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Synthesis of O,O-Diphenyl α-(*p*-Toluenesulfonyl)amino(substituted)-Phenylmethylphosphonates

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ABSTRACT

A series of O,O-diphenyl-α-(p-toluenesulfonamido)phosphonates have been synthesized by the Mannich-type reaction of p-toluenesulfonamide, (substituted)-benzaldehyde, and diphenyl phosphite with acetyl chloride as the solvent. The mechanism of the reaction is suggested, and the structures of new products are confirmed by ^{1}H NMR spectroscopy, elemental analyses, and X-ray diffraction. The results of bioassay showed that some of the compounds possess good anti-TMV (tobacco mosaic virus) activity. © 1997 John Wiley & Sons, Inc. Heteroatom Chem 8*: 203–206, 1997.*

INTRODUCTION

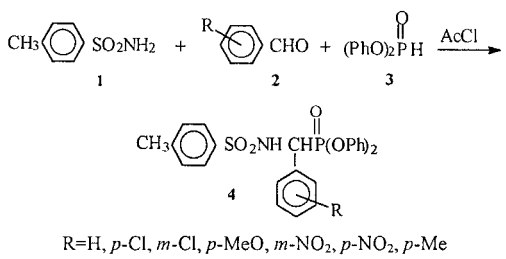
The derivatives of α-aminophosphonic acid have versatile biological activities, [1–3]. Studies on their synthetic methods and biological activities have attracted much attention during the past decades. In 1982, Varaprasad et al. [4] reported that dialkyl α-(*p*-toluenesulfonamido) phenylmethylphosphonates could be synthesized by the addition reaction of a dialkyl phosphite to N-benzylidene-*p*-toluenesulfonamide. In our previous article, we simplified the synthesis process by a three-component reaction and found that some products possess potential herbicidal activity [5]. In this article, we describe the synthesis of the title compounds and their anti-TMV (tobacco mosaic virus) activity.

RESULTS AND DISCUSSION

Synthesis and Reaction Mechanism

With acetyl chloride as the solvent, the title compounds **4** were synthesized by the Mannich-type reaction of *p*-toluenesulfonamide **1**, (substituted)-benzaldehyde **2**, and diphenyl phosphite **3** (as shown in Scheme 1).

In the process of synthesizing **4b** (R = *p* − Cl), we separated an intermediate imine **7b** successfully. Imine **7b** did react with diphenyl phosphite **3** smoothly to give product **4b** under similar reaction conditions. However, when a mixture of acetic acid and acetic anhydride was used as the solvent, only intermediates **5** and **6** were obtained. Therefore, we



R=H, *p*-Cl, *m*-Cl, *p*-MeO, *m*-NO_2, *p*-NO_2, *p*-Me

SCHEME 1

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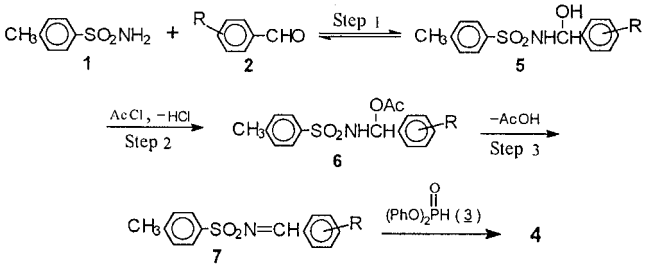
TABLE 1 Physical Data for Compounds **4** and **10**

No.	R	Yield (%)	Mp (°C)	Elemental Analysis (Found/Calcd)		
				C(%)	H(%)	N(%)
4a	H	62.8	206–208	62.80(63.29)	4.99(4.87)	2.84(2.84)
4b	*p*-Cl	53.5	200–202	58.94(59.15)	4.49(4.36)	2.64(2.65)
4c	*m*-Cl	58.2	174–175	59.09(59.15)	4.43(4.36)	2.70(2.65)
4d	*p*-MeO	60.4	214–215	61.97(61.95)	5.20(4.97)	2.70(2.68)
4e	*m*-NO_2	65.1	193–194	57.76(57.99)	4.35(4.28)	5.01(5.20)
4f	*p*-NO_2	68.8	217–219	57.81(57.99)	4.58(4.28)	5.21(5.20)
4g	*p*-Me	69.0	226–228	63.77(63.90)	5.13(5.13)	2.68(2.76)
10a	H	52.5	143–144	57.24(57.55)	4.91(4.80)	3.40(3.36)
10b	Me	65.0	108–109	58.41(58.47)	4.93(5.10)	3.36(3.25)
10c	EtO_2CCH_2	66.7	94–95	58.95(59.14)	5.63(5.54)	2.94(2.87)
10d	*o*-Me-Ph	42.3	103–104	63.87(63.90)	5.06(5.13)	2.84(2.76)



