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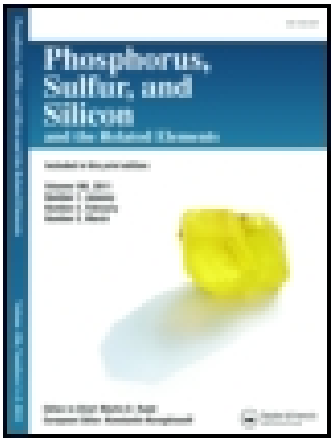

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THE SYNTHESIS OF NOVEL ORGANOGERMANIUM COMPOUNDS CONTAINING PHOSPHONIC ESTERS BY MANNICH-TYPE REACTION

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THE SYNTHESIS OF NOVEL ORGANOGERMANIUM COMPOUNDS CONTAINING PHOSPHONIC ESTERS BY MANNICH-TYPE REACTION

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A new kind of Mannich-type reaction involving an intramolecular catalysis mechanism was applied for the synthesis of α-aminogermyl phosphonic esters. It was found that the carbonyl group was activated by the coordination between the oxygen atom and the germanium atom. Different amines were investigated under the same reaction conditions. The structures of the products were determined by ^{1}H, ^{31}P NMR, IR spectra, and elemental analysis.

Keywords: Mannich reaction; intramolecular catalization; penta-coordination; germasesquioxides; α-aminophosphonates.

INTRODUCTION

The Mannich-type reaction is one of the convenient methods for the preparation of α-aminophosphonic acid derivatives, some of which have herbicidal and antitumor activities.[1,2] The mechanism may involve a nucleophilic attack from amine to aldehyde or acetone to form a hydroxyl intermediate.[3] Many Mannich-type reactions can be catalyzed by Lewis acids, which make carbonyl groups more active.[4] For some Mannich-type reactions, it is very difficult to proceed even in a strong protonic solvent, for example, as the reactant, amines connected with electron-drawing groups or alphatic aldehydes.[5,6] Up to now, Mannich-type reactions involving organogermanium compounds have not been investigated. Germasesquioxides have antitumor and other activities, but their high polymerizing power and poor solubilities often make their activities low.[7]

Recent studies show that germasesqiuoxides when modified by phosphonic acid groups[8] or combined with α-aminophosphonic acid groups[9] have high antitumor or antiinflammatory activities.

In order to find efficient medicines and study new Mannich-type reactions involved organogermanium compounds, we have synthesized a series of γ-organogermyl-α-aminophosphonates **1** by the reaction of different substituted amines, **2** with 3-trichlorogermylbutanal **3** and triphenyl phosphite. The principal advantages of this reaction are: the procedure is simple, the reaction proceeds smoothly under mild conditions, the yield and purity of the corresponding products are good.

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RESULTS AND DISCUSSION

Compound **3** reacted in acetic acid or dichloromethane with substituted amines **2** and triphenyl phosphite at certain temperatures for a short period (Table I) to produce diphenyl γ-trichlorogermyl-α-aminophosphonates **4.** The reaction process was monitored by ^{31}P NMR and TLC method. When no signal was detected for starting materials **2** and triphenyl phosphite, the following reaction sequence was observed. Intermediates **4** could not be isolated in pure form, and were directly converted into germasesquioxides **1** with water.

