Synthesis of methyl(1-aminophosphonate)siloxane oligomers*

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A synthesis of 1-aminophosphonate derivative of methylsiloxane oligomer was developed. A methodology of the introduction of 1-aminophosphonate fragment not only into the stable siloxane structures, but also into hydrolytically unstable alkoxyfunctional organosilicon compounds was suggested.

Key words: hydrosilylation, aminoalkylsiloxanes, aminophosphonates, Kabachnik—Fields reaction.

The development of hybrid materials, in which organosilicon "framework" is combined with functional fragments capable to selectively bind, recognize, and transfer[1—3] biologically important compounds is one of the promising directions of organosilicon chemistry. One of the significant advantages of such materials is their biological inertness; they are low toxic, as well as possess high thermal and mechanical stability. Modification of such organosilicon frameworks allows one to vary their properties within a wide range depending on the demand.

Compounds containing 1-aminophosphonate fragments were characterized by the ability to bind biomolecules. Such compounds are already widely used in different areas, in particular, in medicinal chemistry. Thus, it was shown that aminophosphonates exhibit properties of antibiotics,[4] enzyme inhibitors,[5] and pharmacological agents.[6]

The introduction of 1-aminophosphonate fragment into the siloxane matrix can be used for the increase of its affinity to different biological objects[7] and for the development of a methodology of obtaining new materials with of molecular recognition.

To bring this idea to practice, it is necessary to study model reactions, since there is a possibility of proceeding a number of side processes, including those disturbing the siloxane matrix structure. By the present time, the literature has description of two pathways of the introduction of 1-aminophosphonate fragment into organosilicon cage structures. First, this is the studies[8,9] on the modification of silica gel with propylaminomethylphosphonic group, in which the efficiency of binding the metal ions with the formation of chelate complexes was shown by high-performance liquid chromatography. Second, this is the modification of methyl methacrylate with bis-aminophosphonic ester by the sol—gel technology,[10] leading to the preparation of a copolymer with new thermal and mechanic characteristics (to change fire resistance, glass-transition temperature, and firmness). The indicated works showed a wide range of possible properties of hybrid organosilicon structures with 1-aminophosphonate fragment, however, the authors of none of these works were able to develop highly efficient method for the synthesis of the target compounds. Thus, in the works dealing with modification of silica gel it was indicated that the grafting was not complete, whereas the preparation of the polymer with bis-aminophosphonic graft led to the reaction product which was not an individual compound.

In this connection, it was suggested to use a catalytic hydrosilylation reaction of an unsaturated compound containing 1-aminophosphonate fragment with the hydride-functional model methylsiloxane.

The model siloxane compound with a hydride-silyl functional group, bis(trimethylsiloxy)methylsilane **1**, was obtained according to Scheme 1. The structure of compound **1** was confirmed by ^{1}H NMR spectroscopy and GLC analysis.

Hydrosilylation is one of the most widely used reaction in organosilicon chemistry. This process allows one to obtain both low-molecular-weight compounds and poly-

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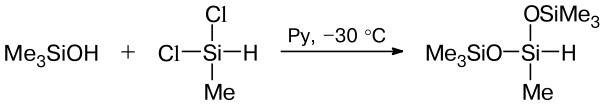
Scheme 1



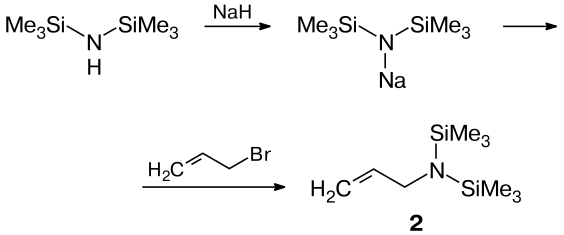
1

meric objects in virtually quantitative yields. The disadvantage of this reaction is the absence of a versatile catalyst for the introduction of unsaturated fragments in the case if reagents bear functional groups such as halogen atom, hydroxy group, amino group. Frequently, the reactions involving such functional compounds due to a number of reasons lead to the formation of a large number of undesired reaction products[11] or the process completely stops.

Apart from that, the tendency of primary amines to oxidation, as well as their high reactivity with respect to siloxane bond, required selection of special reaction conditions. The studies were directed on the development of a versatile synthetic approach to the introduction of an amino group in the siloxane matrices with its subsequent "mild" transformation to 1-aminophosphonate fragment, avoiding the step of the amino derivative isolation. For the introduction of an amino group, it was suggested to initially deactivate the lone electron pair at the nitrogen atom by the introduction of bulky substituents. This approach was considered for the first time in the work.[12] Later, the authors of the work[13] reported the introduction of a protected amine fragment into the polymeric chain containing a silicon-hydride fragment.

