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Synthesis of 3-pyrroline-2-ones from amino acids and an aryl amine

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The conversion of the amino group of amino dicarboxylicacid esters and an aryl amine into N-substituted pyrrolinone derivatives with dimethoxydihydrofurane is described. The conversion also occurs with serine methylester but it decomposes very quickly.

Key Words: Pyrrolinone, synthesis, amino acids

Introduction

More than 55% of organic chemistry publications are about heterocyclic compounds and dedicated to the field of heterocyclic chemistry. Heterocyclic compounds have a wide range of applications. They are predominant among the types of compounds used as pharmaceuticals, as agrochemicals, and as veterinary products.[1,2] Nitrogen-containing 5-membered heterocycles have a vital role in life because of their wide presence in biologically important compounds.[3] One of those heterocyclic systems is α,β-unsaturated-γ-amide heterocycles, which are called pyrrolinones. Some pyrrolinone-containing natural products such as Jatropham (**1**) show antitumor activity[4] and some others are used as platelet aggregation inhibitors.[5] Piracetam (**2**), which is medically used as a nootropic drug, has a pyrrolidinone scaffold similar to that of pyrrolinones.

Pyrrolinones have also been used as precursors for other biologically important compounds[6,7] and a limited number of methods have been published for their synthesis.[8–15] Recently, pyrrolinone-based peptidomimetic compounds have been created and their inhibitory activity demonstrated in vitro.[16,17] Aryl substituted pyrrolinones and pyrrolidinones are pharmaceutically important compounds. Some N-aryl substituted

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pyrrolidinones were synthesized newly and considered as anti-HIV-1 agents.[18] In addition, 1-aryl-3-pyrrolin-2-one derivatives were prepared from the corresponding γ-bromoacetoacetanilides.[19]

The synthesis of 5-membered heterocyclic frameworks was studied by our group before.[21,22] One of these includes the synthesis of pyrrolinone derivatives of some amino acids and we have reported a simple one-pot method for the construction of the pyrrolinone ring system. As part of our ongoing research on *N*-functionalization of pyrrolinone heterocycle[21] we hereby studied the formation of a pyrrolinone ring with amino dicarboxylicacids and also with an aryl amine.

Experimental

All reagents were of commercial quality and reagent quality solvents were used without further purification. ^{1}H- and ^{13}C-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). Melting points were measured on a Thomas Hoover Capillary Melting Point Apparatus in an open capillary. Amino dicarboxylic acid methyl esters (**4a-b**) were synthesized according to the literature[20] and other amino dicarboxylic acid ethyl esters (**4c-d**) were purchased from Aldrich.

General procedure for amino dicarboxylic acid esters[21]

2,5-Dimethoxy-2,5-dihydrofuran **(3)** (1 mmol) was stirred in water (10 mL) adjusted to pH 1 at room temperature over 12 h. Then amino dicarboxylic acid ester (**4a-d**) (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 $NaHCO_3$ and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography to give the product (**5a-d**) as a reddish oil.

Dimethyl 2-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl)pentanedioate *(5a)*: Obtained according to the general procedure, by using **4a** (2.00 g, 8.28 mmol), as a reddish oil (0.58 g, 29%); R_f 0.48 (8:1 EtOAc-hexane); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.16 (1H, d, J = 6.0 Hz, 4′-CH), 6.13 (1H, d, J = 6.0 Hz, 3′-CH), 4.80 (1H, dd, J = 4.4 & 10.7 Hz, 2-CH), 4.06 (2H, AB_q, J = 20.1 Hz, 5′-CH_2), 3.64 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 2.27 (2H, m, 4-CH_2), 2.01 (2H, m, 3-CH_2); ^{13}C-NMR (400 MHz, $CDCl_3$)δ_C 172.79, 172.29 (1-C, 5-C), 171.18 (2′-C), 144.61 (4′-C), 126.92 (3′-C), 53.04 (2-C), 52.56, 51.82 (2 × OCH_3), 50.06 (5′-C), 30.39 (4-C), 25.33 (3-C); MS (EI) m/z 241 (M^+), 209 (M^+-OCH_3), 182 (M^+-$COOCH_3$), 122 (M^+- 2 × $COOCH_3$ 100%), 94 (M^+-pyrrolinone-2 × OCH_3); **IR** (KBr) ν_{max} (neat/cm^{-1}) 3420.16, 3045.43, 2956.70, 1740.33, 1689.78, 1439.07, 1245.67, 1050.52. HRMS (EI) calcd for $C_{11}H_{16}O_5N$ ($M+H^+$) 242.1023, found 242.1020.

