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Synthesis of 3-(3,5-Dioxo-[1,2,4]-oxadiazolidin-2-yl)propylphosphonic Acids

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Abstract

Cyclic carbonylation of hydroxyureas **3** with 1,1'-carbonyldiimidazole gave 3-(3,5-dioxo-[1,2,4]oxadiazolidin-2yl)propylphosphonic acid diethyl esters **4** which were converted into the corresponding phosphonic acids **5** with bromotrimethylsilane.

Keywords

Hydroxyureas - cyclic carbonylation - 1,2,4-oxadiazolidine-3,5-diones - phosphonic acids

Introduction

Since their discovery by Zinner in 1959 1,2,4-oxadiazolidine-3,5-diones have attracted considerable interest in medicinal and agricultural chemistry **[1]**. Quisqualic acid (I), a natural occurring 1,2,4-oxadiazolidine-3,5-dione, is a potent excitatory amino acid that mimics the effects of glutamic acid in both the central and peripheral nervous system **[2]**. Methazol (II) is a potent 1,2,4-oxadiazolidine-3,5-dione herbicide, which was introduced into the market more than 30 years ago **[3]**. Furthermore, 1,2,4-oxadiazolidine-3,5-dione analogues of the thiazolidine-2,4-dione Glitazone display good antihyperglycemic activity **[4,5]**. Recently, we reported on the synthesis of hydroxyurea analogues (III) of the phosphonic acid antibiotic Fosmidomycin **[6]**. As a part of our general interest in the synthesis of bioactive

cyclic hydroxamic acids, cyclic hydroxyureas and phosphonic acids we now investigated the cyclic carbonylation of III (Figure 1).

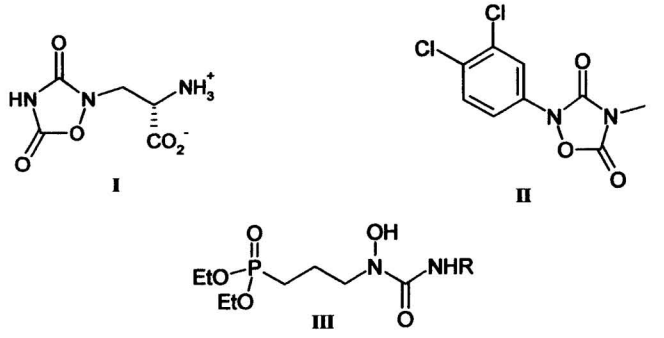
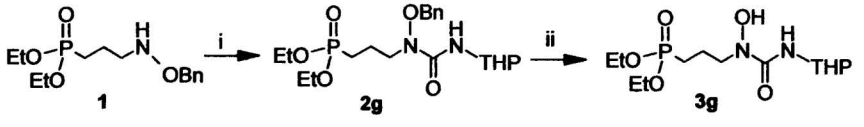


Fig. 1.

RESULTS AND DISCUSSION

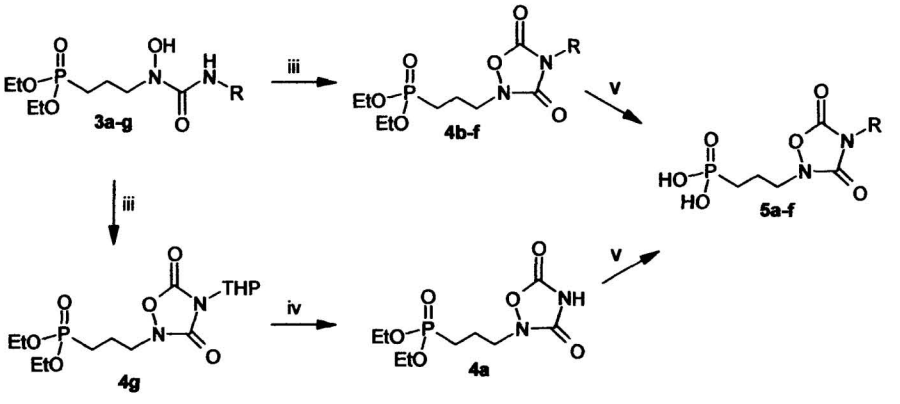
Starting materials **3a-f** were prepared as previously reported by reacting diethyl 3-benzyloxyamino-propylphosphonate **1** with isocyanates, potassium cyanate or 1,1'-carbonyldiimidazole/methylamine followed by catalytic hydrogenation of benzyloxyureas **2a-f** (Table 1) **[6]**. Catalytic hydrogenation of benzyloxyurea **2g**, which was accessible from **1** and tetrahydropyran-2-yl-isocyanate, afforded *N*-THP protected hydroxyurea **3g** (Scheme 1).



