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Reaction of sodium *N*-benzylideneglycinate with dialkyl chlorophosphites in the presence of water

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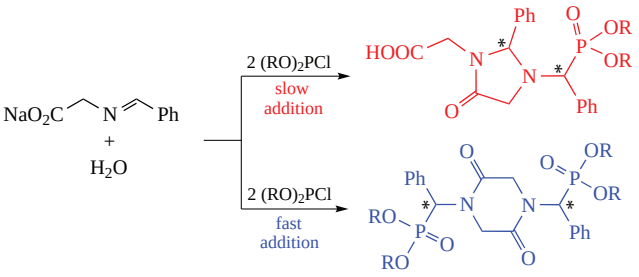
The outcome of reaction of sodium *N*-benzylideneglycinate containing water in its crystal lattice with dialkyl chlorophosphites depends on the mode of addition of the latter. Upon the simultaneous mixing of the reactants, 1,4-bis[α-(dialkoxyphosphoryl)benzyl]piperazine-2,5-diones are formed from two molecules of each reactant. With the slow addition of dialkyl chlorophosphite, the main reaction product is 2-{3-[α-(dialkoxyphosphoryl)benzyl]-5-oxo-2-phenylimidazolidin-1-yl}acetic acid ('1 : 2 adduct'), its formation comprising 1,4-migration of dialkoxyphosphoryl moiety.



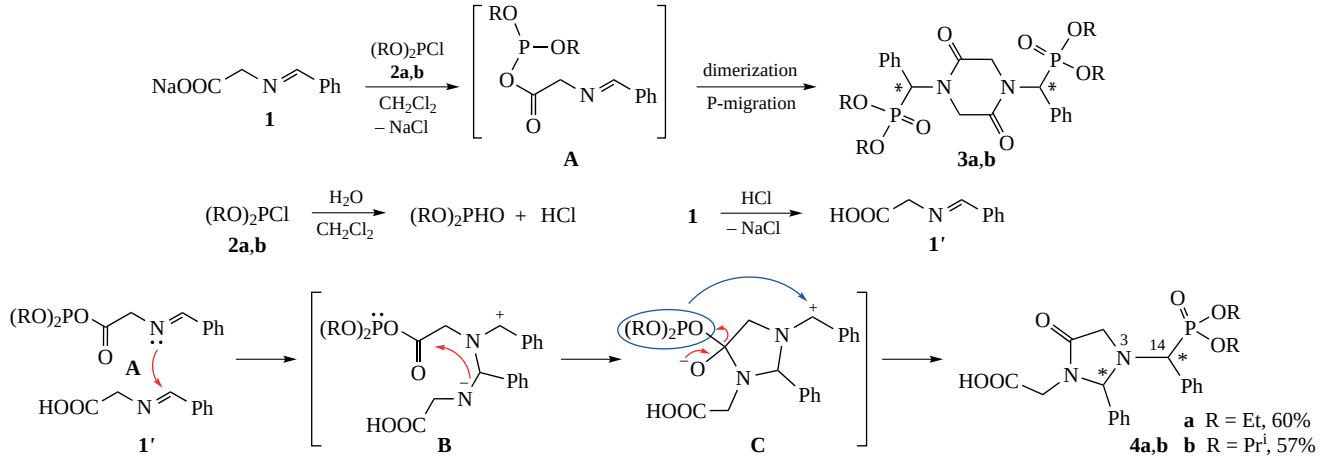
Keywords: sodium *N*-benzylideneglycinate, dialkyl chlorophosphite, 5-oxo-2-phenylimidazolidine, piperazine-2,5-dione, 1-amino-phosphonate, diversity-oriented synthesis.

α-Amino phosphonic acids and their esters (as well as related α-amino phosphinates and α-amino phosphine oxides) are isosteres of aminocarboxylic acids that mimic the transition state in the process of peptide cleavage, and have a high and diverse biological activity.[1] Such compounds and their analogues exhibit antibacterial,[2,3] antifungal,[3] antitumor,[3,4] antioxidant,[5] and antiviral[2(*b*)] activities, and are capable of inhibiting acetyl-cholinesterase[5,6] and α-glucosidase.[7]

Among the main methods for the synthesis of α-amino-phosphonates and related compounds, the Pudovik reaction (addition of hydrophosphoryl compounds to imines) and the Kabachnik–Fields reaction (assembling of aldehyde, amine and hydrophosphoryl compound) are traditionally used. Interest in some other, including catalytic, variants of these reactions is very high [see, *e.g.*, recent works[2(*a*),3,6(*a*),8,9]]. The reaction of the six-membered ring expansion in 1,3,2-benzodioxaphosphorin-4-ones under the action of imines to the seven-membered products and its intramolecular version,[10] the addition of nucleophiles to phosphorus-containing azirines followed by aziridine ring opening,[4(*c*)] and also the reaction of 1,2-imino alcohols with dialkylchlorophosphites leading to 1,4,2-oxazaphosphorines[11] are of note.

