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The Influence of Ring Size on the Selectivity of Phosphorus Heterocycle Aminolysis in the Presence of Water or Alcohols – Case of 2-Oxo- or 2-Thioxo-3-sulfonyl-1,3,2-oxazaphosphorinanes[‡]

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Keywords: Amino alcohols / Sulfonamides / Phosphorus heterocycles / Phosphorylation / Chemoselectivity

Seven phosphorus heterocycles **2** were synthesized in one step by condensing P^{IV} dichlorides **3** with *N*-sulfonyl-3-aminopropanols **4**. In the presence of water, they react selectively with the less bulky amines. No change in selectivity of aminolysis was observed when using these six-membered heterocycles **2** instead of their five-membered analogs **1**.

Introduction

Recently[1] we reported the first observed selective aminolysis of phosphorus heterocycles, namely **1**, in the presence of water. This was attributed to the effect of the good sulfonamide leaving group ($pK_a \approx 10$[2,3]). However, it may also result from the five-membered-ring size effect, as phosphorus displays an extraordinary reactivity in heterocycles of this kind.[4] In that case, the mechanism of phosphorylation is of the addition–elimination (A.E.) type, while with six-membered heterocycles, as with the common acyclic phosphorus compounds, a different SN_2P mechanism is operative.[5] We describe in this paper the previously unreported synthesis and reactivity of the six-membered heterocycles **2**. This should enable us to discriminate between the leaving group and the size (mechanism) effect for heterocycles **1** and eventually to discover an improved aminolysis for heterocycles **2** relative to that for **1** (Figure 1).

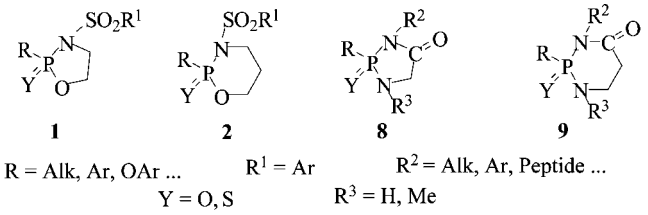

Figure 1. Phosphorous heterocycles **1**, **2**, **8**, and **9**.

[‡] Intramolecular Catalysis of Phosphorus Heterocycles Incorporating an α-Aminoamide Moiety, V. Part IV: Ref.[1]

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Results

Synthesis and Characterization

In a straightforward manner and in analogy with the synthesis of heterocycles **1**, P^{IV} dichlorides **3** and γ-*N*-sulfonylamino alcohols **4** were used, the latter being easily prepared[6] by the selective sulfonylation of 3-aminopropanol. Among the three methods selected for the synthesis of **1**, only using the disodium salts of the *N*-sulfonyl amino alcohols **4** (prepared in situ in anhydrous THF) proved to be satisfactory (Figure 2).

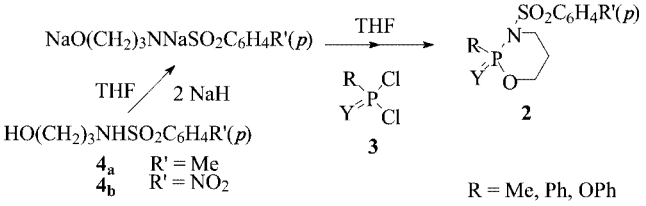
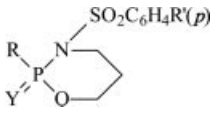


Figure 2. Synthesis of the heterocycles **2**.

The NaCl formed was eliminated either by filtration or by aqueous extraction without any significant loss of heterocycles **2** by hydrolysis. These heterocycles (seven representatives shown in Table 1) are all crystalline in racemic form except $\mathbf{2_f}$. As expected, they display correct elemental analyses and mass spectra, no OH or NH vibration in the IR spectra, a noticeable deshielding of the O and N methylene groups, both in ^{1}H- and ^{13}C NMR spectra, relative to those in compound **4**, and a characteristic complexity of the ^{1}H NMR spectra due to the magnetic nonequivalence of the two protons of each methylene group.[7] Of interest are the shielded values ($\Delta\delta \approx 10$ ppm) of the ^{31}P NMR spectra compared with those of the five-membered analogs **1**, a phenomenon which can be attributed to the reduced strain in 6-membered heterocycles **2**.

Table 1. Heterocycles **2**.



N°	Y	R	R′	M.p. [°C] (solvent of recrystallization)	Yield [%]
2a	S	Me	Me	95–97 (Et_2O-iPr_2O)	70
2b	S	Me	NO_2	117–119 (MeOH)	65
2c	S	Ph	Me	145–147 (Et_2O)	61
2d	S	Ph	NO_2	154–156 (Et_2O)	68
2e	O	Me	Me	123–125 (EtOAc/Et_2O)	65
2f	O	Ph	Me	oil	63
2g	O	OPh	Me	94–96 ($CHCl_3$–Et_2O)	59

Reactivity

Heterocycles **2** are less reactive than their analogs **1** most probably because of the reduced strain discussed in the previous section (for an example, see the reactivity of compound **2a** shown in Figure 3). They are rather resistant to hydrolysis even in the presence of bases, which leads to acids **5**, isolated as dicyclohexylammonium (DCHA) salts. Likewise, with the more bulky alcohols, no reaction leading to esters **6** was observed in the absence of a base or on addition of pyridine or dimethylaminopyridine at room temperature. Only diazabicycloundecene (DBU) promotes alcoholysis at a reasonable rate. The reaction of heterocycles **2** with amines, leading to amides **7**, is rapid with methylamine (a few hours) but rather slow with benzylamine (a few days) and indefinite (no reaction) with secondary amines. More significantly, using methylamine, the selectivity of aminolysis is complete in the presence of an alcohol and very high (> 85%) in the presence of water. However, with more sterically hindered amines such as benzylamine, glycine, or alanine, hydrolysis is more pronounced as the bulkiness of the amine increases (for example with $\mathbf{2_a}$, the yield is 70, 72, and 40%, respectively; see Table 2). In fact, it appears that the selectivity of heterocycles **2** is comparable to that of **1**.[1] For example, with the heterocycle **1** corresponding to $\mathbf{2_d}$ (same environment around phosphorus, numbered[1] **6a**), the ratio aminolysis/hydrolysis in aqueous solutions of methylamine, potassium glycinate, and potassium alaninate is 90:10, 75:25, and 60:40, respectively.[1,17]

