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Synthesis and stereochemical features of 2-oxo-3-cyano-1,2-thiaphosphorinanes

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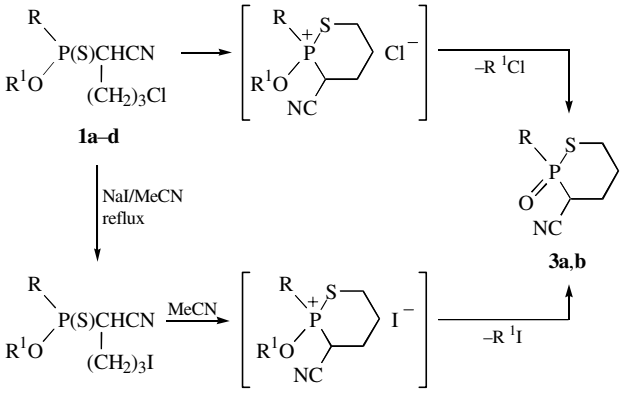
The intramolecular Pishchimuka rearrangement of 3-halopropyl-substituted thiophosphorylacetonitriles results in the corresponding 2-oxo-3-cyano-1,2-thiaphosphorinanes as a statistical mixture of two diastereomers, which transforms to an individual diastereomer with time; in benzene solution, the latter turns again into an equilibrium mixture of diastereomers.

It is well known that 3- and 4-chloro-substituted *O*,*O*-diethyl-thiophosphonates on heating with sodium iodide in acetone form corresponding iodo derivatives, which undergo the intramolecular Pishchimuka rearrangement to yield 2-*O*-ethyl-2-oxo-1,2-thiaphosphacyclanes (so-called thiolphostones).[1,2]

We prepared 3-chloropropyl-substituted thiophosphorylacetonitriles **1** by alkylation of thiophosphorylacetonitriles with 1,3-bromochloropropane under phase-transfer catalysis conditions.[3] Unlike non-functionalised *O*,*O*-diethyl- -chloroalkylthiophosphonates, these compounds are rather reactive. They partially undergo the intramolecular Pishchimuka rearrangement to corresponding 2-oxo-3-cyano-1,2-thiaphosphorinanes **3** under vacuum distillation (Scheme 1). Apparently, the formation of compounds **3** proceeds *via* corresponding phosphonium salts similarly to the previously suggested intramolecular S-alkylation in the series of non-functionalised -haloalkyl-substituted thiophosphoryl compounds.[2] The fact that for the 3-chloropropyl-substituted thiophosphorylacetonitriles with a diphenylthiophosphoryl group we detected (by NMR spectroscopy) the formation of the corresponding phosphonium salt (δ_P 39.4 ppm) in a MeCN solution at room temperature supports this assumption.



Scheme 1 The synthesis of 2-oxo-3-cyano-1,2-thiaphosphorinanes.

Using different 3-chloropropyl-substituted methyl(alkoxy)-thiophosphorylacetonitriles **1b–d** as an example, we found that the yield of thiophosphorinane **3b** obtained by distillation depends on the radical R^1 in the alkoxy group at the phosphorus atom. As should be expected, this yield decreased with increasing volume of the radical and especially when going to the compounds in which R^1 is a secondary alkyl (the yield was about 50% at R^1 = Et, about 32% at R^1 = Bu^i and as low as 7% at R^1 = Pr^i). Although thiaphosphorinanes **3a**,**b** are sparingly soluble in usual organic solvents and can be recovered from distillates by precipitation, nevertheless it is much more suitable to prepare compounds **3** through corresponding iodo derivatives **2** (Scheme 1). On heating a MeCN solution of **1** with NaI, the cyclization was completed in 6–8 h.† The formation of **2** during the reaction and the structure of the compound were confirmed by NMR spectroscopy (^{31}P and ^{1}H). Note that in a MeCN solution the cyclization of iodopropyl-substituted thiophosphorylacetonitriles **2** proceeds slowly even at room temperature (the yield of **3** was 60–65% after 6 months).

