

Synthesis and Properties of Triphenylgermanium Heteroaromatic Carboxylates and Crystal Structure of Triphenylgermanium 2-Furoate

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Ten triphenylgermanium heteroaromatic carboxylates $\text{Ph}_3\text{GeO}_2\text{CR}$ (where R = 2-furanyl, 2-furanvinyl, 2-(5-*tert*-butyl) furanyl, 2-thiophenyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 3-indolyl, 3-indolylmethyl, 3-indolylpropyl) were synthesized by the reaction of sodium heteroaromatic carboxylates with the triphenylgermanium chloride. All compounds were characterized by elemental analysis, ^1H NMR and MS spectra. The compounds were tested against two human tumour cell lines: MCF-7 and WiDr. The results showed that they had high activities. The crystal structure of triphenylgermanium 2-furoate was determined by X-ray single crystal diffraction. The crystal belongs to monoclinic with space group $P2_1/c$, $a = 1.1945(4)$, $b = 0.9934(3)$, $c = 1.6284(5)$ nm, $\beta = 91.59(5)$, $Z = 4$. In this crystal, the structure consists of discrete molecule containing four-coordinate germanium atom in a distorted tetrahedron.

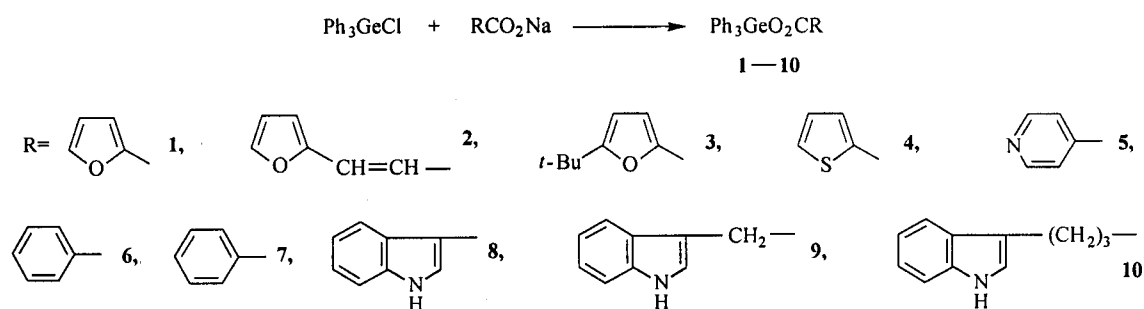
crystal structure

Introduction

Organotin carboxylates are well-known.¹⁻⁵ By contrast, analogous organogermanium carboxylates have not been studied extensively⁶ and their structural chemistry has not been mentioned. In order to study the properties and structures of this kind of compounds, ten triphenylgermanium heteroaromatic carboxylates were synthesized by reaction of triphenylgermanium chloride with sodium heteroaromatic carboxylates. Their structures were characterized by elemental analysis, IR, ^1H NMR and MS spectra. The crystal structure of triphenylgermanium 2-furoate was determined by X-ray single crystal diffraction study.

Keywords Triphenylgermanium, heteroaromatic carboxylates,

Scheme 1



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Experimental

Starting materials and instruments

The triphenylgermanium chloride and sodium heteroaromatic carboxylates were of analytical grade. Dried analytical grade solvents were used in all experiments. Melting points were determined with Kofler micro melting point apparatus and the thermometer was uncorrected. IR spectra were recorded on a Nicolet-460 spectrophotometer in KBr. ^1H NMR spectra were measured on a JEOL-FX-90Q spectrometer using TMS as the internal standard and CDCl_3 as the solvent. MS spectra were recorded on a HP-5988A spectrometer operated at 70 eV. Elemental analyses were performed on a Carlo-Erba 1106 elemental analyzer.

