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A Method for Preparing Phosphinic Acids from Hypophosphites: III.[1] Synthesis of α-Hydroxy Phosphinic Acids

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Abstract — A one-pot method is proposed for preparing unsymmetrical α-hydroxy phosphinic acids from ammonium hypophosphite. Bis(trimethylsilyl) phosphonites formed *in situ* on addition of bis(trimethylsilyl) hypophosphite to activated unsaturated compounds are brought without isolation into the Abramov reaction with an aldehyde or ketone. A series of new α-hydroxy phosphinic acids are obtained.

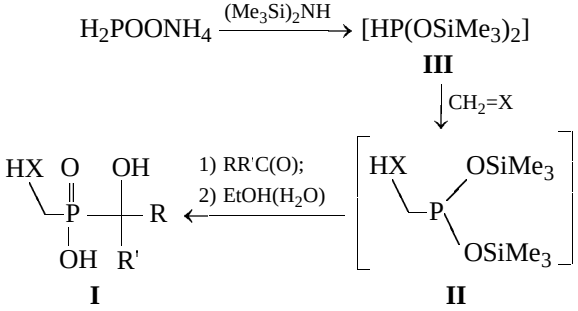
A method for the synthesis of functionally substituted phosphinic acids starting from hypophosphites is based on the ability of hydrophosphoryl compounds to transform into trivalent phosphorus silyl esters. This allows formation of two P–C bond in the sequence of reactions performed in one vessel [1–5]. With haloalkanes, symmetrical phosphinic acids are obtained by two successive reactions of the Arbuzov type [2–5]. Reaction of bis(trimethylsilyl) hypophosphite with aldehydes in the presence of trimethylchlorosilane and triethylamine yields symmetrical bis-α-hydroxy phosphinic acids [6], and with α,ω-dihaloalkanes in hexamethyldisilazane and high-boiling solvents, cyclic phosphinic acids can be obtained [7, 8].

The one-pot procedure with an active unsaturated compound used in the first step and a haloalkane used to form the second P–C bond allows synthesis of unsymmetrical phosphinic acids [1, 4, 9–14].

It was shown previously that trimethylsilyl phosphonites **II** (Scheme 1) formed by *in situ* addition of bis(trimethylsilyl) hypophosphite $HP(OSiMe_3)_2$ (**III**) to the C–C double bond of styrene [1, 4, 10, 11], acrylate [4, 7, 13, 14], or vinylphosphonate [12] react *in situ* with a haloalkane [1, 4], ω-functionalized haloalkane [1, 4, 9, 10], or α,ω-dihaloalkane [1, 11–14] molecule following the scheme of the Arbuzov reaction.

This study further develops this procedure, with an active unsaturated compound used for the formation of the first P–C bond and a carbonyl compound used subsequently for the formation of the second bond. This allows preparation of a series of new unsymmetrical α-hydroxy phosphinic acids **I** (Scheme 1).

Scheme 1.



R = Me, $CHMe_2$, Ph, *p*-C_6H_4OMe, *p*-$C_6H_4NMe_2$; R' = H, Me, Ph; X = CHPh, CHC(O)OEt.

In this work we showed that the phosphonite $HXCH_2P(OSiMe_3)_2$ (**II**) (Scheme 1) formed by *in situ* addition of bis(trimethylsilyl) hypophosphite $HP(OSiMe_3)_2$ (**III**) to activated unsaturated compound CH_2=X further reacts without isolation with an aldehyde or ketone molecule, following the scheme of the Abramov reaction and yielding α-hydroxy phosphinic acid after treatment of the corresponding silyl esters with aqueous ethanol (Scheme 1).

As an unsaturated component, we tested ethyl acrylate and styrene. Acetone, isobutyraldehyde, benzaldehyde, *p*-methoxybenzaldehyde, *p*-dimethylaminobenzaldehyde, acetophenone, and benzophenone were tested as the carbonyl component.

The synthtic potential of the method can be extended by using a Schiff base (imine) as the unsaturated component. We tested *N*-tritylmethanimine and *N*-benzylideneaniline, with *p*-methoxybenzaldehyde as the carbonyl component (Scheme 2). We demonstrated the principal possibility of preparing α-amino α'-hydroxy phosphinic acid derivatives.

[1] For communication II, see [1].