This cyclization is not stereoselective, and compounds **3** are formed as a statistical mixture of two diastereomers **A** and **B**,‡ which exhibit two closely located signals in the ^{31}P NMR spectra. 1,2-Thiaphosphorinanes **3a**,**b** were precipitated as solids with the same ratio between diastereomers on addition of diethyl ether to distillates (Hal = Cl) or to reaction mixtures (Hal = I). At the same time, in the absence of the solvent in distillates or in concentrated reaction mixtures, the slow transformation of equilibrium mixtures to the preferable individual diastereomers was observed. The relative configuration of chiral atoms in the diastereomers was determined by X-ray diffraction. For 2-ethoxy-substituted 1,2-thiaphosphorinane **3a**, the configuration of asymmetric centres was found to be identical, while it was opposite for compound **3b** with a methyl group at the phosphorus atom. A comparison of ^{31}P NMR and X-ray diffraction data allows us to conclude that diastereomer

† *General procedure for the synthesis of* **3a**,**b**. Compounds **1** (obtained according to ref. 3) were heated with a 10% molar excess of NaI in a MeCN solution. After 1.5 h, the NaCl precipitate was filtered off, and heating was continued for 5–6 h. The mixture was evaporated, $CHCl_3$ was added to the residue, and the mixture was filtered once again. The filtrate was evaporated under reduced pressure, the residue was either crystallised from Et_2O (diastereomer mixture) or allowed to stand for spontaneous crystallization (individual diastereomer) followed by washing with benzene. The yield of **3a**,**b** separated was about 73–78%. Compounds **3a**,**b** had the satisfactory elemental analysis regardless of the isolation procedure.

Selected data for **3a**. = 160–190 (1 mmHg), mp 65–70 °C (Et_2O, **A**:**B** = 1:1). Diastereomer **A**: ^{1}H NMR ($CDCl_3$) δ: 1.05 (t, 3H, *Me*CH_2OP, $^3J_{HH}$ 7.0 Hz), 1.75–1.95 and 2.12–2.23 (2m, 1H + 1H, SCH_2CH_2), 2.24–2.33 and 2.43–2.60 [2m, 1H + 1H, C(CN)CH_2], 2.92–3.06 (m, 2H, SCH_2), 3.02 (ddd, CHCN, $^3J_{HH}$ 4.0 Hz, $^3J_{HH}$ 10.4 Hz, $^2J_{PH}$ 19.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 15.7 (Me, $^3J_{PC}$ 7.0 Hz), 23.1 [C(5), $^3J_{PC}$ 6.1 Hz], 29.1 [C(6), $^2J_{PC}$ 5.8 Hz], 30.2 [C(4), $^2J_{PC}$ 3.6 Hz], 31.7 [C(3), $^1J_{PC}$ 100.8 Hz], 62.4 (OCH_2, $^2J_{PC}$ 6.7 Hz), 115.2 (CN, $^3J_{PC}$ 4.5 Hz). ^{31}P NMR, δ: 36.6 ($CDCl_3$), 34.9 (C_6D_6). Diastereomer **B**: mp 116–118 °C. ^{1}H NMR ($CDCl_3$) δ: 1.13 (t, 3H, *Me*CH_2OP, $^3J_{HH}$ 7.0 Hz), 1.86–1.90 and 2.15–2.20 (2m, 1H + 1H, SCH_2CH_2), 2.26–2.32 and 2.50–2.54 [2m, 1H + 1H, C(CN)CH_2], 2.92–3.06 (m, 2H, SCH_2), 3.16 (ddd, CHCN, $^3J_{HH}$ 3.8 Hz, $^3J_{HH}$ 10.0 Hz, $^2J_{PH}$ 18.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 15.9 (Me, $^3J_{PC}$ 6.2 Hz), 25.6 [C(5), $^3J_{PC}$ 4.5 Hz], 29.7 [C(6), $^2J_{PC}$ 5.8 Hz], 30.2 [C(4), $^2J_{PC}$ 3.6 Hz], 32.2 [C(3), $^1J_{PC}$ 96.8 Hz], 62.8 (OCH_2, $^2J_{PC}$ 7.1 Hz), 114.9 (CN, $^3J_{PC}$ 11.2 Hz). ^{31}P NMR, δ: 36.2 ($CDCl_3$), 34.0 (C_6D_6).

