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Dedicated to Full Member of the Russian Academy of Sciences B.A. Trofimov on the 65th Anniversary of His Birth

Synthesis of *N*-(3-Trimethylsilyl-2-propynoyl) Amino Acids

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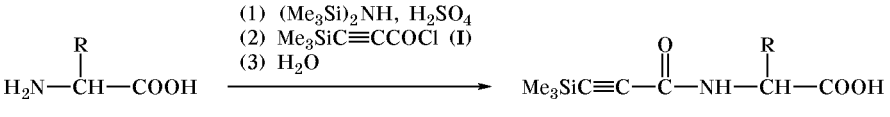
Abstract—An efficient procedure has been developed for the preparation of previously unknown *N*-(3-trimethylsilyl-2-propynoyl) amino acids. The procedure is based on the reaction of 3-trimethylsilyl-2-propynoyl chloride with silylated amino acids which are generated *in situ*.

In the preceding communications [1–4] we reported on the reactions of 3-trimethylsilyl-2-propynoyl chloride with N-, N,N-, N,O-, and N,S-nucleophiles. Depending on the nucleophile nature and conditions, the reaction involved either one or both functional groups. Aliphatic diamines were acylated with trimethylsilylpropynoyl chloride (**I**) at both amino groups, while *o*-phenylenediamine and 2-aminoethanethiol reacted at only one nucleophilic center [4]. 3-Trimethylsilylpropynoic acid amides exhibit a wide spectrum of biological activity, specifically fungicide, nematocide, antiphlogistic, analgetic, and antipyretic activity [5, 6].

The goal of the present study was to synthesize previously unknown *N*-(3-trimethylsilyl-2-propynoyl) amino acids **VIII**–**XIII**. Methods of preparation, physical and chemical properties, and wide industrial applications of *N*-acyl α-amino acids, as well as their importance for vital activity of humans, have been reviewed in [7]. *N*-(Trimethylsilylpropynoyl) derivatives of amino acids, including those of naturally occurring amino acids, attract interest as potential biologically active substances and polyfunctional reagents for fine organic synthesis. Like propynoyloxycarbonyl amino acid chlorides [8], *N*-(trimethylsilylpropynoyl) derivatives can be used in peptide synthesis via conversion into acyl chlorides and subsequent reaction with amino acids. Removal of the trimethylsilyl protection should give rise to analogs having an activated terminal triple bond. A new amino acid fragment can be introduced by conjugate addition of heteronucleophiles, e.g., amino acids containing O-, S-, or N-nucleophilic center in the side chain [9]. α,β-Acetylenic *N*-acyl amino acids have not been reported previously.

As nucleophiles we used natural amino acids **II**–**V** and aromatic amino acids **VI** and **VII**. Insofar as amino acids are poorly soluble in organic solvents, they are usually converted into the corresponding esters and *N*-acetyl derivatives. For this purpose, the initial amino acids were preliminarily treated with excess hexamethyldisilazane in the presence of a catalytic amount of concentrated sulfuric acid. The resulting *N*,*O*-bis-silyl derivatives were then brought (without isolation) into reaction with an equimolar amount of 3-trimethylsilylpropynoyl chloride (**I**). The

Scheme 1.



II–**V** → **VIII**–**XI**

II, **VIII**, R = *i*-Bu; **III**, **IX**, R = $HOCH_2$; **IV**, **X**, R = $HSCH_2$; **V**, **XI**, R = 3-indolylmethyl.

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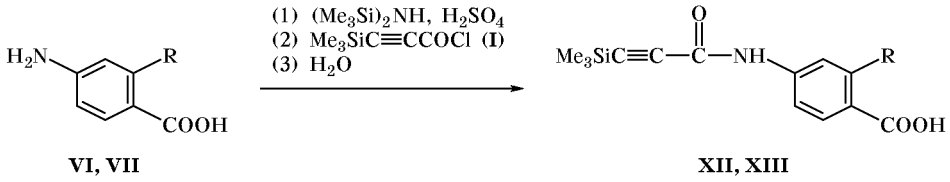
Scheme 2.