Reagents: i: Tetrahydropyran-2-yl-isocyanate; ii: H_2 / Pd-C

Scheme 1

Treatment of **3b-f** with 1,1'-carbonyldiimidazole in dry methylene chloride led to 1,2,4-oxadiazolidine-3,5-diones (**4b-f**) in good yields of 60-89 %. Formation of the 1,2,4-oxadiazolidine-3,5-dione nucleus was monitored by running IR spectra from the reaction mixture, showing the gradual emergence of a (C=O) absorption at 1810-1830 cm^{-1} besides a strong (C=O) absorption at 1730-1750cm^{-1}. In contrast to the smooth cyclic carbonylation of **3b-f** the corresponding cyclisation reaction of **3a** with 1,1'-carbonyldiimidazole failed. However, cyclic carbonylation of *N*-THP-protected hydroxyurea **3g** led smoothly to the expected 1,2,4-oxadiazolidine-3,5-dione **4g**, which could be converted into **4a** by removal of the THP group with Lewatit SC108/H^+ in methanol/water. Dealkylation of phosphonic esters **4a-f** by means of bromotrimethylsilane and subsequent hydrolysis of the intermediate trimethylsilyl esters led to phosphonic acids **5a-f** (Scheme 2). The structures of the novel compounds **3g, 4, 5** were confirmed by IR spectra, NMR spectra, mass spectra and elemental analysis.



Reagents: iii: 1,1'-Carbonyldiimidazole; iv: Lewatit SC 108; v: TMSBr / H_2O

Scheme 2

3,4,5	R	yield 3 [%]	yield 4 [%]	yield 5 [%]
a	H	87	60	25
b	CH_3	87	74	89
c	C_2H_5	87	75	74
d	*i*-C_3H_7	89	70	65
e	*t*-C_4H_9	99	68	77
f	C_6H_5	94	78	69
g	THP	90	89	-

Tab. 1. Hydroxyureas **3** and 1,2,4-oxadiazolidine-3,5-diones **4,5**

Experimental Part

General Methods: Melting points (uncorrected) were determined on a Mettler FP 62 apparatus. Elemental analyses were carried out with a Heraeus CHN-O-Rapid instrument. IR spectra were recorded on a Shimadzu FT-IR 8300. ^{1}H NMR (400.1 MHz) und ^{13}C NMR (100.62 MHz) spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as an internal standard and DMSO-d_6, D_2O and $CDCl_3$ as solvents. Mass spectra were recorded on a VG 70-250S (VG Analytical) instrument. Column chromatography was conducted on silica gel (ICN Silica 100-200, active 60 Å).

Diethyl 3-(1-benzyloxy-3-tetrahydropyran-2-yl-ureido)propylphosphonate (2g)

To a stirred solution of **1** (3.01 g, 10 mmol) in dry methylene chloride (5 mL) was added tetrahydropyran-2-yl-isocyanate (10.5 mmol) at ambient temperature. After stirring over night the reaction mixture was purified by column chromatography on silica gel with EtOAc/MeOH (9.5/0.5) as an eluent to give **2g**. Yellow oil; 80% yield; IR (film): 1676 (C=O), 1238 (P=O), 1055, 1034 (P-O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) 1,21-1.34 (m, 7H, CH_3, CH_2 of THP), 1.43-1.55 (m, 2H, CH_2 of THP), 1.58-1.67 (m, 1H, CH_2 of THP), 1.71-1.99 (m, 6H, PCH_2CH_2, CH_2 of THP), 3.51-3.65 (m, 3H, NCH_2, OCH_2 of THP), 3.88-3.91 (m, 1H, OCH_2 of THP), 4.03-4.13 (m, 4H,