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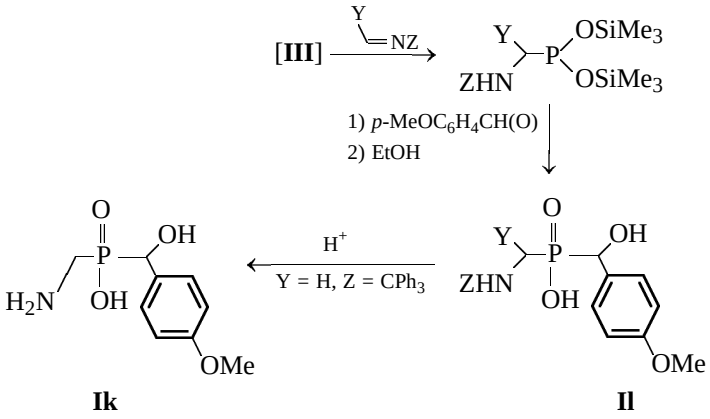
Scheme 2.



Ik **Il**

Il, Y = Z = Ph.

The use of the *N*-trityl protecting group followed by its removal under mild conditions allows synthesis of α-amino α'-hydroxy phosphinic acids with unsubstituted amino group, as we showed by the example of the synthesis of amino acid **Ik** (Scheme 2).

The newly synthesized α-hydroxy phosphinic acids **Ia**–**Il** are crystalline substances showing relatively low thermal stability. α-Hydroxy acids **Ib** and **Ig** containing a 1-hydroxy-1-methylethyl fragment (formed in reaction with acetone) are the least stable. For example, recrystallization of acid **Ib** from an alcohol-ether mixture was accompanied by partial dissociation into 2-ethoxycarbonylethylphosponous acid (δ_P 25 ppm) and acetone. The capability of α-hydroxy phosphinic acids for the similar dissociation in 10% ammonia solution was noted previously [15]. We have not examined systematically the thermal lability of these compounds. Nevertheless, we tried to avoid the use of high-boiling solvents in synthesis, isolation, and recrystallization of α-hydroxy phosphinic acids **I**.

Thus, we suggested a one-pot method for preparing unsymmetrical α-hydroxy phosphinic acids from ammonium hypophosphite, using styrene and acrylate as unsaturated component for the formation of the first P–C bond and carbonyl compounds for the formation of the second bond by the Abramov reaction. It is possible to use *N*-tritylmethanimine and *N*-benzylideneaniline as unsaturated components for the synthesis of α-amino α'-hydroxy phopsphinic acids.

EXPERIMENTAL

The ^{1}H and ^{31}P NMR spectra were taken on Bruker DPX-200 and Bruker CXP-300 Fourier spectrometers, with TMS as internal and 85% H_3PO_4 as external references. The melting points were measured on a Boetius PHMK device or in a block in an open capillary.

All the reactions with silyl hypophosphites and intermediate phosphonous acids were performed under argon. The solvents used were carefully dried. Ammonium hypophosphite was prepared according to [16]. Carbonyl compounds were purchased from Khimeks (St. Petersburg, Russia). TLC of individual compounds and reaction mixtures was performed using Silufol plates [eluent chloroform–acetone, (5–7) : 1] and on Merck glass plates with a 0.2-mm layer of silica gel UV-254 [for the analysis of hydroxy and amino acids, eluent 1-butanol–acetic acid–water, (5–8) : 1 : 1].

Synthesis of α-hydroxy phosphinic acids with ethyl acrylate as unsaturated component. A mixture of 0.05 mol of H_2POONH_4 and 0.06 mol of $(Me_3Si)_2NH$ [17, 18] was stirred for 1.5 h at 120°C, cooled under argon to 40°C, and then freshly distilled ethyl acrylate was added dropwise to the reaction mixture. The mixture was stirred at this temperature for 1.5 h, and then 0.05 mol of the appropriate aldehyde or ketone in 3–5 ml of absolute benzene or chloroform was added slowly dropwise, and the mixture was stirred at 50–80°C for 2–3 h. After cooling to room temperature, 20 ml of alcohol was added dropwise, and the mixture was refluxed for 15 min and then evaporated in a vacuum. The residue was dissolved in 50–70 ml of chloroform and washed with water (2 × 10 ml). The organic layer was dried over $MgSO_4$ and evaporated in a vacuum. The oily residue was crystallized from ether or an ether–acetone or ether–alcohol mixture. Yields of α-hydroxy phosphinic acids **Ia**–**Ie** 43–57% based on H_2POONH_4.

