New reaction pathway of dialkyl phosphorochloridites with salts of α-benzylideneaminocarboxylic acids. Direct synthesis of α-aminophosphonates from isostructural α-benzylideneaminocarboxylic acids

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The reaction of sodium *N*-benzylidenevalinate with dialkyl phosphorochloridites is accompanied by decarboxylation and yields diastereomeric *N*-(1-dialkoxyphosphoryl-2-methylpropyl)-*N*-(1-dialkoxyphosphorylbenzyl)amines.

Key words: α-benzylideneaminocarboxylic acids, phosphorylation, dialkyl phosphorochloridites, α-aminophosphonates.

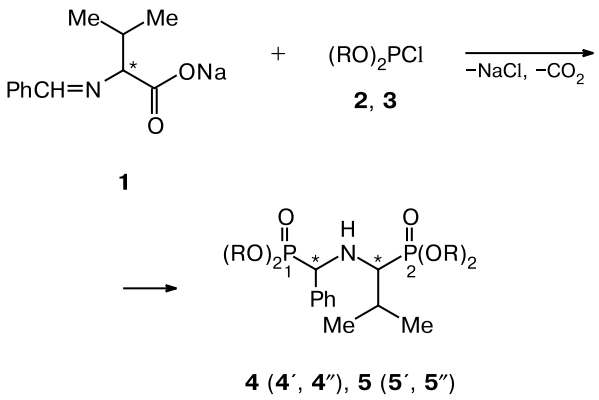
Natural α-amino acids are important representatives of the so-called chiral pool of compounds, which occur in nature in the L form and are widely used in synthetic organic chemistry.[1,2] These compounds can serve as cheap commercially available enantiomerically pure starting reagents for various synthetic purposes. These compounds are rather widely used in the chemistry of heteroorganic compounds, and, in particular, of organophosphorus compounds.[3] In recent years, the synthesis of enantiopure organophosphorus compounds has attracted considerable attention because the latter can be used as biologically active compounds and ligands for preparing homogeneous and heterogeneous catalysts.[3—5]

In this connection, we have recently studied[6] the reaction of sodium *N*-benzylideneglycinate with dialkyl phosphorochloridites and demonstrated that this reaction proceeds under very mild conditions and gives diphosphorylated dipeptides, *viz.*, 1,4-bis[α-(dialkoxyphosphoryl)benzyl]piperazine-2,5-diones, as a mixture of *d*,*l* and *meso* forms. With the aim of examining the possibility of using imino derivatives of chiral α-amino acids in this reaction, we studied the reaction of sodium (±)- and L-(−)-*N*-benzylidenevalinate (**1**)[7] with dialkyl phosphorochloridites **2** and **3**.

This reaction was found to follow an essentially different pathway. The reactions of the above reagents afford *N*-(1-dialkoxyphosphoryl-2-methylpropyl)-*N*-(1-dialkoxyphosphorylbenzyl)amines **4** and **5** (Scheme 1).

Study by ^{31}P and ^{1}H NMR spectroscopy provided evidence that amines **4** and **5** are produced as two diastereomers (**4´**, **4″** and **5´**, **5″** due to the presence of two chiral centers in these compounds) in nonequivalent amounts.

Scheme 1



4 (**4´**, **4″**), **5** (**5´**, **5″**)

R = Et (**2**, **4**), Pr^{i} (**3**, **5**)

The ^{31}P NMR spectra of products **4** and **5** are sufficiently characteristic. For example, the spectrum of amines **5´** and **5″** has two sets of resonances. The major diastereomer (arbitrarily, **5´**) gives two doublets with equal intensity in fields characteristic of the resonance of phosphonate phosphorus nuclei (δ_P 21.72 and 25.34 with the long-range coupling constant $^{4}J_{P(1),P(2)}$ = 7.4 Hz). The coupling constant $^{4}J_{P(1),P(2)}$ for the minor diastereomer is, apparently, substantially smaller and is not manifested as the corresponding splitting in the spectrum, due to which the resonances for the phosphorus nuclei of diastereomer **5″** appear as two slightly broadened singlets

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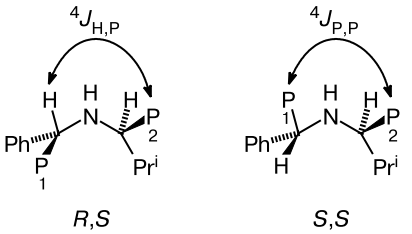
(δ_P 21.85 and 26.21). The integral intensity ratio of the signals for diastereomers **5′** and **5″** is 5 : 1.

