Synthesis and structure of potentially biologically active *N*-(silylmethyl)tetrahydropyrimidin-2-ones

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A transsilylation of 1,3-bis(trimethylsilyl)tetrahydropyrimidin-2-one with (chloromethyl)-chlorosilanes $ClCH_2SiMe_nCl_{3-n}$ (n = 0, 2) gave the corresponding 1,3-bis[(chlorosilyl)-methyl]tetrahydropyrimidin-2-ones. New Si-containing tetrahydropyrimidin-2-ones were synthesized by the exchange reactions at the Si—Cl and Si—N bonds of these compounds. The structures of all the synthesized compounds were confirmed by multinuclear NMR spectroscopy. Virtual screening using the PASS program showed that these compounds can exhibit certain types of biological activity with 40—94% probability.

Key words: 1,3-bis(trimethylsilyl)tetrahydropyrimidin-2-one, 1,3-bis(silylmethyl)tetrahydropyrimidin-2-ones, transsilylation, transetherification, potential biological activity.

In the last decades, chemistry of urea derivatives is under rapid development.[1] Derivatives of cyclic urea are of special interest as building blocks in synthetic organic chemistry,[2—5] unique organic ligands,[6—9] solvents and co-solvents.[10,11] These compounds exhibit considerable antibacterial,[12,13] sedative-hypnotic,[14,15] antitumor,[16,17] and antiviral[18] activity. It should be noted that derivatives of cyclic ureas are active inhibitors of enzymes: β-secretase (BASE1)[19,20] and HIV-1 protease.[21—29] Compounds inhibiting synthesis of BASE1 can be used for treatment of Alzheimer disease. Lopinavir (ABT-378) is one of the main components of highly efficient agent Kaletra used in the therapy of HIV-infected patients.[30,31] Its molecule contains a structural fragment of cyclic urea, *viz.*, tetrahydropyrimidin-2-one. It should be noted that a number of lopinavir analogues were also synthesized, in which the tetrahydropyrimidin-2-one moiety is replaced with other heterocyclic fragments.[32,33] It turned out that in this series lopinavir has the best inhibiting activity against HIV-1 protease and pharmacokinetic profile.

The interest to the study of biological activity of silicon-containing compounds came into being in the middle of last century[34,35] and these studies successfully continue at the present time.[36] Unlike carbon, silicon atom has considerably lower electronegativity and larger covalent radius and contains vacant 3d orbitals. Modification of organic compounds *via* introduction in their molecules of Si-containing groups leads to the change in stereoelectronic structure and, as a consequence, to the change in pharmacological properties of compound: the solubility of medicines in lipids increases, their cell membrane permeability improves, the agents remain active for a longer time. Recently, the data on the formation of silicon hypervalent complexes by siderophores *E. coli* under physiological conditions were obtained.[37,38] These results open very interesting aspects of silicon chemistry concerning the role of hypervalent silicon compounds in biochemical processes *in vivo*. The following data on biological activity of *N*-silylmethylated ureas are known: they exhibit antitumor activity,[39,40] regulate lipid metabolism,[41] inhibit proteases,[42] and are used in dermatology.[43]

Taking into account all the said above, we expect that introduction of silicon-containing groups in the molecules of cyclic ureas can lead to the preparation of compounds possessing biological activity. The purpose of the present work is the development of methods for the synthesis of *N*-(silylmethyl)-substituted tetrahydropyrimidin-3-ones, studies of their structures and chemical properties.

Results and Discussion

There are two main approaches to the synthesis of *N*-(silylmethyl)-substituted tetrahydropyrimidin-2-ones: (1) cyclization of *N*-silylmethylated 1,3-diaminopropanes and (2) substitution reactions at the nitrogen atom of tetrahydropyrimidin-2-one. We used the first method earlier[44] on a model cyclization reaction of *N*,*N*′-bis(silylmethyl)-propylenediamines $(EtO)_{3-n}Me_nSiCH_2N(CH_2)_3NCH_2SiMe_n(OEt)_{3-n}$ (n = 0, 2) to synthesize 1,3-bis(silylmethyl)tetrahydropyrimidin-2-ones, which reacted with BCl_3 to give the corresponding chlorosilanes (Scheme 1).

