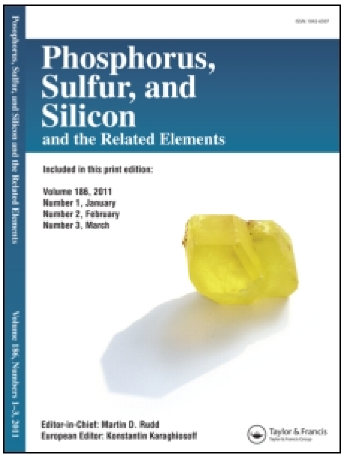

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PHOSPHONIC SYSTEMS. 4. PREPARATION OF TETRAETHYLALKYLPHOSPHONIC DIAMIDES

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The preparation of N,N,N′,N′-tetraethylalkylphosphonic diamides, R-P(O)(NEt_2)$_2$ from the corresponding haloalkanes and the lithium derivative of bis(diethylamino)phosphorous acid is reported.

Key words: Alkylphosphonodiamidates; diamidophosphite ion as a nucleophile in S_N2 reaction.

In our recent work on 1-alkenylphosphonic diamides[1] we have observed that the disubstitution of the corresponding phosphonic dichlorides with dialkylamines is a sluggish reaction, often leading to uncomplete substitution or being accompanied by side reactions. A similar observation was made in an early report[2] on the preparation of these compounds. In his review on hexamethylphosphorictriamide (HMPTA) Normant reported[3] that the anion $(Me_2N)_2PO^-$ (generated by the cleavage of HMPTA with alkali metals) can react with bromoalkanes yielding phosphonic diamides. That observation led to the synthetic application of the diamidophosphite anions, *via* their reaction with epoxides, leading to β-hydroxyphosphonodiamidates.[4] The P-alkylation of the sodium salt of the diamidophosphite in the 1,3,2-benzodiazaphosphorin system has also been reported.[5]

In view of the simple method developed in our Laboratory[6] for the preparation of tetraethyldiamidophosphite (**1**), we decided to investigate the applicability of this substrate to the synthesis of the corresponding phosphonic diamides.

RESULTS AND DISCUSSION

When 2-propenylphosphonic dichloride was treated with an excess of diethyl- and triethylamine at room temperature, only the monosubstitution product, N,N-diethyl-2-propenylphosphonoamidochloridate (**2**) was isolated from the reaction mixture with no indication (^{31}P n.m.r. spectroscopy) of the formation of the corresponding diamide (Equation 1).‡

$$CH_2{=}CH{-}CH_2P(O)Cl_2 \xrightarrow{3Et_2NH,\ 4Et_3N} \underset{\mathbf{2}}{CH_2{=}CH{-}CH_2P(O)(NEt_2)Cl} \qquad (1)$$

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‡ Longer reaction times gave some disubstitution, but parallel formation of the isomerised, α,β-unsaturated products was also observed.

In fact, the reluctance of **2** to undergo second substitution by Et_2NH can be used for the preparation of phosphonic amidoesters (**3**), as illustrated in Equation 2.

$$\mathbf{2} \xrightarrow{\text{RONa/ROH}} CH_2{=}CH{-}CH_2P(O)(NEt_2)(OR) \qquad (2)$$

3 a, R = Me (65%)
b, R = Et (60%)

We have found however, that the phosphonic diamides (**4**) can be prepared successfully from **1**, *via* its lithium derivative, in the reaction with haloalkanes (Equation 3).

$$\underset{\mathbf{1}}{(Et_2N)_2P(O)H} \xrightarrow[\text{2. R—X}]{\text{1. BuLi/THF}} \underset{\mathbf{4}}{R{-}P(O)(NEt_2)_2} \qquad (3)$$

Compounds prepared according to Equation 3 are listed in Table I. All compounds gave single peaks in their ^{31}P n.m.r. spectra, and their ^{1}H and ^{13}C n.m.r. spectra

TABLE I
N,N,N',N'-Tetraethylphosphonodiamidates (**4**)

4	R-X	Yield(%)[a]	δ_P (ppm)[b]	M.S.(M^+,%)
a	MeI	100	32.6	206 (25)
b	PrBr	75	34.8	234 (9)
c	$CH_2{=}CHCH_2Br$	82	30.7	232 (3)
d	$MeCH{=}CHCH_2Br$	54[c]	32.3	246 (4)
e	n-$C_6H_{13}Br$	75	35.8	276 (19)
f	$PhCH_2Br$	85	30.8	282 (7)
g	n-$C_5H_{11}Cl$	16[d]	37.9	262 (10)
h	$Ph(CH_2)_3Br$	30[e]	35.4	310 (26)

[a] Crude products were obtained in a state of purity greater than 95% as determined by ^{31}P n.m.r. spectroscopy. They could be subjected to column chromatography or bulb to bulb distillation, but that did not result in a significant improvement of their purity.