The same integral intensity ratio of the signals for the diastereomers is observed in the ^{1}H NMR spectrum, where the signals for the methine protons at the α-carbon atoms are most characteristic. The α-proton of the benzyl fragment in major diastereomer **5′** appears as a doublet at δ_H 4.30 with the geminal coupling constant $^2J_{H,P}$ = 18.3 Hz, and the α-proton of the substituted isobutyl fragment appears as a doublet of doublets at δ 2.86 with the geminal coupling constant $^2J_{H,P}$ = 18.3 Hz and the vicinal coupling constant $^3J_{H,H}$ = 3.1 Hz. For minor diastereomer **5″**, the α-proton of the isobutyl fragment appears as a doublet of doublets at δ_H 2.46 ($^2J_{H,P}$ = 10.4 Hz, $^3J_{H,H}$ = 2.1 Hz), and the α-proton of the benzyl fragment overlaps with the multiplet of the methine protons of the isopropyloxy group at the phosphorus atom.

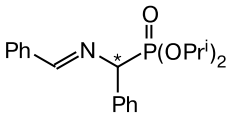
In the ^{1}H NMR spectrum of major diastereomer **4′**, the region of methine protons is virtually identical to that in the spectrum of **5′**. The α-proton of the benzyl fragment of diastereomer **4′** appears as a doublet at δ_H 4.26 with $^2J_{H,P}$ = 18.0 Hz, and the α-proton of the isobutyl fragment appears as a doublet of doublets at δ_H 2.87 with $^2J_{H,P}$ = 18.3 Hz and $^3J_{H,H}$ = 3.1 Hz. The α-proton of the isobutyl fragment of minor diastereomer **4″** is observed as a doublet of doublets at δ_H 2.54 with $^2J_{H,P}$ = 10.2 Hz and $^3J_{H,H}$ = 3.1 Hz. It is noteworthy that the signal for the α-proton of the benzyl fragment of diastereomer **4″**, which is not observed in the spectrum of **5″**, appears as a doublet of doublets at δ_H 4.62 with $^2J_{H,P}$ = 19.2 Hz and also has, apparently, the long-range coupling constant with the second phosphorus atom $^4J_{H,P}$ = 3.9 Hz. As mentioned above, the long-range coupling constant through four bonds, $^4J_{P(1),P(2)}$, in the ^{31}P NMR spectrum is clearly seen only for the major isomer and is not observed for the minor isomer. To the contrary, the long-range coupling constant through four bonds, $^4J_{H,P}$, in the ^{1}H NMR spectrum is observed only for the minor isomer and is not seen for the major isomer. Apparently, this is attributed to the fact that the relative change in the configuration of the chiral centers for different isomers leads to interchange of the spatial positions of the proton and phosphorus atom. The possible conformations of diastereomers **4** and **5** are given below (for one enantiomeric pair, *viz.*, *R*,*S* and *S*,*S*).



The diastereoselectivity of the reaction with diethyl phosphorochloridite appeared to be slightly lower than that with diisopropyl phosphorochloridite (*dr* 3 : 1 and 5 : 1, respectively).

It should be noted that the yields of the products can be increased by performing the reactions with the use of phosphorochloridite and imino acid in a ratio of 2 : 1. However, under these conditions, the reaction mixture contained up to 15% of unconsumed dialkyl phosphorochloridite **2** or **3**. Major diastereomer **5′** prepared by the reaction of phosphite **3** was isolated in pure form.

At the same time, benzylideneaminophosphonate **6** was isolated from the reaction mixture, which was prepared by the reaction with the use of a small excess of salt **1**. Compound **6** is, apparently, the primary reaction product. In addition, the reaction mixture always contained up to 10% of dialkyl phosphites $(RO)_2P(O)H$ easily identifiable by ^{31}P NMR spectroscopy (δ_P 4.50 and 8.50, $J_{H,P} \approx$ 680 Hz).



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The mechanism of this reaction requires additional study. Apparently, this process involves oxidative decarboxylation of α-benzylideneaminocarboxylic acids.[8,9] Thus, CO_2 was eliminated from the reaction mixture, which was detected both visually and by the qualitative reaction with lime water.

