

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^[‡]

Frédéric Dujols^{*[a]} and Michel Mulliez^[a]

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**. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2006)

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 S_N2P 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).

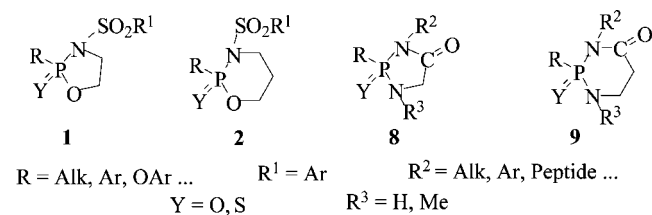


Figure 1. Phosphorous heterocycles **1**, **2**, **8**, and **9**.

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

[a] Laboratoire de Synthèse et Physico-chimie de Molécules d'Intérêt Biologique, Unité Mixte de Recherche no. 5068 associée au Centre National de la Recherche Scientifique, Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse cedex 09, France
Fax: + 33-5-61558255
E-mail: candre@chimie.ups-tlse.fr

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).

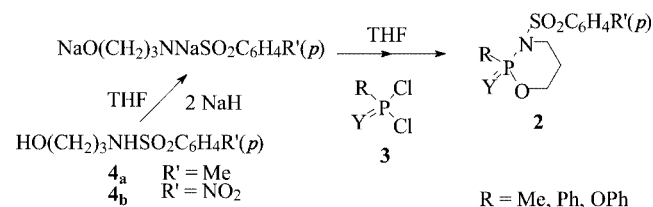
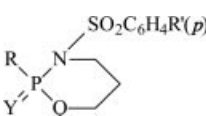


Figure 2. Synthesis of the heterocycles **2**.

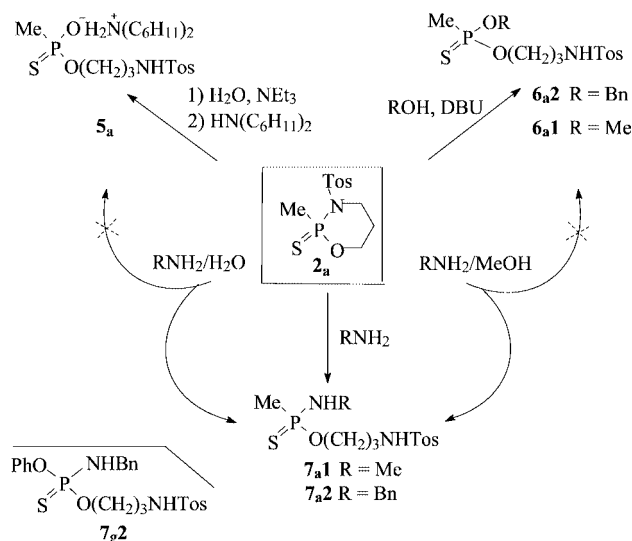
The NaCl formed was eliminated either by filtration or by aqueous extraction without any significant loss of heterocycles **2** by hydrolysis. These heterocycles (seven representatives shown in Table 1) are all crystalline in racemic form except **2_f**. As expected, they display correct elemental analyses and mass spectra, no OH or NH vibration in the IR spectra, a noticeable deshielding of the O and N methylene groups, both in ¹H- and ¹³C NMR spectra, relative to those in compound **4**, and a characteristic complexity of the ¹H 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 ³¹P 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 [%]
2_a	S	Me	Me	95–97 (Et ₂ O- <i>i</i> Pr ₂ O)	70
2_b	S	Me	NO ₂	117–119 (MeOH)	65
2_c	S	Ph	Me	145–147 (Et ₂ O)	61
2_d	S	Ph	NO ₂	154–156 (Et ₂ O)	68
2_e	O	Me	Me	123–125 (EtOAc/Et ₂ O)	65
2_f	O	Ph	Me	oil	63
2_g	O	OPh	Me	94–96 (CHCl ₃ -Et ₂ O)	59

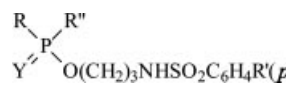
Reactivity

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 **2_a** 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 **2_a**, the yield is 70, 72, and 40%, respectively; see Table 2). In fact,

Figure 3. Reactions of the heterocycle **2_a**.

it appears that the selectivity of heterocycles **2** is comparable to that of **1**.^[1] For example, with the heterocycle **1** corresponding to **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]

