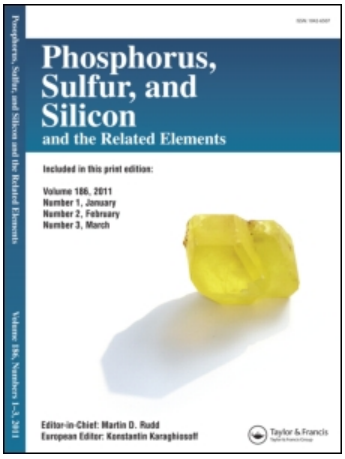


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# A NOVEL SYNTHESIS OF (N-ARYLSULFONYL)-PHOSPHONODIPEPTIDE DERIVATIVES

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# A NOVEL SYNTHESIS OF (N-ARYLSULFONYL)-PHOSPHONODIPEPTIDE DERIVATIVES

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In order to search for highly active and selective herbicides, a new type of phosphonopeptide derivatives were designed and synthesized by Mannich-type or Arbuzov-type reaction directly. The structures of new products were confirmed by $^{1}H$ NMR, $^{31}P$ NMR, IR spectra, MS and elemental analyses. The results of bioassay showed that some of them possess potential herbicidal activity.

*Keywords:* Phosphonopeptide; herbicide; Mannich-type reaction; Arbuzov-type reaction

## INTRODUCTION

The phosphonopeptide derivatives with α-aminophosphonic acid in the C-terminal position possess many kinds of biological activity. For example, Alaphosphin (L-ala-alap) shows remarkable fungicidal activity in very low concentration,[1] while Bialaphos is a good herbicide.[2] Therefore, it is possible to find good pesticides by modifying the structure of phosphonopeptide with active groups. All the DP-X type herbicides contain a sulfonureado group in their structure which plays an important role in their high herbicidal activity. Based on the structural specificity of these compounds, a new type of compound, (N-arylsulfonyl) – phosphonodipeptide derivatives was designed and a good synthetic method for them was sought.

Owing to the possession of various kinds of biological activity, the synthesis of phosphonpeptide derivatives with α- aminophosphonic acid in

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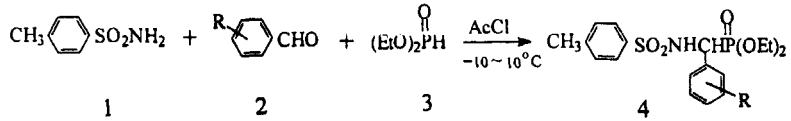
C-terminal has received much attention. Many synthetic routes have been developed, including the acid chloride method,[3,4] activated ester method,[5,6] condensation method (DCC method etc.),[7,8] and the mixed anhydride method[9,10]. All these methods, however, require α-amino-phosphonic esters be synthesized as intermediates, which often need muti-step reactions to obtain[11,12]. On the other hand, the Mannich-type reaction is well-known as an efficient method to build P – C – N bonds by a three-component reaction, therefore, it has been widely applied to the synthesis of α-aminophosphonic derivatives [13–20]. However, it has never been used for the synthesis of phosphonopeptide derivatives directly. In this paper, a facile route for the synthesis of the title compounds is described.



## RESULTS AND DISCUSSION

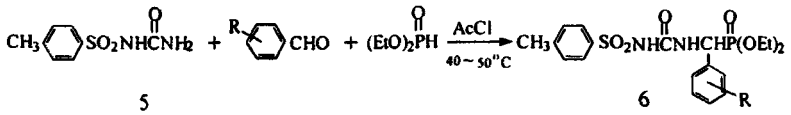
In 1990, Yuan et al. reported for the first time that acetyl chloride was an excellent solvent for the three-component reaction of benzyl carbamate, a benzaldehyde and dialkyl phosphite.[15–17] It was found that with acetyl chloride as the solvent, compound **4** could be prepared readily by the Mannich-type reaction of p-toluenesulfonamide **1**, aromatic aldehydes **2** and diethyl phosphite **3** (Scheme 1): [21]




