Heteroatom Chemistry
Volume 8, Number 3, 1997

Synthesis of Novel Phosphonopeptide Derivatives and Their Biological Activity

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Received 30 July 1996; revised 16 December 1996

ABSTRACT

In order to search for novel herbicides with high activity and selectivity, a series of N-p-toluenesulfonyl phosphonopeptide derivatives has been designed and synthesized by the condensation reaction of diphenyl α-aminoalkylphosphonates and 1-p-toluenesulfonamido-acetyl chloride. Their structures were confirmed by ^{1}H NMR spectroscopy and elemental analyses. The results of bioassay showed that some of these compounds possess potential anti-TMV (Tobacco Mosaic Virus) activity. © *1997 John Wiley and Sons, Inc. Heteroatom Chem* **8***: 279–282, 1997.*

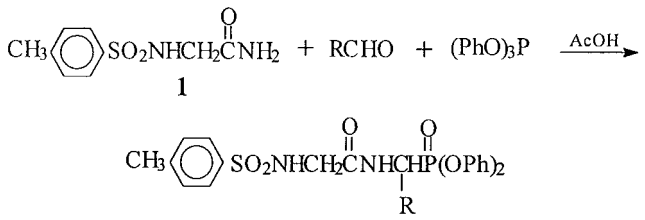
INTRODUCTION

The derivatives phosphonopeptides with an α-aminophosphonic acid in the C-terminal position possess many kinds of biological activities [1]. For example, Alaphosphin (L-ala-alap) shows remarkable fungicidal activity in very low concentration [2], while Bialaphos is a good herbicide [3]. For the purpose of the search for new, effective and selective herbicides, we decided to introduce the arylsulfonureado group, which played an important role in the famous sulfonurea-type herbicides, into the structure of phosphonopeptides, and therefore we synthesized a series of new phosphonopeptide derivatives. The results of bioassay showed that some of them possess potential herbicidal activity.

RESULTS AND DISCUSSION

Synthesis of Phosphonopeptides

There have been many articles concerning the synthesis of phosphonopeptides with an α-aminophosphonic acid in the C-terminal position, including the acid chloride method [4,5], activated ester method [6,7], condensation method [8,9], mixed anhydride method [10,11], and so on. All these methods, however, required an α-aminophosphonic ester to be synthesized as an intermediate, which often required multistep reactions to effectuate. Therefore, we wished to synthesize the title compound by the Mannich-type reaction of an easily obtained material **1** with aldehydes and triphenyl phosphite (as shown in Scheme 1). Unfortunately, we have not been able to isolate the pure title compounds. The possible reason is that there are two reactive sites in **1** making the reaction too complicated as evidenced by the fact that the ^{31}P NMR spectrum of the solution exhibits four peaks, and their chemical shifts are 14.0, 13.3, 9.8, and 5.2, respectively.



SCHEME 1

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Therefore, we designed a synthesis of the title compounds by a multistep route outlined in Scheme 2 (designated method A in the Experimental).

With glacial acetic acid as the solvent, both aliphatic aldehydes **3** and aromatic aldehydes **4** could be used to undergo the Mannich-type reaction with benzyl carbamate **2** and triphenyl phosphite **5** to prepare intermediate **7** [12]; however, when aromatic aldehydes were used, it was more convenient to synthesize **7** by using diphenyl phosphite **6** to replace triphenyl phosphite, due to the fact that there is no phenol produced in the course of the reaction so that the purification of **7** is simplified significantly [13]. Unfortunately, the attempt to use aliphatic aldehydes in this reaction failed to give the corresponding **7** in good yield.

We have also tried to prepare phosphonodipeptide **14** by the DCC condensation reaction of N-*p*-toluenesulfonyl glycine **12** with **9**. Compared with method A, it seemed that the step of chlorination of **12** could be bypassed. However, it was difficult remove the by-product dicyclohexylurea completely, thus making the work-up process complex. On the contrary, **13** reacted readily with **9** in anhydrous benzene with the help of triethylamine. When the reaction was finished, the product **14** precipitated together with triethylamine hydrochloride, which could be removed by washing with water. Then the pure **14** was easily obtained by recrystallization from acetone and petroleum ether.

