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Synthesis of α-triazolyl α-amino acid derivatives

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Summary. We report the synthesis of α-triazolyl α-amino esters by 1,3 dipolar cycloaddition of acetylenic compounds and α-azido α-amino esters.

Keywords: Amino acids – α-Azido α-amino esters – α-Triazolyl α-amino esters – Cycloaddition

Introduction

α-Amino acids play an important role in different areas (Kleeman et al., 1985), e.g. as enzyme inhibitors, antibacterial agents, neuroactive compounds, pharmaceutical starting materials, herbicides and fungicides.

This has led to the development of numerous synthetic methods for a variety of compounds (Haemers et al., 1989; Williams, 1989). However the synthesis of heterocyclic amino acids has not been very well investigated to date.

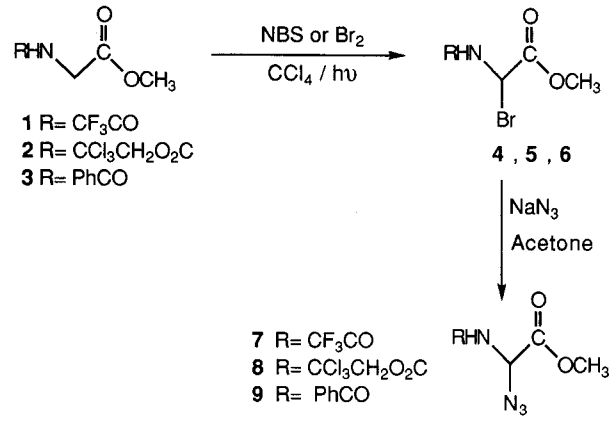
A synthetic method for heterocyclic α-aminophosphonic acids has been elaborated by our laboratory (Elachqar et al., 1994). These compounds are not described in the literature yet they may present interesting biological activity due to the presence of the heterocycle.

We report here the application of the strategy for the preparation of α-triazolyl α-amino acids.

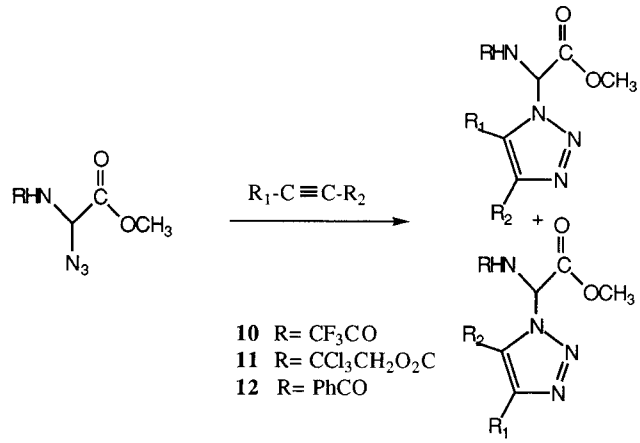
The synthesis is based on the 1,3 dipolar cycloaddition of acetylenic compounds and the azides **7**, **8** and **9** obtained by the reaction of sodium azide on the α-bromo-α-aminoesters **4**, **5**, and **6** (Scheme 1).

Bromination of the N-protected α-amino esters **1**, **2**, and **3** was accomplished by the Steglich method (Steglich and Kober, 1983).

Treatment of the bromides **4**, **5** and **6** by sodium azide in acetone at room temperature for six to twelve hours led to **7**, **8** and **9** respectively in good yields. Cycloaddition with acetylenic compounds led to a mixture of regioisomers (Scheme 2); reaction conditions and results are summarized in



Scheme 1



Scheme 2

Table 1. Purification of the mixture was performed by chromatography over silica gel.

