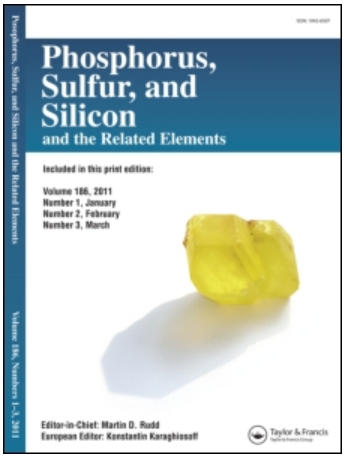

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The Interaction of Bis(chloromethyl) isocyanatophosphinate with Chiral α-Aminoalkylphosphonates: Stereoselective Synthesis of 2,4-Dioxo-5-phenyl-1-phenylethylamino-4-phenoxy-1,3,4-diazaphospholidine

Michael A. Pudovik[a]; Natalia A. Khailova[a]; Alfia A. Shaimardanova[a]; Vladimir A. Alfonsov[a]; Olga N. Kataeva[a]
[a] A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan, Russia

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The Interaction of Bis(chloromethyl) isocyanatophosphinate with Chiral α-Aminoalkylphosphonates: Stereoselective Synthesis of 2,4-Dioxo-5-phenyl-1-phenylethylamino-4-phenoxy-1,3,4-diazaphospholidine

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A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan, Russia

*O,O-Diphenyl-(α-phenylethylamino)benzylphosphonate **6** was synthesized in racemic and enantiopure forms. Its interaction with bis(chloromethyl)isocyanatophosphinate **7** results in the formation of 2,4-dioxo-5-phenyl-1-phenylethylamino-4-phenoxy-1,3,4-diazaphospholidine **10**.*

Keywords α-Aminoalkylphosphonates; bis(chloromethyl)isocyanatophosphinate; diazaphospholidine; enantiomers; organophosphorus compounds

INTRODUCTION

Phosphorus-containing heterocycles with endocyclic P—C bonds have recently attracted significant interest. In particular, five-membered phosphorus and element containing cyclic structures with P—C bonds revealing specific reactivity are of interest as pesticides, drugs, and reagents in organic synthesis.[1—3] One of the most convenient approaches to the synthesis of such phosphacyclanes is based on

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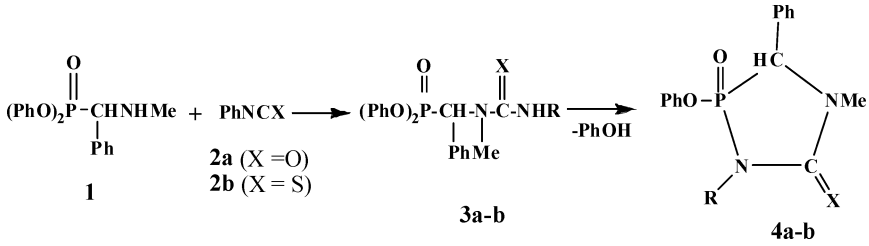
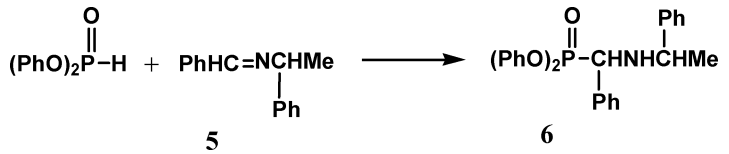
Address correspondence to M. A. Pudovik, Institute of Organic and Physical Chemistry, Russian Academy of Sciences, 420088, Arbuzov Str., 8, Kazan, Russia. E-mail: pudovik@iopc.knc.ru

