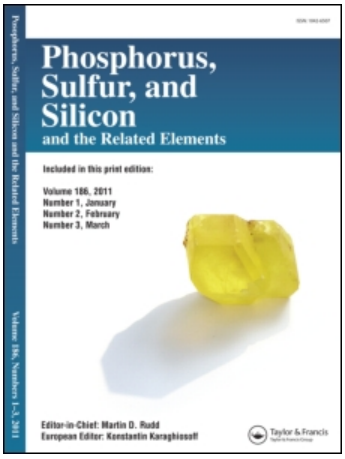

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FRAGMENTATION OF A PHENYLPHOSPHONAMIDIC ACID AS A NEW TECHNIQUE FOR THE GENERATION OF PHENYL DIOXOPHOSPHORANE

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FRAGMENTATION OF A PHENYLPHOSPHONAMIDIC ACID AS A NEW TECHNIQUE FOR THE GENERATION OF PHENYL DIOXOPHOSPHORANE

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(Dedicated to Professor John G. Verkade in honor of his sixtieth birthday)

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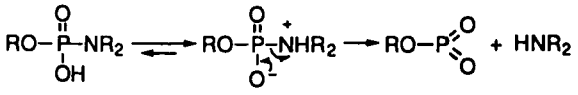
N-(1-Adamantyl) phenylphosphonamidic acid (**3**), an easily prepared solid, on heating in toluene or 1,2-dichloroethane gave the crystalline adamantylamine salt of the anhydride PhP(O)(NHAd)—O—PPh(O)(OH). The mechanism is proposed to involve first the fragmentation of **3** to form phenyl dioxophosphorane, $PhPO_2$, which then acts as a phosphorylating agent to unreacted **3**. This mechanism was supported by the observation of first-order kinetics for the consumption of **3**. When the phosphonamidic acid was fragmented in the presence of an alcohol, the intermediate $PhPO_2$ was trapped as the monoalkyl phenylphosphonate. The OH groups on the surface of silica gel were also phosphonylated by $PhPO_2$. The acidic OH group of a phosphoric acid monoester (thymyl phosphate) was phosphonylated to give Thy—O—P(O)(OH)—O—PPh(O)(OH). It is concluded from this study that N-(1-adamantyl) phenylphosphonamidic acid is a useful precursor of phenyl dioxophosphorane, which can perform valuable phosphonylation operations.

Key words: N-(1-adamantyl) phenylphosphonamidic acid; phenyl dioxophosphorane; phosphonylation.

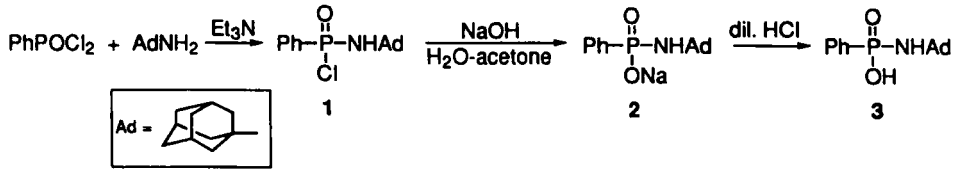
We recently[1,2] described a technique for the generation of alkyl metaphosphates (RO—PO_2) by the thermal fragmentation of certain N-substituted esters of phosphoramidic acids.



By replacing the alkoxy group in the phosphoramidic acid with phenyl, we have now been able to extend this method to the generation of phenyl dioxophosphorane (Ph—PO_2). This is a species that is little known[3] yet is potentially of value as a highly reactive phosphonylating agent. Previously we have generated the dioxophosphorane by fragmentation of derivatives of the 3-phenyl-2,3-oxaphosphabicyclo[2.2.2]octene ring system[4,5]; the new approach to be described here is considerably simpler, and makes phenyldioxophosphorane (and potentially other dioxophosphoranes, and oxothionophosphoranes as well) readily available for evaluation as phosphonylating reagents. Phosphonate synthesis remains an important activity in organophosphorus chemistry; some very recent selected references include the discovery of new synthetic methods for phosphonates (from phosphonyltriethylammonium salts,[6] and from H-phosphinates via phosphonochloridites[7]) and the synthesis of phosphonate esters of biologically significant alcohols (2-hydroxyglutarate,[8] ecgonine[9]).

