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Phospholidines incorporating a β *N*-sulfonylaminoalcohol moiety: first observed selectivity of phosphorus heterocycle aminolysis in the presence of water†

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Eleven 2-oxo or 2-thioxo 3-sulfonyl 1,3,2-oxazaphospholidines were synthesized in one step by condensing P(IV) dichlorides with *N*-sulfonyl-ethanolamines, or -aminothexylalcohols or -*ortho*-aminophenols. These compounds, in contrast to all other phosphorus heterocycles studied so far, reacted easily with amines, sometimes selectively in the presence of water, leading to the corresponding amides. The results are rationalized by the involvement of the addition–elimination mechanism of phosphorylation with direct collapse of the primary zwitterionic intermediate formed by the amine attack on phosphorus

Introduction

Aminolysis of heterocycles **A** (Fig. 1) incorporating an α aminoamide moiety, by α aminoacids, involving attack on phosphorus, is the second of two steps in a scheme of repetitive and controlled peptide synthesis.[1] In aqueous solution, however, *hydrolysis* occurs, irrespective of substituents R and Y.[1,2] In order to achieve aminolysis of **A**, the study of its catalysis was therefore suggested.[1] Recently this has been undertaken,[3] and has led to the proposal of a scheme of intramolecular nucleophilic catalysis, by introducing a catalytic group X into the R group, with conversion of the heterocycle **A** into a new, selectively aminolysed one, **B**, in the presence of water (Fig. 1, top).

However, no phosphorus heterocycle meeting this property was known at the outset of this study. We therefore undertook a preliminary investigation to find at least one such heterocycle **B**. Recently,[4] after studying six-membered heterocycles $\mathbf{B}_1$,[5] we met partial success. Heterocycles $\mathbf{B}_2$, incorporating an *N*,*N*′-disulfonylated ethylenediamine moiety, are actually aminolyzed, by attack on phosphorus, but they are much more easily hydrolyzed. This can be attributed to the steric hindrance around phosphorus: therefore it was of interest to study heterocycles $\mathbf{B}_3$ where one of the bulky *N*-sulfonyl groups of $\mathbf{B}_2$ is replaced by oxygen. The subject of the present paper is therefore: synthesis of $\mathbf{B}_3$ and its reaction with nucleophiles, particularly amines. Together with the simplest heterocycles $\mathbf{B}_3$ *stricto sensu* henceforth referred to as **6** for the sake of consistency in numbering, which are derived from *N*-sulfonyl ethanolamines **2** we also used **7** and **8**, derived from the *N*-sulfonyl aminothexylalcohols **3** and *N*-sulfonyl-*ortho*-aminophenols **4** respectively (Fig. 1). Both are more constrained than **6**, which should make the postulated catalysis,[3] studied in a forthcoming publication,[6] easier.

Results

Synthesis of the heterocycles

Non-sulfonylated phosphorus heterocycles incorporating a β aminoalcohol moiety are well known.[7–9] Their *N*-sulfonylation may therefore be envisaged. However, the acylation of

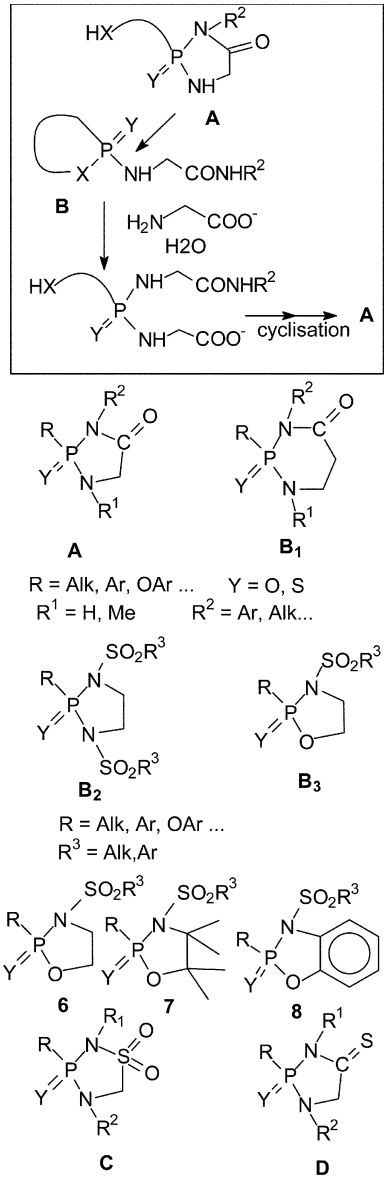

Fig. 1 Heterocycles considered (synthesized or to be synthesized).

† Intramolecular catalysis of phosphorus heterocycles incorporating an α aminoamide moiety. Part IV. Part III: ref. 4.

