Stereochemical evidence for elimination–addition and a methylenethioxophosphorane (thiophosphene) intermediate in nucleophilic substitution at the P=S centre of a benzylic phosphonamidothioic chloride

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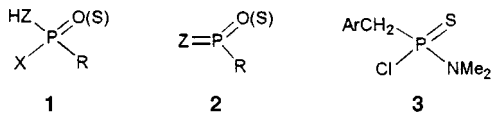
The two diastereoisomers of $ArCH_2P(S)(NMeR^*)Cl$ (Ar = 4-$NO_2C_6H_4$, R* = CHMePh) react with Et_2NH (0.2 mol dm^{-3}) in CH_2Cl_2 to give mixtures of the diastereoisomers of $ArCH_2P(S)(NMeR^*)NEt_2$ in practically the same ratio (54.5 : 45.5 or 53 : 47); such non-stereospecificity points to a thiophosphene intermediate ArCH=P(S)NMeR* as the product-forming species.

Nucleophilic substitution at a phosphoryl (P=O) or thiophosphoryl (P=S) centre generally proceeds by an associative $S_N2(P)$ mechanism with a five-coordinate intermediate or transition-state.[1] An alternative dissociative mechanism, involving elimination–addition (EA) and a transient three coordinate P^V intermediate **2**, is sometimes favoured when the substrate **1**

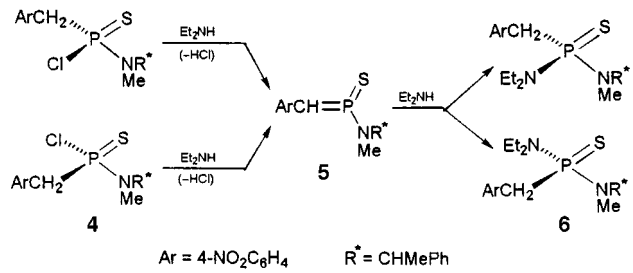


1 **2** **3**

(X = leaving group) has an acidic ligand HZ,[1,2] *i.e.* when Z is an oxygen,[3] sulfur[4] or nitrogen[5] atom. When Z is just a saturated carbon atom however, elimination–addition seems unable to compete with the normal $S_N2(P)$ reaction.[6] An exception may be the benzylic phosphonamidothioic chloride **3**, at least when it is substituted with a nitro group (Ar = 4-$NO_2C_6H_4$).[7] Then it displays remarkably high reactivity towards basic nucleophiles such as Et_2NH, perhaps because the C_α–H bonds are sufficiently acidic for reaction to proceed rapidly by an EA mechanism. To substantiate such a mechanism, and in particular the intermediacy of a three-coordinate methylenethioxophosphorane (thiophosphene) intermediate $[ArCH{=}P(S)NMe_2]$, there is a need of stereochemical information. Working with the individual enantiomers of **3** (Ar = 4-$NO_2C_6H_4$) would present problems, both preparative and analytical, so our attention turned to the related compound **4** (Ar = 4-$NO_2C_6H_4$) (Scheme 1). This is chiral at carbon as well as phosphorus so both substrate and substitution product will exist as diastereoisomers.

The phosphonamidothioic chloride **4** was prepared using 4-nitrobenzylphosphonothioic dichloride $[ArCH_2P(S)Cl_2]$[7] and (*S*)-(−)-PhMeCHNHMe. It is known that benzylic phosphonothioic dichlorides tend to go directly to the diamide when they react with secondary amines,[8] but by keeping the amine concentration low [addition over 5–6 h to a dilute CH_2Cl_2 solution of $ArCH_2P(S)Cl_2$], and having some of the amine hydrochloride (the byproduct of the reaction) present in solution from the outset, the amidic chloride **4** was the major product. Chromatography (silica gel; 15% EtOAc in light petroleum) followed by crystallisation of appropriate fractions afforded pure samples of the two diastereoisomers (**A** and **B**) of **4** [*m*/*z* 370, 368 (M^+, 6%): **A**, mp 108–109 °C, $\delta_P(CDCl_3)$ 90.00; $\delta_H(CDCl_3)$ 3.92 (2H, m, C*H*$_2$Ar), 2.575 (3H, d, J_{PH} 15, N*Me*) and 1.525 (3H, d, J_{HH} 7, CH*Me*Ph); **B**, mp 87–88 °C, $\delta_P(CDCl_3)$ 90.57; $\delta_H(CDCl_3)$ 3.91 (2H, m, C*H*$_2$Ar), 2.61 (3H, d, J_{PH} 15, N*Me*) and 1.30 (3H, d, J_{HH} 7, CH*Me*Ph)].†

