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Methylenethioxophosphorane (thiophosphene) intermediates in the reactions of diphenylmethylphosphonamidothioic chlorides with amines. Differences between the elimination–addition mechanisms of nucleophilic substitution for P=S and P=O substrates

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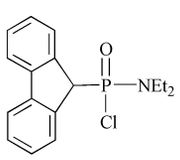
Received (in Cambridge, UK) 31st October 2001, Accepted 28th November 2001
First published as an Advance Article on the web 21st January 2002

In reactions with R_2NH (R = Me or Et) in $CHCl_3$ the P=S substrate $Ph_2CHP(S)(NMe_2)Cl$ differs markedly from its P=O counterpart: the rate of substitution is increased much more by a 4-nitro substituent but is also more sensitive to the bulk of the amine, there is greater discrimination between competing nucleophiles, and with R_2ND there is relatively little H–D exchange at the α carbon atom prior to substitution. Yet the P=S and P=O compounds both seem to react by elimination–addition mechanisms. It is suggested that whereas in the P=O case the conjugate base is formed rapidly and elimination of chloride to give the methyleneoxophosphorane (phosphene) intermediate is rate limiting, the conjugate base of the P=S substrate eliminates chloride rapidly giving a relatively stable methylenethioxophosphorane (thiophosphene) intermediate.

With acyl and sulfonyl substrates it is not unusual for nucleophilic substitution to favour an elimination–addition mechanism with a ketene[1] or sulfene[2] as the product-forming species. With phosphonyl (P=O) substrates,[3] however, elimination–addition (EA) *via* a methyleneoxophosphorane (phosphene) intermediate[4] does not generally compete effectively[5] with the normal associative $S_N2(P)$ mechanism.[3,6] An exception is the fluorenyl phosphonamidic chloride **1**: considerable evidence points to the intermediacy of the phosphene **2** in its substitution reactions with amines.[7,8]



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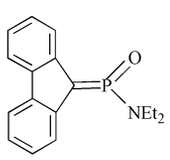

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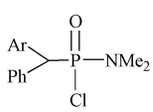
Three-coordinate P^v species, notably monomeric metaphosphate,[9] are more stable when they contain P=S in place of P=O, or at least they are formed more readily.[10] That is certainly the case with the phosphene **2**, to the extent that the P=S analogue of **1** undergoes substitution with Et_2NH ten thousand times faster than the P=O compound itself.[11] Conversely, in $S_N2(P)$ reactions it is P=O compounds that are the more reactive.[12] The likelihood of EA being the preferred mechanism of substitution is therefore much greater for a substrate that contains a P=S group.

Having recently argued that EA competes effectively with $S_N2(P)$ in the reactions of the benzhydryl P=O compound **3a** with Me_2NH and Et_2NH[13] we confidently expected that EA would be dominant for the corresponding P=S compound **5a** and that the reactions would proceed very readily. It was therefore disturbing to find that substitution does *not* occur at all readily, at least with Et_2NH as the nucleophile: if the P=S analogue does *not* react by EA the case for the P=O compound doing so will be hard to sustain. We have therefore examined in some detail the behaviour of the phosphonamidothioic chloride **5a** and also its 4-nitro substituted derivative **5b**.



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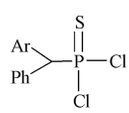

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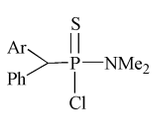

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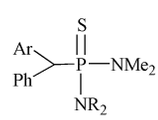
a; Ar = Ph;



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b; Ar = 4-$NO_2C_6H_4$

Results and discussion

Phosphonamidothioic chlorides

The reactions of phosphonic and thiophosphonic dichlorides [$RP(X)Cl_2$; X = O or S] with secondary amines are generally easy to control so that just one of the chlorine atoms is replaced. Unfortunately, as previously noted,[14] that is not the case with the benzhydryl compound **4a**: regardless of the conditions employed, on reaction with Me_2NH it gives largely the diamide **6a** (R = Me). To obtain the amidic chloride **5a** we therefore had to find a way of selectively replacing one of the NMe_2 groups of the diamide by a chlorine atom. The most satisfactory method proved to be exchange with $PSCl_3$ (10-fold excess) at 120–125 °C using DMF as catalyst. Typically the conversion was ⩾95% complete in 24 h (^{31}P NMR), but it was not pushed to completion because the second NMe_2 group began to be exchanged. The same method was also satisfactory for the 4-nitro substituted amidic chloride **5b** which, being chiral at carbon as well as phosphorus, was obtained as a mixture of diastereoisomers: δ_P 95.4 (major) and 95.3; δ_H 5.25 (major) and 5.22 (both d, J_{PH} 21, CH) and 2.83 and 2.805 (major) (both d, J_{PH} 15, NMe_2).

