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Short Communication

An efficient and general route to the synthesis of diethyl α,α-bromofluorophosphonates

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ABSTRACT

An efficient and general two-step halogenation procedure to prepare diethyl α,α-bromofluorophosphonates was described, which included bromination by PPh_3, 2,3-dichloro-5,6-dicyanobenzquinone (DDQ) and *n*-Bu_4NBr, and electrophilic fluorination by N-fluorobisbenzenesulfonimide (NFSI). Both aromatic and aliphatic α,α-bromofluorophosphonates could be prepared by this method.

1. Introduction

Since many of the most important biochemicals are organophosphates, including DNA and RNA as well as many cofactors that are essential for life, the organophosphorus chemistry has been rapidly developed recently [1]. In particular, α-monohalogenated [2] and α,α-dihalogenated phosphonates [3] have been designed as phosphate mimics used as metabolite probes, anticancer drugs, and enzyme inhibitors due to their structural and electronic similarities to the parent phosphate groups. In fact, fluorine as the optimum substitution atom of phosphate mimics, the synthesis strategies of α-monofluoro- and α,α-difluoroalkylphosphonates, including nucleophilic [4] and electrophilic fluorination [5], have been reported a lot. However, the attention which is paid to the synthesis of phosphonates bearing two different halogen substituents in the α-position to the phosphorus atom is limited. α-Bromobenzylphosphonates have been demonstrated to be better enzyme inhibitors compared to α-chlorobenzylphosphonates and α-flurobenzylphosphonates [6]. Since the bromine atom is a better leaving group than chlorine and fluorine atoms, α,α-bromofluorophosphonates may be more effective inhibitors. Therefore, it is necessary to explore a efficient method for the preparation of α,α-bromofluorophosphonate to enrich probe library of protein tyrosine phosphatases (PTPs) based on our reports on the synthesis of diethyl α,α-chlorofluorophosphonates recently [6].

In this paper, we describe the synthesis of a series of diethyl α,α-bromofluorophosphonates. The starting materials 1 were prepared by the Pudovik reaction starting from corresponding aldehydes and diethyl phosphate easily. Followed by a two-step halogenation procedure (Scheme 1), the target products, α,α-bromofluorophosphonates, could be prepared in reasonable yields. This method was applicable for the synthesis of both aromatic and aliphatic α,α-bromofluorophosphonates.

2. Results and discussion

The starting materials, α-hydroxyphosphonates **1**, were obtained in excellent yields from corresponding aldehydes and diethyl phosphate with sodium ethoxide as catalyst [7]. The following step was nucleophilic bromination. In our initial investigation, we adopted the procedure of PPh_3/Br_2/pyridine in CH_3CN according to the literature [8]. To our disappointment, the procedures did not proceed as smoothly as expected. The yields were low (40–56%) (Scheme 2). The plausible explanation was that the secondary hydroxyl possessed larger steric hindrance. Thus, it was difficult for nucleophilic reagent PPh_3Br_2 to approach. In other words, the bromination with PPh_3Br_2 was practically dependent on the structure. The above results prompted us to try another reported method using PPh_3/DDQ/*n*-Bu_4NBr in CH_2Cl_2 [9] to obtain α-bromophosphonates. In order to improve the conversion rates, the reaction was refluxed at 40 °C, and it worked well (Scheme 2). As shown in Table 1, various types of

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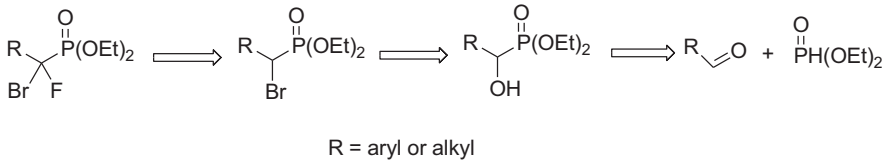
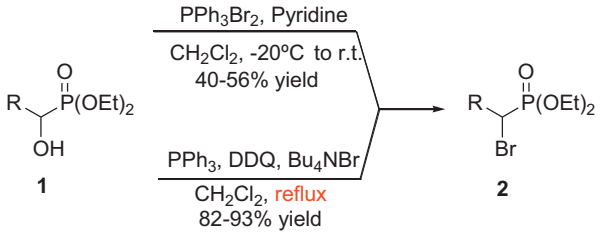


Scheme 1. Strategy for the preparation of α,α-bromofluorophosphonates.

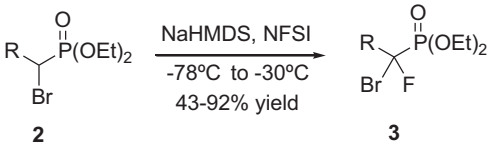
diethyl α-bromophosphonates 2 were obtained in good to excellent yields (82–93%).

Having achieved an efficient synthesis of α-bromophosphonates, we proceeded with the synthesis of α,α-bromofluorophosphonates by treating a solution of the respective compound 2 in dry THF with excess sodium hexamethyldisilazide (NaHMDS) and NFSI. Namely, α-bromophosphonates was deprotonated by NaHMDS (1.5 equiv) in THF at −78 °C for 1 h under an inert atmosphere, followed by treatment with NFSI (1.3 equiv) at −78 °C to −30 °C (Scheme 3). Fortunately, this procedure worked well, and both α,α-bromofluoroalkylphosphonates and α,α-bromofluorobenzylphosphonates (Entries 3a–h, Table 2) were obtained in reasonable to good yields (46–92%). Their structure was unequivocally confirmed by ^{13}C NMR and ^{19}F NMR spectroscopy (Table 2).

