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SYNTHESIS AND CYTOTOXICITY OF 3-(HETARYLTHIO)-1-PROPYNYL-(TRIMETHYL)SILANES

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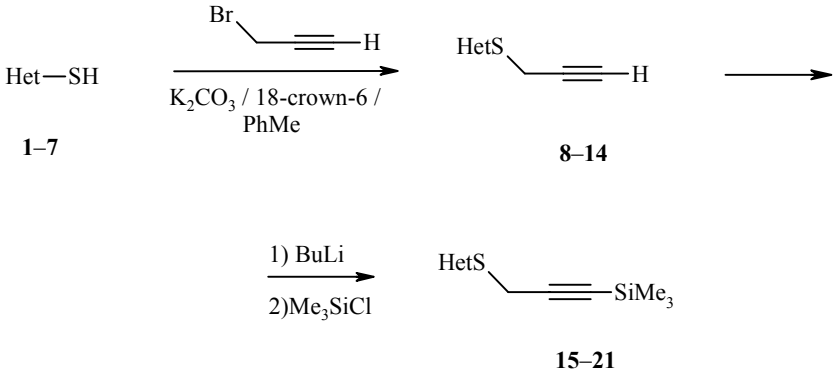
We have developed a two-step method for synthesis of 3-(hetarylthio)-1-propynyl(trimethyl)silanes from thiols in a phase-transfer catalysis system HC≡CCH$_2$Br–solid K$_2$CO$_3$–18-crown-6-toluene followed by reaction with n-BuLi–Me$_3$SiCl in ether or THF. We have observed that 3-[1,3-bis(trimethylsilyl)-2-propynyl]thioindole displays high cytotoxicity in HT-1080 and MG-22A tumor cell lines.

Keywords: alkynes, heteroaromatic compounds, silicon-containing compounds, phase-transfer catalysis, cytotoxicity.

Heteroaromatic sulfides are of interest as biologically active compounds [1]. In particular, high antitumor activity and cytotoxicity have been established for pyridine [2-9], quinoline [10-16], indole [17-21], benzothiazole [22], benzimidazole [23], uracil [24], and purine sulfides [25]. The results of a study of the antitumor activity of different silanes have been summarized in [26]. We have established that heteroaromatic sulfides of the type HetS(CH$_2$)$_n$SiR$_3$ (n = 1,3) lower the blood cholesterol level and exhibit vasodilator properties [27]. The cytotoxicity of heteroaromatic sulfides of the type HetSCH$_2$C≡CSiMe$_3$ was not studied previously, and this is the objective of this work.



1–7 **8–14** **15–21**

We have developed a novel two-step method for synthesis of 3-(hetarylthio)-1-propynyl(trimethyl)silanes from thiols. Heteroaromatic thiols **1-7, 22** in the system HC≡CCH$_2$Br–solid K$_2$CO$_3$–18-crown-6–toluene form hetaryl propargyl sulfides **8-14, 23** in up to 100% yields. The high efficiency of this

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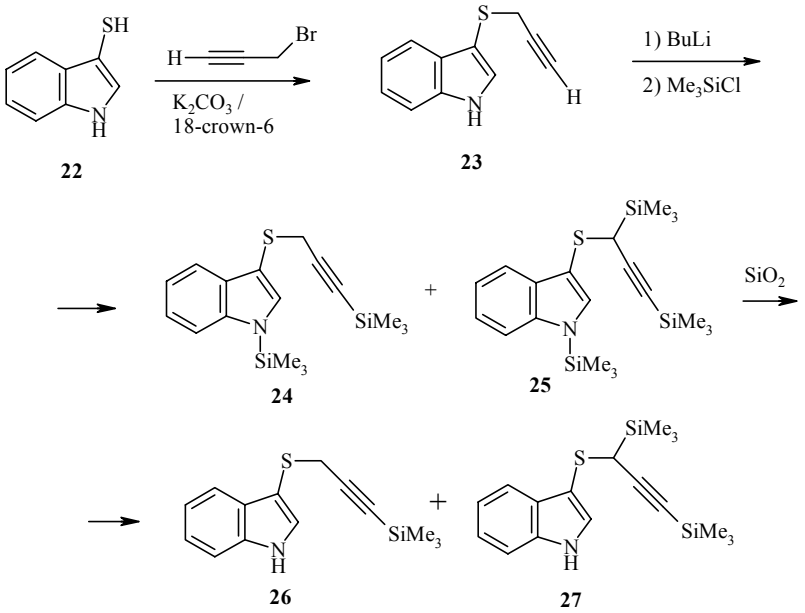
phase-transfer catalysis system for alkylation of thiols has been demonstrated in [1, 27]. Consecutive reactions of sulfides **8-14** with *n*-BuLi and Me_3SiCl in ether lead to formation of 3-(hetarylthio)-1-propynyl(trimethyl)silanes **15-21** in up to 83% yields (Tables 1-3).