Reactions with Me_2NH and Et_2NH

The unsubstituted substrate **5a** gave the expected diamide

DOI: 10.1039/b109944m

Table 1 Pseudo-first order rate constants (k) for reactions of phosphonamidothioic chlorides **5a** and **5b** (and, for comparison, the corresponding P=O compounds **3a** and **3b**) with 2.0 mol dm^{-3} amines in $CHCl_3$ at 30 °C

	$10^5\ k/s^{-1}$	
Substrate	Me_2NH	Et_2NH
5a	2.52	0.052[a]
5b	2200	105[b]
3a	1.04	0.21
3b	13.8	3.87

[a] For consumption of substrate to give diamide product and byproducts (~ 18%). For diamide formation alone would be somewhat smaller. [b] Mean value; for individual diastereoisomers $10^5\ k$ *ca.* 165 and 46 s^{-1}.

product **6a** with R_2NH (R = Me or Et) but in the case of Et_2NH the reaction was very slow. Using an excess of the amine as a 2 mol dm^{-3} solution in $CHCl_3$ some 7% of the substrate still remained unreacted after 8 weeks at 30 °C, and even that may not fully represent the slowness of the substitution as side reactions (most likely hydrolysis) accounted for about a fifth of the substrate consumed.

The nitro-substituted substrate **5b** was much more reactive and side reactions were minimal. In this case the diamide product **6b** formed with Me_2NH (δ_P 84.3) has diastereotopic NMe_2 groups [δ_H 2.45 and 2.44 (both 6 H, d, J_{PH} 11.5)] while that derived from Et_2NH exists as diastereoisomers (δ_P 81.5 and 81.3) [δ_H 4.815 and 4.805 (both 1 H, d, J_{PH} 18, CH); 2.495 and 2.475 (both 6 H, d, J_{PH} 11, NMe_2)].

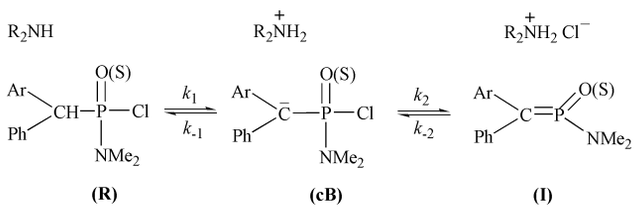
Rate studies were carried out using a large excess of the amine (R_2NH; R = Me or Et) as a 2.0 mol dm^{-3} solution in $CHCl_3$ (containing 0.1 mol dm^{-3} $R_2NH_2^+$ Cl^-) at 30 °C.† The reactions were monitored by ^{31}P NMR spectroscopy to 90% completion. First order plots were linear for the unsubstituted substrate **5a** (Table 1; values of k for the P=O compound **3a** included for comparison) but for the nitro-substituted substrate **5b** reaction was too fast to follow by NMR spectroscopy with Me_2NH ($t_{1/2}$ < 1 min) and with Et_2NH it produced a plot that was distinctly non-linear (successive half lives 16, 18 and 20 min). The curvature seems to be caused by a difference in the reactivity of the two diastereoisomers of the substrate: the lowfield diastereoisomer constituted one third of the substrate initially but only one seventh at 50% completion, implying that it reacts 3 or 4 times more quickly. The value of k shown (Table 1) is the mean of the estimated values for the individual diastereoisomers. The product diastereoisomer ratio (64 : 36) remained constant throughout, however, suggesting that substitution is non-stereospecific. A difference in reactivity was not apparent for the diastereoisomers of the corresponding P=O substrate **3b** but that could be because they equilibrate rapidly under the conditions of substitution.[13] To obtain the rate constant for the fast reaction of **5b** with Me_2NH samples were withdrawn at 15 s intervals and quenched by mixing with MeOH (large excess); they were then analysed by GLC. Curvature of the first-order plot was not as pronounced as with Et_2NH, but the method did not allow the relative reactivity of the individual diastereoisomers of the substrate to be assessed.

