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Alkylgermasesquioxide Derivatives of *tert*-Butyl-diacylhydrazines

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ABSTRACT: N-tert-*Butyl*-N-*benzoylhydrazine was synthesized by a new method. Its condensation and the condensation of its* N,N′*-isomer with 3-(trichlorogermyl)propionyl chloride provided* N-tert-*butyl*-N′*-(3-trichlorogermyl)propionyl*-N-*benzoylhydrazine or its* N,N,N′*-isomer, respectively, in good yields. Subsequent hydrolysis of the trichlorogermyl compounds using saturated sodium carbonate yielded the corresponding germasesquioxide derivatives that have good solubility in organic solvents. The structures of these compounds were confirmed by* ^1H *NMR, IR, MS, and elemental analysis. The hydrolysis of organogermanium trichloride was studied, and the elimination of* $HGeCl_3$ *was observed when the basicity was too high (pH > 10).* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:293–297, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10174

INTRODUCTION

Recently, a new class of insect growth regulators, the *N-tert*-butyl-*N*,*N*′-diacylhydrazines, has been found to mimic the action of 20-hydroxyecdysone in activating the ecdysone receptor, leading to lethal premature molting [1–3]. Relationships between the structure and biological activity of the *N-tert*-butyl-*N*,*N*′-dibenzoylhydrazine larvicides have been extensively investigated. The results indicated that the molecular hydrophobicity is favorable [4–6]. In addition, germasesquioxide compounds have recently attracted considerable attention because of their unusual physical and chemical properties and marked biological activities [7–14]. It is conceivable that the incorporation of the two moieties into one structural unit might produce an unexpected effect on the biological activity. Therefore, we designed and synthesized the novel diacylhydrazines containing a germasesquioxide group.

RESULTS AND DISCUSSION

N-tert-Butyl-*N*-benzoylhydrazine (**3**) is an important intermediate in the synthesis of *N-tert*-butyl-*N*,*N*′-dibenzoylhydrazine derivatives and three synthesizing methods have been published: (1) *N-tert*-Butylhydrazine was reacted with di-*tert*-butyldicarbonate to afford *N-tert*-butyloxycarbonyl-*N*′*-tert*-butylhydrazine, and then condensation with benzoyl chloride and deprotection using hydrochloric acid yielded **3** in 38% yield [15]; (2) *N-tert*-Butylhydrazine was reacted with *N*-(9-fluorenylmethylcarbonyl)succinimide to afford *N-tert*-butyl-*N*′-(9-fluorenylmethylcarbonyl)hydrazine, and then acylation and deprotection using piperidine provided **3** [16]; (3) *N-tert*-Butyl-*N*′-acetonehydrazone was condensed with benzoyl chloride, and then deprotection using hydrochloric acid afforded **3** [17]. However, all of these methods have some problems. In the methods (1) and (3), the yields are low (<50%). Method (2) is

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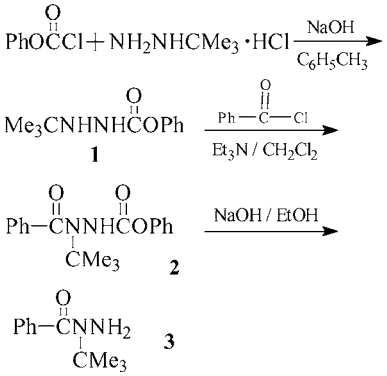
not economical, because the expensive *N*-(9-fluorenylmethylcarbonyl)succinimide is used. Herein we report the synthesis of **3** by a novel procedure.

Phenyl chloroformate was treated with *tert*-butylhydrazine hydrochloride to obtain *N-tert*-butyl-*N′*-phenoxycarbonylhydrazine (**1**), and subsequent acylation with benzoyl chloride yielded *N-tert*-butyl-*N′*-phenoxycarbonyl-*N*-benzoylhydrazine (**2**). Deprotection using sodium hydroxide provided **3**, as shown in Scheme 1. This method has a number of advantages: The reaction is carried out under mild conditions, starting materials are easily prepared, and the experimental procedure is very simple. Because of its simplicity and high efficiency, this method has already been applied to the preparation of *N-tert*-butyl-*N*-benzoylhydrazines in our laboratory.

