New route to amino[$^2H_2$]methylphosphonic acid *via* bis(trifluoroethyl) phosphonate transesterification

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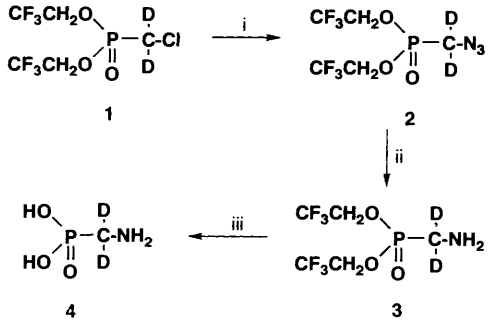
Transesterification of bis(trifluoroethyl) chloromethyl- and azidomethyl-phosphonates with alcohols in the presence of catalytic quantities of alcoholates gives dialkyl chloromethyl- and azidomethyl-phosphonates in good yield. This process has been used for the synthesis of dibenzyl azido[$^2H_2$]methylphosphonate which has been reduced and hydrogenolised to amino[$^2H_2$]methylphosphonic acid under neutral conditions.

The synthesis of α-aminophosphonic acids has attracted considerable interest in recent years. It has been stimulated by the discovery of a great variety of biological properties for these compounds[1] which include potent antibiotics,[2] enzyme inhibitors,[3] pharmacological agents as well as peptidomimetics,[4] herbicides and fungicides.[5] As they are the most important substitutes for the corresponding α-amino acids there is considerable interest in the chemical modification of α-aminophosphonic acids in order to understand the biological significance of their derivatives. A fundamental and interesting modification of these acids is their transformation to α,α-dideuteriated derivatives which may be useful for biomedical applications. Recently, we have employed the nucleophilic amination of cheap and abundant chloromethylphosphonic esters[6] as the first step in this deuteriation process and demonstrated that, with well defined substituents on the phosphorus atom, the amination of the chloromethyl moiety by sodium azide is very specific. Thus, the amination of chloromethylphosphonic ester **1** with sodium azide in dimethyl sulfoxide (DMSO) was shown to afford azidomethylphosphonic ester **2** in good yield (86%) only if the substituents at phosphorus are trifluoroethoxy groups.[7] This methodology was then applied to the development of a simple and effective protocol for the synthesis of the amino[$^2H_2$]methylphosphonic acid **4** (Scheme 1).

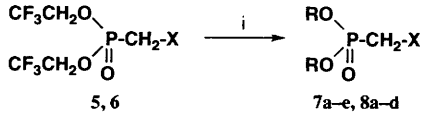


Scheme 1 *Reagents and conditions:* i, NaN_3, DMSO, 90 °C; ii, H_2, EtOH, CF_3CO_2H (1 mol equiv.), Pd/C (10%), 1 bar; iii, HCl (12 mol dm^{-3}), 95 °C, 6 h

However, the trifluoroethoxy protecting groups must be removed with strong aqueous acid and, because of the formation of soluble hydrochloric salts, final treatment with a scavenger to promote precipitation of the free aminophosphonic acid is then required. This operation shows varying degrees of success according to the structure of the acids. Therefore, we proposed to associate the reduction of the azido group with the hydrogenolysis of the two ester functions to provide a new approach to the amino[$^2H_2$]methylphosphonic acid **4** under neutral conditions.

Results and discussion

To investigate the feasibility of this approach, the bis(trifluoroethyl) chloromethylphosphonate **5** and azidomethylphosphonate **6** were transesterified to give two benzyloxy groups at the phosphorus atom which could be easily removed by hydrogenolysis. Modro and Froneman[8] have described the reaction of alcohols with dialkyl phosphites in the presence of titanium tetraalkoxides which results in a displacement of one or both ester functions by the RO groups of the alcohol used, but there are no reports dealing with the facile transesterification of the phosphonate moiety in the presence of an alcohol. Here we describe a new mild and efficient reaction for the transesterification of bis(trifluoroethyl) phosphonates **5** (X = Cl) and **6** (X = N_3) to the corresponding dialkyl phosphonates **7** and **8** by alcohols in the presence of alcoholates catalysts (ROM with M = Li or Na) (Scheme 2). This transesterification,