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

					
N° ^[a]	Y	R	R'	R''	Yield [%]
5_a	S	Me	Me	OH DCHA salt	87
5_e	O	Me	Me	OH DCHA salt	82
6_{a1}	S	Me	Me	OMe	100 ^[b]
6_{c1}	S	Ph	Me	OMe	100 ^[b]
6_{d1}	S	Ph	NO ₂	OMe	100 ^[b]
6_{a2}	S	Me	Me	OBn	89
6_{c2}	S	Ph	Me	OBn	100 ^[b]
6_{b2}	S	Me	NO ₂	OBn	100 ^[b]
7_{a1}	S	Me	Me	NHMe	80, 95 ^[b,c] , 100 ^[b,d]
7_{d1}	S	Ph	NO ₂	NHMe	100, 100 ^[b,c] , 100 ^[b,d]
7_{e1}	O	Me	Me	NHMe	60 ^[c]
7_{a2}	S	Me	Me	NHBn	75, 70 ^[c]
7_{d2}	S	Ph	NO ₂	NHBn	100 ^[b]
7_{g2}	O	OPh	Me	NHBn	67
7_{c2}	O	Me	Me	NHBn	77 ^[c]
7_{a3}	S	Me	Me	NHCH ₂ COOK	72 ^[b,c]
7_{a4}	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 ³¹P 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 phosphoramides **7_{a1}** and **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 **2_g**; there is no loss of phenol, and the cyclic structure is retained, product **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 SN₂P mechanism of phosphorylation is involved (a penta-coordinated *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 SN₂P 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 (2_a) – **Illustrative Procedure:** A THF (50 mL) solution of **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 (**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 (Na₂SO₄), and concentrated to dryness. In each case the product was easily crystallized. ¹H NMR (CDCl₃): δ = 1.73–1.85 (m, 1 H, CCH₂C), 2.01–2.20 (m, 1 H, CCH₂C), 2.31 (d, *J* = 14.7 Hz, 3 H, PCH₃), 2.42 (s, 3 H, tos CH₃), 3.10–3.26 (m, 1 H, NCH₂), 3.50–3.70 (m, 1 H, NCH₂), 3.90–4.20 (m, 1 H, OCH₂), 4.30–4.50 (m, 1 H, OCH₂), 7.59 (qAB *J* = 8.1 Hz, 4 H, tos C₆H₄) ppm. ¹³C NMR (CDCl₃): δ = 21.75 (tos CH₃), 26.18 (d, *J* = 102.2 Hz, PCH₃), 26.34 (d, *J* = 2.7 Hz, CCH₂C), 44.39 (NCH₂), 63.22 (d, *J* = 7.2 Hz, OCH₂), 129.02 (2 CH), 129.42 (2 CH), 133.49 (MeCquat.), 144.82 (SO₂Cquat.) ppm. ³¹P NMR (CDCl₃): δ = +87.12 ppm. IR: 1343, 1164 (νSO₂) cm^{−1}. MS (DCI/CH₄): *m/z* (%) = 306 (100) [MH]⁺. C₁₁H₁₆NO₃PS₂ (305.36): calcd. C 43.27, H 5.28, N 4.59; found C 42.93, H 5.25, N 4.43.

Similarly **2_b** was obtained. ¹H NMR (CDCl₃): δ = 1.70–2.0 (m, 1 H, CCH₂C), 2.09–2.18 (m, 1 H, CCH₂C), 2.33 (d, *J* = 15.7 Hz, 3 H, PCH₃), 3.10–3.30 (m, 1 H, NCH₂), 3.60–3.80 (m, 1 H, NCH₂), 3.90–4.10 (m, 1 H, OCH₂), 4.30–4.50 (m, 1 H, OCH₂), 8.26 (qAB, *J* = 8.8 Hz, 4 H, C₆H₄NO₂) ppm. ¹³C NMR (CDCl₃): δ = 26.12 (d, *J* = 101.5 Hz, PCH₃), 26.27 (d, *J* = 3.1 Hz, CCH₂C), 44.80 (NCH₂), 63.46 (d, *J* = 7.5 Hz, OCH₂), 123.89 (2 CH), 130.42 (2 CH), 141.68 (SO₂Cquat.), 150.87 (NO₂Cquat.) ppm. ³¹P NMR (CDCl₃): δ = +87.22 ppm. IR: ν̄ = 1351, 1172 (νSO₂), 1530, 1355 (νNO₂) cm^{−1}. C₁₀H₁₃N₂O₅PS₂ (336.33): calcd. C 35.71, H 3.89, N 8.33; found C 35.46, H 3.78, N 8.34.

Similarly **2_c** was obtained. ¹H NMR (CDCl₃): δ = 1.80–2.00 (m, 1 H, CCH₂C), 2.10–2.30 (m, 1 H, CCH₂C), 2.42 (s, 3 H, tos CH₃), 3.30–3.50 (m, 1 H, NCH₂), 3.70–3.90 (m, 1 H, NCH₂), 4.10–4.30 (m, 1 H, OCH₂), 4.40–4.60 (m, 1 H, OCH₂), 7.52 (qAB, *J* = 8.1 Hz, 4 H, C₆H₄Me), 7.50–7.60 (m, 3 H, C₆H₅), 8.00–8.20 (m, 2 H, C₆H₅) ppm. ¹³C NMR (CDCl₃): δ = 21.42 (tos CH₃), 26.21 (d, *J* = 3.8 Hz, CCH₂C), 45.38 (NCH₂), 64.08 (d, *J* = 7.5 Hz, OCH₂), 128.19 (d, *J* = 15.7 Hz, 2 CH), 128.76 (CH), 129.53 (CH), 130.56 (d, *J* = 154.5 Hz, PCquat.), 132.08 (d, *J* = 12.3 Hz, 2 CH), 133.10 (d, *J* = 2.9 Hz, CH), 134.41 (MeCquat.), 144.52 (SO₂Cquat.) ppm. ³¹P NMR (CDCl₃): δ = +76.29 ppm. IR: ν̄ = 1352, 1164 (νSO₂) cm^{−1}. MS (DCI/CH₄): *m/z* (%) = 368 (100) [MH]⁺. C₁₆H₁₈NO₃PS₂ (367.43): calcd. C 52.30, H 4.94, N 3.81; found C 52.03, H 4.98, N 3.57.

