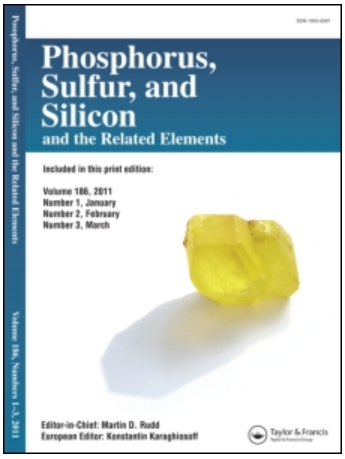

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

THE CHEMISTRY AND STRUCTURE OF THE P(O)NC(O) SYSTEM. PART 1. TRIMETHYLSILYLATION OF O,O-DIETHYL-*N*-FORMYLPHOSPHORAMIDATE AND THE HEXAMETHYLDISILAZANE-PROMOTED CONVERSION TO THE *N*-PHOSPHORYLATED FORMAMIDINE

Sieglinde Bauermeister[a]; Toasz A. Modro[a]
[a] Department of Chemistry, University of Pretoria, Pretoria, South Africa

To cite this Article Bauermeister, Sieglinde and Modro, Toasz A.(1992) 'THE CHEMISTRY AND STRUCTURE OF THE P(O)NC(O) SYSTEM. PART 1. TRIMETHYLSILYLATION OF O,O-DIETHYL-*N*-FORMYLPHOSPHORAMIDATE AND THE HEXAMETHYLDISILAZANE-PROMOTED CONVERSION TO THE *N*-PHOSPHORYLATED FORMAMIDINE', Phosphorus, Sulfur, and Silicon and the Related Elements, 72: 1, 201 — 207
To link to this Article: DOI: 10.1080/10426509208031552
URL: http://dx.doi.org/10.1080/10426509208031552

Phosphorus, Sulfur, and Silicon, 1992, Vol. 72, pp. 201–207
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THE CHEMISTRY AND STRUCTURE OF THE P(O)NC(O) SYSTEM. PART 1. TRIMETHYLSILYLATION OF O,O-DIETHYL-*N*-FORMYLPHOSPHORAMIDATE AND THE HEXAMETHYLDISILAZANE-PROMOTED CONVERSION TO THE *N*-PHOSPHORYLATED FORMAMIDINE

SIEGLINDE BAUERMEISTER* and TOMASZ A. MODRO
Department of Chemistry, University of Pretoria, Pretoria, 0002, South Africa

(Received July 6, 1992)

The reactions of O,O-diethyl-*N*-formylphosphoramidate with trimethylsilylating reagents are described. The silylation occurs invariably at the carbonyl oxygen yielding the unstable O-trimethylsilyl-*N*-phosphorylformimidate which can easily undergo desilylation accompanied by the N → O phosphoryl migration, or substitution of the Me_3SiO group by nucleophiles (water, chloride, ammonia).

Key words: O,O-Diethyl-*N*-formylphosphoramidate; Nucleophilicity/electrophilicity of the P(O)NC(O) system; trimethylsilylation; N → O phosphoryl migration; Nucleophilic displacement of the Me_3SiO group, *N*-phosphorylated formamidine.

INTRODUCTION

N-acylated phosphoramidates, $(RO)_2P(O)NHC(O)R'$ (**1**) represent a system with more than one electrophilic (phosphorus and carbonyl carbon) and nucleophilic (nitrogen and two oxygen atoms of the Y=O groups; Y = P, C) centres. Selectivity in the nucleophilic cleavage was found to depend on the acidity of the medium,[1] and, in the currently investigated[2] alkylation of the conjugate base of **1** we found that the direction of the reaction depends on various factors, such as the bulk of the alkyl group, the nature of the solvent and the counterion of the base, as well as on phase transfer catalysis. In this paper we report on the reactions of a selected substrate **1**, O,O-diethyl-*N*-formylphosphoramidate (**1a**, R = Et; R' = H) with silylating reagents. We have recently observed that the regioselectivity in the reaction of Me_3SiCl (TMSCl) with ambident allylic anions derived from alkenylphosphonates is opposite to that observed for the reaction with haloalkanes.[3] Glidewell[4] demonstrated that O,O-diisopropyl-*N*-benzylphosphoramidate reacts with TMSCl at nitrogen, and calculated (using for the O—Si bond energy the value of 445 kJ mol^{-1} [5]) that the enthalpy change for the migration of the Me_3Si group from oxygen to nitrogen is negative (−30 kJ mol^{-1}). Taking, however, the more recent value of 531 kJ mol^{-1},[6] one arrives at the **positive** (+56 kJ mol^{-1}) ΔH value for that reaction. The equilibrium between the O- and *N*-silylated tautomers of *N*,O,O-triphenylphosphoramidate has been reported.[7] It was therefore difficult to predict regioselectivity in the trimethylsilylation of **1a**, and, as reported below, the final product depends critically on the detailed conditions of the reaction. Recently,

