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Synthesis of heterocyclic compounds containing germanium and nitrogen as hetero-atoms. I

Kazuhiro Shitara, Yoshiro Sato* and Reiko Nakagawa

Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467 (Japan)

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Abstract

Several new five- and six-membered heterocyclic compounds containing both germanium and nitrogen as hetero-atoms in the same ring were synthesized from chloro(chloromethyl)dimethylgermane. Their reactions and those of the related aminomethylgermanes are described.

Introduction

Many cyclic organogermanium compounds have been reported owing to their importance as substances of biological interest and in synthetic organic chemistry [1]. For example, *N*-(3-dimethylaminopropyl)-2-aza-8,8-diethyl-8-germaspiro[4,5]-decene, known as spirogermanium, has received attention for its potential as an anticancer agent [2]. A few heterocyclic compounds containing nitrogen and germanium in the same ring have been reported, but most such compounds contain a nitrogen–germanium bond unstable in water [3–6].

We have reported previously the syntheses of several heterocyclic compounds containing the Si–C–N or Si–C–C–N bond system [7–10]. During our investigation, some five- and six-membered ring compounds containing both of germanium and nitrogen in the same ring were synthesized from chloromethyldimethylchlorogermane (**1**) as starting material.

Results and discussion

The chlorine–germanium bond of **1**, in contrast to the chlorine–carbon bond is more reactive toward ordinary nucleophilic reagents. Treatment of **1** with the Grignard reagents 2-methylphenylmagnesium bromide (**2**) and vinylmagnesium bromide (**6**), gave chloromethyldimethyl(2-methylphenyl)germane (**3**) and chloromethyldimethylvinylgermane (**7**), respectively.

Tetrahydrobenzo[*d*]-1,3-azagermine rings were synthesized from **3** by use of the procedure for the synthesis of its sila-analog [7]. (2-Bromomethylphenyl)chlorometh-

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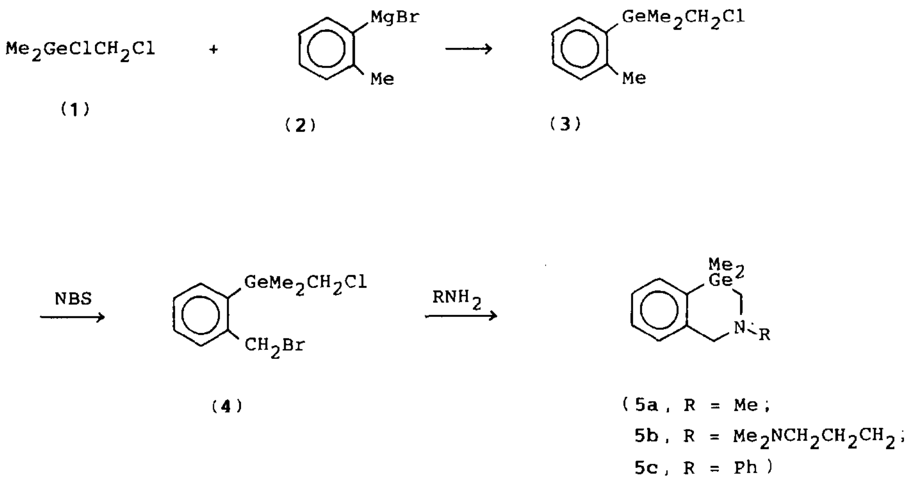
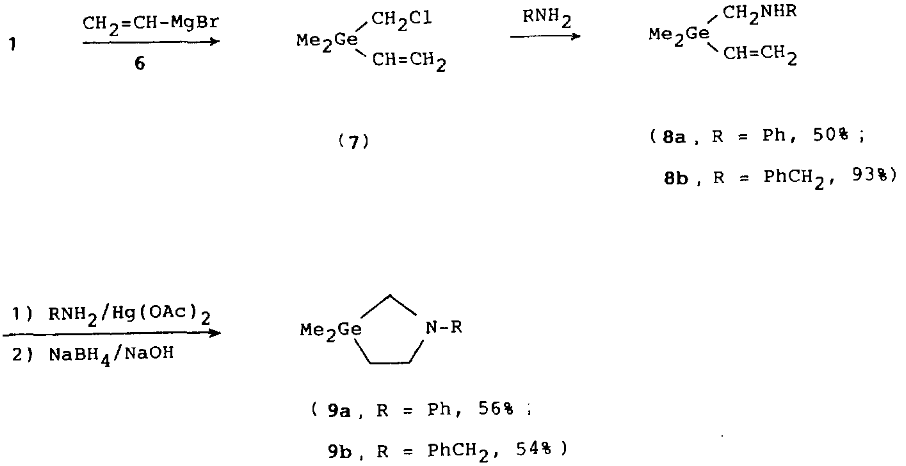


