Pergamon

Tetrahedron Vol. 51, No. 30, pp. 8355-8362, 1995
Copyright © 1995 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4020/95 $9.50+0.00

0040-4020(95)00446-7

FeCl3-Catalyzed Conjugate Addition of Secondary Amines, Imidazole and Pyrazole to Methyl 2-Acetamidoacrylate. Preparation of β-Dialkylamino-α-alanine and β-(*N*-Heteroaryl)-α-alanine Derivatives.

Montserrat Pérez and Roser Pleixats*

Department of Chemistry. Universitat Autònoma de Barcelona.
Bellaterra. 08193-Barcelona. Spain.

Abstract: β-Dialkylamino-α-alanine and β-(*N*-heteroaryl)-α-alanine derivatives are obtained by conjugate addition of nitrogen based nucleophiles (cyclic and acyclic secondary amines, imidazole and pirazole) to methyl 2-acetamidoacrylate, **1**, under iron(III) chloride catalysis.

INTRODUCTION

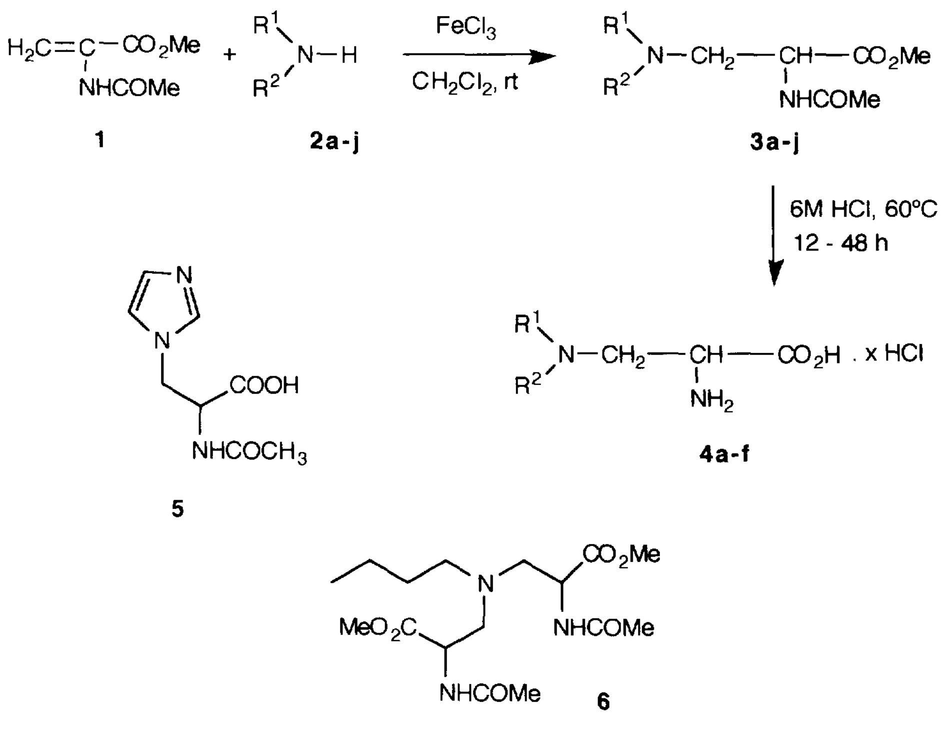
Some β-Dialkylamino-α-alanines and β-(*N*-heteroaryl)-α-alanines are non-proteinogenic amino acids widely found in nature.[1] Attempts to synthesize enantiomerically pure β-aminoalanines by reaction of a nitrogen-based nucleophile with an alanine derivative bearing a suitable leaving group in the β-position often results in β-elimination[2] followed sometimes by conjugate addition of the nucleophile.[3] Several heterocyclic β-substituted alanines have been obtained from *O*-acetylserine and the appropriate heterocycle by enzymatic catalysis[1g] or biomimetic synthesis.[1c] Recently, a method has been reported in which the β-substitution is carried out in an intramolecular sense in order to minimise the β-elimination.[1h] The preparation of *N*-protected β-substituted alanines in optically pure form has also been described by Mitsunobu-type cyclization of serine derivatives followed by regioselective opening of the resulting β-lactones using nitrogen, sulfur, oxygen, halogen and carbon nucleophiles.[4] Careful search of the reaction conditions (solvent, temperature, time) for each nucleophile is required for regiospecificity and stereochemical integrity to be attained. Thus, the reaction of nitrogen nucleophiles with serine β-lactones can give the amino acid arising from alkyl-oxygen cleavage and/or the amide arising from acyl-oxygen cleavage.[4d]

As the strategies mentioned before are based on β-substitution it seems worthwhile to try out the conjugate addition[5] of primary, secondary and heterocyclic amines to the commercially available methyl 2-acetamidoacrylate which would constitute a general, expeditious and simple method to prepare the protected β-substituted α-amino acids. Some precedents exist on the conjugate addition of primary amines and diethyl amine to *N*-acetyldehydroalanine in aqueous solution at 40-50°C.[6] Racemic β-(1-pyrazolyl)alanine has been synthesized by conjugate addition of pyrazole to α-acetamidoacrylic acid in boiling acetic acid and subsequent hydrolysis of the amide group.[7] Base-catalyzed (potassium hydrogenocarbonate) conjugate addition of a purine derivative to methyl trifluoroacetylaminoacrylate in dimethylsulfoxide has also been described.[1f] Furthermore, Belokon has reported the Michael type base-catalyzed addition of oxygen, nitrogen, sulfur and carbon nucleophiles to a chiral Ni(II) dehydroalanine complex leading to enriched mixtures of diastereoisomeric complexes under thermodynamic control.[8]

