A Simple Access to 2-Acyl- and 2,5-Diacyl- Phospholide Ions

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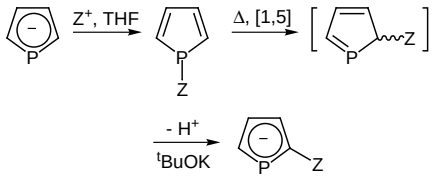
Abstract: Depending on the reaction conditions (rate of addition, temperature, stoichiometry), the reaction of acyl chlorides with 3,4-dimethylphospholide ion in THF gives the 2-acyl- and 2,5-diacyl-phospholides.

Key words: acyl chlorides, 3,4-dimethylphospholide, sigmatropic shift

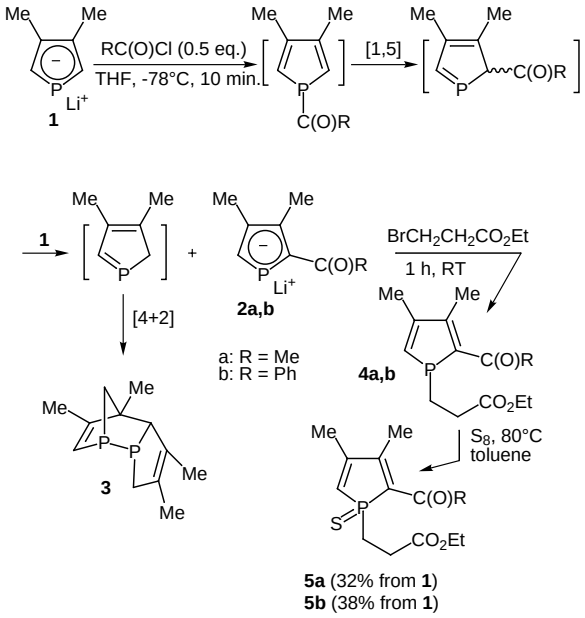
The synthesis of functionalized phospholes is a recurrent problem, which has not received fully satisfactory solutions until now.[1] Electrophilic substitution reactions are indeed impossible except in a few special cases[2] because phospholes are pyramidal and essentially non-aromatic. Besides, the aromatic phospholides ions react with electrophiles exclusively at phosphorus as a result of the high concentration of negative charge at the heteroatom. At the moment, the most versatile solution to get 2-functionalized phospholes involves the reaction of electrophiles with 2-lithiophospholes.[3] Unfortunately, this process relies on the cumbersome synthesis of the appropriate 2-bromophosphole precursors. Besides, it cannot be used for the preparation of reactive 2,5-bis-functionalized derivatives, which are key intermediates en route to polyphosphole macrocycles and chains.

Recently, we have discovered a practical access to 2-functional phospholide ions[4] which is shown in Scheme 1. The functionalized electrophile Z^+ is grafted at P, then a thermal [1,5] sigmatropic shift, is induced by heating and the resulting 2-functionalized 2*H*-phosphole is deprotonated by a base. A limited number of electrophiles have been used, the most interesting in the context of this work being $ClCO_2Et$, which yields both the mono- and the bis-ethoxycarbonyl phospholides under mild conditions. The extreme simplicity of this one-pot process encouraged us to investigate its generality more deeply. Thus, we decided to study the reaction of 3,4-dimethylphospholide **1** with acyl chlorides.

In view of the high reactivity of acyl chlorides towards **1**, a first series of experiments was carried out at –78 °C in THF. The reaction of **1** with acetyl chloride goes to completion in 10 minutes. Monitoring the reaction mixture by ^{31}P NMR shows the replacement of the resonance of **1** (δ ^{31}P +59, t, $^2J_{(P-H)}$ = 40 Hz) by a new resonance corresponding to the 2-acetylphospholide **2a** (δ ^{31}P +135, d, $^2J_{(P-H)}$ = 38.4 Hz) together with the AX system of the 2*H*-phosphole dimer **3**[5] (δ ^{31}P –24 and –63, $^1J_{(P-P)}$ = 185 Hz). The functional phospholide **2a** was also characterized by negative ion mass spectrometry and derivatization leading to phosphole **4a** and its sulfide **5a**.[6] Similar results were observed with benzoyl chloride.[7] The overall reaction sequence is depicted in Scheme 2.