CH_3CH_2), 4.78 (d, J_{AB} = 10.9 Hz, 1H, CH_2Ph), 4.84 (d, J_{AB} = 10.9 Hz, 1H, CH_2Ph), 4.90 (dt, ^3J = 9.6, 2.4 Hz, 1H, CH of THP), 6.12 (d, ^3J = 9.2 Hz, 1H, NH), 7.36-7.39 (m, 5H, arom. H); ^{13}C NMR ($CDCl_3$): δ (ppm) 16.47 (d, $^3J_{C,P}$ = 6.1 Hz, CH_3), 20.21 (d, $^2J_{C,P}$ = 5.1 Hz, PCH_2CH_2), 22.83 (CH_2 of THP), 23.11 (d, $^1J_{C,P}$ = 142.4 Hz, PCH_2), 25.07 (CH_2 of THP), 31.50 (CH_2 of THP), 49.24 (d, $^3J_{C,P}$ = 19.3 Hz, NCH_2), 61.57 (d, $^2J_{C,P}$ = 6.6 Hz, CH_3CH_2), 66.94 (OCH_2 of THP), 77.31 (CH_2Ph), 78.68 (CH of THP), 128.84, 128.99, 129.31, 135.05 (arom. C), 158.68 (C=O); $C_{20}H_{33}N_2O_6P$ (428.5): calcd. C 56.07, H 7.76, N 6.54; found C 55.31, H 7.78, N 6.25; HRMS (FAB): calcd. for $C_{20}H_{33}N_2O_6P$: $[M+H]^+$: 429.2155, found 429.2192.

Diethyl 3-(1-hydroxy-3-tetrahydropyran-2-yl-ureido)propylphosphonate (3g)

2g (2 mmol) was hydrogenated in MeOH at ambient temperature and 1.75 atm. using catalytic amounts of 10% Pd/C for 2h. The suspension was filtrated and the solvent was evaporated to give **3g**. Colourless oil; 90% yield; IR (film): 3433, 3327, 3179 (NH/OH), 1666 (C=O), 1232 (P=O), 1056, 1034 (P-O) cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) 1.31 (t, ^3J = 7.1 Hz, 6H, CH_3), 1.34-1.62 (m, 4H, CH_2 of THP), 1.77-2.00 (m, 6H, PCH_2CH_2, CH_2 of THP), 3.55-3.66 (m, 3H, NCH_2, OCH_2 of THP), 3.92-3.97 (m, 1H, OCH_2 of THP), 4.02-4.12 (m, 4H, CH_3CH_2), 4.96 (dt, ^3J = 9.7, 2.4 Hz, 1H, CH of THP), 6.55 (d, ^3J = 9.7 Hz, 1H, NH), 9.42 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ (ppm) 16.36 (d, $^3J_{C,P}$ = 6.1 Hz, CH_3), 19.54 (d, $^2J_{C,P}$ = 5.6 Hz, PCH_2CH_2), 22.25 (d, $^1J_{C,P}$ = 140.9 Hz, PCH_2), 23.03 (CH_2 of THP), 25.17 (CH_2 of THP), 31.60 (CH_2 of THP), 49.74 (d, $^3J_{C,P}$ = 7.1 Hz, NCH_2), 62.02 (d, $^2J_{C,P}$ = 7.1, OCH_2CH_3), 62.27 (d, $^2J_{C,P}$ = 6.6, OCH_2CH_3), 66.87 (OCH_2 of THP), 78.77 (CH of THP), 159.65 (C=O); $C_{13}H_{27}N_2O_6P$ (338.3): calcd. C 46.15, H 8.04, N 8.28; found C 46.48, H 8.13, N 8.05; HRMS (FAB): calcd. for $C_{13}H_{27}N_2O_6P$: $[M+H]^+$: 339.1686, found 339.1722.