intramolecular cyclization of polyfunctional organophosphorus derivatives containing substituted alkyl groups. 1,2-Azaphospholidines and 1,2-azaphosphorines were obtained by intramolecular cyclization of haloalkylphosphonylated primary amines.[4,5] A series of studies devoted to the synthesis of 1,2-thia- and 1,2-azaphosphacyclanes on the basis of intramolecular alkylation of ω-haloalkyl substituted compounds with thiophosphoryl- or imino-group was carried out.[6–9] Synthesis of saturated and unsaturated polyheterophosphacyclanes was performed by intramolecular cyclization of haloalkylphosphonylated ureas, thioureas, and uretanes.[10–12] α-Aminoalkylphosphonates and their *N*-substituted derivatives are of particular interest for the creation of cyclic structures, since this class of compounds shows wide and various biological activity.[13] The transformation of benzoylaminomethylphosphonate into 1,4,2-oxazaphospholine under the action of phosphorus pentachloride was described.[14] Compounds containing a guanidine fragment in alkyl group of alkylphosphonates are cyclized to give 1,3,4-diazaphospholidines.[15] It is known that phosphonates with the cumulene system N=C=N in alkyl group attach to secondary amines with subsequent cyclization of the adduct and formation of 1,3,4-diazaphospholines with 6-coordinated phosphorus atom.[16] Recently we have shown (Scheme 1) that the addition of *O*,*O*-diphenyl(α-methylamino)benzylphosphonate **1** to phenylisocyanate **2a** or phenylisothiocyanate **2b** is easily carried out in the presence of the catalytic quantities of triethylamine with the formation of N,N′-disubstituted thioureas **3a–b**, which are cyclized to give diastereomeric 1,3,4-diazaphospholidines **4a–b**.[17]

The processes of the cyclization in Scheme 1 are diastereoselective. That provides the way to obtain stereoisomeric phosphacyclanes, including enantiopure ones. In this respect, it is especially important to use enantiopure aminoalkylphosphonates.



SCHEME 1



SCHEME 2

RESULTS AND DISCUSSION

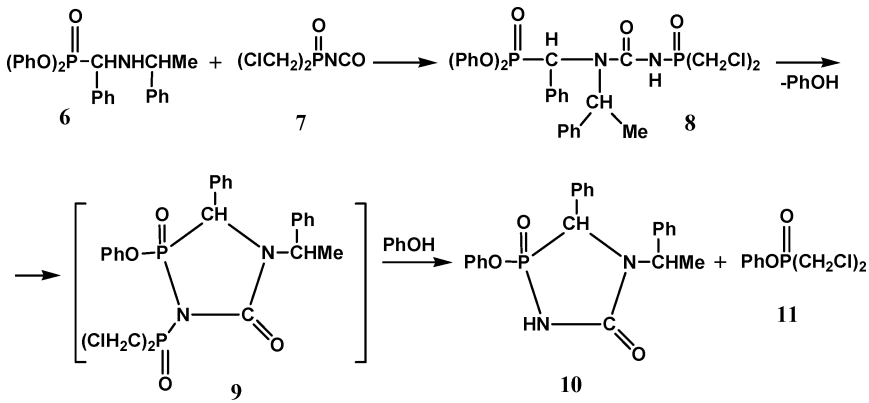
As a preliminary study (Scheme 2), α-aminophosphonate **6** was obtained by addition of diphenylphosphite to racemic benzalphenylethylamine **5**.

Owing to the presence of two chiral centers in **6**, it is formed as a mixture of two diastereomers characterized by two signals at 16.5 and 16.7 ppm in ^{31}P NMR spectrum of the reaction mixture, and the ratio is equal to 30:70. We did not succeed in separation of diastereomers by fractional crystallization, though this separation method is often successful. After each crystallization step, the ratio of diastereomers became worse. The reason that it appeared impossible to separate the diastereomers by fractional crystallization became clear after the X-ray single crystal diffraction study had been carried out. Compound **6** crystallizes in the centrosymmetric space group $P2_1/c$ as a racemic mixture of two diastereomers.

Eventually we took a fraction of crystals with the diastereomeric ratio 40:60 according to the NMR ^{1}H and ^{31}P spectra to study the reactivity of aminophosphonate **6**.

It appeared that in contrast to aminophosphonate **1**, its analogue **6** at 20°C does not react with iso(thio)cyanates **2a**,**2b**, and the heating of the reaction mixture results in its resinification. Such a result, apparently, is caused by the steric factors, owing to the larger volume of the substituent at nitrogen atom. However, the reaction with more reactive bis(chloromethyl)isocyanate **7** proceeds slowly according to Scheme 3. At the first stage, disubstituted urea **8** is formed as a result of the addition of aminophosphonate **6** to isocyanate **7**. The former undergoes intramolecular cyclization with elimination of phenol molecule and the formation of phosphacyclane **9**, containing endo- and exocyclic phosphorus atoms. Labile exocyclic P-N bond of **9** is cleaved upon the action of phenol molecule to give final products diazaphospholidine **10** and *O*-phenyl(chloromethyl)phosphinate **11**.

