

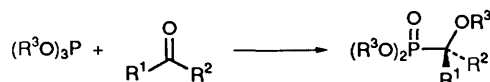
Novel (1,3)-Bifunctional Organophosphorus(III) Phosphonylating Agents

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2-[Bis(trimethylsilyl)amido]-1,3,2-diazaphospholidine, $[N,N'-(\text{CH}_2\text{NMe})_2]\text{P}[\text{N}(\text{SiMe}_3)_2]$ **1**, has been synthesised from $[N,N'-(\text{CH}_2\text{NMe})_2]\text{PCl}$ and $\text{Li}[\text{N}(\text{SiMe}_3)_2]$. The activity of **1** as a phosphonylating agent is demonstrated by its ability to undergo the Abramov reaction with aldehydes.

There are a great variety of biologically desirable organophosphorus compounds possessing structures based on the phosphonate scaffold $(\text{RO})_2\text{P}(=\text{O})\text{R}$ (where R represents either H or a carbon donor residue).¹ Moreover, many of the most useful and potent of these chemicals contain functionality at the α -carbon position; examples include antibiotics such as (1*R*,2*S*)-phosphonmycin $(\text{HO})_2\text{P}(\text{O})\text{CH}-\text{CHMe}-\text{O}$,² antiviral agents such as phosphonoacetic and phosphonoformic acids $[(\text{HO})_2\text{P}(\text{O})\text{CH}_2\text{C}(\text{O})\text{OH}$ and $(\text{HO})_2\text{P}(\text{O})\text{C}(\text{O})\text{OH}$ respectively] used in the treatment of HIV³ and α -amino-phosphonic acids which act as amino acid surrogates.⁴ In recent years, many routes⁵ have been used to α -functionalised phosphonate esters but few combine simplicity, efficiency, generality and high yields. We have been investigating novel phosphonylation methodology based on the Abramov reaction (Scheme 1),⁶ which both achieves these objectives and extends

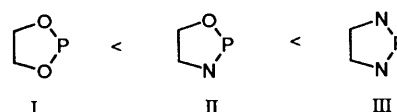


Scheme 1 $\text{R}^1, \text{R}^2 = \text{H, alkyl, aryl}; \text{R}^3 = \text{alkyl, triorganosilyl}$

them to include asymmetric phosphonylation processes where it is possible to control the stereochemistry at the C- α atom.^{6,7} In the search for organophosphorus(III) reagents that will phosphonylate unsaturated substrates under mild conditions, it has been shown that when triorganosilyl groups replace alkyl groups as the ester functionality (R^3 in Scheme 1), the resulting silylated phosphites $(\text{RO})_2\text{POSiR}'_3$ undergo the Abramov reaction far more readily than tertiary alkyl or aryl phosphites since (i) the presence of the more electron-releasing triorganosilyl function increases the nucleophilicity of the phosphorus lone pair and (ii) silyl groups are transferred more readily in the transition state than are alkyl groups.⁸ Upon recognising that compounds of the form $(\text{RO})_2\text{POSiR}'_3$ belong to a wider class of (1,3)-bifunctional reagents in which electrophilic (silicon) and nucleophilic (phosphorus) termini are separated by a single atom spacer group, we reasoned that increased reactivity could be achieved by increasing the relative philicities of either terminus. Here we report on strategies to increase the phosphorus atom nucleophilicity by designing a more electron-releasing phosphorus atom coordination sphere.

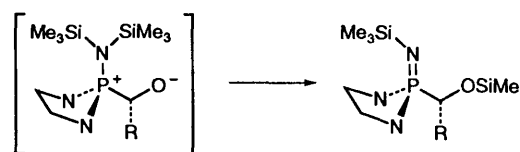
It has been shown that phosphorus atom nucleophilicity is increased if oxygen atom coordinated residues on phosphorus are replaced by nitrogen donor residues.^{8,9} Thus, we have found that the reactivity of silylated organophosphorus(III) compounds varies with the auxiliary as shown in Scheme 2.

Consequently, we envisaged that replacement of the triorganosilyloxy groups in the compounds $[N,N'-(\text{CH}_2\text{NMe})_2]\text{POSiR}'_3$ ($\text{R}_3 = \text{Ph}_3, \text{Bu}'\text{Me}_2, \text{Et}_3$)⁹ by the isoelectronic bis(trimethylsilyl)amido group $(\text{Me}_3\text{Si})_2\text{N}$ -, might result in even further reactivity increase due to (i) greater lone pair-lone



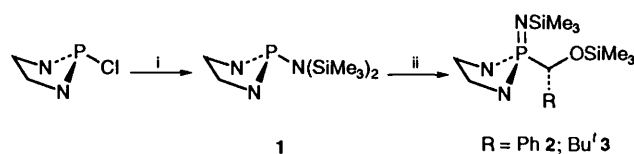
Scheme 2

pair repulsion between nitrogen and phosphorus than between oxygen and phosphorus (*vide supra*), (ii) relief of steric strain accompanying migration of a triorganosilyl group thus converting a three-coordinate nitrogen to a two-coordinate nitrogen atom (Scheme 3).