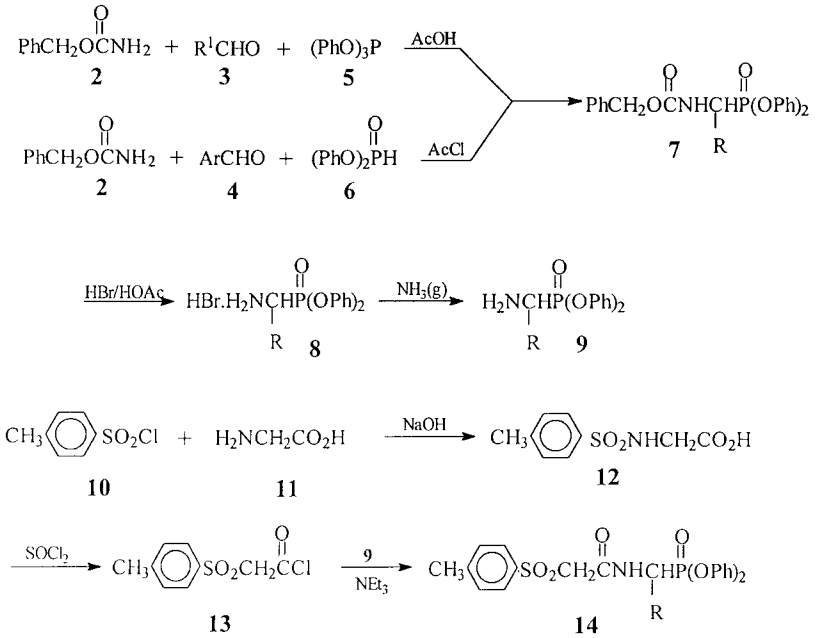
It was reported that the hydrobromide salt of diphenyl α-aminophosphonate **8** could not be used directly in the condensation reaction to prepare the phosphonopeptide [12]; nevertheless, our experiment revealed that **8** reacted smoothly with **12** with the help of two molar equivalents of triethylamine to give product **14**. Compounds **14a**, **14b**, and **14c** were synthesized by this method (method B).

The Structures of the Products

The molecular structures of product **14** were confirmed by ^{1}H NMR spectroscopy and elemental analyses. Their physical constants are listed in Table 1, and those of the ^{1}H NMR spectra, in Table 2. In the ^{1}H NMR spectra, the chemical shift of the H atom in CH (R = aryl) was at the range of δ 5.77–6.42. Owing to the deshielding effect of the α-benzene ring, these chemical shifts were much greater than those of CH (R = alkyl), which were in the range of δ 4.37–4.88. Moreover, the H atom in CH (R = aryl) exhibited a dd peak due to the coupling effects of the P atom and the (N-)H atom ($J^2_{\text{P-H}}$ = 22.00–22.78, $J^3_{\text{H-H}}$ = 5.77–6.42 Hz) while that when R = alkyl exhibited multiple peaks.

Biological Activity

The preliminary screening tests were carried out by spraying the seedlings of the plants with the solu-



SCHEME 2

TABLE 1 Physical Constants of Product **14**

Compounds	R	MP (°C)	Yield (%)	Elemental Analyses (%) Found (Calcd)		
				C	H	N
14a	Ph	189–190	31.5	61.20(61.09)	4.85(4.91)	5.18(5.09)
14b	*p*-Me-Ph	168–169	66.4	61.70(61.70)	5.18(5.14)	4.96(5.07)
14c	*o*-Cl-Ph	180–181	55.5	57.65(57.48)	4.50(4.45)	4.73(4.79)
14d	*m*-Cl-Ph	155–156	43.7	57.46(57.48)	4.36(4.45)	4.78(4.79)
14e	*p*-Cl-Ph	144–145	45.6	57.43(57.48)	4.42(4.45)	4.83(4.79)
14f	2,4-Cl_2-Ph	169–170	52.2	54.50(54.19)	4.51(4.55)	4.73(4.52)
14g	*p*-MeO-Ph	193–195	45.7	60.02(60.00)	5.06(5.00)	4.87(4.83)
14h	*o*-MeO-Ph	202–204	37.1	60.12(60.00)	5.01(5.00)	4.85(4.83)
14i	*m*-NO_2-Ph	177–179	42.5	56.14(56.47)	4.47(4.56)	4.96(5.07)
14j	*p*-NO_2-Ph	160–162	37.8	56.32(56.47)	4.45(4.56)	4.92(5.07)
14k	Me	138–139	53.0	56.53(56.56)	5.13(5.12)	5.64(5.74)
14l	*n*-Pr	150–151	56.7	58.24(58.14)	5.58(5.62)	5.41(5.42)
14m	*n*-Bu	139–141	53.5	58.79(58.87)	5.88(5.58)	5.26(5.28)
14n	*i*-Bu	152–153	81.2	58.90(58.87)	5.89(5.58)	4.98(5.28)

