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LETTERS TO THE EDITOR

Cyclic Amidoalkylation of Hydrophosphorylic Compounds. Synthesis of Proline Analogs

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Abstract—A method for the synthesis of N-Cbz-protected phosphorylic analogs of proline by cyclic amidoalkylation of various hydrophosphorylic compounds was developed. Combination of amide and carbonyl fragments in the 4-N-Cbz-aminobutyraldehyde molecule allows to realize the three-center two-component amide version of the Kabachnik–Fields reaction.

Keywords: phosphorylic analogs of proline, cyclic amidoalkylation, 4-aminobutyraldehyde

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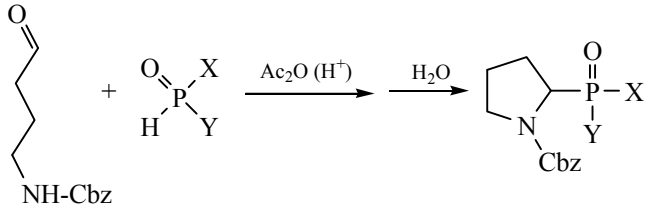
Amidoalkylation of hydrophosphorylic compounds is a promising general method for constructing the α-aminophosphoryl function, which allows preserving the protection at the nitrogen atom of the target molecule. By earlier studies of the amide version of the Kabachnik–Fields reaction we developed an effective convenient procedure for carrying out the reactions of hydrophosphorylic compounds with aldehydes and alkyl carbamates in acetic anhydride under acid catalysis at room temperature [1–4].

This work deals with the development of a two-component three-center amide (carbamate) version of this reaction combining the carbamate and carbonyl reaction sites in one molecule. We proposed a modification of the approach based on the known ability of α,ω-aminoaldehydes to cyclization [5, 6] reported in [5]. 4-N-Cbz-Aminobutyraldehyde **1** was taken as the starting compound, in whose molecule the length of the hydrocarbon chain between two reaction sites makes it possible to obtain a five-membered pyrrolidine ring, present in the best known cyclic amino acid proline.

The reaction of 4-N-Cbz-aminobutyraldehyde **1** with hydrophosphorylic compounds **2** in acetic anhydride under acid catalysis at room temperature led to the formation of phosphorylic proline analogs **3** (Scheme 1).

In accordance with the mechanism of amidoalkylation of the hydrophosphorylic compounds we have suggested earlier the formation of the phosphorus-carbon bond proceeds through the Arbuzov reaction including the nucleophilic attack of the P(III) atom of the acetyloxy derivative on the carbon atom of the

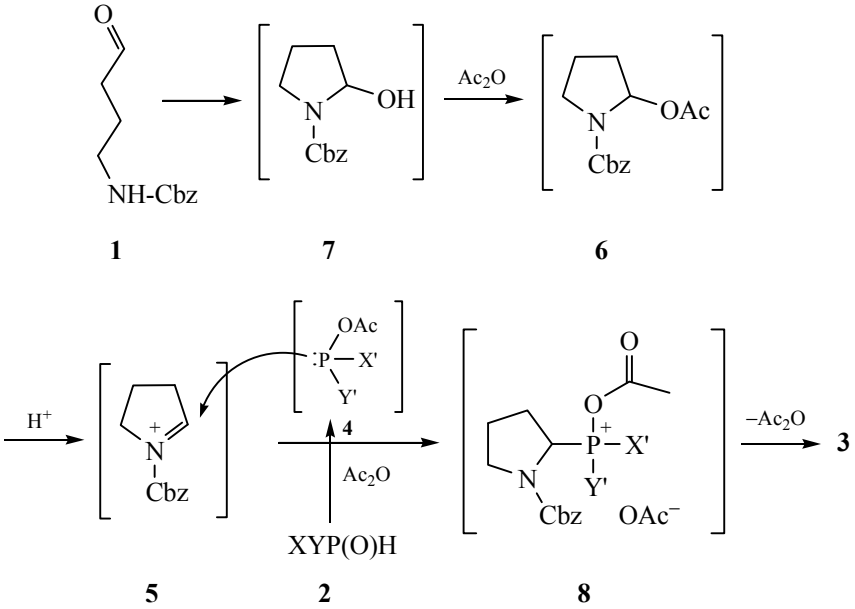
Scheme 1.



