Synthesis of ω-Phthalimidoalkylphosphonates

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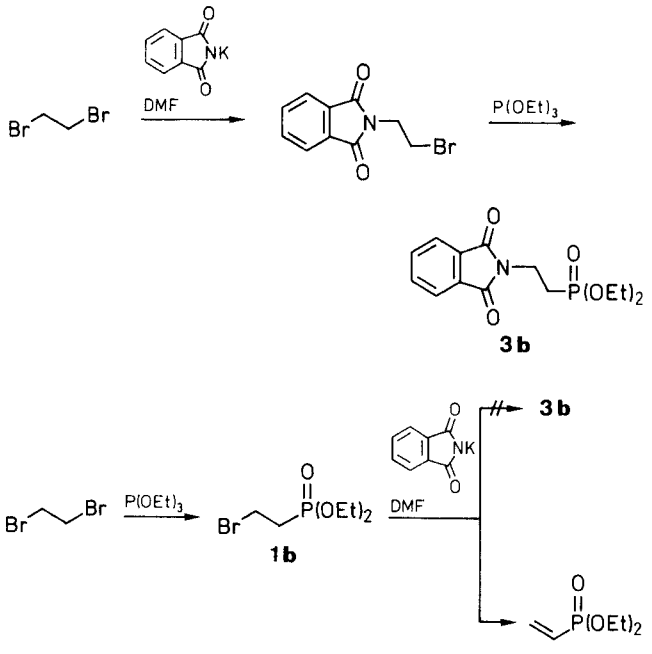
Diethyl phthalimidoalkylphosphonates were synthesized by the reaction of diethyl bromoalkylphosphonates with *N*-(*tert*-butyldimethylsilyl)phthalimide in the presence of tetrabutylammonium fluoride.

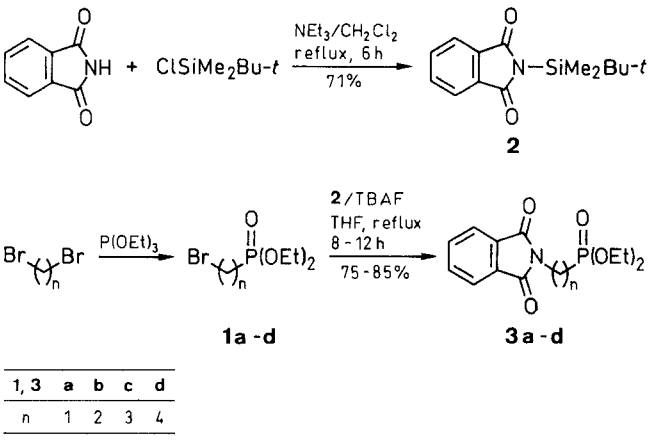
Aminophosphonic acids and their peptide derivatives are of interest due to their biological activities since the first isolation of 2-aminoethylphosphonic acid (2-AEP) from several organisms and human beings.[1-3] For example, 2-AEP shows a considerable herbicidal activity.[4] The phosphonate analogues of γ-aminocarboxylic acid (GABA), which are used for inhibitory central neurotransmitters, have some affinity for GABA binding sites.[5] Phosphonodipeptides and phosphonooligopeptides based on L- and D-1-AEP and aminomethylphosphonic acid (Alaphosphin) inhibit the growth of various types of pathogenic bacteria.[6]

Syntheses of aminoalkylphosphonic acids and their esters **3** have been developed by various methods.[7,8] For example, diethyl phthalimidoethylphosphonate **(3b)** was synthesized by the Michaelis–Arbuzov reaction of *N*-(2-bromoethyl)phthalimide with triethyl phosphite.[9,10] When a reverse process is applied by reacting potassium phthalimide with 2-bromoethylphosphonate, the desired diethyl phthalimidoethylphosphonate **(3b)**, was not formed, instead vinyl phosphonate was obtained by hydrogen bromide elimination[4] as shown in Scheme 1.



Scheme 1

In this paper we wish to report a new synthesis of diethyl phthalimidoalkylphosphonates **3** involving the reaction of diethyl alkylphosphonates **1** with *N*-(*tert*-butyldimethylsilyl)phthalimide **(2)**[11] in the presence of tetrabutylammonium fluoride (TBAF). This method seems to be mild for the synthesis of **3** in fairly good yield as shown in Scheme 2.



Scheme 2

This procedure employs the *N*-(*tert*-butyldimethylsilyl)phthalimide **(2)**/tetrahydrofuran system instead of potassium phthalimide/dimethylformamide in the first stage of Gabriel synthesis, which was easily activated by a naked fluoride ion of TBAF. *N*-(*tert*-Butyldimethylsilyl)phthalimide **(2)** was prepared from *tert*-butyldimethylsilyl chloride (TBDMSCl) and phthalimide in the presence of triethylamine. The yields of phthalimidoalkylphosphonates **3** were increased by decreasing chain length of bromoalkylphosphonates **1** (Table).