The literature indicates two possible pathways for the preparation of protected allylamines: i) the reaction of allylamine with chlorotrimethylsilane[14] and ii) the reaction of allyl bromide with metal hexamethyldisilazane amides.[15,16] The second method, in our viewpoint, is more preferable and was chosen for the in depth studies. A protected allylamine agent was synthesized according to Scheme 2.

Scheme 2



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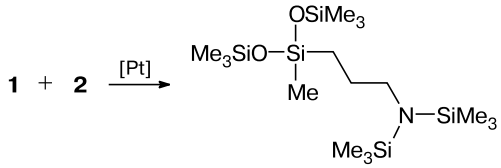
Reaction conditions were optimized in order to obtain maximal yield of compound **2**, which was isolated by vacuum distillation and characterized by ^{1}H, ^{13}C, and ^{29}Si NMR spectroscopy. The yield of the product was 55%.

The reactivity of compound **2** in the presence of the Karstedt catalyst was first tested in the reaction with dimethylphenylhydridesilane. It was shown that the hydrosilylation reaction reached completion. However, since it was important to determine the stability of the Si—O—Si bond in the siloxane system under the reaction conditions, we further used the synthesized compound **1** as a model. At a temperature of 80 °C, a complete conversion of hydridesilane was reached approximately within 10 h.

The hydrosilylation reaction involving bis(trimethylsiloxy)methylsilane (**1**) and *N*,*N*-bis(trimethylsilyl)prop-2-en-1-amine (**2**) in the presence of the Karstedt catalyst is described by Scheme 3.

Scheme 3



3

The reaction progress was monitored by ^{1}H NMR spectroscopy, tracking the disappearance of the signal for the protons of the hydridesilyl group of compound **1** in the region of δ 5.7 and emergence of a multiplet signal for the protons of the $SiCH_2$ fragment in the region of δ 0.3, which indicated the formation of the Si—C bond. The conditions selected directed the reaction to form anti-Markovnikov product, which was indicated by the signals for the propylene bridge in the ^{1}H NMR spectrum of compound **3** (Fig. 1), with the siloxane bonds remaining intact. Compound **3** was characterized by ^{1}H, ^{13}C, and

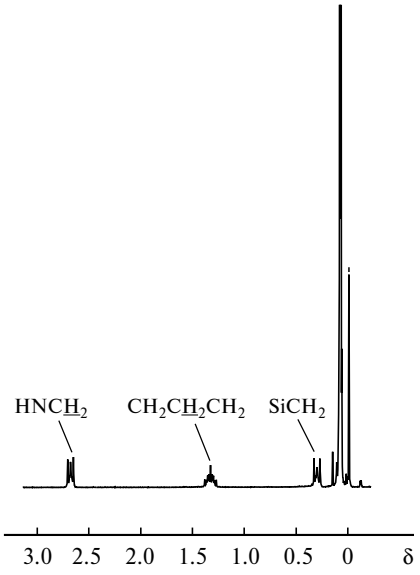


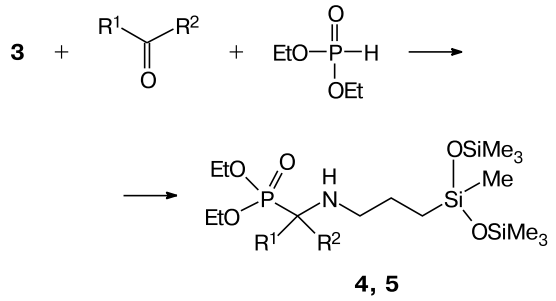
Fig. 1. ^{1}H NMR spectrum ($CDCl_3$) of compound **3**.

^{29}Si NMR spectroscopy and GPC and used in further synthesis without isolation.

Then, to prepare the methylsiloxane aminophosphonate derivative it was necessary to introduce a phosphonate group into the synthesized model compound **3**. The Kabachnik—Fields reaction is the most feasible synthetic method of obtaining α-aminophosphonates, which proceeds in a three-component system ketone—dialkyl phosphite—amine. Therefore, to accomplish the reaction, it was necessary to obtain compound with a primary amino group.