1 2 3 4

SCHEME 1

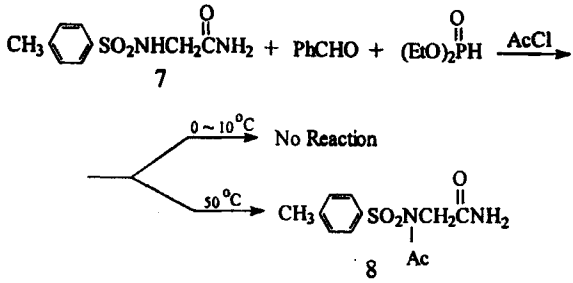
Similarly, compound **6** can be obtained by the Mannich-type reaction of compound **5** with **2** and **3** under higher temperature, 40~45 °C in this case. Obviously, the reaction activity of compound **1** is much higher than compound **5** (Scheme 2).




5 6

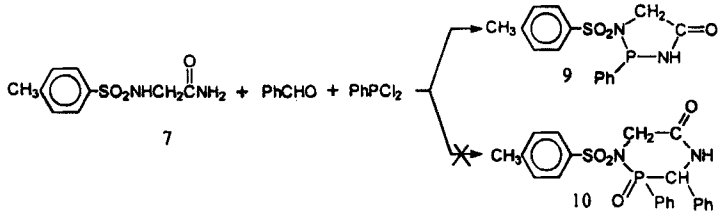
SCHEME 2

However, when N-*p*-toluenesulfonamido acetamide **7** was used instead of **1** or **5** to react with benzaldehyde and diethyl phosphite to synthesize the corresponding phosphonopeptide derivative, it was found that no reaction took place at low temperature while only a by-product **8** was obtained when the mixture is warmed up to 50 °C (Scheme 3).



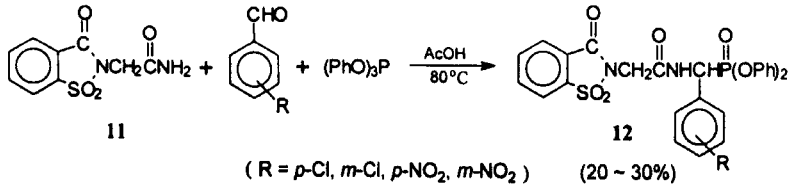

SCHEME 3

The Mannich-type reaction of **7** with benzaldehyde and phenyldichlorophosphine in anhydrous benzene also probably failed because there were two reaction sites in **7** making the reaction complicated. Only a by-product **9**, instead of the cyclic phosphinopeptide **10**, was obtained (Scheme 4)[22].



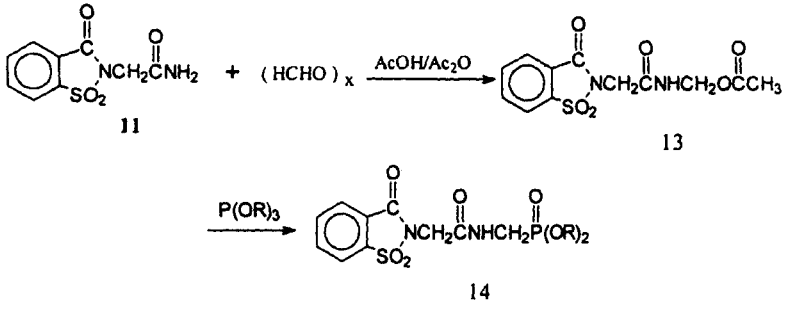

SCHEME 4

In order to protect the sulfonamido group, saccharinyl acetamide **11** was used to replace compound **7.** Although **11** could not react with aromatic aldehyde and diethyl phosphite in acetyl chloride, when Oledsyszyn's procedure was followed using glacial acetic acid as the solvent,[13] **11** reacted with aromatic aldehydes and triphenyl phosphite smoothly at 70–80 °C to give the corresponding phosphonodipeptide derivatives **12**[23] (Scheme 5).