Scheme 1



Scheme 2

From a mechanistic standpoint, this means that the sigmatropic shift of the acyl groups from P to Cα is fast even at –78 °C. The resulting 2*H*-phospholes are very acidic and easily deprotonated by the starting phospholide **1** to give the functionalized phospholides **2a,b**. According to ^{31}P NMR, the reactions are almost quantitative in line with the yields of **5a,b** as measured on the isolated products (32 and 38 *vs* 50% max.). From a practical standpoint, we then tried to modify the technique in order to make a better use of **1**. A more efficient procedure relies on the very fast ad-

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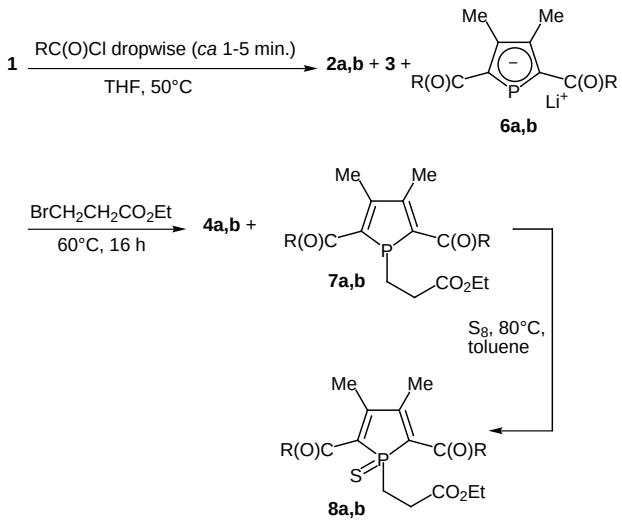
dition of the acyl chloride to the phospholide (in ca. 5 sec), followed by the addition of *t*-BuOK.[6] The overall yields of sulfides **5a,b** from **1** were boosted to 70% (R = Me) and 78% (R = Ph). This approach can also be modified to get the 2,5-diacyl derivatives. The slow addition of ca. one equivalent of acyl chloride to **1** at 50 °C leads to a mixture of mono- and diacyl-phospholides. After alkylation, the resulting phospholes **4** and **7** can be separated by chromatography, then sulfurized[8] (Scheme 3). Since two molecules of **1** are successively used for the deprotonation of the mono- and difunctionalized 2*H*-phospholes, the maximum theoretical yield of **7** and **8a,b** from **1** is only 33%. In practice, we have obtained the sulfides **8a** and **8b** in 10 and 13% yields, respectively after chromatographic purification. No attempt has been made to optimize these yields, although this is certainly possible. Anyhow, the extreme simplicity of this procedure is attractive even at this stage of development. Finally, it is interesting to notice that **6b** displays, by far, the most deshielded ^{31}P resonance of all presently known monophospholides at +209 ppm.