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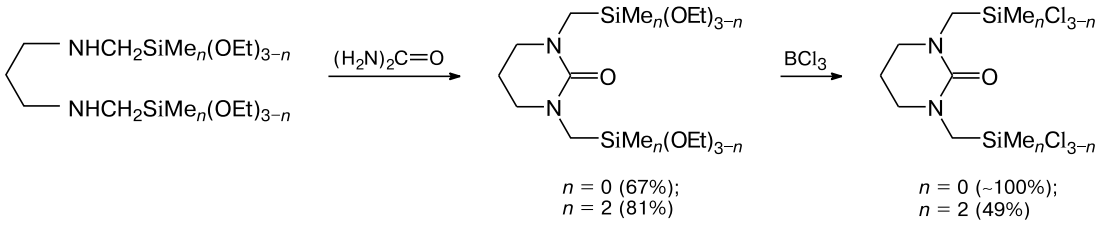
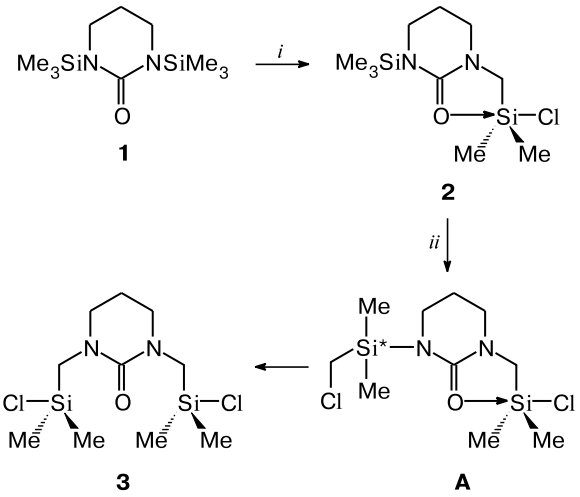
Scheme 1



The second method is the reaction of halomethylsilanes $HalCH_2SiX_3$ with preliminary metallated or silylated ureide nitrogen atom. The transsilylation of carboxylic acid *N*-trimethylsilylamides with chloromethylsilanes $ClCH_2SiMe_nCl_{3-n}$ (n = 0—2) leads to carboxylic acid *N*-(silylmethyl)amides under mild conditions in good yields.[45] As a rule, the silicon atom in these compounds is pentacoordinated. Exchange reactions involving labile Si—Cl bonds can lead to a number of carboxylic acid *N*-(silylmethyl)amides with a broad range of substituents at the silicon atom. We showed that 1,3-bis(trimethylsilyl)tetrahydropyrimidin-2-one (**1**) reacts with $ClCH_2SiMe_2Cl$ (the ratio of reagents 1 : 1) in heptane with the formation of 1-[(chlorodimethyl)silylmethyl]-3-trimethylsilyltetrahydropyrimidin-2-one (**2**) in high yield as the only transsilylation product.[46] In continuation of these findings, we studied the reaction of compound **1** with $ClCH_2SiMe_2Cl$ in the ratio of 1 : 2 (Scheme 2). The substitution of the second trimethylsilyl group takes place under more drastic conditions, the reaction reached completion upon heating the mixture for several hours without solvent and leads to the formation of 1,3-bis[(chlorodimethylsilyl)methyl]tetrahydropyrimidin-2-one (**3**). This method gave compound **3** in higher yield than that in the exchange reaction[44] (69% and 49%, respectively). The transsilylation of compound **1** with two moles of $ClCH_2SiMe_2Cl$ at room temperature in heptane or chloroform comes to completion only after several days. The studies of this process in $CDCl_3$ using ^1H NMR spectroscopy at room temperature showed that this is a two-step reaction (see Scheme 2). The first step gives the transsilylation product at one trimethylsilyl group of compound **1** to form urea **2** with the pentacoordinated silicon atom. This is indicated by the gradual decrease in the intensity of the signal for the Me_3Si group (δ = 0.24) in the ^1H NMR spectra of compound **1** and appearance of new signals at δ 0.27 and 0.60 (Me_3Si and Me_2Si groups, respectively) belonging to compound **2**. In the ^{29}Si NMR spectra, new signals attributable to these groups are observed at δ 14.73 and –41.63. Simultaneously, already ~45 min after the moment of mixing reagents, the ^1H NMR spectrum exhibits weak, but gradually growing signals at δ 0.38 (Me_2Si*), 2.97 ($SiCH_2$), and 3.27 (NCH_2) belonging to compound **A** (see Scheme 2). The intermediate **A** is the product of N-transsilylation of trimethylsilyl group in urea **2**. In the ^{29}Si NMR spectra, the intermediate **A** is represented by the signals at δ 10.01 and —41.28 (Me_2Si* and Me_2Si groups, respectively). This process is slower than N-transsilylation of **1** and reaches completion after 10 h, which is indicated by the gradual decrease in the intensities of signals for the Me_3SiN groups in the ^1H NMR spectra of compound **2**. The intermediate **A** completely rearranges into the final product **3** only within 2 days.