These compounds were stable at −20 °C for at least half a year and for at least one month without solvent at room temperature. It can be seen from Table 2 that an array of electron-withdrawing substituents on aromatic ring could be tolerated. This was because electron-withdrawing groups decreased electron density of the aromatic ring, which enhanced the stability of intermediate phosphonate carbanions. However, inferior results were displayed when the substrates 2 with electron-donating groups on aromatic ring were employed. When some α-bromophosphonates (R = 4-MeC_6H_4, 2-, 3- and 4-$MeOC_6H_4$) were used for the synthesis of α,α-bromofluorophosphonates, only 3f (R = 3-$MeOC_6H_4$) was obtainable in a low yield of 43% (Entry 3f, Table 2). We reasoned that the electron-donating group might contribute to an increased electron density of the aromatic ring, which made it difficult to form intermediate phosphonate carbanions during the reaction process, and these electron-donating groups had stronger influence when they were at the 2- and 4-positions of aromatic rings than at 3-position. In addition, the reaction was also applicable to α-bromophosphonates with aliphatic substituents. Moderate yields were obtained for 3 g (R = Et) and 3 h (R = *n*-Pr) (Entries 3g and h, Table 2).



Scheme 2. Preparation of diethyl α-bromophosphonates **2**.



Scheme 3. Preparation of diethyl α,α-bromofluorophosphonates **3**.

Table 1
Spectroscopic data of diethyl α-bromophosphonates **2**.

Entry	R	^{1}H NMR(δ, ppm, *J*, Hz)	^{13}C NMR(δ, ppm, *J*, Hz)	Yield[a] (%)
2a	4-$NO_2C_6H_4$-	4.91 (d, $^{2}J_{PH}$ = 13.9)	39.6 (d, $^{1}J_{PC}$ = 156.2)	93
2b	3-$NO_2C_6H_4$-	4.93 (d, $^{2}J_{PH}$ = 13.6)	39.6 (d, $^{1}J_{PC}$ = 157.1)	91
2c	2-$NO_2C_6H_4$-	6.00 (d, $^{2}J_{PH}$ = 14.8)	34.0 (d, $^{1}J_{PC}$ = 157.3)	92
2d	4-CNC_6H_4-	4.87 (d, $^{2}J_{PH}$ = 13.7)	40.3 (d, $^{1}J_{PC}$ = 156.5)	90
2e	3-CNC_6H_4-	4.81 (d, $^{2}J_{PH}$ = 13.5)	39.7 (d, $^{1}J_{PC}$ = 157.3)	88
2f	3-$MeOC_6H_4$-	4.81 (d, $^{2}J_{PH}$ = 12.9)	41.4 (d, $^{1}J_{PC}$ = 158.0)	93
2g	Et-	3.74 (dt, $^{2}J_{PH}$ = 12.9)	44.0 (d, $^{1}J_{PC}$ = 156.8)	82
2h	*n*-Pr-	3.79 (dt, $^{2}J_{PH}$ = 10.2)	41.9 (d, $^{1}J_{PC}$ = 157.1)	85

[a] Isolated yields.

Table 2
Spectroscopic data of diethyl α,α-bromofluorophosphonates **3**.

Entry	R	^{13}C NMR(δ, ppm, *J*, Hz)	^{19}F NMR(δ, ppm, *J*, Hz)	Yield[a] (%)
3a	4-$NO_2C_6H_4$-	98.3 (dd, $^{1}J_{PC}$ = 188.1, $^{1}J_{FC}$ = 267.9)	−129.0 (d, $^{2}J_{PF}$ = 80.4 Hz)	87
3b	3-$NO_2C_6H_4$-	98.3 (dd, $^{1}J_{PC}$ = 189.8, $^{1}J_{FC}$ = 267.3)	−128.9 (d, $^{2}J_{PF}$ = 82.3 Hz)	92
3c	2-$NO_2C_6H_4$-	97.4 (dd, $^{1}J_{PC}$ = 189.0, $^{1}J_{FC}$ = 268.9)	−128.9 (d, $^{2}J_{PF}$ = 82.1 Hz)	81
3d	4-CNC_6H_4-	98.5 (dd, $^{1}J_{PC}$ = 190.0, $^{1}J_{FC}$ = 267.8)	−129.6 (d, $^{2}J_{PF}$ = 80.7 Hz)	82
3e	3-CNC_6H_4-	98.5 (dd, $^{1}J_{PC}$ = 189.7, $^{1}J_{FC}$ = 267.6)	−129.6 (d, $^{2}J_{PF}$ = 80.7 Hz)	87
3f	3-$MeOC_6H_4$-	99.4 (dd, $^{1}J_{PC}$ = 189.5, $^{1}J_{FC}$ = 267.1)	−127.4 (d, $^{2}J_{PF}$ = 82.6 Hz)	43
3g	Et-	104.5 (dd, $^{1}J_{PC}$ = 189.5, $^{1}J_{FC}$ = 265.3)	−124.6 (ddd, $^{2}J_{PF}$ = 84.6 Hz)	54
3h	*n*-Pr-	104.6 (dd, $^{1}J_{PC}$ = 189.9, $^{1}J_{FC}$ = 265.4)	−122.9 (ddd, $^{2}J_{PF}$ = 84.6 Hz)	46

[a] Isolated yields.

