Preparation of 3-(trimethylsilanyl)propynoic acid *N*-(hydroxyalkyl)amides

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Dedicated to Academician Michael G. Voronkov on the occasion of his 80th birthday
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Abstract
New 3-(trimethylsilanyl)propynoic acid *N*-(hydroxyalkyl)amides were synthesized by the reaction of silyl-protected aminoalcohols with 3-(trimethylsilanyl)propynoyl chloride in high yields. The reaction of unprotected ethanolamine with 3-(trimethylsilanyl)propynoyl chloride caused N,O-bisacylation and the formation of 2-[3-(trimethylsilanyl)propynoyl)aminoethyl 3-(trimethyl-silanyl)propynoate.

Keywords: *N*-(Hydroxyalkyl)amides of 3-(trimethylsilanyl)propynoic acid, 3-(trimethylsilanyl)-propynoyl chloride, aminoalcohols, N,O-silyl protection

Introduction

Amides of propynoic acid feature a variety of pharmacological profiles;[1-8] they have been used for the synthesis of rapamycin,[9] an immunosuppressant, and they serve as building blocks in organic chemistry, in particular, for the formation of heterocyclic systems which may be of special interest as biologically active compounds.

Silicon-substituted propynoic acid amides have received little attention. 3-(Trimethyl-silanyl)propynoic acid *N*-benzylamide has been prepared from lithiated 2-propynoic acid amide and chlorotrimethylsilane; its reaction with arylisocyanates in the presence of triethylamine has been reported to afford *Z*-trimethylsilydenehydantoin.[10]

Previously, we have described the synthesis of 3-(trimethylsilanyl)propynoic acid *N*,*N*-dialkylamides,[11,12] their fragmentation under electron impact[2] and the determination of their basicity by an IR method.[13] Furthermore, the reaction of trimethylsilanyl- and *tert*-butyl-propynoic acid *N*,*N*-dialkylamides with triethylgermyllithium leads to the corresponding

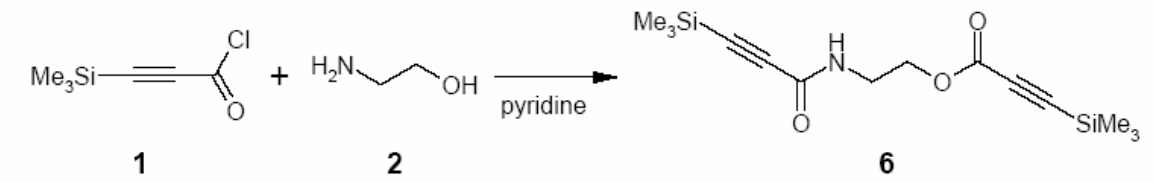
triethylpropynoyl-germanes in high yields.[14]

The goal of this investigation is the synthesis of new amides of 3-(trimethylsilanyl)propynoic acid containing an *N*-hydroxyalkyl group by the reaction of 3-(trimethylsilanyl)propynoyl chloride **1** with hydroxyalkylamines $H_2NCR^1R^2CH_2OH$ **2-4** [$R^1 = R^2 = H$ (**2**), $R^1 = H$, $R^2 = Et$ (**3**), $R^1 = R^2 = Me$ (**4**)] and 1,3-diamino-2-propanol **5**. The target amides may be of interest as biologically active compounds and as the starting material, for example, for the synthesis of acetylenic oxazolines**.**

Results and Discussion

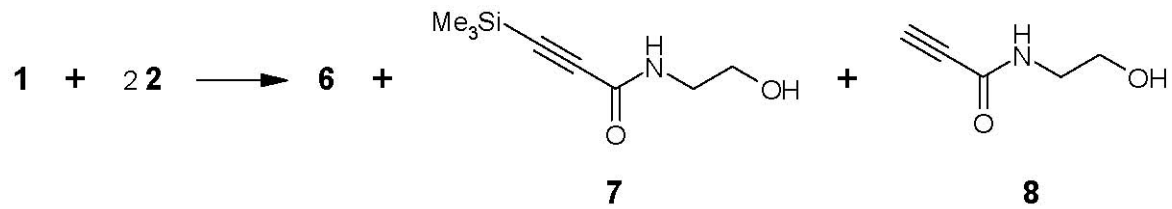
The investigation of the reaction of 3-(trimethylsilanyl)propynoyl chloride (**1**) with ethanolamine (**2**) revealed the influence of the reaction conditions: (1) The ratio of reactants employed, (2) the order and rate at which the reactants were mixed, (3) the nature of the base used and its impact on the type of products formed.