General procedure for the preparation of 1,2,4-oxadiazolidine-3,5-diones 4b-g

To a stirred solution of **3b-g** (5 mmol) in dry methylene chloride (20 mL) was added 1,1'-carbonyldiimidazole (5.5 mmol) at room temperature. After stirring for 12

hours the reaction mixture was washed twice with diluted hydrochloric acid, the organic layer was dried over $MgSO_4$ and concentrated to give **4b-g**.

3-(4-Methyl-3,5-dioxo-[1,2,4]oxazolidin-2-yl)propylphosphonic acid diethyl ester (4b)

Colourless crystals; 74% yield; m.p. 53 °C (EtOAc / hexane); IR (KBr): 1830, 1747 (C=O), 1232 (P=O), 1055, 1026 (P-O) cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) 1.34 (t, ^3J = 7.1 Hz, 6H, OCH_2CH_3), 1.79-1.86 (m, 2H, PCH_2), 1.98-2.09 (m, 2H, PCH_2CH_2), 3.14 (s, 3H, NCH_3), 3.77 (t, ^3J = 6.9 Hz, 2H, NCH_2), 4.05-4.18 (m, 4H, OCH_2); ^{13}C NMR ($CDCl_3$): δ (ppm) 16.47 (d, $^3J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 20.47 (d, $^2J_{C,P}$ = 4.6 Hz, PCH_2CH_2), 22.80 (d, $^1J_{C,P}$ = 144.0 Hz, PCH_2), 26.51 (NCH_3), 49.83 (d, $^3J_{C,P}$ = 17.3 Hz, NCH_2), 61.81 (d, $^2J_{C,P}$ = 6.1 Hz, OCH_2), 152.07, 156.41 (C=O); $C_{10}H_{19}N_2O_6P$ (294.3): calcd. C 40.82, H 6.51, N 9.52; found C 40.69, H 6.58, N 9.32.

3-(4-Ethyl-3,5-dioxo-[1,2,4]oxazolidin-2-yl)propylphosphonic acid diethyl ester (4c)

Colourless crystals; 75% yield; m.p. 41 °C (EtOAc / hexane); IR (KBr): 1817, 1742 (C=O), 1234 (P=O), 1058, 1024 (P-O) cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) 1,31 (t, ^3J = 7.3 Hz, 3H, NCH_2CH_3), 1.34 (t, ^3J = 7.1 Hz, 6H, OCH_2CH_3), 1.78-1.86 (m, 2H, PCH_2), 1.98-2.08 (m, 2H, PCH_2CH_2), 3.63 (q, ^3J = 7.3 Hz, 2H, NCH_2CH_3), 3.76 (t, ^3J = 6.7 Hz, 2H, NCH_2), 4.05-4.18 (m, 4H, OCH_2); ^{13}C NMR ($CDCl_3$): δ (ppm) 12.90 (NCH_2CH_3), 16.47 (d, $^3J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 20.41 (d, $^2J_{C,P}$ = 4.6 Hz, PCH_2CH_2), 22.81 (d, $^1J_{C,P}$ = 143.9 Hz, PCH_2), 36.06 (NCH_2CH_3), 49.76 (d, $^3J_{C,P}$ = 17.3 Hz, NCH_2), 61.80 (d, $^2J_{C,P}$ = 6.1 Hz, OCH_2), 151.81, 156.22 (C=O); $C_{11}H_{21}N_2O_6P$ (308.3): calcd. C 42.86, H 6.87, N 9.09; found C 42.86, H 6.65, N 9.13.