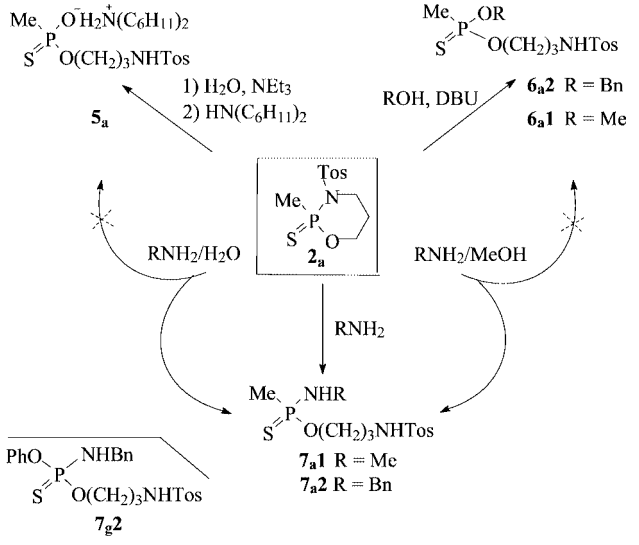


Figure 3. Reactions of the heterocycle $\mathbf{2_a}$.

Table 2. Products of hydrolysis, alcoholysis, and aminolysis of the heterocycles **2**.

N°[a]	Y	R	R′	R"	Yield [%]
5a	S	Me	Me	OH DCHA salt	87
5e	O	Me	Me	OH DCHA salt	82
6a1	S	Me	Me	OMe	100[b]
6c1	S	Ph	Me	OMe	100[b]
6d1	S	Ph	NO_2	OMe	100[b]
6a2	S	Me	Me	OBn	89
6c2	S	Ph	Me	OBn	100[b]
6b2	S	Me	NO_2	OBn	100[b]
7a1	S	Me	Me	NHMe	80, 95[b,c], 100[b,d]
7d1	S	Ph	NO_2	NHMe	100, 100[b,c], 100,[b,d]
7e1	O	Me	Me	NHMe	60[c]
7a2	S	Me	Me	NHBn	75, 70[c]
7d2	S	Ph	NO_2	NHBn	100[b]
7g2	O	OPh	Me	NHBn	67
7e2	O	Me	Me	NHBn	77[c]
7a3	S	Me	Me	$NHCH_2COOK$	72[b,c]
7a4	S	Me	Me	NHCHMeCOOK	40[b,c]

[a] Numbering is as follows: **5**, **6**, and **7** are the products of hydrolysis, alcoholysis, and aminolysis, respectively; the subscript indicates the reacting heterocycle; the following number (for alcoholysis or aminolysis) is 1 for Me, 2 for Bn (benzyl), 3 for potassium glycinate, and 4 for potassium alaninate. [b] By ^{31}P NMR spectroscopy, in the reaction mixture. [c] Reaction performed in the presence of excess water. [d] Reaction performed in the presence of excess methanol.

All the products synthesized (Table 2), **5**, **6**, and **7**, were isolated as oils with the exception of the crystalline phosphonamides $\mathbf{7_a1}$ and $\mathbf{7_g2}$. The latter compound did not show subsequent loss of phenol (i.e. no recyclization), a fact of some importance in light of the postulated participation of the sulfonamide group in the reactions of phosphorylation.[8]

Discussion and Conclusion

A considerable number of studies have been devoted to the reactivity of phosphorus, particularly when it is included in cyclic structures.[4] They are very well documented for hydrolysis, but fewer examples exist for aminolysis[9,10] and even fewer for the selectivity of aminolysis over hydrolysis.[11] However, this is of particular interest from two points of view: (1) general: how to explain, independently of catalysis, the paradox of the usually higher reactivity of water and alcohols relative to that of the better nucleophiles, amines, with activated phosphorus compounds (just the opposite of the cases with carbonyl- and sulfonyl-acti-

vated compounds);[12] (2) particular: the applicability of a scheme of intramolecular peptide synthesis[13] requiring the selective aminolysis in water of phosphorus heterocycles **8** (Figure 1). The purpose of the series of studies we have undertaken[14] is precisely to solve this problem.

For this work (part V of the series[1,14,16,18]), all heterocycles **2** react with cleavage of the P–N bonds, therefore with attack of the nucleophiles opposite to the sulfonamide leaving group. Of particular interest is the case of $\mathbf{2_g}$; there is no loss of phenol, and the cyclic structure is retained, product $\mathbf{7_g2}$ (cf. Figure 3, bottom, left) being isolated. This means either that there is no pseudorotation of the initial addition product resulting from the reaction of amines with phosphorus (A.E. mechanism) or, more probably, that the SN_2P mechanism of phosphorylation is involved (a pentacoordinated *transition state* and not, as in the A.E. mechanism, an *intermediate* compound of sufficient lifetime, which can solely be subject to a pseudorotation), in accordance with the literature.[5] As with *acyclic* phosphorus compounds comparable to **2** (also SN_2P mechanism) with good leaving groups and similar crowding around phosphorus, selective aminolysis has been observed with rather hindered amines such as cyclohexylamine or isopropylamine,[15] one should expect an improvement of the selectivity of aminolysis of the heterocycles **2**. However, this is *not* the case. The conclusion is therefore reached that neither the mechanism nor the size, as previously observed[16] with heterocycles **8** and **9** (Figure 1), significantly influences the selectivity of aminolysis observed with either **1** or **2**, and that the selectivity is fundamentally related to the presence of the good sulfonamide leaving group.