When the reaction was carried out with **1**, **2** and pyridine (1:1:1 ratio) in $CHCl_3$ at –50 to –40 °C, 2-(3-trimethylsilanylpropynoylamino)ethyl 3-(trimethylsilanyl)propynoate (**6**) was isolated in 39% yield (Scheme 1).



Scheme 1

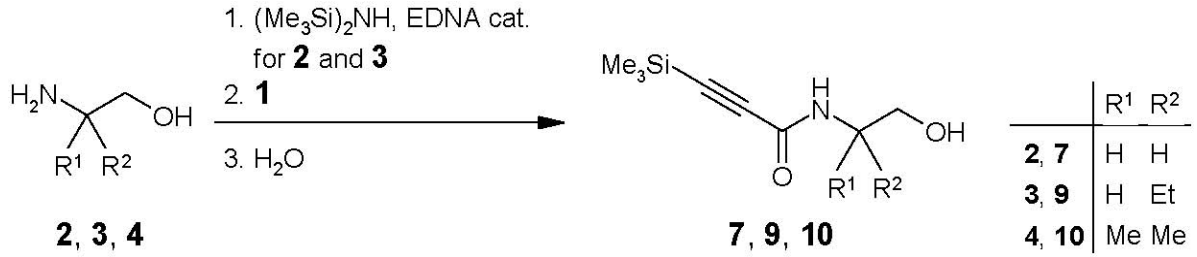
Employing ethanolamine as reactant and base (i.e. carrying out the reaction of **1** and **2** at the ratio 1:2) in $CHCl_3$ or Et_2O afforded a mixture of products: amidoester **6,** 3-(trimethylsilanyl)propynoic acid *N*-(2-hydroxyethyl)amide (**7**), and propynoic acid N-(2-hydroxyethyl)-amide (**8**) (Scheme 2). The reaction mixture was analyzed by IR and ^1H NMR spectra with reference to the spectra of the individual products (vide infra). Amide **8**, which is presumed to be formed upon heterolysis of the Si-C_{sp} bond in amide **7**, was isolated after column chromatography on Al_2O_3.



Scheme 2

Carrying out the reaction by adding ethanolamine (**2**) to 3-(trimethylsilanyl)propynoyl chloride (**1**) favors the formation of amide **6**. However, fast addition of 3-(trimethylsilanyl)propynoyl chloride (**1**) to ethanolamine (**2**) or inverting the order of mixing the reactants, i.e. adding **2** to a solution of **1** gave rise to a mixture of **6** and **8**. Obviously, these conditions (probably due to the excess of base and presence of traces of water in ethanolamine) induce the heterolysis of Si-C_{sp} bond of the presumed precursor of **8**, the hydroxyalkyamide **7**.