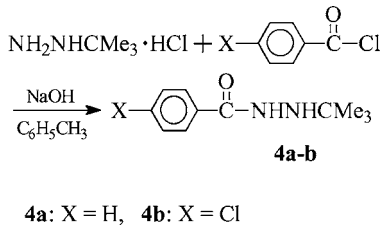
Benzoyl and 4-chlorobenzoyl chloride were condensed with *tert*-butylhydrazine hydrochloride to give *N′-tert*-butyl-*N*-benzoylhydrazines (**4**) in good yields, as shown in Scheme 2.

3-Phenyl-3-(trichlorogermyl)propionyl chloride (**5**) was condensed with **3** to give *N-tert*-butyl-*N′*-(3-phenyl-3-trichlorogermyl)propionyl-*N*-benzoylhydrazine (**6a**) in 82% yield. Subsequent hydrolysis of the trichlorogermyl compound **6a** using saturated sodium carbonate yielded the corresponding germasesquioxide derivative **7a**, as shown in Scheme 3. The compounds **6b–c** and **7b–c** were similarly prepared (Scheme 4).

We found that the hydrolysis of trichlorogermyl derivatives (**6a–c**) must be carried out with saturated sodium carbonate. When the acidity is too high (pH < 7), the hydrolysis of organogermanium trichlorides is incomplete; when the basicity is too high (pH > 10), $HGeCl_3$ can eliminate and a by-product **8** is formed, as shown in Scheme 5. This elimination of $HGeCl_3$from trichlorogermyl derivatives was observed for the first time. Moreover, the pH value of the solution may affect the degree



SCHEME 1



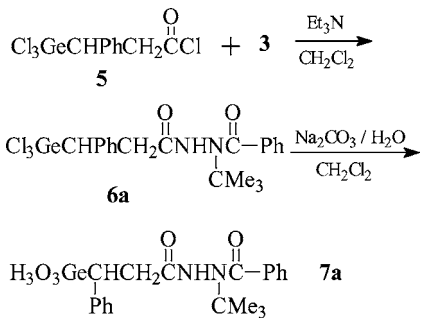
SCHEME 2

of condensation and solubility of germasesquioxide resulting from the hydrolysis of the organogermanium trichlorides. When the pH value of the solution is large, the condensation is small and solubility of germasesquioxide is acceptable. We found that the hydrolysis of trichlorogermyl derivatives (**6a–c**) was carried out with saturated sodium carbonate to give germasesquioxides **7a–c**. ^{1}H NMR, IR, and elemental analysis data supported the structure of the compound **7**. All germasesquioxides **7a–c** melt below 300°C. The IR spectra (KBr) of **7a–c** have a strong absorption (800–900 cm^{-1}), characteristic of germanium–oxygen bonds [18,19]. A strong and broad absorption (3100–3500 cm^{-1}) attributable to Ge—OH species is noted. In ^{1}H NMR spectra of **7a–c**, the proton of group GeOH gives rise to a signal in the range of δ 1.5–4.0 ppm [20,21].

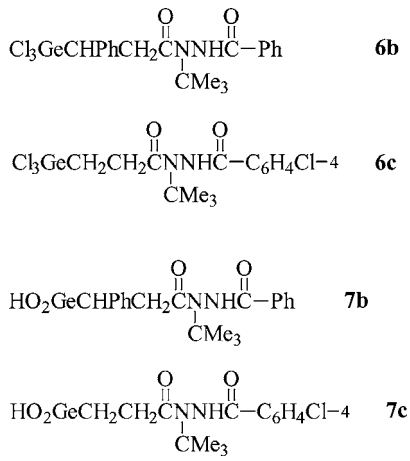
In conclusion, a new method for the synthesis of *N-tert*-butyl-*N*-benzoylhydrazine enjoys a number of advantages. Hydrolysis of organogermanium trichlorides using saturated sodium carbonate yield germasesquioxides that have good solubility in organic solvents. The hydrolysis of organogermanium trichloride was studied. Elimination of $HGeCl_3$ from trichlorogermyl derivatives was observed for the first time when the basicity was too high (pH > 10).

