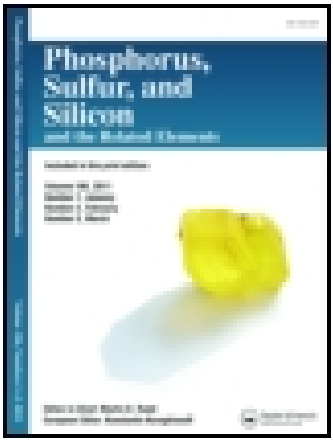

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FORMATION OF AMINOMETHYLPHOSPHONIC ACIDS AND MONOESTERS FROM AMINOMETHYLPHOSPHONATES

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FORMATION OF AMINOMETHYLPHOSPHONIC ACIDS AND MONOESTERS FROM AMINOMETHYLPHOSPHONATES

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Correcting a previous preliminary communication, the reaction between diethyl N-benzoyl α-aminomethylphosphonate and PCl_5 is shown to afford the corresponding aminomethylphosphonic acids and monoesters instead of the previous mentioned oxazaphospholene.

Keywords: aminomethylphosphonates; aminomethylphosphonic acids and monoesters

INTRODUCTION

α -Aminomethylphosphonic acids **1**, mono- **2** and diesters **3** (Fig. 1), analogues of aminoacids in which a COOH group is replaced by PO_3H_2, PO_3HR or PO_3R_2, are of wide interest as biologically active molecules in biochemistry, medicine and plant protection[1].

RESULTS

We directed our research to the synthesis of a heterocyclic five membered ring **4**, with a P-C-N unit, equivalent to an α-aminomethylphosphonic acid twice protected on the nitrogen atom and the phosphorus atom. We tried to

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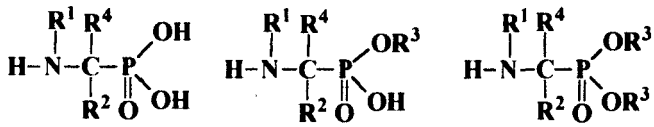


1 2 3

FIGURE 1

apply a cyclisation method first described, in a special case, by Drach and Lobanov[3] (Fig. 2).

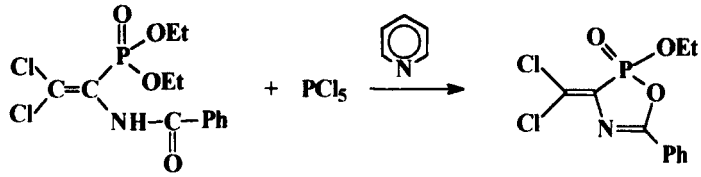


FIGURE 2

First in a preliminary communication[2], we suggested indeed the formation of an oxazaphospholene cyclic structure **4** (Fig. 3), but further informations and analyses showed actually the formation of the corresponding mono ester **5** or the α-aminomethylphosphonic acid **6**, according to the amount of PCl_5 used (Table I). Other activating agents, such as Ph_3PBr_2 or Ph_3P/CCl_4, were also tried to promote the cyclisation but unsuccessfully.

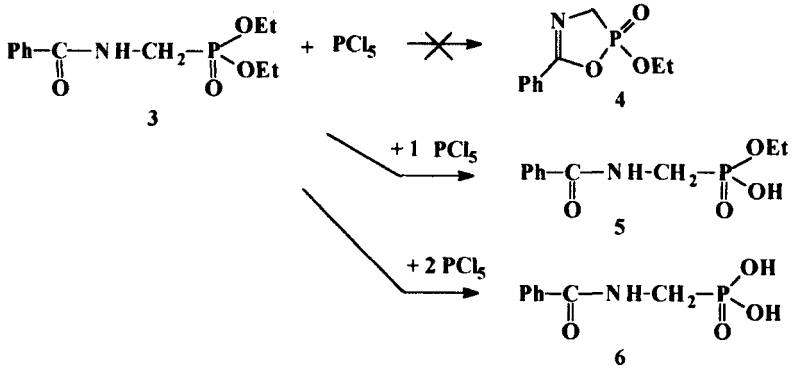
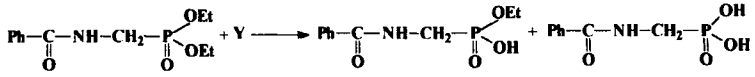


FIGURE 3

TABLE I Dependence of the formation of **5** and **6** from **3** on the amount of PCl_5 used.



3 **5** **6**

Y	*Treatment*	*Product*	*Yield (%)*
1 PCl_5 / pyridine	Saturated solution $NaHCO_3$	**5**	38
2 PCl_5 / pyridine	Saturated solution $NaHCO_3$	**6**	85
Ph_3PBr_2	Filtration	**6**	63
Ph_3P / CCl_4 / Et_3N	Filtration	**No reaction**	0

CONCLUSION

The various reactions investigated did not give the cyclic compound **4**, twice protected on the nitrogen atom and the phosphorus atom, but the mono-ester **5** with one equivalent of PCl_5, and the α-aminomethylphosphonic acid **6** with two equivalents of PCl_5 or Ph_3PBr_2.

EXPERIMENTAL

All the experiments were carried out under nitrogen, with anhydrous solvents. Melting points were determined with a Metler FP5 and a Wild Leitz 350 apparatus. The compounds are characterized by ^{1}H-NMR (200.132 MHz), ^{13}C-NMR (50.323 MHz) and ^{31}P-NMR (81.0 MHz). Elemental analyses were performed by the "Service Central de Micro-analyse du CNRS", in Montpellier. The infrared spectra were obtained using a Perkin-Elmer Spectrum 1000 recording spectrometer. Mass spectra were performed using Fast Atom Bombardment or Electronic Impact (70eV).

