Diastereoselective cycloalkylation of diphenylphosphorylacetonitrile by α,ψ-dibromoalkanes

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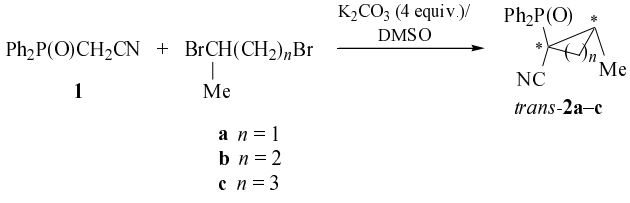
Cycloalkylation of $Ph_2P(O)CH_2CN$ **1** by α,ψ-dibromoalkanes under phase-transfer catalysis conditions (K_2CO_3/DMSO) proceeds diastereoselectively yielding (1*RS*,2*RS*)-1-(diphenylphosphoryl)-2-methylcycloalkane carbonitriles **2**.

Phosphorus-substituted CH acids, in particular, phosphorylacetonitriles having equilibrium p*K* values of 16–17.3 in DMSO,[1] are known to easily undergo alkylation reactions under phase-transfer catalysis (PTC) conditions,[2–5] which proceed at the central carbon atom. Different procedures of phosphorylacetonitrile cycloalkylation by linear α,β-dihaloalkanes were described with systems such as K_2CO_3/DMSO at 20 °C;[6,7] NaH/THF–DMSO (80:20 v/v) at 20 °C (an exothermic interaction)[8] and K_2CO_3/MeCN at 80 °C.[8] The systems based on potassium carbonate were found to be more effective.

Previously,[9,10] we found that (1-diphenylphosphoryl)cycloalkane carbonitriles are appropriate precursors of a novel type of phosphine ligands for metallocomplex catalysis having two possible coordination sites — the phosphorus atom and the cyano group nitrogen along with a rather rigid stereochemical structure. It was of interest to obtain similar *gem*-disubstituted cycloalkanes having an additional, *e.g.*, alkyl, substituent in the ring and two chiral carbon atoms in the molecule. To obtain the desired compounds, we used α,ψ-dibromoalkanes as electrophilic agents in the above cyclization. In this case one could expect the formation of reaction products as a statistical mixture of *cis* and *trans* isomers. However, surprisingly this reaction turned out to proceed stereoselectively when diphenylphosphorylacetonitrile **1** was used as the starting organophosphorus substrate, yielding mainly a single isomer of cycloalkane **2**.†



1

trans-**2a–c**

a $n = 1$
b $n = 2$
c $n = 3$

The cycloalkylation reactions were carried out under PTC conditions using the heterophase system K_2CO_3/DMSO at 20 °C as described previously.[6,7] We used dry DMSO (containing less than 0.1% H_2O, Fluka) and DMSO of technical grade con-

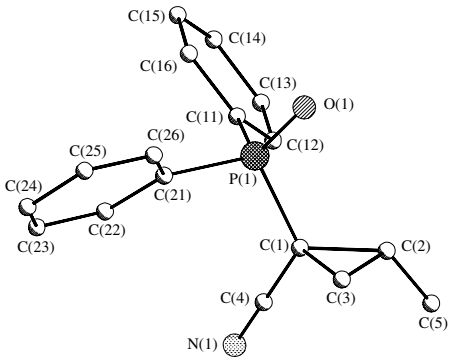


Figure 1 General view of **2a**. Selected bond lengths (Å): P(1)–O(1) 1.490(2), P(1)–C(21) 1.797(2), P(1)–C(11) 1.802(2), P(1)–C(1) 1.819(2), C(1)–C(4) 1.433(3), N(1)–C(4) 1.143(3); selected bond angles (°): O(1)–P(1)–C(21) 113.2(1), O(1)–P(1)–C(11) 113.8(1), C(21)–P(1)–C(11) 107.0(1), O(1)–P(1)–C(1) 109.1(1), C(21)–P(1)–C(1) 105.6(1), C(11)–P(1)–C(1) 107.7(1).

