Preparation and characterization of novel pyrrol-3-ones attached to α/β-amino acids, esters and amides

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Summary. Various α/β amino acid derivatives 5 were attached to compounds 3 to yield 2,3-dihydro-1H-pyrrol-3-ones amino acids derivatives 6. This rare heterocyclic amino acid skeleton including the pyrrolo[1,2-b][1,3]oxazol moiety was also successfully prepared in the esteric form. The structure of the new compounds was characterized by spectroscopic methods.

Keywords: Pyrrol-3-ones – Amino acids – Amino acid esters – Amino acid amides – Pyrrolo[2,1-b][1,3]oxazole – Furan-3(2H)-ones

Introduction

The development and application of new practical methods for the preparation of structurally diverse amino acid derivatives is of fundamental importance due to their widespread use in all areas of physical and life sciences. Non-naturally occurring amino acids and derivatives constitute an important resource for new chemotherapeutic agents, antibacterial compounds and enzyme inhibitors (Hoz et al., 2001). In this respect, heterocyclic amino acids are of much interest for biological and medicinal reasons. Such amino acids, containing isoxazole (Betler and Mullé, 1995), tetrazole (Schoepp et al., 1991), triazole (Ikegami and Murakoshi, 1994), and pyrazole (Dunnill and Fowden, 1965), are bioactive materials. Among these, the pyrrole amino acid derivatives, holds a special important status. Some of them, e.g. domoic acids, kainic acids (Clayden et al., 2005), lamellarins (Bailly, 2004), lukianol A (Yoshida et al., 1992), halitulin (Kashman et al., 1999), were isolated from natural sources. Some act as DNA targeting compounds with considerable cytotoxicity while others function as multi-drug resistant reversal agents (Bailly, 2004; Rudi et al., 1994; Kashman et al., 1999; Boger et al., 1999).

A variety of methods are known for the synthesis of pyrrolo-amino acids and esters. Recently, we have reported (Üngören et al., 2004; Saçmacı et al., 2005) about the reaction of furan-3(2H)-ones with primary amines and hydrazines to yield pyroles containing N-alkyl/aryl/hydroxy substituted β-amino acid esters. We were able (Saçmacı et al., 2005) to prepare the interesting N-acetic acid substituted pyrrole derivative (Scheme 1). This last synthesis paved the way to a general procedure for a new type of pyrrolo-amino acid derivatives. In the present study, we extend the scope to various pyrrole containing α-amino acids, amides and esters. We also describe the successful preparation of the rare heterocyclic amino acid ester skeleton including the pyrrolo[1,2-b][1,3]oxazol moiety.

Materials and methods

4-(4-Methoxybenzoyl)-5-(4-methoxyphenyl)-2,3-dihydro-2,3-furandione 1 was prepared by cyclization of 1,3-bis(4-methoxybenzoyl)propane-1,3-dione with oxalyl chloride (Hökelek et al., 2002). Melting points were determined on an electrothermal 9200 apparatus and are uncorrected. Elemental analyses (C, H, N) were carried out using LECO-932 CHNSO analyzer. IR spectra were recorded on a Jasco Plus Model 460 FT-IR Spectrometer as KBr pellets. 1H (400 MHz) and 13C (100 MHz) NMR spectra were obtained on a Bruker Avance DPX-400 spectrometer in DMSO-d6 and CDCl3 with TMS as an internal standard. Mass spectra, were measured with an Agilent 1100 MSD instrument. All experiments were followed by tlc using DC Alufolien Kieselgel 60 F 254 and Camag TLC lamp (254/366 nm).

Ethyl (Z)-[2,3-Dihydro-4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-3-oxofuran-2-ylidene]acetate (3b)

To a boiling solution of 2,3-dihydro-furan-2,3-dione 1 (0.338 g, 1 mmole) in 25 ml benzene, a solution of 2 (0.348 g, 1 mmole) in dry benzene (15 ml)
was added and the mixture was refluxed for 20 min. After removal of the solvent, the oily residue was triturated with a mixture of petroleum ether (40–60) and diethyl ether (3:1) for 24 h. The bright yellow crystals were filtered off and washed with cyclohexane (0.32 g; 78%). m.p. 99–100°C; 1H NMR (ppm): 7.95–6.91 (m, 8H, Ar–H), 6.13 (s, 1H, –C≡H), 4.34 (q, J = 7.1 Hz, 2H, OCH3), 3.85, 3.81 (s, 6H, OCH3), 1.39 (t, J = 7.1 Hz, 3H, CH3); IR (cm−1): 3139 (OH), 1750, 1690 (C=O). 13C NMR (100 MHz, CDCl3) (ppm): 193.6 (Ar–CO), 188.5 (pyrrol’s CO), 181.2 (pyrrol’s CH2); 1H NMR (400 MHz, CDCl3) (ppm): 7.80–6.83 (m, 8H, Ar–H), no detection (OH), 4.03 (q, J = 6.9 Hz, OCH3), 3.92 (q, J = 17.1 Hz, 2H, NCH3) 3.88, 3.84 (s, 6H, –OCH3), 2.90 (s, 2H, C–CH2COOEt); 13C NMR (100 MHz, CDCl3) (ppm): 193.9, 188.7, 181.2, 170.3 (C=O), 163.1–111.7 (C=C, arom. and aliph.), 88.3 (C=OH), 50.84, 55.74 (OCH3), 45.28 (NCH3), 39.3 (CH2CH2), 14.42 (CH2CH2); IR ν (cm−1): 3420, 3190 (OH), 3280–3050 (OH), 1740, 1696 (C=O). Anal. calcd. for C25H26N2O8: C, 62.23; H, 5.43; N, 5.81. Found C, 62.20; H, 5.85; N, 5.76.