EXPERIMENTAL

Proton NMR spectra were obtained at 200 MHz using a Bruker AC-P 200 spectrometer. Chemical shifts



SCHEME 3

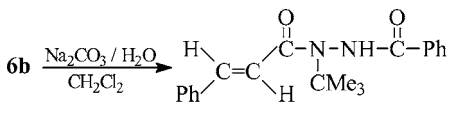


SCHEME 4

(δ) are given in ppm. Infrared spectra were recorded on a Shimadzu-435 spectrometer. Elemental analyses were determined on an MT-3 elemental analyzer. Melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. Mass spectra were recorded with HP 5988A spectrometer using the EI method.

N-tert-*Butyl*-N′-*phenoxycarbonylhydrazine* (**1**)

To a mechanically stirred suspension of *tert*-butylhydrazine hydrochloride (0.092 mol) in toluene (100 ml) was added dropwise a solution of 10% aqueous sodium hydroxide (0.092 mol) at room temperature. After 15 min, the reaction mixture was cooled to −15°C, and solutions of phenyl chloroformate (0.088 mol) in toluene (30 ml) and 10% aqueous sodium hydroxide (0.088 mol) were added dropwise and simultaneously from separate addition funnels, while maintaining the temperature below −10°C. Following the addition, the reaction mixture was warmed to room temperature and stirred for 2 h. The water phase was extracted three times with 100 ml of chloroform. The extraction solvent was combined with the organic phase, and dried with anhydrous magnesium sulfate and filtered. The solvent was removed by distillation to give a white solid. The solid was then recrystallized from isopropanol and petroleum ether to obtain a colorless crystalline solid in 71% yield, mp 106–108°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.12 (s, 9H, Bu^t), 5.14 (br, 2H, NHNH), 7.08–7.56 (m, 5H, Ph).



SCHEME 5

N-tert-*Butyl*-N′-*phenoxycarbonyl*-N-*benzoylhydrazine* (**2**)

A solution of benzoyl chloride (0.054 mol) in methylene dichloride (15 ml) was added dropwise to a solution of **1** (0.054 mol) and triethylamine (0.065 mol) in methylene dichloride (40 ml) under magnetic stirring at 0°C. The resulting mixture was then stirred at room temperature for 2 h. The solid was filtered off and the filtrate was washed successively with 2% aqueous hydrochloric acid and 10% aqueous sodium bicarbonate, and dried with anhydrous magnesium sulfate and filtered. The solvent was removed by distillation to give a white solid. The solid was then recrystallized from ethanol to obtain a colorless crystalline solid in 81% yield, mp 141–143°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.40 (s, 9H, Bu^t), 6.74–7.32 (m, 10H, Ph).

N-tert-*Butyl*-N-*benzoylhydrazine* (**3**)

Compound **2** (8.00 mmol) was dissolved in lukewarm ethanol (40 ml). While the reaction mixture was stirred, a 15% aqueous solution of sodium hydroxide (50 ml) was added. Following the addition, the mixture was stirred at 60°C for 1 h. It was then cooled and extracted three times with 100 ml of chloroform. The extraction solvent was dried with anhydrous magnesium sulfate and filtered. The solvent was removed by distillation to give a white solid. The solid was then recrystallized from isopropanol and petroleum ether to obtain a colorless crystalline solid in 76% yield, mp 127–129°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.48 (s, 9H, Bu^t), 3.90 (s, 2H, NH_2), 7.28–7.56 (m, 5H, Ph). IR (KBr): 3276.0 (NH_2), 1620.5 (C=O), 1573.1, 1529.5, 1508.8 (Ph), 1375.6, 1350.0 (Bu^t), 719.6, 696.7 (Ph) cm^{-1}.

