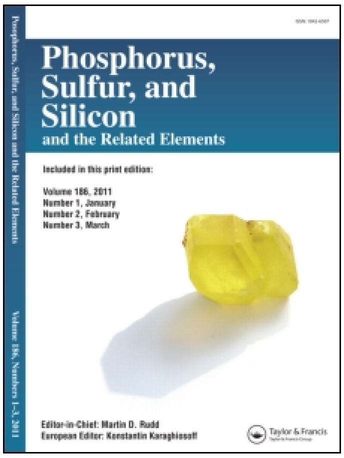

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THE REACTION OF BENZOYLPHOSPHONIC ACID WITH THIONYL CHLORIDE. THE FORMATION OF BENZOYLPHOSPHONIC DICHLORIDE AND P,P'-DIBENZOYLPYROPHOSPHONIC DICHLORIDE

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THE REACTION OF BENZOYLPHOSPHONIC ACID WITH THIONYL CHLORIDE. THE FORMATION OF BENZOYLPHOSPHONIC DICHLORIDE AND P,P′-DIBENZOYLPYROPHOSPHONIC DICHLORIDE

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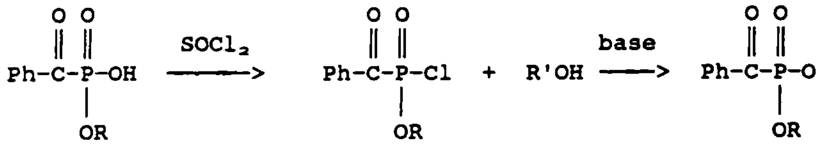
The reaction of benzoylphosphonic acid (3) with thionyl chloride leads to the formation of benzoylphosphonic dichloride (5) and P,P′-dibenzoylpyrophosphonic dichloride (6). These products were identified by ^{31}P nmr spectra and through their products of alcoholysis with 2-propanol.

Key words: Benzoylphosphonic acid; benzoylphosphonic dichloride; P,P′-dibenzoylpyrophosphonic dichloride.

The general approach to the preparation of acylphosphonate mixed esters involves the use of activated acylphosphonic acid derivatives.[1] For preparing nucleoside acylphosphonates, in which the acylphosphonyl moiety serves as a unique protecting group of the phosphorus, aroylphosphonic acids were activated by mesitylene-1,3-disulfonyl chloride in the presence of pyridine or 3-nitro-1,2,4-triazole.[2] One of us with others, on the other hand, recently described the preparation of methyl benzoylphosphonochloridate (**1**, R = Me)[3] which is a simple monoactivated derivative useful for the preparation of mixed acylphosphonate[3,4] (e.g. **2**, R ≠ R′) and acylphosphonamidate esters.[5]

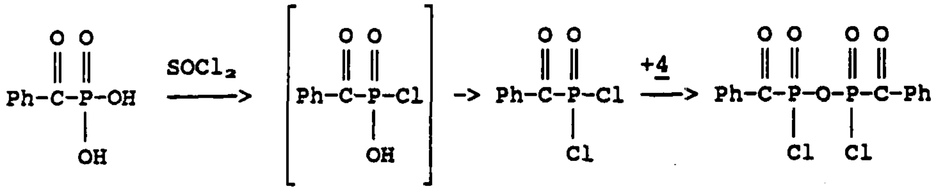


$$\mathrm{Ph{-}\overset{O}{\overset{\|}{C}}{-}\underset{\underset{OR}{|}}{\overset{O}{\overset{\|}{P}}}{-}OH} \xrightarrow{\mathrm{SOCl_2}} \mathrm{Ph{-}\overset{O}{\overset{\|}{C}}{-}\underset{\underset{OR}{|}}{\overset{O}{\overset{\|}{P}}}{-}Cl} + \mathrm{R'OH} \xrightarrow{\mathrm{base}} \mathrm{Ph{-}\overset{O}{\overset{\|}{C}}{-}\underset{\underset{OR}{|}}{\overset{O}{\overset{\|}{P}}}{-}OR'}$$

1　　2

for R = Me,
$\delta^{31}P$ = -0.54 ppm　　13.5 ppm

To expand this approach further we decided to examine whether the reaction of benzoylphosphonic acid (3) with thionyl chloride would yield the analogous benzoylphosphonic dichloride (5). We found that addition of a dioxan solution of benzoylphosphonic acid to 2.1 moles of thionyl chloride in dichloromethane gave a solution which showed in the ^{31}P nmr spectrum two signals at 28 and 8 ppm in the relative intensities of 1:3.