[b] Relative to trimethyl phosphate.

[c] After bulb to bulb distillation; yield of the crude product 78%.

[d] After bulb to bulb distillation.

[e] After column chromatography and bulb to bulb distillation.

were in excellent agreement with the expected structure.The structures of the products were also confirmed by mass spectrometry; all products **4** yielded peaks corresponding to the respective molecular ions, and gave fragmentation patterns in agreement with their structure. For known compounds (**4a**, **b**, **f**), their properties agreed with those reported in the literature. Although compounds **4a**–**h** could be purified by distillation or by column chromatography, the purity of crude products was usually sufficiently high that they could be used without further purification. Only in two cases (preparation of **4g**, **h**), the phosphonic diamides had to be isolated from the reaction mixture, yielding final products with much lower yields. Reaction (3) failed when 2-bromopropane was used as an alkylating agent, presumably because elimination of HBr rather than nucleophilic substitution took place as a major reaction. It seems therefore that the synthetic procedure presented in Equation 3 is limited to the preparation of phosphonic diamides unsubstituted at carbon 1. When instead of the lithium, the sodium derivative of **1** (generated from **1** and sodium hydride) was used, complex mixtures of phosphorus-containing products were obtained. The nucleophilic properties of the anion derived from **1** are therefore strongly dependent on the nature of the counterion.

EXPERIMENTAL

Solvents and commercially available substrates were purified by conventional methods immediately before use. All reactions involving organometallic reagents were carried out in an atmosphere of dry nitrogen. N.m.r. spectra were recorded on a Bruker AC300 MHz spectrometer in $CDCl_3$ and the chemical shift values are given relative to TMS (^1H, ^{13}C) and trimethyl phosphate (^{31}P). Mass spectra were recorded on a Varian MAT-212 double focusing direct inlet spectrometer at an ionization potential of 70 eV. Only the values of M^+ and selected ions, most relevant to structural determinations, are reported. Bulb to bulb distillations were performed on a Buchi GKR-50 apparatus. For column chromatography, Merck Kieselgel 60 (0.063–0.200 mm) was used as a stationary phase.

2-Propenylphosphonodichloridate was prepared according to the literature procedure.[7]

N,N-Diethyl-P-prop-2-enylphosphonoamidochloridate (**2**). 2-Propenylphosphonodichloridate (4.96 g, 0.031 mol) in tetrachloromethane (10 mL) was added dropwise with stirring at room temperature to a solution of diethylamine (7.2 mL, 0.069 mol) and triethylamine (13.7 mL, 0.099 mol) in tetrachloromethane (30 mL). Stirring was continued for 2 h, the mixture was filtered and the filtrate was washed with water (3 × 50 mL), and dried ($MgSO_4$). After removal of the solvent the crude product was purified by distillation. Yield 2.95 g (49%); bp 87–89°C (0.3 mm). ^1H n.m.r.: δ 0.86 (6H, t, J_{HH} 7.1 Hz, 2 × Me of NEt_2), 2.70 (2H, dd, J_{HP}, J_{HH} 19.6, 7.8 Hz, CH_2P), 2.84 (4H, m, 2 × CH_2 of NEt_2), 4.99 (2H, m, γ-CH_2), 5.61 (1H, m, β-CH). ^{31}P n.m.r.: δ 42.0. M.S.: *m/z* 195 (M^+, 8%).

N,N-Diethyl-O-methyl-P-prop-2-enylphosphonoamidate (**3a**). Sodium (0.023 g, 1.0 mmol) was dissolved in methanol (1 mL) and to this solution a solution of **2** (0.20 g, 1 mmol) in methanol (1 mL) was added. The mixture was stirred at room temperature for 2 h and neutralized with aq. ammonium chloride. After extraction with tetrachloromethane (3 × 10 mL) drying ($MgSO_4$) and removal of the solvent, **3a** was obtained as a pale yellow oil; 0.13 g (65%). ^1H n.m.r.: δ 0.95 (6H, t, J_{HH} 7.0 Hz, 2 × Me of NEt_2), 2.40 (2H, m, CH_2P), 2.92 (4H, m, 2 × CH_2 of NEt_2), 3.43 (3H, d, J_{HP} 10.8 Hz, OMe), 5.02 (2H, m, γ-CH_2), 5.62 (1H, m, β-CH). ^{31}P n.m.r.: δ 30.4. M.S.: *m/z* 191 (M^+, 5%), 176 (M^+-Me ·, 16), 119 (M^+-Et_2N ·, 100).