† NMR spectra were recorded on Bruker WP-200SY, DPX-200 and AMX-400 spectrometers in $CDCl_3$ solutions using residual proton signals of the deuterated solvent as an internal standard (^1H, ^{13}C) and 85% H_3PO_4 (^{31}P) as an external standard. IR spectra were recorded in KBr pellets on a Magna-IR750 (Nicolet) Fourier spectrometer; resolution, 2 cm^{-1}; 128 scans.

*Synthesis of (1*RS,2RS*)-1-(diphenylphosphoryl)-2-methylcycloalkane carbonitriles* **2a–c**: A mixture of diphenylphosphorylacetonitrile **1** (1 equiv., 1 g, 4.15 mmol), K_2CO_3 (4 equiv., 2.30 g, 16.60 mmol) and 2 equiv. of a corresponding α,ψ-dibromoalkane (8.3 mmol) in DMSO (40 ml) was stirred at ambient temperature for 8–16 days (dry DMSO, Fluka, 0.1% H_2O) or 20–70 h (technical grade DMSO, ~5% H_2O). Then, the mixture was diluted with water (50 ml) and extracted with CH_2Cl_2 (3×50 ml). In the case of **2a**, wherein a sufficient amount of initial phosphorylacetonitrile **1** remains in the reaction mixture, it was preferable to extract the reaction mixture with Et_2O followed by the extraction with CH_2Cl_2, as this allowed us to separate the product (Et_2O layer) from the remaining starting compound extracted by CH_2Cl_2. The combined organic layers were washed with water (2×30 ml), dried over $MgSO_4$ and evaporated to dryness. The residue was purified by crystallization (petroleum ether–CH_2Cl_2, 9:1). All compounds after purification gave satisfactory elemental analyses.

Selected data for **2a**: yield 53% (according to ^{31}P NMR), 37% after isolation; mp 101–103 °C. ^{31}P-{^1H} NMR ($CDCl_3$) δ: 28.81. ^1H NMR ($CDCl_3$) δ: 1.26–1.34 (m, 1H, CH_2, *trans* to P=O bond), 1.41 (d, 3H, Me, $^3J_{HH}$ 6.1 Hz), 1.89–1.96 (m, 1H, CH_2, *cis* to P=O bond), 2.07–2.18 (m, 1H, CH), 7.48–7.56 (m, 4H, *o*-C_6H_5P), 7.58–7.60 (m, 2H, *p*-C_6H_5P), 7.76–7.84 (m, H, 4H, *m*-C_6H_5P). ^{13}C NMR ($CDCl_3$) δ: 13.74 (d, P–*C*–CN, $^1J_{PC}$ 99.2 Hz), 14.92 (Me), 20.12 (CH_2), 20.88 (CH), 118.84 (d, CN, $^2J_{PC}$ 9.9 Hz), 128.65 and 128.80 (2d, *o*-C_6H_5P, $^2J_{PC}$ 7.4 Hz), 130.03 (d, C–P in C_6H_5P, $^1J_{PC}$ 107.9 Hz), 130.16 (d, C–P in C_6H_5P, $^1J_{PC}$ 107.9 Hz), 131.44 and 131.59 (2d, *m*-C_6H_5P, $^3J_{PC}$ 9.9 and 11.1 Hz), 132.74 (d, *p*-C_6H_5P, $^4J_{PC}$ 3.7 Hz). IR (KBr, ν/cm^{-1}): 1211 (P=O), 2226 (CN).