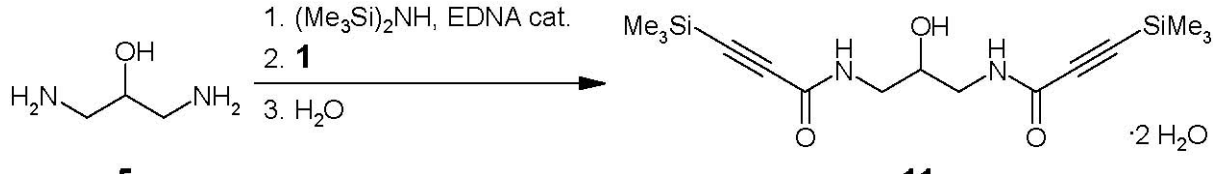
Low solubility of ethanolamine in organic solvents complicates the synthesis of amide **7** substantially. Selective N-acylation of O-silylated ethanolamine with 3-(trimethylsilanyl)-propynoyl chloride (**1**) gave 3-(trimethylsilanyl)propynoic acid *N*-(2-hydroxyethyl)amide (**7**) in high yield. O-Trimethylsilylation of ethanolamine (**2**) with hexamethyldisilazane was catalyzed by 1,4-dinitroethylenediamine (EDNA) (0.01 mol%); the high efficiency of this catalyst in the O-silylation of acetylenic alcohols has been shown by us previously.[15] In an analogous manner, 3-(trimethylsilanyl)propynoic acid *N*-(2-hydroxy-1-ethyl)ethylamide (**9**) was prepared by the reaction of O-silylated 2-amino-1-butanol **3** with **1**. Only the conversion of 2,2-dimethylethanol-amine (**4**) to 3-(trimethylsilanyl)propynoic acid *N*-(2-hydroxy-1,1-dimethylethyl)amide (**10**) (88% yield) was accomplished without preceding silylation of the aminoalcohol **4** (Scheme 3).



2, **3**, **4** **7**, **9**, **10**

Scheme 3

The reaction of O-silylated 1,3-diamino-2-propanol **5** with 3-(trimethylsilanyl)propynoyl chloride (**1**) gave 3-(trimethylsilanyl)propynoic acid *N*-2-[hydroxy-3-(3-trimethylsilanylpropyno-ylaminopropyl)]amide (**11**) in high yield (Scheme 4).



5 **11**

Scheme 4

The ^{1}H NMR spectra of amides **6** and **7** display two sets of spectra with different intensities indicating the presence of the two rotational isomer (*E* and *Z*) due to hindered amide rotation.[16]

The ^{1}H NMR spectrum of **11** displays six NCH_2 group signals, three NH signals and three Me_3Si group signals. This reflects the presence of three amide rotamers (*EE*, *EZ*, and *ZZ*) and

was confirmed by a shift of the signal positions upon heating to 60 °C in $CDCl_3$. Heating a DMSO-d_6 solution of **11** to 120 °C brought about coalescence of the multiple signals. Furthermore, the diastereotopic protons of the NCH_2 groups give rise to an additional splitting pattern.

In conclusion, it has been shown that O-silyl protected aminoalcohols are required (with one exception) to accomplish the selective N-acylation with 3-(trimethylsilanyl)propynoyl chloride furnishing 3-(trimethylsilanyl)propynoic acid *N*-(hydroxyalkyl)amides.

Experimental Section

General Procedures. IR Spectra of products **6–11** (KBr pellets or liquid films) were recorded on a Specord 75 IR instrument. ^1H, ^{13}C, and ^{29}Si NMR spectra of DMSO-d_6 and $CDCl_3$ solutions were recorded on a Bruker DPX-400 spectrometer, with $(Me_3Si)_2O$ or cyclohexane as internal standards. 1,4-Dinitroethylenediamine (EDNA) was used as a solution in THF (0.005 M).

2-(3-Trimethylsilanylpropynoylamino)ethyl 3-(trimethylsilanyl)propynoate (6). To a solution of **1** (2.9 g, 18 mmol) in $CHCl_3$ (10 mL) was added a solution of **2** (1.1 g, 18 mmol) and pyridine (1.42 g, 18 mmol) in $CHCl_3$ (5 mL) at –50 to –40 °C within 15 min. The reaction mixture was allowed to warm up to room temperature, and was then stirred for 2h, before water was added, and the mixture was extracted with $CHCl_3$. The extract was dried ($MgSO_4$), the solvent was removed (15 mm Hg) to give colourless crystals **6** (2.2 g, 39%), mp 56-58 °C (from heptane/benzene). IR (KBr): $\tilde{\nu}$ 3260 (NH), 2170 (C≡C), 1710 (CO_2), 1620 (CONH), 1530 (C═N, δ NH), 1260, 860, 750 (Si−C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.12 (1H, s, NH, amide A, 90%), 6.76 (amide B, 10%), 3.60 (2H, m, NCH_2, 10%), 3.44 (2H, m, NCH_2, 90%), 3.57 (2H, s, OCH_2), 0.09 (18H, s, Me_3Si, 10%), 0.06 (18H, s, Me_3Si, 90%); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.83, 153.27 (C═O), 98.16, 95.42 (SiC≡C), 94.97, 92.49 (SiC≡C), 64.65 (C−O), 39.13 (C−NH), –0.25, –0.06 (Me_3Si), ^{29}Si NMR (79.49 MHz, $CDCl_3$): δ –14.46. Anal. Calcd. for $C_{14}H_{23}NO_3Si_2$ (311.34): C, 54.31; H, 7.48; N, 4.52; Si, 18.14. Found: C, 54.01; H, 7.61; N, 4.62; Si, 18.44.

