

SYNTHESES OF 1-BENZYLOXYAMINOALKYLPHOSPHONATES

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Abstract- A synthesis of 1-benzyloxyaminoalkylphosphonates was achieved via ionic hydrogenation of diethyl 1-benzyloxyiminoalkylphosphonates by triethylsilane-trifluoroacetic acid. Diethyl 1-benzyloxyaminomethylphosphonate, which could not be 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 Chimiak,² Neilands,³ and Meahr.⁴

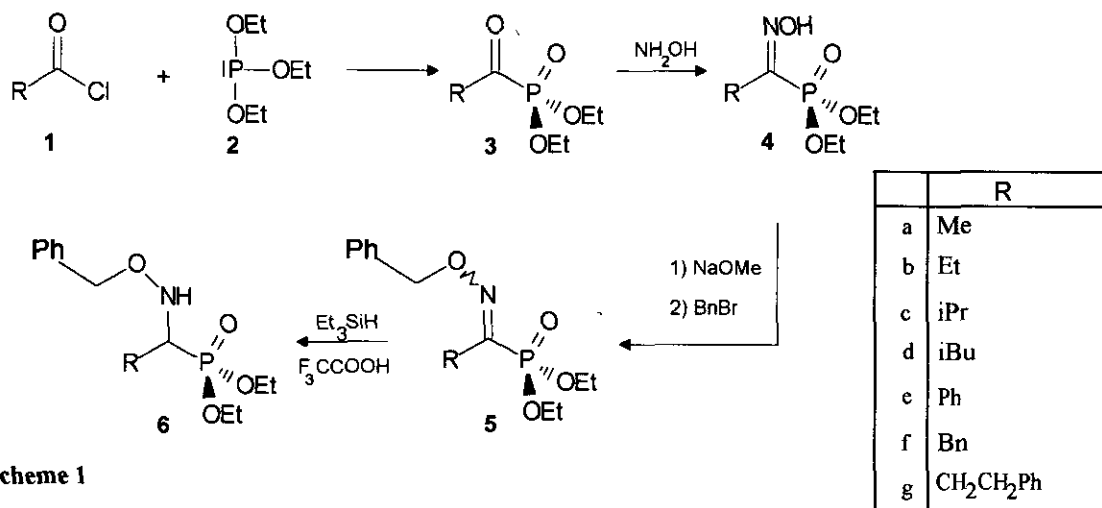
Although the biological role of these compounds is not completely clear, they have been reported to act as growth factors, antibiotics antitumour or fungistatic agents.⁵ Moreover *N*-hydroxy peptides have been found in human and mouse tumours.⁶

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.⁹ Elhaddadi and co-workers reported a direct method of preparing 1-benzyloxyaminophosphonic acids by reaction of phosphorus trichloride with *O*-benzyloximes.¹⁰ 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 -benzyloxyimino acids esters.¹¹ Application of this method using the corresponding 1-benzyloxyiminoalkylphosphonates,¹² 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.¹³

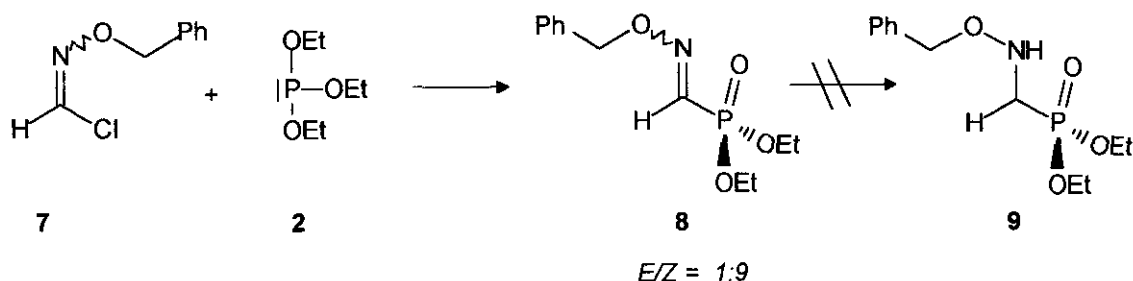


Scheme 1

Recently Hiyama and co-workers reported the reduction of oximes with triethylsilane-trifluoroacetic acid.¹⁴ We were able to apply this method with a slight modification for the selective reduction of 1-benzyloxyiminoalkyl phosphonates (5) to the corresponding 1-benzyloxyaminomethylphosphonates (6).

