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Synthesis and biological activity of novel *N-tert*-butyl-*N,N′*-substitutedbenzoylhydrazines containing 2-methyl-3-(triphenylgermanyl)propoxycarbonyl

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In a search for new insect growth regulators with unusual biological properties and different activity spectrum, we thought that the preservation of the bioactive unit and the introduction of 2-methyl-3-(triphenylgermanyl)propoxycarbonyl in *N-tert*-butyl-*N,N′*-dibenzoylhydrazine would enhance their larvicidal activities to a significant degree. Therefore, we designed and synthesized *N′-tert*-butyl-*N′*-[2-methyl-3-(triphenylgermanyl)propoxycarbonyl]-*N*-benzoylhydrazine and analogs by two procedures. These novel compounds were characterized by elemental analyses, IR, and ^{1}H NMR. At the same time, *N-tert*-butyl-*N*-substitutedbenzoylhydrazines were prepared by a new method, and some reactions involved were studied. The preliminary results indicate that some compounds have inhibitory effects against plant pathogenetic bacteria such as early blight of tomato.

KEYWORDS: *N-tert*-butyl-*N,N′*-dibenzoylhydrazine; insect growth regulators; 2-methyl-3-(triphenylgermanyl)propoxycarbonyl; *N-tert*-butyl-*N*-substitutedbenzoylhydrazines; fungicidal activities

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 to activate the ecdysone receptor, leading to lethal premature molting.[1,2] 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 and that *N-tert*-butyl-*N*-benzoylhydrazine is the biologically active unit.[3,4] In addition, both the *β*-triphenylgermanyl propanoic acid and its derivatives often possess unexpected biological activity.[5–8] What is more, the introduction of the 2-methyl-3-(triphenylgermanyl)propoxycarbonyl group into the bioactive compound may be expected to induce great changes in molecular properties, such as solubility and hydrophobicity. Hence, in a search for new insect growth regulators with unusual biological properties and a different activity spectrum, we considered that the preservation of the bioactive unit and the introduction of 2-methyl-3-(triphenylgermanyl)propoxycarbonyl in *N-tert*-butyl-*N,N′*-dibenzoylhydrazine would enhance their larvicidal activities to a significant degree. Therefore, we designed and synthesized the novel title compounds **8**, **11**, and **12**.

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EXPERIMENTAL

General

All the melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded with a Shimadzu-435 spectrometer. ^{1}H NMR and ^{31}P NMR spectra were recorded with a Bruker ACP200 instrument, with tetramethylsilane and 85% H_3PO_4 being used as the internal and external standards respectively. Elemental analyses were carried out with a Yanaco CHN Corder MT-3 elemental analyzer. Mass spectra were recorded with an HP5988A spectrometer using the electron impact method.

Synthesis

N′-tert-Butyl-*N*-benzoylhydrazine (**4**) was obtained according to reported procedures.[9–12] 2-Methyl-3-(triphenylgermyl)propanoic acid (**1**) was synthesized by the reaction of 2-methyl-3-(trichlorogermyl)propanoic acid with phenylmagnesium bromide in molar ratio 1:4; yield: 70.5%; m.p.: 150–152 °C.

*Methyl 2-methyl-3-(triphenylgermyl)propanoate (**2**)*

2-Methyl-3-(triphenylgermyl)propanoic acid (0.023 mol) was added to anhydrous methanol (50 ml), then the resulting mixture was refluxed for 2 h. The solvent was evaporated to give a yellow solid. The solid was then recrystallized from methylene dichloride and petroleum ether (60–90 °C) to yield a white crystalline solid in 75.0% yield; m.p.: 81–83 °C.

