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A facile synthesis of 1-halo- and 1-organoxygermatranes

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Abstract

Interaction of the readily available 1-trimethylsiloxygermatranes (**1a**, **1b**) with various halogenating reagents (Me_3SiBr, Me_3SiI, HF and $SOCl_2$) has given the 1-halogermatranes (**2a–2f**). The 1-halogermatranes (**2a**, **2b**) have been converted into the corresponding 1-organoxygermatranes by treatment with trialkylalkoxystannanes (**3a–3f**). The corresponding 1-organoxygermatranes (**4d**, **4e**, **4f**) were made by interaction of 1-hydroxygermatrane monohydrate with the corresponding hydroxy derivatives).

Introduction

Germatranes show unusual physical and chemical properties and marked biological activity [1]. 1-Halo- and 1-organoxygermatranes are of special interest as potential sources of functionally-substituted organogermanium compounds [2,3]. Two methods have usually been used for the synthesis of 1-halo- and 1-alkoxygermatranes: (i) transalkoxylation of trialkoxyhalogermanes and tetraalkoxygermanes and (ii) interaction of tetrahalogermanes with $(R_3SnOCH_2CH_2)_3N$. Other possible methods of producing 1-halo- and 1-alkoxygermatranes involve the exchange of the substituents in 1-substituted germatranes with halogen or alkoxy groups [1]. However, these methods have their limitations for the synthesis of more complex molecules owing to the difficulty of preparing the starting materials [4].

Results and discussion

Mironov and co-workers recently demonstrated that the Ge–O bond in 1-alkoxygermatranes is easily cleaved by nucleophilic reagents [5]. We have found that 1-trimethylsiloxygermatrane (**1a**) and 1-trimethylsiloxy-3,7,10-trimethylgermatrane (**1b**) react readily with Me_3SiBr, Me_3SiI, HF and $SOCl_2$ to give the corresponding

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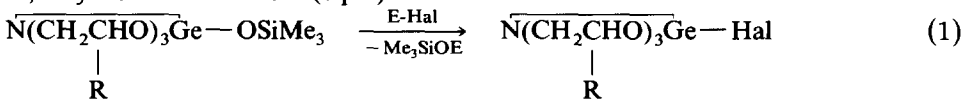
1-halogermatranes, **2a** and **2e** and 1-halo-3,7,10-trimethylgermatranes **2b**, **2c**, **2d** and **2f**, in yields of > 60–85% (eq. 1).



(1)

(1a, b) **(2a–2f)**

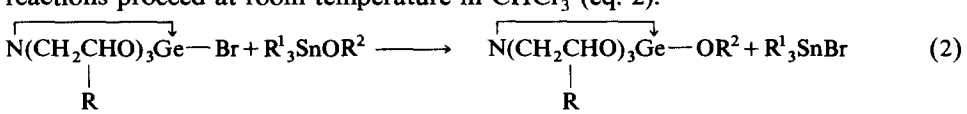
1	R
a	H
b	Me

E–Hal
Me_3SiBr
Me_3SiI
$SOCl_2$
HF

2	R	Hal
a	H	Br
b	Me	Br
c	Me	I
d	Me	F
e	H	Cl
f	Me	Cl

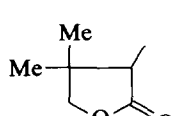
The preparations of compounds **2a** and **2e** by other methods have been described previously [5] and we have briefly reported the syntheses of these 1-halogermatranes and 1-halo-3,7,10-trimethylgermatranes **2b** and **2f** by the route outlined in eq. 1 [6]. The 1-iodo- and 1-fluoro-3,7,10-trimethylgermatranes **2c** and **2d** have not previously been reported. It should be noted that the attempted synthesis of 1-iodogermatrane by interaction of 1-ethoxygermatrane with Me_3SiI was unsuccessful, cleavage of the endocyclic Ge–O bond of the "atrane" skeleton apparently taking place [7]. The 1-halogermatranes (**2**) are crystalline substances, soluble in polar and insoluble in nonpolar organic solvents, and decompose above 200 °C without melting (table 1).