Metalation of 3-(2-propynyl)thioindole **23** with butyllithium was carried out in THF due to problems connected with the solubility of the dilithium salt of **23** in ether. Reaction of sulfide **23** with *n*-BuLi (2.2 equivalents) in THF followed by treatment of the reaction mixture with excess of Me_3SiCl leads to a mixture of silylated products **24** and **25** (45:55). During their separation by column chromatography on silica gel, N-desilylation of compounds **24** and **25** occurs. As a result, we isolated 3-(3-trimethylsilyl-2-propynyl)thioindole **26** (18% yield) and 3-[1,3-bis(trimethylsilyl)-2-propynyl]thioindole **27** (22% yield).



The biological activity of the compounds obtained were studied for two tumor cell lines: HT-1080 (human fibrosarcoma) and MG-22A (mouse hepatoma) (Table 4). The greatest cytotoxic effect is exhibited by 3-[1,3-bis(trimethylsilyl)-2-propynyl]thioindole (**27**), and specifically IC_{50} is 5 μg/ml (CV test) for fibrosarcoma and 2 μg/ml (CV and MTT tests) for mouse hepatoma. We should note the very high level of NO generation for the indole derivative **27** (900% for the HT-1080 line, and 300% for the MG-22A line).

TABLE 1. Synthesis of Hetaryl Propargyl Sulfides **8-14** and 3-(Hetarylthio)-1-propynyl(trimethyl)silanes **15-21**

Thiol	Het	$t_{reaction}$, h	Sulfide	Yield **8-14**, %	Silane	Yield of silanes, %
1	Ph	6	**8** [28]	78	**15** [29]	65
2	2-Pyridyl	4	**9**	95	**16**	54
3	2-Quinolyl	9	**10**	70	**17**	83
4	2-Pyrimidyl	6	**11**	100	**18**	23
5	1-Methyl-2-imidazolyl	10	**12**	91	**19**	51
6	2-Benzoxazolyl	3	**13**	86	**20**	13
7	2-Benzthiazolyl	6	**14**	63	**21**	77

