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Synthesis of New 3-Pyrrolin-2-One Derivatives

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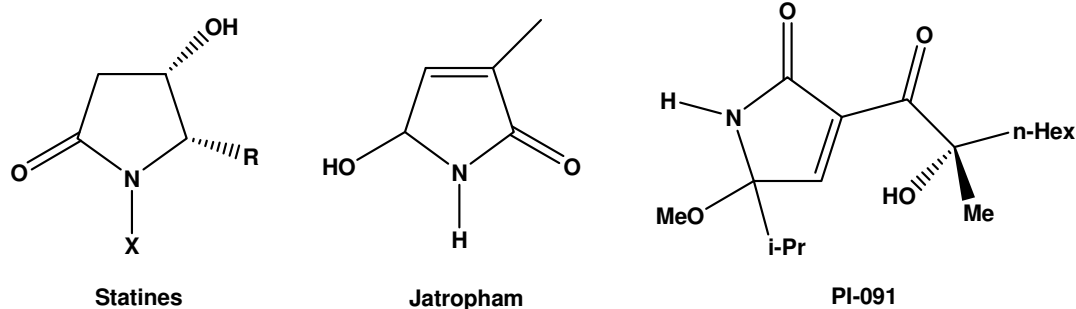
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Six new 3-pyrrolin-2-one derivatives were synthesized via the condensation reaction of amino acid esters (**2a-f**) with 2,5-dimethoxy-2,5-dihydrofuran (**1**) in acidic medium. This simple one-pot reaction furnished the corresponding pyrrolinones (**3a-f**) in acceptable yields.

Key Words: Pyrrolinone, synthesis, dimethoxydihydrofuran.

Introduction

3-Pyrrolin-2-ones are important starting materials for the preparation of a variety of biologically active compounds. These α,β -unsaturated- γ -lactams have been used as precursors for statines¹ and various alkaloids². Moreover, antitumor alkaloid Jatropham³ and the platelet aggregation inhibitor PI-091⁴ are pyrrolinone-containing natural products. In the literature there are several synthetic routes to 3-pyrrolin-2-one derivatives. Those derivatives were synthesized via reduction of simple maleimides⁵,



photoisomerization and intramolecular cyclization of α,β -unsaturated amide aldehydes³ and ketones⁶, oxidative substitution of organotin pyrrole compounds⁷, condensation reaction of α,β -diketones with acetamides⁸, photooxidation of N-substituted pyrroles^{9,10}, and reaction with furanone⁴. There are several examples in the literature of methoxyfuranones that have been converted to pyrrolinones. In these reactions the ring nitrogen is introduced by a reaction with ammonia in appropriate solvent or with primary amine. Although

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dimethoxydihydrofuran has similar synthon as furanones, not much work has been done in this chemistry. Jacques Royer and co-workers^{11,12} studied the reaction of dimethoxydihydrofuran with an amino alcohol.

In order to further explore the reactions of dimethoxydihydrofuran in the synthesis of pyrrolinones, we hereby report 6 new pyrrolinone derivatives formed using various amino acid esters. As shown in Figure 1, this simple one-pot condensation reaction of amino acid esters with dimethoxydihydrofuran gave the corresponding pyrrolinones (**3a-f**) in acceptable yields. Those new derivatives have the potential to be biologically active and are versatile building blocks for further transformations like conjugate additions¹³, cuprate additions¹⁴, and cycloadditions^{15,16}.

