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The Facile Synthesis of *O,O*-Dialkyl 1-Aminoalkanephosphonates

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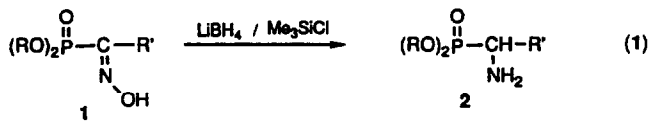
Abstract. *O,O*-Dialkyl 1-hydroxyiminoalkanephosphonates **1**, may be conveniently reduced to *O,O*-dialkyl 1-aminoalkanephosphonates **2**, at ambient temperature by application of lithium borohydride/trimethylsilyl chloride

Biologically active *O,O*-dialkyl 1-aminoalkanephosphonates **2**: are important inhibitors of aminopeptidases[1]; are structural units in peptide analogues functioning as antibacterial agents, which inhibit bacterial cell wall biosynthesis[2,3]; are structural units in peptidic phosphonylating agents that irreversibly inhibit a wide variety of serine proteases[4,5,6]; are structural units in butyloxycarbonyl protected phosphonate esters that complex with alpha-lytic proteases[7]; and are structural units in peptidylphosphonate diphenyl esters which powerfully inhibit the enzyme thrombin[8,9,10].



1 **2** (1)

A number of methods already exist for the reduction of oximes[11]. *O,O*-Dialkyl 1-hydroxyiminoalkanephosphonate derivatives **1** may be reduced by: (a) Catalytic hydrogenation over 5% Pd/C, with trace amounts of water, using methanol or acetic acid as the solvent for the reaction[12]; (b) catalytic hydrogenation over Raney nickel, using methanol or liquid ammonia as the solvent for the reaction[13,14] (c) reduction over aluminium amalgam in anhydrous ether[15,16,17,18]; and (d) reduction over activated zinc dust in formic acid[19]. Herein we report that the facile synthesis of *O,O*-

dialkyl 1-aminoalkanephosphonates **2** may be conveniently achieved in good yield by treating the corresponding hydroxyimino precursor **1** with a lithium borohydride/trimethylsilyl chloride mixture in dry THF, as the solvent for the reaction (equation **2**)[20].

$$LiBH_4 + Me_3SiCl \xrightarrow{THF} Me_3SiH + BH_3\text{-}THF + LiCl \qquad (2)$$

It has been suggested that this combination exerts its affect by forming a borane-THF complex which acts as the reducing agent. The addition of trimethylsilyl chloride makes it possible to carry out chemical reductions with $LiBH_4$, which are either very slow or do not occur in its absence. The fact that $LiBH_4/Me_3SiCl$ reductions of 1-hydroxyiminophosphonates **1** can take place at ambient temperature and normal pressure, ensures that the substrate is derivatised with minimum decomposition. It has been observed that *O,O*-dialkyl 1-hydroxyiminoalkanephosphonates are particularly unstable at elevated temperature, and in some cases violently decompose if attempts are made to purify them by distillation[21]. Using the conditions required to carry out catalytic hydrogenations of 1-hydroxyiminophosphonates, prolonged heating of these substrates, particularly under high pressure, results in their marked decomposition; as evidenced by the poor yield of the desired product.

TABLE (1) The preparation of *O,O*-dialkyl 1-aminoalkanephosphonates **2** of the corresponding *O,O*-dialkyl 1-hydroxyiminoalkanephosphonates **1** using $Me_3SiCl/LiBH_4$

No.	R	R'	yield(%)[23]	^{31}P(ppm) ($CDCl_3$)	FABMS[24] M+H(%)
1	CH_3CH_2	CH_3	43	30.28	182(100)
2	CH_3CH_2	CH_2CH_3	59	29.82	196(100)
3	$(CH_3)_2CH$	CH_2CH_3	68	27.93	224(100)
4	$CH_3(CH_2)_3$	CH_2CH_3	60	29.66	252(100)
5	$ClCH_2CH_2$	CH_2CH_3	55	27.61	265(41)
6	CH_3CH_2	$CH_2CH_2CH_3$	70	30.02	210(100)
7	$(CH_3)_2CH$	$CH_2CH_2CH_3$	80	28.21	238(7)
8	$ClCH_2CH_2$	$CH_2CH_2CH_3$	57	27.72	279(5)
9	CH_3CH_2	$(CH_2)_4CH_3$	90	29.98	238(18)
10	$(CH_3)_2CH$	$(CH_2)_4CH_3$	95	28.71	266(15)

Table 1, shows that the 1-aminoalkanephosphonates may be afforded in very good yields. Further distillation of these compounds under reduced pressure generates a spectroscopically pure product, although distillation is not always necessary as the compounds are normally very pure. The use of this facile method means that a wider variety of 1-aminophosphonates may be synthesised without fear of thermal decomposition of the hydroxyimino substrate.

General method for the preparation of *O,O*-dialkyl 1-aminoalkanephosphonates

Trimethylsilyl chloride (4 mol eq.) was carefully added dropwise and with stirring to a suspension of lithium borohydride (2 mol eq.) in freshly distilled dry THF. The *O,O*-dialkyl 1-hydroxyiminoalkanephosphonate precursor[22], also in dry THF, was then carefully added dropwise to the above mixture amidst considerable effervescence. The solution was allowed to stir at ambient temperature for 12 h. Methanol was carefully added dropwise to dissolve any volatile material, and the resultant solution was concentrated under reduced pressure on a rotary evaporator. The residue so formed, was treated with aqueous KOH (20 %) and extracted exhaustively with dichloromethane. The combined organic extracts were washed with water, and dried by vigorous stirring over anhydrous $MgSO_4$. The desiccant was filtered off, and the filtrate was concentrated under reduced pressure to afford the 1-amino derivative as a clear oil. Further purification, if necessary, was achieved by distillation under high vacuum, to give rise to the product as a colourless free-flowing oil.

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22. The isolation procedure for the *O,O*-dialkyl 1-hydroxyiminoalkanephosphonates used in this study, involved extraction from a crude solution of the product acidified with 10% hydrochloric acid. It is likely that this treatment caused isomerisation of the Z-isomer which is present in small quantity, to the E-isomer which is always present in large excess. The ^{31}P N.M.R. spectra of these worked-up 'oximes', always showed one peak, characteristic of the chemical shift for the E-isomer; afforded in very high yield.
23. The 1-aminophosphonates **2** were fully characterised by: ^{1}H, ^{13}C, and ^{31}P N.M.R. spectroscopy($CDCl_3$); FAB mass spectrometry and C,H,N analyses.
24. FAB mass spectra were obtained with a Vacuum Generator (VG) Analytical ZAB-E spectrometer with a primary beam of xenon atoms generated in an ion gun operating at 8 kv. The 1-aminophosphonates **2** were inserted immediately into the spectrometer after mixing them with a matrix of 3-nitrobenzyl alcohol (except in the case of aminophosphonate no. 4, table 1, which was mixed in a matrix of glycerol). The intensities of the protonated ions were expressed in percent relative to the intensity of the most abundant peak. C,H,N values were obtained for the 1-aminophosphonates **2**, using a Carlo Erba Model 1106 Elemental Analyser, as further confirmation of their identity, and found to be in good agreement with the expected structures. As an example, this was shown by aminophosphonate no. 10; b.pt. 94^{0}C/0.08-0.10mm; C,H,N - Calc. for $C_{12}H_{28}NO_3P$: C-54.34, H-10.57, N-5.28. Found: C-54.42, H-10.54; N-5.16.

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