

The Synthesis of Novel Phosphonodipeptides and Their Herbicidal Activity

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ABSTRACT

A series of novel phosphonodipeptides has been synthesized from diphenyl α -aminoalkylphosphonates and *N*-chloroacetyl-*N*-alkyl (or aryl)glycine ethyl esters. The structures of all the compounds prepared were proved by ^1H NMR, IR, MS, and elemental analyses. The bioassay tests showed that some of the compound have good herbicidal activity.

INTRODUCTION

The biologically active aminoalkanephosphonic acids have stimulated the development of methodology to obtain new compounds in this field [1-7]. The α -aminoalkane (or aralkyl)phosphonic acids and their derivatives have been prepared by various methods [1-16].

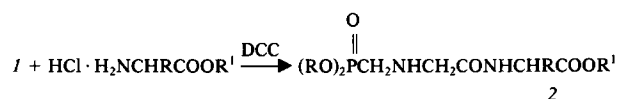
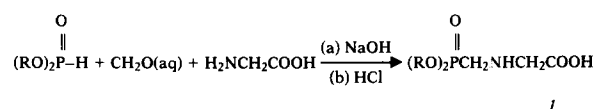
For the purpose of finding new, effective, and selective herbicides, we have designed and synthesized a number of new phosphonodipeptides **5** and cyclic peptides **6** containing a glyphosate group. Preliminary bioassays indicate that **5** and **6** have high herbicidal activity.

RESULTS AND DISCUSSION

A. Synthesis of Phosphonodipeptides and Cyclodipeptides

An attempt to prepare the chain phosphonodipeptides **2** by the method shown in Scheme 1 failed,

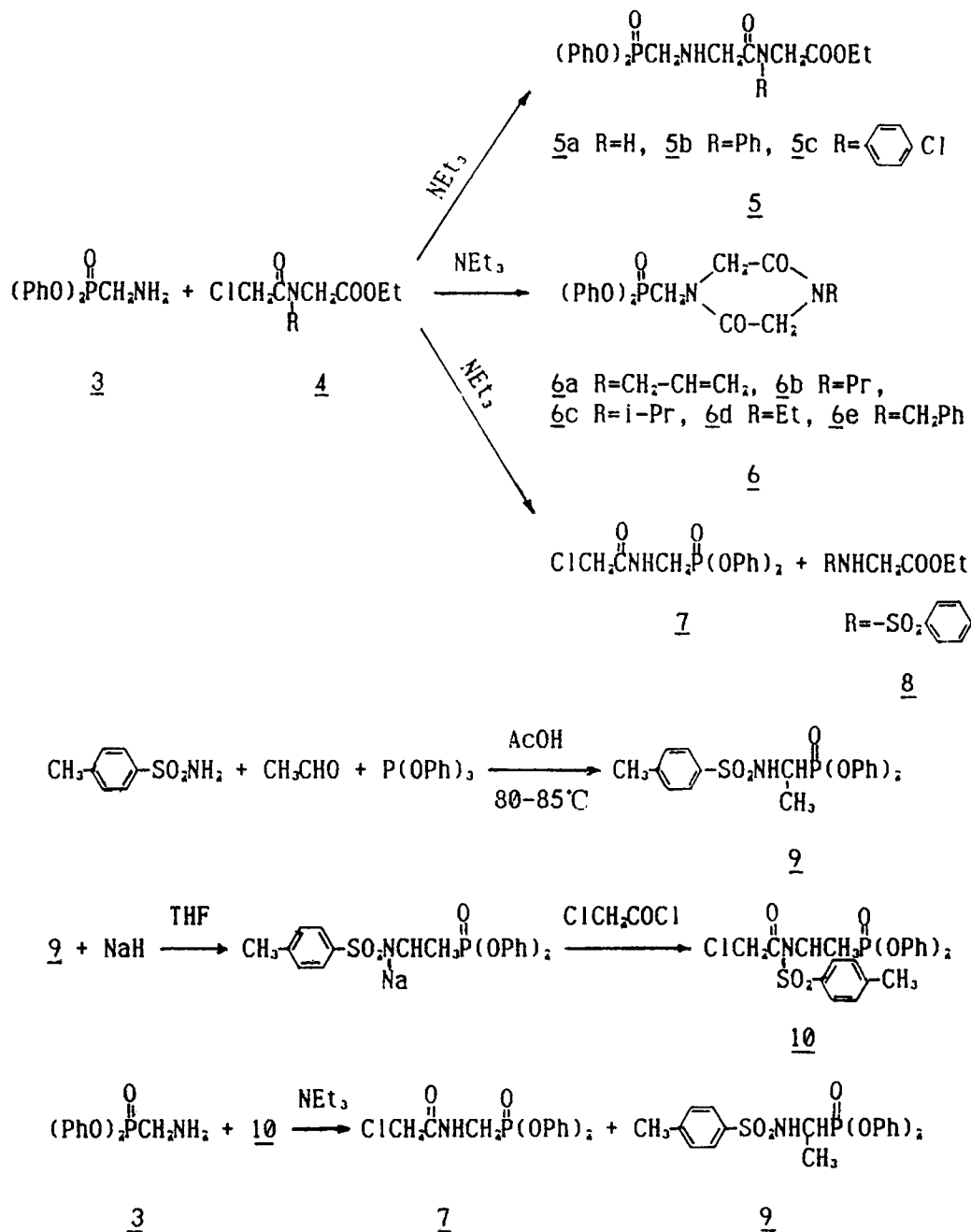
because it was very difficult to purify intermediate **1** from the mixture which was very viscous and hygroscopic.