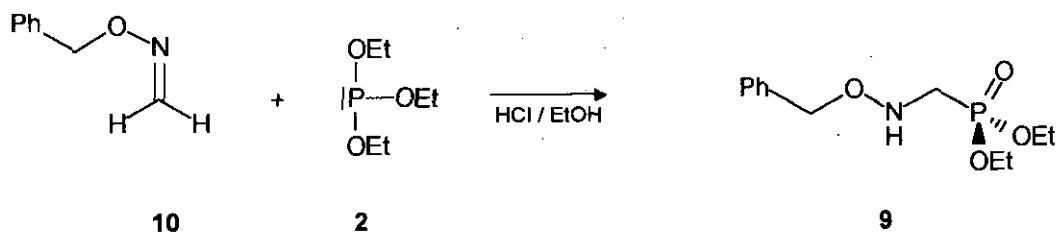
Reduction of **5** by 2 eq. of triethylsilane in trifluoroacetic acid at 40°C afforded **6** in good yields (50 - 79%) as colourless oils, which were isolated by column chromatography on silica gel, using ether/pentane. The progress of reduction could be observed by ^1H -nmr spectroscopy. After evaporation of all volatile compounds under reduced pressure (40°C / 0.01 torr) monitoring by ^1H -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

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*-benzylformaldoxime (**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

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. ^1H - 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_3PO_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-benzyloxyiminophosphonate¹⁰ (**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_2CO_3 (25 ml). The organic phase was dried over anhydrous Na_2SO_4 , evaporated to dryness and the oily residue was chromatographed on silica gel with ether to give **6** as colorless oils.

Diethyl 1-benzyloxyaminoethylphosphonate (6a) - 1.9 g (66%) were obtained after chromatographic separation, colorless oil. ^1H -Nmr (CDCl_3) δ = 1.30 (m, 6H, O- CH_2 - CH_3), 1.38 (dd, $^2J_{\text{PH}}$ = 16 Hz, $^3J_{\text{HH}}$ = 7 Hz, 3H, **H-2**), 3.38(dq, $^2J_{\text{PH}}$ = 14 Hz, $^3J_{\text{HH}}$ = 7.1 Hz, 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 }) δ =13.3 (s, C-2, $^2J_{\text{PC}}$ = 0 Hz), 16.3 (d, $^3J_{\text{PC}}$ = 3 Hz, O- CH_2 - CH_3), 53.9 (d, $^1J_{\text{PC}}$ = 146 Hz, C-1), 62.1 (d, $^2J_{\text{PC}}$ = 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) δ = 24.8. Ir (film) ν = 3215(m) **N-H**, 3100(w), 3070(w), 3040(m), 2990(s), 2940(m), 2910(m), 2870(m), 1500(m), 1480(m), 1465(m,sh), 1455(s), 1395(m), 1370(s), 1235(vs) **P=O**, 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 $\text{C}_{13}\text{H}_{22}\text{NO}_4\text{P}$: 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. ^1H -Nmr (CDCl_3) δ = 1.05 (t, $^3J_{\text{HH}}$ = 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, $^3J_{\text{HHa}}$ = 5.5 Hz, $^3J_{\text{HHb}}$ = 7.5 Hz, $^2J_{\text{PH}}$ = 15 Hz, 1H, **H-1**), 4.10 (m, 4H, O- CH_2 -