Dimethyl 2-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl)succinate *(5b)*: Obtained according to the general procedure, by using **4b** (1.00 g, 6.02 mmol), as a reddish oil (0.39 g, 29%); R_f 0.51 (8:1 EtOAc-hexane); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.17 (1H, d, J = 6.0 Hz, 4′-CH), 6.18 (1H, d, J = 6.0 Hz, 3′-CH), 5.15 (1H, m,

2-CH), 4.14 (2H, AB_q, J = 20.0 Hz, 5′-CH), 3.74 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.01 (2H, m, 3-CH_2); ^{13}C-NMR (400 MHz, $CDCl_3$)δ_C 169.93, 169.08 (1-C, 4-C), 168.61 (2′-C), 142.66 (4′-C), 125.45 (3′-C), 51.00 (5′-C), 50.43, 49.68 (2 × OCH_3), 49.18 (2-C), 33.19 (3-C); **MS** (EI) m/z 227 (M^+), 195 (M^+-OCH_3), 168 (M^+-$COOCH_3$), 136 (M^+-$COOCH_3$ -OCH_3), 108 (M^+-2 × $COOCH_3$), 81 (pyrrolinone); IR (KBr) ν_{max} (neat/cm^{-1}) 3462.10, 3048.23, 2955.63, 2852.61, 1740.22, 1690.79, 1438.76, 1240.43, 1005.17. HRMS (EI) calcd for $C_{10}H_{14}O_5N$ ($M+H^+$) 228.0866, found 228.0900.

Dimethyl 2-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl)malonate *(5c)*: Obtained according to the general procedure, by using **4c** (2.00 g, 9.40 mmol), as a reddish oil (0.75 g, 33%); R_f 0.76 (8:1 EtOAc-hexane); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.25 (1H, d, J = 6.0 Hz, 4′-CH), 6.21 (1H, d, J = 6.2 Hz, 3′-CH), 5.70 (1H, s, 2-CH), 4.39 (2H, s, 5′-CH_2), 4.22 (4H, m, 2 × OCH_2), 1.30 (6H, t, J = 7.15 Hz, 2 × CH_3); ^{13}C-NMR (400 MHz, $CDCl_3$)δ_C 171.54, 171.56 (1-C, 3-C), 168.23 (2′-C), 145.40 (4′-C), 126.13 (3′-C), 62.24 (5′-C), 57.40 (2-C), 51.03, 13.92 (2 × OCH_2CH_3); MS (EI) m/z 213 (M^+), 168 (M^+-OEt, 100%), 140 (M^+-COOEt), 96 (M^+-COOEt-OEt), 68 (M^+-2 × COOEt); IR (KBr) ν_{max} (neat/cm^{-1}) 3473.10, 3043.78, 2984.96, 2939.71, 2875.12, 1747.12, 1694.22, 1446.20, 1238.76, 1025.14. HRMS (EI) calcd for $C_{11}H_{16}O_5N$ ($M+H^+$) 242.1023, found 242.1033.

Diethyl 2-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl)pentanedioate *(5d)*: Obtained according to the general procedure, by using **4d** (1.06 g, 6.06 mmol), as a reddish oil (0.53 g, 32%); R_f 0.45 (8:1 EtOAc-hexane); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.20 (1H, d, J = 6.0 Hz, 4′-CH), 6.19 (1H, d, J = 6.0 Hz, 3′-CH), 4.87 (1H, dd, J = 4.4 Hz & 10.8 Hz, 2-CH), 4.19 (2H, q, J = 7.2 Hz, OCH_2), 4.14 (2H, AB_q, J = 20.0 Hz, 5′-CH_2), 4.11 (2H, q, J = 7.2 Hz OCH_2), 1.28 (3H, t, J = 7.2 Hz, CH_3), 1.24 (3H, t, J = 7.2 Hz, CH_3); ^{13}C-NMR (400 MHz, $CDCl_3$)δ_C 175.1, 174.3 (1-C, 5-C), 169.51 (2′-C), 142.00 (4′-C), 128.00 (3′-C), 60.39 & 59.45 (2 × OCH_2), 58.20 (5′-C), 52.10 (2-C), 49.20 (3-C), 27.88 (4-C), 23.37, 15.03 (2 × CH_3); MS (EI) m/z 269 (M^+), 223 (M^+-OCH_2CH_3), 196 (M^+-$COOCH_2CH_3$), 181 (M^+-$COOCH_2CH_3$-CH_3), 150 (M^+-CO_2Et-OEt), 122 (M^+-2 × CO_2Et, 100%); IR (KBr) ν_{max} (neat/cm^{-1}) 3356.91, 3042.27, 2983.21, 1720.00, 1694.37, 1244.54, 1193.47, 1024.30. HRMS (EI) calcd for $C_{13}H_{20}O_5N$ ($M+H^+$) 270.1336, found 270.1296.