The chemical yields of the cycloaddition reactions depend on the nature of the substituents R_1 and R_2 of the acetylenic compounds. According to literature data (Tsypin, et al., 1977) the yields of the cycloaddition reactions are better with electron withdrawing substituents (R_1 or R_2 = CO_2 CH_3, CH_2Cl) than with electron donating substituents (R_1 = $(CH_2)_2)CH_3$). Moreover the nature of the substituents R_1 an R_2 has a great effect on the orientation of the cycloaddition reactions, the best regioselectivity being obtained with electron with-drawing substituents (L'Abbe, 1969). The structures of the two regioisomers were assigned on the basis of literature data (Birkofer et al., 1963) concerning the chemical shifts of triazolic protons. The studies carried out (Tsypin et al., 1977) have shown that the proton signal for the 1,4 isomer lies downfield from the corresponding signal for the 1,5 isomer.

Table 1. Synthesis of α-triazolyl α-amino acids derivatives **10**, **11** and **12**

Product	R_1	R_2	Time (h)	Yield. (%)	Ratio of isomers
10a	CO_2Me	CO_2Me	16	63[a]	–
10b	H	Ph	48	86[b]	83/17
10c	H	CH_2Cl	48	75[b]	75/25
11a	CO_2Me	CO_2Me	18	89[a]	–
11b	H	Ph	48	70[b]	69/31
11c	H	CH_2Cl	48	75[b]	67/33
11d	H	$CH_3(CH_2)_3$	72	29[b]	52/48
12a	CO_2Me	CO_2Me	16	85[a]	–
12b	H	Ph	48	80[b]	63/37
12c	H	CH_2Cl	48	73[b]	65/35
12d	Ph	Ph	168	20[b]	–
12e	H	$(CH_2)_2$-OH	120	54[b]	60/40
12f	H	CO_2Et	72	87[a]	94/6
12g	H	CH(OH)-CH_3	48	74[b]	67/33
12h	H	CH(OH)-C_2H_5	48	77[b]	91/9

[a] Room temperature, without solvent; [b] Benzene, reflux.

This new synthetic method, which is simple and efficient, leads to α-amino carboxylic esters carrying in the α-position, a variety of triazole 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 and 400 MHz) instruments, TMS as internal standard. Microanalyses were performed by the Centre of Microanalyses I.C.S.N. – CNRS (Paris). Mass spectra were measured on a JEOL – JMS – DX 300 FAB instrument.

Bromides **4**, **5** and **6** have been prepared using Steglich's method (Steglich and Kober, 1983). The solid compounds are crystallized from ether/hexane mixture and recrystallized from benzene.

*Synthesis of the azides **7**, **8** and **9***

The bromide **4**, **5** or **6** (2 mmol) and sodium azide (5 mmol) in acetone were stirred between 6 and 12 hrs at room temperature. After reaction the solution was filtered, the solvent evaporated and the residue chromatographed on silica column.

7: Yield = 90% m.p. = 46°C Rf = 0.59 ether/hexane 2/1
^{1}H NMR ($CDCl_3$) δ: 3.98 (s, 3H), 5.86 (d, 1H, J = 7 Hz), 7.8 (m, 1H).

8: Yield = 70% oil Rf = 0.6 ether/hexane 1/1
^{1}H NMR ($CDCl_3$) δ: 3.88 (s, 3H), 4.7 (s, 2H), 5.56 (d, 1H, J = 10Hz), 6.8 (m, 1H)

9: Yield = 80% m.p. = 81°C Rf = 0.7 ether
^{1}H NMR ($CDCl_3$) δ: 3.76 (s, 3H), 5.96 (d, 1H, J = 7Hz), 7.2–8 (m, 6H).
MS(FAB) M + 1 = 235

Cycloaddition reaction: general procedure

The azide **7**, **8** or **9** (6.4mmol) and the dipolarophile (7.6mmol) were stirred without solvent or in benzene at reflux (see Table 1 for the reaction conditions). After evaporation of the solvent, the residue was chromatographed over silica.

10a: Yield = 63% m.p. = 106°C Rf = 0.54 ether/hexane 3/1
^{1}H NMR ($CDCl_3$) δ: 3.9 (s, 3H), 4.0 (s, 3H), 4.05 (s, 3H), 7.65 (m, 1H), 8.66 (1H, ma).
Anal. calcd. for $C_{11}H_{11}F_3N_4O_7$: C,35.87; H,2.99; N,15.22.
Found. C,35.94; H,3.02; N,15.34.

