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A. Elachqar ^a , A. El Hallaouiq ^a , M. L. Roumestant ^b & Ph. Viallefont ^b

^a Laboratoire de Chimie Organique, Faculté des Sciences, Université Sidi Mohamed Ben Abdellah, BP 1796 - FES - ATLAS (MAROC)

^b URA 468, Université Montpellier II, Place E. Bataillon, 34095, MONTPELLIER, Cedex 5 Published online: 23 Sep 2006.

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SYNTHESIS OF HETEROCYCLIC α-AMINOPHOSPHONIC ACIDS

A. Elachqar¹, A. El Hallaoui*¹, M.L. Roumestant² and Ph. Viallefont²

1- Laboratoire de Chimie Organique,
Faculté des Sciences - Université Sidi Mohamed Ben Abdellah
BP 1796 - FES - ATLAS (MAROC)
2- URA 468, Université Montpellier II,
Place E. Bataillon, 34095 MONTPELLIER - Cedex 5

Abstract: Heterocyclic α -aminophosphonic acids derivatives were easily obtained by 1,3 dipolar cycloaddition of acetylenic compounds on azido α -aminophosphonic esters.

α-Aminophosphonic acids, analogues of α-amino acids display diverse and useful biological properties¹: enzymatic inhibitors, antibacterial agents, neuroactive compounds, anticancer drugs, pesticides.

Numerous methods have been described in the literature for the synthesis of racemic compounds ^{2,3} but to our knowledge the synthesis of

^{*} To whom correspondence should be addressed

heterocyclic α -aminophosphonic acids has received little attention. We propose in this letter one efficient method for the obtention of α -triazolyl α -aminophosphonic acids.

The synthesis is based on the 1,3 dipolar cycloadditions of acetylenic compounds on the azides 8 and 9 obtained by reaction of sodium azide on the bromides 4 6 and 7.

RHN
$$P(OEt)_2$$
 NBS/CCl₄ RHN $P(OEt)_2$

Br

1 R = PhCO
2 R = CCl₃ CH₂O₂ C
3 R = PhCH₂
4 R = CF₃ CO
5 R = PhCH₂O₂ C

RHN $P(OEt)_2$

Scheme 1

For the bromination reaction the nature of the protective group plays a great role; bromination did not take place for 4 (R= CF3 CO) and took place on the benzylic methylenic group for 3 (R = Ph CH₂) and 5 (R= Ph CH₂ O₂ C).

Treatment of the bromides 6 and 7 by sodium azide in acetone at room temperature during 3 hrs gave 8 and 9 in good yields.

Cycloadditions led to a mixture of regioisomers (scheme 2); reaction conditions and results are summarized in the table.

According to the data of the literature ^{5,6} the yields depend on the nature of the groups R₁ and R₂ of the starting acetylenic compounds, they are better with electron withdrawing groups.

$$RHN \stackrel{O}{\longrightarrow} P(OEt)_{2}$$

$$RHN \stackrel{O}{\longrightarrow} P(OEt)_{2}$$

$$R_{1} \stackrel{N}{\longrightarrow} N$$

$$R_{2} \stackrel{N}{\longrightarrow} N$$

$$RHN \stackrel{P}{\longrightarrow} P(OEt)_{2}$$

$$RHN \stackrel{P}{\longrightarrow} P(OEt)_{2}$$

$$RHN \stackrel{P}{\longrightarrow} P(OEt)_{2}$$

$$RHN \stackrel{N}{\longrightarrow} P(OEt)_{2}$$

$$R_{1} \stackrel{N}{\longrightarrow} N$$

$$R_{2} \stackrel{N}{\longrightarrow} N$$

$$RHN \stackrel{N}{\longrightarrow} P(OEt)_{2}$$

$$R_{1} \stackrel{N}{\longrightarrow} N$$

$$R_{1} \stackrel{N}{\longrightarrow} N$$

$$R_{1} \stackrel{N}{\longrightarrow} N$$

$$R_{2} \stackrel{N}{\longrightarrow} N$$

$$R_{1} \stackrel{N}{\longrightarrow} N$$

$$R_{1} \stackrel{N}{\longrightarrow} N$$

$$R_{2} \stackrel{N}{\longrightarrow} N$$

$$R_{1} \stackrel{N}{\longrightarrow} N$$

$$R_{1} \stackrel{N}{\longrightarrow} N$$

$$R_{1} \stackrel{N}{\longrightarrow} N$$

$$R_{2} \stackrel{N}{\longrightarrow} N$$

$$R_{1} \stackrel{N}{\longrightarrow} N$$

$$R_{1} \stackrel{N}{\longrightarrow} N$$

$$R_{2} \stackrel{N}{\longrightarrow} N$$

$$R_{1} \stackrel{N}{\longrightarrow} N$$

$$R_{2} \stackrel{N}{\longrightarrow} N$$

$$R_{1} \stackrel{N}{\longrightarrow} N$$

$$R_{2} \stackrel{N}{\longrightarrow} N$$

$$R_{3} \stackrel{N}{\longrightarrow} N$$

$$R_{4} \stackrel{N}{\longrightarrow} N$$

The ratio of the two regioisomers (separated by chromatography column on silicagel) is dependent not only on the nature of R_1 and R_2 , but also on the reaction conditions : temperature and time.

