A Straightforward Synthesis of 3-Acylphospholes

Magali Clochard, Joanna Grundy, Bruno Donnadieu, and François Mathey*

UCR-CNRS Joint Research Chemistry Laboratory, Department of Chemistry, University of California Riverside, Riverside, California 92521-0403

fmathey@citrus.ucr.edu

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ABSTRACT

The reaction of 2,5-diphenylphospholide, first with acyl chlorides, then with 'BuOK, provides a direct access to 3-acyl-2,5-diphenylphospholides via a 1*H*-, 2*H*-, 3*H*-phosphole equilibrium.

Functionalization is the central synthetic problem of phosphole chemistry. The nonplanar nonaromatic structure of phospholes prevents the use of the classical methods that allow the synthesis of a wide range of functional pyrroles such as electrophilic substitution and α -metalation reactions. Today the simplest functionalization method in use in phosphole chemistry relies on the equilibrium between 1*H*- and 2*H*-phospholes.^{1–7} Its principle is depicted in Scheme 1. The role of the base is to displace the equilibrium by

Scheme 1. Synthesis of 2-Functional Phospholides from the Equilibrium Mixture between 1*H*- and 2*H*-Phospholes



abstracting the acidic proton from the 2H-phosphole.

These [1,5] shifts have been studied from a theoretical standpoint on the parent phosphole.^{8,9} The equilibrium

involves not only the 1*H*- and the 2*H*- but also the 3*H*-phosphole. The three species lie very close in energy, but the barrier between the 1*H*- and the 2*H*-phosphole is substantially smaller than the barrier between the 2*H*- and the 3*H*-phosphole (19.6 vs 30.7 kcal mol⁻¹).

We reasoned that, if we took a phosphole with substituents on the two α -positions of the ring and chose a Z-functionality whose migration was especially easy, it might be possible to use the same principle to prepare 3-functional phospholes.

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Scheme 2. Equilibrium between 1*H*-, 2*H*-, and 3*H*-Phospholes with a Formyl Migrating Group: Variation of the Electronic + Zero Point Energies (data in kcal mol⁻¹)



To check the feasibility of this approach, we performed DFT calculations at the B3LYP/6-311+G(d,p) level¹⁰ on the 2,5dimethylphosphole ring with formyl as the migrating group. The carbonyl groups are, indeed, known to migrate very easily.⁴ The results are shown in Scheme 2. The transition states display one imaginary frequency and IRC calculations have shown that they connect the 1H, 2H, and 3H minima. As can be seen, the TS_{2-3} transition state is sufficiently low to allow a practical use of the 3H-phosphole for synthetic purposes. We thus allowed the 2,5-diphenylphospholide ion (made by cleavage of the P-Ph bond of 1,2,5-triphenylphosphole¹¹ by lithium in THF) to react with several acyl chlorides and then studied the evolution of the resulting 1-acyl-2,5-diphenylphospholes in the presence of 'BuOK at 50-60 °C. The reaction mixture is conveniently monitored by ³¹P NMR spectroscopy. For R = Ph, the starting 2,5diphenylphospholide ($\delta^{31}P = 71$ ppm) is first transformed into the 1-benzoyl-2,5-diphenylphosphole ($\delta^{31}P = 18$ ppm). Upon addition of 'BuOK, the 1-acylphosphole reacts to give a mixture of the starting phospholide resulting from the nucleophilic attack of the base at the P-acyl bond and the expected 3-acylphospholide 1 ($\delta^{31}P = 139$ ppm) resulting from the abstraction of the acidic proton from the 3Hphosphole. Similar results were observed with the other acyl chlorides (Scheme 3). The formula of the 3-acylphospholides



was definitively established by transformation into the corresponding 1-methylphosphole sulfides 4-6.¹² The X-ray



Figure 1. Crystal structure of sulfide 4.

crystal structure analysis of **4** (Figure 1) shows that the carbonyl group lies out of the plane of the phosphole ring $(C8-C9-C10-O1 \text{ torsion angle} = 36.8^{\circ})$ and is not conjugated with the C=C double bond (C1-C8 = 1.3526 Å); C9-C17 = 1.3565 Å).

The yields of this synthesis of 3-acylphospholes are sometimes quite modest due to the competing nucleophilic attack of 'BuOK at the P-acyl bond. Nevertheless, this synthesis is attractive by its simplicity, can probably be