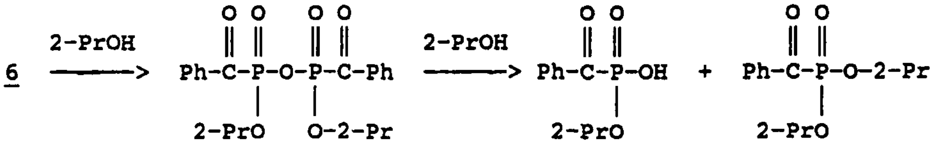
$$\mathrm{Ph{-}C(=O){-}P(=O)(OH){-}OH} \xrightarrow{SOCl_2} \left[\mathrm{Ph{-}C(=O){-}P(=O)(OH){-}Cl}\right] \rightarrow \mathrm{Ph{-}C(=O){-}P(=O)(Cl){-}Cl} \xrightarrow{+4} \mathrm{Ph{-}C(=O){-}P(=O)(Cl){-}O{-}P(=O)(Cl){-}C(=O){-}Ph}$$

3 4 5 6

$\delta^{31}P$

-1.2 ppm 28 ppm 8 ppm

Considering the deshielding effect of the chlorine on the phosphorus, the chemical shift of 28 ppm of the minor product seems reasonable for benzoylphosphonic dichloride (**5**). This structure is assigned therefore, to the minor product. In order to confirm this and to elucidate the structure of the main product (**6**) of the reaction, 2 equivalents of 2-propanol and of pyridine were added to the product mixture. After stirring for 30 min at room temperature, ^{31}P nmr examination of the reaction mixture showed the presence of two absorptions: $\delta = 0.15$ ppm (d, $J = 7.9$ Hz, 45%) and $\delta = -0.2$ ppm (t, $J = 7.3$ Hz, 55%). The two absorptions were identified as 2-propyl hydrogen benzoylphosphonate (**7**) and di-2-propyl benzoylphosphonate (**8**), respectively, by admixture with authentic samples of **7** and **8**. Di-2-propyl benzoylphosphonate (**8**) was prepared by the Arbuzov reaction of benzoyl chloride with tri-2-propyl phosphite. Compound **8** was monodealkylated and acidified to yield **7**. Reaction of **5** with 2-propanol is expected to yield **8**. Similarly reaction of 2-propanol with P,P'-dibenzoylpyrophosphonic dichloride (**6**) should be expected to give di-2-propyl P,P'-dibenzoylpyrophosphonate (**9**), which upon further alcoholysis should lead to equal amounts of **7** and **8**. These considerations lend support to the structure assignments **5** and **6** to the products having the ^{31}P chemical shifts at 28 and 8 ppm, respectively.

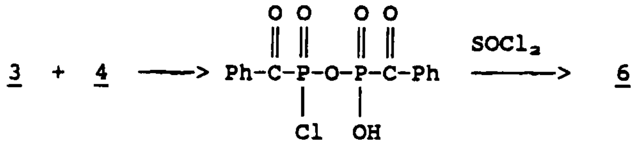


$$\mathbf{6} \xrightarrow{2\text{-PrOH}} \mathrm{Ph{-}C(=O){-}P(=O)(O{-}2{-}Pr){-}O{-}P(=O)(O{-}2{-}Pr){-}C(=O){-}Ph} \xrightarrow{2\text{-PrOH}} \mathrm{Ph{-}C(=O){-}P(=O)(2{-}PrO){-}OH} + \mathrm{Ph{-}C(=O){-}P(=O)(2{-}PrO){-}O{-}2{-}Pr}$$

9 7 8

It seems reasonable to assume that the reaction of thionyl chloride with **3** should lead, in the first step, to the formation of benzoylphosphonochloridic acid, **4**. This compound may react with an additional molecule of thionyl choride to give benzoylphosphonic dichloride (**5**). The formation of the P,P'-dibenzoylpyrophosphonic dichloride (**6**), can be assumed to result from the interaction of **4** with **5**. Consequently, an increase in the yield of **5** at the expense of **6** should be expected if the reaction of **3** would be carried out in a dilute solution, using a large excess of thionyl chloride. Under such conditions bimolecular reactions, involving two phosphonate derivatives, should be suppressed. To test this, we caused to react **3** with ten fold and one hundred fold excess of thionyl chloride. Examination of the reaction mixtures obtained in both experiments showed the presence of the same signals in the ^{31}P nmr spectra in approximately equal intensities. The apparent failure to raise the yield of **5** even with the use of 100 fold excess of thionyl chloride indicates a kinetic preference for the reaction of **4** and **5**.

An alternative way for the formation of **6** which cannot be ignored, is the possible reaction of **3** and **4** leading to the asymmetrical pyrophosphonate **9**, which in turn may give **6** through the action of thionyl chloride.



$$\underline{3} + \underline{4} \longrightarrow \mathrm{Ph{-}\overset{O}{\overset{\|}{C}}{-}\underset{\underset{Cl}{|}}{\overset{\overset{O}{\|}}{P}}{-}O{-}\underset{\underset{OH}{|}}{\overset{\overset{O}{\|}}{P}}{-}\overset{O}{\overset{\|}{C}}{-}Ph} \xrightarrow{SOCl_2} \underline{6}$$

9

EXPERIMENTAL

General. Nuclear magnetic resonance spectra were recorded on a Varian VXR-300S instrument. Chemical shifts are reported in ppm downfield from TMS or TSP as internal standards in ^1H spectra and from 85% H_3PO_4 as external standard in ^{31}P spectra. Positive chemical shifts are at low field with respect to the standard. Peak multiplicities are given in parentheses. Dioxan was dried over sodium, dichloromethane was dried over phosphorus pentoxide and acetonitrile was dried over calcium hydride. All solvents were freshly distilled before use.

