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Reactions of α-Phosphoryl-α-haloacetaldehydes with Difunctional Nucleophiles

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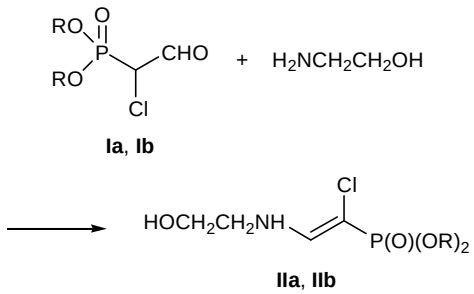
Abstract—Reactions of phosphorylated α-haloacetaldehydes with difunctional nitrogen-, oxygen-, and sulfur-containing nucleophiles were performed with a view to synthesize C-phosphorylated heterocyclic compounds.

Reactions of α-halocarbonyl compounds with di- and polyfunctional nucleophiles are widely used for the preparation of various heterocyclic systems; some products obtained in such a way turned out to be effective drugs, pesticides, etc. [1–4]. In order to elucidate the effect of a phosphoryl group on the reaction direction and synthesize C-phosphorylated heterocycles we examined reactions of phosphoryl-substituted α-haloacetaldehydes with difunctional nitrogen-, oxygen-, and sulfur-containing nucleophiles.

The condensation of phosphorylated chloroacetaldehydes **Ia** and **Ib** with 2-aminoethanol was performed in methylene chloride at –8 to –5°C. According to the IR and ^{1}H NMR data, instead of expected heterocyclic compounds, the products were enamines **IIa** and **IIb**, respectively (Scheme 1). The IR spectra of **IIa** and **IIb** contained absorption bands at about 1580 cm^{-1}, which are typical of stretching vibrations of double C=C bond, and broadened bands at 3200–3300 cm^{-1}, which correspond to NH and OH groups. In the ^{1}H NMR spectra of enamines **IIa** and **IIb**, we observed two doublets at δ 7.25–7.30 ppm ($^3J_{PH}$ = 7.5 Hz) due to proton at the double bond, a signal at δ 7.60 ppm due to the NH proton, and a triplet at δ 4.25 ppm (^3J = 5.25 Hz) due to the hydroxy proton.

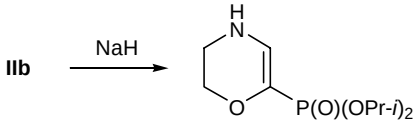
Scheme 1.



R = Et (**a**), *i*-Pr (**b**).

By reaction of enamine **IIb** with sodium hydride in diethyl ether at –5°C we obtained 2-(diisopropoxyphosphoryl)-5,6-dihydro-4*H*-1,4-oxazine (**III**) (Scheme 2). Presumably, the cyclization involves the imino tautomer of **IIb**. Compound **III** showed in the IR spectrum absorption bands at 1605 and 3240 cm^{-1} due to stretching vibrations of the C=C and N–H bonds, respectively. Unlike initial compound **IIb**, the CH=C proton in **III** appeared in the ^{1}H NMR spectrum as a doublet at δ 7.50 ppm. The spectrum contained no OH signal, and the NH signal was located in a stronger field (δ 7.30 ppm) relative to the corresponding signal of phosphonate **IIb**.

Scheme 2.



III

Phosphorylated chloroacetaldehydes **Ia** and **Ib** reacted with *o*-aminophenol in boiling chloroform to give enamines **IVa** and **IVb** in high yield (Scheme 3). Compounds **IVa** and **IVb** are crystalline substances. Their structure was proved by the spectral and analytical data. In the ^{1}H NMR spectra of **IVa** and **IVb**, proton at the double bond resonates as two doublets with an intensity ratio of 2:1, indicating the presence of two isomers.

The reaction of more electrophilic chloro(diethoxyphosphoryl)phenylacetaldehyde (**Ic**) with nitrogen-containing nucleophiles, in particular 2-aminoethanol,

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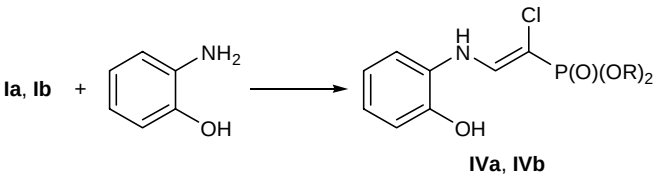
Scheme 3.