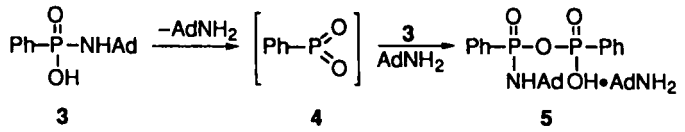
†On leave from the Chemistry Department, Technical University of Lodz.

SCHEME 1



In the generation of the alkyl metaphosphates,[1] best results were obtained when the N-substitutent on the phosphoramidic acid was a large bulky group such as 1-adamantyl or mesityl. The fragmentations then followed first-order kinetics, both in the presence and absence of a trapping agent for the released metaphosphate, which supports the proposed mechanism of a slow elimination step followed by fast addition of the trapping agent. With smaller groups, such as diethylamino, mixed first and second order kinetics were observed in the trapping reactions, implying some participation of the bimolecular addition-elimination mechanism. We therefore started our investigation of the proposed method for $PhPO_2$ generation by preparing the N-1-adamantyl derivative of phenylphosphonamidic acid as the precursor (Scheme 1).

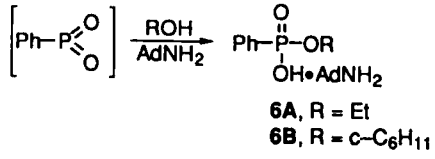
Possibly because of the bulk of the adamantyl group when placed on phosphorus, there is little difficulty in obtaining the desired substitution of only one chlorine in the phosphonic dichloride so as to give phosphonochloramidate **1**. Hydrolysis of the chloramidate with NaOH occurs smoothly in water-acetone; the sodium salt can be isolated but this is not necessary, since acidification with dil. HCl causes precipitation of the desired phosphonamidic acid **3** in purity sufficient for its direct use as a precursor of $PhPO_2$. Compound **3** was found to decompose so rapidly in various solvents that it is unlikely conventional recrystallization or chromatographic procedures would be successful. The ^{31}P NMR spectrum in $CDCl_3$ (δ 22.2) could be recorded successfully if the measurement was made immediately upon preparing the solution, but after a few minutes signals for the decomposition product began to appear. This product displayed a doublet of doublets (δ12.4; δ6.5; $^2J_{PP}$ = 31.3 Hz) suggestive of a derivative with a P—O—P link. Anhydride formation is common when metaphosphate precursors are allowed to fragment in the absence of a trapping agent; they are formed from attack of the metaphosphate on unreacted phosphoramidic acid. Therefore structure **5** was proposed for the decomposition product of the phosphonamidic acid.



The decomposition was somewhat slower at room temperature in toluene, but a sample on being heated at 100°C for 15 min was completely decomposed. The anhydride crystallized from the solution, and was recrystallized from $CHCl_3$-hexane. The ^{31}P shift of δ 6.5 was appropriate for a phosphonate moiety, and the shift of δ 12.4 for the phosphonamide moiety, both shifted several ppm upfield due to the well-known shielding effect of the pyro linkage. The ^{31}P NMR spectrum was also recorded

on solid **3** by the CP-MAS technique. The shift (δ 22.5) matched that in $CDCl_3$ solution, and no signals for the anhydride were present.

Experiments on decomposition of **3** in the presence of alcohols have shown that the suspected $PhPO_2$ intermediate can be effectively trapped, with the formation of the adamantylamine salt of a mono-ester of phenylphosphonic acid (**6**).