Similarly **2_d** was obtained. ¹H NMR (CDCl₃): δ = 1.90–2.10 (m, 1 H, CCH₂C), 2.20–2.40 (m, 1 H, CCH₂C), 3.40–3.60 (m, 1 H, NCH₂), 3.80–4.00 (m, 1 H, NCH₂), 4.20–4.40 (m, 1 H, OCH₂), 4.40–4.60 (m, 1 H, OCH₂), 7.50–7.70 (m, 3 H, C₆H₅), 8.00–8.20 (m, 2 H, C₆H₅), 8.18 (qAB, *J* = 8.9 Hz, 4 H, C₆H₄NO₂) ppm. ¹³C NMR (CDCl₃): δ = 26.27 (d, *J* = 3.7 Hz, CCH₂C), 45.86 (NCH₂), 64.33 (d, *J* = 7.4 Hz, OCH₂), 123.91 (2 CH), 128.42 (d, *J* = 16.1 Hz, 2 CH), 129.23 (d, *J* = 154.7 Hz, PCquat.), 130.09 (2 CH), 132.19 (d, *J* = 12.8 Hz, 2 CH), 133.6 (d, *J* = 2.9 Hz, CH), 142.76 (SO₂Cquat.), 150.55 (NO₂Cquat.) ppm. ³¹P (CDCl₃): δ = +76.34 ppm. IR: ν̄ = 1311, 1162 (νSO₂), 1533, 1350 (νNO₂) cm^{−1}. C₁₅H₁₅N₂O₅PS₂ (366.33): calcd. C 45.22, H 3.80, N 7.03; found C 45.29, H 3.64, N 6.76.

Similarly **2_e** was obtained. ¹H NMR (CDCl₃): δ = 1.60–1.90 (m, 2 H, CCH₂C), 1.87 (d, *J* = 17.7 Hz, 3 H, PCH₃), 2.33 (s, 3 H, tos CH₃), 2.90–3.20 (m, 1 H, NCH₂), 3.50–3.60 (m, 1 H, NCH₂), 3.90–4.20 (m, 2 H, OCH₂), 7.56 (qAB, *J* = 7.9 Hz, 4 H, C₆H₄Me) ppm. ¹³C NMR (CDCl₃): δ = 16.34 (d, *J* = 135.7 Hz, PCH₃), 21.59 (tos CH₃), 25.53 (d, *J* = 5.2 Hz, CCH₂C), 44.75 (NCH₂), 64.99 (d, *J* = 7.9 Hz, OCH₂), 128.35 (2 CH), 129.75 (2 CH), 134.97 (MeCquat.), 144.66 (SO₂Cquat.) ppm. ³¹P NMR (CDCl₃): δ = +25.34 ppm. IR: ν̄ = 1210 (νPO), 1341, 1162 (νSO₂) cm^{−1}. MS (DCI/CH₄): *m/z* (%) = 290 (100) [MH]⁺. C₁₁H₁₆NO₄PS (289.29): calcd. C 45.67, H 5.57, N 4.84; found C 45.84, H 5.34, N 4.81.

Similarly **2_f** was obtained. ¹H NMR (CDCl₃): δ = 1.60–2.10 (m, 2 H, CCH₂C), 2.36 (s, 3 H, tos CH₃), 3.35–3.85 (m, 2 H, NCH₂), 3.80–4.45 (m, 2 H, OCH₂), 7.20–7.90 (m, 5 H, PC₆H₅), 7.59 (qAB *J* = 8.4 Hz, 4 H, C₆H₄Me) ppm. ¹³C NMR (CDCl₃): δ = 21.66 (tos CH₃), 25.66 (d, *J* = 5.4 Hz, CCH₂C), 45.43 (NCH₂), 65.76 (d, *J* = 7.9 Hz, OCH₂), 128.32 (2 CH), 128.49 (d, *J* = 16.6 Hz, 2 CH), 129.74 (2 CH), 131.24 (d, *J* = 151.6 Hz, PCquat.), 132.10 (d, *J* = 11.1 Hz, 2 CH), 132.93 (d, *J* = 2.7 Hz, CH), 135.48 (MeCquat.), 144.59 (SO₂Cquat.) ppm. ³¹P NMR (CDCl₃): δ = +11.92 ppm. IR: ν̄ = 1339, 1165 (νSO₂) cm^{−1}. C₁₆H₁₈NO₄PS (351.36): C 54.69, H 5.16, N 3.98; found C 54.31, H 5.01, N 3.63.