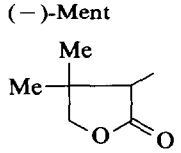
The availability of the 1-halogermatranes **2** makes it possible to synthesize various 1-organoxygermatranes, including those containing potentially biologically-active fragments. We describe here an efficient conversion of 1-bromogermatranes into the 1-organoxygermatranes by the method outlined previously [8] for the synthesis of normal alkoxygermanes, and also the novel synthesis of 1-organoxy-germatranes by reaction of trialkylorganoxystannanes with 1-bromogermatranes **2a** and **2b**. In the case of 1-bromogermatranes **2a** and compounds **3a**, **3b**, **3c** and **3f** the reactions proceed at room temperature in $CHCl_3$ (eq. 2).



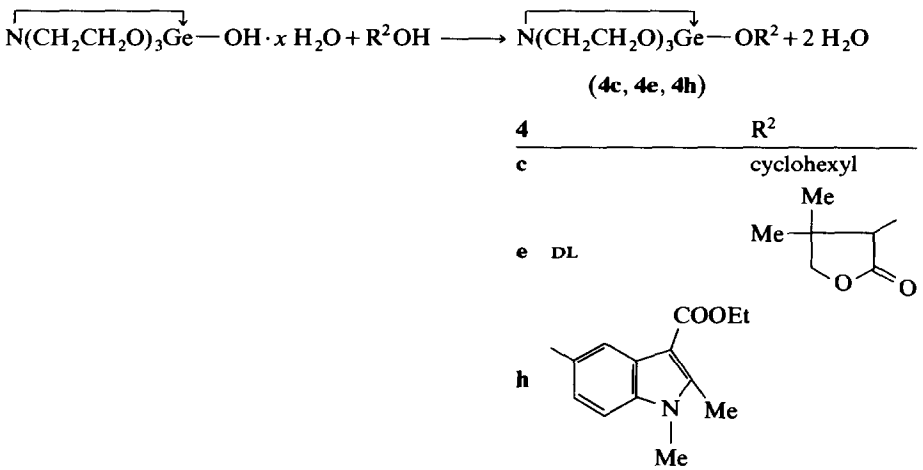
(2)

(2a, 2b) **(3a–3f)** **(4a–4g)**

3	R^1	R^2
a	Et	Me
b	Et	Et
c	Et	cyclohexyl
d	Et	(−)-Ment
e	Bu	(−)-Ment
f	Et	 DL

4	R	R^2
a	H	Me
b	H	Et
c	H	cyclohexyl
d	H	(−)-Ment
e	H	 DL
f	Me	Me
g	Me	(−)-Ment

The reaction of 1-bromogermatrane **2a** with trialkyl-(−)menthoxystannanes **3d** or **3e** in $CHCl_3$ and $CHBr_3$ gave (−)-1-menthoxygermatrane **4d** which forms complexes with the solvents, e.g. **4d** · *x* $CHCl_3$ and **4d** · *x* $CHBr_3$. An X-ray study [9] has shown that in the complex **4d** · *x*$CHCl_3$ the hydrogen atom of $CHCl_3$ forms a hydrogen bridge with the endocyclic (bond distance 243.7 pm) and exocyclic (bond distance 245.9 pm) oxygen atoms; the length of the transannular coordinative Ge–N bond is 214,9 pm and that of the Ge–OMent bond 176 pm [9]. Reaction of triethyl-(−)-menthoxystannane **3d** with 1-bromogermatrane **2a** was also carried out in other solvents, e.g. CH_2Cl_2, CCl_4 and C_6H_6, but in no case was compound **4d** obtained. We were able to make (−)-1-menthoxygermatrane **4d** by heating the complex **4d** · *x* $CHCl_3$ at 110–120 °C (2 Torr) for 4 h. No complex formation with $CHCl_3$ was observed in the case of 1-methoxy- (**4a**), 1-ethoxy- (**4b**), 1-cyclohexoxy- (**4c**) germatranes, or with germatrane (**4e**). 1-Bromo-3,7,10-trimethylgermatrane (**2b**) is considerably less reactive than 1-bromogermatrane (**2a**) towards the alkoxystannanes, the reactions requiring refluxing in xylene for several hours. Because compound **3g*** is prone to hydrolysis we could not obtain the corresponding 1-organoxygermatrane **4h** by the method of eq. 2, but it was made in almost quantitative yield by the reaction of 1-hydroxygermatrane monohydrate with 1,2-dimethyl-3-carbethoxy-5-hydroxyindole in xylene with azeotropic distillation of water (eq. 3):



