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# Synthesis of Cyclic Esters of N-Toluenesulfonyl α-Aminophosphonic Acid

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ABSTRACT: *Many new cyclic esters of N-toluenesulfonyl α-aminophosphonic acids were synthesized by the three-component reaction of p-toluenesulfonamide, an aromatic aldehyde, and 2-chloro-1,3,2-benzodioxaphosphole in anhydrous benzene. Different reaction conditions have been investigated, and the related reaction mechanisms have been suggested.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9:511–516, 1998

## *INTRODUCTION*

We reported previously the synthesis of a series of diethyl (or diphenyl) N-*p*-toluenesulfonyl α-aminophosphonates and their potential herbicidal activities [1]. Recently, Chris Meier [2] reported that when a biologically active nucleoside analog was connected with a cyclic phosphoryl group to form a prodrug with higher lipophilicity, it could overcome the difficulty of the intracellular delivery of the nucleoside analog because it is easier for the prodrug to pass through a membrane than the free nucleoside. Furthermore, the prodrug can be readily hydrolyzed to release the biologically active nucleoside analog under the physiological conditions [2]. This strategy prompted us to synthesize the corresponding cyclic esters of α-aminophosphonic acids that might improve the lipophilicity of the biologically active N-substituted α-aminophosphonic acid and thus improve their biological activity. So far, numerous methods have been developed to synthesize N-protected acyclic diesters of α-aminophosphonic acid [3–11], the important building blocks for peptide synthesis [12]; however, a survey of the literature revealed that there is no general method to synthesize the cyclic esters of α-aminophosphonic acids. In this article, a simple and direct method has been introduced for the synthesis of these kinds of compounds.

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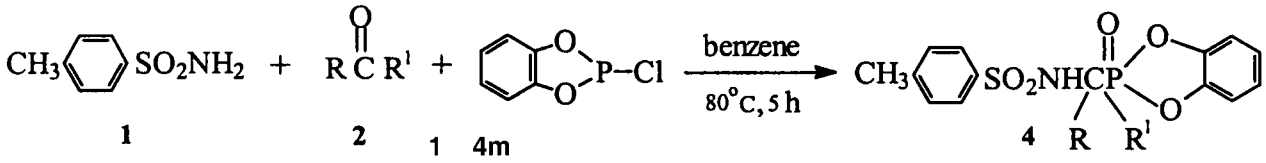
## *RESULTS AND DISCUSSION*

We reported previously that acetyl chloride is a good solvent for the three-component reaction of *p*-toluenesulfonamide **1**, an aldehyde and a dialkyl (or diphenyl) phosphite to synthesize a dialkyl (or diphenyl) 1-*p*-toluenesulfonamido benzylphosphonate [1]. We have also extended the reaction to phenyldichlorophosphine (or trichlorophosphine) and found that acetyl chloride is an excellent solvent for synthesis of the corresponding α-aminophosphinic chloride (or α-aminophosphonic dichloride), which can be converted readily to the corresponding phosphinic acid and phosphinopeptide [13]. Naturally, we thought of using acetyl chloride as the solvent to synthesize the title compounds. Thus, we have utilized 2-chloro-1,3,2-benzodioxaphosphole **3** as the phosphorus component instead of a dialkyl phosphite (or phenyldichlorophosphine). When benzaldehyde was used as the carbonyl component, the corresponding title compound was obtained in a yield of 32.4% (method A, see Experimental section). However, when *p*-nitrobenzaldehyde (or *p*-chlorobenzaldehyde) was employed instead of benzalde-

hyde, we failed to isolate the corresponding title compounds but obtained rather the imine intermediates. However, when anhydrous benzene was used as the solvent, almost all of the aromatic aldehydes reacted with **1** and **3** to give products smoothly in yields of 44.8–84.6% (method B, see Experimental section). Thus, after the mixture of **1**, *2*, and **3** was heated under 80°C for 5 hours and then cooled to room temperature, the solid that had formed was collected by filtration and then recrystallized from a mixture of ethyl acetate and petroleum ether to give the title compounds **4** in pure form. The yields are satisfactory, and the procedure is simple (Scheme 1). Furthermore, when the aromatic aldehyde was replaced by an aliphatic aldehyde (e.g., propionaldehyde) or ketone (e.g., 2-pentanone), the reaction also took place smoothly to give the corresponding products **4l** and **4m**.

