1-Aminoalkanephosphonates. Part II. A Facile Conversion of 1-Aminoalkanephosphonic Acids into *O,O*-Diethyl 1-Aminoalkanephosphonates.†

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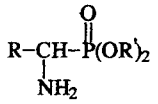
Dedicated to Professor Harry R. Hudson on the occasion of his retirement from the School of Applied Chemistry, University of North London.

1-(*N*-Trifluoroacetylamino)alkanephosphonate *O,O*-diethyl esters **2C**, obtained from parent 1-aminoalkanephosphonic acids **1**, have been selectively deprotected on the amino function affording *O,O*-diethyl 1-aminoalkanephosphonates **3**. Protonation constants of all amino esters **3** synthesized have been determined by potentiometric titration.

1-Aminoalkanephosphonates **3** have received considerable attention since they are key substrates in the synthesis of phosphonopeptides **I**[1] and also due to their biological activity.[2,3]



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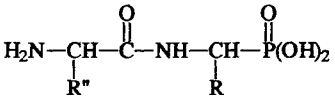


I

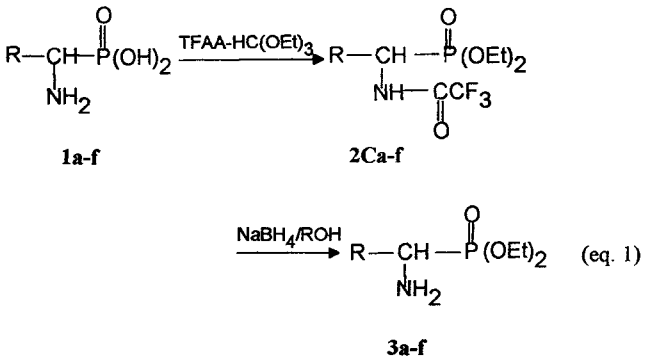
The compounds **3**, however, are obtained by a limited number of mostly specific and rather laborious, synthetic methods.[1,4] Thus, 1-aminoalkanephosphonates **3** have been prepared by addition of diethyl[5] or dimethyl[6] phosphites to the specific Schiff bases and subsequent deprotection of the amino function in the *N*-substituted 1-aminoalkanephosphonates formed. Amino esters **3** have also been obtained via reduction of oximes[7–10] or hydrazones[11] of 1-oxoalkanephosphonates.

O,O-Diphenyl 1-aminoalkanephosphonates have been synthesized by hydrolytic degradation of corresponding 1-(*N*-benzyloxycarbonylamino)alkanephosphonates.[12] The subsequent transesterification of the latter compounds afforded various *O,O*-dialkyl 1-aminoalkanephosphonates.[13] The group of methods of increasing synthetic importance is based on the esterification of free 1-aminoalkanephosphonic acids,[14,17] since the latter compounds are now easily accessible.[4,21] These procedures lead to *O,O*-dialkyl 1-*N*-acylamino)alkanephosphonates **2**, which have been used as substrates in the selective (also enantioselective) *N*-acyl hydrolysis.[12,14–16]

Recently we have reported on the highly efficient conversion of 1-aminoalkanephosphonic acids **1** into corresponding 1-(*N*-acylamino)alkanephosphonates **2** by means of anhydride-orthoester systems.[17] These compounds proved to be easy to isolate by distillation and/or crystallization and stable while stored at room temperature for a long time.

Among them, the derivatives **2C** containing the *N*-trifluoroacetylamino (*N*-TFA-amino) group are particularly interesting due to their volatility and liability of the *N*-TFA linkage (compounds **2A** and **2B** present *N*-formylamino and *N*-acetylamino derivatives).[17]

In this communication we would like to report on the new one-pot synthesis of 1-aminoalkanephosphonates **3** based on the conversion of the amino acids **1** into 1-(*N*-trifluoroacetylamino)alkanephosphonates **2C**, followed by the amino group deprotection.



1a-f **2Ca-f** **3a-f** (eq. 1)

The deprotection of the 1-(*N*-TFA-amino)alkanephosphonates **2C** has been conveniently achieved in alcoholic solution of sodium borohydride, (this reagent has also been applied in peptide chemistry[18,19]), affording with high yields the title *O,O*-diethyl 1-aminoalkanephosphonates **3**, isolated in the form of oxalates **4**. Conversion of stable oxalates **4** into free amino esters **3** was found to be nearly quantitative.

An attempt to apply an alternative procedure of deprotection using basic conditions[20] (EtOH/EtONa) has been unsuccessful due to the formation of stable amidate salts **5**. The formation of **5a** has been indicated in the ^{31}P NMR spectra [increase of chemical shifts from $\delta = 25.0$ for **2Ca**, (EtOH) to $\delta = 28$ for **5a** (EtOH/EtONa)] and also in ^{1}H NMR experiments (disappearance of the NH-TFA proton of **2Ca** after treatment with potassium *t*-butanolate). This formed salt **5a** remained unchanged for a week at ambient temperature, and regenerated quantitatively to the parent amide **2Ca** after treatment with acetic acid (eq. 2).

