LETTERS
TO THE EDITOR

Synthesis and Structure of 4-Het(aryl)-3,5,5-trimethoxycarbonyl-2-pyrrolidones

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Received February 28, 2019; revised February 28, 2019; accepted March 7, 2019

Abstract—Condensation of 2-het(aryl)-1,1-dimethoxycarbonylethenes with acetylaminomalonic acid ester afforded (3*R**,4*S**)-4-(4-methoxyphenyl)-, (3*R**,4*S**)-4-(3,4-methylenedioxyphenyl)-, (3*R**,4*S**)-4-(4-dimethylaminophenyl)-, (3*R**,4*S**)-4-(2-furyl)-, (3*R**,4*S**)-4-(indol-3-yl)-, (3*R**,4*S**)-4-(1-methylindol-3-yl)-, and (3*R**,4*S**)-4-(1-benzylindol-3-yl)-3,5,5-tris(methoxycarbonyl)-2-pyrrolidones.

Keywords: heterocyclic compounds, 2-pyrrolidone, pyrrolidone-2-carboxylic acids esters

DOI: 10.1134/S1070363219070260

Pyrrolidonecarboxylic acids esters are known to be very suitable and promising precursors for the synthesis of biologically active derivatives of γ -aminobutyric [1–3] and glutamic [4, 5] acids. For example, 4-het(aryl)-2-pyrrolidone-3,5,5-tricarboxylates are key compounds in the synthesis of (2*R**,3*R**)-3-(het)arylglutamic acids hydrochlorides, among which substances with a wide spectrum of pharmacological activity in combination with relatively low toxicity were found [5]. The reactions of the corresponding 1,1-dimethoxycarbonylethenes with acetylaminomalonic acid ester are of undoubted interest in this respect, since they proceed stereospecifically and lead to diastereohomogeneous (3*R**,4*S**)-1-acetyl-3,5,5-tris(methoxycarbonyl)-4-het(aryl)-2-pyrrolidones [5].

In continuation of these studies, we performed the reactions of 2-(4-methoxyphenyl)-, 2-(3,4-methylenedioxyphenyl)-, 2-(4-dimethylaminophenyl)-, 2-(2-furyl)-, 2-(indol-3-yl)-, 2-(1-methylindol-3-yl)-, and 2-(1-benzylindol-3-yl)-1,1-dimethoxycarbonylethenes **1–7** with acetylaminomalonic acid ester to obtain new representatives of 4-het(aryl)-2-pyrrolidone-3,5,5-tricarboxylates series. Compounds **1–7** were synthesized according to the procedure described in [6]. It turned out that only compounds **1**, **2** and **4** reacted with acetylaminomalonic acid ester under the conditions described by us (equimolar ratio of reactants, 10–15°C, 2 h [5]) to form previously unknown 1-acetyl-3,5,5-trimethoxycarbonyl-

2-pyrrolidones **8**, **9**, and **11** with yields of 65–77% (Scheme 1). The reactions of dimethoxycarbonylethenes **3**, **5–7** with acetylaminomalonic acid ester occurred in the presence of a 1.5-fold excess of acetylaminomalonic acid ester within 4 h. As a result, triesters **10**, **12–14** were obtained with yields from 30 to 70% (Scheme 1).

Note that the reaction of 2-(indol-3-yl)-1,1-dimethoxycarbonylethenes **1** and **3** with acetylaminomalonic acid ester proceeded for 24 h to afford new *N*-unsubstituted pyrrolidonecarboxylates **15** and **16** with yields of 43 and 50%, respectively. The formation of these compounds can be explained, apparently, not only by intramolecular acylation of the amino group of the initially formed linear adduct, but also by subsequent deacylation of the *N*-acetyl groups under the reaction conditions. All the synthesized compounds **8–16** are colorless crystalline substances. Their structure was characterized by IR, ¹H and ¹³C NMR spectroscopy methods using the ¹H–¹³C HMBC technique. The ¹H NMR spectra of compounds **8–16** contain one set of the proton signals, which indicates their diastereohomogeneity. Note that the values of the spin-spin coupling constants for the C³H and C⁴H protons (³*J*_{HH} = 10.0–12.0 Hz) in the spectra of compounds **8–16** indicate their *trans* arrangement, which corresponds to 3*R* and 4*S* relative configuration of two asymmetric centers (C³ and C⁴ atoms) in the molecules of these substances. These data are in good agreement with those given in the literature for

Scheme 1.