Competition experiments were also performed, using an equimolar mixture of Me_2NH and Et_2NH (2.0 mol dm^{-3} total amine). The unsubstituted substrate **5a** gave only the product derived from Me_2NH (product ratio ≥ 99 : 1) but the nitro compound was not completely selective and gave a 97 : 3 mixture of products.

The results in Table 1 show that the P=S substrate **5a** is indeed less reactive than its P=O counterpart with Et_2NH ($t_{1/2}$ 15.3 day; k^S/k^O 0.25). It is the more reactive with Me_2NH (k^S/k^O 2.5) but with both amines it is the closeness of the P=S and P=O reactivity that is really striking. Such similarity would not be expected for $S_N2(P)$ reactions,[12] or for EA either based on such precedent as there is ($k^S/k^O \geq 10^4$ for **1** and its P=S counterpart with Et_2NH).[11]

The Me_2NH/Et_2NH rate difference for the P=S substrate **5a** (k^M/k^E = 50) is an order of magnitude greater than for the P=O substrate **3a** (k^M/k^E = 5)[13] or for the fluorenyl substrate **1** (k^M/k^E = 4)[7] and its P=S counterpart (k^M/k^E = 4).[11] It is not quite as great as is seen in the $S_N2(P)$ reactions of $PhP(S)(NMe_2)Cl$ (k^M/k^E = 200),[15] but the complete selectivity for Me_2NH in the competition experiment is exactly what would be expected for $S_N2(P)$.[7,15] The nitro-substituted substrate **5b** shows rather less discrimination against Et_2NH, both in terms of rate of reaction (k^M/k^E = 21) and competitive product formation (NMe_2 : NEt_2 product ratio 97 : 3), but its behaviour is still hardly supportive of an EA mechanism.

In spite of all this there is one feature of the results in Table 1 that seems inexplicable without recourse to an EA mechanism. With either amine, introduction of the 4-nitro substituent into the substrate (**5a** ⟶ **5b**) increases the reactivity about a thousand fold. An increase of this magnitude is not only inconceivable for an $S_N2(P)$ mechanism but is also at least 60 times greater than was seen for the P=O substrate **3**.[13] Our preferred explanation is that the P=S and P=O substrates differ not in the *type* of substitution mechanism—for both it is EA—but in the detail, specifically as regards the elimination stage leading to the transient phosphene or thiophosphene intermediate (Scheme 1). For the P=O substrate removal of the



Scheme 1

proton from the α carbon atom is fast and reversible and expulsion of chloride ion from the conjugate base (phosphene formation) is rate limiting ($k^2 < k^{-1}$) (Fig. 1, P=O line *a*). With the

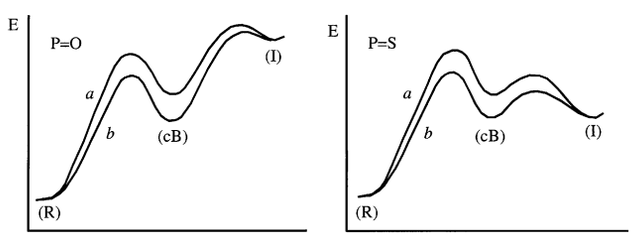


Fig. 1 Postulated reaction energy profiles for formation of phosphene and thiophosphene intermediates (I) from P=O and P=S reactants (R) *via* conjugate bases (cB); *a*, Ar = C_6H_5; *b*, Ar = 4-$NO_2C_6H_4$.