To our knowledge the only precedent of conjugate addition to the weak acceptor methyl 2-acetamidoacrylate, **1**, involves the use of Grignard reagents as nucleophiles in the presence of CuI.[9] Attempts of asymmetric conjugate addition by diastereoselective protonation of the intermediate enolate derived from chiral 2-acetamidoacrylates resulted in moderate diastereomeric excess.[9b] On the other hand, it has been found that Lewis acids catalyze the 1,4- addition of amine nucleophiles to acrylates under mild conditions, ferric chloride being the best choice.[10] Very recently, it has been shown[11] that the combined use of high pressure and ytterbium triflate catalysis allows the preparation of hindered β-aminoesters from amines and α,β-unsaturated esters.

RESULTS

In the course of a synthetic project, we were confronted with the preparation of some *N,N*-disubstituted β-aminoalanines. With the above-mentioned precedents in mind we decided to study the scope and limitations of the ferric chloride-catalyzed conjugate addition of nitrogen nucleophiles **2** to methyl 2-acetamidoacrylate **1**. Our results for the catalyzed and uncatalyzed (blank experiments) reactions are collected in Scheme I and Table I. Blank experiments were carried out under the same conditions of the corresponding catalyzed reactions except that no catalyst was added.



Scheme 1

The reactions were performed in dichloromethane at room temperature with a 10% molar of catalyst unless otherwise stated. Great improvements in the yields were achieved by the catalytic method for some secondary cyclic and acyclic (only dibutylamine) amines (see Table 1). Specially remarkable are the results obtained for the substrates **2c** and **2d** and for the aromatic heterocycles imidazole and pyrazole since no or very little reaction took place in those cases in the absence of catalyst (entries 3,4,7 and 8 of Table 1).

Table 1. Conjugate addition of nitrogen-based nucleophiles to **1**.

Entry	**2**	t (h)	**3** (%)[a]		**4** (%)[a]
			No catalyst	10% FeCl$_3$	
1	piperidine, **2a**	2	**3a** (50)	**3a** (98)	**4a** (68)
2	morpholine, **2b**	48	**3b** (50)[b]	**3b** (94)[b]	**4b** (56)
3	2-methoxycarbonylpiperidine, **2c**	168	**3c** (0)	**3c** (40)[c]	**4c** (79)
4	3-methoxycarbonylpiperidine, **2d**	48	**3d** (traces)	**3d** (95)[c]	**4d** (100)
5	4-methoxycarbonylpiperidine, **2e**	168	**3e** (33)[b]	**3e** (84)[b]	**4e** (74)
6	pyrrolidine, **2f**	15	**3f** (30)	**3f** (91)	**4f** (80)
7	imidazole, **2g**[d]	168	**3g** (0)	**3g** (27)	—
			5 (0)[e]	**5** (72)[e]	—
8	pyrazole, **2h**	144	**3h** (traces)[f]	**3h** (54)[f]	—
9	dibutylamine, **2i**	144	**3i** (20)	**3i** (51)	—
10	butylamine, **2j**	192	**3j** (49)[g]	**3j** (13)[g]	—
			6 (0)[h]	**6** (41)[h]	—

a) Isolated yields except for the uncatalyzed reactions leading to **3a**, **3b**, **3d**, **3e** and **3h** where the yields are based on integration of ^{1}H-NMR spectra of the crude mixtures containing **1**. b) The reaction was run in acetonitrile. c) Inseparable mixture of diastereoisomers. d) Ultrasound irradiation. e) 2-Acetamido-3-(1-imidazolyl)propanoic acid. f) The reaction was run in chloroform at reflux temperature. g) Upon standing after several days it undergoes spontaneous ester hydrolysis. h) *N,N*-Bis(2-acetamido-2-methoxycarbonylethyl)butylamine.

Ultrasound irradiation was found to increase the yield in the case of imidazole (entry 7). The corresponding β-substituted acid **5** was isolated as the major compound (72%) together with the acetamidoester **3g** (27%). The reaction with pyrazole (entry 8) was run in chloroform at reflux temperature because under the general conditions the rate was too slow. The effect of catalyst in the reaction with butylamine, **2j**, which was the only primary amine tested, it is worth to mention; with a molar ratio **1**:**2j** of 1:1 the catalyzed reaction gave the product of double addition **6** as the major compound (41%) together with the monoaddition product **3j** (13%) whereas the only isolated compound in the uncatalyzed reaction was **3j** (49%) (entry 10). This acetamidoester undergoes spontaneous ester hydrolysis upon standing. 2-Pyridone failed to react with **1** under FeCl$_3$ catalysis.

In some cases (entries 1-6) acid hydrolysis of the α-acetamidoesters **3** thus obtained was performed, affording the corresponding amino acid hydrochlorides **4** . These compounds were very hygroscopic solids, their melting points could not be measured and some of them did not give correct elemental analysis, although their spectroscopic behaviour is as expected.