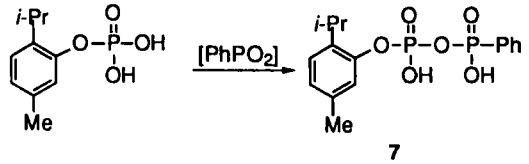


6A, R = Et
6B, R = c-C_6H_{11}

Thus, when a solution of **3** in toluene containing six equivalents of cyclohexanol was heated at 80°C, the product was salt **6B** which crystallized from the solution. It had a ^{31}P NMR shift of δ 11.8. The phosphonamidic acid was also decomposed in the presence of ethanol in toluene or 1,2-dichloroethane; from the former, the salt (**6A**) of the ethyl ester (^{31}P NMR δ 12.2) crystallized from the reaction mixture.

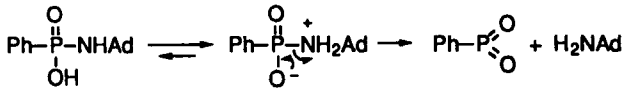
In our work with phosphoramidic acids, we employed silica gel, acting through its surface OH groups, as a novel trap for metaphosphates,[1] which created a phosphate function bonded to the surface. This function is easily detected by solid-state ^{31}P NMR; the signals are shifted some 10 ppm upfield of simple phosphates, an effect we confirmed by using a simple silanol as a trap. Phenyl dioxophosphorane was therefore generated from **3** in the presence of silica gel suspended in various solvents. The recovered silica gel gave a pronounced signal at δ 7, with a smaller signal, sometimes a shoulder, at around δ 12–13. The major signal at δ 7 is tentatively assigned to a surface-bonded phosphonate group.

The ability of the dioxophosphorane to react with the P—OH group of the starting phosphonamidic acid to form the P—O—P group in **5** suggested that this reactivity could be put to use for synthetic purposes. One preliminary experiment has been performed to test the phosphonylation of a phosphoric acid mono ester. A solution of thymyl phosphate, a crystalline easily dried solid, was heated in toluene with one equiv. of phosphonamidic acid **3**. The ^{31}P NMR signals expected for mixed anhydride **7** formed (δ 7.3 and −18.2; $^2J_{PP}$ = 23 Hz), along with those for a smaller amount (about 20%) of anhydride **5**. Probably the use of an excess of the trapping acid would improve the yield of desired anhydride. It was also noticed that continuing the heating after all **3** had decomposed caused the slow disappearance of **5** with increased amounts of the desired product **7**. Apparently anhydride **5** is capable of functioning as a phosphonylating agent toward the thymyl phosphate. Such behavior has also been observed in work with certain phosphoramidic acid-alcohol combinations.[10] We consider these preliminary results to be quite promising for the development of a new method for constructing the P—O—P link and further work on the phosphonylation of phosphorus acids is in progress.



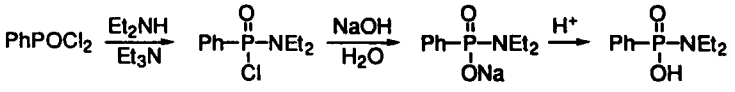
7

We return now to the question of the mechanism of the fragmentation of phosphonamidic acid **3**. If the proposed elimination of phenylphosphorane occurs as a slow step, the kinetics should be first order, as indeed was observed for the fragmentation of phosphoramidic acids.[1] We have determined the rate of reaction of phosphonamidic acid **3** in toluene solution at 64.5°C, using ^{31}P NMR as the analytical method as was done for phosphoramidic acids.[1] In the present case, the rate of fragmentation was so fast that some of the starting **3** had already decomposed, forming anhydride **5**, before the first measurement of the concentration of **3** could be made. Nevertheless, it was possible to follow the reaction for a period of about two half-lives, during which time first-order kinetics with $k = (2.57 \pm 0.14) \cdot 10^{-3}\ s^{-1}$ were observed. The fact that the released phenyl dioxophosphorane reacted with the starting **3** does not change the kinetic order, as has been discussed for the similar problem in phosphoramidic acid fragmentations.[1] The half-life of **3** at 64.5°C is only 4.5 min, significantly less than observed for phosphoramidic acids (e.g., 58 min for O-ethyl N-1-adamantylphosphoramidic acid at 80°C). The kinetics measurement rules out the possibility that the observed reaction product **5** could have been formed in a bimolecular reaction of phosphonamidic acid **3**, and leaves the mechanism involving phenyl dioxophosphorane as a short-lived intermediate as the most probable. The phosphonamidic acid may exist in equilibrium with a zwitterionic form, which is true of phosphoramidic acids.[2] In that event, it is likely that the zwitterion is the species that fragments to the dioxophosphorane, as was established by kinetic isotope effects with the phsophoramidic acids,[2] but no evidence bears on this point at this time.