SCHEME 5

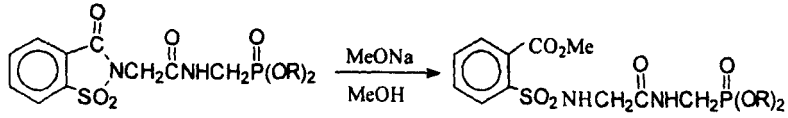
The advantage of using compound **11** as the starting material is that it can be prepared easily from the Na salt of saccharin and chloroacetamide in DMF[24]; unfortunately the yields of product **12** were only 20~30%. In order to improve the yields of product **12, 11** was reacted with paraformaldehyde first in the mixture of acetic acid and acetic anhydride at 90~100°C for 5 hours and then in 110°C for 2 hours. After removal of the volatile components in vacuo, a white solid obtained was recrystallized from a mixture of acetone and petroleum ether with a yield of 67%, The product was confirmed by $^1$H NMR spectrum and elemental analysis as N-acetoxymethylene-2-saccharinyl acetamide **13,** which then reacted with trialkyl phosphite at 110~130 °C for 2 hours to give compound **14** in yields of 86.6 ~93.1 %. This reaction is somewhat like the Arbuzov reaction (Scheme 6)[25,26].




SCHEME 6

To make the molecular structure as close as possible to that of the DP-X type herbicides, the bond between carbonyl group and N atom of the ring in compound **14** was attempted to be opened with NaOMe and MeOH to

give *ortho*-methoxycarbonyl-phenylsulfonglycyl-α-aminomethylenephosphonate **15** (Scheme 7).




14 15

SCHEME 7

The bioassays showed that compounds **14** and **15** possess potential herbicidal activity. Further tests are in progress.



TABLE I Physical Data of Compound **12**, **14** and **15**

| *Compd* | *R* | *Yield (%)* | *m.p (°C)* | *Calcd. (%)* | | | *Found (%)* | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *C* | *H* | *N* | *C* | *H* | *N* |
| **12a** | *p*-Cl | 22.1 | 209–210 | 56.34 | 3.69 | 4.69 | 56.51 | 3.77 | 4.67 |
| **12b** | m-Cl | 25.6 | 174–175 | 56.34 | 3.69 | 4.69 | 56.41 | 3.65 | 4.48 |
| **12c** | *p*-$NO_2$ | 31.2 | 235–236 | 55.3.5 | 3.62 | 6.92 | 55.57 | 3.49 | 6.70 |
| **12d** | *m*-$NO_2$ | 15.6 | 205–206 | 55.35 | 3.62 | 6.92 | 55.13 | 3.64 | 6.74 |
| **14a** | Me | 86.6 | 139–140 | 39.78 | 4.14 | 7.73 | 39.76 | 4.21 | 7.70 |
| **14b** | Et | 87.2 | 145–146 | 43.08 | 4.87 | 7.18 | 43.06 | 4.91 | 7.13 |
| **14c** | Pr | 92.5 | 152–154 | 45.93 | 5.50 | 6.70 | 46.00 | 5.53 | 6.87 |
| **14d** | *i*-Pr | 90.9 | 162–163 | 45.93 | 5.50 | 6.70 | 45.99 | 5.46 | 6.89 |
| **14e** | Bu | 87.5 | 130–131 | 48.43 | 6.05 | 6.29 | 48.43 | 6.11 | 6.35 |
| **14f** | *i*-Bu | 93.1 | 170–171 | 48.43 | 6.05 | 6.29 | 48.28 | 6.09 | 6.19 |
| **15a** | Me | 30.6 | oil | 39.74 | 4.97 | 6.96 | 39.59 | 4.86 | 7.11 |
| **15b** | Pr | 32.4 | oil | 45.48 | 5.94 | 6.96 | 45.33 | 6.10 | 6.93 |

## EXPERIMENTAL

*General notes.* the melting points were uncorrected. Elemental analyses were measured by Yanaco CHN Corder MT-3 apparatus $^1$H NMR were recorded on a Bruker AC-P 200 spectrometer by using TMS as internal and standards.