Phthalimidoalkylphosphonates **3** are precusors of aminoalkylphosphonic acid (conversion via the well-known hydrazinolysis followed by acid hydrolysis of the ester) and their peptide derivatives.

IR spectra were measured on a Perkin-Elmer 710B IR spectrometer. ^{1}H NMR spectra were obtained on a JNM-PMX 60 NMR spectrometer.

***N*-(*tert*-Butyldimethylsilyl)phthalimide (2):**
To a stirred and cooled (ice-salt bath) mixture of phthalimide (14.71 g, 0.1 mol) and TBDMSCl (15.07 g, 0.1 mol) in CH_2Cl_2 (100 mL) was slowly added NEt_3 (10.12 g, 0.1 mol). The mixture was refluxed for 6 h and cooled. The precipitated triethylammonium chloride was filtered and the filtrate was washed successively with 5% HCl solution (2 × 50 mL), H_2O (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure; white crystals; yield: 18.59 g (71%); mp 117°C (Lit.[11] mp 115.5–117°C).

Diethyl Phthalimidoalkylphosphonates 3: General Procedure:
TBAF (5.23 g, 0.02 mol) was slowly added to a mixture of diethyl bromoalkylphosphonates **1** (0.01 mol) and *N*-(*tert*-butyldimethylsilyl)phthalimide (**2**; 0.01 mol) in anhydr. THF (25 mL) in a round-bottomed flask equipped with a reflux condenser under N_2 atmo-

Table. Diethyl Phthalimidoalkylphosphonates **3** Prepared

Product	n	Yield (%) found[a]	Yield (%) reported[4]	mp (°C) (solvent)	Lit.[4] mp (°C)	IR (neat) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
3a	1	85	70	67 (hexane)	64–66	1250, 1020[b]	1.40 (t, 6H, J = 7, $2CH_3$), 3.85 (d, 2H, NCH_2), 4.05 (m, 4H, $2OCH_2$), 7.45 (s, $4H_{arom}$)
3b	2	84	67	oil	–	1225, 1020	1.35 (t, 6H, J = 7, $2CH_3$), 1.81–2.55 (dd, 2H, CH_2P), 3.97 (m, 2H, NCH_2), 4.25 (m, 4H, $2OCH_2$), 7.48 (s, $4H_{arom}$)
3c	3	79	95	oil	–	1250, 1030	1.32 (t, 6H, J = 7, $2CH_3$), 1.51–2.25 [m, 4H, $(CH_2)_2$], 3.68 (m, 2H, NCH_2), 4.15 (m, 4H, $2OCH_2$), 7.75 (s, $4H_{arom}$)
3d	4	75	85	oil	72–75	1230, 1020	1.30 (t, 6H, J = 7, $2CH_3$), 1.47–2.10 [m, 6H, $(CH_2)_3$], 3.63 (m, 2H, NCH_2), 4.05 (m, 4H, $2OCH_2$), 7.75 (s, $4H_{arom}$)

[a] Yield of isolated product **3** based on **1**.

[b] Measured as KBr pellet.

sphere at r.t. The mixture was refluxed for 8 h[12] and concentrated under reduced pressure. The oily residue was diluted with CH_2Cl_2 (25 mL), washed successively with H_2O (2 × 25 mL) and brine (2 × 25 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude products were submitted to chromatography on a silica gel column (EtOAc/hexane, 4:1) to give the desired compounds **3** (Table).

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(1) Itasaka, O. *Biochemistry of Natural C–P Compounds;* Maruzen Ltd.; Kyoto, 1984.
(2) Hoagland, R.E. In *Biologically Active Natural Products*; Culter, H.G.; Ed.; ACS Symposium Series 380; American Chemical Society: Washington D.C., 1988.
(3) Toy, A.D.; Walsh, E.N. *Phosphorus and Chemistry in Everyday Living;* American Chemical Society; Washington D.C., 1987.
(4) Tanaka, J.; Kuwano, E.; Eto, M. *J. Fac. Agr. Kyushu Univ.* **1986**, *30*, 209.
(5) Kerr, D.I.B.; Ong, J.; Prager, R.H. *Br. J. Pharmacol.* **1990**, *99*, 422.
(6) Atherton, F.R.; Hassall, C.H.; Lambert, R.W. *J. Med. Chem.* **1986**, *29*, 29, and references cited therein.
(7) Engel, R. *Org. React.* **1988**, *36*, 175.
(8) Engel, R. *Synthesis of Carbon–Phosphorus Bonds*; CRC Press: Boca Raton, FL, 1988.
(9) Kosolapoff, G.M. *J. Am. Chem. Soc.* **1947**, *69*, 2112.
(10) Yamauchi, K.; Ohtsuki, S.; Kinoshita, M. *J. Org. Chem.* **1984**, *49*, 1158, and references cited therein.
(11) Kita, Y.; Haruta, J.; Fujii, T.; Segawa, J.; Tamura, Y. *Synthesis* **1981**, 451.
(12) For n = 1, 12 h.