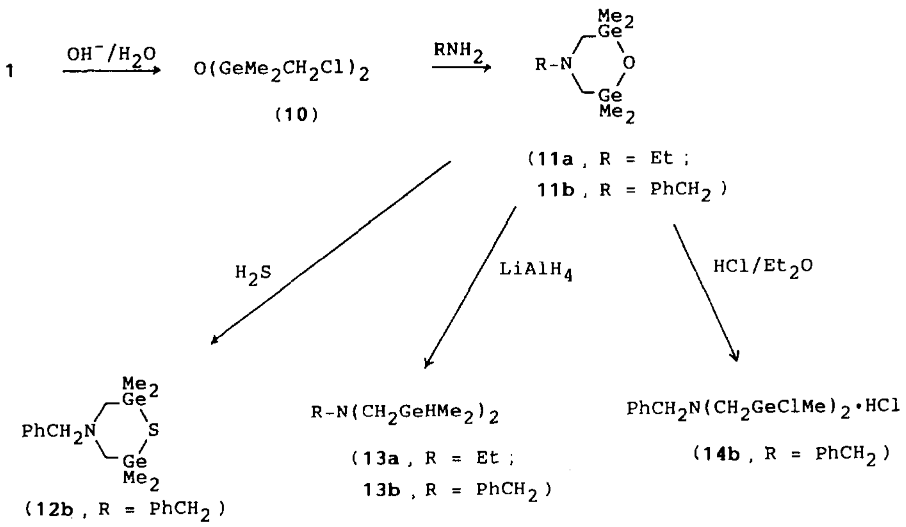
Scheme 1

yldimethylgermane (**4**) was prepared by bromination of **3** with *N*-bromosuccinimide followed by heating with methylamine, 3-(dimethylamino)propylamine and aniline to give new heterocyclic compounds, 3-substituted 1,1-dimethyl-1,2,3,4-tetrahydrobenzo[*d*]-1,3-azagermines (**5a–5c**) (Scheme 1).

Dimethyl(substituted aminomethyl)vinylgermanes (**8**), prepared by the reaction of **7** with primary amines (aniline and benzylamine), were treated with mercuric acetate followed by sodium borohydride to give 1-substituted 3,3-dimethyl-1,3-azagermolidine (**9**) in moderate yields (Scheme 2). Voronkov et al. reported the reaction of alkenyl(chloromethyl)dimethylsilane with aniline/mercuric acetate system to give initially an addition product of the amine to the alkene, which was cyclized to give the 1,3-azasiloline ring [11]. However, similar treatment of **7** with



Scheme 2



Scheme 3

aniline gave a mixture of **8a** and **9a** in low yields, but benzylamine afforded only **8b**. Substitution reactions of the amines with the chloro group of **7** occurred initially but there was no addition of the amino group to the vinyl group in this reaction.

1,3-Bis(chloromethyl)-1,1,3,3-tetramethyldigermoxane (**10**), readily obtained from **1** by alkaline treatment, was converted to a new cyclic compound, 4-substituted 2,2,6,6-tetramethylperhydro-1,4,2,6-oxazadigermine (**11**) by reaction with primary amines (Scheme 3). The oxygen atom of germoxane was easily replaced by sulfur [12], thus becoming 4-benzyl-2,2,6,6-tetramethylperhydro-1,4,2,6-thiazadigermine (**12b**) when heated with hydrogen sulfide in water. The reduction of **11** using lithium aluminum hydride afforded a high yield of *N*,*N*-bis[(dimethylgermyl)methyl]alkylamine (**13**). Compound **13**, a stable oil in air, converted to the chlorogermane in a chloroform solution containing carbon tetrachloride. Treatment of **11b** with hydrogen chloride in ether resulted not in the corresponding amine hydrochloride, but in *N*,*N*-bis(chlorodimethylgermylmethyl)benzylamine hydrochloride (**14b** · HCl).