 $\begin{aligned} \textbf{Table}: & \text{Synthesis of triazolyl} \\ & \alpha\text{-aminophosphonic acid derivatives 10 and 11} \end{aligned}$

Product	R1	R2	Time (h)	Yield	Ratio of isomers
10 a	CO ₂ Me	CO ₂ Me	18	90 a	-
10 b	Н	CO ₂ Et	96	82 a	98/2
10 c	Н	Ph	48	65 b	98/2
10 d	Н	CH2 Br	72	92 b	83/17
10 e	Н	CH2 Cl	48	82 b	67/33
10 f	Ph	Ph	312	33 b	-
10 g	Н	CH3 (CH2)3	52	26 b	65/35
10 h	Н	C ₃ H ₇ CH OH	24	91 b	98/2
11 a	CO2 Me	CO2 Me	18	86 a	-
11 b	Н	CO2 Et	96	68 a	98/2
11 c	Н	Ph	48	53 b	98/2
11d	Н	CH2 Br	48	63 b	70/30

a: room temperature, without solvent

b: benzene, reflux

The method described here allowed us to prepare differently substituted α -triazolyl α -aminophosphonic acid derivatives.

Experimental

Melting points were obtained on a Electrothermal melting point apparatus and are uncorrected. ¹H NMR spectra were obtained on VARIAN EM - 360 (60 MHz) and BRUCKER (250 MHz) instruments, TMS as internal standard. Microanalyses were performed by the centre of analyses in Montpellier, Mass Spectra were measured on a JEOL - JMS - DX 300 FAB or EI.

Bromides 6 and 7 have been prepared using Steglich's 4 method.

Synthesis of the azides 8 and 9:

The bromide 6 or 7 (2 mmol) and sodium azide (7 mmol) in acetone (10 ml) were stirred during 3 hrs at room temperature. After reaction, the solution was filtered, the solvent evaporated and the residue chromatographed on silica column.

- 8 : Yield = 92 % m.p. = 76° C. ¹HNMR (CDCl₃) δ : 1. 23 (t, 3H, J = 7 Hz); 1. 33 (t, 3 H, J, = 7 Hz); 4. 2 (m, 2 H); 4. 25 (m, 2 H); 6. 1 (d x d, 1 H, J = 13 Hz, J = 10 Hz); 7. 66 - 8. 2 (m, 5 H); 8. 9 (d, 1 H, J = 10 Hz).
- 9 : Yield = 87 % m. p. = 57 ° C. 1 HNMR (CDCl₃) δ : 1. 33 (t, 3 H, J = 7 Hz) ; 1.

4 (t, 3 H, J = 7 Hz); 4. 25 (m, 2 H); 4. 3 (m, 2 H); 4. 83 (s, 2 H); 5. 36 (d x d, 1 H, J = 14 Hz, J = 10 Hz); 8. 4 (m, 1 H). Anal. calcd. for C8 H₁₄ Cl₃ N₄ 05 P C, 25. 0; H, 3. 65; N, 14. 60 Found C, 25. 85; H, 3. 31; N, 14. 52.

Reaction of cycloaddition, general procedure:

The azide 8 or 9 (6. 4 mmol) and the acetylenic compound (7. 6 mmol) were stirred without solvent or in benzene at reflux (see table for the reaction conditions). After evaporation of the solvent, the residue was chromatographed on silica column.

10 a: m. p. = 114° C MS (FAB) M + 1 = 455. ¹H NMR (CD Cl₃) δ: 1. 26 (t, 3 H, J = 8 Hz); 1. 36 (t, 3 H, J = 8 Hz); 4 (s, 6 H); 4. 30 (m, 2 H); 4. 36 (m, 2 H); 7. 33 (d x d, 1 H, J = 15 Hz, J = 10 Hz); 7. 53 (m, 5 H); 8. 2 (m, 5 H); 8. 36 (m, 1 H).

10 b: major regioisomer m. p. = 136°C. ¹H NMR (CD Cl₃) δ : 1. 22 (t, 3 H, J = 8 Hz); 1. 32 (t, 3 H, J = 8 Hz); 1. 36 (t, 3 H, J = 6 Hz); 4. 05 (m, 2 H); 4. 3 (m, 2 H); 4. 38 (q, 2 H, J = 6 Hz); 7. 15 (d x d, 1 H, J = 16 Hz, J = 10 Hz); 7. 25 (m, 5 H); 7. 93 (m, 5 H); 8. 6 (s, 1 H). 8. 65 (m, 1 H).