After careful study of the mechanism of the three-component reaction of *p*-toluenesulfonamide, an aldehyde and a phosphorus reagent, it was suggested that two conditions are necessary for the reaction to proceed smoothly: (1) There must exist a P–H bond in the molecule of the phosphorus reagent, or a P–H bond can be formed readily in the course of the reaction. (2) An imine intermediate can be formed smoothly. This suggestion can explain the following facts:

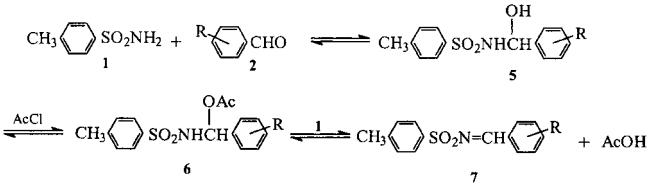
1. When acetyl chloride was used as the solvent, the reaction was often performed at low temperature ( − 10°C–r.t.). No matter what kind of phosphorus reagent was used, the carbonyl attack of **1** on **2** formed intermediate **5**, which was then converted to intermediate **6** in acetyl chloride. By elimination of one molecule of acetic acid, the reactive imine intermediate **7** was formed, which had previously been isolated and characterized [1]. Obviously, the solvent acetyl chloride helped the formation of imine **7** (Scheme 2).
   A. When the dialkyl phosphite containing a P–H bond in an acidic medium was used as the phosphorus reagent, it reacted directly with the imine intermediate **7** to give the dialkyl aminophosphonate [4].
   B. When the phenyldichlorophosphine was used as the phosphorus reagent, there was no P–H bond in the molecule. However, it was reported that phenyldichlorophosphine could react with acetic acid to form a reactive intermediate **8** [14]. In fact, this was an equilibrium reaction. The concentration of **8** should be very low in the course of the reaction due to the high concentration of acetyl chloride. Moreover, **8** could be isomerized to intermediate **9** readily in an acidic medium, which then could react with **7** to form the corresponding phosphinic chloride **10**. Therefore, the possibility for **8** to undergo side reactions was very little at a low temperature. A monitoring of the reaction by using $^{31}$P NMR spectroscopy revealed that almost all the phenyldichlorophosphine was converted into aminophosphinic chloride **10** (two indentical peaks at $\delta = 51.6$ and 49.1), and no side reaction was observed [13] (Scheme 3).
   C. When 2-chloro-1,3,2-benzodioxaphosphole (**3**) was used as the phosphorus reagent, a similar reaction took place as with phenyldichlorophosphine, and the corresponding cyclic aminophosphonates **4** could also be obtained. However, in contrast to phenyldichlorophosphine, the reactivity of **3** was much lower, which might explain the low yields of **4** under similar reaction conditions.
2. The foregoing reactions have also been investigated by using anhydrous benzene as the solvent.
   A. When the dialkyl phosphite was used as the phosphorus reagent, the diamide intermediate **7** could not be formed effectively without the participation of acetyl chloride. Therefore, no corresponding dialkyl phosphonates were isolated, although there exists a P–H bond in a dialkyl phosphite.
   B. When phenyldichlorophosphine was utilized as the phosphorus reagent, the reaction monitored by $^{31}$P NMR spectroscopy revealed that it was very complicated. In this reaction, intermediate **7** was also formed because phenyldichlorophosphine reacted with intermediate **5** to form intermediate **11**, which was then transformed into intermediates **7** and **12**. Of course, it was possible for **12** to isomerize into **13**, which then reacted with **7** to form the product **10**. Actually, the formation of **10** was observed in the $^{31}$P NMR spectrum ($\delta = 51.8$ and 49.3) [13]. However, it was also observed that many other phosphorus components were formed during the reaction by a $^{31}$P NMR spectroscopy tracing experiment ($19 < \delta < 44$), and the concentration of **10** was so low that this reaction



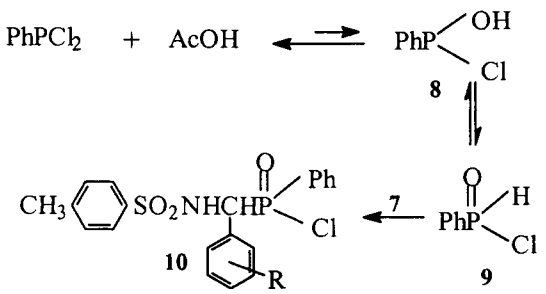

1 2 1 4m 4

For **4a~4l**, $R^1$ = H, **4a**: R = Ph, **4b**: R = *p*-$NO_2$-Ph, **4c**: R = *p*-Me-Ph, **4d**: R = *m*-$NO_2$-Ph, **4e**: R = 2,4-$Cl_2$- Ph, **4f**: R = *o*-MeO- Ph, **4g**: R = *p*-Cl-Ph, **4h**: R = *o*-Cl-Ph, **4i**: R = *p*-MeO-Ph, **4j**: R = *p*-$NMe_2$-Ph, **4k**: R = 3,4-$OCH_2O$-Ph, **4l**: R = Me, **4m**: R = Me, $R^1$ = *n*-Pr

