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Competing sulfonylation and phosphonylation following rearrangement of an *O*-sulfonyl-*N*-phosphinoylhydroxylamine with *tert*-butylamine: demonstration of a phosphonamidic-sulfonic anhydride intermediate and ^{18}O-labelling evidence on how it may be formed [1]

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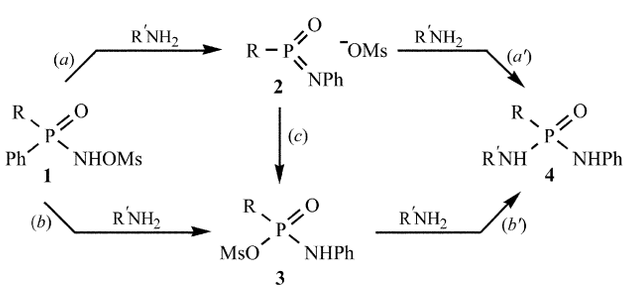
Received 16th May 2003, Accepted 5th August 2003
First published as an Advance Article on the web 28th August 2003

Reaction of R(Ph)P(O)NHOSO$_2$Bn (R = PhMeCH) with Bu^{t}NH$_2$ in CH$_2$Cl$_2$ gives a mixture of RP(O)(NHPh)-NHBu^t and Bu^{t}NHSO$_2$Bn, the proportion of the sulfonamide increasing steadily (14.6% to 32.9%) as the concentration of amine is reduced (8.0 to 0.2 mol dm^{-3}). Apparently the phenyl and sulfonate groups in the substrate become transposed, giving a phosphonamidic-sulfonic anhydride RP(O)(NHPh)OSO$_2$Bn which then reacts at the phosphorus or sulfur atom to give the final products; an authentic sample of the anhydride gives similar mixtures of products. Substrate labelled with ^{18}O in the sulfonyl position (57 mol% one ^{18}O atom) gives sulfonamide containing most but not all of the label (43.7 mol% one ^{18}O atom with 2.0 mol dm^{-3} amine). This implies partial equilibration of the three sulfonate oxygen atoms during rearrangement, or after the anhydride intermediate has been formed.

Introduction

N-Phosphinoylhydroxylamines [R$_2$P(O)NHOH] are the phosphorus analogues of hydroxamic acids and when suitably activated they undergo rearrangement on treatment with alkoxides or aliphatic amines.[2,3] Thus, for example, the *O*-methylsulfonate **1** (R = Ph) gives the phosphonic diamide **4** with R′NH$_2$, a phenyl group having migrated from phosphorus to nitrogen.[2] Benzyl groups will also migrate,[4] and even simple alkyl groups,[5] but they do so only reluctantly and the unsymmetrical substrate **1** (R = alkyl or benzyl) gives exclusively the product **4** of phenyl migration (Scheme 1).[3,6]



Scheme 1

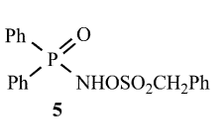
Rearrangement may proceed *via* a monomeric metaphosphonimidate **2**, analogous to the isocyanate formed in a Lossen rearrangement,[7] and some features of the reactions do accord well with a reactive three coordinate P^V intermediate.[8] Other aspects, however, are difficult to reconcile with such an intermediate, at least as the sole product-forming species.[8–10] One possible alternative or competing pathway involves attack of the nucleophile (R′NH$_2$) prior to migration of the phenyl group, forming a five coordinate phosphorane. However, the modest sensitivity to steric effects in both the substrate (R = Me, Et, Pr^i) and the nucleophile (R′ = Me, Pr^i, Bu^t) argues against such an associative mechanism.[8] Another possibility is that the phenyl and sulfonate groups in the substrate become transposed, resulting in a phosphonamidic-sulfonic mixed anhydride **3** (Scheme 1). Nucleophilic attack at the phosphorus atom of the mixed anhydride would then give the phosphonic diamide **4**, but attack at the sulfur atom would give a sulfonic amide (R′NHMs) instead. In practise products corresponding to attack at sulfur have not been observed. That may be of little significance, however, since it seems that P^V-sulfonic mixed anhydrides often react exclusively at the phosphorus atom.[11,12] The observation of products corresponding to nucleophilic attack at sulfur would obviously afford important support for a phosphonamidic-sulfonic anhydride. Also, it would open the way to an exploration of how the anhydride is formed, using substrate labelled with ^{18}O in one of the sulfonate positions.

As regards the possibility of attack at sulfur, alkylsulfonyl compounds (RCH$_2$SO$_2$X; X = leaving group) can react with nucleophiles both by direct (associative) displacement of the leaving group and by a dissociative elimination–addition (EA) mechanism with a sulfene intermediate (RCH=SO$_2$).[13] Increased acidity of the C$_\alpha$–H bond (*e.g.* RCH$_2$SO$_2$X; R = Ph) should accelerate the EA pathway, and in doing so might make reaction at the sulfur atom of a phosphonamidic-sulfonic anhydride more competitive with reaction at phosphorus.

Results and discussion

Evidence for a phosphonamidic-sulfonic anhydride intermediate

The benzylsulfonyl derivative **5** [δ_P 30.0; δ_H 4.56 (2H, s)] was prepared from Ph$_2$P(O)NHOH using benzylsulfonyl chloride. On treatment with Bu^{t}NH$_2$ (2 mol dm^{-3}) it gave overwhelmingly the normal phosphonic diamide rearrangement product **4** (R = Ph, R′ = Bu^t). A trace of the sulfonic amide Bu^{t}NHSO$_2$-CH$_2$Ph was detected by comparison (^{1}H NMR, GLC, MS) with an authentic sample,[14] but as it amounted to ≤1% of the total product it is of little mechanistic significance.