Experimental

All reactions were carried out under nitrogen. Diethyl ether and tetrahydrofuran were dried by distillation from sodium benzophenone ketyl before use. ^1H NMR spectra were recorded on a JEOL JNM-MH-100 spectrometer using Me_4Si as internal standard. ^{13}C NMR spectra were recorded on a JEOL JNM FX-100 spectrometer. IR spectra were recorded on a JASCO IRA-2 spectrometer. Mass spectral data were obtained by using a JEOL JMS-DX300 GC/MS system (70 eV). Gas chromatographic analyses were carried out with Gasukuro Kogyo Model 370 equipped with FID and TCD detectors. All melting points and boiling points are uncorrected.

Chloromethyldimethyl(2-methylphenyl)germane (3)

A solution of 2-methylphenylmagnesium bromide, prepared from *o*-bromotoluene (9.49 g, 55.5 mmol) and magnesium turnings (1.41 g, 57.8 m atom) in THF (40 ml), was added to a solution of chloro(chloromethyl)dimethylgermane (6.21 g, 33.1 mmol) in THF (30 ml) at room temperature. After 3 h of stirring at reflux, the reaction mixture was quenched with saturated aqueous NH_4Cl (30 ml), and extracted with ether (50 ml × 3). The extract was dried over anhydrous $MgSO_4$, concentrated, and distilled to give 7.178 g (89%) of **3**: b.p. 106–109 °C. ^1H NMR ($CDCl_3$): δ 0.56 (6H, s, $GeCH_3$), 2.40 (3H, s, $PhCH_3$), 3.17 (2H, s, CH_2), 7.1–7.4 (4H, m, ArH). Anal. Found: C, 49.09; H, 6.14. $C_{10}H_{15}ClGe$ calc: C, 49.37; H, 6.21%.

2-(Bromomethylphenyl)chloromethyldimethylgermane (4)

A mixture of **3** (1.44 g, 5.90 mmol), *N*-bromosuccinimide (1.05 g, 5.91 mmol) and benzoyl peroxide (24 mg) in carbon tetrachloride (25 ml) was heated at reflux for 3 h. The filtrate of the reaction mixture was distilled to give **4** (1.40 g, 74%): b.p. 124–127 °C (2 Torr). ^1H NMR ($CDCl_3$): δ 0.68 (6H, s, $GeCH_3$), 3.26 (2H, s, CH_2Cl), 4.58 (2H, s, CH_2Br), 7.2–7.5 (4H, m, ArH). Anal. Found: C, 37.00; H, 4.34. $C_{10}H_{14}BrClGe$ calc: C, 37.28; H, 4.38%.

3-Substituted 1,1-dimethyl-1,2,3,4-tetrahydrobenzo[d]-1,3-azagermine (5a–5c): general procedure

A solution of **4** (644 mg, 2.0 mmol) and 5.0 mmol of primary amine (methylamine, 3-dimethylaminopropylamine, or aniline) in benzene (8 ml) was heated at reflux for 3 h (10 h for aniline). The reaction mixture was extracted with 5% HCl (20 ml × 4). The acid extract was made alkaline and extracted with ether. The ether extract was dried, concentrated, and distilled to give 3-methyl- (**5a**), 3-(3-dimethylaminopropyl)- (**5b**), or 3-phenyl-1,1-dimethyl-1,2,3,4-tetrahydrobenzo[*d*]-1,3-azagermine (**5c**). Their yields and properties are summarized in Table 1.

Chloromethyldimethylvinylgermane (7)

A solution of vinylmagnesium bromide, prepared from vinyl bromide (6.9 g, 65 mmol) and magnesium turnings (1.50 g, 61.5 mmol) in THF (23 ml), was added to a stirring solution of **1** (7.14 g, 38.0 mmol) in THF (50 ml). After 12 h of reflux, the mixture was quenched with saturated aqueous NH_4Cl (50 ml) and extracted with ether (70 ml × 3). The ether extract was dried ($MgSO_4$), concentrated, and distilled to give 4.90 g (72%) of **7**: b.p. 136–139 °C. ^1H NMR ($CDCl_3$): δ 0.36 (6H, s, $GeCH_3$), 2.98 (2H, s, CH_2Cl), 5.67 (1H, dd, *J* 4, *J* 19 Hz, $=CH_2$), 6.01 (1H, dd, *J* 4, *J* 14 Hz, $=CH_2$), 6.32 (1H, dd, *J* 14, *J* 19 Hz, $-CH=$). Anal. Found: C, 33.60; H, 5.96. $C_5H_{11}ClGe$ calc: C, 33.52; H, 6.19%.