Similarly **2_g** was obtained. ¹H NMR (CDCl₃): δ = 1.80–2.00 (m, 2 H, CCH₂C), 2.41 (s, 3 H, tos CH₃), 3.50–3.70 (m, 1 H, NCH₂),

3.80–4.00 (m, 1 H, NCH₂), 4.30–4.50 (m, 2 H, OCH₂), 7.10–7.40 (m, 5 H, OC₆H₅), 7.59 (qAB, $J = 8.3$ Hz, 4 H, C₆H₄Me) ppm. ¹³C NMR (CDCl₃): $\delta = 21.70$ (tos CH₃), 25.90 (d, $J = 5.4$ Hz, CCH₂C), 46.93 (NCH₂), 69.90 (d, $J = 8.4$ Hz, OCH₂), 120.24 (d, $J = 4.8$ Hz, 2 CH), 125.49 (CH), 127.89 (CH), 129.65 (CH), 129.82 (CH), 136.60 (MeCquat.), 144.69 (NO₂Cquat.), 150.22 (d, $J = 7.6$ Hz, OCquat.) ppm. ³¹P NMR (CDCl₃): $\delta = -13.71$ ppm. IR: $\tilde{\nu} = 1246$ (vPO), 1336, 1167 (vSO₂) cm⁻¹. C₁₆H₁₈NO₃PS (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 **2a** (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 ³¹P 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 (Na₂SO₄) and concentrated to dryness. ¹H NMR (CDCl₃): $\delta = 0.9$ – 1.9 (m, 22 H, 10 CH₂ DCHA + CCH₂C), 1.60 (d, $J = 14.5$ Hz, 3 H, PCH₃), 2.39 (s, 3 H, tos CH₃), 2.90–3.20 (m, 4 H, 2 CH DCHA + NCH₂), 3.60–4.10 (m, 2 H, OCH₂), 7.48 (qAB, $J = 8.4$ Hz, 4 H, C₆H₄Me) ppm. ¹³C NMR (CDCl₃): $\delta = 21.52$ (tos CH₃), 24.75 (4 CH₂ DCHA), 25.05 (2 CH₂ DCHA), 29.18 (4 CH₂ DCHA), 30.08 (d, $J = 6.9$ Hz, CCH₂C), 39.59 (NCH₂), 53.08 (2 CH DCHA), 60.87 (d, $J = 5.8$ Hz, OCH₂), 127.07 (2 CH), 129.56 (2 CH), 137.63 (MeCquat.), 142.92 (SO₂Cquat.) ppm. ³¹P NMR (CDCl₃): $\delta = +75.29$ ppm. IR: $\tilde{\nu} = 1327$, 1158 (vSO₂), 2800–2400 (vN⁺H), 3245 (vNH) cm⁻¹.

Similarly **5e** was obtained. ¹H NMR (CDCl₃): $\delta = 1.10$ – 2.05 (m, 22 H, 10 CH₂ DCHA + CCH₂C), 1.27 (d, $J = 10.5$ Hz, 3 H, PCH₃), 2.37 (s, 3 H, tos CH₃), 2.65–3.12 (m, 4 H, 2 CH DCHA + NCH₂), 3.70–4.05 (m, 2 H, OCH₂), 7.46 (qAB, $J = 8.3$ Hz, 4 H, C₆H₄Me) ppm. ¹³C NMR (CDCl₃): $\delta = 12.47$ (d, $J = 140$ Hz, PCH₃), 21.53 (tos CH₃), 24.73 (4 CH₂ DCHA), 25.11 (2 CH₂ DCHA), 29.17 (4 CH₂ DCHA), 29.17 (4 CH₂ DCHA), 30.26 (d, $J = 4.5$ Hz, CCH₂C), 39.31 (NCH₂), 52.96 (2 CH DCHA), 60.85 (d, $J = 5.7$ Hz, OCH₂), 126.99 (2 CH), 129.58 (2 CH), 137.91 (MeCquat.), 142.90 (SO₂Cquat.) ppm. ³¹P NMR (CDCl₃): $\delta = -25.48$ ppm. IR: $\tilde{\nu} = 1326$ (et), 1159 (vSO₂), 1198 (vPO), 2800–2400 (vNH⁺), 3244 (vNH) cm⁻¹.