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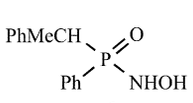

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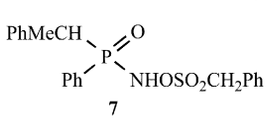

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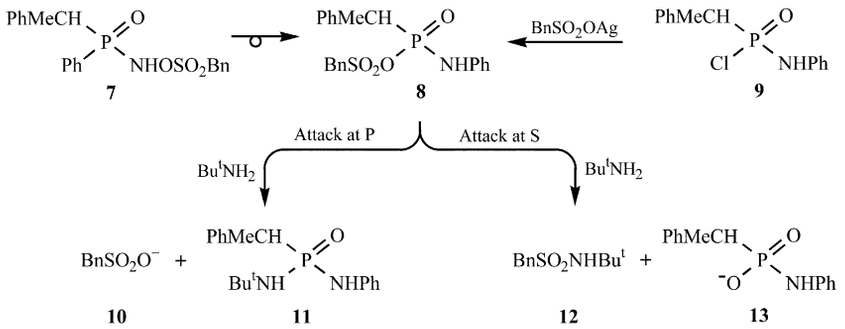
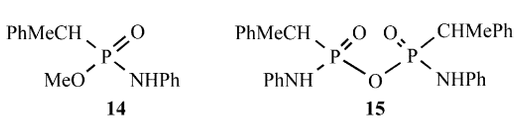


Scheme 2

To further encourage attack at sulfur we considered replacing one of the *P*-phenyl groups in the substrate by a bulky alkyl or benzyl group. Such groups have much lower migratory aptitudes than phenyl,[3,6] so any phosphonamidic-sulfonic anhydride that is formed in the rearrangement will retain the bulky group on the phosphorus atom. Steric factors may then retard attack of the nucleophile at phosphorus and give attack at sulfur more chance to compete. The *N*-phosphinoylhydroxylamine **6** has an α-methylbenzyl group on the phosphorus atom. This is bulky but it is also chiral, so **6** exists as diastereoisomers and was previously prepared for stereochemical studies.[9] A mixture of the diastereoisomers of **6** (δ_P 41.9 and 40.1; ratio ~3 : 1) was now treated briefly with $PhCH_2SO_2Cl$ in ice-cold pyridine to give the benzylsulfonyl derivative **7** (75%) as a mixture of diastereoisomers, $\delta_P(CDCl_3)$ 42.6 and 41.0 (ratio 3.3 : 1 after crystallisation). The two benzylic protons in each of the diastereoisomers of **7** are themselves diastereotopic, and they appear in the ^{1}H NMR spectrum as an AB quartet centred at δ_H 4.60 (major diastereoisomer) or 4.19.

With $MeNH_2$ (2 mol dm^{-3}) in CH_2Cl_2 the only substantial phosphorus-containing product obtained from the benzylsulfonate **7** was the expected phosphonic diamide **4** (R = PhMeCH, R′ = Me) (diastereoisomers, δ_P 27.7 and 27.1), corresponding to migration of the phenyl group. However, the ^{1}H NMR spectrum of the reaction mixture suggested a small but significant amount of the sulfonamide $MeNHSO_2CH_2Ph$ [δ_H 4.26 (s) and 2.70 (d, J_{HH} 5, NH*Me*); *ca.* 5%], and this was confirmed by GLC (by comparison with an authentic sample[15]) and MS (M^+ 185) after isolation by TLC.

With Bu^tNH_2 (2 mol dm^{-3}) the corresponding phosphonic diamide **11** (diastereoisomers, δ_P 22.7 and 22.4) was again the dominant product (see Scheme 2) but now the ^{31}P NMR spectrum of the reaction mixture also contained a minor peak at δ_P 19.0 (8%), corresponding to the phosphonamidate anion **13** (isolated and characterised as the methyl phosphonamidate **14**) and several small peaks δ_P 26–23 (10% of total phosphorus), apparently due to the phosphonamidic anhydride **15** (several diastereoisomers). The anion **13** is the expected byproduct of nucleophilic attack at the sulfur atom of the phosphonamidic-sulfonic mixed anhydride **8**, while the phosphonamidic anhydride **15** would result from subsequent attack of the anion **13** at the phosphorus atom of **8**. More conclusive evidence for involvement of the phosphonamidic-sulfonic anhydride was the formation of the sulfonamide **12** [δ_H 4.23 (s) and 1.34 (s, $NHBu^t$)] in *ca.* 17% yield; it was isolated chromatographically and fully characterised.



Extent of involvement of the phosphonamidic-sulfonic anhydride

The foregoing observations clearly implicate a phosphonamidic-sulfonic anhydride in the rearrangement but they do not reveal the extent of its involvement: the phosphonic diamide (but not the sulfonamide) can also be formed directly from the metaphosphonimidate **2** (Scheme 1, step *a′*) without involvement of the anhydride **3**, and this could well be the major pathway. At lower concentrations of amine a smaller proportion of the metaphosphonimidate might be expected to go directly to the phosphonic diamide; more would form the phosphonamidic-sulfonic anhydride (Scheme 1, step *c*) and thence, to some extent, the sulfonamide instead of the phosphonic diamide, so that the proportion of the sulfonamide in the product would be increased. As a test of this the reaction of the benzylsulfonate **7** with Bu^tNH_2 was repeated using a wide range of amine concentrations (in CH_2Cl_2) and the relative yields of sulfonamide **12** and phosphonic diamide **11** were determined by GLC. The results (Table 1) show that the proportion of the sulfonamide (mol%) in the amide product (**11** + **12**) does indeed increase steadily on dilution, from 14% in neat Bu^tNH_2 to 32.9% with 0.2 mol dm^{-3} amine.