Dimethyl(phenylaminomethyl)vinylgermane (8a)

A mixture of **7** (3.41 g, 19.0 mmol) and aniline (6.74 g, 72.3 mmol) in DMSO (15 ml) was heated at 80 °C for 10 h. The reaction mixture was mixed with water (200 ml) and extracted with ether (50 ml × 3). The ethereal extract was dried ($MgSO_4$), concentrated, and distilled to give 2.23 g (50%) of **8a**: b.p. 120 °C (1.5 Torr, oven temperature of a Kugelrohr distillation apparatus). ^1H NMR ($CDCl_3$): δ 0.32 (6H, s, $GeCH_3$), 1.54 (1H, br. NH), 2.74 (2H, s, NCH_2), 5.68 (1H, dd, *J* 4, *J* 19 Hz,

Table 1

3-Substituted 1,1-dimethyl-1,2,3,4-tetrahydrobenzo[*d*]-1,3-azagermine (**5a**–**5c**)

Compound	Yield (%)	B.p. (°C/ mmHg) [a]	Elemental analysis (Found (calc)(%))			^{1}H NMR ($CDCl_3$) δ (ppm)
			C	H	N	
5a, R = Me	73	90/5	55.93 (56.02)	7.35 (7.26)	5.92 (5.94)	0.41 (6H, s, $GeCH_3$), 2.42 (2H, s, $GeCH_2$), 2.45 (3H, s, NCH_3), 3.49 (2H, s, $PhCH_2$), 7.0–7.4 (4H, m, Ar–H)
5b, R = Me_2NCH_2-CH_2CH_2	95	150/1.5	58.63 (58.69)	8.62 (8.54)	9.01 (9.13)	0.42 (6H, s, $GeCH_3$), 1.5–1.9 (2H, m, CH_2), 2.22 (6H, s, NCH_3), 2.30 (2H, t, *J* 7 Hz, NCH_2), 2.48 (2H, s, $GeCH_2$), 2.54 (2H, t, *J* 7 Hz, NCH_2), 3.59 (2H, s, $PhCH_2$), 6.9–7.4 (4H, m, ArH)
5c, R = Ph	73	160/0.2 m.p. 70–72	64.34 (64.51)	6.45 (6.43)	4.86 (4.70)	0.42 (6H, s, $GeCH_3$), 3.43 (2H, s, $GeCH_2$), 4.43 (2H, s, NCH_2), 6.6–7.5 (9H, m, ArH)

[a] Oven temperature of Kugelrohr distillation apparatus.

$=CH_2$), 6.02 (1H, dd, *J* 4, *J* 14 Hz, $=CH_2$), 6.34 (1H, dd, *J* 14, *J* 19 Hz, –CH=), 6.6–7.2 (5H, m, ArH). Anal. Found: C, 56.17; H, 7.24; N, 5.99. $C_{11}H_{17}GeN$ calc: C, 56.02; H, 7.26; N, 5.94%.

*(Benzylaminomethyl)dimethylvinylgermane (**8b**)*

In a manner similar to that described for **8a**, **7** (3.54 g, 19.8 mmol) and benzylamine (7.17 g, 66.9 mmol) in DMSO (15 ml) were treated to give 4.60 g (93%) of **8b**: b.p. 110 °C (1.5 Torr, Kugelrohr). ^{1}H NMR ($CDCl_3$): δ 0.26 (6H, s, $GeCH_3$), 1.36 (1H, br, NH), 2.35 (2H, s, $GeCH_2$), 3.77 (2H, s, $PhCH_2$), 5.61 (1H, dd, *J* 4, *J* 19 Hz, $=CH_2$), 5.95 (1H, dd, *J* 4, *J* 14 Hz, $=CH_2$), 6.31 (1H, dd, *J* 14, *J* 19 Hz, –CH=), 7.27 (5H, s, ArH). Anal. Found: C, 57.45; H, 7.76; N, 5.83. $C_{12}H_{19}GeN$ calc: C, 57.68; H, 7.66; N, 5.61%.