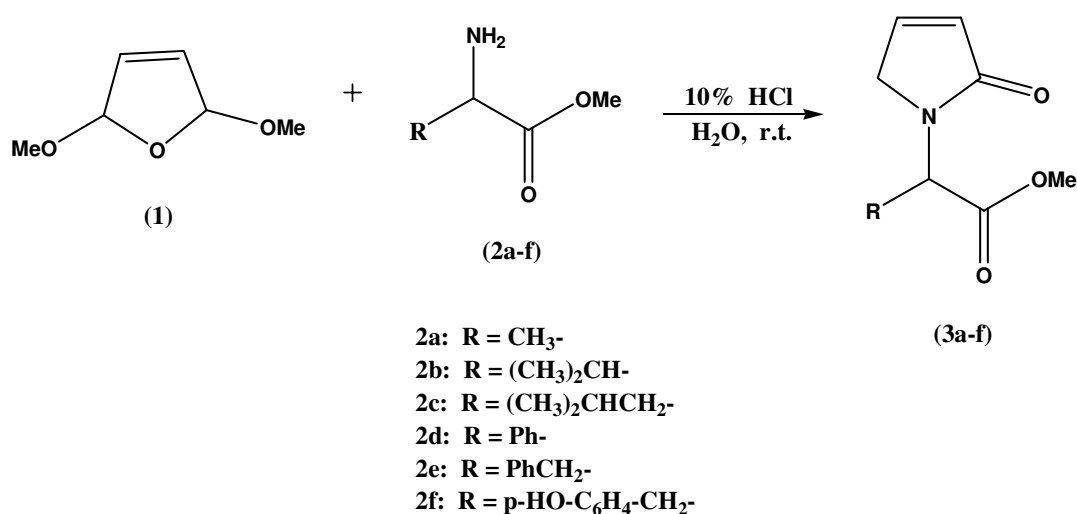


Figure 1. The one-pot synthesis of pyrrolinones (**3a-f**).

Experimental

All reagents were of commercial quality and reagent quality solvents were used without further purification. ¹H and ¹³C NMR spectra were determined on a Bruker DPX 400 MHz FT spectrometer. Mass spectra were obtained on an Agilent 5973 Network Mass Selective Detector via HPP7-M Direct Insertion Probe. IR spectra (KBr) were recorded on a Shimadzu FT-IR DR-8001 FT infrared spectrophotometer. The purity of the compounds was assessed by thin layer chromatography on silica gel 60 F₂₅₄. Column chromatography was conducted on silica gel 60 (mesh size 0.063–0.200 mm). LC-MS (ESI) spectrum was determined on an Agilent 1100 MSD spectrometer at an ionization energy of 70 eV and A: 0.01 mM HAc + 0.2% formic acid, B: MeOH (A:B 70:30, v:v) solvent system was used as the mobile phase. Melting points were measured on a Thomas Hoover Capillary Melting Point Apparatus in an open capillary. Amino acid methyl esters (**2a-f**) were synthesized according to the literature.¹⁷

General procedure for amino acid esters

2,5-Dimethoxy-2,5-dihydrofuran (**1**) (1 mmol) was stirred in water (10 mL) adjusted to pH 1 at room temperature over 12 h. Then amino acid methyl ester (**2a-f**) (1 mmol) was added and the mixture was stirred at this temperature with monitoring by TLC. After the reaction was complete the mixture was neutralized with solid NaHCO₃ and extracted with dichloromethane (3 × 10 mL). The combined organic

layers were dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography to give the product (**3a-f**) as a colorless oil.

Methyl 2-(2-oxo-2,5-dihydro-pyrrol-1-yl)propanoate (3a): Obtained according to the general procedure, by using **2a** (0.188 g, 1.825 mmol), as a colorless oil (0.078 g, 25%); R_f 0.70 (8:1 EtOAc-hexane); ¹H-NMR (CDCl₃, 400 MHz) δ_H 7.08 (1H, d, J=5.9 Hz, 4'-CH), 6.13 (1H, d, J=5.8 Hz, 3'-CH), 4.90 (1H, q, J=7.5 Hz, 2-CH), 4.05 (2H, AB_q, J=19.7 Hz, 5'-CH₂), 3.66 (3H, s, OCH₃), 1.43 (3H, d, J=7.5 Hz, 3-CH₃); ¹³C-NMR (CDCl₃, CCl₄, 400 MHz) δ_C 171.7 (1-C), 170.6 (2'-C), 142.9 (4'-CH), 127.1 (3'-CH), 51.7 (2-CH), 49.0 (OCH₃), 48.2 (5'-CH₂), 15.6 (3-CH₃); IR (KBr) ν_{max} (neat/cm⁻¹); 2950, 1740, 1690, 1688; MS (EI) m/z 170.1 (M+H⁺, 48%); HRMS (EI) calcd for C₈H₁₂O₃N (M+H⁺) 170.08116, found 170.08117.