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Table 1 Heterocycles prepared

No.	R	Y	R^3	Method	Yield (%)	Mp/°C (recrystallization solvent)	δ^{31}P (solvent)
6a	Ph	S	$(p)NO_2C_6H_4$	c	65	186–187 (MeCN)	+85.8 (CD_3SOCD_3)
6b	PhO	S	$(p)NO_2C_6H_4$	b	37	130–134 (CH_2Cl_2)	+63 ($CDCl_3$)
6c	Me	S	$(p)MeC_6H_4$	c	48	168–170 (MeCN)	+97 ($CDCl_3$)
6d	Ph	S	$(p)MeC_6H_4$	c	17	139–141 (EtOAc)	+85 (CD_3SOCD_3)
7a	PhO	O	$(p)MeC_6H_4$	c	83	132–134 (EtOAc–iPr_2O)	+1 ($CDCl_3$)
7b	PhO	O	$(p)NO_2C_6H_4$	a	64	173–175 (EtOAc–iPr_2O)	+1 ($CDCl_3$)
7c	PhO	O	C_6H_5	a	74	112–114 (EtOAc–Et_2O)	+1 ($CDCl_3$)
8a	PhO	S	$(p)MeC_6H_4$	b	69	104–105 (EtOH)	+61 (MeCN)
8b	PhO	O	$(p)MeC_6H_4$	a	90	oil	−0.1 (pyridine)
8c	SarOEt[a]	O	$(p)MeC_6H_4$	a	58	135–138 (iPrOH)	+13.9 (CH_2Cl_2)
8d	PhGlyOMe[a]	O	$(p)MeC_6H_4$	a	55	139–142 (MeOH)	+10 (CD_3SOCD_3)

[a] Abbreviations: Sar = -N(Me)CH_2CO-; Gly = -NHCH_2CO-.

phosphoramides is not a clean reaction.[10] Consequently we turned to the use of preformed *N*-sulfonylamino-alcohols **2, 3** or -phenols **4** which are easily prepared, as described elsewhere.[11] Compounds **4** have in fact already been used by Ugi *et al.*[12] for the synthesis of a few heterocycles **8**, not for reactions with amines, but with alcohols (oligonucleotide synthesis). Several steps are then necessary due to the use of tricoordinated phosphorus compounds.

Our option was to use P(IV) dichlorides **1** to afford heterocycles **6**, **7** or **8** in a single step. The direct condensation of **1** with the *N*-sulfonylated compounds even in refluxing toluene or carbon tetrachloride is very sluggish, making the use of bases necessary. These in turn may cause adverse effects: i) rather slow decomposition of dichlorides **1** by tertiary aliphatic amines such as triethylamine (in contrast to pyridine in which they are both stable and activated by nucleophilic catalysis[13]); ii) alkylation of the bases by the phosphoric ester function when present in the R group of **1** or in heterocycles **6** themselves.[14] Moreover, the formation of phosphoranes, as already observed with dichlorides **1** reacting with non-sulfonylated amino-alcohols[9] or- phenols,[15] must be avoided. Three methods were finally selected: a) reaction in pyridine, with non-alkylating dichlorides; b) reaction in the presence of triethylamine when, especially with the PS dichlorides, the initial phosphorylation proved to be faster than the decomposition of dichloride **1**; c) use of the disodium salt of sulfonylated aminoalcohols, first prepared *in situ*. Method c) is particularly suitable for the preparation of potentially alkylating heterocycles **6** and methods a) and b) for **7** and **8**. Thus, a representative series of eleven *N*-sulfonylated heterocycles **6**, **7** and **8** was obtained (Table 1).

Only with the less constrained (found, as expected, to be less prone to cyclization) *N*-sulfonylaminoalcohols **2** were intermediate monochlorides **5** detected by ^{31}P NMR spectroscopy with characteristic chemical shifts indicative of (in agreement with values from the literature) a selective *O*- rather than *N*-sulfonyl phosphorylation. As expected, their cyclization affords the five membered ring heterocycles **6** (Fig. 2). Their ^{1}H NMR spectra show that the *N*-CH_2 methylene is strongly coupled with phosphorus, excluding the seven membered ring form **6′**. This is also the case for heterocycles **7** and **8**, after examination of the IR spectra showing the persistence of the characteristic νSO_2 absorptions at ~1350 and 1150 cm^{-1}.

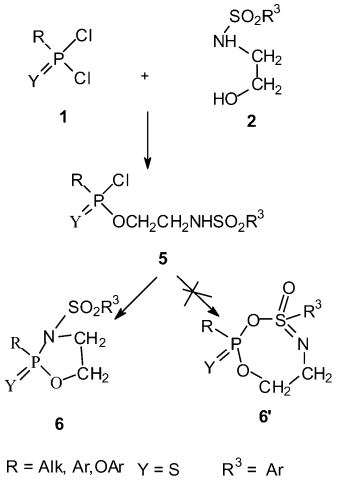

Fig. 2 Synthesis of heterocycles **6**.