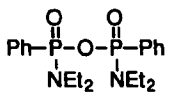


An attempt was made to use the less expensive diethylamino derivative of phenylphosphonic acid (Scheme 2) as the precursor of phenyldioxophosphorane, but this phosphonamidic acid (**10**) could not be isolated. Acidification of **9** on an ion-exchange column (Amberlyst-15 H^+) with wet acetone as eluent gave phenylphosphonic acid, and with ethanol as eluent the product was ethyl phenylphosphonate (suggestive of fragmentation to phenyl dioxophosphorane as an intermediate, but not further studied). An attempt to hydrolyze chloride **8** with water-triethylamine gave only the symmetrical anhydride **11** from interaction of **8** and **10**.

SCHEME 2



8 **9** **10**



11

EXPERIMENTAL[11]

N-(1-Adamantyl) Phenylphosphonochloramidate (**1**). A solution of 7.56 g (0.05 mol) of 1-adamantanamine and 7.0 mL (0.05 mol) of triethylamine in 120 mL of ether was added at room temperature over a 1-h period to a solution of 9.75 g (0.050 mol) of phenylphosphonic dichloride in 120 mL of ether, with vigorous stirring. White solid precipitated, and the mixture was stirred for an additional 6 h at room temperature. The solid was filtered from the mixture and washed with ether. The residue (15.2 g) was a mixture of amine hydrochloride and chloramidate **1**; it gave a ^{31}P NMR signal in $CDCl_3$ at δ 28.6. The solid was used directly in the next step.

N-(1-Adamantyl) Phenylphosphonamidic Acid (**3**). The solid from the preceding step was added in small portions to a solution of 5 g (0.125 mol) of sodium hydroxide in 80 mL of water and 50 mL of acetone at room temperature. All solid dissolved during a 1 h period of stirring, giving a solution with a single ^{31}P NMR signal, at δ 11.4. The amine released from the hydrochloride was removed by extraction with two 20-mL portions of benzene. The water-acetone solution containing salt **2** was acidified with 0.36% HCl to pH 3 (pH paper). Acid **3** precipitated and was recovered by filtration; it was washed with water until the washings were neutral, and then with ether. It was thoroughly dried in a high vacuum. Yield 6.7 g (46%); m.p. 151°C dec; ^{31}P NMR δ 22.2 ($CDCl_3$), δ 20.3 (toluene), δ 19.1 (THF); all solutions developed signals for anhydride **5** on standing. CP-MAS ^{31}P NMR of the solid δ 22.5 (with no signals for **5**); ^1H NMR ($CDCl_3$) δ 1.54, 1.77, 1.93 (15 H total, adamantyl), 5.2 (2 H, OH and NH), 7.28–8.0 (5 H, phenyl). Anal. Calcd. for $C_{16}H_{22}NO_2P$: C, 65.96; H, 7.61; N, 4.81. Found: C, 65.25; H, 7.43; N, 4.63.

Acid **3** was stable as the solid when stored in the refrigerator. Solutions, especially in chloroform, were unstable and developed ^{31}P NMR signals for the anhydride **5** (described below); in $CDCl_3$, decomposition was complete in 20 h.