### 1. Synthesis of N-exthoxycarbonylmethylene 2- saccharinyl acetamide 13

A mixture of saccharinyl acetamide **11** (0.05 mol), 30 mL of acetic anhydride, 5 mL of acetic acid and paraformaldehyde (0.05 mol) was stirred in 90°C for 5 hours. Extra paraformaldehyde (0.025 mol) was added and stirring continued in 120°C for 2 hours. The volatile components was then removed under reduced pressure to give a white solid. The solid was then recrystallized from a mixture of acetone and petroleum ether to give pure product **13.** m.p. 147~148 °C, yield 67.1%, $^1$H NMR ($CDCl_3$, TMS, δ): 7.90~8.11 (4H, m, Ph), 5.25 (2H. d, $CH_2O$), 4.43 (2H, s, $CH_2C(O)$), 2.07 (3H, s, $CH_3$).

Anal. calcd.: C 46.15, H 3.85, N 8,97%

found: C 46.13, H 4.03, N 8.83%

### 2. Synthesis of product 12

A mixture of 5 mL of AcOH, saccharinyl acetamide **11** (5 mmol), substituted benzaldehyde (5 mmol) and triphenyl phosphite (5 mmol) was heated slowly to 70 °C. The temperature was kept at 70~80 °C for five hours and then the reaction mixture was cooled to room temperature. After standing overnight, the solid was filtered, washed with methanol, and then recrystallized from chloroform and methanol to give pure product. (In the case of no solid being produced directly, the volatile components was removed in vacuo. The oily residue was taken to a silica gel column and eluted with petroleum: ethyl acetate = 3:1 to give the pure product **12.** Physical data are listed in **table I**, and $^1$H NMR data in **table II.**

### 3. Synthesis of product 14

A mixture of **13** (0.01 mol) and 7 mL of trialkyl phosphite was stirred in 110~130 °C until the solid disappeared. After cooling to room temperature, the product **14** was filtered and washed with a mixture of petroleum ether and ethylacetate (4: 1). Physical data are listed in **table I**, $^1$H NMR data in **table II**.