For **3b**: = 170–190 °C (1 mmHg). Diastereomer **A**: mp 136–137 °C; ^{1}H NMR ($CDCl_3$) δ: 1.98 (d, 3H, MeP, $^2J_{PH}$ 13.4 Hz), 2.12–2.19 (m, 2H, SCH_2CH_2), 2.25–2.39 and 2.52–2.56 [2m, 1H + 1H, C(CN)CH_2], 2.87–2.92 and 3.36–3.28 (2m, 1H + 1H, SCH_2), 3.25 (dt, CHCN, $^3J_{HH}$ 3.88 Hz, $^2J_{PH}$ 16.66 Hz). ^{31}P NMR, δ: 42.5 ($CDCl_3$), 39.4 (C_6D_6). Diastereomer **B**: ^{31}P NMR, δ: 40.01 ($CDCl_3$), 37.4 (C_6D_6).

‡ The diastereomer having a downfield signal in the ^{31}P NMR spectra was designated as diastereomer **A**.

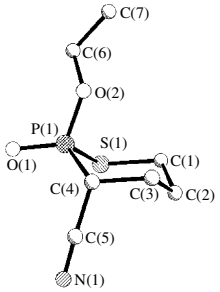


Figure 1 The general view of diastereomer **B** (2*R**,3*R**) of **3a**. Selected bond lengths (Å): P(1)–O(1) 1.456(3), P(1)–O(2) 1.573(3), P(1)–C(4) 1.817(4), P(1)–S(1) 2.044(2), S(1)–C(1) 1.807(6); selected bond angles (°): O(1)–P(1)–O(2), 116.7(2), O(1)–P (1)–C(4) 117.0(2), O(2)–P(1)–C(4) 98.2(2), O(1)–P(1)–S(1) 109.4(2), O(2)–P(1) –S(1) 109.0(1), C(4)–P(1)–S(1) 105.5(1), C(1)–S(1)–P(1) 99.2(2), C(6)–O(2)–P(1) 119.0(3), C(2)–C(1)–S(1) 114.3(3), C(5)–C(4)–P(1) 109.5(3), C(3)–C (4)–P(1) 113.2(3).

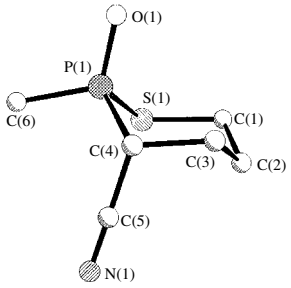


Figure 2 The general view of diastereomer **A** (2*S**,3*R**) of **3b**. Selected bond lengths (Å): P(1)–O(1) 1.488(2), P(1)–C(6) 1.785(3), P(1)–C(4) 1.838(4), P(1)–S(1) 2.062(2), S(1)–C(1) 1.835(3); selected bond angles (°): O(1)–P(1)–C(6) 114.6(1), O(1)–P(1)–C(4) 108.3(1), C(6)–P(1)–C(4) 109.1(2), O(1)–P(1) –S(1) 116.4(1), C(6)–P(1)–S(1) 103.8(1), C(4)–P(1)–S(1) 103.9(1), C(1)–S(1)–P(1) 97.9(2), C(2)–C(1)–S(1) 113.7(3), C(5)–C(4)–P(1) 112.1(2), C(3)–C(4)–P(1) 108.7(3).

A is characterised by the configuration (2*S**,3*R**) with the fully staggered disposition of the cyano group and the oxygen atom of the P=O group, while the identical configuration of asymmetric centres, *i.e.* (2*R**,3*R**), with the skew arrangement of the above groups corresponds to isomer **B**. Note that in spite of different surroundings at the phosphorus atom (phosphonate and phosphinate structures in **3a** and **3b**, respectively) the signals in the ^{31}P NMR spectra of these compounds are close to one another and upfield shifted with respect to the signals of linear compounds with similar surroundings at the phosphorus. Thus the chemical shift primarily depend on the presence of a 1,2-thiaphosphorinane ring in the molecule.

According to X-ray diffraction data,§ bond lengths and angles in both molecules (Figures 1 and 2) exhibit expected values.[4,5] The phosphorus atoms are characterised by a slightly distorted tetrahedral configuration with the endocyclic angles 105.1(1)° and 103.9(1)° in the structures of **3a**(**B**) and **3b**(**A**), respectively. In both molecules, six-membered rings exhibit a slightly distorted chair conformation.