P=S compound the conjugate base is formed more or less as readily[16] but the thiophosphene intermediate is relatively stable; loss of chloride ion (thiophosphene formation) is now fast ($k^2 \geq k^{-1}$), so formation of the conjugate base becomes rate limiting (Fig. 1, P=S line *a*). A 4-nitro substituent will greatly increase the stability of the anionic conjugate base (cB), and hence its rate of formation, but the influence it has on the stability of the uncharged phosphene or thiophosphene intermediate (I) is unlikely to be large (Fig. 1, lines *b*; for simplicity

† In substitution reactions of phosphonamidic chlorides with amines the amine hydrochloride byproduct can accelerate the reaction slightly, causing deviations from linearity in the first-order rate plots (ref. 7). In the present study a small amount of the appropriate amine hydrochloride (Et_2NH_2Cl or Me_2NH_2Cl) (0.1 mol dm^{-3}) was included in each reaction mixture; now the rate plots showed little if any curvature.

the NO_2 group is shown as having no effect on the stability of the intermediate). The nitro group therefore has a major impact on the rate of formation of the thiophosphene intermediate from **5** (Fig. 1, P=S) but a much smaller effect on the rate of phosphene formation from **3** (Fig. 1, P=O). More extreme stabilisation of the conjugate base should increase still further the difference in reactivity between P=O and P=S substrates—hence, we suppose, the dramatic difference seen for the fluorenyl substrate **1** and its P=S counterpart ($k^S/k^O \geqslant 10^4$).[11]

As regards the differences in the rates of reaction with Me_2NH and Et_2NH, the congested environment of the C_α–H bond in these benzhydryl compounds may make proton removal more sensitive than usual to the bulk of the base, so that formation of the conjugate base will be markedly slower in the case of Et_2NH. This will be reflected strongly in the rate of thiophosphene formation from **5** (proton removal rate-limiting) but only modestly in the rate of phosphene formation from **3**. It should be noted, however, that the behaviour of the P=S substrate does not actually require that the elimination stage of the EA mechanism be E1cB; it could equally well be E2 with an ElcB-like transition state.

As regards product formation it is a characteristic of three-coordinate P^v intermediates (monomeric metaphosphate *etc.*) that they discriminate little between competing nucleophiles.[17,18] If substrate **5** does indeed react with Me_2NH and Et_2NH by way of a thiophosphene intermediate the observed selectivity for Me_2NH ($\geqslant$ 99 : 1 for **5a**; 97 : 3 for **5b**) is unprecedented. It far exceeds what is seen in the EA reactions of either the corresponding P=O compound **3** (~ 75 : 25)‡ or the less hindered P=S substrate $ArCH_2P(S)(NMe_2)Cl$ (Ar = 4-$NO_2C_6H_4$) (70 : 30).[13,15] Perhaps with this thiophosphene (Scheme 1) the combined effect of the stabilisation afforded by the P=S group and the steric shielding imposed by the benzhydryl group is enough to confer selectivity. If the thiophosphene lies in a sufficiently deep energy well the activation energy for product formation is going to vary considerably from one nucleophile to another. To the extent that reaction of the thiophosphene mirrors its formation it will have a transition state or intermediate that resembles the conjugate base of the substrate except that the leaving group has been replaced by the nucleophile. Structural features that stabilise the conjugate base will then lower the energy barrier not only for return of the thiophosphene (Scheme 1) but also its progression on to product. That may be why the fluorenyl substrate (the P=S analogue of **1**) discriminates much less than the benzhydryl substrate **5** between competing nucleophiles.

Reactions with Me_2ND and Et_2ND

Although selectivity does not necessarily detract from the case for a thiophosphene intermediate it certainly lends no support. Non-stereospecificity of substitution would be powerful supporting evidence for a planar three-coordinate intermediate and, as noted earlier, there was an indication of this in the reaction of **5b** with Et_2NH. It is no more than an indication, however: the diastereoisomers of the substrate have not been separated, and they are only partially resolved in the ^{31}P NMR spectrum of the mixture ($\Delta\delta_P$ 0.08), so any conclusion concerning the behaviour of the individual diastereoisomers cannot be very secure.

