ORGANIC LETTERS

2005
Vol. 7, No. 20
4511−4513

A Straightforward Synthesis of 3-Acylphospholes

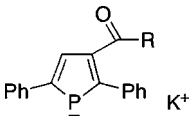
Magali Clochard, Joanna Grundy, Bruno Donnadieu, and François Mathey*

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

fmathey@citrus.ucr.edu

Received July 29, 2005

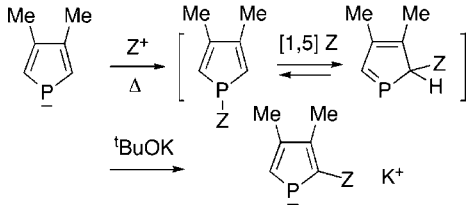
ABSTRACT



The reaction of 2,5-diphenylphospholide, first with acyl chlorides, then with ^{t}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 abstracting the acidic proton from the 2*H*-phosphole.

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



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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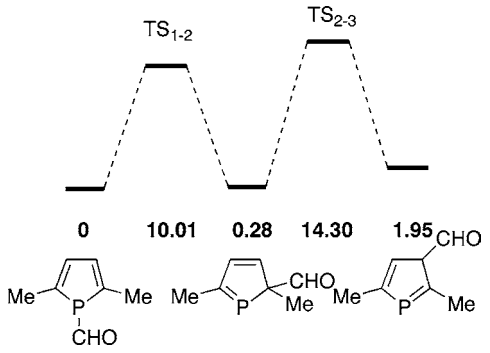
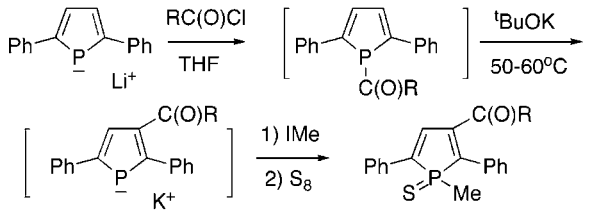
10.1021/ol051816d CCC: $30.25
Published on Web 09/08/2005

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) level[10] on the 2,5-dimethylphosphole 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 1*H*, 2*H*, and 3*H* minima. As can be seen, the TS_{2-3} transition state is sufficiently low to allow a practical use of the 3*H*-phosphole for synthetic purposes. We thus allowed the 2,5-diphenylphospholide ion (made by cleavage of the P−Ph bond of 1,2,5-triphenylphosphole[11] 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 ^{t}BuOK at 50−60 °C. The reaction mixture is conveniently monitored by ^{31}P NMR spectroscopy. For R = Ph, the starting 2,5-diphenylphospholide (δ^{31}P = 71 ppm) is first transformed into the 1-benzoyl-2,5-diphenylphosphole (δ^{31}P = 18 ppm). Upon addition of ^{t}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** (δ^{31}P = 139 ppm) resulting from the abstraction of the acidic proton from the 3*H*-phosphole. Similar results were observed with the other acyl chlorides (Scheme 3). The formula of the 3-acylphospholides

Scheme 3. Synthesis of 3-Acyl-2,5-diphenylphospholides



1 R = Ph δ^{31}P 139.1
2 R = 2-thienyl δ^{31}P 131.7
3 R = Me δ^{31}P 142.5

4 R = Ph (49%)
5 R = 2-thienyl (33%)
6 R = Me (10%)

was definitively established by transformation into the corresponding 1-methylphosphole sulfides **4**−**6**.[12] The X-ray

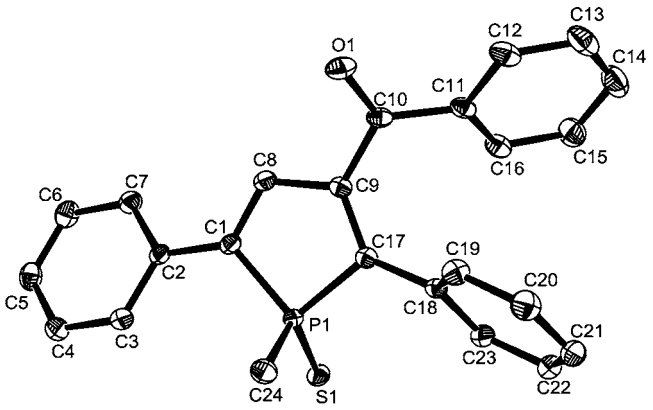


Figure 1. Crystal structure of sulfide **4**.