Selected data for **2b**: yield 80% (according to ^{31}P NMR), 62% after isolation, mp 92–94 °C. ^{31}P-{^1H} NMR ($CDCl_3$) δ: 28.14. ^1H NMR ($CDCl_3$) δ: 0.88 (d, 3H, Me, $^3J_{HH}$ 6.9 Hz), 1.91–2.03 (m, 1H, CH_2), 2.19–2.29 (m, 2H, CH_2), 2.86–2.98 (m, 1H, C–CH_2), 3.17–3.29 (m, 1H, CH), 7.45–7.49 (m, 4H, *o*-C_6H_5P), 7.50–7.53 (m, 2H, *p*-C_6H_5P), 7.75–7.92 (m, 4H, *m*-C_6H_5P). ^{13}C NMR ($CDCl_3$) δ: 18.22 (Me), 24.71 (d, C–CH_2, $^2J_{PC}$ 2.5 Hz), 26.98 (d, C–CH_2CH_2, $^3J_{PC}$ 12.9 Hz), 33.35 (d, C–*C*HMe, $^2J_{PC}$ 2.5 Hz), 41.03 (d, P–*C*–CN, $^1J_{PC}$ 70.7 Hz), 120.05 (d, CN, $^2J_{PC}$ 5.0 Hz), 128.40 (d, C–P in C_6H_5P, $^1J_{PC}$ 100.5 Hz), 128.58 and 128.76 (2d, *o*-C_6H_5P, $^2J_{PC}$ 12.4 Hz), 129.35 (d, C–P in C_6H_5P, $^1J_{PC}$ 102.3 Hz), 131.38 and 131.92 (2d, *m*-C_6H_5P, $^3J_{PC}$ 8.7 Hz), 132.67 and 132.72 (2d, *p*-C_6H_5P, $^4J_{PC}$ 2.5 Hz). IR (KBr, ν/cm^{-1}): 1199 (P=O), 2226 (CN).

Selected data for **2c**: yield 87% (according to ^{31}P NMR), 50% after isolation, mp 123–124 °C. ^{31}P-{^1H} NMR ($CDCl_3$) δ: 28.05. ^1H NMR ($CDCl_3$) δ: 0.80 (d, 3H, Me, $^3J_{HH}$ 6.9 Hz), 1.39–1.57 (m, 1H, CH_2), 1.75–1.88 (m, 2H, CH_2), 1.95–2.21 (m, 2H, CH_2), 2.43–2.69 (m, 1H, CH_2), 2.73–2.91 (m, 1H, CH), 7.48–7.61 (m, 6H, *o*-, *p*-C_6H_5P), 8.06–8.16 (m, 4H, *m*-C_6H_5P). ^{13}C NMR ($CDCl_3$) δ: 17.43 (Me), 23.90 (d, P–C–$CH_2CH_2CH_2$, $^3J_{PC}$ 5.3 Hz), 35.13 (d, P–C–CH_2CH_2, $^3J_{PC}$ 6.8 Hz), 35.84 (P–C–CH_2), 38.89 (CH), 46.10 (d, P–*C*–CN, $^1J_{PC}$ 70.1 Hz), 121.00 (d, CN, $^2J_{PC}$ 2.3 Hz), 128.50 and 128.72 (2d, *o*-C_6H_5P, $^2J_{PC}$ 13.4 Hz), 130.16 (d, P–C in C_6H_5P, $^1J_{PC}$ 60.3 Hz), 131.51 and 132.03 (2d, *m*-C_6H_5P, $^3J_{PC}$ 8.3 Hz), 132.46 and 132.49 (2d, *p*-C_6H_5P, $^4J_{PC}$ 4.0 Hz). IR (KBr, ν/cm^{-1}): 1196, 1212 (P=O), 2226 (CN).

taining ~5% H_2O. The amount of water in the organic phase used in the PTC reactions is known to influence the reaction rate (participation of a so-called 'omega-phase').[11] In the above case, a change in water amount had a profound effect on the reaction rate (^{31}P NMR monitoring of reaction).‡

In the presence of ~5% H_2O, reactions proceeded for 20–80 h (**2a**, 80 h; **2b**, 35 h; **2c**, 20 h) and in dry DMSO it required 8–16 days (**2a**, 16 days; **2b**, 13 days, **2c**, 8 days). Note that under other conditions being equal the reaction rate and the yield of the resulting product increased with increasing length of the alkylene chain in dihaloalkane. However, the amount of water in the solvent did almost not influence the stereochemical result of the reaction.