5, 6 **7a–e, 8a–d**

a R = Et,
b R = C_5H_{11},
c R = $C_{10}H_{21}$,
d R = Bn,
e R = Bu^i

5, 7a–e	X = Cl	M = Li
6, 8a, b	X = N_3	M = Li
8c	X = N_3	M = Li + Na
8d	X = N_3	M = Na

Scheme 2 *Reagents and conditions:* i, ROH (2.1 mol equiv.), ROM (cat), THF, 20 °C, 1–24 h

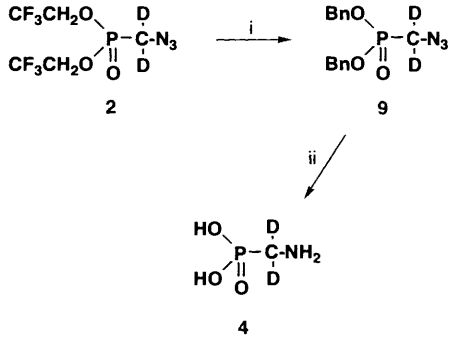
moderated by the trifluoroethoxy attracting groups, allows the introduction of a large variety of alkoxy groups at phosphorus.

Treatment of bis(trifluoroethyl) phosphonates **5** (X = Cl) and **6** (X = N_3) with primary alcohols (ROH, 2.1 equiv.) in the presence of catalytic quantities of the corresponding lithium or sodium alcoholates, in tetrahydrofuran (THF) at room temperature gave the desired transesterified dialkoxy phosphonates **7a–e** and **8a–d** in excellent yield (80–96%) after purification and isolation (Table 1). The clean and complete transesterification of **5** and **6** to give **7** and **8** resulted in a displacement of both trifluoroethoxy ester functions and no product resulting from partial transesterification was isolated.

Table 1

Entry	ROH	Reaction 5 ⟶ 7a–e		Reaction 6 ⟶ 8a–d	
		Time (h)	Product (yield %)	Time (h)	Product (yield %)
1	EtOH	0.25	**7a** (80)	1.25	**8a** (93)
2	$C_5H_{11}OH$	2.5	**7b** (88)	25	**8b** (94)
3	$C_{10}H_{21}OH$	3.5	**7c** (95)	24	**8c** (93)
4	BnOH	10	**7d** (90)	1	**8d** (96)
5	Bu^iOH	3.5	**7e** (80)	—	—

Attention was next turned to the use of **2** as starting material for the synthesis of dibenzyl azido[$^2H_2$]methylphosphonate **9**. Transesterification of **2** by reaction with benzyl alcohol in THF in the presence of catalytic amount of sodium metal gave the desired dibenzyloxy derivative **9** in high yield (95%) (Scheme 3).



Scheme 3 *Reagents and conditions:* i, BnOH (2.1 mol equiv.), BnONa (cat), THF, 20 °C; ii, H_2, EtOH, Pd/C (10%), 3 bar, 25 °C, 24 h

The associated reduction of the azide and hydrogenolysis of the benzyloxy ester functions of **9** were then investigated. Although the reaction of **9** with hydrogen in ethanol at room temperature and atmospheric pressure in the presence of a catalyst (Pd/C, 10%) gave the aminophosphonic acid **4** in reasonable yield (50%), the reaction was very slow and several by-products, which could be identified by ^{31}P NMR, were generated. Subsequently a more efficient synthesis was developed using higher pressure (3 bar) of H_2 which afforded **4** in satisfactory yield (88%) and without contamination by these side products.

In conclusion, a new approach to amino[$^2H_2$]methylphosphonic acid has been described, based on the transesterification of bis(trifluoroethyl) phosphonate followed by a one-pot reduction of the azido group and the hydrogenolysis of the benzyloxy ester functions simultaneously, under neutral conditions. The application of this approach to aminophosphonic acid synthesis is currently being investigated.