Scheme 3

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(6) **2a**: A solution of 1-phenyl-3,4-dimethylphosphole (0.94 g, 5×10^{-3} mol) in distilled THF (25 mL) was stirred with lithium wire (70 mg, 1×10^{-2} mol) for 2 h at 25 °C. The complete transformation of the phosphole into the phospholide was checked by ^{31}P NMR. The remaining lithium wire was removed, *tert*-butyl chloride (0.55 mL) was added, and the solution was refluxed for 30 min. The resulting reaction mixture was cooled to –78 °C and acetyl chloride (0.36 mL, 5×10^{-3} mol) was added over 5 sec. After warming to r.t., potassium *tert*-butoxide (0.784 g) was added to the solution which turned from orange to red. ^{31}P NMR (THF): δ = +135, $^1J_{(P\text{-}H)}$ = 38.4 Hz; mass (ICN, NH_3): *m/z* (%) = 153(100) [M^-]. **4a**: ^{31}P NMR ($CDCl_3$): δ = +3.3; ^{13}C NMR ($CDCl_3$): δ = 61.11 (s, OCH_2), 151.24 (d, $^2J_{(C\text{-}P)}$ = 5.3 Hz, Cβ), 157.81 (d, $^2J_{(C\text{-}P)}$ = 12.1 Hz, Cβ), 173.21 (d, $^3J_{(C\text{-}P)}$ = 5.3 Hz, CO_2Et), 196.60 (d, $^2J_{(C\text{-}P)}$ = 21.9 Hz, COMe). **5a**: Purified by chromatography on silica gel with hexane/ether 70/30: ^{31}P NMR ($CDCl_3$): δ = +48.6; ^1H NMR ($CDCl_3$): δ = 1.25 (t, $^3J_{(H\text{-}H)}$ = 7.2 Hz, CH_3-CH_2), 2.13 (dd, CH_3 cycle), 2.38 (d, CH_3 cycle), 2.57 (s, $COCH_3$), 4.13 (q, CH_2O), 6.19 (dd, $^2J_{(H\text{-}P)}$) = 30.8 Hz, CH-P); ^{13}C NMR ($CDCl_3$): δ = 14.15 (s, CH_3(Et)), 16.32 (d, $^3J_{(C\text{-}P)}$ = 12.1 Hz, CH_3 cycle), 17.70 (d, $^3J_{(C\text{-}P)}$ = 15.8 Hz, CH_3 cycle), 26.78 (d, $^1J_{(C\text{-}P)}$ = 51.3 Hz, CH_2P), 28.04 (s, $COCH_3$), 32.01 (s, $COCH_2$), 61.13 (s, OCH_2), 125.98 (d, $^1J_{(C\text{-}P)}$ = 77.7 Hz, P-CH), 134.28 (d, $^1J_{(C\text{-}P)}$ = 70.2 Hz, P-CCO) 153.17 (d, $^2J_{(C\text{-}P)}$ = 15.1 Hz, Cβ), 160.24 (d, $^2J_{(C\text{-}P)}$ = 21.1 Hz, Cβ), 171.66 (d, $^3J_{(C\text{-}P)}$ = 13.6 Hz, CO_2Et), 194.55 (d, $^2J_{(C\text{-}P)}$ = 15.8 Hz, CO); mass (ICP, NH_3): *m/z* (%) = 287(100) [M^+ + H].

(7) **2b**: ^{31}P NMR (THF): δ = +151.5, $^1J_{(P\text{-}H)}$ = 36.6 Hz; mass: *m/z* (%) = 215(100) [M^-]. **4b**: ^{31}P NMR ($CDCl_3$): δ = +10.3; mass (ICP, NH_3): *m/z* (%) = 316(6) [M^+], 216(24) [M^+ – CH_2CHCO_2Et], 105 (100). **5b**: ^{31}P NMR ($CDCl_3$): δ = +58.8; ^1H NMR ($CDCl_3$): δ = 1.25 (t, CH_3 (Et)), 1.86 (d, CH_3 cycle), 2.12 (dd, CH_3 cycle), 4.14 (q, $^3J_{(H\text{-}H)}$ = 7.2 Hz, CH_2O), 6.23 (dd, $^2J_{(H\text{-}P)}$ = 32.3 Hz, CH-P); ^{13}C NMR ($CDCl_3$): δ = 14.84 (s, CH_3 (Et)), 17.01 (d, $^3J_{(C\text{-}P)}$ = 13.4 Hz, CH_3 cycle), 18.13 (d, $^3J_{(C\text{-}P)}$ = 16.5 Hz, CH_3 cycle), 27.71 (d, $^1J_{(C\text{-}P)}$ = 50.8 Hz, CH_2-P), 28.66 (s, $COCH_2$), 61.59 (s, OCH_2), 125.90 (d, $^1J_{(C\text{-}P)}$ = 77.2, P-CH), 153.00 (d, $^2J_{(C\text{-}P)}$ = 20.3 Hz, Cβ), 153.41 (d, $^2J_{(C\text{-}P)}$ = 15.1 Hz, Cβ), 172.74 (d, $^3J_{(C\text{-}P)}$ = 14.2 Hz, CO_2Et), 194.07 (d, $^2J_{(C\text{-}P)}$ = 10.2 Hz, CO); mass (IE): *m/z* (%) = 348(3) [M^+], 248(91) [M^+ – CH_2CHCO_2Et], 105 (100).