One may expect the formation of four diastereomers in this reaction, as the third chiral center at the phosphorus atom is formed in phospholidine **10** upon cyclization. The ^{31}P NMR spectrum of the



SCHEME 3

reaction mixture, recorded after 45 days, had a singlet signal of phenylbis(chloromethyl)phosphinate **11** (δ_P 37.5 ppm), and two broad unresolved signals (at δ_P 20.8 and 21.5 ppm) assigned to diastereomers of phospholidine **10** were observed. After crystallization from the reaction mixture, solid product was obtained as a composition of three diastereomers in a 16:42:42 ratio. In the ^{1}H NMR spectra, there are six doublet signals: three of them in the region of 4.93–5.24 ppm assigned to the protons of the CHP-fragments of three diastereomers and three others at 1.52–1.84 ppm corresponding to the resonance of methyl group of phenylethylamino-substituent. One of the diastereomers **10** with δ_P 21.50 ppm was isolated as a result of fractional crystallization, and its molecular structure was determined by X-ray single crystal diffraction.

One of the enantiomers of this diastereomer is presented in Figure 1 and has the following configurations of the chiral centers: C5(R), C6(S), and P4(R). This diastereomer forms a racemic centrosymmetric crystal. A heterocyclic fragment of a molecule of isolated diastereomer adopts a P-envelope, and the phosphorus atom is out of plane $C^5N^1C^2N^3$ (0.02 Å) by 0,328 (2) Å. The orientation of phenyl group at the C_6 atom is orthogonal to a plane of the heterocycle that reduces an opportunity of steric contacts. The phosphoryl substituent is in an equatorial position, and the phenoxy group occupies an axial position. In the crystal molecules of compound **10**, intermolecular hydrogen bonds N^3–$H^3 \ldots O^{2|}$[1-x,-y,-z] with the parameters are formed: N^3–H^3 0.68(4)Å, $H^3 \ldots O^{2|}$ 2.13(4)Å, $N^3 \ldots O^{2|}$ 2.804(8)Å, $\angle(N^3$–$H^3 \ldots O^{2|})$ 177(5)°.

The next step was to involve the enantiopure α-aminophosphonate **6A** in the reaction with isocyanate **7**. It is necessary to note that the compound **6A** was registered in reaction of catalytic addition of

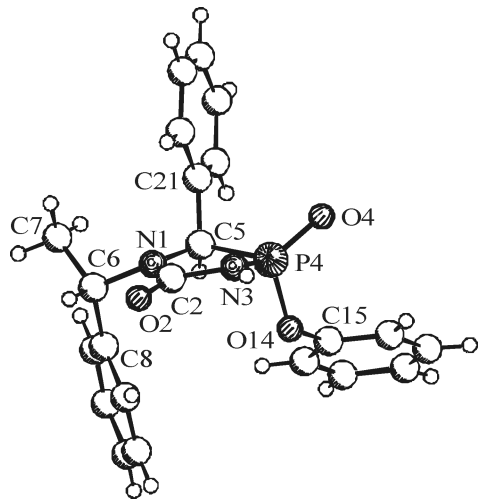


FIGURE 1 Molecular structure of the diastereomer **10** in the crystal.

diphenylphosphite to (S)-(-)-benzal(1-phenyl)ethylamine **5A** (catalyst BF_3) as a mixture of diastereomers by ^{31}P NMR method[18] without separation. We obtained aminophosphonate in the same reaction, but sodium phenolate was used as a catalyst. The reaction proceeds with the formation of aminophosphonate diastereomers composition (74:26 ratio in the reaction mixture with δ_P 16.64 and 16.25 ppm). In contrast to the racemic sample, we succeed in fractional crystallization of aminophosphonate diastereomers and isolated one of the isomers in the enantiopure form ($[\alpha]_D^{20}$–53.7).