Antitumour activity tests

The samples of antitumour activity tests were prepared by dissolving the compounds in DMSO, and diluting with water. The cell lines were maintained in a continuous logarithmic culture in Dulbecco's medium supplemented with 10% foetal calf serum, penicillin (100 IU cm^{-3}) and streptomycin (100 $\mu\text{g} \cdot \text{cm}^{-3}$). The cells were mildly trypsinized for passage and for use in experiments. Stock solutions of the compounds to be tested were prepared in DMSO and full growth medium.

Preparation of title compounds

The preparation of title compounds were carried out under nitrogen atmosphere. Ph_3GeCl (1.0 mmol) and sodium heteroaromatic carboxylates (1.2 mmol) were added to 20 mL of dry dichloromethane and the resultant solution was stirred 8 h at 30°C. The precipitated salts were removed by filtration and the filtrate was concentrated to about 5 mL under reduced pressure. Adequate amount of ether and hexane were added to this solution. Immediately a precipitate was formed. The product was recrystallized from dichloromethane-ether-hexane.

1 Colorless crystals, 323 mg, yield 78 %, m.p. 118—119°C; ^1H NMR δ : 6.5 (q, $J = 6.50$ Hz, 1H), 7.18—7.31 (m, 1H), 7.41—7.64 (m, 15H), 7.64—7.78 (m, 1H); IR (KBr) ν : 1613, 1347, 1095, 922 cm^{-1} ; Anal. calcd for $\text{C}_{23}\text{H}_{18}\text{O}_3\text{Ge}$: C 66.56, H 4.37; found C 66.24, H 4.39.

2 Colorless crystals, 357 mg, yield 81 %, m.p. 96—98°C; ^1H NMR δ : 6.46—6.78 (m, 2H), 7.18—7.29 (m, 1H), 7.36—7.56 (m, 17H); IR (KBr) ν : 1608, 1328, 1096, 928 cm^{-1} ; Anal. calcd for $\text{C}_{25}\text{H}_{20}\text{O}_3\text{Ge}$: C 68.08, H 4.57; found C 68.41, H 4.68.

3 Colorless crystals, 329 mg, yield 70 %, m.p. 125—127°C; ^1H NMR δ : 1.35 (s, 9H), 6.08—6.17 (m, 1H), 6.94—7.06 (m, 1H), 7.31—7.60 (m, 15H); IR (KBr) ν : 1610, 1336, 1091, 925 cm^{-1} ; Anal. calcd for $\text{C}_{27}\text{H}_{26}\text{O}_3\text{Ge}$: C 68.84, H 5.56; found C 68.52, H 5.44.

4 Colorless crystals, 312 mg, yield 75 %, m.p. 121—123°C; ^1H NMR δ : 6.85—7.06 (m, 1H), 7.35—7.63 (m, 16H), 7.81—7.90 (m, 1H); IR (KBr) ν : 1615, 1324, 1095, 922 cm^{-1} ; Anal. calcd for $\text{C}_{23}\text{H}_{18}\text{O}_3\text{Ge}$: C 64.09, H 4.21; found C 64.33, H 4.36.

5 Colorless crystals, 383 mg, yield 90 %, m.p. 152—154°C; ^1H NMR δ : 7.25—7.43 (m, 15H), 7.53 (d, $J = 8.36$ Hz, 2H), 7.94 (d, $J = 8.02$ Hz, 2H); IR (KBr) ν : 1634, 1340, 1095, 926 cm^{-1} ; Anal. calcd for $\text{C}_{24}\text{H}_{19}\text{NO}_2\text{Ge}$: C 67.66, H 4.50, N 3.29; found C 64.33, H 4.36, N 3.28.

6 Colorless crystals, 387 mg, yield 91 %, m.p. 158—160°C; ^1H NMR δ : 7.20—7.40 (m, 15H), 7.52 (d, $J = 8.20$ Hz, 1H), 7.80 (d, $J = 8.42$ Hz, 1H), 8.56 (d, $J = 8.22$ Hz, 1H), 8.82—8.95 (br, 1H); IR (KBr) ν : 1633, 1338, 1093, 931 cm^{-1} ; Anal. calcd for $\text{C}_{24}\text{H}_{19}\text{NO}_2\text{Ge}$: C 67.66, H 4.50, N 3.29; found C 67.49, H 4.54, N 3.32.

