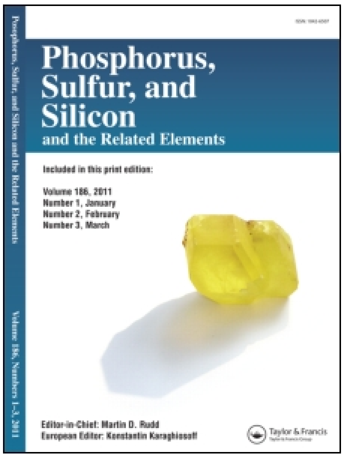

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CONDENSATION REACTION OF ß-TRIPHENYLGERMANYL PROPANOIC ACID WITH DIPHENYL α-AMINOPHOSPHONATES AND BIOACTIVITIES OF PRODUCTS

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The condensation reaction of β-triphenylgermanyl propanoic acid with diphenyl α-aminophosphonates was studied. A variety of novel diphenyl N-triphenylgermanylpropiono-α-aminophosphonates were synthesized successfully in good yields by using DCC catalyzed by pyridine. The structures of all of the products were confirmed by ^{1}HNMR, ^{31}PNMR, IR, MS and elemental analysis. The results of bioassay showed that the new products have good anticancer activities and very strong anti-inflammatory activities.

Keywords: anticancer activities; anti-inflammatory activities; diphenyl N-triphenylgermanylpropiono-α-aminophosphonates; condensation reaction

INTRODUCTION

Both the β-triphenylgermanyl propanoic acid and its derivatives exhibit anti-inflammatory and antibacteria activities.[1] Both α-aminophosphonic acids and their derivatives have bioactivity e.g. antibacteria, antitumor, etc.[2,3] Synthesis and bioactivity of organogermanic compounds containing α-aminophosphonyl structures have seldom been reported. In order to look for new compounds having potent efficient anticancer and anti-inflammatory activities, we developed the idea that the incorporation

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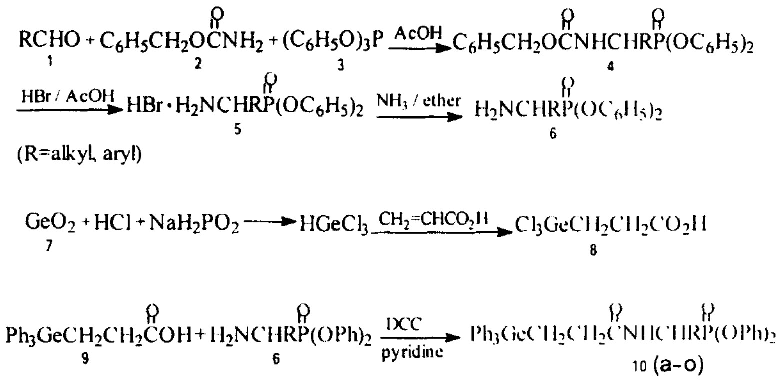
* Correspondence Author.

of a germanium residue into α-aminophosphonic acids and their derivatives would enhance their antitumor activities to a significant degree, while their toxicity would be reduced at the same time. Therefore, we designed and synthesized a series of novel diphenyl N-triphenylgermanylpropiono-α-aminophosphonates, and studied the condensation reaction of β-triphenylgermanyl propanoic acid with diphenyl α-aminophosphonates. We have investigated anticancer and anti-inflammatory activities of the products.

RESULTS AND DISCUSSION

Synthesis of products

A series of diphenyl N-triphenylgermanylpropiono-α-aminophosphonates were synthesized by the multistep route outlined in Scheme **I**.



$$\underset{1}{RCHO} + \underset{2}{C_6H_5CH_2O\overset{O}{\overset{\|}{C}}NH_2} + \underset{3}{(C_6H_5O)_3P} \xrightarrow{AcOH} \underset{4}{C_6H_5CH_2O\overset{O}{\overset{\|}{C}}NHCHR\overset{O}{\overset{\|}{P}}(OC_6H_5)_2}$$

$$\xrightarrow{HBr/AcOH} \underset{5}{HBr\cdot H_2NCHR\overset{O}{\overset{\|}{P}}(OC_6H_5)_2} \xrightarrow{NH_3/ether} \underset{6}{H_2NCHR\overset{O}{\overset{\|}{P}}(OC_6H_5)_2}$$

