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SILA-SUBSTITUTED PERFUMES

IV *. SILA DERIVATIVES OF SOME MUSK SCENTS **

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Summary

The sila derivatives XII and XIII and the germa derivative XIV of the artificial musk scents 3,5-di(tert.butyl)benzaldehyde (A) and 3,5-di(tert.butyl)acetophenone (B) as well as the sila and germa derivatives XVIII and XIX of the "xylene musk" scent C, 2,4-dimethyl-6-tert.butyl-trinitrobenzene, were synthesized and characterized in their chemical and structural properties. Astonishingly, the musk odor of A and B disappeared on sila or germa substitution of the quarternary C atom of a tert-butyl group whereas it became more brilliant and intense on sila substitution of a similar C atom in "xylene musk" and was still active in the germa derivative.

Introduction

In preceding papers of the title series we investigated the influence of sila and germa substitution of the central C atom in tertiary carbinols (→ silanols, but digermoxanes) of the linalool class of compounds which is abundant in many fragrances of flowers, for instance, lilies, hyacinthes, even roses. Intensity and note of the odour did not change significantly on sila substitution, but a shift from the lily to the hyacinth component could be observed in nearly all cases. A very important class of perfumes is that of musk scents. Apart from the natural product muscone — a large, 15-membered cycle with a keto group — an astonishingly large number of artificial compounds are known (>50) which possess, in spite of quite different structural principles, the typical musk odour (urine-like/sweaty). One of the most important technical musk scents is the

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[*] For part III see ref. 1.

[**] In honor of Professor Henry Gilman for his outstanding research in the field of organometallic chemistry.

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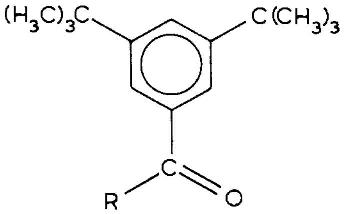
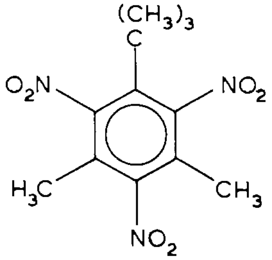
"xylene musk" (C), 2,4-dimethyl-6-tert.butyl-trinitrobenzene. The musk scents A and B are similar in structure and, although not commercially prepared, are often used in literature discussions about connections of structure and smell [2]. We hoped to effect sila and germa substitution in A, B and C and to contribute in this way to the question of structure—smell relationships.



(A, R = H,
(B, R = CH_3)

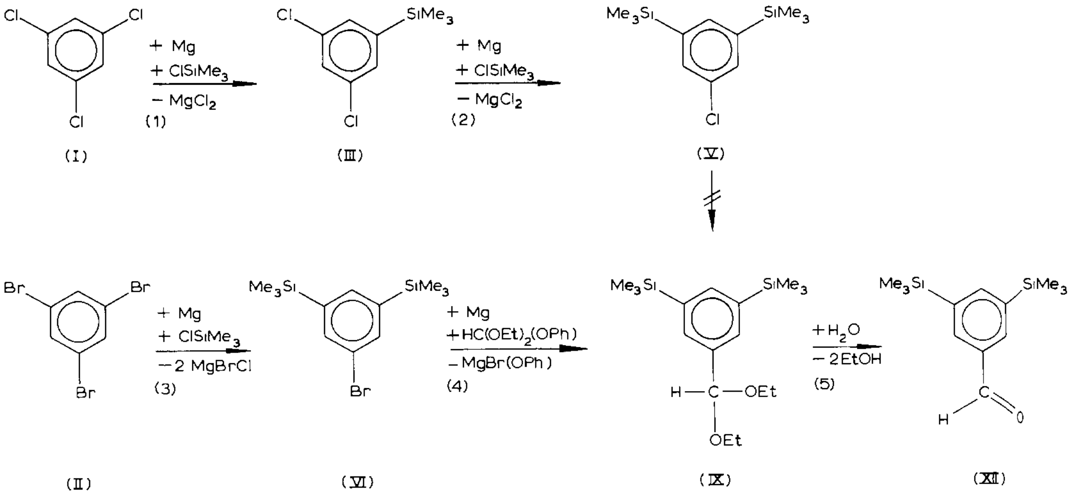


(C)