Methyl 3-Methyl-2-(2-oxo-2,5-dihydro-pyrrol-1-yl)butanoate (3b): Obtained according to the general procedure, by using **2b** (0.459 g, 2.740 mmol), as a colorless oil (0.189 g, 35%); R_f 0.60 (8:1 EtOAc-hexane); ¹H-NMR (CDCl₃, 400 MHz) δ_H 7.01 (1H, d, J=6.00 Hz, 4'-CH), 6.04 (1H, d, J=6.00 Hz, 3'-CH), 4.44 (1H, d, J=10 Hz, 2-CH), 4.05 (2H, AB_q, J=20.4 Hz, 5'-CH₂), 3.59 (3H, s, OCH₃), 2.08 (1H, m, 3-CH), 0.87 (3H, d, J=6.6 Hz, 4-CH₃), 0.75 (3H, d, J=6.7 Hz, CH₃); ¹³C-NMR (CDCl₃, CCl₄, 400 MHz) δ_C 170.9 (1-C), 170.8 (2'-C), 143.0 (4'-CH), 126.6 (3'-CH), 58.7 (2-CH), 51.2 (OCH₃), 49.5 (5'-CH₂), 28.9 (3-CH), 19.0 (4-CH₃), 18.8 (CH₃); IR (KBr) ν_{max} (neat/cm⁻¹) 2965, 1740, 1688; MS (EI) m/z 198.1 (M+H⁺, 21%); HRMS (EI) calcd for C₁₀H₁₆O₃N (M+H⁺) 198.11246, found 198.11247; LCMS (ESI) (A: 0.01 mM HAc + 0.2% formic acid, B: MeOH (A:B 70:30, v:v) rt = 12.102 min, m/z 198.1 (M+H⁺, 15%), 138.1 (M+H⁺-CO₂CH₃, 100%), 110.1 (M+H⁺-CO₂CH₃-CO, 15%).

Methyl 4-Methyl-2-(2-oxo-2,5-dihydro-pyrrol-1-yl)pentanoate (3c): Obtained according to the general procedure, by using **2c** (0.330 g, 1.825 mmol), as a colorless oil (0.123 g, 32%); R_f 0.60 (8:1 EtOAc-hexane); ¹H-NMR (CDCl₃, 400 MHz) δ_H 7.09 (1H, d, J=5.9 Hz, 4'-CH), 6.12 (1H, d, J=5.9 Hz, 3'-CH), 4.90 (1H, dd, J=6.00 & 10.1 Hz, 2-CH), 4.04 (2H, AB_q, J=20.00 Hz, 5'-CH₂), 3.63 (3H, s, OCH₃), 1.69 (2H, m, 3-CH₂), 1.38 (1H, m, 4-CH), 0.88 (6H, d, J=6.60 Hz, 2xCH₃); ¹³C-NMR (CDCl₃, CCl₄, 400 MHz) δ_C 172.5 (1-C), 171.8 (2'-C), 143.9 (4'-CH), 127.3 (3'-CH), 52.1 (2-CH), 51.5 (OCH₃), 49.7 (5'-CH₂), 38.3 (3-CH₂), 24.9 (4-CH), 23.0 (5-CH₃), 21.2 (CH₃); IR (KBr) ν_{max} (neat/cm⁻¹) 2960, 1742, 1690; MS (EI) m/z 212.1 (M+H⁺, 40%); HRMS (EI) calcd for C₁₁H₁₈O₃N (M+H⁺) 212.12807, found 212.12812.

Methyl 2-(2-oxo-2,5-dihydro-pyrrol-1-yl)-2-phenylethanoate (3d): Obtained according to the general procedure, by using **2d** (0.55 g, 2.74 mmol), as a colorless oil (0.123 g, 32%); R_f 0.50 (8:1 EtOAc-hexane); ¹H-NMR (CDCl₃, 400 MHz) δ_H 7.20 (5H, m, Ar-H₅), 6.94 (1H, d, J=6.0 Hz, 4'-CH), 6.01 (1H, d, J=6.00 Hz, 3'-CH), 5.92 (1H, s, 2-CH), 3.82 (2H, AB_q, J=20.0 Hz, 5'-CH₂), 3.62 (3H, s, OCH₃); ¹³C-NMR (CDCl₃, CCl₄, 400 MHz) δ_C 170.5 (1-C), 170.2 (2'-C), 143.8 (4'-CH), 134.2 (Ar-C), 128.5 (2xAr-CH), 128.1 (Ar-CH), 127.9 (2xAr-CH), 126.3 (3'-CH), 56.7 (2-CH), 51.7 (OCH₃), 49.8 (5'-CH₂); IR (KBr) ν_{max} (neat/cm⁻¹) 2953, 1744, 1688; MS (EI) m/z 232.1 (M+H⁺, 5%); HRMS (EI) calcd for C₁₃H₁₄O₃N (M+H⁺) 232.09682, found 232.09682.

