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SHORT COMMUNICATIONS

Dedicated to M.A. Pudovik on his 80th anniversary

Reaction of *N*-(4,4-Diethoxybutyl)phosphamides with Chloro(diphenyl)phosphine. Synthesis of 2-(Diphenylphosphoryl)pyrrolidines

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Abstract—The reaction of *N*-(4,4-diethoxybutyl)phosphamides with chloro(diphenyl)phosphine in chloroform in the presence of acetic acid gave previously unknown 2-(diphenylphosphoryl)pyrrolidines, and hydrolysis of the latter afforded 2-(diphenylphosphoryl)pyrrolidine.

Keywords: acetals, chloro(diphenyl)phosphine, *N*-(4,4-diethoxybutyl)phosphamides, 2-(diphenylphosphoryl)-pyrrolidines

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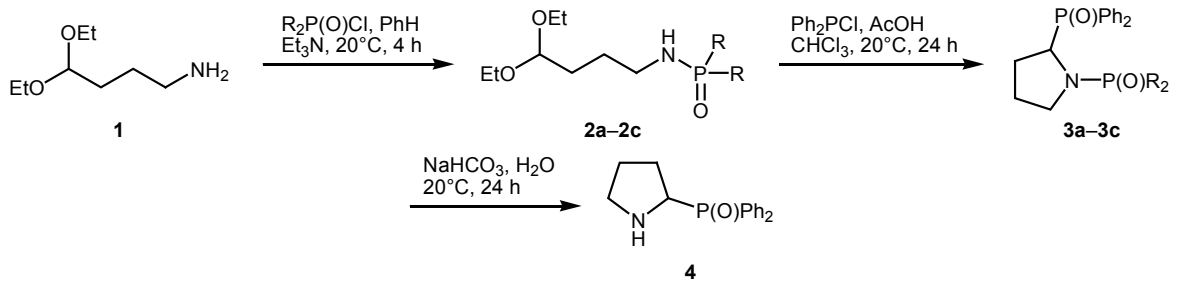
Pyrrolidine ring is a structural fragment of many known biologically active compounds [1–4]. Of particular interest are derivatives of proline which is a proteinogenic amino acid involved in biosynthesis of proteins and other biological processes [5]. In recent years, phosphorus-containing analogs of proline have attracted much interest due to their diverse biological activity. In particular, such compounds inhibit angiotensin-converting enzyme 2 [6, 7] and separase [8], and they can be used to monitor post-proline protease activity [9].

The known methods of synthesis of phosphoproline can be classed with two main approaches. The first one is based on phosphorylation of already synthesized cyclic precursors, derivatives of pyrrolidine and 1-pyrroline [10–12]. The necessity of preliminary preparation of the initial heterocycle complicates the synthetic scheme and reduces the overall yield. The second approach involves heterocyclization of linear precursors [13–15]. However, in this case, expensive metal-containing catalysts are often required. On the other hand, its advantage is that no laborious synthesis of initial cyclic compounds is necessary.

We previously proposed a procedure for the synthesis of 2-(diphenylphosphoryl)pyrrolidines by acid-catalyzed reaction of *N*-(4,4-diethoxybutyl)ureas with chloro(diphenyl)phosphine [16]. In order to determine the scope of this approach, it seemed important to study the effect of the nature of the electron-withdrawing fragment on the nitrogen atom in the amino acetal molecule on the reaction outcome. For this purpose, by reaction of 4,4-diethoxybutan-1-amine (**1**) with four-coordinate phosphorus acid chlorides in benzene in the presence of triethylamine we obtained *N*-(4,4-diethoxybutyl)phosphamides **2a**–**2c**. Acetals **2a**–**2c** were then reacted with an equimolar amount of chloro(diphenyl)-phosphine in anhydrous chloroform in the presence of acetic acid at room temperature. As a result, we isolated previously unknown diphosphorylated pyrrolidines **3a**–**3c**. Treatment of the latter with aqueous sodium hydrogen carbonate afforded 2-(diphenylphosphoryl)-pyrrolidine (**4**) (Scheme 1).

