SYNTHESSES OF 1-BENZYLAMINOALKYLPHOSPHONATES

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Abstract- A synthesis of 1-benzylaminoalkylphosphonates was achieved via ionic hydrogenation of diethyl 1-benzylaminoalkylphosphonates by triethylsilane-trifluoroacetic acid. Diethyl 1-benzylaminoethylphosphonate, which could not prepared by reduction, was synthesized by a simple one pot reaction.

INTRODUCTION

N-Hydroxyamino acids have been known for over 100 years but their derivatives have only recently been identified as constituents of natural products \(^1-^4\). Hydroxylamine derivatives are found chiefly in metabolites of microorganisms.\(^3\) Reviews of such hydroxamic acids have been given by Mikes,\(^1\) Chimiac,\(^2\) Neilands,\(^3\) and Meahr.\(^4\)

Although the biological role of these compounds is not completely clear, they have been reported to act as growth factors, antibiotics antitumour or fungistatic agents.\(^5\) Moreover N-hydroxypeptides have been found in human and mouse tumours.\(^6\)

Phosphonate analogs of amino acids, either isolated from nature or obtained synthetically, display a wide range of interesting properties which may have considerable economic and clinical potential.\(^7\) In addition to phosphonoamino acids, their peptides also show interesting activity mainly antibacterial and as inhibitors of proteases.\(^8\) Compounds containing phosphonate and N-hydroxyamino functions are until now poorly explored; only a few reports describe the synthesis of N-hydroxyaminoalkylphosphonates. Vasella obtained alkyl N-
glycosyl-N-hydroxyaminoalkylphosphonates in good yields and high diastereomeric excess by nucleophilic addition of lithium dialkylphosphite to N-glycosylnitrones. Elhaddadi and co-workers reported a direct method of preparing 1-benzyloxyaminophosphonic acids by reaction of phosphorus trichloride with O-benzyl oximes. The present paper describes the results of our studies concerning the reduction of diethyl 1-benzyloxyiminoalkylphosphonates by triethylsilane-trifluoroacetic acid and the preparation of diethyl 1-benzyloxyaminomethylphosphonate via a simple one pot synthesis.

RESULTS AND DISCUSSION

The reduction of 1-oxyiminocarboxylic acids or esters by boron complexes is an attractive and simple route for the synthesis of the corresponding hydroxyamino compounds. While cyanoborohydrides are required for the reduction of 1-oxyiminocarboxylic acids, the use of borane amine complexes under acidic conditions is described for reduction of α-benzyloxyimin acids esters. Application of this method using the corresponding 1-benzyloxyiminoalkylphosphonates, however, was unsatisfactory; yields were low and the resulting products were mainly composed of unreacted 1-benzyloxyiminophosphonates, which hardly could be separated from the desired products.

Recently Hiyama and co-workers reported the reduction of oximes with triethylsilane-trifluoracetic acid. We were able to apply this method with a slight modification for the selective reduction of 1–benzyloxyiminoalkyl phosphonates (5) to the corresponding 1-benzyloxyaminoalkylphosphonates (6).
Reduction of 5 by 2 eq. of triethylsilane in trifluoracetic acid at 40°C afforded 6 in good yields (50 - 79%) as colourless oils, which were isolated by column chromatography on silica gel, using ether/pentane. The progress of reduction could be observed by $^1$H-nmr spectroscopy. After evaporation of all volatile compounds under reduced pressure (40°C / 0.01 torr) monitoring by $^1$H-nmr spectroscopy revealed slow decrease of the signal at $\delta = 5.2 - 5.3$ ppm, attributed to the benzylic protons of 5, and a concomitant growth of a singlet at $\delta = 4.7 - 4.8$ ppm belonging to the benzylic protons of 6.

Compound (8) could not be prepared according to Scheme 1 and was synthesized by the Michaelis-Arbusov reaction as depicted in Scheme 2; contrary to 5a - g it was not possible to reduce 8 by ionic hydrogenation.