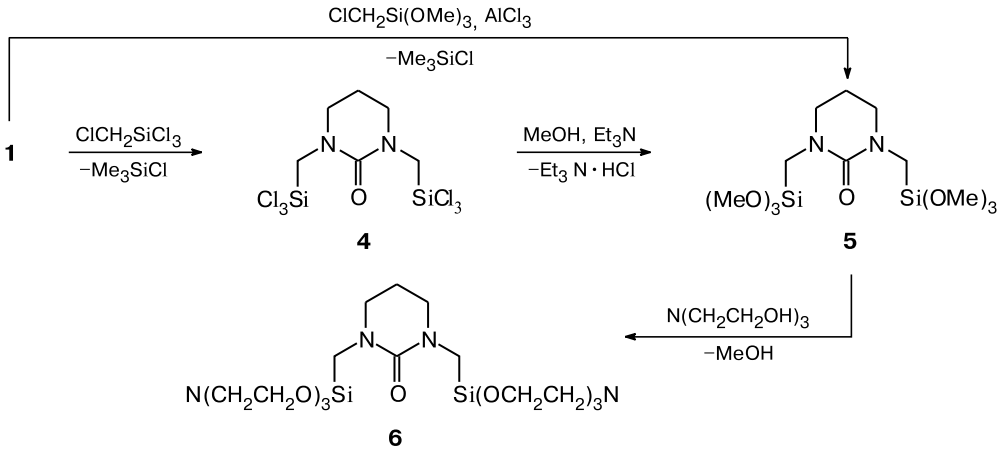
Scheme 2



Reagents and conditions: *i*. $ClCH_2SiMe_2Cl$, $CDCl_3$; *ii*. $ClCH_2SiMe_2Cl$.

Urea **1** reacts with (chloromethyl)trichlorosilane $ClCH_2SiCl_3$ (the ratio of reagents 1 : 2) in thoroughly dried hexane, forming 1,3-bis[(trichlorosilyl)methyl]tetrahydropyrimidin-2-one (**4**) in high yield (Scheme 3). The product is a fine white powder, extremely sensitive to the air moisture: the powder deliquesces in air already after several minutes. According to NMR spectroscopy, compound **4** contains only insignificant amount of impurities (no more than 3—5%). The spectral characteristics do not change for several days if the sample is stored in a sealed evacuated tube at –78 °C. Unfortunately, any attempts to obtain a pure sample by recrystallization failed, these manipulations led only to the appearance of addi-

Scheme 3



tional signals in the NMR spectra, some of which can be assigned to the hydrolysis products. Compound **4** decomposes upon heating and prolonged storage at room temperature even in a sealed tube.