Reactions of the heterocycles

Further proof, chemical this time, of the size of the heterocycles stems from the reactivity of phosphorus: it is very high, characteristic of five-membered heterocycles containing phosphorus. This was particularly studied by Westheimer *et al.*[16] with molecules incorporating a glycol moiety. Correlatively no alkylation by the phosphoric ester function takes place.

With water or alcohols we observed, as did Ugi *et al.*,[12] that the phosphorylation leading to acids **9** or esters **10** is very fast. *This is also the case with amines*. We thus prepared a representative series (Table 2) of amides **11, 12, 13** derived from heterocycles **6, 7, 8** respectively, establishing that this phenomenon is general, not dependent on structural variations of the heterocycles. Separating the products from the reacting amines was straightforward when amines had low boiling points (procedure 1). Otherwise direct crystallization in the presence of aqueous citric acid solution (procedure 2) or extraction in water immiscible organic solvents (procedure 3) were used. Here, aqueous bicarbonate solutions, included to eliminate any acids generated by hydrolysis, did not significantly lower the yields by ionization of the sulfonamide group. Also, they did not induce *quick* recyclization to the parent heterocycles, as observed with **13a**, comparable to that observed with phosphordiamides bearing an amino*acid* residue[1] instead of the hydroxy*sulfonamide* one.

More importantly for our purposes (see introduction), aminolysis is often *selective* in the presence of a large excess of water, particularly with primary aliphatic amines, such as methylamine (see for example **11a** Fig. 3) or aminoacids like glycine (with secondary amines hydrolysis prevails).

Irrespective of the nucleophile, the opening of the heterocycles always takes place with P–N cleavage, even with those containing a phenol which is a better leaving group (in **8**, or in phenyl ester (R = OPh) heterocycles **6,7**). So, the cyclic structure is not maintained as seen by the formation of amides **13a–c** using PS heterocycle **8a**. With the corresponding PO compound **8b**, loss of phenol is observed but this results from a second aminolysis (**13d** → **13e**: Fig. 4). Unlike with **6b**, this is also the case with constrained heterocycle **7a**, leading to diamides **12a** or **12b**. These interesting reactions are best interpreted by the participation of the sulfonamide group in the apparently nucleophilic catalysis

Table 2 Phosphor(n)amides synthesized

No.	R	Y	NHR^3	NHR^4	Procedure	Yield (%)	Mp/°C (recrystallization solvent)	$\delta^{31}P$ (solvent)
11a	Ph	S	$C_6H_4NO_2(p)$	Me	1	90	98–100 (Et_2O)	+77.9 (CD_3SOCD_3)
11b	Ph	S	$C_6H_4NO_2(p)$	Me_2[a]	1	71	95–97 (Et_2O–iPr_2O)	+85 ($CDCl_3$)
11c	Me	S	$C_6H_4Me(p)$	Me	1	75	69–71 (EtOAc–iPr_2O)	+86 ($CDCl_3$)
11d	Me	S	$C_6H_4Me(p)$	Bn[a]	3	95	oil	+85 ($CDCl_3$)
12a	MeNH	O	$C_6H_4Me(p)$	Me	3	61	113–115 (Et_2O)	+15 ($CDCl_3$)
12b	Me_2CHNH	O	$C_6H_4Me(p)$	Me_2CH	3	52	oil	+14 ($CDCl_3$)
13a	PhO	S	$C_6H_4Me(p)$	Me	3	97	105–106 (95% EtOH)	+71 (EtOH)
13b	PhO	S	$C_6H_4Me(p)$	Gly-OEt	3	46	94–95 (EtOH)	+64 (PhMe)
13c	PhO	S	$C_6H_4Me(p)$	Sar-OEt	3	49	74–76 (iPr_2O)	+66 ($CDCl_3$)
13d	PhO	O	$C_6H_4Me(p)$	Bn[b]	3	18	129–130 (95% EtOH)	+1 ($CDCl_3$)
13e	BnNH[b]	O	$C_6H_4Me(p)$	Bn[b]	3	73	139–141 (95% EtOH)	+13 ($CDCl_3$)
13f	Sar-OEt	O	$C_6H_4Me(p)$	Bn[b]	2	71	91–93 (EtOAc–iPr_2O)	+15 ($CDCl_3$)
13g	PhGly-OMe	O	$C_6H_4Me(p)$	Bn[b]	2	62	127–128 (95% EtOH)	+12 (CH_2Cl_2)
13h	PhGly-OMe	O	$C_6H_4Me(p)$	Me_2[a]	2	68	oil	+12 (pyridine)

[a] Me_2 = *di*methylamino derivatives (aminolysis by dimethylamine). [b] Bn = CH_2Ph.