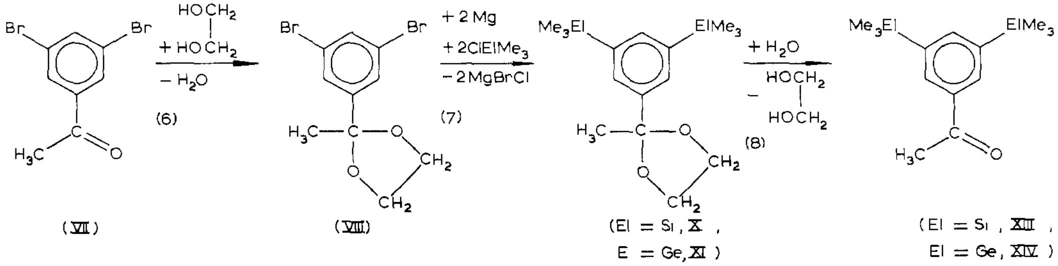
Synthetic routes

It is not possible to synthesize sila and germa analogues of artificial musk scents A—C by methods used for the preparation of the original carbon compounds, where the molecules are constructed stepwise by electrophilic substitution of the aromatic skeleton: at first, tertiary butyl groups are introduced, and only later, formyl, acetyl or nitro groups. As trimethylsilyl and trimethylgermyl groups bound to aromatic systems are especially good leaving groups in electrophilic substitution, they have to be introduced in the last or at least next to the last step of synthesis. Therefore only in compound XII does the introduction of the formyl group by Grignard reaction follow that of the trimethylsilyl group.

An attempt to synthesize 3,5-bis(trimethylsilyl)benzaldehyde (XII) from



3,5-bis(trimethylsilyl)chlorobenzene (V) failed. V was prepared according to reaction 2 from 1,3-dichloro-5-trimethylsilylbenzene, which was already known before but obtained here by a different method in reaction 1 with 1,3,5-trichlorobenzene as starting material. However, a route beginning with 1,3,5-tribromobenzene was successful. Substitution of two bromine atoms by trimethylsilyl groups (reaction 3) and, subsequently, of the third by a bis(ethoxy)-methyl group (reaction 4) via Grignard reactions followed by hydrolysis of the acetal IX produced the disila analogue XII of the musk scent A in a total yield of 30%.



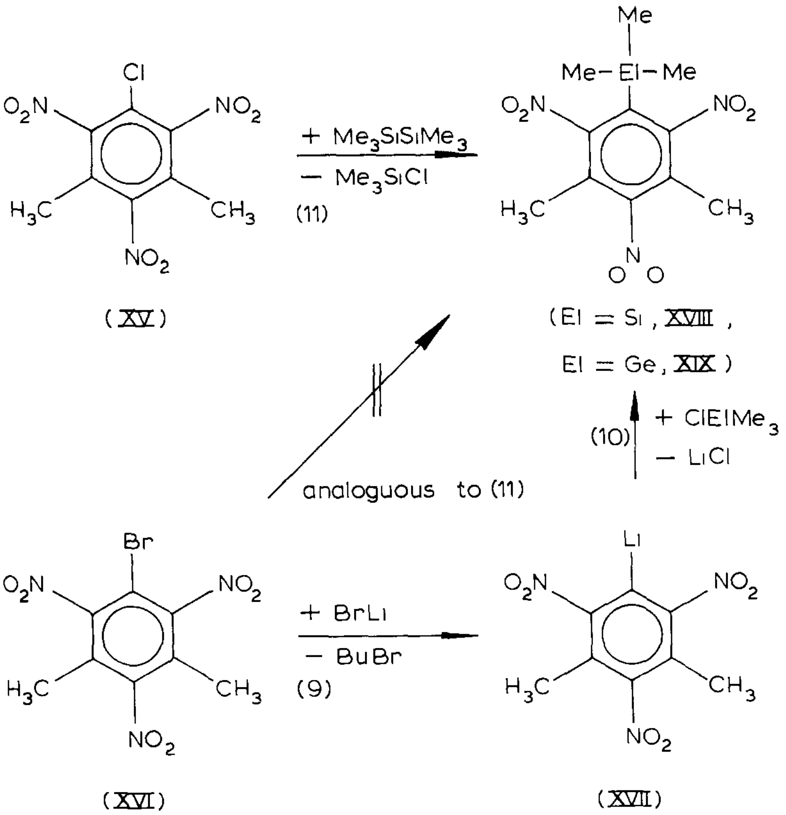
(VII)