SCHEME 1

In view of the above fact, we designed a new route, as shown in Scheme 2. Treatment of diphenyl aminomethanephosphonate (**3**) with *N*-chloroacetyl-*N*-alkyl(aryl or hydrogen or phenylsulfonyl)glycine ethyl ester (**4**) in the presence of triethylamine gave various products, depending on the substituent R on the N atom of compounds **4**. When R = aryl or hydrogen, the chain dipeptides **5** were formed. When R = alkyl, the products were the cyclic dipeptides **6**. However, when R = phenylsulfonyl, the products **7** and **8** were obtained, resulting from the cleavage of the C-N bond. Similarly, the reaction of **3** with **10** produced esters **7** and **9** via cleavage of the C-N bond. This is probably due to the fact that the strong electron withdrawing groups, phenylsulfonyl and p-tolylsulfonyl, decrease the electronic density at N so that the C-N bond becomes weak.

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SCHEME 2

B. The Structures of the Products

The molecular structures of **3**, **4**, **5**, **6**, **7**, **8**, **9**, and **10** were confirmed by ¹H NMR and MS spectra as well as by IR and/or elemental analysis. Results of **5** and **6** have been listed in Table 1.

The ¹H NMR spectral data of the dipeptides **5** and **6** are listed in Table 1. The ¹H NMR spectra of cyclodipeptides **6** showed the resonance of the two protons of the methylene group near the phosphorus atom (a doublet, δ = 4.18–4.25) at a lower field than that of the chain dipeptides **5** (a doublet,

δ = 3.30–3.80). The difference results from the deshielding effects of the carbonyl group in the ring. The methylene and methyl protons of the ethoxy group and the NH proton of **5** appeared as a quartet (δ = 4.20), a triplet (δ = 1.18–1.30), and a broad singlet (δ = 2.25), separately. In contrast, compounds **6** did not show the resonance of these groups. This is consistent with their structures.

The ³¹P NMR spectrum of **6a** showed a singlet at δ = 12.7410, which was attributable to the P-atom of the diphenoxyphosphinoyl group (Ref. [17]: δ = 11–13).

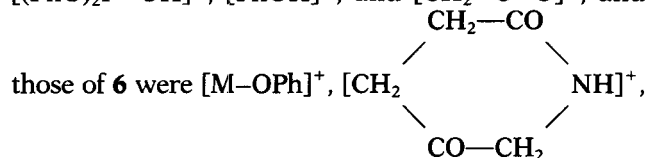
TABLE 1 The Data of Compounds 5 and 6 [22]