Methyl [2-hydroxy-4-(4-methoxybenzoyl)-2-(2-ethoxy-2-oxoethyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrryl-1-yl]acetate (6c)

White crystal from toluene; m.p. 151–153°C; yield 0.417 g, 84%; 1H NMR (400 MHz, CDCl3) (ppm): 7.80–6.83 (m, 8H, Ar–H), no detection (OH), 4.23 (q, J = 18.8 Hz, 2H, –NCH3), 4.20 (q, J = 7.1 Hz, 2H, OCH3), 3.84, 3.82, 3.72 (s, 9H, –OCH3), 2.99 (q, J = 16.1 Hz, 2H, C–CH2–COOMe), 1.29 (t, J = 7.0 Hz, 3H, –CH3); 13C NMR (100 MHz, CDCl3) (ppm): 194.0, 188.6, 181.1, 170.25 (C=O), 169.9–111.8 (C=C, arom. and aliph.), 88.2 (C=O), 61.3 (OCH3), 55.6, 55.3, 52.6 (OCH3), 44.6 (N–CH3), 40.1 (CH2 COOEt), 14.07 (OCH2CH2); IR ν (cm−1): 3137 (OH), 1753, 1747, 1687 (C=O).

Anal. calcd. for C22H25NO9: C, 72.7; H, 5.47; N, 2.82. Found C, 72.60; H, 5.55; N, 2.61.

**Scheme 1**

1 mmole amino acid derivatives (5a–e) and 1 mmole 3a,b were refluxed in a mixture of 50 ml methanol and 2 ml pyridine for 5 h. After the solvents were removed by evaporation, the oily residue was triturated with mixtures of dry diethyl ether and n-hexane (3:1) to get the corresponding crude pyrrolones (6a–i), which were purified by recrystallization.

Melhyt [2-hydroxy-4-(4-methoxybenzoyl)-2-(2-ethoxy-2-oxoethyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrryl-1-yl]acetate (6a)

White crystal from water; m.p. 156–157°C; yield 0.270 g, 56%; 1H NMR (400 MHz, CDCl3) (ppm): 7.80–6.83 (m, 8H, Ar–H), no detection (OH), 4.23 (q, J = 18.2 Hz, 2H, NCH3 COOMe), 3.84, 3.82, 3.75, 3.73 (s, 12H, –OCH3), 3.0 (q, J = 16.2 Hz, 2H, –CH2COOEt), 13C NMR (100 MHz, CDCl3) (ppm): 193.6 (Ar–CO), 188.5 (pyrrol’s CO), 181.2 (CH2COOMe), 170.9 (NCH3COOMe), 163.2–111.7 (C=C, arom. and aliph.), 88.1 (C=OH), 55.4, 55.4, 52.7, 52.3 (OCH3), 44.6 (N–CH3), 39.7 (C–CH3). IR ν (cm−1): 3139 (OH), 1750, 1690 (C=O).

Anal. calcd. for C23H25NO9: C, 72.6; H, 5.21; N, 2.90. Found C, 72.27; H, 5.22; N, 2.93.

Ethyl [2-hydroxy-4-(4-methoxybenzoyl)-2-(2-ethoxy-2-oxoethyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrryl-1-yl]acetate (6b)

White crystal from water; m.p. 156–157°C; yield 0.427 g, 86%; 1H NMR (400 MHz, CDCl3) (ppm): 7.75–6.76 (m, 8H, Ar–H), 6.22 (s, 1H, OH), 4.17 (q, J = 18.2 Hz, 2H, –NCH3), 4.15 (q, J = 7.1 Hz, 2H, OCH3), 3.79, 3.77, 3.70 (s, 9H, –OCH3), 3.02 (q, J = 16.2 Hz, 2H, CH2COOEt), 1.21 (t, J = 7.1 Hz, 3H, CH2CH3); 13C NMR (100 MHz, CDCl3) (ppm): 194.2, 188.8, 180.9, 170.0 (C=O), 169.9–111.7 (C=C, arom. and aliph.), 88.1 (C=OH), 61.8 (OCH3), 55.3, 55.1 (OCH3), 44.6 (N–CH3), 40.1 (CH2COOEt), 14.05 (OCH2CH2); IR ν (cm−1): 3136 (OH), 1749, 1688 (C=O).

Anal. calcd. for C25H24NO9: C, 72.7; H, 5.47; N, 2.82. Found C, 72.50; H, 5.36; N, 2.95.

Ethyl 3-[2-hydroxy-4-(4-methoxybenzoyl)-2-(2-ethoxy-2-oxoethyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrryl-1-yl]propanoate (6h)

White crystal from CCl4–CH2Cl2 (1:1); m.p. 113–115°C; yield 0.245 g, 48%; 1H NMR (400 MHz, CDCl3) (ppm): 7.68–6.75 (m, 8H, Ar–H),