Experimental Section[17]

The general conditions are the same as in the preceding article of this series.[1]

Synthesis of the Heterocycles 2

2-Methyl-3-*p*-methylbenzenesulfonyl-2-thioxo-1,3,2-oxazaphosphorinane ($\mathbf{2_a}$) – Illustrative Procedure: A THF (50 mL) solution of $\mathbf{4_a}$[6] (1 g, 4.36 mmol) was heated to reflux first for 1 h in the presence of NaH (95%, 0.22 g, 9.16 mmol) and finally for 3 h after addition of methanethiophosphonyl dichloride ($\mathbf{3_a}$) (0.715 g, 4.75 mmol). The cooled suspension was centrifuged (10 min, 6000 rpm), and the supernatant concentrated to dryness. Alternatively, after concentration, the residue was taken up in chloroform (50 mL), and the organic layer was extracted with water (3 × 50 mL), dried (Na_2SO_4), and concentrated to dryness. In each case the product was easily crystallized. ^{1}H NMR ($CDCl_3$): δ = 1.73–1.85 (m, 1 H, CCH_2C), 2.01–2.20 (m, 1 H, CCH_2C), 2.31 (d, J = 14.7 Hz, 3 H, PCH_3), 2.42 (s, 3 H, tos CH_3), 3.10–3.26 (m, 1 H, NCH_2), 3.50–3.70 (m, 1 H, NCH_2), 3.90–4.20 (m, 1 H, OCH_2), 4.30–4.50 (m, 1 H, OCH_2), 7.59 (qAB J = 8.1 Hz, 4 H, tos C_6H_4) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.75 (tos CH_3), 26.18 (d, J = 102.2 Hz, PCH_3), 26.34 (d, J = 2.7 Hz, CCH_2C), 44.39 (NCH_2), 63.22 (d, J = 7.2 Hz, OCH_2), 129.02 (2 CH), 129.42 (2 CH), 133.49 (Me*C*quat.), 144.82 (SO_2C-quat.) ppm. ^{31}P NMR ($CDCl_3$): δ = +87.12 ppm. IR: 1343, 1164 (νSO_2) cm^{-1}. MS (DCI/CH_4): *m*/*z* (%) = 306 (100) $[MH]^+$. $C_{11}H_{16}NO_3PS_2$ (305.36): calcd. C 43.27, H 5.28, N 4.59; found C 42.93, H 5.25, N 4.43.

Similarly $\mathbf{2_b}$ was obtained. ^{1}H NMR ($CDCl_3$): δ = 1.70–2.0 (m, 1 H, CCH_2C), 2.09–2.18 (m, 1 H, CCH_2C), 2.33 (d, J = 15.7 Hz, 3 H, PCH_3), 3.10–3.30 (m, 1 H, NCH_2), 3.60–3.80 (m, 1 H, NCH_2), 3.90–4.10 (m, 1 H, OCH_2), 4.30–4.50 (m, 1 H, OCH_2), 8.26 (qAB, J = 8.8 Hz, 4 H, $C_6H_4NO_2$) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.12 (d, J = 101.5 Hz, PCH_3), 26.27 (d, J = 3.1 Hz, CCH_2C), 44.80 (NCH_2), 63.46 (d, J = 7.5 Hz, OCH_2), 123.89 (2 CH), 130.42 (2 CH), 141.68 (SO_2Cquat.), 150.87 (NO_2Cquat.) ppm. ^{31}P NMR ($CDCl_3$): δ = +87.22 ppm. IR: $\tilde{\nu}$ = 1351, 1172 (νSO_2), 1530, 1355 (νNO_2) cm^{-1}. $C_{10}H_{13}N_2O_5PS_2$ (336.33): calcd. C 35.71, H 3.89, N 8.33; found C 35.46, H 3.78, N 8.34.

Similarly $\mathbf{2_c}$ was obtained. ^{1}H NMR ($CDCl_3$): δ = 1.80–2.00 (m, 1 H, CCH_2C), 2.10–2.30 (m, 1 H, CCH_2C), 2.42 (s, 3 H, tos CH_3), 3.30–3.50 (m, 1 H, NCH_2), 3.70–3.90 (m, 1 H, NCH_2), 4.10–4.30 (m, 1 H, OCH_2), 4.40–4.60 (m, 1 H, OCH_2), 7.52 (qAB, J = 8.1 Hz, 4 H, C_6H_4Me), 7.50–7.60 (m, 3 H, C_6H_5), 8.00–8.20 (m, 2 H, C_6H_5) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.42 (tos CH_3), 26.21 (d, J = 3.8 Hz, CCH_2C), 45.38 (NCH_2), 64.08 (d, J = 7.5 Hz, OCH_2), 128.19 (d, J = 15.7 Hz, 2 CH), 128.76 (CH), 129.53 (CH), 130.56 (d, J = 154.5 Hz, P*C*quat.), 132.08 (d, J = 12.3 Hz, 2 CH), 133.10 (d, J = 2.9 Hz, CH), 134.41 (Me*C*quat.), 144.52 (SO_2Cquat.) ppm. ^{31}P NMR ($CDCl_3$): δ = +76.29 ppm. IR: $\tilde{\nu}$ = 1352, 1164 (νSO_2) cm^{-1}. MS (DCI/CH_4): *m*/*z* (%) = 368 (100) $[MH]^+$. $C_{16}H_{18}NO_3PS_2$ (367.43): calcd. C 52.30, H 4.94, N 3.81; found C 52.03, H 4.98, N 3.57.