We have previously reported[12] that the reaction beetwen sodium *N*-benzylideneaminoacetate and dialkyl phosphites (20 °C, $CHCl_3$) led to 1,4-bis[α-(dialkoxyphosphoryl)benzyl] piperazine-2,5-diones (52–58%), which can be considered as a new method for obtaining α-aminoalkylphosphonic acid derivatives. It turned out that the outcome of reaction between imino carboxylic acid salts and dialkyl phosphites was affected by water which was formed in the course of synthesis of the imino acids and was often incorporated in the crystal lattice of the salts. Thus, the reaction of *N*-benzylidenephenylglycine and *N*-benzylidenealanine sodium salts with dialkylchlorophosphites in the presence of water proceeded in a new way to afford stereoisomers of bis[α-(dialkoxyphosphoryl)alkyl]amines.[13] Noticeable amounts of dialkyl phosphites, products of the side dialkylchlorophosphite hydrolysis, were also formed.

In this work, we found that the composition and ratio of the resulting compounds depended not only on the presence of water (in the crystal lattice of sodium *N*-benzylideneglycinate **1**), but also on the mode of addition of dialkyl chlorophosphite **2** (Scheme 1). If an excess of chlorophosphite **2** is slowly added to a suspension of salt **1** in chloroform (in contrast to the data of ref. 12 when all chlorophosphite was added immediately), the main reaction products turn to be not 1,4-bis[α-(dialkoxy-phosphoryl)benzyl]piperazine-2,5-diones **3a**,**b** but rather different novel derivatives of (5-oxo-2-phenylimidazolidin-1-yl)-acetic acid **4a**,**b**. We associate this with the formation of free *N*-benzylideneglycine **1′** in the course of acidification of sodium salt **1** with hydrogen chloride. Obviously, HCl is generated from crystalline water and chlorophosphites **2** to give also dialkyl phosphites $(RO)_2P(O)H$ as side products. In this case, the contribution of the reaction between the intermediate phosphite **A** and free acid **1′** which would readily migrate into chloroform solution should greatly increase. Apparently, the nitrogen atom of intermediate **A** attacks the imino group of compound **1′**, leading to a bipolar ion **B** which would undergo intramolecular cyclization followed by migration of the phosphorus moiety to the carbocation center to afford intermediate **C** and finally imidazolidinone derivative **4**.



Scheme 1

Major reaction products **4** and side compounds **3** were separated by column chromatography.† Their structure has been confirmed by the 1D and 2D NMR spectroscopy (^{1}H, ^{1}H-{^{31}P}, ^{13}C, ^{13}C-{^{1}H}, ^{13}C-{^{1}H}-dept, C,H-HMBC, C,H-HSQC, ^{31}P, ^{31}P-{^{1}H}) as well as ESI and MALDI mass spectrometry. As for compound **4a**, we succeeded in isolating one of two possible diastereomers and confirming its structure by the XRD (Figure 1).‡ A non-centrosymmetric crystal consists only of molecules of the pure enantiomer, in which the configuration of chiral atoms is $C_S^2C_R^{14}N_S^3$. However, since compound **4a** is racemate in a solution, its crystals should be a conglomerate of non-centrosymmetric crystals of enantiomers. In the single crystal of (2*S*,14*R*)-**4a** (see Figure 1), the phosphorus atom has the usual distorted tetrahedral configuration. One nitrogen atom [N(1)] has a planar trigonal configuration, and the other one [N(3)] has a flattened trigonal pyramidal configuration and becomes chiral. The imidazolidinone ring has a distorted envelope conformation [the N(1)C(2)C(3)C(5) fragment is planar within 0.038(4) Å, the N(3) atom is deviated from this plane by –0.491(4) Å], the N(1)–C(2)–N(3)–C(4) torsion angle is –34.0(4)°. The C(8) and C(14) atoms are deviated from this plane by –0.839(4) and –0.286(5) Å, the corresponding torsion angle C(8)–N(2)–C(3)–N(14) is 73.2(4)°.

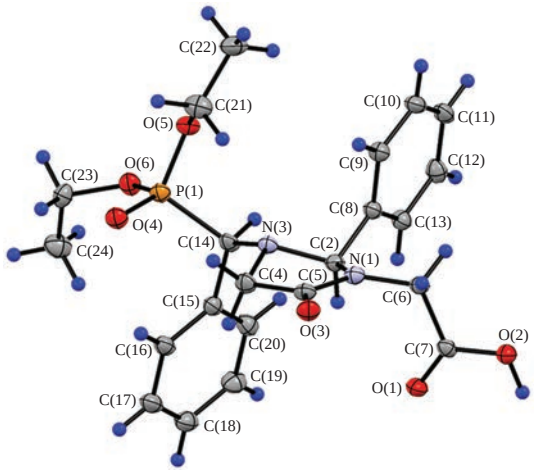


Figure 1 Geometry of molecule **4a** in the crystal (for the $C_S^2C_R^{14}N_S^3$-enantiomer of the diastereomer d_1). Selected bond lengths (Å) and bond angles (°): P(1)–O(4) 1.467(3), P(1)–O(5) 1.566(4), P(1)–O(6) 1.556(3), P(1)–C(14) 1.816(5), N(1)–C(2) 1.470(5), N(1)–C(5) 1.349(6), N(3)–C(2) 1.476(5), N(3)–C(4) 1.463(6), C(2)–N(1)–C(6) 124.0(3), C(5)–N(1)–C(6) 122.2(3), C(2)–N(1)–C(5) 112.0(3), C(2)–N(3)–C(4) 106.2(3), C(4)–N(3)–C(14) 118.8(3), C(2)–N(3)–C(14) 114.3(4).