![Scheme 2](image)

Since no starting material was recovered, we are inclined to contribute this failure to decomposition of 8. Consequently we sought a more mild and convenient way for the preparation of 9. We found, that reaction of O-benzylformaldehyde (10) with triethylphosphite (2) in 0.5 M ethanolic HCl resulted in formation of diethyl 1-benzyloxyaminomethylphosphonate (9). It is especially noteworthy, that this reaction was limited to compound (10); attempts to prepare 5 by this method failed.

![Scheme 3](image)
EXPERIMENTAL

Melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. IR spectra were recorded on a Carl Zeiss DMR4 spectrophotometer. $^1$H- and $^{13}$C-Nmr spectra were obtained with a Bruker WM-250 instrument using CDCl$_3$ as solvent unless otherwise indicated. All chemical shifts are reported in ppm downfield from internal tetramethylsilane; coupling constants J are given in Hz. $^{31}$P-Nmr spectra were recorded on a Bruker AC 200 at 81.0 MHz (internal standard 85% H$_3$PO$_4$). EI-mass spectra were recorded on a Varian MAT 311A spectrometer (70eV).

General procedure for preparation of 1-benzyloxyaminophosphonates (6):
To a solution of 10 mmol of 1-benzyloxyiminophosphonate$^{10}$ (5) (5a: 2.85 g, 5b: 2.99 g, 5c: 3.15 g, 5d: 3.3 g, 5e: 3.48 g, 5f: 3.61 g, 5g: 3.75 g) in trifluoroacetic acid (20 ml) under nitrogen was added 2.4 g (20 mmol) of triethylsilane. The pale yellow solution was stirred at 40°C for 12 h. Evaporation of all volatile compounds under reduced pressure (40°C/ 0.01 torr) afforded a pale yellow oil. The residue was taken up in ether and washed with 1M Na$_2$CO$_3$ (25 ml). The organic phase was dried over anhydrous Na$_2$SO$_4$, evaporated to dryness and the oily residue was chromatographed on silica gel with ether to give 6 as colorless oils.

Diethyl 1-benzyloxyaminomethylphosphonate (6a) - 1.9 g (66%) were obtained after chromatographic separation, colorless oil. $^1$H-Nmr (CDCl$_3$) $\delta$= 1.30 (m, 6H, O-CH$_2$-CH$_3$), 1.38 (dd, $^2$J$_{PH}$= 16 Hz, $^3$J$_{HH}$= 7 Hz, 3H, H-2), 3.38 (dq, $^2$J$_{PH}$= 14 Hz, 3.64 (1H, H-1), 4.09 (m, 4H, O-CH$_2$-CH$_3$), 4.72 (s, 2H, O-CH$_2$-Ph), 6.85 (bs, 1H, N-H), 7.25 - 7.40 (m, 5H, H$_{Ar}$). $^{13}$C-Nmr (CDCl$_3$, {1H}) $\delta$= 13.3 (s, C-2, $^2$J$_{PC}$= 0 Hz), 16.3 (d, $^3$J$_{PC}$= 3 Hz, O-CH$_2$-CH$_3$), 53.9 (d, $^2$J$_{PC}$= 6.5 Hz, O-CH$_2$-CH$_3$), 76.9 (s, O-CH$_2$-Ph), 127.9, 128.3, 128.5 (s, C$_{Ar}$), 137.5 (s, C$_i$). $^{31}$P-Nmr (CDCl$_3$) $\delta$= 24.8. IR (film) v= 3215(m) N-H, 1165(s), 1100(s, sh), 1055(vs), 1030(vs) P-O-C, 970(vs), 920(m), 880(w), 800(s), 750(s), 700(s), 610(m) cm$^{-1}$. Anal. Calcd for C$_{13}$H$_{22}$N$_2$O$_4$P: C, 54.35; H, 7.72; N, 4.88. Found: C, 54.08; H 7.81; N, 4.89.-