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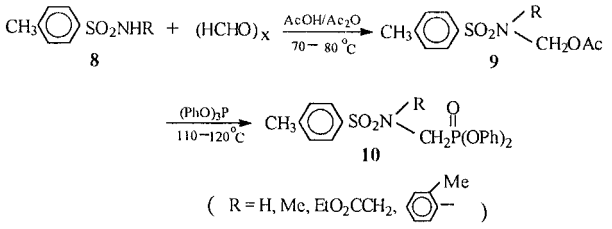

SCHEME 3

suggest the reaction mechanism to be as follows (as shown in Scheme 2).

At first, the amino group in **1** attacked the carbonyl group in **2** to give **5**, then **5** was acetylated to give **6**. Then one molecule of acetic acid was removed from **6** to give **7**. Finally, **4** was obtained by addition of **3** to **7**.

The possible reason why the mixture of acetic acid and acetic anhydride failed as solvents in this reaction was that acetic acid was unfavorable for **6** to be converted to **7**, although it could catalyze the attack of the amino group in **1** on the carbonyl group of **2**. However, when the more powerful acetylating reagent acetyl chloride was used as the solvent, it could not only acetylate **5** quickly, but also reacted with acetic acid, produced in step 3, to give acetic anhydride. Furthermore, the hydrochloride produced in step 2 could also catalyze step 1, and thus the whole reaction could proceed easily. Obviously, the acetyl chloride, which was used as the solvent in the Mannich-type reaction for the first time by Yuan et al. [6–8] was also an excellent solvent in this reaction. However, when the N-substituted *p*-toluenesulfonamide **8** was used instead of **1**, it easily reacted with acetyl chloride but did not undergo the Mannich-type reaction. For example, N-methyl-*p*-toluenesulfonamide could be acetylated by acetyl chloride even below 0 °C to give N-methyl-N-acetyl-*p*-toluenesulfonamide. For this reason, acetyl chloride could not be used as the solvent in the Mannich-type reaction of **8**. In this case, we treated **8** with paraformaldehyde in $AcOH/Ac_2O$ at 80 °C to form intermediate **9** first, and then caused this to react with triphenyl phosphite at 110–120 °C to give the corresponding product **10** [9] (as shown in Scheme 3).

The structures of all the compounds prepared were confirmed by ^1H NMR spectroscopy and elemental analyses. Some of them were also confirmed by IR, MS, and ^{31}P NMR spectroscopy (see Table 1).

In the ^1H NMR spectrum of **10a**, the CH_2 group exhibited dd peaks due to the coupling of the N–H and P atom, while in the ^1H NMR spectra of **10b** and **10c**, the CH_2 group exhibited d peaks because N–H was replaced by N–R (R = Me or $EtO_2CCH_2^-$). Therefore, it could have been seen that the two H atoms at the α-C were magnetically equivalent. However, in the ^1H NMR spectrum of **10d**, the two H atoms at the α-C were magnetically nonequivalent. One hydrogen H(1) exhibited a triplet at δ 4.52, while the other hydrogen H(2) exhibited dd peaks at δ 3.92. In order to explain this magnetic nonequivalence, a sin-