By the method of eq. 3 1-organoxygermatranes **4c** and **4e** were synthesized in high yields, but treatment of (−)-menthol with 1-hydroxygermatrane monohydrate did not give the expected product.

Yields, melting points and analytical data for the obtained compounds are given in Table 1. All the compounds were also completely characterized by ^1H and ^{13}C NMR spectroscopy: the signals of the methylene protons of the germatrane skeleton

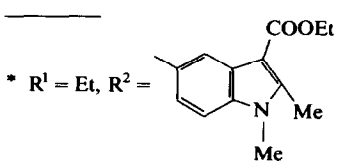


Table 1

Yields, melting points and analytical data for compounds (**2c**, **2d**) and (**4c–4h**)

Compound (Method of preparation)	Molecular formula	Yield, % (recrystallization solvent)	m.p., °C	Analysis (found (calc.) (%))		
				C	H	Ge
2c (eq. 1)	$C_9H_{18}IGeNO_3$	69 ($CHCl_3$)	115–116 dec.	27.45 (27.88)	4.66 (4.68)	18.62 (18.72)
2d (eq. 1)	$C_9H_{18}FGeNO_3$	60 ($CHCl_3$)	275–275 dec.	38.45 (38.63)	6.29 (6.48)	25.80 (25.94)
4c (eq. 2)	$C_{12}H_{23}GeNO_4$	76 (CH_3CN)	244–245	44.98 (45.34)	7.42 (7.29)	22.03 (22.03)
4d	$C_{16}H_{31}GeNO_4$	[a]	175–176	51.47 (51.38)	8.18 (8.35)	19.84 (19.10)
4d·x $CHCl_3$ (eq. 2)	$C_{17}H_{32}Cl_3GeNO_4$	82	182–184	40.80 (41.38)	6.70 (6.54)	15.05 (14.71)
4d·x $CHBr_3$ (eq. 2)	$C_{17}H_{32}Br_3GeNO_4$	84	134–135	32.98 (32.58)	5.25 (5.15)	11.60 (11.58)
4e (eq. 3)	$C_{12}H_{21}GeNO_6$	96 (CH_3CN)	248–249	41.40 (41.43)	6.09 (6.08)	20.19 (20.08)
4f (eq. 2)	$C_{10}H_{21}GeNO_4$	95 ($CHCl_3$)	140–141	41.23 (41.15)	7.13 (7.25)	24.82 (24.87)
4g (eq. 2)	$C_{19}H_{37}GeNO_4$	60	136–137	54.52 (54.84)	8.66 (8.96)	17.87 (17.44)
4h (eq. 3)	$C_{19}H_{26}GeN_2O_6$	99 (CH_3CN)	264–265	51.19 (50.60)	6.03 (5.81)	16.06 (16.09)

[a] Quantitative yield.

appear in the ^1H NMR spectra as two markedly broadened triplets at 2.8–2.95 (NCH_2) and 3.6–3.85 (OCH_2) ppm forming the AA'BB' spin system (J 5.6–5.8 Hz). In the ^{13}C NMR spectra signals of the carbon atoms of the "atrane" skeleton appear at 50.5–51.0 (NCH_2) and 56.1–56.85 (OCH_2) ppm. The ^1H NMR spectra of the 3,7,10-trimethylgermatranes are extremely complex due to the asymmetry of the methylsubstituted carbon atoms, which results in inequivalence of the protons of the skeleton and also because of the presence of two diasteromers [10]; in this case ^{13}C NMR spectroscopy is more informative [11].

