Synthesis of substituted 1-thia-3-aza- $4\lambda^5$ -phosphacyclohex-2-ene

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The addition of dimethylamine to *O*-phenyl 2-chloropropylisothiocyanatophosphonate afforded the six-membered cyclic product, *viz.*, 1-thia-3-aza- $4\lambda^5$ -phosphacyclohex-2-ene.

Key words: chloroalkylphosphonates, functionalization, heterocyclization, thiaaza-phosphacyclohexene.

Earlier, we have found¹ that in the presence of bases, phosphorylated thioureas in which the phosphorus atom is bound to the chloromethyl group can undergo cyclization to give 1,3,4-thiaazaphospholines. With the aim of examining the possibility of the synthesis of large rings, in particular, six-membered rings, according to this procedure, we introduced the 2-chloroalkyl group instead of the chloromethyl fragment at the P atom. Taking into account the published data,² we prepared tris(2-chloropropyl) phosphite (1) by the reaction of phosphorus trichloride with propylene oxide. Compound 1 was isomerized to bis(2-chloropropyl) 2-chloropropylphosphonate (2) on prolonged heating (Scheme 1). Chlorination of the latter with PCl₅ afforded the target product, *viz.*, 2-chloropropylphosphonyl dichloride (3).

Scheme 1



The reaction of equimolar amounts of dichloride **3** and phenol produced monochlorophosphonate **4**, which was transformed into isothiocyanatophosphonate **5** on heating in the presence of KSCN over a long period of time (Scheme 2).

According to the ³¹P NMR spectroscopic data, products **4** and **5** containing two chiral centers exist as two diastereomers in an approximately equal amounts. Com-

Scheme 2



pound **5** was used without additional purification because it decomposes in the course of vacuum distillation.

After passing an excess of dimethylamine through a benzene solution of isothiocyanatophosphonate 5, cocrystals of cyclic product 7 and Me₂NH·HCl formed (Scheme 3). Cyclization occurs, apparently, through the intermediate formation of phosphorylated thiourea 6, which is rapidly transformed into the final product 7. Since the reaction was carried out in the presence of an excess of dimethylamine, we hypothesize that the most probable cyclization mechanism involves the initial formation of the complex between the base (dimethylamine) and thiourea, which is accompanied by weakening of the N-H bond, to give, presumably, the ion pair $6^{-} \cdot Me_2 NH_2^{+}$. The subsequent nucleophilic attack of the S atom of the thiourea fragment on the C_{β} atom of the chloropropyl group is accompanied by the simultaneous displacement of the Cl atom from the latter group to form a cyclic system. We have proposed³ an analogous reaction mechanism for the formation of five-membered heterocycles from the corresponding chloromethylphosphorylthioureas based on the results of calculations by the semiempirical MNDO and ab initio HF/6-31G* methods and the density functional theory (DFT/PBE/TZ2P).

Triple recrystallization of the precipitate from benzene afforded individual phosphacyclane 7 as one diastereomer (δ_P 15.74). In the ¹H NMR spectrum of com-

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pound 7, the signal of the Me group at the C atom appears as a doublet of doublets (δ 1.36, ${}^{3}J_{H,H} = 6.8$ Hz, ${}^{4}J_{H,P} =$ 2.7 Hz). The composition and structure of product 7 were confirmed also by the results of EI mass spectrometry and elemental analysis. In the mass spectrum of phosphacyclane 7, the peak at m/z 284 corresponds to the molecular ion [M]⁺⁺. The first step of fragmentation of molecule 7 under EI is associated with elimination of the Me group from the dimethylamino fragment resulting in the appearance of the ion peak $[M - Me]^+$ at m/z 269. Elimination of the dimethylamino group gives rise to the ion peak $[M - NMe_2]^+$ at m/z 240. The cleavage of the C–S and P-C bonds in the phosphorus-containing heterocycle gives rise to the $[M - C_3H_6]^+$ ion at m/z 242. The ion peak $[M - OPh]^+$ at m/z 191 is, apparently, attributable to the cleavage of the P-O bond with localization of the charge on the phosphorus-containing fragment. Subsequent fragmentation of this ion accompanied by the cleavage of the C-S and P-C bonds in the heterocycle affords the $[M - OPh - C_3H_6]^+$ ion at m/z 149, which is the most abundant ion in the mass spectrum of compound 7. The presence of other fragment ions at small



Fig. 1. Molecular geometry of compound 7 in the crystal and C-H...O hydrogen bonds (indicated by dashed lines).

m/z in the mass spectrum of compound 7 is, apparently, associated with successive fragmentation of the abovementioned ions under EI.