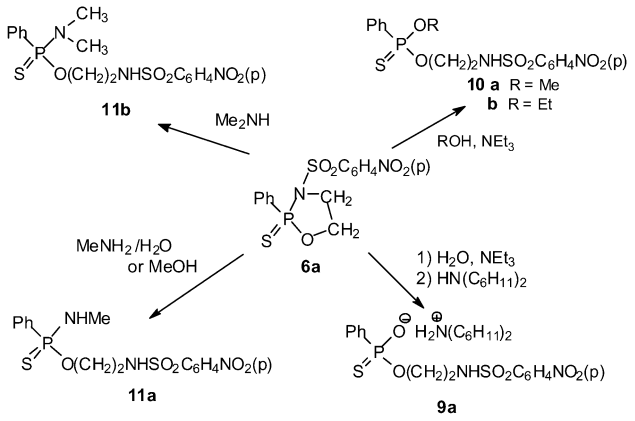

Fig. 3 Reactions of heterocycle **6a**.

of the phenylester aminolysis. They prefigure the postulated[3] intramolecularly catalyzed aminolysis of heterocycles **A** (Fig. 1, top: displacement of carboxamide instead of phenol; XH = $NHSO_2R$) and will be studied with it.[6]

Discussion

The most widely accepted mechanism of phosphorylation using five-membered phosphorus heterocycles is *addition–elimination* (AE), with formation of pentacoordinated intermediates. According to the rules of stability, in the present case, (Fig. 5) two *addition* intermediates **X** and **Y** may be formed, corresponding to the location of the bulky *N*-sulfonyl group either in the apical, preferential reaction, or the equatorial position. However, **Y** cannot intervene in the course of the reaction: to do so a pseudorotation (ψ) placing the *N*-sulfonyl group in the apical position is required for the observed cleavage of the P–N bond to take place. This can be excluded since the resulting new intermediate formed, **Z**, would be destabilized by the apical position of the R group in known cases where R is a carbon or amino group. With the "apicophilic" OPh group ψ is conceivable but must also be excluded because no loss of phenol, with conservation of the cyclic structure, is observed.

The *elimination* step starting from zwitterion **X** may intervene directly, (a) or (b), after loss of a proton leading to anion **X′**. In the case of aminolysis, possibility (b) is excluded as above for **Z** (destabilization of intermediate compounds with an amino group in the apical position). However direct decomposition (a) is possible unlike for the analogous zwitterions derived from heterocycles **A** (Fig. 1) with a carboxamide endocyclic leaving group ($pK_a \geq 14$), as the pK_a of sulfonamides (~10) is of the same order of magnitude as that of aliphatic ammoniums.[17]

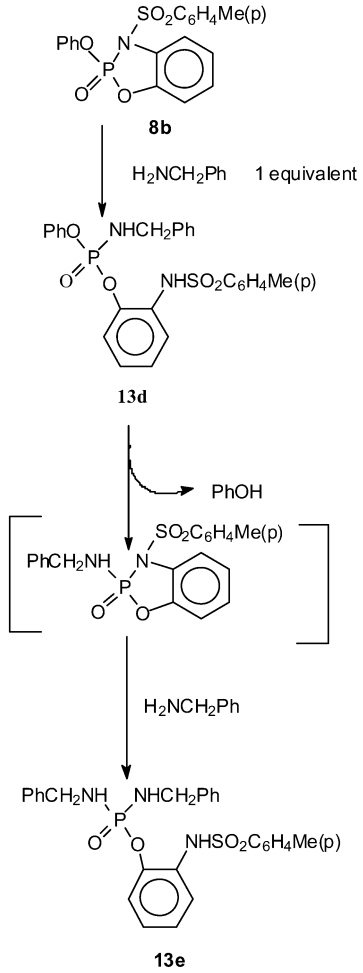

Fig. 4 Benzylaminolyses of heterocycle **8b**.