Experimental

The ^1H and ^{13}C NMR spectra were recorded on a Varian XR-400 spectrometer with tetramethylsilane as an internal standard. The NMR spectra of compounds **4d**, **4d**·x $CHCl_3$, **4d**·x $CHBr_3$ and **4h** were recorded in DMSO-d_6, all other compounds in $CDCl_3$. Chemical shifts are quoted in ppm downfield from TMS.

Trimethylsiloxygermatrane **1a** was obtained by heating 1-hydroxygermatrane monohydrate with an excess of hexamethyldisilazane at reflux temperature [12]. 1-Hydroxygermatrane monohydrate was previously synthesized by the reaction of germanium dioxide with water and triethanolamine [12]; triisopropanolamine reacts readily in the same manner, but isolation of the corresponding pure 1-hydroxygermatrane becomes difficult due to decreasing crystallizability of the formed

product. We were able to obtain **1b** without isolating 1-hydroxy-3,7,10-trimethylgermatrane pure [6].

1-Iodo-3,7,10-trimethylgermatrane (2c)

To a solution of **1b** (0.5 g, 1.4 mmol) in 5 ml *m*-xylene was added trimethyliodosilane (0.8 g, 4 mmol) and set aside for 24 h at room temperature to give fine crystals of **2c**. The precipitate was dried in vacuo; yield 0.38 g (69%). ^{13}C NMR: 1st diastereomer: 59.69 (NCH_2); 64.56 (OCH); 20.24 (CH_3); 2nd diastereomer: 62.86, 62.56, 65.57 (NCH_2); 66.19, 66.23, 68.24 (OCH); 20.48, 20.64, 23.28 (CH_3).

1-Fluoro-3,7,10-trimethylgermatrane (2d)

A solution of 1-trimethylsiloxy-3,7,10-trimethylgermatrane **1b** (1.9 g, 5.4 mmol) in 10 ml of isopropyl alcohol was mixed with a solution of 0.2 g of 46% HF in 8 ml of the same solvent. The mixture was set aside at room temperature for 1 h in a hermetically sealed polyethylene vessel. Then compound **2d** that had separated was filtered off and dried in vacuo. Yield: 0.9 g (60%). ^{13}C NMR: 1st diastereomer: 57.95 (NCH_2); 62.21 (OCH); 19.95 (CH_3); 2nd diastereomer: 61.17, 60.65, 63.75 (NCH_2); 63.91, 64.20, 65.58 (OCH); 19.22, 20.26, 23.02 (CH_3).

Triorganoxystannanes were prepared in high yields by treatment of trialkylmethoxystannanes with the corresponding hydroxy derivatives:

Triethylcyclohexoxystannane (3c). A mixture of cyclohexanol (3.2 g, 32 mmol) and triethylmethoxystannane **3a** (11.8 g, 50 mmol) was heated and the formed methanol was removed continuously during the reaction. Distillation of the residue yielded 9.0 g (95%) of **3c**, b.p. 118–119 °C (1 Torr), n_D^{20} 1.4825. Found: C, 47.61; H, 8.63; Sn, 38.75. $C_{12}H_{26}OSn$ calcd.: 47.25; H, 8.59; Sn, 38.91%. ^{13}C NMR: 71.82 (C-1); 36.30 (C-2, C-6); 25.72 (C-4); 24.25 (C-3, C-5).

Compounds 3d–3f. These were prepared analogously, and had the properties shown below:

Tributyl-(−)-menthoxystannane (3e). Yield 99%, b.p. 148–150 °C (2 Torr), n_D^{20} 1.4818, α_D^{21} −30.7 ($c = 1.0$, $CHCl_3$). ^{13}C NMR: 8.64, 13.49, 27.08, 27.94 (SnBu); carbon atoms of the menthoxy group: 15.90, 21.19, 22.37, 23.05, 25.07, 31.93, 34.78, 47.93, 51.48, 71.84 (O–C). Found: C, 59.33; H, 10.34; Sn, 26.91. $C_{22}H_{46}OSn$ calcd.: C, 59.34; H 10.41; Sn 26.65%.

