Phosphorus Heterocycles

One-Pot Conversion of Phospholide Ions into β-Functional Phosphinines

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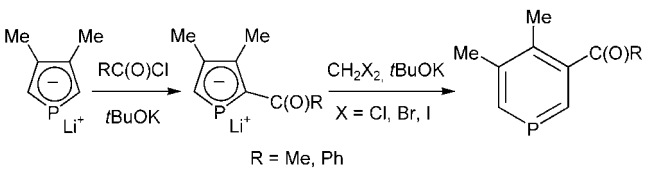
Although the first β-functional phosphinine, a 3-phosphaphenol, was synthesized by Märkl et al. as early as 1977,[1] only a few such compounds are known,[2] particularly if we exclude a series of polyfunctional derivatives obtained by [4+2] cycloaddition between 1-phosphadienes or synthetic equivalents and functional alkynes.[3] As a result, the reactivity of this class of compounds is almost unexplored.[4] Herein, we describe a straightforward access to such compounds from the readily available phospholide ions.

In 1997, we described a simple method which converts α-unsubstituted into α-functional phospholides.[5] This method has been applied to the synthesis of 2-acylphospholides.[6] In the course of a systematic investigation of the reactivity of these species, we discovered that their reaction with dihalomethanes unexpectedly leads to the formation of 3-acylphosphinines (Scheme 1).

The whole sequence takes place at room temperature or below. The reaction is best run with dibromomethane. The 3-functional phosphinines appear to be the sole products of the transformation as determined by monitoring the reaction mixture by ^{31}P NMR spectroscopy. Whatever the nature of the β-substituent, the ^{31}P resonance signal is observed at $\delta = 188 \pm 1$ ppm ($CDCl_3$) as for the 3-unsubstituted species.[7] This observation underlines the weakness of the electronic interaction between phosphorus and the functional *meta* substituent. The phosphinines are purified by chromatography on silica gel or by distillation in a Kugelrohr apparatus. They were completely characterized by NMR spectroscopy and mass spectrometry. The final yields of isolated products based on the starting 1-phenyl-3,4-dimethylphosphole (three reactions in one pot) remain modest (8–20%), probably because of substantial losses during the purification procedure. We have also checked that the conversion into phosphinine does not take place in the absence of the functional substituent.



Scheme 1.

Since we had no precise idea about the mechanism of formation of these functional phosphinines, we decided to investigate various possibilities by DFT calculations at the B3LYP/6-311+G(d,p) level[8] using the Gaussian 03 package.[9] We decided to check the possibility of a carbenoid mechanism. We admitted the formation of a carbenoid species by deprotonation of the P-CH_2X unit of the initially formed 1-haloalkylphosphole. The process was modeled using the anion derived from 1-chloromethyl-2-acetylphosphole. The theoretical investigation of the reaction pathway suggested that the conversion into phosphinine proceeded by the initial opening of the phosphole ring, to give the 1-chloro-6-acetyl-2-phosphahexatriene anion as a first intermediate. The transition state (one imaginary frequency) between the phosphole and the phosphahexatriene anions was computed to lie 25.3 kcal mol^{-1} higher in energy than the starting phosphole anion (zero-point energy (ZPE) included). Thus, this mechanism was discarded because it needed too much energy to be operative at RT and provided no explanation for the role of the acyl substituents.

It is possible to deprotonate one methyl group of 3,4-dimethylphosphole sulfides[10] or borane complexes.[11] We thus decided to investigate the possibility of a similar deprotonation in the present case, the role of the electron-withdrawing functional groups being to facilitate this deprotonation. The process was modeled using the anion derived from 1-chloromethyl-2-acetyl-3-methylphosphole **A**. The computed structure is shown in Figure 1. The exocyclic C=CH_2 unit has a strong double bond character (1.371 Å), the internal C1–C2 bond is essentially a single bond (1.450 Å), thus the negative charge is mainly localized at C1. Since, C1, P7, C8, and Cl11 are coplanar and the C1-C8-Cl11 angle is 153°, the geometrical situation is ideal for a S_N2 backside attack of C1 onto C8–Cl11, leading to the bicyclic phosphirane **B** whose computed structure is shown in Figure 2. The transition state between **A** and **B** (one imaginary frequency, intrinsic reaction coordinate (IRC) calculations) was computed to lie 13.8 kcal mol^{-1} higher in energy than the starting anion. Thus, this pathway is acceptable both in terms of energy and because it rationalizes the role of the functional substituent. We detected no acceptable pathway between the bicyclic phosphirane **B** and the final phosphinine. But we noted that H10 lies only at 2.433 Å from O12 and bears a

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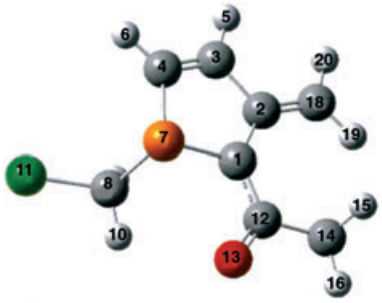


Figure 1. Computed structure of the anion **A** derived from 1-chloromethyl-2-acetyl-3-methylphosphole. Selected interatomic distances [Å], angles, and torsion angles [°]: C1···C8 2.825, C8-Cl11 1.851, C2-C18 1.371, C1-C2 1.450, C1-C12 1.415; C1···C8-Cl11 153.0, C1-P7-C8-Cl11 173.7. Gray C, green Cl, orange P, red O.