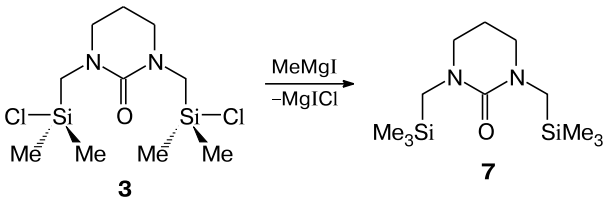
Treatment of compound **4** with thoroughly dried methanol in the presence of triethylamine in pentane leads to the formation of 1,3-bis[(trimethoxysilyl)methyl]tetrahydropyrimidin-2-one (**5**) in 78% yield. The reaction was carried out with vigorous stirring at 0±5 °C, raising the reaction temperature above 10 °C leads to a sharp decrease in the yield of compound **5** (down to 30%). Urea **5** was also synthesized by an alternative method in satisfactory yield (51%) by the reaction of (chloromethyl)trimethoxysilane with compound **1** (see Scheme 3). This reaction requires heating of the mixture of reagents in the ratio of 1 : 2 in xylene in the presence of a catalytic amount of anhydrous $AlCl_3$, simultaneously distilling off chlorotrimethylsilane. Despite the fact that chlorotrimethylsilane in this reaction was isolated in almost quantitative yield, the yield of compound **5** was only 51% because of formation of considerable amounts of unidentified polymeric products. The corresponding 1,3-bis(silatranylmethyl)tetrahydropyrimidin-2-one (**6**) was synthesized by transetherification of compound **5** with triethanolamine.

Compound **3** smoothly reacts with MeMgI in diethyl ether or tetrahydrofuran with the formation of the corresponding 1,3-bis[(trimethylsilyl)methyl]tetrahydropyrimidin-2-one (**7**) (Scheme 4), with the carbonyl group remaining intact under these conditions.

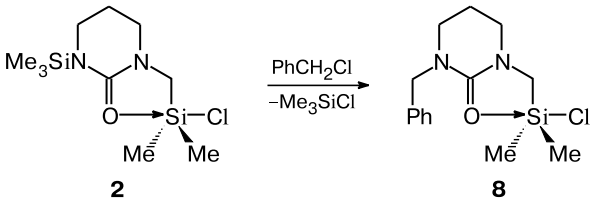
The reaction of compound **2** with benzyl chloride gives 1-benzyl-3-[(chlorodimethylsilyl)methyl]tetrahydropyrimidin-2-one (**8**) (Scheme 5).

The structures of all the *N*-silylmethylated cyclic ureas were confirmed by multinuclear NMR spectroscopy. Some specific features of these structures should be highlighted. Thus, according to the ^{29}Si NMR spectra the two silicon atoms in compound **3** are equivalent. The signal for the

Scheme 4



Scheme 5



silicon atom in the ^{29}Si NMR spectra of compound **3** was found in considerably more low-field region as compared to that for compound **2** existing as a (O—Si)-chelate with a pentacoordinated silicon atom[46] (δ –6.65 and –41.63, respectively). This can be caused by a competitive interaction of two silyl groups with the carbonyl group C=O well known as a "flip—flop" rearrangement.[47,48] The involvement of the carbonyl group in the C=O→Si coordinative binding is indicated by the downfield displacement of its chemical shift in the ^{13}C NMR spectra as compared to that in the structurally close urea **7**, in which such an interaction is absent (δ 157.96 and 155.96, respectively). 1-Benzyl-3-[(chlorodimethylsilyl)methyl]tetrahydropyrimidin-2-one (**8**) is a bright representative of (O—Si)-chelates. The pentacoordination of the silicon atom in compound **8** is indicated by a considerable upfield displacement of its chemical shift in the ^{29}Si NMR spectra,

which is close to that in compound **2**. In the ^{1}H NMR spectrum of urea **6**, the protons of the NCH_2 and OCH_2 groups of the silatrane framework resonate as two triplets (δ 2.79 and 3.72, respectively) in the region indicative for silatranes.[49] The pentacoordination of the silicon atom in compound **6** is indicated by the upfield shift of its signal in the ^{29}Si NMR spectrum as compared to that in the model compound **5** (−79.96 and −56.85, respectively).