Unfortunately, the reaction with sodium L-(−)-*N*-benzylidenevalinate is accompanied by racemization of the optically active center of the α-amino acid. The specific rotation of the crude material (after removal of the precipitate and the solvent) obtained by the reaction of **1** with **2** (in a ratio of 1 : 1) was $[\alpha]_D^{20}$ −2.70 (*c* 3.59, $CHCl_3$), and the specific rotation of the product prepared by the reaction of **1** with **3** (in a ratio of 1 : 2) was $[\alpha]_D^{20}$ −4.71 (*c* 3.58, $CHCl_3$). For comparison, the specific rotation of the starting compound **1** is $[\alpha]_D^{20}$ −63.60 (*c* 2.12, methanol). After chromatographic purification, the reaction products have no optical activity. Apparently, racemization of the chiral carbon atom of the amino acid occurs in early steps of the reaction, and the formation of the first P—C bond occurs non-enantioselectively. The observed diastereoselectivity is conditioned by the addition of the second equivalent of phosphite to the imine fragment giving rise to the second chiral center. The diastereomer ratio is approximately equal to that obtained in the reaction with racemic compound **1**.

It should be noted that we prepared analogous products (**4** and **5**) by the reaction of *N*-benzylidenevaline trimethylsilyl ester with diisopropyl phosphorochloridite. Apparently, this reaction afforded also products with a structure of piperazine-2,5-dione (analogous compounds were prepared as the major products by the reactions of dialkyl phosphorochloridites with sodium *N*-benzylideneglycinate).[6] The NMR spectra of the reaction mixtures and intermediate fractions isolated by column chroma-

tography show signals, which could belong to these products (singlets at δ_P 17—18 in the ^{31}P NMR spectrum and doublets at δ_H ~5—6 with $^2J_{H,P} \approx 20$ Hz in the ^1H NMR spectrum).[6] However, attempts to isolate these product in pure form failed because of low yields and difficulties of chromatographic separation.

To conclude, the above-described reaction provides the straightforward replacement of the carboxy group in α-aminocarboxylic acids with the phosphonic group and makes it possible to synthesize isostructural α-aminophosphonates directly from the corresponding α-benzylideneaminocarboxylic derivatives. The close precedents of the direct transformation of amino acids into the corresponding phosphonates are scarce in the literature[10—12] and have limitations.

Experimental

The $^{31}P\{^1H\}$ NMR spectra were recorded on a CXP 100 spectrometer in $CDCl_3$ with 85% H_3PO_4 as the external standard. The ^1H NMR spectra were measured on an AVANCE-600 instrument in $CDCl_3$. The ^{13}C NMR spectra were recorded on a Bruker MSL-400 instrument in $CDCl_3$. The IR spectra were measured on a Vector 22 Fourier-transform IR spectrometer (Bruker) in a thin layer. The EI mass spectra (70 eV) were obtained on a Finnigan MAT TRACE MS instrument (ion source temperature was 200 °C, direct inlet of the sample, the evaporator tube was heated from 35 to 150 °C with a step of 35 °C min^{-1}). The mass-spectrometric data were processed using the Xcalibur program. The CI mass spectra were obtained on a Finnigan MAT-212 instrument (pentane as the reagent gas, direct inlet of the sample, the ion source temperature was 120 °C, the temperature of the evaporator tube was 100—200 °C). The mass-spectrometric data were processed using the MASPEC 32 system program. The optical rotation was measured on a Perkin—Elmer 341 polarimeter.

Sodium salt **1** was prepared by the reaction of (±)- and L-(+)-valine with benzaldehyde in an aqueous-ethanolic solution.[7] For the L-(+)-valine derivative, m.p. 280 °C, $[\alpha]_D^{20}$ −63.60 (*c* 2.12, methanol).

***N*-(1-Dialkoxyphosphoryl-2-methylpropyl)-*N*-(1-dialkoxyphosphorylbenzyl)amines 4′, 4″ and 5′, 5″ (general procedure).** An equimolar amount of dialkyl phosphorochloridite **2** or **3** in $CHCl_3$ (5 mL) was added with stirring to a suspension of sodium *N*-benzylidenevalinate (**1**) (1.00 g, 4.4 mmol) in anhydrous $CHCl_3$ (20 mL) at ~20 °C. The reaction mixture was stirred for 4 h and then allowed to stand for ~24 h. The precipitate that formed was filtered off and the filtrate was concentrated. The residue was chromatographed on SiO_2 (Chemapol, L 100/160 mesh) in the 1 : 4 acetonitrile—toluene system, the eluate was monitored by TLC on Silufol UV-254 plates. After chromatography, the total yield of products **4′**, **4″** and **5′**, **5″** was 33 and 35%, respectively. In the reaction of compound **1** with **3** in a ratio of 1 : 2, the total yield of products **5′**, **5″** increased to 54%, and the major isomer **5′** was isolated in the individual state by chromatography (12% yield).