The amidic chloride **4** reacted readily with Et_2NH as a dilute solution in CH_2Cl_2, giving the expected diamide product **6** as a mixture of diastereoisomers [$\delta_P(CDCl_3)$ 81.24 and 81.20; $\delta_H(CDCl_3)$ 2.475 and 2.435 (d, J_{PH} 10.5, N*Me*), 1.48 and 0.97 (d, J_{HH} 7, CH*Me*Ph) and 1.135 and 1.015 (t, J_{HH} 7, CH_2*Me*), *m*/*z* 405 (M^+, 15%)]. Whichever diastereoisomer of the substrate was used, the product **6** was obtained as practically the same 54 : 46 mixture having the low-field diastereoisomer (δ_P 81.24; δ_H 2.475, 1.48 and 1.135) in slight excess. As long as the diastereoisomers are configurationally stable under the conditions of reaction, it follows that substitution is non-stereospecific but slightly stereoselective. Such behaviour is not compatible with the normal $S_N2(P)$ mechanism of nucleophilic substitution,[9] but it is entirely reasonable for an EA mechanism in which both diastereoisomers of substrate form the thiophosphene intermediate **5** (Scheme 1). This is planar (trigonal) at phosphorus and can be attacked by Et_2NH at either face (non-stereospecificity), but the two faces are diastereotopic (chirality in NMeR*) so they will not necessarily be attacked with equal ease (diastereoselectivity).



Scheme 1

To assess the stability of the configuration at phosphorus the reactions of the two diastereoisomers of **4** were monitored by ^{31}P NMR spectroscopy, using a 0.2 mol dm^{-3} solution of Et_2NH (large excess) in CH_2Cl_2. In both cases the diastereoisomer composition of the product **6** (*ca.* 54 : 46) remained constant throughout the reaction ($t_{\frac{1}{2}}$ = 35–40 min at 19 °C) and the stereochemical integrity of the substrate was retained (≥95% one diastereoisomer at ≥90% completion).‡ It is therefore certain that non-stereospecificity is an integral part of the process of substitution.

In the course of the NMR experiments it became apparent that the products from the two diastereoisomers of the substrate were in fact not quite identical, the diastereoisomer ratios being 54.5 : 45.5 for **A** and 53 : 47 for **B**. The most obvious explanation is that elimination–addition is not completely dominant, so that a small proportion (1.5%) of the substrate is able to react stereospecifically by the normal $S_N2(P)$ mechanism. This, however, is difficult to reconcile with the behaviour observed using an amine less bulky than Et_2NH. As a base there is not much difference between Et_2NH and Me_2NH but as a nucleophile at a tetrahedral phosphorus centre there is;[10] with $PhP(S)(NMe_2)Cl$, for example, Me_2NH reacts at least a hundred times faster than Et_2NH.[7] If $S_N2(P)$ does compete with the EA

mechanism, it will surely do so much more effectively in the case of Me_2NH. In fact the reaction of **4** with Me_2NH is hardly more stereospecific at all. Using 0.2 mol dm^{-3} Me_2NH in CH_2Cl_2 the diamide product (**6** with Me_2N in place of Et_2N) [*m*/*z* 377 (M^+, 15%)] was formed ($t_{\frac{1}{2}}$ = *ca.* 15 min at 19 °C) with diastereoisomer ratios of 52.5 : 47.5 and 50.5 : 49.5 from **A** and **B** respectively, and again the low-field diastereoisomer [$\delta_P(CDCl_3)$ 85.04; $\delta_H(CDCl_3)$ 2.58 (d, J_{PH} 13, NMe_2), 2.46 (d, J_{PH} 10.5, NMe) and 1.45 (d, J_{HH} 7, CH*Me*Ph)] was formed in slight excess of the other (δ_P 84.97; δ_H 2.41, 2.41 and 0.88).‡ Here too, then, substitution is almost completely non-stereospecific. Any contribution from $S_N2(P)$ must be slight (2%) even with Me_2NH, and with Et_2NH it will surely be negligible. That being so, it seems likely that the reaction of **4** with Et_2NH proceeds entirely by an EA mechanism, with a thiophosphene intermediate, and that slight differences in the composition of the product from the two diastereoisomers are a consequence of the structure of the thiophosphene and/or the environment in which it is formed.§

Notes and references

† The substrate **4** and the products derived from it were fully characterised by NMR (^1H and ^{31}P) and IR spectroscopy, mass spectrometry (EI), and elemental analysis and/or accurate mass measurement.

‡ In CH_2Cl_2 the relative ^{31}P NMR chemical shifts of the two diastereoisomers of the diamide product are reversed (relative to $CDCl_3$) so the product formed in excess appeared at high field [$\delta_P(CH_2Cl_2)$ 80.96 and 81.02 with Et_2NH; 84.71 and 84.82 with Me_2NH].

§ The thiophosphene **5** has a (formal) C–P double bond so (in principle) it exists as *E* and *Z* isomers; these may be formed in differing proportions from the two diastereoisomers of the substrate and react with the nucleophile with differing stereoselectivities. Also, the thiophosphene may be so short-lived that some of it is trapped by the nucleophile before it is able to diffuse away from the chloride ion (or amine hydrochloride) released in the elimination step of the EA mechanism. In these ways the stereochemistry of the product could be influenced by the configuration of the substrate, notwithstanding the planarity at the phosphorus atom of the thiophosphene intermediate.

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