Heteroatom Chemistry
Volume 10, Number 1, 1999

Synthesis of O,O-Diphenyl N-Trichlorogermanylpropiono-α-aminophosphonates

Qingmin Wang, Qiang Zeng, and Zhi Chen

Institute of Elemento-Organic Chemistry, State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin, 300071, P. R. China

Received 27 January 1998; revised 21 April 1998

ABSTRACT: *A variety of novel O,O-Diphenyl N-(trichlorogermanyl)propiono-α-aminophosphonates were synthesized by the reaction of β-(trichlorogermanyl) propionyl chloride with diphenyl α-aminophosphonates in the presence of triethylamine. The structures of all of the products were confirmed by ^{1}H-NMR spectroscopy, elemental analyses, and IR spectroscopy. Data of ^{1}H-NMR and IR spectroscopic determinations indicated the title compounds to be pentacoordinated organogermanium compounds. The results of bioassay showed that some of the title compounds possess potential anticancer activity.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 5–8, 1999

INTRODUCTION

Both α-aminophosphonic acids and their derivatives have bioactivities, for example, antibacterial and antitumor [1–3]. For the purpose of our search for new compounds having potent and efficient antitumor or antiinflammatory activities, we decided to introduce the organogermanium group, which has versatile biological activities in its own right [4], into the structures of various α-aminophosphonates, and therefore, we designed and synthesized a series of the title compounds.

Correspondence to: Qingmin Wang.
Contract grant sponsor: National Natural Science Foundation of China.
 CCC 1042-7163/99/010005-04

RESULTS AND DISCUSSION

Synthesis of the Products

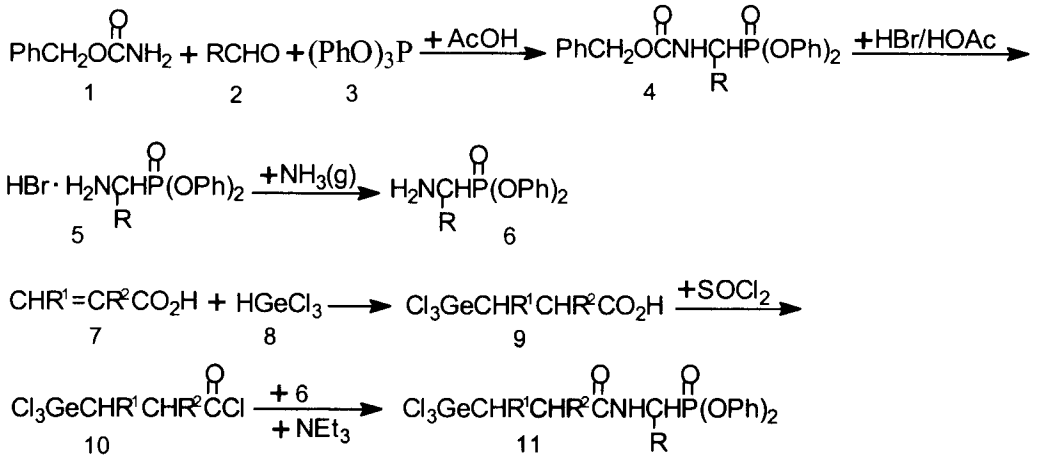
We synthesized the title compounds by the multistep route outlined in Scheme 1.

With glacial acetic acid as the solvent, aldehydes (**2**) can undergo a Mannich-type reaction with benzyl carbamate (**1**) and triphenyl phosphite (**3**) to give the N-benzyloxycarbonyl derivatives **4** [5]. However, this method could not be used for the synthesis of diphenyl benzyloxycarbonylaminomethanephosphonate (**15**). Therefore, we synthesized **15** by the route depicted in Scheme 2 [6]. Benzyl carbamate (**1**) was used to react with acetic anhydride (**12**) and paraformaldehyde (**13**) in glacial acetic acid to give benzyl N-(acetoxymethyl)-carbamate (**14**). Crude **14** was then reacted with triphenyl phosphite in acetic acid to give **15** as a crystalline product.

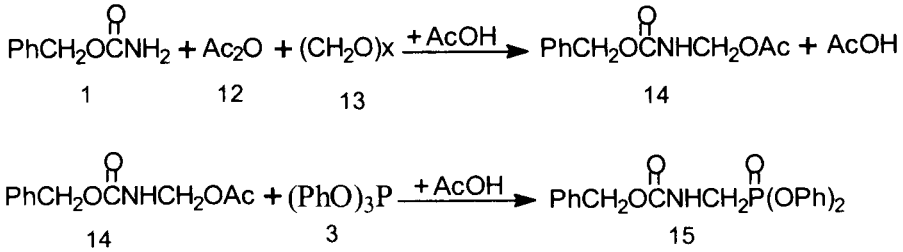
β-(Trichlorogermanyl)propionic acid (**9**) was prepared by the addition of **7** to **8** [7]. We transformed the β-(trichlorogermanyl)propionic acid into the corresponding acyl chloride (**10**) by the action of thionyl chloride. Then, β-(trichlorogermanyl)propionyl chloride was condensed with various diphenyl α-aminophosphonates (**6**), with the help of triethylamine, to give the title compounds (**11**). When each reaction had been completed, the product (**11**) was easily purified by recrystallization from methylene dichloride and petroleum ether.