In both structures, the CN group occupies an axial position, while the positions of oxygen atoms of the phosphoryl group are different. In 1,2-thiaphosphorinane **3a**(**B**) (R = OEt), it occupies an equatorial position with the torsion angle O(1)–P(1) – C(4)–C (5) equal to 48.9°, while it is in an axial position in **3b**(**A**) (R = Me) and is fully staggered to the CN group with the torsion angle equal to 170.6°. Evidently, the strength of the possible stereoelectronic *n*– * interaction between the lone electron pair of sulfur and the antibonded orbital of the axial group at the phosphorus atom [P(1)–O(2) in **3a**(**B**) and P(1)=O(1) in **3b**(**A**)] is different in these two cases.[6] This *n*– * interaction will result in shortening the P(1)–S(1) bond. Taking into account that the P(1)–S (1) bond in **3a**(**B**) is significantly shorter [2.044(2) Å tha n that in **3b**(**A**) [2.062(2) Å], we can conclude that the above interaction is more pronounced in the case of the P(1)–O(2) antibonded orbital in diastereomer **B** of 1,2-thiaphosphorinane **3a**. The appreciable shortening of the P(1)=O(1) bond length up to 1.456(2) Å in the above structure in comparison with **3b**(**A**) [1.488(2) Å] is not only due to the difference in the *n*– * interaction, but also due to the alteration of the coordination sphere of the phosphorus atom (replacement of OEt with Me).[7]

Note that P–S bond lengths in cyano-substituted 1,2-thiaphosphorinanes **3** are similar to those [2.048(2)–2 .068(2) Å in the series of 2,2-diphenyl-1,2 ^{4}-thiaphospholanium and 2,2-diphenyl-1,2 ^{4}-thiaphosphorinanium salts.[2] Furthermore, the S(1)–C(1) bond in the crystal structure of **3b**(**A**) is significantly elongated up to 1.835(1) Å as compared with that in **3a**(**B**) [1.807(5) Å] and also is very similar to the corresponding bond in the above thiaphosphorinanium salts [1.837(5) Å]. The P(1)–C(4) bonds in 1,2-thiaphosphorinanes **3a**,**b** are significantly longer [1.817(4) Å]. Thus, the phosphorus atom in the crystal structures of **3a**,**b** possesses a significant positive charge which is larger in **3b**(**A**), where the *n*– * interaction is less pronounced.

In both of the crystal structures of **3**, molecules are assembled by the C(4)–H(4)···O(1)=P(1) H-bonds in two centrosymmetric dimers, which in turn are interlinked by the C–H ···O=P bonds in double H-bonded layers (Figures 3 and 4). Note that, from the geometrical point of view (C···O and H···O distances), the C–H ···O=P H-bonds in **3b**(2*S**,3*R**) molecules are significantly stronger than those in the crystal structure of **3a**(2*R**,3*R**). This

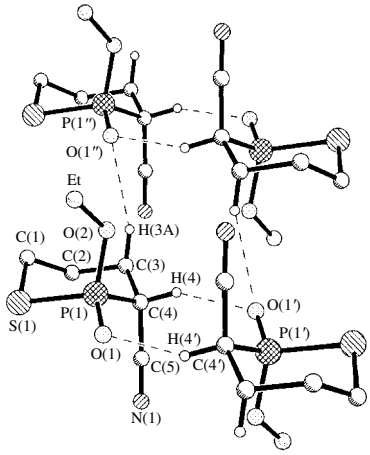


Figure 3 The doubly bonded layers in the crystal structure of **3a**(**B**). The shortened contacts are: C(4)–H(4)···O(1′) (–*x*, 1 – *y*, –*z*) [H(4)···O(1′) 2.31 Å C(4)···O(1′) 3.266(4) Å, C(4)–H(4)···O(1′) 147°]; C(3)–H(3A)···O(1″) (*x*, –1 + *y*, *z*) [H(3A)···O(1″) 2.36 Å C(3)···O(1″) 3.345(4) Å, C(3)–H(3A)···O(1″) 153°].

