N-methyl-*N*-(triethoxysilylmethyl) and *N*-methyl-*N*-(silatran-1-ylmethyl) substituted glycine and alanine

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Organosilicon derivatives of glycine, α- and β-alanine, and α-methylalanine were prepared by the reaction of methyl esters of α- and β-halocarboxylic acids with *N*-methylaminomethyltriethoxysilane in the presence of triethylamine. The compounds synthesized were converted into the corresponding *N*-silatran-1-ylmethyl derivatives. Trimethylsilyliodoacetate reacts with *N*-methylaminomethyltrietoxysilane to give 2,2-diethoxy-4-methyl-1-oxa-4-aza-2-silacyclohexane-6-one. Its reaction with triethanolamine leads to *N*-methyl-*N*-(silatran-1-ylmethyl)glycine.

Key words: (*N*-methyl)aminomethyltriethoxysilane, *N,O*-dimethyl-*N*-(triethoxysilylmethyl), and *N,O*-dimethyl-*N*-(silatran-1-ylmethyl) substituted aminoacids.

Organosilicon compounds containing aminoacid moieties in their molecules exhibit biological activity.[1] Optically pure compounds of this type are rather promising for chiral ligand-exchange liquid chromatography.[2] Unlike the *N,O*-silyl derivatives of amino acids used in peptide synthesis, which have been investigated in detail, organosilicon compounds containing aminoacid groups in their organic radicals have been poorly investigated. Compounds of this type were obtained for the first time by the reaction of haloalkylsilanes with derivatives of aminomalonic acid.[4—8] *N*-[2-(*R,S*)-hydroxy-3-ethoxysilylpropyl]-(L)-phenylalanine was prepared by the reaction of L-phenylalanine with glycidoxypropyltriethoxysilane.[2] Hydrobromides of triorganylsilylmethyl substituted amino acids and their esters and hydrochlorides of trimethoxysilylpropyl substituted aminocarboxylic acids and their esters are formed by the *N*-alkylation of the corresponding (aminoalkyl)silanes with haloalkylcarboxylic acids and their esters.[9—11] Enantiomerically pure β-trimethylsilylalanine was synthesized from (*S*) alanine, trimethylchloromethylsilane and pyrazinyllithium.[12]

We obtained *N,O*-dimethyl-*N*-(triethoxysilylmethyl) substituted glycine (**2a**), α-alanine (**2b**), β-alanine (**2c**), and α-methylalanine (**2d**) by reacting methyl α- and β-halocarboxylates with *N*-methylaminomethyltriethoxysilane (**1**) in the presence of triethylamine:

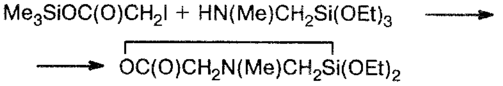
$$\mathrm{MeOC(O)CRR'(CH_2)_{\mathit{n}}X + MeNHCH_2Si(OEt)_3 \xrightarrow[-Et_3N\cdot HX]{Et_3N}}$$
$$\mathrm{\longrightarrow MeOC(O)CRR'(CH_2)_{\mathit{n}}N(Me)CH_2Si(OEt)_3}$$

2a—d

a: R, R' = H, *n* = 0; **c:** R, R' = H, *n* = 1;
b: R = H, R' = Me, *n* = 0; **d:** R, R' = Me, *n* = 0;
X = Br, I

The yields of aminoacid derivatives **2a, b, d** decrease noticeably as the number of methyl groups at the carbon atom of the halocarboxylic acid increases (Table 1).