In summary, racemic β-dialkylamino-α-alanine, β-(*N*-pyrazolyl)-α-alanine and β-(*N*-imidazolyl)-α-alanine derivatives are efficiently obtained under mild conditions by FeCl$_3$-catalyzed conjugate addition reaction of the corresponding nucleophile to the commercially available α-acetamidoacrylate, **1**. Probably, the coordination of Lewis acid catalyst with the acetamido moiety counteracts the donor properties of this group thus enhancing the activity of **1** as a Michael acceptor.

EXPERIMENTAL

Methyl 2-acetamidoacrylate and most of the amines used are commercially available. 2-Methoxycarbonylpiperidine **2c**, 3-methoxycarbonylpiperidine **2d**[12] and 4-methoxycarbonylpiperidine **2e**[12] were prepared from their corresponding carboxylic acids by standard procedures. ^{1}H-NMR (^{13}C-NMR) spectra were registered at 250 MHz (62.5 MHz). NMR values are given in δ units.

Methyl 2-acetamido-3-piperidinopropanoate **3a**. A mixture of piperidine (0.148 g, 1.74 mmole), methyl 2-acetamidoacrylate (0.250 g, 1.75 mmole), anhydrous iron(III) chloride (0.028 g, 0.18 mmole) and dichloromethane (15 mL) was stirred at room temperature for 2 h (TLC monitoring). The crude mixture was washed with an aqueous solution of sodium sulfate to eliminate iron species[10] and the aqueous phase extracted with dichloromethane. The combined organic layers were dried with anhydrous sodium sulfate and the solvent was evaporated to afford **3a** as an oil which crystallized upon digestion in diethyl ether (0.390 g, 1.70 mmole, 98 %); m.p. 67-69ºC (from diethyl ether); IR (KBr): 3256, 1757, 1646 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.4 (m, 2H), 1.5 (m, 4H), 2.0 (s, 3H), 2.4 (m, 4H), 2.6 (dd, J = 12.8 Hz, J = 5.9 Hz, 1H), 2.7 (dd, J = 12.8 Hz, J = 7.1 Hz, 1H), 3.7 (s, 3H), 4.5 (ddd (aparent q), J = 7.1 Hz, J = 5.9 Hz, J = 4.3 Hz, 1H), 6.5 (broad d, J = 4.3 Hz, 1H); ^{13}C-NMR ($CDCl_3$): 22.9, 23.9, 25.8, 50.6, 52.1, 54.4, 58.7, 169.93, 172.3. Anal.: Calcd. for $C_{11}H_{20}N_2O_3$: C, 57.87; H, 8.83; N, 12.27. Found: C, 57.79; H, 8.61; N, 12.23.

3-Piperidinoalanine dihydrochloride **4a**. A solution of **3a** (0.328 g, 1.43 mmole) in 6M hydrochloric acid (15 mL) was heated at 60ºC for 12 h (^{1}H-NMR monitoring). Then the solvent was evaporated to yield **4a** (0.240 g, 0.98 mmole, 68 %) as a white hygroscopic solid; m.p. 147-152ºC (dec.); IR(KBr): 2994-2430, 1749 cm^{-1}; ^{1}H-NMR (D_2O): 1.5 (m, 6H), 2.8 (t, J = 11.7 Hz, 2H), 3.3 (dd, J = 14.2 Hz, J = 5.8 Hz, 1H), 3.4 (m, 2H), 3.5 (dd, J = 14.2 Hz, J = 7.1 Hz, 1H), 4.4 (dd (aparent t), J = 7.1 Hz, J = 5.8 Hz, 1H); ^{13}C-NMR (D_2O + 1,4-dioxane): 20.0, 21.89, 21.93, 46.9, 53.4, 53.9, 54.4, 167.8. Anal.: Calcd. for $C_8H_{16}N_2O_2 \cdot 2HCl$: C, 39.20; H, 7.40; N, 11.43. Found: C, 39.23; H, 7.37; N, 11.15.

Methyl 2-acetamido-3-morpholinopropanoate **3b**. It was prepared from morpholine in 94% yield as for **3a** except that acetonitrile was used as solvent; m.p. 88-90ºC (from ethyl acetate); IR (KBr): 3267, 1754, 1639 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.0 (s, 3H), 2.5 (m, 4H), 2.67 (dd, J = 12.8 Hz, J = 5.8 Hz, 1H), 2.74 (dd, J = 12.8 Hz, J = 6.6 Hz, 1H), 3.67 (m, 4H), 3.74 (s, 3H), 4.6 (ddd (aparent q) J = 6.6 Hz, J = 6.2 Hz, J = 5.8 Hz, 1H), 6.6 (d, J = 6.2 Hz, 1H); ^{13}C-NMR ($CDCl_3$): 22.7, 50.3, 52.1, 53.4, 58.7, 66.6, 169.8, 171.9. Anal: Calcd. for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.41; H, 7.59; N, 12.17.

3-Morpholinoalanine dihydrochloride **4b**. Prepared from **3b** in 56% yield as for **4a** (reaction time 48 h). Hygroscopic solid. IR(KBr): 3436, 3292-2466, 1746 cm^{-1}; ^{1}H-NMR (D_2O): 3.3 (m, 4H), 3.5 (dd, J = 13.5 Hz, J = 5.3 Hz, 1H), 3.6 (dd, J = 13.5 Hz, J = 8.0 Hz, 1H), 3.8 (m, 4H), 4.3 (dd, J = 8.0 Hz, J = 5.3 Hz, 1H). Anal.: Calcd. for $C_7H_{14}N_2O_3 \cdot 2HCl \cdot H_2O$: C, 31.71; H, 6.84; N, 10.56. Found: C, 31.87; H, 7.37, N 10.72.