2-Ethoxycarbonylethyl-α-hydroxybenzylphosphinic acid Ia. Yield 43%, mp 111–113°C (ether–alcohol). ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1 : 3), δ, ppm: 1.25 t (3H, CH_3), 1.83 m (2H, CH_2), 2.42 m (2H, CH_2), 4.07 q (2H, CH_2O), 4.75 d (1H, CH, J_{PH} 11 Hz), 7.25 m (3H, Ph), 7.45 m (2H, Ph). ^{31}P NMR spectrum (DMSO-d_6–CCl_4, 1 : 3), δ_P, ppm: 45.4. Found, %: C 52.67, 52.49; H 6.47, 6.41; P 10.87, 11.03. $C_{12}H_{17}O_5P$. Calculated, %: C 52.94; H 6.29; P 11.38.

2-Ethoxycarbonylethyl(1-hydroxy-1-methylethyl)phosphinic acid Ib. Yield 57%, mp 101–103°C (ether). ^{1}H NMR spectrum (CD_3OD), δ, ppm: 1.25 t (3H, CH_3), 1.38 d (6H, $2CH_3$, J_{PH} 14 Hz), 2.10 m (2H, CH_2), 2.63 m (2H, CH_2), 4.13 q (2H, CH_2O). ^{31}P NMR spectrum (CD_3OD), δ_P, ppm: 52.0. Found, %: C 43.05, 42.91; H 7.59, 7.50; P 13.70, 13.73. $C_8H_{17}O_5P$. Calculated, %: C 42.86; H 7.64; P 13.82.

2-Ethoxycarbonylethyl(1-hydroxy-1-phenylethyl)phosphinic acid Ic. Yield 47%, mp 105–107°C (ether–acetone). ^{1}H NMR spectrum (CD_3OD), δ, ppm: 1.22 t (3H, CH_3), 1.75 d (3H, CH_3, J_{PH} 14 Hz), 1.86 m (2H, CH_2), 2.35 m (2H, CH_2), 4.08 q (2H, CH_2), 7.32 m (3H), 7.60 m (2H) (Ph). ^{31}P NMR spectrum (CD_3OD), δ_P, ppm: 51.4.

2-Ethoxycarbonylethyl(1-hydroxy-1,1-diphenylmethyl)phosphinic acid Id. Yield 53%, mp 128–129°C (ether). ^{1}H NMR spectrum (CD_3OD), δ, ppm: 1.19 t (3H, CH_3), 1.95 m (2H, CH_2), 2.36 m (2H, CH_2), 4.05 q (2H, CH_2), 7.28 m (6H), 7.71 m (4H) (2Ph). ^{31}P NMR spectrum (CD_3OD), δ_P, ppm: 50.0. Found, %: C 62.25, 62.15; H 5.93, 6.02; P 8.61, 8.77. $C_{18}H_{21}O_5P$. Calculated, %: C 62.07; H 6.08; P 8.89.

2-Ethoxycarbonylethyl(α-hydroxy-*p*-methoxybenzyl)phosphinic acid Ie. Yield 51%, mp 141–143°C (ether–alcohol). ^{1}H NMR spectrum (CD_3OD), δ, ppm: 1.25 t (3H, CH_3), 2.05 m (2H, CH_2), 2.55 m (2H, CH_2), 3.77 s (3H, CH_3O), 4.13 q (2H, CH_2O), 4.85 d (1H, CH, J_{PH} 10 Hz), 6.90 s (1H, Ph), 6.92 s (1H, Ph), 7.38 s (1H, Ph), 7.40 s (1H, Ph). ^{31}P NMR spectrum (CD_3OD), δ_P, ppm: 48.0. Found, %: C 51.95, 52.09; H 6.59, 6.50; P 9.90, 9.83. $C_{13}H_{19}O_6P$. Calculated, %: C 51.66; H 6.34; P 10.25.

2-Ethoxycarbonylethyl(α-hydroxy-*p*-dimethylaminobenzyl)phosphinic acid If. Yield 43%, mp 133–135°C (ether). ^{1}H NMR spectrum (CD_3OD), δ, ppm: 1.20 t (3H, CH_3), 1.81 m (2H, CH_2), 2.45 m (2H, CH_2), 2.88 s (6H, $2CH_3N$), 4.10 q (2H, CH_2O), 4.75 d (1H, CH, J_{PH} 13.5 Hz), 6.88 s (1H, Ph), 6.90 s (1H, Ph), 7.39 s (1H, Ph), 7.41 s (1H, Ph). ^{31}P NMR spectrum (CD_3OD), δ_P, ppm: 39.0. Found, %: C 52.95, 53.09; H 7.19, 7.20; P 9.90, 9.83. $C_{14}H_{22}NO_5P$. Calculated, %: C 53.33; H 7.03; P 9.82.