Note that in reaction mixtures the formation of the second minor product was revealed (monitoring by ^{31}P NMR spectroscopy) in a somewhat higher concentration in dry DMSO (5–12% in dry DMSO and 2–6% in wet DMSO). Since the respective signal is downfield shifted one may assign it either to the second geometric isomer or to the product of double C,C-alkylation. However, after typical water work-up, we isolated only one isomer in all the cases.

In the ^{31}P-{^{1}H} NMR spectra of **2a–c**, singlet signals were observed at 28.05–28.81 ppm. In the ^{1}H NMR spectra, the signal of a methyl group appeared as a doublet with chemical shifts of 1.41, 0.88 and 0.80 ppm for **2a**, **2b** and **2c**, respectively. Here, the spin–spin interaction was observed only with a geminal proton, and there was no spin–spin coupling at phosphorus. According to the single-crystal X-ray diffraction analysis of substituted cyclopropane **2a** and cyclobutane **2b**,§ the products obtained are the *trans*-isomers (racemic mixture, identical configuration of chiral centres $R^*_CR^*_C$). Similar chemical shifts for compounds **2a–c** in ^{31}P-{^{1}H} NMR spectra, the similarity in the shift values for the methyl group in **2b**,**c** and in the multiplicity of the latter for all cycloalkanes **2a–c** obtained in ^{1}H and ^{13}C NMR spectra allowed us to assert that corresponding substituted cyclopentane **2c** also presents the *trans*-isomer. Note that the difference in the signal positions in the ^{1}H and ^{13}C NMR spectra of **2a** in comparison with those of **2b**,**c**, namely, their upfield shifting, is typical of such a type of compounds, and it may be explained by the presence of a strained cyclopropane ring.[6,7]

Thus, according to the X-ray data, in compounds **2a** and **2b**, the Ph_2P=O group is disposed in the *trans* position with respect to the methyl substituent in the ring with the torsion angles P(1)C(1)C(2)C(5) equal to –144.5 and 105.4°, respectively (Figures 1 and 2). The cyano group in **2a** and **2b** is antiperiplanarly situated with respect to the P=O bond with the torsion angle O(1)P(1)C(1)C(4) of 176°. The main geometric parameters are close to the expected values. The P(1)–C(1) bond is the only one exception, which apparently is shortened up to 1.819(2) Å due to an increase in the electronegativity of the C(1) atom in **2a** in comparison with the similar bond length in **2b** [1.839(2) Å].

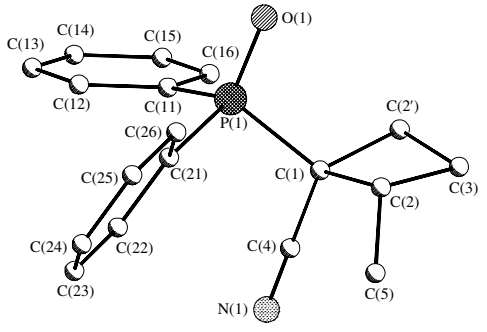


Figure 2 General view of **2b**. Selected bond lengths (Å): P(1)–O(1) 1.482(1), P(1)–C(11) 1.793(2), P(1)–C(21) 1.799(2), P(1)–C(1) 1.839(2), N(1)–C(4) 1.141(2); selected bond angles (°): O(1)–P(1)–C(11) 114.69(8), O(1)–P(1)–C(21) 112.20(8), C(11)–P(1)–C(21) 108.32(8), O(1)–P(1)–C(1) 109.77(8), C(11)–P(1)–C(1) 106.80(8), C(21)–P(1)–C(1) 104.43(8).

‡ In contrast to linear α,ω-dihaloalkanes, with the use of their α,ψ-isomers a certain amount of unreacted starting phosphorylacetonitrile almost always remained in the reaction mixture.