**SCHEME 1**



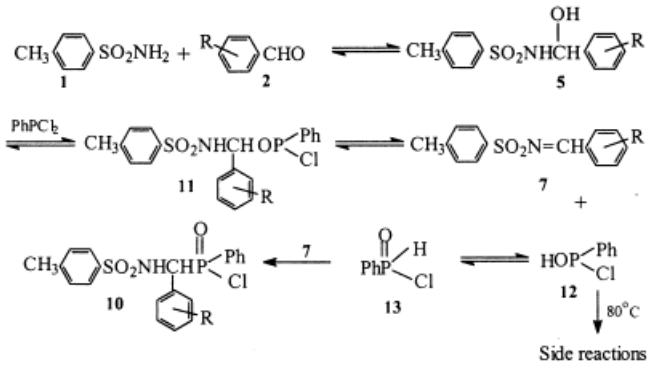
**SCHEME 2**



**SCHEME 3**

cannot be used as an efficient method to synthesize **10**. The possible reason for the complication of this reaction was due to the high reactivity of **12**, which contains both a reactive P–Cl bond and a reactive hydroxyl group at the same time. At refluxing temperature, intermediate **12** might undergo many side reactions (Scheme 4).

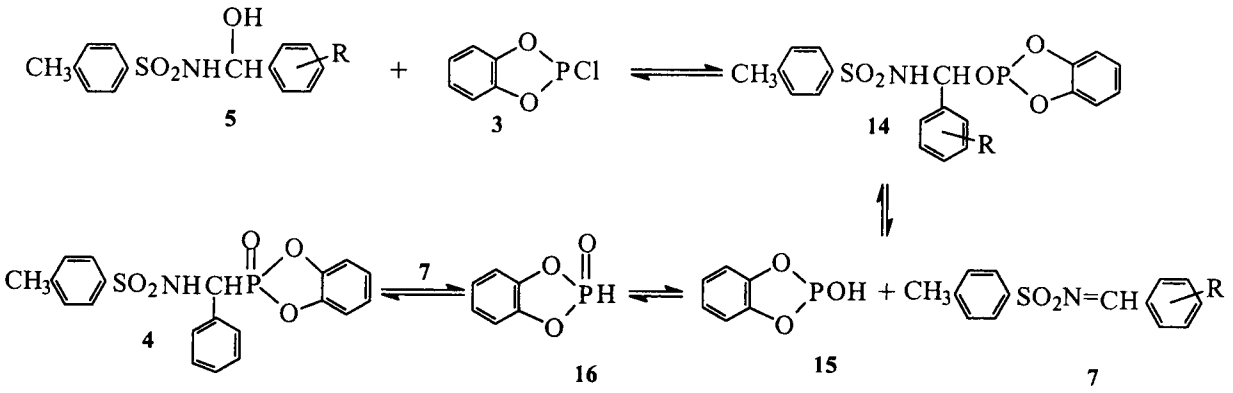
C. When 2-chloro-1,3,2-benzodioxaphosphole (**3**) was employed as the phosphorus reagent, it could react similarly with **5** to form intermediate **14**, which was then transformed to imine **7** and intermediate **15**. What made the difference was that **15** did not contain the reactive P–Cl bond and thus is more stable than **13**. Therefore, **15** could be isomerized readily into **16**, which then reacted with **7** to give products **4** (Scheme 5).




**SCHEME 4**

We also successfully extended the reaction described earlier to other substrates, such as benzyl carbamate, phenylurea, and so on. When benzyl carbamate was used as the substrate instead of *p*-toluenesulfonamide, the reaction mechanism was very similar except that the intermediate formed was a diamide compound [14] instead of the corresponding imine.