3-(Trimethylsilanyl)propynoic acid *N*-(2-hydroxyethyl)amide (7). Method A. A mixture of **2** (5.08 g, 83 mmol), hexamethyldisilazane (6.71 g, 42 mmol) and ethylenedinitramine (0.005 M THF solution; 1.7 mL, 0.01 mol%) was heated at 110 to 140 °C for 0.5 h to give 2-amino-1-(trimethylsiloxy)ethane (9.97 g, 90%) upon distillation, bp 137–138 °C (lit.[17] 134–135 °C). To a solution of 2-amino-1-(trimethylsiloxy)ethane (1.37 g, 10 mmol) in diethyl ether (15 mL) was added a solution of **1** (1.66 g, 10 mmol) in diethyl ether (5 mL) at 0 °C; the reaction mixture was stirred for 1h. After addition of water and extraction with diethyl ether, the extract was dried ($MgSO_4$), and the solvent was distilled off (25 mm Hg). A viscous liquid **7** (1.3 g, 80%) was isolated. IR (liquid film): $\tilde{\nu}$ 3400 (OH), 3200 (NH), 2180 (C≡C), 1640 (C═O), 1540 (C═N, δ

NH), 1260, 850, 750 (Si−C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (1H, s, NH, amide A, 90%), 6.72 (amide B, 10%), 3.72 (2H, t, OCH_2), 3.23 (1H, s, OH), 3.49 (2H, m, NCH_2, 10%), 3.42 (2H, m, NCH_2, 90%), 0.29 (9H, s, Me_3Si, 10%), 0.23 (9H, s, Me_3Si, 90%); ^{13}C: NMR (100 MHz, $CDCl_3$): δ 153.69 (C═O), 97.46 (SiC^o ≡C), 92.27 (SiC≡C), 61.33 (C−O), 42.46 (C−NH), –0.68 (Me_3Si). Anal. Calcd. for $C_8H_{15}NO_2Si$ (185.29): C, 51.86; H, 8.16; N, 7.55; Si, 15.16. Found: C, 51.56; H, 8.29; N, 7.32; Si, 14.86.

Method B. A mixture of **2** (2.21 g, 30 mmol), hexamethyldisilazane (4.88 g, 30 mmol), and ethylenedinitramine (0.005 M THF solution; 0.4 mL, 0.01 mol%) was heated at 110 to 140 °C for 1 h. Hexamethyldisiloxane was distilled off (15 mm Hg), and the residue was dissolved in $CHCl_3$ (15 mL). To this solution was added a solution of **1** (2.43 g, 15 mmol) in $CHCl_3$ (10 mL) at 0 to 10 °C. The reaction mixture was stirred at room temperature for 1 h, then water was added, and the aqueous solution was neutralized with sodium bicarbonate (5% in water). The extract with $CHCl_3$ was dried ($MgSO_4$), and after removal of the solvent (15 mm Hg) a viscous liquid **7** (2.15 g, 77%) was obtained.