Methyl 3-hydroxy-2-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl)propanoate *(7)*: Obtained according to the general procedure, by using **6** (3.92 g, 24.7 mmol), as a yellow oil (1.00 g, 22%); R_f 0.34 (8:1 EtOAc-hexane); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.06 (1H, d, J = 6.0 Hz, 4′-CH), 6.01 (1H, d, J = 6.0 Hz, 3′-CH), 4.72 (1H, m, 2-CH), 4.11 (2H, AB_q, J = 20.0 Hz, 5′-CH_2), 3.90 (2H, dd, J = 5.5 Hz & 10.2 Hz, 3-CH_2), 3.53 (3H, s, OCH_3).

1-(2-hydroxyphenyl)-1H-pyrrol-2(5H)-one *(9)*: Obtained according to the general procedure, by using **8** (4.02 g, 36.5 mmol), as a brown oil (1.9 g, 30%); R_f 0.45 (3:2 EtOAc-hexane); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 8.87 (1H, br-s, OH), 7.26 (1H, d, J = 6.0 Hz, 4′-CH), 7.15 (1H, t, J = 8.1 Hz, 4-CH), 7.08 (1H, d, J = 8.1 Hz, 6-CH), 7.04 (1H, d, J = 8.1 Hz, 3-CH), 6.90 (1H, t, J = 8.1 Hz, 5-CH), 6.23 (1H, d, J = 6.0 Hz, 3′-CH), 4.46 (2H, s, 5′-CH_2); ^{13}C-NMR (400 MHz, $CDCl_3$) δ_C 171.9 (2′-C), 150.5 (2-C), 146.2 (4′-C), 128.1 (4-C), 127.3 (3′-C), 126.6 (1-C), 123.2 (5-C), 120.9 (6-C), 120.2 (3-C), 55.3 (5′-C); MS (EI) m/z 175 (M^+, 100%), 158, 94, 82; **IR** (KBr) ν_{max} (neat/cm^{-1}) 3239.0, 1668.6, 1595.3, 1514.3, 1498.9, 1460.3, 1415.9, 1288.6, 1236.5, 754.3. HRMS (EI) calcd for $C_{10}H_{10}O_2N$ ($M+H^+$) 176.0706 found 176.0695.

Results and discussion

As shown in Figure 1, the condensation reaction of amino dicarboxylicacid esters with dimethoxydihydrofurane gave the corresponding pyrrolinones (**5a-d**) in reasonable yields.

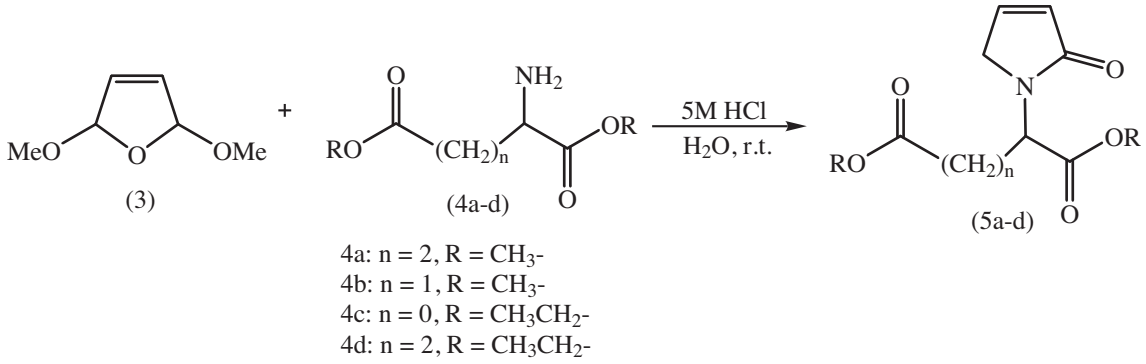


Figure 1. The synthesis of pyrrolinones (**5a-d**).