Methyl 2-acetamido-3-(2-methoxycarbonylpiperidino)propanoate **3c**. (Diastereoisomeric mixture which could not be separated). Prepared from **2c** in 40% yield as for **3a**; the initial molar ratio **1**:**2c** was 1:1 but after 48 h of reaction 0.4 equivalents of **2c** were added. Oil; b.p. 190ºC (oven temperature)/0.1 mm Hg; IR (film): 3295, 1736, 1659 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.3-1.7 (m, 4H+4H), 1.8 (m, 2H+2H), 2.066 (s, 3H), 2.069 (s, 3H), 2.2 (m, 1H), 2.3 (m, 1H), 2.6 (dd, J = 13.2 Hz, J = 5.1 Hz, 1H), 2.7 (dd, J = 13.2 Hz, J = 9.2 Hz, 1H), 2.9 (m, 1H+1H+1H), 3.0 (dt, J = 10.9 Hz, J = 3.8 Hz, 1H), 3.1 (dd, J = 8.8 Hz, J = 3.7 Hz, 1H), 3.2 (t, J = 5.8 Hz, 1H), (3.703 (s) + 3.706 (s), 3H), (3.715 (s) +3.718 (s) 3H), (3,730 (s) + 3,734 (s), 6H), 4.36 (aparent dd, J = 9.2 Hz, J = 4.4 Hz, 1H), 4.44 (m, 1H), 6.8 (d, J = 5.5 Hz, 1H), 7.0 (d, J = 4.0 Hz, 1H); by irradiation at 7.06 ppm (NH of one diastereoisomer) the signal at 4.36 ppm is observed as a dd (J = 9.2 Hz, J = 5.1 Hz); by irradiation at 6.83 ppm (NH of the other diastereoisomer) the signal at 4.44 ppm is observed as a dd (J = 9.5 Hz, J = 5.1 Hz); ^{13}C-NMR ($CDCl_3$): 21.8, 22.5, 22.6, 22.8, 24.94, 24.98, 29.3, 29.8, 50.3, 51.0, 51.4, 51.5, 51.8, 52.1, 56.5, 56.7, 64.2, 64.5, 170.3, 170.6, 171.8, 172.2, 174.1, 174.8. Anal: Calcd. for $C_{13}H_{22}N_2O_5$: C, 54.53; H, 7.74; N, 9.78. Found: C, 54.09; H, 7.45; N, 9.77.

3-(2-Carboxypiperidino)alanine hydrochloride **4c**. (Diastereoisomeric and mono and dihydrochlorides mixtures). Prepared from **3c** in 79% yield as for **4a** (reaction time 17 h); hygroscopic solid; IR(KBr): 3397-2564, 1740, 1678 cm^{-1}; ^{1}H-NMR (D_2O): 1.5-2.2 (m, 6H), 3.0-3.9 (m, 5H), 4.4 (m, 1H); ^{13}C-RMN (D_2O+

1,4-dioxane): 20.8, 21.3, 21.7, 23.2, 23.3, 23.7, 49.1, 49.2, 49.4, 49.6, 55.0, 55.4, 62.4, 62.6, 165.7, 169.3, 171.0; MS(m/e): 198 (M-18, 35), 155 (65), 125 (68), 83 (100), 55 (33). Anal.: Calcd. for $C_9H_{16}N_2O_4$·1.5 HCl: C, 39.90; H, 6.51; N, 10.34. Found: C, 39.78; H, 6.63; N, 10.78.

Methyl 2-acetamido-3-(3-methoxycarbonylpiperidino)propanoate **3d**. (Diastereoisomeric mixture which could not be separated). Prepared from **2d** in 95% yield as for **3a**; oil; IR(film): 3417 (broad), 1741, 1673 cm^{-1}; ^{1}H-NMR (CDCl$_3$): 1.6 (m, 4H+4H), 2.01 (s, 3H), 2.03 (s, 3H), 2.2 (m, 2H), 2.3-2.8 (m, 8H), 3.0 (m, 2H), 3.4-3.8 (partially masked m, 2H), 3.65 (s, 3H), 3.66 (s, 3H), 3.69 (s, 3H), 3.70 (s, 3H), 4.5 (m, 1H + 1H), 6.7 (d, J = 6.2 Hz, 1H), 6.8 (d, J = 6.6 Hz, 1H); ^{13}C-RMN (CDCl$_3$): 22.5, 22.6, 23.88, 23.94, 25.8, 26.0, 41.0, 41.1, 50.6, 51.0, 51.37, 51.41, 51.9, 52.0, 53.6, 53.7, 54.8, 55.4, 58.1, 170.1, 170.2, 171.9, 172.1, 174.1, 174.2. Anal.: Calcd. for $C_{13}H_{22}N_2O_5$: C, 54.53; H, 7.74; N, 9.78. Found: C, 54.14; H, 7.63; N, 9.68.

