50 (H^+) (30 mL) and eluted with H_2O (50 mL). The eluate was evaporated to dryness under reduced pressure to yield the desired product as a viscous colorless liquid (0.80 g, 87%). ^{31}P NMR (D_2O): δ_P = 22 ppm(m). Anal: found: C, 35.15; H, 6.84%. $C_6H_{13}PO_5 \cdot 1/2\ H_2O$ requires C, 35.13; H, 6.88%.

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