Equally good evidence for a thiophosphene intermediate would be the incorporation of deuterium into the product as it is formed using a deuteriated amine (R_2ND). The reactions of **5a** and **5b** with Me_2NH and Et_2NH were therefore repeated using amine containing 80–85 atom% D and in every case the product was seen to be substantially deuteriated at the α carbon atom (^1H NMR; CH integral < 1 H). Provided the substrate does not become deuteriated by exchange with R_2ND before it undergoes substitution, this is compelling evidence for an intermediate with a (formal) C=P bond. To assess the importance of exchange the reactions were monitored by ^1H and ^{31}P NMR spectroscopy, focusing on the H/D composition of the methine group of the substrate (CH integral) at various stages of reaction. It was not possible to obtain relevant data for the fast reaction of **5b** with Me_2ND—no substrate remained when the first spectrum was recorded—but with Et_2ND it could be seen that there was no appreciable exchange to at least 70% completion (substrate CH integral still ~1 H). For the unsubstituted substrate **5a** there was some exchange, at a rate comparable with the rate of substitution, but useful information could still be obtained. Thus, for example, when the reaction with Me_2ND was about half complete (^{31}P NMR) the product contained practically as much deuterium as the amine (CH: 0.2 H/0.8 D) whereas the substrate contained substantially less (CH: 0.63 H/0.37 D). Most of the product at that time would have been derived from substrate containing even less deuterium (less H–D exchange) so there can be no doubt that a thiophosphene is important in product formation. This result is all the more significant because it relates to the less acidic substrate (no NO_2 group) and the more nucleophilic (less hindered) amine; if EA is able to compete effectively with $S_N2(P)$ in this reaction it will surely be dominant in all the others. That being so, it is interesting to note that with the nitro-substituted substrate **5b** the products as formed contained less deuterium than expected (CH: ~0.5 H/0.5 D) and that only after reaction was complete did the deuterium content gradually increase to the expected level (CH: ~0.2 H/0.8 D), by slow exchange with R_2ND. This suggests that there is a D kinetic isotope effect in the product-forming addition of the amine (80–85 atom% D) to the thiophosphene intermediate.

The extent of H–D exchange in the substrate is itself of mechanistic significance. In the case of the nitro-substituted P=O substrate **3b** exchange is very much faster than substitution so that the deuterium content of the substrate practically matches that of the amine (Et_2ND) before any detectable product formation has occurred. The contrast with the P=S substrate **5b**—no exchange even at 70% completion—could hardly be greater. As implied by the energy profiles in Fig. 1 (lines *b*) the preferred fate of the conjugate base is return to substrate (protonation) in the case of the P=O compound but formation of the intermediate (elimination of Cl^-) in the case of the P=S compound. The contrast should be less pronounced when the substrates have no nitro substituent (Fig. 1; lines *a*) and that indeed is so: with the P=S compound **5a** exchange occurs at about the same rate as substitution and with the P=O compound **3a** it is not very much faster (2 and 10 times faster with Et_2ND and Me_2ND respectively). It is surprising that for the P=S substrate exchange is less important, relative to substitution, when the nitro substituent is present. Intuitively we would expect it to be more important, as it is for the P=O substrate, but perhaps the nitro group assists return of the thiophosphene intermediate less than it assists progression on to product.

Conclusion

The P=S substrates **5** resemble their P=O counterparts **3** in as much as they react with amines by an EA mechanism rather than by $S_N2(P)$. The elimination stage is most likely ElcB for both types, but differences emerge because the three-coordinate P^v intermediates differ in stability. In the case of the P=S compounds the intermediate thiophosphene is relatively stable and elimination of chloride from the conjugate base is fast. The overall rate of substitution is therefore determined mainly by the rate of formation of the conjugate base (large effect of NO_2

‡ The NMe_2 : NEt_2 product ratio is 3.1 : 1 for **3b**, and 3.05 : 1 for **3a** when a small amount of DBU (strong base) is included in the reaction mixture. In the absence of DBU some **3a** reacts by $S_N2(P)$ rather than EA so substitution appears to be more selective (product ratio 6.4 : 1).

substituent), there is little return of the conjugate base to substrate (little H–D exchange), and the intermediate discriminates quite strongly between competing nucleophiles. For the P=O compounds the intermediate phosphene is relatively unstable and elimination of chloride from the conjugate base is slow. There is extensive return of the conjugate base to substrate and little discrimination between competing nucleophiles.

For phosphonic acid derivatives generally there may not always be a clear mechanistic distinction between the EA pathways of P=O and P=S compounds. However, as long as the thiophosphene intermediate is more stable than the phosphene, the tendency will be towards dissimilar types of behaviour as identified now for the P=O and P=S benzhydryl phosphonamidic chlorides **3** and **5**.