Scheme 3

$[N,N'-(\text{CH}_2\text{NMe})_2]\text{P}[\text{N}(\text{SiMe}_3)_2]$ **1** is readily isolated as an orange liquid in high yield upon treatment of $[N,N'-(\text{CH}_2\text{NMe})_2]\text{PCl}$ ¹⁰ with $\text{Li}[\text{N}(\text{SiMe}_3)_2]$ in tetrahydrofuran (Scheme 4).



Scheme 4 Reagents and conditions: i, $\text{Li}[\text{N}(\text{SiMe}_3)_2]$, THF, -78°C then **1** at 25°C . Yield: 85%, ii, RCHO ($\text{R} = \text{Ph, Bu}'$), 1 equiv., pentane, 25°C . Yield: 79% **2**, 78% **3**. No specific conformation of the diazaphospholidine ring is implied in the structures shown.

A single high frequency ^{31}P NMR resonance is observed at δ 126.7 ppm (C_6D_6), characteristic of phosphorus(III) and similar to values found for related amidodiazaphospholidines.¹¹ As found also for $[N,N'-(\text{CH}_2\text{NMe})_2]\text{POSiR}'_3$,⁹ **1** does not undergo rapid inversion of configuration at phosphorus on the NMR timescale as evidenced by the retention of a complex AA'BB' spin system for the diamine methylene hydrogens up to 100°C in C_7D_8 (by $^1\text{H}\{^{31}\text{P}\}$ NMR). **1** is sensitive to moist air; exposure of a C_6D_6 solution for 17 h results in the appearance of ^{31}P NMR signals characteristic of four-coordinate phosphorus species.¹²

Compound **1** will phosphonylate benzaldehyde and pivaldehyde (1 equiv.) cleanly at room temperature *via* the Abramov reaction to afford **2** and **3**, respectively (Scheme 4). No other phosphorus-containing products can be observed in this reaction and both **2** and **3** are isolated in high yields. Spectroscopic data are fully consistent with the empirical formulae $[N,N'$

(CH₂NMe)₂]P(=NSiMe₃)CHR(OSiMe₃) (R = Ph **2**, Bu' **3**). For instance, characteristic low frequency ³¹P NMR resonances are observed at δ 19.2 and 20.9 ppm (C₆D₆) respectively and high resolution mass spectrometry confirms the empirical formulae.

As predicted, **1** is more reactive than [N,N'-(CH₂NMe)₂]-POSiR₃:⁹ thus, in a competition experiment a mixture comprising 53% **1** and 47% [N,N'-(CH₂NMe)₂]POSiEt₃,⁹ reacts with PhCHO (1 equiv.) at room temperature in toluene solvent to afford both **2** and [N,N'-(CH₂NMe)₂]P(=O)CHR(OSiEt₃) respectively, but **1** can be seen to react faster since after 80 min the ratio of starting reagents has altered to 33% **1** and 67% [N,N'-(CH₂NMe)₂]POSiEt₃ and after 20 h **1** has been completely consumed but unchanged [N,N'-(CH₂NMe)₂]-POSiEt₃ is still present in the mixture (by ³¹P NMR). Furthermore, from the ratio of products it appears that **1** is somewhat less than twice as reactive as [N,N'-(CH₂NMe)₂]-POSiEt₃. A similar result is obtained with Bu'CHO.

Hydrolysis of **2** (2 mol dm⁻³ HCl in aq. THF, 16 h, room temp.) results in the conversion of the P=NSiMe₃ function into the P=O function showing that the parent phosphonic moiety can be readily unmasked.

Studies are currently in progress on, (i) an asymmetric variant of the process described here, (ii) methods of increasing phosphorylation reactivity by moving to more activating substituents on phosphorus and (iii) catalytic asymmetric phosphorylation processes based on chiral metallophosphite esters.