In the case of alcoholysis and hydrolysis, anion **X′** is not destabilized (OR and OH groups being apicophilic) and in basic media (conditions for the competition aminolysis/hydrolysis or aminolysis/alcoholysis) it should be formed directly without passing through **X**. The selectivity of aminolysis could then result from the higher stability of **X** formed with amines (zwitterion) than of **X′** with alcohols or water (anions). Otherwise considered, the presence of the sulfonamide leaving group with a relatively low pK_a also implies that the *elimination* cannot be the limiting step in the overall process of phosphorylation unlike *addition*, which is easier with amines, better nucleophiles compared to

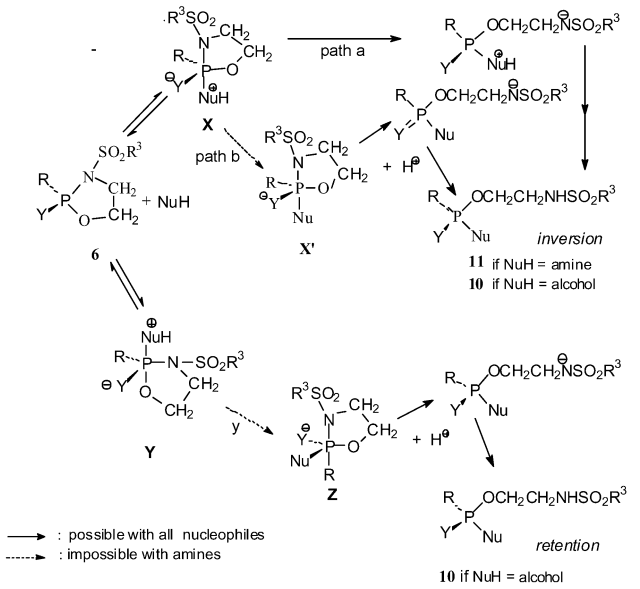

Fig. 5 Possible mechanism (indicated with heterocycles **6**, one enantiomer, but also valid for **7** and **8**).

alcohols or water (without catalysis), when the amines are not too bulky.

In conclusion the heterocycles studied here are easily aminolyzed, often even in the presence of water. To the best of our knowledge this represents the first observed case of selective aminolysis in water of phosphorus heterocycles. This appears related to the presence of the good sulfonamide leaving group. One may note that although many studies have been devoted to the fascinating extreme reactivity of phosphorus included in five-membered heterocycles,[16] much less attention has been paid to its selectivity towards nucleophiles,[18] specially depending on the leaving groups.[19–21] The improvement of aminolysis *versus* hydrolysis or alcoholysis with a good leaving group, as observed here, was not clearly anticipated. In order to determine whether this is a general phenomenon, opening the way to intramolecular α[1,3] and β[5] peptide and also pseudopeptide synthesis, we will examine the effect of changing the endocyclic carboxamide, poor leaving group, in **A**, by the good sulfonamide-[22] and thioamides,[23] in heterocycles **C** and **D** respectively (Fig. 1).

Experimental[24]

General remarks

Solvents and commercial grade reagents, were used without special purification. Melting points were determined in capillaries using Dr Tottoli's apparatus (Büchi) and are uncorrected. ^{1}H, ^{31}P, and ^{13}C (*J*-modulated) NMR spectra were recorded on a Bruker AC 80 spectrometer at 80.13, and (proton decoupled) 32.44 and 20.15 MHz with lock-on internal or external deuteriated solvents. Chemical shifts are expressed relative to Me_4Si (^{1}H and ^{13}C), 85% H_3PO_4 (^{31}P) and coupling constants *J* are given in Hertz. IR spectra (KBr pellets or Nujol mulls) were recorded on a Fourier transform Perkin Elmer model 1600 apparatus. Frequencies are expressed in cm^{-1}. Mass spectra were obtained using a Nermag R10-10C apparatus. Elemental analyses were carried out on a Carlo Erba model G 1106 by the "Service interuniversitaire de microanalyse" in Toulouse.