Stec and Baraniak reported on the TMSCl-catalyzed N → O migration of the phosphoryl group in *N*-benzoyl-*N*-phenylphosphoramidate.[8] For that substrate no substitution leading to a stable product is possible, but the rearrangement was explained in terms of the initial attack of the phosphoryl oxygen at silicon, followed by the N → O migration *via* a pentacoordinated, P^v intermediate.

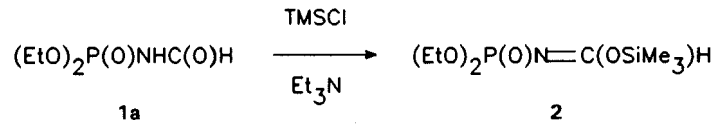
RESULTS AND DISCUSSION

Reactions with TMSCl

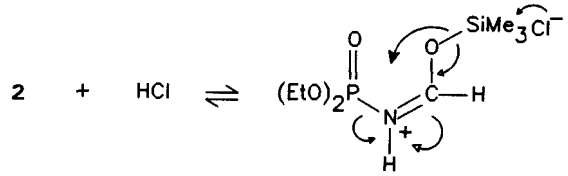
When **1a** was treated with some excess of TMSCl and triethylamine, it was quantitatively converted into a single phosphorus-containing product (single signal in the ^{31}P NMR spectrum). Attempts to purify the product led to extensive decomposition; when exposed to atmosphere, the compound was converted completely to the starting material **1a**. NMR spectroscopy (^{31}P, ^1H) allowed us to identify the product as O-trimethylsilyl-*N*-diethoxyphosphorylformimidate (**2**), thus the nucleophilic attack at silicon in TMSCl occurred *via* the carbonyl oxygen atom (Scheme I).

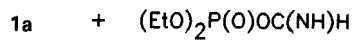
The ^{31}P chemical shift of the product (3.23 ppm) corresponds closely to that observed for the C—O-ethyl (δ_P 3.54) and C—O-isopropyl (two stereoisomers, δ_P 3.70, 3.44) analogues of **2**.[2] The ^1H NMR spectrum contained, in addition to the signals of the ethoxyphosphoryl group, a signal indicating the incorporation of the Me_3Si group (δ_H 0.11, s, 9 H), and the signal of the C(sp^2)—H (δ_H 8.27, d, J_{HP} 13.9 Hz, 1 H), corresponding to the analogous signals (δ_H 8.12, 7.97, 7.93; J_{HP} 15.3, 15.3, 15.5 Hz) of the C—OEt and C—O^{i}Pr derivatives.[2] Upon hydrolysis, formimidate **2** underwent simple desilylation back to the starting material. When treated with dry HCl, **2** underwent, however, not only simple desilylation, but also the desilylation accompanied by the rearrangement, yielding the O-phosphorylated formimidate **3**. Under those conditions, the protonation pre-equilibrium activates the P—N bond, so it can also be cleaved in the desilylation step (Scheme II). Compound **3** was identified by NMR (^{31}P, ^1H) spectroscopy: its ^{31}P chemical shift (δ_P −15.6) corresponds well to that (δ_P −16.4) reported for the analogous rearrangement product.[8] The ^1H NMR spectrum showed disappearance of the Me_3Si signal, and the low-field shift of the C(sp^2)H signal (δ_H 8.60, br. s). It seems therefore that the N → O migration of the phosphoryl group can result not only from the electrophilic catalysis operating *via* the phosphoryl oxygen (as reported[8]), but also *via* a reaction occurring at the carbonyl oxygen.