Synthesis of α-hydroxy phosphinic acids with styrene as unsaturated component. A mixture of 0.05 mol of H_2POONH_4, 0.08 mol of $(Me_3Si)_2NH$, and 0.05 mol of styrene was stirred for 2 h under argon at 120–130°C. The reaction mixture was cooled under argon to 50°C, and 0.05 mol of the corresponding carbonyl compound in 3–5 ml of absolute benzene was slowly added dropwise. The stirring was continued at 50–80°C for 3 h. The subsequent alcoholysis and isolation of compounds **I** were performed similarly to acids **Ia**–**Ie**. The yields of α-hydroxy phosphinic acids **Ig**–**Ii** were 53–73% based on H_2POONH_4.

2-Phenylethyl(1-hydroxy-1-methylethyl)phosphinic acid Ig. Yield 53%, mp 153–155°C (ether). ^{1}H NMR spectrum (CD_3OD), δ, ppm: 1.40 d (6H, $2CH_3$, J_{PH} 13.3 Hz), 2.08 m (2H, CH_2), 2.94 m (2H, CH_2), 7.23 m (5H, Ph). ^{31}P NMR spectrum (CD_3OD), δ_P, ppm: 54.7. Found, %: C 57.76, 58.05; H 8.06, 7.59; P 13.41, 13.37. $C_{11}H_{17}O_3P$. Calculated, %: C 57.89; H 7.51; P 13.57.

2-Phenylethyl(1-hydroxy-2-methylpropyl)phosphinic acid Ih. Yield 67%, mp 123–125°C (ether). ^{1}H NMR spectrum (CD_3OD), δ, ppm: 1.10 d (6H, $2CH_3$, J_{HH} 7 Hz), 2.12 m [3H, CH_2 + C*H*(Me_2)], 2.92 d.t (2H, CH_2), 3.50 d.d (1H, J_{PH} 7 Hz), 7.23 m (5H, Ph). ^{31}P NMR spectrum (CD_3OD), δ_P, ppm: 52.6. Found, %: C 57.11, 56.85; H 8.06, 8.39; P 12.11, 12.01. $C_{12}H_{19}O_3P \cdot 0.5H_2O$. Calculated, %: C 57.36; H 8.02; P 12.33.

2-Phenylethyl-α-hydroxybenzylphosphinic acid Ii. Yield 70%, mp 143–145°C (hexane–acetone). ^{1}H NMR spectrum (CD_3OD), δ, ppm: 1.95 m (2H, CH_2), 2.80 m (2H, CH_2), 4.90 d (1H, CH, J_{PH} 11 Hz), 7.20 m (10H, 2Ph). ^{31}P NMR spectrum (CD_3OD), δ_P, ppm: 46.0. Found, %: C 62.87, 63.03; H 6.53, 6.57; P 10.51, 10.37. $C_{15}H_{17}O_3P \cdot 0.5H_2O$. Calculated, %: C 63.15; H 6.36; P 10.86.

2-Phenylethyl(α-hydroxy-*p*-methoxybenzyl)phosphinic acid Ij. Yield 73%, mp 173–174°C (hexane–acetone). ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1 : 3), δ, ppm: 1.87 m (2H, CH_2), 2.77 m (2H, CH_2), 3.75 m (3H, CH_3O), 4.70 d (1H, CH, J_{PH} 11 Hz), 6.83 d (2H, Ph), 7.15 m (5H, Ph), 7.35 d (2H, Ph). ^{31}P NMR spectrum (DMSO-d_6–CCl_4, 1 : 3), δ_P, ppm: 46.5. Found, %: C 62.47, 62.44; H 6.43, 6.31; P 9.90, 9.67. $C_{16}H_{19}O_4P$. Calculated, %: C 62.74; H 6.25; P 10.11.