Alcoholysis – Illustrative Procedure: To a DMF (0.8 g) solution of **2a** (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 (MgSO₄), and concentrated to dryness, leaving **6a1** as a colorless oil. ¹H NMR (CDCl₃): $\delta = 1.67$ – 2.00 (m, 2 H, CCH₂C), 1.73 (d, $J = 15.5$ Hz, 3 H, PCH₃), 2.39 (s, 3 H, tos CH₃), 2.70–3.20. max 2.99 (m, 2 H, NCH₂), 3.65 (d, $J = 13.8$ Hz, 3 H, OCH₃), 3.60–4.20 (m, 2 H, OCH₂), 7.49 (qAB, $J = 8.3$ Hz, 4 H, C₆H₄Me) ppm. ¹³C NMR (CDCl₃): $\delta = 20.83$ (d, $J = 114.9$ Hz, PCH₃), 21.56 (tos CH₃), 30.29 (d, $J = 6.9$ Hz, CCH₂C), 39.53 (NCH₂), 53.02 (d, $J = 6.6$ Hz, OCH₃), 65.18 (d, $J = 6.6$ Hz, OCH₂), 127.13 (2 CH), 129.77 (2 CH), 137.02 (MeCquat.), 143.46 (SO₂Cquat.) ppm. ³¹P NMR (CDCl₃): $\delta = +98.86$ ppm. IR: $\tilde{\nu} = 1328$, 1159 (vSO₂), 3279 (vNH) cm⁻¹. Only 56% reaction was observed after 18 days in the presence of NEt₃ (5 equiv.) in place of DBU.

Similarly **6c1** was obtained after 2 days in acetonitrile. ¹H NMR (CDCl₃ + D₂O): $\delta = 1.80$ (pseudo q, $J = 6.2$ Hz, 2 H, CCH₂C),

2.38 (s, 3 H, tos CH₃), 3.02 (t, $J = 6.2$ Hz, 2 H, NCH₂), 3.66 (d, $J = 13.7$ Hz, 3 H, OCH₃), 3.95–4.31 (m, 2 H, OCH₂), 7.19–7.96 (m, 5 H, PC₆H₅), 7.47 (qAB, $J = 8.4$ Hz, 4 H, C₆H₄NO₂) ppm. ¹³C NMR (CDCl₃ + D₂O): $\delta = 21.59$ (tos CH₃), 30.13 (d, $J = 6.5$ Hz, CCH₂C), 39.50 (NCH₂), 63.69 (d, $J = 5.7$ Hz, OCH₂), 53.33 (d, $J = 4.9$ Hz, OCH₃), 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 (MeCquat.), 143.45 (SO₂Cquat.) ppm. ³¹P NMR (CDCl₃): $\delta = +87.97$ ppm. IR: $\tilde{\nu} = 1331$, 1158 (vSO₂), 3288 (vNH) cm⁻¹.

Similarly **6a1** was obtained after 24 h in acetonitrile. The sulfonic acid Amberlyst 15 resin was used for the removal of DBU. ¹H NMR (CDCl₃): $\delta = 1.6$ – 1.9 (m, 2 H, CCH₂C), 3.03 (t, $J = 6.4$ Hz, 2 H, NCH₂), 3.65 (d, $J = 13.7$ Hz, 3 H, OCH₃), 3.95–4.22 (m, 2 H, OCH₂), 7.35–7.88 (m, 5 H, C₆H₅C), 8.10 (qAB, $J = 9.2$ Hz, 4 H, C₆H₄NO₂) ppm. ¹³C NMR (CDCl₃): $\delta = 30.72$ (d, $J = 7$ Hz, CCH₂C), 40.05 (NCH₂), 53.34 (d, $J = 5.5$ Hz, OCH₃), 63.98 (d, $J = 5.9$ Hz, OCH₂), 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, PCquat.), 147.49 (MeCquat.), 149.52 (SO₂Cquat.) ppm. ³¹P NMR (CDCl₃): $\delta = +89.83$ ppm. IR: $\tilde{\nu} = 1311$, 165 (vSO₂), 1530, 1349 (vNO₂), 3286 (vNH) 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 **6a2** was obtained after 3 weeks. ¹H NMR (CDCl₃ + D₂O): $\delta = 1.71$ (pseudo q, $J = 6.5$ Hz, 2 H, CCH₂C), 1.72 (d, $J = 15.5$ Hz, 3 H, PCH₃), 2.37 (s, 3 H, tos CH₃), 2.94 (t, $J = 6.5$ Hz, 2 H, NCH₂), 3.70–4.20 (m, 2 H, OCH₂), 4.94–5.11 (m, 2 H, OCH₂), 7.19–7.32 (m, 5 H, C₆H₅CH₂), 7.48 (qAB, $J = 8.3$ Hz, 4 H, C₆H₄Me) ppm. ¹³C NMR (CDCl₃): $\delta = 21.54$ (tos CH₃), 21.59 (d, $J = 115.3$ Hz, PCH₃), 30.17 (d, $J = 7.2$ Hz, CCH₂C), 39.53 (NCH₂), 63.13 (d, $J = 6.7$ Hz, OCH₂), 68.16 (d, $J = 6.2$ Hz, benzylic CH₂), 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, CH₂Cquat.), 137.03 (MeCquat.), 143.44 (SO₂Cquat.) ppm. ³¹P (CDCl₃): $\delta = +97.52$. IR: $\tilde{\nu} = 1327$, 1159 (vSO₂), 3277 (vNH) cm⁻¹.

