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Synthesis and neurotropic activity of silyl propargyl alcohols and sulfides

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New silicon derivatives of hetaryl propargyl sulfides and propargyl alcohols were synthesized using phase-transfer catalytic and organometallic methods. These compounds were tested for acute toxicity and neurotropic activity in the pentylenetetrazole test, and for phenamine hypothermia, phenamine hyperactivity and passive avoidance response tests. We have found that the silyl propargyl alcohols and sulfides are low toxicity compounds, the LD_{50} being 700–1300 mg kg^{-1}. In the PAR test, the synthesized compounds exerted some memory-improving activity. For di-1-(3-methyl-3-hydroxybutyn-1-yl)methyl(3-iodopropyl)silane (16) the effect was statistically significant and amounted to 250% of the control level. In the pentylenetetrazole test, all compounds possessed anticonvulsant activity, the most active compounds being 3-(benzoxazolylthio)-1-propynyl(trimethyl)silane (6) and di-[2-(1-hydroxycyclohexyl)ethynyl]methyl(3-iodopropyl)silane (17). The phenamine-induced hyperactivity was significantly elevated after treatment with (3-trimethylsilyl-2-propynyl)thiobenzene (1) or di-[1-(3-methyl-3-hydroxybutyn-1-yl)diphenylsilane (12). Our data show that these silicon derivatives of hetaryl propargyl sulfides and propargyl alcohols possess certain memory improving and anticonvulsant activity that should be studied in detail to evaluate the receptor systems involved.

KEYWORDS: hetaryl propargyl sulfides; silyl propargyl alcohols; neurotropic activity

INTRODUCTION

Aromatic and heterocyclic sulfides and related compounds are widely used as central nervous system (CNS) agents. Recently, the neuroprotective activity of *N*-[(methylsulfinyl)phenyl]guanidines[1] and the antidepressant activity of 1-piperidinylpropan-2-ols[2] containing sulfide groups were described. Heteroaromatic sulfur-containing derivatives were also used successfully in the treatment of CNS diseases. Pyridine sulfides have been used as neurotropic,[3] antidepressant,[4–7] anticonvulsant[4] and antipsychotic[8] agents. High neurotropic activity of pyridine, furan and thiophene thiosemicarbazones was also described.[9,10] Quinoline sulfides were used as CNS agents[11] and exhibit anticonvulsant activity.[12] The CNS activity of indole sulfur derivatives has been described in several articles.[13–18] The CNS depressant activity of pyrimidine sulfides[19] and the anticonvulsant activity of benzoxazole sulfides[20] was also studied. In addition, the dopaminergic activity of aromatic and heteroaromatic alkynes[21] and their application in the treatment of psychiatric and neurological disorders[22] have also been reported. Recently, diarylenyne glucine derivatives were investigated as glucine transport inhibitors and used for the treatment of schizophrenia, cognitive dysfunction, and Alzheimer's disease.[23] Alkynylamides were used as anticonvulsants.[24] 5-(Arylalkynyl)pyrimidines exhibited neurotropic activity and were proposed for the treatment of neurodegenerative disorders.[25] High neurotropic activity of pyrimidine-containing heterocyclic compounds was also described.[26]

In many cases, the presence of a silyl or germyl group in the molecule increases the neurotropic activity of aromatic and heteroaromatic compounds.[27] Thus, silicon-containing

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thiosemicarbazones[9] and silyl- and germyl-isoxazolines[28] exhibited high neurotropic activity. Moreover, silylisoxazolines protected animals against hypoxia and pentylenetetrazole convulsions. The silyl-substituted compounds are thought to penetrate the blood–brain barrier better than less lipophilic unsilylated substances.[29,30] It has been shown that some silyl derivatives of α-pyrrolidone exert a tranquilizing effect on emotional behavior of animals in conflict situations and decrease shock-induced emotional reactions.[31] Silyl-substituted dopamine derivatives and benzyldimethylsilylmethamines possessed anti-Parkinsonian activity.[32,33] It was suggested that the appearance of marked pharmacological activity of the compounds could be related to a better penetration of these substances via the hematoencephalic barrier and to their effect on GABA and dopaminergic processes in the CNS.[31]

Taking into account the above-mentioned data, we have synthesized new organosilicon derivatives of alkynes (silyl propargyl alcohols and hetaryl propargyl sulfides) and investigated their neurotropic activity.