Similarly $\mathbf{2_d}$ was obtained. ^{1}H NMR ($CDCl_3$): δ = 1.90–2.10 (m, 1 H, CCH_2C), 2.20–2.40 (m, 1 H, CCH_2C), 3.40–3.60 (m, 1 H, NCH_2), 3.80–4.00 (m, 1 H, NCH_2), 4.20–4.40 (m, 1 H, OCH_2), 4.40–4.60 (m, 1 H, OCH_2), 7.50–7.70 (m, 3 H, C_6H_5), 8.00–8.20 (m, 2 H, C_6H_5), 8.18 (qAB, J = 8.9 Hz, 4 H, $C_6H_4NO_2$) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.27 (d, J = 3.7 Hz, CCH_2C), 45.86 (NCH_2), 64.33 (d, J = 7.4 Hz, OCH_2), 123.91 (2 CH), 128.42 (d, J = 16.1 Hz, 2 CH), 129.23 (d, J = 154.7 Hz, P*C*quat.), 130.09 (2 CH), 132.19 (d, J = 12.8 Hz, 2 CH), 133.6 (d, J = 2.9 Hz, CH), 142.76 (SO_2C-quat.), 150.55 (NO_2Cquat.) ppm. ^{31}P ($CDCl_3$): δ = +76.34 ppm. IR: $\tilde{\nu}$ = 1311, 1162 (νSO_2), 1533, 1350 (νNO_2) cm^{-1}. $C_{15}H_{15}N_2O_5PS_2$ (366.33): calcd. C 45.22, H 3.80, N 7.03; found C 45.29, H 3.64, N 6.76.

Similarly $\mathbf{2_e}$ was obtained. ^{1}H NMR ($CDCl_3$): δ = 1.60–1.90 (m, 2 H, CCH_2C), 1.87 (d, J = 17.7 Hz, 3 H, PCH_3), 2.33 (s, 3 H, tos CH_3), 2.90–3.20 (m, 1 H, NCH_2), 3.50–3.60 (m, 1 H, NCH_2), 3.90–4.20 (m, 2 H, OCH_2), 7.56 (qAB, J = 7.9 Hz, 4 H. C_6H_4Me) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.34 (d, J = 135.7 Hz, PCH_3), 21.59 (tos CH_3), 25.53 (d, J = 5.2 Hz, CCH_2C), 44.75 (NCH_2), 64.99 (d, J = 7.9 Hz, OCH_2), 128.35 (2 CH), 129.75 (2 CH), 134.97 (Me*C*quat.), 144.66 (SO_2Cquat.) ppm. ^{31}P NMR ($CDCl_3$): δ = +25.34 ppm. IR: $\tilde{\nu}$ = 1210 (νPO), 1341, 1162 (νSO_2) cm^{-1}. MS (DCI/CH_4): *m*/*z* (%) = 290 (100) $[MH]^+$. $C_{11}H_{16}NO_4PS$ (289.29): calcd. C 45.67, H 5.57, N 4.84; found C 45.84, H 5.34, N 4.81.

Similarly $\mathbf{2_f}$ was obtained. ^{1}H NMR ($CDCl_3$): δ = 1.60–2.10 (m, 2 H, CCH_2C), 2.36 (s, 3 H, tos CH_3), 3.35–3.85 (m, 2 H, NCH_2), 3.80–4.45 (m, 2 H, OCH_2), 7.20–7.90 (m, 5 H, PC_6H_5), 7.59 (qAB J = 8.4 Hz, 4 H, C_6H_4Me) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.66 (tos CH_3), 25.66 (d, J = 5.4 Hz, CCH_2C), 45.43 (NCH_2), 65.76 (d, J = 7.9 Hz, OCH_2), 128.32 (2 CH), 128.49 (d, J = 16.6 Hz, 2 CH), 129.74 (2 CH), 131.24 (d, J = 151.6 Hz, P*C*quat.), 132.10 (d, J = 11.1 Hz, 2 CH), 132.93 (d, J = 2.7 Hz, CH), 135.48 (Me*C*quat.), 144.59 (SO_2Cquat.) ppm. ^{31}P NMR ($CDCl_3$): δ = +11.92 ppm. IR: $\tilde{\nu}$ = 1339, 1165 (νSO_2) cm^{-1}. $C_{16}H_{18}NO_4PS$ (351.36): C 54.69,H5.16, N 3.98; found C 54.31, H 5.01, N 3.63.

Similarly $\mathbf{2_g}$ was obtained. ^{1}H NMR ($CDCl_3$): δ = 1.80–2.00 (m, 2 H, CCH_2C), 2.41 (s, 3 H, tos CH_3), 3.50–3.70 (m, 1 H, NCH_2),

3.80–4.00 (m, 1 H, NCH_2), 4.30–4.50 (m, 2 H, OCH_2), 7.10–7.40 (m, 5 H, OC_6H_5), 7.59 (qAB, J = 8.3 Hz, 4 H, C_6H_4Me) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.70 (tos CH_3), 25.90 (d, J = 5.4 Hz, CCH_2C), 46.93 (NCH_2), 69.90 (d, J = 8.4 Hz, OCH_2), 120.24 (d, J = 4.8 Hz, 2 CH), 125.49 (CH), 127.89 (CH), 129.65 (CH), 129.82 (CH), 136.60 (Me*C*quat.), 144.69 (NO_2*C*quat.), 150.22 (d, J = 7.6 Hz, O*C*quat.) ppm. ^{31}P NMR ($CDCl_3$): δ = –13.71 ppm. IR: $\tilde{\nu}$ = 1246 (νPO), 1336, 1167 (νSO_2) cm^{-1}. $C_{16}H_{18}NO_5PS$ (367.36): calcd. C 52.32, H 4.94, N 3.81; found C 52.13, H 4.82, N 3.80.