Benzoylphosphonic acid (**3**). Bromotrimethylsilane (4.6 mL, 0.035 mol) was added dropwise with stirring to dimethyl benzoylphosphonate (2.5 g, 0.012 mol) dissolved in dry acetonitrile (20 mL) at room temperature. After 90 min. stirring at room temperature, examination of the reaction mixture by ^{31}P nmr showed a singlet at −18 ppm corresponding to bistrimethylsilyl benzoylphosphonate. The solvent and the excess of bromotrimethylsilane were evaporated in vacuo, methanol (50 mL) was added to the residue and the solution was stirred at room temperature for 30 min. After removal of the volatile components the residue was crystallized from methanol-toluene, m.p. 212°, $\delta^{31}P$ −1.2 ppm (s), lit. m.p. 213°, $\delta^{31}P$ −1.29 ppm.[6]

Reactions of benzoylphosphonic acid (**3**) *with thionyl chloride.* 1) A solution of **3** (185 mg, 1 mmol) in dry dioxan (5 mL) was added slowly dropwise to a solution of thionyl chloride (0.21 mL, 2.1 mmol) in dichloromethane (5 mL). The solution was stirred at room temperature for 2 h. Examination of the solution by ^{31}P nmr showed the presence of two absorptions: 28.03 ppm (2) 25% and 7.98 ppm (s) 75%. 2) In the second experiment a solution of **3** (185 mg, 1 mmol) in dioxan (10 mL) was added in small portions over 90 min. to a solution of thionyl chloride (2 mL, 21 mmol) in dichloromethane (10 mL). Examination of the solution by ^{31}P nmr showed the presence of the same two absorptions: 28.03 ppm (s) 48% and 7.98 ppm (s) 52%. 3) In the third experiment a solution of **3** (19 mg, 0.1 mmol) in (dioxan 1 mL) was added to a solution of thionyl chloride (2 mL, 21 mmol) in dichloromethane (10 mL). Examination of the solution by ^{31}P nmr showed the presence of the same two absorptions: 28.03 ppm (s) 50% and 7.98 ppm (s) 50%.

Diisopropyl benzoylphosphonate (**8**). Triisopropyl phosphite (23.7 mL, 0.1 mol) was added dropwise to benzoyl chloride (11.6 mL, 0.1 mol) cooled to −5°C by an ice-salt bath. After completion of the addition the reaction mixture was stirred at room temperature for 48 h. NMR: ^1H: ($CDCl_3$) 8.25, (2 H, d, J = 7.6 Hz); 7.58 (1 H, t, J = 7.3 Hz); 7.47 (2 H, t, J = 7.1 Hz); 4.79 (2 H, m); 1.49 (12 H, d, J = 6.3); ^{31}P: −2.79.

Monodealkylation of diisopropyl benzoylphosphonate. A solution of diisopropyl benzoylphosphonate (**8**, 8.1 g, 0.03 mol) and of lithium bromide (2.86 g, 0.033 mol) in acetonitrile (50 mL) was refluxed for 3 h and then was left to stand at room temperature for 72 h. The precipitated lithium isopropyl benzoylphosphonate was filtered, 4.8 g. NMR (D_2O): ^1H: 8.24 (2 H, d, J = 7.3 Hz); 7.76, (1 H, t, J = 7.6 Hz); 7.63 (2 H, t, J = 7.5 Hz); 4.54 (1 H, m) 1.30 (6 H, d, J = 6.3 Hz); ^{31}P: −2.79 (d).

Lithium isopropyl benzoylphosphonate (2.35 g, 10 mmol) was dissolved in water (5 mL) concentrated hydrochloric acid (2 mL) was added and the liberated acidic ester **6** was extracted by dichloromethane (3 × 10 mL). The solvent was evaporated after drying over magnesium sulfate, to leave behind **7** as an oil. NMR ($CDCl_3$) ^1H: 8.2 (2 H, d, $J = 7.1$ Hz) 7.58 (1 H, t, $J = 7.3$ Hz) 7.42 (2 H, t, $J = 7.3$ Hz) 4.79 (1 H, m); 1.32 (6 H, d, $J = 6.1$ Hz); ^{31}P: -2.6 (d).

REFERENCES AND NOTES

1. An alternative approach to mixed esters could be based on the Arbuzov reaction of mixed phosphites. This would necessitate the preparation of such compounds, which might be rather tedious. In addition, the Arbuzov reaction of mixed phosphites may lead in many instances to product mixtures.
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