Recently, the use of microwave irradiation as a convenient source of energy in organic synthesis has become a popular procedure with the advantages of rapid heating of reactants and thus resulting in a dramatic reduction in reaction time. It has been reported that certain reactions such as Diels–Alder [15,16], ethenoid [17], Claisen reaction [18], Fischer cyclization [19], synthesis of heterocycles [20], hydrolysis of esters [21,22], phosphoanhydride [23] and adenosine triphosphate formation [24], rapid hydrogenation [25], deprotection of benzyl esters [26], deacetylation of diacetates [27], Graebe–Ullmann synthesis [28], oxazoline formation [29,30], Knoevengel condensation [31], and aromatic ether formation [32,33] could be facilitated by microwave irradiation. However, to the best of our knowledge, no such application has been devised for the previously described Mannich-type reaction. The pro-



**SCHEME 5**

gress in the application of microwave irradiation as a new energy source attracted us to investigate the previous reactions under microwave irradiation. Thus, with anhydrous benzene as the solvent (15 mL), the three-component reaction of **1**, benzaldehyde, and **3** was completed within 20 minutes under the microwave irradiation (270 W, method C, see Experimental section). Compared with the 5 hours needed for the conventional heating method, much time and energy were saved. Meanwhile, it was also observed that 3 minutes were needed to cause benzene to reflux in the course of this reaction, while only 0.5 minute was needed to cause benzene to reflux, and 4 minutes to complete the reaction when *p*-nitrobenzaldehyde was employed instead of benzaldehyde. However, after pure anhydrous benzene (15 mL) was irradiated under the same microwave (270 W) irradiation for 30 minutes, no refluxing was observed, and the temperature of the benzene was found to be only 61°C. Thus, it can be concluded that the energy was transferred from the reactants to the solvent, which was just opposite to the operation of the conventional heating method. The polar reactants can absorb microwave energy quickly and efficiently, while it is difficult for benzene to absorb microwave irradiation because of its weak polarity. This is perhaps the reason why the reactions took place so fast under microwave irradiation. However, in contrast to method B, the yields of the products have not been improved. In most cases, the yields were lower than those of method B (Table 1), and in some cases, even no corresponding products were isolated. Despite this, the microwave irradiation offers a new alternative heating method for the Mannich-type reaction.

## *EXPERIMENTAL*

The melting points were uncorrected. Elemental analyses were carried out by use of a Yanaco CHN Corder MT-3 apparatus. $^1$H NMR spectra were recorded on a Bruker AC-200 spectrometer with use of TMS as an internal standard.

### *2-[1-(Benzyloxycarbonylamino)-benzyl] 1,3,2-Benzodioxaphosphole-2-oxides* (**4**)*: General Procedures*

*Method A.* Aldehyde **2** (5 mmol) was slowly added to a mixture of *p*-toluenesulfonamide (**1**, 0.76 g, 5 mmol), 2-chloro-1,3,2-benzodioxaphosphole **3** (0.87 g, 5 mmol), and acetyl chloride (10 mL) under cooling with an ice salt bath. After having been stirred at 0°C for 0.5 hour and then at room temperature for 4 hours, a solid that had formed was collected by filtration and then recrystallized from a mixture of ethyl acetate and petroleum ether to give product **4** in pure form (Table 1).

*Method B.* Aldehyde **2** (5 mmol) was slowly added to a mixture of *p*-toluenesulfonamide (**1**, 0.76 g, 5 mmol), 2-chloro-1,3,2-benzodioxaphosphole **3** (0.87 g, 5 mmol), and anhydrous benzene (15 mL) at ambient temperature. After having been stirred at r.t. for 0.5 hour and then heating to reflux for 5 hours, the mixture was allowed to cool to room temperature. The solid was then collected by filtration and recrystallized from a mixture of ethyl acetate and petroleum ether to give product **4** in pure form (Table 1).

*Method C.* Aldehyde **2** (5 mmol) was slowly added to a mixture of *p*-toluenesulfonamide (**1**, 0.76 g, 5 mmol), 2-chloro-1,3,2-benzodioxaphosphole **3** (0.87 g, 5 mmol), and anhydrous benzene (15 mL) at r.t. After irradiation under the microwave (270 W) for 4 to 20 minutes, the mixture was allowed to cool