N,N,O-Triethyl-P-prop-2-enylphosphonoamidate (**3b**). Prepared as **3a** from **2** and EtONa/EtOH. Yield: 60%. ^1H n.m.r.: δ 0.95 (6H, t, J_{HH} 7.1 Hz, 2 × Me of NEt_2), 1.14 (3H, t, J_{HH} 7.1 Hz, Me of OEt), 2.40 (2H, m, CH_2P), 2.92 (4H, m, 2 × CH_2 of NEt_2), 3.80 (2H, m, CH_2 of OEt), 5.01 (2H, m, γ-CH_2), 5.64 (1H, m, β-CH). ^{31}P n.m.r.: δ 28.9. M.S.: *m/z* 205 (M^+, 5%), 133 (M^+-Et_2N ·, 31), 72 (Et_2N^+, 25).

N,N,N',N'-Tetraethylalkylphosphonodiamidates (**4**). *General procedure*. n-Butyllithium (33 mL, solution in hexane, 53 mmol) was added to a solution of **1** (10.0 g, 52 mmol) in THF (70 mL) at −78°C.

The mixture was stirred at that temperature for 15 min, and the required haloalkane (51 mmol) was added dropwise with stirring. Stirring was continued for 30 min at −78°C and the mixture was allowed to warm up to room temperature. Volatile materials were removed under reduced pressure, water (50 mL) was added and extracted with ether (4 × 30 mL). After drying ($MgSO_4$) and removal of the solvent, crude products **4** were obtained as pale yellow oils. For yields, δ_P, and molecular ions, see Table I. All products **4** showed in their ^1H and ^{13}C n.m.r. spectra signals corresponding to the $P(O)(NEt_2)_2$ group: $\delta_H \approx 0.8$ (12H, t, $J_{HH} \approx 7$ Hz, 4 × Me of NEt_2), ≈2.7 (8H, m, 4 × CH_2 of NEt_2). $\delta_C \approx 13$ (d, $J_{CP} \approx 3$Hz, Me of NEt_2), ≈37 (d, $J_{CP} \approx 5$ Hz). Further characterization of compounds **4a–4h** is given below.

4a: n_D^{24} 1.4574 (lit.[8] n_D^{30} 1.4565). ^1H n.m.r.: δ 1.15 (3H, d, J_{HP} 14.6 Hz, Me-P). ^{13}C n.m.r.: δ 28.5 (d, J_{CP} 87.0 Hz, Me-P). M.S.: *m/z* 191 (M^+-Me · , 23%), 134 (M^+-Et_2N · , 100), 120 (Et_2NPOH^+, 38), 72 (Et_2N^+, 65).

4b: n_D^{17} 1.4655 (lit.[2] n_D^{30} 1.4580). ^1H n.m.r.: δ 0.88 (3H, t, J_{HH} 7.1 Hz, γ-Me), ≈1.54 (4H, overlapping m, α-CH_2, β-CH_2). ^{13}C n.m.r.: δ 14.9 (d, J_{CP} 24.0 Hz, γ-Me), 15.1 (d, J_{CP} 9.2 Hz, β-CH_2), 27.8 (d, J_{CP} 115.6 Hz, α-CH_2). M.S.: *m/z* 191 [$(Et_2N)_2PO^+$, 22%], 162 (M^+-Et_2N · , 100), 120 (Et_2NPOH^+, 85), 72 (Et_2N^+, 63).

4c: n_D^{17} 1.4732. ^1H n.m.r.: δ 2.40 (2H, dd, J_{HP}, J_{HH} 17.3, 7.3 Hz, CH_2P), 4.91 (2H, m, γ-CH_2), 5.63 (1H, m, β-CH). ^{13}C n.m.r.: δ 30.5 (d, J_{CP} 111.7 Hz, CH_2P), 115.4 (d, J_{CP} 12.2 Hz, γ-CH_2), 127.3 (d, J_{CP} 9.1 Hz, β-CH). M.S.: *m/z* 191 [$(Et_2N)_2PO^+$, 100%], 160 (M^+-Et_2N · , 27), 120 (Et_2NPOH^+, 29) 72 (Et_2N^+, 65).