Reactions of the Heterocycles 2

Hydrolysis – Illustrative Procedure: A DMF (2 g) solution of $\mathbf{2_a}$ (0.20 g, 0.6 mmol), water (0.22 g, 12.2 mmol), and triethylamine (0.19 g, 1.9 mmol) were kept at room temperature. After 4 weeks, only 25% reaction was observed by ^{31}P NMR spectroscopy. After addition of more water (0.86 g) and triethylamine (0.82 g) and heating to 60 °C, the reaction was terminated in less than a week. The reaction mixture was concentrated to dryness, diluted with an aqueous solution (20 mL) of mono-dicyclohexylammonium citrate (0.54 g, 1.45 mmol), and extracted with chloroform (3×20 mL). The organic extracts were dried (Na_2SO_4) and concentrated to dryness. ^1H NMR ($CDCl_3$): δ = 0.9–1.9 (m, 22 H, 10 CH_2 DCHA + CCH_2C), 1.60 (d, J = 14.5 Hz, 3 H, PCH_3), 2.39 (s, 3 H, tos CH_3), 2.90–3.20 (m, 4 H, 2 CH DCHA + NCH_2), 3.60–4.10 (m, 2 H, OCH_2), 7.48 (qAB, J = 8.4 Hz, 4 H, C_6H_4Me) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.52 (tos CH_3), 24.75 (4 CH_2 DCHA), 25.05 (2 CH_2 DCHA), 29.18 (4 CH_2 DCHA), 30.08 (d, J = 6.9 Hz, CCH_2C), 39.59 (NCH_2), 53.08 (2 CH DCHA), 60.87 (d, J = 5.8 Hz, OCH_2), 127.07 (2 CH), 129.56 (2 CH), 137.63 (MeCquat.), 142.92 (SO_2C-quat.) ppm. ^{31}P NMR ($CDCl_3$): δ = +75.29 ppm. IR: $\tilde{\nu}$ = 1327, 1158 (νSO2), 2800–2400 (νN^+H), 3245 (νNH) cm^{-1}.

Similarly $\mathbf{5_e}$ was obtained. ^1H NMR ($CDCl_3$): δ = 1.10–2.05 (m, 22 H, 10 CH_2 DCHA + CCH_2C), 1.27 (d, J = 10.5 Hz, 3 H, PCH_3), 2.37 (s, 3 H, tos CH_3), 2.65–3.12 (m, 4 H, 2 CH DCHA + NCH_2), 3.70–4.05 (m, 2 H, OCH_2), 7.46 (qAB, J = 8.3 Hz, 4 H, C_6H_4Me) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.47 (d, J = 140 Hz, PCH_3), 21.53 (tos CH_3), 24.73 (4 CH_2 DCHA), 25.11 (2 CH_2 DCHA), 29.17 (4 CH_2 DCHA), 29.17 (4 CH_2 DCHA), 30.26 (d, J = 4.5 Hz, CCH_2C), 39.31 (NCH_2), 52.96 (2 CH DCHA), 60.85 (d, J = 5.7 Hz, OCH_2), 126.99 (2 CH), 129.58 (2 CH), 137.91 (Me*C*-quat.), 142.90 (SO_2*C*quat.) ppm. ^{31}P NMR ($CDCl_3$): δ = –25.48 ppm. IR: $\tilde{\nu}$ = 1326 (et), 1159 (νSO_2), 1198 (νPO), 2800–2400 (νNH^+), 3244 (νNH) cm^{-1}.

Alcoholysis – Illustrative Procedure: To a DMF (0.8 g) solution of $\mathbf{2_a}$ (0.1 g, 0.33 mmol), were added methanol (0.12 g, 3.74 mmol) and DBU (0.05 g, 0.33 mmol). After completion of the reaction (≈ 3 weeks), the reaction mixture was diluted with chloroform (10 mL), and the organic layer was extracted with citric acid solution (10%, 2×10 mL), dried ($MgSO_4$), and concentrated to dryness, leaving $\mathbf{6_a1}$ as as a colorless oil. ^1H NMR ($CDCl_3$): δ = 1.67–2.00 (m, 2 H, CCH_2C), 1.73 (d, J = 15.5 Hz, 3 H. PCH_3), 2.39 (s, 3 H, tos CH_3), 2.70–3.20. max 2.99 (m, 2 H, NCH_2), 3.65 (d, J = 13.8 Hz, 3 H, OCH_3), 3.60–4.20 (m, 2 H, OCH_2), 7.49 (qAB, J = 8.3 Hz, 4 H, C_6H_4Me) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.83 (d, J = 114.9 Hz, PCH_3), 21.56 (tos CH_3), 30.29 (d, J = 6.9 Hz, CCH_2C), 39.53 (NCH_2), 53.02 (d, J = 6.6 Hz, OCH_3), 65.18 (d, J = 6.6 Hz, OCH_2), 127.13 (2 CH), 129.77 (2 CH), 137.02 (Me*C*quat.), 143.46 (SO_2*C*quat.) ppm. ^{31}P NMR ($CDCl_3$): δ = +98.86 ppm. IR: $\tilde{\nu}$ = 1328, 1159 (νSO_2), 3279 (νNH) cm^{-1}. Only 56% reaction was observed after 18 days in the presence of NEt_3 (5 equiv.) in place of DBU.

Similarly $\mathbf{6_c1}$ was obtained after 2 days in acetonitrile. ^1H NMR ($CDCl_3$ + D_2O): δ = 1.80 (pseudo q, J = 6.2 Hz, 2 H, CCH_2C), 2.38 (s, 3 H, tos CH_3), 3.02 (t, J = 6.2 Hz, 2 H, NCH_2), 3.66 (d, J = 13.7 Hz, 3 H, OCH_3), 3.95–4.31 (m, 2 H, OCH_2), 7.19–7.96 (m, 5 H, PC_6H_5), 7.47 (qAB, J = 8.4 Hz, 4 H, $C_6H_4NO_2$) ppm. ^{13}C NMR ($CDCl_3$ + D_2O): δ = 21.59 (tos CH_3), 30.13 (d, J = 6.5 Hz, CCH_2C), 39.50 (NCH_2), 63.69 (d, J = 5.7 Hz, OCH_2), 53.33 (d, J = 4.9 Hz, OCH_3), 127.13 (2 CH), 128.50 (d, J = 14.7 Hz, 2 CH), 129.77 (2 CH), 131.03 (d, J = 11.7 Hz, 2 CH), 132.64 (d, J = 2.9 Hz, CH), 136.88 (Me*C*quat.), 143.45 (SO_2*C*quat.) ppm. ^{31}P NMR ($CDCl_3$): δ = +87.97 ppm. IR: $\tilde{\nu}$ = 1331, 1158 (νSO_2), 3288 (νNH) cm^{-1}.

