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LETTERS TO THE EDITOR

Synthesis of Phosphonic Analog of (*S*)-Homoproline

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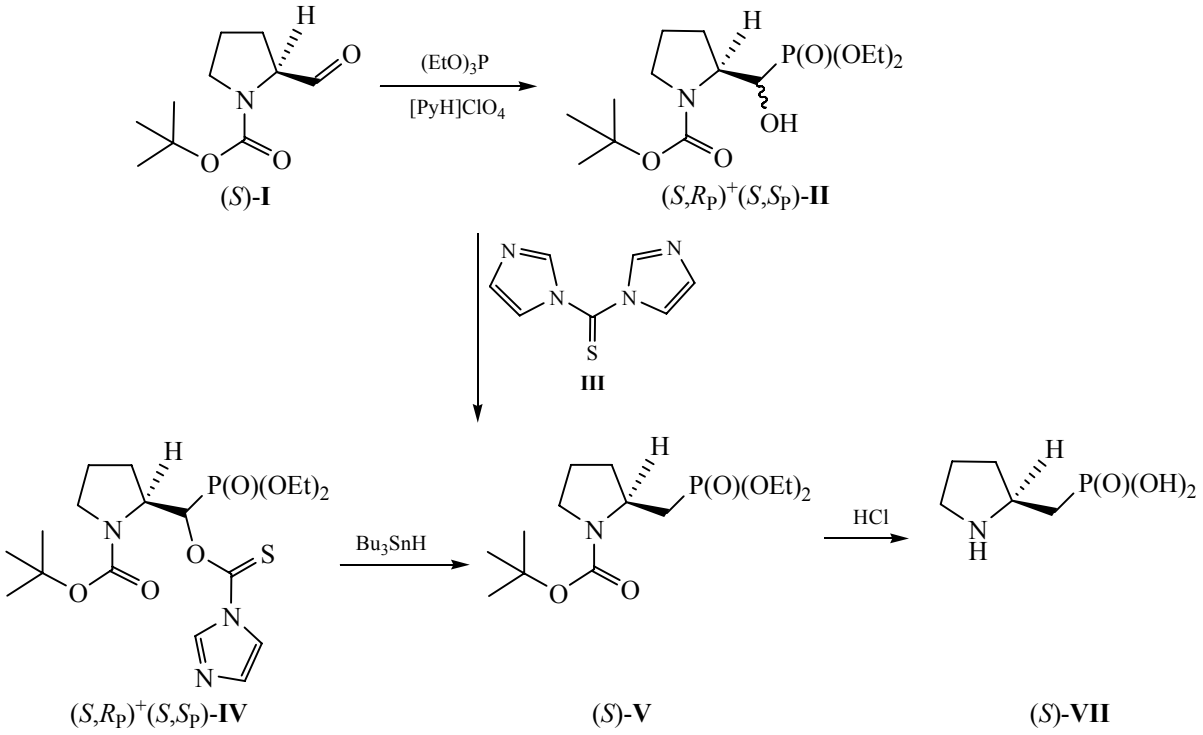
The reaction scheme for the synthesis of phosphonic analogue of homoproline was developed with application of Barton-McCombie reaction on the key step [1] (see Scheme 1).

N-Boc-Prolinal **I** was obtained by reduction of *N*-Boc-Proline methyl ester with H-DIBAL [2] and used as a starting compound. The phosphonylation of *N*-Boc-Prolinal **I** with triethylphosphite in the presence of pyridinium perchlorate as a catalyst [3] led to the formation of hydroxyphosphonate **II**, which was obtained as a mixture of (S,R_P) and (S,S_P) diastereoisomers in very high yield. After that the hydroxyphosphonate **II** was dehydroxylated according to Barton–McCombie method. The treatment of compound **II** with thiocarbonylbis (imidazole) **III** in dichloroethane at reflux afforded the compound **IV**, which was purified by column chromatography and its structure was confirmed by ^{1}H, ^{13}C, and ^{31}P NMR spectra.

Compound **IV** was then treated with tributylstannane in boiling toluene during several hours, in the presence of azobisisobutyrylnitrile to initiate the radical reaction (the reaction did not occur in the absence of azobisisobutyrylnitrile). The reaction progress was monitored by TLC and NMR spectroscopy. The protected *S*-homoproline **V** was isolated and purified by column chromatography on silica gel. Deprotection

Scheme 1.



(*S*)-**I** (S,R_P)$^+$(S,S_P)-**II** **III**

(S,R_P)$^+$(S,S_P)-**IV** (*S*)-**V** (*S*)-**VII**

of **V** was performed by hydrochloric acid treatment. The obtained *S*-homoproline analog is of potential interest as an organocatalyst [cf. 4, 5].

Diethyl 1-(*N*-Boc-2-pyrrolidine)-1-hydroxymethylphosphonate [a mixture of (S,R_P) and (S,S_P) diastereoisomers] **(II).** Pyridinium perchlorate (0.9 g, 0.05 mol) was added to solution of diethyl phosphite (3.1 g, 0.022 mol) and *N*-Boc-prolinal (4 g, 0.02 mol) in methylene chloride. The mixture was stirred at room temperature during 3 h, then filtered and evaporated. The residue was distilled under high vacuum. Yield 4.4 g (65 %), colorless liquid, bp 145°C (0.01 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ_H, ppm: 1.36 t (3H, CH_3, J_{HH} 7 Hz), 1.38 t (3H, CH_3, J_{HH} 7 Hz), 1.46 s (9H, CH_3C), 1.78–1.83 m (2H, CH_2), 2.17–2.23 m (2H, CH_2), 3.25–3.30 m (1H, CHO), 3.7–3.8 m (2H, CH_2), 4.05–4.12 m (1H, CHN), 4.25–4.33 m (4H, CH_2O). ^{31}P NMR spectrum, ($CDCl_3$): δ_P 24.90 and 24.31 ppm.