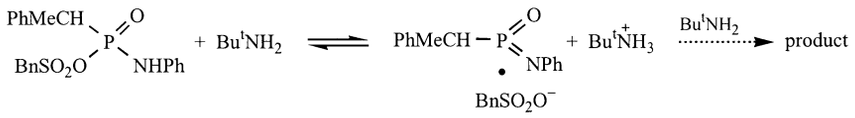
Table 1 Proportion (mol% by GLC[a]) of sulfonamide **12** in the amide product (**11** + **12**) obtained from **7** or **8** with Bu^tNH_2 in CH_2Cl_2[b]

	Sulfonamide **12** (mol%)	
$[Bu^tNH_2]$/mol dm^{-3}	Reactant **7**	Reactant **8**
0.2	32.9	34.7
0.4	27.0	27.0
0.8	22.0	24.9
1.4	19.0	20.9
2.0	17.3	19.3
4.0	14.7	15.3
8.0	14.6	16.0

[a] GLC peak areas corrected for different responses of detector for products **11** and **12**. [b] For **7** with neat Bu^tNH_2, 14.0 mol% **12** was produced.

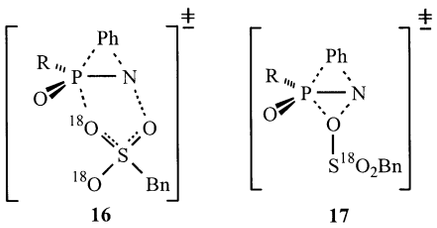
The symmetrical phosphonamidic anhydride **15** was a byproduct in these reactions (^{31}P NMR), especially at low amine concentrations. That is an inevitable consequence of nucleophilic attack at the sulfur atom of the phosphonamidic-sulfonic mixed anhydride **8**, since the displaced phosphonamidate anion **13** (the leaving group) is itself an effective nucleophile and will attack the mixed anhydride (at the P atom) in competition with the amine. The absolute yields of the amide products **11** and **12** will be reduced but, because the symmetrical anhydride does not react with Bu^tNH_2 under the conditions employed, their relative yields will not be affected.

To extract full mechanistic value from these results we would need precise knowledge of the behaviour of the phosphonamidic-sulfonic anhydride **8** with Bu^tNH_2, *i.e.* reaction at phosphorus *vs.* reaction at sulfur. Fortunately we were able to obtain an authentic sample of **8** (diastereoisomers, δ_P 29.15 and 28.7), contaminated with only a little of the symmetrical anhydride **15**, by heating the phosphonamidic chloride **9** with silver benzylsulfonate in MeCN (Scheme 2).[16]



Scheme 3

As expected, this anhydride gave a mixture of the phosphonic diamide **11** and the sulfonamide **12** when treated with Bu^tNH_2 (2.0 mol dm^{-3}) in CH_2Cl_2. Surprisingly, however, the proportion of the sulfonamide (19.3 mol%) was only slightly greater than for the rearrangement of **7** under the same conditions (17.3%). Still more surprising was the effect of varying the amine concentration. Not only did the relative yield of the sulfonamide change, showing that the behaviour of the anhydride **8** is not constant, but the changes paralleled closely those seen in the rearrangement (Table 1). Indeed, given that the diastereoisomer composition of any phosphonamidic-sulfonic anhydride formed by rearrangement is unlikely to be the same as that of the authentic sample, and that the diastereoisomers may differ somewhat in their behaviour with Bu^tNH_2, the discrepancies between the two sets of results (Table 1) can probably be discounted. Certainly there is not the anticipated divergence between the two sets of results at high amine concentrations. The implication is clear and mechanistically very important: most of the rearrangement of **7**, and possibly all of it, proceeds *via* the phosphonamidic-sulfonic anhydride *even at the highest concentrations of amine*. Little if any of the rearrangement product is formed directly from the metaphosphonimidate. It is not difficult to reconcile this with path *a* in Scheme 1 when the amine concentration is low: the metaphosphonimidate **2** might reasonably be formed without any amine in its solvation shell, and recombine with the sulfonate anion (step *c*) before it can diffuse away and react with the amine. But at the highest amine concentrations, and especially in neat Bu^tNH_2, the metaphosphonimidate will be formed in contact with amine molecules. One of these will surely be as well placed as the sulfonate anion to form a bond to phosphorus, yet apparently it does not do so. Unless the metaphosphonimidate has a marked preference for combination with the sulfonate anion, path *a* becomes untenable. The alternative is a concerted rearrangement of the conjugate base of the substrate (Scheme 1, path *b*). Then the sulfonate group would migrate to phosphorus at the same time as the phenyl group migrates to nitrogen, *via* a transition state such as **16** or **17**, and there would be no opportunity for products to be formed without the intervention of the phosphonamidic-sulfonic anhydride. Experiments with ^{18}O-labelled substrate would, we hoped, confirm the identity of the sulfonylating agent and also shed light on the mechanism of the rearrangement.