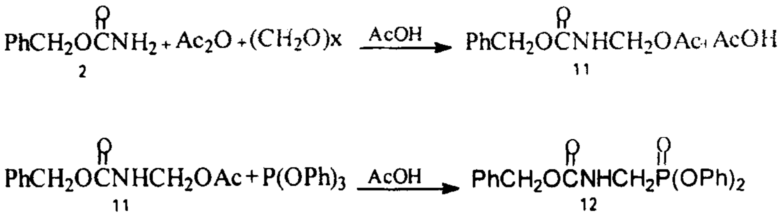
(R=alkyl, aryl)

$$\underset{7}{GeO_2} + HCl + NaH_2PO_2 \longrightarrow HGeCl_3 \xrightarrow{CH_2=CHCO_2H} \underset{8}{Cl_3GeCH_2CH_2CO_2H}$$

$$\underset{9}{Ph_3GeCH_2CH_2\overset{O}{\overset{\|}{C}}OH} + \underset{6}{H_2NCHR\overset{O}{\overset{\|}{P}}(OPh)_2} \xrightarrow[pyridine]{DCC} \underset{10\,(a\text{-}o)}{Ph_3GeCH_2CH_2\overset{O}{\overset{\|}{C}}NHCHR\overset{O}{\overset{\|}{P}}(OPh)_2}$$

SCHEME I

With glacial acetic acid as the solvent, aldehydes(**1**) can undergo the Mannich-type reaction with benzyl carbamate(**2**) and triphenyl phosphite(**3**) to prepare the N-benzyloxycarbonyl derivatives **4**.[4] This method cannot be used for the synthesis of diphenyl benzyloxycarbonylaminomethanephosphonate(**12**). Compound **12** was synthesized by the route shown in Scheme **II**. Benzyl carpamate(**2**) reacted with acetic anhydride and paraformaldehyde in glacial acetic acid to obtain benzyl N-(acetoxymethyl)-carbamate(**11**) Crude **11** reacted with triphenyl phosphite in acetic acid to give **12** as a crystalline product. β-Trichlorogermanyl propanoic acid(**8**) was prepared from germanium dioxide(**7**).[5] β-Triphenylgermany propanoic acid(**9**) was prepared by the reaction of β-trichlorogermanyl propanoic acid(**8**) with phenylmagnesium bromide in molar ratio 1:4.[5]



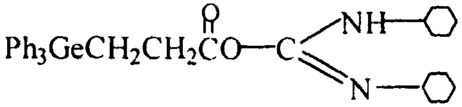
$$\underset{2}{PhCH_2O\overset{O}{\overset{\|}{C}}NH_2} + Ac_2O + (CH_2O)x \xrightarrow{AcOH} \underset{11}{PhCH_2O\overset{O}{\overset{\|}{C}}NHCH_2OAc \cdot AcOH}$$

$$\underset{11}{PhCH_2O\overset{O}{\overset{\|}{C}}NHCH_2OAc} + P(OPh)_3 \xrightarrow{AcOH} \underset{12}{PhCH_2O\overset{O}{\overset{\|}{C}}NHCH_2\overset{O}{\overset{\|}{P}}(OPh)_2}$$

SCHEME II

The transformation of β-triphenylgermanyl propanoic acid with thionyl chloride into β-triphenylgermanyl propionyl chloride was attempted, then the corresponding acyl chloride would be condensed with diphenyl α-aminophosphonates to give diphenyl N-triphenylgermanylpropiono-α-aminophosphonates. This did not succeed. In the molecule of β-triphenylgermanyl propanoic acid, there are three weak aromatic Ge-C bonds, which might be easily replaced by chloride in thionyl chloride. The reaction of β-triphenylgermanyl propanoic acid with thionyl chloride became too complicated, and the viscous intermediate was very difficult to purify. Using DCC in the presence of pyridine, β-triphenylgermanyl propanoic acid was condensed with diphenyl α-aminophosphonates successfully in good yields.