TABLE 2 ^{1}H NMR of Products **14**

Compd.	*p*-CH_3-Ph (*s, 3H*)	R (*s, 3H*)	CH_2 (*d, 2H*)	CH (*dd, 1H*)	$J^3_{H\text{-}H}$ (*Hz*)	$J^2_{P\text{-}H}$ (*Hz*)	Ph (*m*)	SO_2NH (*br. 1H*)	C(*O*)NH (*br. 1H*)
14a	2.32		3.49	5.85	9.56	22.04	6.76–7.64(19H)	5.19	7.87
14b	2.32	2.31	3.42	5.80	9.56	22.00	6.99–7.51(18H)	5.49	8.42
14c	2.31		3.49	6.42	9.54	22.78	6.78–7.51(18H)	5.20	8.00
14d	2.26		3.46	5.77	9.54	22.04	6.84–7.56(18H)	5.36	8.25
14e	2.33		3.49	5.80	9.55	22.24	6.84–7.63(18H)	5.39	8.07
14f	2.32		3.50	6.37	9.56	22.06	6.84–7.60(17H)	5.58	8.29
14g	2.29	3.78	3.40	5.77	9.56	21.32	6.75–7.55(18H)	5.25	8.02
14h	2.33	3.76	3.50	6.19	9.56	22.04	6.82–7.30(18H)	5.15	7.88
14i	2.30		3.51	5.95	9.54	22.78	6.95–7.63(18H)	5.51	8.29
14j	2.35		3.52	5.94	9.54	22.78	6.89–8.14(18H)	5.35	8.00
14k	7.08–7.68 (m, 15H, 2 × C_6H_5 + C_6H_4 + NH); 5.60 (br., 1H, SO_2NH); 4.81 (m, 1H, CH); 3.48 (d, 2H, CH_2); 2.38 (s, 3H, CH_3-Ph); 1.40 (dd, 3H, CH_3, $J^3_{H\text{-}H}$ = 7.23Hz, $J^3_{P\text{-}H}$ = 18.3Hz)								
14l	7.08–7.66 (m, 15H, 2 × C_6H_5 + C_6H_4 + NH); 5.62 (br., 1H, SO_2NH); 4.79 (m, 1H, CH); 3.46 (d, 2H, $CH_2C(O)$); 2.36 (s, 3H, CH_3-Ph); 1.85 (m, 2H, CH_2); 1.52 (m, 2H, CH_2); 0.86 (t, 3H, CH_3)								
14m	7.10–7.68 (m, 15H, 2 × C_6H_5 + C_6H_4 + NH); 5.63 (br., 1H, SO_2NH); 4.37 (m, 1H, CH); 3.48 (d, 2H, $CH_2C(O)$); 2.37 (s, 3H, CH_3-Ph); 1.95 (m, 2H, CH_2); 1.73 (m, 2H, CH_2); 1.32 (m, 2H, CH_2); 0.85 (t, 3H, CH_3)								
14n	7.10–7.68 (m, 15H, 2 × C_6H_5 + C_6H_4 + NH); 5.79 (br., 1H, SO_2NH); 4.88 (m, 1H, CH); 3.47 (d, 2H, $CH_2C(O)$); 2.37 (s, 3H, CH_3-Ph); 1.85 (m, 2H; CH_2); 1.43 (m, 1H, CH); 0.85 (t, 6H, 2 × CH_3)								

tions of the compounds **14**, respectively, in acetone at the dosage of 100 g/ha. Unfortunately, it was found that most of the products showed a low inhibiting effect (<50%) against herbicidal barnyard grass. However, we found, by chance, that some of the compounds possess potential anti-TMV (Tobacco Mosaic Virus) activity. For example, at 100 ppm, the inhibitory rate of compound **14e** to TMV attained 40%. Although phosphonopeptide derivatives have been reported to possess various biological activities, as far as we know, there is no report on their anti-TMV activity.

EXPERIMENTAL

Instruments

Elemental analyses were performed with a CHN CORDERD MT-3 elementary analyzer. ^{1}H NMR spectra were recorded with a Bruker AC-P200 spectrometer. TMS was used as an internal standard for ^{1}H NMR spectroscopy.

Glycine, paraformaldehyde, (substituted) benzaldehyde, and *p*-toluenesulfonyl chloride were available commercially and used without purification. Both triphenyl phosphite and triethylamine were

freshly distilled before being used. Benzyl carbamate **2**, diphenyl 1-benzyloxycarbonylaminomethylphosphonates **7** were prepared according to the literature [13,14] and diphenyl aminomethylphosphonate **9** [15], and N-toluenesulfonyl glycine [16] 1-*p*-toluenesulfonamidoacetyl chloride were prepared according to conventional methods.

Phosphonodipeptides (**14**)

Method A. To a solution of 1-*p*-toluenesulfonamidoacetyl chloride **12** (1.34 g, 5.4 mmol) and anhydrous benzene (10 mL), a mixture of anhydrous benzene (10 mL), diphenyl α-aminophosphonate (5.4 mmol), and triethylamine (0.55 g, 5.4 mmol) was added dropwise at 0°C. After the solution had been stirred at 0°C for 0.5 hours and then at ambient temperature for 1.5 hours, the solid produced was filtered off and washed repeatedly with water. The solid was then recrystallized from acetone and petroleum ether to give pure compound **14**. Compounds **14d–n** were synthesized by this method. Their data are listed in Tables 1 and 2.

Diphenyl p-toluenesulfonamido-acetyl-α-amino Phosphonates (**14**)

Method B. A mixture of anhydrous benzene (20 mL), 1-*p*-toluenesulfonamidoacetyl chloride 0.74 g (3 mmol) of **12** and the hydrobromide salt of diphenyl α-aminophosphonate (3 mmol) **8** was stirred in an ice-salt bath, and then 0.6 g of triethylamine (6 mmol) was added dropwise. After stirring had been continued at 0°C for 0.5 hour and then at room temperature for 6 hours, the solid was filtered off under reduced pressure and washed with water. The solid was then recrystallized from acetone and petroleum ether to give pure compound **14**. Compounds **14a**, **14b**, and **14c** were synthesized by this method. Their data are listed in Table 1 and 2.

ACKNOWLEDGMENT

This project was supported by the National Natural Science Foundation of China.

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