Compounds	R	Yield (%)	mp (°C) or Rf	MS (M ⁺)	¹ H NMR and ³¹ P NMR (ppm)	IR (cm ⁻¹)
8a ^a	H	78.8	0.220	406	7.54 (m, 1 H, NH), 7.18 (m, 10 Harom), 4.10 (q, 2 H, CH ₂), 3.90 (d, 2 H, CH ₂), 3.80 (s, 2 H, CH ₂), 3.60–3.30 (d, 2 H, CH ₂), 2.25 (s, 1 H, NH), 1.18 (t, 3 H, CH ₃)	3289 3051 2939 1739 1663 1589 1486 1206 1184 927
8b	C ₄ H ₅	50.0	0.443	482	7.41–7.12 (m, 15 Harom), 4.38 (s, 2 H, CH ₂), 4.26–4.15 (q, 2 H, CH ₂), 3.40 (s, 2 H, CH ₂), 3.37–3.31 (d, 2 H, CH ₂), 2.25 (s, 1 H, NH), 1.30–1.24 (t, 3 H, CH ₃)	3277 3046 2938 1738 1661 1589 1486 1203 1181 925
8c	p-ClC ₆ H ₅	53.0	0.565	516	7.34–7.13 (m, 14 Harom), 4.35 (s, 2 H, CH ₂), 4.21–4.18 (q, 2 H, CH ₂), 3.47 (s, 2 H, CH ₂), 3.34–3.37 (d, 2 H, CH ₂), 2.26 (s, 1 H, NH), 1.30–1.23 (t, 3 H, CH ₃)	3290 3050 2940 1740 1660 1588 1485 1205 1182 927
9a ^b	CH-CH=CH ₂	60.0	88–89	400	7.36–7.14 (m, 10 Harom), 5.72–5.64 (m, 1 H, CH), 5.28–5.71 (m, 2 H, CH ₂), 4.29 (s, 2 H, CH ₂), 4.25–4.19 (d, 2 H, CH ₂), 4.01–3.97 (d, 2 H, CH ₂), 3.914–3.910 (d, 2 H, CH ₂), 31P NMR: 12.7410	3051 2909 1646 1587 1464 1206 1183 945
9b	Pr	55.0	0.315	402	7.37–7.14 (m, 10 Harom), 4.27 (s, 2 H, CH ₂), 4.25–4.20 (d, 2 H, CH ₂), 3.96 (s, 2 H, CH), 3.38–3.30 (t, 2 H, CH ₂), 1.62–1.51 (m, 2 H, CH ₂), 0.94–0.87 (t, 3 H, CH ₃)	3052 2919 1658 1588 1487 1207 1180 950
9c	1-Pr	55.0	0.400	402	7.36–7.14 (m, 10 Harom), 4.83–4.72 (m, 1 H, CH), 4.25 (s, 2 H, CH ₂), 4.25–4.20 (d, 2 H, CH ₂), 3.88 (s, 2 H, CH ₂), 1.16–1.11 (d, 6 H, CH ₃)	3049 2916 1660 1589 1486 1206 1181 945
9d	Et	47.4	0.320	388	7.37–7.17 (m, 10 Harom), 4.26 (s, 2 H, CH ₂), 4.24–4.19 (d, 2 H, CH ₂), 3.96–3.95 (d, 2 H, CH ₂), 3.49–3.38 (q, 2 H, CH ₂), 1.18–1.10 (t, 3 H, CH ₃)	3053 2913 1661 1588 1484 1204 1182 942
9e	CH ₂ Ph	50.0	0.572	450	7.31–7.17 (m, 15 Harom), 4.55 (s, 2 H, CH ₂), 4.33 (s, 2 H, CH ₂), 4.23–4.18 (d, 2 H, CH ₂), 3.84 (s, 2 H, CH ₂)	3051 2915 1662 1580 1489 1204 1183 945

^aSatisfactory microanalyses obtained: C, ±0.32; H, ±0.10; N, ±0.15.

^bSatisfactory microanalyses obtained: C, ±0.30; H, ±0.21; N, ±0.31.

The EI mass spectra of **5a**, **5b**, and **5c** showed the molecular ion peaks (M: 406, 482, and 516, respectively), and those of compounds **6a**, **6b**, **6c**, **6d**, and **6e** also indicated molecular ion peaks (M: 388, 402, 402, 400, 450, separately). The main fragmentation products of **5** were [(PhO)₂P(O)CH₂NHCH₂]⁺, [(PhO)₂P=OH]⁺, [PhOH]⁺, and [CH₂=C=O]⁺, and



The IR spectra of **5** showed the normal stretching absorption bands, indicating the existence of the NH (~3290 cm⁻¹), P = O (~1200 cm⁻¹), P-O-Ar (~975 cm⁻¹), Ar C=C (~3050, 1580, 1480 cm⁻¹),

and carbonyl of amide and ester group (~1660, 1740 cm⁻¹). The compounds **6** also showed the stretching absorption bands of P=O, (~1200 cm⁻¹), P-O-Ar, (~945 cm⁻¹), Ar C=C (~3050, 1580, 1480 cm⁻¹), and carbonyl of the amide group (~1660 cm⁻¹) but did not show those of NH and carbonyl of the ester group.

Herbicidal Activity

The preliminary screening tests were carried by spraying the seedlings of the plants with the solutions of the compounds **5** and **6**, respectively, in DMF at the rate of 0.01 kg/ha. The results are given in Table 2. It was found that most of them showed herbicidal activities. Compound **5a** had a high inhibiting effect against barnyard grass and crabgrass, and compounds **5c**, **6a**, **6b**, **6c**, **6d**, and **6e** could inhibit the growth of rape significantly.