16 **17**

Mechanism of rearrangement to the phosphonamidic-sulfonic anhydride

Isotopically labelled $PhCH_2SO_2Cl$ was prepared from the unlabelled compound by hydrolysis with $H_2{}^{18}O$–pyridine followed by treatment of the hydrolysis product with oxalyl chloride. Reaction of labelled $PhCH_2SO_2Cl$ with the *N*-phosphinoylhydroxylamine **6** afforded the sulfonyl derivative **7** (5 : 1 mixture of diastereoisomers) having *ca.* 57% of the molecules enriched with one ^{18}O atom in the SO_2 group (FAB mass spectrometry; negligible double-labelled material).

Table 2 ^{18}O Content (mol%) of products from rearrangement of ^{18}O-sulfonyl-*N*-phosphinoylhydroxylamine **8** with Bu^tNH_2

	$[Bu^tNH_2]$/mol dm^{-3}		
	8.0	2.0	0.4
Sulfonate anion **10**	57.6	57.6	57.7
Phosphonic diamide **11**	0.0	0.0	0.0
Sulfonamide **12**	49.1	43.7	41.4
Phosphonamidate anion **13**	8.4	13.7	(16.3)[a]

[a] Not measured directly; value shown is ^{18}O content of (**12** + **13**) unaccounted for by **12** [^{18}O in (**12** + **13**) = ^{18}O in (**10** + **11**)].

The rearrangement of ^{18}O-labelled **7** was examined using 2.0 mol dm^{-3} Bu^tNH_2 in CH_2Cl_2. The phosphonic diamide **11** (mixture of diastereoisomers) and the sulfonamide **12** (*ca.* 17%) were isolated directly by TLC but the (water-soluble) salts **10** and **13** were first converted into the methyl esters by treatment with diazomethane. The amount of ^{18}O in each of the products was determined by mass spectrometry (EI generally but CI for **12**). † For the products resulting from nucleophilic attack at the P atom of the phosphonamidic-sulfonic anhydride **8** the results were as expected: all of the label was located in the sulfonate anion **10** (methyl ester: 57.6% one ^{18}O atom) and none in the phosphonic diamide **11**. Of more concern are the products that result from attack at the sulfur atom, since it is these that will reflect the distribution of the ^{18}O label between the bridging and non-bridging sulfonate positions in the anhydride **8**. The sulfonamide **12** was found to contain 76% of the available label (43.7% one ^{18}O atom) and the phosphonamidate anion **13** 24% (methyl ester **14**: 13.7% one ^{18}O atom). This implies a 24 : 76 distribution of label between the bridging and non-bridging positions of the phosphonamidic-sulfonic anhydride **8**.

If the anhydride **8** was formed by concerted rearrangement of the conjugate base of the substrate (*i.e.* **7** less the NH proton) the expected distribution of the label would be 50 : 50 for a transition state such as **16** or 0 : 100 for a transition state such as **17**. The measured distribution (24 : 76) is equally far removed from either. The experimentally observed value does, however, relate to the anhydride as it is when it forms the product (**10** + **11** or **12** + **13**), and some scrambling of the label might occur after the anhydride has been formed but before it is converted into product. Like a phosphonamidic chloride,[17] the phosphonamidic-sulfonic anhydride will tend to react at phosphorus by a stepwise preassociative elimination–addition mechanism.[18] The reverse of the base-induced elimination shown in Scheme 3 is therefore likely to be important, especially at lower amine (nucleophile) concentrations, so there could well be some equilibration of bridge and non-bridge labelled anhydrides. At higher concentrations of amine there is a greater probability that the nucleophile will already be in place (preassociation) when the elimination occurs, ready to take the metaphosphonimidate on to product; return to the anhydride should be less important and scrambling of the ^{18}O label less extensive. As a test of this the rearrangement of the labelled substrate **7** was

† In all mass spectrometric measurements of ^{18}O enrichment, allowance was made for ^{34}S and natural abundance ^{18}O by comparing directly the spectrum of the enriched material with that of a sample of natural abundance.

repeated using other amine concentrations (Table 2). The distribution of the label (bridge *vs*. non-bridge) in the anhydride, as inferred from examination of the reaction products, was 15 : 85 when the Bu^tNH_2 concentration was increased to 8.0 mol dm^{-3} and 28 : 72 when it was reduced to 0.4 mol dm^{-3}.

Scrambling will, of course, tend to even out the distribution of the label, but not beyond the statistical value of 33 : 67. If the rearrangement is concerted, the transition state cannot be as in **16**: an initial 50 : 50 distribution of label could never give rise to an experimental (average) value of 24 : 76. The transition state could conceivably be like **17**, although there would have to be extensive scrambling in the anhydride, even with 2.0 mol dm^{-3} amine, for the initial 0 : 100 distribution of label to result in the observed 24 : 76 (average) value.