***N*-(1-Diethoxyphosphoryl-2-methylpropyl)-*N*-(1-diethoxyphosphorylbenzyl)amine (4) (mixture of diastereomers 4′ and 4″).** Colorless viscous oil, n_D^{20} 1.5110. Found (%): C, 52.40; H, 8.03; N, 3.32; P, 14.26. $C_{19}H_{35}NO_6P_2$. Calculated (%): C, 52.41; H, 8.10; N, 3.22; P, 14.23. ^1H NMR, δ: 0.89—1.35 (m, 18 H, $OCH_2C\underline{H}_3$, $CH(C\underline{H}_3)_2$ (**4′**, **4″**)); 2.02—2.20 (m, 1 H, $C\underline{H}(CH_3)_2$ (**4′**, **4″**)); 2.54 (dd, 0.25 H, $Pr^iC\underline{H}N$, $^2J_{H,P}$ = 10.2 Hz, $^3J_{H,H}$ = 3.1 Hz (**4″**)); 2.87 (dd, 0.75 H, $Pr^iC\underline{H}N$, $^2J_{H,P}$ = 18.3 Hz, $^3J_{H,H}$ = 3.1 Hz (**4′**)); 3.77—4.15 (m, 8 H, $OC\underline{H}_2CH_3$ (**4′**, **4″**)); 4.26 (d, 0.75 H, $PhC\underline{H}N$, $^2J_{H,P}$ = 18.0 Hz (**4′**)); 4.62 (dd, 0.25 H, $PhC\underline{H}N$, $^2J_{H,P}$ = 19.2 Hz, $^4J_{H,P}$ = 3.9 Hz (**4″**)); 7.10—7.44 (m, 5 H, Ph (**4′**, **4″**)). ^{31}P NMR, δ: 23.01 and 26.76 (both d, $^4J_{P(1),P(2)}$ = 7.4 Hz (**4′**)); 23.11 and 27.68 (both s (**4″**)). The integral intensity ratio of the signals of **4′** and **4″** was 3 : 1. IR, ν/cm^{-1}: 1026, 1051 (P—O—C), 1245 (P=O), 3469 (NH). MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 435 $[M]^+$ (1.0), 298 $[M - (EtO)_2PO]^+$ (73.5), 242 $[M - (EtO)_2PO - Et - Et']^+$ (51.5), 161 $[M - (EtO)_2PO - (EtO)_2PO']^+$ (100). MS (CI, 200 eV), *m*/*z* (I_{rel} (%)): 436 $[M + H]^+$ (100).

***N*-(1-Diisopropoxyphosphoryl-2-methylpropyl)-*N*-(1-diisopropoxyphosphorylbenzyl)amine (5) (mixture of diastereomers 5′ and 5″).** Colorless viscous oil, n_D^{20} 1.5011. Found (%): C, 56.23; H, 8.70; N, 2.83; P, 12.60. $C_{23}H_{43}NO_6P_2$. Calculated (%): C, 56.20; H, 8.82; N, 2.85; P, 12.60. ^1H NMR, δ: 0.91—1.35 (20 d, 30 H, $OCH(C\underline{H}_3)_2$, $CCH(C\underline{H}_3)_2$, $^3J_{H,H}$ = 6.5 Hz (**5′**, **5″**)); 2.05—2.21 (m, 1 H, $CC\underline{H}(CH_3)_2$ (**5′**, **5″**)); 2.46 (dd, 0.15 H, $Pr^iC\underline{H}N$, $^2J_{H,P}$ = 10.4 Hz, $^3J_{H,H}$ = 2.1 Hz (**5″**)); 2.86 (dd, 0.85 H, $Pr^iC\underline{H}N$, $^2J_{H,P}$ = 18.3 Hz, $^3J_{H,H}$ = 3.1 Hz (**5′**)); 4.30 (d, 0.85 H, $PhC\underline{H}N$, $^2J_{H,P}$ = 18.3 Hz (**5′**)); 4.45—4.79 (m, 4.15 H, $OC\underline{H}(CH_3)_2$ (**5′**, **5″**) and $PhC\underline{H}N$ (**5″**)); 4.62 (dd, 0.15 H, $PhC\underline{H}N$, $^2J_{H,P}$ = 19.2 Hz, $^3J_{H,P}$ = 3.9 Hz (**5″**)); 7.15—7.48 (m, 5 H, Ph (**5′**, **5″**)). ^{31}P NMR, δ: 21.72 and 25.34 (both d, $^4J_{P(1),P(2)}$ = 7.4 Hz (**5′**)); 21.85 and 26.21 (both s (**5″**)). The integral intensity ratio of the signals of **5′** and **5″** was 5 : 1. IR, ν/cm^{-1}: 1024 (P—O—C), 1245 (P=O), 3464 (NH). MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 492 $[M]^+$ (3.4), 326 $[M - (Pr^iO)_2PO]^+$ (80.5), 270 $[M - (Pr^iO)_2PO - Et - Et']^+$ (46.0), 160 $[M - (Pr^iO)_2PO - (Pr^iO)_2POH]^+$ (100). MS (CI, 200 eV), *m*/*z* (I_{rel} (%)): 492 $[M + H]^+$ (100).