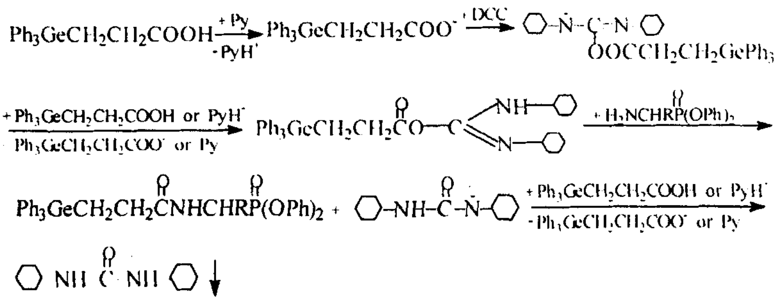
It was found that pyridine acted as a catalyst, which plays an important role. In the absence of pyridine, the reaction required 12 hrs to synthesize **10b,** whereas when 2 mol pyridine was added, it required 5 hrs only. When pyridine was used as the catalyst, the amount became the key factor of the reaction. If less than 2 mol was added to the reaction system, pyridine did not take effect; only when 2 mol or more was used, could the condensation reaction accelerate. It is probably due to the formation of a complex between Ge and pyridine. During the process of reaction, an intermediate **A** was trapped. Its structure was confirmed by ^{1}HNMR as follows:



A

A, white solid, m.p. 172–174 °C. ^{1}HNMR(CDCl$_3$, δppm): 0.8–1.8(m, 22H, $(CH_2)_5$, CH_2Ge), 2.48–2.62(m, 2H. CH_2CO), 3.49–3.61(m, 1H, NCH), 3.70–3.80(m, 1H, C=NCH), 6.75(br., 1H, NH), 7.20–7.60 (m, 15H, 3Ph).

Taking into account the existence of intermediate **A**, the mechanism illustrated in Scheme **III** was proposed.



SCHEME III

The structure of products

All products were colorless crystalline solids, and their structures were confirmed by ^{1}HNMR, ^{31}PNMR, IR, MS and elemental analysis. The data are listed in Table **I**, and the ^{1}HNMR spectra are listed in Table **II**. The ^{1}HNMR data indicated that all the protons of groups $GeCH_2$ and CH_2CO showed multiplet peaks and the protons of $GeCH_2$ appeared at the higher field. When substituent R is aryl, the H atom at the α-C exhibited dd peaks due to the coupling of the P atom and the (N-)H atom.

TABLE I Data of Products diphenyl N-triphenylgermanylpropiono-α-aminophosphonates **10**

Compds.	*R*	*Yelid (%)*	*MP (°C)*	*Ele. Ana. (%)*					
				Calcd.			*Found*		
				C	*H*	*N*	*C*	*H*	*N*
10a	H	84.8	128–130	65.63	5.18	2.25	65.36	5.26	2.45
10b	Me	77.0	147–149	66.08	5.39	2.20	66.25	5.37	2.42
10c	Pr^n	77.8	144–145	66.90	5.77	2.11	66.48	5.61	2.07
10d	Pr^i	72.2	160–162	66.90	5.77	2.11	66.63	5.98	2.16
10e	Bu^n	85.6	146–147	67.29	5.94	2.06	66.92	5.74	2.08
10f	CH_2Ph	92.1	164–166	69.13	5.38	1.97	68.98	5.42	1.77
10g	Ph	89.7	134–135	68.80	5.20	2.01	68.66	5.14	2.23
10h	$4\text{-OH-}C_6H_4$	64.6	174–175	67.26	5.08	1.96	67.32	5.16	1.86
10i	$4\text{-OMe-}C_6H_4$	70.5	164–166	67.61	5.26	1.92	67.74	5.24	1.88
10j	$4\text{-Me-}C_6H_4$	79.4	176–178	69.13	5.38	1.97	69.36	5.22	2.06
10k	$3\text{-Cl-}C_6H_4$	71. 1	154–156	65.57	4.81	1.91	65.80	5.12	1.62
10l	$4\text{-Cl-}C_6H_4$	89.7	191–193	65.57	4.81	1.91	65.49	4.78	1.93
10m	$3\text{-}NO_2\text{-}C_6H_4$	82.2	173–175	64.64	4.75	3.77	64.46	4.36	3.66
10n	$4\text{-}NO_2\text{-}C_6H_4$	87.3	195–197	64.64	4.75	3.77	64.52	4.45	3.64
10o	$2,4\text{-}Cl_2\text{-}C_6H_3$	69.5	148–149	62.62	4.47	1.83	62.54	4.45	1.64