Superficially the results of the labelling experiments might seem to rule out entirely a non-concerted route to the phosphonamidic-sulfonic anhydride (Scheme 1, step *a* + step *c*). The sulfonate group would in that case become completely detached from the nitrogen atom before it begins to bond to phosphorus, and the ^{18}O label must, in the limit, end up evenly distributed between the bridging position of the anhydride and the two non-bridging positions (ratio 33 : 67). Initially, however, the sulfonate oxygen atom (unlabelled) released from the N–O bond will not be equivalent to the other two because of differences in association (with $Bu^tNH_3^+$) or solvation (by Bu^tNH_2 or CH_2Cl_2). If the new bond to phosphorus is formed before equilibration of the oxygen atoms is complete, and makes preferential use of this (unlabelled) oxygen atom, the anhydride will be formed with less than a third of the available ^{18}O label located in the bridging position. The observed result, 24% of the available ^{18}O in the bridge, could then be rationalised by a fairly modest bias for incorporation of the unlabelled sulfonate oxygen in the new P–O bond, or a strong bias with some subsequent scrambling. With regard to the latter possibility, an exceptionally high reactivity for one of the oxygen atoms of the sulfonate anion might also resolve the dilemma noted earlier, *viz*. the failure of Bu^tNH_2, even at the highest concentration, to suppress anhydride formation (Scheme 1, step *c*) by intercepting the metaphosphonimidate and taking it directly to the phosphonic diamide product (step *a′*). There are several examples of racemisation and isomerisation in which a carboxylate[19] or sulfonate[20] anion is released and recaptured with only partial equilibration of the oxygen atoms, and at least one example of a more profound rearrangement (migration from N to C) in which the sulfonate oxygen atom released by bond-breaking is preferentially employed in subsequent bond making.[21] In all of these, however, the anion recombines with a cation, not an uncharged species like a metaphosphonimidate. Nonetheless, it does seem quite possible that rearrangement to the phosphonamidic-sulfonic anhydride is non-concerted, notwithstanding the incomplete equilibration of the sulfonate oxygen atoms.

Conclusion

The sulfonamide **12** is a substantial product in the reaction of the *O*-benzylsulfonyl derivative of the *N*-phosphinoylhydroxylamine **6** with Bu^tNH_2. It is formed at the expense of the normal phosphonic diamide rearrangement product **11**, but not by direct transfer of the sulfonyl group; substrate **7** specifically labelled with ^{18}O in the sulfonyl (SO_2) group produces sulfonamide containing considerably less isotope. Rather, transposition of the phenyl and sulfonate groups in **7** gives the phosphonamidic-sulfonic mixed anhydride **8** and it is this that sulfonylates the amine. Whether the anhydride is formed concertedly after deprotonation (N*H*) of the substrate, or non-concertedly *via* a metaphosphonimidate (Scheme 1, step *a* + step *c*), is not clear; if it is concerted, however, the ^{18}O-labelling experiments show that the transition state must resemble **17** rather than **16**.

The yield of sulfonamide relative to phosphonic diamide declines as the concentration of the amine is increased, but *not* because less anhydride is formed: it is the balance between the competing reactions at the sulfur and phosphorus atoms of the anhydride that changes, and over a wide range of amine concentrations the product mixtures obtained from the hydroxylamine derivative **7** parallel closely those obtained from an authentic sample of the anhydride **8**.‡ Regardless of the concentration of amine, most and possibly all of the rearrangement of **7** must, it seems, proceed *via* the anhydride **8**. The same is likely to be true for all *O*-sulfonyl-*N*-phosphinoylhydroxylamines, but it is only in exceptional cases that attack at sulfur competes substantially with attack at phosphorus and makes manifest the involvement of the phosphonamidic-sulfonic anhydride.

Experimental

Mps were determined using a Kofler hot-stage apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker ARX 250 spectrometer (Me_4Si internal standard; coupling constants *J* given in Hz) and ^{31}P NMR spectra (^1H decoupled) were recorded on the same instrument at 101.3 MHz (positive chemical shifts downfield from 85% H_3PO_4). Mass spectra were recorded on a Kratos Concept spectrometer in EI (70 eV), CI (NH_3) or FAB (*m*-nitrobenzyl alcohol matrix) mode, or a Perkin Elmer TurboMass GC-MS instrument (in EI mode). IR spectra were recorded as Nujol mulls on a Perkin Elmer 298 spectrometer. GLC analyses were performed using a Philips PU 4500 chromatograph (flame-ionisation detector) fitted with an OV 1701 wide bore capillary column (1 μm film; 15 m × 0.53 mm) using helium as carrier gas (19 ml min^{-1}); peak areas were measured with a Spectra-Physics SP4270 integrator. Amines were dried over and distilled from KOH, and CH_2Cl_2 was distilled from CaH_2. Light petroleum refers to the fraction bp 60–80 °C and ether to diethyl ether.

O-Benzylsulfonyl-*N*-(diphenylphosphinoyl)hydroxylamine 5

While cooling constantly in ice, pyridine (0.4 ml) was added to *N*-(diphenylphosphinoyl) hydroxylamine[2] (117 mg, 0.5 mmol), followed immediately by $PhCH_2SO_2Cl$ (114 mg, 0.6 mmol). The mixture was shaken for 8 min. Much of the pyridine was evaporated *in vacuo* (no heating) and iced water was added, giving an oil that soon solidified. Thorough washing of the solid with MeOH–H_2O (2 : 1) and drying at 35 °C at 0.1 mmHg afforded the *sulfonate* **5** (161 mg, 83%); $\delta_P(CDCl_3)$ 30.0; $\delta_H(CDCl_3)$ 8.29 (1H, d, J_{PH} 7.5, NH), 8.0–7.3 (15H, Ph) and 4.56 (2H, s, SO_2CH_2Ph); *m*/*z* (FAB) 388 [$(M + H)^+$, 100] and 201 (30). A sample crystallised from MeOH had mp 132–133 °C (decomp.) (Found: C, 58.9; H, 4.7; N, 3.4. $C_{19}H_{18}NO_4PS$ requires C, 58.9; H, 4.7; N, 3.6%).