VI, VII **XII, XIII**

VI, **XII**, R = H; **VII**, **XIII**, R = OH.

reaction occurred under mild conditions (in diethyl ether at room temperature; reaction time 1 h) and with high regioselectivity. The products, *N*-(3-trimethylsilyl-2-propynoyl) amino acids **VIII**–**XI** were obtained in 74–95% yield (Scheme 1). Previously, a similar procedure was successfully applied to the synthesis of *N*-hydroxy-3-trimethylsilylpropynamides [3].

Aromatic amino acids **VI** and **VII** reacted with acyl chloride **I** in a similar way, affording the corresponding *N*-(trimethylsilylpropynoyl)aminobenzoic acids **XII** and **XIII** in 62–77% yield (Scheme 2). It should be noted that 4-(3-trimethylsilyl-2-propynoylamino)benzoic acid (**XII**) was also synthesized in 65% yield without preliminary silylation of *p*-aminobenzoic acid (**VI**) which is relatively readily soluble in organic solvents.

Compounds **VIII**–**XIII** are colorless crystalline substances which are poorly soluble in water and weakly polar organic solvents. Their structure was proved by elemental analyses and IR and ^{1}H and ^{13}C NMR spectra. The IR spectra of amides **VIII**–**XIII** contained absorption bands belonging to vibrations of the amide carbonyl group (1630–1640 cm^{-1}), acid carbonyl group (1680–1740 cm^{-1}), triple C≡C bond (2160–2180 cm^{-1}), and NH and OH groups (2500–3400 cm^{-1}.

In the ^{1}H NMR spectrum of 3-sulfanyl-2-(3-trimethylsilyl-2-propynoylamino)propanoic acid (**X**), weak signals from protons of the NH, NCH, and CH_2 groups were present in addition to the expected signals. These signals are likely to appear due to the presence of the second rotational isomer which originates from restricted rotation about the amide C–N bond [10]. A similar pattern was observed by us previously in the spectra of *N*-hydroxyamides derived from 3-trimethylsilylpropynoic acid [3].

When free amino acids, DL-serine (**III**) and L-cysteine (**IV**), were used in the reaction with chloride **I**, no target amides were isolated. We also tried to obtain *N*,*O*-bis-acylated products by reaction of 2 mol of chloride **I** with *N*,*O*-bis(trimethylsilyl) derivatives of DL-tryptophane (**V**) and 4-amino-2-hydroxybenzoic acid (**VII**). However, only compounds **XI** and **XIII**, respectively, were isolated.

Thus, the reaction of 3-trimethylsilylpropynoyl chloride with *N*,*O*-bis-silylated amino acids prepared *in situ* provides an efficient and mild procedure for the synthesis of *N*-(3-trimethylsilyl-2-propynoyl) amino acids.

EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR spectrometer in KBr. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX-400 instrument using HMDS as internal reference and DMSO-d_6, $CDCl_3$, and acetone-d_6 as solvents.

***N*-(3-Trimethylsilyl-2-propynoyl) amino acids VIII–XIII.** A mixture of 6.2 mmol of amino acid **II**–**VII** and 15.6 mmol of hexamethyldisilazane containing a catalytic amount of concentrated sulfuric acid was heated for 20 min under reflux. Excess hexamethyldisilazane was removed under reduced pressure, the residue was dissolved in 10 ml of anhydrous diethyl ether, and a solution of 6.2 mmol of 3-trimethylsilyl-2-propynoyl chloride (**I**) in 5 ml of ether was added dropwise over a period of 10 min at room temperature. The mixture was stirred for 1 h, treated with 5 ml of water, and extracted with ether or chloroform. The extract was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by recrystalliztion.