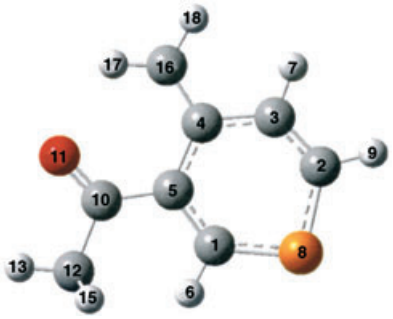
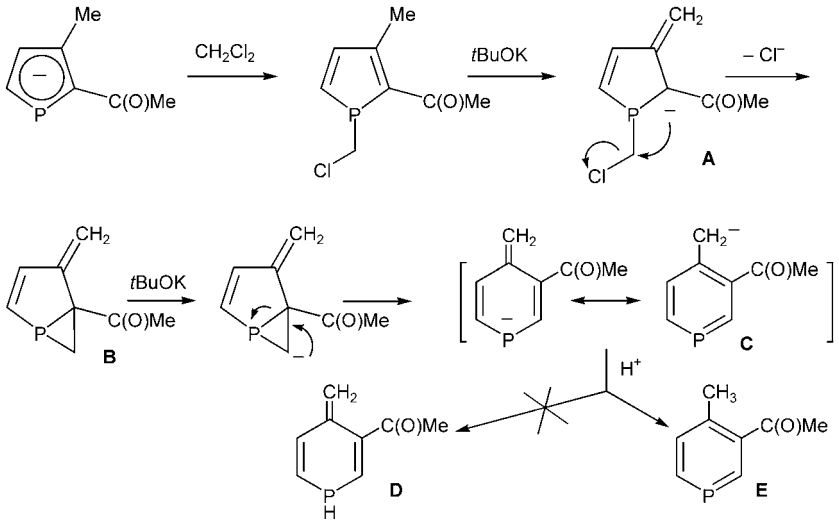


Figure 3. Computed structure of phosphinine anion **C**. Selected bond lengths [Å] and angles [°]: C1-P8 1.740, C2-P8 1.797, C1-C5 1.403, C2-C3 1.354, C3-C4 1.465, C5-C4 1.483, C4-C16 1.368; C1-P8-C2 97.6. Gray C, orange P, red O.

significantly higher positive Mulliken charge than H9 (+0.068 versus +0.014). We thus investigated the conversion of the phosphirane anion obtained from **B** by abstraction of H10 into the corresponding phosphinine anion **C** whose computed structure is shown in Figure 3. The exocyclic C=CH_2 unit has a strong double bond character (C4–C16 1.368 Å). The negative charge appears to be essentially localized at phosphorus (−0.47) and at the carbon center of the exocyclic =CH_2 group (C16 −0.49). The conversion of the anion derived from **B** into **C** is equivalent to the ring opening of a phosphirane anion and is extremely easy.[12] The first transition state between the anion of **B** and **C** lies very close to the starting anion and is only 2.3 kcal mol^{-1} higher in energy than the starting product. The phosphinine anion is more stable than the phosphirane anion by 59.6 kcal mol^{-1} (ZPE included). The protonation of **C** can either occur at the phosphorus center to give **D**, or at the exocyclic =CH_2 group to give **E** (Scheme 2). However, the phosphinine **E** is more stable than **D** by 26.7 kcal mol^{-1} and thus, will be the sole final product of the reaction by a protonation–deprotonation equilibrium. The mechanism of the conversion is thus well established and is summarized in Scheme 2.



Scheme 2.

What the DFT calculations show is that the methyl β-substituent (this was partly verified using 2,5-diphenylphospholide ion whose ring expansion fails) and the electron-withdrawing functional group that activates the methyl are necessary. Within the limits of these requirements, numerous variations on the functional substituent are still possible (a preliminary experiment has shown that the ring expansion works with the ethoxycarbonyl α-substitution).

Figure 2. Computed structure of bicyclic phosphirane **B**. Significant bond lengths [Å] and angles [°]: C1-C8 1.501, C2-C17 1.342, C1-C2 1.504, C1-C11 1.506; C1-P7-C8 46.6. Gray C, orange P, red O.