General procedure for the synthesis of compound 5

To a solution of compound **3** (17.5 mmoles, 4.75 g) in anhydrous toluene (60 ml) and pyridine (19.25 mmoles, 1.4 ml), at −5°C, is added dropwise a

solution of PCl_5 (17.5 mmoles, 3.64 g) in anhydrous toluene (60 ml) during 30 min. After 12 h at 20°C, pyridinium chloride is filtered and the filtrate is dried under vacuum. The oil is washed by a saturated solution of sodium bicarbonate until pH = 7, then extracted with chloroform. The aqueous phase is dried under vacuum and the white solid is washed with anhydrous ethanol and dried. A white solid (1.75 g, 38 % yield) is isolated and characterized by m.p. (145–150°C), IR, ^{31}P, ^{1}H, ^{13}C NMR spectra.

General procedure for the synthesis of compound 6

a. To a solution of compound **3** (46 mmoles, 12.5 g) in anhydrous toluene (100 ml) and pyridine (8.2 ml), at −5°C, is added dropwise a solution of PCl_5 (92 mmoles, 19.16 g) in anhydrous toluene (150 ml) during 1 h. After 12 h at 20°C, pyridinium chloride is filtered and the filtrate is dried under vacuum. The oil is washed by a saturated solution of sodium bicarbonate until pH = 7, then extracted with chloroform. The aqueous phase is dried under vacuum and the white solid, washed with ether and anhydrous ethanol, is isolated (9.3 g, 85 % yield) and characterized by IR, ^{31}P, ^{1}H, ^{13}C NMR spectra.
b. To a solution of triphenylphosphine (4 mmoles, 1.05 g) in anhydrous toluene (20 ml), at −5°C, is added dropwise Br_2 (4 mmoles) and after 2 h at 0°C, a solution of compound **3** (3.7 mmoles, 0.97 g) in anhydrous toluene (20 ml). After 24 h at 20°C, the solution is filtered and the solid is washed with chloroform. A white solid is isolated (0.5 g, 63 % yield) and characterized by IR, ^{31}P, ^{1}H, ^{13}C NMR spectra.

Selected physical and spectral data : IR, ^{31}P, ^{1}H and ^{13}C NMR:

5 IR KBr (cm^{-1}) : 3430 f (NH), 1655 F (C=O), 1605 f, 1595 f, 1525 f, 1485 F (C=C arom.), 1260 F (P=O), 1140–1060 F (P-O); **^{31}P-NMR** (D_2O) : δ 18.12; **^{1}H-NMR** (D_2O) : δ 1.25 t (3H, CH_3, $^{3}J_{H-H}$ = 7.1), 3.75 d (2H, CH_2, $^{2}J_{H-P}$ = 12 ; $^{3}J_{H-P}$ = 12) ; 3.95 dd (2H, OCH_2, $^{3}J_{H-H}$ = $^{3}J_{H-P}$ = 7.1) ; 7.81 m (2H arom.), 7.57 m (3H arom.), **^{13}C-NMR** (D_2O) : δ 18.85 d (1C, CH_3, $^{3}J_{C-P}$ = 5.8), 39.15 d (1C, CH_2, $^{1}J_{C-P}$ = 147.7) ; 64.45 d (1C, OCH_2, $^{2}J_{C-P}$ = 5.8) ; 136.31 s (1C, C_i) ; 173.17 d (1C, C=O, $^{3}J_{C-P}$ = 4.9); **M.S. FAB+**(NBA) : M+H = 266; **mp** = 145–150°C.

6a (mono-sodium salt) **IR** KBr (cm^{-1}) 3440 F (NH), 1635 F (C=O), 1600 f, 1575 f, 1550 F, 1490 m (C=C arom.), 1255 F (P=O), 1215 m, 1155

F, 1120 F, 1050 F (P-O); **^{31}P-NMR** (D_2O) : δ 14.95; **^{1}H-NMR** (D_2O) : δ 3.63 d (2H, CH_2, $^{2}J_{H-P}$= 12 ; $^{3}J_{H-P}$ = 12.6) ; 7.90 m (2H arom.), 7.65 m (3H arom.), **^{13}C-NMR** (D_2O) : δ 41.65 d(1C, CH_2, $^{1}J_{C-P}$ = 140.7) ; 136.10 s (1C, C_i) ; 173.30 d(1C, C=O, $^{3}J_{C-P}$ = 6.36): **M.S. FAB+**(NBA) : M+H = 238.

6b Anal. Calcd. for $C_8H_{10}NO_4P$: C, 44.6; H,4.68; N, 6.51 ; O, 29.75. Found : C, 44.29; H, 4.40; N, 6.44; O, 29.34; **IR** KBr (cm^{-1}) : 3372 F (NH), 1601 F (C=O), 1553 F, 1488 f, 1447 m, 1401 m (C=C arom.), 1214 F (P=O), 1145F, 1078 f, 1002 F (P-OH); **^{31}P-NMR** (D_2O) δ 20.09; **^{1}H-NMR** (D_2O) : δ 3.76 d (2H, CH_2, $^{2}J_{H-P}$ = 12 ; $^{3}J_{H-P}$ = 12.1) ; 7.73 m (2H arom.), 7.5 m (3H arom.), **^{13}C-NMR** (D_2O) : δ 37.74 d (1C, CH_2, $^{1}J_{C-P}$ = 151) ; 139.96 s (1C, C_i) ; 173.29 d(1C, C=O, $^{3}J_{C-P}$ = 4.2); **M.S. FAB+** (NBA) : M+H = 216.

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