Thus, the acid-catalyzed reaction of *N*-(4,4-diethoxybutyl)phosphamides with chloro(diphenyl)-phosphine leads to the formation of new diphosphorylated pyrrolidine derivatives under mild condi-

Scheme 1.



R = OPh (**a**), Ph (**b**), CH_2Cl (**c**).

tions. Obvious advantages of the proposed procedure are mild reaction conditions and the use of commercially available acetic acid as catalyst.

***N*-(4,4-Diethoxybutyl)phosphamides 2a–2c (*general procedure*).** A mixture of 1.9 g of 4,4-diethoxybutan-1-amine (**1**), 2.4 g of triethylamine, and 11.8 mmol of the corresponding phosphoryl compound in 20 mL of anhydrous benzene was stirred for 4 h at room temperature. The precipitate was filtered off, and the filtrate was evaporated under reduced pressure to leave a yellow oily product.

Diphenyl *N*-(4,4-diethoxybutyl)phosphoramidate (2a). Yield 90%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.17 t (6H, CH_3, J = 7.1 Hz), 1.49–1.63 m (4H, CH_2), 3.02–3.12 m (2H, CH_2), 3.38–3.37 m (2H, CH_2), 3.52–3.62 m (2H, CH_2), 4.41 t (1H, CH, J = 5.2 Hz), 7.15 t (2H, H_{arom}, J = 6.9 Hz), 7.23–7.28 m (4H, H_{arom}), 7.29–7.36 m (4H, H_{arom}). ^{31}P NMR spectrum ($CDCl_3$): δ_P 0.47 ppm.

***N*-(4,4-Diethoxybutyl)diphenylphosphinamide (2b).** Yield 89%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.11 t (6H, CH_3, J = 7.0 Hz), 1.57–1.65 m (4H, CH_2), 2.88–2.99 m (2H, CH_2), 3.32–3.45 m (2H, CH_2), 3.48–3.62 m (2H, CH_2), 4.36–4.42 m (1H, CH), 7.32–7.46 m (6H, H_{arom}), 7.78–7.89 m (4H, H_{arom}). ^{31}P NMR spectrum ($CDCl_3$): δ_P 23.40 ppm.

***N*-(4,4-Diethoxybutyl)bis(chloromethyl)phosphinamide (2c).** Yield 84%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.17 t (6H, CH_3, J = 7.1 Hz), 1.56–1.69 m (4H, CH_2), 3.02–3.11 m (2H, CH_2), 3.42–3.54 m (4H, CH_2), 3.57–3.67 m (4H, CH_2), 3.69–3.76 m (2H, CH_2), 4.46 t (1H, CH, J = 5.2 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.30, 24.23 d (J = 5.0 Hz), 30.69, 34.41 d (J = 95.8 Hz), 39.82, 61.47, 102.60. ^{31}P NMR spectrum ($CDCl_3$): δ_P 31.87 ppm.

2-(Diphenylphosphoryl)pyrrolidines 3a–3c (*general procedure*). A mixture of *N*-(4,4-diethoxybutyl)-phosphamide **2a**–**2c** (1.52 mmol), 0.39 g of chloro(diphenyl)phosphine, 10 mL of anhydrous chloroform, and 0.1 mL of acetic acid was stirred for 24 h at 20°C. The mixture was evaporated, and the residue was treated with 5 mL of anhydrous diethyl ether. The white solid was filtered off and dried under reduced pressure (10 mm Hg). Compounds **3a**–**3c** were isolated as white powders.

1-(Diphenoxyphosphoryl)-2-(diphenylphosphoryl)pyrrolidine (3a). Yield 82%, mp 103–105°C. IR spectrum, ν, cm^{-1}: 2863, 2758, 1598, 1441, 1348. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.62–1.76 m (1H, CH_2), 1.84–1.99 m (3H, CH_2), 3.13–3.21 m (1H, CH_2), 3.23–3.37 m (1H, CH_2), 4.74–4.88 m (1H, CH), 7.06–7.42 m (2H, H_{arom}), 7.48–7.69 m (10H, H_{arom}), 7.79–7.92 m (4H, H_{arom}), 7.97–8.12 m (4H, H_{arom}). ^{31}P NMR spectrum (DMSO-d_6), δ_P, ppm: –1.37 d (J = 17.2 Hz), 30.81 d (J = 17.1 Hz). Mass spectrum (ESI-TOF): m/z 504 $[M + H]^+$. Found, %: C 66.99; H 5.49; N 2.91; P 12.46. $C_{28}H_{27}NO_4P_2$. Calculated, %: C 66.80; H 5.41; N 2.78; P 12.30.

