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Tetraethyl(pyrrolidine-2,2-diyl)bisphosphonate

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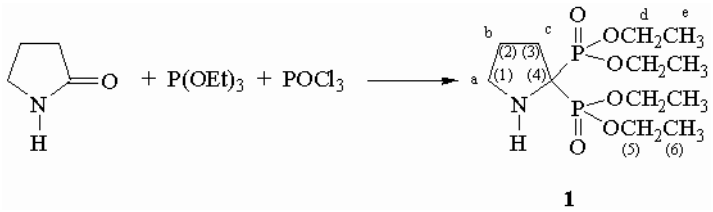

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The synthesis of the title compound is already described [1, 2] and we report here the fully optimized procedure. In a double walls flask, under nitrogen, phosphorus oxychloride (20 ml; 0.22 mol) is added for 1 h 00 time to a mixture at -7.5 °C of 2-pyrrolidinone (9.3 g; 0.11 mol) and triethylphosphite (35.1 g; 0.21 mol; 1.9 eq.). The reaction mixture is stirred for 1 hour at room temperature and then poured over a mixture of ice (200 g) and ammonia 30 % (400 ml). The aqueous layer is extracted with methylene chloride (3x100 ml) and then the latter is removed to obtain a yellow oil. The oil is dissolved in 100 ml of methylene chloride. An aqueous solution of hydrochloric acid (10 ml of 32 % HCl solution, 190 ml of water) is added (check that pH 1) and the aqueous layer is washed with methylene chloride (3x100 ml). A solution of sodium hydroxide (20 g of NaOH in 200 ml of water) is added up to pH 10 and the aqueous layer is extracted with methylene chloride (4x100 ml). The organic layer is dried over sodium sulfate, filtered and the removal of the solvent affords **1** (20.9 g; 58 %) as a colourless oil.

Formula: $C_{12}H_{27}NO_6P_2$.

Molecular weight: 343.13 $g.mol^{-1}$.

M.p: -36 °C.

B.p: 140 °C under 6.10^{-2} mmHg.

Rf: 0.39 (Acetone) ; 0.43 (CH_2Cl_2 / EtOH 19:1).

UV (EtOH, 25 °C): lmax (e) 205 (1622), 221 (1737), 264 (212) nm ($mol^{-1}.dm^3.cm^{-1}$).

pKa: 3.5 - Krebs at 20 °C: 3.59 - Krebs at 37 °C: 3.47. [3]

IR (Neat): 3481 (n_{NH}); 2982 (n_{CH2} ring + n_{CH3} As.); 2932 (n_{CH2} ethoxy); 2909; 2869 (n_{CH3} Sym.); 1670 (d_{NH}); 1595; 1478; 1457 (d_{CH2} ring + ethoxy); 1392 or 1368 (d_{CHsp3} Sym.); 1324; 1293; 1243 (P=O); 1164 (P-OEt); 1098 (n_{C-N}); 1044; 968; 794; 732; 645; 580; 536 cm^{-1}.

Raman: 2979 (n_{CH2} ring + n_{CH3} As.); 2934 (n_{CH2} ethoxy); 2874 (n_{CH3} Sym.); 2778; 2725; 1594 (d_{NH} in plane); 1482; 1458 and 1449 (d_{CH2} ring + ethoxy); 1394 or 1369 (d_{CHsp3} Sym.); 1289; 1240 (P=O); 1190; 1162 (P-OEt); 1100 (n_{C-N}); 1027; 918; 877; 812; 757; 653; 291; 271 cm^{-1}.

^{1}H-NMR: d in ppm referring to TMS (multiplicity, J in Hz) ; a, b, c, d and e as assigned in scheme.

Solvent	Frequency (MHz)	a	b	c	d	e
$CDCl_3$	400	2.92 (t, 6.4)	1.74 (quint., 6.4)	2.16 (m)	4.07 (m)	1.20 (t, 7.0) 1.20 (t, 6.8)
C_6D_6	400	2.88 (t, 6.5)	1.69 (quint., 6.5, 7.2)	2.42 (tt, 7.2[a], 17.7[b])	4.17 (m)	1.10 (t, 7.1) 1.11 (t, 7.1)
D_2O	500	2.98 (t, 6.4)	1.87 (quint., 6.4)	2.28 (tt, 7.2[a], 18.7[b])	4.21 (m)	1.34 (t, 7.1)
DMSO 55 °C = 328 K	500	2.92 (t, 6.9)	1.74 (quint., 7.2)	2.14 (tt, 7.2[a], 17.9[b])	4.08 (m)	1.23 (t, 7.2)
Acetone-d_6[c]	500	3.10 (t, 6.5)	1.91 (quint., 6.8)	2.33 (tt, 7.2[a], 17.7[b])	4.26 (m)	1.38 (t, 7.1)
$CDCl_3$[d]	500	0.87 s	0.79 s	0.58 s	1.78 s	1.85 s

[a] J_{H-H}
[b] J_{P-H}
[c] Additional: 3.28 (ls, NH)
[d] Value of T_1

^{13}C-NMR: d in ppm referring to TMS (multiplicity, J_{CP} in Hz) (multiplicity, $^{1}J_{CH}$ in Hz for $CDCl_3$ and Acetone-d_6) ; (1), (2), (3), (4), (5) and (6) as assigned in scheme.