3-(4-Isopropyl-3,5-dioxo-[1,2,4]oxazolidin-2-yl)propylphosphonic acid diethyl ester (4d)

Colourless oil; 70% yield; IR: 1815, 1738 (C=O), 1238 (P=O), 1055, 1028 (P-O) cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) 1.34 (t, ^3J = 7.0 Hz, 6H, OCH_2CH_3), 1.47 (d, ^3J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.77-1.86 (m, 2H, PCH_2), 1.97-2.08 (m, 2H, PCH_2CH_2), 3.73 (t, ^3J = 6.7 Hz, 2H, NCH_2), 4.05-4.18 (m, 4H, OCH_2), 4.26 (sept., ^3J = 6.9 Hz, 1H, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ (ppm) 16.47 (d, $^3J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 19.31 ($CH(CH_3)_2$), 20.44 (d, $^2J_{C,P}$ = 5.1 Hz, PCH_2CH_2), 22.82 (d, $^1J_{C,P}$ = 143.9 Hz, PCH2), 46.17 ($CH(CH_3)_2$), 49.76 (d, $^3J_{C,P}$ = 17.3 Hz, NCH_2), 61.80 (d, $^2J_{C,P}$ = 6.6 Hz, OCH_2), 151.31, 156.17 (C=O); $C_{12}H_{23}N_2O_6P$ (322.3): calcd. C 44.72, H 7.19, N 8.69; found C 44.79, H 7.35, N 8.69.

3-(4-tert-Butyl-3,5-dioxo-[1,2,4]oxazolidin-2-yl)propylphosphonic acid diethyl ester (4e)

Colourless oil; 68% yield; IR: 1811, 1732 (C=O), 1236 (P=O), 1053, 1028 (P-O) cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) 1.33 (t, ^3J = 7.1 Hz, 6H, OCH_2CH_3), 1.62 (s, 9H, $C(CH_3)_3$), 1.77-1.85 (m, 2H, PCH_2), 1.95-2.06 (m, 2H, PCH_2CH_2), 3.69 (t, ^3J = 6.7 Hz, 2H, NCH_2), 4.05-4.18 (m, 4H, OCH_2); ^{13}C NMR ($CDCl_3$): δ (ppm) 16.47 (d, $^3J_{C,P}$ = 5.6 Hz, OCH_2CH_3), 20.36 (d, $^2J_{C,P}$ = 4.6 Hz, PCH_2CH_2), 22.85 (d, $^1J_{C,P}$ = 143.9 Hz, PCH_2), 27.88 ($C(CH_3)_3$), 49.46 (d, $^3J_{C,P}$ = 17.3 Hz, NCH_2), 59.22 ($C(CH_3)_3$), 61.79 (d, $^2J_{C,P}$ = 6.6 Hz, OCH_2), 151.40, 156.73 (C=O); $C_{13}H_{25}N_2O_6P$ (336.3): calcd. C 46.43, H 7.49, N 8.33; found C 46.23, H 7.38, N 8.29.

3-(3,5-Dioxo-4-phenyl-[1,2,4]oxadiazolidin-2-yl)propylphosphonic acid diethyl ester (4f)

Colourless oil; 78% yield; IR (film): 1821, 1747 (C=O), 1242 (P=O), 1055, 1028 (P-O) cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) 1.35 (t, ^3J = 7.0 Hz, 6H, CH_3), 1.83-1.92 (m, 2H, PCH_2), 2.04-2.16 (m, 2H, PCH_2CH_2), 3.88 (t, ^3J = 6.7 Hz, 2H, NCH_2), 4.06-4.20 (m, 4H, OCH_2), 7.41-7.47 (m, 1 H, arom. H), 7.48-7.51 (m, 4H, arom. H); ^{13}C NMR ($CDCl_3$): δ (ppm) 16.45 (d, $^3J_{C,P}$ = 6.1 Hz, CH_3), 20.54 (d, $^2J_{C,P}$ = 4.6 Hz, PCH_2CH_2), 22.85 (d, $^1J_{C,P}$ = 143.9 Hz, PCH_2), 49.74 (d, $^3J_{C,P}$ = 16.8 Hz, NCH_2), 61.86 (d, $^2J_{C,P}$ =

6.6 Hz, OCH_2); 125.08, 129.09, 129.48, 130.36 (arom. C), 150.50, 154.72 (C=O); $C_{15}H_{21}N_2O_6P$ (356.3): calcd. C 50.56, H 5.94, N 7.86; found C 50.70, H 5.87, N 7.95.