(8) **6a**: ^{31}P NMR (THF): δ = +188.9. **6b**: The solution of 3,4-dimethylphospholide was prepared as for **2a**. The reaction mixture was warmed to 50 °C and benzoyl chloride (0.58 mL, 5×10^{-3} mol) was added dropwise over 1 min. A condenser was used to avoid THF evaporation. ^{31}P NMR (THF): δ = +209.6. **7a**: ^{31}P NMR (THF): δ = +13.2. **7b** : Purified by chromatography on silica gel with hexane/ether 70/30. ^{31}P NMR ($CDCl_3$): δ = +23; ^{13}C NMR ($CDCl_3$): δ = 14.64 (s, CH_3 (Et)), 17.54 (s, CH_3 cycle), 18.09 (d, $^1J_{(C\text{-}P)}$ = 24.5 Hz, CH_2-P), 31.27 (s, CH_2CO), 61.24 (s, OCH_2), 148.33 (d, $^1J_{(C\text{-}P)}$ = 7.8 Hz, Cα), 153.92 (d, $^2J_{(C\text{-}$

$_{P)}$ = 12.4 Hz, Cβ), 172.55 (d, $^{3}J_{(C\text{-}P)}$ = 6.8 Hz, CO_2Et), 194.51 (d, $^{2}J_{(C\text{-}P)}$ = 16.6 Hz, CO); mass (IE): *m/z* (%) = 421(4) [M^+ + H], 256 (67) 105 (100, PhCO). **8a**: Purified by chromatography on silica gel with hexane/ether 50/50. ^{31}P NMR ($CDCl_3$): δ +57.9; ^{1}H NMR ($CDCl_3$): δ = 1.21 (t, CH_3 (Et)), 2.35 (d, $^{4}J_{(H\text{-}P)}$ = 2.3 Hz, CH_3 cycle), 2.59 (s, $COCH_3$), 4.07 (q, $^{3}J_{(H\text{-}H)}$ = 7.1 Hz, OCH_2); ^{13}C NMR ($CDCl_3$): δ = 14.12 (s, CH_3 (Et)), 16.08 (d, $^{3}J_{(C\text{-}P)}$ = 11.3 Hz, CH_3 cycle), 27.65 (d, $^{1}J_{(C\text{-}P)}$ = 50.6 Hz, CH_2P), 27.85 (d, $^{3}J_{(C\text{-}P)}$ = 2.6 Hz, $COCH_3$), 32.38 (s, $COCH_2$), 61.30 (s, OCH_2), 135.08 (d, $^{1}J_{(C\text{-}P)}$ = 68.7 Hz, Cα), 157.66 (d, $^{2}J_{(C\text{-}P)}$ = 18.1 Hz, Cβ), 171.22 (d, $^{3}J_{(C\text{-}P)}$ = 13.6 Hz, CO_2Et), 195.69 (d, $^{2}J_{(C\text{-}P)}$ = 15.1 Hz, CO); mass (ICP, NH_3): *m/z* (%) = 345(27) [M^+ + NH_3], 328(100) [M^+]. **8b**: ^{31}P NMR ($CDCl_3$): δ +63.7; ^{1}H NMR ($CDCl_3$): δ = 1.10 (t, CH_3 (Et)), 1.77 (s, CH_3 cycle), 2.54 (m, CH_2), 2.69 (m, CH_2), 3.99 (q, $^{3}J_{(H\text{-}H)}$ = 7.2 Hz, OCH_2); ^{13}C NMR ($CDCl_3$): δ = 13.67 (s, CH_3 (Et)), 15.78 (d, $^{3}J_{(C\text{-}P)}$ = 12.8 Hz, CH_3 cycle), 27.80 (d, $^{1}J_{(C\text{-}P)}$ = 52.1 Hz, CH_2P), 60.40 (s, OCH_2), 135.62 (d, $^{1}J_{(C\text{-}P)}$ = 67.9 Hz, Cα), 150.64 (d, $^{2}J_{(C\text{-}P)}$ = 17.4 Hz, Cβ), 171.25 (d, $^{3}J_{(C\text{-}P)}$ = 21.9 Hz, CO_2Et), 192.28 (d, $^{2}J_{(C\text{-}P)}$ = 10.6 Hz, CO).