† *2-{3-[α-(Diethoxyphosphoryl)benzyl]-5-oxo-2-phenylimidazolidin-1-yl}acetic acid* **4a**. To a suspension of sodium *N*-benzylideneglycinate **1** (2.22 g, 12.0 mmol) in dry CH_2Cl_2 (30 ml) at 20–25 °C and vigorous stirring under argon, a solution of diethyl chlorophosphite **2a** (3.76 g, 24 mmol) in CH_2Cl_2 (20 ml) was added dropwise over 1.5 h, and the mixture was stirred for another 1 h. The next day, the precipitate was filtered off in a Schott funnel, the filtrate was concentrated *in vacuo*, and the light brown oily residue was treated with water (3 × 10 ml). After drying *in vacuo*, the residue turned into a powder of the similar color, which was further purified by column chromatography on silica gel (gradient benzene/MeCN, 3 : 1 → 0 : 1, TLC control). First, 1,4-bis[α-(diethoxyphosphoryl)benzyl]piperazine-2,5-dione **3a** (1.36 g, 20%) as a mixture of *d*,*l* and *meso* diastereomers was eluted, its spectral data corresponding to previously published.[12] Further elution gave a fraction with one of diastereomers of compound **4a** (d_1) with the configuration of chiral centers (2*S**,14*R**), from which it was isolated in pure form. Upon slow evaporation of the solvent from a solution of **4a** (d_1) in chloroform, the stereoisomer crystallizes with the formation of crystals suitable for investigation by XRD, mp 209–211 °C. In total, 3.25 g (60%) of compound **4a** was obtained as a light brown oil (mixture of two diastereomers) from fractions with different ratios.

2-{3-[α-(Diisopropoxyphosphoryl)benzyl]-5-oxo-2-phenylimidazolidin-1-yl}acetic acid **4b** was obtained similarly from diisopropyl chlorophosphite **2b** (2.50 g, 13.55 mmol) and sodium benzylideneglycinate **1** (1.25 g, 6.76 mmol) as a light brown oil (1 : 1.2 diastereomer mixture), yield 0.91 g (57%).

1,4-Bis[α-(diisopropoxyphosphoryl)benzyl]piperazine-2,5-dione **3b**, a minor product, was isolated as a 1 : 1 mixture of *meso* and *d*,*l* diastereomers in a yield of 0.50 g (24%), its ^{1}H and ^{31}P NMR spectra corresponding to those reported.[12]

For the characterization of compounds, see Online Supplementary Materials.

‡ *Crystal data for* **4a**. $C_{22}H_{27}N_2O_6P$, M_r = 446.42, monoclinic, space group $P2_1$, at 100 K, a = 8.1686(3), b = 13.0294(4) and c = 10.9124(3) Å, β = 107.327(3)°, V = 1108.72(6) Å^3, Z = 2, Z' = 1, d_{calc} = 1.337 g cm^{-3}, μ(CuK$_\alpha$) = 1.451 mm^{-1}, F(000) = 472. Total of 24033 reflections were collected (4395 of which were unique, R_{int} = 0.0704) and used in refinement, which converged to wR_2 = 0.1667, GOOF 1.095 for all data, R_1 = 0.0614, wR_2 = 0.1641 for 4149 reflections with $I > 2\sigma(I)$.

The X-ray diffraction analysis was carried out on a Rigaku Xta Lab Synergy S instrument with a HyPix detector and a Photon Jet microfocus X-ray tube using CuK$_\alpha$ (1.54184 Å) radiation at 100 K. Images were indexed and integrated using the CrysAlisPro data reduction package. The structure was solved by direct methods using SHELXT[14] and refined by the full-matrix least-squares on F^2 using SHELXL.[15] Non-hydrogen atoms were refined anisotropically. The hydrogen atoms were inserted at the calculated positions and refined as riding atoms. The figures were generated using Mercury 4.1 program.[16] Absolute configuration established by anomalous-dispersion effects in diffraction measurements on the crystal, Flack parameter –0.01(4).

CCDC 2032718 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

To conclude, the reaction of *N*-arylideneamino carboxylic acids sodium salts with dialkylchlorophosphites is strongly dependent on the experimental processing and the presence of water. We herein accomplished an example of diversity-oriented synthesis leading to fundamentally different structures of the amino phosphonate type. The results seem promising for extention to other types of amino carboxylic acids.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.01.033.

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