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 torsion angle = 36.8°) 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 ^{t}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 × 10^{-3} mol) and heated at 60 °C for 1 h. Benzoyl chloride (0.2 mL, 1.6 × 10^{-3} mol) was added dropwise at −50 °C. The mixture was warmed to room temperature and monitored by ^{31}P NMR. A yellow color is observed upon completion of the reaction. After 10 min at 60 °C, ^{t}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, 12.8 × 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. ^{31}P NMR ($CDCl_3$) δ + 46.1 (dq, ^2J(P−H) = 12 Hz, ^3J(P−H) = 40 Hz); ^{1}H NMR ($CDCl_3$) δ 1.84 (d, ^2J(H−P) = 12 Hz, 3H, C**H**$_3$), 7.09−7.88 (m, 16H, **Ph** + **H**$_\beta$); ^{13}C NMR ($CDCl_3$) δ 19.92 (d, ^1J(C−P) = 49.5 Hz, −**C**H$_3$), 126.96−129.95 (m, **C** ortho, meta, para), 132.28 (d, ^2J(C−P) = 21.9 Hz, **C**$_\beta$H), 140.32 (d,^1J(C−P) = 74.8 Hz, **C**$_\alpha$), 140.40 (d, ^1J(C−P) = 72.2 Hz, **C**$_\alpha$), 142.37 (d, ^2J(C−P) = 23.0 Hz, **C**$_\beta$), 195.36 (d, ^3J(C−P)= 15 Hz, −**C**(O)Ph); mass spectrum (EI, 70 eV) *m*/*z* 386 (M$^+$, 100%), 371 (M$^+$ − CH$_3$, 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%). ^{31}P NMR ($CDCl_3$) δ + 41.3 (dq, ^2J(P−H) = 11 Hz, ^3J(P−H) = 37 Hz); ^{1}H NMR ($CDCl_3$) δ 1.84 (d, ^2J(H−P) = 13.5 Hz, 3H, C**H**$_3$), 6.82−7.87 (m, 14H, **Ph** + **Th** + **H**$_\beta$); ^{13}C NMR ($CDCl_3$) δ 19.81 (d, ^1J(C−P) = 48.0 Hz, −**C**H$_3$), 126.95−136.43 (m, **Ph** + **Th**), 131.97 (d, ^2J(C−P) = 20.7 Hz, **C**$_\beta$H), 139.78 (d, ^1J(C−P) = 72.5 Hz, **C**$_\alpha$), 148.48 (d, ^1J(C−P) = 73.7 Hz, **C**$_\alpha$), 142.42 (d, ^2J(C−P) = 27.6 Hz, **C**$_\beta$), 187.24 (d, ^3J(C−P)= 16.1 Hz, −**C**(O)Th); mass spectrum (EI, 70 eV) *m*/*z* 392 (M$^+$, 63%), 377 (M$^+$ − CH$_3$, 10%), 361 (M$^+$ − S, 100%), 383 (M$^+$ − C(O)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%). ^{31}P NMR ($CDCl_3$) δ +44.9; ^{1}H NMR ($CDCl_3$) δ 1.74 (d, ^2J(H−P) = 12.9 Hz, 3H, P−C**H**$_3$), 1.97 (s, 3H, $COCH_3$), 7.20−7.85 (m, 11H, **Ph** + **H**$_\beta$); ^{13}C NMR ($CDCl_3$) δ 18.96 (d, ^1J(C−P) = 49.0 Hz, P−**C**H$_3$), 29.83 (s, CH_3), 126.69−132.05 (m, **Ph**), 131.17 (d, ^2J(C−P) = 21.0 Hz, **C**$_\beta$H), 139.36 (d, ^1J(C−P) = 73.8 Hz, **C**$_\alpha$), 142.63 (d, ^2J(C−P) = 22.1 Hz, **C**$_\beta$), 143.63 (d, ^1J(C−P) = 69.9 Hz, **C**$_\alpha$), 198.95 (d, ^3J(C−P)= 15 Hz, −**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 3*H*-phosphole chemistry. As far as we know, only one 3-acylphosphole[13] and one 3*H*-phosphole with tetracoordinate phosphorus[14] have been described so far.

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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.

OL051816D