The reaction of aminophosphonate **6A** with isocyanate **7** proceeds stereoselectively. In the ^{31}P NMR spectra of the reaction mixture, there are two signals (δ_P21.5 and 22.8 ppm) of diazaphospholidines diastereomeric mixture **10A** and **10B** in rather good 83:17 ratio. 1-Phenyl-2,4-dioxo-4-phenoxy-5-phenyl-1,3,4-diazaphospholidine **10A** ($[\alpha]_D^{20}$+31.0°) was isolated by fractional crystallization.

Thus the reaction of enantiopure aminophosphonate with the chiral inductor at nitrogen atom can be successfully used as a synton for stereoselective cyclization reactions with the formation of enantiopure phosphorus-nitrogen containing heterocycles.

EXPERIMENTAL

IR spectra were obtained using a UR-20 spectrophotometer. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker MSL-400

spectrometer in $CDCl_3$, and chemical shifts reported in ppm downfield from TMS. MS were recorded on a TRACE MS Finnigan MAT mass spectrometer.

The X-ray data for compound **10** were collected on a CAD-4 Enraf-Nonius automatic diffractometer with graphite-monochromated Mo Kα radiation at 20°C. The stability of the crystal and of experimental conditions was checked every 2 h using three control reflections, while the orientation was monitored every 200 reflections by centering two standards. Corrections for Lorentz and polarization effects were applied. Twenty five centered reflections were used to determine unit cell dimensions.

The following programs were used: Data collection and reduction, MoLEN[19]; structure solution, SHELXS-97[20]; and structure refinement by full-matrix least-squares against F^2 using, SHELXL-97.[21]

X-ray crystal data for **10**: formula $C_{22}H_{21}N_2O_3P$, $M = 392.38$, colorless crystal $0.50 \times 0.40 \times 0.40$ mm, $a = 14.933(2)$, $b = 10.476(3)$, $c = 14.003(2)$ Å, $\beta = 110.80(1)$ $V = 2047.8(7)$ Å^3, $\rho_{calc} = 1.273$ g cm^{-3}, $\mu = 0.159$ mm^{-1}, empirical absorption correction ($0.925 \leq T \leq 0.939$), $Z = 4$, monoclinic, space group $P2_1/c$ (No. 14), $\lambda = 0.71073$ Å, $T = 293$ K, 5656 reflections collected, $[(\sin\theta)/\lambda] = 0.60$ Å^{-1}, 3450 independent ($R_{int} = 0.096$) and 1240 observed reflections [$I \geq 2\,\sigma(I)$], 257 refined parameters, $R = 0.065$, $wR^2 = 0.133$, max. residual electron density 0.25 (-0.29) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms, except the NH-group hydrogen, located from the difference Fourier map and refined isotropically.

O,O-Diphenyl-(α-phenylethylamino)benzylphosphonate (6)

Benzalphenylethylamine (4.20 g, 20.1 mmol) was added to a solution of diphenylphosphite (4.70 g, 20.1 mmol) and sodium phenolate (0.1 g) in dry acetonitrile (20 mL), and the mixture was heated at 80°C for 5 h. The next day, acetonitrile was removed. White needles were obtained after recrystallization from diethyl ether (5.9 g, 66%), mp 102–104°C. IR: 3320 (NH), 1590 (Ph), 1265 (P=O) cm^{-1}; ^{1}H NMR (acetone-d_6): $\delta =$ 1.33 (d, $^3J_{HH} = 6.4$ Hz, 3H, MeC), 1.36 (d, $^3J_{HH} = 6.4$ Hz, 3H, MeC), 3.68 (major isomer) (q, $^3J_{HH} = 6.7$ Hz, 1H, NCH), 4.00 (minor isomer) (q, $^3J_{HH} = 6.71$ Hz, 1H, NCH), 4.11 (major isomer) (d, $^2J_{PH} = 23.6$ Hz, 1H, PCH), 4.57 (minor isomer) (d, $^2J_{PH} = 20.2$ Hz, 1H, PCH), 7.15 (m, 20H, Ph). ^{31}P NMR (acetone-d_6): $\delta = 16.5$, 16.7. Anal. Calcd. for $C_{27}H_{26}NO_3P$: C, 73.12; H, 5.91; N, 3.16; P, 6.99. Found: C, 72.85; H, 6.07; N, 3.33; P, 6.88%.