1 **2** **3a–3e**

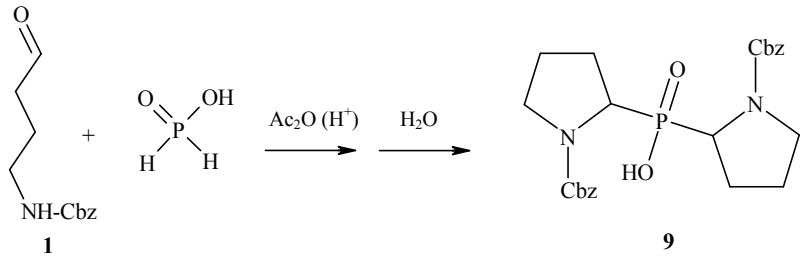
X = Y = OH (**a**); X = Y = OEt (**b**); X = Me, Y = OH (**c**); X = CH_2OH, Y = OH (**d**); X = Y = Ph (**e**).

Scheme 2.



X', Y' = X, Y or OAc.

Scheme 3.



positively charged Schiff base form [1–4]. Probably, the $P^{III}OAc$ derivative **4** generated in situ in the acetic anhydride medium from the startig hydrophosphorylic compound **2** (Scheme 2) also acts as a nucleophilic agent in the studied reaction.

We assumed the formation of a highly reactive positively charged form of the cyclic Schiff base **5** as an electrophilic component. Probably, it was generated in situ from 2-acetyloxy-N-Cbz-pyrrolidine **6** under the acid catalysis. The compound **6** was formed by acylating 2-hydroxy-N-Cbz-pyrrolidine **7** in acetic anhydride (Scheme 2). Perhaps the process of cyclization of 4-N-Cbz-aminobutyraldehyde **1** into 2-hydroxy-N-Cbz-pyr-rolidine **7** begins immediately after the removal of the acetal protection under acidic conditions.

The proposed procedure is a convenient method for the synthesis of phosphorylic proline analogs **3**, which includes one-pot formation of the pyrrolidine ring and its phosphorylation in acetic anhydride medium under acid catalysis at room temperature. The known methods for the synthesis of phosphorylic proline analogs are based on the use of various starting compounds already containing the pyrrolidine ring [8–11]. Phosphorous acid, diethyl phosphite, methylphosphonous, hydroxymethylphosphonous and diphenylphosphinic acids were studied as a hydrophosphorylic component. In general, acid catalysis is carried out by the addition of p-toluenesulfonic acid, as well as in the presence of acetyl chloride. The latter is especially necessary when using phosphorous acid, since in this case acylation of three acid groups occurs to form triacetyl phosphite as a nucleophilic three-coordinated component [4]. The use of hypophosphorous acid (0.5 equiv.) in this reaction resulted in symmetric phosphinic acid **9** as a double cyclization product (Scheme 3).

The obtained phosphorylic analogs of proline are a mixture of diastereomers and conformers, which is due

to the presence of several chiral centers and the relative conformational rigidity of the pyrrolidine ring, which was registered by the NMR spectra [8–11].

In summary, an approach to the synthesis of phosphorylic proline analogs by cyclic amidoalkylation of hydrophosphorylic compounds using 4-N-Cbz-aminobutyraldehyde in acetic anhydride medium under acid catalysis at room temperature was developed.

Dimethyl acetal 4-aminobutyraldehyde, acetic anhydride, acetyl chloride, and hypophosphorous acid were purchased from the Reakor company (Alfa Aesar). 4-[*N*-(Benzyloxycarbonyl)]aminobutyric aldehyde **1** was prepared by acylation of 4-aminobutyraldehyde dimethyl acetal using benzyloxycarbonyl chloride [12] in aqueous dioxane followed by gentle removal of acetal protection with hydrochloric acid and thorough drying of the compound in a vacuum [13].

