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LETTERS TO THE EDITOR

Double Michael–Pudovik Addition of Generated *in situ* Silylic Esters of Trivalent Phosphorus to Unsaturated Compounds

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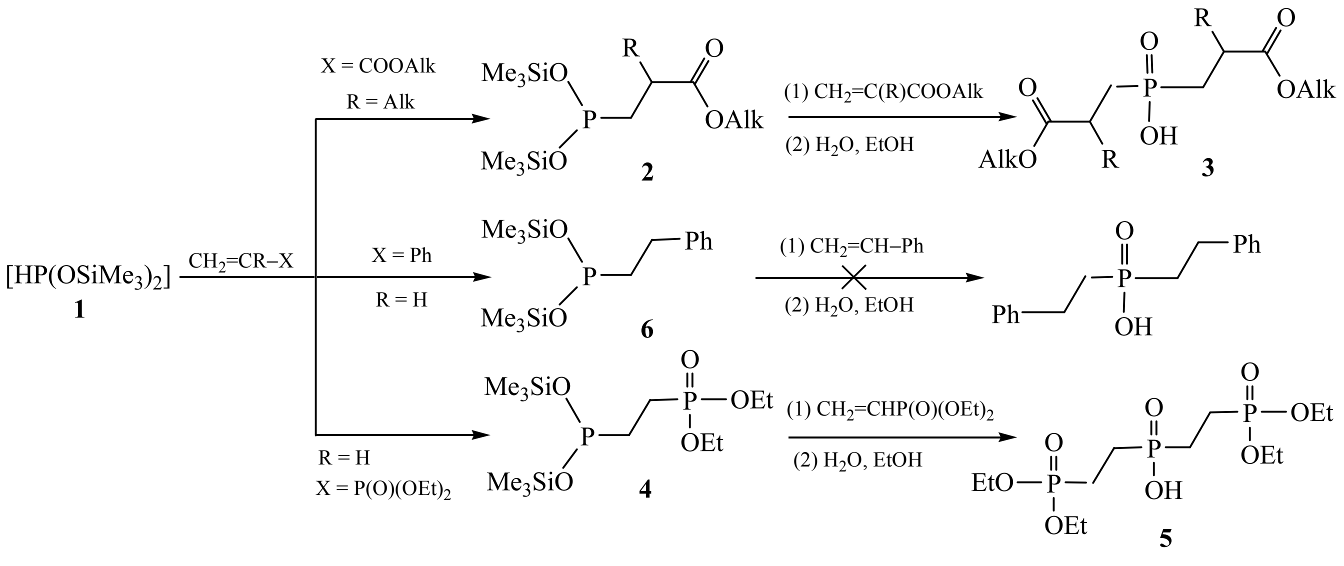
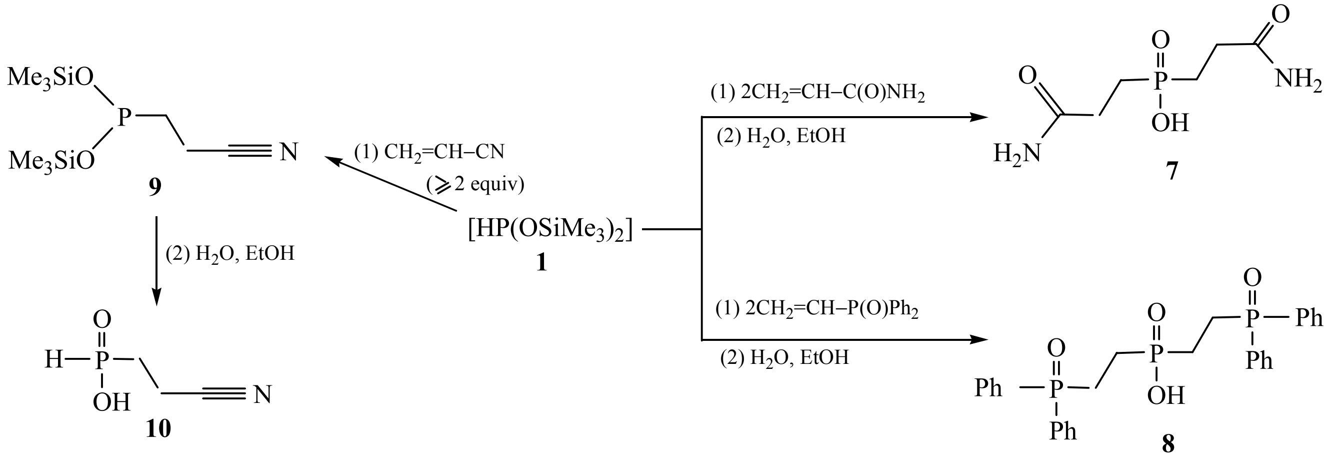
Among hypophosphorous acid derivatives, bis(trimethylsilyl) hypophosphite is distinguished as a highly reactive reagent capable of participating in transformations like the Arbuzov reaction [1–3], as well as of addition to unsaturated compounds according to Michael–Pudovik reaction [4–7]. We have proposed and are developing a methodology for the synthesis of phosphinic acids, which ensures most effective utilization of unique properties of bis(trimethylsilyl)-phosphonite (**1**) for building up phosphorus–carbon bonds via its generation *in situ* from hypophosphorous acid salts [5–10]. The low-temperature addition of bis-(trimethylsilyl) hypophosphite (**1**) to α-substituted acrylates with formation of phosphonites **2** containing isosteric fragment of natural amino acids underlies syntheses of pseudopeptides that are phosphinic acid analogs of natural peptides [8–10] (Scheme 1). Under more severe conditions in the presence of excess acrylate, 1:2 addition products (phosphinic acids **3**) were obtained [4–7]. When vinyl phosphonate was used as unsaturated component, bis(trimethylsilyl diethoxyphosphinylethylphosphonite **4** was obtained [11]. Bis[2-(diethoxyphosphinyl)ethyl]phosphinic acid (**5**; 1:2 addition product) was isolated in the synthesis of a bisphosphorylic analogue of γ-amino-butyric acid [12]. Unlike acrylates and diethyl vinylphosphonate,