O-Benzylsulfonyl-*N*-[phenyl(1-phenylethyl)phosphinoyl]-hydroxylamine 7

The *N*-phosphinoylhydroxylamine **6**[9] (mixture of diastereoisomers) (104 mg, 0.4 mmol) was sulfonylated as above to give, after crystallisation from CH_2Cl_2–ether and drying (35 °C, 0.1 mmHg), the *sulfonate* **7** (124 mg, 75%), mp 75–78 °C; $\delta_P(CDCl_3)$ 42.6 and 41.0 (ratio 3.3 : 1; diastereoisomers); $\delta_H(CDCl_3)$ major diastereoisomer: 8.30 (1H, d, J_{PH} 7, NH), 8.0–7.1 (Ph groups), 4.60 (2H, AB; δ_A 4.66, δ_B 4.54, J_{AB} 14; $PhCH_2SO_2$), 3.74 (1H, dq, J_{PH} 14.5, J_{HH} 7.5, PhMeC*H*) and 1.74 (3H, dd, J_{PH} 16.5, J_{HH} 7.5, Ph*Me*CH); minor diastereoisomer: 7.72 (1H, d, J_{PH}

‡ For substitution by a preassociative stepwise elimination–addition mechanism the amine will be involved in the rate-limiting elimination stage as both base and nucleophile; the order in amine will therefore be greater than for a simple (no preassociation) stepwise elimination–addition mechanism. If attack at sulfur is less dependent on preassociation than attack at phosphorus it will benefit less from any increase in the concentration of amine.

4.5, NH), 8.0–7.1 (Ph groups), 4.19 (2H, AB; δ_A 4.27, δ_B 4.12, J_{AB} 14), 3.64 (1H, dq, J_{PH} 12, J_{HH} 7.5, PhMeC*H*) and 1.54 (3H, dd, J_{PH} 17.5, J_{HH} 7.5, Ph*Me*CH); *m/z* (FAB) 416 [$(M + H)^+$, 100%] (Found: C, 60.8; H, 5.6; N, 3.2. $C_{21}H_{22}NO_4PS$ requires C, 60.7; H, 5.5; N, 3.4%).

O-Benzyl[^{18}O]sulfonyl-*N*-[phenyl(1-phenylethyl)phosphinoyl]-hydroxylamine

(a) A solution of $H_2{}^{18}O$ (22 mg, 1.1 mmol) in pyridine (200 µl) was stirred and cooled in ice while $PhCH_2SO_2Cl$ (191 mg, 1.0 mmol) was added. After 10 min the mixture was moved to a 60 °C bath and heated for 15–20 min. The pyridinium sulfonate was converted into the *tert*-butylammonium sulfonate by adding CH_2Cl_2 (2.5 ml) and, in portions, Bu^tNH_2 (146 mg, 2.0 mmol), evaporating the volatile material *in vacuo*, and treating the residue with CH_2Cl_2 and Bu^tNH_2 again. Trituration with ether gave the solid *tert*-butylammonium salt. This salt was suspended in CH_2Cl_2 (2.5 ml) and stirred with oxalyl chloride (254 mg, 2.0 mmol) and a catalytic quantity of DMF (2 µl). After 0.5 h the volume was reduced and ether was added. The precipitate (Bu^tNH_3Cl) was removed and the filtrate was concentrated. The residue was extracted with a little warm ether and the extract was diluted with light petroleum to give crystals of *benzyl[^{18}O]sulfonyl chloride* (145 mg, 75%), mp 90–91 °C; $\delta_H(CDCl_3)$ 7.47 (5H, s) and 4.87 (2H, s); *m/z* (EI) 190, 192, 194 (M^+, 5%; ratio 1.9 : 2.9 : 1) and 91 (100).

(b) The *N*-phosphinoylhydroxylamine **6** was treated with benzyl[^{18}O]sulfonyl chloride using the method previously employed for the unlabelled material (see above). The resulting *^{18}O-labelled sulfonate* **7**, $\delta_P(CDCl_3)$ 42.6 and 41.0 (ratio 5.0 : 1; diastereoisomers), *m/z* (FAB) 416 and 418 [$(M + H)^+$], had 57% of the molecules singly labelled and <1% doubly labelled.

Phosphonamidic-sulfonic anhydride 8

(a) Benzylsulfonyl chloride (300 mg) was hydrolysed by heating in H_2O–EtOH (1 : 9) (2 ml) at 80 °C for 2 h. Volatile material was evaporated and the residue was extracted with water (1 ml). The aqueous extract was washed with CH_2Cl_2 (2 × 0.3 ml) and was then kept *in vacuo* until solid benzylsulfonic acid was obtained. The sulfonic acid (*ca*. 1.6 mmol) was added to a stirred suspension of Ag_2O (232 mg, 1.0 mmol) in MeCN (3 ml). After 10 min the mixture was filtered through Celite, the filtrate was concentrated, and the residual solid was washed repeatedly with CH_2Cl_2 to give silver benzylsulfonate which was dried *in vacuo* over P_2O_5.

(b) With careful exclusion of moisture MeCN (0.35 ml) was added to $PhCH_2SO_3Ag$ (70 mg, 0.25 mmol) and *N*-phenyl-*P*-(1-phenylethyl)phosphonamidic chloride **9** (mixture of diastereoisomers)[9] (56 mg, 0.20 mmol) in a septum-capped tube. The mixture was maintained at 50–55 °C overnight (16 h) giving the *phosphonamidic-sulfonic anhydride* **8** contaminated with some of the symmetrical phosphonamidic anhydride **15** [10% of total phosphorus (^{31}P NMR); 5 mol%]. The MeCN was evaporated *in vacuo via* a needle inserted through the septum and then CH_2Cl_2 (0.5 ml) was added. The mixture was shaken and was left to stand until the silver salts had settled. Portions of the solution of **8** were removed by syringe and used immediately; $\delta_H(CDCl_3)$ (mixture of diastereoisomers) 7.5–6.9 (Ph groups), 5.87 and 5.40 (both d, J_{PH} 8, NH), 4.67 (s) and 4.34 (AB quartet; δ_A 4.45, δ_B 4.23, J_{AB} 14.5) (SO_2CH_2Ph), 3.585 and 3.525 (both dq, J_{PH} 21, J_{HH} 7.5, PhMeC*H*), 1.64 and 1.595 (both dd, J_{PH} 20, J_{HH} 7.5, Ph*Me*CH); $\delta_P(CDCl_3)$ 29.15 and 28.7 (ratio *ca*. 1 : 1; diastereoisomers) [impurity **15**, 26.1–25.4 (several diastereoisomers)].

