Synthesis of 1-Phthalimidoalkanephosphonates

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The discovery of the antibacterial activity of alaphosphin, an α-aminophosphonic acid dipeptide (L-alanyl-L-1-aminoethanephosphonic acid) which inhibits alanine racemase[1], prompted several research groups to elaborate new methods for the synthesis of 1-aminoalkanephosphonic acids and esters. The methods presently available for their preparation can be divided into four general classes:

- addition of dialkyl phosphites to aldimines[2];
- reaction of aldehydes with trialkyl phosphites and ureas[3], thioureas[4], or alkyl carbamates[5];
- *reduction of imines, oximes, or hydrazones of* 1-oxoalkanephosphonic esters[6];
- alkylation of diethyl isocyanomethanephosphonates[7].

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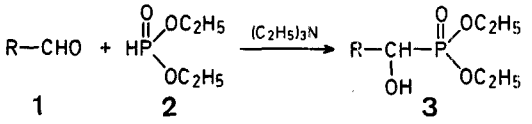
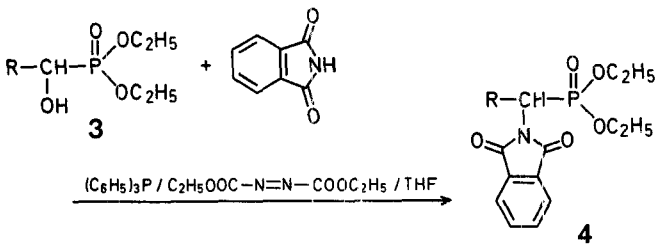
Apparently, no attempts have been made to use dialkyl 1-hydroxyalkanephosphonates (**3**) as starting material. Compounds **3** are conveniently available by the acid- or base-catalyzed addition of aldehydes (**1**) to dialkyl hydrogen phosphites[8,9] (**2**) (Table 1).



It is known that the reaction of alcohols with phthalimide in the presence of the complex formed from diethyl diazenedicarboxylate and triphenylphosphine results in the formation of *N*-alkylphthalimides in good yields[10,11]. We have utilized this reaction for the preparation of dialkyl 1-phthalimidoalkanephosphonates (**4**).



Compounds **4** are precursors of 1-aminoalkanephosphonic acids (conversion via the well-known hydrazinolysis followed by acid hydrolysis[12] of the ester) and they may also find application in peptide synthesis[12] (via transformation to the acid chlorides) and as carbonyl olefination reagents (removal of the phthaloyl group and protection of the amino group by benzylidenation)[13].

Diethyl 1-Hydroxyalkanephosphonates (3); General Procedure:
The appropriate aldehyde (**1**; 0.11 mol) is added dropwise to a stirred ice-cooled mixture of diethyl hydrogen phosphite (**2**; 13.81 g, 0.1 mol) and triethylamine (5.06 g, 0.05 mol) and the mixture is heated at 75 °C for 30 min. The product is isolated by distillation in vacuo.

Diethyl 1-Phthalimidoalkanephosphonates (4); General Procedure:
To a stirred mixture of the appropriate diethyl 1-hydroxyalkanephosphonate (**3**; 12.7 mmol), triphenylphosphine (4.984 g, 19 mmol), and phthalimide (1.87 g, 12.7 mmol) in tetrahydrofuran (20 ml), a solution