N′-tert-*Butyl*-N-*substituted Benzoylhydrazines* (**4**)

N′-tert-Butyl-*N*-benzoylhydrazine (**4a**) was prepared similar to **1**. Yield: 91%, mp 92–94°C (Ref. [22], Yield: 54%, mp 92–94°C)

N′-tert-Butyl-*N*-(4-chlorobenzoyl)hydrazine (**4b**) was prepared similar to **4a**. Yield: 98%, mp 118–120°C (Ref. [22], mp 116–122°C).

3-Phenyl-3-(trichlorogermanyl)propionyl Chloride (**5**)

3-Phenyl-3-(trichlorogermanyl)propionyl chloride (**5**) was prepared according to the reported

procedure [23–25]. Yield: 86%, bp 124–126°C/0.3 mmHg (Ref. [23–25], Yield: 83%, bp 118–119°C/0.2 mmHg).

3-(Trichlorogermanyl)propionyl chloride was prepared similar to **5**. Yield: 93%, bp 90–91°C/4 mmHg (Ref. [23–25], Yield: 89%, bp 109°C/10 mmHg).

Compound **6a**

A mixture of *N-tert*-butyl-*N*-benzoylhydrazine (**3**) (2.5 mmol), triethylamine (3.0 mmol), and methylene dichloride (20 ml) was stirred in an ice-salt bath, and then a solution of **5** (2.5 mmol) in 10 ml of methylene dichloride was added dropwise at 0°C. After the solution had been stirred at 0°C for 1 h and then at ambient temperature for 10 h, the solid was filtered off and the filtrate was washed with hydrochloric acid. The washed solution was dried with anhydrous magnesium sulfate and filtered. The solvent was removed by distillation to give a white solid. The solid was then recrystallized from methylene dichloride and petroleum ether to obtain a colorless crystalline solid **6a**. Yield: 82%, mp 201–203°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.48 (s, 9H, Bu^t), 2.04 (m, 2H, $CH_2C{=}O$), 3.50 (m, 1H, CHGe), 7.00–7.68 (m, 10H, Ph), 6.56 (br, 1H, NH). IR (KBr): 3180.0, 1660.0, 1628.7, 1396.6, 1363.7, 750.2, 692.4, 656.3, 523.2 cm^{-1}. Anal. Calcd for $C_{20}H_{23}Cl_3GeN_2O_2$: C, 47.81; H, 4.61, N, 5.57. Found C, 47.83, H, 4.61, N, 5.84.

6b and **6c** were prepared similar to **6a**.

Compound **6b**

Yield: 83%, mp 160–162°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.57 (s, 9H, Bu^t), 3.16 (d, 2H, $^3J_{HH}$ = 6.2 Hz, $CH_2C{=}O$), 3.66 (m, 1H, CHGe), 7.12–7.78 (m, 10H, Ph), 8.12 (br, 1H, NH). IR (KBr): 3140.0, 1656.0, 1607.0, 1394.4, 1364.3, 763.2, 695.9, 649.4, 517.6 cm^{-1}. Anal. Calcd for $C_{20}H_{23}Cl_3GeN_2O_2$: C, 47.81, H, 4.61, N, 5.57. Found: C, 47.92; H, 4.90; N, 5.53. EIMS *m/z* (%): 502.25 (M^+, 1), 192.40 (100), 177.30 (39), 136.30 (57), 131.30 (14).

Compound **6c**

Yield: 79%, mp 204–205°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.50 (s, 9H, Bu^t), 2.18 (m, 1H, CH_2Ge), 2.82 (m, 2H, $CH_2C{=}O$), 7.49, 7.73 (dd, 4H, $^3J_{HH}$ = 8.50 Hz, Ph), 7.89 (br, 1H, NH). IR (KBr): 3229.5, 1658.0, 1602.2, 1396.7, 1367.5, 841.9, 671.8, 527.9 cm^{-1}. Anal. Calcd. for $C_{14}H_{18}Cl_4GeN_2O_2$: C, 36.49; H, 3.93; N, 6.08. Found: C, 36.38; H, 3.63; N, 5.99.