General procedure of cyclic amidoalkylation of hydrophosphoryl compounds using 4-N-Cbz-aminobutyraldehyde. *p*-Toluenesulfonic acid (0.15–0.50 mmol) was added to a mixture of the hydrophosphorylic component (5 mmol) and 4-N-Cbz-aminobutyraldehyde (5 mmol) in 5 mL of acetic anhydride. When using phosphorous acid as the hydrophosphorylic component, acetyl chloride (~5 mL) was used as the catalyst. After 24 h, the reaction mixture was treated with water and evaporated. The residue was partitioned between 10 mL of chloroform and 25–35 mL of a saturated $NaHCO_3$ solution. The aqueous layer was separated, washed with 5–7 mL of diethyl ether, acidified to pH ~ 1–3 and extracted with ethyl acetate or chloroform (3 × 15 mL). If necessary, the purification procedure was repeated until the signal of the starting hydrophosphorylic compound in the ^{31}P NMR spectrum (20–30 ppm) disappeared. The organic layer was dried with sodium or magnesium sulfate and evaporated. The residue was chromatographed on silica gel eluting with chloroform, chloroform–isopropanol (3–7% or up to 12% in the case of compound **3a**). The obtained compounds were oily substances, that is typical for compounds containing N-protected pyrrolidine fragment [8–10].

1-*N*-(Benzyloxycarbonyl)pyrrolidin-2-yl-phosphonic acid (3a). Yield 57% (mixture of diastereomers and conformers). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.49–2.48 m (4H, CH_2CH_2, ring), 3.36–4.12 m (3H, CH_2N + CHN), 4.12 m (2H, CH_2O), 5.15 d (2H, PhC$\underline{H}_2$O, $^2J_{HH}$ = 6.4 Hz), 7.35 br.m (5H, Ph), 11.04 br.s (OH). ^{31}P NMR spectrum ($CDCl_3$), δ_C, ppm (the signals marked with an asterisk refer to minor isomers): 27.13*, 27.38*, 28.06, 28.62*, 29.07*. Mass spectrum (LCMS), *m/z*: 286.3711 [*M* + H] (calculated for $C_{12}H_{16}NO_5P$: 285.2329).

Diethyl 1-*N*-(benzyloxycarbonyl)pyrrolidin-2-yl-phosphonate (3b). Yield 68%, R_f ~0.6 ($CHCl_3$: *i*-PrOH = 10 : 1), ~0.5 [$CHCl_3$: $(CH_3)_2CO$ = 3 : 1]. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.19 t (6H, CH_3, $^3J_{HH}$ = 6.9 Hz), 1.70–2.30 m (4H, CCH_2CH_2C, ring), 3.35–3.55 m (2H, CH_2N), 3.85–4.30 m (5H, $2CH_2O$ + NCH), 5.08 br.m (2H, PhC$\underline{H}_2$O), 7.28 br.s (5H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.09* d and 16.16 d ($2CH_3$, $^3J_{PC}$ = 5.8 Hz), 23.10, 24.08* (CH_2, CH_2CH, ring), 26.42 and 27.22* (CH_2, CH_2CH_2, ring), 46.44 (CH_2N), 53.35 d (PCH, $^1J_{PC}$ = 162.6 Hz), 61.85 d (CH_2O, $^2J_{PC}$ = 6.9 Hz), 62.09* d (CH_2O, $^2J_{PC}$ = 7.3 Hz), 66.84 (Ph$\underline{C}H_2O$), 127.70* and 128.12 (Ph), 154.7 [NC(O)]. ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 14.82, 12.31*. Found, %: C 55.94, 56.03; H 7.34, 7.23. N 3.93, 3.96. $C_{16}H_{24}O_5P$. Calculated, %: C 56.30; H 7.09; N 4.10.

1-*N*-(Benzyloxycarbonyl)pyrrolidin-2-ylmethyl-posphinic acid (3c). Yield 65%, R_f~0.3–0.4 ($CHCl_3$:*i*-PrOH = 10 : 1), ~0.1–0.3 [$CHCl_3$: $(CH_3)_2CO$ = 3 : 1]. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.32*d and 1.52 d (3H, CH_3, $^3J_{HH}$ = 14.0 Hz), 1.70–2.50 m (4H, CCH_2CH_2C, ring), 3.40–3.55 m (2H, CH_2N), 4.10 br.s (1H, NCH), 5.11 br.s (2H, CH_2O), 7.33 br.m (5H, Ph), 8.08 br.s (OH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.4 d (CH_3, $^1J_{PC}$ = 90.9 Hz), 13.8* d (CH_3, $^1J_{PC}$ = 93.8 Hz), 23.52* and 24.52 (CH_2, CH_2CH_2, ring), 25.24 and 25.85 (CH_2, CH_2CH, ring), 47.06 and 51.21* (CH_2N), 56.62 d (PCH, $^1J_{PC}$ = 110.4 Hz), 56.25* (PCH, $^1J_{PC}$ = 113.9 Hz), 64.84* and 67.27 (Ph$\underline{C}H_2O$), 127.74*, 128.01* and 128.42 (Ph), 155.79 and 154.82* d [NC(O), $^3J_{PC}$ = 14.6 Hz]. ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 55.18*, 55.72, 56.05*, 56.96*. Found, %: C 54.94, 55.02; H 6.63, 6.46. N 4.77; 4.83. $C_{13}H_{18}O_4P$. Calculated, %: C 55.12; H 6.41; N 4.94.