**TABLE 1** Compounds **4** Prepared

| *Product* | *Method* | *Reaction Time (h)* | *Yields (%) mp* | *Mp (°C)* | *$^1$H NMR (DMSO-$d_6$)* |
|---|---|---|---|---|---|
| **4a** | A<br>B<br>C | 4<br>5<br>1/3 | 32.6<br>67.0<br>64.2 | 163–166 | 8.32–7.96 (br, 1H, NH); 7.76–6.56 (m, 13H, 2 × $C_6H_4$ + $C_6H_5$); 5.08–4.60 (dd, 1H, CH); 2.24–2.12 (s, 3H, $CH_3$) |
| **4b** | A<br>B<br>C | 4<br>5<br>1/3 | 0<br>65.8<br>28.8 | 200–202 | 8.80–8.48 (t, 1H, NH); 8.40–6.40 (m, 12H, 3 × $C_6H_4$); 5.24–4.76 (dd, 1H, CH); 2.40–2.10 (s, 3H, $CH_3$) |
| **4c** | B<br>C | 5<br>1/3 | 68.9<br>45.6 | 246–249 | 8.60–8.08 (br, 1H, NH); 8.00–6.40 (m, 12H, 3 × $C_6H_4$); 5.04–4.40 (dd, 1H, CH); 2.40–2.08 (s, 3H, $CH_3$) |
| **4d** | B<br>C | 5<br>1/15 | 49.9<br>0 | 250–252 | 8.88–8.40 (br, 1H, NH); 8.40–6.40 (m, 12H, 3 × $C_6H_4$); 5.16–4.64 (dd, 1H, CH); 2.48–2.08 (s, 3H, $CH_3$) |
| **4e** | B<br>C | 5<br>1/3 | 44.8<br>54.2 | 104–106 | 8.00–6.20 (m, 12H, 2 × $C_6H_4$ + $C_6H_3$ + NH); 5.88–5.36 (dd, 1H, CH); 2.36–2.20 (s, 3H, $CH_3$) |
| **4f** | B<br>C | 5<br>1/3 | 56.3<br>0 | 86–89 | 7.80–6.40 (m, 13H, 3 × $C_6H_4$ + NH); 5.80–5.20 (dd, 1H, CH); 3.88–3.50 (s, 3H, $OCH_3$); 2.40–2.08 (s, 3H, $CH_3$) |
| **4g** | B<br>C | 5<br>1/3 | 66.3<br>64.8 | 115–117 | 8.00–6.20 (m, 13H, 3 × $C_6H_4$ + NH); 5.96–5.40 (dd, 1H, CH); 2.30–1.88 (s, 3H, $CH_3$) |
| **4h** | B<br>C | 5<br>1/3 | 50.0<br>0 | 65–70 | 7.96–6.40 (m, 13H, 3 × $C_6H_4$ + NH); 5.96–5.50 (dd, 1H, CH); 2.32–2.08 (s, 3H, $CH_3$) |
| **4i** | B<br>C | 5<br>1/3 | 84.6<br>48.5 | 208–210 | 8.00–6.44 (m, 13H, 3 × $C_6H_4$ + NH); 5.24–4.72 (dd, 1H, CH); 3.84–3.56 (s, 3H, $OCH_3$); 2.40–2.12 (s, 3H, $CH_3$) |
| **4j** | B<br>C | 5<br>1/3 | 74.7<br>0 | 169–171 | 8.08–6.40 (m, 13H, 3 × $C_6H_4$ + NH); 5.04–4.50 (dd, 1H, CH); 3.30–1.80 (m, 9H, 3 × $CH_3$) |
| **4k** | B<br>C | 5<br>1/3 | 77.4<br>54.5 | 192–195 | 8.00–6.40 (m, 12H, 2 × $C_6H_4$ + $C_6H_3$ + NH); 6.00–5.68 (d, 2H, $CH_2$); 5.24–4.72 (dd, 1H, CH); 2.52–2.16 (s, 3H, $CH_3$) |
| **4l** | B | 5 | 70.9 | 124–130 | 8.20–5.40 (m, 9H, 2 × $C_6H_4$ + NH); 3.92–3.32 (dd, 1H, CH); 2.46–2.20 (s, 3H, $C_6H_5$ − $CH_3$); 2.00–1.20 (br, 2H, $CH_2$); 0.92–0.52 (t, 3H, $CH_2$ − $CH_3$) |
| **4m** | B | 5 | 66.3 | 215–220 | 8.80–8.44 (br, 1H, NH); 8.40–6.40 (m, 12H, 3 × $C_6H_4$); 5.20–4.60 (dd, 1H, CH); 2.36–2.12 (s, 3H, $CH_3$) |

Satisfactory microanalyses: C ± 0.40; H ± 0.25; N ± 0.28.

to room temperature. The solid was then collected by filtration and recrystallized from a mixture of ethyl acetate and petroleum ether to give product **4** in pure form (Table 1).

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