MATERIALS AND METHODS

Chemistry

^{1}H and ^{13}C NMR spectra were recorded on a Mercury 200 (Varian) instrument at 200 and 50.3 MHz using $CDCl_3$ as a solvent and tetramethylsilane (TMS) as internal standard. Mass spectra were registered on a GC-MS HP 6890 (70 eV). Gas chromatography analysis was performed on a Chrom-5 instrument equipped with flame-ionization detector using glass column packed with 5% OV-101/Chromosorb W-HP (80–100 mesh, 1.2 m × 3 mm, 170–250 °C, 7–10 min).

Intermediates **8** and **9** were not isolated.

*Synthesis of silyl hetaryl propargyl sulfides **1–7***

3-(Hetarylthio)-1-propynyl(trimethyl)silanes (**1–6**) and 3-[1,3-bis(trimethylsilyl)-2-propynyl]thioindole (**7**) were prepared as described in Ref. 34.

*Synthesis of silyl dialkyndiols **10–15***

Propargyl alcohol (0.1 M) in dry tetrahydrofuran (THF; 20 ml) was added dropwise to the Grignard reagent (prepared from 0.2 M magnesium and 0.2 M ethyl bromide) in THF (100 ml). The mixture was stirred for 3 h at room temperature. Then, diorganyldichlorosilane (0.05 M) in THF (20 ml) was added dropwise at 0 °C to the reaction mixture containing intermediate **8** or **9**. The mixture was stirred for 8 h, followed by workup with 15% HCl. The product was extracted with diethyl ether; the organic phase was then dried over Na_2SO_4 overnight, filtered and evaporated under reduced pressure. The product was purified by crystallization from pentane or chromatographed on silica using hexane as eluent.

*Di(3-methyl-3-hydroxybutyn-1-yl)dimethylsilane (**10**)*

M.p. 108 °C. The synthesis of **10** is described in Ref. 35. Anal. Found: C, 63.82; H, 8.96. Calc. for $C_{12}H_{20}SiO_2$: C, 64.24; H, 8.98.

*Di(3-Methyl-3-hydroxybutyn-1-yl)methylphenylsilane (**11**)*

M.p. 117–118 °C. Anal. Found: C, 69.50; H, 7.00. Calc. for $C_{17}H_{22}SiO_2$: C, 71.28; H, 7.74%. ^{1}H NMR δ ppm: 0.30 (3H, s, SiMe); 2.08 (2H, s, OH); 2.47 (12H, s, Me); 7.22–7.36 (5H, m, Ph). ^{13}C NMR δ ppm: −3.6; 22.9; 39.7; 68.4; 72.1; 87.8; 120.2; 126.4; 131.2; 131.9. Purity was established by NMR. The compound was very hygroscopic and elemental analysis data was approximate.

*Di(3-methyl-3-hydroxybutyn-1-yl)diphenylsilane (**12**)*

M.p. 126–127 °C. Anal. Found: C, 75.13; H, 6.22. Calc. for $C_{22}H_{24}SiO_2$: C, 75.82; H, 6.94%. ^{1}H NMR δ ppm: 1.58 (12H, s); 2.09 (2H, s, OH); 7.36–7.44 (4H, m, Ph); 7.68–7.75 (6H, m, Ph). ^{13}C NMR δ: 31.1; 65.6; 80.1; 114.3; 128.0; 130.2; 132.7; 134.7.

*Di(3-methyl-3-hydroxybutyn-1-yl)chloromethylmethylsilane (**13**)*

M.p. 66–67 °C. Anal. Found: C, 55.37; H, 7.64. Calc. for $C_{12}H_{19}ClSiO_2$: C, 55.69; H, 7.40%. ^{1}H NMR δ ppm: 0.41 (3H, s, SiMe); 1.52 (12H, s, Me); 2.08 (2H, s, OH), 2.88 (2H, s, CH_2). ^{13}C NMR δ ppm: −2.8; 1.0; 29.0; 31.1; 65.5; 79.5; 113.0.

