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Synthesis of *N*-(2-Hydroxyalkyl)trimethylsilylpropynamides

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Abstract—A number of previously unknown *N*-(2-hydroxyethyl)trimethylsilylpropynamides were synthesized by reactions of 2-aminoethyl trimethylsilyl ethers with trimethylsilylpropynoyl chloride. 2-Hydroxyethylamine reacts with trimethylsilylpropynoyl chloride at both nitrogen and oxygen atoms to afford 2-(3-trimethylsilylpropynoylamino)ethyl trimethylsilylpropynoate.

In the preceding communications [1, 2] we reported on the synthesis of a number of trimethylsilylpropynamides; and their relative baicity was studied by IR spectroscopy [3]. By reactions of *N*,*N*-dialkyltrimethylsilylpropynamide and *N*,*N*-dialkyl-4,4-dimethyl-2-pentynamide with triethylgermyllithium we obtained, respectively, triethyl(trimethylsilylpropynoyl)germane and triethyl(4,4-dimethyl-2-pentynoyl)germane in high yields [4]. Fragmentation under electron impact of α,β-silicon-containing *N*-arylamides of acetylenic acids was also studied [2].

Silicon-containing acetylenic acid amides are polyfunctional compounds having a conjugated bond sequence Si–C≡CC(O)N; they are valuable intermediate products in fine organic synthesis, specifically in the synthesis of naturally occurring compounds and their analogs. Terminal alkynamides and their silicon-substituted analogs exhibit biological activity over a wide range [5–14]. Further functionalization of trimethylsilylpropynamides was expected to diversify their chemical properties and biological activity.

The goal of the present work was to synthesize new hydroxy-containing trimethylsilylpropynamides from trimethylsilylpropynoyl chloride (**I**) and amino-alcohols of the general formula $NH_2CRR'CH_2OH$ (**II**–**IV**) and 1,3-diamino-2-propanol (**V**).

We have found that the reaction of trimethylsilylpropynoyl chloride (**I**) with 2-aminoethanol (**II**) takes different pathways, depending on the conditions (reactant ratio, order of their mixing and rate of addition, and nature of hydrogen chloride acceptor). When the reaction was carried out with equimolar amounts of the reactants at –50 to –40°C in chloroform containing pyridine, we obtained previously unknown 2-(trimethylsilylpropynoylamino)ethyl trimethylsilylpropynoate (VI) (Scheme 1).

Scheme 1.

$$\underset{\mathbf{I}}{Me_3Si{-}C{\equiv}C{-}COCl} + \underset{\mathbf{II}}{H_2NCH_2CH_2OH} \xrightarrow{\text{Pyridine}} \underset{\mathbf{VI}}{Me_3SiC{\equiv}CCONHCH_2CH_2OCOC{\equiv}CSiMe_3}$$

The yields, physical properties, IR spectra, and elemental analyses of products **VI**, **VII**, and **IX**–**XI** are given in Table 1. The IR spectrum of amido ester **VI** contains absorption bands belonging to stretching vibrations of the triple bond (SiC≡C (2170 cm^{-1}), stretching vibrations of the Si–Me bonds (1260, 850, and 750 cm^{-1}), bending vibrations of the NH group (1530 cm^{-1}), and stretching vibrations of the amide carbonyl (1620 cm^{-1}), ester carbonyl (1710 cm^{-1}), and N–H bond (3260 cm^{-1}). The structure of amide **VI** was also confirmed by the ^1H, ^{13}C, and ^{29}Si NMR spectra (Tables 2, 3).

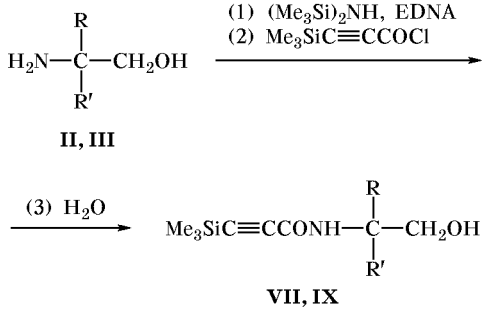
When the reaction of **I** was performed with 2 equiv of 2-aminoethanol (i.e., the latter was also used as hydrogen chloride acceptor) in chloroform or ether, a mixture of several products was formed. It showed in the IR spectrum the following absorption bands, cm^{-1}: 2170 (SiC≡C), 2100 and 3290 (H–C≡C), 1620 (CONH), 1720 (C=O, ester), 1530 and 3260 (δN–H and νN–H) and 3400–3600 (OH). These data indicate formation of amido ester **VI** and hydroxy amide