Diethyl 1-benzyloxyaminopropylphosphonate (6b) - 1.87 g (62%) were obtained after chromatographic separation, colorless oil. $^1$H-Nmr (CDCl$_3$) $\delta$= 1.05 (t, $^3$J$_{HH}$= 7.5 Hz, 3H, H-3.), 1.30 (virt. q, 6H, O-CH$_2$-CH$_3$), 1.82 (m, 2H, H-2), 3.12 (ddd, $^3$J$_{HHa}$= 5.5 Hz, $^3$J$_{HHb}$= 7.5 Hz, $^2$J$_{PH}$= 15 Hz, 1H, H-1), 4.10 (m, 4H, O-CH$_2$-
CH₂), 4.72 (s, 1H, O-CH₂-Ph), 5.96 (br s, 1H, N-H). 7.12-7.40 (m, 5H, H̃_{AR}). ¹³C-Nmr (CDCl₃, {¹H}) δ= 111.1 (d, 3J_{PC}= 9.4 Hz, C-3), 16.2 (d, 3J_{PC}= 5.0 Hz, OCH₂-CH₃), 16.3 (d, 3J_{PC}= 5.0 Hz, OCH₂-CH₃), 20.7 (s, 2J_{PC}= 0 Hz, C-2), 60.0 (d, 1J_{PC}= 142.7 Hz, C-1), 61.7 (d, 2J_{PC}= 6.3 Hz, OCH₂-CH₃), 61.8 (d, 3J_{PC}= 6 Hz, OCH₂-CH₃), 76.5 (s, O-CH₂-Ph), 127.7, 128.2, 128.4 (s, C_{AR}), 137.5 (s, C_q). ³¹P-Nmr (CDCl₃) δ= 25.4. Ir (film) ν= 3230(m) N-H, 3090(w), 3070(m), 3040(m), 2980(vs), 2940(s), 2910(s), 2890(s), 1640(m), 1500(m), 1460(s), 1395(s), 1370(s), 1250(vs) P=O, 1230(m), 1165(s), 1100(s), 1050(vs, b) P-O-C, 1030(vs, b), 970(vs, b), 950(vs, b), 785(m), 750(s), 700(s) cm⁻¹. Anal. Calcd for C₁₄H₂₄N₂O₄P: C, 55.81; H, 8.02; N, 4.65; P, 10.28. Found: C, 55.66; H 8.27; N, 4.62; P, 10.13.

**Diethyl 1-benzyloxyamino-2-methylpropylphosphonate (6c)**

2.50 g (79%) were obtained after chromatographic workup, colorless oil. ¹H-Nmr (CDCl₃) δ= 1.06 (d, 3J_{HH}= 6 Hz, 3H, H-3), 1.10 (d, 3J_{HH}= 6 Hz, 3H, H-4), 1.29 (m, 6H, O-CH₂-CH₃), 2.29 (m, 1H, H-2), 3.08 (dd, 2J_{PH}= 16 Hz, 3J_{HH}= 5.5 Hz, 1H, H-1), 4.1 (m, 4H, O-CH₂-CH₃), 4.71 (s, 2H, O-CH₂-O), 6.05 (br s, 1H, N-H), 7.25-7.40 (m, 5H, H̃_{AR}). ¹³C-Nmr (CDCl₃, {¹H}) δ= 16.3 (d, 3J_{PC}= 3.6 Hz, O-CH₂-CH₃), 16.4 (d, 3J_{PC}= 5.7 Hz, O-CH₂-CH₃), 18.9 (d, 3J_{PC}= 5.3 Hz, C-3), 20.8 (d, 3J_{PC}= 8.9 Hz, C-4), 27.5 (s, 2J_{PC}= 0 Hz, C-2), 61.7 (d, 2J_{PC}= 8.6 Hz, O-CH₂-CH₃), 64.6 (d, 1J_{PC}= 139.4 Hz, C-1), 76.1 (s, O-CH₂-Ph), 127.8, 128.3, 128.4 (s, C_{AR}), 137.6 (s, C_q). ³¹P-Nmr (CDCl₃) δ= 25.3. Ir (film) ν= 3240(w) NH, 3100(w), 3070(w), 3040(w), 2980(m), 2940(m) 2910(m), 2870(m), 1650(w), 1500(w), 1475(m), 1455(m), 1390(m), 1370(m), 1250(s) P=O, 1165(m), 1100(m), 1050(s, sh) P-O, 1025(s) P-O, 960(s), 850(s), 790(m), 745(m), 700(s) cm⁻¹. Anal. Calcd for C₁₅H₂₆N₂O₄P: C, 57.13; H, 8.31; N, 4.44; P, 9.82. Found: C, 57.0; H 8.21; N, 4.55; P, 9.82.