Thermal Fragmentation of N-(1-Adamantyl) Phosphonamidic Acid **3**. In an NMR tube, a solution of 20 mg of acid **3** in 1,2-dichloroethane was heated at 50°C for 30 min. All **3** disappeared and the only ^{31}P NMR signals were found at δ 11.0 and 5.0 (d of d, $^2J_{PP}$ = 32 Hz) for the mixed anhydride **5**. The fragmentation was also performed in toluene. The reaction was complete at 64.5°C after 40 min giving the anhydride **5** with ^{31}P NMR δ 12.4 and 6.5 (d of d, $^2J_{PP}$ = 31.1 Hz). This mixture was used for isolation of **5**; the solution was evaporated to half its volume and placed in the freezer, causing precipitation of anhydride **5**. The solid (m.p. 234–236°C) was washed with ether and recrystallized from $CHCl_3$-hexane (m.p. 244–245°C); on TLC (silica) in 2-propanol/ethyl acetate, a single spot was observed (R_f = 0.35), but the elemental anlaysis for C, H, N was not within the limits.

Thermal Fragmentation of Acid **3** *in the Presence of Alcohols*

Ethanol: Acid **3** (50 mg) was heated at 50°C in 3 mL of 10% (v/v) ethanol in 1,2-dichloroethane. Analysis by ^{31}P NMR showed the major product to be the adamantylamine salt (**6A**) of ethyl phenylphosphonate, δ 12.1, with only about 5% of unassigned signals at δ 6.1 and 5.2; none of anhydride **5** was present. The fragmentation was also conducted on 50 mg of **3** in 4 mL of 10% (v/v) ethanol in toluene at 120°C for 30 min, during which solid **6A** precipitated. It was recovered by filtration (39.6 mg, 68.4%); ^{31}P NMR ($CDCl_3$) δ 12.2; ^1H NMR ($CDCl_3$) δ 1.14 (t, J = 7 Hz, CH_3), 1.47 and 1.78 (adamantyl, 15 H), 3.78 (m, CH_2), 7.3–7.9 (ArH), 8.5 (broad, OH, NH). The solid was analyzed without recrystallization. Anal. Calcd. for $C_{18}H_{28}NO_3P$: C, 64.07; H, 8.36; N, 4.15. Found: C, 63.52; H, 8.38; N, 4.07. Addition of **6A** to an ethereal solution of diazomethane gave a solution containing ethyl methyl phenylphosphonate, identified by ^{31}P NMR δ 21.4 ($CDCl_3$) and ^1H NMR ($CDCl_3$) δ 1.32 (t, J = 7 Hz, $CH_2\underline{CH_3}$), 3.73 (d, J = 11.1 Hz, OCH_3), 4.12 (m, OCH_2), 7.3–8.0 (ArH).

Cyclohexanol: A warm solution of 200 mg (2.0 mmol) of cyclohexanol in 3 mL of benzene under argon in an NMR tube was treated with 100 mg (0.34 mmol) of phosphonamidic acid **3**. The temperature was raised to 80°C; after about 5 min, a clear solution resulted. Heating was continued for 2 h, during which time a white solid precipitated. The supernatant solution showed the presence of the mixed anhydride **5**; heating was continued for an additional 16 h to utilize **5** in continued reaction with cyclohexanol. The solid was recovered by filtration. It was insoluble in most solvents except methanol, in which it had ^{31}P NMR δ 11.8. It was washed with benzene and then recrystallized from methanol containing acetone. Yield of **6A**, 40 mg (29.8%), m.p. 266–270°C. Anal. Calcd. for $C_{22}H_{34}NO_3P$: C, 67.49; H, 8.75; N, 3.57. Found: C, 66.87; H, 8.66; N, 3.49.

Thermal Fragmentation of Acid **3** *in the Presence of Silica Gel.* Using the procedure described previously for phosphoramidic acids,[1] a suspension of 0.7 g of dried silica gel in 10 mL of THF containing 0.10 g of acid **3** was heated for 4 h at 60°C. The solid was recovered and washed with methylene chloride, 2-propanol, and again with methylene chloride; ^{31}P NMR (CP-MAS) δ 6.8 with a shoulder at

δ 12.5. Similar results were obtained when the reaction was conducted in toluene (δ 7.7) or 1,2-dichloroethane (δ 7.25). Elemental analysis of the product from THF gave 3.83% C, 1.16% H, 0.07% N.