Experimental

^{31}P NMR and ^1H NMR spectra were recorded on a Bruker AC 200 spectrometer with 85% H_3PO_4 as external standard (positive δ values are downfield of this reference) for ^{31}P NMR and $CDCl_3$ as internal standard for ^1H and ^{13}C NMR; ^2H NMR spectra were recorded on a Bruker AM 400 spectrometer with $CDCl_3$ as internal standard; J values are quoted in Hz. Low-resolution mass spectra were recorded on a Hewlett Packard 5989 B mass spectrometer. High-resolution mass spectra (HRMS) were recorded on VG ZAB-HSQ or Bruker CMS 47X ICR FT mass spectrometers. All reactions, including deuteriolysis, were carried out under an inert atmosphere and rigorously anhydrous conditions. A Buchi GKR-50 apparatus with three flasks was used for distillation.

General experimental details for the preparation of compounds **1**, **2** and **3** (Scheme 1) have been described earlier.[7]

Dialkyl chloromethyl- and azidomethyl-phosphonates 7a–e and 8a–d

To a stirred solution of compound **5** (X = Cl) or **6** (X = N_3) (50 mmol) in THF (200 cm^3) were successively added at room temperature, the appropriate primary alcohol (105 mmol) and a piece of lithium (0.052 g, 7.5 mmol) or sodium (0.175 g, 7.5 mmol). When the transesterification was finished (see Table 1) the reaction mixture was treated with hydrochloric acid (3 mol dm^{-3}) until the pH of the mixture was acidic. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 cm^3), after which the organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The crude products **7a–e** were purified by bulb-to-bulb distillation; products **8a–d** were checked for purity (^1H and ^{31}P spectra) before use but never purified by distillation. Compound **7a** (80%), bp (20 mmHg) 150–155 °C; $\delta_P(CDCl_3)$ +19.30; $\delta_H(CDCl_3)$ 1.36 (t, $^3J_{H,H}$ 7, CH_3), 3.52 (d, $^2J_{P,H}$ 10.5, PCH_2) and 4.20 (dq, $^3J_{H,H}$ and $^3J_{P,H}$ 7, OCH_2CH_3); $\delta_C(CDCl_3)$ 16.10 (d, $^3J_{P,C}$ 5, CH_3), 32.9 (d, $^1J_{P,C}$ 159.2, PCH_2) and 63.24 (d, $^2J_{P,C}$ 6.6, OCH_2CH_3); *m/z* (CI, NH_3) 187 $(M + H)^+$.

Compound **7b** (88%), bp (20 mmHg) 220–225 °C; $\delta_P(CDCl_3)$ +19.40; $\delta_H(CDCl_3)$ 0.91 (t, $^3J_{H,H}$ 7, CH_3), 1.33–1.74 [m, $OCH_2(CH_2)_3CH_3$], 3.56 (d, $^2J_{P,H}$ 10.5, PCH_2) and 4.13 [dt, $^3J_{P,H}$ and $^3J_{H,H}$ 7, $OCH_2(CH_2)_3CH_3$]; $\delta_C(CDCl_3)$ 13.48 (s, CH_3), 21.84 [s, $O(CH_2)_3CH_2CH_3$], 27.21 [s, $O(CH_2)_2CH_2CH_2CH_3$], 29.83 [d, $^3J_{P,C}$ 5, $OCH_2CH_2(CH_2)_2CH_3$], 32.75 (d, $^1J_{P,C}$ 159.3, PCH_2) and 66.86 [d, $^2J_{P,C}$ 7, $OCH_2(CH_2)_3CH_3$]; *m/z* (CI, NH_3) 271 $(M + H)^+$.

Compound **7c** (95%), crude; $\delta_P(CDCl_3)$ +19.40; $\delta_H(CDCl_3)$ 0.89 (t, $^3J_{H,H}$ 7, CH_3), 1.27–1.70 [m, $OCH_2(CH_2)_8CH_3$], 3.61 (d, $^2J_{P,H}$ 10.5, PCH_2) and 4.14 [dt, $^3J_{P,H}$ and $^3J_{H,H}$ 7, $OCH_2(CH_2)_8CH_3$]; *m/z* (CI, NH_3) 411 $(M + H)^+$.