Experimental

Synthesis of [N,N'-(CH₂NMe)₂]P[N(SiMe₃)₂] **1.**—A solution of Li[N(SiMe₃)₂] in THF (1.0 mol dm⁻³ solution; 5.42 cm³) was added dropwise at -78 °C to a stirred solution of [N,N'-(CH₂NMe)₂]PCl (0.83 g, 5.42 mmol) in THF (ca. 50 cm³) under an atmosphere of dinitrogen. The mixture was allowed to warm to room temperature and stirred thus for 1 h prior to work-up by removal of the volatiles under reduced pressure and extraction of the desired product into pentane (30 cm³). Subsequent removal of the pentane under reduced pressure afforded the product as an orange liquid (1.28 g, 85%); ν_{max}/cm⁻¹ 1260s [δ(SiCH₃)]; δ_H(C₆D₆) 2.63 (m, 4 H, CH₂), 2.43 (d, 6 H, ³J_{PH} 12.0, NMe) and 0.27 (d, 18 H, ⁴J_{PH} 1.7, SiMe₃); δ_C(C₆D₆) 52.01 (d, ²J_{PC} 8.0, CH₂N), 34.58 (d, ²J_{PC} 29.1, NMe) and 4.85 (d, ³J_{PC} 9.3, SiMe₃); δ_P(C₆D₆) 126.7 (s) (Found: M⁺, 277.155 587. Calc. for C₁₀H₂₈N₃PSi₂: M, 277.155 943).

Reactions of **1 with Benzaldehyde and Pivaldehyde.**—Benzaldehyde (0.16 cm³, 1.61 mmol) was added dropwise at room temperature to a stirred solution of **1** (0.44 g, 1.61 mmol) in pentane solvent (15 cm³). After 80 min, the yellow solution was filtered and removal of the volatile materials under reduced pressure afforded [N,N'-(CH₂NMe)₂]P(=NSiMe₃)CHPh(OSiMe₃) **2** as an orange oil (0.49 g, 79%); ν_{max}/cm⁻¹ 1265s [δ(SiCH₃)]; δ_H(C₆D₆) 7.7–7.2 (m, 5 H, PhH), 5.05 (d, 1 H, ²J_{PH}

11.4, PhCHP), 2.84 (m, 2 H, CH₂N), 2.70 (m, 2 H, CH₂N), 2.58 (d, 3 H, ³J_{PH} 9.4, NMe), 2.16 (d, 3 H, ³J_{PH} 9.3, NMe), 0.34 (s, 9 H, SiMe₃) and 0.09 (s, 9 H, SiMe₃); δ_C(C₆D₆) 138–126 (phenyl carbons), 75.54 (d, ¹J_{PC} 147.2, PhCHP), 47.94 (d, ²J_{PC} 6.8, CH₂N), 47.87 (d, ²J_{PC} 7.9, CH₂N), 33.36 (d, ²J_{PC} 5.2, NMe), 32.25 (d, ²J_{PC} 5.0, NMe), 4.03 (d, ³J_{PC} 4.0, P=NSiMe₃) and 0.29 (s, OSiMe₃); δ_P(C₆D₆) 19.2 (s) (Found: M⁺, 383.197 730. Calc. for C₁₇H₃₄N₃OPSi₂: M, 383.197 808). Compound **3** was prepared and isolated in a similar manner (78%); ν_{max}/cm⁻¹ 1270s [δ(SiCH₃)]; δ_H(C₆D₆) 3.62 (d, 1 H, ²J_{PH} 8.0, Bu'CHP), 2.86 (m, 2 H, CH₂N), 2.62 (m, 2 H, CH₂N), 2.38 (d, 6 H, ³J_{PH} 8.0, NMe), 1.09 (s, 9 H, CMe₃), 0.23 (s, 9 H, SiMe₃) and 0.17 (s, 9 H, SiMe₃); δ_C(C₆D₆) 82.10 (d, ¹J_{PC} 155.5, Bu'CHP), 48.41 (d, ²J_{PC} 6.6, CH₂N), 47.77 (d, ²J_{PC} 6.5, CH₂N), 35.99 (d, ²J_{PC} 4.6, CMe₃), 33.46 (d, ²J_{PC} 6.7, NMe), 32.22 (d, ²J_{PC} 4.7, NMe), 28.34 (d, ³J_{PC} 5.5, CMe₃), 4.15 (d, ³J_{PC} 4.3, P=NSiMe₃) and 1.16 (s, OSiMe₃); δ_P(C₆D₆) 20.9 (s) (Found: M⁺, 363.229 208. Calc. for C₁₅H₃₈N₃OPSi₂: M, 363.229 108).

Acknowledgements

We thank the SERC for a studentship (to V. S.).

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Paper 3/02508J

Received 4th May 1993

Accepted 18th May 1993