3-(3-Carboxypiperidino)alanine hydrochloride **4d**. Prepared in quantitative yield from **3d** as for **4a** (reaction time 18 h); hygroscopic solid; IR(KBr): 3428, 3200-2400, 1726 cm^{-1}; ^{1}H-NMR (D$_2$O) : 1.6-2.1 (m, 5H), 2.9 (m, 1H), 3.42 (m, 5H), 4.2 (t, J = 6.4 Hz, 1H); ^{13}C-NMR (D$_2$O + 1,4-dioxane): 28.3 (broad), 31.0, 45.1 (broad), 54.5, 60.5, 61.1, 176.5; MS (m / e): 215 (M-1, 2), 198 (M-18, 18), 155 (39), 125 (54), 97 (22), 84 (100), 83 (86), 82 (29), 69 (20), 56 (31), 55 (49).

Methyl 2-acetamido-3-(4-methoxycarbonylpiperidino)propanoate **3e**. Prepared from **2e** in 84% yield as for **3a** except that acetonitrile was used as solvent; the initial ratio **1**:**2e** was 1:1 but after 164 h of reaction 0.5 equivalents of **2e** were added; m.p. 92-93°C (after digestion on diethyl ether); IR(KBr): 3308, 1755, 1731, 1652 cm^{-1}; ^{1}H-NMR (CDCl$_3$): 1.5 (m, 2H), 1.7 (m, 2H), 1.9 (s, 3H), 1.9-2.2 (m, 3H), 2.5 (dd, J = 10.8 Hz, J = 5.8 Hz, 1H), 2.6 (dd, J = 10.8 Hz, J = 6.9 Hz, 1H), 2.7 (m, 2H), 3.5 (s, 3H), 3.6 (s, 3H), 4.4 (ddd (aparent q), J = 6.9 Hz, J = 6.2 Hz, J = 5.8 Hz, 1H), 6.4 (d, J = 6.2 Hz, 1H); by irradiation at 6.35 ppm (NH) the signal at 4.39 ppm is observed as an aparent t (J = 6.2 Hz); ^{13}C-NMR (CDCl$_3$): 22.8, 28.2, 40.4, 50.6, 51.5, 52.1, 52.6, 53.0, 58.2, 169.9, 172.1, 175.2. Anal.: Calcd. for $C_{13}H_{22}N_2O_5$: C, 54.53; H, 7.74; N, 9.78. Found: C, 54.69; H, 7.45; N, 9.76.

3-(4-carboxypiperidino)alanine dihydrochloride **4e**. It was prepared from **3e** in 74% yield as for **4a** (reaction time 18 h); hygroscopic solid recrystallized in absolute ethanol; IR(KBr): 3429, 3274-2400, 1725 cm^{-1}; ^{1}H-NMR (D$_2$O): 1.8 (m, 2H), 2.0 (m, 2H); 2.6 (m, 1H), 3.0 (m, 2H), 3.4 (dd, J = 13.9 Hz, J = 5.9 Hz, 1H), 3.49 (m, 2H), 3.51 (dd, J = 13.9 Hz, J = 6.6 Hz, 1H), 4.3 (aparent t, J = 6.2 Hz, 1H); ^{13}C-NMR (D$_2$O + 1,4-dioxane): 12.5, 16.1, 24.5 (broad), 37.0 (broad), 46.9, 52.0 (broad), 54.6 (broad), 56.7, 61.4, 168.0, 174.4, 176.2.

Methyl 2-acetamido-3-(1-pyrrolidinyl)propanoate **3f**. Prepared from pyrrolidine in 91% yield as for **3a**; m.p. 80-82°C (from diethyl ether); IR(KBr); 3330, 2970, 2795, 1754, 1654 cm^{-1}; ^{1}H-NMR (CDCl$_3$): 1.7 (m, 4H), 2.0 (s, 3H), 2.4 (m, 4H), 2.8 (dd, J = 12.4 Hz, J = 5.5 Hz, 1H), 2.9 (dd, J = 12.4 Hz, J = 6.2 Hz, 1H), 3.7 (s, 3H), 4.5 (ddd (aparent q), J = 6.2 Hz, J = 5.5 Hz, J = 5.1 Hz, 1H), 6.4 (broad d, J = 5.1 Hz, 1H); by irradiation at 6.41 ppm (NH) the signal at 4.47 ppm is observed as an aparent t (J = 5.7 Hz); by irradiation at 2.81 ppm the signal at 4.47 ppm is observed as a d (J = 6.2 Hz); by irradiation at 4.47 ppm (CH) the signal at 2.77 is observed as a d (J = 12.4 Hz), the signal at 2.85 ppm is observed as a d (J = 12.4 Hz) and the signal at 6.41 ppm is observed as a broad s; ^{13}C-NMR (CDCl$_3$): 23.0, 23.6, 51.9, 52.2, 54.2, 56.3, 170.1, 172.2. Anal.: Calcd. for $C_{10}H_{18}N_2O_3$: C, 56.06; H, 8.47; N, 13.07. Found: C, 56.18; H, 8.28; N, 12.97.

3-(1-Pyrrolidinyl)alanine dihydrochloride **4f**. It was prepared from **3f** in 80% yield as for **4a** (reaction time 48 h); hygroscopic solid; IR(KBr): 3400-2200, 1717 cm^{-1}; ^{1}H-NMR (CD$_3$OD): 2.1 (m, 4H), 3.3 (partially masked m, 2H), 3.8 (dd, J = 13.9 Hz, J = 6.6 Hz, 1H), 3.9 (m, 2H), 4.0 (dd, J = 13.9 Hz, J = 5.5 Hz, 1H), 4.7 (aparent t, J = 6.2 Hz, 1H); ^{13}C-RMN (D$_2$O + 1,4-dioxane): 22.3, 22.6, 48.6, 53.0, 54.4, 56.1, 168.9. Anal.: Calcd. for $C_7H_{14}N_2O_2$·2HCl: C, 36.38; H, 6.98; N, 12.12. Found: C, 36.15; H, 7.06; N, 11.85.