1,2-Bis(diphenylphosphoryl)pyrrolidine (3b). Yield 75%, mp 135–137°C. IR spectrum, ν, cm^{-1}: 2869, 2786, 1597, 1441, 1348. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.48–1.60 m (1H, CH_2), 1.81–1.94 m (1H, CH_2), 1.97–2.03 m (2H, CH_2), 3.02–3.12 m (1H, CH_2), 3.24–3.31 m (1H, CH_2), 4.79–4.86 m (1H, CH), 7.23–7.38 m (4H, H_{arom}), 7.44–7.60 m (10H, H_{arom}), 7.63–7.68 m (2H, H_{arom}), 7.70–7.76 m (4H, H_{arom}). ^{31}P NMR spectrum (DMSO-d_6), δ_P, ppm: 31.98 d (J = 24.0 Hz), 32.94 d (J = 24.1 Hz). Mass spectrum (ESI-TOF), m/z: 472 $[M + H]^+$, 495 $[M + Na]^+$. Found, %: C 71.04; H 6.01; N 3.12; P 13.00. $C_{28}H_{27}NO_2P_2$. Calculated, %: C 71.33; H 5.77; N 2.97; P 13.14.

1-[Bis(chloromethyl)phosphoryl]-2-(diphenylphosphoryl)pyrrolidine (3c). Yield 48%, mp 115–116°C. IR spectrum, ν, cm^{-1}: 2884, 2746, 1597, 1430, 1346. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.85–2.03 m (4H, CH_2), 3.14–3.23 m (1H, CH_2), 3.27–3.32 m (1H, CH_2), 3.62–3.74 m (4H, CH_2), 4.77–4.86 m (1H, CH), 7.56–7.72 m (6H, H_{arom}), 7.82–7.90 m (2H, H_{arom}), 7.94–8.03 m (2H, H_{arom}). ^{31}P NMR

spectrum (DMSO-d_6), δ_P, ppm: 28.66 d (J = 22.1 Hz), 38.64 d (J = 22.2 Hz). Mass spectrum (ESI-TOF): m/z 416 $[M + H]^+$. Found, %: C 52.16; H 5.20; Cl 16.89; N 3.45; P 14.98. $C_{18}H_{21}Cl_2NO_2P_2$. Calculated, %: C 51.94; H 5.09; Cl 17.03; N 3.37; P 14.88.

2-(Diphenylphosphoryl)pyrrolidine (4). A mixture of compound **3a**–**3c** (0.99 mmol) and 0.8 g of sodium hydrogen carbonate in 20 mL of water was stirred for 24 h at room temperature. The mixture was extracted with chloroform (3×10 mL), and the combined extracts were evaporated under reduced pressure. The spectral characteristics of **4** coincided with those reported previously [17].

The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 600 spectrometer at 600 and 150 MHz, respectively; the chemical shifts were measured relative to the residual proton and carbon signals of the solvent (DMSO-d_6, $CDCl_3$). The ^{31}P NMR spectra were recorded on a Bruker Avance II-400 instrument at 161.9 MHz using 85% H_3PO_4 as external standard. The IR spectra were recorded on a UR-20 spectrometer in the range 400–3600 cm^{-1}; crystalline products were examined as KBr discs. Elemental analysis was performed on a Carlo Erba EA 1108 analyzer. The mass spectra (electrospray ionization, positive ion detection, a.m.u. range 100–2800) were obtained with a Bruker Daltonik AmazonX mass spectrometer (Bremen, Germany). The melting points were measured in glass capillaries using a Stuart SMP 10 melting point apparatus.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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