*2-Methyl-3-(triphenylgermyl)propanol (**3**)*

Methyl 2-methyl-3-(triphenylgermyl)propanoate (0.015 mol) in anhydrous tetrahydrofuran (20 ml) was added in small portions to a mixture of lithium aluminum hydride (0.03 mol) and anhydrous tetrahydrofuran (30 ml) at room temperature under nitrogen. After the addition, the reaction mixture was refluxed for 2 h, and then cooled. 5% aqueous sodium hydroxide and ether were added. The organic layer was separated, washed with water and dried with anhydrous sodium sulfate. The solvent was evaporated to give a white solid. The solid was then recrystallized from petroleum ether (60–90 °C) to obtained a colorless crystal in 53.3% yield; m.p.: 112–114 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 0.90 (d, 3H, $^3J_{HH}$ = 6.5 Hz, Me), 1.35–2.04 (m, 4H, $GeCH_2CH$, OH), 3.38–3.43 (m, 2H, CH_2O), 7.43–7.51 (m, 15H, Ph).

Compound **5**

A solution of isophthaloyl dichloride (16.45 mmol) in methylene dichloride (10 ml) was added dropwise to a solution of *N′-tert*-butyl-*N*-benzoylhydrazine (32.90 mmol) and triethylamine (39.48 mmol) in methylene dichloride (40 ml) under magnetic stirring at 0 °C. After the addition, the reaction mixture was stirred at room temperature for 8 h, and washed successively with 2% aqueous hydrochloric acid, distilled water, 5% aqueous sodium bicarbonate and distilled water. The washed solution was dried with anhydrous sodium sulfate and filtered, and the solvent was removed by distillation to give a white solid. The solid was then recrystallized from acetic acid to obtain a colorless crystalline solid in 80.4% yield; m.p.: 178–179 °C. ^{1}H NMR (200 MHz, DMSO): 1.47 (s, 18H, ^{t}Bu), 7.11–7.67 (m, 14H, Ph), 10.67 (s, 1H, NH), 10.69 (s, 1H, NH). Anal. Found: C, 69.53; H, 6.72; N, 10.73. Calc. for $C_{30}H_{34}N_4O_4$: C, 70.02; H, 6.66; N, 10.89%. IR (KBr, cm^{-1}): 3264 (NH), 1678 (CONH), 1636 (CON^tBu), 1390 and 1366 (^{t}Bu), 655 (NH).

N′-tert-*Butyl*-N′-*(3-carboxybenzoyl)*-N-*benzoylhydrazine (**6**)*

Compound **5** (5.76 mmol) was dissolved in lukewarm ethyl acetate (40 ml). While the reaction mixture was stirred, a 5% aqueous solution of sodium hydroxide (120 ml) was added. Following the addition, the mixture was stirred at 30 °C for 30 min, then cooled, and acidified with dilute hydrochloric acid to give a white solid. The solid was collected by suction-filtration and washed with water. The material was then air-dried, then crystallized from acetic acid and water to afford a colorless crystalline solid in 61.5% yield; m.p.: 251–253 °C. ^{1}H NMR (200 MHz, DMSO): 1.49 (s, 9H, ^{t}Bu), 7.35–8.03 (m, 9H, Ph), 10.75 (s, 1H, CO_2H). Anal. Found: C, 66.71; H, 5.74; N, 7.92. Calc. for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23%. IR (KBr, cm^{-1}): 3178 (NH, OH), 1725 (CO_2H), 1669 (CONH), 1626 (CON^tBu), 1392 and 1362 (^{t}Bu), 1232 (C—O).

N′-tert-*Butyl*-N′-*[3-[2-methyl-3-(triphenylgermanyl)propoxycarbonyl]benzoyl]*-N-*benzoylhydrazine (**8**)*