Scheme 1.



Scheme 2.



styrene reacted with hypophosphite **1** to give only 1:1 addition product **6** even at elevated temperature in the presence of excess unsaturated reagent [13].

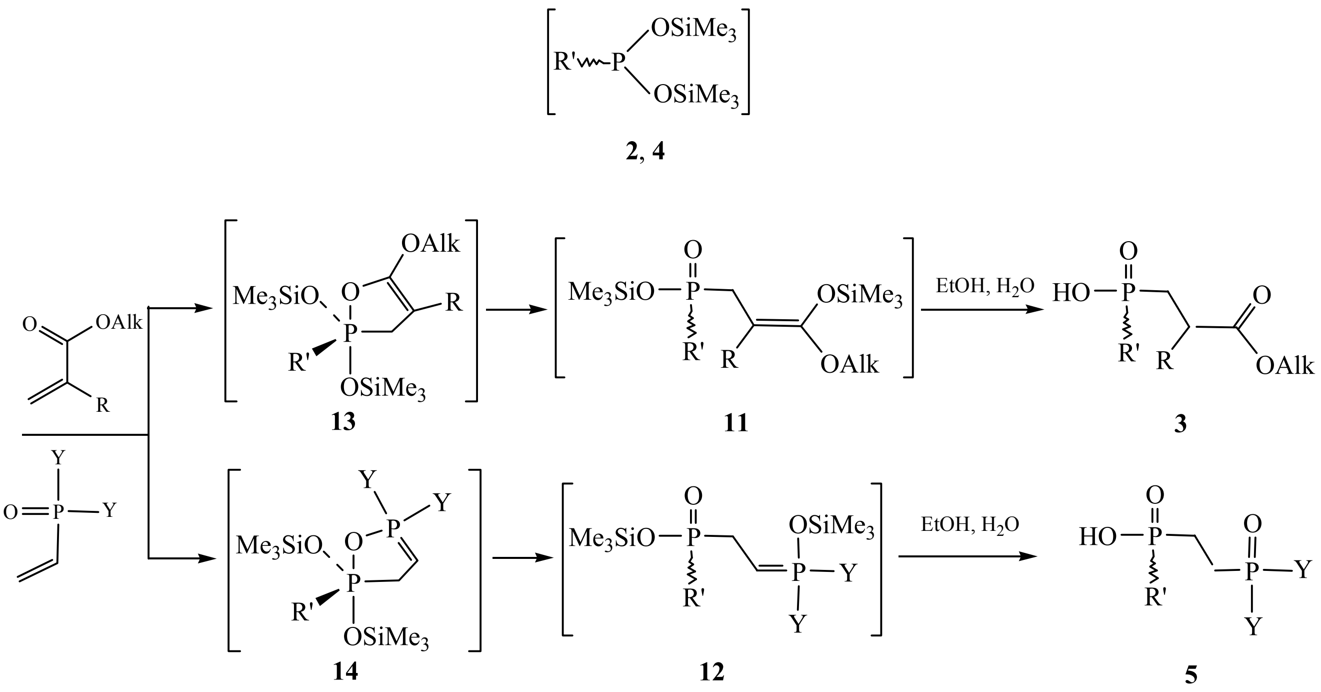
In this work, I studied the reactions of acrylonitrile, acrylamide, and diphenyl(vinyl)phosphine oxide as unsaturated components with bis(trimethylsilyl) hypophosphite (**1**) generated *in situ* with the goal of obtaining the corresponding 1:2 addition products, symmetrically substituted phosphinic acids. As shown previously, the reaction of acrylamide with hypophosphorous acid gives 1:1 adduct [14]. I have found that one-pot reaction of 2 equiv of acrylamide with generated *in situ* bis(trimethylsilyl) hypophosphite (**1**) yields 1:2 addition product, bis(3-amino-3-oxopropyl) phos-phinic acid (**7**), after treatment of the reaction mixture with excess of aqueous alcohol (Scheme 2). Analogous one-pot reaction of **1** with 2 equiv of diphenyl(vinyl)phosphine oxide affords bis[2-(diphenylphosphinyl)-ethyl]phosphinic acid (**8**) in good yield (Scheme 2).