TABLE 2 ^{1}H NMR Data of Compounds **4** and **10**

No.	*δ(CDCl$_3$)*
4a	6.88–7.48 (19H, m, 3 × C_6H_5 + C_6H_4); 6.70 (1H, br., NH); 5.20 (1H, dd, CH, J^2_{P-H} = 25.2 Hz, J^2_{N-H} = 5.4 Hz); 2.32 (3H, s, CH_3)
4b	6.96–7.48 (18H, m, 2 × C_6H_5 + 2 × C_6H_4); 6.84(1H, br., NH); 5.12 (1H, dd, CH, J^2_{P-H} = 21.6 Hz, J^2_{N-H} = 5.4 Hz); 2.28 (3H, s, CH_3)
4c	6.84–7.40 (18H, m, 2 × C_6H_5 + 2 × C_6H_4); 6.76 (1H, br., NH); 5.18 (1H, dd, CH, J^2_{P-H} = 27.0 Hz, J^2_{N-H} = 4.5 Hz); 2.24 (3H, s, CH_3)
4d	6.56–7.56 (18H, m, 2 × C_6H_5 + 2 × C_6H_4); 6.84 (1H, br., NH); 5.12 (1H, dd, CH, J^2_{P-H} = 25.2 Hz, J^2_{N-H} = 5.4 Hz); 2.24 (3H, s, CH_3)
4e	6.88–7.08 (18H, m, 2 × C_6H_5 + 2 × C_6H_4); 8.92 (1H, br., NH); 5.28 (1H, dd, CH, J^2_{P-H} = 25.2 Hz, J^2_{N-H} = 5.4 Hz); 2.20 (3H, s, CH_3)
4f	6.96–8.00 (18H, m, 2 × C_6H_5 + 2 × C_6H_4); 9.28 (1H, br., NH); 5.32 (1H, dd, CH, J^2_{P-H} = 25.2 Hz, J^2_{N-H} = 5.4 Hz); 2.24 (3H, s, CH_3)
4g	6.78–7.44 (18H, m, 2 × C_6H_5 + 2 × C_6H_4); 6.54 (1H, br., NH); 5.10 (1H, dd, CH, J^2_{P-H} = 25.2 Hz, J^2_{N-H} = 5.4 Hz); 2.28 (3H, s, CH_3), 2.12 (3H, s, CH_3)
10a	7.04–7.80 (14H, m, 2 × C_6H_5 + C_6H_4); 6.02 (1H, br., NH); 3.50 (2H, dd, CH_2, J^3_{N-H} = 9.0 Hz, J^2_{P-H} = 14.4 Hz); 2.35 (3H, s, CH_3)
10b	7.20–7.88 (14H, m, 2 × C_6H_5 + C_6H_4); 3.86 (2H, d, CH_2, J^2_{P-H} = 10.8 Hz); 3.03 (3H, s, N–CH_3); 2.44 (3H, s, CH_3–Ph)
10c	7.20–7.92 (14H, m, 2 × C_6H_5 + C_6H_4); 4.48 (2H, s, CH_2); 4.36 (2H, d, CH_2–P, J^2_{P-H} = 10.8 Hz); 4.08 (2H, m, CH_2CH_3); 2.44 (3H, s, CH_3–Ph); 1.16 (3H, t, CH_3)
10d	6.52–7.60 (18H, m, 2 × C_6H_5 + 2 × C_6H_4); 4.52 (1H, t, C–H_a, J^2_{P-Ha} = J^2_{Hb-Ha} = 16.1 Hz); 3.92 (1H, dd, C–H_b, J^2_{P-H} = 5.64 Hz, J^2_{Ha-Hb} = 16.0 Hz); 2.40 (3H, s, CH_3–Ph); 2.36 (3H, s, CH_3)

gle crystal of **10d** was prepared in a mixture of chloroform and petroleum ether for X-ray diffraction analysis, as shown in Figure 1. Because of the big steric effect of the ortho-methylbenzyl group, the free rotation of the P–C and C–N bonds are hindered so that the two hydrogen atoms at α-C are magnetically nonequivalent. Of them, H(1) is near the benzene ring **3** and lies in its deshielding area, while H(2) is far from it. Therefore, H(1) should lie at lower field in the ^{1}H NMR spectrum. Its chemical shift is 4.52, while H(2) lies at higher field with the chemical shift being 3.92 ppm. In addition, due to the nonequivalence, H(1) is coupled not only to the P atom but also to H(2) so that H(1) should exhibit dd peaks. However, since the coupling constant of the P atom to H(1) ($J^2_{P-H(1)}$ = 16.1 Hz) is equal to that of H(2) to H(1) ($J^2_{H(2)-H(1)}$ = 16.1 Hz), H(1) exhibits a triplet resonance, whereas H(2) exhibits dd peaks ($J^2_{P-H(2)}$ = 5.6 Hz, $J^2_{H(1)-H(2)}$ = 16.1 Hz). In compounds **10a**, **10b**, and **10c**, the substituting group R is not big enough to cause the magnetical nonequivalence.