*3,3-Dimethyl-1-phenyl-1,3-azagermolidine (**9a**)*

To a stirring mixture of mercuric acetate (354 mg, 1.11 mmol), THF (3 ml) and water (3 ml) was added **8a** (261 mg, 1.11 mmol) at room temperature. After 4 h 0.5 *N* NaOH (5 ml) was added, followed by a solution of $NaBH_4$ (44 mg, 1.16 mmol) in 2.5 *N* NaOH (1 ml) with additional stirring for 2 h. The reaction mixture was filtered and the filtrate was extracted with ether (10 ml × 3). The residue of the ether extract was mixed with acetic anhydride (1 ml) in order to separate it from the **8a** remaining. After 2 h stirring, the mixture was added to 5% HCl, and extracted with ether. The acid layer was neutralized with aqueous NaOH and extracted with ether. The extract was dried ($MgSO_4$), concentrated, and distilled to give 146 mg (56%) of **9a**: b.p. 130 °C (2 Torr, Kugelrohr). ^{1}H NMR ($CDCl_3$): δ 0.42 (6H, s, $GeCH_3$), 1.17 (2H, t, *J* 7 Hz, $GeCH_2C$), 2.64 (2H, s, $GeCH_2N$), 3.45 (2H, t, *J* 7 Hz,

NCH_2C), 6.6–7.3 (5H, m, ArH). Anal. Found: C, 56.28; H, 7.31; N, 6.16. $C_{11}H_{17}GeN$ calc: C, 56.02; H, 7.26; N, 5.94%.

*1-Benzyl-3,3-dimethyl-1,3-azagermolidine (**9b**)*

In a manner similar to that described for **9a**, treatment of **8b** (277 mg, 1.11 mmol) gave 150 mg (54%) of **9b**: b.p. 110 °C (1 Torr). ^1H NMR ($CDCl_3$): δ 0.28 (6H, s, $GeCH_3$), 0.94 (2H, t, J 7Hz, $GeCH_2C$), 1.84 (2H, s, $GeCH_2N$), 2.54 (2H, t, J 7 Hz, NCH_2C), 3.58 (2H, s, $PhCH_2$), 7.24 (5H, s, ArH). Anal. Found: C, 57.56; H, 7.70; N, 5.68. $C_{12}H_{19}GeN$ calc: C, 57.68; H, 7.66; N, 5.61%.

*1,3-Bis(chloromethyl)-1,1,3,3-tetramethyldigermoxane (**10**)*

A mixture of **1** (2.41 g, 12.85 mmol), saturated aqueous $NaHCO_3$ (20 ml), and ether (20 ml) was stirred for 1 h. The ether layer was separated, and the aqueous layer extracted with ether. The combined extract was dried ($MgSO_4$), concentrated, and distilled to give 1.91 g (93%) of **10**: b.p. 110 °C (20 Torr, Kugelrohr). ^1H NMR ($CDCl_3$): δ 0.48 (12H, s, $GeCH_3$), 3.04 (4H, s, CH_2Cl).

*4-Ethyl-2,2,6,6-tetramethylperhydro-1,4,2,6-oxazadigermine (**11a**)*

A solution of **10** (776 mg, 2.42 mmol), ethylamine (134 mg, 2.97 mmol), and triethylamine (857 mg, 847 mmol) in benzene (10 ml) was stirred for 2 d. The reaction mixture was filtered and the filtrate was extracted with 5% HCl (25 ml × 4). The acid extract was neutralized with NaOH and extracted with ether. The ether extract was dried ($MgSO_4$), concentrated, and distilled to give 497 mg (70%) of **11a**: b.p. 100 °C (27 Torr, Kugelrohr). ^1H NMR ($CDCl_3$): δ 0.50 (12H, s, $GeCH_3$), 1.15 (3H, t, J 7 Hz, CH_3C), 2.27 (4H, s, $GeCH_2$), 2.62 (2H, q, J 7 Hz, CH_2C). Anal. Found: C, 32.62; H, 7.28; N, 4.68. $C_8H_{21}Ge_2NO$ calc: C, 32.86; H, 7.24; N, 4.79%.

*4-Benzyl-2,2,6,6-tetramethylperhydro-1,4,2,6-oxazadigermine (**11b**)*

In a manner similar to that described for **11a**, a mixture of **10** (1.85 g, 5.77 mmol), benzylamine (956 mg, 8.92 mmol), triethylamine (1.54 g, 15.22 mmol) and benzene (30 ml) yielded 1.66 g (81%) of **11b**: b.p. 90 °C (0.15 Torr, Kugelrohr). ^1H NMR ($CDCl_3$): δ 0.42 (12H, s, $GeCH_3$), 2.21 (4H, s, $GeCH_2$), 3.64 (2H, s, $PhCH_2$), 7.44 (5H, s, ArH). Anal. Found: C, 44.02; H, 6.64; N, 4.02. $C_{13}H_{23}Ge_2NO$ calc: C, 44.04; H, 6.54; N, 3.95%.