Experimental

Instrumentation and general experimental methods were as previously described.[13]

Phosphonothioic dichlorides

The phosphonic dichloride $Ph_2CHP(O)Cl_2$ or $ArPhCHP(O)Cl_2$ (4 mmol) was stirred with $PSCl_3$ (20 mmol), P_4S_{10} (1 mmol) and DMF (catalyst; 0.15 mmol) at 130 °C (bath temp.) until the P=O ⟶ P=S transformation was complete (*ca.* δ_P 45 ⟶ 85) (2–3 h). The mixture was diluted with CH_2Cl_2 and filtered, and volatile material (including $PSCl_3$) was removed by warming under vacuum. The crude product was passed down a short column of silica (CH_2Cl_2 eluent) and was then crystallised:

Diphenylmethylphosphonothioic dichloride 4a. Mp 84.5–85 °C (from light petroleum), *m*/*z* 304, 302, 300 (M^+, <1%), *m*/*z* (CI; NH_3) 322, 320, 318 [$(M + NH_4)^+$, 15%], 305, 303, 301 [$(M + H)^+$, 3] and 167 (Ph_2CH^+, 100); δ_P ($CDCl_3$) 89.2; δ_H ($CDCl_3$, 250 MHz) 7.69 (4 H, m), 7.38 (6 H, m) and 5.22 (1 H, d, J_{PH} 21) (Found: C, 51.9; H, 3.6. $C_{13}H_{11}Cl_2PS$ requires C, 51.8; H, 3.7%).

4-Nitrophenyl(phenyl)methylphosphonothioic dichloride 4b. Mp 107–108 °C (from CH_2Cl_2–light petroleum), *m*/*z* 349, 347, 345 (M^+, 0.5%) and 212 ($ArPhCH^+$, 100); δ_P ($CDCl_3$) 84.2; δ_H ($CDCl_3$, 250 MHz) 8.26 (2 H, dd, J_{PH} 1, J_{HH} 9), 7.89 (2 H, dd, J_{PH} 3, J_{HH} 9), 7.7–7.6 (2 H, m), 7.45–7.35 (3 H, m) and 5.34 (1 H, d, J_{PH} 21); ν_{max} (Nujol)/cm^{-1} 1520 and 1345 (NO_2) (Found: C, 45.7; H, 2.8; N, 3.8; M^+, 344.9548. $C_{13}H_{10}Cl_2NO_2PS$ requires C, 45.1; H, 2.9; N, 4.05%; *M*, 344.9547 for ^{35}Cl).

Phosphonamidothioic chlorides

The phosphonothioic dichloride **4a** or **4b** (0.5 mmol) was treated with an excess of Me_2NH (≥ 2 mmol) in CH_2Cl_2 (2 ml), the solvent was evaporated, and the residue was extracted thoroughly with ether to give the phosphonothioic diamide **6a** or **6b**. The crude diamide was dissolved in $PSCl_3$ (0.5 ml, 5 mmol) containing DMF (catalyst; 3.5 mg, 0.05 mmol) and the solution was heated in an NMR tube at 120–125 °C until practically all the diamide had been converted into the amidic chloride **5a** or **5b** (≥ 18 h; δ_P ~ 85 ⟶ 95). Volatile material was evaporated by warming under vacuum and the product was extracted into ether and purified by crystallisation or chromatography:

***N*,*N*-Dimethyl-*P*-(diphenylmethyl)phosphonamidothioic chloride 5a.** Yield 66%, mp 128–129 °C (from ether–light petroleum), *m*/*z* 311,309 (M^+, 3%) and 167 (Ph_2CH^+, 100); δ_P ($CDCl_3$) 99.3; δ_H ($CDCl_3$) 7.7–7.6 (4 H, m), 7.4–7.25 (6 H, m), 5.13 (1 H, d, J_{PH} 21) and 2.80 (6 H, d, J_{PH} 15) (Found: C, 58.0; H, 5.5; N, 4.4; M^+, 309.0508. $C_{15}H_{17}ClNPS$ requires C, 58.15; H, 5.5; N, 4.5%; *M*, 309.0508 for ^{35}Cl).