The yields and physical properties of synthesized *O,O*-diethyl 1-aminoalkanephosphonates **3** and their oxalates **4** are given in Table 1 and 2, respectively. The results of protonation investigations of **3** are summarized in Table 3.

Table 1. Conversion of 1-Aminoalkanephosphonic Acids **1** into *O,O*-Diethyl 1-Aminoalkanephosphonates **3**

Compound 3/4		Yields [%][a]		mp of **4**		Molecular equivalent of **4**[b]			DCIMS of **3**[d]	
Nr	R	A (**3**)	B (**4**)	Found	Reported	Found	Calculated	Formula of **4**	M + 1	Formula of **3**
a	Me	97	85	120–122	101–103[10]	292.0	289.2	**3a** × $C_2H_2O_4$ × H_2O[c]	182	$C_6H_{16}NPO_3$
b	Pr	75	70	127–129		312.0	317.2	**3b** × $C_2H_2O_4$ × H_2O[c]	210	$C_8H_{20}NPO_3$
c	*i*-Pr	88	70	127–129	121–123[10]	303.9	299.2	**3c** × $C_2H_2O_4$	210	$C_8H_{20}NPO_3$
d	Bu	84	75	138–139		331.3	331.3	**3d** × $C_2H_2O_4$ × H_2O[c]	224	$C_9H_{22}NPO_3$
e	Bz	86	76	129–132	131–132[10]	375.4	383.2	**3e** × $C_2H_2O_4$ × $2H_2O$[c]	258	$C_{12}H_{20}NPO_3$
f	Ph	85	70	165–167		334.7	333.2	**3f** × $C_2H_2O_4$[c]	244	$C_{11}H_{18}NPO_3$

[a] Yields: A – NMR yields of **3**, B – isolation in the form of oxalates **4** yields.
[b] Molecular equivalent derived from potentiometric titration (first inflection point).
[c] The microanalyses were in fair agreement with the calculated values (N ± 0.10, P ± 0.29).
[d] Intensity of 100%.

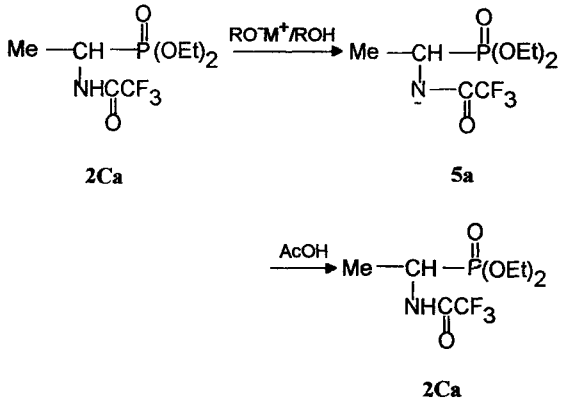
Table 2. Spectroscopic Properties of 1-Aminoalkanephosphonates **3**

Compound	^{31}P NMR δ, *J* (Hz)		^{1}H NMR[a,c] δ, *J* (Hz)
3/4	**3**[a]	**4**[b]	**3**[a(c)]
a	30.1	22.6	1.15–1.30 (m, 9H, $2CH_3CH_2O$, CH_3CH); 1.35–1.55 (br s, 2H, NH_2); 2.88–3.08 (m, 1H, CH_3CH); 4.02 (qd, *J* = 0.76, 7.1, 4H, $2CH_3CH_2O$).
a[c]			1.41 (td, *J* = 1.03, 6.10, 6H, $2CH_3CH_2O$); 1.61 (dd, *J* = 7.0, 16.8, 3H, CH_3CH); 3.70–4.0 (br s, 1H, CHP); 4.30 (qd, *J* = 1.03, 7.00, 4H, $2CH_3CH_2O$); 7.35–7.70 (br s, 3H, NH_3).
b	30.0	22.3	0.90 (t, *J* = 6.9, 3H, $CH_3(CH_2)_2$); 1.30 (t, *J* = 7.08, 6H, $2CH_3CH_2O$); 1.32–1.95 (m, 6H, $NH_2 + CH_2(CH_2)_2$); 2.82–3.02 (m, 1H, CHP); 4.11 (qd, *J* = 0.80, 7.18, 4H, $2CH_3CH_2O$).
c	29.1	21.9	0.99 (t, *J* = 6.98, 6H, $(CH_3)_2CH$); 1.29 (t, *J* = 7.06, 6H, $2CH_3CH_2O$); 1.46–1.60 (br s, 2H, NH_2); 1.96–2.20 (m, 1H, $(CH_3)_2CH$); 2.80 (dd, *J* = 3.43, 14.2, 1H,PCH); 4.09 (qd, *J* = 0.80, 7.18, 4H, $2CH_3CH_2O$).
d	29.9	22.4	0.89 (t, *J* = 6.80, 3H, $CH_3(CH_2)_3$); 1.31 (t, *J* = 7.1, 6H, $2CH_3CH_2O$); 1.40–2.00 (m, 8H, $CH_3(CH_2)_3 + NH_2$); 2.86–2.98 (m, 1H, CHP); 4.11 (qd, *J* = 0.87, *J* = 7.18, 4H, $2CH_3CH_2O$).
e	28.4	21.8	1.31 (td, *J* = 0.80, *J* = 6.30, 6H, $2CH_3CH_2O$); 1.40–1.70 (br s, 2H, NH_2); 2.35–2.75 (m, 1H, CHP); 3.10–3.85 (m, 2H, $PhCH_2$); 4.14 (qd, *J* = 1.50, 6.90, 4H, $2CH_3CH_2O$); 7.10–7.40 (m, $5H_{ar}$).
f	25.4	21.4	1.21 (td, *J* = 7.07, 19.5, 6H, $2CH_3CH_2O$); 1.89 (s, 2H, NH_2); 3.78–4.10 (m, 4H, $2CH_3CH_2O$); 4.24 (d, *J* = 17.2, 1H, CHP); 7.20–7.50 (m, $5H_{ar}$).