Propynoic acid *N*-(2-hydroxyethyl)amide (8). To a solution of **2** (1.2 g, 20 mmol) in dry diethyl ether (50 mL) was added a solution of **1** (1.6 g, 10 mmol) in diethyl ether (10 mL) at –20 °C over a period of 1 h, and the reaction mixture was stirred for an additional 1 h. After dissolving the reaction mixture in water and extraction with ether, the extract was dried ($MgSO_4$), the solvent was distilled off (15 mm Hg), and a viscous substance (0.6 g) was obtained. Column chromatography (Al_2O_3, chloroform/methanol 10:1) of a portion (0.2 g) of this product afforded amidoester **6** (0.08 g, 16%) and amide **8** (0.05 g, 27%), a viscous liquid. IR (liquid film): $\tilde{\nu}$ 1530 (δ NH), 1615 (CO), 2100 (H-C≡C), 3290 (H-C≡), 3200 (NH), 3400 (OH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.90 (s, 1H, H-C≡C), 3.45 (m, 2H, CH_2N), 3.67 (t, 2H, CH_2O), 6.75 (s, 1H, NH), the OH signal is masked by the multiplet at 3.5.

3-(Trimethylsilanyl)propynoic acid *N*-(2 hydroxy-1-ethyl)ethylamide (9). A mixture of **3** (4.45 g, 50 mmol), hexamethyldisilazane (4 g, 25 mmol) and ethylenedinitramine (0.005 M THF solution; 1.0 mL, 0.01 mol%) was heated at 110 °C for 5 h. Vacuum distillation afforded a colourless liquid 2-amino-1-(trimethylsiloxy)butane (5.34 g, 67%), bp 65–68 °C (25 mm Hg), n_{20D} 1.4190. IR (liquid films): $\tilde{\nu}$ 3270 (broad signal, NH), 1580 (δ NH), 1240, 870, 830 (Si-C), 1082 (Si-O-C) cm^{-1}. Anal. Calcd. for C_7H_{19} NOSi (161.33): C, 52.11; H, 11.87; N, 8.67; Si, 17.41. Found: C, 51.62; H, 11.74; N, 8.19; Si, 17.02.

To a solution of 2-amino-1-(trimethylsiloxy)butane (2.77 g, 12 mmol) in dry diethyl ether (10 mL) at –30 °C under argon was added a solution of (**1**) (0.95 g, 6 mmol) in ether (10 mL). The reaction mixture was allowed to slowly warm up to room temperature, it was diluted with water (10 mL) and extracted with ether; the extract was dried ($MgSO_4$) and concentrated (25 mm Hg) until the crystalline product separated; after recrystallization from diethyl ether and heptane colourless crystals **9** (1.05 g, 84%) were obtained, mp 68–70 °C. IR: $\tilde{\nu}$ 3400, 3250 (NH, OH), 2170 (C≡C), 1640 (C═O), 1538 (C═N, δ NH), 1245, 845, 760 (Si−C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.13 (1H, s, NH), 3.63 (2H, m, OCH_2), 2.65 (1H, m, C−NH), 1.53, 1.47

(2H, m, $\underline{CH_2}CH_3$), 0.91 (3H, t, $CH_2\underline{CH3}$), 0.23 (9H, s, (Me_3Si); the OH signal is masked by the multiplet at 3.5. ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.25 (C═O), 97.60 (SiC≡$\underline{C}$), 91.85 (Si$\underline{C}$≡C), 64.34 (C−O), 53.52 (C−NH), 24.12 ($\underline{CH_2}CH_3$), 10.46 ($CH_2\underline{CH3}$), –0.72 (Me_3Si); ^{29}Si NMR (79.49 MHz, $CDCl_3$): δ –15.06. Anal. Calcd. for $C_{10}H_{19}NO_2Si$ (213.19): C, 56.28; H, 8.97; N, 6.56; Si, 13.16. Found: C, 55.70; H, 9.37; N, 6.16; Si, 12.84.