3-[3,5-Dioxo-4-(tetrahydropyran-2-yl)-[1,2,4]oxazolidin-2-yl]propylphosphonic acid diethyl ester (4g)

Colourless oil; 89% yield; IR (film): 1825, 1747 (C=O), 1242 (P=O), 1059, 1028 (P-O) cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) 1.33 (t, ^3J = 7.1 Hz, 6H, CH_3), 1.51-1.73 (m, 4H, CH_2 of THP), 1.77-1.85 (m, 2H, PCH_2), 1.97-2.08 (m, 3H, PCH_2CH_2, CH_2 of THP), 2.53-2.63 (m, 1H, CH_2 of THP), 3.58-3.64 (m, 1H, OCH_2 of THP), 3.76 (t, ^3J = 6.7 Hz, 2H, NCH_2), 4.04-4.18 (m, 5H, OCH_2CH_3, OCH_2 of THP), 5.04-5.07 (m, 1H, CH of THP); ^{13}C NMR ($CDCl_3$): δ (ppm) 16.46 (d, $^3J_{C,P}$ = 6.1 Hz, CH_3), 20.50 (d, $^2J_{C,P}$ = 4.6 Hz, PCH_2CH_2), 22.77 (d, $^1J_{C,P}$ = 143.4 Hz, PCH_2), 23.00 (CH_2 of THP), 24.51 (CH_2 of THP), 26.86 (CH_2 of THP), 49.49 (d, $^3J_{C,P}$ = 17.3 Hz, NCH_2), 61.80 (d, $^2J_{C,P}$ = 6.6 Hz, OCH_2CH_3), 68.89 (OCH_2 of THP), 81.28 (CH of THP), 150.39, 154.91 (C=O); $C_{14}H_{25}N_2O_7P$ (364.3): calcd. C 46.15, H 6.92, N 7.69; found C 46.24, H 7.06, N 7.25; HRMS (FAB): calcd. for $C_{14}H_{25}N_2O_7P$: $[M+H]^+$: 365.1478, found 365.1501.

3-(3,5-Dioxo-[1,2,4]oxazolidin-2-yl)propylphosphonic acid diethyl ester (4a)

To a solution of **4g** (2 mmol) in methanol (15 mL) / water (0.25 mL) was added Lewatit SC108/H^+ (1.5 g) and the suspension was refluxed for 4 h. After cooling to room temperature Lewatit SC108/H^+ was removed by filtration, the filter was washed with MeOH/NH_4OH and the filtrate was concentrated. The remaining residue was dissolved in methylene chloride and extracted with aqueous $NaHCO_3$ (3 x 10mL). The aqueous layer was adjusted to pH 1 with 0.5 M HCl and extracted twice with methylene chloride. The organic layer was dried over $MgSO_4$, concentrated and hexane was added to give **4a** as white solid. Colourless crystals; 60% yield; m.p. 58 °C (EtOAc); IR (KBr): 1827, 1744 (C=O), 1204 (P=O), 1053, 1022 (P-O) cm^{-1}; ^1H NMR (DMSO-d_6): δ (ppm) 1.23 (t, ^3J = 7.0 Hz, 6H, CH_3), 1.74-

1.85 (m, 4H, PCH_2CH_2), 3.66 (t, ^3J = 6.6 Hz, 2H, NCH_2), 3.92-4.06 (m, 4H, OCH_2CH_3), 12.32 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ (ppm) 16.17 (d, $^3J_{C,P}$ = 5.6 Hz, CH_3), 19.99 (d, $^2J_{C,P}$ = 4.6 Hz, PCH_2CH_2), 21.45 (d, $^1J_{C,P}$ = 140.4 Hz, PCH_2), 49.15 (d, $^3J_{C,P}$ = 17.8 Hz, NCH_2), 60.92 (d, $^2J_{C,P}$ = 6.6 Hz, OCH_2CH_3), 152.38, 157.81 (C=O); $C_9H_{17}N_2O_6P$ (280.22): calcd. C 38.58, H 6.12, N 10.00; found C 38.94, H 5.94, N 9.74.