Synthesis of the Heterocycles

Method a (in pyridine)—illustrative procedure: 1-tosyl-2,3-dioxo-4,5-benzo-2-ethylsarcosinate-1,2-diazaphospholidine (8c). To a cooled (4 °C) and well stirred pyridine (~10 cm^3) solution of phosphoryl chloride (2.81 g, 18.3 mmol) were successively added: first, dropwise, in 10 min, a pyridine (~10 cm^3) solution of sarcosine ethyl ester hydrochloride[25] (2.81 g, 18 mmol) (^{31}P NMR: single signal of dichloride **1** δ +17.3), then *N*-tosyl *ortho*-aminophenol[11] (4.82 g, 18.3 mmol) (^{31}P NMR: after 50 min: δ +17.2 (80%): **1** and +4.35 (20%): monochloride **5**; after 1 h 30 min: +17.5 (50%) and 14.3 (45%): **8c**, and 4.2 (5%); after 5 h 30 min: +14 (100%)). The solution was then concentrated to dryness. THF (~50 cm^3) added to the residue and the homogeneous suspension obtained after overnight stirring was centrifuged (15 min, 7000 rpm). The supernatant was concentrated to dryness and the residue dissolved in toluene (~8 cm^3) resulting in quick crystallization at room temperature (Found: C, 50.5; H, 5.0; N, 6.6. $C_{18}H_{21}N_2O_6PS$ requires C, 50.8; H, 5.0; N, 6.5%); ν_{max} no band NH and OH, 1750, 1358, 1173; δ_H ($CDCl_3$) 1.29 (3H, t, *J* 7.1, CH_2CH_3), 2.37 (3H, s, CH_3 tosyl), 2.79 (3H, d, *J* 11.6, NCH_3), 4.00 (2H, octet ABX, CH_2 aminoacid), 4.24 (2H, q, *J* 7.1, OCH_2), 6.89–7.34 max 6.99 (4H, m, C_6H_4 aminophenol), 7.70 (4H, qAB, J_{AB} 8.5, C_6H_4 tosyl); δ_C ($CDCl_3$) 14.2 (CH_3 ethyl), 21. 7 (CH_3 tosyl), 34.9 (d, *J* 3.9, NCH_3), 50.9 (d, *J* 6.5, CH_2 aminoacid), 61.4 (CH_2 ethyl), from 112.8 to 129.9: 6 CH (expected: 6), including one, δ 112.8 (d, *J* 2.7), 128. 7 (d, *J* 14. 7), 134.7, 142.0, 145.6: 4 quat. C (expected: 4), 169.4 (d, *J* 5.2, CO); δ_P (CH_2Cl_2) +13.9.

Method b (in the presence of triethylamine)—illustrative procedure: 3-oxo-2-thioxo-1-tosyl-2-phenoxy-4,5-benzo-1,2-azaphospholidine (8a). To a solution of phenyldichlorothiophosphate[26] (4 g, 17.62 mmol) and *N*-tosyl-*ortho*-aminophenol[11] (4.21 g, 16 mmol) well stirred in THF (~80 cm^3), triethylamine (4.93 cm^3, 35 mmol) was added dropwise, in 2–3 min. After 20 min the reaction mixture was refluxed. Monitoring by ^{31}P NMR: after 15 min: δ = +52 (80%): dichloride **1**, +60 (20%): **8a**; after 1 h 30 min: δ = +53 (5%), +61 (95%). The insoluble material (quantitative yield for triethylamine hydrochloride) was filtered off. After concentration to dryness and dilution in absolute ethanol (a few cm^3) the product soon crystallized (Found: C, 54.7; H, 3.9; N, 3.35. $C_{19}H_{16}NO_4PS_2$ requires C, 54. 6; H, 3.9; N, 3.2%);ν_{max} no band OH and NH; δ_H ($CDCl_3$) 2.39 (3H, s, CH_3), 6.98–8.15 max 7.32 (13H, m, C_6H_5 + 2 C_6H_4); δ_C ($CDCl_3$) 21.8 (CH_3), 112.9 (d, *J* 10.5), 113.7 (d, *J* 7.5), 121.8 (d, *J* 4.8), 124, 124.4, 126.4 (d, *J* 2.3), 129.1, 130 (d, *J* 2), 130 (CH, 9 expected), 128.9 (d, *J* 13.8), 134.7, 143,5 (d, *J* 4.2), 145.9, 150.6 (d, *J* 10.3) (quat.C, 5 expected); δ_P ($CDCl_3$) +61.

Method c (with disodium salts)—illustrative procedure: 3-oxo-2-thioxo-1-*para*-nitrophenylsulfonyl-2-phenyl-1,2-azaphospholidine (6a). To a ~30% dispersion in mineral oil of sodium hydride (0.69 g, ~8.6 mmol) were added THF (40 cm^3) and *N*-*para*-nitrophenylsulfonylethanolamine[11] (1.93 g, 7.84 mmol). After refluxing for 15 min, phenylthiophosphonyl dichloride (1.34 cm^3, 8.64 mmol) was added and the reaction mixture was refluxed for a further 6 h. The suspension was centrifuged (10 min, 6000 rpm) and the supernatant was concentrated to approximately half volume. After standing overnight at −30 °C crystals of **6a** were collected, rinsed with THF (a few cm^3) and dried (Found: C, 43.75; H, 3.4; N, 7.3; P, 8.1; S, 16.7. $C_{14}H_{13}N_2O_5PS_2$ requires C, 44.0; H, 3.6; N, 7.2; P, 8,3; S, 16.6%); ν_{max}: no band OH and NH; δ_H (DMSO-d_6) 3.6–4.2 max 3.89 (2H, m, NCH_2), 4.3–4.8 max 4.5 (2H, m, OCH_2), 7.5–8.15 max 7.65 (5H, m, C_6H_5), 8.28 (4H, qAB, *J* 9.1, C_6H_4); δ_C (DMSO-d_6) 47.5 (d, *J* 9.3, NCH_2), 66.6 (d, *J* 6.3, OCH_2), 124.5 and 129.1 (2 C *ortho*, 2 C *meta* $C_6H_4NO_2$), 128.7 (d, *J* 15.6, 2 C *ortho* PhPS), 131. 5 (d, *J* 13.9, 2 C *meta* PhPS), 132.5 (d, *J* 148, C *ipso*), 133.5 (d, *J* 3.2, C *para* PhPS), 142.4 and 150.3 (2 quat. C $C_6H_4NO_2$); δ_P (DMSO d_6) +85.8; *m/z* (DCI, ammonia) 385 (M + H^+, $C_{14}H_{14}N_2O_5PS_2$ requires 385) (100%), 402 (M + NH_4^+, $C_{14}H_{17}N_3O_5PS_2$ requires 402) (35%).

