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SYNTHESIS OF HETEROCYCLIC α-AMINOPHOSPHONIC ACIDS

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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 properties[1]: 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

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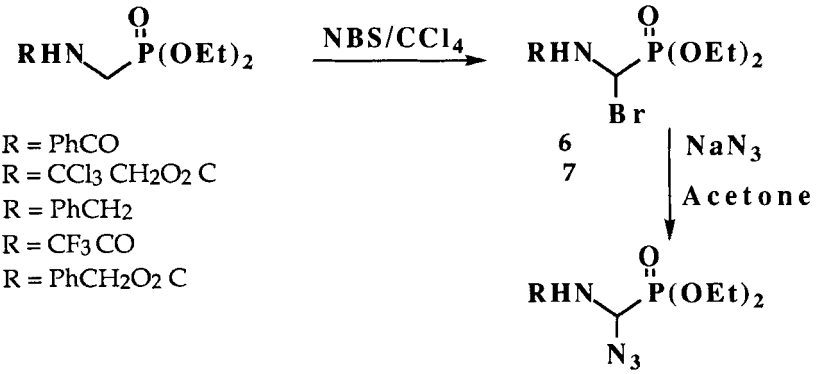
heterocyclic α-aminophosphonic acids has received little attention. We propose in this letter one efficient method for the obtention of α-triazolyl α-aminophosphonic acids.

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**.



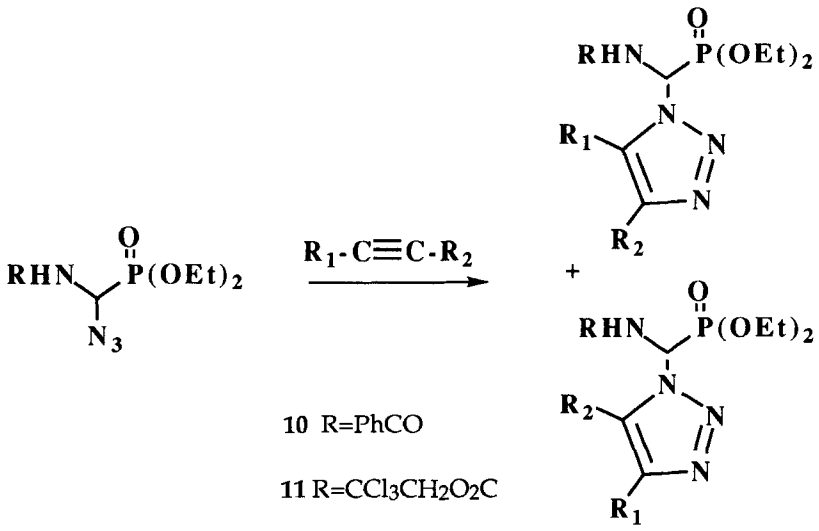
Scheme 1

For the bromination reaction the nature of the protective group plays a great role ; bromination did not take place for **4** (R= CF_3 CO) and took place on the benzylic methylenic group for **3** (R = Ph CH_2) and **5** (R= Ph CH_2 O_2 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 R_1 and R_2 of the starting acetylenic compounds, they are better with electron withdrawing groups.



10 R=PhCO

11 R=$CCl_3CH_2O_2C$

Scheme 2

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.

Table : Synthesis of triazolyl α-aminophosphonic acid derivatives **10** and **11**

Product	R1	R2	Time (h)	Yield	Ratio of isomers
10 a	CO_2 Me	CO_2 Me	18	90 [a]	-
10 b	H	CO_2 Et	96	82 [a]	98/2
10 c	H	Ph	48	65 [b]	98/2
10 d	H	CH2 Br	72	92 [b]	83/17
10 e	H	CH2 Cl	48	82 [b]	67/33
10 f	Ph	Ph	312	33 [b]	-
10 g	H	$CH_3 (CH_2)_3$	52	26 [b]	65/35
10 h	H	$C_3 H_7$ CH OH	24	91 [b]	98/2
11 a	CO_2 Me	CO_2 Me	18	86 [a]	-
11 b	H	CO_2 Et	96	68 [a]	98/2
11 c	H	Ph	48	53 [b]	98/2
11d	H	CH_2 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. ^{1}H 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. ^{1}HNMR ($CDCl_3$) 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 ($CDCl_3$) 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 $C_8 H_{14} Cl_3 N_4 O_5 P$ 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 ($CDCl_3$) 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, 1H).

10 b : major regioisomer m. p. = 136°C. ^1H NMR ($CDCl_3$) 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 ($CDCl_3$) 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 Cl_3) 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. ^{1}H NMR (CD Cl_3) 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. ^{1}H NMR($CDCl_3$) 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 C_{15} H_{20} Cl N_4 O_4 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($CDCl_3$) 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. ^{1}H NMR ($CDCl_3$) 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 C_{14} H_{20} Cl_3 N_4 O_9 P: C, 31. 96 ; H, 3. 8 ; N, 10. 65. Found C, 32. 09 ; H, 3. 69 ; N, 10. 45.

11b : oil. ^{1}H NMR ($CDCl_3$) 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. ^{1}H NMR ($CDCl_3$) 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).

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