Methyl 2-(2-oxo-2,5-dihydro-pyrrol-1-yl)-3-phenylpropanoate (3e): Obtained according to the general procedure, by using **2e** (0.394 g, 1.825 mmol), as a colorless oil (0.314 g, 30%); R_f 0.60 (8:1

EtOAc-hexane); ¹H-NMR (CDCl₃, 400 MHz) δ_H 7.15 (5H, m, Ar-H₅), 6.97 (1H, d, J=5.96 Hz, 4'-CH), 6.03 (1H, d, J=5.98 Hz, 3'-CH), 5.11 (1H, dd, J=5.86 & 10.24 Hz, 2-CH), 3.95 (2H, AB_q, J=19.89 Hz, 5'-CH₂), 3.64 (3H, s, OCH₃), 3.33 (1H, dd, J=5.90 & 14.57 Hz, 3-CH_α), 3.02 (1H, dd, J=10.31 & 14.56 Hz, 3-CH_β); ¹³C-NMR (CDCl₃, CCl₄, 400 MHz) δ_C 171.6 (1-C), 171.4 (2'-C), 143.9 (4'-C), 136.4 (Ar-C), 128.6 (2xAr-CH), 128.5 (2xAr-CH), 127.1 (Ar-CH), 126.9 (3'-CH), 56.6 (2-CH), 54.4 (OCH₃), 52.3 (5'-CH₂), 36.0 (3-CH₂); IR (KBr) ν_{max} (neat/cm⁻¹) 2953, 1742, 1690; MS (EI) m/z 232.1 (M+H⁺, 5%); MS (EI) m/z 246.1 (M+H⁺, 5%); HRMS (EI) calcd for C₁₄H₁₆O₃N (M+H⁺) 246.11254, found 246.11247.

Methyl 3-(4-Hydroxy-phenyl)-2-(2-oxo-2,5-dihydro-pyrrol-1-yl)propanoate (3f): Obtained according to the general procedure, by using **2f** (0.421 g, 1.825 mmol), as a colorless oil (0.157 g, 33%); R_f 0.50 (8:1 EtOAc-hexane); ¹H-NMR (CDCl₃, 400 MHz) δ_H 7.08 (1H, d, J=6.00 Hz, 4'-CH), 7.01 (2H, A₂B₂, J_{ab} = 8.3 Hz, Ar-H₂), 6.73 (2H, A₂B₂, J=8.3 Hz, Ar-H₂), 6.10 (1H, d, J=6.00 Hz, 3'-CH), 5.30 (1H, dd, J=4.9 & 11.5 Hz, 2-CH), 4.12 (2H, AB_q, J=20.2 Hz, 5'-CH₂), 3.76 (3H, s, OCH₃), 3.38 (1H, dd, J=4.80 & 14.80 Hz, 3-CH_α), 2.97 (1H, dd, J=11.60 & 14.70, 3-CH_β); ¹³C-NMR (CDCl₃, CCl₄, 400 MHz) δ_C 172.6 (1-C), 171.4 (2'-C), 155.9 (Ar-C(OH)), 144.6 (4'-CH), 129.3 (2 x Ar-CH), 126.7 (Ar-C), 126.6 (3'-CH), 115.7 (2 x Ar-CH), 54.4 (2-CH), 52.5 (OCH₃), 50.4 (5'-CH₂), 35.3 (3-CH₂); IR (KBr) ν_{max} (neat/cm⁻¹) 2953, 1740, 1695; MS (EI) m/z 262.1 (M+H⁺, 100%); HRMS (EI) calcd for C₁₄H₁₆O₄N (M+H⁺) 262.10735, found 262.10738.