[a] Solutions of **3** in $CDCl_3$.
[b] Solutions of **4** in CD_3OD.
[c] Solutions of **3** in CD_3Cl – TFA (20%).

Table 3. Comparison of Protonation Constants of 1-Aminoalkanephosphonic Acids **1**, *O,O*-Diethyl 1-Aminoalkanephosphonates **3**, 1-Aminoalkanoic Acids and their Ethyl Esters.

R	1-aminoalkanephosphonates				1-aminoalkanoates		
	O,O-diethyl ester amino acid				*O*-ethyl ester amino acid		
	pK	pK_1	pK_2	pK_3	pK[22]	pK_1[23]	pK_2[23]
Me	6.40		5.55	10.11[26]	7.80	2.34	9.69
		0.47	5.58	10.20[24]			
Et					7.53		
Pr	6.43		5.67	10.29[24]			
i-Pr	6.28	1.23	5.68	10.46[26]			
		0.62	5.80	10.35[24]			
Bu	6.45	0.68	5.70	10.29[24]			
i-Bu					7.63	2.39	9.60
$PhCH_2$	5.95		5.43	9.62[26]			
Ph	5.70						



2Ca 5a

(eq. 2)

2Ca

1-Aminoalkanephosphonic acids **1** have been prepared according to ref. 21. Other reagents were purchased from Aldrich. All compounds obtained were characterized by DCIMS, ^{13}P NMR and ^{1}H NMR. All melting points (Boetius apparatus) are uncorrected. ^{31}P NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 81.01 MHz. Positive chemical shift values are reported for compounds absorbing at lower fields than phosphoric acid. ^{1}H NMR spectra were recorded at 200 MHz. The direct isobutane chemical ionization mass spectra (DCIMS) were obtained on a Finnigan MAT 95 spectrometer.

Potentiometric Measurements:

The acid protonation constants of the *O,O*-diethyl 1-aminoalkanephosphonates were determined by pH-metric titration of their oxalate salts **4** by means of an automatic titrator EMU connected to an IBM PC computer (Politechnika Wrocławska, Poland), fitted with a combined glass-calomel electrode TRIZMA E 5259 (Sigma). The electrode system was calibrated using standard buffer solutions ($2 < pH < 10$), so that the pH-meter readings could be converted into hydrogen-ion concentrations. In all cases the temperature was 20.0 ± 0.5 °C. The exact concentrations of solutions of **4** were determined by titration; the concentrations (in samples 5 mL) were approximately 2×10^{-3} mol dm^{-3}. The ionic strength was adjusted to 0.1 mol dm^{-3} with KNO_3. The titrations (100 to 200 measurements) with increment of 0.001 mL were performed with a KOH solution of known concentration (0.1 mol dm^{-3}).

1-Aminoalkanephosphonates 3; General Procedure:

The 1-aminoalkanephosphonic acid **1** (1 mmol) was dissolved in a TFA (0.1 mL) – TFAA (0.6 mL) mixture and the resulting solution was heated with stirring at 45–55 °C for 15 min. The triethyl orthoformate (5 mL) was carefully added, the resulting mixture was heated at 100–110 °C for 2 h, and followed by evaporation (at 50 °C at 20 Torr and at 0.1 Torr) giving crude derivative **2C**. This compound was dissolved in EtOH (10 mL), followed by addition of $NaBH_4$ (6 mmol, 228 mg). The resulting mixture was stirred for 1 h at r.t. and for 0.5 h at reflux temperature, and evaporated under reduced pressure. The residue so formed, was treated with 1M aq $NaHCO_3$ (10 mL) and extracted with $CHCl_3$. The combined organic extracts were dried by vigorous stirring over $MgSO_4$. The desiccant was filtered, and the filtrate was concentrated under reduced pressure to afford crude 1-aminoalkanephosphonate **3** which was dissolved in Et_2O (1.5 mL) and precipitated in the form of oxalate **4** after treatment with oxalic acid (5 ml of 1M ethereal solution of oxalic acid). This mixture was allowed to stand for 2 h in a refrigerator and the product **4** was collected by filtration. The conversion of oxalates **4** into 1-aminoalkanephosphonates **3** was performed using described above extractive system based on 1M $NaHCO_3$ and $CHCl_3$.

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