$Me_3SiC{\equiv}CCONHCH_2CH_2OH$ (**VII**), as well as of products resulting from heterolytic dissociation of the $Si-C_{sp}$ bond. By column chromatography on Al_2O_3 we succeeded in isolating only *N*-(2-hydroxyethyl)propynamide $HC{\equiv}CCONHCH_2CH_2OH$ (**VII**) with a terminal triple bond. It was characterized by the IR and NMR spectra. The formation of amide **VI** is favored by addition of 2-aminoethanol to acid chloride (**I**); the reverse order of mixing of the reactants and fast addition of chloride **I** favors heterolysis of the $Si-C_{sp}$ bond (according to the data of IR monitoring). Presumably, cleavage of the $Si-C_{sp}$ bond is facilitated by the presence of excess basic reagent and moisture which cannot be removed by evacuation or azeotropic distillation with benzene. A considerable problem in the synthesis of amide **VII** is insufficient solubility of 2-aminoethanol in organic solvents. To overcome this difficulty, 2-aminoethanol was treated with hexamethyldisilazane in the presence of ethylenedinitramine (EDNA) as catalyst (0.01 mol). The high catalytic activity of ethylenedinitramine was demonstrated by us previously in the silylation of acetylenic alcohols [15].

The reaction of 2-aminoethyl trimethylsilyl ether with trimethylsilylpropynoyl chloride (**I**) occurred regioselectively at the amino group to afford hitherto unknown *N*-(2-hydroxyethyl)trimethylsilylpropynamide (**VII**). Its structure was proved by the IR and ^1H, ^{13}C, and ^{29}Si NMR spectra (Tables 2, 3). In the ^1H NMR spectra of compounds **VI** and **VII**, apart from the expected signals, we observed weak signals from NH, NCH_2, and Me_3Si groups (Table 2). Their appearance may be explained by the presence of another rotational isomer which is stabilized due to restricted rotation about the amide group [16].

Under analogous conditions, from 2-aminobutyl trimethylsilyl ether (**III**) and chloride **I** we obtained silicon-containing acetylenic hydroxy amide **IX**,

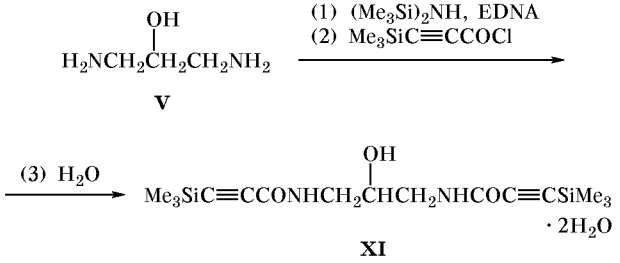
Scheme 2.



II, **VII**, R = R′ = H; **III**, **IX**, R = H, R′ = Et.

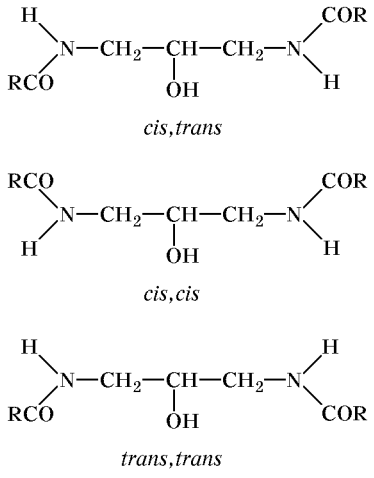
N-(1-hydroxymethylpropyl)trimethylsilylpropynamide (Scheme 2). We succeeded in synthesizing hydroxy amide $Me_3SiC{\equiv}CCONHC(Me)_2CH_2OH$ (**X**) without preliminarily silylation of the initial amino alcohol only from 2-amino-2-methyl-1-propanol (**IV**). The reaction of silylated 1,3-diamino-2-propanol **V** with trimethylsilylpropynoyl chloride (**I**) gave *N*-[2-hydroxy-3-(trimethylsilylpropynoylamino)propyl]trimethylsilylpropynamide (**XI**) (Scheme 3).