TABLE II ^{1}HNMR of Products **10**

Compds	*δ(CDCl$_3$)*
10a	1.70–1.78(m, 2H, $GeCH_2$), 2.27–2.37(m, 2H, CH_2CO), 4.00(dd, 2H, CH_2PO, $^2J_{PH}$ 12.76Hz, $^3J_{HH}$=6.80Hz), 5.66(br., 1H, CONH), 7.11–7.42(m. 25H, Ph).
10b	1.43(dd, 3H, CH_3, $^3J_{PH}$=18.30Hz, $^3J_{HH}$=7.30Hz), 1.67–1.75(m, 2H, $GeCH_2$), 2.18–2.28(m, 2H, CH_2CO), 4.86–4.92(m, 1H, CHPO), 5.88(d, 1H, CONH, $^3J_{HH}$=9.38Hz), 7.10–7.46(m, 25H, Ph).
10c	0.91(t, 3H, CH_3, $^3J_{HH}$=8.0Hz), 1.21–1.60(m, 4H, CH_2CH_2), 1.69–1.77(m, 2H, $GeCH_2$), 2.19–2.28(m. 2H, CH_2CO), 4.81–4.87(m, 1H, CHPO), 5.59(br., 1H, CONH), 7.10–7.45(m, 25H, Ph).
10d	1.03(d, 6H, CH_3, $^3J_{HH}$=8.0Hz), 1.65–1.77(m, 3H, CH, $GeCH_2$), 2.22–2.30(m, 2H, CH_2CO), 4.78–4.83(m, 1H, CHPO), 5.74(br., 1H, CONH), 7.19–7.45(m, 25H, Ph).
10e	0.86(t, 3H, CH_3, $^3J_{HH}$=8.0Hz), 1.23–1.56(m, 6H, $CH_2CH_2CH_2$), 1.67–1.75(m, 2H, $GeCH_2$), 2.19–2.28(m, 2H, CH_2CO), 4.78–4.85(m, 1H, CHPO), 5.58(br., 1H, CONH), 7.10–7.45(m, 2511, Ph).