TABLE II $^1$H NMR Data of Compound **12, 14** and **15**

| *Compd.* | $\delta$ *$^1$H NMR ($CDCl_3$)* |
|---|---|
| **12a** | 6.76 ~ 7.94 (18H, m, 2 × $C_6H_5$+ 2 × $C_6H_4$); 8.38 (1H, br., N-H); 5.88 (1H, dd C-H, $J^2_{N-H}$ = 4.20 Hz, $J^2_{P-H}$ =23.53 Hz); 4.23 (2H, m, $CH_2$); 2.21 (3H, s, $CH_3$) |
| **12b** | 6.78 ~ 8.09 (18H, m, 2 × $C_6H_5$ + 2 × $C_6H_4$); 8.39 (1H, br., N-H); 5.91 (1H, dd C-H, $J^2_{N-H}$ = 5.00 Hz, $J^2_{P-H}$ =24.78 Hz); 4.26 (2H, m, $CH_2$); 2.23 (3H, s, $CH_3$) |
| **12c** | 6.87 ~ 8.19 (19H, m, 2 × $C_6H_5$+ 2 × $C_6H_4$ + N-H); 5.94 (1H, dd C-H, $J^2_{N-H}$ = 4.48 Hz, $J^2_{P-H}$=22.38 Hz); 4.37 (2H, m, $CH_2$); 2.26 (3H, s, $CH_3$) |
| **12d** | 6.80 ~ 8.25 (18H, m, 2 × $C_6H_5$+ 2 × $C_6H_4$); 8.40 (1H, br., N-H); 5.96 (1H, dd C-H, $J^2_{N-H}$ =5.240 Hz, $J^2_{P-H}$ =23.04 Hz); 4.23 (2H, m, $CH_2$); 2.24 (3H, s, $CH_3$) |
| **14a** | 7.85 ~ 7.94 (4H, m, Ph); 7.63 (1H, br. N-H); 4.87 (2H, s, $CH_2C$= O); 3.75 (6H, d, 2 × $CH_3$, $J^3_{P-H}$ = 11.0 Hz); 3.76 (2H, dd, O=$PCH_2$, $J^2_{N-H}$=3.8Hz, $J^2_{P-H}$=12.4Hz) |
| **14b** | 7.86 ~ 7.93 (4H, m, Ph); 7.53 (1H, br. N-H); 4.47 (2H, s, $CH_2C$= O); 4.11 (4H, m, 2 × $CH_2O$), 3.72 (2H, dd, O=$PCH_2$, $J^2_{N-H}$=3.8Hz, $J^2_{P-H}$=10.6Hz); 1.30 (6H, t, 2 × $CH_3$, $J^3_{H-H}$=7.0Hz) N. P. |
| **14c** | 7.89 ~ 7.94 (4H, m, Ph); 7.26 (1H, br. N-H); 4.47 (2H, s, $CH_2C$= O); 3.99 (4H, m, 2 × $CH_2O$), 3.71 (2H, dd, O=$PCH_2$, $J^2_{N-H}$=3.3Hz, $J^2_{P-H}$=13.3Hz); 1.66 (4H, m, 2 × $CH_2CH_3$); 0.91 (6H, t, 2 × $CH_2CH_3$, $J^3_{H-H}$=7.3Hz) |
| **14d** | 7.88 ~ 7.94 (4H, m, Ph); 7.32 (1H, br. N-H); 4.66 (2H, m, 2 × CH); 4.47 (2H, s, $CH_2C$=O); 3.68 (2H, dd, O=$PCH_2$, $J^2_{N-H}$=2.8Hz, $J^2_{P-H}$=12.5Hz); 1.28 (12H, d, 2 × $CHMe_3$, $J^3_{H-H}$=6.1 Hz) |
| **14e** | 7.79 ~ 8.14 (4H, m, Ph); 7.50 (1H, br. N-H); 4.47 (2H, s, $CH_2C$= O); 4.00 (4H, m, 2 × $CH_2O$), 3.71 (2H, dd, O=$PCH_2$, $J^2_{N-H}$=3.0Hz, $J^2_{P-H}$=12.3Hz); 1.61 (4H, m, 2 × $CH_2$); 1.37 (4H, m, 2 × $CH_2$); 0.89 (6H, t, 2 × $CH_3$) |
| **14f** | 7.90 ~ 7.96 (4H, m, Ph); 7.26 (1H, br. N-H); 4.46 (2H, s, $CH_2C$=O); 3.83(4H, m, 2 × $CH_2$); 3.83 (2H, dd, O=P-$CH_2$); 1.92 (2H, m, 2 × CH); 0.92 (12H, d, 2 × $CHMe_2$) |
| **15a** | 7.84 ~ 7.94 (4H, m, Ph); 7.26 (1H, br. N-H); 4.87 (s, 2H,$CH_2$-N); 3.97 (s, 3H, $CH_3$); 3.76 (d, 2H, $CH_2$-P); 3.76 (d, 6H, 2 × $CH_3$) |
| **15b** | 7.64 ~ 8.01 (4H, m, Ph); 7.26 (1H, br. N-H); 3.97 (3H, s, $CH_3$); 3.96 (4H, m, 2 × $CH_2$); 3.94 (2H, s, $CH_2$-N); 3.78 (dd, 2H, $CH_2$); 1.66 (4H, m, 2 × $CH_2$); 0.92(6H, d, 2 × $CH_3$) |

## 4. Synthesis of product 15

0.0575 g sodium (2.5 mmol) was put into 10 mL anhydrous methanol. After there was no hydrogen being produced, compound **14** (2.5 mmol) was added and the mixture was stirred at room temperature for 1 hour. After vacuum distillation of the volatile components, the oily residue was

taken to a silica gel column and eluted with petroleum ether: acetone = 3: 2 to give product **15.** Physical data are listed in **Table I**, $^1$H NMR data in **table II**.

***Acknowledgements***

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