Relative Ease of Formation of Alkylidine(oxo and thioxo)phosphorane Intermediates in Nucleophilic Substitution at Phosphonyl and Thiophosphonyl Centres†

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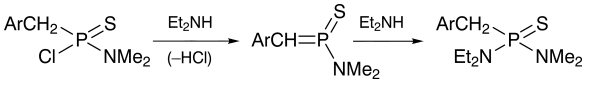
The conversion of $R_2CHP(X)(NEt_2)Cl$ (R_2CH = 9-fluorenyl) into $R_2CHP(X)(NEt_2)_2$ *via* the intermediate $R_2C{=}P(X)NEt_2$ (elimination–addition mechanism) is much faster when X = S than when X = O.

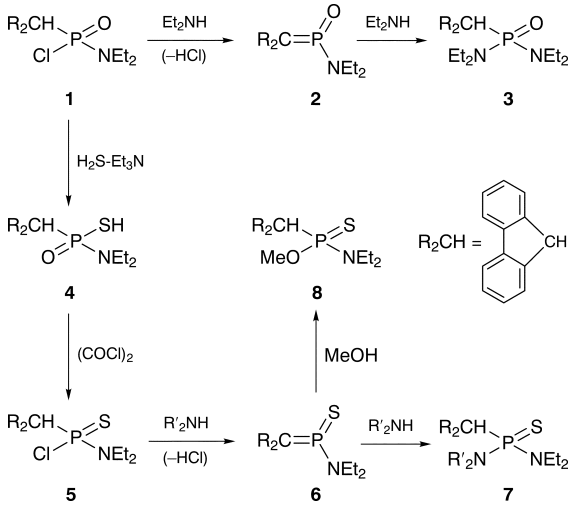
Nucleophilic substitution by elimination–addition (EA) is not uncommon for acyl and sulfonyl substrates, with ketenes or sulfenes as the product-forming intermediates.[1,2] An EA mechanism may also be favoured in some substitution reactions of $PhCH_2P(S)Cl_2$ and other benzylic thiophosphonyl (P=S) compounds (Scheme 1, Ar = 4-nitro or 4-cyanophenyl), the intermediates now being three-coordinate P^V alkylidinethioxophosphoranes (thiophosphenes).[3–5] For phosphonyl (P=O) substrates, however, it seems that formation of alkylidineoxophosphoranes (phosphenes) cannot compete with the normal associative [$S_N2(P)$] substitution mechanism.[6] An exception is the fluorenyl compound **1** (R_2CH = 9-fluorenyl); this gives **3** with Et_2NH, apparently by way of the phosphene intermediate **2**.[7] That being so, successful preparation of the thiophosphonyl analogue of **1** would make possible a direct comparison of the ease of formation of phosphenes and thiophosphenes as intermediates in nucleophilic substitution.



Scheme 1

9-Fluorenylphosphonothioic dichloride [$R_2CHP(S)Cl_2$] was readily obtained from the phosphonic dichloride [$R_2CHP(O)Cl_2$][7] by O/S exchange ($PSCl_3$–P_4S_{10}; DMF catalyst; 140 °C), but selective replacement of one of the chlorine atoms proved impossible. Using a stoichiometric amount of Et_2NH (2 equiv.), the required amidic chloride **5** (δ_P 93.8) was formed in only 40% yield, together with the diamide **7** (R′ = Et) (δ_P 85.0) and unchanged dichloride (δ_P 89.0) (both ~30%). Such a lack of selectivity is remarkable, although in this case not entirely unexpected: similar behaviour has been noted in the reactions of some other benzylic phosphonothioic dichlorides with Et_2NH.[3]

Attempts to convert the phosphonamidic chloride **1** into its P=S counterpart **5** by direct O/S exchange were not successful; with Lawesson's reagent, for example, there was practically no reaction over 16 h in boiling toluene. An indirect route from **1** to **5** was therefore examined (Scheme 2). Using a concentrated solution of H_2S–Et_3N in MeCN at 45 °C, **1** could be converted into the phosphonamidothioic acid **4** (as its Et_3NH^+ salt, δ_P 68.0), and this with oxalyl chloride gave the required thioic chloride **5**. Neither reaction was entirely clean (^{31}P NMR spectroscopy) but the final product was easily obtained pure by chromatography (47% yield) and crystallisation.



