A Novel Synthetic Route to 1-Aminoalkylphosphinic Acids

Xian-Yun Jiao,[a] Christophe Verbruggen,[a] Marianne Borloo,[a] Willy Bollaert,[a] Alex De Groot,[b] Roger Dommisse,[b] Achiel Haemers*[a]

[a] Department of Pharmaceutical Chemistry, University of Antwerp (UIA), Universiteitsplein, 1, B-2610 Antwerp, Belgium
[b] Department of Organic Chemistry, University of Antwerp (RUCA), Groenenborgerlaan, 171, B-2020 Antwerp, Belgium

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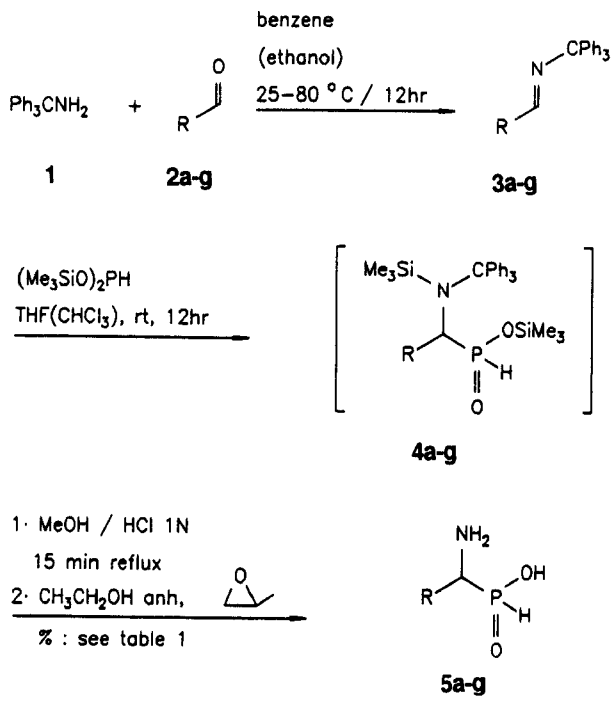
A "one-pot" synthesis of various 1-aminoalkylphosphinic acids is described. They were obtained in high yield by the deprotection of the corresponding bis(trimethylsilyl) *N*-tritylaminoalkylphosphites. The latter were prepared by addition of bis(trimethylsilyl) phosphonite to a *N*-tritylalkanimine.

1-Aminoalkylphosphinic acids are interesting compounds in the design of enzyme inhibitors. They are isoesters of the aminoalkylcarboxylic acids and could interfere with the biochemical mechanism of the enzyme–substrate reaction. Phosinopril, an angiotensin-converting-enzyme inhibitor,[1] inhibitors of CN-ligases as bacterial D-Ala-D-Ala ligase[2] and glutamine synthetase[3] and HIV protease,[4] an aspartic protease, are examples of aminophosphinic acid based enzyme inhibitors.

A general method to prepare functionalized 1-aminoalkylphosphinic acids was published by Baylis et al. and consists of the addition of hypophosphorous acid to *N*-(diphenylmethyl)imines.[5] Grobelny slightly modified this method and used bis(trimethylsilyl) phosphonite instead of hypophosphorous acid.[6]



2, 3, 4, 5	R	2, 3, 4, 5	R
a	H	d	$CH(CH_3)_2$
b	CH_3	e	C_6H_5
c	$CH_2CH_2CH_2OH$*	f	3-pyridyl

* 3 and 4: OTMS-protected

We propose an easy and fast general "one-pot" method to prepare differently functionalized 1-aminoalkylphosphinic acids in high yield, using an addition of bis(trimethylsilyl) phosphonite to *N*-tritylalkanimines. Trityl protection has already been used by Soroka et al. for the synthesis of 1-aminoalkylphosphonic acids[7] and has the advantage of being rapidly removed by dilute acid.

The tritylimine **3** in THF or chloroform was added to a THF or chloroform solution of bis(trimethylsilyl) phosphonite at 0 °C. The reaction mixture was stirred overnight at room temperature, and the solvent was evaporated under reduced pressure. The resulting bis(trimethylsilyl) derivative **4** of the corresponding 1-tritylaminoalkylphosphinic acid was, without isolation, hydrolyzed in methanol and hydrochloric acid, and, after evaporation of the solvent, the 1-aminoalkylphosphinic acid **5** was isolated from an ethanolic solution with propylene oxide.

The results are summarized in Table 1.

Tritylamine (**1**) was prepared from trityl chloride and ammonia but is also commercially available. Aldehyde **2c** ws prepared from dihydrofuran by treatment with 0.2 M HCl[5] and the corresponding imine was *O*-trimethylsilyl protected to give **3c** before the phosphonite was added. Bis(trimethylsilyl) phosphonite was prepared as described,[8] except that THF was used as solvent. *N*-Tritylalkanimines **3a–b, f** were prepared as described[7] and used after recrystallisation in the solvents given. In the preparation of *N*-tritylalkanimines **3c–e**, benzene was substituted for anhydr. EtOH and the water formed was removed with Na_2SO_4; EtOH was evaporated under vacuum.

