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**New Route to α,α -Dideuteriated Aminomethylphosphonic Acid via
bis(Trifluoroethyl)phosphonic Esters Transesterification**

Sylvie Berté-Verrando, Rachel Dizière, Mohammad Samadi and Philippe Savignac

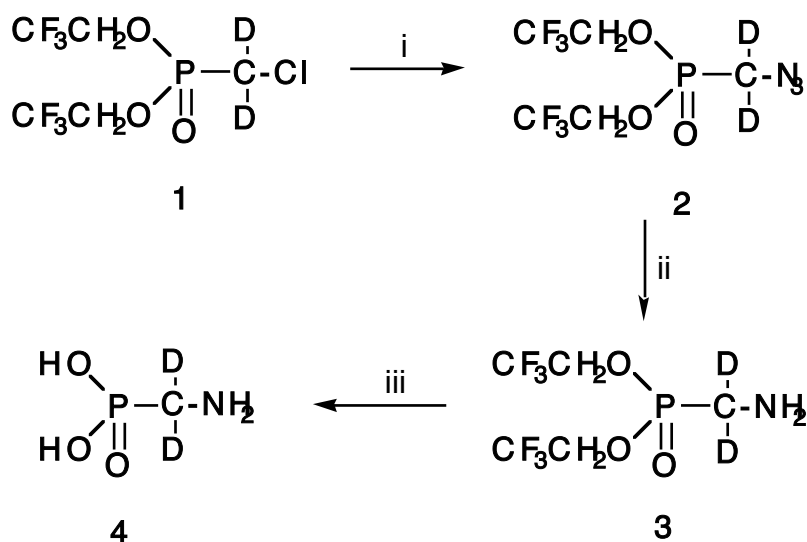
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Transesterification of bis(trifluoroethyl)chloromethyl and azidomethyl phosphonates with alcohols in the presence of catalytic quantities of alcoholates gives access to dialkyl chloromethyl and azidomethyl phosphonates in good yield. This process has been used for the synthesis of α,α -dideuteriated dibenzyl azidomethylphosphonate which has been reduced and hydrogenolised to α,α -dideuteriated aminomethylphosphonic 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 a 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 first step in this deuteration 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 α,α -dideuteriated aminomethylphosphonic acid **4** (Scheme 1).

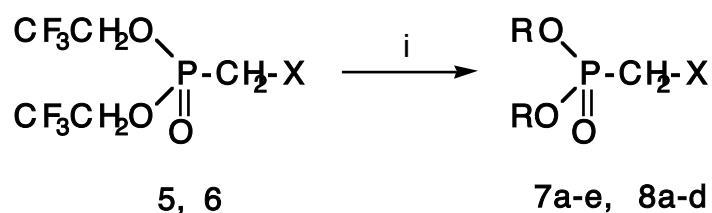


Scheme 1 Reagents and conditions : i, NaN₃, DMSO, 90°C; ii, H₂, EtOH, CF₃COOH (1 mol equiv), Pd/C (10%), 1 bar; iii, HCL 12 N, 95°C, 6h.

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 free aminophosphonic acids is then required. This operation shows varying degrees of success according to the structure of the acids. Thus, we envisaged to associate the reduction of the azido group with the hydrogenolysis of the two esters functions to provide a new approach to the α,α -dideuteriated aminomethylphosphonic acid **4** in neutral conditions.

Results and discussion

To investigate the feasibility of this approach the bis(trifluoroethyl)chloromethylphosphonate **5** and azidomethylphosphonate **6** were submitted to transesterification. This introduces two benzyloxy groups at phosphorus which are easily removed by hydrogenolysis. Modro and Froneman⁸ have described a reaction of alcohols with dialkyl phosphites in the presence of titanium tetraalkoxides which results in a displacement of both or one ester function by the RO groups of the alcohol used, but there are no reports dealing with the ready 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=N₃) to the corresponding dialkyl phosphonic esters **7** and **8** by alcohols in the presence of alcoholates catalysts (ROM with M=Li or Na) (Scheme 2). This transesterification, moderated by the trifluoroethoxy attracting groups allows the introduction of a large variety of alkoxy groups at phosphorus.