*Di(3-methyl-3-hydroxybutyn-1-yl)methyl(3-chloropropyl)silane (**14**)*

M.p. 94–95 °C. Anal. Found: C, 57.98; H, 7.74. Calc. for $C_{14}H_{23}ClSiO_2$: C, 58.62; H, 8.08%. ^{1}H NMR δ ppm: 0.30 (3H, s, $SiMe_3$); 0.79–0.88 (2H, m, $SiCH_2$); 1.52 (12H, s, Me); 1.83–1.98 (2H, m, $CH_2CH_2CH_2$); 2.13 (2H, s, OH); 3.58 (2H, t, J = 6.82 Hz, CH_2Cl). ^{13}C NMR δ ppm: −1.4; 13.6; 27.1; 47.2; 66.4; 81.4.

*Di[2-(1-hydroxycyclohexyl)ethynyl]methyl(3-chloropropyl)silane (**15**)*

Oil. Anal. Found: C, 64.83; H, 7.67. Calc. for $C_{20}H_{31}ClSiO_2$: C, 65.02; H, 7.75%. ^{1}H NMR δ ppm: 0.13 (3H, s, CH_3); 0.60–0.78 (2H, m, CH_2); 1.13–1.15 (2H, m, CH_2); 1.46–1.74 (12H, m, CH_2); 1.81–1.95 (8H, m); 2.00 (2H, s, OH); 3.17–3.26 (2H, m) ^{13}C NMR δ ppm: 23.07, 25.05, 39.7, 68.5, 72.1, 87.8.

*Synthesis of iodopropyl silanes **16** and **17***

The solution of chloropropyl silane **14** or **15** (0.02 mol) and excess of sodium iodide (0.03 mol) in dry acetone (50 ml) was refluxed for 48 h. Then the reaction mixture was filtered from inorganic salts and evaporated under reduced pressure. The product was purified by crystallization from pentane.

*Di(3-methyl-3-hydroxybutynyl)methyl(3-iodopropyl)silane (**16**)*

M.p. 86–88 °C. Anal. Found: C, 44.53; H, 6.04. Calc. for $C_{14}H_{23}ISiO_2$: C, 44.45; H, 6.13%. ^{1}H NMR δ ppm: 0.31 (3H, s,

$SiMe_3$); 0.79–0.90 (2H, m, $SiCH_2$); 1.53 (12H, s, Me); 1.86–2.03 (4H, m, OH and $CH_2CH_2CH_2$); 3.23–3.31 (2H, t, $J = 6.9$ Hz, CH_2I) ^{13}C NMR δ ppm: −1.35; 10.3; 13.7; 17.7; 27.1; 47.2; 65.4; 81.4.

*Di[2-(1-hydroxycyclohexyl)ethynyl]methyl(3-iodopropyl)silane (**17**)*

M.p. 44–47 °C. Anal. Found: C, 52.07; H, 6.32. Calc. for $C_{20}H_{31}ISiO_2$: C, 51.58; H, 6.15%. ^1H NMR δ ppm: 0.08 (3H, s); 0.1–0.19 (2H, m); 0.59–0.80 (2H, m); 1.17 (2H, m); 1.45–1.75 (10H, m); 1.81–2.04 (12H, m). ^{13}C NMR δ ppm: −0.16; 23.0; 23.1; 25.0; 39.7; 68.4; 72.0; 87.7.

Pharmacology

The biological investigations were performed using the experimental methods described elsewhere.[36–42]

The neurotropic activity of all the silicon-containing alkynes synthesized was studied for the first-time on ICR male mice weighing 20–30 g in the autumn–winter season. Mice were housed under standard conditions (21–23 °C, 12 h light–dark cycle) with free access to food pellets (diet R3, Lactima, Sweden) and water. All experimental procedures were performed in accordance with the regulations of the Animal Ethical Committee of BaltLASA, Riga, Latvia.