4-Methyl-2-(3-trimethylsilyl-2-propynoylamino)-pentanoic acid (VIII). IR spectrum, ν, cm^{-1}: 850, 1240 [Si(CH$_3$)$_3$]; 1530 [CN, δ(NH)]; 1630, 1640 (C=O); 1710, 1720 (COO); 2500–3400 (NH, OH). ^{1}H NMR spectrum, δ, ppm: 0.23 s [9H, (CH$_3$)$_3$Si], 0.96 d [6H, (C**H**$_3$)$_2$CH], 1.62 m [1H, (CH$_3$)$_2$C**H**], 1.73 m (2H, CH$_2$), 4.68 m (1H, NCH), 6.11 br.s (1H, NH). ^{13}C NMR spectrum, δ$_C$, ppm: –0.86 (CH$_3$Si), 21.67 [(**C**H$_3$)$_2$CH], 22.66 [(CH$_3$)$_2$**C**H], 24.71 (CH$_2$), 50.64 (CH), 92.32 (Si**C**≡C), 96.65 (SiC≡**C**), 151.42 (C=O), 175.98 (COOH).

3-Hydroxy-2-(3-trimethylsilyl-2-propynoylamino)propynoic acid (IX). IR spectrum, ν, cm^{-1}:

Yields, melting points, and elemental analyses of compounds **VIII**–**XIII**

Comp. no.	Yield, %	mp, °C	Found, %				Formula	Calculated, %			
			C	H	N	Si		C	H	N	Si
VIII	80	162–164[a]	56.29	8.25	5.26	10.87	$C_{12}H_{21}NO_3Si$	56.43	8.29	5.48	11.00
IX	95	141–142[b]	46.87	6.96	5.94	12.01	$C_9H_{15}NO_4Si$	47.14	6.59	6.11	12.25
X	88	259–263[c]	43.46	7.23	5.23	11.10	$C_9H_{15}NO_3SiS$	43.88	6.54	5.68	11.40
XI	74	62–63[d]	62.10	6.27	7.91	7.95	$C_{17}H_{20}N_2O_3Si$	62.17	6.14	8.03	8.55
XII	77	190–191[b]	59.40	5.89	5.35	10.45	$C_{13}H_{15}NO_3Si$	59.74	5.78	5.36	10.71
XIII	62	179–180[d]	55.76	5.56	5.04	10.40	$C_{13}H_{15}NO_4Si$	56.09	5.43	5.03	10.09

[a] From benzene.
[b] From heptane.
[c] With decomposition. Found S, %: 12.50. Calculated S, %: 13.01.
[d] From heptane–benzene.

850, 1260 [Si(CH_3)]; 1510 [CN, δ(NH)]; 1630 (C=O); 1740 (COO); 2180 (C≡C); 2520–3400 br (NH, OH). ^{1}H NMR spectrum, δ, ppm: 0.20 s [9H, (CH_3)$_3$Si], 3.92 m and 3.87 m (2H, CH_2), 4.54 m (1H, NCH), 7.67 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: –0.69 (CH_3Si), 55.72 (CH), 62.54 (CH_2), 90.87 (Si**C**≡C), 99.02 (SiC≡**C**), 152.94 (C=O), 171.27 (COOH).

2-(3-Trimethylsilyl-2-propynoylamino)-3-sulfanylpropanoic acid (X). IR spectrum, ν, cm^{-1}: 840, 1260 [Si(CH_3)]; 1520 [CN, δ(NH)]; 1640 (C=O); 1710, 1730 (COO); 2170 (C≡C); 2500–3400 (NH, OH); 2570 (SH). ^{1}H NMR spectrum, δ, ppm: 0.22 s [9H, (CH_3)$_3$Si], 3.09 m and 3.28 m (2H, CH_2, 80%), 2.72 m (2H, CH_2, 20%), 4.75 m (1H, NCH, 80%), 4.26 m (1H, NCH, 20%), 8.03 d (1H, NH, 80%), 8.95 d (1H, NH, 20%); at 80°C: 2.79 m, 2.89 m, 3.02 m, 3.19 m (CH_2); 4.37 m, 4.50 m (CH); 8.58 d (NH). ^{13}C NMR spectrum, δ_C, ppm: 0.34 (CH_3Si), 39.25 (CH), 52.46 (CH_2), 91.85 (Si**C**≡C), 99.49 (SiC≡**C**), 152.98 (C=O), 172.30 (COOH).