In the search for possible practical application of the synthesized compounds, we carried out their virtual screening using the PASS program[50] developed in the V. N. Orekhovich Research Institute of Biomedical Chemistry of the Russian Academy of Medical Sciences and successfully used for the prediction of biological activity of new compounds.[51—53] Based on the structural formula of compound, this program predicts more than 500 kinds of biological activity and helps to determine the scope of experimental screening when looking for compounds with useful properties. All the synthesized compounds were predicted to have various kinds of biological activity with more than 50% probability. It should be noted that a real screening for biological activity could have been done for only compounds **5**—**7**, since compounds with the labile Si—Cl bond are not suitable for this purpose. According to the virtual screening data, compound **5** can potentially possess inhibiting activity against a number of enzymes (with 53—73% probability), stimulation of leukopoesis (with 52% probability), stimulation of kidney function (with 63% probability); for compound **6** — antitumor activity (with 78% probability), inhibitory activity against a number of enzymes (with 40—59% probability), stimulation of kidney function (with 52% probability), analeptic activity (with 41—46% probability). Compound **7** can regulate metabolism (with 94% probability), exhibit antidiabetic effect (with 84% probability), antiviral activity against HIV (with 81% probability), general antiviral activity (with 77% probability), antispasmodic properties (with 60% probability). These data show that experimental biological testing of ureas **5**—**7** can give interesting results.

In conclusion, in the present work we have shown that the transsilylation of 1,3-bis(trimethylsilyl)tetrahydropyrimidin-2-one with silanes $ClCH_2SiMe_nCl_{3-n}$ (n = 0—2) can be successfully used not only for the formation of one C(O)N—C—Si fragment in ureas, but also in the preparation of 1,3-bis(silylmethyl)tetrahydropyrimidin-2-ones. New 1-organyl-3-(silylmethyl)- and 1,3-bis(silylmethyl)-tetrahydropyrimidin-2-ones were synthesized by the exchange reactions of the Si—Cl and N—$SiMe_3$ bonds. Virtual screening using the PASS program showed that the synthesized compounds can potentially exhibit various kinds of biological activity with high probability.

Experimental

NMR spectra of 10—20% solutions of compounds were recorded on JEOL-90Q and Bruker DPX-400 spectrometers (400.1 (^{1}H), 100.6 (^{13}C), 79.5 (^{29}Si) MHz) in $CDCl_3$ using Me_4Si or cyclohexane as internal standards. Tetrahydropyrimidin-2-one was commercially available from Aldrich and used without additional purification. 1,3-Bis(trimethylsilyl)tetrahydropyrimidin-2-one (**1**) and 1-[(chlorodimethylsilyl)methyl]-3-trimethylsilyltetrahydropyrimidin-2-one (**2**) were synthesized according to the procedure described by us earlier.[46] Silanes were distilled immediately before use with addition of 3—5% of Bu_3N to bind HCl. Solvents were purified according to the known procedures.[54] Syntheses which used hydrolytically unstable compounds were carried out in the Schlenk glassware under dry argon.