Experimental Section

Synthesis of 3-acetyl-4,5-dimethylphosphinine: 1-Phenyl-3,4-dimethyl phosphole (1.88 g, 10 mmol) was stirred with lithium wire (0.14 g, 20 mmol) in THF (20 mL) for about 3 h. After removal of excess lithium by filtration, PhLi was quenched by the addition of $AlCl_3$ (3.33 mmol, 0.45 g) at −30 °C and warming the stirred solution to ambient temperature over 1 h. The reaction solution was cooled to −78 °C and acetyl chloride (10 mmol, 0.68 mL) was added, the solution was then warmed to room temperature over about 7 min, then *t*BuOK (2.24 g, 20 mmol) was added. The reaction solution was cooled to −78 °C and CH_2Br_2 (10 mmol, 0.70 mL) was added, then the mixture stirred at ambient temperature for ca. 3 h. The crude product was extracted with diethyl ether (3 × 10 mL) and column chromatography on silica gel with hexane:diethyl ether 90:10 to give the pure 3-acetyl-4,5-dimethylphosphinine as a colorless oil (0.13 g, 7.8 % yield).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.53$ (dd, 1H, $^2J_{PH} = 37$ Hz, $^4J_{HH} = 3$ Hz, PC*H*), 8.39 (dd, 1H, $^2J_{PH} = 34$ Hz, $^4J_{HH} = 3$ Hz, PC*H*), 2.55 (s, 3H, COCH_3) 2.45 (s, 3H, CH_3), 2.30 ppm (d, $^4J_{PH}$ 4 Hz, 3H, CH_3); ^{31}C NMR (75 MHz, $CDCl_3$): $\delta = 205.7$ (*C*O), 155.7 (d, $^1J_{PC} = 50$ Hz, P*C*H), 148.0 (d, $^2J_{PC} = 15$ Hz, C_β), 147.3 (d, $^1J_{PC} = 52$ Hz, P*C*H), 144.7 (d, $^2J_{PC} = 15$ Hz, C_β), 134.5 (d, $^3J_{PC} = 19.2$ Hz, C_γ), 30.8 (s, *C*H$_3$), 24.1 (d, $^3J_{PC} = 3.1$ Hz, *C*H$_3$), 18.1 ppm (*C*H$_3$); ^{31}P NMR (121 MHz, $CDCl_3$, external standard 85% H_3PO_4): $\delta = 188.5$ ppm; Mass spectrum: *m*/*z* 166 [M^+], (80%), 151 [M^+−Me] (59%), 123 [M^+−COMe] (100%).

Synthesis of 3-benzoyl-4,5-dimethylphosphinine: 3-Benzoyl-4,5-dimethylphosphinine was prepared using the procedure described above, with benzoyl chloride (10 mmol, 1.16 mL) instead of acetyl chloride. However instead of chromatographic separation the crude reaction mixture was distilled at 175 °C, 10^{-2} mbar over 8 h using a Glaskugelrohr 51 (Büchi) to give the pure 3-benzoyl-4,5-dimethylphosphinine (0.50 g, 22% yield) as a colorless oil, which turned yellow immediately on contact with air. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.60$ (dd, 1H, $^2J_{PH} = 36.9$ Hz, $^4J_{HH} = 3$ Hz, PC*H*), 8.37 (dd, 1H, $^2J_{PH} = 34.8$ Hz, $^4J_{HH} = 3$ Hz, PC*H*), 7.81–7.43 (m, 5H, Ph), 2.50 (s, 3H, CH_3), 2.22 ppm (d, $^4J_{PH} = 3.6$ Hz, 3H, CH_3); ^{31}C NMR (75 MHz, $CDCl_3$): $\delta = 199.2$ (*C*O), 155.6 (d, $^1J_{PC} = 50$ Hz, P*C*H), 148.8 (d, $^1J_{PC} = 52.4$ Hz, P*C*H), 146.2 (d, $^2J_{PC} = 15.4$ Hz, C_β), 144.5 (d, $^2J_{PC} = 15.1$ Hz, C_β), 136.5 (s, ipso C(Ph)), 135 (d, $^3J_{PC} = 19$ Hz, C_γ), 133.8, 130.2, 128.7 (3s, *C*H(Ph)), 24.1 (d, $^3J_{PC} = 3$ Hz, *C*H$_3$), 18.7 ppm (*C*H$_3$); ^{31}P NMR (121 MHz, $CDCl_3$ external standard 85% H_3PO_4: $\delta = 187.4$ ppm; Mass spectrum: *m*/*z* 228 [M^+] (62%), 105 [PhCO], 100%); Exact mass: calcd: 228.0704; found: 228.0738.

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