Methyl 2-acetamido-3-(1-imidazolyl)propanoate **3g**. Imidazole (0.118 g, 1.74 mmol) was added to a sonicated solution of **1** (0.250 g, 1.75 mmole) and anhydrous iron(III) chloride (0.028 g, 0.17 mmole) in dichloromethane (20 mL). The mixture was sonicated for 3 days (TLC monitoring), then more imidazole was added (0.118 g, 1.74 mmole) and the mixture left 4 days more under the same conditions. The solution was washed with an aqueous solution of sodium sulfate and the aqueous phase extracted with dichloromethane.

The combined organic layers were dried with anhydrous sodium sulfate and the solvent evaporated to afford **3g** (0.098 g, 0.47 mmole, 27%); IR(film): 3410, 1747, 1680, 1671 cm^{-1}; ^{1}H-NMR (d_6-DMSO): 1.8 (s, 3H), 3.7 (s, 3H), 4.2 (dd, J = 13.9 Hz, J = 9.1 Hz, 1H), 4.3 (dd, J = 13.9 Hz, J = 4.8 Hz, 1H), 4.6 (ddd, J = 9.1 Hz, J = 8.0 Hz, J = 4.8 Hz, 1H), 6.8 (s, 1H), 7.1 (s, 1H), 7.5 (s, 1H), 8.4 (d, J = 8.0 Hz, 1H). The aqueous layer was evaporated and the residue was chromatographed through a silica gel column under pressure. Elution with methanol yielded 2-acetamido-3-(1-imidazolyl)propanoic acid, **5** (0.249 g, 1.26 mmole, 72%) as an oil which crystallized in diethyl ether; m.p. 125-127°C; IR(KBr): 3382-2849, 1652, 1508 cm^{-1}; ^{1}H-NMR (d_6-DMSO): 1.8 (s, 3H), 4.2 (dd, J = 13.9 Hz, J = 8.6 Hz, 1H), 4.3 (dd, J = 13.9 Hz, J = 4.2 Hz, 1H), 4.5 (m, 1H), 6.9 (s, 1H), 7.1 (s, 1H), 7.6 (s, 1H), 8.2 (d, J = 7.6 Hz, 1H); MS(m/e): 197 (M, 6), 129 (M-68, 10), 87 (36), 68 (66), 43 (100) . Anal.: Calcd. for $C_8H_{11}N_3O_3 \cdot H_2O$: C, 44.65; H, 6.09; N, 19.52. Found: C, 45.20; H, 5.40; N, 19.65.

Methyl 2-acetamido-3-(1-pyrazolyl)propanoate **3h**. A mixture of pyrazole (0.119 g, 1.75 mmole), methyl 2-acetamidoacrylate, **1** (0.250g, 1.75 mmole) and iron(III) chloride (0.029g, 0.18 mmol) in chloroform (30 mL) was refluxed for 2 days (GLC monitoring). Then more pyrazole was added (0.119 g, 1.75 mmole) and the mixture left 6 days more under the same conditions. The solvent was evaporated and the residue was chromatographed through a silica gel column under pressure. Elution with diethyl ether gave **1** (0.111g, 0.78 mmole) and elution with diethyl ether-methanol 1:1 gave pyrazole (0.114 g, 1.67 mmole); finally elution with methanol afforded **3h** (0.197 g, 0.93 mmole, 54 % yield); m.p. 93-95 °C (from chloroform-diethyl ether); IR (KBr): 3323, 1729, 1641, 1545 cm^{-1}; ^{1}H-NMR ($CDCl_3$) : 2.0 (s, 3H), 3.7 (s, 3H), 4.5 (dd, J= 13.9 Hz, J = 4.0 Hz, 1H), 4.7 (dd, J = 13.9 Hz, J = 3.6 Hz, 1H), 4.9 (ddd (aparent quint.), J = 6.2 Hz, J = 4.0 Hz, J = 3.6 Hz, 1H), 6.2 (aparent t , J = 1.8 Hz, 1H), 6.6 (broad d, J = 6.2 Hz, 1H), 7.3 (d, J = 2.2 Hz, 1H), 7.5 (d, J = 1.5 Hz, 1H); ^{13}C-NMR (d_4-MeOH) : 21.9, 52.4, 52.7, 54.0, 106.4, 131.8, 140.5, 170.5, 172.8. Anal.: Calcd. for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.89. Found : C, 51.07; H, 5.95; N, 19.56. .