(VIII)

(El = Si, X,
E = Ge, XI)

(El = Si, XIII,
El = Ge, XIV)

Dibromoacetophenone (VII) is the starting compound for the sila (XIII) and the germa analogue (XIV) of the artificial musk scent B. Conversion to the ketal VIII with ethanediol (reaction 6) and subsequent substitution of two bromine atoms by trimethylsilyl and trimethylgermyl groups, respectively, via



(XV)

(El = Si, XVIII,
El = Ge, XIX)

(XVI)

(XVII)

Grignard reaction 7, followed by hydrolysis (reaction 8) of the intermediate dioxolanes X and XI gave XIII and XIV in total yields of 60% and 85%, respectively.

In the case of the sila (XVIII) and germa analogues (XIX) of the musk scent C we first chose a reported preparation [9] where Cl atoms in aromatic compounds are substituted by application of hexamethyldisilane at 160°C in the presence of a catalyst. But the yield of XVIII in reaction 11 was very low and the compound was difficult to separate from byproducts. A different route starting from 6-bromo-2,4-dimethyl-1,3,5-trinitrobenzene (XVI) (which can be lithiated at temperatures below —100°C according to the preparation of similar organolithium compounds from nitrobenzenes in the literature [3] proved satisfactory. The 6-lithio-derivative XVII is stable for some time at very low temperatures and reacts with trimethylchlorosilane (or -germane) to give XVIII and XIX in total yields of 26 and 42%, respectively.

Properties. Proof of structure. Comment on smell

The compounds prepared here for the first time are colourless liquids (V, IX) or low melting (below 100°C), white solids. Only the analogues of the musk scent C, XVIII and XIX, are faint yellow, and they change colour in the same way as C under action of light.

The composition of the compounds is confirmed by elemental analysis, molar refractivities and their peaks in mass spectra. The proton NMR spectra are (chemical shifts and relative intensities) in accord with the different groups suggested for the molecular framework. Fragments and isotopic patterns in the mass spectra give additional proof of the structure.

Of greatest interest is here, of course, the question of the change of odour. In the case of the "xylene musk" C, the smell becomes more brilliant and perfumisticaly more valuable on sila substitution (XVIII) of the quarternary C atom, but the germa derivative XIX is weaker than C, but with a natural, brutish side tone. Contrary to the musk scents A and B, the sila and germa derivatives XII, XIII and XIV are odourless. The change of smell may be due to the change in the size of the molecules, especially by substitution of the bulky $C(CH_3)_3$ groups on the mostly flat aromatic systems by the still more voluminous $Si(CH_3)_3$ and $Ge(CH_3)_3$ groups. The greatest distance (Van der Waals radii) changes from 11.4 Å in the molecules of A and B to 12.1 Å in XIII (and XII) and 12.6 Å in XIV, corresponding to 6% and 10.5% enlargement, respectively. This is a low effect in correspondence to the wide range of different compounds with a musk scent. Therefore, a disturbance of the aromatic π system by the adjacent Si or Ge *d* orbitals or even the changed polarity in SiC and GeC bonds, compared with CC bonds, may be of some influence on the interaction of the molecules with receptor sites in cells of the olfactory sense. This is the more evident as the change in the largest distances of the molecules from C with 11.2 Å to XVIII and XIX with 11.7 Å and 12.0 Å (4.5% and 7% enlargement, respectively) is nearly the same as in the trio of analogues B/XIII/XIV whereas the effect on the sense of smell was quite different in both cases.