O,O-Diphenyl-(α-phenylethylamino)benzylphosphonate (6A)

Compound **6A** was obtained from diphenylphosphite (4.9 g, 20.9 mmol) and (S)-(-)-benzalphenylethylamine (4.37 g, 20.9 mmol) as described for phosphonate **6**, yield: (1.3 g, 14%); mp 122–123 °C; $[\alpha]_D^{20}$ −53.7°(c = 1.22, CH_3CN). IR: 3325 (NH), 1590 (Ph), 1275 (P=O) cm^{-1}. ^1H NMR (acetone-d_6): δ = 1.41 (d, $^3J_{HH}$ = 6.3 Hz, 3H, MeC), 3.73 (q, $^3J_{HH}$ = 6.7 Hz, 1H, NCH), 4.16 (d, $^2J_{PH}$ = 23.6 Hz, 1H, PCH), 7.3 (m, 20H, Ph). ^{31}P NMR (acetone-d_6): δ = 16.2. Anal. Calcd. for $C_{27}H_{26}NO_3P$: C, 73.12; H 5.91; N 3.16; P, 6.99. Found: C, 72.93; H, 5.88; N, 3.22; P, 6.76%.

2,4-Dioxo-5-phenyl-1-phenylethylamino-4-phenoxy-1,3,4 -diazaphospholidine (10)

Isocyanate **7** (0.89 g, 2 mmol) was added to a solution aminophosphonate **6** (0.38 g, 2 mmol) in acetonitrile (20 mL). In 45 days, crystalline product **10** (0.30 g, 38%) was separated, mp 201–207 °C. IR: 1190, 1210 (POPh), 1278 (P=O), 1590 (Ph), 1700 (C=O), 3080 (NH) cm^{-1}. ^1H NMR (acetone-d_6): δ = 1.10 (d, $^3J_{HH}$ = 5.9 Hz, 3H, MeC), 1.22 (d, $^3J_{HH}$ = 7.4 Hz, 3H, MeC), 1.34 (d, $^3J_{HH}$ = 7.1 Hz, 3H, MeC), 4.45 (d, $^2J_{PH}$ = 21.1 Hz, 1H, PCH), 4.67 (d, $^2J_{PH}$ = 21.5, 1H, PCH), 4.86 (d, $^2J_{PH}$ = 29.3 Hz, 1H, PCH), 5.6 (m, 1H, NCH), 5.33 (m, 1H, NCH), 7.01 (m, 15H, Ph).^{31}P NMR (acetone-d_6): δ = 21.5, 20.8. MS: m/z (%) 392.36 (M^+). Anal. Calcd. for $C_{22}H_{21}N_2O_3P$: C, 67.33; H, 5.39; N, 7.13; P, 7.89. Found: C, 67.14; H, 5.11; N, 6.98; P, 7.67%.

2,4-Dioxo-5-phenyl-1-phenylethylamino-4-phenoxy-1,3,4 -diazaphospholidine (10A)

Compound **10A** was obtained similarly from aminophosphonate **6A** (0.45 g, 1.0 mmol) and isocyanate **7** (0.19 g, 1.0 mmol). Yield: (0.18 g, 46%); mp 182–183°C. $[\alpha]_D$ 31.0° (c = 1.09, CH_3CN). IR: 1190, 1215 (POPh), 1255 (P=O), 1595 (Ph), 1695 (C=O), 3070 (NH). ^1H NMR (acetone-d_6): δ = 1.62 (d, $^3J_{HH}$ = 4.6 Hz, 3H, MeC), 4.86 (q, $^3J_{HH}$ = 5.0 Hz, 1H, NCH), 5.07 (d, $^2J_{PH}$ = 13.1 Hz, 1H, PCH), 7.2 (m, 15H, Ph), 8.54 (s, 1H, NH). ^{31}P-NMR (acetone-d_6): δ = 21.6. Anal. Calcd. for $C_{22}H_{21}N_2O_3P$: C, 67.33; H, 5.39; N, 7.13; P, 7.89. Found: C, 67.05; H, 5.16; N, 6.80; P, 7.72%.

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