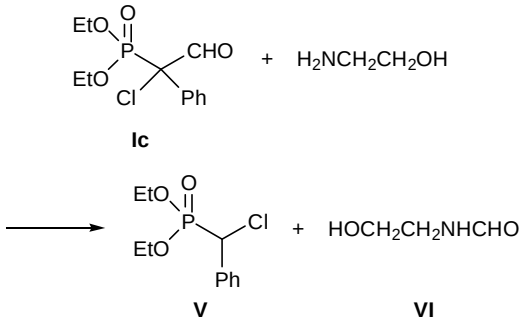


IVa, **IVb**

R = Et (**a**), *i*-Pr (**b**).

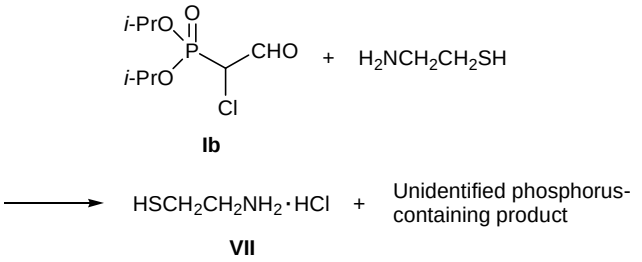
followed the haloform decomposition scheme with rupture of the C–CHO bond and formylation of the amino group in the nucleophile. The products of this reaction were diethyl α-chlorobenzylphosphonate (**V**) and *N*-(2-hydroxyethyl)formamide (**VI**) (Scheme 4); they were isolated and identified by spectral methods. The ^{1}H NMR spectrum of **V** contained a doublet at δ 4.90 ppm with a coupling constant typical of P–CHCl interaction.

Scheme 4.



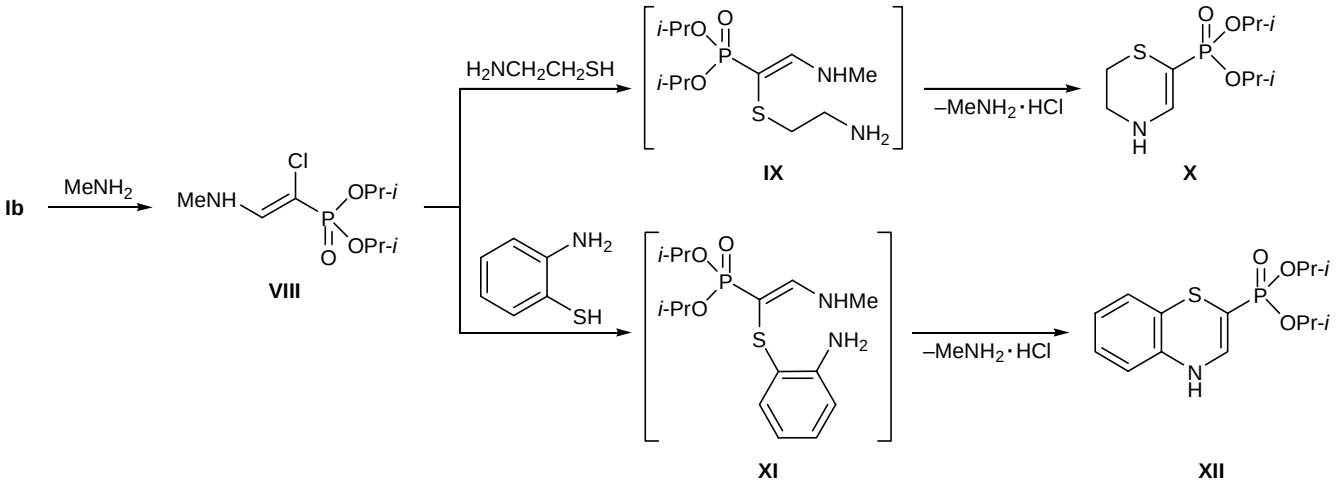
2-Aminoethanethiol, which is a weaker base than 2-aminoethanol, reacted with aldehyde **Ib** (regardless of the reaction conditions) to give 2-aminoethanethiol hydrochloride and an oily phosphorus-containing substance which showed in the ^{31}P NMR spectrum three signals at δ_P 10.2, 15.1, and 19.2 ppm. Unfortunately, we failed to identify this product (Scheme 5). Analogous results were obtained in the reaction of aldehyde **Ib** with 2-aminobenzenethiol.

