Aminomethanephosphonic Acid and its Diphenyl Ester

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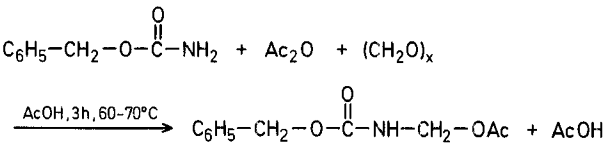
We have previously reported the synthesis of aminoalkanephosphonic acids and their diphenyl esters from carbonyl compounds, benzyl carbamate, and phosphorus(III) chloride[1] or triphenyl phosphite[2]. Although this method provides an access to higher alkanephosphonic acids it cannot be used for the synthesis of aminomethanephosphonic acid or its diphenyl ester.

We have now found that diphenyl benzyloxycarbonylaminomethanephosphonate (**2**) can be easily obtained by an Ivanov-type aminoalkylation[3] of triphenyl phosphite with benzyl *N*-(acetoxymethyl)-carbamate (**1**). Reagent **1** may be obtained by reaction of benzyl carbamate with acetic anhydride and paraformaldehyde in glacial acetic acid.



$$C_6H_5-CH_2-O-\overset{O}{\overset{\|}{C}}-NH_2 + Ac_2O + (CH_2O)_x \xrightarrow{AcOH, 3h, 60-70°C} C_6H_5-CH_2-O-\overset{O}{\overset{\|}{C}}-NH-CH_2-OAc + AcOH$$

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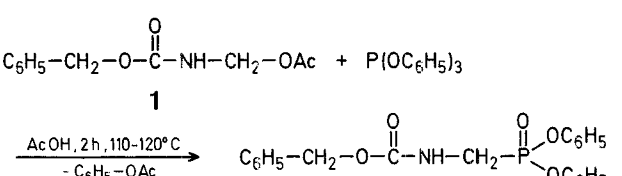
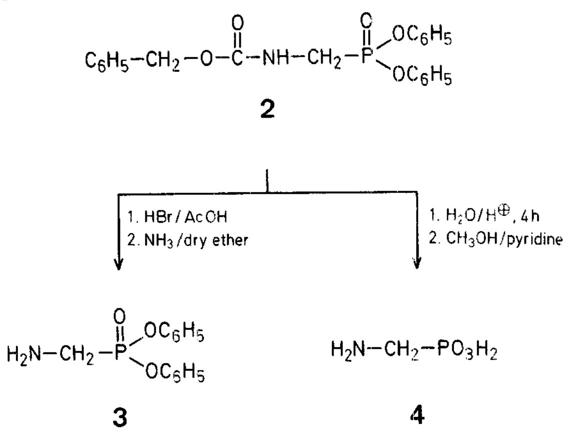
The reaction of crude **1** with triphenyl phosphite in acetic acid affords diphenyl benzyloxycarbonylaminomethanephosphonate (**2**) as a crystalline product in 45–54% yield.



$$\underset{\mathbf{1}}{C_6H_5-CH_2-O-\overset{O}{\overset{\|}{C}}-NH-CH_2-OAc} + P(OC_6H_5)_3 \xrightarrow[-C_6H_5-OAc]{AcOH, 2h, 110-120°C} \underset{\mathbf{2}}{C_6H_5-CH_2-O-\overset{O}{\overset{\|}{C}}-NH-CH_2-\overset{O}{\overset{\|}{P}}\genfrac{}{}{0pt}{}{OC_6H_5}{OC_6H_5}}$$

The benzyloxycarbonyl group in **2** is removed by treatment with hydrogen bromide in acetic acid to give diphenyl aminomethanephosphonate (**3**) in nearly quantitative yield whereas acid hydrolysis of **2** affords free aminomethanephosphonic acid (**4**).



Our procedure appears to offer some preparative advantages over the known methods for the synthesis of aminomethanephosphonic acid[4,5]. In addition, the ester **3** is of interest as reactive intermediate and substrate in peptide synthesis.

Diphenyl Benzyloxycarbonylaminomethanephosphonate (2):

A mixture of benzyl carbamate (30.6 g, 0.2 mol), paraformaldehyde (6 g, 0.2 mol), acetic anhydride (23.8 ml, 0.25 mol), and acetic acid (20 ml) is stirred for 3 h at 60–70 °C. Triphenyl phosphite (62.06 g, 0.2 mol) is then added and the mixture is stirred for 2 h at 110–120 °C. After evaporation of acetic acid and excess acetic anhydride, the residue is dissolved in methanol (150 ml). The solution is allowed to stand at − 10 °C for 4 h. The precipitated product is isolated by suction, washed with methanol, and air-dried; yield: 35.8–42.9 g (45–54%). For use in the synthesis of **3**, the product is recrystallized from chloroform/methanol; yield: 38 g (48%); m.p. 114–116 °C.

$C_{21}H_{20}NO_5P$	calc.	N 3.52	P 7.80
(397.2)	found	3.44	7.73

I.R. (KBr): ν = 3300, 3080, 1720, 1595, 1555, 1490, 1455, 1390, 1320, 1250, 1235, 1220, 1210, 1160, 1070, 1025, 1005, 960, 950, 930 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 7.4–7 (m, 15 H_{arom}); 5.4 (m, 1 H, NH); 5.1 (s, 2 H, CH_2); 3.95 ppm (dd, 2 H, CH_2—P).

Aminomethanephosphonic Acid (4):

A solution of crude diphenyl benzyloxycarbonylaminomethanephosphonate (**2**; 19.8 g, 0.05 mol) in 36% hydrochloric acid (40 ml) is heated to reflux for 4 h, and then allowed to cool. The organic layer is removed and the aqueous solution evaporated to dryness in vacuo. To the residue, methanol (50 ml) is added followed by the addition of pyridine until pH 4 is reached. The mixture is then refluxed for 5 min, cooled, and treated with pyridine until pH 4 is reached again. The precipitated product is isolated by suction, washed with methanol, and dried; yield: 5.2 g (94%); m.p. 308–310 °C (Ref.[5], m.p. 310 °C).

CH_6NO_3P	calc.	N 12.62	P 27.89
(111.0)	found	12.50	27.50

Diphenyl Aminomethanephosphonate (3):

This compound is obtained according to the procedure of Ref.[2]. The product is very hygroscopic and is easily hydrolyzed to the monoester.

Hydrobromide of **3**; yield: 17.5 g (100%); m.p. 147–149 °C.

$C_{13}H_{15}BrNO_3P$	calc.	N 4.07	P 9.01
(344.1)	found	4.20	8.84

I.R. (KBr): ν = 3200–2300, 1605, 1595, 1585, 1565, 1520, 1480, 1400, 1230, 1210, 1170, 1160, 1065, 1020, 1005, 955, 935 cm^{-1}.

^{1}H-N.M.R. (D_2O): δ = 7.9–7.5 (m, 10 H_{arom}); 4.4 ppm (d, 2 H).

Diphenyl Aminomethanephosphonate: yield: 12.6 g (96%); oil.

$C_{13}H_{14}NO_3P$	calc.	N 5.32	P 11.76
(263.2)	found	5.20	11.58

I.R. (film): ν = 3400, 3310, 3070, 1590, 1490, 1250, 1210, 1185, 1160, 1070, 1020, 1005, 930.

^{1}H-N.M.R. ($CDCl_3$): δ = 7.4–7.0 (m, 10 H_{arom}); 3.30 (d, 2 H); 2.9 ppm (m, 2 H, NH_2).

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