The test substances were administered intraperitoneally (i.p.) 1 h prior to the assay at a dose of 5 mg kg^{-1}. The solutions were made by adding of one or two drops of 0.6% Tween-80 solution and then dissolved up to final concentration in saline (0.9% NaCl solution). Control animals received injections of an equal amount of saline with addition of Tween-80. Statistical significance was determined using the Student *t*-test with a confidence interval accepted when $p < 0.05$.

Rectal temperatures were recorded with a Thermaler TH5 (Physitemp, USA) electrothermometer. An effect on the duration of ethanol-induced (20% 5 g kg^{-1} i.p.) sleeping time was also evaluated. The influence on learning and memory processes was evaluated in a passive avoidance response (PAR) test.[38,39] The influence of phenamine-induced (10 mg kg^{-1}, s.c.) locomotor activity and rectal temperature was tested after 0.5 and 1.0 h following the phenamine administration.[40] Anticonvulsant activity was measured using pentylenetetrazole[41,42] (1% solution, intravenous 0.01 ml s^{-1}) seizure tests. Acute toxicity was determined in accordance with 'Guidance Document on Using *In Vitro* Data to Estimate *In Vivo* Starting Doses for Acute Toxicity Based on Recommendations from an International Workshop Organized by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)' and the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) (National Institute of Environmental Health Sciences National Institutes of Health US Public Health Service Department of Health and Human Services).[43] Reference chemicals were selected from the RC (registry of cytotoxicity/ZEBET) and tested in a standardized cytotoxicity 3T3 (BALB/c mouse fibroblast cells) Neutral Red Uptake test. The regression equation from the candidate test was calculated by linear regression using the candidate IC_{50} values and corresponding LD_{50} values from the RC. The resulting regression was then compared with the RC regression: $\log(LD_{50}) = 0.435 \times \log(IC_{50}) + 0.625$.

RESULTS AND DISCUSSION

Chemistry

S-Propargyl derivatives of heterocycles were prepared by the interaction of hetaryl thiols with propargyl bromide in the phase-transfer catalytic system solid K_2CO_3–18-crown-6–toluene. Reaction of propargylation of thiols occurred smoothly in good yields (53–100%) for all heterocyclic thiols. The silicon derivatives of hetaryl propargyl sulfides were obtained by metallation of propargylated thiols with *n*-BuLi followed by addition of trimethylchlorosilane.[34]

The results of the synthesis of the silylated propargyl sulfides **1**–**7** are shown in Table 1. The yield of silylated indole propargyl sulfide (**7**) was diminished due to dilithium salt producion in the metallation process, with subsequent by-product formation. The problems in the purification of the silylated products led to the reduced yield.

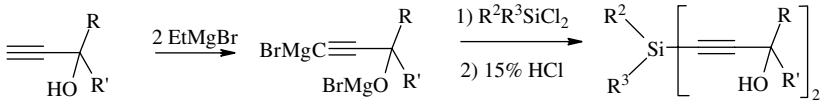
Silyl propargyl alcohols **10**–**15** were synthesized by Grignard reaction in 17–89% yields (Scheme 1 and Table 1). The C-silylation of propargyl alcohols was successful because bis(C,O-MgBr) intermediates **8** and **9** reacted with dichlorosilanes specifically yielding only C-silyl products **10**–**15**. Iodopropylsilanes **16** and **17** were prepared from chloropropyl analogues (**14**, **15**) in the reaction with sodium iodide in dry acetone (50–56%; Scheme 2).

Neurotropic activity

Four types of activity test, i.e. acute toxicity, PAR, pentylenetrazole convulsions and phenaminum hyperactivity, were used to study the neurotropic activity of 15 silyl propargyl alcohols and hetaryl propargyl sulfides. The experimental evaluations of neurotropic properties of the synthesized compounds **1**–**7** and **10**–**17** are presented in Table 2. Biological investigations were performed using the methods described in Refs 36–42.

