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FORMATION OF AMINOMETHYLPHOSPHONIC ACIDS AND MONOESTERS FROM AMINOMETHYLPHOSPHONATES

Henri-Jean Cristau $^{\rm a}$, Jean-Marc Lambert $^{\rm a}$ & Jean-Luc Pirat $^{\rm a}$

^a Laboratoire de Chimie Organique, ESA 5076 du C.N.R.S., Ecole Nationale Supérieure de Chimie, de Montpellier 8, rue de l'Ecole Normale, 34296, MONTPELLIER Cedex 5, FRANCE Published online: 24 Sep 2006.

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FORMATION OF AMINOMETHYLPHOSPHONIC ACIDS AND MONOESTERS FROM AMINOMETHYLPHOSPHONATES

HENRI-JEAN CRISTAU^{*}, JEAN-MARC LAMBERT and JEAN-LUC PIRAT^{*}

Laboratoire de Chimie Organique, ESA 5076 du C.N.R.S., Ecole Nationale Supérieure de Chimie de Montpellier, 8, rue de l'Ecole Normale, 34296 MONTPELLIER Cedex 5, FRANCE

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Correcting a previous preliminary communication, the reaction between diethyl N-benzoyl α -aminomethylphosphonate and PCl₅ 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 PO₃H₂, PO₃HR or PO₃R₂, 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

^{*} Correspondence Author: E-mail : pirat@cit.enscm.fr.



apply a cyclisation method first described, in a special case, by Drach and Lobanov^[3] (Fig. 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 PCl₅ used (Table I). Other activating agents, such as Ph₃PBr₂ or Ph₃P/CCl₄, were also tried to promote the cyclisation but unsuccessfully.



Ph-C-NH-CH ₂ -P O O O O O O O C D Et O Et O Et O Et O Et	+Y>Ph-C-NH-CH₂-P U O O O O O H	t + PhCNHC 0	H ₂ -P OH
3	5	6	
Ŷ	Treatment	Product	Yield (%)
1 PCl ₅ / pyridine	Saturated solution NaHCO3	5	38
2 PCl ₅ / pyridine	Saturated solution NaHCO3	6	85
Ph ₃ PBr ₂	Filtration	6	63
Ph ₃ P / CCl ₄ / Et ₃ N	Filtration	No reaction	0

TABLE I Dependence of the formation of 5 and 6 from 3 on the amount of PCl₅ used.

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 PCl₅, and the α -aminomethylphosphonic acid 6 with two equivalents of PCl₅ or Ph₃PBr₂.

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 ¹H-NMR (200.132 MHz), ¹³C-NMR (50.323 MHz) and ³¹P-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 Per-kin-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 PCl₅ (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, ³¹P, ¹H, ¹³C 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 PCl₅ (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, ³¹P, ¹H, ¹³C NMR spectra.
- b. To a solution of triphenylphosphine (4 mmoles, 1.05 g) in anhydrous toluene (20 ml), at -5°C, is added dropwise Br₂ (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, ³¹P, ¹H, ¹³C NMR spectra.

Selected physical and spectral data : IR, ³¹P, ¹H and ¹³C 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); ³¹P-NMR (D₂O) : δ 18.12; ¹H-NMR (D₂O) : δ 1.25 t (3H, CH₃, ³J_{H-H} = 7.1), 3.75 d (2H, CH₂, ²J_{H-P} = 12 ; ³J_{H-P} = 12) ; 3.95 dd (2H, OCH₂, ³J_{H-H} = ³J_{H-P} = 7.1) ; 7.81 m (2H arom.), 7.57 m (3H arom.), ¹³C-NMR (D₂O) : δ 18.85 d (1C, CH₃, ³J_{C-P} = 5.8), 39.15 d (1C, CH₂, ¹J_{C-P} = 147.7) ; 64.45 d (1C, OCH₂, ²J_{C-P} = 5.8) ; 136.31 s (1C, C₁) ; 173.17 d (1C, C=O, ³J_{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); ³¹P-NMR (D₂O) : δ 14.95; ¹H-NMR (D₂O) : δ 3.63 d (2H, CH₂, ²J_{H-P} = 12 ; ³J_{H-P} = 12.6) ; 7.90 m (2H arom.), 7.65 m (3H arom.), ¹³C-NMR (D₂O) : δ 41.65 d(1C, CH₂, ¹J_{C-P} = 140.7) ; 136.10 s (1C, C_i) ; 173.30 d(1C, C=O, ³J_{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); ³¹P-NMR (D₂O) δ 20.09; ¹H-NMR (D₂O) : δ 3.76 d (2H, CH₂, ²J_{H-P} = 12; ³J_{H-P} = 12.1); 7.73 m (2H arom.), 7.5 m (3H arom.), ¹³C-NMR (D₂O) : δ 37.74 d (1C, CH₂, ¹J_{C-P} = 151); 139.96 s (1C, C_i); 173.29 d(1C, C=O, ³J_{C-P} = 4.2); M.S. **FAB+** (NBA) : M+H = 216.

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55