ISSN 1070-3632, Russian Journal of General Chemistry, 2012, Vol. 82, No. 6, pp. 1178–1179. © Pleiades Publishing, Ltd., 2012.
Original Russian Text © A.V. Lebedev, V.D. Sheludyakov, O.L. Ustinova, A.B. Lebedeva, 2012, published in Zhurnal Obshchei Khimii, 2012, Vol. 82, No. 6, pp. 1044–1045.

LETTERS TO THE EDITOR

Silylation of Hydroxyalkylidenediphosphonic Acids as an Effective Method of Their Purification

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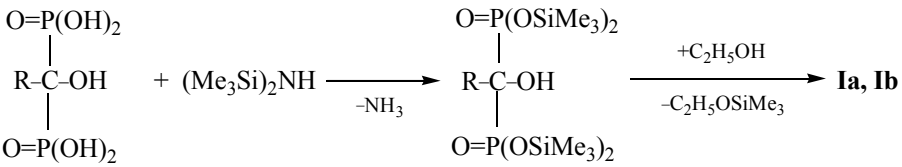
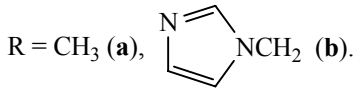
Received November 21, 2011

DOI: 10.1134/S1070363212060254

As known, the silylation of hydroxyl-containing organic compounds significantly increases their volatility. Therefore it seemed interesting to study the silylation of some hydroxyalkylidenediphosphonic acids and to test the possibility of using this procedure for a deep purification of these substances. Alkylidenediphosphonic acids are widely used as complex forming agents in chemistry and medicine [1], and significant difficulties are often met while isolating them in a pure state [2, 3].

We have found that hydroxyalkylidenediphosphonic acids **Ia, Ib** react with hexamethyldisilazane (HMDS) to form the silylation products of four of the five hydroxy groups, that is, tetrakistrimethylsilyl esters **IIa, IIb** were obtained, according to the following scheme.





Recently it was reported on the synthesis of pentasilylated alkenylidenediphosphonic acids by the reaction of unsaturated carboxylic acid chlorides with tris(trimethylsilyl)phosphite [4]. The formation of tetrasilyl derivatives in our case may be ascribed to the decrease in the acidity of the hydroxy group on the carbon atom due to the decrease in electron-acceptor properties of both oxyphosphonic groups due to the arising double bonding between the silicon and oxygen atoms, and also to the insufficient reactivity of the silylating agent because of this effect.

The structure of compounds **IIa, IIb** was established from the data of elemental analysis, mass spectra, and ^{1}H NMR spectra. In the ^{1}H NMR spectra the signals of protons of four trimethylsilyl groups, of hydroxy group, and of the protons on α-carbon atom which take part in coupling with phosphorus atoms are observed.

The synthesis of compounds **IIa, IIb** is complicated by the formation of poorly soluble salts of starting diphosphonic acids due to their reaction with liberating ammonia. These salts decompose above 100°C with the separation of ammonia and the liberation of starting phosphonic acids. Due to that the reaction requires a prolonged boiling in the excess of HMDS. More stable compound **Ia** forms the silyl derivative **IIa** in 85–87% yield. In the case of zoledronic acid **Ib** a partial tarring of reaction mixture takes place, and the yield of sililated compound **IIb** does not exceed 65%.

The alcoholysis of the silyl derivative **IIa** with ethanol gives spectroscopically pure acid **Ia** in 95% yield. The hydrolysis of compound **IIb** with ethanol containing 10% of water gives pure zoledronic acid **Ib** in 97% yield.

The high value of chemical shift (δ 8.68 ppm) of the signal of proton in the position 2 of imidazole ring of compound **Ib** indicates that the zolendronic acid molecule exists in a zwitterion form resulting in its extremely low solubility in organic solvents and water. A gradual addition of potassium hydroxide to the solution of acid **Ib** in D_2O causes the appearance of two triplets of protons of the CH_2 group and an upfield shift of the signal of proton in the position 2 of imidazole ring (δ 7.7 ppm or less). Note that after the addition of four equivalents of alkali to the four-basic acid **Ib** small signal at δ 8.7 ppm remains in its ^{1}H NMR spectrum which is apparently due to the low value of the dissociation constant of the fourth hydroxy group on phosphorus.

NMR spectra were taken on a Bruker AM-360 spectrometer in $CDCl_3$ for compounds **IIa, IIb**, and in D_2O for acid **Ib** against the residual signals of solvents as an internal references. Mass spectra were measured on a MAT-311A mass spectrometer at the ionizing electrons energy 70 eV.

Silylation of hydroxyalkylidenediphosphonic acids. A mixture of 0.1 mol of acids **Ia, Ib** and 0.1 mol of HMDS was quickly heated to the temperature of evolution of ammonia gas (about 90–100°C). At first the mixture self-heated from 25 to 70–75°C due to the formation of solid ammonium salts. After the beginning of liberation of ammonia controlled by indicator the mixture was slowly heated to 140°C with the simultaneous addition of HMDS until its total amount reached 0.4 mol. The mixture obtained was refluxed for 1 h at 140°C and distilled in a vacuum. Target products **IIa, IIb** were colleted as the last high boiling fractions.

Tetrakis(*O*-trimethylsilyl)hydroxyethylidenediphosphonic acid (IIa). Yield 87%, bp 134–136°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 0.30 t (36H, $4SiMe_3$), 1.67 m (3H, CH_3), 6.72 s (1H, OH). Found, %: C 33.92, 33.78; H 8.05, 9.02. $C_{14}H_{40}O_6P_2Si_4$. Calculated.%: C 33.99; H 8,15. Mass spectrum *m/z*: 495 [M^+], calculated molecular mass 494.7306.

Tetrakis(*O*-trimethylsilyl)hydroxy(1-imidazolyl)-ethylidenediphosphonic acid (IIb). Yield 65%, bp 175–177°C (0.5 mm Hg). ^{1}H NMR spectrum, δ, ppm: 0.29 t (36H, $4SiMe_3$), 5.63 t (2H, CH_2), 6.52 s (1H, OH), 6.98 s ($1H_{arom}$), 7.12 s ($1H_{arom}$), 7.81 s ($1H_{arom}$). Found, %: C 36.18, 36.21; H 7.52, 7.46. $C_{17}H_{12}N_2O_7 \cdot P_2Si_4$. Calculated, %: C 36.41, H 7.55. Mass spectrum, *m/z*: 545 [$M - CH_3$]$^+$, calculated molecular mass 560.7954.

Alcoholysis and hydrolysis of silyl esters of hydroxyalkylidenediphosphonic acids. Compound **IIa, IIb,** 0.1 mol, was stirred for 0.5 h in 75 ml of ethanol or 90% aqueous ethanol respectively. After removing of volatile substances in a vacuum in the case of compound **IIa** or filtration of the precipitate formed in the case of compound **IIb** pure diphosphonic acids were obtained.

Zoledronic acid Ib. ^{1}H NMR spectrum, δ, ppm: 4.65 t (2H, CH_2), 7.33 s ($1H_{arom}$), 7.48 s ($1H_{arom}$), 8.67 s ($1H_{arom}$).

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