Reaction of **1a** with TMSCl in the absence of a base led to a mixture of three products, proportions of which varied from experiment to experiment. None of the products contained the Me_3Si group incorporated into the molecule, and, on the basis of the NMR (^{31}P, ^1H) spectroscopy, those products were identified as the

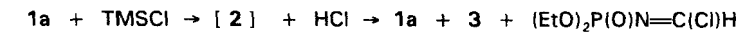


SCHEME I





SCHEME II



SCHEME III

starting material (**1a**), O-phosphorylated formimidate **3**, and *N*-diethoxyphosphorylformidoyl chloride **4**. We believe that all three compounds result from the reaction of HCl with the common intermediate **2**, formed directly by the O-silylation of the carbonyl group of the substrate (Scheme III).

The variation of the proportion of products **1a**, **3**, and **4** with the reaction time clearly showed that **1a** present in the reaction mixture does not result from an incomplete conversion, but from a subsequent reaction of the intermediate. The desilylation-rearrangement of **2** to **3**, promoted by HCl, has been demonstrated in the experiment described before (Scheme II). We have also shown in an independent experiment that when **1a** was treated with dry HCl, it rearranged to **3**, probably *via* the mechanism analogous to that proposed by Baraniak and Stec[8] for the rearrangement of the tertiary substrate. It is therefore possible that at least some of **3** has been formed directly *via* this route. The structure of product **4** is tentative and based on the spectroscopic evidence, as we were unable to isolate this compound from the reaction mixture. ^{1}H NMR spectroscopy demonstrated for this compound the presence of only two ethoxy groups and one C(sp^2)H atom (δ_H 8.16, br s). ^{31}P chemical shift (δ 8.50) indicated the presence of the P—N bond, and corresponds well to the δ_P value of 8.20 ppm obtained for the structurally analogous *N*-phosphorylated formamidine (*vide infra*). The formation of **4** can be envisaged as a result of the nucleophilic displacement of the trimethylsilyloxy group by Cl^- in the unprotonated 2. In the presence of the excess of HCl (Scheme II), the fully protonated **2** undergoes exclusively the cleavage of the O—Si bond leading to the formation of the starting material, or the rearranged product **3**.

Reaction with Hexamethyldisilazane (HMDS)

The *N*-trimethylsilylation of phosphoramidates achieved by the action of HMDS has been reported,[9] and was used in synthetic work[10] to enhance the acidity of the

NH function. When **1a** was treated with HMDS, a new, crystalline, product was formed which did not contain the Me_3Si group. The ^{31}P NMR spectrum (δ_P 8.2) indicated that no rearrangement took place, as the chemical shift value was in the range of that observed for *N*-phosphoryl derivatives. ^1H NMR spectroscopy demonstrated the presence of two ethoxy groups, one C(sp^2)H atom (δ_H 8.41, d, J_{HP} 22.2 Hz), and a strong signal for the N—H hydrogens (δ_H 8.26, br s). In the ^{13}C NMR spectrum, in addition to the signals derived from the OEt groups, we observed only one signal of the C(sp^2) atom (δ_C 161.9, d, J_{CP} 5.5 Hz). The chemical shift value of that signal corresponds closely to that reported[11] for the amidine carbon in *N*-methyl-*N'*-(2,6-dichlorophenyl)acetamidine (δ_C 158.6). The IR spectrum indicated the retention of the phosphoryl group (ν_{PO} = 1223 cm^{-1}), the presence of the NH groups (ν_{NH} = 3279, 3150 cm^{-1}), and contained the absorption at 1668 cm^{-1}, which was identified as the C=N stretching band, very close to the value of $\nu_{C=N}$ = 1657 cm^{-1} observed before [12] for $(MeO)_2P(O)N{=}C(Ph)OEt$. Elemental analysis clearly demonstrated the presence of **two** nitrogen atoms in the molecule, and the structure of the product was finally proved by X-ray diffraction[13] (and confirmed by MS), as that of *N*-diethoxyphosphorylformamidine **5**.