a R = Et, **b** R = C₅H₁₁, **c** R = C₁₀H₂₁, **d** R = Bn, **e** R = iBu

Bn = Benzyl

5, 7a-e X = Cl M = Li

6, 8a,b X = N₃ M = Li

8c X = N₃ M = Li + Na

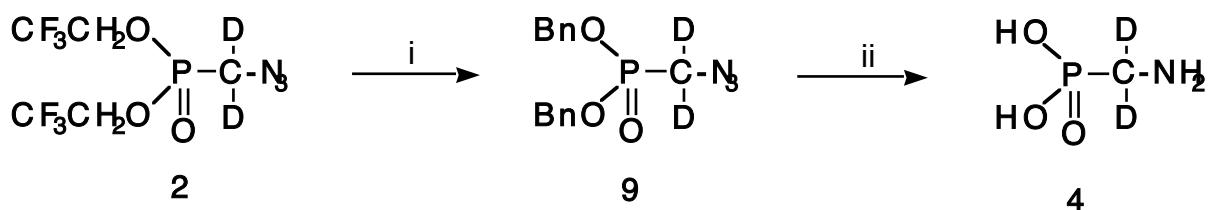
8d X = N₃ M = Na

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

Treatment of bis(trifluoroethyl) phosphonates **5** (X=Cl) and **6** (X=N₃) with primary alcohols (ROH, 2.1 equiv) in the presence of catalytic quantities of the corresponding alcoholates, lithium or sodium, 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, no product resulting from partial transesterification was isolated.

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 ₅ H 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	iBuOH	3.5	7e (80)	—	—

Attention was next turned to the use of **2** as starting material for the synthesis of α,α -dideuteriated dibenzyl azidomethylphosphonate **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, H₂, EtOH, Pd/C (10%), 3 bar, 25°C, 24h.

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 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 can be identified by ³¹P NMR. were generated. Subsequently a more efficient synthesis was developed under pressure (3 bar) which afforded **4** in satisfactory yield (88%) and without contamination by these side products .

In conclusion, this work describes a new approach to α,α -dideuteriated aminomethylphosphonic acid based on a transesterification reaction of a bis(trifluoroethyl) phosphonate and an associated reaction permitting a one pot reduction of the azido group and hydrogenolysis of the benzyloxy ester functions simultaneously. in neutral conditions. The application of this approach in aminophosphonic acid synthesis is currently being investigated.

Experimental

³¹P NMR and ¹H NMR spectra were recorded on a Bruker AC 200 spectrometer with 85% H₃PO₄ as external standard (positive chemical shifts are downfield of this reference) for ³¹P NMR and CDCl₃ as internal standard for ¹H NMR; ²H NMR spectra were recorded on a Bruker AM 400 spectrometer with CDCl₃ as internal standard; coupling constants 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 scrupulously anhydrous conditions. A Buchi GKR-

50 apparatus with three flasks was used for distillation. The flask containing the crude product was in the upper part of the oven, and the collecting flask just outside.

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

O,O-Dialkyl Chloromethyl and Azidomethylphosphonates 7a-e and 8a-d (Scheme 2). To a solution of compounds **5** (X=Cl) or **6** (X=N₃) (50 mmol) in THF (200 cm³) were successively added at room temperature under stirring, a primary alcohol (105 mmol) and a piece of lithium (0.052g, 7.5 mmol) or sodium (0.175g, 7.5 mmol). When the transesterification was finished (see Table 1) the reaction mixture was treated with 3N hydrochloric acid until acidic pH. The aqueous phase was extracted with CH₂Cl₂ (3x50cm³), the organic layer was dried (MgSO₄), and the solvents were evaporated off under reduced pressure. The crude products **7a-e** were purified by bulb-to-bulb distillation, products **8a-d** were checked for purity (¹H and ³¹P spectra) before use but never purified by distillation.

Compound **7a** (80%), b.p. (20 mmHg) 150-155°C; δ_P (CDCl₃) + 19.30; δ_H (CDCl₃) 1.36 (t, ³J_{H-H} 7, O-CH₂-CH₃), 3.52 (d, ²J_{P-H} 10.5, P-CH₂), 4.20 (dq, ³J_{H-H} and ³J_{P-H} 7, O-CH₂-CH₃); δ_C (CDCl₃) 16.10 (d, ³J_{P-C} 5, O-CH₂-CH₃), 32.9 (d, ¹J_{P-C} 159.2, P-CH₂), 63.24 (d, ²J_{P-C} 6.6, O-CH₂-CH₃). Found : CI NH₃ (M+H)⁺, 187. C₅H₁₂ClO₃P requires M, 186.

Compound **7b** (88%), b.p. (20 mmHg) 220-225°C; δ_P (CDCl₃) + 19.40; δ_H (CDCl₃) 0.91 (t, ³J_{H-H} 7, O-CH₂-(CH₂)₃-CH₃), 1.33 -1.74 (m, O-CH₂-(CH₂)₃-CH₃), 3.56 (d, ²J_{P-H} 10.5, P-CH₂), 4.13 (dt, ³J_{P-H} and ³J_{H-H} 7, O-CH₂-(CH₂)₃-CH₃); δ_C (CDCl₃) 13.48 (s, O-(CH₂)₄-CH₃), 21.84 (s, O-(CH₂)₃-CH₂-CH₃), 27.21 (s, O-(CH₂)₂-CH₂-CH₂-CH₃), 29.83 (d, ³J_{P-C} 5, O-CH₂-CH₂-(CH₂)₂-CH₃), 32.75 (d, ¹J_{P-C} 159.3, P-CH₂), 66.86 (d, ²J_{P-C} 7, O-CH₂-(CH₂)₃-CH₃). Found : CI NH₃ (M+H)⁺, 271. C₁₁H₂₄ClO₃P requires M, 270.