Reactions of heterocycles

Aminolysis—illustrative procedure no. 1: methylamide 11a. A suspension of **6a** (0.3 g, 0.78 mmol) in a ~33% solution of

methylamine in ethanol was stirred until complete dissolution (25 min). After concentration to dryness and scratching with a glass rod to induce crystallization, the product was rinsed with ether (Found C, 43.4; H, 4.4; N, 10.1. $C_{15}H_{18}N_3O_5PS_2$ requires C, 43.3; H, 4.3; N, 10.1%); ν_{max} 3380, 3320, 3180; δ_H (DMSO-d_6) 2.39 (3H, dd, J 5.6 and 13.6, CH_3), 3.21 (2H, m, NCH_2), 4.93 (2H, dt (apparent q), J 7.8, OCH_2), 5.26 (1H, dq (apparent sext.), J 5.6 and 11.2, NHCH$_3$), 7.41–8.42 max 8.3 (10H, m, C_6H_5 + C_6H_4 + $NHSO_2$); δ_C (DMSO-d_6) 27.3 (d, J 2.2, CH_3), 42.6 (d, J 8.9, NCH_2), 62.2 (d, J 5.6, OCH_2), 124.3 and 128.5 (2 C *ortho*, 2 C *meta* $C_6H_4NO_2$), 128.2 (d, J 12.9, 2 C *ortho* PhPS), 130.2 (d, J 10.9, 2 C *meta* PhPS), 131.3 (d, J 3, C *para* PhPS), 133.9 (d, J 141.5, C *ipso*), 146.1 and 149.4 (2 quat.C $C_6H_4NO_2$); δ_P (DMSO-d$_6$) +77.9. After dissolution in DMF containing an excess of ~40% aqueous methylamine solution the reaction reached completion in less than 5 min (δ_P +78 (90%): **11a**, + 65 (10%): **9a**).

Illustrative procedure no. 2 (crystallization in the presence of citric acid): benzylamide 13f. A dichloromethane (20 cm^3) solution of **8c** (5.13 g, 12.08 mmol) and benzylamine (1.5 cm^3, 1.1 eq.) was concentrated to dryness after 2 h (^{31}P NMR: the single signal of **13f** δ +15.2). The residue was triturated ~5 min in a ~10% acid solution (a few cm^3). After addition of ~1 volume of alcohol the product soon crystallized (Found: C, 56.5; H, 5.7; N, 7.9. $C_{25}H_{30}N_3O_6PS$ requires: C, 56.7; H, 5.7; N, 7.8%); ν_{max} 3260, 3170, 1730; δ_H (DMSO-d_6) 1.14 (3H, t, J 7.1, CH_2CH_3), 2.31 (3H, s, CCH_3), 2.52 (3H, d, J 9.4, NCH_3), 3.74 (2H, apparent dd (ABX spectrum), CH_2 sarcosine), 3.93–4.19 max 4.02 (4H, m, 2 CH_2: benzylic and ethyl), 5.58 (1H, dt, J 10.4 and 6.5, NHCH$_2$), 6.96–7.67 max 7.34 (13H, m, C_6H_5 + 2 C_6H_4), 9.1 (1H, s, NH tosyl).