10b: Yield = 86%
Major regioisomer: m.p. = 74°C Rf = 0.5 ether/hexane 1/1
^{1}H NMR ($CDCl_3$) δ: 3.76 (s, 3H), 7.1 (d, 1H, J = 8Hz), 7.26–7.83 (m, 5H), 7.9 (s. 1H), 8.4 (d, 1H, J = 8Hz).
Anal. calcd. for $C_{13}H_{11}F_3N_4O_3$: C,47.56; H,3.35; N,17.07.
Found. C,47.45; H,3.34; N,17.2.

Minor isomer: m.p. = 132°C Rf = 0.48 ether/hexane 3/1
^{1}H NMR ($CDCl_3$) δ: 3.86 (s, 3H), 6.83 (m, 1H), 7.2–7.9 (m, 5H), 8.1 (s, 1H), 8.43 (m, 1H).
Anal. calcd. for $C_{13}H_{11}N_4O_3$: C,47.56; H,3.35; N,17.07.
Found: C,47.51; H,3.34; N,17.15.

10c: Yield = 75%
Major isomer: m.p. = 67°C Rf = 0.7 ether/hexane 2/1
^{1}H NMR ($CDCl_3$) δ: 3.7 (s, 3H), 4.5 (s, 2H), 6.88 (d, 1H, J = 8Hz), 7.6 (s, 1H), 8.1 (d, 1H, J = 8Hz).
Anal. calcd. for $C_8H_8ClN_4O_3$: C,32.0; H,2.66; N,18.66
Found. C,32.07; H,2.46; N,18.14.
Minor isomer: m.p. = 108°C Rf = 0.5 ether/hexane 2/1
^{1}H NMR ($CDCl_3$) δ: 3.86 (s, 3H), 4.7 (s, 2H), 6.83 (d, 1H, J = 8Hz), 8.0 (s, 1H), 8.9 (d, 1H, J = 8Hz).

11a: Yield = 89% m.p. = 134°C Rf = 0.5 ether/hexane 3/1
^{1}H NMR ($CDCl_3$) δ: 3.85 (s, 3H), 3.98 (s, 3H), 4.02 (s, 3H,), 4.73 (s, 2H), 7.1 (ma, 1H), 7.4 (d, 1H, J = 9Hz).
Anal. calcd. for $C_{12}H_{13}Cl_3N_4O_8$: C,32.17; H,2.9; N,12.5.
Found. C,32.37; H,3.0; N,12.42.

11b: Yiled = 70%
Major isomer: m.p. = 150°C Rf = 0.45 ether/hexane 2/1
^{1}H NMR ($CDCl_3$) δ: 3.9 (s, 3H), 4.8 (s, 2H), 6.76 (d, 1H, J = 8Hz), 7–8.1 (ma, 6H), 8.23 (s, 1H).
Anal. calcd. for $C_{14}H_{13}Cl_3N_4O_4$: C,41.22; H,3.19; N,13.74.
Found. C,41.41; H,2.99; N,13.47
Minor isomer: m.p. = 135°C Rf = 0.7 ether/hexane 2/1
^{1}H NMR ($CDCl_3$) δ: 3.86 (s, 3H), 4.8 (s, 2H), 6.93 (ma, 1H), 7.3–8.0 (m, 6H), 8.03 (s, 1H).

11c: Yield = 75%
Major isomer: m.p. = 105°C Rf = 0.52 ether/hexane 2/1
^{1}H NMR ($CDCl_3$) δ: 3.93 (s, 3H), 4.73 (s, 2H), 4.8 (s, 2H), 6.75 (d, 1H, J = 8Hz), 7.4 (d, 1H, J = 8Hz), 8.1 (s, 1H).
Anal. calcd. for $C_9H_{10}Cl_4N_4O_4$: C,28.42; H,2.63; N,14.73.
Found. C,28.69; H,3.05; N,14.38.