7 Colorless crystals, 370 mg, yield 87 %, m.p. 142—143°C; ^1H NMR δ : 7.22—7.43 (m, 16H), 7.50—7.58 (br, 1H), 7.68—7.76 (br, 1H), 8.81—8.90 (br, 1H); IR (KBr) ν : 1632, 1347, 1095, 923 cm^{-1} ; Anal. calcd for $\text{C}_{24}\text{H}_{19}\text{NO}_2\text{Ge}$: C 67.66, H 4.50, N 3.29; found C 67.38, H 4.41, N 3.24.

8 Colorless crystals, 380 mg, yield 82 %, m.p. 135—137°C; ^1H NMR δ : 4.18 (s, 1H), 6.91—7.73 (m, 20H); IR (KBr) ν : 1620, 1342, 1096, 923 cm^{-1} ; Anal. calcd for $\text{C}_{27}\text{H}_{21}\text{NO}_2\text{Ge}$: C 69.88, H 4.56, N 3.02; found C 69.64, H 4.51, N 3.11.

9 Colorless crystals, 420 mg, yield 88 %, m.p. 110—112°C; ^1H NMR δ : 2.98 (s, 2H), 3.90 (s, 1H), 6.94—7.62 (m, 20H); IR (KBr) ν : 1616,

1335, 1094, 929 cm^{-1} ; Anal. calcd for $\text{C}_{28}\text{H}_{23}\text{NO}_2\text{Ge}$: C 70.34, H 4.85, N 2.93; found C 70.58, H 4.90, N 2.96.

10 Colorless crystals, 435 mg, yield 86 %, m.p. 104—106°C; ^1H NMR δ : 1.77—1.92 (m, 2H), 2.90—2.94 (m, 4H), 4.10 (s, 1H), 6.95—7.70 (m, 20H); IR (KBr) ν : 1605, 1327, 1094, 916 cm^{-1} ; Anal. calcd for $\text{C}_{30}\text{H}_{27}\text{NO}_2\text{Ge}$: C 71.19, H 5.38, N 2.77; found C 71.23, H 5.40, N 2.79.

Crystallographic measurements

Crystals of $\text{Ph}_3\text{GeO}_2\text{CC}_4\text{H}_9\text{O}$ are colorless prisms $\text{C}_{23}\text{H}_{18}\text{GeO}_3$, $M_r = 414.96$. A single crystal having approximate dimensions $0.70 \times 0.60 \times 0.50$ nm was mounted in a fiber. All measurements were made on a Bruker smart-1000 CCD diffractometer with graphite monochromated Mo K_α (0.071073 nm) radiation. The data were collected at temperature of 293(2) K to maximum θ value of 26.53°. The crystal structure belongs to monoclinic, space group $P2_1/c$: $a = 1.1945(4)$ nm, $b = 0.9934(3)$ nm, $c = 1.6284(5)$ nm, $\beta = 91.590(5)^\circ$, $V = 1.9317(11)$ nm^3 , $Z = 4$, $D_c = 1.427$ Mg/m^3 , $F(000) = 848$. The structure was solved by direct method and expanded using Fourier techniques. The non-hydrogen atoms were refined by full-matrix least-squares calculation to $R_1 = 0.0238$ and $wR_2 = 0.0637$ for 3937 ($R_{\text{int}} = 0.0140$) independent reflections with $I > 2\sigma(I)$. In the final difference map, the residuals are 2.49×10^2 and -4.16×10^2 e/nm^3 , respectively.

