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An Efficient Synthesis of Diethyl 1-Aminoalkylphosphonate Hydrochlorides via the Intermediate Diethyl 1-Azidoalkylphosphonates

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AN EFFICIENT SYNTHESIS OF DIETHYL 1-AMINOALKYLPHOSPHONATE HYDROCHLORIDES VIA THE INTERMEDIATE DIETHYL 1-AZIDOALKYLPHOSPHONATES

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Abstract: The title compounds **4** have been obtained in high yields in a one-step sequence by the Mitsunobu reaction of diethyl 1-hydroxyalkylphosphonates **1** with hydrazoic acid, and subsequence treatment of the intermediate azides **2** with triphenylphosphine, followed by hydrolysis of the iminophosphoranes **3** with water.

Synthesis of 1-aminoalkylphosphonates, the phosphonic analogues of α-amino acids, due to their interesting biological properties[1] still attracts considerable attention.[2-7] Among numerous synthetic methods for the preparation of 1-aminoalkylphosphonic acid derivatives, the application of 1-azidoalkylphosphonates[8-10] or 1-azidoalkylphosphonoamidates[11] as intermediates has received little attention.

Results and Discussion

Diethyl 1-hydroxyalkylphosphonates **1**, which are easily available from diethyl phosphite and appropriate aldehydes,[12,13] can be applied as convenient precursor for further transformations.[14,15] Recently we have devised[16] the new,

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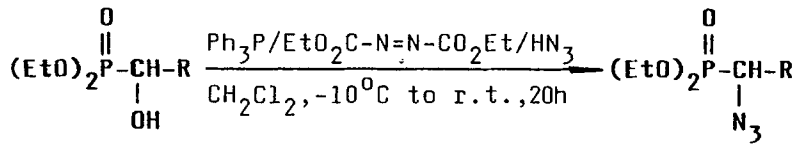


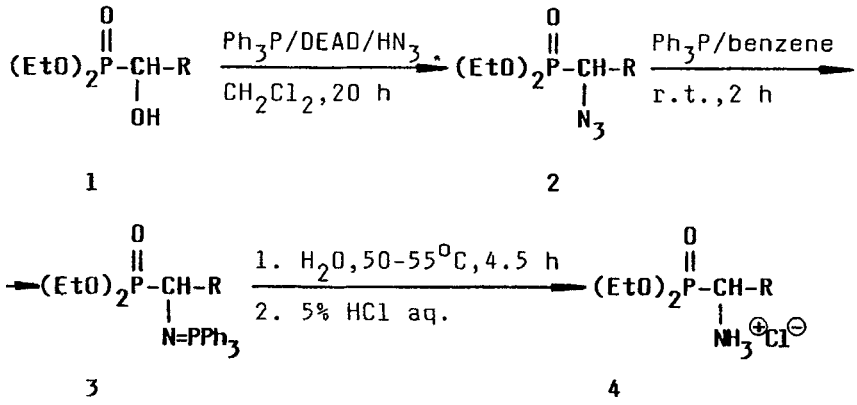
1 R:H, Alkyl, Ph. 2

Equation 1

general and efficient route to diethyl 1-azidoalkylphosphonates **2**, based on the reaction between diethyl 1-hydroxyalkylphosphonates **1** with hydrazoic acid in the presence of triphenylphosphine/diethyl azodicarboxylate (DEAD) system (the Mitsunobu reaction[17]). (Equation 1).

The reaction presented above takes place under very mild conditions, via the preformed betaine-type adduct of triphenylphosphine to diethyl azodicarboxylate to give the diethyl 1-azidoalkylphosphonates **2** in high yields and excellent purity.

These results and the earlier investigations of Baraldi et al.[14] on phthaloylamination of 1-hydroxyalkylphosphonates prompted us to develop one-pot transformation of diethyl 1-hydroxyalkylphosphonates **1** directly into diethyl 1-aminoalkylphosphonate hydrochlorides **4**, without the necessity of isolation of the intermediate azides **2**. Such methodology was succesfuly applied by Golding et



1-4	R	1-4	R	1-4	R
a	H	e	i-Pr	h	4-MeO-C_6H_4
b	Me	f	Bn	i	4-Br-C_6H_4
c	Et	g	Ph	j	$BnOCH_2$
d	Pr				

Scheme 1

al.[18] for one-pot conversion of alcohols into amines and amino acids.

According to this strategy (Scheme 1), the azide **2** prepared from diethyl 1-hydroxyalkylphosphonate **1** by te Mitsunobu reaction is converted "in situ" by the Staudinger reaction[19] with triphenylphosphine into the iminophosphorane **3**. This, in turn is hydrolysed with an excess of water and directly transformed by treatment with dilute hydrochloric acid into the corresponding hydrochloride **4** in high overall yield (71-92%) and purity.