3. Conclusions

A new methodology for the synthesis of α,α-bromofluorophosphonates is developed from the corresponding α-hydroxyphosphonates via nucleophilic bromination and then electrophilic fluorination. Both aromatic and aliphatic α,α-bromofluorophosphonates could be obtained by this method. These compounds are potential non-peptidyl inhibitors of PTPs. Study of asymmetric fluorination and biological activity of the products are in progress.

4. Experimental

4.1. General methods

All reactions were carried out under an atmosphere of dry argon. THF was freshly distilled from sodiumbenzophenone ketyl. ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) and ^{19}F NMR (282 MHz) spectra were recorded on a Bruker AV-300. TMS (^{1}H), $CDCl_3$ (^{13}C) were used as internal standards and $CFCl_3$ (^{19}F) was used as external standard. Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. High-resolution mass spectrometry (HRMS) spectra were recorded on a high resolution ESI-FTICR mass spectrometry (Varian 7.0 T).

4.2. Typical procedure for the preparation of α-hydroxyphosphonates 1

To a solution of sodium ethoxide (0.765 g, 11.25 mmol) in CH_2Cl_2 (10 ml) was added diethyl phosphite (1.05 ml, 7.6 mmol) via syringe at −35 °C under argon. The reaction was stirred for 30 min. and a solution of 4-nitrobenzaldehyde (1 g, 6.62 mmol) in CH_2Cl_2 (5 ml) was added. The mixture was stirred for 3–5 h. The reaction was quenched with 0.1 N HC1 and the resulting solution was extracted with ethyl acetate. The organic layer was dried with $MgSO_4$ and the solvents were removed in vacuo. The crude material was purified via flash column chromatography to yield 1a as white solid (1.81 g, 95% yield).

4.2.1. Diethyl α-hydroxy-4-nitrobenzylphosphonate (1a) [6]

White solid, mp 86–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24–1.32 ppm (m, 6H, CH_3), 4.05–4.18 ppm (m, 4H, OCH_2), 5.18 ppm (d, $^2J_{PH}$ = 12.2 Hz, 1H, CHOH), 7.68 ppm (d, J = 7.6 Hz, 2H, Ar-H), 8.23 ppm (d, J = 8.3 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.3 ppm (d, $^3J_{PC}$ = 5.6 Hz), 63.2 ppm (d, $^2J_{PC}$ = 7.6 Hz), 63.9 ppm (d, $^2J_{PC}$ = 7.2 Hz), 69.9 ppm (d, $^1J_{PC}$ = 158.4 Hz), 123.1, 127.6, 144.5, 147.3 ppm.

4.2.2. Diethyl α-hydroxy-3-nitrobenzylphosphonate (1b) [6]

White solid, mp 88–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25–1.33 ppm (m, 6H, CH_3), 4.04-4.19 ppm (m, 4H, OCH_2), 5.18 ppm (dd, $^2J_{PH}$ = 11.3 Hz, J = 5.6 Hz, 1H, CHOH), 5.47 ppm (br, 1H, OH), 7.53 ppm (t, J = 7.9 Hz, 1H, Ar-H), 7.82 ppm (d, J = 7.5 Hz, 1H, Ar-H), 8.17 ppm (d, J = 8.0 Hz, 1H, Ar-H), 8.42 ppm (s, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.0 ppm (d, $^3J_{PC}$ = 5.7 Hz), 63.1 ppm (d, $^2J_{PC}$ = 7.5 Hz), 63.6 ppm (d, $^2J_{PC}$ = 7.2 Hz), 69.3 ppm (d, $^1J_{PC}$ = 161.0 Hz), 121.7, 122.4, 128.7, 132.9, 139.5, 147.8 ppm.

4.2.3. Diethyl α-hydroxy-2-nitrobenzylphosphonate (1c) [6]

Yellowish solid, mp 127–129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 ppm (t, J = 7.0 Hz, 3H, CH_3), 1.28 ppm (t, J = 7.0 Hz, 3H, CH_3), 4.06–4.15 ppm (m, 4H, OCH_2), 6.26 ppm (d, $^2J_{PH}$ = 14.2 Hz, 1H, CHOH), 7.46 ppm (t, J = 7.8 Hz, 1H, Ar-H), 7.69 ppm (t, J = 7.5 Hz, 1H, Ar-H), 8.00 ppm (d, J = 8.0 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2 ppm (d, $^3J_{PC}$ = 8.7 Hz), 63.2 ppm (d, $^2J_{PC}$ = 7.5 Hz), 64.1 ppm (d, $^2J_{PC}$ = 7.0 Hz), 65.5 ppm (d, $^1J_{PC}$ = 159.4 Hz), 124.6, 128.3, 128.9, 133.1, 133.2, 147.5 ppm.