Commercially available compounds and reagents were purchased from Janssen Chimica. Mp were taken using a Electrothermal digital melting apparatus and are uncorrected. IR spectra were obtained using a Beckmann Acculab 4 spectrometer and NMR spectra were obtained using a Varian Unity 400 spectrometer.

1-Aminoalkylphosphinic Acids 5; General Procedure:
THF (10 mL) was added from a syringe to the *in situ* generated bis(trimethylsilyl) phosphonite (18.8 mmol) at 0 °C under N_2 and stirring was continued for 5 min. A solution of **3** (18.8 mmol) in THF (**5a, f**) or $CHCl_3$ (**5b–e**) (20 mL) was then gradually injected at 0 °C and stirring continued at r.t. for 12 h. The solvent was removed under reduced pressure, the residue was dissolved in 1 M HCl in MeOH (30 mL) and refluxed for 15 min. The solvent was evaporated under reduced pressure, H_2O (30 mL) was added and the mixture was extracted three times with Et_2O. The aqueous layer was evaporated under reduced pressure, the residue[9] solubilized in anhydr. EtOH (30 mL) and treated with an excess of propylene oxide. The precipitated product **5** was isolated by suction, washed with EtOH and dried in vacuum. If precipitation was insufficient, the compound could be isolated by evaporation of the solution and lyophilization.

***N*-Trityl-4-trimethylsilyloxy-1-butanimine (3c)**
The imine (22 mmol) of tritylamine and 4-hydroxybutanal (**2**) was prepared in the usual way[7] and dissolved without purification in $CHCl_3$ (15 mL). The solution was cooled to 0 °C and Et_3N (22 mmol) was added. Trimethylsilyl chloride (22 mmol) was added

Table 1. 1-Aminoalkylphosphinic Acids **5**[a]

	Yield[b] as HCl (%)	Yield as base (%)	Yield reported[5] (%)	mp (°C)	IR (KBr) ν_{max} (cm^{-1})	^{31}P NMR (D_2O) δ	^1H NMR (D_2O) δ
5a	83	81	6	179–185	1040 s (PO), 1170 s (PO), 2360 w (PH)	14.2	3.04 (2H, dd, J_{P-CH} = 11.1, J_{PH-CH} = 1.8, CH_2), 7.15 (1H, dt, J_{PH} = 542.0, J_{PH-CH} = 1.8, PH)
5b	95	88	68	216–218	960–1040 s (PO), 1180 s (PO), 2290 w (PH)	21.4	1.41 (3H, dd, J = 7.3–16.0, CH_3), 3.24 (1H, m, CH), 6.97 (1H, dd, J_{PH} = 532.0, J_{PH-CH} = 1.5, PH)
5c	91	75	–	143–144	1050 s (PO), 1180 s (PO) 2340 m (PH, 3200–3400 s (OH)	20.1	1.74–1.96 (4H, m, $CH_2CH_2CH_2OH$, 3.14 (1H, d, CH), 3.65 (2H, t, CH_2OH), 7.03 (1H, d, J_{PH} = 535.4, PH)
5d	78	67	59	198–200	1030 s (PO), 1170 s (PO), 2350 m (PH)	18.6	1.09–1.13 (6H, 2d, J = 6.9, CH_3), 2.26 (1H, m, CH), 2.95 (1H, ddd, J_{PH-CH} = 0.8, J_{P-cH} = 11.5, J = 6.6, CH), 7.10 (1H, dd, J_{PH} = 535.0, J_{PH-CH} = 0.8, PH)
5e	89	70	–	234–235	1060 s (PO), 1210 s (PO), 2310 s (PH), 1550–1640 m (phenyl)	18.6	4.36 (1H, d, J_{P-CH} = 13.6, CH), 7.10 (1H, dd, J_{PH} = 543.0, J_{PH-CH} = 1.4, PH), 7.45 (2H, d, J = 7.0, H_{ar}), 7.53 (3H, m, J = 7.0, H_{ar})
5f	94	90	–	162–163	960–1050 m (PO) 1170 m (PO), 2320 w (PH), 1555 m, 1620 m (pyridyl)	22.9	5.07 (1H, d, J_{P-CH} = 9.3, CH), 6.95 (1H, d, J_{PH} = 535.0, PH), 8.11 (1H, m, H_{ar}-5), 8.62 (1H, m, H_{ar}-4), 8.74 (1H, m, H_{ar}-2), 8.79 (1H, m, H_{ar}-6)

[a] Satisfactory microanalyses were obtained: C H N, within 0.4%.
[b] No attempt has been made to optimize the yield.

dropwise to this solution and stirring was continued for 1 h. The mixture was passed through a short (r: 1 cm, l: 2 cm) column with silica gel H (10–40 μ) and washed with $CHCl_3$ (20 mL). The solvent was evaporated under reduced pressure and **3c** was used directly without further purification.

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(9) Crystalline hydrochlorides of **5** could be obtained at this stage by lyophilization but are very hygroscopic.