In the work,[17] it was found that the stirring a methanolic solution of a siloxane polymer with protected amino groups led to the removal of the trimethylsilyl fragments. The use of methanol allows one to obtain primary amine under mild conditions, however, in the work[17] it was also indicated that this approach does not exclude a possibility of the Si—O—Si bond cleavage. Earlier, the work[18] described the Kabachnik—Fields reaction which used hexamethyldisilazane in the presence of crystalline iodine as a catalyst. This method allows one to exclude the step of the removal of trimethylsilyl protecting group at the nitrogen atom. The advantage of this approach consists in the absence of water in the system, which was eliminated in the course of a traditional Kabachnik—Fields reaction. Thus, the reaction mechanism indicated in these studies substantiated a possibility to carry out the Kabachnik—Fields reaction without preliminary isolation of the intermediate unprotected amino derivative. However, the use of iodine and drastic conditions of product isolation used in the work[18] are absolutely unacceptable in the synthesis of siloxane structures. Therefore, we suggested to carry out the Kabachnik—Fields reaction in ethanol (Scheme 4).

Scheme 4



4, 5

$R^1 = R^2 = Me$ (**4**), $R^1 + R^2 = (CH_2)_5$ (**5**)

Reagents and conditions: acetone ($R^1 = R^2 = Me$) for **4** or cyclopentanone ($R^1 + R^2 = (CH_2)_5$) for **5**, hexane, EtOH, 20 °C.

Stirring a three-component system consisting of ketone (acetone, cyclopentanone), diethyl phosphite, and compound **3** in ethanol gave 1-aminophosphonates **4** and **5** in good yields (92—95%). Compounds **4** and **5** were isolated by column chromatography.

In conclusion, in the course of our studies we obtained model compounds containing 1-aminophosphonate groups. The suggested method can be regarded as a versatile approach to the introduction of this polyfunctional fragment into the siloxane structures, since this version of a traditional Kabachnik—Fields reaction leads to the preparation of inert disiloxane instead of the formation of water, that allows one to extend this scheme on functional organosilicon compounds sensitive to moisture.

Experimental

Hexane, pyridine, ethanol, 1,1,1,3,3,3-hexamethyldisilazane, sodium hydride (Acros), dichloromethylsilane (Acros), allyl bromide (Acros), diethyl phosphite (Acros), acetone, and cyclopentanone were purified according to standard procedures. ^{1}H, ^{13}C, ^{31}P, and ^{29}Si NMR spectra were recorded on a Bruker WP-250 SY spectrometer (250.13 MHz (^{1}H)) in $CDCl_3$. Chemical shifts in the ^{1}H NMR spectra are given relative to residual signals of chloroform (δ_H 7.25, δ_C 77.00), in the ^{31}P NMR spectra relative to 85% aqueous solution of H_3PO_4 (an external standard), in the ^{29}Si NMR spectra relative to Me_4Si (an internal standard).

Gas liquid chromatography was performed on a Khromatek Analitik 5000 chromatograph (Russia), detector catarometer, carrier gas helium, 2 m×3 mm columns, stationary phase SE-30 (5%) on Chromaton-H-AW. Liquid chromatography was performed on a chromatographic system, which included a STAIER, series 2 high pressure pump (Akvilon, Russia), a RIDK 102 refractometric detector (Czech Republic) and a JETSTREAM 2 PLUS column thermostat (KNAUER, Germany). The thermostat temperature was 40 °C (±0.1 °C). Eluent was tetrahydrofuran, the flow rate 1.0 mL min^{-1}. A 300×7.8-mm column was filled with Phenogel (Phenomenex, USA), particle size 5 μm, pore size 10^3 Å (the passport range of separation up to 75000 Da). The data were recorded and processed using the UniChrom 4.7 program (Belarussia). Molecular weight was evaluated with respect to linear polystyrene standards. Electrospray ionization (ESI) high resolution mass spectra were obtained on Bruker micrOTOF II spectrometer.

Trimethylsilanol. A 0.1 *M* solution of hydrochloric acid was added dropwise to hexamethyldisilazane (110 g, 0.683 mol) with stirring over 1 h (114 mL). Then, the reaction mixture was stirred for 1 h. The GLC data showed that the starting hexamethyldisilazane did not react completely, therefore, additional portion of 0.1 *M* hydrochloric acid (100 mL) was slowly added dropwise to the reaction mixture. The GLC data showed that hexamethyldisilazane was completely consumed. The organic phase was separated, treated with calcium chloride (20 g), and allowed to stand for 16 h. Calcium chloride was filtered off, the product was obtained with 95% content of trimethylsilanol (GLC data).