Table 1. Diethyl 1-Hydroxyalkanephosphonates (**3**) prepared

3	R	Yield [%]	b.p./torr [°C]	Molecular formula[a] or b.p./torr [°C] reported	I.R. (fiom) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
a	H	55	110°/0.5	112–115°/1.5[8]	3280, 1240, 1050	1.32 (t, 6H, J=7 Hz, CH_3); 3.9 (d, 2H, J=7 Hz, CH_2—P); 4–4.3 (m, 4H, $2CH_2$—O); 5.12 (sb, 1H, OH)
b	CH_3	72	87°/0.1	116–119°/1.5[8]	3300, 1225, 1050	1.3 (t, 6H, J=7 Hz, CH_3); 1.42 (dd, 3H, $J_{H,H}$=6 Hz, $J_{H,P}$=16 Hz, CH_3); 3.7–4 (m, 1H, CH); 4–4.4 (m, 4H, $2CH_2$—O); 4.75 (sb, 1H, OH)
c	*n*-C_3H_7	75	95°/0.1	111–112°/0.5[9]	3300, 1230, 1040	0.92 (t, 3H, J=7 Hz, CH_3); 1.3 (t, 6H, J=7 Hz, $2CH_3$); 1.5–1.8 (m, 4H, $2CH_2$); 3.7–4.1 (m, 1H, CH); 4–4.3 (m, 4H, $2CH_2$—O); 4.8 (sb, 1H, OH)
d	*n*-C_6H_{13}	78	108°/0.1	$C_{11}H_{25}O_4P$ (252.3)	3290, 1225, 1035	0.9 (t, 3H, J=7 Hz, CH_3); 1.3 (t, 6H, J=7 Hz, $2CH_3$); 1.45–1.85 (m, 10H, $5CH_2$); 3.75–4 (m, 1H, CH); 4.05–4.35 (m, 5H, $2CH_2$—O, OH)
e	*n*-C_7H_{15}	75	110°/0.1	$C_{12}H_{27}O_4P$ (266.3)	3300, 1230, 1040	0.9 (t, 3H, J=7 Hz, CH_3); 1.3 (t, 6H, J=7 Hz, $2CH_3$); 1.4–1.8 (m, 12H, $6CH_2$); 3.5 (sb, 1H, OH); 3.7–4 (m, 1H, CH); 4.0–4.4 (m, 4H, $2CH_2$—O)

[a] The microanalyses were in good agreement with the calculated values: C, ±0.17; H, ±0.22; P, ±0.30.

Table 2. Diethyl 1-Phthalimidoalkanephosphonates (**4**) prepared

4	R	Yield [%]	m.p. [°C] (solvent) or b.p. [°C]/torr	Molecular formula[a] or Lit. m.p. [°C]	I.R. ($CHCl_3$) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
a	H	62	66–67° (hexane)	67° (hexane)[12]	1770, 1720, 1240, 1050	1.32 (t, 6H, J=7 Hz, CH_3); 4.1 (d, 2H, J=11 Hz, CH_2); 4.0–4.4 (m, 4H, $2CH_2$—O); 7.7–8.0 (m, $4H_{phthal}$)
b	CH_3	60	131–132°/ 0.0005	$C_{14}H_{18}NO_5P$ (311.3)	1770, 1720, 1240, 1050	1.3 (t, 6H, J=7 Hz, CH_3); 1.7 (dd, 3H, $J_{H,H}$=8 Hz, $J_{H,P}$=17 Hz, CH_3); 4.0–4.4 (m, 4H, $2CH_2$—O); 4.5–5.0 (dq, 1H, $J_{H,H}$=8 Hz, $J_{H,P}$=17 Hz, CH); 7.7–8.0 (m, $4H_{phthal}$)
c	*n*-C_3H_7	63	142–143°/ 0.0005	$C_{16}H_{22}NO_5P$ (339.9)	1770, 1720, 1250, 1050	0.9 (t, 3H, J=7 Hz, CH_3); 1.3 (t, 6H, J=7 Hz, $2CH_3$); 1.2–1.5 (m, 4H, $2CH_2$); 4.0–4.3 (m, 4H, $2CH_2$—O); 4.4–4.8 (m, 1H, CH); 7.7–8.0 (m, $4H_{phthal}$)
d	*n*-C_6H_{13}	65	155–156°/ 0.0005	$C_{19}H_{28}NO_5P$ (381.4)	1770, 1720, 1250, 1050	0.9 (t, 3H, J=7 Hz, CH_3); 1.3 (t, 6H, J=7 Hz, $2CH_3$); 1.2–1.6 (m, 10H, $5CH_2$); 4.0–4.3 (m, 4H, CH_2—O); 4.4–4.8 (m, 1H, CH); 7.7–8.0 (m, $4H_{phthal}$)
e	*n*-C_7H_{15}	71	160–161°/ 0.0005	$C_{20}H_{30}NO_5P$ (395.4)	1770, 1720, 1250, 1050	0.9 (t, 3H, J=7 Hz, CH_3); 1.3 (t, 6H, J=7 Hz, $2CH_3$); 1.1–1.6 (m, 12H, $6CH_2$); 4.0–4.3 (m, 4H, $2CH_2$—O); 4.4–4.8 (m, 1H, CH); 7.7–8.0 (m, $4H_{phthal}$)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.27; H, ±0.25; N, ±0.17; P, ±0.30.

of diethyl diazenedicarboxylate (3.31 g, 19 mmol) in tetrahydrofuran (10 ml) is added dropwise at room temperature. Stirring is continued for 2 days and the solvent then removed in vacuo. Ether (50 ml) is added to the residue to precipitate triphenylphosphine oxide and diethyl hydrazine-*N,N'*-dicarboxylate which are filtered off. The filtrate is evaporated and the residue column-chromatographed on silica gel (120 g) using ethyl acetate/petroleum ether (b.p. 40–70°C) (1/1) as eluent.