Experimental

Chemical shifts, δ, of proton NMR spectra are given in ppm relative to TMS (low-field); solvent and internal standard in parentheses. Mass spectra: all at 70 eV; most abundant mass units of isotopic patterns; * confirmed by transition ions (metastable peaks).

1,3-Dichloro-5-trimethylsilylbenzene (III)

According to eq. 1, 18.6 g (0.1 mol) 1,3,5-trichlorobenzene (I) in 30 ml THF are added dropwise to 2.43 g (0.1 mol) Mg in 21.6 g (0.2 mol) boiling trimethylchlorosilane/40 ml THF and refluxed (~5 h) until complete reaction of the magnesium. After removing the solvent, addition of ligroin (50/70°C), filtration of the Mg salts, concentration of the filtrate and fractional distillation of the residue (61—67°C/0.8 mmHg), 9.9 g (45%) of III are obtained. Lit. [4] b.p. 117—123°C/20 mmHg.

3,5-Bis(trimethylsilyl)chlorobenzene (V)

According to eq. 2, 9.8 g (0.09 mol) trimethylchlorosilane are added dropwise to the Grignard reagent prepared by 5 h refluxing of 1.09 g (0.045 mol) Mg and 9.8 g (0.045 mol) III. After 6 h reflux and a work-up similar to that used in reaction 1, a mixture of 2.4 g (24%) unreacted III and 2.6 g (25%) of V results. V is separated and purified by distillation (75°C/5.5 mmHg) through a split-tube column. Colourless liquid, b.p. 75°C/5.5 mmHg, n_D^{20} 1.5028, d_4^{20} 0.9506, molar refractivity: calcd./found MR_L (Lorentz/Lorenz) 79.0/79.9, MR_E (Eisenlohr) 390/386.

$C_{12}H_{21}ClSi_2$ (256.93). Calcd./Found: C, 56.1/55.9; H, 8.24/8.1; Si, 21.9/21.0; Cl, 13.8/13.5%. NMR: (CCl_4/CH_2Cl_2) δ 0.48 (s, 18, $SiCH_3$), 7.4 (s, 3, ArH). Mass spectrum: 256 (21) M^+, 241 (100)* [$M^+ - Me$], 73 (23)* [241 − C_8H_9ClSi], 45 (8)* [73 − C_2H_4].

3,5-Bis(trimethylsilyl)bromobenzene (VI)

According to eq. 3, a solution of 62.9 g (0.2 mol) 1,3,5-tribromobenzene (II) in 200 ml THF was added dropwise to 9.72 g (0.4 mol) magnesium and held at a temperature of 30—35°C. After stirring for 2 h at room temp., 43.4 g (0.4 mol) trimethylchlorosilane was added slowly, the mixture refluxed for 30 min and shaken with a saturated solution of NH_4Cl in water. The organic layer was separated, washed with NaCl (sat. solution in water), the solvent removed by vacuum rotary evaporation at room temp. and the residue distilled (Vigreux column) in vacuo. Yield: 17—24 g (28—40%) VI, b.p. 72—75°C at 4 mmHg. By recrystallization from 96% ethanol (2 times) small amounts of 1,3-dibromo-5-trimethylsilylbenzene (IV) could be removed. Melting point of the pure compound: 53—54°C.

$C_{12}H_{21}BrSi_2$ (301.38). Calcd./Found: C, 47.8/48.0; H, 7.0/7.0; Br, 26.5/26.4; Si, 18.6/18.6%. NMR: (CCl_4/TMS) δ 0.29 (s, 18, $SiCH_3$), 7.42 (t, 1, ArH), 7.49 (d, 2, ArH, $J = 1$ Hz). Mass spectrum: 302 (26) M^+, 287 (100)* [$M^+ - Me$], 73 (28)* [287 − C_8H_9BrSi], 45 (7)* [73 − C_2H_4].