Results and Discussion

The condensation reaction of amino acid esters (**2a-f**) with 2,5-dimethoxy-2,5-dihydrofuran (**1**) gave the corresponding pyrrolinones (**3a-f**) in 25%–35% yields. 3-Pyrrolin-2-ones are suitable building blocks since the topology of the pyrrolinone ring provides regiocontrol for the functionalization of different sites in the molecule. We preferred to synthesize simple, unsubstituted pyrrolinones that can be functionalized at a later stage. Previously N-boc protected amino acids were used in the synthesis of 5-alkyl-pyrrolinones¹ and the carbon chain of the amino acid was used for the construction of pyrrolinone heterocycle. In this respect our method gives a different application of amino acid derivatives in the synthesis of pyrrolinone scaffold. With this method, racemic N-substituted pyrrolinones (**3a-f**) were obtained starting from racemic amino acid esters (**2a-f**). Currently, the synthesis starting from homochiral amino acid esters is under investigation. Unfortunately, LCMS results showed that those new compounds are not stable and presumably give the isomers **3**, **4** and **5** (Figure 2).

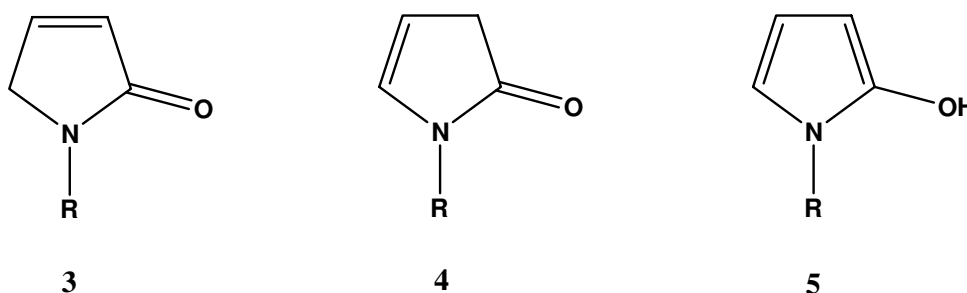


Figure 2. The pyrrolinone heterocycle (**3**) and its probable isomers (**4** and **5**).

LC-MS (ESI) analysis of **3b** showed one main strong peak (with r.t. of 12.102 min) and many other small peaks. The main peak fragmentations are 198.1 ($M+H^+$, 15%), 138.1 ($M+H^+-CO_2CH_3$, 100%), and 110.1 ($M+H^+-CO_2CH_3-CO$, 15%) and confirm the structure **3b**. Furthermore, 2 of the small peaks (r.t. 7.115 and 15.740 min) determine the same fragmentations, which may prove the 2 other isomeric structures of **4** and **5**. Those results are consistent with the literature.¹⁸ The rest of the other peaks on the chromatogram are the decomposition products.

The 1NMR spectra of the pyrrolinone ring showed a doublet at 6.94–7.09 ppm for 4'-CH with a coupling constant of 5.9–6.0 Hz, a doublet at 6.01–6.13 ppm for 3'-CH with a coupling constant of 5.8–6.0 Hz and an AB system at 3.82–4.12 ppm with a geminal coupling constant of 19.7–20.2 Hz for all derivatives (**3a-f**). Other protons appeared in the expected region. The ^{13}NMR spectra of the pyrrolinone ring showed cyclic amide carbon at 170.6–171.8 ppm and the peaks at 142.9–144.6, 126.3–127.3, and 48.2–52.3 ppm correspond to 4'-CH, 3'-CH, and 5'-CH₂, respectively. In the IR spectra, ester and amide carbonyl absorptions were observed at 1740 and 1690 cm^{-1} , and olefinic stretching at 1688 cm^{-1} . Mass spectra (EI) confirmed the protonated molecular ion [$M+H^+$] for all products (**3a-f**) with 5%–100% abundance. The high resolution mass spectrum gave perfect values for $M+H$, which corresponded well to the calculated value for this molecular formula for all pyrrolinones (**3a-f**).

Acknowledgments

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