Scheme 5.



We previously showed that phosphorylated enamines like **VIII**, which are readily available via reaction of phosphoryl-substituted α-chloroacetaldehydes with primary amines, are convenient electrophilic substrates for the preparation of heterocyclic systems. In continuation of our studies on the synthetic potential of these difunctional electrophiles, we examined the reactions of enamine **VIII** with 2-aminoethanethiol and 2-aminobenzenethiol in boiling acetonitrile. These reactions did not stop at the stage of formation of compounds **IX** and **XI** (as might be expected) but afforded 2-diisopropoxyphosphoryl-substituted 1,4-thiazine **X** and 1,4-benzothiazine **XII**, respectively (Scheme 6). The assumed reaction scheme was confirmed by the ^{31}P NMR data. After 5 h, the ^{31}P NMR spectrum of the reaction mixture contained signals at δ_P 13.94 and 13.4 ppm, which corresponded to the initial enamine and intermediate **IX** or **XI**, respectively. After 10 h, the signal at δ_P 13.94 ppm disappeared, and a new signal appeared at δ_P 16.3 ppm.

Scheme 6.



After 16 h, the spectrum contained only the signal at δ_P 16.3 ppm due to the final heterocyclic product.

The structure of compounds **X** and **XII** was confirmed by the ^{1}H NMR and IR spectra and elemental analyses. In the IR spectra of **X** and **XII** we observed absorption bands belonging to stretching vibrations of the phosphoryl group (1285 cm^{-1}), C=C bond (1620 cm^{-1}), and secondary amino group (3140 cm^{-1}). In the ^{1}H NMR spectra of the products (acetone-d_6), the CH= signal appeared as a doublet at δ 7.10–7.20 ppm, and the NH proton resonated at δ 6.50–6.70 ppm as a singlet. In addition, thiazine **X** showed in the ^{1}H NMR spectrum signals from the SCH_2 and NCH_2 protons, and compound **XII**, aromatic proton signals; their relative intensities were consistent with the assumed structures.

EXPERIMENTAL

The melting points were determined on a Boetius melting point apparatus. The ^{1}H NMR spectra were recorded on a Tesla BW-57 spectrometer (100 MHz) from solutions in acetone-d_6 using HMDS as internal reference. The ^{31}P NMR spectra were measured on a Bruker WR-80 instrument at 32.38 MHz relative to 85% H_3PO_4. The IR spectra were obtained on a UR-20 spectrometer from samples prepared as thin films or KBr pellets.

Reaction of aldehydes Ia and Ib with 2-aminoethanol. A solution of 0.25 g (4 mmol) of 2-aminoethanol in 10 ml of dry methylene chloride was added dropwise under stirring to a solution of 0.86 g (4 mmol) of aldehyde **Ia** in 15 ml of dry methylene chloride, maintaining the temperature at –8 to –5°C. The mixture was stirred for 0.5 h on cooling and for 3 h at room temperature. Removal of the solvent left oily product **IIa**. Yield 0.74 g (72%). IR spectrum, ν, cm^{-1}: 1287 (P=O), 1580 (C=C), 3240 (NH), 3310 (OH). ^{1}H NMR spectrum, δ, ppm: 1.00 d.t (12H, CH_3), 3.00 t (2H, NCH_2), 3.60 t (2H, OCH_2), 4.25 t (1H, OH), 4.60 m (2H, OCH), 7.30 d.d (1H, =CH), 7.60 s (1H, NH). ^{31}P NMR spectrum: δ_P 14.5 ppm. Found, %: Cl 12.38; N 4.75; P 10.81. $C_{10}H_{21}ClNO_4P$. Calculated, %: Cl 12.43; N 4.90; P 10.86.