Trimethylsilyl iodoacetate reacts with compound **1** under the same conditions to give 2,2-diethoxy-4-methyl-1-oxa-4-aza-2-silacyclohexane-6-one (**3**):

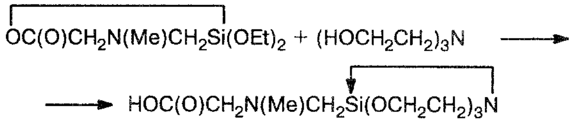


$$\mathrm{Me_3SiOC(O)CH_2I + HN(Me)CH_2Si(OEt)_3 \longrightarrow \overline{OC(O)CH_2N(Me)CH_2Si}(OEt)_2}$$

3

Compounds **2a—c** were converted into the corresponding *N*-silatran-1-yl derivatives of aminoacids, $\mathrm{MeOC(O)CRR'(CH_2)_{\mathit{n}}\overline{Si(OCH_2CH_2)_3N}}$ (**4a—c**), by transesterification with triethanolamine according to the standard procedure (see Table 1).[13]

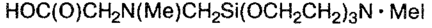
When heterocyclic compound **3** was treated with triethanolamine, the endocyclic Si—O bond cleaved, and *N*-methyl-*N*-(silatran-1-ylmethyl)glycine (**5**) was formed



$$\mathrm{\overline{OC(O)CH_2N(Me)CH_2Si}(OEt)_2 + (HOCH_2CH_2)_3N \longrightarrow HOC(O)CH_2N(Me)CH_2\overline{Si(OCH_2CH_2)_3N}}$$

5

The reaction of compound **5** with methyl iodide yielded its iodomethylate



$$\mathrm{HOC(O)CH_2N(Me)CH_2\overline{Si(OCH_2CH_2)_3N}\cdot MeI}$$

6

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Table 1. Physicochemical properties of organosilicon derivatives of aminoacids

Compound	B.p. (m.p.) /°C	Yield (%)	n_D^{20}	$\frac{\text{Found}}{\text{Calculated}}$ (%)				Molecular formula
				C	H	N	Si	
2a	99—101	72	1.4238	48.36 47.99	9.47 9.02	4.98 5.01	8.90 10.05	$C_{11}H_{25}NO_5Si$
2b	101—104	44	1.4269	48.94 49.12	9.38 9.27	4.80 4.77	9.49 9.57	$C_{12}H_{27}NO_5Si$
2c	111—114	61	1.4268	49.07 49.14	9.41 9.34	5.18 4.78	9.57 9.46	$C_{12}H_{27}NO_5Si$
2d	112—113/1	20	1.4245	51.03 50.78	9.98 9.50	4.78 4.55	10.08 9.13	$C_{13}H_{29}NO_5Si$
3	93—94/1	32	1.4396	43.71 43.81	8.62 7.31	— —	12.50 12.81	$C_8H_{17}NO_4Si$
4a	(69—71)	25	—	45.72 45.50	7.35 7.64	9.46 9.67	10.30 9.97	$C_{11}H_{22}N_2O_5Si$
4b	(38—41)	45	—	46.96 47.36	7.39 7.94	8.69 9.20	8.75 9.22	$C_{12}H_{24}N_2O_5Si$
4c	(28—30)	46	—	—	—	—	—	$C_{12}H_{24}N_2O_5Si$
5	180$_{\text{decomp.}}$	100	—	43.44 43.46	7.41 7.29	9.81 10.10	10.29 10.15	$C_{10}H_{20}N_2O_5Si$
6	—	96	—	31.96 31.68	5.81 5.54	6.71 6.70	— —	$C_{11}H_{23}IN_2O_5Si$

Table 2. Chemical shifts ($CDCl_3$, δ) in the ^1H NMR spectra of silicon-containing aminoacids $ROC(O)CR^1R^2(CH_2)_nN(CH_3)CH_2SiX_3$