R = 4-methoxyphenyl (**1**, **8**), 3,3-methylenedioxyphenyl (**2**, **9**), 4-dimethylaminophenyl (**3**, **10**), 2-furyl (**4**, **11**), indol-3-yl (**5**, **12**, **15**), 1-methylindol-3-yl (**6**, **13**), 1-benzylindol-3-yl (**7**, **14**, **16**).

(3*R**,4*S**)-1-acetyl-3,5,5-trimethoxycarbonyl-4-(het-aryl)-2-pyrrolidones [2]. The close coupling constants of the whole series of compounds **8–16** make it possible to attribute the relative (3*R*,4*S*) configuration for all the reaction products obtained.

Compounds **8**, **9**, **11** were obtained according to the procedure reported in [5].

(3*R,4*S**)-1-Acetyl-4-(4-methoxyphenyl)-3,5,5-tris(methoxycarbonyl)-2-pyrrolidone (**8**)** was prepared from 2-(4-methoxyphenyl)-1,1-dimethoxycarbonyl-2-ethene **1** and acetamidomalonic ester. Yield 77%, mp 93–95°C (CH₃OH). IR spectrum (CHCl₃), ν , cm⁻¹: 1760, 1740 (C=O). ¹H NMR spectrum (CDCl₃), δ , ppm: 2.57 s [3H, NC(O)CH₃]; 3.46 s, 3.74 s and 3.82 s (9H, COOCH₃), 3.77 s (3H, OCH₃), 4.18 d and 4.22 d (2H, CH, ³*J* = 11.7 Hz), 6.85 m (2H, Ph), 7.06 m (2H, Ph). ¹³C NMR spectrum (CDCl₃), δ , ppm: 25.23 (COCH₃), 47.49, 53.42, 73.10 (CH), 53.28, 55.34, 53.55, 53.69 (CH₃), 114.26, 124.02, 129.59, 160.10 (Ph), 166.01, 166.38, 167.07, 168.66, 171.30 (C=O). Found, %: C 56.15, 56.19; H 5.15, 5.18; N 3.33, 3.37. C₁₉H₂₁NO₉. Calculated, %: C 56.02; H 5.20; N 3.44.

(3*R,4*S**)-1-Acetyl-4-(3,4-methylenedioxyphenyl)-3,5,5-tris(methoxycarbonyl)-2-pyrrolidone (**9**)** was obtained from 2-(3,4-methylenedioxyphenyl)-1,1-dimethoxycarbonyl-2-ethene **2** and acetamidomalonic ester. Yield 72%, mp 154–156°C (CH₃OH). IR spectrum (CHCl₃), ν , cm⁻¹: 1761, 1745 (C=O). ¹H NMR spectrum (CDCl₃), δ , ppm: 2.56 s [3H, NC(O)CH₃]; 3.53 s, 3.73 s and 3.82 s (9H, COOCH₃), 4.23 d and 4.27 d (2H, CH, ³*J* = 12.0 Hz), 5.95 s (2H, CH₂O), 6.59 m and 6.73 m (3H, Ph). ¹³C NMR spectrum (CDCl₃), δ , ppm: 25.15

(COCH₃), 47.94, 53.39, 72.98 (CH), 53.31, 53.55, 53.74 (CH₃), 101.56 (CH₂O), 108.52, 108.66, 121.95, 125.69, 148.17, 148.32 (Ph), 165.87, 166.27, 166.91, 168.40, 171.22 (C=O). Found, %: C 54.23, 54.22; H 4.48, 4.49; N 3.30, 3.29. C₁₉H₁₉NO₁₀. Calculated, %: C 54.16; H 4.55; N 3.32.