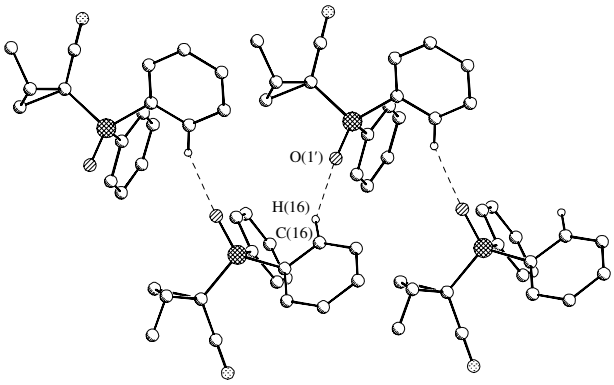


Figure 3 Schematic diagram of C–H···O-bonded chains in **2a**. Parameters C(16)–H(16)···O(1′) (3/2 – *x*, *y*, –0.5 + *z*): H(16)···O(1′) 2.20 Å, C(16)–H(16)–O(1′) 151°, C(16)···O(1′) 3.177(2) Å.

It should be noted that a cyclobutane ring is not flat in **2b**, and it has the puckering angle along the line C(2)···C(2′) equal to 18.2°.

Supramolecular structures in **2a** and **2b** are also different. Thus, in cyclopropane **2a**, the formation of the strong intermolecular C–H···O contact is observed [H(16)···O(1′) 2.20 Å], assembling the molecules into infinite chains elongated along the *c* axis while in cyclobutane **2b** the corresponding C–H···O contacts are considerably weaker (H···O is longer than 2.5 Å).

In order to estimate whether the preferential formation of a *trans* isomer is caused by thermodynamic reasons, we carried out quantum-chemical investigation of both possible isomers for corresponding cyclopropane derivative **2a**. The calculations with full geometry optimization (B3LYP/6-31G*) using G98W[12] suite resulted in satisfactory agreement with experimental data with the exception of an insignificant (*ca.* 0.02 Å) elongation of bond lengths formed by the phosphorus atom. The comparison of full energies of the isomers demonstrated that, though the *trans* isomer exhibits a lower energy, the advantage constitutes only 1.7 kcal mol^{-1} with respect to the *cis* isomer. Therefore, the stereochemical result obtained is more likely connected with steric factors in the intermediate monoalkylated product rather than with the thermodynamical benefit of the *trans* isomer.

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§ *Crystallographic data for* **2a** *and* **2b**: at 110 K, the crystals of $C_{17}H_{16}NOP$ **2a** are orthorhombic, space group *Aba*2, a = 23.103(13), b = 15.708(9) and c = 8.187(5) Å, V = 2971(3) Å^3, Z = 8, M = 281.28, d_{calc} = 1.258 g cm^{-3}, μ(MoKα) = 1.80 cm^{-1}, F(000) = 1184; the crystals of $C_{18}H_{18}NOP$ **2b** are triclinic, space group $P\bar{1}$, a = 7.602(3), b = = 10.182(4) and c = 11.042(5) Å, α = 87.526(9)°, β = 79.305(9)°, γ = = 68.679(2)°, V = 782.0(6) Å^3, Z = 2, M = 295.30, d_{calc} = 1.254 g cm^{-3}, μ(MoKα) = 1.74 cm^{-1}, F(000) = 312. Intensities of 11516 (**2a**) and 6633 (**2b**) reflections were measured with a Smart 1000 CCD diffractometer at 110 K [λ(MoKa) = 0.71072 Å, ω-scans with a 0.3° step in ω and 10 s per frame exposure, $2\theta < 60°$], and 4242 (**2a**) and 4476 (**2b**) independent reflections (R_{int} = 0.0260 and 0.0223, respectively) were used in a further refinement. The structures were solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. Hydrogen atoms were located from the Fourier synthesis and refined in the isotropic approximation. The refinement converged to wR_2 = 0.1186 and GOF = 1.146 for all independent reflections [R_1 = 0.0494 was calculated against F for 3434 observed reflections with $I > 2\sigma(I)$] for **2a**; wR_2 = 0.1391 and GOF = 0.951 for all independent reflections [R_1 = 0.0544 was calculated against F for 3229 observed reflections with $I > 2\sigma(I)$] for **2b**. All calculations were performed using SHELXTL PLUS 5.0 on 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.*, Issue 1, 2002. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/112.

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