The formation of product **5** is presented in Scheme IV and involves a sequence of C=O group silylation, followed by the addition-elimination reaction with ammonia, released in the first step.[9,10,14]

As demonstrated before in the reaction of **1a** with $TMSCl/Et_3N$, the derivative **2** can easily lose the Me_3SiO group in reaction with nucleophiles; in Scheme IV HMDS acts as both, activating (silylating) agent, and as a precursor of a nucleophile (NH_3). The formamidine **5** was, in fact, prepared previously[15] by treating O-^{i}butyl-*N*-diethoxyphosphorylformimidate with ammonia, and similar reactions with amines have been reported recently.[16] Although intermediate **2** was unstable under reaction conditions (Scheme IV), its intermediacy was demonstrated when the reaction was carried out at low temperatures (−5°C). ^{31}P NMR spectra (also recorded at −5°C) of the reaction mixture showed the formation (followed by the disappearance) of the species with δ_P in the range of 3.20–3.30, corresponding to that of **2** (*vide supra*). The variation of the relative concentrations of **1a**, **2**, and **5** at −5°C (measured by the relative intensities of the corresponding signals in the ^{31}P NMR spectra) with time is presented in Figure 1. With **1a** itself was treated with an excess of ammonia at elevated temperature, we observed very slow (*ca.* 4% conversion after 4.5 h) formation of amidine **5**, thus confirming the activating effect of the O-silylation in the formation of the amidine derivative.

In conclusion, we have demonstrated that the reaction of **1a** with electrophilic silicon occurs exclusively *via* the carbonyl oxygen. The fate of the O-silylated derivative depends on the reaction conditions. In the presence of nucleophiles (water, Cl, NH_3, etc.) it can undergo displacement of the Me_3SiO group without

$$2\ \mathbf{1a} + (Me_3Si)_2NH \rightarrow 2\ \underset{\mathbf{2}}{(EtO)_2P(O)N{=}C(OSiMe_3)H} + NH_3$$

$$\mathbf{2} + NH_3 \rightarrow \underset{\mathbf{5}}{(EtO)_2P(O)N{=}C(NH_2)H} + Me_3SiOH$$

SCHEME IV

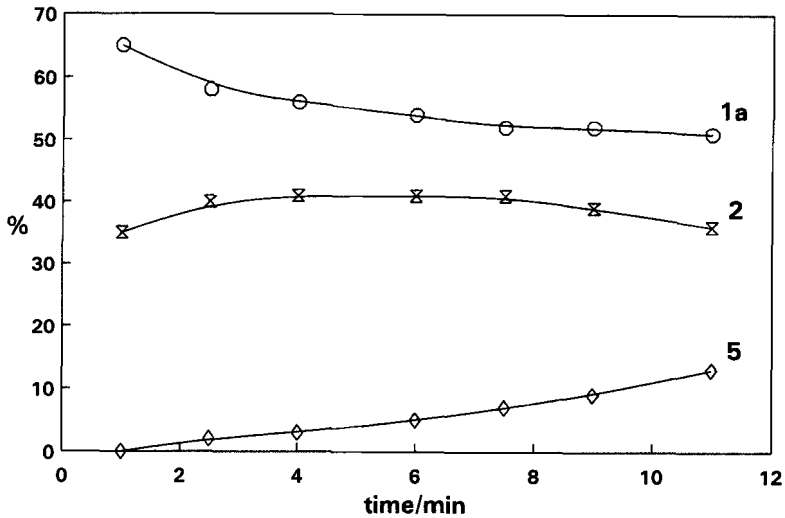
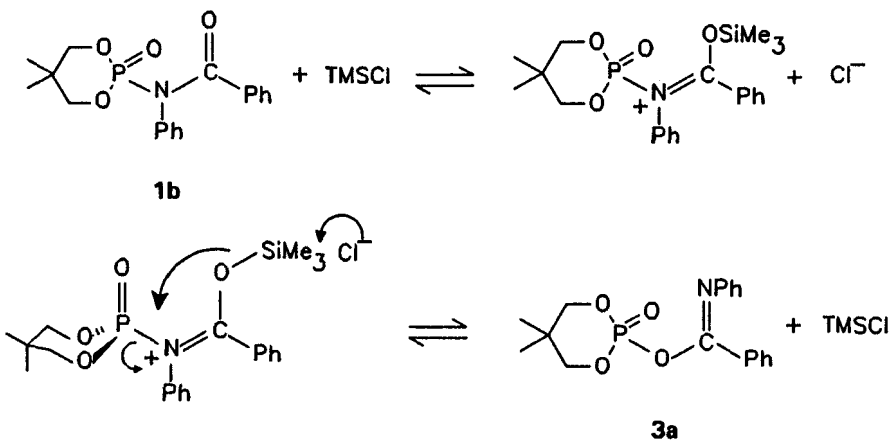