(3*R,4*S**)-1-Acetyl-3,5,5-tris(methoxycarbonyl)-4-(2-furyl)-2-pyrrolidone (**11**)** was obtained from 2-(2-furyl)-1,1-dimethoxycarbonyl-2-ethene **4** and acetamidomalonic ester. Yield 65%, mp 80–82°C (CH₃OH). IR spectrum (CHCl₃), ν , cm⁻¹: 1763, 1742 (C=O). ¹H NMR spectrum (CDCl₃), δ , ppm: 2.56 s [3H, NC(O)CH₃]; 3.60 s, 3.80 s and 3.85 s (9H, COOCH₃), 4.21 d and 4.40 d (2H, CH, ³*J* = 11.6 Hz); 6.29 m, 6.33 m and 7.38 m (3H, Fur). ¹³C NMR spectrum (CDCl₃), δ , ppm: 25.21 (COCH₃), 42.13, 52.13, 71.68 (CH), 53.56, 53.66, 53.77 (CH₃), 110.21, 111.05, 143.52, 146.22 (Fur), 165.49, 166.16, 166.68, 167.87, 171.13 (C=O). Found, %: C 52.15, 52.15; H 4.70, 4.78; N 3.63, 3.65. C₁₆H₁₇NO₉. Calculated, %: C 52.32; H 4.67; N 3.81.

(3*R,4*S**)-1-Acetyl-4-(4-dimethylaminophenyl)-3,5,5-tris(methoxycarbonyl)-2-pyrrolidone (**10**)**. To a solution of sodium methylate [prepared from 10 mL of methanol and 0.69 g (0.03 mol) of sodium] was added with stirring 6.51 g (0.03 mol) of acetamidomalonic ester. The resulting mixture was kept until the precipitate was completely dissolved, then cooled to 10–15°C, and a solution of 5.26 g (0.02 mol) of 2-(4-dimethylaminophenyl)-1,1-dimethoxycarbonyl-2-ethene **3** in 19 mL of methanol was added maintaining a temperature of 10–15°C. The reaction mixture was stirred at 20°C for 4 h, then poured into

finely crushed ice with 12 N hydrochloric acid (~2.5 mL, relative to sodium amount) to adjust pH ~ 7. The resulting crystalline product was filtered off, washed with cold water and dried in air. Yield 5.90 g (70%), mp 193–195°C (CH₃OH). IR spectrum (CHCl₃), ν , cm⁻¹: 1759, 1740 (C=O). ¹H NMR spectrum (CDCl₃), δ , ppm: 2.57 s [3H, NC(O)CH₃], 2.93 s (6H, NCH₃); 3.48 s, 3.73 s and 3.82 s (9H, COOCH₃), 4.14 d and 4.22 d (2H, CH, ³J = 11.9 Hz), 6.63 m and 6.97 m (4H, Ph). ¹³C NMR spectrum (CDCl₃), δ , ppm: 25.23 (COCH₃), 40.37 (NCH₃), 47.76, 53.26, 73.27 (CH), 53.24, 53.44, 53.74 (CH₃), 112.17, 129.14, 150.09 (Ph), 166.10, 166.51, 167.24, 169.02, 171.34 (C=O). Found, %: C 57.35, 57.36; H 5.61, 5.61; N 6.49, 6.55. C₂₀H₂₄N₂O₈. Calculated, %: C 57.14; H 5.75; N 6.66.

Compounds **12**–**14** were prepared similarly; the reaction mixture was neutralized with glacial acetic acid (relative to sodium amount, pH ~ 7).

(3*R,4*S**)-1-Acetyl-4-(indol-3-yl)-3,5,5-tris(methoxycarbonyl)-2-pyrrolidone (12).** Yield 36%, mp 193–195°C (CH₃OH). IR spectrum (CHCl₃), ν , cm⁻¹: 3500–3320 br (NH), 1759, 1740 (C=O). ¹H NMR spectrum (CDCl₃), δ , ppm: 2.62 s [3H, NC(O)CH₃]; 3.38 s, 3.71 s and 3.81 s (9H, COOCH₃), 4.35 d and 4.63 d (2H, CH, ³J = 11.6 Hz), 6.99–7.45 m (5H, Ind), 8.54 s (1H, NH). ¹³C NMR spectrum (CDCl₃), δ , ppm: 25.27 (COCH₃), 41.33, 53.67, 73.27 (CH), 53.18, 53.36, 53.63 (CH₃), 107.73, 111.84, 118.64, 120.18, 122.73, 123.55, 126.63, 136.35 (Ind), 166.48, 167.06, 167.30, 168.94, 171.52 (C=O). Found, %: C 57.52, 57.58; H 4.93, 4.93; N 6.61, 6.63. C₂₀H₂₀N₂O₈. Calculated, %: C 57.69; H 4.84; N 6.73.