Compound **7c** (95%), crude; δ_P (CDCl₃) + 19.40; δ_H (CDCl₃) 0.89 (t, ³J_{H-H} 7, O-CH₂-(CH₂)₈-CH₃), 1.27-1.70 (m, O-CH₂-(CH₂)₈-CH₃), 3.61 (d, ²J_{P-H} 10.5, P-CH₂), 4.14 (dt, ³J_{P-H} and ³J_{H-H} 7, O-CH₂-(CH₂)₈-CH₃). Found : CI NH₃ (M+H)⁺, 411. C₂₁H₄₄ClO₃P requires M, 410.

Compound **7d** (90%), b.p. (20 mmHg) 230-235°C; δ_P (CDCl₃) + 20.30; δ_H (CDCl₃) 3.50 (d, ²J_{P-H} 10.5, P-CH₂), ABX system, δ_{HA} 5.16, δ_{HB} 5.09, J_{AX} and J_{BX} 9, J_{AB} 11.7, $\delta_{P-O-CH_AH_B-C_6H_5}$, 7.38 (s, O-CH₂-C₆H₅). Found : CI NH₃ (M+H)⁺, 311. C₁₅H₁₆ClO₃P requires M, 310.

Compound **7e** (80%), b.p. (20 mmHg) 200-205°C; δ_P (CDCl₃) + 18.90; δ_H (CDCl₃) 0.94 (d, ³J_{H-H} 7, O-CH₂-CH(CH₃)₂), 1.95 (h, ³J_{H-H} 6.6, O-CH₂-CH(CH₃)₂), 3.55 (d, ²J_{P-H} 10.5, P-CH₂), 3.89 (dd, ³J_{P-H} and ³J_{H-H} 7, O-CH₂-CH(CH₃)₂); δ_C (CDCl₃) 18.45 (s, O-CH₂-CH(CH₃)₂), 29.14 (d, ³J_{P-C} 6, O-CH₂-CH(CH₃)₂), 33.00 (d, ¹J_{P-C} 160, P-CH₂), 72.93 (d, ²J_{P-C} 6.2, O-CH₂-CH(CH₃)₂). HRMS (Found : M⁺, 242.08385. Calc. for C₉H₂₀ClO₃P : M, 242.08386).

Compound **8a** (93%), crude; δ_P (CDCl₃) + 19.30; δ_H (CDCl₃) 1.36 (t, ³J_{H-H} 7, O-CH₂-CH₃), 3.46 (d, ²J_{P-H} 11.8, P-CH₂), 4.19 (dq, ³J_{P-H} and ³J_{H-H} 7, O-CH₂-CH₃); δ_C (CDCl₃) 16.03 (d, ³J_{P-C} 5.7, O-CH₂-CH₃), 44.50 (d, ¹J_{P-C} 155.0, P-CH₂), 62.70 (d, ²J_{P-C} 6.3, O-CH₂-CH₃). Found : CI NH₃ (M+H)⁺, 194. C₅H₁₂N₃O₃P requires M, 193.

Compound **8b** (94%), crude; δ_P (CDCl₃) + 20.60; δ_H (CDCl₃) 0.92 (t, ³J_{H-H} 7, O-CH₂-(CH₂)₃-CH₃), 1.34-1.75 (m, O-CH₂-(CH₂)₃-CH₃), 3.48 (d, ²J_{P-H} 11.8, P-CH₂), 4.13 (q, ³J_{P-H} and ³J_{H-H} 7, O-CH₂-(CH₂)₃-CH₃); δ_C (CDCl₃) 14.00 (s, O-(CH₂)₄-CH₃), 22.36 (s, O-(CH₂)₃-CH₂-CH₃), 27.73 (s, O-(CH₂)₂-CH₂-CH₂-CH₃), 30.37 (d, ³J_{P-C} 5.9, O-CH₂-CH₂-(CH₂)₂-CH₃), 44.00 (d, ¹J_{P-C} 155.5, P-CH₂), 67.2 (d, ²J_{P-C} 6.6, O-CH₂-(CH₂)₃-CH₃). Found : CI NH₃ (M+H)⁺, 278. C₁₁H₂₄N₃O₃P requires M, 277.