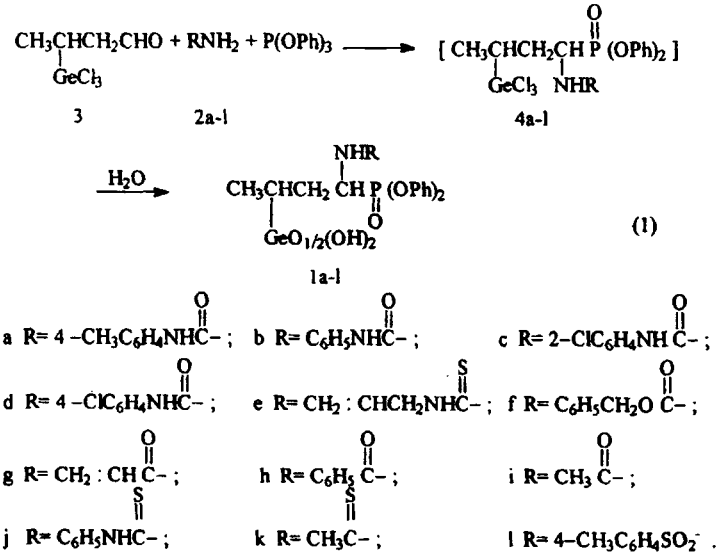

TABLE I The results and conditions of reaction of 3 with 2 and (PhO)P in AcOH

Compds.	*Reaction Conditions*		*Yields by ^{31}P NMR (%)*	*δp*	
	Temperature (°C)	*Time(min.)*			
4a	11	60	82.1	15.75,	16.28
4b	17	60	88.4	16.69,	17.23
4c	11	60	87.5	15.39,	16.02
4d	11	60	84.6	15.34,	15.88
4e	17	30	90.3	16.15,	16.69
4f	17	60	73.5	15.48,	16.02
4g	12	60	60.1	15.75,	16.69
4h	12	150	47.6	15.75,	16.64
4i	12	150	69.8	15.48,	16.02
4j	17	30	92.5	15.34,	16.02
4k	12	150	90.1	16.69,	17.23
4l	40	360	74.4	15.75,	16.15

The structures of compounds **1** have been confirmed by spectroscopic criteria (Tables II, III) and quantitative elemental analysis.

Table II ^{1}H and ^{31}P NMR data of compounds 1[a]

Compd.	^{1}H chemical shifts					^{31}P
	R[b]	CH_3CHGe[b]	CH_2[b]	CHP[b]	C_6H_5O[b]	
1a	8.39(s, 4-$CH_3C_6H_4\underline{NHC}$(=O)-) 2.21(s, 4-$\underline{CH_3}C_6H_4NHC$(=O)-) 7.00-7.82(m, 4-$CH_3\underline{C_6H_4}NHC$(=O)-)	1.06-1.15	1.90-2.19	3.40-3.77	7.00-7.82	19.65
1b	8.50(s, $C_6H_5\underline{NHC}$(=O)-) 6.72-7.62(m, $\underline{C_6H_5}NHC$(=O)-)	1.04-1.10	1.94-2.26	3.37-3.62	6.72-7.62	18.15 20.59

a. Solvent is CDCl3
b. Unresolved multiples

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Table II ^{1}H and ^{31}P NMR data of compounds 1[a] (continued)

1c	7.49(s, 2-ClC$_6$H$_4$NHC(=O)-) 7.00-7.80(m, 2-ClC$_6$H$_4$NHC(=O)-)	1.07-1.14	1.89-2.17	3.42-3.71	7.00-7.80	18.57
1d	7.43(s, 4-ClC$_6$H$_4$NHC(=O)-) 7.20-7.60(m, 4-ClC$_6$H$_4$NHC(=O)-)	1.08-1.17	1.94-2.26	3.37-3.62	7.20-7.60	18.17 18.66
1e	5.82(s, CH$_2$: CHCH$_2$NHC(=S)-) 5.10(s, CH$_2$: CHCH$_2$NHC(=S)-) 4.20(s, CH$_2$: CHCH$_2$NHC(=S)-)	1.06-1.13	1.96-2.13	3.31-3.60	7.00-7.65	19.73 20.77
1f	4.86(s, C$_6$H$_5$CH$_2$OC(=O)-) 6.60-7.40(s, C$_6$H$_5$CH$_2$OC(=O)-)	0.90-1.50	2.02-2.24	3.50-3.82	6.60-7.40	15.48 16.69
1g	6.26(s, CH$_2$: CHC(=O)-) 5.61(s, CH$_2$: CHC(=O)-)	1.10-1.21	2.00-2.23	3.47-3.74	7.00-7.60	16.69
1h	7.00-8.20(m, C$_6$H$_5$C(=O)-)	1.04-1.10	1.99-2.26	3.35-3.76	7.00-8.70	18.03 18.57
1i	2.46(s, CH$_3$C(=O)-)	1.05-1.24	1.92-2.18	3.23-3.54	6.92-7.54	18.14 18.96
1j	9.07(s, C$_6$H$_5$NHC(=S)-) 6.90-7.60(m, C$_6$H$_5$NHC(=S)-)	1.13-1.25	1.98-2.25	3.50-3.76	6.90-7.60	18.75 19.66
1k	2.40(s, CH$_3$C(=S)-)	1.00-1.23	1.88-2.21	3.20-3.49	7.00-7.41	18.26 19.32
1l	2.46(s, 4-CH$_3$C$_6$H$_4$SO$_2$-) 7.02-7.95(s, 4-CH$_3$C$_6$H$_4$SO$_2$-)	1.02-1.13	1.96-2.28	3.29-3.59	7.02-7.95	16.96 18.17

a. Solvent is CDCl3
b. Unresolved multiples

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TABLE III IR data of compounds 1