§ *Crystallographic data for* **3a** *and* **3b** at –8 0 °C: crystals of $C_7H_{12}N_2PS$ **3a** are monoclinic, space group C_2/c, a = 21.034(9) Å, b = 6.076(4) Å, c = 18.015(9) Å β = 118.16(2)°, V = 2030(2) Å^3, Z = 8, M = 205.21, d_{calc} = 1.343 g cm^{-3}, μ(MoK) = 4.39 cm^{-1}, F(000) = 864; crystals of $C_6H_{10}NOPS$ **3b** are triclinic, space group $P\bar{1}$, a = 6.978(7) Å, b = = 7.132(3) Å c = 9.813(6) Å, V = 414.7(5) Å^3, α = 101.72(4)°, β = = 101.79(6)°, γ = 113.77(5)°, Z = 2, M = 175.17, d_{calc} = 1.403 g cm^{-3}, μ(MoK) = 5.16 cm^{-1}, F(000) = 184. Intensities of 3049 reflections for **3a** and 1445 reflections for **3b** were measured with a Syntex $P2_1$ diffractometer at –8 0 °C (λ MoK radiation, $\theta/2\theta$ scan technique, $2\theta_{max} < 60°$ for **3a** and 50° for **3b**) and 2977 for **3a** and 980 for **3b** independent reflections were used in further calculations and refinement. The structures were solved by a direct method and refined by a full-matrix least-squares against F^2 in the anisotropic-isotropic approximation. Hydrogen atoms were located from the difference Fourier synthesis and refined in the isotropic approximation. The refinement converged to wR_2 = 0.2615 and COF = 0.869 for all independent reflections [R_1 = = 0.0736 for 1102 observed reflections with $I > 2\sigma(I)$] for structure **3a** and to wR_2 = 0.1629 and COF = 1.059 for all independent reflections [R_1 = 0.0437 for 880 observed reflections with $I > 2\sigma(I)$] for structure **3b**. All calculations were performed using the SHELXTL PLUS 5.0 program on an IBM PC/AT. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, 1999, Issue 1. Any request to the CCDC should quote the full literature citation and the reference number 1135/51.

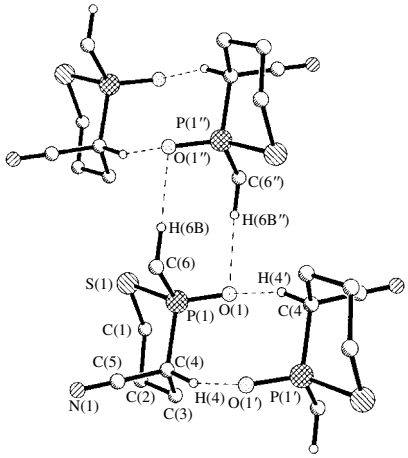


Figure 4 The doubly bonded layers in the crystal structure of **3b**(**A**). The shortened contacts are: C(4)–H(4)···O(1′) (–*x*, 1 – *y*, 1 – *z*) [H(4)···O(1′) 2.22 Å C(4)···O(1′) 3.246(4) Å C(4)–H(4)···O(1′) 161°]; C(6)–H(6B)···O(1″) (1 – *x*, 1 – *y*, 1 – *z*) [H(6B)···O(1″) 2.42 Å C(3)···O(1″) 3.469(4) Å C(3)–H(3A)···O(1″) 167°].

can be due to additional accumulation of the negative charge at the phosphoryl oxygen atom O(1). These O···H contacts, according to Desiraju,[8] can be considered as medium-strength contacts, which play an important role in the crystal packing. It is likely that the formation of these contacts in the crystals of preferential individual diastereomers of 1,2-thiaphosphorinanes **3a**,**b** resulted in the crystallization from concentrated reaction mixtures. At the same time, an equilibrium mixture of both diastereomers is formed in solutions where these contacts are impossible.

In benzene solutions, slow reverse transformation of individual diastereomers **3a**(**B**) and **3b**(**A**) to the corresponding equilibrium mixtures, where the ratio **A**:**B** = 1:1 was achieved in about 3 months, was observed. Evidently, mutual transformations of the diastereomers proceed through opening of the six-membered ring (at either a P–S or S–C bond), inversion of the configuration of one of the asymmetric centres and subsequent recyclization.

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