**Diethyl 1-benzyloxyamino-3-methylbutylphosphonate (6d)**

2.4 g (73%) were obtained after chromatographic separation, colorless oil. ¹H-Nmr (CDCl₃) δ= 0.88 (d, 3H, 3J_{HH}= 7.5 Hz, H-4), 0.91 (d, 3J_{HH}= 7.5 Hz, 3H, H-5), 1.29 (virt. q, 6H, O-CH₂-CH₃), 1.39-1.72 (m, 2H, H-2), 1.79-1.96 (m, 1H, H-3), 3.21 (ddd, 3J_{HH}= 9.7 Hz, 3J_{HHb}= 4.6 Hz, 2J_{PH}= 14.3 Hz, 1H, H-1), 4.08 (m, 4H, O-CH₂-CH₃), 4.69 (s, 2H, O-CH₂-Ph), 5.93 (bs, 1H, N-H), 7.25-7.40 (m, 5H, H̃_{AR}). ¹³C-Nmr (CDCl₃, {¹H}) δ= 16.2 (d, 3J_{PC}= 5 Hz, O-CH₂-CH₃), 16.3 (d, 3J_{PC}= 4.7 Hz, O-CH₂-CH₃), 21.5 (s, C-4), 23.1 (s, C-5), 24.8 (d, 3J_{PC}= 10.8 Hz, C-3), 36.3 (d, 2J_{PC}= 0 Hz, C-2), 56.5 (d, 1J_{PC}= 142.9 Hz, C-I), 61.7 (d, 2J_{PC}= 3 Hz, O-CH₂-CH₃), 61.8 (d, 2J_{PC}= 6 Hz, O-CH₂-CH₃), 76.6 (s, O-CH₂-Ph), 127.7, 128.1, 128.4 (s, C_q). Ir (film) ν= 3230(N-H), 3090(w), 3065(w), 3035(w), 2960(s), 2940(s, sh), 2870(m), 1500(w), 1470(m), 1455(m), 1390(m), 1370(m), 1300(w), 1240(s) P=O, 1210(m, sh), 1170(m), 1100(m, sh), 1065(vs, sh), 1030(vs) P-O-C, 980(vs), 750(m), 700(m) cm⁻¹. Anal. Calcd for C₁₆H₂₈N₂O₄P: C, 58.35; H, 8.56; N, 4.25; P, 9.40. Found: C, 58.21; H 8.52; N, 4.28; P, 9.24.
Diethyl benzylxyaminobenzylphosphonate (6e) - 2.75 g (79%) were obtained after chromatographic separation, colorless oil. 1H-Nmr (CDCl3) δ= 1.12 (t, 3JPh= 6.9 Hz, 3H, O-CH2-CH3), 1.24 (t, 3JPh= 6.9 Hz, 3H, O-CH2-CH3), 3.71-4.08 (m, 4H, O-CH2-CH3), 4.48 (d, 2JPh= 20.4 Hz, 1J/ 1H, H-1 ), 6.43 (vbr, d, J= 8.4 Hz, 2H, O-CH2-Ph), 4.64 (d, 2JPh= 26.9 Hz, 1J/ 1H, H-1), 6.25 (br s, 1H, N-H), 7.15 - 7.50 (m, 5H, HAr). 13C-Nmr (CDCl3, {1H}) δ= 16.2 (d, 3JPC= 5.9 Hz, O-CH2-CH3), 16.3 (d, 3JPC= 5.9 Hz, O-CH2-CH3), 62.9 (d, 1Jpc= 143.7 Hz, C-1), 76.7 (s, O-CH2-Ph), 127.9, 128.1, 128.3, 128.4, 128.7 (s, CAr), 134.8 (d, 2JPC= 5 Hz, C-2), 137.5 (s, C3). Ir (film) ν= 3230(m) N-H, 1495(m), 1475(w), 1455(m), 1390(m), 1370(m), 1250(s) P=O, 1180(w), 1165(m), 1100(m), 1050(vs), 1025(vs) P-O-C, 970(s), 915(m), 850(w), 795(m), 750(s), 700(s) cm⁻¹. Anal. Calcd for C13H22NO4P: C, 61.88; H, 6.92; N, 4.01. Found: C, 61.59; H 6.86; N, 4.31.