1-N-(Benzyloxycarbonyl)pyrrolidin-2-yloxymethylphosphinic acid (3d). Yield 56%. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.70–2.50 m (4H, CCH_2CH_2C, ring), 3.40–3.54 m (2H, CH_2N), 3.55–4.10 m (2H, C$\underline{H}_2$OH), 4.35 br.s (1H, NCH), 5.23 br.s (2H, CH_2O), 7.42 br.m (5H, Ph), 8.50 br.s (2H, OH). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 45.03*, 47.02, 49.53*, 52.03*. Mass spectrum (LCMS), *m/z*: 300.3787 [*M* + H] (calculated for $C_{12}H_{16}NO_5P$: 299.2595).

1-*N*-(Benzyloxycarbonyl)pyrrolidin-2-yldiphenylphosphine oxide (3e). Yield 67%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.75–2.56 m (4H, CCH_2CH_2C, ring), 3.38–3.70 m (2H, CH_2N), 3.80–4.15 m (1H, CHN), 4.88 br.s (2H, CH_2O), 7.14–8.01 m (15H, Ph). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 32.21*, 34.24. Mass spectrum (LCMS), *m/z*: 406.4298 [*M* + H] (calculated for $C_{24}H_{24}NO_3P$: 405.4261).

Bis{*N*-(benzyloxycarbonyl)pyrrolidin-2-yl}phosphinic acid (9). A solution of 10 mmol of 4-N-Cbz-aminobutyraldehyde in 5 mL of glacial acetic anhydride was added to a solution of 5 mmol of hypophosphorous acid in 5 mL of glacial acetic anhydride at 0–10°C. Next, 0.5 mmol of p-toluenesulfonic acid was added to the resulting mixture. After 24 h, the reaction mixture was treated with water and evaporated. The oily residue was partitioned between 20–25 mL of chloroform or ethyl acetate and 10 mL of water. The organic layer was separated, washed with a $NaHCO_3$ solution until the hypophos-phorous acid signal in the ^{31}P NMR spectrum dis-appeared, dried with sodium or magnesium sulfate, and evaporated. The residue was chromatographed on silica gel eluting with chloroform, chloroform–iso-propanol (5%). Yield 41% (mixture of diastereomers and conformers), viscous oil, $R_f \sim 0.5$ ($CHCl_3$: *i*-PrOH = 10 : 1), ~ 0.2–0.3 [$CHCl_3$: $(CH_3)_2CO$ = 3 : 1]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.35–2.50 m (8H, CH_2CH_2, ring), 3.05–3.85 m (6H, CH_2N + CHN), 5.12 br.s (4H, $PhC\underline{H_2}O$), 7.33 m (10H, Ph). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 48.26*, 48.84*, 50.02*, 50.37, 50.59*, 51.89*, 52.35*. Mass spectrum (LCMS), *m/z*: 473.4913 [*M* + H] (calculated for $C_{24}H_{29}N_2O_6P$: 472.4707).

The ^{1}H, ^{31}P and ^{13}C NMR spectra were recorded on a Bruker DPX-200 Fourier spectrometer, internal reference TMS (^{1}H, ^{13}C) and external reference 85% H_3PO_4 (^{31}P). Chromatographic analysis was performed on an Agilent 1100 LC/MSD system with DAD, ELSD and a one-quadrupole mass-selective detector at electrospray ionization. TLC analysis was carried out on Silufol plates, Merck glass plates coated with 0.2 mm UV-254 silica gel, and Alufol (Kavalier) plates (neutral alumina on aluminum foil), developing with iodine vapor or UV light. N-Benzyloxycarbonyl-protected phosphorylic proline analogs were isolated by column chromatography on Silpearl and L100/160 (Chemapol) silica gel.

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