TABLE 2. ^{1}H and ^{13}C NMR Spectra of Alkynes **9-14, 16-21, 26, 27**

Alkyne	^{1}H NMR, δ, ppm, *J* (Hz)	^{13}C NMR, δ, ppm	
		Het	$SCH_2C{\equiv}CR$
9	2.18 (1H, t, *J* = 2.6, CH); 3.95 (2H, d, *J* = 2.6, SCH_2); 7.00, 7.18, 7.50 and 8.44 (4H, m, ring protons)	119.85 (C-5), 122.00 (C-3), 136.09 (C-4), 149.52 (C-6), 157.05 (C-2)	18.16 (CH_2), 70.42 (≡CH), 80.06 (≡C)
10	2.19 (1H, t, *J* = 2.8, CH); 4.16 (2H, d, *J* = 2.8, SCH_2); 7.22, 7.42, 7.66, 7.92 (6H, m, ring protons)	120.33 (C-3), 125.52 (C-6), 126.07 (C-4a), 127.59 (C-5), 128.11 (C-7), 129.76 (C-8), 135.70 (C-4), 148.17 (C-8a), 157.05 (C-2)	17.91 (CH_2), 70.48 (≡CH), 80.02 (≡C)
11	2.18 (1H, t, *J* = 2.6, CH); 4.00 (2H, d, *J* = 2.6, SCH_2); 6.98 (1H, m, 5-H); 8.51 (2H, m and m, 4- and 6-H)	116.77 (C-5), 157.28 (C-4 and C-6), 170 (C-2)	19.15 (CH_2), 70.38 (≡CH), 79.49 (≡C)
12	2.18 (1H, t, *J* = 2.6, CH); 3.67 (3H, s, CH_3); 3.67 (2H, d, *J* = 2.6, SCH_2); 6.9-7.2 (2H, m, ring protons)	122.80 (C-5), 129.59 (C-4), 139.29 (C-2), 33.42 (NCH_3)	23.14 (CH_2), 71.77 (≡CH), 79.18 (≡C)
13	2.30 (1H, t, *J* = 2.8, CH); 4.07 (2H, d, *J* = 2.8, SCH_2); 7.26 (2H, m, 5- and 6-H); 7.45 and 7.62 (2H, m and m, 7- and 4-H)	109.99 (C-6), 118.67 (C-5), 124.15 (C-7), 124.40 (C-4), 141.74 (C-7a), 152.00 (C-3a), 162.99 (C-2)	20.66 (CH_2), 72.38 (≡CH), 77.86 (≡C)
14	2.29 (1H, t, *J* = 2.6, CH); 4.11 (2H, d, *J* = 2.6, SCH_2); 7.2-7.9 (4H, m, ring protons)	121.02 (C-7), 121.75 (C-4), 124.47 (C-6), 126.11 (C-5), 135.40 (C-7a), 152.95 (C-3a), 164.51 (C-2)	21.52 (CH_2), 72.28 (≡CH), 76.37 (≡C)
16	0.05 (9H, s, $SiMe_3$); 3.91 (2H, s, CH_2); 6.90, 7.13, 7.41 and 8.35 (4H, m, ring protons)	119.61 (C-5), 121.85 (C-3), 135.88 (C-4), 149.29 (C-6), 157 (C-2)	-0.24 ($SiMe_3$), 19.41 (CH_2), 87.41 (≡CSi), 101.36 (SC≡)
17	0.06 (9H, s, $SiMe_3$); 4.12 (2H, s, CH_2); 7.14, 7.34, 7.60 and 7.83 (6H, m, ring protons)	120.32 (C-3), 125.44 (C-6), 126.01 (C-4a), 127.59 (C-5), 128.06 (C-7), 129.72 (C-8), 135.59 (C-4), 148.15 (C-8a), 157.52 (C-2)	-0.12 ($SiMe_3$), 19.22 (CH_2), 87.68 (≡CSi), 101.37 (SC≡)
18	0.13 (9H, s, $SiMe_3$); 3.97 (2H, s, CH_2); 6.98 (1H, m, 5-H); 8.52 (2H, m, 4- and 6-H)	116.67 (C-5), 157.22 (C-4 and C-6), 171.20 (C-2)	-0.20 ($SiMe_3$), 20.42 (CH_2), 87.59 (≡CSi), 100.82 (SC≡)
19	0.11 (9H, s, $SiMe_3$); 3.70 (2H, s, CH_2); 3.74 (3H, s, NCH_3); 6.97 and 7.11 (2H, both d, *J* = 0.6, ring protons)	122.61 (C-5), 129.46 (C-4), 139.10 (C-2), 33.35 (NCH_3)	-0.68 ($SiMe_3$), 24.49 (CH_2), 88.35 (≡CSi), 100.59 (SC≡)
20	0.13 (9H, s, $SiMe_3$); 4.11 (2H, s, CH_2); 7.2-7.6 (4H, m, ring protons)	109.94 (C-6), 118.61 (C-5), 124.08 (C-7), 124.36 (C-4), 141.83 (C-7a), 151.98 (C-3a), 163.22 (C-2)	-0.29 ($SiMe_3$), 21.92 (CH_2), 89.81 (≡CSi), 98.92 (SC≡)
21	0.16 (9H, s, $SiMe_3$); 4.16 (2H, s, CH_2); 7.1-7.9 (4H, m, ring protons)	121.02 (C-7), 121.76 (C-4), 124.07 (C-6), 124.46 (C-5), 126.12 (C-7a), 135.50 (C-3a), 153.05 (C-2)	-0.24 ($SiMe_3$), 22.93 (CH_2), 89.90 (≡CSi), 99.39 (SC≡)
26	0.05 (9H, s, $SiMe_3$); 3.36 (2H, s, CH_2); 7.1-7.4 and 7.80 (5H, m, ring protons); 8.37 (1H, br. s, NH)	111.43 (C-5), 119.44 (C-4), 119.44 (C-6), 120.52 (C-3), 122.66 (C-7), 129.32 (C-3a), 130.35 (C-7a), 136.13 (C-2)	-0.19 ($SiMe_3$), 26.14 (CH_2), 88.19 (≡CSi), 102.92 (SC≡)
27	0.05 and 0.22 (18H, s and s, $SiMe_3$); 3.02 (1H, s, CH); 7.2-7.4 and 7.82 (5H, m, ring protons); 8.22 (1H, br. s, NH)	106.80 (C-5), 111.29 (C-4), 119.69 (C-6), 120.35 (C-3), 122.53 (C-7), 129.45 (C-3a), 132.88 (C-7a), 136.13 (C-2)	-2.99 ($CHSi(\underline{C}H_3)_3$), 0.07 ($SiMe_3$), 29.87 (CH_2), 87.33 (≡CSi), 106.50 (SC≡)