Compound **7d** (90%), bp (20 mmHg) 230–235 °C; $\delta_P(CDCl_3)$ +20.30; $\delta_H(CDCl_3)$ 3.50 (d, $^2J_{P,H}$ 10.5, PCH_2), 5.16 and 5.09 (ABX system, J_{AX} and J_{BX} 9, J_{AB} 11.7, $P_XOCH_AH_BC_6H_5$) and 7.38 (s, C_6H_5); *m/z* (CI, NH_3) 311 $(M + H)^+$.

Compound **7e** (80%), bp (20 mmHg) 200–205 °C; $\delta_P(CDCl_3)$ +18.90; $\delta_H(CDCl_3)$ 0.94 (d, $^3J_{H,H}$ 7, CH_3), 1.95 [h, $^3J_{H,H}$ 6.6, $OCH_2CH(CH_3)_2$], 3.55 (d, $^2J_{P,H}$ 10.5, PCH_2) and 3.89 [dd, $^3J_{P,H}$ and $^3J_{H,H}$ 7, $OCH_2CH(CH_3)_2$]; $\delta_C(CDCl_3)$ 18.45 (s, CH_3), 29.14 [d, $^3J_{P,C}$ 6, $OCH_2CH(CH_3)_2$], 33.00 (d, $^1J_{P,C}$ 160, PCH_2) and 72.93 [d, $^2J_{P,C}$ 6.2, $OCH_2CH(CH_3)_2$]; HRMS (Found: M^+, 242.083 85. Calc. for $C_9H_{20}ClO_3P$: *M*, 242.083 86).

Compound **8a** (93%), crude; $\delta_P(CDCl_3)$ +19.30; $\delta_H(CDCl_3)$ 1.36 (t, $^3J_{H,H}$ 7, CH_3), 3.46 (d, $^2J_{P,H}$ 11.8, PCH_2) and 4.19 (dq, $^3J_{P,H}$ and $^3J_{H,H}$ 7, OCH_2CH_3); $\delta_C(CDCl_3)$ 16.03 (d, $^3J_{P,C}$ 5.7, CH_3), 44.50 (d, $^1J_{P,C}$ 155.0, PCH_2), 62.70 (d, $^2J_{P,C}$ 6.3, OCH_2CH_3); *m/z* (CI, NH_3) 194 $(M + H)^+$.

Compound **8b** (94%), crude; $\delta_P(CDCl_3)$ +20.60; $\delta_H(CDCl_3)$ 0.92 (t, $^3J_{H,H}$ 7, CH_3), 1.34–1.75 [m, $OCH_2(CH_2)_3CH_3$], 3.48 (d, $^2J_{P,H}$ 11.8, PCH_2) and 4.13 [q, $^3J_{P,H}$ and $^3J_{H,H}$ 7, $OCH_2(CH_2)_3CH_3$]; $\delta_C(CDCl_3)$ 14.00 (s, CH_3), 22.36 [s, $O(CH_2)_3CH_2CH_3$], 27.73 [s, $O(CH_2)_2CH_2CH_2CH_3$], 30.37

[d, $^3J_{P,C}$ 5.9, $OCH_2CH_2(CH_2)_2CH_3$], 44.00 (d, $^1J_{P,C}$ 155.5, PCH_2) and 67.2 [d, $^2J_{P,C}$ 6.6, $OCH_2(CH_2)_3CH_3$]. *m/z* (CI, NH_3) 278 $(M + H)^+$.