Compound **7a**

To a solution of the compound **6a** (2.5 mmol) in methylene dichloride (10 ml), a saturated solution of sodium carbonate was added with vigorous stirring. After the addition, the resulting mixture was stirred at room temperature for 12 h. The water phase was extracted three times with 20 ml of methylene dichloride. The extraction solvent was combined with the organic phase. The solvent was removed by distillation to give a white solid. The solid was then washed successively with distilled water and ether. Finally, a white powder **7a** was obtained. Yield: 90%, mp 212–214°C. ^{1}H NMR (CF_3CO_2D, 200 MHz) δ: 1.38 (s, 9H, Bu^t), 2.06 (m, 2H, $CH_2C{=}O$), 3.36 (m, 1H, CHGe), 3.60 (br, 1H, GeOH), 6.80–7.68 (m, 10H, Ph). IR (KBr): 3404.0, 1685.5, 1634.5, 1381.4, 1364.0, 875.0, 757.9, 694.5, 658.2, 585.9 cm^{-1}. Anal. Calcd for $C_{20}H_{26}GeN_2O_5$: C, 53.70; H, 5.86; N, 6.27. Found: C, 53.86; H, 5.49; N, 6.54.

7b and **7c** were prepared similar to **7a**.

Compound **7b**

Yield: 90%, mp 180–192°C. ^{1}H NMR (CF_3CO_2D, 200 MHz) δ: 1.46 (s, 9H, ^{t}Bu), 2.12 (m, 2H, CH_2CO), 3.12 (br, 1H, GeOH), 3.76 (m, 1H, CHGe), 7.04–7.86 (m, 10H, Ph). IR (KBr): 3393.0, 3053.5, 2916.0, 1665.4, 1608.7, 1579.8, 1518.2, 1481.4, 1450.8, 1389.3, 1362.3, 1272.7, 1235.4, 1210.4, 1185.0, 1069.1, 1023.0, 867.6, 804.3, 772.0, 692.6, 646.7, 459.3 cm^{-1}. Anal. Calcd for $C_{20}H_{24}GeN_2O_4$: C, 55.99; H, 5.63; N, 6.52. Found: C, 56.07; H, 6.00; N, 6.43.

Compound **7c**

Yield: 88%, mp 252–300°C. ^{1}H NMR (CF_3CO_2D, 200 MHz) δ: 1.42 (s, 9H, Bu^t), 2.10 (m, 2H, CH_2Ge), 3.00 (m, 3H, $CH_2C{=}O$, GeOH), 7.42, 7.66 (dd, 4H, $^3J_{HH}$ = 8.00 Hz, Ph). IR (KBr): 3400.0, 1658.7, 1594.4, 1384.0, 1363.4, 862.8, 842.0, 692.7, 522.3 cm^{-1}. Anal. Calcd for $C_{14}H_{19}ClGeN_2O_4$: C, 43.41; H, 4.94; N, 7.23. Found: C, 42.99; H, 4.97; N, 7.13.

Compound **8**

A colorless crystalline solid, mp 186–188°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.50 (s, 9H, Bu^t), 6.78 (d, 1H, $^3J_{HH}$ = 15.6 Hz, C=CH), 7.52 (d, 1H, $^3J_{HH}$ = 15.6 Hz, C=CH), 7.21–7.86 (m, 10H, Ph), 9.14 (br, 1H, NH). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.60; H, 6.48; N, 8.39. IR (KBr): 3219 (NH), 3072 (C–H), 1683 (C=0), 1664 (C=C), 1633

(C=O), 1388 and 1360 (CMe_3), 971 (trans HC=CH), 662 (NH).

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