4.2.4. Diethyl α-hydroxy-4-cyanobenzylphosphonate (1d) [6]

Yellowish solid, mp 78–80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23–1.30 ppm (m, 6H, CH_3), 4.04–4.13 ppm (m, 4H, OCH_2), 5.12 ppm (d, $^2J_{PH}$ = 12.2 Hz, 1H, CHOH), 7.61 ppm (d, J = 8.7 Hz, 2H, Ar-H), 7.65 ppm (d, J = 8.5 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.4 ppm (d, $^3J_{PC}$ = 2.6 Hz), 16.5 ppm (d, $^3J_{PC}$ = 2.4 Hz), 63.3 ppm (d, $^2J_{PC}$ = 7.6 Hz), 63.9 ppm (d, $^2J_{PC}$ = 7.1 Hz), 70.2 ppm (d, $^1J_{PC}$ = 157.8 Hz), 111.7, 118.8, 127.7, 132.0, 142.5 ppm.

4.2.5. Diethyl α-hydroxy-3-cyanobenzylphosphonate (1e) [6]

White solid, mp 84–86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24–1.32 ppm (m, 6H, CH_3), 4.08–4.15 ppm (m, 4H, OCH_2), 5.08 ppm (d, $^2J_{PH}$ = 11.1 Hz, 1H, CHOH), 7.48 ppm (t, J = 7.7 Hz, 1H, Ar-H), 7.61 ppm (d, J = 7.4 Hz, 1H, Ar-H), 7.73 ppm (d, J = 7.6 Hz, 1H, Ar-H), 7.83 ppm (s, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.1 ppm (d, $^3J_{PC}$ = 1.6 Hz), 16.2 ppm (d, $^3J_{PC}$ = 1.4 Hz), 63.1 ppm (d, $^2J_{PC}$ = 7.5 Hz), 63.5 ppm (d, $^2J_{PC}$ = 7.2 Hz), 69.3 ppm (d, $^1J_{PC}$ = 161.2 Hz), 111.9, 118.5, 128.7, 130.4, 131.3, 139.0 ppm.

4.2.6. Diethyl α-hydroxy-3-methoxybenzylphosphonate (1f) [6]

Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 ppm (t, J = 7.0 Hz, 3H, CH_3), 1.28 ppm (t, J = 7.0 Hz, 3H, CH_3), 3.82 ppm (s, 3H, OCH_3), 3.95–4.11 ppm (m, 4H, OCH_2), 5.01 ppm (d, $^2J_{PH}$ = 10.8 Hz, 1H, CHOH), 6.86 ppm (d, J = 8.1 Hz, 1H, Ar-H), 7.07 ppm (s, 2H, Ar-H), 7.30 ppm (d, J = 8.1 Hz, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ16.3 ppm (d, $^3J_{PC}$ = 1.4 Hz), 16.4 ppm (d, $^3J_{PC}$ = 1.6 Hz), 55.2 ppm, 63.0 ppm (d, $^2J_{PC}$ = 7.3 Hz), 63.4 ppm (d, $^2J_{PC}$ = 7.0 Hz), 70.6 ppm (d, $^1J_{PC}$ = 158.6 Hz), 112.4, 113.8, 119.5, 129.1, 138.5, 159.5 ppm.

4.2.7. Diethyl α-hydroxyethylphosphonate (1g) [6]

Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 ppm (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.34 ppm (t, J = 7.0 Hz, 6H, OCH_2CH_3), 1.71–1.86 ppm (m, 2H, CH_2CH_3), 3.77 ppm (dd, $^2J_{PH}$ = 9.9 Hz, J = 5.8 Hz, 1H, CHOH), 4.12–4.22 ppm (m, 4H, OCH_2).

4.2.8. Diethyl α-hydroxypropylphosphonate (1h) [6]

Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 ppm (t, J = 6.8 Hz, 3H, CH_2CH_3), 1.34 ppm (t, J = 7.0 Hz, 6H, OCH_2CH_3), 1.45–1.74 ppm (m, 4H, CH_2CH_2), 3.87 ppm (t, $^2J_{PH}$ = 4.9 Hz, 1H, CHOH), 4.13–4.22 ppm (m, 4H, OCH_2).

4.3. Typical procedure for the preparation of α-bromophosphonates 2 from α-hydroxyphosphonates 1

To a stirring mixture of DDQ (0.908 g, 4 mmol) and PPh_3 (1.048 g, 4 mmol) in dry CH_2Cl_2 (10 mL) was added n-Bu_4NBr (1.288 g, 4 mmol) at room temperature. Then 1a (0.648 g, 2 mmol) was added to the reaction mixture. The reaction was refluxed at 40 °C. The reaction mixture was turned dark red. After 8 h, the reaction mixture was washed with saturated Na_2CO_3 solution (3 mL × 20 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent afforded a crude product that was purified by column chromatography on silica gel using hexane/ethyl acetate (3:1) as an eluent to afford 2a as a yellow oily compound (0.653 g, 93% yield).