CH₃), 4.72 (s, 1H, O-CH₂-Ph), 5.96 (br s, 1H, N-H), 7.12-7.40 (m, 5H, H_{AR}). ¹³C-Nmr (CDCl₃, {¹H}) δ= 11.1 (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_i). 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(s), 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 C₁₄H₂₄NO₄P: 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, H_{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_i). 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 C₁₅H₂₆NO₄P: 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_{HHa}= 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, H_{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-1), 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_i). 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 C₁₆H₂₈NO₄P: 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 benzyloxyaminobenzylphosphonate (6e) - 2.75 g (79%) were obtained after chromatographic separation, colorless oil. $^1\text{H-Nmr}$ (CDCl_3) δ = 1.12 (t, $^3J_{\text{PH}} = 6.9$ Hz, 3H, O-CH₂-CH₃), 1.24 (t, $^3J_{\text{PH}} = 6.9$ Hz, 3H, O-CH₂-CH₃), 3.71-4.08 (m, 4H, O-CH₂-CH₃), 4.48 (d, $^2J_{\text{PH}} = 20.4$ Hz, $^{4/5}$ v. 1H, **H-1**), 4.63 (virt. d, $J = 8.4$ Hz, 2H, O-CH₂-Ph), 4.64 (d, $^2J_{\text{PH}} = 26.9$ Hz, $^{1/5}$ v. 1H, **H-1**), 6.25 (br s, 1H, N-H), 7.15 - 7.50 (m, 5H, **H_{Ar}**). $^{13}\text{C-Nmr}$ (CDCl_3 , { ^1H }) δ = 16.2 (d, $^3J_{\text{PC}} = 5.9$ Hz, O-CH₂-CH₃), 16.3 (d, $^3J_{\text{PC}} = 5.9$ Hz, O-CH₂-CH₃), 62.9 (d, $^1J_{\text{PC}} = 143.7$ Hz, **C-1**), 76.7 (s, O-CH₂-Ph), 127.9, 128.1, 128.1, 128.3, 128.4, 128.5, 128.7 (s, **C_{Ar}**), 134.8 (d, $^2J_{\text{PC}} = 5$ Hz, **C-2**), 137.5 (s, **C_i**). 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 $\text{C}_{13}\text{H}_{22}\text{NO}_4\text{P}$: 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. $^1\text{H-Nmr}$ (CDCl_3) δ = 1.32(virt. t, $J = 7.6$ Hz, 3H, O-CH₂-CH₃), 1.38 (virt. t, 3H, O-CH₂-CH₃), 3.10 - 3.32 (m, 2H, **H-2**), 3.57 (ddd, $^2J_{\text{PH}} = 15.5$ Hz, $^3J_{\text{HHa}} = 5.3$ Hz, $^3J_{\text{HHb}} = 8.5$ Hz, 1H, **H-1**), 4.17 (m, 4H, O-CH₂-CH₃), 4.80 (s, 2H, O-CH₂-Ph), 6.98 (br s, 1H, N-H), 7.15-7.38 (m, 10H, **H_{Ar}**). $^{13}\text{C-Nmr}$ (CDCl_3 , { ^1H }) δ = 16.1 (d, $^3J_{\text{PC}} = 2.6$ Hz, O-CH₂-CH₃), 16.2 (d, $^3J_{\text{PC}} = 2.9$ Hz, O-CH₂-CH₃), 33.1 (s, $^2J_{\text{PC}} = 0$ Hz, **C-2**), 59.8 (d, $^2J_{\text{PC}} = 148$ Hz, **C-1**), 61.7 (d, $^2J_{\text{PC}} = 6.7$ Hz, O-CH₂-CH₃), 61.9 (d, $^2J_{\text{PC}} = 6.5$ 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, **C_{Ar}**), 137.3 (s, **C_i**), 137.7 (d, $^3J_{\text{PC}} = 11.6$ 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 $\text{C}_{13}\text{H}_{22}\text{NO}_4\text{P}$: 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. $^1\text{H-Nmr}$ (CDCl_3) δ = 1.28 (m, 6H, O-CH₂-CH₃), 2.09 (m, 2H, **H-2**), 2.82 (m, 2H, **H-3**), 3.19 (ddd, $^3J_{\text{HHa}} = 6$ Hz, $^3J_{\text{HHb}} = 6$ Hz, $^2J_{\text{PH}} = 17$ Hz, 1H, **H-1**), 4.09 (m, 4H, O-CH₂-CH₃), 4.75 (s, 2H, O-CH₂-Ph), 7.15 - 7.40 (m, 10H, **H_{Ar}**). $^{13}\text{C-Nmr}$ (CDCl_3 , { ^1H }) δ = 16.4 (d, $^3J_{\text{PC}} = 6.5$ Hz, O-CH₂-CH₃), 29.1 (s, $^2J_{\text{PC}} = 0$ Hz, **C-2**), 32.6 (d, $^3J_{\text{PC}} = 11.6$ Hz, **C-3**), 57.8 (d, $^1J_{\text{PC}} = 142$ Hz, **C-1**), 61.9 (d, $^2J_{\text{PC}} = 5.5$ Hz, O-CH₂-CH₃), 76.7 (s, O-CH₂-Ph), 126.0, 127.0, 128.3, 128.4, 128.5 (s, **C_{Ar}**), 137.5 (s, **C_i**), 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(s, sh), 1025(s), 965(s), 910(m, sh), 860(m), 790 (m, sh), 735(s), 695(s), 600(m)

cm^{-1} . Anal. Calcd for $\text{C}_{20}\text{H}_{28}\text{NO}_4\text{P}$: 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.-