Method I (see Scheme 4). To the stirred solution of *N′-tert*-butyl-*N′*-(3-carboxybenzoyl)-*N*-benzoylhydrazine (**6**) (0.47 mmol) in methylene dichloride (5 ml), distilled thionyl chloride (0.47 mmol) and dimethylformamide (one drop) was added. Then the resulting mixture was stirred at room temperature for 24 h, and evaporated *in vacuo* to dryness. The residue was dissolved in methylene dichloride (5 ml) and added to the stirred solution of 2-methyl-3-(triphenylgermyl)propanol (**3**) (0.47 mmol) and distilled triethylamine (0.99 mmol) in methylene dichloride (10 ml) at 0 °C. After the addition, the reaction mixture was stirred at room temperature for 8 h. The solvent was removed by distillation to give a white solid. The solid was purified by column chromatography on a silica gel using a mixture of petroleum ether (60–90 °C) and ethyl acetate as the eluent. Finally, a white powder was obtained in 63.6% yield; m.p.: 148–149 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 0.84 (d, 3H, $^3J_{HH}$ = 6.3 Hz, Me), 1.25 (m, 2H, $GeCH_2$), 1.60 (s, 9H, ^{t}Bu), 1.86 (m, 1H, CH), 3.83 (m, 2H, CH_2O), 5.28 (s, 1H, NH), 7.24–8.06 (m, 24H, Ph). Anal. Found: C, 70.17; H, 6.09; N, 4.03. Calc. for $C_{41}H_{42}GeN_2O_4$: C, 70.42; H, 6.05; N, 4.01%. IR (KBr, cm^{-1}): 3218 (NH), 1718 (CO_2), 1677 (CONH), 1629 (CON^tBu), 1381 and 1358 (^{t}Bu), 1227 (C—O), 582 (Ge—CH_2).

Method II (see Scheme 6). To the stirred solution of isophthaloyl dichloride (0.597 mmol) in methylene dichloride (15 ml), a solution of 2-methyl-3-(triphenylgermyl)propanol (**3**) (0.299 mmol) and distilled triethylamine (0.299 mmol) in methylene dichloride was added dropwise at room temperature. After the addition was completed, stirring was continued for 1 h at room temperature. Then, to the resulting mixture, a solution of *N′-tert*-butyl-*N*-benzoylhydrazine (0.299 mmol) and distilled triethylamine (0.299 mmol) in methylene dichloride (10 ml) was added dropwise. The mixture was stirred at room temperature for 8 h, and washed with dilute hydrochloric acid and water, then dried with anhydrous sodium sulfate and filtered. The solvent was removed by distillation to give a white solid. The solid was purified by column chromatography on silica gel

using a mixture of petroleum ether (60–90 °C) and ethyl acetate as the eluent. Finally, a white powder was obtained in 82.1% yield. Spectra end elemental analysis were as for Method I.

Compounds **11** and **12** were prepared similarly.

N′-tert-Butyl-*N′*-[2-[2-methyl-3-(triphenylgermanyl)propoxycarbonyl]benzoyl]-*N*-benzoylhydrazine (**11**); yield: 83.8%; m.p.: 165–166 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 0.94 (d, 3H, $^3J_{HH}$ = 6.3 Hz, Me), 1.58 (s, 9H, ^{t}Bu), 1.74 (m, 2H, $GeCH_2$), 2.26 (m, 1H, CH), 4.12 (m, 2H, OCH_2), 7.24–7.74 (m, 24H, Ph), 8.31 (d, 1H, NH). Anal. Found: C, 70.35; H, 6.08; N, 4.08. Calc. for $C_{41}H_{42}GeN_2O_4$: C, 70.42; H, 6.05; N, 4.01%. IR (KBr, cm^{-1}): 3240 (NH), 1723 (CO_2), 1667 (CONH), 1641 (CON^{t}Bu), 1392 and 1363 (^{t}Bu), 1231 (C—O), 589 (Ge—CH_2).

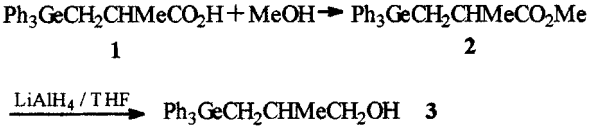
N′-tert-Butyl-*N′*-[4-[2-methyl-3-(triphenylgermanyl)propoxycarbonyl]benzoyl]-*N*-benzoylhydrazine (**12**); yield: 71.1%; m.p.: 90–92 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 0.91 (d, 3H, $^3J_{HH}$ = 6.3 Hz, Me), 1.59 (s, 9H, ^{t}Bu), 1.80 (m, 2H, $GeCH_2$), 2.24 (m, 1H, CH), 4.05 (m, 2H, OCH_2), 7.16–7.81 (m, 24H, Ph), 8.57 (br, 1H, NH). Anal. Found: C, 70.50; H, 6.36; N, 4.30. Calc. for $C_{41}H_{42}GeN_2O_4$: C, 70.42; H, 6.05; N, 4.01%. IR (KBr, cm^{-1}): 3260 (NH), 1717 (CO_2), 1671 (CONH), 1634 (CON^{t}Bu), 1391 and 1364 (^{t}Bu), 1226 (C—O), 597 (Ge—CH_2).