In general, the silyl propargyl alcohols and sulfides are low toxicity compounds (LD_{50} in the 700–1300 mg kg^{-1} range). Compounds **1**, **2**, **6**, **10**, and **14** have $LD_{50} \gg 2000$ mg kg^{-1}. Only two compounds exhibited medium toxicity, i.e. 3-[(2-quinolyl)thio]-1-propynyl(trimethyl)silane (**3**; 413 mg kg^{-1}) and 3-[(3-indolyl)thio]-3-trimethylsilyl-1-propynyl(trimethyl)silane (**7**; 375 mg kg^{-1}).

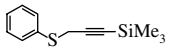
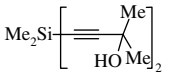
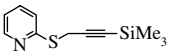
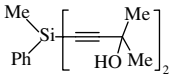
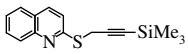
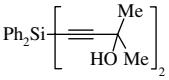
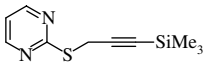
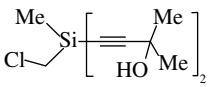
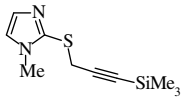
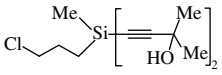
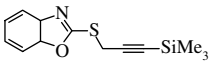
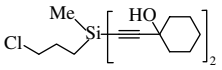
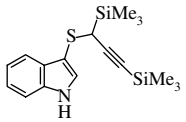
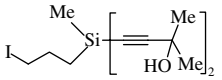
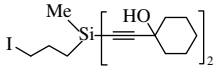
The silyl derivatives possess some memory-improving activity in the PAR test. However, in most cases the effect was not statistically significant (Table 2). Only the memory-improving effect of di(3-methyl-3-hydroxybutyn-1-yl)methyl(3-iodopropyl)silane (**16**) was 250% of the control level (the highest amongst silyl dialkyndiols) and it was found to be statistically significant ($p < 0.5$).



8, 9 **10 – 15**

Scheme 1.

Table 1. Synthesis of silicon-containing alkynes

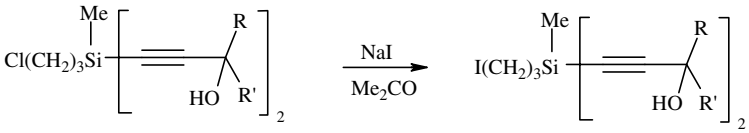
No.	Silyl propargyl sulfide	Yield (%)	No.	Silyl propargyl alcohol	Yield (%)
1		65	**10**		20
2		54	**11**		18
3		83	**12**		89
4		23	**13**		63
5		51	**14**		79
6		13	**15**		17
7		22	**16**		50
			17		56

All substances tested, with the exception of di(3-methyl-3-hydroxybutyn-1-yl)dimethylsilane (**10**), di(3-methyl-3-hydroxybutyn-1-yl)methylphenylsilane (**11**; not pure), and di(3-methyl-3-hydroxybutyn-1-yl)methylchloromethylsilane (**13**), showed anticonvulsant activity in the pentylenetetrazole test. The pentylenetetrazole dose inducing clonic convulsions after the treatment with the sulfides (Table 2) increased in the following order of substituted hetaryl derivatives: 2-pyridinyl (**2**) and 3-indolyl (**7**) > phenyl (**1**) > 2-pyrimidinyl (**4**) > 2-benzoxazolyl (**6**). The change of isopropyl substituent (**16**) for the cyclohexyl (**17**) also increased the activity. Furthermore, the chlorine (**14**) substitution by iodine (**16**) leads to a better protection in the pentylenetetrazole test. The most active compounds were 3-(benzoxazolylthio)-1-propynyl(trimethyl)silane (**6**) and di[2-(1-hydroxycyclohexyl)ethynyl]methyl(3-iodopropyl)silane (**17**), which not only significantly increased the pentylenetetrazole dose inducing the clonic convulsions, but also increased the *exitus letalis* dose (169% and 173% respectively). In addition, compounds **1**, **14**, and **16** statistically significantly prolonged the animal survival time (Table 2).