10 c : major isomer m. p. = 160° C M. S (FAB) M+1= 415. ¹H NMR (CD Cl₃) δ = 1. 16 (t, 3 H, J = 8 Hz); 1. 3 (t, 3 H,J= 8 Hz); 3. 7 (m, 2 H); 4. 56 (m, 2 H); 7. 36 (d x d, 1 H, J = 16 Hz, J = 10 Hz); 7. 3 - 8. 2 (m, 10 H); 8. 66 (s, 1 H); 9. 53 (m, 1 H).

10 d: major isomer m.p. = 102° C MS (FAB) M + 1 = $432.^{1}$ H NMR (CD Cl₃) δ = 1. 15 (t, 3H, J = 7 Hz); 1. 36 (t, 3 H, J = 7 Hz) 4. (m, 2 H); 4. 26 (m, 2 H); 4. 53 (s, 2 H); 7. 06 (d x d, 1 H, J = 15 Hz, J = 10 Hz); 7. 36 - 7. 9 (m, 5 H); 7.7 (s, 1 H); 7. 93 (m, 1 H).

minor isomer m.p. = 138° C MS (FAB) M + 1 = 432. ¹H NMR (CD Cl₃) δ = 1. 15 (t, 3H, J = 7 Hz); 1. 26 (t, 3 H, J = 7 Hz); 4. (m, 2 H); 4. 2 (m, 2 H); 4. 5 (s, 2 H); 7. 15 (d x d, 1 H, J = 17 Hz, J = 10 Hz); 7. 26 - 8 (m, 5 H); 8.16 (s, 1 H); 8. 93 (m, 1 H).

10 e: major isomer m.p. = 136° C. ¹H NMR(CDCl₃) δ : 1. 15 (t, 3H, J = 7 Hz); 1. 32 (t, 3 H, J = 7 Hz); 4. (m, 2 H); 4. 24 (m, 2 H); 4. 70 (S, 2 H); 7. 12 (d x d, 1 H, J = 17 Hz, J = 10 Hz); 7. 38 - 7. 92 (m, 5 H); 8. 17 (s, 1 H); 8. 75 (m, 1 H). Anal. Calcd. for C₁₅ H₂₀ Cl N₄ O₄ P C, 62. 09; H, 5. 17; N, 14. 48. Found C, 62. 22; H, 5. 06 · N, 14. 95.

minor isomer. m.p. = 103° C MS (FAB) M + 1 = $387.^{1}$ H NMR(CDCl₃) δ : 1. 15 (t, 3H, J = 7 Hz) ; 1. 32 (t, 3 H, J = 7 Hz) ; 3. 96 (m, 2 H) ; 4. 24 (m, 2 H) ; 4. 70 (s, 2 H) ; 7. 12 (d x d, 1 H, J = 15 Hz, J = 10 Hz); 7. 38 - 7. 88 (m, 5 H); 7. 68 (s, 1 H) ; 7. 93 (m, 1 H).

11 a: m.p. = 134°C. ¹H NMR (CDCl₃) δ: 1.29(t, 3H, J=7Hz); 1.42(t, 3 H, J=7 Hz); 4.15 (s,6H); 4.25 (m, 2 H); 4.32 (m, 2 H); 4.85 (s, 2 H);7.3 (dxd, 1 H, J=15 Hz, J = 10 Hz); 8.36(m, 1 H). Anal. Calcd. for C₁₄ H₂₀ Cl₃ N₄ O₉ P: C, 31. 96; H, 3. 8; N, 10. 65. Found C, 32. 09; H, 3. 69; N, 10. 45.

11**b** : oil. ¹H NMR (CDCl₃) δ : 1.16(t,3H, J=7Hz); 1.36(t,3H, J= 7Hz); 1.43(t, 3H, J=7Hz); 3.6-4.7(m,6H); 4.8(s,2H); 6.8(dd, 1H, J=17Hz, J≈12Hz); 8.76(s,1H); 8.9(m,1H).

11c: m.p.=155°C. ¹H NMR (CDCl₃) δ: 1.17(t,3H,J=7Hz); 1.4(t,3H,J=7Hz); 3.85-4.4(m,4H); 4.6-4.9(2H;AB); 6.6(dd,1H,J=18Hz, J=10Hz); 7.3-7.9(m,6H); 8.16(s,1H).

References:

- 1 Kafarski, P., Lejczak, B., Phosphorus Sulfur and Silicon, 1991, 63, 193.
- 2- Kukhar, V.P. and Solodenko, V.A., Russ. Chem. Rev., 1987, 56, 859.
- 3- Gajda, T. and Matusiak, M., Synthetic Commun. 1992, 22, 2193 and references cited.
- 4- Schrader, T., Kober, R., Steglich, W., Synthesis, 1986, 372.
- 5- Atmani, A., El Hallaoui, A., El Haji, S., Roumestant, M.L., Viallefont, Ph., Synthetic Commun., 1991, 21, 2383.
- 6- Birkofer, L., Ritter, A. and Uhlenbravick, H., Chem. Ber., 1963, 96, 3280.

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