Scheme 2

The phosphonamidothioic chloride **5** reacted rapidly with Me_2NH or Et_2NH to give the expected diamide **7** (R′ = Me or Et) as the only product. Under the conditions previously employed for the P=O compound **1** (1.2 mol dm^{-3} amine in $CHCl_3$ at 31 °C)[7] the reactions were too fast to follow; even with Et_2NH, quenching with MeOH (large excess) after just 3 seconds produced none of the ester **8**, indicating that the substrate had already been fully converted into the diamide product. By contrast, the reaction of the P=O compound with Et_2NH has a half-life of 2.2 h.[7] Thus the P=S substrate ($t_{1/2} \leqslant 0.8$ s) is at least ten thousand times as reactive as its P=O counterpart. A measure of its reactivity could be obtained at higher dilution: with 0.2 mol dm^{-3} amine in $CHCl_3$ ($T \sim 31$ °C) the substrate remaining after 5 seconds, as indicated by the amount of the ester **8** formed on quenching, was 50% with Et_2NH ($t_{1/2} \sim 5$ s) and 6% with Me_2NH ($t_{1/2} \sim 1.2$ s).

The fact that the P=S substrate **5** is more reactive than its P=O counterpart **1** is compelling evidence for an EA mechanism, since P=O compounds are the more reactive in normal $S_N2(P)$ reactions.[8,9] Also, the reaction with Et_2NH is only about four times slower than that with Me_2NH, indicating a low sensitivity to steric hindrance. This is reasonable for a mechanism in which the amine acts as a base in the rate-limiting stage, removing a proton from the α carbon atom, but not for one in which it acts as a nucleophile at a tetrahedral P^V centre. The contrast with a P=S substrate that cannot react by elimination–addition is striking. The phenyl phosphonamidothioic chloride $PhP(S)(NMe_2)Cl$ reacts 200 times faster with Me_2NH than with Et_2NH ($t_{1/2}$ 4 min and 13.5 h with 0.6 mol dm^{-3} amine in CH_2Cl_2 at 33 °C),[4] and with both amines its reactivity is much less than that of the fluorenyl compound **5**. Also, in competition experiments using a 1:1 mixture of Me_2NH and

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Et_2NH, the phenyl substrate forms only the product derived from Me_2NH,[4] whereas the fluorenyl substrate **5** gives a substantial amount of the product **7** (R′ = Et) derived from the less nucleophilic (more hindered) Et_2NH (Me_2N:Et_2N product ratio 5:1). The relative lack of discrimination in the case of the fluorenyl compound is consistent with a reactive and sterically accessible thiophosphene intermediate as the product-forming species.

To conclude, a P=O compound is more reactive than its P=S counterpart in S_N2(P) reactions and the difference can be large (10^2–10^3 fold).[9] An EA mechanism is preferred for the reactions of the fluorenyl compounds **1** and **5** with Et_2NH, however, and here it is the P=S compound that is the more reactive and the difference is even greater ($\geqslant 10^4$ fold). If this is typical, thiophosphene formation (easy) may quite often compete effectively with S_N2(P) (slow) at a thiophosphonyl centre but phosphene formation (difficult) will not often be competitive with S_N2(P) (fast) at a phosphonyl centre.

Experimental

^{1}H NMR spectra were recorded at 250 MHz (Me_4Si internal standard; *J* in Hz) and ^{31}P NMR spectra at 101 MHz (positive δ_P downfield from 85% H_3PO_4). Amines were dried over KOH, $CHCl_3$ was passed through alumina and dried over molecular sieves, and CH_2Cl_2 was distilled from CaH_2. Light petroleum refers to the fraction bp 60–80 °C and ether to diethyl ether. GLC analysis employed a 15 m × 0.53 mm column containing a 1 μm film of OV 1701 at 220 °C (He carrier gas; 16 ml min^{-1}).