4d: n_D^{17} 1.4739. ^1H n.m.r.: δ 1.48 (3H, m, δ-Me), 2.41 (2H, dd, J_{HP}, J_{HH} 16.6, 5.5 Hz, CH_2P), 5.30 (2H, m, β-CH, γ-CH). ^{13}C n.m.r.: δ 16.6 (s, δ-Me), 30.4 (d, J_{CP} 112.8 Hz, CH_2P), 127.8 (d, J_{CP} 13.1 Hz, β-CH), 129.6 (d, J_{CP} 9.3 Hz, γ-CH). M.S.: *m/z* 191 [$(Et_2N)_2PO^+$, 100%], 120 (Et_2NPOH^+, 51), 72 (Et_2N^+, 68), 55 ($C_4H_7^+$, 38).

4e: n_D^{24} 1.4601. Distilled bulb to bulb (oven temp 176–178°C/0.1 mm). ^1H n.m.r.: δ 0.77 (3H, t, J_{HH} 6.7 Hz, 6-Me), 1.10–1.68 (8H, overlapping m, 2,3,4,5-CH_2), 1.74 (2H, dd, J_{HP}, J_{HH} 14.7, 7.3 Hz, CH_2P). ^{13}C n.m.r.: δ 12.6 (s, 6-Me and 5-CH_2), 12.7 (d, J_{CP} 2.7 Hz, δ-CH_2), 20.9 (d, J_{CP} 3.6 Hz, γ-CH_2), 21.1 (S, β-CH_2), 25.2 (d, J_{CP} 115.0 Hz, CH_2P). M.S.: *m/z* 261 (M^+-Me · , 10%), 204 (M^+-Et_2N · , 58), 191 [$(Et_2N)_2PO^+$, 26], 120 (Et_2NPOH^+, 42), 72 (Et_2N^+, 100).

4f: n_D^{17} 1.5186. ^1H n.m.r.: δ 3.08 (2H, d, J_{HP} 16.6 Hz, CH_2P), 7.10–7.40 (5H, m, Ph). ^{13}C n.m.r.: δ 32.5 (d, J_{CP} 109.5 Hz, CH_2P), 125.0, 126.8, 128.9, 131.9 (s, aromatic C). M.S.: *m/z* 191 [$(Et_2N)_2PO^+$, 100%], 120 (Et_2NPOH^+, 12), 91 ($C_7H_7^+$, 82), 72 (Et_2N^+, 23).

4g: n_D^{24} 1.4570. Distilled bulb to bulb (oven temp 162–164°C/0.2 mm). ^1H n.m.r.: δ 0.80 (3H, t, J_{HH} 7.1 Hz, 5-Me), 0.95–1.05 (2H, m, δ-CH_2), 1.25 (2H, m, γ-CH_2), 1.48 (2H, m, β-CH_2), 1.61 (2H, m, α-CH_2). ^{13}C n.m.r.: δ 13.8 (s, 5-Me), 14.0 (d, J_{CP} 2.8 Hz, δ-CH_2), 21.9 (d, J_{CP} 3.7 Hz, γ-CH_2), 22.3 (s, β-CH_2), 26.5 (d, J_{CP} 115.5 Hz, α-CH_2). M.S.: *m/z* 191 [$(Et_2N)_2PO^+$, 46%], 190 (M^+-Et_2N · , 32), 120 (Et_2NPOH^+, 54), 72 (Et_2N^+, 100).

4h: n_D^{24} 1.5019. Purified by column chromatography (benzene, followed by ethanol, R_f (EtOH) 0.87) and by bulb to bulb distillation (oven temp 248–250°C/0.1 mm). ^1H n.m.r.: δ 1.67 (2H, m, CH_2P), 1.83 (2H, m, β-CH_2), 2.64 (2H, t, J_{HH} 7.4 Hz, γ-CH_2), 7.05–7.28 (5H, m, Ph). ^{13}C n.m.r.: δ 23.7 (d, J_{CP} 3.3 Hz, β-CH_2), 25.5 (d, J_{CP} 115.7 Hz, α-CH_2), 36.5 (d, J_{CP} 17.4 Hz, γ-CH_2), 125.4, 127.8, 128.0 (aromatic C). M.S.: *m/z* 238 (M^+-Et_2N · , 24%), 191 [$(Et_2N)_2PO^+$, 39], 120 (Et_2NPOH^+, 23), 91 ($C_7H_7^+$, 20), 72 (Et_2N^+, 100).

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