1-Aminoethanephosphonic Acid; Typical Procedure:
A solution of diethyl 1-phthalimidoethanephosphonate (**4b**; 3.1 g, 0.01 mol) and 99% hydrazine hydrate (1 ml) in methanol (20 ml) is stirred at room temperature overnight and then refluxed for 2 h. The precipitated phthalic hydrazide is filtered and the filtrate is evaporated in vacuo. The crude oily residue is refluxed for 6 h with concentrated hydrochloric acid (30 ml). The cooled solution is evaporated in vacuo to dryness, the residue is dissolved in methanol (10 ml), and treated with propene oxide to pH 6. The precipitated 1-aminoethanephosphonic acid is filtered off, washed with cold methanol and diethyl ether; yield: 0.87 g (70%); m.p. 272–274°C (Lit.[7], m.p. 273–274°C).

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[1] J. G. Allen et al., *Nature* **272**, 56 (1978).

[2] A. Kotynsky, W. J. Stec, *J. Chem. Research* [S] **1978**, 41.
J. Lukszo, J. Kowalik, P. Mastalerz, *Chem. Lett.* **1978**, 1103.
D. Redmore, *J. Org. Chem.* **43**, 992, 996 (1978).
J. Lukszo, R. Tyka, *Synthesis* **1977**, 239.
R. Gancarz, J. S. Wieczorek, *Synthesis* **1977**, 625.
T. Glowiak et al., *Tetrahedron Lett.* **1977**, 3965.
R. Tyka, *Tetrahedron Lett.* **1970**, 677.

[3] J. W. Huber, W. F. Gilmore, *Tetrahedron Lett.* **1979**, 3049.
G. H. Birum, *J. Org. Chem.* **39**, 209 (1974).
J. Oleksyszyn, R. Tyka, *Synthesis* **1978**, 5.

[4] Z. H. Kudzin, *Synthesis* **1981**, 643.
Z. H. Kudzin, W. J. Stec, *Synthesis* **1978**, 469; **1980**, 1032.
J. Oleksyszyn, R. Tyka, P. Mastalerz, *Synthesis* **1977**, 571.

[5] J. Oleksyszyn, *Synthesis* **1980**, 722.
J. Oleksyszyn, L. Subotkowska, P. Mastalerz, *Synthesis* **1979**, 985.
J. Oleksyszyn, R. Tyka, *Tetrahedron Lett.* **1977**, 2823.
J. Oleksyszyn, R. Tyka, P. Mastalerz, *Synthesis* **1978**, 479.
W. J. Stec, K. Lesiak, *J. Org. Chem.* **41**, 3757 (1976).

[6] J. Kowalik, L. Kupczyk-Subotkowska, P. Mastalerz, *Synthesis* **1981**, 57.
Z. H. Kudzin, A. Kotynski, *Synthesis* **1980**, 1028.
K. D. Berlin, R. T. Claunch, E. J. Gaudy, *J. Org. Chem.* **33**, 3090 (1968).
K. D. Berlin, N. K. Roy, R. T. Claunch, D. Bude, *J. Am. Chem. Soc.* **90**, 4494 (1968).

[7] J. Rachon, U. Schöllkopf, T. Wintel, *Justus Liebigs Ann. Chem.* **1981**, 709.
J. Rachon, U. Schöllkopf, *Justus Liebigs Ann. Chem.* **1981**, 1186, 1693.

[8] C. G. Overberger, E. Sarlo, *J. Org. Chem.* **26**, 4711 (1961).

[9] M. S. Kharasch, R. A. Mosher, I. S. Bengelsdorf, *J. Org. Chem.* **25**, 1000 (1960).

[10] O. Mitsunobu, M. Wada, T. Sano, *J. Am. Chem. Soc.* **94**, 679 (1972).

[11] For a recent review, see: O. Mitsunobu, *Synthesis* **1981**, 1.

[12] K. Yamauchi, M. Kinoshita, M. Imoto, *Bull. Chem. Soc. Jpn.* **45**, 2528, 2531 (1972).
K. Yamauchi, Y. Mitsuda, M. Kinoshita, *Bull. Chem. Soc. Jpn.* **48**, 3285 (1975).

[13] S. F. Martin, *Synthesis* **1979**, 533.

0039-7881/82/0832-0655 $ 03.00