9-*Fluorenylphosphonothioic Dichloride*.—9-Fluorenylphosphonic dichloride (3.56 g, 12.6 mmol) was stirred with $PSCl_3$ (10.6 g, 63 mmol), P_4S_{10} (1.4 g, 3.15 mmol) and DMF (catalyst; 25 μl) at 140 °C (bath temp.) for 1.5 h. Volatile material was evaporated and the residue was extracted with CH_2Cl_2. The extract was concentrated and ether and light petroleum were added to give 9-fluorenylphosphonothioic dichloride (2.39 g, 64%), mp 138–140 °C, *m*/*z* 298, 300, 302 (M^+, 8%) and 165 (100), δ_P ($CDCl_3$) 89.1 δ_H ($CDCl_3$) 8.04 (2 H, dd, J_{PH} 4, J_{HH} 7.5), 7.82 (2 H, d, J_{HH} 7.5), 7.52 (2 H, ddd, J_{PH} 3, J_{HH} 7.5, 7.5), 7.39 (2 H, dd, J_{HH} 7.5, 7.5) and 5.14 (1 H, d, J_{PH} 17) (Found: C, 52.5; H, 2.9. $C_{13}H_9Cl_2PS$ requires C, 52.2; H, 3.0%).

N,N-Diethyl-P-(9-*fluorenyl*)*phosphonamidothioic Chloride* **5**.—A solution of Et_3N (0.71 g, 7.0 mmol) in dry MeCN (4 ml) was saturated with H_2S. The phosphonamidic chloride **1** (0.55 g, 1.72 mmol) was added and the mixture was heated at 45 °C (pressure released at 30 °C) in a septum-capped bottle for 3.3 h to give the Et_3NH^+ salt of the phosphonamidothioic acid **4**, δ_P 68.0 (75%) [minor products, δ_P 86.6 (15%) and 16.3 (10%)].‡ Volatile material was evaporated and the salt of **4** was extracted into ether. The extract was concentrated to 3 ml, filtered, acidified with CF_3CO_2H (1 equiv.) and immediately added dropwise over 5 min to oxalyl chloride (0.8 g, 6.3 mmol) in CH_2Cl_2 (8 ml). Reaction was complete after 45 min (product δ_P 94.7). Chromatography on silica, eluting with light petroleum containing ether (7%), gave the phosphonamidothioic chloride **5** (0.27 g, 47%), crystallised from light petroleum, mp 79.5–80.5 °C, *m*/*z* 335, 337 (M^+, 3.5%), 170, 172 (M^+–$C_{13}H_9$, 70) and 165 (100), δ_P ($CDCl_3$) 93.8, δ_H ($CDCl_3$) 8.15 (1 H, dd, J_{PH} 3.5, J_{HH} 8), 7.79 (3 H, m), 7.5–7.2 (4 H, m), 5.09 (1 H, d, J_{PH} 23), 3.17 (4 H, m) and 0.95 (6 H, t, J_{HH} 7) (Found: C, 61.0; H, 5.6; N, 4.3. $C_{17}H_{19}ClNPS$ requires C, 60.8; H, 5.7; N, 4.2%).

Reactions of 9-*Fluorenylphosphonothioic Dichloride*.—(*a*) The phosphonothioic dichloride was added to Et_2NH (6 equiv.) in CH_2Cl_2 (0.65 mol dm^{-3} solution) containing Et_2NH_2Cl (1 equiv.). Volatile material was evaporated to give, after washing with water, the phosphonothioic diamide **7** (R′ = Et), crystallised from light petroleum, mp 101.5–102.5 °C, *m*/*z* (CI) 373 ($M + H^+$, 35%), δ_P ($CDCl_3$) 85.0, δ_H ($CDCl_3$) 8.17 (2 H, d, J_{HH} 7.5), 7.78 (2 H, d, J_{HH} 7), 7.40 (2 H, dd, J_{HH} 7, 7), 7.31 (2 H, dd, J_{HH} 7, 7), 4.98 (1 H, d, J_{PH} 20), 2.93 (8 H, m) and 0.86 (12 H, t, J_{HH} 7) (Found: C, 68.2; H, 7.9; N, 7.5. $C_{21}H_{29}N_2PS$ requires C, 67.7; H, 7.85; N, 7.5%).

‡Minor products thought to be the corresponding salts with two S atoms or two O atoms.

(*b*) Et_2NH (2 equiv.) was added to a solution of the phosphonothioic dichloride in CH_2Cl_2 (0.2 mol dm^{-3}). The mixture was diluted with CH_2Cl_2 and washed with water. NMR spectroscopy ($CDCl_3$ solution) indicated a mixture of the phosphonamidothioic chloride **5** (40%), δ_P 93.8, δ_H 5.08 (d, J_{PH} 23), the phosphonothioic diamide **7** (R′ = Et) (30%), δ_P 85.0, δ_H 4.97 (d, J_{PH} 20), and unreacted phosphonothioic dichloride (30%), δ_P 89.0, δ_H 5.14 (d, J_{PH} 17).