*4-Benzyl-2,2,6,6-tetramethylperhydro-1,4,2,6-thiazadigermine (**12b**)*

To a stirring mixture of **11b** (2.724 g, 7.68 mmol), benzene (20 ml) and water (15 ml) was introduced hydrogen sulfide gas at 80 °C for 10 h, then extracted with ether. The extract was dried ($MgSO_4$), concentrated, and distilled to give 2.387 g (84%) of **12b**: b.p. 140 °C (5 Torr, Kugelrohr), m.p. 38–41 °C. ^1H NMR ($CDCl_3$): δ 0.50 (12H, s, $GeCH_3$), 2.28 (4H, s, $GeCH_2$), 3.57 (2H, s, $PhCH_2$), 7.33 (5H, s, ArH). Anal. Found: C, 42.03; H, 6.11; N, 3.78. $C_{13}H_{23}Ge_2NS$ calc: C, 42.14; H, 6.26; N, 3.74%.

*N,N-Bis[(dimethylgermyl)methyl]ethylamine (**13a**)*

A mixture of **11a** (314 mg, 1.07 mmol), $LiAlH_4$ (105 mg, 2.77 mmol) in THF (10 ml) was heated at reflux for 2 h. The reaction mixture was quenched with AcOEt (0.3 ml), 10% NaOH (0.3 ml), then H_2O (0.9 ml). The mixture was filtered and the precipitate was washed with ether. The combined ether layer was dried over $MgSO_4$, concentrated, and distilled to give 213 mg (72%) of **13a**: b.p. 90 °C (26 Torr, Kugelrohr). ^1H NMR ($CDCl_3$): δ 0.28 (12H, d, J 4 Hz, $GeCH_3$), 1.04 (3H, t, J 7 Hz, CH_3C), 2.41 (4H, d, J 2.4 Hz, $GeCH_2$), 2.52 (2H, q, J 7 Hz, CCH_2), 3.9–4.1 (2H, m, GeH). IR (film): 2025 (GeH) cm^{-1}. Anal. Found: C, 34.53; H, 4.98; N, 8.38. $C_8H_{23}Ge_2N$ calc: C, 34.51; H, 5.03; N, 8.33%.

N,N-Bis[(dimethylgermyl)methyl]benzylamine (13b)

In a manner similar to that described for **13a**, a mixture of **11b** (2.21 g, 6.24 mmol), $LiAlH_4$ (815 mg, 21.5 mmol) and THF (30 ml) yielded 1.51 g (71%) of **13b**: b.p. 110 °C (2.5 Torr, Kugelrohr). ^1H NMR ($CDCl_3$): δ 0.27 (12H, d, J 4 Hz, $GeCH_3$), 2.15 (4H, d, J 3 Hz, $GeCH_2$), 3.55 (2H, s, $PhCH_2$), 4.0–4.2 (2H, m, GeH), 7.31 (5H, s, ArH). IR (film): 2050 (GeH) cm^{-1}. Anal. Found: C, 45.70; H, 7.12; N, 4.41. $C_{13}H_{25}Ge_2N$ calc: C, 45.85; H, 7.40; N, 4.11%.

N,N-Bis[(chlorodimethylgermyl)methyl]benzylamine hydrochloride (14b)

To a solution of **11b** (100 mg, 0.28 mmol) in ether (15 ml) was added saturated HCl/Et_2O (1 ml). The precipitated crystals were filtered and recrystallized from a mixture of hexane/benzene to give 124 mg (98%) of **14b**: m.p. 142–143 °C. ^1H NMR ($CDCl_3$): δ 1.14 (12H, s, $GeCH_3$), 3.05 (4H, bs, $GeCH_2$), 4.35 (2H, bs, $PhCH_2$), 7.62 (5H, bs, ArH). Anal. Found: C, 35.09; H, 5.39; N, 3.19. $C_{13}H_{24}Cl_3Ge_2N$ calc: C, 35.02; H, 5.43; N, 3.14%.

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