As a complementary study to the above syntheses, the reaction of serine methylester (**6**) with 2,5-dimethoxy-2,5-dihydrofuran (**3**) was carried out (Figure 2). The expected compound (**7**) was formed as a crude product, which was decomposed quickly to an unresolved compound.

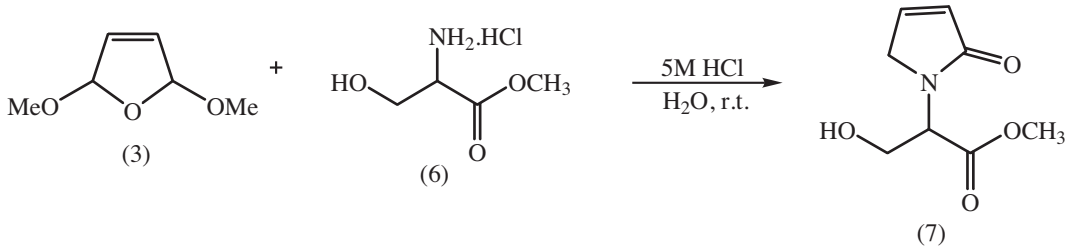


Figure 2. Serine methylester derived pyrrolinone synthesis.

On the other hand, aromatic amines can also be used for the construction of pyrrolinone heterocycle. However, aromatic amines such as aniline, *p*-anisidine, or *p*-toluidine are much weaker bases and nucleophiles than the corresponding nonaromatic amines. For this reason they are seldom used as nucleophiles since the delocalization of the unshared electron pair of the nitrogen into the ring makes them poor nucleophiles. Nevertheless, reacting aromatic amines with 2,5-dimethoxy-2,5-dihydrofuran to form *N*-aryl substituted pyrrolinones offers a convenient route to the synthesis of some pharmaceutically important compounds. Therefore, we also tried some primary aromatic amines and reported here the synthesis of *N*-(*o*-hydroxyphenyl) substituted pyrrolinone, which was formed from the reaction of 2,5-dimethoxy-2,5-dihydrofuran with *o*-aminophenol (Figure 3).

The ^{1}H-NMR spectra of the pyrrolinone ring showed a doublet at 7.06-7.26 ppm for 4′-CH with a coupling constant of 6.0 Hz, a doublet at 6.01-6.23 ppm for 3′-CH with a coupling constant of 6.0-6.2 Hz, and an AB system at 4.06-4.14 ppm with a geminal coupling constant of 20.0-20.1 Hz for **5a**, **5b**, **5d**, and **7** but a singlet at 4.39-4.46 ppm for **5c** and **9** (Table). Other protons appeared in the expected region. The ^{13}C-NMR spectra of the pyrrolinone ring showed cyclic amide carbon at 168.2-171.9 ppm and the peaks at 142.0-146.2,

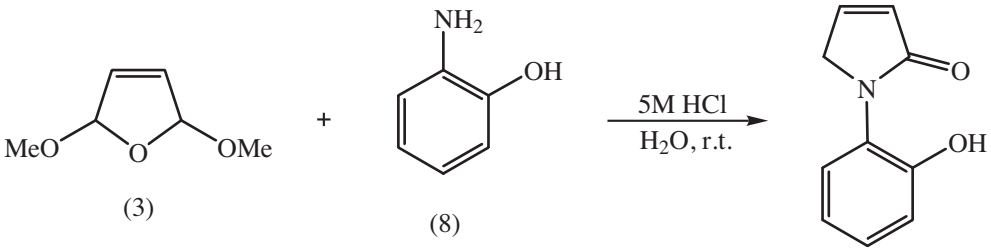
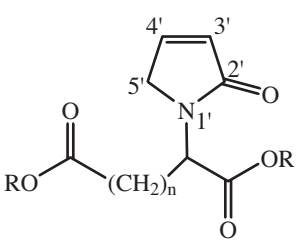
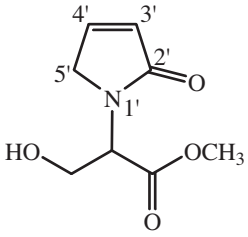


Figure 3. The synthesis of o-hydroxyphenyl substituted pyrrolinone.