The Structures of the Products

The structures of all of the title compounds were confirmed by ^{1}H-NMR spectroscopy and elemental



SCHEME 1



SCHEME 2

TABLE 1 Physical Constants of Products **11**

Compds.	R^1	R^2	R	MP (°C)	*Yield* (%)	*Elemental Analyses* (%) *Found* (*Calcd*)		
						C	*H*	*N*
11a	H	H	H	138–139	87.9	38.43 (38.65)	3.26 (3.45)	3.06 (2.82)
11b	H	H	Me	173–175	93.0	39.86 (39.94)	3.79 (3.75)	2.71 (2.74)
11c	H	Me	Me	166–168	87.0	41.13 (41.16)	4.03 (4.03)	2.40 (2.67)
11d	Me	H	Me	158–160	88.6	41.03 (41.16)	4.05 (4.03)	2.64 (2.67)
11e	H	H	Pr^n	166–168	74.1	42.57 (42.31)	4.54 (4.30)	2.62 (2.60)
11f	H	H	Pr^i	165–167	71.1	41.98 (42.31)	4.46 (4.30)	2.33 (2.60)
11g	H	H	Bu^n	151–153	69.6	43.39 (43.41)	4.65 (4.55)	2.32 (2.53)
11h	H	H	CH_2Ph	144–146	75.5	46.84 (47.03)	4.06 (3.95)	2.24 (2.38)
11i	H	H	Ph	164–166	78.1	45.82 (46.09)	3.44 (3.69)	2.48 (2.44)
11j	H	H	4-OMe-C_6H_4	181–183	70.9	45.44 (45.79)	3.50 (3.84)	2.25 (2.32)
11k	H	H	4-Me-C_6H_4	156–158	87.1	47.20 (47.03)	3.74 (3.95)	2.18 (2.38)
11l	H	H	3-Cl-C_6H_4	154–156	75.0	43.26 (43.28)	3.10 (3.32)	2.63 (2.30)
11m	H	H	4-Cl-C_6H_4	153–155	76.3	43.24 (43.28)	3.57 (3.32)	2.33 (2.30)
11n	H	H	3-NO_2-C_6H_4	165–167	81.9	42.88 (42.73)	3.22 (3.26)	4.33 (4.53)
11o	H	H	4-NO_2-C_6H_4	176–178	77.4	42.55 (42.73)	3.56 (3.26)	4.48 (4.53)
11p	H	H	2,4-Cl_2-C_6H_3	147–149	87.3	40.98 (41.14)	2.87 (2.98)	2.26 (2.18)