4.3.1. Diethyl α-bromo-4-nitrobenzylphosphonate (2a) [9]

Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 ppm (t, J = 7.0 Hz, 3H, CH_3), 1.35 ppm (t, J = 7.0 Hz, 3H, CH_3), 3.95–4.16 ppm (m, 2H, OCH_2), 4.21–4.30 ppm (m, 2H, OCH_2), 4.91 ppm (d, $^2J_{PH}$ = 13.9 Hz, 1H, CHBr), 7.74 ppm (d, J = 8.5 Hz, 2H, Ar-H), 8.22 ppm (d, J = 8.6 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.1 ppm (dd, $^3J_{PC}$ = 1.8 Hz, 5.6 Hz), 16.3 ppm (dd, $^3J_{PC}$ = 1.9 Hz, 5.6 Hz), 39.6 ppm (d, $^1J_{PC}$ = 156.2 Hz), 64.1 ppm (dd, $^2J_{PC}$ = 2 Hz, 7 Hz), 64.6 ppm (dd, $^2J_{PC}$ = 2 Hz, 7 Hz), 123.6, 130.4, 141.9, 147.8 ppm.

*4.3.2. Diethyl α-bromo-3-nitrobenzylphosphonate (**2b**) [9]*

Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 ppm (t, *J* = 7.0 Hz, 3H, CH_3), 1.35 ppm (t, *J* = 7.0 Hz, 3H, CH_3), 4.00–4.13 ppm (m, 2H, OCH_2), 4.14–4.30 ppm (m, 2H, OCH_2), 4.93 ppm (d, $^2J_{PH}$ = 13.6 Hz, 1H, CHBr), 7.56 ppm (t, *J* = 8.0 Hz, 1H, Ar-H), 7.95 ppm (d, *J* = 7.7 Hz, 1H, Ar-H), 8.20 ppm (d, *J* = 8.0 Hz, 1H, Ar-H), 8.39 ppm (s, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2 ppm (d, $^3J_{PC}$ = 5.8 Hz), 16.3 ppm (d, $^3J_{PC}$ = 5.8 Hz), 39.6 ppm (d, $^1J_{PC}$ = 157.1 Hz), 64.2 ppm (d, $^2J_{PC}$ = 7.0 Hz), 64.5 ppm (d, $^2J_{PC}$ = 7.0 Hz), 124.7, 124.3, 129.6, 135.4, 136.9, 148.0 ppm.

*4.3.3. Diethyl α-bromo-2-nitrobenzylphosphonate (**2c**) [9]*

Yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 ppm (t, *J* = 7.0 Hz, 3H, CH_3), 1.35 ppm (t, *J* = 7.0 Hz, 3H, CH_3), 3.92–4.09 ppm (m, 2H, OCH_2), 4.23–4.33 ppm (m, 2H, OCH_2), 6.00 ppm (d, $^2J_{PH}$ = 14.8, 1H, CHBr), 7.49 ppm (t, *J* = 7.7 Hz, 1H, Ar-H), 7.66 ppm (t, *J* = 7.5 Hz, 1H, Ar-H), 7.91 ppm (d, *J* = 8.1 Hz, 1H, Ar-H), 8.17 ppm (d, *J* = 7.9 Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.0 ppm (d, $^3J_{PC}$ = 5.7 Hz), 16.3 ppm (d, $^3J_{PC}$ = 5.8 Hz), 34.0 ppm (d, $^1J_{PC}$ = 157.3 Hz), 64.0 ppm (d, $^2J_{PC}$ = 7.1 Hz), 64.7 ppm (d, $^2J_{PC}$ = 7.1 Hz), 124.7, 129.4, 129.5, 133.2, 133.3, 148.1 ppm.

*4.3.4. Diethyl α-bromo-4-cyanobenzylphosphonate (**2d**) [9]*

Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 ppm (t, *J* = 6.0 Hz, 3H, CH_3), 1.35 ppm (t, *J* = 6.0 Hz, 3H, CH_3), 3.96–4.14 ppm (m, 2H, OCH_2), 4.22–4.27 ppm (m, 2H, OCH_2), 4.87 ppm (d, $^2J_{PH}$ = 13.7, 1H, CHBr), 7.67 ppm (s, 4H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.0 ppm (d, $^3J_{PC}$ = 5.7 Hz), 16.5 ppm (d, $^3J_{PC}$ = 5.7 Hz), 40.3 ppm (d, $^1J_{PC}$ = 156.5 Hz), 64.3 ppm (d, $^2J_{PC}$ = 6.9 Hz), 64.7 ppm (d, $^2J_{PC}$ = 7.1 Hz), 112.8, 118.3, 130.4, 132.4, 140.1 ppm. HRMS for $C_{12}H_{15}BrNO_3PH$ $[M+H]^+$: calculated 332.0051; found 332.0047.