The reaction of acrylonitrile with an equimolar amount of previously isolated bis(trimethylsilyl) hypophosphite (**1**) was studied previously by Pudovik and coworkers [15], but attempts to obtain 1:2 addition product were not reported. Our results showed that, generated *in situ* hypophosphite **1** reacts with acrylonitrile in the cold, as well as on heating with excess acrylonitrile [1 : (2–4)], to give only the corresponding 1:1 adduct bis(trimethylsilyl) 2-cyanoethylphosphonite (**9**) [15], i.e., in a way similar to the reaction of **1** with styrene. The ^{31}P NMR spectrum of the reaction mixture contained signals typical of trivalent phosphorus compounds, in particular at δ_P ~142 (**1**) and ~154 ppm (**9**). Signals were not detected in the region δ_P ~50±5 ppm typical for dialkylphosphinic acid. Mild hydrolysis of phosphonite **9** gave 2-cyanoethylphosphinic acid **10** (Scheme 2) which is promising reagent for further transformations.

The formation of 1:1 addition products, phosphonites **6** and **9**, and the absence of 1:2 adducts in the reactions of **1** with styrene and acrylonitrile suggest that these reactions involve 1,2-addition of phosphonite **1** as PH component to the C=C double bond of the unsaturated reagent, where the P–C bond is formed with the β-carbon atom. Furthermore, our results rule out 1,2-addition of intermediate phosphonites **2** and **4** as the $POSiMe_3$ reagent to the second molecule of acrylate or vinylphosphonate. Presumably, the reaction proceeds as 1,4-addition of the phosphorus atom to the β-carbon atom of the unsaturated reagent and of the trimethylsilyl group to the C=O or P=O oxygen atom of the latter with intermediate formation of silyl enol ether **11** or ylide **12** (Scheme 3).

The obtained data are consistent with the hypothesized initial formation of phosphorane structure **13** or **14** via 1,4-cycloaddition of acrylate or vinylphosphonate to phosphonite **2** or **4** to give unstable five-coordinate phosphorus compounds containing a 2,3-dihydro-1,2λ^5-oxaphosphole ring [16]. Probably, unsaturated compounds incapable of 1,4-cycloaddition to phosphorus(III) acid silyl esters generated *in situ* could not give rise to 1:2 addition products. Opening of the five-membered ring through cleavage of the P–O bond and migration of the trimethylsilyl group to the oxygen atom lead to silyl enol ether **11** or ylide **12**, and mild hydrolysis of the latter yields phosphinic acid **3** or **5**.

Scheme 3.



Bis[2-(diphenylphosphinyl)ethyl]phosphinic acid (8). A mixture of 1.6 g (0.02 mol) of ammonium hypophosphite and 9.2 g (0.04 mol) of diphenyl(vinyl)phosphine oxide in 10.0 mL (0.04 mol) of hexamethyldisilazane was refluxed for 5 h with stirring. The mixture was cooled, 40 mL of aqueous ethanol (1 : 1) was slowly added dropwise, and the mixture was evaporated under reduced pressure. The residue was dissolved in 50 mL of chloroform, and the solution was washed in succession with a saturated aqueous solution of sodium carbonate (3 × 15 mL), 0.5 N aqueous HCl, and water. The organic phase was dried over $MgSO_4$ and evaporated, and the residue was crystallized from diethyl ether. Recrystallization from ethanol gave 7.2 g (71%) of **8**, R_f 0.4 (Silufol, $CHCl_3$–Me_2CO, 4 : 1), mp 199–200°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.90 m (4H, CH_2), 2.60 m (4H, CH_2), 7.40 m and 7.70 m (20H, Ph), 10.12 s [1H, P(O)OH]. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.5 d.d ($^1J_{PC}$ = 91.4, $^3J_{PC}$ = 4.0 Hz), 21.6 d.d ($^1J_{PC}$ = 70.4, $^3J_{PC}$ = 4.0 Hz), 128.6, 128.8, 130.5, 130.7, 132.0. ^{31}P NMR spectrum ($CDCl_3$): δ_P 35.8 ppm, d [2P, $P(O)Ph_2$, $^3J_{PP}$ = 48.4 Hz], 49.2 t [1P, P(O)OH, $^3J_{PP}$ = 48.4 Hz]. Found, %: C 64.90, 64.42; H 5.66, 5.59; P 17.77, 17.87. $C_{28}H_{29}O_4P_3$. Calculated, %: C 64.37; H 5.60; P 17.79.