Compds.	*IR(cm^{-1}, KBr)*					
1a	3355.5	3045.5	2911.0	1649.4	1594.4	1540.0
	1511.6	1487.2	1452.4	1311.6	1291.2	1201.6
	1157.2	1064.8	933.1	868.8	786.4	714.0
1b	3362.5	3086.0	2941.0	1683.0	1651.9	1593.4
	1544.0	1507.2	1486.3	1439.8	1309.9	1200.8
	1179.6	1156.3	1063.8	978.5	932.1	867.8
	752.2	686.5				
1c	3369.5	3109.5	2939.0	1693.0	1652.4	1590.3
	1531.2	1486.9	1453.7	1229.8	1201.6	1180.6
	1156.9	1065.0	1022.0	934.4	871.5	752.9
	704.0					
1d	3367.2	3108.8	2919.7	1694.4	1658.5	1587.6
	1529.8	1486.7	1452.9	1227.6	1201.8	1182.7
	1160.4	1065.0	1028.1	934.4	869.6	748.8
1e	3383.5	3248.0	3046.0	2908.0	1634.8	1588.2
	1540.9	1486.6	1452.7	1249.6	1202.3	1180.1
	1157.0	1065.2	1021.6	981.9	935.4	873.7
	762.5	686.1				
1f	3375.5	3046.5	2916.0	1697.1	1649.0	1588.4
	1565.7	1509.3	1486.4	1451.6	1375.2	1248.9
	1204.1	1182.0	1021.1	932.3	868.4	761.8
	709.0	685.9				
1g	3378.5	3091.5	2914.5	1714.0	1658.2	1623.6
	1589.6	1562.5	1487.4	1453.2	1204.5	1180.2
	1157.5	1021.3	994.6	930.4	872.6	761.7
	727.4	686.8				
1h	3377.5	3146.2	2938.5	1643.1	1589.3	1524.8
	1486.8	1452.8	1306.0	1250.1	1204.7	1156.7
	1021.3	930.9	871.0	763.4	686.3	
1i	3369.4	3042.1	2938.4	1645.7	1587.4	1521.9
	1486.7	1452.8	1306.5	1250.1	1201.9	1155.8
	1021.3	930.7	869.0	762.9	687.5	
1j	3296.5	3043.5	2911.0	1702.7	1588.8	1527.9
	1486.1	1448.0	1380.2	1348.7	1314.6	1201.7
	1180.4	1157.2	1065.5	1021.6	935.8	872.8
	759.3	708.8	628.6			
1k	3272.0	3047.7	2907.9	1635.7	1587.7	1521.3
	1486.7	1452.7	1243.8	1203.9	1178.3	1157.0
	1065.3	1023.8	1021.7	11805	1149.8	1038.9
	1022.7	935.8	872.9	758.3	686.4	
1l	3371.5	3252.0	3053.0	2910.5	2591.5	2484.0
	1589.1	1486.4	1451.4	1328.4	1204.5	1181.2
	1153.7	1111.9	1020.3	990.6	930.4	871.8
	761.6	701.0	662.0			

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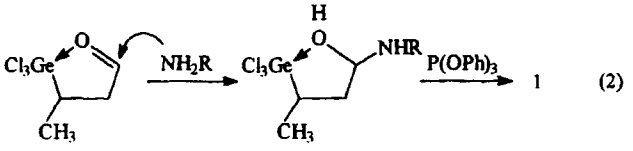
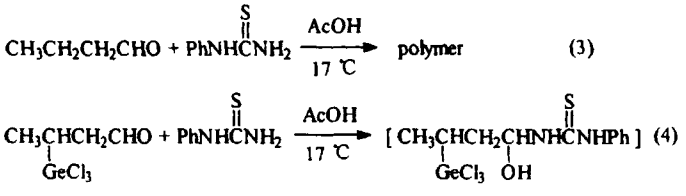
Compared with similar Mannich-type reactions without an organogermanium group involved, the reaction (Equation (1)) conditions are mild. It can proceed easily at low temperature in a short time in a protonic solvent or even in a non-protonic solvent. This can be explained as being due to the intramolecular catalytic mechanism. The existence of empty 4d orbitals made the germanium atom easily form a oordinated bond with an electron-donor(intramolecular coordination or intermolecular coordination). When the germaniums-atom was bonded to strong electron-drawing atoms or groups, the coordination trend would be increased. In compound 3, the germanium atom was bonded tp the three chlorine atoms, the oxygen atoms of the carboxyl group interacted with germanium atom to form the fifth coordinated bond, which made the carbon atom more positive, and easily attacked by nucleophilic agents.