3-(Trimethylsilanyl)propynoic acid *N*-(2-hydroxy-1,1-dimethylethyl)amide (10). To a solution of **4** (1.78 g, 20 mmol) in dry benzene (10 mL) at –1 to +5 °C was added **1** (1.82 g, 11 mmol) in benzene (10 mL) over a period of 25 min. The mixture was refluxed for 4 h, diluted with water (10 mL), extracted with Et_2O; the extract was dried ($MgSO_4$) and concentrated (25 mm Hg) to give white crystals **10** (1.86 g, 88%), mp 105–107 °C (hexane). IR (KBr): $\tilde{\nu}$ 3400 (OH), 3200 (NH), 2170 (C≡C), 1630 (C═O), 1500–1530 (C═N, δ NH), 1250, 840, 750 (Si−C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91 (1H, s, NH), 3.61 (1H, s, OCH_2), 1.33 (6H, s, C−CH_3), 0.23 (9H, s, Me_3Si); the OH signal is masked by the multiplet at 3.5; ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.26 (C═O), 97.93 (SiC≡$\underline{C}$), 91.23 (Si$\underline{C}$≡C), 69.84 (C−O), 57.10 (C−NH), –0.74 (Me_3Si); ^{29}Si NMR (79.49 MHz, $CDCl_3$): δ –15.10. Anal. Calcd. for $C_{10}H_{19}NO_2Si$ (213.19): C, 56.28; H, 8.97; N, 6.56; Si, 13.16. Found: C, 56.22; H, 9.30; N, 6.76; Si, 13.25.

Trimethylsilanylpropynoic acid *N*-[2-hydroxy-3-[(3-trimethylsilanylpropynoyl)]amino]-propylamide (11). Mixture of **5** (1.05 g, 11.6 mmol), hexamethyldisilazane (2.81 g, 17 mmol), and ethylenedinitramine (0.005 M THF solution; 1.7 mL, 0.25 mol%) was heated at 80 °C for 7 h. Hexamethyldisiloxane and excess of hexamethyldisilazane were removed in vacuo (25 mm Hg), the residue was dissolved in dry diethyl ether (20 mL), and a solution of **1** (1.87 g, 11.6 mmol) in dry diethyl ether (10 mL) was added at –5 °C over a period of 12 min; the reaction mixture was stirred for 3 h at room temperature, then diluted with water, neutralized with $NaHCO_3$ (5% in water), and extracted with ether. The extract was dried ($MgSO_4$), and after evaporation of the solvent (15 mm Hg) a slightly yellow viscous liquid **11** (1.91 g, 88%) was obtained. IR (liquid film): $\tilde{\nu}$ 3500 (OH), 3200 (NH), 2170 (C≡C), 1630 (C═O), 1500–1530 (C═N, δ NH), 1250, 840, 750 (Si−C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (2H, s, NH, amide A, 15%), 7.10 (2H, s, NH, amide B, 60%), 6.98 (2H, s, NH, amide C, 25%), [at 60 °C: 6.84, 6.78, 6.60 (NH)], 3.85 (1H, m, OCH), 3.61, 3.55 (2H, m, NCH_2, 25%), 3.45, 3.28 (2H, m, NCH_2, 60%), 3.38, 3.32 (2H, m, NCH_2, 15 %), 0.28 (18H, s, Me_3Si, 25%), 0.25 (18H, s, Me_3Si, 15%), 0.21 (18H, s, Me_3Si, 60%); the OH signal is masked by the multiplet at 3.5; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.61 (NH, 75%), 8.27 (NH, 15%), 8.01 (NH, 10%); at 120 °C: 7.85 (coalescence of all NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.76, 151.07, 150.44 (C═O), 97.58, 95.25, 93.84 (SiC≡$\underline{C}$), 87.93, 87.73 (Si$\underline{C}$≡C), 67.06, 66.39, 66.11 (C−O), 41.74, 41.58, 41.50 (C−NH), 0.40, –1.75, –2.18 (Me_3Si); ^{29}Si NMR (79.49 MHz, DMSO-d_6): δ –14.07, –14.97, –15.00. Anal. Calcd. for $C_{15}H_{26}N_2O_3Si_2 \cdot 2H_2O$ (374.33): C, 48.09; H, 7.53; N, 7.40; Si, 14.99. Found: C, 48.37; H, 7.25; N, 7.63; Si, 14.82.

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