2-(3,5-Dibromophenyl)-2-methyl-(1,3)-dioxolane (VIII)

According to eq. 6, 12.1 g (0.044 mol) 3,5-dibromoacetophenone (VII) [5], 2.7 g (0.044 mol) 1,2-ethanediol and 35 mg *p*-toluenesulfonic acid in 45 ml benzene are refluxed for 6 h in a water separator. The resulting mixture is neutralized by $NaHCO_3$ and washed with sat. NaCl solution. The organic layer is separated and dried with Na_2SO_4. After removal of the solvent and sublimation (80°C/0.01 mmHg) of the residue, 12.9 g (92%) of pure VIII are obtained. The white crystals of VIII melt at 74—75°C.

$C_{10}H_{10}Br_2O_2$ (322.01). Calcd./Found: C, 37.3/37.4; H, 3.13/3.3; Br, 49.6/ 49.5%. NMR: ($CDCl_3$/TMS) δ 1.52 (s, 3, CH_3CO), 3.84 (m, 4, CH_2CH_2), 7.5 (s, 3, ArH). Mass spectrum: 322 (11) M^+, 307 (100)* [$M^+ - $Me], 263 (30)* [307 $- C_2H_4O$], 235 (9)* [263 $-$ CO], 87 (52) [$M^+ - C_6H_3Br_2$], 43 (49)* [87 $- C_2H_4O$].

Bis(ethoxy)-3,5-bis(trimethylsilyl)phenyl-methane (IX)

According to eq. 4, 2 drops of methyl iodide are added to a stirred suspension of 0.40 g (0.0165 mol) Mg and 4.4 g (0.015 mol) VI in 6 ml THF. After completion of the reaction and 0.5 h of stirring at 20°C, 3.24 g (0.0165 mol) orthoformic diethylphenylester [6] are added dropwise. The mixture is stirred for another 0.5 h at 20°C. Shaking with sat. NH_4Cl solution, separation of the organic layer, washing (2 times) with 10% NaOH and with sat. NaCl solution, evaporation of the solvent and fractional distillation of the residue (Vigreux column, 84°C/0.05 mmHg) give 3.8 g (78%) IX.

Colourless liquid, b.p. 84°C/0.05 mmHg, n_D^{20} 1.4808, d_4^{20} 0.9146 [g/ml], calcd./ found MR_L 101.0/101.0, MR_E 487/481.

$C_{17}H_{32}O_2Si_2$ (324.62). Calcd./Found: C, 62.9/62.5; H, 9.94/10.07; Si, 17.3/ 17.5%. NMR: (CCl_4/TMS) δ 0.29 (s, 18, $SiCH_3$), 1.20 (t, 6, CCH_3, J = 7 Hz), 3.46 (q, 4, OCH_2), 5.37 (s, 1, HCO), 7.41 (s, 3, ArH). Mass spectrum: 324 (4) M^+, 309 (6) [$M^+ - $Me], 279 (93) [$M^+ - OC_2H_5$], 207 (29) ?, 73 (100) $SiMe_3^+$.

2-Methyl-(1,3)-dioxolanes: 2-[3,5-bis(trimethylsilyl)phenyl]- (X) and 2-[3,5-bis(trimethylgermyl)phenyl] - (XI)

According to eq. 7, a solution of 6.4 g (0.02 mol) VIII in 30 ml THF is added dropwise to a suspension of 1.07 g (0.044 mol) Mg and 6.5 g (0.06 mol) trimethylchlorosilane [or 7.7 g (0.05 mol) trimethylchlorogermane, respectively] at 40—50°C and stirred for 14 h at 20°C. The reaction mixture is treated with 20 ml ether, filtrated and removed from the solvent, the residue treated with 20 ml ligroin, filtrated, concentrated and finally sublimed (80°C/0.01 mmHg and 100°C/0.01 mmHg, respectively). X results in a yield of 4.0 g (65%), XI of 7.35 g (93%). The melting points are 48°C for X and 56°C for XI.