All compounds synthesized enhanced phenamine-induced hyperactivity. However, only for two compounds, i.e. (3-trimethylsilyl-2-propynyl)thiobenzene (**1**) and di(3-methyl-3-hydroxybutyn-1-yl)diphenylsilane (**12**), was the effect found to be statistically significant. Thus, the activity counts 60 min after administration of the compounds **1** and **12** were 325% and 318% respectively of the control value.

Thus, the silyl derivatives possessed a greater effect probably due to a better penetration of these substances via the hematoencephalic barrier and to their effect on GABA and dopaminergic processes in the CNS, as was described by Tsareva *et al*.[31]

Our data show that the compounds studied possess some neurotropic activity. These should be studied in detail to evaluate the receptor systems and molecular targets involved



14, 15 **16, 17**

Scheme 2.

Table 2. Neurotropic[a] activity of silyl propargyl alcohols and sulfides[a]

Compound	Toxicity (mg kg^{-1})	PAR (s)	Pentylenetetrazole test: Clonic convulsion (mg kg^{-1})	Pentylenetetrazole test: Exitus letalis (mg kg^{-1})	Phenamine hyperactivity, activity counts: After 30 min	After 60 min	30–60 min
Saline		48.8 ± 24.1	27.2 ± 1.6	83.1 ± 9.3	1121 ± 368	1593 ± 534	472 ± 200
1	>2000	58.6 ± 29.3	35.6 ± 2.0*	103.3 ± 17.5*	1927 ± 253	3462 ± 677**	1534 ± 455**
2	>2000	85.9 ± 23.9	34.1 ± 0.7*	107.6 ± 14.3	1476 ± 103	2467 ± 222	992 ± 231
3	413	70.4 ± 21.2	33.4 ± 2.4**	92.1 ± 17.3	1164 ± 435	2040 ± 851	875 ± 434
4	1866	78.6 ± 21.9	37.8 ± 1.9*	105.5 ± 14.5	966 ± 297	2325 ± 717	1359 ± 550
5	1044	97.1 ± 26.2	32.6 ± 1.9**	77.1 ± 14.4	1118 ± 239	1913 ± 331	796 ± 185
6	2452	68.1 ± 22.6	38 ± 3.3*	140.8 ± 21.2*	1149 ± 299	1972 ± 620	823 ± 339
7	375	65.5 ± 34.1	34.5 ± 2.9*	90.9 ± 11.6	1516 ± 262	2653 ± 536	1137 ± 412
10	>2000	80.8 ± 28.6	32.2 ± 1.8	86.8 ± 13	961 ± 223	1776 ± 538	816 ± 334
11	976	82.5 ± 32.5	29.7 ± 3.1	86.3 ± 15.9	832 ± 205	1436 ± 520	605 ± 324
12	769	79.6 ± 26.3	34.9 ± 0.6*	115.3 ± 16.8	1656 ± 163	3159 ± 420**	1503 ± 316*
13	1189	77.4 ± 25.8	27.1 ± 1.8	77.6 ± 10.9	1400 ± 319	2780 ± 509	1380 ± 364
14	>2000	84.8 ± 21.9	34.8 ± 1.7*	117.8 ± 9.9*	1447 ± 296	2250 ± 303	803 ± 210
15	>500	122.2 ± 16.8*	41.3 ± 6.2*	106.8 ± 13.1	1114 ± 395	1410 ± 521	297 ± 183
16	1297	10.1 ± 20.1	32.8 ± 1.1*	134.8 ± 17.3*	1699 ± 521	2702 ± 967	1003 ± 459
17	690	75.6 ± 25.5	37.8 ± 2.2*	143.5 ± 25.6*	1402 ± 519	2155 ± 929	752 ± 416

[a] All values represent means ± SEM of at least five independent experiments. * $p < 0.05$ compared with control; ** $p < 0.06$ compared with control. The chemicals references are described in accordance with 'Guidance Document on Using *In Vitro* Data to Estimate *In Vivo* Starting Doses for Acute Toxicity Based on Recommendations from an International Workshop Organized by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)' and the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) (National Institute of Environmental Health Sciences National Institutes of Health US Public Health Service Department of Health and Human Services).

that give rise to the biological activities of these organosilicon compounds.

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