Compound **8c** (93%), crude; δ_P (CDCl₃) + 20.60; δ_H (CDCl₃) 0.89 (t, ³J_{H-H} 7, O-CH₂-(CH₂)₈-CH₃), 1.27-1.74 (m, O-CH₂-(CH₂)₈-CH₃), 3.48 (d, ²J_{P-H} 11.8, P-CH₂), 4.13 (q, ³J_{H-H} 7, O-CH₂-(CH₂)₈-CH₃); δ_C (CDCl₃) 14.46 (s, O-CH₂-CH₂-CH₂-CH₂-(CH₂)₃-CH₂-CH₂-CH₃), 23.09 (s, O-CH₂-CH₂-CH₂-CH₂-(CH₂)₃-CH₂-CH₂-CH₃),

25.85 (s, O-CH₂-CH₂-CH₂-CH₂-(CH₂)₃-CH₂-CH₂-CH₃), 29.73 (s, O-CH₂-CH₂-CH₂-CH₂-(CH₂)₃-CH₂-CH₂-CH₃), 29.94 (s, O-CH₂-CH₂-CH₂-CH₂-(CH₂)₃-CH₂-CH₂-CH₃), 30.93 (d, ³J_{P-C} 5.6, O-CH₂-CH₂-CH₂-CH₂-(CH₂)₃-CH₂-CH₂-CH₃), 32.31 (s, O-CH₂-CH₂-CH₂-CH₂-(CH₂)₃-CH₂-CH₂-CH₃), 45.25 (d, ¹J_{P-C} 155.4, P-CH₂), 67.4 (d, ²J_{P-C} 6.7, O-CH₂-CH₂-CH₂-CH₂-(CH₂)₃-CH₂-CH₂-CH₃). Found : CI NH₃ (M+H)⁺, 418. C₂₁H₄₄N₃O₃P requires M, 417.

Compound **8d** (96%), crude; δ_PX (CDCl₃) + 21.40; δ_H (CDCl₃) 3.41 (d, ²J_{P-H} 12, P-CH₂), ABX system, δ_{HA} 5.14, δ_{HB} 5.06, J_{AX} and J_{BX} 9, J_{AB} 11.6, P_X-O-CH_AH_B-C₆H₅), 7.38 (s, O-CH₂-C₆H₅); δ_C (CDCl₃) 44.50 (d, ¹J_{P-C} 155.5, P-CH₂), 69.10 (d, ²J_{P-C} 7.3, O-CH₂-C₆H₅) 127.10 (s, C_p C₆H₅), 128.50 (s, C_o C₆H₅) 128.90 (s, C_m C₆H₅), 135.80 (d, ³J_{C-P} 4.3, C_{ipso} C₆H₅). Found : CI NH₃ (M+H)⁺, 318. C₁₅H₁₆N₃O₃P requires M, 317.

α,α-Dideuteriated Dibenzyl Azidomethylphosphonate **9** (Scheme 3). Experimental conditions were the same as those described above. The crude product was checked for purity (¹H and ³¹P spectra) before use but never purified by distillation.

Compound **9** (95%), crude; δ_P (CDCl₃) + 19, 2; δ_H (CDCl₃) 5.07 (m, CH₂-C₆H₅) 7.36 (s, CH₂-C₆H₅); δ_C (CDCl₃) 44.95 (dp, ¹J_{P-C} 155.6, ¹J_{C-D} 22.9, P-CD₂), 69.07 (d, ²J_{P-C} 7.3, O-CH₂-C₆H₅) 127.12 (s, C_p C₆H₅), 125.46 (s, C_o C₆H₅), 128.91 (s, C_m C₆H₅) 135.81 (d, ³J_{P-C} 4.3, C_{ipso} C₆H₅); (Found: M⁺, 319.1055. Calc. for C₁₅H₁₄D₂N₃O₃P; M, 319, 1055.

a,a-Dideuteriated Aminomethylphosphonic Acid **4** (Scheme 4). In a Parr apparatus equipped with a 500 cm³ flask were introduced, *α,α*-Dideuteriated Dibenzyl Azidomethylphosphonate **9** (9.6 g, 30 mmol) in ethanol (95%) (120cm³) and Pd/C (10%) (1g). Under pressure of H₂ (3 bar) the reaction mixture was shaken at room temperature for 24 h. The catalyst was removed by suction filtration over celite, and the filter cake washed with hot water. Water

was evaporated off under reduced pressure .The crude product was worked-up with ethanol (95%), and acid **4** spontaneously precipitated.

Compound **4** (88%), m.p. > 260°C; δ_P (D₂O) + 11,4 ; δ_D (C₃D₅OD/H₂O) 2.93 (s , 2D, P-CD₂); δ_C (C₃D₆O/H₂O) 36.6 (dp, ¹J_{P-C} = 141, ¹J_{C-D} = 21.5, P-CD₂); All the attempts to obtain an HRMS by electronic impact ionization with this compound failed completely. The compound has the same data as a sample previously obtained^{7b}.

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