Similarly $\mathbf{6_d1}$ was obtained after 24 h in acetonitrile. The sulfonic acid Amberlyst 15 resin was used for the removal of DBU. ^1H NMR ($CDCl_3$): δ = 1.6–1.9 (m, 2 H, CCH_2C), 3.03 (t, J = 6.4 Hz, 2 H, NCH_2), 3.65 (d, J = 13.7 Hz, 3 H, OCH_3), 3.95–4.22 (m, 2 H, OCH_2), 7.35–7.88 (m, 5 H, C_6H_5C), 8.10 (qAB, J = 9.2 Hz, 4 H, $C_6H_4NO_2$) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.72 (d, J = 7 Hz, CCH_2C), 40.05 (NCH_2), 53.34 (d, J = 5.5 Hz, OCH_3), 63.98 (d, J = 5.9 Hz, OCH_2), 123.88 (2 CH), 128.24 (2 CH), 128.49 (d, J = 15 Hz, 2 CH), 130.98 (d, J = 11.8 Hz, 2 CH), 132.65 (d, J = 2.7 Hz, CH), 132.07 (d, J = 151 Hz, P*C*quat.), 147.49 (Me*C*quat.), 149.52 (SO_2*C*quat.) ppm. ^{31}P NMR ($CDCl_3$): δ = +89.83 ppm. IR: $\tilde{\nu}$ = 1311,165 (νSO_2), 1530, 1349 (νNO_2), 3286 (νNH) cm^{-1}. In the presence of a large excess of methanol in little DMF, the reaction is accelerated by DBU (2 equiv.): $t_{1/2} \approx 2$ h and is very slow with DMAP (1 equiv.): $t_{1/2} \approx 7$ weeks.

Similarly $\mathbf{6_a2}$ was obtained after 3 weeks. ^1H NMR ($CDCl_3$ + D_2O): δ = 1.71 (pseudo q, J = 6.5 Hz, 2 H, CCH_2C), 1.72 (d, J = 15.5 Hz, 3 H, PCH_3), 2.37 (s, 3 H, tos CH_3), 2.94 (t, J = 6.5 Hz, 2 H, NCH_2), 3.70–4.20 (m, 2 H, OCH_2), 4.94–5.11 (m, 2 H, OCH_2), 7.19–7.32 (m, 5 H, $C_6H_5CH_2$), 7.48 (qAB, J = 8.3 Hz, 4 H, C_6H_4Me) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.54 (tos CH_3), 21.59 (d, J = 115.3 Hz, PCH_3), 30.17 (d, J = 7.2 Hz, CCH_2C), 39.53 (NCH_2), 63.13 (d, J = 6.7 Hz, OCH_2), 68.16 (d, J = 6.2 Hz, benzylic CH_2), 127.13 (2 CH), 128.68 (CH), 128.68 (2 CH), 129.68 (2 CH), 129.77 (2 CH), 136.31 (d, J = 6.3 Hz, CH_2*C*quat.), 137.03 (Me*C*quat.), 143.44 (SO_2*C*quat.) ppm. ^{31}P ($CDCl_3$): δ = +97.52. IR: $\tilde{\nu}$ = 1327, 1159 (νSO_2), 3277 (νNH) cm^{-1}.

Similarly $\mathbf{6_c2}$ was obtained after 11 days. IR: $\tilde{\nu}$ = 1327, 1159 (νSO_2), 3317 (νNH). ^1H NMR ($CDCl_3$ + D_2O): δ = 1.73 (pseudo q, J = 6.2 Hz, 2 H, CCH_2C), 2.37 (s, 3 H, tos CH_3), 2.85–2.99 (m, 2 H, NCH_2), 3.88–4.12 (m, 2 H, OCH_2), 4.98–5.15 (m, 2 H, OCH_2), 7.45 (qAB, J = 8.1 Hz, 4 H, C_6H_4Me), 7.10–8.00 (m, 10 H, 2 C_6H_5) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.59 (tos CH_3), 30.12 (d, J = 7.2 Hz, CCH_2C), 39.54 (NCH_2), 63.68 (d, J = 5.9 Hz, OCH_2), 68.44 (d, J = 5.3 Hz, benzylic CH_2), 127.12 (2 CH), 128.19 (2 CH), 128.51 (d, J = 15.4 Hz, 2 CH), 128.56 (CH), 128.66 (CH), 129.78 (2 CH), 131.01 (d, J = 11.8 Hz, 2 CH), 132.56 (d, J = 153.5 Hz, P*C*quat.), 132.61 (d, J = 2.9 Hz, CH), 136.10 (d, J = 7.7 Hz, CH_2*C*quat.), 141.06 (Me*C*quat.), 143.39 (SO_2*C*quat.) ppm. ^{31}P NMR ($CDCl_3$): δ = +88.71 ppm. IR: $\tilde{\nu}$ = 1327, 1159 (νSO_2), 3317 (νNH) cm^{-1}. No reaction was observed in the presence of excess benzyl alcohol and a catalytic amount of DMAP after 2 months at 65 °C.