Compds	$\delta(CDCl_3)$
10f	1.54–1.62(m, 2H, $GeCH_2$), 2.02–2.10(m, 2H, CH_2CO), 3.14–3.24(m, 2H, CH_2Ph), 5.12–5.18(m, 1H, CHPO), 5.60(d, 1H, CONH, $^3J_{HH}$=10Hz), 7.00–7.36(m, 30H, Ph).
10g	1.62–1.71(m, 2H, $GeCH_2$), 2.20–2.29(m, 2H, CH_2CO), 5.94(dd, 1H, CHPO, $^2J_{PH}$=20.40Hz, $^3J_{HH}$=8.16Hz), 6.45(br., 1H, CONH), 6.79–7.43(m, 30H, Ph).
10h	1.69–1.78(m, 2H, $GeCH_2$), 2.23–2.32(m, 2H, CH_2CO), 5.82(dd, 1H, CHPO, $^2J_{PH}$=20.90Hz, $^3J_{HH}$=9.39Hz), 6.36(br., 1H, CONH), 6.58–7.41(m, 29H, Ph).
10i	1.63–1.72(m, 2H, $GeCH_2$), 2.18–2.27(m, 2H, CH_2CO), 3.77(s. 3H, OMe), 5.87(dd. 1H, CHPO, $^2J_{PH}$=22.20Hz $^3J_{HH}$=8.80 Hz) 6.36(br., 1H CONH) 6.76–7.43(m, 29H, Ph).
10j	1.65–1.76(m, 2H, $GeCH_2$), 2.13–2.23(m, 2H, CH_2CO), 2.31(s, 3H, Me), 5.90(dd, 1H, CHPO, $^2J_{PH}$=20.41Hz, $^3J_{HH}$=8.16 Hz), 6.29(br., 1H, CONH), 6.80–7.39(M, 29H, Ph).
10k	1.63–1.73(m, 2H, $GeCH_2$), 2.16–2.27(m, 2H, CH_2CO), 5.88(dd, 1H, CHPO, $^2J_{PH}$=20.00Hz, $^3J_{HH}$=12.00Hz), 6.37(br., 1H, CONH), 7.04–7.41(m, 29H, Ph).
10l	1.62–1.70(m, 2H, $GeCH_2$), 2.19–2.28(m, 2H, CH_2CO), 5.86(dd, 1H, CHPO, $^2J_{PH}$=21.90Hz. $^3J_{HH}$=9.38Hz), 6.29(br., 1H, CONH), 6.80–7.39(m, 29H, Ph).
10m	1.65–1.74(m, 2H, $GeCH_2$), 2.24–2.34(m, 2H, CH_2CO), 5.96(dd, 1H, CHPO, $^2J_{PH}$=22.94Hz, $^3J_{HH}$=9.40Hz), 6.43(br., 1H, CONH), 6.86–8.29(m, 29H, Ph).
10n	1.65–1.74(m, 211, $GeCH_2$). 2.24–2.34(m, 2H, CH_2CO). 5.96(dd, 1H, CHPO, $^2J_{PH}$=22.94Hz, $^3J_{HH}$=9.40Hz), 6.43(br., 1H, CONH), 6.86–8.14(m, 29H, Ph).
10o	1.63–1.72(m, 2H, $GeCH_2$), 2.15–2.25(m, 2H, CH_2CO), 6.40(dd, 1H, CHPO, $^2J_{PH}$=21.90Hz, $^3J_{HH}$=9.16Hz), 6.58(br., 1H, CONH), 7.14–7.44(m, 28H, Ph).

The ^{31}PNMR data of products **10b, 10d, 10o** and the corresponding intermediate diphenyl α-aminophosphonate are listed in Table **III.** We saw from Table **III** that the more bulky substituent R is, the greater δ_p of the product; and δ_p of the product is less than δ_p of the corresponding intermediate α-aminophosphonate. This is due to a sterically hindered effect.

TABLE III ^{31}PNMR of **10b**, **10d**, **10o** and the corresponding diphenyl α-aminophosphonates

Compds.	*δ_p of product*	*δ_p of corresponding diphenyl α-aminophosphonate*
10b	18.53	22.52
10d	17.15	21.77
10o	13.12	16.15

The IR data of some products are listed in Table **IV**. Table IV shows that all absorption bands appeared as expected. For **10b,** 3244.0 cm^{-1} (s) was N-H stretching absorption band, 1675.7 cm^{-1}(s) was C=O stretching absorption band, 1589.2 cm^{-1} (s) and 1483.1 cm^{-1} (s) were phenyl ring stretching absorption bonds in group OPh, 1539.6 cm^{-1} (s) and 1429.5 cm^{-1} (s) were phenyl ring stretching absorption bands in group $GePh_3$, 1256.5 cm^{-1} (s) and 1229.8 cm^{-1} (s) were P=O stretching absorption bands, 575.9 cm^{-1} (w) was Ge-CH_2 stretching absorption band.