(2)

Besides mild reaction conditions and a short reaction period, other experimental observations that could explain the mechanism were investigated.

1. IR spectrum of 3-trichlorogermylbutanal and that of butanal were different. The strengthening and winging vibration of the carbonyl group in 3-trichlorogermylbutanal were very weak compared with those of butanal, which might be due to the coordination betwen the carbonyl group and the germanium atom resulting in the formation of a five-membered ring. It has also been proven by ^{35}Cl NMR that intramolecular coordination exists in organogermanium compounds containing trichlorogermyl and carbonyl groups.
2. Two reactions below were investigated:



The product of reaction (3) was reported by G.H. Birum in 1974. The product of reaction (4) could not be isolated in pure form, and its structure was directly determined by ^{1}H NMR with CF_3CO_2H as the solvent. The reactions were monitored by TLC method.

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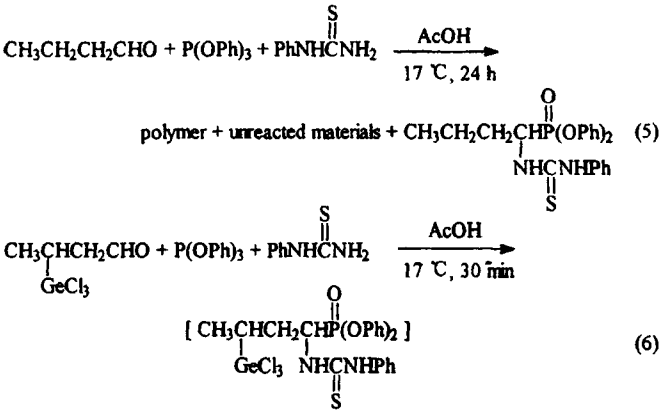
Similar reactions were also investigated:

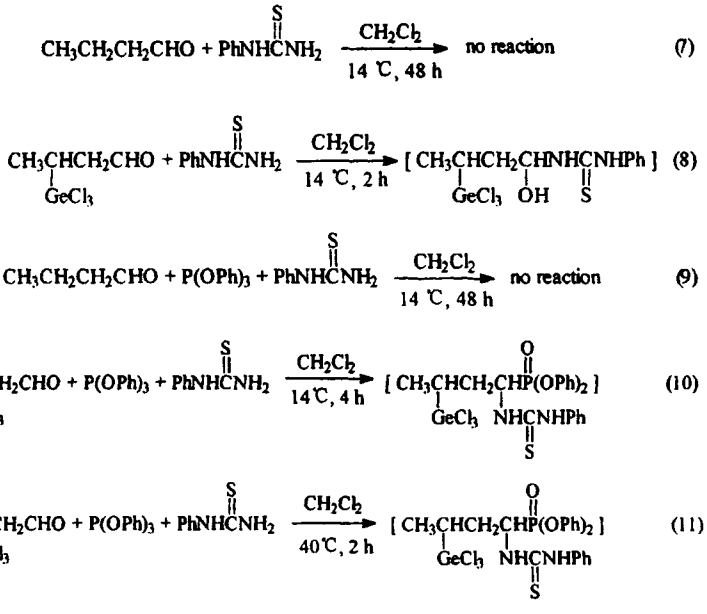


(5)

(6)

The reactions were monitored by ^{31}P NMR and TLC. Reaction (5) could not stop until the polymer product was formed.

3. Five reactions below were investigated:



(7)

(8)

(9)

(10)

(11)

The above reactions were monitored by ^{31}PNMR and TLC method. Reactions (7) and (9) could not occur without acidic catalysts. Reactions(8), (10) and (11) proceed smoothly and rapidly.

4. The reaction of 3-trichlorogermylbutanal with substituted amines and triphenyl phosphite could not be inhibited by weak Lewis base (e.g. $P(OEt)_3$) or strong Lewis base(e.g. Et_3N).

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Reactions (3) and (5) produced polymeric products, but reaction (4) and (6) did hot. This could be explained by the coordination between hydroxyl and germanium atom (see Equation (2)). The coordination between oxygen atom and germanium atom weakened the nucleophilic ability of the oxygen atom to the carbonyl group of the aldehyde, and resulted in no polymer formation. Reactions (8), (10) and (11) could take place in non-protonic solvent without catalyst, but reactions(7) and (9) could not. All of these were ascribed to the ability of germanium to form penta-coordination structures.