TABLE 3. Mass Spectra of Alkynes **9-14, 16-21, 23-27**

Alkyne	*m/z* (I_{rel}, %)
9	148 (100, M^+), 117 (28),104 (24), 83 (17), 79 (47), 69 (17), 57 (14), 51 (40)
10	198 (100, M^+), 167 (10), 129 (17)
11	149 (100, M^+), 123 (12), 118 (14), 84 (9), 80 (13), 69 (12), 57 (14), 53 (18)
12	152 (100, M^+), 137 (41), 113 (37), 106 (17), 72 (100), 55 (8)
13	189 (98, M^+), 160 (18), 150 (43), 122 (100), 63 (10)
14	205 (100, M^+), 173 (15), 166 (32), 160 (13), 129 (13), 122 (17), 108 (34), 102 (10) 69 (10)
16	220 (97, M^+), 206 (100), 191 (14), 168 (21), 162 (10), 138 (13), 83 (17), 73 (14)
17	271 (18, M^+), 256 (40), 198 (100), 180 (8), 128 (17), 101 (7), 73 (10)
18	221 (100, M^+), 207 (97), 168 (19), 163 (14), 131 (12), 96 (8), 83 (23), 73 (17), 53 (13)
19	224 (100, M^+), 209 (92), 191 (33), 171 (87), 165 (34), 151 (13), 141 (10), 133 (15), 119 (15), 113 (33), 96 (15), 83 (45), 72 (37), 55 (17)
20	260 (100, M^+), 246 (42), 208 (25), 176 (17), 150 (25), 122 (40), 96 (17), 83 (47), 73 (20)
21	277 (100, M^+), 262 (43), 244 (17), 186 (13), 166 (21), 108 (22), 83 (18), 73 (17)
23	186 (100, M^+), 154 (7), 115 (9), 93 (6)
24	331 (23, M^+), 220 (100), 73 (54), 45 (9)
25	403 (27, M^+), 330 (20), 298 (27), 286 (11), 261 (27), 246 (23), 220 (100), 183 (22), 73 (54)
26	259 (24, M^+), 186 (23), 148 (100), 121 (9), 73 (9)
27	331 (35, M^+), 258 (100), 242 (19), 226 (22), 183 (42), 174 (58), 148 (39), 73 (59)

Quinoline derivative **17** and indole derivative **26** also displayed high cytotoxicity for the MG-22A line (1 μg/ml, MTT test).

TABLE 4. Cytotoxic Activity *in vitro* of Silanes **15-21***

Com-pound	Cell lines					
	HT-1080			MG-22A		
	IC_{50}, μg/ml		NO, CV *[2]	IC_{50}, μg/ml		NO, CV
	CV	MTT		CV	MTT	
15	44	77	31	35	24	91
16	27	35	500	25	18	83
17	24	36	83	3	1	500
18	27	36	150	28	14	73
19	57	*[3]	28	87	21	14
20	42	50	100	11	13	500
21	*[3]	*[3]	13	*[3]	*[3]	13
26	9	14	250	3	1	200
27	5	11	900	2	2	300

* IC_{50} is the concentration killing 50% of the cells; CV is staining by crystal violet; MTT is staining by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.