Table 1
Diethyl 1-aminoalkylphosphonate hydrochlorides 4a-j prepared.

Product	Yield (%)[a]	m.p.(°C)[b] [solvent]	Lit.m.p. or Molecular Formula
4a	89[c]	67-69[d,e]	298-300[23], oil[24]
4b	85	74-77[d,e]	oil[25]
4c	89	65-68[d,e]	oil[25]
4d	88	131-132 [AcOEt]	135[25]
4e	75	112-113 [AcOEt]	116[25]
4f	80	100-101[e] [EtOH-Et_2O]	230-232[27]
4g	87	163-164 [EtOH-Et_2O]	162.2-163.4[28]
4h	87	162-163 [EtOH-AcOEt]	169.3-169.7[28]
4i	92	160-161 [EtOH-AcOEt]	154-155[29]
4j	71	132-133 [EtOH-Et_2O]	$C_{13}H_{23}ClNO_4P$[f] (323.8)

[a]Yield of isolated pure product based on **1**. [b]All hydrochlorides decomposed at m.p.with vigorous gas evolution when heated in open capillaries. [c]Iminophosphorane **3a** was hydrolysed with water at r.t. for 6 h. [d]Hygroscopic crystals. M.ps. were measured in sealed capillaries. [e]Due to the hygroscopicity and/or confusing discrepancies in the m.ps. of some hydrochlorides reported, the following aminoalkylphosphonates were additionally characterized as oxalates: **4a** m.p.122-123°C, Lit.[24] m.p.121-123°C; **4b** m.p. 114-115°C, Lit.[26] m.p.114-117°C; **4c** m.p.108-109°C, Lit.[26] m.p.109-110°C; **4f** m.p.123-125°C, Lit.[26] m.p.125-127°C. [f]Elemental Analyses: calc. C 48.22, H 7.16, P 9.57, found C 48.18, H 7.22, P 9.57.

Table 2

Spectroscopic data of diethyl 1-aminoalkylphosphonate hydrochlorides 4a-j.

Compound	^{1}H-NMR (D_2O/DSS$_{int}$)[a] δ (ppm), J(Hz)	^{31}P-NMR (D_2O/H_3PO_4 ext)[b] δ (ppm)
1.	2.	3.
4a	1.37(t,6H,J=7.1,2CH_3),3.50(d,2H,$^2J_{PH}$=13.97,CH_2), 4.27(dq,4H,J=7.1,$^3J_{PH}$=8.67,2CH_2)	19.7
4b	1.37(t,6H,J=7.1,2CH_3),1.52(dd,3H,J=7.35,$^3J_{PH}$=17.28,CH_3), 3.83(dq.1H,J=7.35,$^2J_{PH}$=13.68,CH),4.1-4.47(m,4H,2CH_2)	22.2
4c	1.09(t,3H,J=7.4,CH_3),1.37(t,6H,J=7.06,2CH_3)1.55-2.26(m, 2H,CH_2),3.48-3.83(m,1H,CH),4.09-4.45(m,4H,2CH_2)	21.3
4d	0.95(t,3H,J=6.3,CH_3),1.37(t,6H,J=7.06,2CH_3),1.45-2.13(m, 4H,2CH_2)3.54-3.91(m,1H,CH),4.09-4.47(m,4H,2CH_2)	21.8
4e	1.11,1.14(2d,6H,J=6.83,2CH_3),1.37(t,6H,J=7.06,2CH_3), 2.04-2.66(m,1H,CH),3.61(dd,1H,J=5.59,$^2J_{PH}$=15.3,CH), 4.08-4.48(m,4H,2CH_2)	21.1
4f	1.33(bt,3H,J=7.06,2CH_3),2.84-3.55(m,2H,CH_2),3.86-4.49 (m,5H,2CH_2,CH),7.4(s,5H$_{arom}$)	20.3
4g	1.28,1.30(2t,6H,J=7.06,2CH_3),3.96-4.35(m,4H,2CH_2),4.96(d, 1H,$^2J_{PH}$=17.79,CH),7.73(bs,5H$_{arom}$)	18.0

(continued)

Table 2 (continued)

1.	2.	3.
4h	1.26,1.31(2t,6H,J=7.06,$2CH_3$),3.86(s,3H,CH_3), 3.94-4.35(m,4H,$2CH_2$),4.90(d,1H,J=17.65,CH), 7.05-7.58(AA´BB´of p-C_6H_4,4H)	18.0
4i	1.28,1.30(2t,6H,J=7.06,$2CH_3$),3.96-4.26(m,4H,$2CH_2$), 4.96(d,1H,J=17.72,CH),7.36-7.78(AA´BB´of p-C_6H_4,4H)	17.2
4j	1.31,1.34(2t,6H,J=7.1,$2CH_3$),3.78-4.45(m,7H,$3CH_2$,CH), 4.65(s,2H,CH_2),7.45(s,$5H_{arom}$)	18.6

[a]Recorded at 80 MHz with a Tesla BS 587 FT spectrometer.