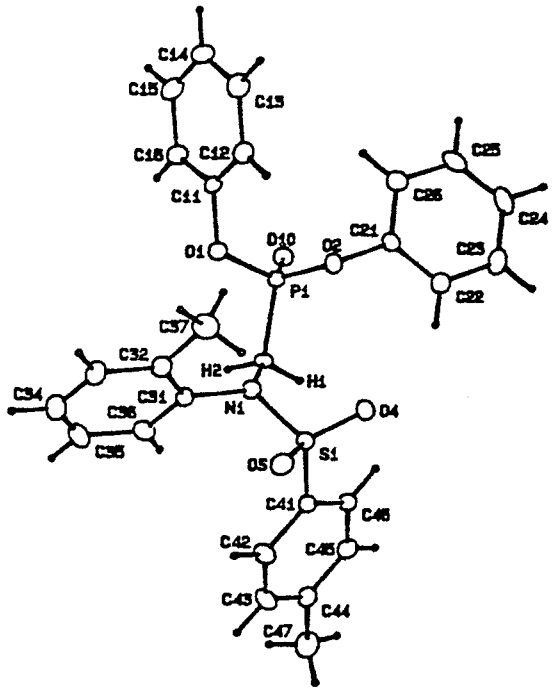

FIGURE 1 X-ray diffraction of compound **10d**.

Biological Activities

The preliminary biological tests showed that the herbicidal activity of the products is low. However, we found by chance that some of the compounds possess good anti-TMV activity. For example, at 100 ppm, the inhibitory rate of compound **4f** to TMV at-

tained 55%, even better than that of the commercial NS-83. Although α-amino phosphonic acid derivatives have been reported to possess various biological activities, as far as we know, there is no report on their anti-TMV activity. The further study on the anti-TMV activity of the products is on the way.

EXPERIMENTAL

The melting points were uncorrected. Elemental analyses were measured by a Yanaco CHN Corder MT-3 apparatus. ^{1}H NMR and ^{31}P NMR spectra were recorded on a Bruker AC-P 200 spectrometer by using TMS and 85% H_3PO_3 as internal and external standards, respectively.

The reagents and solvents were available commercially and purified according to conventional methods.

O,O-Diphenyl α-(N-p-Toluenesulfonyl) Amino(substituted)-Phenylmethylphosphonates (**4**)*: General Procedures*

A mixture of *p*-toluenesulfonamide **1** (5 mmol); diphenyl phosphite **3** (5 mmol), and 15 mL of AcCl was stirred at room temperature. The aldehyde **2** (6 mmol) was added dropwise. After the mixture had been stirred at room temperature for 4 hours, the solvent was removed under reduced pressure. The residue was recrystallized from $CHCl_3$/MeOH to give pure products **4**. Their physical constants are listed in Table 1; those of ^{1}H NMR, in Table 2.

O,O-Diphenyl α-(N-p-Toluenesulfonyl)aminomethylphosphonates (**10**)*: General Procedure*

A mixture of 3 mL of acetic acid, 5 mL of acetic anhydride, the N-substituted *p*-toluenesulfonamide **8** (5 mmol), and paraformaldehyde (6 mmol) was stirred at 70–80 °C for 2–3 hours. Then triphenyl phosphite (5 mmol) was added, and the mixture was stirred at 110–120 °C for 3 hours. After the solvent had been removed under reduced pressure, the residue was dissolved in 5 mL of methanol and kept in refrigerator overnight. The solid was filtered off and recrystallized from chloroform and methanol to give pure **10**. Their physical constants are listed in Table 1, and the ^{1}H NMR data, in Table 2.

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