TABLE 2 ^{1}HNMR of Products **11**

Compds.	$\sigma(CDCl_3)$
11a	2.03–2.15 (m, 2H, $GeCH_2$); 2.43–2.46 (m, 2H, CH_2CO); 4.05 (dd, 2H, CH_2PO, $^2J_{PH}$ = 14.0 Hz, $^3J_{HH}$ = 6.0 Hz); 7.10–7.36 (m, 10H, Ph).
11b	1.40 (dd, 3H, CH_3, $^3J_{PH}$ = 18.0 Hz, $^3J_{HH}$ = 7.2 Hz); 1.94–2.07 (m, 2H, $GeCH_2$); 2.38–2.50 (m, 2H, CH_2CO); 4.80–4.87 (m, 1H, CHPO); 7.05–7.40 (m, 10H, Ph).
11c	1.06 (dd, 3H, CH_3(CHPO), $^3J_{PH}$ = 31.9 Hz, $^3J_{HH}$ = 7.1 Hz); 1.41–1.54 [m, 3H, CH_3(CHCO)]; 1.96–2.09 (m, 2H, $GeCH_2$); 2.52–2.67 (m, 2H, CH_2CO); 4.90–4.97 (m, 1H, CHPO); 8.12 (dd, 1H, CONH, $^3J_{PH}$ = 18.2 Hz, $^3J_{HH}$ = 9.9 Hz); 7.05–7.34 (m, 10H, Ph).
11d	1.20 [d, 3H, CH_3(CHGe), $^3J_{HH}$ = 7.2 Hz]; 1.42 [dd, 3H, CH_3(CHPO), $^3J_{PH}$ = 18.0 Hz, $^3J_{HH}$ = 7.2 Hz]; 2.10–2.23 (m, 1H, $GeCH_2$); 2.28–2.40 (m, 2H, CH_2CO); 4.91–4.98 (m, 1H, CHPO); 8.32 (br., 1H, CONH); 6.98–7.36 (m, 10H, Ph).
11e	0.91 (t, 3H, CH_3, $^3J_{HH}$ = 7.8 Hz); 1.18–1.53 (m, 4H, CH_2CH_2); 2.00–2.13 (m, 1H, $GeCH_2$); 2.38–2.51 (m, 2H, CH_2CO); 4.86–4.93 (m, 1H, CHPO); 9.16 (br., 1H, CONH); 7.05–7.34 (m, 10H, Ph).
11f	1.03 (d, 6H, CH_3, $^3J_{HH}$ = 6.9 Hz); 1.81–1.90 (m, 1H, CH); 2.02–2.14 (m, 2H, $GeCH_2$); 2.46–2.57 (m, 2H, CH_2CO); 4.85–4.90 (m, 1H, CHPO); 6.95 (br., 1H, CONH); 7.05–7.34 (m, 10H, Ph).
11g	0.86 (t, 3H, CH_3, $^3J_{HH}$ = 7.8 Hz); 1.12–1.48 (m, 6H, $CH_2CH_2CH_2$); 2.00–2.11 (m, 2H, $GeCH_2$); 2.37–2.50 (m, 2H, CH_2CO); 4.85–4.91 (m, 1H, CHPO); 7.59 (br., 1H, CONH); 7.03–7.34 (m, 10H, Ph).
11h	1.80–1.91 (m, 2H, $GeCH_2$); 2.15–2.27 (m, 2H, CH_2CO); 3.15–3.24 (m, 2H, CH_2Ph); 5.17–5.24 (m, 2H, CHPO); 7.08–7.36 (m, 15H, Ph).
11i	1.87–2.00 (m, 2H, $GeCH_2$); 2.22–2.32 (m, 2H, CH_2CO); 6.02 (dd, 1H, CHPO, $^2J_{PH}$ = 22.0 Hz, $^3J_{HH}$ = 10.0 Hz); 8.66 (d, 1H, CONH, $^3J_{HH}$ = 10.0 Hz); 6.49–7.51 (m, 15H, Ph).
11j	1.95–2.05 (m, 2H, $GeCH_2$); 2.26–2.38 (m, 2H, CH_2CO); 3.77 (s, 3H, OMe); 5.95 (dd, 1H, CHPO, $^2J_{PH}$ = 20.9 Hz, $^3J_{HH}$ = 9.4 Hz); 8.17 (br., 1H, CONH); 6.62–7.48 (m, 14H, Ph).
11k	1.88–2.00 (m, 2H, $GeCH_2$); 2.24–2.44 (m, 5H, Me, CH_2CO); 5.97 (dd, 1H, CHPO, $^2J_{PH}$ = 21.9 Hz, $^3J_{HH}$ = 9.4 Hz); 8.58 (d, 1H, CONH, $^3J_{HH}$ = 9.4 Hz); 6.54–7.39 (m, 14H, Ph).
11l	1.93–2.05 (m, 2H, $GeCH_2$); 2.27–2.38 (m, 2H, CH_2CO); 5.96 (dd, 1H, CHPO, $^2J_{PH}$ = 22.0 Hz, $^3J_{HH}$ = 10.0 Hz); 8.30 (d, 1H, CONH, $^3J_{HH}$ = 10 Hz); 6.64–7.55 (m, 14H, Ph).
11m	1.95–2.07 (m, 2H, $GeCH_2$); 2.33–2.43 (m, 2H, CH_2CO); 5.96 (dd, 1H, CHPO, $^2J_{PH}$ = 21.9 Hz, $^3J_{HH}$ = 9.4 Hz); 8.11 (br., 1H, CONH); 6.67–7.45 (m, 14H, Ph).
11n	2.00–2.11 (m, 2H, $GeCH_2$); 2.40–2.41 (m, 2H, CH_2CO); 6.08 (dd, 1H, CHPO, $^2J_{PH}$ = 22.4 Hz, $^3J_{HH}$ = 9.9 Hz); 6.84–8.38 (m, 14H, Ph).
11o	2.00–2.11 (m, 2H, $GeCH_2$); 2.40–2.52 (m, 2H, CH_2CO); 6.07 (dd, 1H, CHPO, $^2J_{PH}$ = 22.9 Hz, $^3J_{HH}$ = 9.4 Hz); 6.74–8.10 (m, 14H, Ph).
11p	1.96–2.05 (m, 2H, CH_2); 2.28–2.40 (m, 2H, CH_2CO); 6.51 (dd, 1H, CHPO, $^2J_{PH}$ = 22.4 Hz, $^3J_{HH}$ = 9.9 Hz); 8.25 (br., 1H, CONH); 6.72–7.59 (m, 13H, Ph).