Similarly $\mathbf{6_b2}$ was obtained after 3 days in benzyl alcohol as solvent. ^1H NMR ($CDCl_3$ + D_2O): δ = 1.77 (pseudo q, J = 6.2 Hz, 2 H, CCH_2C), 3.01 (t, J = 6.2 Hz, 2 H, NCH_2), 3.88–4.20 (m, 2 H, OCH_2), 4.95–5.14 (m, 2 H, OCH_2), 7.06–7.70 (m, 5 H, C_6H_5), 8.07 (qAB, J = 9 Hz, 4 H, $C_6H_4NO_2$) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.05 (d, J = 7.2 Hz, CCH_2C), 39.46 (NCH_2), 63.29 (d, J = 5.9 Hz, OCH_2), 68.65 (d, J = 5.3 Hz, benzylic CH_2), 124.37 (2 CH), 127.67 (2 CH), 127.92 (CH), 128.39 (2 CH), 128.45 (d, J = 14.2 Hz, 2 CH), 128.97 (2 CH), 130.97 (d, J = 11.7 Hz, 2 CH), 132.53 (d, J =

151 Hz, CH), 132.76 (d, J = 3 Hz, CH_2*C*quat.), 135.92 (d, J = 7.3 Hz, CH_2*C*quat.), 145.89 (SO_2*C*quat.), 149.99 (NO_2*C*-quat.) ppm. ^{31}P NMR ($CDCl_3$): δ = +88.82 ppm. IR: $\tilde{\nu}$ = 1311, 1165 (νSO_2), 1529, 1348 (νNO_2), 3282 (νNH) cm^{-1}.

Aminolysis – Illustrative Procedure: After 3 hours (no more $\mathbf{2_a}$ by ^{31}P NMR), the initial solution of methylamine (0.24 g, 7.41 mmol) and $\mathbf{2_a}$ (0.19 g, 0.62 mmol) in anhydrous pyridine (10.9 g) was concentrated and taken up with chloroform (20 mL). The organic solution was extracted with citric and hydrogen carbonate (5%) solutions, dried (Na_2SO_4), and concentrated to dryness. The product $\mathbf{7_a1}$ was crystallized: m.p. 69–71 °C (EtOAc/*i*Pr_2O). Alternatively, the product was obtained (95% yield by NMR, 75% isolated yield) in a 1:1 DMF/methylamine(40% aqueous solution, 45 equiv.) mixture after 2 h. ^{1}H NMR ($CDCl_3$): δ = 1.65 (d, J = 13 Hz, 3 H, PCH_3), 1.46–1.67 (m, 2 H, CCH_2C), 2.33 (s, 3 H, tos CH_3), 2.51 (d, J = 13.1 Hz, 3 H, NCH_3), 2.60–2.99 (m, 2 H, NCH_2), 3.60–4.08 (m, 2 H, OCH_2), 7.45 (qAB, J = 8.2 Hz, 4 H, C_6H_4Me) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.57 (d, J = 106.6 Hz, PCH_3), 21.55 (tos CH_3), 27.93 (d, J = 2.8 Hz, NCH_3), 29.96 (d, J = 7.5 Hz. C*C*H_2C), 39.57 (NCH_2), 60.65 (d, J = 6.3 Hz, OCH_2), 127.07 (2 CH), 129.76 (2 CH), 139.61 (Me*C*quat.), 143.36 (SO_2*C*quat.) ppm. ^{31}P NMR ($CDCl_3$): δ = +85.66. IR: $\tilde{\nu}$ = 1324, 1158 (νSO_2), 3275 (νNH) cm^{-1}. $C_{11}H_{19}N_2O_3PS_2$ (290.32): calcd. C 40.98, H 5.94, N 8.69; found C 40.77, H 5.92, N 8.48. With excess diethylamine (28 equiv.) no reaction was observed after 1 month.

Similarly $\mathbf{7_d1}$ was obtained after 30 min in DMF. ^{1}H NMR ($CDCl_3$ + D_2O): δ = 1.91 (pseudo q, J = 5.9 Hz, 2 H, CCH_2C), 2.46 (d, J = 13.3 Hz, 3 H, NCH_3), 3.05–3.20 (m, 2 H, NCH_2), 3.95–4.30 (m, 2 H, OCH_2), 7.35–7.80 (m, 5 H, PC_6H_5), 8.11 (qAB, J = 9.2 Hz, 4 H, C_6H_4Me) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.15 (d, J = 2.4 Hz, NCH_3), 30.09 (d, J = 6.9 Hz, C*C*H_2C), 39.46 (NCH_2), 60.99 (d, J = 5.8 Hz, OCH_2), 124.35 (2 CH), 128.39 (2 CH), 128.63 (d, J = 14.5 Hz, 2 CH), 130.65 (d, J = 11.1 Hz, 2 CH), 132.03 (d, J = 2.6 Hz, CH), 132.94 (d, J = 118.2 Hz, P*C*quat.), 145.70 (SO_2*C*-quat.), 149.95 (NO_2*C*quat.) ppm. ^{31}P NMR ($CDCl_3$): δ = +79.18. IR: $\tilde{\nu}$ = 1309, 1163 (νSO_2), 1529, 1347 (νNO_2), 3287 (νNH) cm^{-1}.

Similarly $\mathbf{7_e1}$ was obtained after 5 h in DMF. ^{1}H NMR ($CDCl_3$): δ = 1.37 (d, J = 16.5 Hz, 3 H, PCH_3), 1.76 (pseudo q, J = 6 Hz, 2 H. CCH_2C), 2.36 (s. 3 H, tos CH_3), 2.51 (d, J = 11.8 Hz, 3 H, NCH_3), 2.95 (t, J = 6.0 Hz, 2 H, NCH_2), 3.65–4.05 (m, 2 H, OCH_2), 7.47 (qAB, J = 8.3 Hz, 4 H, C_6H_4Me) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.54 (d, J = 132.7 Hz, PCH_3), 21.51 (tos. CH_3), 27.02 (NCH_3), 30.29 (d, J = 5.5 Hz, C*C*H_2C), 39.21 (NCH_2), 60.31 (d, J = 6.3 Hz, OCH_2), 127.02 (2 CH), 129.65 (2 CH), 137.44 (Me*C*-quat.), 143.07 (SO_2*C*quat.) ppm. ^{31}P NMR ($CDCl_3$): δ = +36.98 ppm. IR: $\tilde{\nu}$ = 1208 (νPO), 1321, 1163 (νSO_2), 3266 (νNH) cm^{-1}.