1,3-Bis[(chlorodimethylsilyl)methyl]tetrahydropyrimidin-2-one (3). An excess of (chloromethyl)chlorodimethylsilane (15 mL, 0.11 mol) was added dropwise to compound **1** (7.4 g, 0.03 mol) with vigorous stirring. After an exothermic reaction ceased, the mixture was refluxed for 3 h with a reflux condenser. Then, Me_3SiCl was evaporated from the reaction mixture, the residue was distilled *in vacuo* to give compound **3** (6.5 g, 69%), b.p. 203—205 °C (1.5 Torr), n_D^{20} 1.4712. ^{1}H NMR, δ: 0.57 (s, 12 H, Me_2Si); 2.08 (m, 2 H, CCH_2C); 2.90 (s, 4 H, NCH_2Si); 3.38 (m, 4 H, NCH_2C). ^{13}C NMR, δ: 4.94 (Me_2Si); 21.07 (CCH_2C); 43.24 (NCH_2C); 47.02 (NCH_2Si); 157.96 (C=O). ^{29}Si NMR, δ: −6.65 (25 °C). Found (%): C, 38.36; H, 6.93; N, 8.97; Si, 17.70; Cl, 22.26. $C_{10}H_{22}Cl_2N_2OSi_2$. Calculated (%): C, 38.33; H, 7.08; N, 8.94; Si, 17.92; Cl, 22.63.

1,3-Bis([trichlorosilylmethyl)tetrahydropyrimidin-2-one (4). A solution of (chloromethyl)trichlorosilane (3.66 g, 0.02 mol) in hexane (15 mL) was added dropwise (slowly, over ~3 h) to a solution of (compound **1** (2.44 g, 0.01 mol) in hexane (50 mL) under dry argon with vigorous stirring. After 24 h, a precipitate formed was filtered off under argon using reverse filtration, washed with dry pentane, and dried *in vacuo*. The yield was 3.8 g (96%). ^{1}H NMR, δ: 1.99 (m, 2 H, CCH_2C); 2.96 (s, 4 H, NCH_2Si); 3.39 (m, 4 H, NCH_2C). ^{13}C NMR, δ: 21.07 (CCH_2C); 45.15 (NCH_2C); 45.99 (NCH_2Si); 159.82 (C=O). ^{29}Si NMR, δ: −13.08. Found (%): C, 18.65; H, 2.71; N, 7.21. $C_6H_{10}Cl_6N_2OSi_2$. Calculated (%): C, 18.24; H, 2.55; N, 7.09.

1,3-Bis[(trimethoxysilyl)methyl]tetrahydropyrimidin-2-one (5). ***A.*** A mixture of urea **1** (24.4 g, 0.1 mol) and chloromethyl(trimethoxy)silane (34 g, 0.2 mol) was heated in the presence of catalytic amount of anhydrous $AlCl_3$ (~0.1 g) with simultaneous distillation of Me_3SiCl. The residue was distilled *in vacuo*, the yield was 18.7 g (51%), b.p. 221—226 °C (1 Torr).

B. Compound **4** (3.95 g, 0.01 mol) was carefully added with vigorous stirring to a solution of anhydrous methanol (3.2 g, 0.1 mol) and triethylamine (15 mL, 0.1 mol) in dry pentane (150 mL) cooled to 0 °C, the temperature of the reaction mixture was maintained within 0±5 °C. Then, the temperature was slowly raised to ambient and the reaction mixture was stirred at room temperature for 10 h and then allowed to stand for 18 h. A precipitate of triethylamine hydrochloride was filtered off and washed with pentane (2×30 mL). Pentane was evaporated *in vacuo*, the residue was distilled *in vacuo* to obtain compound **5** (2.8 g, 78%), b.p. 220—223 °C (1 Torr). ^{1}H NMR, δ: 1.95 (m, 2 H, CCH_2C); 2.88 (s, 4 H, NCH_2Si); 3.30 (m, 4 H, NCH_2C); 3.57 (s, 18 H, SiOMe). ^{13}C NMR, δ: 21.07 (CCH_2C); 39.73 (NCH_2C); 47.89 (NCH_2Si); 56.45 (SiOMe); 156.56 (C=O). ^{29}Si NMR, δ: −56.85. Found (%): C, 39.33; H, 7.89; N, 7.87. $C_{12}H_{28}N_2O_7Si_2$. Calculated (%): C, 39.11; H, 7.66; N, 7.60.