According to the results of X-ray diffraction study, molecule 7 adopts a chair conformation. The S(1)-C(2)-N(3)-P(4) fragment is planar (within 0.02(1) Å), and the C(5) and C(6) atoms deviate from this plane by 0.440(7) and -0.380(6) Å, respectively, *i.e.*, in opposite directions from the planar fragment (Fig. 1, Table 1). The chiral P(4) and C(6) atoms have an *R* configuration. The O atom of the phosphoryl group is in an equatorial position and the phenoxy group is in an axial position. The methyl group at the chiral C atom is in an equatorial position. The P=O and exocyclic P-O bond lengths (1.468(4) and 1.601(4) Å, respectively) have stan-

Table 1. Selected bond lengths (d) and bond angles (ω) in compound 7

Bond	$d/{ m \AA}$	Angle	ω/deg	Angle	ω/deg
S(1)–C(2)	1.772(7)	C(2) - S(1) - C(6)	104.7(3)	N(2) - C(2) - N(3)	120.4(6)
S(1)-C(6)	1.818(6)	O(4) - P(4) - O(5)	113.0(2)	P(4) - C(5) - C(6)	111.3(4)
P(4)-O(4)	1.468(4)	O(4) - P(4) - N(3)	114.6(2)	S(1) - C(6) - C(5)	111.5(4)
P(4)-O(5)	1.601(4)	O(4) - P(4) - C(5)	113.3(3)	C(10) - C(11) - C(12)	122.0(6)
P(4) - N(3)	1.619(4)	O(5) - P(4) - N(3)	102.0(2)	C(11) - C(12) - C(13)	118.9(6)
P(4) - C(5)	1.795(7)	O(5) - P(4) - C(5)	105.0(3)	C(12) - C(13) - C(14)	120.5(6)
O(5)-C(9)	1.410(6)	N(3) - P(4) - C(5)	107.9(3)	S(1) - C(6) - C(15)	106.7(4)
N(2) - C(2)	1.333(8)	P(4) - O(5) - C(9)	119.7(3)	C(5) - C(6) - C(15)	112.3(5)
N(2) - C(7)	1.440(9)	C(2) - N(2) - C(7)	119.1(5)	O(5) - C(9) - C(10)	116.2(5)
N(2) - C(8)	1.439(8)	C(2) - N(2) - C(8)	124.0(5)	O(5) - C(9) - C(14)	121.4(5)
N(3) - C(2)	1.292(7)	C(7) - N(2) - C(8)	116.8(5)	C(10) - C(9) - C(14)	122.4(6)
C(5) - C(6)	1.534(8)	P(4) - N(3) - C(2)	129.1(4)	C(9) - C(10) - C(11)	117.7(6)
C(6) - C(15)	1.493(9)	S(1) - C(2) - N(2)	113.5(4)	C(9) - C(14) - C(13)	118.5(6)
		S(1)-C(2)-N(3)	126.0(5)		

dard values. The N atom in the dimethylamino group adopts a planar-trigonal configuration (the sum of the bond angles is 360(1)°). Analysis of intermolecular interactions, which was carried out using the PLATON program,⁴ demonstrated that the molecular packing in the crystal is stabilized by weak C-H...O hydrogen bonds. The molecules are linked to each other through the bifurcate C(6)-H(6)...O(4)' (1 + x, y, z) (C(6)-H(6), 1.04 Å; H(6)...O(4)', 2.24 Å; C(6)...O(4)', 3.145(7) Å; C(6)-H(6)-O(4)', 145°) and C(10)-H(10)...O(4)'(1 + x, y, z) hydrogen bonds (C(10)-H(10), 0.99 Å; H(10)...O(4)', 2.38 Å; C(10)...O(4)', 3.362(7) Å; C(10)-H(10)-O(4)', 172°) to form infinite chains along the 0a axis. The molecules are also linked in infinite zigzag chains along the 0c axis through the intermolecular $C(12) - H(12) \dots O(4)'$ hydrogen bonds (-x, -1/2 + y, -z)(C(12)-H(12), 0.98 Å; H(12)...O(4)', 2.51 Å; C(12)...O(4)', 3.427(7) Å; C(12)-H(12)-O(4)', 154°). These two types of chains form together a two-dimensional network. It should be noted that compound 7 crystallizes in the chiral polar space group $P2_1$, and the molecule is chiral. We established its absolute configuration in the crystal. The crystals of compound 7 can be considered as a conglomerate, *i.e.*, crystallization leads to spontaneous resolution of enantiomers.

Therefore, cyclization of 2-chloropropylphosphonylsubstituted thiourea afforded a new representative of P,N,S-containing unsaturated six-membered heterocycles, *viz*., substituted 1-thia-3-aza- $4\lambda^5$ -phosphacyclohex-2-ene.

Experimental

The ¹H NMR spectrum was recorded on a Bruker WM-250 instrument (250 MHz) in a mixture of CDCl₃ and C_6D_6 (1 : 1). The ³¹P NMR spectra were measured on a CXP-90 instrument (36.47 MHz) with 85% H₃PO₄ as the external standard. The IR spectrum of heterocycle 7 was recorded on a UR-20 spectrometer in the frequency range of 400–3600 cm⁻¹ in Nujol mulls. The mass spectra (EI) were obtained on a TRACE MS Finnigan MAT instrument with direct inlet of the sample into the ion source; the energy of ionizing electrons was 70 eV; the temperature of the ion source was 200 °C. The evaporator tube was heated in programmed mode from 35 to 150 °C with a step of 35 °C min⁻¹. The mass-spectrometric data were processed using the Xcalibur program.