TABLE 2 Herbicidal Activities of 5 and 6

Compounds	[Lucerne]	Rape	Inhibiting Rate (%)			
			Oat	Barnyard Grass	Crabgrass	Sorghum
5a	55.6	61.7	—	100	100	—
5b	19.4	20.2	14.5	56.8	—	31.3
5c	27.6	73.2	37.7	29.7	—	29.3
6a	33.3	96.2	23.2	30.0	—	24.6
6b	32.8	28.6	13.3	0.0	—	31.7
6c	28.0	90.6	24.5	28.1	—	40.6
6d	31.2	92.3	4.9	54.8	—	31.3
6e	48.8	100	8.5	26.6	—	28.7

EXPERIMENTAL

Instruments

Elemental analysis was performed with a CHN CORDERD MT-3 elementary analyzer. Mass spectra were recorded with a VG-7070E spectrometer using the GAB method. ^1H NMR was recorded with a JEOL-FX-90Q spectrometer and BRUKER AC-P200. TMS was used as an internal standard for ^1H NMR, and 85% H_3PO_4 was used as an external standard for ^{31}P NMR. The IR spectra were measured by using a SHIMADZU-435 instrument. Melting points were determined with a model YANACO MP-500 apparatus. Column chromatography was performed on silica gel H (10–40 μm HaI Yang Chemical Factory of Qingdao) using 1,4-dioxane/chloroform (1:10 or 1:20) as the eluent.

Amino acids were available commercially and used without purification. Chloroform was freed from ethanol by washing with concentrated H_2SO_4 , and water, dried, and distilled from P_2O_5 . 1,4-dioxane was dried with potassium hydroxide, and benzene was dried with sodium. Both $\text{P}(\text{OPh})_3$ and NEt_3 were freshly distilled before being used. Benzyl carbamate [18], diphenyl aminomethylphosphonate [11], the N-alkyl(aryl)glycine ethyl ester [19], the N-alkyl(aryl or hydrogen)-N-chloroacetyl-glycine ethyl ester [20], and N-chloroacetyl-N-phenylsulfonylglycine ethyl ester [21] were prepared according to conventional methods.

Diphenyl 1-(*p*-tolylsulfonamido)ethane Phosphonate (9)

A mixture of 15.5 g (0.05 mol) of triphenyl phosphite, 8.6 g (0.05 mol) of *p*-tolylsulfonamide, 3.3 g (0.075 mol) of freshly distilled acetaldehyde, and 7.5 ml of glacial acetic acid was stirred for 1 hour until the exothermic reaction subsided. The mixture was then heated at 80–85°C for 3 hours and decolorized with activated carbon. The solvent was removed on a rotary evaporator under reduced pressure with heating on a boiling water bath. The product was recrystallized (chloroform-petroleum

ether) and had a melting point of 156–157°C (12.5 g, 58.0%). ^1H NMR (CDCl_3) δ : 7.71–6.95 (m, 14 Harom), 5.73–5.56 N (q, 1 H, NH), 4.31–3.94 (m, 1 H, CH), 2.31 (s, 3 H, CH_3), 1.34–1.21 (q, 3 H, CH_3). Elemental analysis: $\text{C}_{21}\text{H}_{22}\text{NO}_5\text{PS}$ (%) Calc.: C, 58.47; H, 5.10; N, 3.25. Found: C, 58.61; H, 5.34; N, 3.05.

Diphenyl N-chloroacetyl-1-(*p*-tolylsulfonamide)ethanephosphonate (10)

To a solution of 8.6 g (0.02 mol) of diphenyl 1-(*p*-tolylsulfonamido)ethanephosphonate (9) in 30 ml anhydrous tetrahydrofuran was added 0.6 g (0.02 mol, 80%) of sodium hydride in portions with vigorous stirring at room temperature. After the addition, the mixture was stirred for 1 hour and a solution of 2.3 g (0.02 mol) of chloroacetyl chloride in anhydrous THF was added dropwise. The mixture continued to be stirred for 3 hours at room temperature. After removal of the precipitate of sodium chloride, the solvent was concentrated by use of a rotary evaporator. The product was recrystallized from acetone-petroleum ether, (4.6 g, 45.3%), mp 117–119°C. ^1H NMR (DCCl_3) δ : 7.75–7.01 (m, 14 Harom), 4.85–4.70 (m, 1 H, CH), 4.79–4.40 (q, 2 H, CH_2Cl), 2.41 (s, 3 H, CH_3), 1.87–1.75 (q, 3 H, CH_3). Elemental analysis: $\text{C}_{23}\text{H}_{23}\text{ClNO}_4\text{PS}$ (%) Calc.: C, 54.38; H, 4.53; N, 2.76. Found: C, 54.15; H, 4.64; N, 2.57.