Compound **9**

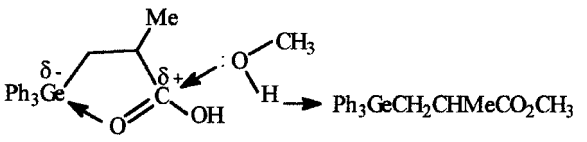
To the stirred and cooled (0 °C) solution of *N′-tert*-butyl-*N*-benzoylhydrazine (1.40 mmol) and dicyclohexylcarbodiimide (DCC; 2.10 mmol) in anhydrous tetrahydrofuran (15 ml) was added dropwise a solution of compound **6** (1.40 mmol) in anhydrous tetrahydrofuran (10 ml). After the addition, the mixture was stirred for 9 h at room temperature. Then, a few drops of glacial acetic were added to destroy any unreacted DCC and the mixture was filtered. The filtrate was evaporated *in vacuo*; the residue was purified by chromatography on a silica gel. Elution with ethyl acetate and petroleum ether (60–90 °C) gave compound **9** in 73.7% yield. ^{1}H NMR (200 MHz, $CDCl_3$): 1.59 (s, 9H, ^{t}Bu), 1.00–2.08 (m, 20H, $(CH_2)_5$), 3.80 (m, 2H, NCH), 6.24 (br, 1H, NH), 7.18–7.86 (m, 9H, Ph), 8.88 (br, 1H, NHC=O). Anal. Found: C, 69.99; H, 7.39; N, 9.89. Calc. for $C_{32}H_{42}N_4O_4$: C, 70.30; H, 7.74; N, 10.25%. IR (KBr, cm^{-1}): 3210 (NH), 1720 (OC=O), 1675 (NHC=O), 1632 (N^{t}BuC=O, C=N).

RESULTS AND DISCUSSION

2-Methyl-3-(triphenylgermyl)propanoic acid (**1**) was synthesized by the reaction of 2-methyl-3-(trichlorogermyl)propanoic acid with phenylmagnesium bromide at molar ratio 1:4. Esterification of 2-methyl-3-(triphenylgermyl)propanoic acid with methanol seemed especially easy. When **1** was dissolved in lukewarm methanol, methyl 2-methyl-3-(triphenylgermyl)propanoic (**2**) formed immediately. The resultant ester can be reduced by $LiAlH_4$ to yield 2-methyl-3-(triphenylgermyl)propanol (**3**) as shown in Scheme 1.



Scheme 1.



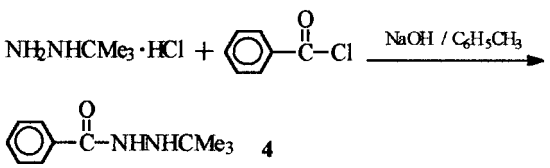
Scheme 2.

Because there are empty d-orbitals in the outer sphere of the germanium atom, the oxygen atoms of the carboxylic group can coordinate with the germanium atom to form the pentacoordinated germanium-centered complex illustrated in Scheme 2. Electrons of the oxygen atom can partly transfer to the empty d-orbital of the germanium atom; thus, the carbon atom in the carboxylic group becomes more electrophilic and can be more easily attacked by nucleophilic reagents, such as methanol. Here, the triphenylgermyl group acts as an intramolecular Lewis acid catalyst.