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⁽¹²⁾ Synthesis of 4: 1,2,5-Triphenylphosphole (0.5 g, 1.6×10^{-3} mol) in dry THF (20 mL) was allowed to react with an excess of lithium wire until the P-Ph bond cleavage was completed. After removing excess lithium, the solution was treated with *tert*-butyl chloride (0.2 mL, $1.6 \times$ 10^{-3} mol) and heated at 60 °C for 1 h. Benzoyl chloride (0.2 mL, 1.6 \times 10^{-3} mol) was added dropwise at -50 °C. The mixture was warmed to room temperature and monitored by ³¹P NMR. A yellow color is observed upon completion of the reaction. After 10 min at 60 °C, 'BuOK (0.18 g, 1.6×10^{-3} mol) was slowly added and the solution was stirred at the same temperature for a further 60 min. Iodomethane (0.1 mL, 1.6×10^{-3} mol) was added through a syringe at -50 °C, and the solution was warmed to room temperature. Sulfurization was performed by addition of sulfur powder (0.05 g, $\bar{1}2.8$ \times 10^{-3} mol). After vacuum distillation of the solvent, the residue was chromatographed with dichloromethane-hexane 60:40 to yield 0.3 g (49%) of a bright-yellow solid. ³¹P NMR (CDCl₃) δ + 46.1 (dq, $^{2}J(P-H) = 12 \text{ Hz}, ^{3}J(P-H) = 40 \text{ Hz}); ^{1}H \text{ NMR} (CDCl_{3}) \delta 1.84 (d, ^{2}J(H-H)); ^{1}H \text{ NMR} (d, ^{2}J(H)); ^{1}H \text{ NMR} (d, ^{2}J(H)); ^{1}H \text{ NMR} (d, ^{2}J(H)); ^{1}H \text{ NM} (d, ^$ P) = 12 Hz, 3H, CH₃), 7.09–7.88 (m, 16H, Ph + H_{β}); ¹³C NMR (CDCl₃) δ 19.92 (d, ¹*J*(C–P) = 49.5 Hz, –CH₃), 126.96–129.95 (m, C ortho, meta, para), 132.28 (d, ${}^{2}J(C-P) = 21.9$ Hz, $C_{\beta}H$), 140.32 (d, ${}^{1}J(C-P) = 74.8$ Hz, C_α), 140.40 (d, ¹*J*(C-P) = 72.2 Hz, C_α), 142.37 (d, ²*J*(C-P) = 23.0 Hz, C_β), 195.36 (d, ³*J*(C-P) = 15 Hz, -C(O)Ph); mass spectrum (EI, 70 eV) m/z 386 (M⁺, 100%), 371 (M⁺ - CH₃, 16%), 354 (M⁺ - S, 20%), 281 (M⁺ – C(O)Ph, 9%), 233 (M⁺ – 2Ph, 8%). Synthesis of 5: As for 4 with 2-thienoyl chloride (0.17 mL, 1.6×10^{-3} mol). Yield 0.2 g (33%). ³¹P NMR (CDCl₃) δ + 41.3 (dq, ²J(P-H) = 11 Hz, ³J(P-H) = 37 Hz); ¹H NMR (CDCl₃) δ 1.84 (d, ²*J*(H–P) = 13.5 Hz, 3H, CH₃), 6.82–7.87 (m, 14H, **Ph** + **Th** + **H**_{β}); ¹³C NMR (CDCl₃) δ 19.81 (d, ¹*J*(C–P) = 48.0 Hz, $-CH_3$), 126.95–136.43 (m, Ph + Th), 131.97 (d, ${}^2J(C-P) = 20.7$ Hz, C_{β} H), 139.78 (d, ${}^{1}J(C-P) = 72.5$ Hz, C_{α}), 148.48 (d, ${}^{1}J(C-P) = 73.7$ Hz, C_{α}), 142.42 (d, ²*J*(C–P) = 27.6 Hz, C_{β}), 187.24 (d, ³*J*(C–P)= 16.1 Hz, -C(0)Th; mass spectrum (EI, 70 eV) m/z 392 (M⁺, 63%), 377 (M⁺ - CH₃, 10%), 361 (M⁺ - S, 100%), 383 (M⁺ - C(0)Thiophene, 12%). Synthesis of 6: Same conditions as for 4 and 5, except that a higher concentration of 1,2,5-triphenylphosphole is used (0.5 g in 5 mL of THF). Yield 0.05 g (10%). ³¹P NMR (CDCl₃) δ +44.9; ¹H NMR (CDCl₃) δ 1.74 $(d_1^{-2}J(H-P) = 12.9 \text{ Hz}, 3H, P-CH_3), 1.97 (s, 3H, COCH_3), 7.20-7.85 (m, 11H, Ph + H_{\beta}); {}^{13}C NMR (CDCl_3) \delta 18.96 (d, {}^{1}J(C-P) = 49.0 \text{ Hz},$ $P-CH_3$, 29.83 (s, CH₃), 126.69–132.05 (m, **Ph**), 131.17 (d, ²*J*(C–P) = 21.0 Hz, C_{β} H), 139.36 (d, ¹*J*(C-P) = 73.8 Hz, C_{α}), 142.63 (d, ²*J*(C-P) = 22.1 Hz, C_{β}), 143.63 (d, ¹*J*(C-P) = 69.9 Hz, C_{α}), 198.95 (d, ³*J*(C-P)= 15 Hz, $-\mathbf{C}(O)$ Me); mass spectrum (EI, 70 eV) m/z 324 (M⁺, 100%).

generalized to other good migrating groups, and represents the first synthetic application of 3H-phosphole chemistry. As far as we know, only one 3-acylphosphole¹³ and one 3Hphosphole with tetracoordinate phosphorus¹⁴ have been described so far. Acknowledgment. The authors thank the University of California Riverside and the CNRS for financial support of this work.

Supporting Information Available: Theoretical calculations (structures and energies) and X-ray data for sulfide **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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