Illustrative procedure no. 3 (purification by acid–base extractions): glycine ethyl ester derivative 13b. To a pyridine (3 cm^3) solution of **8a** (0.48 g, 1.15 mmol) and glycine ethyl ester hydrochloride (0.16 g, 1.15 mmol), triethylamine (0.17 cm^3, 1.2 eq.) was added after 17 h. ^{31}P NMR control: after 16 h: δ + 64.3 (10%): **13b**, + 59.7 (90%): **8a**; after 17 h 45: δ +65 (100%). The solution was concentrated to a small volume, diluted with ether (~20 cm^3) extracted with ~10% citric acid and ~5% bicarbonate solutions (3 × ~15 cm^3 each) and dried (Na_2SO_4). After concentrating to dryness and diluting in absolute ethanol (a few cm^3) the product soon crystallized (Found: C, 53.1; H, 4.8; N, 5.4. $C_{23}H_{25}N_2O_6PS_2$ requires C, 53.3; H, 4.9; N, 5.3%); δ_H (DMSO-d_6) 1.19 (3H, t, J 7.1, CH_2CH_3), 2.29 (3H, s, CH_3 tosyl), 3.85 (2H, d, J 14.9, CH_2 glycine), 4.04 (2H, q J 7.1, CH_2CH_3), 7–7.69 max 7.24 (15H, m, C_6H_5 + 2 C_6H_4 + 2 NH); δ_C ($CDCl_3$) 14.2 (CH_3 ethyl), 21.6 (CH_3 tosyl), 44 (CH_2 gly), 62.2 (CH_2 ethyl), 121.1 (d, J 4.3), 122.3, 125.2, 125.8, 127.3, 129.6, 129.9 (CH, 9 expected), 129.1 (d, J 6.1), 136.5, 141.6 (d, J 7.5), 143.9, 150.4 (d, J 7.2) (quat C, 5 expected), 170.8 (d, J 6.9, CO); δ_P ($CDCl_3$) +63.6.

Hydrolysis—illustrative procedure: dicyclohexylammonium salt 9a. To a suspension of **6a** in a ~2 : 1 (v/v) DMF–water mixture, triethylamine (1.5 eq.) was added after 2 h 15 min, and dicyclohexylamine (1.1 eq.) after complete solubilization (4 h 15 min). ^{31}P NMR control: after 2 h: δ +85.8 (70%): **6a**; +74.2 (30%): acid corresponding to **9a**; after 4 h: a single signal δ +66.2: triethylammonium salt. After concentration to dryness, the product was crystallized in a methanol–water mixture, mp 85–87 °C (Found: C, 51.9; H, 6.7; N, 6.7. $C_{26}H_{38}N_3O_6PS_2$. H_2O requires C, 51.7; H, 6.5; N, 6.6%); δ_H (DMSO-d_6) 1–1.9, max 1.64 (20H, m, 10 CH_2 DCHA), 3.16 (2H, t, J 5.3, NCH_2), 3.16 (2H, m, 2 CH DCHA), 3.7 (2H, s, H_2O), 3.9 (2H, m, OCH_2), 7.32–8 max 7.36 (7H, m, C_6H_5 + NH_2), 8.25 (4H, qAB, J 9, C_6H_4); δ_P (DMSO-d_6) +67.5.

The reaction of tetrabutylammonium glycinate (~15 eq.) and water (~200 eq.) in DMF solution went to completion in less than 5 min. (^{31}P NMR: two signals δ = + 66.5 (25%): potassium salt, + 75.7 (75%): aminolysis product attributed by comparison with δ of **11a**.) Similarly with potassium alaninate (~8 eq.) and water (~100 eq.) after 5 min ^{31}P NMR showed 3 signals: δ = +66.79 (60%): hydrolysis, +75.9 (20%), +75.0 (20%): aminolysis (two diastereoisomers).

Alcoholysis—illustrative procedure: methyl ester 10a. To a DMF solution of **6a**, triethylamine (~1.9 eq.), then methanol (~40 eq.) were added. After 30 min (^{31}P NMR control: a single signal δ +88.6), the solution was concentrated to dryness and the product crystallized quantitatively in a mixture of ethyl acetate–ether (1/1), mp 102–104 °C (Found: C, 43.3; H, 4.1; N, 6,7. $C_{15}H_{17}N_2O_6PS_2$ requires C, 42.9; H, 4.1; N, 6.4%); ν_{max} 3214, 1348, 1166, 1529, 1311; δ_H ($CDCl_3$) 3.31 (2H, dt, J 5.1 and 5.5, NCH_2), 3.66 (3H, d, J 13.8, CH_3), 4.11 (2H, dt, J 5.5 and 10, OCH_2), 6.9–7.3 max 7.2 (5H, m, C_6H_5), 7.9 (4H, qAB, J 9.1, C_6H_4); δ_C ($CDCl_3$) 43.5 (d, J 7.3, NCH_2), 53.5 (d, J 5.3, OCH_3), 64.6 (d, J 5.5, OCH_2), 124.4 (2 C *ortho* $C_6H_4NO_2$), 128.3 (2 C *meta* $C_6H_4NO_2$), 128.3 (d, J 15.1, 2 C *ortho* PhPS), 131 (d, J 11.9, 2 C *meta* PhPS), 132.9 (d, J 2,8, C *para* PhPS), 131.5 (d, J 151.2, C *ipso*), 145.9 and 149.9 (2 quat.C $C_6H_4NO_2$); δ_P ($CDCl_3$) +91.4.

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