Scheme 3.



Compound **XI** showed in the ^1H NMR spectrum six signals from NCH_2 groups, three NH signals, and three signals from Me_3Si groups, which are likely to belong to three different rotamers (Scheme 4); the position of these signals changes on heating (Table 2).

Scheme 4.



R = $Me_3SiC{\equiv}C$.

An additional doubling of the NCH_2 signals is explained by the proximity of CHOH prochiral center.

Thus we have demonstrated the efficiency of using amino alcohol trimethylsilyl ethers in reactions with trimethylsilylpropynoyl chloride, which ensure regioselective N-acylation leading to formation of silicon-containing acetylenic hydroxy amides in high yield.

Table 1. Yields, melting points, IR spectra, and elemental analyses of compounds **VI**, **VII**, and **IX**–**XI**

Comp no.	Yield, %	mp, °C (solvent)	IR spectrum, ν, cm^{-1}				
			Si–C	C=O	C≡C	C=N, δNH	NH, OH
VI	78	56–58 (heptane–benzene)	750, 860, 1260	1620 (amide), 1710 (ester)	2170	1530	3260
VII	80	Viscous liquid	750, 850, 1260	1640	2180	1540	3200, 3400
IX	84	68–70 (ether–heptane)	760, 845, 1245	1640	2170	1538	3250, 3400
X	88	105–107 (hexane)	760, 845, 1245	1630	2170	1545	3200, 3400
XI	88	Viscous liquid	750, 840, 1250	1630	2170	1500–1530	3200, 3500

Comp. no.	Found, %				Formula	Calculated, %			
	C	H	N	Si		C	H	N	Si
VI	54.01	7.61	4.62	18.44	$C_{14}H_{23}NO_3Si_2$	54.31	7.48	4.52	18.14
VII	51.56	8.29	7.32	14.86	$C_8H_{15}NO_2Si$	51.86	8.16	7.55	15.16
IX	55.70	9.57	6.16	12.84	$C_{10}H_{19}NO_2Si$	56.28	8.97	6.56	13.16
X	56.22	9.30	6.76	13.25	$C_{10}H_{19}NO_2Si$	56.28	8.97	6.56	13.16
XI	48.37	7.25	7.63	14.82	$C_{15}H_{26}N_2O_3Si_2 \cdot 2H_2O$	48.09	7.53	7.40	14.99

EXPERIMENTAL

The IR spectra of compounds **VI**–**XI** were recorded on a Specord 75IR spectrometer from samples prepared as KBr pellets or thin films (for liquids). The ^1H, ^{13}C, and ^{29}Si NMR spectra were measured on a Bruker DPX-400 spectrometer in DMF-d_7 or $CDCl_3$, using HMDS and cyclohexane as internal references.

2-(Trimethylsilylpropynoylamino)ethyl trimethylsilylpropynoate (VI). To a solution of 2.9 g (18 mmol) of compound **I** in 10 ml of chloroform we added at –50 to –40°C over a period of 15 min 1.1 g (18 mmol) of 2-aminoethanol (**II**) and 1.42 g (18 mmol) of pyridine in 5 ml of chloroform. The mixture was allowed to gradually warm up to room temperature, stirred for 2 h, treated with water, and extracted with chloroform. The extract was dried over $MgSO_4$, and the solvent was removed under reduced pressure to isolate 2.2 g of compound **VI**.

***N*-(2-Hydroxyethyl)trimethylsilylpropynamide (VII).** *a.* A mixture of 5.08 g (83 mmol) of 2-aminoethanol (**II**), 6.71 g (42 mmol) of hexamethyldisilazane, and 0.01 mol % of *N*,*N*′-dinitroethylenediamine was heated for 0.5 h at 110–140°C. Vacuum distillation gave 9.97 g (90%) of 1-amino-2-trimethylsiloxyethane, bp 137–138°C (published data [17]: bp 134–135°C). A 1.37-g (10-mmol) portion of the product was dissolved in 15 ml of dry diethyl ether, a solution of 1.66 g (10 mmol) of chloride **I** in 5 ml of ether was added at 0°C, and the mixture was stirred for 1 h, treated with water, and extracted with ether. The extract was dried over $MgSO_4$, and the solvent was removed to isolate 1.3 g (80%) of amide **VII** as a viscous liquid.