Authentic samples used for analysis of products of rearrangement reactions

The following were prepared from benzylsulfonyl chloride and the appropriate amine or MeOH–Et_3N.

$PhCH_2SO_2NHMe$, crystallised from $CHCl_3$–light petroleum, mp 110 °C (lit.,[15] 109–110 °C); $\delta_H(CDCl_3)$ 7.40 (5H, s), 4.26 (2H, s), 4.04 (br s, NH) and 2.71 (3H, d, J_{HH} 5, NH*Me*); *m/z* (EI) 185 (M^+, 3%) and 91 (100).

$PhCH_2SO_2NHBu^t$, crystallised from CH_2Cl_2–light petroleum, mp 107–108 °C (lit.,[14] 107.5–109.5 °C); $\delta_H(CDCl_3)$ 7.35 (5H, s), 4.22 (2H, s), 4.11 (s, NH) and 1.35 (9H, s); *m/z* (EI) 227 (M^+, ≤1%); *m/z* (CI) 245 [$(M + NH_4)^+$, 35%], 228 [$(M + H)^+$, 10], 148 (55) and 91 (100).

$PhCH_2SO_2OMe$, crystallised from ether–light petroleum, mp 59–61 °C (lit.,[22] 60–62 °C); $\delta_H(CDCl_3)$ 7.41 (5H, s), 4.36 (2H, s) and 3.75 (3H, s); *m/z* (EI) 186 (M^+, 15%) and 91 (100).

Samples of the following compounds were available from previous work.

The phosphonic diamide **4** (R = Ph, R′ = Bu^t),[2] $\delta_P(CH_2Cl_2)$ 12.1.

The phosphonic diamide **4** (R = PhMeCH, R′ = Me),[9] $\delta_P(CH_2Cl_2)$ 26.2 and 25.7 (diastereoisomers); *m/z* (EI) 274 (M^+, 40%) and 169 (M^+ − CHMePh, 100).

The phosphonic diamide **11**,[9] $\delta_P(CDCl_3)$ 22.5 and 22.75 (diastereoisomers); *m/z* (EI) 316 (M^+, 25%), 211 (M^+ − CHMePh, 45) and 155 (M^+ − CHMePh − C_4H_8, 100).

The methyl phosphonamidate **14**,[10] $\delta_P(CDCl_3)$ 31.0 and 30.8 (diastereoisomers); *m/z* (EI) 275 (M^+, 100%).

The phosphonamidic anhydride **15**,[10] $\delta_P(CDCl_3)$ 25.65–24.23 (several diastereoisomers; 5 principal peaks); *m/z* (EI) 504 (M^+, 20%) and 105 ($PhMeCH^+$, 100).

Rearrangement reactions of *O*-benzylsulfonyl-*N*-phosphinoyl-hydroxylamines

(a) The substrate **5** (0.05 mmol) was added to a 2.0 mol dm^{-3} solution of Bu^tNH_2 in CH_2Cl_2. After 20 min at 25–30 °C the volatile material was evaporated. The ^{31}P NMR spectrum of the crude product consisted of a single peak, $\delta_P(CDCl_3)$ 12.7, and the ^{1}H NMR spectrum ($CDCl_3$) indicated that the yield of $PhCH_2SO_2NHBu^t$ (δ_H 4.22 for the authentic sample) was only 0.5% relative to $PhCH_2SO_3^-$ (δ_H 4.03). The NMR solution was diluted, washed with water and examined by GLC, which indicated a trace amount of $PhCH_2SO_2NHBu^t$ (t_R 1.0 min at 210 °C) in addition to the dominant product (t_R 7.2 min). Crystallisation from ether–light petroleum afforded the phosphonic diamide **4** (R = Ph, R′ = Bu^t), mp 176–178 °C (lit.,[2] 176–178 °C), IR and ^{1}H NMR spectra as previously described,[2] and the mother liquor afforded (TLC) a trace of $PhCH_2SO_2NHBu^t$; *m/z* (CI) 245 [$(M + NH_4)^+$, 60%] and 228 [$(M + H)^+$, 20].

(b) The substrate **7** (mixture of diastereoisomers) (0.02 mmol) was added to a 2.0 mol dm^{-3} solution of $MeNH_2$ in CH_2Cl_2 (0.3 ml). After 20 min the mixture was concentrated, diluted with CH_2Cl_2, and washed with a very small volume of water; the phosphonic diamide **4** (R = PhMeCH, R′ = Me) was isolated as a mixture of diastereoisomers; $\delta_P(CDCl_3)$ 27.6 and 26.85 (ratio 3 : 2). The ^{1}H NMR spectrum was as previously reported[9] with small additional peaks attributable to $PhCH_2SO_2NHMe$ (5%); $\delta_H(CDCl_3)$ 4.26 (s, $PhCH_2$) and 2.70 (d, J_{HH} 5, NH*Me*). The presence of the sulfonamide was confirmed by GLC, t_R 8.4 min at 150 °C. TLC (silica, ether) afforded separate samples of the phosphonic diamide, R_f 0.1, *m/z* (EI) 274 (M^+, 50%) and 169 (M^+ − CHMePh, 100), and the sulfonamide, R_f 0.4, *m/z* (CI) 203 [$(M + NH_4)^+$, 100%] and 186 [$(M + H)^+$, 10].