Minor isomer: m.p. = 91°C Rf = 0.76 ether/hexane 2/1
^{1}H NMR ($CDCl_3$) δ: 3.85 (s, 3H), 4.66 (s, 2H), 4.78 (s, 2H), 6.63–7.06 (ma, 2H), 7.83 (s, 1H).

11d: Yield = 29%
Major isomer: m.p. = 92°C Rf = 0.5 ether/hexane 3/1
^{1}H NMR ($CDCl_3$) δ: 0.93 (t, 3H, J = 7Hz), 1.1–2.0 (m, 4H), 2.73 (t, 2H, J = 7Hz), 3.88 (s, 3H), 4.76 (s, 2H), 6.65 (d, 1H, J = 8Hz), 7.1 (d, 1H, J = 8Hz), 7.66 (s, 1H).
Anal. calcd. for $C_{12}H_{17}Cl_3N_4O_4$: C,37.16; H,4.38; N,14.45.
Found. C,37.16; H,4.27; N,14.49.

12a: Yield = 85% m.p. = 107°C Rf = 0.46 ether
^{1}H NMR ($CDCl_3$) δ: 3.81 (s, 3H), 3.93 (s, 3H), 4.02 (s, 3H), 7.24–7.8 (m, 6H), 7.98 (d, 1H, J = 8Hz).
Anal. calcd. for $C_{16}H_{16}N_4O_7$: C,51.06; H,4.26; N,14.89.
Found. C,51.10; H,4.09; N,14.55.

12b: Yield = 80%
Major isomer: m.p. = 131°C Rf = 0.61 ether
^{1}H NMR ($CDCl_3$) δ: 3.9 (s, 3H), 7.13 (d, 1H, J = 8Hz), 6.7–8.1 (m, 10H), 8.2 (d, 1H, J = 8Hz), 8.4 (s, 1H).
Anal. calcd. for $C_{18}H_{16}N_4O_3$: C,64.28; H,4.76; N,16.67.
Found. C,64.03; H,4.73; N,16.71.

Minor isomer: m.p. = 94°C Rf = 0.79 ether
^{1}H NMJR ($CDCl_3$) δ: 3.86 (s, 3H), 7.3–8.0 (m, 12H), 8.06 (s, 1H).

12c: Yield = 73%
Majon isomer: m.p. = 116°C Rf = 0.75 ether/hexane 5/1
^{1}H NMR ($CDCl_3$) δ: 3.83 (s, 3H), 4.66 (s, 2H), 7.36 (d, 1H, J = 8Hz), 7.43–8.1 (m, 6H), 7.8 (s, 1H).
Anal. calcd. for $C_{13}H_{13}ClN_4O_3$: C,50.56; H,4.21; N,18.15.
Found. C,50.45; H,4.32; N,18.12.

Minor isomer: m.p. = 141°C Rf = 0.44 ether/hexane 5/1
^{1}H NMJR ($CDCl_3$) δ: 3.9 (s, 3H), 4.78 (s, 2H), 7.2 (d, 1H, J = 8 Hz), 7.4–8.1 (m, 5H), 8.23 (s, 1H), 8.33 (d, 1H, J = 8 Hz).
Anal. calcd. for $C_{13}H_{13}ClN_4O_3$: C,50.56; H,4.21; N,18.15.
Found. C,50.4; H,4.23; N,17.95.

12d: Yield = 20% m.p. = 176°C Rf = 0.64 AcOEt/hexane 1/1
^{1}H NMR ($CDCl_3$) δ: 3.83 (s, 3H), 7.0 (d, 1H, J = 8 Hz), 7.7 (s, 5H), 7.26–8.43 (m, 11H).
Anal. calcd. for $C_{24}H_{20}N_4O_3$: C,69.90; H,4.85; N,13.59.
Found. C,69.21; H,4.37; N,13.21.