*4.3.5. Diethyl α-bromo-3-cyanobenzylphosphonate (**2e**)*

Yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 ppm (t, *J* = 7.1 Hz, 3H, CH_3), 1.29 ppm (t, *J* = 6.0 Hz, 3H, CH_3), 3.90–4.11 ppm (m, 2H, OCH_2), 4.14–4.24 ppm (m, 2H, OCH_2), 4.81 (d, $^2J_{PH}$ = 13.5, 1H, CHBr), 7.43 ppm (t, *J* = 7.5 Hz, 1H, Ar-H), 7.57 ppm (d, *J* = 7.7 Hz, 1H, Ar-H), 7.78 ppm (d, *J* = 8.4 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2 ppm (d, $^3J_{PC}$ = 5.7 Hz), 16.3 ppm (d, $^3J_{PC}$ = 5.8 Hz), 39.7 (d, $^1J_{PC}$ = 157.3 Hz), 64.1 ppm (d, $^2J_{PC}$ = 7.0 Hz), 64.5 ppm (d, $^2J_{PC}$ = 7.1 Hz), 112.8, 118.0, 129.5, 132.4, 132.9, 133.9, 136.5 ppm. HRMS for $C_{12}H_{15}BrNO_3PH$ $[M+H]^+$: calculated 332.0051; found 332.0047.

*4.3.6. Diethyl α-bromo-3-methoxybenzylphosphonate (**2f**)*

Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 ppm (t, *J* = 7.1 Hz, 3H, CH_3), 1.32 ppm (t, *J* = 7.1 Hz, 3H, CH_3), 3.80 ppm (s, 3H, OCH_3), 3.82–3.93 ppm (m, 1H, OCH_2), 3.98–4.11 ppm (m, 1H, OCH_2), 4.15–4.26 ppm (m, 2H, OCH_2), 4.81 (d, $^2J_{PH}$ = 12.9 Hz, CHBr), 6.85 ppm (d, *J* = 8.1 Hz, 1H, Ar-H), 7.10 ppm (d, *J* = 9.0 Hz, 2H, Ar-H), 7.24 ppm (t, *J* = 7.9 Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2 ppm (d, $^3J_{PC}$ = 5.9 Hz), 16.4 ppm (d, $^3J_{PC}$ = 5.9 Hz), 41.4 ppm (d, $^1J_{PC}$ = 158.0 Hz), 55.3, 64.1 ppm (d, $^2J_{PC}$ = 4.6 Hz), 64.2 ppm (d, $^2J_{PC}$ = 4.7 Hz), 114.7, 115.0, 112.8, 129.6, 135.8, 159.5 ppm. HRMS for $C_{12}H_{18}BrO_4PH$ $[M+H]^+$: calculated 337.0204; found 337.0199.

*4.3.7. Diethyl α-bromoethylphosphonate (**2g**) [8]*

Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 ppm (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.32 ppm (t, *J* = 7.1 Hz, 6H, OCH_2CH_3), 1.80–1.94 ppm (m, 1H, CH_2), 2.09-2.22 ppm (m, 1H, CH_2), 3.74 (dt, $^2J_{PH}$ = 12.9 Hz, *J* = 3.3 Hz, 1H, CHBr), 4.13–4.25 ppm (m, 4H, OCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.4, 12.6, 16.3 ppm (d, $^3J_{PC}$ = 5.9 Hz), 20.7, 25.9 ppm (dd, $^3J_{PC}$ = 1.9 Hz, *J* = 5.9 Hz), 44.0 ppm (d, $^1J_{PC}$ = 156.8 Hz), 63.5 ppm (d, $^2J_{PC}$ = 6.9 Hz), 63.8 ppm (d, $^2J_{PC}$ = 6.9 Hz).

*4.3.8. Diethyl α-bromopropylbenzylphosphonate (**2h**) [8]*

Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 ppm (t, *J* = 7.3 Hz, 3H, CH_2CH_3), 1.34 ppm (t, *J* = 7.1 Hz, 6H, OCH_2CH_3), 1.39–1.49 ppm (m, 1H, CH_2CH_3), 1.61–1.76 ppm (m, 1H, CH_2CH_3), 1.81–1.94 ppm (m, 1H, CH_2CHBr), 1.96–2.09 ppm (m, 1H, CH_2CHBr), 3.79 ppm (dt, $^2J_{PH}$ = 10.2 Hz, *J* = 3.3 Hz, CHBr), 4.13–2.26 ppm (m, 4H, OCH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.94, 16.3 ppm (d, $^3J_{PC}$ = 5.8 Hz), 20.8 ppm (d, $^3J_{PC}$ = 12.8 Hz), 34.1 ppm, 41.9 ppm (d, $^1J_{PC}$ = 157.1), 63.3 ppm (d, $^2J_{PC}$ = 6.8 Hz), 63.6 ppm (d, $^2J_{PC}$ = 7.0 Hz).

*4.4. Typical procedure for the preparation of α,α-bromofluorophosphonates **3** from α-bromophosphonates **2***

To a solution of α-bromophosphonate **2a** (0.31 g, 0.88 mmol) in dry THF (10 ml) at −78 °C was added a solution of NaHMDS (0.66 ml, 2.0 M in THF, 1.32 mmol) over a period of 10 min under an atmosphere of dry argon. The resulting dark red solution was stirred for 1 h at −78 °C. A solution of NFSI (0.36 g, 1.15 mmol) in dry THF (5 ml) was added over a period of 10 min and the resulting solution stirred at −78 °C for 2 h. The solution was allowed to warm to −30 °C and a precipitate formed and quenched with 0.01 M hydrochloric acid. Volatiles were removed under reduced pressure and the residue extracted with CH_2Cl_2. The organic layers were combined and concentrated by rotary evaporation. The crude material was purified via flash column chromatography of silica gel to yield **3a** as yellow oil (0.28 g, 87% yield).