Methyl 2-acetamido-3-(dibutylamino)propanoate **3i**. A mixture of **1** (0.250 g, 1.74 mmole), dibutylamine (0.225 g, 1.74 mmole) and iron(III) chloride (0.028 g, 0.17 mmole) in dichloromethane (15 mL) was stirred at room temperature for 4 days (GLC monitoring), then more dibutylamine was added (0.112 g, 0.87 mmole) and left 2 days more. The crude mixture was washed with an aqueous solution of sodium sulfate and the aqueous phase extracted with dichloromethane. The combined organic layers were dried with anhydrous sodium sulfate and the solvent evaporated. The residue was chromatographed on a silica gel column; with ethyl acetate as eluent **1** was obtained (0.037 g, 0.26 mmole, 15% recovery); elution with methanol afforded **3i** as an oil (0.241 g, 0.85 mmole, 51% yield); IR(film): 3291, 2958, 2933, 1750, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 0.9 (t, J = 6.6 Hz, 6H), 1.4 (m, 8H), 2.0 (s, 3H), 2.3 (m, 4H), 2.7 (dd, J = 13.3 Hz, J = 5.9 Hz, 1H), 2.8 (dd, J = 13.3 Hz, J = 6.2 Hz, 1H), 3.7 (s, 3H), 4.4 (ddd (aparent q), J = 6.2 Hz, J = 5.9 Hz, J = 5.5 Hz, 1H), 6.3 (d, J = 5.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$): 14.0, 20.4, 22.9, 29.0, 51.4, 52.1, 53.9, 54.9, 169.9, 172.4. Anal.: Calcd. for $C_{14}H_{28}N_2O_3$: C, 61.73; H, 10.36; N, 10.28. Found: C, 61.49; H, 10.02; N, 10.02.

Methyl 2-acetamido-3-butylaminopropanoate **3j**. (Uncatalyzed reaction). A mixture of butylamine (0.127 g, 1.74 mmole) and **1** (0.250 g, 1.74 mmole) in dichloromethane (15 mL) was stirred at room temperature for 8 days (TLC monitoring). The solution was washed with water, the aqueous phase extracted with dichloromethane and the combined organic layers dried with anhydrous sodium sulfate and the solvent evaporated to give **3j** (0.183 g, 0.85 mmole, 49%) as an oil; IR(film): 3307, 3284, 1745, 1657 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 0.9 (t, J = 6.9 Hz, 3H), 1.4 (m, 4H), 2.0 (s, 3H), 2.6 (t, J = 6.9 Hz, 2H), 2.9 (dd, J = 12.4 Hz, J = 4.4 Hz, 1H), 3.1 (dd, J = 12.4 Hz, J = 4.8 Hz, 1H), 3.7 (s, 3H), 4.6 (ddd, J = 6.6 Hz, J = 4.8 Hz, J = 4.4 Hz, 1H), 6.6 (d, J = 6.6 Hz, 1H); ^{13}C-NMR ($CDCl_3$): 13.8, 20.1, 22.9, 31.9, 49.2, 50.7, 52.2, 52.3, 170.1, 172.1; MS(m / e): 217 (M+1, 10), 173 (2), 144 (6), 86 (100), 44 (41). Anal.: Calcd. for $C_{10}H_{20}N_2O_3$: C, 55.53; H, 9.32; N, 12.95. Found: C, 55.98; H, 9.53; N, 13.17. Compound **3j** undergoes spontaneous ester hydrolysis upon standing after several days giving 2-acetamido-3-butylaminopropionic acid as an hygroscopic solid; IR(KBr): 3600-2400, 1677, 1646 cm^{-1}; ^{1}H-NMR (CD_3OD): 1.0 (t, J =7.3 Hz, 3H), 1.4 (m, 2H), 1.6 (m, 2H), 2.0 (s, 3H), 3.0 (t, J = 7.4 Hz, 2H), 3.1 (dd, J = 12.3 Hz, J = 6.8 Hz, 1H), 3.2 (dd, J = 12.3 Hz, J = 6.7 Hz), 4.4 (aparent t, J = 6.7 Hz, 1H); ^{13}C-NMR (CD_3OD): 14.0, 20.9, 22.8, 29.7, 51.0, 52.4, 173.7, 175.0; MS(m/e): 203 (M+1, 3), 139 (M-64, 10), 86 (100), 44(48). Anal.: Calcd. for $C_9H_{18}N_2O_3 \cdot 1.5\ H_2O$: C, 47.14; H, 9.23; N, 12.21. Found: C, 46.68; H, 8.44; N, 12.20.

N,N-Bis(2-acetamido-2-methoxycarbonylethyl)butylamine **6**. (Catalyzed reaction). A mixture of **1** (0.490 g, 3.42 mmole), butylamine (0.250 g, 3.42 mmole) and anhydrous iron(III) chloride (0.055 g, 0.34 mmole) was stirred at room temperature for 8 days (TLC monitoring). The crude mixture was washed with an aqueous solution of sodium sulfate, the aqueous phase was extracted with dichloromethane, the combined organic layers were dried with anhydrous sodium sulfate and the solvent was evaporated. The residue was chromatographed through a silica gel column under pressure; elution with ethyl acetate afforded methyl 2-acetamidoacrylate, **1** (0.035 g, 0.24 mmole); elution with methanol gave first **3j** (0.096 g, 0.44 mmole, 13%) and then **6** as an oil (0.252 g, 0.70 mmol, 41%); IR(film): 3285, 2957, 2932, 1743, 1656 cm^{-1}; ^1H-NMR ($CDCl_3$): 0.9 (m, 3H), 1.3 (m, 4H), 2.05 (s, 3H), 2.07 (s, 3H), 2.4 (t, J = 7.0 Hz, 2H), 2.8 (m, 4H), 3.7 (s, 6H), 4.6 (m, 2H), 6.5 (d, J = 7.2 Hz, 1H), 6.7 (d, J = 6.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$): 13.9, 20.1, 20.2, 22.8, 28.8, 51.3, 51.8, 52.4, 53.7, 54.6, 56.2, 56.3, 170.2, 170.6, 171.9, 172.2. Anal.: Calcd. for $C_{16}H_{29}N_3O_6$: C, 53.47; H, 8.13; N, 11.69. Found: C, 54.31; H, 8.32; N, 11.94.