12e: Yield = 54%
Major isomer: oil Rf = 0.61 AcOEt
^{1}H NMR ($CDCl_3$) δ: 2.83 (t, 2H, J = 7 Hz), 3.7 (s, 3H), 3.8 (t, 2H, J = 7 Hz), 5.4 (m, 1H), 8 (7H, m), 8.4 (d, 1H, J = 8 Hz).

Minor isomer: m.p. = 124°C Rf = 0.47 AcOEt
^{1}H NMR (DMSO d_6) δ: 2.85 (t, 2H, J = 7 Hz), 3.69 (m, 2H), 3.79 (s, 3H), 4.79 (ma, 1H), 7.17 (d, 1H, J = 8 Hz), 7.52–7.98 (m, 5H), 8.04 (s, 1H), 10.26 (d, 1H, J = 8 Hz).
Anal. calcd. for $C_{14}H_{16}N_4O_4$: C,55.26; H,5.26; N,18.42.
Found. C,55.29, H,5.25; N,17.89.

12f: Yield = 87%
Major isomer: m.p. = 149°C Rf = 0.36 ether/hexane 4/1
^{1}H NMR ($CDCl_3$) δ: 1.31 (t, 3H, J = 7 Hz), 3.84 (s, 3H), 4.43 (q, 2H, J = 7 Hz), 7.05 (d, 1H, J = 8 Hz), 7.34–8.91 (m, 5H), 8.16 (d, 1H, J = 8 Hz), 8.54 (s, 1H). MS(FAB) M + 1 = 333.
Anal. calcd. for $C_{15}H_{16}N_4O_5$: C,54.21; H,4.81; N,18.56.
Found. C,54.4; H,4.61; N,16.70.

Minor isomer: m.p. = 152°C Rf = 0.64 ether/hexane 4/1
^{1}H NMR ($CDCl_3$) δ: 1.46 (t, 3H, J = 7 Hz), 3.85 (s, 3H), 4.5 (q, 2H, J = 7 Hz), 7.33–8.2 (m, 7H), 8.3 (s, 1H).
MS(FAB) M + 1 = 333.

12g: Yield = 74%
Major isomer: m.p. = 150°C Rf = 0.2 acetone/hexane 2/1
^{1}H NMR ($CDCl_3$) δ: 1.56 (d, 3H, J = 7 Hz), 2.52 (m, 1H), 3.88 (s, 3H), 4.83–5.4 (m, 1H), 7.06 (d, 1H, J = 8 Hz), 7.33–8.2 (m, 5H), 8.06 (s, 1H), 8.36 (d, 1H, J = 8 Hz).
Anal. calcd. for $C_{14}H_{16}N_4O_4$: C,55.26; H,5.26; N,18.42.
Found. C,55.20; H,5.20; N,17.94.

12h: Yield = 77%
Major isomer: m.p. = 112°C Rf = 0.17 ether
^{1}H NMR ($CDCl_3$) δ: 0.91 (t, 3H, J = 7 Hz), 1.45–2.2 (m, 2H), 3.78 (s, 3H), 3.93 (ma, 1H), 4.78 (t, 1H, J = 7 Hz), 7.06 (d, 1H, J = 8 Hz), 7.26–8.23 (m, 5H), 8.08 (s, 1H), 8.86 (d, 1H, J = 8 Hz).

Anal. calcd. for $C_{15}H_{18}N_4O_4$: C,56.60; H,5.66; N,17.61
Found. C,56.45; H,5.74; N,17.06.

Minor isomer: m.p. = 129°C Rf = 0.3 ether
^{1}H NMR ($CDCl_3$) δ: 1.0 (t, 3H, J = 7 Hz), 1.63–2.3 (m, 2H), 3.8 (s, 3H), 4.2 (m, 1H) 5.0 (t, 1H, J = 7 Hz), 7.16 (d, 1H, J = 8 Hz), 7.36–8.1 (m, 5H), 7.63 (s, 1H), 8.3 (d, 1H, J = 8 Hz).

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