Similarly **6c2** was obtained after 11 days. IR: $\tilde{\nu} = 1327$, 1159 (vSO₂), 3317 (vNH). ¹H NMR (CDCl₃ + D₂O): $\delta = 1.73$ (pseudo q, $J = 6.2$ Hz, 2 H, CCH₂C), 2.37 (s, 3 H, tos CH₃), 2.85–2.99 (m, 2 H, NCH₂), 3.88–4.12 (m, 2 H, OCH₂), 4.98–5.15 (m, 2 H, OCH₂), 7.45 (qAB, $J = 8.1$ Hz, 4 H, C₆H₄Me), 7.10–8.00 (m, 10 H, 2 C₆H₅) ppm. ¹³C NMR (CDCl₃): $\delta = 21.59$ (tos CH₃), 30.12 (d, $J = 7.2$ Hz, CCH₂C), 39.54 (NCH₂), 63.68 (d, $J = 5.9$ Hz, OCH₂), 68.44 (d, $J = 5.3$ Hz, benzylic CH₂), 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, PCquat.), 132.61 (d, $J = 2.9$ Hz, CH), 136.10 (d, $J = 7.7$ Hz, CH₂Cquat.), 141.06 (MeCquat.), 143.39 (SO₂Cquat.) ppm. ³¹P NMR (CDCl₃): $\delta = +88.71$ ppm. IR: $\tilde{\nu} = 1327$, 1159 (vSO₂), 3317 (vNH) 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 **6b2** was obtained after 3 days in benzyl alcohol as solvent. ¹H NMR (CDCl₃ + D₂O): $\delta = 1.77$ (pseudo q, $J = 6.2$ Hz, 2 H, CCH₂C), 3.01 (t, $J = 6.2$ Hz, 2 H, NCH₂), 3.88–4.20 (m, 2 H, OCH₂), 4.95–5.14 (m, 2 H, OCH₂), 7.06–7.70 (m, 5 H, C₆H₅), 8.07 (qAB, $J = 9$ Hz, 4 H, C₆H₄NO₂) ppm. ¹³C NMR (CDCl₃): $\delta = 30.05$ (d, $J = 7.2$ Hz, CCH₂C), 39.46 (NCH₂), 63.29 (d, $J = 5.9$ Hz, OCH₂), 68.65 (d, $J = 5.3$ Hz, benzylic CH₂), 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, CH₂Cquat.), 135.92 (d, $J = 7.3$ Hz, CH₂Cquat.), 145.89 (SO₂Cquat.), 149.99 (NO₂Cquat.) ppm. ³¹P NMR (CDCl₃): $\delta = +88.82$ ppm. IR: $\tilde{\nu} = 1311$, 1165 (vSO₂), 1529, 1348 (vNO₂), 3282 (vNH) cm⁻¹.

Aminolysis – Illustrative Procedure: After 3 hours (no more **2a** by ³¹P NMR), the initial solution of methylamine (0.24 g, 7.41 mmol) and **2a** (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 (Na₂SO₄), and concentrated to dryness. The product **7a1** was crystallized: m.p. 69–71 °C (EtOAc/iPr₂O). 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. ¹H NMR (CDCl₃): $\delta = 1.65$ (d, $J = 13$ Hz, 3 H, PCH₃), 1.46–1.67 (m, 2 H, CCH₂C), 2.33 (s, 3 H, tos CH₃), 2.51 (d, $J = 13.1$ Hz, 3 H, NCH₃), 2.60–2.99 (m, 2 H, NCH₂), 3.60–4.08 (m, 2 H, OCH₂), 7.45 (qAB, $J = 8.2$ Hz, 4 H, C₆H₄Me) ppm. ¹³C NMR (CDCl₃): $\delta = 19.57$ (d, $J = 106.6$ Hz, PCH₃), 21.55 (tos CH₃), 27.93 (d, $J = 2.8$ Hz, NCH₃), 29.96 (d, $J = 7.5$ Hz, CCH₂C), 39.57 (NCH₂), 60.65 (d, $J = 6.3$ Hz, OCH₂), 127.07 (2 CH), 129.76 (2 CH), 139.61 (MeCquat.), 143.36 (SO₂Cquat.) ppm. ³¹P NMR (CDCl₃): $\delta = +85.66$. IR: $\tilde{\nu} = 1324$, 1158 (vSO₂), 3275 (vNH) cm⁻¹. C₁₁H₁₉N₂O₃PS₂ (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 **7a1** was obtained after 30 min in DMF. ¹H NMR (CDCl₃ + D₂O): $\delta = 1.91$ (pseudo q, $J = 5.9$ Hz, 2 H, CCH₂C), 2.46 (d, $J = 13.3$ Hz, 3 H, NCH₃), 3.05–3.20 (m, 2 H, NCH₂), 3.95–4.30 (m, 2 H, OCH₂), 7.35–7.80 (m, 5 H, PC₆H₅), 8.11 (qAB, $J = 9.2$ Hz, 4 H, C₆H₄Me) ppm. ¹³C NMR (CDCl₃): $\delta = 28.15$ (d, $J = 2.4$ Hz, NCH₃), 30.09 (d, $J = 6.9$ Hz, CCH₂C), 39.46 (NCH₂), 60.99 (d, $J = 5.8$ Hz, OCH₂), 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, PCquat.), 145.70 (SO₂Cquat.), 149.95 (NO₂Cquat.) ppm. ³¹P NMR (CDCl₃): $\delta = +79.18$. IR: $\tilde{\nu} = 1309$, 1163 (vSO₂), 1529, 1347 (vNO₂), 3287 (vNH) cm⁻¹.