1,1,1,3,5,5,5-Heptamethyltrisiloxane (1). A solution of dichloromethylsilane (20 g, 0.174 mol) in hexane (60 mL) was added dropwise to a solution of trimethylsilanol (40 g, 0.45 mol) in pyridine (33.2 g, 0.42 mol) at a temperature of −30 °C. The reaction mixture was heated to room temperature and stirred for 16 h. Then, the solution was filtered from the precipitate, washed with water, and dried with sodium sulfate. The product was isolated by distillation at atmospheric pressure. The yield was 34%. A colorless liquid, b.p. 141—142 °C. ^{1}H NMR, δ: 4.64 (s, 1 H, SiH); 0.12 (s, 21 H, $SiCH_3$).

***N*,*N*-Bis(trimethylsilyl)prop-2-en-1-amine (2).** A mixture of hexamethyldisilazane (131.12 g, 0.81 mol) and sodium hydride (6.48 g, 0.27 mol) was refluxed for 3 h at 110 °C under argon. Then, the solution obtained was cooled, followed by the addition of allyl bromide (30 g, 0.24 mol). The mixture was stirred for 16 h. A suspension obtained was filtered from the precipitate. The protected allylamine was isolated by vacuum distillation. The compound was obtained as a colorless liquid, the yield was 55% (27.36 g), b.p. 85 °C (35 Torr) (*cf.* Ref. 13: b.p. 82 °C (30 Torr)). ^{1}H NMR, δ: 0.11 (s, 18 H, $Si(CH_3)_3$); 3.46 (d, 2 H, CH_2N); 5.06 (dd, 2 H, CH=); 5.79 (m, 1 H, =CH). ^{13}C NMR, δ: 2.15, 47.50, 113.50, 141.46.

***N*-(3-(1,1,1,3,5,5,5-Heptamethyltrisiloxan-3-yl)propyl)-1,1,1-trimethyl-*N*-(trimethylsilyl)silanamine (3).** A Karstedt catalyst (25 μL) was added to a solution of compound **1** (1 g, 4.49 mmol) and protected allylamine **2** (0.99 g, 4.9 mmol) in toluene (20 mL). The reaction mixture was stirred for 10 h at 80 °C. The solvent was evaporated on rotary evaporator. The compound was dried over 1 h under oil pump vacuum. The reaction product was used without additional purification, the yield was 95% (1.8 g). ^{1}H NMR, δ: –0.01 (s, 3 H, $Si(CH_3)$); 0.08 (s, 36 H, $Si(CH_3)_3$); 0.30 (m, 2 H, CH_2Si); 1.33 (m, 2 H, $CH_2CH_2CH_2$); 2.68 (m, 2 H, $NHCH_2CH_2$). ^{13}C NMR, δ: –0.39, 1.86, 2.09, 15.03, 28.85, 49.02. ^{29}Si NMR, δ: –21.79, 5.09, 7.00.

Synthesis of diethyl {2-[(3-(1,1,1,3,5,5,5-heptamethyltrisiloxan-3-yl)propyl)amino]R^1R^2}phosphonates 4 and 5 (general procedure). A ketone (acetone or cyclopentanone) (2.6 mmol) and diethyl phosphite (0.35 g, 2.6 mmol) were added to a solution of compound **3** (1 g, 2.36 mmol) in a mixture of hexane—ethanol (1 : 1). The reaction mixture was stirred for 10 h, the solvent was evaporated on a rotary evaporator, the reaction products were isolated by column chromatography on silica gel (eluent chloroform—isopropyl alcohol (9 : 1)).

Diethyl (2-{[3-(1,1,1,3,5,5,5-heptamethyltrisiloxane-3-yl)-propyl]amino}prop-2-yl)phosphonate (4). The yield was 86%. ^{1}H NMR, δ: –0.03 (s, 3 H, $Si(CH_3)$); 0.05 (s, 18 H, $Si(CH_3)_3$); 0.43 (m, 2 H, CH_2Si); 1.26 (d, 6 H, $C(CH_3)_2$, $^3J_{P,H}$ = 15.6 Hz); 1.30 (t, 6 H, $CH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.1 Hz); 1.40 (m, 2 H, $CH_2C\underline{H}_2CH_2$); 2.65 (m, 2 H, $NHC\underline{H}_2CH_2$); 4.11 (m, 4 H, $OC\underline{H}_2CH_3$). ^{31}P NMR, δ: 31.51. ^{13}C NMR, δ: –0.42, 1.80, 15.16, 16.59, 23.00, 24.64, 46.09, 52.24, 54.18. ^{29}Si NMR, δ: –21.56, 7.13. MS, *m/z*: 458.2338 $[M + H]^+$, 480.2157 $[M + Na]^+$. Calculated for $C_{17}H_{44}NO_5PSi_3$: [M] = 458.2327, [M + Na] = 480.2145.