Compound **IIb** was obtained in a similar way. Yield 76%. IR spectrum, ν, cm^{-1}: 1280 (P=O), 1580 (C=C), 3250 (NH), 3300 (OH). ^{1}H NMR spectrum, δ, ppm: 1.00 d.t (6H, CH_3), 3.00 t (2H, NCH_2), 3.50 t (2H, OCH_2), 4.00 q (4H, OCH_2), 4.20 t (1H, OH), 7.25 d.d (1H, =CH), 7.60 s (1H, NH). ^{31}P NMR spectrum: δ_P 14.2 ppm. Found, %: Cl 13.68; N 5.36; P 11.95. $C_8H_{17}ClNO_4P$. Calculated, %: Cl 13.79; N 5.44; P 12.04.

2-(Diisopropoxyphosphoryl)-5,6-dihydro-4*H*-1,4-oxazine (III). Sodium hydride, 0.12 g (5 mmol), was dispersed in 10 ml of anhydrous diethyl ether, and a solution of 1.43 g (5 mmol) of compound **IIb** in 5 ml of diethyl ether was added dropwise in a stream of dry nitrogen under stirring and cooling to –5°C. The mixture was stirred for 1 h on cooling and for 2 h at room temperature. The precipitate was filtered off, and the filtrate was evaporated to isolate oily product **III** in 81% yield. IR spectrum, ν, cm^{-1}: 1285 (P=O), 1605 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.15 d.t (12H, CH_3), 3.00 t (2H, NCH_2), 3.50 m (2H, OCH_2), 4.60 m (2H, OCH), 7.30 s (1H, PNH), 7.50 d (1H, =CH). Found, %: N 5.64; P 12.51. $C_{10}H_{20}NO_4P$. Calculated, %: N 5.62; P 12.45.

Reaction of aldehydes Ia–Ic with *o*-aminophenol. A mixture of 2.14 g (10 mmol) of aldehyde **Ia** and 1.00 g (10 mmol) of *o*-aminophenol in 20 ml of chloroform was heated for 2 days under reflux. The solvent was distilled off, the residue was treated with 5 ml of diethyl ether, and the precipitate of compound **IVa** was filtered off, washed with diethyl ether, and dried. Yield 2.38 g (78%), mp 130–131°C. IR spectrum, ν, cm^{-1}: 1280 (P=O), 1605 (C=C), 3270 (NH), 3400 (OH). ^{1}H NMR spectrum, δ, ppm: 1.00 d.t (6H, CH_3), 4.00 m (4H, OCH_2), 6.80 m (2H, H_{arom}), 7.10 m (2H, H_{arom}), 7.40 s (1H, NH), 7.80 d.d (1H, =CH), 9.20 s (1H, OH). ^{31}P NMR spectrum: δ_P 11.5 ppm. Found, %: Cl 11.68; N 4.62; P 10.21. $C_{12}H_{17}ClNO_4P$. Calculated, %: Cl 11.62; N 4.58; P 10.15.

Compound **IVb** was synthesized in a similar way. Yield 80%, mp 142-144°C. IR spectrum, ν, cm^{-1}: 1285 (P=O), 1600 (C=C), 3250 (NH), 3410 (OH). ^{1}H NMR spectrum, δ, ppm: 1.15 d.t (12H, CH_3), 4.50 m (2H, OCH), 6.80 m (2H, H_{arom}), 7.10 m (2H, H_{arom}), 7.45 s (1H, NH), 7.80 d.d (1H, =CH), 9.25 s (1H, OH). ^{31}P NMR spectrum: δ_P 11.8 ppm. Found, %: Cl 10.56; N 4.15; P 9.24. $C_{14}H_{21}ClNO_4P$. Calculated, %: Cl 10.64; N 4.20; P 9.29.