Phosphonodipeptides (5)

A mixture of 0.005 mol of N-aryl(or hydrogen)-N-chloroacetyl-glycine ethyl ester, 0.005 mol of diphenyl aminomethanephosphonate, 0.006 mol of triethylamine, and 15 ml of benzene was refluxed at 80°C for 10 hours with stirring. Triethylamine hydrochloride was removed by filtration. The product was purified by flash chromatography on a silica gel column using a mixture of chloroform and dioxane (10:1 v/v) as the eluent. The results are given in Table 1.

Cyclophosphonodipeptides (6)

A mixture of 0.005 mol of N-alkyl-N-chloroacetyl-glycine ethyl ester, 0.005 mol of diphenyl aminomethanephosphonate, 0.006 mol of triethylamine, and 15 ml of benzene was refluxed for 27 hours with stirring and then allowed to cool. After removal of the precipitate of triethylamine hydrochloride by filtration, the filtrate was concentrated by rotary evaporation. The product was chromatographed on a silica gel column using a mixture of chloroform and dioxane (10:1 v/v) as solvent. The results are given in Table 1.

The Reaction of Diphenyl Aminomethanephosphonate and N-chloroacetyl-N-phenylsulfonylglycine Ethyl Ester

A mixture of 1.3 g (0.005 mol) of diphenyl aminomethanephosphonate, 1.6 g (0.005 mol) of N-chloroacetyl-N-phenylsulfonylglycine ethyl ester, 0.5 g (0.005 mol) of triethylamine, and 15 ml of benzene was refluxed for 10 hours with stirring. The solution showed that the spots of the original materials had disappeared on silica gel TLC with the solvent mixture of chloroform and dioxane (20:1 v/v). The solution was concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 1:1 and chloroform:dioxane = 20:1, successively). Two products, **7** and **8**, were obtained. The first was diphenyl N-chloroacetylaminomethanephosphonate (**7**) (0.4 g, 23.5%), mp 106–108°C. Elemental analysis: C₁₅H₁₅ClNO₄P(%) Calc.: C, 53.02; H, 4.42; N, 4.12. Found: C, 53.06; H, 4.35; N, 4.04. ¹H NMR(CDCl₃) δ: 7.44–7.08 (m, 10 Harom), 4.14–4.00 (q, 2 H, CH₂, J_{PH} = 5.5 Hz), 4.01 (s, 2 H, CH₂). The second was N-phenylsulfonylglycine ethyl ester (**8**) (0.5 g, 41.7%), mp 63–64°C. Elemental analysis: C₁₈H₁₃NO₄S(%) Calc.: C, 49.38; H, 5.35; N, 5.76. Found: C, 49.58; H, 5.70; N, 5.87. ¹H NMR(CDCl₃) δ: 7.96–7.56 (m, 5 Harom), 5.40–5.24 (t, 1 H, NH), 4.22–3.98 (q, 2 H, CH₂), 3.84–3.78 (d, 2 H, CH₂), 1.28–1.12 (t, 3 H, CH₃).

Similarly, the reaction of diphenyl aminomethanephosphonate (**3**) with diphenyl N-chloroacetyl-1-(*p*-tolylsulfonamido)ethanephosphonate (**10**) gave compounds **7** and **9**. For compound **7**, yield

24.2%, mp 106–108°C. ¹H NMR(CDCl₃) δ: 7.44–7.08 (m, 10 Harom), 4.14–4.00 (q, 2 H, CH₂, J_{PH} = 5.5 Hz), 4.01 (s, 2 H, CH₂). For compound **9**, yield 50.0%, mp 156–157°C, ¹H NMR(CDCl₃) δ: 7.70–6.94 (m, 14 Harom), 5.73–5.56 (q, 1 H, NH), 4.31–3.94 (m, 1 H, CH), 2.31 (s, 3 H, CH₃), 1.34–1.21 (q, 3 H, CH₃).

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- [22] Note added in proof: Rhone-Poulenc has several patents (U. S. 4675429, 4738708, 4894082, and 4868269), describing a highly efficient synthesis of a compound that is closely related to some of the compounds described in this article.