Phosphite **1** and phosphonate **2** were synthesized according to known procedures.^{2,5}

2-Chloropropylphosphonyl dichloride (3). Phosphorus pentachloride (49.5 g, 236 mmol) was added gradually with stirring to compound **2** (37 g, 118 mmol), which was heated to 140 °C, in the presence of catalytic amounts (0.3 g) of CuCl. The reaction mixture was kept at 140 °C for 3 h, volatile compounds were removed, and compound **3** was obtained by fractionation in a yield of 10 g (43%), b.p. 70–74 °C (0.06 Torr). Found (%): Cl, 54.12; P, 15.54. C₃H₆Cl₃OP. Calculated (%): Cl, 54.47; P, 15.86. 31 P NMR, δ : 44.22.

O-Phenyl 2-chloropropylchlorophosphonate (4). A mixture of dichloride **3** (7.7 g, 39.4 mmol) and phenol (3.7 g, 39.4 mmol) was heated at 160 °C for 18 h, and compound **4** was obtained by fractionation in a yield of 4 g (40%), b.p. 105–110 °C (0.06 Torr). Found (%): Cl, 28.04; P, 12.90. $C_9H_{11}Cl_2O_2P$. Calculated (%): Cl, 28.06; P, 12.25. ³¹P NMR (C_6H_6), δ : 32.07, 33.08.

2-Dimethylamino-6-methyl-4-oxo-4-phenoxy-1-thia-3-aza-4 λ^5 -**phosphacyclohex-2-ene (7).** A mixture of acid chloride **4** (2 g, 7.9 mmol) and KSCN (0.77 g, 7.9 mmol) in anhydrous MeCN (5 mL) was heated at 80 °C for 10 h. Potassium chloride was separated from a solution of product **5** (δ_P 8.03, 9.86) in a yield of 0.58 g (100%). Then MeCN was removed, the residue was dissolved in anhydrous benzene (5 mL), and an excess of Me₂NH was passed through the solution. After 24 h, product **7** was filtered off, recrystallized three times from benzene, and dried *in vacuo*. The yield was 1.2 g (53%), m.p. 200–202 °C. Found (%): C, 51.15; H, 6.00; N, 10.13; P, 10.86; S, 10.86. C₁₂H₁₇N₂O₂PS. Calculated (%): C, 50.70; H, 5.98; N, 9.85; P, 10.91; S, 11.26. IR, v/cm⁻¹: 1580 (C=N), 1250 (P=O). ¹H NMR, δ : 1.36 (dd, MeC, ³J_{H,H} = 6.8 Hz, ⁴J_{H,P} = 2.7 Hz); 1.71 and 2.28 (both m, H_A, H_B, CH₂); 3.07 (br.s, MeN); 3.60 (m, CHS); 7.00–7.30 (m, Ph). ³¹P NMR (DMSO-d₆), δ : 15.03.

X-ray diffraction study of compound 7. Pale-yellow crystals of compound 7 (from DMF) ($C_{12}H_{17}N_2O_2PS$, M = 284.31) are monoclinic, space group $P2_1$, a = 6.1513(8) Å, b = 7.749(2) Å, c = 14.470(2) Å, $\beta = 97.99(1)^{\circ}$, V = 683.1(2) Å³, Z = 2, $d_{calc} =$ 1.382 g cm⁻³, F(000) = 284. The intensities of 2423 reflections were measured on an Enraf Nonius CAD-4 diffractometer at 20 °C (λ (Mo-K α), ω /2 θ scanning technique, $2\theta_{max} \le 27.8^{\circ}$), of which 1385 reflections were with $I > 3\sigma$. The intensities of three check reflections showed no decrease in the course of X-ray data collection. Because of a low value of the coefficient ($\mu(Mo)$ = 3.29 cm^{-1}), absorption was ignored. The structure was solved by direct methods using the SIR program⁶ and refined first isotropically and then anisotropically. All H atoms were revealed from difference electron density syntheses. Their contributions to the structure factors were taken into account in the final step of the refinement with fixed positional and thermal parameters. With the aim of establishing the absolute structure and, consequently, the absolute configuration of the molecule, the direct and inverted structures were refined taking into account anomalous scattering by all nonhydrogen atoms. The reliability factors were as follows: R = 0.04488, $R_w = 0.04981$ for the direct structure, and R = 0.04496, $R_w = 0.04992$ for the inverted structure based on 1303 independent reflections for 162 refinement parameters. All calculations were carried out using the MOLEN complex program⁷ on an AlphaStation 200 computer. According to the Hamilton test,⁸ the direct structure corresponds to the absolute structure with the probability of 95%. The final reliability factors were R = 0.045, $R_w = 0.050$ based on 1303 independent reflections with $F^2 \ge 3\sigma$. The complete tables of the atomic coordinates, bond lengths, and bond angles were deposited with the Cambridge Structural Database.

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