The reaction of aldehyde **Ic** with 2-aminoethanol was performed in a similar way. After removal of the solvent, the residue was distilled under reduced pressure to isolate diethyl α-chlorobenzylphosphonate (**V**). Yield 83%, bp 115–116°C (0.05 mm). ^{1}H NMR spectrum, δ, ppm: 1.15 d.t (6H, CH_3), 4.00 m (4H, OCH_2), 4.90 d (1H, CHCl), 7.35 m (5H, H_{arom}). ^{31}P NMR spectrum: δ_P 17.1 ppm. Found, %: Cl 13.57; P 11.85. $C_{11}H_{16}ClO_3P$. Calculated, %: Cl 13.52; P 11.81.

Reactions of chloro(diisopropoxyphosphoryl)-acetaldehyde (Ib) with 2-aminoethanethiol and 2-aminobenzenethiol. 2-Aminoethanethiol or 2-aminobenzenethiol, 0.002 mol, was added to a solution of 2.42 g (0.01 mol) of aldehyde **Ib** in 10 ml of acetonitrile, and the mixture was kept for 20 h at room temperature. The precipitate of aminothiol hydrochloride was filtered off, and the filtrate was evaporated to obtained an oily substance which we failed to identify.

Diisopropyl 1-chloro-2-methylaminoethenylphosphonate (VIII). A stream of dry methylamine was passed over a period of 1.5 h through a solution of 0.98 g (4 mmol) of aldehyde **Ib** in 40 ml of methylene chloride while stirring at –5°C. The mixture was stirred for 2 h at room temperature, the solvent was removed under reduced pressure, and the residue, a jelly-like material, was crystallized from acetonitrile. Yield 0.72 g (70%), mp 96°C. ^{1}H NMR spectrum, δ, ppm: 1.25 t (12H, CH_3), 3.00 d (3H, CH_3), 4.60 m (2H, OCH), 6.00 s (1H, NH), 7.25 d.d (1H, CH, $^3J_{PH}$ = 7.5 Hz). ^{31}P NMR spectrum: δ_P 13.94 ppm. Found, %: Cl 13.78; N 5.44; P 12.08. $C_9H_{19}ClNO_3P$. Calculated, %: Cl 13.90; N 5.48; P 12.13.

2-Diisopropoxyphosphoryl-4*H*-1,4-benzothiazine (XII). A mixture of 2.7 g (0.01 mol) of enamine **VIII** and 1.25 g (0.01 mol) of 2-aminobenzenethiol in 20 ml of acetonitrile was heated for 16 h under reflux. The mixture was cooled, the precipitate of methylamine hydrochloride was filtered off, the filtrate was evaporated, the residue was treated with 3 ml of a 2:1 diethyl ether–ethanol mixture, and the precipitate was filtered off and dried. Yield 2.03 g (65%), mp 139–141°C. IR spectrum, ν, cm^{-1}: 1285 (P=O), 1620 (C=C), 3140 (NH). ^{1}H NMR spectrum, δ, ppm: 1.15 d (12H, CH_3), 4.60 m (2H, OCH), 6.50 s (1H, NH), 6.75 m (4H, H_{arom}), 7.10 d (1H, =CH). ^{31}P NMR spectrum: δ_P 16.3 ppm. Found, %: N 4.44; P 9.81; S 10.26. $C_{14}H_{20}NO_3PS$. Calculated, %: N 4.47; P 9.90; S 10.22.

2-Diisopropoxyphosphoryl-5,6-dihydro-4*H*-1,4-thiazine (X) was synthesized in a similar way. Yield 67%, oily substance. IR spectrum, ν, cm^{-1}: 1287 (P=O), 1640 (C=C), 3110 (NH). ^{1}H NMR spectrum, δ, ppm: 1.10 t (12H, CH_3), 2.85 m (2H, SCH_2), 3.45 m (2H, NCH_2), 4.60 m (2H, 2OCH), 6.70 s (1H, NH), 7.10 d (1H, =CH). ^{31}P NMR spectrum: δ_P 16.2 ppm. Found, %: N 5.22; P 11.64; S 12.11. $C_{10}H_{20}NO_3PS$. Calculated, %: N 5.28; P 11.70; S 12.07.

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