Similarly $\mathbf{7_a2}$ was obtained after 4 weeks. ^{1}H NMR ($CDCl_3$): δ = 1.71 (d, J = 15 Hz, 3 H, PCH_3), 1.6–1.86 (m, 2 H, CCH_2C), 2.36 (s, 3 H, tos CH_3), 2.60–3.00 (m, 2 H, NCH_2), 3.45–4.30 (m, 4 H, OCH_2 + benzylic CH_2), 7.25 (s, 5 H, C_6H_5), 7.46 (qAB, J = 8.3 Hz, 4 H, C_6H_4Me) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.93 (d, J = 106.3 Hz, PCH_3), 21.57 (tos CH_3), 29.99 (d, J = 7.7 Hz, C*C*H_2C), 39.49 (NCH_2), 60.87 (d, J = 6.4 Hz, OCH_2), 127.36 (CH), 127.62 (2 CH), 127.78 (2 CH), 128.76 (2 CH), 129.77 (2 CH), 137.07 (Me*C*quat.), 139.37 (d, J = 5.5 Hz, CH_2*C*quat.), 143.38 (SO_2*C*-quat.) ppm. ^{31}P NMR ($CDCl_3$): δ = +84.47 ppm. IR: $\tilde{\nu}$ = 1323,1156 (νSO_2), 3276 (νNH) cm^{-1}.

Similarly $\mathbf{7_d2}$ was obtained after 2 weeks. ^{1}H NMR ($CDCl_3$): δ = 1.84 (pseudo q, J = 6 Hz, 2 H, CCH_2C), 2.36 (s, 3 H, tos CH_3), 3.05 (t, J = 6 Hz, 2 H, NCH_2), 3.85–4.20 (m, 4 H, OCH_2 + CH_2), 7.18–7.85 (m, 5 H, C_6H_5), 8.09 (m, 5 H, PC_6H_5), 8.09 (qAB, J = 9.1 Hz, 4 H, $C_6H_4NO_2$) ppm. ^{31}P NMR ($CDCl_3$): δ = +77.64 ppm. IR: $\tilde{\nu}$ = 1324, 1157 (νSO_2), 3276 (νNH) cm^{-1}.

Similarly $\mathbf{7_g2}$ was obtained after 5 days. M.p. 183–185 °C. ^{1}H NMR ([D_6]DMSO): δ = 1.70–2.20 max 1.80 (m, 2 H, CCH_2C), 2.36 (s, 3 H, tos CH_3), 2.60–2.80, max 2.76 (m, 2 H, NCH_2), 3.25–3.60 (m, 2 H, OCH_2), 3.87 (broad s, 2 H, benzylic CH_2), 7.00–7.40 (m, 5 H, OC_6H_5), 7.61 (qAB, J = 7.9 Hz, 4 H, C_6H_4Me) ppm. ^{13}C NMR ([D_6]DMSO): δ = 20.89 (tos CH_3), 26.09 (C*C*H_2C), 42.96 (NCH_2), 44.01 (benzylic CH_2), 49.92 (OCH_2), 120.85 (d, J = 4.3 Hz, 2 CH), 122.85 (CH), 127.62 (CH), 128.54 (CH), 128.88 (CH), 129.46 (CH), 132.56 (CH_2*C*quat.), 138.21 (Me*C*quat.), 142.55 (SO_2*C*quat.), 152.8 (d, J = 7.5 Hz, O*C*quat.) ppm. ^{31}P NMR ([D_6]DMSO): δ = –8.23 ppm. IR: $\tilde{\nu}$ = 1322, 1154 (νSO_2), 3271 (νNH) cm^{-1}. $C_{23}H_{27}N_2O_5PS$:(474.52): calcd. C 58.21, H 5.73, N 5.90; found C 57.91, H 5.58, N 5.71.

Similarly $\mathbf{7_e2}$ was obtained after 20 days. ^{1}H NMR ($CDCl_3$ + D_2O): δ = 1.41 (d, J = 17.7 Hz, 3 H, PCH_3), 1.79 (pseudo q, J = 6.4 Hz, 2 H, CCH_2C), 2.38 (s, 3 H, tos CH_3), 3.01 (t, J = 6.4 Hz, 2 H, NCH_2), 3.99–4.45 (m, 4 H, benzylic CH_2 + OCH_2), 7.15–7.40 (m, 5 H,C_6H_5), 7.48 (qAB, J = 8.3 Hz, 4 H, C_6H_4Me) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.88 (d, J = 132.3 Hz, PCH_3), 21.52 (tos CH_3), 39.21 (d, J = 5.9 Hz, C*C*H_2C), 39.20 (NCH_2), 44.64 (benzylic CH_2), 60.47 (d, J = 6.3 Hz, OCH_2), 127.51 (CH), 126.99 (2 CH), 127.74 (2 CH), 128.69 (2 CH), 129.68 (2 CH), 137.36 (C*C*quat.), 139.74 (d, J = 5.2 Hz, CH_2*C*quat.), 143.15 (SO_2*C*quat.) ppm. ^{31}P NMR ($CDCl_3$ + D_2O): δ = +32.41 ppm. IR: $\tilde{\nu}$ = 1194 (νPO), 1319, 1157 (νSO_2), 3252 (νNH) cm^{-1}.

Similarly $\mathbf{7_a3}$ was obtained after 3 days at 60 °C in a mixture of DMF with a solution of potassium glycinate (8 equiv.) in water (5.6 equiv.). ^{31}P NMR: δ = +83.5 ppm.

Similarly $\mathbf{7_a4}$ was obtained after 5 days at 60 °C in a mixture of DMF with a solution of potassium alaninate (8 equiv.) in water (64 equiv.). ^{31}P NMR: δ = +83.9, + 83.3 ppm (2 couples of diastereoisomers, 1:1 ratio).

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