***N*,*N*-Dimethyl-*P*-[4-nitrophenyl(phenyl)methyl]phosphonamidothioic chloride 5b.** Yield 45%, eluted from silica using light petroleum–ethyl acetate (5 : 1), mixture of diastereoisomers, mp 60–67 °C (from ether–light petroleum); δ_P ($CDCl_3$) 95.4 and 95.3 (major); δ_H ($CDCl_3$) (300 MHz) 8.20 (2 H, d, J_{HH} 9), 7.81 (2 H, dd, J_{PH} 3, J_{HH} 9), 7.67–7.60 (2 H, m), 7.4–7.3 (3 H, m), 5.25 (major) and 5.22 (total 1 H; both d, J_{PH} 21), and 2.83 and 2.805 (major) (total 6 H; both d, J_{PH} 15); ν_{max} (Nujol)/cm^{-1} 1520 and 1350 (NO_2); *m*/*z* 356, 354 (M^+, 6%), 212 ($ArPhCH^+$, 80) and 196 (100) (Found: C, 50.6; H, 4.6; N, 7.7; M^+, 354.0358. $C_{15}H_{16}ClN_2O_2PS$ requires C, 50.8; H, 4.55; N, 7.9%; *M*, 354.0359 for ^{35}Cl).

Phosphonamidothioic chloride rate studies

All materials and glassware were dried and moisture was excluded as completely as possible. The reaction medium was a 2.0 mol dm^{-3} solution of R_2NH (R = Me or Et) in $CHCl_3$ containing $R_2NH_2^+$ Cl^- (0.1 mol dm^{-3}). The substrate (10–15 μmol) was dissolved in the reaction medium [240 μl, but 60 μl for **5a** with Et_2NH (to reduce hydrolytic side reactions)] and the solution was transferred to a 4 mm (or capillary) NMR tube housed in a 5 mm tube containing D_2O (NMR lock). Faster reactions were conducted in the probe of the NMR spectrometer at 30 °C. Slower reactions (sealed tubes) were maintained at 30 °C (block heater) and transferred to the spectrometer periodically. The reaction of **5b** with Me_2NH was complete within 8 min but in other cases the ^{31}P NMR spectrum (^1H decoupled) was recorded at regular intervals so that 9 spectra were obtained as reaction progressed to 90% completion. For each spectrum the relative amounts of substrate and product were deduced from the integral. In the case of **5a** with Et_2NH byproducts (hydrolysis) accounted for *ca.* 20% of the substrate consumed. The values of *k* were deduced from first order plots (Table 1).

When reaction was complete the volatile material was evaporated and the residue was dissolved in CH_2Cl_2. The solution was washed with water and the product was isolated and characterised spectroscopically (see below).

The very fast reaction of **5b** with Me_2NH was repeated and samples (8 μl) were withdrawn at intervals (15 s), diluted with MeOH (100 μl), and left overnight to allow the remaining substrate to be converted completely into the methyl ester [$ArPhCHP(S)(NMe_2)OMe$]. The samples were then analysed by GLC [OV 1701 widebore capillary column (1 μm film; 15 m × 0.53 mm); He carrier (35 ml min^{-1}); 235 °C; FID] and the relative amounts of the methyl ester (R_t 3.6 min) and the amide product (R_t 6.3 min) were deduced from the peak areas. The value of *k* (Table 1) was deduced as before.

Deuterium incorporation studies

Stock solutions of R_2ND (R = Me or Et) (80–85 atom% D; 1.9–2.0 mol dm^{-3}) in $CDCl_3$ (containing 0.1 mol dm^{-3} $R_2ND_2^+$ Cl^-) were prepared as previously described.[13] The substrate **5** (12–16 μmol) was dissolved in the appropriate stock solution (65 μl) and the solution was transferred to a capillary NMR tube. At intervals the ^{31}P and ^1H NMR spectra were recorded and from them the extent of reaction and the approximate deuterium content of the CH(D) group of the substrate (and sometimes the product) were estimated as before. The temperature was maintained at *ca.* 30 °C generally but 19 °C for **5b** + Et_2ND. The deuterium content of the product from **5b** was seen to increase gradually (by H–D exchange) from the level when reaction was just complete (CH: 0.7 D increasing to 0.85 D in 36 h at room temp. with Me_2ND; 0.5 D increasing to 0.85 D in 4 days at 30 °C then 3 days at room temp. with Et_2ND).