General procedure for the preparation of phosphonic acids 5a-f

To a stirred solution of **4a-f** (2 mmol) in dry methylene chloride (5 mL) bromotrimethylsilane (6 mmol) was added at room temperature. After 24 h the solvent was removed under reduced pressure, the remaining residue was dissolved in THF (3 mL) and treated with water (0.05 mL). After stirring for 10 minutes the solvent was evaporated and the residue was dried in vacuo. **5a-f** were crystallised from ethyl acetate.

3-(3,5-Dioxo-[1,2,4]oxazolidin-2-yl)propylphosphonic acid (5a)

Colourless crystals; 25% yield; m.p. 156 °C (EtOAc); IR (KBr): 3157 (NH), 2735, 2291 (P-OH), 1813, 1738, 1717 (C=O), 1121 (P=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ (ppm) 1.53-1.61 (m, 2H, PCH_2), 1.74-1.84 (m, 2H. PCH_2CH_2), 3.65 (t, ^3J = 7.1 Hz, 2H, NCH_2), 4.12, (s, 2H, P$(OH)_2$), 12.45 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ (ppm) 21.03 (d, $^2J_{C,P}$ = 4.1 Hz, PCH_2CH_2), 24.92 (d, $^1J_{C,P}$ = 137.8 Hz, PCH_2), 49.99 (d, $^3J_{C,P}$ = 17.8 Hz, NCH_2), 152.88, 158.30 (C=O); HRMS (FAB): calcd. for $C_5H_9N_2O_6P$: $[M+H]^+$: 225.0277, found 225.0280.

3-(4-Methyl-3,5-dioxo-[1,2,4]oxazolidin-2-yl)propylphosphonic acid (5b)

Colourless crystals; 89% yield; m.p. 113 °C (EtOAc); IR (KBr): 2735, 2276 (P-OH), 1817, 1747, 1732 (C=O), 1171 (P=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ (ppm) 1.55-1.63 (m, 2H, PCH_2), 1.76-1.87 (m, 2H, PCH_2CH_2), 2.97 (s, 3H, CH_3), 3.70 (t, ^3J = 7.0 Hz, 2H, NCH_2), 8.14 (s, 2H, P$(OH)_2$); ^{13}C NMR (DMSO-d_6): δ (ppm) 21.06 (d,

$^2J_{C,P}$ = 4.1 Hz, PCH_2CH_2), 24.84 (d, $^1J_{C,P}$ = 137.3 Hz, PCH_2), 26.58 (CH_3), 50.50 (d, $^3J_{C,P}$ = 17.3 Hz, NCH_2), 152.75, 157.53 (C=O); $C_6H_{11}N_2O_6P$ (238.1): calcd. C 30.26, H 4.66, N 11.76; found C 30.39, H 4.78, N 11.50.

3-(4-Ethyl-3,5-dioxo-[1,2,4]oxazolidin-2-yl)propylphosphonic acid (5c)

Colourless crystals; 74% yield; m.p. 93 °C (EtOAc); IR (KBr): 2860, 2278 (P-OH), 1817, 1724 (C=O), 1168 (P=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ (ppm) 1.18 (t, ^3J = 7.3 Hz, CH_3), 1.55-1.63 (m, 2H, PCH_2), 1.76-1.87 (m, 2H, PCH_2CH_2), 3.48 (q, ^3J = 7.2 Hz, 2H, CH_2CH_3), 3.71 (t, ^3J = 7.0 Hz, 2H, NCH_2), 6.46 (s, 2H, $P(OH)_2$); ^{13}C NMR (DMSO-d_6): δ (ppm) 12.80 (CH_3), 21.01 (d, $^2J_{C,P}$ = 4.1 Hz, PCH_2CH_2), 24.85 (d, $^1J_{C,P}$ = 137.8 Hz, PCH_2), 35.80 (CH_3CH_2), 50.37 (d, $^3J_{C,P}$ = 16.8 Hz, NCH_2), 152.32, 157.07 (C=O); $C_7H_{13}N_2O_6P$ (252.2): calcd. C 33.34, H 5.20, N 11.11; found C 33.38, H 5.22, N 10.82.