TABLE IV IR of some Products

Compds	*IR(cm^{-1})(KB_r)*
10b	3244.0(N-H); 3022.0, 2988.0, 2840.5(C-H); 1675.7(C=O); 1589.2, 1483.1(OPh); 1539.6, 1429.5($GePh_3$); 1256.5, 1229.8(P=O); 1181.3, 1155.8(C-O in Ph-O-P); 948.8, 936.0(P-O in P-O-Ph); 778.3, 758.3, 732.6, 695.1(Ph); 575.9(Ge-CH_2).
10d	3269.0(N-H); 3109.0, 2921.0, 2905.0(C-H); 1676.1(C=O); 1590.4, 1489.3(OPh); 1527.7, 1428.7($GePh_3$); 1262.0, 1205.9(P=O); 1086(C-O in P-O-Ph); 942.9, 928.5(P-O in P-O-Ph); 769.6, 735.2, 695.8(Ph); 584.6(Ge-CH_2).
10g	3246.0(N-H); 3055.5, 2917.5(C-H); 1670.4(C=O); 1588.6, 1529.4(OPh); 1487.1, 1428.5 ($GePh_3$); 1265.9, 1206.9(P=O); 1086.7, 1021.1(C-O in P-O-Ph) 958.3. 929.1(P-O in P-O-Ph); 772.7, 752.7, 732.7, 696.3(Ph): 593.6(Ge-CH_2).
10o	3295.0(N-H); 3061.5, 2948.5(C-H); 1688.1(C=O); 1590.5, 1532.2(OPh); 1505.4, 1429.8 ($GePh_3$); 1259.3, 1224.0(P=O); 1179.2, 1156.6(C-O in P-O-Ph); 949.4, 933.4(P-O in P-O-Ph); 794.3, 771.6, 735.0, 697.8(Ph); 589.5(Ge-CH_2).

The El-MS of product **10b** gave the molecular ion peaks 637(M^+) and the main fragments were those cleaving the bond of Ge-C [e.g. 305(Ph_3Ge^+), 227(Ph_2Ge^+), 151($PhGe^+$), 466($Ph_2GeCH_2CH_2C(O)NHC(Me) = P(O)OPh^+$), 326($Ph_2GeCH_2CH_2C(O)N{=}CHMe$)].

Biological activities of products

The results of bioassay showed that the new products have good anticancer activities and very strong anti-inflammatory activities. Table V and VI were listed anticancer activities and anti-inflammatory activities of some products, respectively.

TABLE V Anticancer Activities of some Products (in vitro)

Compds.	*Target of drag*	*Concention of drag*	*Inhibition rate (%)*	*IC50 (ug/ml)*
10b	KB	10ug/ml	53.0	9.4
	Bel-7402		32.7	>10
	HCT-8		42.3	>10
10d	KB		65.0	7.7
	Bel-7402		52.3	9.5
	HCT-8		77.3	6.1

TABLE VI Anti-inflammatory Activities of some Products on mice shedding granule from mast cells (in vitro)

Compds.	*Target of drag*	*Concention of drag*	*Inhibition rate(%)*	*IC50 (ug/ml)*
10b	mast cell	10ug/ml	100	2.42
10k			92.8	1.5
10o			100	0.3

EXPERIMENTAL

All the melting points were determined with Thomas-Hoover melting point apparatus and the thermometer was not standardized. IR spectra were recorded with a Shimadu-435. ^{1}HNMR spectra were recorded with Bruker AC-P200 using tetramethylsilane as an internal standard. ^{31}PNMR spectra were recorded with Bruker AC-P200 using 85% H_3PO_4 as an external standard. Mass spectra were recorded with HP5988A spectrometer using the EI method. Elemental analysis were carried out with a Yanaco CHN Corder MT-3 elemental analyzer.

General procedure for synthesis of Diphenyl N-triphenylgermanylpropiono-α-aminophosphonates **10:**

2.65 mmol of diphenyl α-aminophosphonate **6,** 0.60 g (2.92 mmol) of DCC and 0.41 g (5.3 mmol) of pyridine were dissolved in 25 mL of dried dichloromethane (or THF). The reaction mixture was cooled to below 0 °C in an ice-salt bath and stirred for 0.5 hr. To the stirred mixture was added dropwise I g (2.65 mmol) of β-triphenylgermanyl propanoic acid **9**, dissolved in 10 mL of dried dichloromethane (or THF), in a period of 20 minutes. After the addition, the mixture was stirred for approximately 5 hrs at 30–40 °C. To the reaction mixture was added several drops glacial acetic to destroy excess of DCC. The precipitate was filtered off, the filtrate was washed successively 2% aqueous hydrochloric acid, distilled water, 10% aqueous sodium bicarbonate, distilled water. The washed solution was dried with anhydrous magnesium sulfate and filtered, and the solvent was removed by distillation to give white solid. The white solid was purified by vacuum column chromatography on a silica gel using a mixture of petroleum ether (60–90 °C) and ethyl acetate as the eluent. Finally, colourless crystalline solid **10** was obtained.

Acknowledgements

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