Solvent	Frequency (MHz)	(1)	(2)	(3)	(4)	(5)	(6)
$CDCl_3$	125	47.4 (t, 4.7) (t, 139.4)[a]	26.1 (t, 3.7) (t, 133.8)[a]	30.5 (t, 3.6) (t, 135.4)[a]	61.7 (t, 152.3)	62.8 (t, 3.8) (tsext.[c], 148.3)[a] 63.3 (t, 3.6) (tsext.[c], 149.3)[a]	15.4[b] (qh, 127.1)[a] 15.5[b] (qh, 127.1)[a]
C_6D_6	100	47.7 (t, 4.0)	26.5 (t, 3.1)	31.2 (t, 3.0)	62.8 (t, 151.8)	62.7 (t, 5.8) 63.4 (t, 5.8)	16.5 (t, 7.2) 16.6 (t, 5.5)
D_2O	125	47.0 (m)	25.4 (t, 3.1)	30.0 (m)	62.0	64.7 (q, 3.8)	15.6 (t, 2.7)
DMSO 30 °C = 303 K	125	47.0	25.6	30.5	61.4 (t, 151.3)	62.3 (t, 3.6) 62.6[b]	16.3
DMSO 55 °C = 328 K	125	46.7 (t, 4.7)	25.3 (t, 3.7)	30.3 (t, 3.5)	61.6 (t, 151.7)	62.0 (t, 3.8) 62.3 (t, 3.4)	15.9 (t, 3.1) 16.0 (t, 2.3)
DMSO 70 °C = 343 K	125	46.9	25.6	30.6	62.1 (t, 151.5)	62.3 (t, 3.7) 62.5 (t, 3.5)	16.2
Acetone-d_6	125	48.0 (t, 4.5) (t, 138.9)[a]	26.7 (t, 3.6) (t, 133.2)[a]	31.5 (d, 3.7) (t, 133.8)[a]	62.9 (t, 151.8)	63.2 (t, 3.7) (t, 148.04)[a] 63.6 (d, 3.4) (t, 147.9)[a]	16.8 (t, 3.8) (q, 130.5)[a]

[a] Proton coupled (multiplicity, $^{1}J_{CH}$ in Hz)

[b] Unresolved triplet

[c] Triplet of sextuplet

Variable temperature in DMSO at 63 MHz [4]

Temp. °C	Temp. K	(1)	(2)	(3)	(4)	(5)	(6)
30	303	46.9 (t, 4.7)	25.6 (t, 3.5)	30.5 (t, 3.2)	61.4 (t, 151.7)	62.3 (t, 3.8) 62.6 (t, 3.6)	16.3 (t, 3.0)
50	323	46.9 (t, 4.8)	25.6 (t, 3.5)	30.5 (t, 3.2)	61.6[a]	62.3 (t, 3.8) 62.5 (t, 3.6)	16.2 (t, 2.9)
60	333	46.9 (t, 4.7)	25.6 (t, 3.6)	30.5 (t, 3.2)	61.8 (t, 151.0)	62.3 (t, 3.8) 62.5 (t, 3.6)	16.2 (t, 2.7)
70	343	46.9 (t, 4.8)	25.6 (t, 3.7)	30.5 (t, 3.2)	61.9[a]	62.3 (t, 3.8) 62.5 (t, 3.5)	16.2
90	363	46.9 (t, 4.8)	25.5 (t, 3.7)	30.5 (t, 3.2)		62.3 (t, 3.8) 62.5 (t, 3.7)	16.1 (t, 2.5)
110	383	46.9 (t, 4.8)	25.5 (t, 3.7)	30.6 (t, 3.1)		62.3 (t, 3.9) 62.5 (t, 3.7)	16.1

[a] Only the central line

^{31}P-NMR: d in ppm referring to external 85 % H_3PO_4
d ($CDCl_3$, 40 MHz): 22.5 ppm.
d ($CDCl_3$, 162 MHz): 24.7 ppm.
d (C_6D_6, 40 MHz): 22.8 ppm.
da (Krebs at 20 °C, 162 MHz): 16.51 ppm - db (Krebs at 20 °C, 162 MHz): 24.09 ppm. [3]
da (Krebs at 37 °C, 162 MHz): 16.53 ppm - db (Krebs at 37 °C, 162 MHz): 24.18 ppm. [3]
T_1 ($CDCl_3$, 202 MHz): 1.89 s.

^{31}P MAS NMR: d (10 KHz spinning at 200 K): 22.39 ppm. [5]

^{15}N-NMR: d in ppm referring to external CD_3NO_2: d ($CDCl_3$, 50 MHz): -341.6 (t, J_{NP} = 8.6) ppm.
d (C_6D_6, 50 MHz): -340.7 (t, J_{NP} = 8.7) ppm.

^{17}O-NMR: d in ppm referring to external H_2O: d (DMSO, 68 MHz): 95.4 (P=O) ppm.
d (Acetone d_6, 68 MHz): 84.6 (P=O) and 53.9 (P-O) ppm.

References and Notes

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Sample Availability: Available from the author and from MDPI.