DL-2-Triethylstannoxy-3,3-dimethyl-γ-butyrolactone (3f). Yield 99%, b.p. 125–126 °C (1 Torr). ^1H NMR: 0.99 (s, 3H, CH_3); 1.15 (s, 3H, CH_3); 1.13 (m, 6H, CH_2); 4.04 (s, 1H, CH); system AB CH_2 group: 3.85 (H_A), 3.94 (H_B), J_{AB}: 8.8 Hz. ^{13}C NMR: 7.55 ($SnCH_2$); 9.84 ($SnCH_2CH_3$); 18.75 (CH_3); 23.19 (CH_3); 42.08 (C-3); 76.04 (C-4); 78.64 (C-2); 180.57 (C=O). Found: C, 43.24; H, 7.42; Sn, 35.42. $C_{12}H_{24}O_3Sn$ calcd.: C, 43.02; H, 7.22; Sn, 35.43.

1,2-Dimethyl-3-carboethoxy-5-triethylstannoxyindole (3g). The procedure was as described for **3c**, except that the residue was washed with n-pentane and dried in vacuo. Yield: 91%, m.p. 62–63 °C. ^1H NMR: 1.28 (m, 6H, $SnCH_2$); 1.32 (t, 9H, $SnCH_2CH_3$); 1.43 (t, 3H, $COOCCH_3$); 4.78 (q, 2H, $COOCH_2$); 3.61 (s, 3H, NCH_3); 2.71 (s, 3H, CH_3C=); 7.43 (d, 1H, H-4); 7.06 (d, 1H, H-7); 6.73 (dd, 1H, H-6). ^{13}C NMR: 7.11 ($SnCH_2$); 9.78 ($SnCH_2CH_3$); 11.85 (=C–CH_3); 29.52 (N–CH_3); 14.89 ($OCCH_3$); 59.00 (OCH_2); 166.44 (C=O). Found: C, 52.04; H, 6.40; Sn, 27.20%. $C_{19}H_{29}NO_3Sn$ calcd.: C, 52.09; H, 6.67; Sn, 27.09%.

1-Methoxygermatrane (4a). To a mixture of **2a** (1.3 g, 4.3 mmol) in 4 ml $CHCl_3$ at room temperature was added **3a** (1.18 g, 5 mmol). After 15 min all of **2a** had dissolved. The mixture was stirred for 1 h and the product precipitated by addition of 10 ml of n-pentane, filtered off, and dried in vacuo. Yield: 1.05 g (97%), m.p. 173–175 °C, lit. [13] 174–178 °C.

Compounds 4b, 4c, 4e. These were made analogously:

1-Ethoxygermatrane (4b). Reaction time 3 h, yield 92%, m.p. 125–126 °C, lit. [13] 126–130 °C.

1-Cyclohexoxygermatrane (4c). Reaction time 50 h, yield 76%, m.p. 244–245 °C. ^{1}H NMR: 2.87 (t, 6H, NH_2); 3.85 (t, 6H, OCH_2). ^{13}C NMR: 51.97 (NCH_2); 56.82 (OCH_2); 71.85 (C-1); 36.31 (C-2, C-6); 25.70 (C-4); 24.27 (C-3, C-5).

DL-2-Germatranoxy-3,3-dimethyl-γ-butyrolactone (4e). Reaction time 50 h, yield 88%, m.p. 248–249 °C. ^{1}H NMR: 2.83 (t, 6H, NH_2); 3.63 (t, 6H, OCH_2); 0.90 (s, 3H, CH_3); 1.08 (s, 3H, CH_3); 3.94 (s, 1H, CH), system AB CH_2 group: 3.93 (H_A), 3.95 (H_B), J_{AB} 8.8 Hz. ^{13}C NMR: 50.51 (NCH_2); 55.83 (OCH_2); 74.41 (C-4); 74.93 (C-2); 39.52 (C-3); 22.09 (CH_3); 18.79 (CH_3).