Similarly **7a1** was obtained after 5 h in DMF. ¹H NMR (CDCl₃): $\delta = 1.37$ (d, $J = 16.5$ Hz, 3 H, PCH₃), 1.76 (pseudo q, $J = 6$ Hz, 2 H, CCH₂C), 2.36 (s, 3 H, tos CH₃), 2.51 (d, $J = 11.8$ Hz, 3 H, NCH₃), 2.95 (t, $J = 6.0$ Hz, 2 H, NCH₂), 3.65–4.05 (m, 2 H, OCH₂), 7.47 (qAB, $J = 8.3$ Hz, 4 H, C₆H₄Me) ppm. ¹³C NMR (CDCl₃): $\delta = 11.54$ (d, $J = 132.7$ Hz, PCH₃), 21.51 (tos CH₃), 27.02 (NCH₃), 30.29 (d, $J = 5.5$ Hz, CCH₂C), 39.21 (NCH₂), 60.31 (d, $J = 6.3$ Hz, OCH₂), 127.02 (2 CH), 129.65 (2 CH), 137.44 (MeCquat.), 143.07 (SO₂Cquat.) ppm. ³¹P NMR (CDCl₃): $\delta = +36.98$ ppm. IR: $\tilde{\nu} = 1208$ (vPO), 1321, 1163 (vSO₂), 3266 (vNH) cm⁻¹.

Similarly **7a2** was obtained after 4 weeks. ¹H NMR (CDCl₃): $\delta = 1.71$ (d, $J = 15$ Hz, 3 H, PCH₃), 1.6–1.86 (m, 2 H, CCH₂C), 2.36 (s, 3 H, tos CH₃), 2.60–3.00 (m, 2 H, NCH₂), 3.45–4.30 (m, 4 H, OCH₂ + benzylic CH₂), 7.25 (s, 5 H, C₆H₅), 7.46 (qAB, $J = 8.3$ Hz, 4 H, C₆H₄Me) ppm. ¹³C NMR (CDCl₃): $\delta = 20.93$ (d, $J = 106.3$ Hz, PCH₃), 21.57 (tos CH₃), 29.99 (d, $J = 7.7$ Hz, CCH₂C), 39.49 (NCH₂), 60.87 (d, $J = 6.4$ Hz, OCH₂), 127.36 (CH), 127.62 (2 CH), 127.78 (2 CH), 128.76 (2 CH), 129.77 (2 CH), 137.07 (MeCquat.), 139.37 (d, $J = 5.5$ Hz, CH₂Cquat.), 143.38 (SO₂Cquat.) ppm. ³¹P NMR (CDCl₃): $\delta = +84.47$ ppm. IR: $\tilde{\nu} = 1323$, 1156 (vSO₂), 3276 (vNH) cm⁻¹.

Similarly **7a2** was obtained after 2 weeks. ¹H NMR (CDCl₃): $\delta = 1.84$ (pseudo q, $J = 6$ Hz, 2 H, CCH₂C), 2.36 (s, 3 H, tos CH₃), 3.05 (t, $J = 6$ Hz, 2 H, NCH₂), 3.85–4.20 (m, 4 H, OCH₂ + CH₂), 7.18–7.85 (m, 5 H, C₆H₅), 8.09 (m, 5 H, PC₆H₅), 8.09 (qAB, $J =$

9.1 Hz, 4 H, C₆H₄NO₂) ppm. ³¹P NMR (CDCl₃): $\delta = +77.64$ ppm. IR: $\tilde{\nu} = 1324$, 1157 (vSO₂), 3276 (vNH) cm⁻¹.

Similarly **7g2** was obtained after 5 days. M.p. 183–185 °C. ¹H NMR ([D₆]DMSO): $\delta = 1.70$ –2.20 max 1.80 (m, 2 H, CCH₂C), 2.36 (s, 3 H, tos CH₃), 2.60–2.80, max 2.76 (m, 2 H, NCH₂), 3.25–3.60 (m, 2 H, OCH₂), 3.87 (broad s, 2 H, benzylic CH₂), 7.00–7.40 (m, 5 H, OC₆H₅), 7.61 (qAB, $J = 7.9$ Hz, 4 H, C₆H₄Me) ppm. ¹³C NMR ([D₆]DMSO): $\delta = 20.89$ (tos CH₃), 26.09 (CCH₂C), 42.96 (NCH₂), 44.01 (benzylic CH₂), 49.92 (OCH₂), 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 (CH₂Cquat.), 138.21 (MeCquat.), 142.55 (SO₂Cquat.), 152.8 (d, $J = 7.5$ Hz, OCquat.) ppm. ³¹P NMR ([D₆]DMSO): $\delta = -8.23$ ppm. IR: $\tilde{\nu} = 1322$, 1154 (vSO₂), 3271 (vNH) cm⁻¹. C₂₃H₂₇N₂O₅PS₂ (474.52): calcd. C 58.21, H 5.73, N 5.90; found C 57.91, H 5.58, N 5.71.