(c) The substrate **7** (3.3 : 1 diastereoisomer mixture) (0.24 mmol) was added to a 2.0 mol dm^{-3} solution of Bu^tNH_2 in CH_2Cl_2 (4.8 ml). After 30 min at *ca*. 30 °C the volatile material was evaporated and the crude product was examined spectroscopically; $\delta_P(CDCl_3)$ 22.8 and 22.7 (80%, ratio 2 : 1; diastereoisomers of **11**) and 18.95 (8%; anion **13**) (also several peaks 25.9–23.3); $\delta_H(CDCl_3)$ included 4.23 ($PhCH_2SO_2NHBu^t$) and 4.07 ($PhCH_2SO_3^-$) in a 1 : 5 ratio. The crude product was partitioned between CH_2Cl_2 and water. Preparative TLC (silica, ether) of the organic portion gave the phosphonic diamide **11**

(mixture of diastereoisomers), R_f 0.2, crystallised from light petroleum, mp 121–123 °C (lit.,[9] 120–124 °C); $\delta_P(CDCl_3)$ 22.65 and 22.4 (ratio 3 : 2); *m/z* (EI) 316 (M^+, 60%); IR and ^1H NMR spectra as previously reported.[9] The sulfonamide **12** was also obtained, R_f 0.6, crystallised from light petroleum, mp 107–108 °C (lit.,[14] 107.5–109.5 °C); *m/z* (CI) 245 [$(M + NH_4)^+$, 100%] and 228 [$(M + H)^+$, 30]; $\delta_H(CDCl_3)$ 7.35 (5H, s), 4.24 (2H, s), 3.93 (s, NH) and 1.36 (9H, s).

The aqueous portion was freeze dried, methylated (CH_2N_2), and washed with water. GLC (*T* 160 °C for 1 min then 8 °C min^{-1} to 240 °C) indicated a mixture of $PhCH_2SO_2OMe$ (t_R 2.1 min) (major) and PhMeCHP(O)(NHPh)OMe (t_R 8.4 and 9.0 min; diastereoisomers) by comparison with authentic samples. Preparative TLC (silica, ether) afforded samples of the methyl sulfonate, R_f 0.5, mp 60–60.5 °C, *m/z* (EI) 186 (M^+, 15%) and 91 (100), and the methyl phosphonamidate, R_f 0.15, *m/z* (EI) 275 (M^+, 100%), $\delta_P(CDCl_3)$ 30.85 and 30.5 (diastereoisomers); the ^1H NMR spectra of these were as for the authentic samples.

(d) The reaction of ^{18}O-labelled substrate **7** (5.0 : 1 diastereoisomer mixture) with 2.0 mol dm^{-3} Bu^tNH_2 in CH_2Cl_2 was conducted as in (c) above (on one-tenth scale). The ^{31}P NMR signal for the phosphonamidate anion **11** now consisted of two peaks, δ_P 19.46 (^{16}O) and 19.42 (^{18}O) (ratio 88 : 12). The ^{18}O content of the products (after methylation of the anions **10** and **13**) was determined by mass spectrometry (EI generally but CI for the sulfonamide **12**) on isolated samples (TLC). The isolated sample of the methyl phosphonamidate **14** contained some impurities and GC-MS was used for the analysis.

Comparable experiments were also carried out using 0.4 and 8.0 mol dm^{-3} solutions of Bu^tNH_2 in CH_2Cl_2.

Comparison of reactions of *O*-sulfonyl-*N*-phosphinoylhydroxylamine 7 and phosphonamidic-sulfonic anhydride 8

The substrate **7** or **8** in CH_2Cl_2 was added to a solution of Bu^tNH_2 (4–160 equiv.) in CH_2Cl_2 to give a reaction mixture of the required concentration in amine (Table 1) and 0.05 mol dm^{-3} in substrate. The reaction of **7** was also carried out in neat Bu^tNH_2. When the reaction was complete (2–90 min) the volatile material was evaporated and the product mixture was dissolved in CH_2Cl_2 and washed with water. It was then analysed in duplicate by GLC (*T* 150 °C for 1 min then 8 °C min^{-1} to 220 °C) and the peak areas of the sulfonamide **12** (t_R 4.6 min) and the phosphonic diamide **11** (diastereoisomers, t_R 10.6 and 11.2 min) were determined by integration. In some cases the mixture was also examined by ^1H NMR spectroscopy ($CDCl_3$), using NBu^t signals to deduce the relative amounts of the sulfonamide **12** (δ_H 1.36) and phosphonic diamide **11** (δ_H 1.305 and 1.19). Comparison of the GLC and NMR measurements indicated that the GLC detector response for the sulfonamide was 0.75 mol^{-1} relative to the response for the phosphonic diamide; the GLC results shown in Table 1 have been corrected to allow for this. Control experiments showed that the symmetrical phosphonamidic anhydride **15**, a byproduct of the reactions, did not react with Bu^tNH_2 under the conditions employed (amine concentration and reaction time) for the reactions of **7** and **8**.

Acknowledgements

Thanks are due to Dr G. Eaton for recording mass spectra and Professor P. M. Cullis for valuable discussions.

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