[b]Recorded at 36.43 MHz with a Bruker HFX-90 spectrometer. Positive chemical shifts are downfield from H_3PO_4 (85%).

The method is limited to primary and secondary diethyl 1-hydroxyalkylphosphonates **1**. The results are summarized in Table **1**. The structure of the diethyl 1-aminoalkylphosphonate hydrochlorides **4** was confirmed by ^{31}P-NMR and ^{1}H-NMR spectroscopy (Table 2).

In conclusion, the described procedure provides a new, simple and efficient route to diethyl 1-aminoalkylphosponate hydrochlorides **4** with a wide range of aliphatic and aromatic substituents at C-1 carbon. Easily available starting materials are used and isolation of the intermediate azides is not necessery. It may be a useful alternative for the synthesis of 1-aminoalkylphosphonates proposed recently by Chakraborty and Engel.[8]

Experimental

Benzyloxyacetaldehyde was prepared according to the described procedure by oxidative cleavage of the 1-benzylglycerol with sodium metaperiodate in $CH_2Cl_2/H_2O/SiO_2$ system.[20] Diethyl azodicarboxylate (DEAD) was obtained by the conventional procedure.[21]

Diethyl 1-hydroxyalkylphosphonates **1**, were prepared according to the previously described procedure,[14] from diethyl phosphite and appropriate aldehydes in the presence of Et_3N.

Diethyl 2-benzyloxy-1-hydroxyethylphosphonate 1j; yield: 60 %, b.p. 155-157°C/0.1 Torr; n_D^{20} = 1.5006

$C_{13}H_{21}O_5P$ (288.3) calc. C 54.16 H 7.34 P 10.74

found 54.07 7.56 10.51

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.29, 1.31 (2t, 6H, J=7.06 Hz, $2CH_3$), 3.45-4.34 (m, 8H, $3CH_2$, CH, OH), 4.59 (s, 2H,CH_2), 7.32 (s, $5H_{arom}$).

^{31}P-NMR (neat/H_3PO_4 ext.): δ = 23.3 ppm

Diethyl 1-amionoalkylphosphonate hydrochlorides 4a-j; General procedure.

A solution of DEAD (2.09 g, 0.012 mol) in CH_2Cl_2 (5 mL) was added dropwise with stirring and external cooling (dry ice/acetone bath) to a solution of Ph_3P (3.14 g, 0.012 mol) in anhydr. CH_2Cl_2 (20 mL) at -5^{o}C. The mixture was cooled to -10^{o}C, and 1.85 molar solution of HN_3 in benzene[22] (0.0125 mol) was added dropwise. Stirring was continued for 5 min. at 0^{o}C, and diethyl 1-hydroxyalkylphosphonate **1** (0.01 mol) was then added. After the addition had been completed, the mixture was kept for 30 min. at 0^{o}C,and stirring was then continued for 20 h at r.t. White precipitate of ethyl 3-(ethoxycarbonyl)carbazate was filtered off, the filtrate was evaporated under reduced pressure, and the semi-solid residue was extracted with hexane (3 x 50 mL). The combined extracts were evaporated in vacuo. The oily residue was dissolved in benzene (15 mL) and Ph_3P (2.75 g, 0.0105 mol) was added in one portion to the solution. Stirring was continued for 2 h at r.t. Water (1.8 mL, 0.1 mol) was then added and the mixture was heated for 4.5 h at 50-55^{o}C. The product was cooled

to r.t. and extracted with 5% HCl aq. (3 x 5 mL). The combined acid extracts were then reextracted with CH_2Cl_2 (3 x 20 mL).

The acid phase, was decolorized with charcoal, evaporated under reduced pressure to dryness (below 35°C), washed with ether (20 mL) and dried over P_2O_5 in vacuo to give pure diethyl 1-aminoalkylphosphonate hydrochloride **4**.

In the case of the diethyl **1-amino-2-benzyloxyethylphosphonate hydrochloride 4j**, the crude reaction mixture, after azidation of **1j** and evaporation of CH_2Cl_2, was directly subjected for further steps without extraction of **2j** into hexane.

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