***N*-Tritylmethanimine and *N*-benzylideneaniline as unsaturated component. Aminomethyl(α-hydroxy-*p*-methoxybenzyl)phosphinic acid Ik.** A mixture of 0.8 g of H_2POONH_4 and 5.5 ml of $(Me_3Si)_2 \cdot NH$ was stirred for 1.5 h at 120–130°C [17, 18]. After cooling to room temperature, a suspension of 2.7 g of

N-tritylmethanimine suspended in 10 ml of absolute benzene was added under argon. The mixture was slowly heated to 70–80°C and stirred at this temperature for 5 h. Then 1.2 ml of *p*-methoxybenzaldehyde was added, and stirring at 70–80°C was continued for 4 h. After cooling to room temperature, 20 ml of alcohol was slowly added dropwise, and the mixture was refluxed for 15 min and then evaporated in a vacuum. The residue was dissolved in 50 ml of chloroform and washed with water (2 × 10 ml). The organic layer was evaporated. The residue consisted mainly of *N*-tritylaminomethyl(α-hydroxy-*p*-methoxybenzyl)-phosphinic acid [^{31}P NMR data ($CDCl_3$): 40 ppm], which without isolation was dissolved in 20 ml of chloroform and mixed with 30 ml of 1 M HCl; the resulting two-phase mixture was vigorously stirred for 3-4 h. The acidic aqueous phase was evaporated, then again evaporated with water, and the residue was dissolved in aqueous ethanol and treated with excess propylene oxide. The free amino acid was additionally purified by chromatography on Diasorb-Sulfo (weakly acidic) cation exchanger, eluent water. The fractions with positive ninhydrin reaction were collected and evaporated, and the residue was recrystallized from acetone. After recrystallization from aqueous ethanol, acid **Ik** was isolated. Yield 0.53 g (23% based on ammonium hypophosphite), mp 168–169°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 3.07 d (2H, CH_2, J_{PH} 10 Hz), 3.13 d (1H, CH, J_{PH} 10 Hz), 3.78 s (3H, CH_3), 6.93 s (1H, Ph), 6.98 s (1H, Ph), 7.32 s (1H, Ph), 7.36 s (1H, Ph). ^{31}P NMR spectrum (D_2O), δ_P, ppm: 27.3 (pH 1), 36.7 (pH 9). Found, %: C 46.51, 46.45; H 6.26, 6.09; P 13.21, 13.33. $C_9H_{14}NO_4P$. Calculated, %: C 46.76; H 6.10; P 13.40.

α-(*N*-Phenylamino)benzyl(α-hydroxy-*p*-methoxybenzyl)phosphinic acid Il. A mixture of 0.8 g of H_2POONH_4 and 5.0 ml of $(Me_3Si)_2NH$ was stirred for 1.5 h at 120–130°C [17, 18]. After cooling under argon to 80°C, a solution of 1.8 g of *N*-benzylideneaniline in 3 ml of absolute benzene was added, and the mixture was stirred at this temperature for 3 h. Then 1.2 ml of *p*-methoxybenzaldehyde was added, and the mixture was stirred at 80°C for 3 h. After cooling to room temoerature, 15 ml of alcohol was slowly added dropwise, and the reaction mixture was evaporated in a vacuum. The residue was dissolved in minimal amount of methylene chloride and passed through a Celite bed (eluent methylene chloride). The organic phase was washed with water (2 × 10 ml), dried over $MgSO_4$, and evaporated in a vacuum. The residue was recrystallized from petroleum ether and then from alcohol–ether, 1 : 4. 1.1 g (29%) of acid **Il** was obtained as a diastereomeric mixture (resolved signals of the minor diastereomer are marked with an asterisk), mp 178–181°C. ^{1}H NMR spectrum (CD_3OD), δ, ppm: 3.70 s (3H, CH_3), 4.40 d (1H, CH, J_{PH} 13 Hz), 4.50* d (1H, CH, J_{PH} 13 Hz), 4.70 d (1H, CH, J_{PH} 13 Hz), 6.40 m (1H, Ph), 6.55 m (1H, Ph), 6.80 m (3H, Ph), 6.95 m (1H, Ph), 6.95 m (3H, Ph), 7.37 m (5H, Ph). ^{31}P NMR spectrum (CD_3OD), δ_P, ppm: 32.1, 31.0* (2:1). Found, %: C 66.13, 65.91; H 5.66, 5.43; P 8.21, 8.03. $C_{21}H_{22}NO_4P$. Calculated, %: C 65.79; H 5.78; P 8.08.

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