Results and discussion

IR, ^1H NMR and MS spectra

The assignment of IR bands of these compounds has been made by comparison with the IR spectra of related organogermanium compounds, carboxylates and Ph_3GeCl . It is noted that the difference $\Delta\nu$ of $\nu_{\text{as}}(\text{CO}_2)$ and $\nu_{\text{s}}(\text{CO}_2)$ is of importance since these frequencies

can be used for determining the type of bonding between metal and carboxyl group.^{7,8} The magnitude of $\Delta\nu$ [$\nu_{\text{as}}(\text{CO}_2) - \nu_{\text{s}}(\text{CO}_2)$] for compounds **1**—**10** are 266—295 cm^{-1} . It is much greater than the magnitude $\Delta\nu$ for the appropriate sodium heteroaromatic carboxylates,⁸ which indicates the presence of monodent carboxylate groups.⁹ The absorption frequencies in the regions 916—931 cm^{-1} and 1081—1096 cm^{-1} were tentatively assigned to $\nu(\text{Ge—O})$ ¹⁰ and $\nu(\text{Ge—Ph})$,¹¹ respectively.

The values of the $\text{Ge—C}_6\text{H}_5$ chemical shifts are 7.72—7.70, and shift upfield as compared with those at of the triphenylgermanium chloride. It is possible that the oxygen atom of carboxylate group is more electronegative than chlorine atom, and this leads to the decrease of circulating of phenyl group.¹¹ The values of the chemical shift (δ 6.46—8.90) for the protons of heteroaromatic ring in these compounds slightly increase or are close to those of the corresponding free heteroaromatic acid. It is showed that the O, S or N hetero atom in carboxylate ligands does not coordinate to the germanium atom.¹²

In mass spectra, parent molecular ions were not be detected for all compounds. The most abundant ion is germanium-containing fragment at $m/z = 365$, which could be assigned to Ph_3Ge^+ . In addition, $[\text{M} - \text{C}_6\text{H}_5]^+$ is main germanium-containing fragment in all compounds. No ions of mass higher than the parent molecular ions are detected, nor are there fragments containing more than one germanium atom. So these compounds are of the monomeric structure.

Antitumour activity

The compounds were tested against two human tumour cell lines, MCF-7 and WiDr. All compounds showed growth inhibition of the two tumours higher than 50% activity. The percentages of growth inhibition of MCF-7 and WiDr tumour cell lines are listed in Table 1. The triphenylgermanium compounds with furanyl carboxylates are tremendously less active than triphenylgermanium pyridinyl and indolyl carboxylates.

Table 1 Percentage of growth inhibition data (in 10 $\mu\text{g}/\text{cm}^3$)

Tumour cell line	Compounds									
	1	2	3	4	5	6	7	8	9	10
MCF-7	55.2	56.4	52.5	61.5	79.4	78.8	83.2	74.5	81.3	76.6
WiDr	50.8	52.5	50.3	54.2	70.5	69.4	72.3	75.8	73.1	64.5

Molecular structure of $\text{Ph}_3\text{GeO}_2\text{CC}_4\text{H}_3\text{O}$

The crystal structure of $\text{Ph}_3\text{GeO}_2\text{CC}_4\text{H}_3\text{O}$ was determined by single crystal X-ray diffraction. The selected bond lengths and angles are listed in Table 2. The molecular structure figure is given in Fig. 1. In the crystal, the structure consists of discrete molecule containing four-coordinate germanium atom in a slightly distorted tetrahedral configuration. This structure is similar to organotin carboxylates (C_6H_{11})₃SnO₂C₆H₄Cl-*m* and (C_6H_{11})₃-SnO₂C₆H₄CBr-*m*.¹³

The mean Ge(1)—O(1) distance of 0.18425(13) nm is slightly shorter than Ge—O sum of covalent radii (0.195 nm), and should be considered as a bonding interaction. But the Ge(1)—O(2) distance of 0.29341 nm is much greater than the sum of covalent radii for Ge and O atoms, which showed the O(2) atom does not make any significant contacts with the Ge(1) atom. It is showed that only one oxygen atom of 2-furoate ligand coordinates to the germanium atom. So the germanium atom in $\text{Ph}_3\text{GeO}_2\text{CC}_4\text{H}_3\text{O}$ must be considered four coordinate with a tetrahedron environment.