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EXPERIMENTAL

^{1}H, ^{31}P NMR spectra were run on a JEOL FX–90Q spectrometer. ^{1}H chemical shifts are reported in parts per million-- relative to internal tetramethylsilane. All ^{31}P NMR chemical shifts are reported in parts per million relative to 85% phosphoric acid(external). In all cases the nuclei which are deshielded relative to their respective standard are assigned a positive chemical shift. ^{31}P NMR spectra were obtained using full proton coupling. ^{31}P NMR spectra were acquired by using a 90°C tip angle and a 2-40 repetition rate with no pulse delay. IR spectra were run on a DS-301 spectrometer. Quantitative elemental analyses were run on a Yana MT-3. The wave length of UV light used in TLC was 253.7nm, and the spreading agent was petroleum ether-acetone (4:1).

3-Trichlorogermylbutanal / amines / triphenylphosphite reaction

To the solution of 3-trichlorogermylbutanal(5mmol) in gl. acetic acid (25ml). amine (5mmol) was added. The reaction mixture was stirred at room temperature until the solid was dissolved completely. Then triphenyl phosphite(5mmol) was added. The reaction was examined by TLC and ^{31}P NMR per half an hour. A sealed capillary tube containing trimethyl phosphate was placed in the NMR tube. The disappearance of the signal meant the cessation of the reaction.

General procedure for the preparation of compounds 1a-l

The above procedure was carried out, and then the reaction mixture was concentrated by evaporation under vacuum. The residue was hydrolysed with water to give a white solid which was recrystallized from a mixture of DMF and benzene to give compounds **1a-l.**

1a. 76.2% yield, mp>300°C . Anal. Calcd. for $C_{24}H_{28}GeN_2PO_{6.5}$:
C, 52.72; H, 4.94; N, 5.08. Found: C, 51.83; H, 4.64; N, 4.97

1b. 84.9% yield, mp>300°C. Anal. Calcd. for $C_{23}H_{26}GeN_2PO_{6.5}$:
C, 51.35; H, 4.87; N, 5.21. Found: C, 51.24; H, 4.28; N, 5.36
1c. 82.7% yield, mp>300°C. Anal. Calcd. for $C_{23}H_{25}ClGeN_2PO_{6.5}$:
C, 48.26; H, 4.40; N, 4.89. Found: C, 48.26; H, 4.80; N, 4.80
1d. 80.7% yield, mp>300°C. Anal. Calcd. for $C_{23}H_{25}ClGeN_2PO_{6.5}$:
C, 48.26; H, 4.40; N, 4.89. Found: C, 48.34; H, 4.65; N, 4.84
1e. 87.3% yield, mp>300°C. Anal. Calcd. for $C_{20}H_{26}GeN_2PO_{5.5}S$:
C, 46.38; H, 5.06; N, 5.41. Found: C, 46.20; H, 4.71; N, 5.62
1f 86.6% yield, mp>300°C. Anal. Calcd. for $C_{24}H_{27}GeNPO_{7.5}$:
C, 52.13; H, 4.92; N, 2.53. Found: C, 52.16; H, 4.63; N, 2.55
1g. 69.8% yield, mp>300°C. Anal. Calcd. for $C_{19}H_{23}GeNPO_{6.5}$:
C, 48.26; H, 4.90; N, 2.96. Found: C, 48.30; H, 4.60; N, 2.81
1h. 68.4% yield, mp>300°C. Anal. Calcd. for $C_{23}H_{25}GeNPO_{6.5}$:
C, 52..82; H, 4.82; N, 2.69. Found: C, 52.77; H, 4.87; N, 2.56
1i. 64.5% yield, mp>300°C. Anal. Calcd. for $C_{18}H_{23}GeNPO_{6.5}$:
C, 45.33; H, 4.86; N, 2.93. Found: C, 45.19; H, 4.61; N, 3.05
1j. 89.4% yield, mp>300°C. Anal. Calcd. for $C_{23}H_{26}GeN_2PO_{5.5}S$:
C, 49.87; H, 4.73; N, 5.06. Found: C, 49.81; H, 4.99; N, 5.34
1k. 42.3% yield, mp>300°C. Anal. Calcd. for $C_{18}H_{23}GeNPO_{5.5}S$:
C, 45.33; H, 4.86; N, 2.93. Found: C, 45.19; H, 4.61; N, 3.05
1l. 51.4% yield, mp>300°C Anal. Calcd. for $C_{23}H_{27}GeNPO_{7.5}$:
C, 48.22; H, 4.75; N, 2.45. Found: C, 47.98; H, 4.71; N, 2.52

Acknowledgements

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