(3*R,4*S**)-1-Acetyl-4-(1-methylindol-3-yl)-3,5,5-tris(methoxycarbonyl)-2-pyrrolidone (13).** Yield 55%, mp 173–175°C (CH₃OH). IR spectrum (CHCl₃), ν , cm⁻¹: 1760, 1740 (C=O). ¹H NMR spectrum (CDCl₃), δ , ppm: 2.61 s [3H, NC(O)CH₃]; 3.41 s, 3.72 s and 3.82 s (9H, COOCH₃), 3.75 s (3H, NCH₃), 4.32 d and 4.61 d (2H, CH, ³J = 11.9 Hz), 6.92–7.45 m (5H, Ind). ¹³C NMR spectrum (CDCl₃), δ , ppm: 25.33 (COCH₃), 33.11 (NCH₃), 41.19, 54.79, 73.41 (CH), 53.17, 53.34, 53.60 (CH₃), 106.46, 109.83, 118.91, 119.91, 122.42, 127.38, 127.71, 137.13 (Ind), 166.75, 166.99, 167.25, 168.90, 171.46 (C=O). Found, %: C 58.60, 58.68; H 5.20, 5.23; N 6.44, 6.45. C₂₁H₂₂N₂O₈. Calculated, %: C 58.60; H 5.15; N 6.51.

(3*R,4*S**)-1-Acetyl-4-(1-benzylindol-3-yl)-3,5,5-tris(methoxycarbonyl)-2-pyrrolidone (14).** Yield

30%, mp 150–152°C (CH₃OH). IR spectrum (CHCl₃), ν , cm⁻¹: 1761, 1740 (C=O). ¹H NMR spectrum (CDCl₃), δ , ppm: 2.60 s [3H, NC(O)CH₃]; 3.24 s, 3.72 s and 3.80 s (9H, COOCH₃), 4.25 d and 4.65 d (2H, CH, ³J = 11.9 Hz), 5.21 d and 5.32 d (2H, CH₂, ²J = 15.9 Hz), 7.08–7.45 m (5H, Ind), 7.21–7.35 m (5H, Ph). ¹³C NMR spectrum (CDCl₃), δ , ppm: 25.32 (COCH₃), 40.94, 54.88, 73.52 (CH), 50.17 (NCH₂), 53.01, 53.36, 53.64 (CH₃), 107.63, 110.15, 119.06, 120.18, 122.71, 126.97, 128.00, 136.69 (Ind), 126.71, 127.72, 128.97, 137.03 (Ph), 166.51, 167.11, 167.23, 168.84, 171.46 (C=O). Found, %: C 64.11, 64.21; H 5.22, 5.25; N 5.42, 5.48. C₂₇H₂₆N₂O₈. Calculated, %: C 64.02; H 5.17; N 5.53.

(3*R,4*S**)-4-(Indol-3-yl)-3,5,5-tris(methoxycarbonyl)-2-pyrrolidone (15)** was obtained by the procedure for the synthesis of compound **10** from 3.25 g (0.015 mol) of acetamidomalonic ester and 2.59 g (0.01 mol) of 2-(indol-3-yl)-1,1-dimethoxycarbonyl-ethene **1**; reaction time – 24 h. Yield 1.95 g (43%), mp 215–217°C (CH₃OH). IR spectrum (KBr), ν , cm⁻¹: 3470–3310 br (NH), 1745, 1729, 1716 (C=O). ¹H NMR spectrum (DMSO-*d*₆), δ , ppm: 3.22 s, 3.56 s and 3.69 s (9H, COOCH₃), 4.03 d and 4.78 d (2H, CH, ³J = 11.0 Hz), 6.97–7.63 m (5H, Ind), 9.40 s and 11.08 s (2H, NH). ¹³C NMR spectrum (DMSO-*d*₆), δ , ppm: 41.92, 54.48, 72.25 (CH), 53.09, 53.13, 53.73 (CH₃), 109.15, 112.05, 119.34, 119.68, 121.82, 124.80, 127.33, 136.55 (Ind), 168.55, 169.32, 169.92, 171.28 (C=O). Found, %: C 57.60, 57.62; H 4.90, 5.06; N 6.72, 6.80. C₁₈H₁₈N₂O₇. Calculated, %: C 57.75; H 4.85; N 7.48.