FIGURE 1 Reaction of **1a** with HMDS at −5°C. Proportions of **1a**, **2**, and **5** as a function of the reaction time.



1b

3a

SCHEME V

(Scheme III, IV) or with (Scheme II) rearrangement involving the N → O phosphoryl migration. In view of our results, we suggest that the TMSCl-catalyzed rearrangement of 2-*N*-benzoyl-*N*-phenylamino-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane **1b** to the corresponding (5,5-dimethyl-1,3,2-dioxaphosphorinyl)(*N*-phenyliminobenzoyl)oxide **3a**, reported by Baraniak and Stec,[8] also involves the carbonyl (and not, as proposed, the phosphoryl) oxygen atom. For that reaction we propose the mechanism (Scheme V) that corresponds closely to the formation of product **3** (see Scheme II).

It is worth to note at this stage that the retention of configuration at phosphorus, demonstrated for the N → O phosphoryl rearrangement[17] is also compatible with the mechanism presented in Scheme V (equatorial/apical stereochemistry of bond-making and bond-breaking steps).

EXPERIMENTAL

Solvents and commercially available substrates were purified by conventional methods immediately before use. All reactions were carried out and worked up under an atmosphere of dry argon. Mass spectra were recorded on a Varian MAT-212 double-focusing direct-inlet spectrometer at an ionization potential of 70 eV. IR spectra were recorded as neat liquids, with a Bruker IFS 133v FT-IR spectrometer. NMR spectra were recorded on a Bruker AC 300 MHz spectrometer for solutions in C_6D_6, and the chemical-shift values are given relative to $SiMe_4$ (^1H, ^{13}C) and trimethyl phosphate (^{31}P). Elemental analysis (C/H/N) was carried out at the Council for Scientific and Industrial Research (Pretoria). O,O-diethyl-*N*-formylphosphoramidate **1a** was prepared as described elsewhere.[2]

Reactions of **1a** *with TMSCl.* (a) To the solution of **1a** (1.03 g, 5.66 mmol) in benzene (4 cm^3) the solution of TMSCl (1.23 g, 11.35 mmol) in benzene (3 cm^3), followed by the solution of Et_3N (1.15 g, 11.33 mmol) in benzene (3 cm^3) were added with stirring at room temperature. The mixture was stirred for 21 h, the amine salt was filtered off, washed with benzene, and the solvent was evaporated under reduced pressure. The crude product **2** was obtained as a viscous, pale-yellow oil; 1.24 g (87%). δ_H 0.11 (9H, s, Me_3Si), 1.12 (6H, t, J_{HH} 6.8, 2 × Me of POEt), 3.96 (4H, quint, J_{HH}, J_{HP} 6.8, 2 × CH_2 of POEt), 8.27 (1H, d, J_{HP} 13.9, N=CH); δ_P 3.23. When a sample of the product was exposed to the atmosphere, or when the compound was treated with a small amount of water, its NMR spectra (^1H and ^{31}P) showed rapid hydrolysis to the starting material (**1a**). Similarly, attempts to record the IR spectrum of **2**, resulted in the complex spectrum, corresponding mostly to that of **1a**. The instability of **2** also prevented us from obtaining an unambiguous MS of the product.