*4.4.1. Diethy α,α-bromofluoro-4-nitrobenzylphosphonate (**3a**)*

White. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 ppm (t, *J* = 7.0 Hz, 3H, CH_3), 1.43 (t, *J* = 7.0 Hz, 3H, CH_3), 3.97–4.18 ppm (m, 2H, OCH_2), 4.39–4.45 ppm (m, 2H, OCH_2), 7.87 ppm (d, *J* = 8.4 Hz, 2H, Ar-H), 8.28 ppm (d, *J* = 8.5 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2 (d, $^3J_{PC}$ = 5.6 Hz), 16.3 (d, $^3J_{PC}$ = 5.6 Hz), 65.4 ppm (d, $^2J_{PC}$ = 7.5 Hz), 66.4 ppm (d, $^2J_{PC}$ = 6.2 Hz), 98.3 ppm (dd, $^1J_{PC}$ = 188.1 Hz, $^1J_{FC}$ = 267.9 Hz), 123.4, 127.1, 143.6 ppm (d, $^2J_{FC}$ = 20.1 Hz), 148.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −129.0 ppm (d, $^2J_{PF}$ = 80.4 Hz). HRMS for $C_{11}H_{14}BrFNO_5PNa$ $[M+Na]^+$: calculated 391.9669; found 391.9671.

*4.4.2. Diethy α,α-bromofluoro-3-nitrobenzylphosphonate (**3b**)*

Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 ppm (t, *J* = 7.0 Hz, 3H, CH_3), 1.43 (t, *J* = 7.0 Hz, 3H, CH_3), 4.03–4.22 ppm (m, 2H, OCH_2), 4.36–4.45 ppm (m, 2H, OCH_2), 7.64 ppm (t, *J* = 8 Hz, 1H, Ar-H), 8.06 ppm (d, *J* = 7.8 Hz, 1H, Ar-H), 8.28 ppm (d, *J* = 8.2 Hz, 1H, Ar-H), 8.53 ppm (s, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.1 ppm (d, $^3J_{PC}$ = 5.6 Hz), 16.3 ppm (d, $^3J_{PC}$ = 5.6 Hz), 65.5 ppm (d, $^2J_{PC}$ = 7.3 Hz), 66.3 ppm (d, $^2J_{PC}$ = 7.3 Hz), 98.3 ppm (dd, $^1J_{PC}$ = 189.8 Hz, $^1J_{FC}$ = 267.3 Hz), 120.9, 125.3, 129.3, 132.2, 139.3 ppm (d, $^2J_{FC}$ = 20.8 Hz), 147.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −128.9 ppm (d, $^2J_{PF}$ = 82.3 Hz). HRMS for $C_{11}H_{14}BrFNO_5PNa$ $[M+Na]^+$: calculated 391.9669; found 391.9667.

*4.4.3. Diethy α,α-bromofluoro-2-nitrobenzylphosphonate (**3c**)*

Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 ppm (t, *J* = 7.0 Hz, 3H, CH_3), 1.44 (t, *J* = 7.0 Hz, 3H, CH_3), 4.00–4.16 ppm (m, 2H, OCH_2), 4.25–4.53 ppm (m, 2H, OCH_2), 7.44 ppm (d, *J* = 7.1 Hz, 1H, Ar-H), 7.51–7.61 ppm (m, 2H, Ar-H), 8.08 (d, *J* = 7.4 Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.1 ppm (d, $^3J_{PC}$ = 5.6 Hz), 16.4 ppm (d, $^3J_{PC}$ = 5.6 Hz), 65.7 ppm (d, $^2J_{PC}$ = 7.7 Hz), 66.9 ppm (d, $^2J_{PC}$ = 7.5 Hz), 97.4 ppm (dd, $^1J_{PC}$ = 189.0 Hz, $^1J_{FC}$ = 268.9 Hz), 123.5, 124.4, 129.1, 129.6, 130.6, 131.1 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −128.9 ppm (d, $^2J_{PF}$ = 82.1 Hz). HRMS for $C_{11}H_{14}BrFNO_5PNa$ $[M+Na]^+$: calculated 391.9669; found 391.9666.

*4.4.4. Diethy α,α-bromofluoro-4-cyanobenzylphosphonate (**3d**)*

Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 ppm (t, J = 7.0 Hz, 3H, CH_3), 1.39 ppm (t, J = 7.0 Hz, 3H, CH_3), 3.91–4.16 ppm (m, 2H, OCH_2), 4.35–4.46 ppm (m, 2H, OCH_2), 7.73 ppm (d, J = 7.1 Hz, 2H, Ar-H), 7.80 ppm (d, J = 8.0 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.3 ppm (d, $^3J_{PC}$ = 5.6 Hz), 16.5 ppm (d, $^3J_{PC}$ = 5.6 Hz), 65.5 ppm (d, $^2J_{PC}$ = 7.2 Hz), 66.5 ppm (d, $^2J_{PC}$ = 7.2 Hz), 98.5 ppm (dd, $^1J_{PC}$ = 190.0 Hz, $^1J_{FC}$ = 267.8 Hz), 113.9, 118.1, 126.9 ppm (d, $^3J_{FC}$ = 9.0 Hz), 132.2, 142.2 ppm (d, $^2J_{FC}$ = 20.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −129.6 ppm (d, $^2J_{PF}$ = 80.7 Hz). HRMS for $C_{12}H_{14}BrFNO_3PNa$ $[M+Na]^+$: calculated 371.9771; found 371.9767.

