Borane Reduction of Dialkoxyphosphorylcarboxamides as a New Route to Aminoalkylphosphonic Acids

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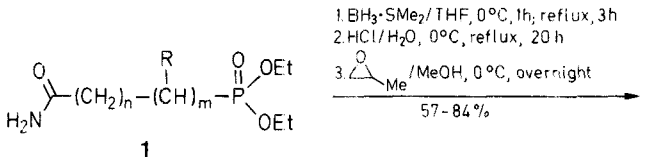
A new, simple method for the synthesis of aminoalkylphosphonic acids is based on the reduction of dialkoxyphosphorylcarboxamides with the borane–dimethyl sulfide complex.

The structural similarity of aminoalkylphosphonic acids to the natural amino acids as well as their biological activity[1] gave rise to the elaboration of novel methods for their synthesis.[2] The selective reduction of the amide group of the easily accessible dialkoxyphosphorylcarboxamides leading to give aminoalkylphosphonic acids has hitherto not been reported.

Several well known reducing agents may be applied to the reduction of carboxamides. The borane complexes with dimethyl sulfide[3] and tetrahydrofuran[4] presumably are most suitable for the reduction of dialkoxyphosphorylcarboxamides **1** to aminoalkylphosphonic acids **2**.

In an early approach, the use of lithium aluminum hydride as reducing agent for esters **1** led to concomitant reduction of phosphonic ester groups, even if stoichiometric quantities of the substrates were used. The resultant mixture of products contained various trivalent phosphorus species apart from the desired aminoalkylphosphonic acid. By using the borane–methyl sulfide complex as reducing agent we were able to selectively reduce the carboxamide group in dialkoxyphosphorylcarboxamides **1**. Several aminoalkylphosphonic acids were thus obtained in good yields.



1

2

1, 2	n	m	R	1, 2	n	m	R
a	1	0	H	**d**	0	1	CH_3
b	2	0	H	**e**	1	1	CH_3
c	3	0	H	**f**	1	1	C_6H_5

The starting amides **1** were prepared from methyl diethoxyphosphorylcarboxylates by treatment with methanolic ammonia according to the known procedures.[5] The reduction reactions were carried out in dry tetrahydrofuran by adding the borane–dimethyl sulfide complex to the solution of **1** at 0 °C followed by heating for 3 hours. After hydrolysis of the B–N bonds with hydrochloric acid the resultant boric acid was removed by esterification with methanol and evaporation. The crude diethyl aminoalkylphosphonates were not isolated but hydrolyzed with concentrated hydrochloric acid. Finally, the free aminoalkylphosphonic acids **2** were precipitated from methanol solution upon treatment with methyloxirane. All products **2** were homogenous on TLC using two solvent systems. The yields of products **2** were generally good, ranging from 57 to 84%.

We also tried to reduce diethyl aminocarbonylphosphonate (**1**, n = 0, m = 0) to obtain aminomethylphosphonic acid, the phosphonic analogue of glycine. This compound was found in the reaction mixture (TLC, comparison with an authentic sample) but its yield and purity has been poor so far. This latter reduction is presently being investigated in our laboratory.

Borane–dimethyl sulfide complex was purchased from Fluka Chemical Co. Tetrahydrofuran was dried with K–Na alloy and freshly distilled. Melting points are uncorrected. IR spectra were obtained using a Jena-Zeiss IR 10 apparatus. ^{1}H-NMR spectra were obtained using a Varian EM 360 (60 MHz) spectrometer.

The purity of products **2** was checked by TLC on Merck Silica Gel plates, solvent systems: *n*-BuOH/AcOH/pyridine/H_2O (6:6:3:5), and *i*-PrOH/aq. NH_3/H_2O (2:1:1).

Aminophosphonic Acids 2; General Procedure:

The diethoxyphosphorylcarboxamide **1a–f** (20 mmol) is dissolved in THF (50 mL) and the reaction flask is chilled with ice. The $BH_3 \cdot SMe_2$ complex (5 mL, a slight stoichiometric excess) is added to the vigorously stirred solution maintaining the temperature around 0 °C. The amide **1** dissolves during 1 h at 0 °C; then, the mixture is refluxed for 3 h. The flask is cooled again with ice and 6 N aq. HCl (40 mL) is added very cautiously to decompose the remaining borane and to hydrolyze the B–N bonds. The solvents are then removed at reduced pressure and the residue is repeatedly evaporated with methanol (4 × 20 mL) to

Table. Aminoalkylphosphonic Acids **2a–f** Prepared

Product	Yield (%)	mp (°C)	Molecular Formula[a] or Lit. mp (°C)	IR (KBr) ν(cm^{-1})	^{1}H-NMR (TFA/TMS) δ, J(Hz)
2a	84	280–285	271–278[6]	3600–2400, 1660, 1570, 1170, 1050	1.60–2.70 (m, 2H, CH_2P); 2.70–3.76 (m, 2H, $CH_2NH_3^+$); 6.73 (s, 3H, NH_3^+)
2b	74	282–288	$C_3H_{10}NO_3P$ (139.1)	3600–2050, 1630, 1540, 1130, 1030	1.00–2.66 (m, 4H, CH_2CH_2P); 2.66–3.73 (m, 2H, $CH_2NH_3^+$); 6.73 (s, 3H, NH_3^+)
2c	60	255–260	$C_4H_{12}NO_3P$ (153.1)	3600–2000, 1660, 1550, 1130, 1050	0.66–2.80 (m, 6H, $CH_2CH_2CH_2P$); 2.80–3.73 (m, 2H, $CH_2NH_3^+$); 6.65 (s, 3H, NH_3^+)
2d	62	277–279	282–286[6]	3600–2000, 1630, 1540, 1150, 1040	0.97 (dd, 3H, J = 17, CH_3); 1.77–2.60 (m, 3H, CH_3); 2.60–3.60 (m, 2H, CH_2); 6.60 (s, 3H, NH_3^+)
2e	57	262–265	$C_4H_{12}NO_3P$ (153.1)	3600–2000, 1620, 1510, 1120, 1060	1.00 (dd, 3H, J = 5, 20, CH_3); 1.40–2.50 (m, 3H, CH_2CH); 2.56–3.56 (m, 2H, $CH_2NH_3^+$); 6.70 (s, 3H, NH_3^+)
2f	61	260–265	$C_9H_{14}NO_3P$ (215.2)	3600–2100, 1640, 1560, 1500, 1450, 1140, 1050	2.10–2.90 (m, 2H, CH_2); 2.90–3.80 (m, 3H, $CHCH_2NH_3^+$); 6.73 (s, 3H, NH_3^+); 7.30 (s, 5H$_{arom}$)

[a] Satisfactory microanalyses: C ±0.30, H ±0.23, N ±0.30.

remove boric acid. The crude aminoalkylphosphonic acids esters are subsequently hydrolyzed with conc. aq. HCl/AcOH (1:1, 60 mL) for about 20 h with TLC control. The volatile acids are removed under reduced pressure and the oily residue is evaporated several times with H_2O and then with MeOH. The free aminoalkylphosphonic acids **2** are set free from their hydrochlorides by adding methyloxirane (3–5 g) to the methanol solution and allowing this mixture to stand overnight at 0 °C. The acids **2** are isolated by suction, washed with MeOH and Et_2O, and dried. Analytical samples are obtained by recrystallization from H_2O/EtOH.

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