ACKNOWLEDGEMENTS

Financial support from DGICYT (Ministry of Education and Science of Spain) through projects PB90-0063 and PB93-0896 is gratefully acknowledged. We are also indebted to DGICYT for a predoctoral scholarship to M.P. and to Prof. M. Moreno-Mañas for helpful comments.

REFERENCES

1. a) Hart, N.K.; Hofmann, A.; Lamberton, J.A.; Richards, C.M. *Heterocycles* **1977**, *7*, 265-272.
   b) Tsuchida, K.; Ikeda, K.; Mizuno, Y. *Chem. Pharm. Bull.* **1980**, *28*, 2748-2752.
   c) Murakoshi, I.; Ikegami, F.; Hinuma, Y.; Hanma, Y. *Phytochemistry* **1984**, *23*, 1905-1908.
   d) Baldwin,J.E.; Adlington, R.M.; Birch, D.J. *Tetrahedron Lett.* **1985**, *26*, 5931-5934.
   e) Murakoshi, I.; Ikegami, F.; Yoneda, Y.; Ihara, H.; Sakata, K.; Koide, Ch. *Chem. Pharm. Bull.* **1986**, *34*, 1473-1478.
   f) Shadid, B.; van der Plas, H.C.; Boesten, W.H.J.; Kamphuis, J.; Meijer, E.M.; Schoemaker, H.E. *Tetrahedron* **1990**, *46*, 913-920.
   g) Ikegami, F.; Itagaki, S.; Ishikawa, T.; Onhena, G.; Kuo, Y.-H.; Lambein, F.; Murakoshi, I. *Chem. Pharm. Bull.* **1991**, *39*, 3376-3377.
   h) Baldwin, J.E.; Adlington, R.M.; Mellor, L.C. *Tetrahedron* **1994**, *50*, 5049-5066.
2. Van Rompuy, L.; Schamp, N.; De Kimpe, N.; Van Parijs, R. *J. Chem. Soc. Perkin Trans I*, **1973**, 2503-2506.
3. a) Benoiton, L. *Can. J. Chem.* **1968**, *46*, 1549-1552.
   b) Lancini, G.C.; Diena, A.; Lazzari, E. *Tetrahedron Lett.* **1966**, *16*, 1769-1772.
   c) Otsuka, M.; Kittaka, A.; Iimori, T.; Yamashita, H.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1985**, *33*, 509-514.
4. a) Arnold, L.D.; Kalantar, T.H.; Vederas, J.C. *J. Am. Chem. Soc.* **1985**, *107*, 7105-7109.
   b) Arnold, L.D.; Drover, J.C.G.; Vederas, J.C. *J. Am. Chem. Soc.* **1987**, *109*, 4649-4659.
   c) Arnold, L.D.; May, R.G.; Vederas, J.C. *J. Am. Chem. Soc.* **1988**, *110*, 2237-2241.
   d) Ratemi, E.S.; Vederas, J.C. *Tetrahedron Lett.* **1994**, *35*, 7605-7608.
   e) Lewis, I.; Bruns, C. *Tetrahedron* **1994**, *50*, 7485-7494.
5. P. Perlmutter. *Conjugate Addition Reactions in Organic Synthesis.* Tetrahedron Organic Chemistry Series, Volume 9. Pergamon Press: Oxford, **1992**.
6. a) Asquith, R.S.; Carthew, P. *Tetrahedron* **1972**, *28*, 4769-4773.
   b) Asquith, R.S.; Yeung, K.W.; Otterburn, M.S. *Tetrahedron* **1977**, 133, 1633-1635.
7. Murakoshi, I.; Ohmiya, S.; Haginiwa, J. *Chem. Pharm. Bull.* **1972**, *20*, 609-611.
8. Belokon, Y.N.; Sagyan, A.S.; Djamgaryan, S.M.; Bakhmutov, V.I.; Belikov, V.M. *Tetrahedron* **1988**, *44*, 5507-5514.

9. a) Cardellicchio, C.; Fiandese, V.; Marchese, G.; Naso, F.; Ronzini, L. *Tetrahedron Lett.* **1985**, *26*, 4387-4390.
   b) Cativiela, C.; Díaz-de-Villegas, M.D.; Gálvez, J.A. *Can. J. Chem.* **1992**, *70*, 2325-2328.
10. Cabral, J.; Laszlo, P.; Mahé, L.; Montaufier, M.T.; Randriamahefa, S.L. *Tetrahedron Lett.* **1989**, *30*, 3969-3972.
11. Jenner, G. *Tetrahedron Lett.* **1995**, *36*, 233-236.
12. Freifelder, M.; Stone, G.R. *J. Org. Chem.* **1961**, *26*, 3805-3808.

(*Received in UK* 19 *April* 1995; *revised* 1 *June* 1995; *accepted* 9 *June* 1995)