(−)-1-Menthoxygermatranes 4d · x $CHBr_3$ and 4d · x $CHCl_3$. A mixture of **2a** (0.2 g, 1 mmol), of $CHBr_3$ (4 ml) and **3d** (1 g, 3 mmol) was stirred 2 h at room temperature, then set aside for 50 h. The solid obtained was filtered off, washed with n-pentane, and dried in vacuo. Yield of 4d · x $CHBr_3$ 0.53 g (84%), m.p. 134–135 °C.

A similar procedure gave **4d** · x $CHCl_3$. Yield 83%, m.p. 182–183 °C, α_D^{21} −23.93 (c = 1.63, DMSO).

(−)-1-Menthoxygermatrane (4d). Complex **4d** · x $CHCl_3$ (0.5 g) was heated at 110–120 °C(2 Torr), for 4 h, until $CHCl_3$ evolution ceased, to give 0.38 g (ca. 100%) of compound **4d**. ^{1}H NMR: 2.83 (t, 6H, NCH_2), 3.64 (t, 6H, OCH_2); 0.72 (d, 3H, CH_3). ^{13}C NMR: 56.08 (OCH_2); 50.62 (NCH_2); carbon atoms of the menthoxy group: 71.41; 50.54; 45.60; 35.41; 31.19; 24.44; 22.80; 22.40; 21.28; 16.06.

1-Methoxy-3,7,10-trimethylgermatrane (4f). A mixture of **2b** (0.7 g, 2.1 mmol), **3a** (1.31 g, 5 mmol), and *m*-xylene (3 ml) was refluxed for 3 h. The mixture was cooled and n-pentane (5 ml) added, to give fine crystals, which were filtered off and dried in vacuo: yield of **4f** 0.5 g (95%), m.p. 140–141 °C. ^{13}C NMR: 1st diastereomer: 52.91 (OCH_3); 59.66 (NCH_2); 62.32 (OCH); 20.41 (CH_3); 2nd diastereomer: 52.93 (OCH_3); 62.88, 62.99, 63.93 (NCH_2); 64.25, 65.92, 66.03 (OCH); 20.63, 20.82, 23.24 (CH_3).

(−)-1-Menthoxy-3,7,10-trimethylgermatrane (4g). This was made analogously. Yield 61%, m.p. 136–137 °C, α_D^{25} −35.5 (c = 0.31, $CHCl_3$).

1,2-Dimethyl-3-carboethoxy-5-germatranoxyindole (4h). A mixture of 1,2-dimethyl-3-carboethoxy-5-hydroxyindole (1.1 g, 4.7 mmol), 1-hydroxygermatrane monohydrate (1.2 g, 4.7 mmol) and *m*-xylene (25 ml) was refluxed and the water formed was continuously removed by azeotropic distillation. The residue was filtered off and the precipitate washed with n-pentane and recrystallized from CH_3CN. Yield of **4h**: 2.1 g (99%), m.p. 264–265 °C. ^{1}H NMR: 2.94 (t, 6H, NCH_2); 3.73 (t, 6H, OCH_2); 3.63 (s, 3H, NCH_3); 2.67 (s, 3H, CH_3–C=); 1.36 (t, 3H, $OCCH_3$), 4.24 (q, 2H, OCH_2); 7.47 (d, 1H, H-4); 7.16 (d, 1H, H-7); 6.76 (dd, 1H, H-6). ^{13}C NMR: 165.17 (C=O); 58.39 (OCH_2CH_3); 56.38 (OCH_2); 50.72 (NCH_2); 29.43 (NCH_3); 14.39 (OCH_2CH_3); 11.50 (CH_3–C=); carbon atoms of the heterocycle: 154.02; 144.80; 130.63; 126.42; 115.74; 110.37; 109.10; 101.7.

Compounds 4c and 4e. These were made analogously in 96% yield.

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