Reactions of N,N-Diethyl-P-(9-*fluorenyl*)*phosphonamidothioic Chloride* **5**.—(*a*) The substrate **5** in CH_2Cl_2 was added to Me_2NH (4 equiv.) in CH_2Cl_2 to give, after washing with water, the phosphonothioic diamide **7** (R′ = Me), crystallised from light petroleum, mp 119.5–120.5 °C, *m*/*z* 344 (M^+, 1.5%), 179 (M^+–$C_{13}H_9$, 100) and 165 (25), δ_P ($CDCl_3$) 88.2, δ_H ($CDCl_3$) 8.51 (1 H, d, J_{HH} 7.5), 7.85–7.73 (3 H, m), 7.46–7.25 (4 H, m), 4.93 (1 H, d, J_{PH} 20), 2.66 (4 H, m), 2.61 (6 H, d, J_{PH} 14) and 0.46 (6 H, t, J_{HH} 7) (Found: C, 66.0; H, 7.2; N, 8.1. $C_{19}H_{25}N_2PS$ requires C, 66.25; H, 7.3; N, 8.1%).

(*b*) The substrate **5** was added to a 0.2 mol dm^{-3} $CHCl_3$ solution of Et_2NH (4 equiv.) mixed with an equal volume of MeOH (> 100 mol equiv. relative to Et_2NH). Analysis by GLC indicated a single product (t_R 3.1 min) and showed that none of the diamide **7** (R′ = Et) (t_R 7.6 min) had been formed. Volatile material was evaporated and the crude product was washed with water to give the methyl phosphonamidothioate **8**, mp 72–73 °C (from light petroleum), *m*/*z* 331 (M^+, 10%), 166 (M^+–$C_{13}H_9$, 100) and 165 (30), δ_P ($CDCl_3$) 90.6, δ_H ($CDCl_3$) 8.16 (1 H, d, J_{HH} 7.5), 7.81–7.71 (3 H, m), 7.46–7.25 (4 H, m), 4.79 (1 H, d, J_{PH} 25.5), 3.735 (3 H, d, J_{PH} 13.5), 2.83 (4 H, m) and 0.66 (6 H, t, J_{HH} 7) (Found: M^+ 331.1160. $C_{18}H_{22}NOPS$ requires *M* 331.1160). In a similar experiment with Me_2NH–MeOH, the diamide **7** (R′ = Me) (t_R 5.4 min) was formed but only in trace amount (1–2%). It is therefore possible to use MeOH to quench substitution of **5** by Et_2NH or Me_2NH.

(*c*) The substrate **5** (0.5 μmol) in $CHCl_3$ (2.5 μl) was added to a solution (50 μl) of Me_2NH or Et_2NH ($\geqslant$20 equiv.) in $CHCl_3$, $T \sim 31$ °C, to give a reaction mixture having an amine concentration of 0.20 or 1.2 mol dm^{-3}. Some seconds later MeOH (50 μl) was added. Analysis by GLC indicated the amount of the diamide product **7** [t_R 5.4 (R′ = Me) or 7.6 min (R′ = Et)], relative to the methyl ester **8** (t_R 3.1 min) corresponding to unreacted substrate at the time of quenching. The results were as follows:

With 0.20 mol dm^{-3} Me_2NH, 94% conversion into **7** (R′ = Me) at *t* = 5 s; 100% at *t* = 20 s.

With 0.20 mol dm^{-3} Et_2NH, 50% conversion into **7** (R′ = Et) at *t* = 5 s; 75% at *t* = 10 s; 100% at *t* = 40 s.

With 1.2 mol dm^{-3} Et_2NH, $\geqslant$99% conversion into **7** (R′ = Et) at *t* = 3 s.

(*d*) The substrate **5** was added to an equimolar mixture of Me_2NH and Et_2NH (20 equiv.) in $CHCl_3$ (1.2 mol dm^{-3} total amine concentration). The crude product, after washing with water, was seen (^{31}P and ^{1}H NMR) to be a 5:1 mixture of **7** (R′ = Me) and **7** (R′ = Et).

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