The distortions from true tetrahedron symmetry are

reflected in the interatomic angles. The angles O(1)—Ge(1)—C(1) [100.33(7)°], O(1)—Ge(1)—C(7) [109.09(6)°], O(1)—Ge(1)—C(13) [108.83(7)°] are less than 109.5°. In contrast, the angles C(1)—Ge(1)—C(7) [111.16(7)°], C(1)—Ge(1)—C(13) [119.91(7)°] and C(7)—Ge(1)—C(13) [114.53(7)°] are greater than 109.5°. It is showed that the phenyl group comes close to the carboxylate. This is due to that the phenyl group has more sterical hindrance than the furanylcarboxylate group.

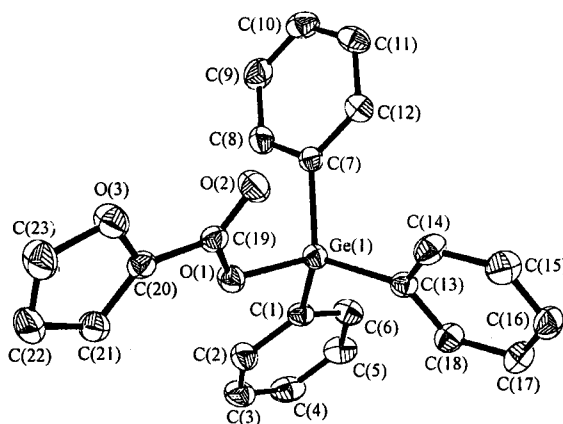


Fig. 1 Molecular structure of triphenylgermanium 2-furoate.

Table 2 Selected bond lengths (nm) and bond angles (°) for triphenylgermanium 2-furoate

Bond	Length (nm)	Bond	Length (nm)
Ge(1)—O(1)	0.18425(13)	C(1)—C(2)	0.1388(2)
Ge(1)···O(2)	0.29341	C(1)—C(6)	0.1390(2)
Ge(1)—C(1)	0.19406(16)	C(2)—C(3)	0.1390(3)
Ge(1)—C(7)	0.19437(17)	C(3)—C(4)	0.1370(3)
Ge(1)—C(13)	0.19446(17)	C(4)—C(5)	0.1370(3)
O(1)—C(19)	0.1334(2)	C(5)—C(6)	0.1390(3)
O(2)—C(19)	0.1212(2)	C(19)—C(20)	0.1455(2)
O(3)—C(20)	0.1367(2)	C(20)—C(21)	0.1347(3)
O(3)—C(23)	0.1364(2)	C(21)—C(22)	0.1410(3)
Bond	Angle (°)	Bond	Angle (°)
O(1)—Ge(1)—C(1)	100.33(7)	C(8)—C(7)—Ge(1)	119.70(13)
O(1)—Ge(1)—C(7)	109.09(6)	C(12)—C(7)—Ge(1)	121.93(13)
C(1)—Ge(1)—C(7)	111.16(7)	C(18)—C(13)—Ge(1)	119.39(13)
O(1)—Ge(1)—C(13)	108.83(7)	C(14)—C(13)—Ge(1)	122.82(13)
C(1)—Ge(1)—C(13)	111.91(7)	O(2)—C(19)—O(1)	123.53(16)
C(7)—Ge(1)—C(13)	114.53(7)	O(2)—C(19)—C(20)	124.09(16)
C(19)—O(1)—Ge(1)	117.99(11)	O(1)—C(19)—C(20)	112.37(15)
C(23)—O(3)—C(20)	105.87(15)	C(21)—C(20)—O(3)	109.51(15)
C(2)—C(1)—Ge(1)	122.79(14)	O(3)—C(20)—C(19)	116.49(15)
C(6)—C(1)—Ge(1)	118.96(11)	C(22)—C(23)—O(3)	111.10(19)

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