Competition experiments

The substrate **5** (~ 10 μmol) was added to a mixture of Me_2NH

and Et_2NH (each 1.0 mol dm^{-3}) in $CHCl_3$ (containing 0.05 mol dm^{-3} $Me_2NH_2^+$ Cl^- and $Et_2NH_2^+$ Cl^-) (250 μl) at 30 °C (sealed ampoule for **5a**). The NMe_2 : NEt_2 product ratio was determined by ^{31}P NMR spectroscopy after 3 h (for **5b**) or 9 days (for **5a**; some substrate still present).

Phosphonothioic diamide products

The identities of the products formed in the rate studies were confirmed as detailed below.

From **5a** and Me_2NH, *product* **6a** (R = Me), crystallised from light petroleum, mp 104.5–105.5 °C; *m*/*z* 318 (M^+, 1.5%) and 151 ($M^+ - Ph_2CH$, 100); δ_P ($CDCl_3$) 85.7; δ_H ($CDCl_3$, 250 MHz) 7.8–7.7 (4 H, m), 7.35–7.15 (6 H, m), 4.64 (1 H, d, J_{PH} 18) and 2.43 (12 H, d, J_{PH} 11) (Found: C, 64.4; H, 7.3; N, 8.7; M^+, 318.1319. $C_{17}H_{23}N_2PS$ requires C, 64.1; H, 7.3; N, 8.8%; *M*, 318.1320).

From **5a** and Et_2NH, *product* **6a** (R = Et), purified by chromatography (silica; 1 : 1 CH_2Cl_2–light petroleum) and crystallisation from ether–light petroleum, mp 101.5–103.5 °C; *m*/*z* 346 (M^+, 1.5%) and 179 ($M^+ - Ph_2CH$, 100); δ_P ($CDCl_3$) 83.1; δ_H ($CDCl_3$; 250 MHz) 7.8–7.7 (4 H, m), 7.3–7.15 (6 H, m), 4.68 (1 H, d, J_{PH} 18), 3.01 (4 H, dq, J_{PH} 11, J_{HH} 7), 2.46 (6 H, d, J_{PH} 11) and 0.86 (6 H, t, J_{HH} 7) (Found: M^+, 346.1632; $C_{19}H_{27}N_2PS$ requires *M*, 346.1633).

From **5b** and Me_2NH, *product* **6b** (R = Me), non-crystalline (glass), *m*/*z* 363 (M^+, 0.3%) and 151 ($M^+ - ArPhCH$, 100); δ_P ($CDCl_3$) 84.3; δ_H ($CDCl_3$, 250 MHz) 8.15 (2 H, d, J_{HH} 8.5), 7.95 (2 H, d, J_{PH} 1.5, J_{HH} 8.5), 7.75–7.65 (2 H, m), 7.35–7.2 (3 H, m), 4.76 (1 H, d, J_{PH} 18), 2.45 (6 H, d, J_{PH} 11.5) and 2.44 (6 H, d, J_{PH} 11.5); ν_{max} (film)/cm^{-1} 1520 and 1350 (NO_2) (Found: M^+, 363.1170; $C_{17}H_{22}N_3O_2PS$ requires *M*, 363.1170).

From **5b** and Et_2NH, *product* **6b** (R = Et) (mixture of diastereoisomers), non-crystalline, *m*/*z* 391 (M^+, 0.5%) and 179 ($M^+ - ArPhCH$, 100); δ_P ($CDCl_3$) 81.5 (major) and 81.3; δ_H ($CDCl_3$, 250 MHz) 8.13 (2 H, d, J_{HH} 9), 8.0–7.9 (2 H, m), 7.8–7.7 (2 H, m), 7.35–7.2 (3 H, m), 4.815 (major) and 4.805 (total 1 H; both d, J_{PH} 18), 3.1–2.9 (4 H, m), 2.495 (major) and 2.475 (total 6 H; both d, J_{PH} 11), and 0.91 and 0.86 (major) (total 6 H; both t, J_{HH} 7); ν_{max} (film)/cm^{-1} 1520 and 1350 (NO_2) (Found: M^+, 391.1483. $C_{19}H_{26}N_3O_2PS$ requires *M*, 391.1483).

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