Compound **8c** (93%), crude; $\delta_P(CDCl_3)$ +20.60; $\delta_H(CDCl_3)$ 0.89 (t, $^3J_{H,H}$ 7, CH_3), 1.27–1.74 [m, $OCH_2(CH_2)_8CH_3$], 3.48 (d, $^2J_{P,H}$ 11.8, PCH_2) and 4.13 [q, $^3J_{H,H}$ 7, $OCH_2(CH_2)_8CH_3$]; $\delta_C(CDCl_3)$ 14.46 (s, CH_3), 23.09 [s, $O(CH_2)_8CH_2CH_3$], 25.85 [s, $O(CH_2)_2CH_2(CH_2)_6CH_3$], 29.73 [s, $O(CH_2)_3CH_2(CH_2)_5CH_3$], 29.94 [s, $O(CH_2)_4(CH_2)_3(CH_2)_2CH_3$], 30.93 [d, $^3J_{P,C}$ 5.6, $OCH_2CH_2(CH_2)_7CH_3$], 32.31 [s, $O(CH_2)_7CH_2CH_2CH_3$], 45.25 (d, $^1J_{P,C}$ 155.4, PCH_2) and 67.4 [d, $^2J_{P,C}$ 6.7, $OCH_2(CH_2)_8CH_3$]; *m/z* (CI, NH_3) 418 $(M + H)^+$.

Compound **8d** (96%), crude; $\delta_P(CDCl_3)$ +21.40; $\delta_H(CDCl_3)$ 3.41 (d, $^2J_{P,H}$ 12, PCH_2), 5.06 and 5.14 (ABX system, J_{AX} and J_{BX} 9, J_{AB} 11.6, $P_XOCH_AH_BC_6H_5$) and 7.38 (s, C_6H_5); $\delta_C(CDCl_3)$ 44.50 (d, $^1J_{P,C}$ 155.5, PCH_2), 69.10 (d, $^2J_{P,C}$ 7.3 $OCH_2C_6H_5$), 127.10 (s, C_p C_6H_5), 128.50 (s, C_o C_6H_5), 128.90 (s, C_m C_6H_5) and 135.80 (d, $^3J_{C,P}$ 4.3, C_{ipso} C_6H_5); *m/z* (CI, NH_3) 318 $(M + H)^+$.

Dibenzyl azido[$^2H_2$]methylphosphonate 9

Experimental conditions were the same as those described above. The crude product was checked for purity (^1H and ^{31}P spectra) before use but never purified by distillation.

Compound **9** (95%), crude; $\delta_P(CDCl_3)$ +19.2; $\delta_H(CDCl_3)$ 5.07 (m, $CH_2C_6H_5$) and 7.36 (s, $CH_2C_6H_5$); $\delta_C(CDCl_3)$ 44.95 (dp, $^1J_{P,C}$ 155.6, $^1J_{C,D}$ 22.9, PCD_2), 69.07 (d, $^2J_{P,C}$ 7.3 $OCH_2C_6H_5$), 127.12 (s, C_p C_6H_5), 128.46 (s, C_o C_6H_5), 128.91 (s, C_m C_6H_5) and 135.81 (d, $^3J_{P,C}$ 4.3, C_{ipso} C_6H_5) (Found: M^+, 319.1055. Calc. for $C_{15}H_{14}D_2N_3O_3P$; *M*, 319.1055).

Amino[$^2H_2$]methylphosphonic acid 4

Dibenzyl azido[$^2H_2$]methylphosphonate **9** (9.6 g, 30 mmol) in ethanol (95%; 120 cm^3) and Pd/C (10%; 1 g) were placed in a Parr apparatus equipped with a 500 cm^3 flask. The reaction mixture was shaken at room temperature under H_2 (3 bar) for 24 h after which the mixture was filtered through Celite and the filter cake washed with hot water. The combined filtrates were evaporated under reduced pressure and the crude product was worked-up with ethanol (95%) whereupon acid **4** (88%) precipitated spontaneously, mp >260 °C; $\delta_P(D_2O)$ +11.4; $\delta_D(C_2D_5OD–H_2O)$ 2.93 (s, 2 D, PCD_2); $\delta_C(C_2D_5OD–H_2O)$ 36.6 (dp, $^1J_{P,C}$ 141, $^1J_{C,D}$ 21.5, PCD_2). All attempts to obtain an HRMS by electronic impact ionization for this compound failed. The compound was spectroscopically identical with that previously reported.[7b]

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