Diastereomer 5′. White crystals, m.p. 188—190 °C. ^1H NMR, δ: 1.03—1.30 (10 d, 30 H, $OCH(C\underline{H}_3)_2$, $CCH(C\underline{H}_3)_2$, $^3J_{H,H}$ = 6.5 Hz); 2.11—2.21 (m, 1 H, $CC\underline{H}(CH_3)_2$); 2.86 (dd, 1 H, $Pr^iC\underline{H}N$, $^2J_{H,P}$ = 18.3 Hz, $^3J_{H,H}$ = 3.1 Hz); 4.30 (d, 0.85 H, $PhC\underline{H}N$, $^2J_{H,P}$ = 18.3 Hz); 4.49—4.71 (m, 4 H, $OC\underline{H}(CH_3)_2$); 7.15—7.48 (m, 5 H, Ph). ^{31}P NMR, δ: 21.7 and 25.3 (both d, $^4J_{P(1),P(2)}$ = 7.4 Hz). ^{13}C NMR, δ: 18.74 (s, $CCH(\underline{C}H_3)_2$); 20.24 (d, $CCH(\underline{C}H_3)_2$, $^3J_{C,P}$ = 10.6 Hz); 22.64—24.49 (m, $OCH(\underline{C}H_3)_2$); 28.66 (s, $C\underline{C}H(CH_3)_2$); 58.40 (dd, $Pr^i\underline{C}HP$, $^1J_{C,P}$ = 55.2 Hz, $^3J_{C,P'}$ = 10.2 Hz); 59.90 (dd, $P\underline{C}HPh$, $^1J_{C,P}$ = 49.9 Hz, $^3J_{C,P'}$ = 13.2 Hz); 127.96—136.00 (m, C arom.).

***O*,*O*-Diisopropyl (benzylideneamino)(phenyl)methanephosphonate (6)** was prepared according to an analogous reaction, **1** : **3** ≈ 1.1 : 1, in 9.4% yield, colorless viscous oil, n_D^{20} 1.5211. Found (%): C, 66.82; H, 7.25; N, 3.88; P, 8.64. $C_{20}H_{26}NO_3P$. Calculated (%): C, 66.84; H, 7.29; N, 3.90; P, 8.62. ^1H NMR, δ: 1.18, 1.21, 1.25, and 1.27 (all d, 12 H, $OCH(C\underline{H}_3)_2$, $^3J_{H,H}$ = 6.3 Hz); 4.61—4.68 (m, 2 H, $OC\underline{H}(CH_3)_2$); 4.87 (d, 1 H, PCH, $^2J_{H,P}$ = 18.8 Hz); 7.25—7.84 (m, 10 H, Ph); 8.41 (d, 1 H, $PhC\underline{H}N$, $^4J_{H,P}$ = 4.7 Hz). ^{31}P NMR, δ: 18.60. ^{13}C NMR, δ: 23.71, 23.90, 24.13, and 24.30 (all d, 2 $OCH(\underline{C}H_3)_2$ + 2 $OCH(\underline{C}'H_3)_2$, $^3J_{C,P}$ = 6.6 Hz and $^3J_{C,P}$ = 4.0 Hz, respectively); 71.66 and 71.73 (both d, $O\underline{C}H(CH_3)_2$ + $O\underline{C}'H(CH_3)_2$, $^2J_{C,P}$ = 9.3 Hz); 73.95 (d, CP, $J_{C,P}$ = 255.2 Hz); 127.60—136.88 (m, C arom.); 164.0 (d, C=N, $J_{C,P}$ = 15.9 Hz). IR, ν/cm^{-1}:

989—1072 (P—O—C), 1249 (P=O), 1639 (C=N). MS (EI, 70 eV), m/z (I_{rel} (%)): 359 $[M]^+$ (0.2), 194 $[M - (Pr^iO)_2PO]^+$ (100).

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