Diethyl (1-{[3-(1,1,1,3,5,5,5-heptamethyltrisiloxane-3-yl)-propyl]amino}cyclopentylidene)phosphonate (5). The yield was 84%. ^{1}H NMR, δ: –0.03 (s, 3 H, $Si(CH_3)$); 0.06 (s, 18 H, $Si(CH_3)_3$); 0.44 (m, 2 H, CH_2Si); 1.30 (t, 6 H, $CH_2C\underline{H}_3$, $^3J_{H,H}$ = = 7.1 Hz); 1.36 (m, 2 H, $CH_2C\underline{H}_2CH_2$); 1.59—2.02 (m, 10 H, $(CH_2)_5$); 2.64 (m, 2 H, $NHC\underline{H}_2CH_2$); 4.10 (m, 4 H, $OC\underline{H}_2CH_3$). ^{31}P NMR, δ: 31.61. ^{13}C NMR, δ: –0.37, 1.64, 15.14, 16.61, 16.68, 24.56, 24.70, 24.82, 34.23, 34.32, 47.01, 47.05, 61.62, 61.72, 62.59, 64.53. ^{29}Si NMR, δ: –21.36, 7.10. MS, *m/z*: 484.2483 $[M + H]^+$, 506.2303 $[M + Na]^+$. Calculated for $C_{19}H_{46}NO_5PSi_3$: [M] = 484.2483, [M + Na] = 506.2314.

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References

1. O. A. Mostovaya, M. N. Agafonova, A. V. Galukhin, B. I. Khayrutdinov, D. Islamov, O. N. Kataeva, I. S. Antipin, I. I. Stoikov, *J. Phys. Org. Chem.*, 2014, **27**, 57—65.
2. M. N. Agafonova, O. A. Mostovaya, I. S. Antipin, A. I. Konovalov, I. I. Stoikov, *Mendeleev Commun.*, 2012, **22**, 80—82.
3. R. R. Khairova, L. S. Yakimova, V. G. Evtugyn, I. Kh. Rizvanov, I. I. Stoikov, *J. Organomet. Chem.*, 2014, **772—773**, 84.
4. P. P. Giannousis, P. A. Bartlett, *J. Med. Chem.*, 1987, **30**, 1603.
5. M. C. Allen, W. Fuhrer, B. Tuck, R. Wade, J. M. Wood, *J. Med. Chem.*, 1989, **32**, 1652.
6. C. H. Hassal, in *Antibiotics*, Ed. F. E. Hahn, Springer, Vol. **6**, Berlin, 1983, p. 1—11.
7. P. Kafarski, B. Lejczak, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1991, **63**, 193.
8. P. N. Nesterenko, O. S. Zhukova, O. A. Shpiguna, P. Jones, *J. Chromatogr. A*, 1998, **813**, 47—53.
9. P. N. Nesterenko, M. J. Shaw, S. J. Hill, P. Jones, *Microchem. J.*, 1999, **62**, 58—69.
10. S. Jiang, G. Chen, Y. Hu, Zh. Gui, Zh. Hu, *Ind. Eng. Chem. Res.*, 2015, **54**, 473.
11. P. Gigler, M. Drees, K. Riener, B. Bechlars, W. A. Herrmann, F. E. Kuhn, *J. Catal.*, 2012, **295**, 1—14.
12. B. N. Ghose, *J. Organomet. Chem.*, 1979, **164**, 11.
13. R. P. Quirk, H. Kim, M. J. Polce, C. Wesdemiotis, *Macromolecules*, 2005, **38**, 7895.
14. M. Schorr, W. Schmitt, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1992, **68**, 25—35.
15. J. L. Speier, R. Zimmerman, J. Webster, *J. Am. Chem. Soc.*, 1956, **78**, 2278.
16. M. Schorr, W. Schmitt, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1992, **68**, 25.
17. M. A. Peters, A. M. Belu, R. W. Linton, L. Dupray, T. J. Meyer, J. M. DeSimone, *J. Am. Chem. Soc.*, 1995, **117**, 3380.
18. S. Sobhani, A. Vafaee, *J. Iran. Chem. Soc.*, 2010, **7**, 227—236.

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