1,3-Bis(silatranylmethyl)tetrahydropyrimidin-2-one (6). One drop of a 10% solution of MeONa in methanol was added to a mixture of compound **5** (3.68 g, 0.01 mol) and triethanolamine

(2.98 g, 0.02 mol), the mixture was vigorously stirred until complete homogenization (10 min). Methanol was removed *in vacuo*, the residue was recrystallized from benzene. The yield was 2.97 g (63%). ^{1}H NMR, δ: 1.82 (m, 2 H, CCH_2C); 2.73 (s, 4 H, NCH_2Si); 2.79 (t, 12 H, NCH_2CH_2O, ^3J = 5.9 Hz); 3.27 (m, 4 H, NCH_2C); 3.72 (t, 12 H, NCH_2CH_2O, ^3J = 5.9 Hz). ^{13}C NMR, δ: 22.45 (CCH_2C); 38.31 (NCH_2C); 47.20 (NCH_2Si); 50.78 (NCH_2CH_2O); 57.63 (NCH_2CH_2O); 157.23 (C=O). ^{29}Si NMR, δ: –79.96. Found (%): C, 45.71; H, 7.42; N, 11.71. $C_{18}H_{34}N_4O_7Si_2$. Calculated (%): C, 45.55; H, 7.22; N, 11.80.

1,3-Bis[(trimethylsilyl)methyl]tetrahydropyrimidin-2-one (7). Urea **3** (6 g, 0.02 mol) was slowly added to a solution of freshly prepared methylmagnesium bromide (0.06 mol) in diethyl ether with stirring, maintaining the temperature of the reaction mixture at ~5 °C. Then, the mixture was stirred for 10 h at room temperature. The ethereal solution was decanted, a precipitate was washed with diethyl ether, the organic solutions were combined. The solvent was evaporated *in vacuo*, the residue was distilled *in vacuo* to obtain compound **7** (4.2 g, 78%), b.p. 135—137 °C (1.5 Torr), n_D^{20} 1.4497. ^{1}H NMR, δ: 0.06 (s, 18 H, Me_3Si); 1.92 (m, 2 H, CCH_2C); 2.85 (s, 4 H, NCH_2Si); 3.22 (m, 4 H, NCH_2C). ^{13}C NMR, δ: –1.49 (Me_3Si); 22.61 (CCH_2C); 39.78 (NCH_2C); 48.45 (NCH_2Si); 155.96 (C=O). ^{29}Si NMR, δ: –1.05. Found (%): C, 52.61; H, 10.19; N, 10.37. $C_{12}H_{28}N_2OSi_2$. Calculated (%): C, 52.88; H, 10.36; N, 10.28.

1-Benzyl-3-[(chlorodimethylsilyl)methyl]tetrahydropyrimidin-2-one (8). A mixture of compound **2** (2.78 g, 0.01 mol) and benzyl chloride (1.5 g, 0.012 mol) was refluxed for 1 h, then, chlorotrimethylsilane was distilled off. Compound **8** (1.86 g, 63%) was isolated by distillation *in vacuo*, b.p. 230—232 °C (1 Torr), a dense pale yellow liquid with a weak specific odor of benzyl chloride, slowly crystallizes in bulk. ^{1}H NMR, δ: 0.65 (s, 6 H, Me_2Si); 1.97 (m, 2 H, CCH_2C); 2.88 (s, 4 H, NCH_2Si); 3.32 (t, 4 H, NCH_2C, ^3J = 6.10 Hz); 4.47 (s, 2 H, $PhCH_2$); 7.29 (5 H, Ph). ^{13}C NMR, δ: 7.41 (Me_2Si); 20.81 (CCH_2C); 45.59 (NCH_2Si); 43.70; 44.42 (NCH_2C); 51.96 ($PhCH_2$); 127.85, 128.76, 128.34, 136.04 (Ph); 158.03 (C=O). ^{29}Si NMR, δ: –41.76. Found (%): C, 56.71; H 7.39; N, 9.49. $C_{14}H_{21}ClN_2OSi$. Calculated (%): C, 56.64; H, 7.13; N, 9.44.

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