Bis(3-amino-3-oxopropyl)phosphinic acid (7). A mixture of 0.8 g (0.01 mol) of ammonium hypophosphite and 1.4 g (0.02 mol) of acrylamide in 5.0 mL (0.02 mol) of hexamethyldisilazane was refluxed for 6 h with stirring. The mixture was cooled, 20 mL of aqueous ethanol (1 : 1) was slowly added dropwise, and the mixture was evaporated under reduced pressure. The residue was treated with weakly acidic water, the mixture was evaporated, and the residue was crystallized from ethanol. Recrystallization from a minimum volume of water gave 1.4 g (67%) of phosphinic acid **7** with mp 195–196°C. ^1H NMR spectrum (D_2O), δ, ppm: 1.95 m (4H, PCH_2), 2.42 m [4H, $CH_2C(O)$]. ^{13}C NMR spectrum (D_2O), δ_C, ppm: 23.9 d ($^1J_{PC}$ = 92.4 Hz), 27.3 d ($^2J_{PC}$ = 2.7 Hz), 177.4 d ($^3J_{PC}$ = 14.2 Hz). ^{31}P NMR spectrum (D_2O): δ_P 54.7 ppm. Found, %: C 34.55, 34.50; H 6.46, 6.52; N 13.45, 13.34. $C_6H_{13}N_2O_4P$. Calculated, %: C 34.62; H 6.30; N 13.46.

2-Cyanoethylphosphinic acid (10). *a*. A mixture of 0.8 g (0.01 mol) of ammonium hypophosphite and 7.5 mL (0.03 mol) of hexamethyldisilazane was refluxed for 3 h with stirring. The mixture was cooled to room temperature in a stream of dry argon, 1.1–2.2 g (0.02–0.04 mol) of acrylonitrile was added, and the mixture spontaneously warmed up to 60–80°C. After cooling, the mixture was stirred for 48 h, unreacted acrylonitrile and excess hexamethyldisilazane were distilled off under reduced pressure, and the residue was distilled in a high vacuum to isolate 1.6–1.8 g (62–69%) of bis(trimethylsilyl) 2-cyanoethylphosphonite (**9**) as a colorless oily liquid, bp 68–74°C (1 mm). ^{1}H NMR spectrum (neat), δ, ppm: 0.00 s (18H, Me_3Si), 1.80–1.95 m (2H, CH_2P), 2.30–2.45 m (2H, CH_2C). ^{31}P NMR spectrum (neat): δ_P 153.8 ppm.

Aqueous ethanol (1:1), 10 mL, was added to phosphonite **9** isolated as described above, and the mixture was stirred until it cooled down and evaporated under reduced pressure. The residue was treated with toluene, the mixture was evaporated, and the residue was dried under reduced pressure. The product was ~0.6 g of 2-cyanoethylphosphinic acid **10** as a low-melting semi-crystalline material. ^{1}H NMR spectrum (CD_3CN), δ, ppm: 1.95–2.20 m (2H, CH_2P), 2.60–2.80 m (2H, CH_2C), 7.10 d (1H, PH, $^1J_{PH}$ = 549.8 Hz). 31C NMR spectrum (CD_3CN), δ_C, ppm: 10.6 s ($\underline{C}$CN), 26.0 d (PC, $^1J_{PC}$ = 92.5 Hz), 120.4 d (CN, $^3J_{PC}$ = 15.5 Hz). ^{31}P NMR spectrum: in CD_3CN: δ_P 29.0 ppm; in D_2O: δ_P 31.0 ppm; in CD_3OD: δ_P 36.5 ppm. Found, %: P 14.40, 14.33. $C_3H_6NO_2P$. Calculated, %: P 14.88.

b. A mixture of 0.8 g (0.01 mol) of ammonium hypophosphite, 7.5 mL (0.03 mol) of hexamethyldisilazane, and 1.1–2.2 g (0.02–0.04 mol) of acrylonitrile was refluxed for 3 h with stirring. The mixture was then treated as described above in *a*.

All operations were carried out under argon. The ^{1}H, ^{31}P, and ^{13}C NMR spectra were recorded on a Bruker DPX-200 spectrometer with Fourier transform. The melting points were determined on a Boetius PHMK melting point apparatus or in open capillaries.

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