b. A mixture of 2.21 g (30 mmol) of 2-aminoethanol (**II**), 4.88 g (30 mmol) of hexamethyldisilazane, and 0.01 mol % of *N*,*N*′-dinitroethylenediamine was heated for 1 h at 110–140°C. The resulting hexamethyldisiloxane was removed under reduced pressure. The residue was dissolved in 15 ml of chloroform, and a solution of 2.43 g (15 mmol) of propynoyl chloride **I** in 10 ml of chloroform was slowly added at 0–10°C. The mixture was stirred for 1 h at room temperature, treated with water, and neutralized with a 5% solution of $NaHCO_3$. The product was extracted into chloroform, and the extract was dried over $MgSO_4$ and evaporated under reduced pressure to isolate 2.15 g of hydroxy amide **VII**.

***N*-(2-Hydroxyethyl)propynamide (VIII).** A solution of 1.6 g (10 mmol) of propynoyl chloride **I** in 10 ml of dry diethyl ether was added dropwise over a period of 1 h to a suspension of 1.2 g (20 mmol) of

Table 2. ^{1}H NMR spectra of compounds **VI**, **VII**, and **IX**–**XI**

Comp. no.	Chemical shifts δ, ppm			
	Me_3Si	NH	NCH_2	OCH_2 (OCH)
VI	0.06 s (9H), 0.09 s	7.12 s (1H), 6.76 s[a]	3.44 m (2H), 3.60 m	3.57 s (2H)
VII[b]	0.23 s (9H), 0.29 s[a]	7.45 s (1H), 6.72 s[a]	3.42 m (2H), 3.49 m[a]	3.72 t (2H)
IX[c]	0.13 s (9H)	6.13 s (1H)		3.63 m (2H)
X[d]	0.23 s (9H)	5.91 s (1H)		3.61 s (2H)
XI[e]	0.21 s (18H), 0.25 s,[f] 0.28 s[f]	6.98 br.s,[f] 7.10 br.s[f] (2H), 7.25 br.s (2H)	3.28 m (2H), 3.32 m (2H),[f] 3.38 m (2H),[f] 3.45 m (2H), 3.55 m (2H),[f] 3.61 m (2H)[f]	3.84 m (1H), 3.85 m

[a] Fraction of the second rotamer 10%.
[b] δ(OH) 3.23 ppm, s (1H); in the spectra of the other compounds the OH signal is obscured in the region of δ 3.5 ppm.
[c] Other signals, δ, ppm: 0.91 t (3H, $CH_2C\mathbf{H}_3$), 1.47 m and 1.53 m (2H, $C\mathbf{H}_2CH_3$), 2.65 m (1H, CHN).
[d] δ(CCH_3) 1.33 ppm, s (6H).
[e] Chemical shifts at 60°C, δ, ppm: 3.33, 3.39, 3.42, 3.49, 3.57, 3.64 (NCH_2); 6.60, 6.78, 6.84 (NH).
[f] Fractions of the other rotamers 15 and 25%.

Table 3. ^{13}C and ^{29}Si NMR spectra of compounds **VI**, **VII**, and **IX**–**XI**

Comp. no.	Chemical shifts δ_C, ppm						δ_{Si}, ppm
	CH_3Si	$Si\mathbf{C}\equiv C$	$SiC\equiv\mathbf{C}$	C=O	C–NH	C–O	
VI	–0.06, –0.25	94.97, 92.49	98.16, 95.42	153.83, 153.27	39.13	64.65	–14.46, –15.41
VII	–0.68	92.27	97.46	153.69	42.46	61.33	
IX[a]	–0.72	91.85	97.60	153.25	53.52	64.34	–15.06
X[b]	–0.74	91.23	97.93	153.26	57.10	69.84	–15.10
XI	–0.80, –0.41	92.70, 93.04	96.94, 97.00	153.98, 154.17	42.57, 42.28	68.90, 70.54	–14.07, –14.97, –15.03

[a] Other signals, δ_C, ppm: 10.46 ($C\mathbf{H}_3CH_2$), 24.12 ($CH_3C\mathbf{H}_2$).
[b] $\delta_C(CH_3)$ 24.29 ppm.