Diethyl 1-benzyloxyamino-2-phenylethylphosphonate (6f) - 2.35 g (65%) were obtained after chromatographic separation, colorless oil. 1H-Nmr (CDCl3) δ= 1.32 (vbr, t, J= 7.6 Hz, 3H, O-CH2-CH3), 1.38 (vbr, t, 3H, O-CH2-CH3), 3.10 - 3.32 (m, 2H, H-2), 3.57 (ddd, 2JPh= 15.5 Hz, 3JHHA= 5.3 Hz, 3JHHB= 8.5 Hz, 1H, H-1), 4.17 (m, 4H, O-CH2-Ph), 4.80 (s, 2H, O-CH2-Ph), 6.98 (br s, 1H, N-H), 7.15-7.38 (m, 10H, HAr). 13C-Nmr (CDCl3, {1H}) δ= 16.1 (d, 3JPC= 2.6Hz, O-CH2-CH3), 16.2 (d, 3JPC= 2.9 Hz, O-CH2-CH3), 33.1 (s, 2Jpc= 0 Hz, C-2), 59.8 (d, 2Jpc= 148 Hz, C-1), 61.7 (d, 2Jpc= 6.7 Hz, O-CH2-CH3), 61.9 (d, 2Jpc= 6.5 Hz, O-CH2-CH3), 76.2 (s, O-CH2-Ph), 126.3, 127.6, 128.1, 128.2, 128.2, 129.2, 129.5 (s, CAr), 137.3 (s, C3), 137.7 (d, 3JPC= 11.6 Hz, C-3). Ir (film) ν= 3240(w) N-H, 3100(w), 3070(m), 3040(m), 2990(s), 2940(m), 2920(m), 2870(m), 1610(w), 1500(s), 1480(m, sh), 1455(s), 1445(m), 1395(m), 1370(m), 1250(vs) P=O, 1165(m), 1100(s, sh), 1055(vs, sh) 1030(vs) P-O-C, 840(w), 790(s), 750(s), 700(s) cm⁻¹. Anal. Calcd for C13H22NO4P: C, 63.65; H, 7.47; N, 3.71; P, 8.21. Found: C, 63.62; H 7.43; N, 3.72; P, 8.08.

Diethyl 1-benzyloxyamino-3-phenylpropylphosphonate (6g) - 2.05 g (54%) were obtained after chromatographic separation, colorless oil. 1H-Nmr (CDCl3) δ= 1.28 (m, 6H, O-CH2-CH3), 2.09 (m, 2H, H-2), 2.82 (m, 2H, H-3), 3.19 (ddd, 3JHHA= 6 Hz, 3JHHB= 6 Hz, 2JPh= 17 Hz, 1H, H-1), 4.09 (m, 4H, O-CH2-CH3); 4.75 (s, 2H, O-CH2-Ph), 7.15 - 7.40 (m, 10H, HAr). 13C-Nmr (CDCl3, {1H}) δ= 16.4 (d, 3JPC= 6.5 Hz, O-CH2-CH3), 29.1 (s, 2Jpc= 0 Hz, C-2), 32.6 (d, 3Jpc= 11.6 Hz, C-3), 57.8 (d, 1Jpc= 142 Hz, C-1), 61.9 (d, 2JPC= 5.5 Hz, O-CH2-CH3), 76.7 (s, O-CH2-Ph), 126.0, 127.0, 128.3, 128.4, 128.5 (s, CAr), 137.5 (s, C3), 141.5 (s, C-4). Ir (film) ν= 3240(m) N-H, 3090(w), 3060(w), 3030(s), 2980(vs), 2960(vs), 2940(vs, sh), 2910(vs), 2880(s), 1610(w), 1495(m), 1455(m), 1455(m), 1415(m, sh), 1390(m), 1370(m), 1235(s) P=O, 1165(m), 1100(m, sh), 1050(sh, sh), 1025(s), 965(s), 910(m, sh), 860(m), 790 (m, sh), 735(s), 695(s), 600(m).
Preparation of diethyl benzoximinomethyloxonate (8)