Similarly **7e2** was obtained after 20 days. ¹H NMR (CDCl₃ + D₂O): $\delta = 1.41$ (d, $J = 17.7$ Hz, 3 H, PCH₃), 1.79 (pseudo q, $J = 6.4$ Hz, 2 H, CCH₂C), 2.38 (s, 3 H, tos CH₃), 3.01 (t, $J = 6.4$ Hz, 2 H, NCH₂), 3.99–4.45 (m, 4 H, benzylic CH₂ + OCH₂), 7.15–7.40 (m, 5 H, C₆H₅), 7.48 (qAB, $J = 8.3$ Hz, 4 H, C₆H₄Me) ppm. ¹³C NMR (CDCl₃): $\delta = 12.88$ (d, $J = 132.3$ Hz, PCH₃), 21.52 (tos CH₃), 39.21 (d, $J = 5.9$ Hz, CCH₂C), 39.20 (NCH₂), 44.64 (benzylic CH₂), 60.47 (d, $J = 6.3$ Hz, OCH₂), 127.51 (CH), 126.99 (2 CH), 127.74 (2 CH), 128.69 (2 CH), 129.68 (2 CH), 137.36 (CCquat.), 139.74 (d, $J = 5.2$ Hz, CH₂Cquat.), 143.15 (SO₂Cquat.) ppm. ³¹P NMR (CDCl₃ + D₂O): $\delta = +32.41$ ppm. IR: $\tilde{\nu} = 1194$ (vPO), 1319, 1157 (vSO₂), 3252 (vNH) cm⁻¹.

Similarly **7a3** 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.). ³¹P NMR: $\delta = +83.5$ ppm.

Similarly **7a4** 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.). ³¹P NMR: $\delta = +83.9$, + 83.3 ppm (2 couples of diastereoisomers, 1:1 ratio).

- [1] F. Dujols, L. Marty, M. Mulliez, *Org. Biomol. Chem.* **2005**, *3*, 227–232.
- [2] F. G. Bordwell, F. G. Algrim, *J. Org. Chem.* **1976**, *41*, 2507–2508.
- [3] G. Dauphin, A. Kergomard, *Bull. Soc. Chim. France* **1961**, 486–492.
- [4] See *inter alia*: F. H. Westheimer, *Acc. Chem. Res.* **1968**, *1*, 70–78.
- [5] J. Emsley, D. Hall, *The Chemistry of Phosphorus*, Harper and Row, London, **1976**, pp. 329–336.
- [6] P. Cazabonne, F. Dujols, M. Mulliez, *Synthesis of Constrained N-Sulfonylated Amino Alcohols*, in preparation; F. Dujols' doctoral thesis [Université Paul Sabatier, Toulouse (France), 4–10–99], ch. VI.
- [7] No definite structure, such as chair or boat, could be determined.
- [8] M. Mulliez, *Participation of Sulfonamides in the Reactions of Phosphorylation*, in preparation; F. Dujols' doctoral thesis [Université Paul Sabatier, Toulouse (France), 4–10–99], ch. VII.
- [9] For acyclic compounds, see for example: V. E. Belskii, L. S. Novikova, L. A. Kudryatseva, B. E. Ivanov, *Bull. Acad. Sci. USSR, Div. Chem. Sci., (Izv. Akad. Nauk SSSR, Ser. Khim Transl.)* **1977**, 1188–1202.
- [10] For cyclic compounds, see for example: M. Revel, J. Navech, F. Mathis, *Bull. Soc. Chim. France* **1971**, 105–112.
- [11] See particularly: L. Horner, *J. Prakt. Chem.* **1992**, *234*, 645–6553 and references cited therein.
- [12] J. M. Grévy, M. Mulliez, *J. Chem. Soc., Perkin Trans. 2* **1995**, 1809–1816.

- [13] M. Mulliez, *Tetrahedron* **1981**, 37, 2027–2041.
- [14] F. Dujols, P. Jollet, M. Mulliez, *Phosphorus Sulfur Silicon* **1998**, 134–135, 231–254.
- [15] G. Sosnovsky, M. Konieczny, *Synthesis* **1977**, 618–619.
- [16] F. Dujols, M. Mulliez, *Phosphorus Sulfur Silicon* **2000**, 157, 165–191.
- [17] More details are available in: F. Dujols' doctoral thesis: no. 3497, **1999**, Université Paul Sabatier, Toulouse (France) .
- [18] F. Dujols, M. Mulliez, *J. Heterocycl. Chem.* **2001**, 38, 475–480.

Received: September 30, 2005

Published Online: February 6, 2006