2-aminoethanol (**II**) in 50 ml of dry diethyl ether, stirred at –18 to –20°C. The mixture was stirred for an additional 1 h, treated with water, and extracted with ether. The extract was dried over $MgSO_4$, and the solvent was removed to obtain 0.6 g of a viscous substance. A 0.2-g portion of this material was subjected to chromatography on Al_2O_3 using chloroform–methanol (10:1) as eluent. We isolated 0.05 g of a viscous liquid whose spectral data corresponded to *N*-(2-hydroxyethyl)propynamide (**VIII**). IR spectrum (film), ν, cm^{-1}: 1530 (δNH), 1615 (C=O), 2100 (HC≡C), 3290 (H–C≡), 3200–3400 (NH, OH). ^{1}H NMR spectrum, δ, ppm: 2.90 s (1H, HC≡C), 3.45 m (2H, CH_2N), 3.67 t (CH_2O), 6.75 s (NH).

***N*-(1-Hydroxymethylpropyl)trimethylsilylpropynamide (IX).** A mixture of 4.45 g (50 mmol) of 2-aminobutanol (**III**), 4 g (25 mmol) of hexamethyldisilazane, and 0.01 mol % of *N*,*N*′-dinitroethylenediamine was heated for 5 h at 110°C. The subsequent vacuum distillation gave 5.34 g (67%) of 2-amino-1-trimethylsiloxybutane, bp 65–68°C (25 mm), n_D^{20} = 1.4190. IR spectrum (film), ν, cm^{-1}: 1082 (Si–O–C); 830, 870, 1240 (Si–C); 1580 (δNH); 3270 br (NH). Found, %: C 51.62; H 11.74; N 8.19; Si 17.02.

$C_7H_{19}NOSi$. Calculated, %: C 52.11; H 11.87; N 8.67; Si 17.41. A 2.77-g (12-mmol) portion of 2-amino-1-trimethylsiloxybutane was dissolved in 10 ml of dry diethyl ether, and a solution of 0.95 g (6 mmol) of propynoyl chloride **I** in 10 ml of diethyl ether was added dropwise at –30°C under argon. The mixture was allowed to warm up to room temperature and was decomposed with 10 ml of water. After appropriate treatment, the residue was recrystallized from diethyl ether–heptane. Yield 1.05 g.

***N*-(2-Hydroxy-1,1-dimethylethyl)trimethylsilylpropynamide (X).** A solution of 1.82 g (11 mmol) of propynoyl chloride **I** in 10 ml of dry benzene was added dropwise over a period of 25 min at –1 to 5°C a solution of 1.78 g (20 mmol) of 2-amino-2-methyl-1-propanol (**IV**) in 10 ml of dry benzene. The mixture was heated for 4 h at 80°C, cooled to room temperature, and decomposed with 10 ml of water. The aqueous layer was extracted with ether, and the organic layer was separated and dried over $MgSO_4$. The solvent was removed under reduced pressure to isolate 1.86 g of compound **X**; mp 105–107°C (from hexane).

***N*-[2-Hydroxy-3-(trimethylsilylpropynoylamino)propyl]trimethylsilylpropynamide (XI).** A mixture of 1.05 g (11.6 mmol) of 1,3-diamino-2-propanol (**V**), 2.81 g (17 mmol) of hexamethyldisilazane, and 0.01 mol % of *N*,*N*′-dinitroethylenediamine was stirred for 7 h at 80°C. The resulting hexamethyldisiloxane and excess hexamethyldisilazane were removed under reduced pressure, 20 ml of dry diethyl ether was added, and a solution of 1.87 g (11.6 mmol) of propynoyl chloride **I** in 10 ml of dry diethyl ether was added dropwise at –5°C over a period of 12 min. The mixture was stirred for 3 h at room temperature, treated with water, neutralized with an aqueous solution of $NaHCO_3$, and extracted with ether. The extract was dried over $MgSO_4$, and the solvent was removed to isolate 1.91 g of amide **XI**.

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