X: $C_{16}H_{28}O_2Si_2$ (308.57). Calcd./Found: C, 62.3/60.0; H, 9.15/9.20; Si, 18.2/18.8%. NMR: (CCl_4/CH_2Cl_2) δ 0.40 (s, 18, $SiCH_3$), 1.67 (s, 3, CH_3CO), 3.90 (m, 4, CH_2CH_2), 7.52 (s, 3, ArH). Mass spectrum: 308 (2.4) $M^{+\cdot}$, 293 (100)* [$M^+ - $Me], 249 (3.6)* [293 $- C_2H_4O$], 221 (1)* [249 $-$ CO], 73 (13) $SiMe_3^+$, 45 (4)* [73 $- C_2H_4$].

XI: $C_{16}H_{28}Ge_2O_2$ (397.58). Calcd./Found: C, 48.3/48.4; H, 7.10/7.15%. NMR: (CCl_4/CH_2Cl_2) δ 0.52 (s, 18, $GeCH_3$), 1.69 (s, 3, CH_3CO), 3.92 (m, 4, CH_2CH_2), 7.43 (t, 1, ArH), 7.48 (d, 2, ArH, J = 1 Hz). Mass spectrum: 398 (11)

M^+, 383 (100)* [M^+ − Me], 339 (18)* [383 − C_2H_4O], 119 (37) $GeMe_3^+$, 87 (48) [M^+ − $C_{12}H_{21}Ge_2$], 43 (22) [87 − C_2H_4O].

3,5-Bis(trimethylsilyl)benzaldehyde (XII), 3,5-bis(trimethylsilyl)acetophenone (XIII) and 3,5-bis(trimethylgermyl)acetophenone (XIV)

According to eqs. 5 and 8, 1 g of IX (or X or XI, respectively) is dissolved in 10 ml THF, treated with 1 ml 10% HCl and stirred for 2 h at 20°C. After removal of the solvent and the byproduct ethanol [or ethanediol respectively] at 20°C and 0.01 mmHg, the residue is crystallized from n-pentane. Yield: 95—98%. The missing small amounts of the compounds may be obtained from the mother liquor by renewed hydrolysis.

The melting points of the white, crystalline compounds are: XII 66°C, XIII 48°C and XIV 57°C.

XII: $C_{13}H_{22}OSi_2$ (250.49). Calcd./Found: C, 62.3/62.2; H, 8.85/8.98; Si, 22.4/22.5%. NMR: ($CDCl_3$/TMS) δ 0.33 (s, 18, $SiCH_3$), 7.80 (t, 1, ArH), 7.88 (d, 2, ArH, J = 1 Hz), 10.01 (s, 1, HCO). Mass spectrum: 250 (21) M^+, 235 (100)* [M^+ − Me], 221 (2.5) [M^+ − CHO], 73 (14) $SiMe_3^+$, 45 (4)* [73 − C_2H_4].

XIII: $C_{14}H_{24}OSi_2$ (264.52). Calcd./Found: C, 63.6/63.4; H, 9.15/9.23, Si, 21.2/21.5%. NMR: ($CDCl_3$/CH_2Cl_2) δ 0.40 (s, 18, $SiCH_3$), 2.68 (s, 3, CH_3CO), 7.87 (t, 1, ArH), 8.10 (d, 2, ArH, J = 1.2 Hz). Mass spectrum: 264 (18) M^+, 249 (100)* [M^+ − Me], 221 (2)* [249 − C_2H_4], 73 (20) $SiMe_3^+$, 45 (5)* [73 − C_2H_4].