Compound **16** was obtained similarly.

(3*R,4*S**)-4-(1-Benzylindol-3-yl)-3,5,5-tris(methoxycarbonyl)-2-pyrrolidone (16).** Yield 55%, mp 175–177°C (CH₃OH). IR spectrum (KBr), ν , cm⁻¹: 3420–3090 (NH), 1759, 1739, 1719 (C=O). ¹H NMR spectrum (DMSO-*d*₆), δ , ppm: 3.13 s, 3.58 s and 3.70 s (9H, COOCH₃), 3.98 d and 4.80 d (2H, CH, ³J = 11.0 Hz), 5.33 d and 5.40 d (2H, CH₂, ²J = 15.7 Hz), 6.98–7.72 m (5H, Ind), 7.14–7.25 m (5H, Ph), 9.43 s (1H, NH). ¹³C NMR spectrum (DMSO-*d*₆), δ , ppm: 41.61, 54.71, 72.27 (CH), 49.54 (NCH₂), 53.01, 53.11, 53.74 (CH₃), 109.19, 110.75, 119.70, 120.06, 122.14, 127.91, 127.99, 136.26 (Ind), 127.55, 127.92, 129.02, 138.60 (Ph), 168.48, 169.16, 169.75, 171.05 (C=O). Found, %: C 64.56, 64.63; H 5.31, 5.32; N 5.97, 5.99. C₂₅H₂₄N₂O₇. Calculated, %: C 64.65; H 5.21; N 6.03.

Spectral characteristics and elemental analysis data were taken using the equipment of the Center for

Collective Use of the Faculty of Chemistry of the Herzen State Pedagogical University of Russia. ^1H , $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were recorded on a Jeol ECX400A spectrometer with operating frequencies of 399.78 (^1H), 100.525 MHz (^{13}C). IR spectra were recorded on a Shimadzu IRPrestige-21 Fourier spectrometer. Elemental analysis was performed on a EuroVector EA 3000 analyzer (CHN Dual mode). Melting points were determined on a PTP(M) device.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Berestovitskaya, V.M., Vasil'yeva, O.S., and Ostroglyadov, E.S., *2-Pyrrolidon i ego proizvodnye* (2-Pyrrolidone and Its Derivatives), St. Petersburg: Asterion, 2013.
2. Maltsev, O.V., Beletskaya, I.P., and Zlotin, S.G., *Russ. Chem. Rev.*, 2011, vol. 80, no. 11, p. 1067. doi 10.1070/RC2011v080n11ABEH004249
3. Reznikov, A.N., Golovin, E.V., and Klimochkin, Yu.N., *Russ. J. Org. Chem.*, 2013, vol. 49, no. 5, p. 663. doi 10.1134/S1070428013050047
4. Bunch, L., Johansen, T.H., Brauner-Osborne, H., Stensbol, T., Johansen, T.N., Krosgaard-Larsen, P., and Madsen, U., *Bioorg. Med. Chem.*, 2001, vol. 9, no. 4, p. 875. doi 10.1016/S0968-0896(00)00304-7
5. Berestovitskaya, V.M., Vasil'yeva, O.S., Ostroglyadov, E.S., Tyurenkov, I.N., Anan'ev, I.V., Lyssenko, K.A., Perfilova, V.N., and Bagmetova, V.V., *Russ. Chem. Bull.*, 2013, vol. 62, no. 11, p. 2401. doi 10.1007/s11172-013-0348-y
6. Berestovitskaya, V.M., Ostroglyadov, E.S., and Vasil'yeva, O.S., *Russ. J. Org. Chem.*, 2003, vol. 39, no. 2, p. 282. doi 10.1023/A:1025517025582