Preparation of diethyl benzyloxyiminomethyl phosphonate (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/ hexane (9:1) to give 8 as colorless oil. yield: 1.1 g (40%). $^1\text{H-Nmr}$ (CDCl_3) Z-isomer: δ = 2.90 (m, 6H, $\text{O-CH}_2\text{-CH}_3$), 4.14 (m, 4H, $\text{O-CH}_2\text{-CH}_3$), 5.29 (s, 2H, $\text{O-CH}_2\text{-Ph}$), 7.10 (d, $^2J_{\text{PH}} = 37$ Hz, 1H, **H-1**), 7.28 - 7.42 (m, 5H, **H_{Ar}**). E-isomer: δ = 2.90 (m, 6H, $\text{O-CH}_2\text{-CH}_3$), 4.14 (m, 4H, $\text{O-CH}_2\text{-CH}_3$), 5.22 (s, 2H, $\text{O-CH}_2\text{-Ph}$), 7.28 - 7.42 (m, 5H, **H_{Ar}**), 7.59 (d, $^2J_{\text{PH}} = 36.5$ Hz, 1H, **H-1**). $^{13}\text{C-Nmr}$ (CDCl_3 , { ^1H }). Z-isomer: δ = 16.2 (d, $^3J_{\text{PC}} = 7$ Hz, $\text{O-CH}_2\text{-CH}_3$), 62.58 (d, $^2J_{\text{PC}} = 23.4$ Hz, $\text{O-CH}_2\text{-CH}_3$), 77.55 (s, $\text{O-CH}_2\text{-Ph}$), 128.1, 128.2, 128.4, (s, **C_{Ar}**), 136.6 (s, **C_i**), 141.76 (d, $^1J_{\text{PC}} = 161.6$ Hz, **C-1**). E-isomer: δ = 16.2 (d, $^3J_{\text{PC}} = 7$ Hz, $\text{O-CH}_2\text{-CH}_3$), 62.58 (d, $^2J_{\text{PC}} = 23.4$ Hz, $\text{O-CH}_2\text{-CH}_3$), 77.43 (s, $\text{O-CH}_2\text{-Ph}$), 128.1, 128.2, 128.4, (s, **C_{Ar}**), 136.6 (s, **C_i**), 141.83 (d, $^1J_{\text{PC}} = 219.6$ Hz, **C-1**). Ir (film) ν = 3110(w), 3100(w), 3070(w), 3040(w), 3090(s), 2940(s), 2910(s), 1595(m) **C=N**, 1500(m), 1480(m), 1455(s), 1445(s), 1395(s), 1370(s), 1255(s, b) **P=O**, 1165(s), 1100(s), 1030(s, b) **P-O-C**, 975(s, b), 890(m), 730(m), 700(s), 670(s, b), 580(s) cm^{-1} . Anal. Calcd for $\text{C}_{13}\text{H}_{22}\text{NO}_4\text{P}$: C, 53.14; H, 6.69; N, 5.16; P, 11.42. Found: C, 53.03; H 6.76; N, 5.03; P, 11.25.-

Preparation of diethyl benzyloxyaminomethylphosphonate (9)

To a solution of *O*-benzylformaldoxime (10)(1.35 g, 10mmol) in 0.5M 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_2CO_3 (6 g). After 3 h stirring, the organic phase was separated and dried over anhydrous Na_2SO_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. $^1\text{H-Nmr}$ (CDCl_3) δ = 1.30 (virt. t, $J = 8$ Hz, 6H, $\text{O-CH}_2\text{-CH}_3$), 3.32 (d, $^2J_{\text{PC}} = 12$ Hz, 2H, **H-1**), 4.11 (m, 4H, $\text{O-CH}_2\text{-CH}_3$), 4.72 (s, 2H, $\text{O-CH}_2\text{-Ph}$, 5.79 (br. s, 1H, **NH**, H/D exchange), 7.28 - 7.42 (m, 5H, **H_{Ar}**). $^{13}\text{C-Nmr}$ (CDCl_3 , { ^1H }) δ = 16.2 (d, $^3J_{\text{PC}} = 6.1$ Hz, $\text{O-CH}_2\text{-CH}_3$), 47.9 (d, $^1J_{\text{PC}} = 146$ Hz, **C-1**), 61.9 (d, $^2J_{\text{PC}} = 6.7$ Hz, $\text{O-CH}_2\text{-CH}_3$), 75.9 (s, $\text{O-CH}_2\text{-Ph}$), 127.7, 128.2, 128.3, (s, **C_{Ar}**), 137.3 (s, **C_i**). Ir (film) ν = 3235(m) **NH**, 370(w), 3040(m), 2990(s), 2940(m), 2920(m), 1500(w), 1480(w), 1455(m), 1395(m), 1370(m), 1245(s) **P=O**, 1165(m), 1100(m, sh), 1030(vs), **P-O-C**, 750(m), 700(s) cm^{-1} . Anal. Calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_4\text{P}$: C, 52.75; H, 7.37; N, 5.13; P, 11.34. Found: C, 52.57; H 7.42; N, 4.93; P, 11.56.

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