XIV: $C_{14}H_{24}Ge_2O$ (353.53). Calcd./Found: C, 47.6/47.1; H, 6.84/6.76%. NMR: (CCl_4/TMS) δ 0.42 (s, 18, $GeCH_3$), 2.50 (s, 3, CH_3CO), 7.53 (t, 1, ArH), 7.80 (d, 2, ArH, J = 1.1 Hz). Mass: 354 (11) M^+, 339 (100)* [M^+ − Me], 309 (12)* [339 − C_2H_6], 119 (44) $GeMe_3^+$, 89 (19) $GeMe^+$.

2,4-Dimethyl-6-trimethylsilyl-1,3,5-trinitrobenzene (XVIII)

a) According to eqs. 9 and 10, 7.5 ml (0.012 mol) of a 15% solution of n-butyllithium in hexane are added dropwise during 15 min and at −105/−108°C to a solution of 3.2 g (0.01 mol) 6-bromo-2,4-dimethyl-1,3,5-trinitrobenzene [7] (XVI, purified by crystallization from 96% ethanol (2 times) and sublimation) in 120 ml THF (dried with $LiAlH_4$ and distilled directly into the reaction vessel) and stirred for 1 h. A black-red solution of XVII results, into which 1.41 g (0.013 mol) trimethylchlorosilane are now dropped. Stirring is continued for 2.5 h, the low temperature maintained during all the steps. The solution is then warmed slowly to room temp. during 15 h, the solvent removed at 0.01 mmHg, the residue treated with 50 ml ether, the organic layer washed with sat. NaCl solution, dried over Na_2SO_4 and finally distilled (removal of the solvent). After sublimation of the residue at 80°C/0.01 mmHg and crystallization from n-pentane XVIII results in 0.8 g (26%) yield.

b) According to eq. 11 1.1 g (0.004 mol) 6-chloro-2,4-dimethyl-1,3,5-trinitrobenzene (XV) [8], 1.2 g (0.08 mol) hexamethyldisilane and 50 mg tetrakis(triphenylphosphane)palladium(0) [10] are heated together with 10 ml toluene to 160°C in a sealed tube (20 ml) for 44 h. The tube is cooled with liquid nitrogen and opened in an N_2 atmosphere, the reaction mixture filtered and liberated from the solvent. After sublimation of the residue a mixture results which consists, according to NMR analysis, of 0.50 g (45%) XV, 0.2 g (20%) 2,4-dimethyl-1,3,5-trinitrobenzene (XX) and only 0.06 g (5%) XVIII.

A similar reaction with XVI instead of XV showed no Br/SiMe$_3$ exchange at all, XVI remained nearly unmodified, and only small amounts (<5%) of XX were observed.

The white crystals of XVIII melt at 89°C.

$C_{11}H_{15}N_3O_6Si$ (313.34). Calcd./Found: C, 42.2/42.1; H, 4.83/4.96; N, 13.4/13.1; Si, 8.96/8.91%. NMR: ($CDCl_3/CH_2Cl_2$) δ 0.32 (s, 9, $SiCH_3$), 2.23 (s, 6, CH_3Ar). Mass spectrum: 298 (100) [$M^+ - Me$], 281 (2.7)* [298 − OH], 252 (19)* [298 − NO_2].

2,4-Dimethyl-6-trimethylgermyl-1,3,5-trinitrobenzene (XIX)

Prepared according to eqs. 9 and 10 and similar to the preparation of XVIII (a) but with 2.3 g (0.015 mol) trimethylchlorogermane instead of trimethylchlorosilane. Yield: 1.5 g (42%). White crystals, m.p. 89°C.

$C_{11}H_{15}GeN_3O_6$ (357.85). Calcd./Found: C, 36.9/36.9; H, 4.23/4.24; N, 11.7/11.7%. NMR: (CCl_4/CH_2Cl_2) δ 0.55 (s, 9, $GeCH_3$), 2.30 (s, 6, CH_3Ar). Mass spectrum: 344 (100) [$M^+ - Me$], 327 (14)* [344 − OH], 298 (51)* [344 − NO_2], 89 (34) $GeMe^+$, 74 (36) Ge^+.

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