TABLE 3 IR of Some of Products **11**

Compds.	*IR* (cm^{-1}) (*KBr*)
11a	3224.5, 3086.0, 2923.0, 1622.0, 1587.0, 1486.6, 1241.2, 1208.1, 1181.9, 1158.2, 963.6, 937.1, 756.9, 684.2, 533.7.
11b	3207.5, 3064.0, 2949.0, 1615.7, 1588.0, 1486.3, 1256.9, 1202.9, 1180.1, 1157.2, 941.0, 767.2, 688.0, 538.6.
11c	3214.0, 3070.0, 2925.5, 1614.9, 1588.4, 1486.8, 1255.2, 1206.0, 1181.8, 1158.0, 954.2, 761.7, 687.3, 535.6.
11d	3205.5, 3061.5, 2945.0, 1621.0, 1587.0, 1487.5, 1254.0, 1201.8, 1178.0, 1156.6, 947.1, 928.0, 763.0, 684.8, 534.9.
11e	3212.0, 3075.5, 2954.5, 1617.0, 1588.1, 1486.0, 1239.2, 1202.8, 1180.2, 1156.5, 953.5, 933.5, 767.1, 687.8, 527.1.
11f	3206.0, 3070.5, 2957.5, 1612.9, 1589.4, 1485.2, 1249.8, 1207.7, 1178.5, 1156.0, 951.0, 927.3, 764.9, 687.5, 522.0.
11o	3230.5, 3104.5, 2852.5, 1623.7, 1615.7, 1521.0, 1486.2, 1364.3, 1255.4, 1206.9, 1178.7, 1158.7, 960.4, 870.5, 758.9, 686.0, 501.6.

analyses. Their physical constants are listed in Table 1, and data of the ^{1}H-NMR spectra are listed in Table 2. The H atom at the α-C(R = aryl) and the two H atoms at the α-C(R = H) exhibited dd peaks due to the coupling of the P atom and the (N-)H atom, and, when R = alkyl, the H atom at the α-C exhibited multiple peaks. An intramolecular Ge–O interaction in 3-(trichlorogermanyl)propanoic acid and its derivatives has previously been observed [8,9]. The Ge atom is pentacoordinated and distorted toward a trigonal bipyramid. We concluded from data of the ^{1}H-NMR and IR spectroscopic studies that the title compounds are also pentacoordinated organogermanium compounds. The IR data of some of the title compounds are listed in Table 3. The C = O stretching absorption band is about 1620 cm^{-1}, whereas the C = O stretching absorption band in diphenyl N-triphenylgermanylpropiono-α-aminophosphonates, whose Ge atom has a tetrahedral configuration, is about 1670 cm^{-1} [10,11]. It has been reported that a single cyclic pentacoordination of a germanium atom can result when the germanium atom is linked to one or more strongly electron-withdrawing atoms or groups, for example, the chlorine atom [8,12]. On consideration of the fact that there are empty d-orbitals in the outer sphere of the Ge atom, it is reasonable to suppose that the oxygen atoms of the C = O group can coordinate with the germanium atom with formation of a five-membered ring. This leads to a red shift of the C = O stretching absorption band. Moreover, this brings about the situation that all the protons of groups $GeCH_2$ and CH_2CO exhibit multiplet peaks.

BIOLOGICAL ACTIVITY

The preliminary biological tests showed that some of the products exhibit activity against KB in vitro. A further study of anticancer activities is underway.

EXPERIMENTAL

All of the melting points were determined with a Thomas–Hoover melting point apparatus, and the values are uncorrected. ^{1}H-NMR spectra were recorded with a Bruker AC-P200 spectrometer with use of TMS as an internal standard. Elemental analyses were carried out with a Yanaco CHN Corder MT-3 elemental analyzer. IR spectra were recorded with a Shimadu-435 instrument.

O,O-Diphenyl N-(trichlorogermanyl)propiono-α-aminophosphonates (11): General Procedure

A mixture of each diphenyl α-aminophosphonate (**6**) (2.5 mmol), triethylamine (3.0 mmol), and methylene dichloride (40 mL) was stirred in an ice–salt bath, and then a solution of β-(trichlorogermanyl)propionyl chloride or a substituted **10** in 10 mL of methylene dichloride was added dropwise at 0°C. After the solution had been stirred at 0°C for 1 hour and then at ambient temperature for 7 hours, 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 **11**. The appropriate data are listed in Tables 1 and 2.

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