3-(4-Isopropyl-3,5-dioxo-[1,2,4]oxazolidin-2-yl)propylphosphonic acid (5d)

Colourless crystals; 65% yield (EtOAc); m.p. 82 °C; IR (KBr): 2802, 2324 (P-OH), 1827, 1736 (C=O), 1209 (P=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ (ppm) 1.36 (d, ^3J = 6.9 Hz, 6H, CH_3), 1.54-1.62 (m, 2H, PCH_2), 1.75-1.86 (m, 2H, PCH_2CH_2), 3.70 (t, ^3J = 7.0 Hz, 2H, NCH_2), 4.11 (sept., ^3J = 6.9 Hz, 1H, CH), 4.55 (s, 2H, $P(OH)_2$); ^{13}C-NMR (DMSO-d_6): δ (ppm) 18.85 (CH_3), 20.52 (d, $^2J_{C,P}$ = 4.1 Hz, PCH_2CH_2), 24.42 (d, $^1J_{C,P}$ = 137.3 Hz, PCH_2), 45.16 (CH), 49.79 (d, $^3J_{C,P}$ = 16.8 Hz, NCH_2), 151.23, 156.30 (C=O); $C_8H_{15}N_2O_6P$ (266.2): calcd. C 36.10, H 5.68, N 10.52; found C 36.16, H 5.35, N 10.39.

3-(4-tert-Butyl-3,5-dioxo-[1,2,4]oxazolidin-2-yl)propylphosphonic acid (5e)

Colourless crystals; 77% yield (EtOAc); m.p. 102 °C; IR (KBr): 2810, 2311 (P-OH), 1809, 1734 (C=O), 1209 (P=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ (ppm) 1.54 (s, 9H, CH_3), 1.57-1.62 (m, 2H, PCH_2), 1.74-1.84 (m, 2H, PCH_2CH_2), 3.66 (t, ^3J = 7.0 Hz, 2H, NCH_2), 7.40 (s, 2H, $P(OH)_2$); ^{13}C-NMR (DMSO-d_6): δ (ppm) 20.86 (d, $^2J_{C,P}$ =

4.1 Hz, PCH_2CH_2), 24.90 (d, $^1J_{C,P}$ = 137.8 Hz, PCH_2), 27.67 (CH_3), 49.99 (d, $^3J_{C,P}$ = 17.3 Hz, NCH_2), 58.50 ($C(CH_3)_3$), 151.64, 157.18 (C=O); $C_9H_{17}N_2O_6P$ (280.2): calcd. C 38.58, H 6.12, N 10.00; found C 38.75, H 6.11, N 9.91.

3-(4-Phenyl-3,5-dioxo-[1,2,4]oxazolidin-2-yl)propylphosphonic acid (5f)

Colourless crystals; 69% yield; m.p. 193 °C (EtOAc); IR (KBr): 2883, 2299 (P-OH), 1815, 1800, 1734 (C=O), 1182 (P=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ (ppm) 1.62-1.70 (m, 2H, PCH_2), 1.85-1.94 (m, 2H, PCH_2CH_2), 3.83 (t, ^3J = 7.0 Hz, 2H, NCH_2), 7.33 (s, 2H, $P(OH)_2$), 7.46-7.57 (m, 5H, arom. H); ^{13}C NMR (DMSO-d_6): δ (ppm) 21.23 (d, $^2J_{C,P}$ = 4.1 Hz, PCH_2CH_2), 24.93 (d, $^1J_{C,P}$ = 137.8 Hz, PCH_2), 50.47 (d, $^3J_{C,P}$ = 16.8 Hz, NCH_2), 126.70, 129.34, 129.52, 131.00 (arom. C), 151.25, 157.83 (C=O); $C_{11}H_{13}N_2O_6P$ (300.2): calcd. C 44.01, H 4.36, N 9.33; found C 44.02, H 4.49, N 9.31.

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