*4.4.5. Diethy α,α-bromofluoro-3-cyanobenzylphosphonate (**3e**)*

Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 ppm (t, J = 7.0 Hz, 3H, CH_3), 1.39 ppm (t, J = 7.0 Hz, 3H, CH_3), 3.89–4.03 ppm (m, 2H, OCH_2), 4.34–4.45 ppm (m, 2H, OCH_2), 7.70 ppm (d, J = 8.4 Hz, 2H, Ar-H), 7.80 ppm (d, J = 7.2 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2 ppm (d, $^3J_{PC}$ = 5.6 Hz), 16.4 ppm (d, $^3J_{PC}$ = 5.6 Hz), 65.4 ppm (d, $^2J_{PC}$ = 7.3 Hz), 66.4 ppm (d, $^2J_{PC}$ = 7.3 Hz), 98.5 ppm (dd, $^1J_{PC}$ = 188.4 Hz, $^1J_{FC}$ = 267.8 Hz), 111.4, 113.7, 117.9, 126.7, 132.1, 141.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −129.6 ppm (d, $^2J_{PF}$ = 80.7 Hz). HRMS for $C_{12}H_{14}BrFNO_3PNa$ $[M+Na]^+$: calculated 371.9771; found 371.9768.

*4.4.6. Diethy α,α-bromofluoro-3-methoxycyanobenzylphosphonate (**3f**)*

Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 ppm (t, J = 7.0 Hz, 3H, CH_3), 1.40 ppm (t, J = 7.0 Hz, 3H, CH_3), 3.83 ppm (s, 3H, OCH_3), 3.85–3.97 ppm (m, 1H, OCH_2), 4.02–4.15 ppm (m, 1H, OCH_2), 4.33–4.43 ppm (m, 2H, OCH_2), 6.92 ppm (d, J = 7.0 Hz, 1H, Ar-H), 7.26–7.35 ppm (m, 3H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2 ppm (d, $^3J_{PC}$ = 5.6 Hz), 16.4 ppm (d, $^3J_{PC}$ = 5.5 Hz), 55.4 ppm, 65.2 ppm (d, $^2J_{PC}$ = 7.1 Hz), 65.9 ppm (d, $^2J_{PC}$ = 7.3 Hz), 99.4 ppm (dd, $^1J_{PC}$ = 189.5 Hz, $^1J_{FC}$ = 267.1 Hz), 111.2, 115.8, 118.2, 129.4, 137.9 159.3 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −127.4 ppm (d, $^2J_{PF}$ = 82.6 Hz). HRMS for $C_{12}H_{17}BrFO_4PNa$ $[M+Na]^+$: calculated 376.9924; found 376.9923.

*4.4.7. Diethy α,α-bromofluoroethylphosphonate (**3g**)*

Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 ppm (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.39–1.42 ppm (m, 6H, OCH_2CH_3), 2.30–2.48 ppm (m, 2H, CH_2), 4.23–4.41 ppm (m, 4H, OCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.18 ppm (d, $^3J_{PC}$ = 4.9 Hz), 16.3 ppm (d, $^3J_{PC}$ = 4.9 Hz), 33.2 ppm (d, $^2J_{PC}$ = 19.9 Hz), 64.6 ppm (d, $^2J_{PC}$ = 7.1 Hz), 65.3 ppm (d, $^2J_{PC}$ = 7.0 Hz), 104.5 ppm (dd, $^1J_{PC}$ = 189.5 Hz, $^1J_{FC}$ = 265.3 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −124.6 ppm (ddd, $^2J_{PF}$ = 84.6 Hz). HRMS for $C_7H_{15}BrFO_3PH$ $[M+H]^+$: calculated 277.0004; found 277.0002.

*4.4.8. Diethy α,α-bromofluoropropylphosphonate (**3h**)*

Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 ppm (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.39 ppm (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.40 ppm (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.67–1.85 ppm (m, 2H, CH_2CH_3), 2.11–2.37 ppm (m, 2H, CH_2CH_2), 4.23-4.44 ppm (m, 4H, OCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5, 16.4, 17.3 ppm (d, $^3J_{PC}$ = 6.6 Hz), 40.4 ppm (d, $^2J_{PC}$ = 6.1 Hz), 41.8 ppm (d, $^2J_{PC}$ = 6.1 Hz), 64.6 ppm (d, $^2J_{PC}$ = 6.9 Hz), 65.4 ppm (d, $^2J_{PC}$ = 7.1 Hz), 104.6 ppm (dd, $^1J_{PC}$ = 189.9 Hz, $^1J_{FC}$ = 265.4 Hz), ^{19}F NMR (282 MHz, $CDCl_3$): δ −122.9 ppm (ddd, $^2J_{PF}$ = 84.6 Hz). HRMS for $C_8H_{17}BrFO_3PH$ $[M+H]^+$: calculated 291.0162; found 291.0157.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2011.06.016.

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