1.69 g (10 mmol) N-Benzyloxyformhydroxamic chloride15 (7) and 1.66 g (10 mmol) triethylphosphite (2) were stirred at 160°C for 2 h under nitrogen. The crude product was chromatographed on silica gel, using ether/n-hexane (9:1) to give 8 as colorless oil. Yield: 1.1 g (40%).

\[ \text{C}_20\text{H}_{28}\text{NO}_4\text{P} : \text{C}, 63.65; \text{H}, 7.47; \text{N}, 3.71; \text{P}, 8.21. \]

Preparation of diethyl benzylxoyaminomethyl phosphonate (9)

To a solution of O-benzylformaldoxime (10) (1.35 g, 10 mmol) in 0.5 M ethanolic HCl (50 ml) was added triethylphosphite (1.66 g, 10 mmol). The mixture was stirred for 2 h at 65°C. The solvent was removed under reduced pressure. Then ether (50 ml) and water (50 ml) were added together with Na$_2$CO$_3$ (6 g). After 3 h stirring, the organic phase was separated and dried over anhydrous Na$_2$SO$_4$. Evaporation of all volatile compounds under reduced pressure (40°C/0.01 torr) left a colorless oil, which was subjected to column chromatography (silica gel, ether). Yield 1.4 g (51%), colorless oil. \[ \text{I}^1\text{H-Nmr (CDCl}_3) \delta = 1.30 \text{ (virt. t, J = 8 Hz, 6H, O-CH}_2\text{-CH}_3), 3.32 \text{ (d, } ^2\text{J}_\text{PC} = 12 \text{ Hz, 2H, H-I, )}, 4.11 \text{ (m, 4H, O-CH}_2\text{-CH}_3), 4.72 \text{ (s, 2H, O-CH}_2\text{-Ph, 5.79 (br. s, 1H, NH, H/D exchange), 7.28 - 7.42 (m, 5H, H}_\text{Ar}, \text{) } \text{C}_3\text{Nmr (CDCl}_3, {^1}\text{H}) \delta = 16.2 \text{ (d, } ^3\text{J}_\text{PC} = 6.1 \text{ Hz, O-CH}_2\text{-CH}_3), 47.9 \text{ (d, } ^1\text{J}_\text{PC} = 146 \text{ Hz, C-1), 61.9 \text{ (d, } ^2\text{J}_\text{PC} = 6.7 \text{ Hz, O-CH}_2\text{-CH}_3, 75.9 \text{ (s, O-CH}_2\text{-Ph, 127.7, 128.2, 128.3, (s, C}_\text{Ar}, \text{), 137.3 (s, C}_i\text{). Ir (film) v } = 3235 (\text{m, NH}, 370(\text{w}), 3040(\text{m}), 2990(\text{s}), 2940(\text{m}), 2920(\text{m}), 1500(\text{w}), 1480(\text{w}), 1455(\text{m}), 1395(\text{m}), 1370(\text{m}), 1245(\text{s, P-O-C, 1165(\text{m), 1100(\text{m, sh), 1030(\text{vs), P-O-C, 750(m), 700(s)) cm}^-1. \text{Anal. Calcd for C}_{13}\text{H}_{22}\text{NO}_4\text{P: C}, 58.14; \text{H}, 7.69; \text{N}, 5.16; \text{P}, 11.25.} \]
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REFERENCES AND NOTES


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