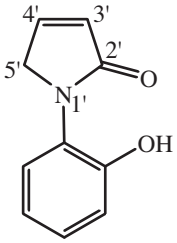
Table. ^{1}H-NMR data of **5a-d**, **7**, and **9**.



5



7



9

	^{1}H-NMR ($CDCl_3$); δ (ppm); J (Hz)
5a	7.16 (1H, d, J = 6.0 Hz, 4′-CH), 6.13 (1H, d, J = 6.0 Hz, 3′-CH), 4.80 (1H, dd, J = 4.4 & 10.7 Hz, 2-CH), 4.06 (2H, AB_q, J = 20.1 Hz, 5′-CH_2), 3.64 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 2.27 (2H, m, 4-CH_2), 2.01 (2H, m, 3-CH_2)
5b	7.17 (1H, d, J = 6.0 Hz, 4′-CH), 6.18 (1H, d, J = 6.0 Hz, 3′-CH), 5.15 (1H, m, 2-CH), 4.14 (2H, AB_q, J = 20.0 Hz, 5′-CH), 3.74 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.01 (2H, m, 3-CH_2)
5c	7.25 (1H, d, J = 6.0 Hz, 4′-CH), 6.21 (1H, d, J = 6.2 Hz, 3′-CH), 5.70 (1H, s, 2-CH), 4.39 (2H, s, 5′-CH_2), 4.22 (4H, m, 2 × OCH_2), 1.30 (6H, t, J = 7.15 Hz, 2 × CH_3)
5d	7.20 (1H, d, J = 6.0 Hz, 4′-CH), 6.19 (1H, d, J = 6.0 Hz, 3′-CH), 4.87 (1H, dd, J = 4.4 Hz & 10.8 Hz, 2-CH), 4.19 (2H, q, J = 7.2 Hz, OCH_2), 4.14 (2H, AB_q, J = 20.0 Hz, 5′-CH_2), 4.11 (2H, q, J = 7.2 Hz OCH_2), 1.28 (3H, t, J = 7.2 Hz, CH_3), 1.24 (3H, t, J = 7.2 Hz, CH_3)
7	7.06 (1H, d, J = 6.0 Hz, 4′-CH), 6.01 (1H, d, J = 6.0 Hz, 3′-CH), 4.72 (1H, m, 2-CH), 4.11 (2H, AB_q, J = 20.0 Hz, 5′-CH_2), 3.90 (2H, dd, J = 5.5 Hz & 10.2 Hz, 3-CH_2), 3.53 (3H, s, OCH_3)
9	8.87 (1H, br-s, OH), 7.26 (1H, d, J = 6.0 Hz, 4′-CH), 7.15 (1H, t, J = 8.1 Hz, 4-CH), 7.08 (1H, d, J = 8.1 Hz, 6-CH), 7.04 (1H, d, J = 8.1 Hz, 3-CH), 6.90 (1H, t, J = 8.1 Hz, 5-CH), 6.23 (1H, d, J = 6.0 Hz, 3′-CH), 4.46 (2H, s, 5′-CH_2)

125.5-128.0, and 50.1-62.2 ppm correspond to 4′-CH, 3′-CH, and 5′-CH_2, respectively. In the IR spectra, ester and amide carbonyl absorptions were observed at 1740 and 1690 cm^{-1}, and olefinic stretching at 1440 cm^{-1}. Mass spectra (EI) confirmed the protonated molecular ion [M+H^+] for the products **5a-d** and **9** with 5%-100% abundance. The high resolution mass spectrum gave good values for M+H, which corresponded well to the calculated value for this molecular formula for all pyrrolinones (**5a-d** and **9**).

Conclusion

2,5-Dimethoxy-2,5-dihydrofuran is the masked equivalent of 1,4-dicarbonyl compounds and it was used in this work for the construction of the carbon chain of pyrrolinone heterocycle. The condensation reaction of amino dicarboxylicacid esters (**4a-d**) with 2,5-dimethoxy-2,5-dihydrofuran (**3**) gave the corresponding 3-pyrroline-2-ones (**5a-d**) in 29%-33% yields. The amino group of serine methylester also reacted with 2,5-dimethoxy-2,5-dihydrofuran but the product (**7**) was unstable. Moreover, the amino group of *o*-aminophenol reacted readily with 2,5-dimethoxy-2,5-dihydrofuran to form **9**.

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