Reaction of **2** *with HCl.* Dry HCl was passed through a solution of **2** (1.20 g, 4.74 mmol) in benzene (10 cm^3) at room temperature for 30 min. The slightly turbid mixture was filtered through a layer of Celite and $MgSO_4$, the layer was washed with benzene, and the solvent and volatile products were evaporated on a rotary evaporator, followed by high vacuum. The residue was examined by NMR spectroscopy which indicated the complete disappearance of the substrate and the formation of two products: **1a** and the new product **3** in a ratio 1.4:1, as determined by ^{31}P NMR spectroscopy. **3**; δ_H 1.07 (6H, t, J_{HH} 7.1, 2 × Me of POEt, overlapping with the corresponding signal of **1a**), 3.94 (4H, quint, J_{HH}, J_{HP} 7.1, 2 × CH_2 of POEt), 8.60 (1H, br s, C(sp^2)H); δ_P −15.6. Attempts to separate the mixture of **1a** and **3** by column chromatography led to extensive decomposition. (b) The solution of **1a** (4.0 g, 22.08 mmol) and TMSCl (2.40 g, 22.08 mmol) in benzene (14 cm^3) was stirred at room temperature for 3 days. Solvent and volatile products were removed under reduced pressure and the residue was examined by NMR (^1H and ^{31}P) spectroscopy. ^{31}P NMR spectrum showed the presence of three components: **3** (δ_P −15.6), **1a** (δ_P −3.9), and **4** (δ_P 8.5). The proportion of these products varied with the reaction time; for example, after 4.5 h, the ratio **1a:3:4** was 15:2.3:1, while after 2.5 days this ratio changed to 7.2:0.7:1 (as determined by ^{31}P NMR spectroscopy). The ^1H NMR spectrum showed only the presence of the POEt groups (overlapping for all three compounds), the C(sp^2)H groups (br s,δ_H 8.16 for **4**, 8.5–8.6 for **1a** and **3**), and the NH functions (δ_H 9.55, br s, overlapping for all three compounds).

Reaction of **1a** *with HCl.* **1a** (1.03 g, 5.69 mmol) was dissolved in benzene (10 cm^3) and the excess of dry HCl was passed through this solution at room temperature for 30 min. The solution was filtered through a layer of Celite and $MgSO_4$, and after washing the layer with benzene, the combined benzene solutions were evaporated under reduced pressure. The NMR (^1H and ^{31}P) spectra of the product demonstrated that it consisted of two compounds, **3** and **1a** in a ratio of 1.2:1.

Reaction of **1a** *with HMDS.* Hexamethyldisilazane (310 mg, 1.9 mmol) in dimethoxyethane or benzene (0.6 cm^3) was added slowly to a solution of phosphoramidate **1a** in the same solvent (0.5 cm^3). The reaction mixture was heated under reflux for 3.5 h, cooled to room temperature and the solvent was evaporated under reduced pressure, yielding the product as a viscous liquid which crystallized on standing in a cold room. Colourless cubic crystals (80–90%), m.p. 68–69°C (from benzene) (lit.,[15] m.p. 76–78°C (Found: C, 32.8; H, 7.3; N, 15.4. $C_5H_{13}N_2O_3P$ requires C, 33.3; H, 7.3; N, 15.5%). ν_{max}/cm^{-1} 3279, 3150 (NH), 1688 (C=N), 1223 (P=O), 1098 (P—O); δ_H 1.19 (6H, t, J_{HH} 7.2, 2 × Me of POEt), 4.01 (4 H, quint, J_{HH}, J_{HP} 7.2, 2 × CH_2 of POEt), 8.26 (2H, br s, 2 × NH), 8.41 (1 H, d, J_{HP} 22.2, N=CH); δ_C 16.1 (d, J_{CP} 6.9, 2 × Me of POEt), 61.9 (d, J_{CP} 5.8, 2 × CH_2 of POEt), 161.9 (d, J_{CP} 5.5, N=C); δ_P 8.2; m/z 180 (M^+, 26%), 153 (38, M − C_2H_3), 152 (12, M − C_2H_4), 136 (41, 152 − NH_2), 126 (79, 153 − HCN), 108 (70, 136 − C_2H_4), 98 (98, 126 − C_2H_4), 81 (100, 108 − HCN), 80 (90, 98 − H_2O), 43 (52, M − Et_2O_3P).

ACKNOWLEDGEMENTS

Financial assistance from the University of Pretoria and the Foundation for Research Development is gratefully acknowledged.

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