3-(1*H*-Indol-3-yl)-2-(3-trimethylsilyl-2-propynoylamino)propanoic acid (XI). A mixture of 0.26 g (1.25 mmol) of DL-tryptophane and 0.81 g (5.0 mmol) of hexamethyldisilazane containing a catalytic amount of concentrated sulfuric acid was heated for 20 min under reflux. Excess hexamethyldisilazane was removed under reduced pressure, the residue was dissolved in 10 ml of anhydrous diethyl ether, and a solution of 0.4 g (2.5 mmol) of compound **I** in 5 ml of diethyl ether was added dropwise over a period of 10 min at room temperature. The mixture was stirred for 1 h and was then treated as described above. Yield 73%. IR spectrum, ν, cm^{-1}: 840, 1250 [Si(CH_3)]; 1530 [CN, δ(NH)]; 1580 (C=C_{arom}); 1630 (C=O); 1730 (COO); 2170 (C≡C); 2500–3400 (NH, OH). ^{1}H NMR spectrum, δ, ppm: 0.21 s [9H, (CH_3)$_3$Si], 3.32 m (2H, CH_2), 4.95 m (1H, NCH), 6.49 d (1H, NH), 7.08 m (1H, 6-H), 7.15 m (1H, 5-H), 7.29 m (1H, 2-H), 7.33 m (1H, 4-H), 7.55 m (1H, 7-H), 8.34 br.s (1H, 1-H). ^{13}C NMR spectrum, δ_C, ppm: –1.10 (CH_3Si), 27.11 (CH_2), 53.27 (CH), 93.55 (Si**C**≡C), 96.54 (SiC≡**C**), 108.89 (C^7), 111.35 (C^3), 118.46 (C^6), 119.63 (C^4), 122.06 (C^5), 123.31 (C^2), 128.22 (C^{3a}), 136.06 (C^{7a}), 152.68 (C=O), 174.87 (COOH).

2-Hydroxy-4-(3-trimethylsilyl-2-propynoylamino)benzoic acid (XIII) was synthesized as described above for compound **XI**. IR spectrum, ν, cm^{-1}: 840, 1260 [Si(CH_3)]; 1560 [CN, δ(NH)]; 1580 (C=C_{arom}); 1630 (C=O); 1680 (COO); 2180 (C≡C); 2400–3400 (NH, OH). ^{1}H NMR spectrum, δ, ppm: 0.27 s [9H, (CH_3)Si], 6.94 d (1H, 3-H), 7.77 d (1H, 2-H), 8.31 d (1H, 6-H), 10.95 br.s (1H, NH), 10.97 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: –0.69 (CH_3Si), 91.48 (Si**C**≡C), 99.33 (SiC≡**C**), 112.78 (C^4), 118.27 (C^3), 122.29 (C^6), 129.07 (C^2), 131.07 (C^1), 150.80 (C^5), 159.70 (C=O), 172.36 (COOH).

4-(3-Trimethylsilyl-2-propynoylamino)benzoic acid (XII). A solution of 0.19 g (1.18 mmol) of compound **I** in 5 ml of diethyl ether was added dropwise over a period of 10 min at room temperature to a solution of 0.16 g (1.18 mmol) of *p*-aminobenzoic acid (**VI**) in 10 ml of diethyl ether. The mixture was stirred for 3 h, treated with 5 ml of water, and extracted with ether. The extract was dried over $MgSO_4$, and the solvent was distilled off under reduced pressure to obtain 0.19 g (65%) of acid **XII**, mp 189–191°C. IR

spectrum, ν, cm^{-1}: 840, 1250 [$Si(CH_3)$]; 1530 [CN, δ(NH)]; 1580 ($C=C_{arom}$); 1640 (C=O); 1680 (COO); 2160 (C≡C); 2530–3400 (NH, OH). ^1H NMR spectrum, δ, ppm: 0.36 s [9H, $(CH_3)_3Si$], 7.90 d (2H, 2-H, 6-H), 8.12 d (2H, 3-H, 5-H), 10.15 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: –0.75 (CH_3Si), 92.41 (Si**C**≡C), 98.98 (SiC≡**C**), 118.96 (C^2, C^6), 125.90 (C^1), 130.66 (C^3, C^5), 142.55 (C^4), 151.00 (C=O), 167.08 (COOH).

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