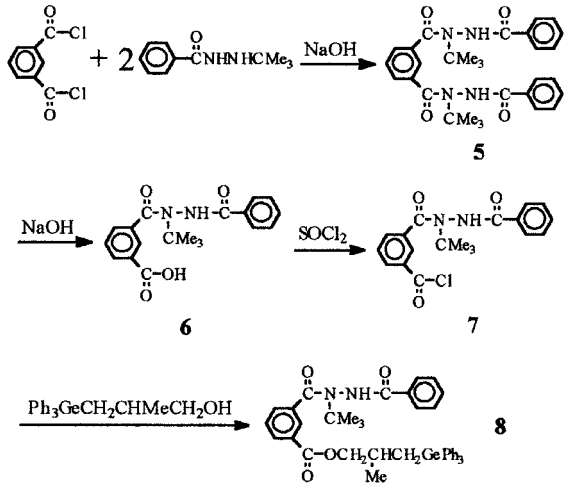
Benzoylchloride was condensed with *tert*-butylhydrazine hydrochloride to give *N′-tert*-butyl-*N*-benzoylhydrazine (**4**) as shown in Scheme 3.

Isophthaloyl dichloride was condensed with *N′-tert*-butyl-*N*-benzoylhydrazine to give compound **5** in 80.4% yield. Selective hydrolysis of compound **5** using sodium hydroxide provided compound **6** in 61.5% yield. This novel hydrolysis was observed for the first time. Compound **6** was reacted with thionyl chloride to give the corresponding acyl chloride **7** without purification; subsequent condensation with 2-methyl-3-(triphenylgermyl)propanol (**3**) in the presence of triethylamine yielded *N′-tert*-butyl-*N′*-[2-methyl-3-(triphenylgermanyl)propoxycarbonyl]benzoyl-*N*-benzoylhydrazine (**8**) as shown in Scheme 4.

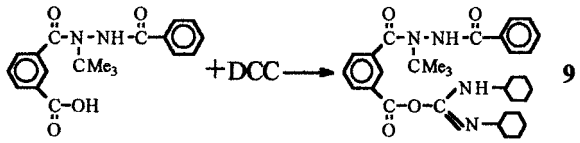
Our attempts to prepare compound **8** directly from compound **6** and *N′-tert*-butyl-*N*-benzoylhydrazine using DCC as dehydrating agent were unsuccessful. However, we obtained compound **9** in 73.7% yield as shown in Scheme 5. It is interesting to note that compound **9** cannot react with compound **3** in dioxane at reflux temperature. We believe that the oxygen atoms of **3** can coordinate with the germanium atom to result in less electron density in the



Scheme 3.



Scheme 4.

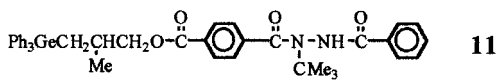


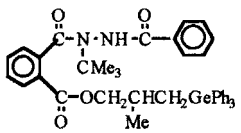
Scheme 5.

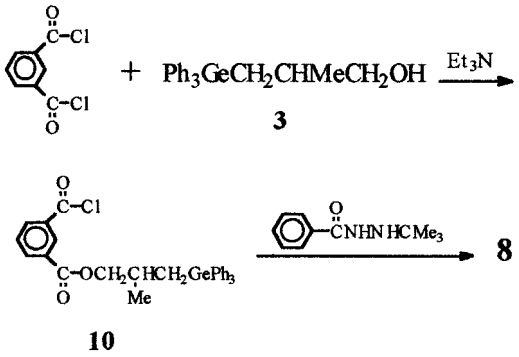
oxygen atoms and a more difficult reaction of **3** with compound **9**.

Compound **8** was synthesized according to another procedure, as shown in Scheme 6. Isophthaloyl dichloride was reacted with equimolar 2-methyl-3-(triphenylgermyl)-propanol (**3**) to give the intermediate **10**, and further condensation with *N′-tert*-butyl-*N*-benzoylhydrazine provided compound **8** in 82.1% yield.

Compounds **11** and **12** were prepared similarly.







Scheme 6.

BIOLOGICAL ACTIVITY

The preliminary biological tests showed that the insectcidal activities of the products are low. However, we found that some of the compounds exhibit significant fungicidal activities. For example, at 500 ppm, the inhibitory rate of compound **8** to EBT (early blight of tomato) is 33.3%. Further investigation on the biological activity of the products is in progress.

Acknowledgements

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