Kinetics of Fragmentation of Acid **3**. The procedure for rate measurements has been previously described.[1] A 29.6 mg (0.102 mmol) sample of **3** in 2 mL of toluene was sealed in an NMR tube and placed in a constant temperature bath at 64.5°C. As soon as all solid **3** dissolved, ^{31}P NMR was recorded, with triphenylphosphine oxide as external standard. At this point, 64% of **3** had already decomposed. The reaction was continued for 8 min. The first-order plot (y = ln c/c_o, x = time) was linear with k = $(2.57 \pm 0.14) \cdot 10^{-3}$ s^{-1} ($t_{1/2}$ = 4.5 min) and correlation coefficient (r) of -0.995.

N,N-Diethylamino Phenylphosphonochloramidate (**8**). To a solution of 9.75 g (0.05 mol) of $PhPOCl_2$ in 60 mL of ether was added a solution of 3.65 g (0.05 mol) of diethylamine and 5.08 g (0.05 mol) of triethylamine in 60 mL of ether at room temperature over a period of 45 min. Triethylamine hydrochloride precipitated as a white solid, and was filtered off. The solution of **8** had ^{31}P NMR δ 35.8. It was concentrated to dryness and used directly in the next step.

Sodium Salt (**9**) *of N,N-Diethylamino Phenylphosphonamidic Acid* (**10**). The residue from above was dissolved in 60 mL of acetone, and added to a solution of 4.5 g (0.11 mol) of sodium hydroxide in 60 mL of water cooled to 0°C over a period of 30 min. The solution of **9** had ^{31}P NMR δ 15.0. It was concentrated to dryness at 25°C with a vacuum pump. The solid residue was washed with 100 mL of ether, and then mixed with 100 mL of absolute ethanol. Some insoluble material was filtered off and discarded. The filtrate was mixed with 200 mL of benzene and then reduced to one-fourth of its volume. The solution was cooled and the precipitated solid salt **9** was filtered off (9.1 g, 77%); ^{31}P NMR (D_2O) δ 17.9; ^{1}H NMR δ 1.04 (t, J = 7 Hz, 6 H, CH_3), 2.96 (m, 4 H, CH_2), 7.3–7.8 (5 H, ArH).

Attempted Preparation of N,N-Diethylamino Phenylphosphonamidic Acid. The sodium salt **9** was passed through Amberlyst-15 H^+ in a wet acetone solution; hydrolysis to phenylphosphonic acid occurred, as indicated by the ^{1}H NMR spectrum. With ethanol as the solvent, ethyl phenylphosphonate was formed. An attempt to hydrolyze chloramidate **8** with water-triethylamine gave anhydride **11**: m.p. 85–88°C (from pentane); ^{31}P NMR ($CDCl_3$) δ 16.5, 16.9 (diastereomers); ^{1}H NMR ($CDCl_3$) δ 1.02 (t, J = 6 Hz, 6 H, CH_3), 3.14 (m, 4 H, CH_2), 7.3–7.8 (5 H, ArH). Anal. Calcd. for $C_{20}H_{30}N_2O_3P_2$: C, 58.81; H, 7.40; N, 6.86. Found: C, 58.39; H, 7.38; N, 6.48.

ACKNOWLEDGEMENT

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11. ^{31}P NMR spectra were recorded on a Bruker 80 MHz Spectrometer, with 85% phosphoric acid as reference. Downfield shifts are positive. ^{1}H NMR spectra were recorded on the same instrument. Phenylphosphonic dichloride was purchased from Aldrich Chemical Co.; it must be redistilled with fractionation before use, as it contains a significant amount of phenylphosphonous dichloride (lower boiling) that will interfere with later reactions. The fractionation is easily monitored by ^{31}P NMR: $PhPOCl_2$, δ 31.6; $PhPCl_2$, δ 160.6. All solvents were carefully dried and distilled before use, and apparatus was generally flame-dried. Reactions were conducted under argon.