*[2] NO concentration, % (CV staining).

*[3] No cytotoxic activity.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian 200 Mercury spectrometer (200 and 50 MHz) in $CDCl_3$, internal standard hexamethyldisiloxane. The mass spectra were recorded on a GC-MS HP 6890 chromatograph/mass spectrometer with ionizing electron energy 70 eV. GLC analysis was carried out on a Chrom-5 chromatograph with flame-ionization detector and glass column (1.2 × 3 mm), packed with 5% OV-101 on Chromosorb W-HP (80-100 mesh). The carrier gas was nitrogen (60 cm^3/min). The analysis temperature was varied over the range 180-250°C, depending on the composition of the reaction mixture. Thiophenol (**1**), 2-mercaptopyridine (**2**), 2-mercaptoquinoline (**3**), 2-mercaptopyrimidine (**4**), 2-mercapto-1-methylimidazole (**5**), 2-mercaptobenzoxazole (**6**), 2-mercaptobenzothiazole (**7**), and 18-crown-6 (Acros) were used without additional purification. Propargyl bromide and trimethylchlorosilane were distilled before the experiment. 3-Mercaptoindole was obtained from indole in the system iodine–KI–NH_2CSNH_2–H_2O, as described in the literature [30]. Diethyl ether and THF were distilled over sodium and benzophenone.

General Procedure for Obtaining Hetaryl Propargyl Sulfides (8-14, 23). Propargyl bromide (2.7 ml, 30 mmol) were added to a suspension of thiol **1-7, 22** (20 mmol), 18-crown-6 (0.132 g, 0.5 mmol), powdered K_2CO_3 (4.14 g, 30 mmol) in toluene (20 ml). The reaction mixture was stirred for 4-10 h at 20°C and then filtered, and the filtrate was evaporated down on a rotary evaporator. The residue was purified by column chromatography (eluent hexane–ethyl acetate in different ratios) and compounds **8-14, 23** were obtained (see Tables 1-3).

General Procedure for Obtaining 3-(Hetarylthio)-1-propynyl(trimethyl)silanes (15-21). 2.5 M solution of *n*-BuLi in hexane (4.4 ml, 11 mmol) was added to a solution of hetaryl propargyl sulfide **8-14** (10 mmol) in dry diethyl ether (40 ml) at 0°C, and the reaction mixture was stirred for 3 h at 20°C under a nitrogen atmosphere. Then trimethylchlorosilane (1.9 ml, 15 mmol) were added, and the reaction mixture was refluxed for 3 h and then washed with a saturated aqueous solution of ammonium chloride (2 × 30 ml), and the organic layer was dried with $MgSO_4$; the ether was evaporated off under reduced pressure. The residue was purified by column chromatography (eluent hexane–ethylacetate in different ratios). As a result, compounds **15-21** were obtained (see Tables 1-3).

Silylation of 3-(2-Propynyl)thioindole (23). 3-(3-Trimethylsilyl-2-propynyl)-thioindole (26), and 3-[1,3-Bis(trimethylsilyl)-2-propynyl]thioindole (27). *n*-BuLi (4.0 ml, 10 mmol, 2.5 M in hexane) was added to a solution of compound **23** (1.03 g, 5.5 mmol) in tetrahydrofuran (50 ml) at 0°C, and the reaction mixture was stirred for 3 h at 20°C under a nitrogen atmosphere. Then trimethylchlorosilane (1.74 ml, 13.6 mmol) were added and the reaction mixture was refluxed for 3 h, then washed with a saturated aqueous solution of ammonium chloride (2 × 30 ml); the organic layer was dried with $MgSO_4$, the ether was evaporated off under reduced pressure. The residue, consisting of compounds **24** and **25** was purified by column chromatography (eluent hexane–ethylacetate, 10:1). As a result, we obtained compounds **26** (0.25 g, 18% yield) and **27** (0.40 g, 22%) (see Tables 2 and 3).

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