Compound	RO	$CR^1R^2(CH_2)_n$	NCH_2Si	$N—CH_3$	X	
					$(OC_2H_5)_3$	$(OCH_2CH_2)_3N$
2a	3.68 s	3.31	2.20 s	2.44 s	1.22 t 3.86 q	
2b	3.57	3.31 q 1.17 d	2.05 s	2.28 s	1.12 t 3.74 q	
2c	3.64	2.66 t 2.45 t	1.97 s	2.28 s	1.21 t 3.84 q	
2d	3.67	1.27	2.04 s	2.35 s	1.23 t 3.86 q	
3		3.15	2.05	2.36	1.24 t 3.93 q	
4a	3.66 s	3.36 s	1.94 s	2.44 s		2.81 t 3.76 t
4b	3.65 s	4.13 q 1.23 d	1.87 s	2.42 s		2.83 t 3.77 t
4c	3.64 s		1.76 s	2.31 s		2.82 t 3.78 t
5	5.79 s	3.78 s	2.34 s	2.85 s		2.96 t 3.83 t
5*	5.95 s	3.43 s	2.29 s	2.81 s		2.94 t 3.81 t
6	5.96 s	3.49 s	2.35 s	2.89 s		3.04 t 3.83 t
6*	6.46 s	3.45 s	2.31 s	2.81 s		2.97 t 3.81 t

* The spectrum was recorded in CD_2Cl_2.

The compositions and structures of compounds **2—6** were confirmed by the data of elemental analysis and ^{1}H NMR spectroscopy (see Tables 1 and 2). Unlike 3-(germatran-1-yl)propionic acid, which has a similar structure,[14] compound **5** exhibits no tendency toward prototropic rearrangement of the 3-carboxylic and 2-oxyethyl groups in solution. The ^{1}H NMR signal of the protons of the OCH_2 and NCH_2 groups in silatranes **4a—c** occurs in the region typical of carbofunctionally substituted 1-alkylsilatranes (see Table 2). A downfield shift of the signal of the protons of these groups has been noted for compounds **5** and **6**. Deshielding of the protons of the silatrane skeleton of the *N*-methyl-*N*-(silatran-1-ylmethyl)glycine (**5**) may result from the zwitterion form of the aminoacid fragment, which is characteristic of α-aminoacids.[17] This is in agreement with the low-frequency shift of the ν(C=O) stretching vibration band in the IR spectrum of compound **5** (1625 cm^{-1} in KBr pellets) with respect to its position in the spectra of **4a—d** (1720—1760 cm^{-1}), which is typical of an ionized carboxylic group.[18]

Experimental

The yields, physicochemical properties, and elemental analysis data for the compounds prepared are presented in Table 1.

Methyl *N*-methyl-*N*-(triethoxysilylmethyl)aminocarboxylates (2a—d). A methyl halocarboxylate (0.01 mol) was slowly added dropwise (in an argon atmosphere) to a stirred mixture of *N*-methylaminomethyltriethoxysilane (0.01 mol) and Et_3N (0.01 mol) in 30 mL of anhydrous pentane. The reaction mixture was stirred for 4 h at ~20 °C. The resulting precipitate was filtered off and washed with pentane (2×20 mL). The pentane was evaporated from the filtrate, and the residue was distilled *in vacuo.*

2,2-Diethoxy-4-methyl-1-oxa-4-aza-2-silacyclohexane-6-one (3). Trimethylsilyl iodoacetate (0.02 mol) was slowly added dropwise under an argon atmosphere to a stirred mixture of *N*-methylaminomethyltriethoxysilane (0.02 mol) and Et_3N (0.02 mmol) in 100 mL of anhydrous Et_2O. The reaction mixture was stirred for 3 h at ~20 °C. The resulting precipitate was filtered off and washed with Et_2O (2×25 mL). The ether was evaporated from the filtrate, and the residue was distilled *in vacuo.*

Silatranes 4a—c and 5 were prepared by transesterification of compounds **2a—c** and **3** with triethanolamine according to the known method,[13] and silatranes **4a—c** were recrystallized from a benzene : heptane mixture (1 : 2).

***N*-Methyl-*N*-(silatran-1-ylmethyl)glycine iodomethylate (6).** Freshly distilled MeI (0.05 mol) in 10 mL of anhydrous ethanol was added dropwise to a solution of compound **5** (0.05 mol) in 15 mL of anhydrous ethanol. The reaction mixture was kept for 12 h at ~20 °C and the precipitate that formed was washed with ether and dried.

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