Diethyl 1-(*N*-Boc-2-pyrrolidine)-1-(1*H*-imidazolthiocarboxy)methylphosphonate (*S*)-(IV). Solution of hydroxyphosphonate **II** (4.4 g, 0.013 mol) and 1,1-thiocarbonyldiimidazole (4.6 g, 0.026 mol) in 100 mL of 1,2-dichloroethane was heated at 70°C during 3 h. After the reaction was completed (TLC), the mixture was subsequently washed with 1 mol/L HCl, $NaHCO_3$, and saturated NaCl solutions, dried, and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate–ethanol, 4 : 1). Yield (5.6 g, 90 %), yellowish solid. ^{1}H NMR spectrum ($CDCl_3$), δ_H, ppm: 1.28 t (3H, CH_3, J_{HH} 7 Hz), 1.32 t (3H, CH_3, J_{HH} 7 Hz), 1.55 s [9H, $(CH_3)C$], 2.00–2.40 m (4H, CH_2), 3.10–3.4 m (2H, CH), 4.12–4.18 m (4H, OCH_2), 4.39 br. s (1H, PCH), 6.80 d (1H, J_{HH} 12 Hz), 7.70 d (1H, J_{HH} 7 Hz), 8.35 d (1H, imidazolyl, J_{HH} 15 Hz). ^{31}P NMR spectrum ($CDCl_3$): δ_P 15.86 ppm.

Diethyl *N*-Boc-2-pyrrolidinemethylphosphonate (*S*)-(V). Tributylstannane (6.8 g, 0.024 mmol) and 0.3 g of azobisisobutyronitrile were added to solution of thiocarbamate **IV** (5.2 g, 0.012 mol) in 15 mL of anhydrous toluene. The mixture was refluxed during about 5 h, adding small portions of azobisisobutyronitrile from time to time. The mixture was cooled down and evaporated under reduced pressure. The residue was purified by silica gel column chromatography. Yield 1.6 g (40%), $[\alpha]_D^{20}$ –35 (*c* 1, $CDCl_3$). ^{1}H NMR spec-trum ($CDCl_3$), δ_H, ppm: 1.29 t (6H, CH_3, J_{HH} 7 Hz), 1.4 s (9H, CH_3C), 1.8 m (2H, PCH_2), 1.5 m (2H, CH_2), 2.1 m (2H, CH_2), 3.35 m (2H, CH_2), 3.8 m (1H, CH), 4.33 m (4H, OCH_2). ^{31}P NMR spectrum ($CDCl_3$): δ_P 28.3 ppm.

Diethyl (2-pyrrolidinmethyl)phosphonate (*S*)-(VI). Compound **V** (0.23 g, 0.5 mmol) was treated with 2 mol/L HCl under short-term heating. After cooling, the mixture was washed with ethyl acetate and water, and then evaporated to give phosphonate **VI**, $[\alpha]_D^{20}$ +15 (*c* 1, CH_3OH). ^{1}H NMR spectrum ($CDCl_3$), δ_H, ppm: 1.30–1.33 m (6H, CH_3), 1.5–1.6 m (1H, CH_2), 1.88–1.92 m (3H, CH_2), 2.15–2.25 m (3H, CH_2), 3.0–3.10 m (2H, CH_2), 3.45–3.53 m (1H, CHN), 4.16–4.23 m (4H, CH_2O). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 18.4 d ($^3J_{CP}$ 6 Hz), 26.4, 31.7 d ($^1J_{CP}$ 140 Hz), 66.4 d ($^2J_{CP}$ 6 Hz), 34.5 d ($^3J_{CP}$ 9.0 Hz), 48.0, 56.5. ^{31}P NMR spectrum (D_2O): δ_P 28 ppm.

(2-Pyrrolidinemethyl)phosphonic acid (*S*)-(VII). Mixture of solution of **V** (0.9 g, 0.002 mol) in dioxane and 8 mol/L hydrochloric acid was refluxed during 25–30 h. After the reaction was completed (TLC), the mixture was cooled, washed with ethyl acetate and water, and then evaporated. The residue was dissolved in ethanol and treated with 0.5 g of propylene oxide. Yield 0.14 g (40%), colorless solid, mp >200°C. ^{1}H NMR spectrum ($CDCl_3$), δ_H, ppm: 1.6–2.0 m (4H, CH_2), 2.17–2.22 m (2H, CH_2), 3.17–3.23 m (2H, CH_2N), 4.1 d. d (1H, CHN, J_{HP} 11 Hz, J_{HH} 3.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 23.0 d and 24.0 d (J_{PH} 100.0 Hz), 34.0, 49, 56.0. ^{31}P NMR spectrum (DMSO): δ_P 18.0 ppm. Found P, %: 18.9. $C_5H_{12}NO_3P$. Calculated P, %: 18.76.

NMR spectra were registered with Varian-300 spectrometer relative to internal TMS (^{1}H and ^{13}C) and to external 85% H_3PO_4 in D_2O (^{31}P).

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