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Synthesis of new substituted saturated γ-lactones from 2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetyl chloride

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Abstract

New derivatives of substituted saturated γ-lactones were synthesized from 2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl) acetyl chloride. All new compounds were characterized by NMR and IR and elemental analysis.

Keywords: amine; isothiocyanate; potassium thiocyanate; saturated γ-lactone.

Introduction

Saturated γ-lactones are an important class of heterocyclic compounds. They display a wide range of biological activities and can be used in medicine, pharmacology, cosmetology, and agriculture. Artemisinin and Santonin, endowed with valuable biological activity, are compounds containing saturated lactone rings (Dayson and Mey, 1964; Mashkovskiy, 1978; Shukla et al., 1995; Arantes et al., 2009). Many compounds, such as pilocarpine, a cholinergic drug, are also derivatives of lactones. Synthesis of new derivatives of saturated lactones is thus of great interest (Pinner et al., 1900, 1901; Davies et al., 2009).

Results and discussion

Here we report a general synthetic route to lactone derivatives starting from readily available 2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetyl chloride (**1**) (Avetisyan and Ovsepyan, 1984). Products **5a–d** were obtained by reaction of compound **1** with potassium thiocyanate (**2**) followed by treatment of the resultant intermediate product **3**, without isolation, with aniline (**4a**), benzylamine (**4b**), cyclohexylamine (**4c**) or diethylamine (**4d**). The overall yield of this one-pot synthesis is 82–84%. Amides **6a–d** were synthesized by reaction of compound **1** with amines **4a–d** (Schemes 1 and 2).

Compounds **5** and **6** were tested for antibacterial activity at the chemotherapy laboratory, A.L. Mndzhoyan Institute of Fine Organic Chemistry, National Academy of Sciences of the Republic of Armenia. These compounds showed a moderate antibacterial activity *in vitro*, making it expedient to conduct further investigations in this area.

Experimental section

All solvents were dried by standard methods. Melting points were measured with an Electrothermal 9100 apparatus. Elemental analyses (C, H and N) were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a Specord 75 IR spectrometer with samples dispersed in mineral oil. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6/CCl_4 (1:3) solutions on a Varian Mercury-300 VX spectrometer at 300 MHz and 75 MHz, respectively. The purity of synthesized compounds was tested by means of thin-layer chromatography (TLC) on Silufol UV-25 plates, eluent acetone/benzene (1:2), visualization with iodine vapors.

Compound **1** was synthesized by using a published procedure (Avetisyan and Ovsepyan, 1984).

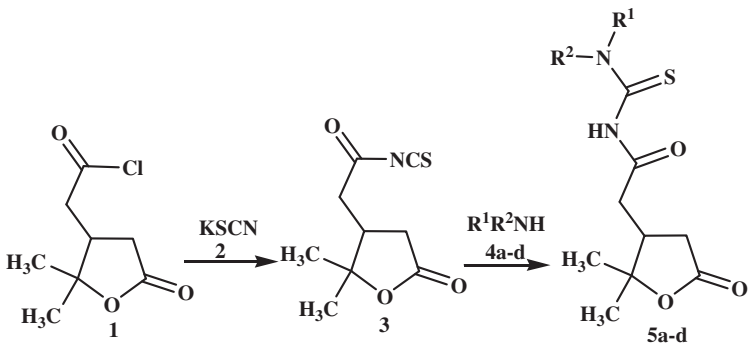
General procedure for 5a–d

A mixture of **1** (0.41 g, 2.2 mmol) and excess potassium thiocyanate (**2**) in anhydrous acetone (10 mL) was stirred at room temperature for 30 min, then treated with amine **4a–d** (4.4 mmol) and heated under reflux for an additional 1 h. The solvent was removed under reduced pressure and water was added to the residue. The precipitated solid was filtered, washed with water and crystallized from ethanol.

2-(2,2-Dimethyl-5-oxotetrahydrofuran-3-yl)-*N*-(phenylcarbamothioyl)acetamide (5a) This compound was obtained as a pale yellow solid; yield 84%; mp 188–189°C; R_f = 0.55; IR: 1580, 1600, 1690, 1775, 3250, 3270 cm^{-1}; ^{1}H NMR: δ_H 1.35 and 1.50 (2s, 6H), 2.25–2.90 (m, 5H), 6.9–8.0 (m, 5H), 11.4 and 12.5 (2s, 2H); ^{13}C NMR: δ_C 24.1, 33.8, 38.5, 40.2, 87.6, 126.8, 128.5, 131.1, 139.1, 177.2, 178.1, 179.5. Anal. Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14. Found: C, 58.83; H, 5.95; N, 9.21.

***N*-(Benzylcarbamothioyl)-2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetamide (5b)** This compound was obtained as a pale yellow solid; yield 83%; mp 195–196°C; R_f = 0.53; IR: 1580, 1600, 1690, 3250, 3270 cm^{-1}; ^{1}H NMR: δ_H 1.35 and 1.50 (2s, 6H); 2.25–2.90 (m, 5H); 4.46 (d, 2H, J = 6.0 Hz) 6.9–8.0 (m, 5H); 11.4 (t, 1H, *J* = 6.0 Hz), 12.5 (s, 1H); ^{13}C NMR: δ_C 24.1, 33.8, 38.5, 40.2, 52.9, 87.6, 128.8, 128.9, 130.6, 142.6, 177.2, 178,1, 189.5. Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N, 8.74. Found: C, 59.99; H, 6.31; N, 8.77.

***N*-(Cyclohexylcarbamothioyl)-2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetamide (5c)** This compound was obtained as a pale yellow solid; yield 84%; mp 182–183°C; R_f = 0.54; IR: 1580, 1600, 1690, 1775, 3250, 3270 cm^{-1}; ^{1}H NMR: δ_H 1.35 and 1.50 (2s, 6H), 1.58–1.95 (m, 10H), 2.25–2.90 (m, 5H), 3.46–3.60 (m, 1H), 7.5 (d, 1H, *J* = 6.0 Hz), 12.5 (s, 1H); ^{13}C NMR: δ_C 24.1, 25.5, 30.0, 33.8, 36.0, 38.5, 40.2, 56.3, 87.6, 177.2, 178,1, 189.5. Anal. Calcd for $C_{15}H_{24}N_2O_3S$: C, 57.67; H, 7.74; N, 8.97. Found: C, 57.74; H, 7.81; N, 8.99.



5a: $R^1 = H$, $R^2 = C_6H_5$; **5b:** $R^1 = H$, $R^2 = CH_2C_6H_5$;
5c: $R^1 = H$, $R^2 = C_6H_{11}$; **5d:** $R^1 = R^2 = C_2H_5$.

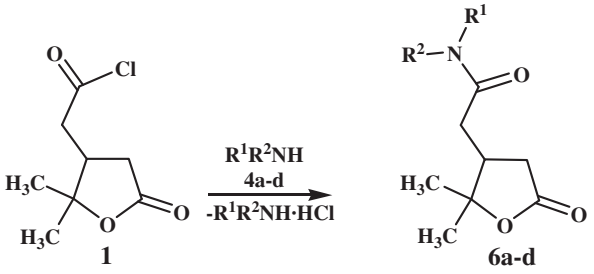
Scheme 1 Synthesis of **5a-d**.

***N*-(Diethylcarbamothioyl)-2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetamide (5d)** This compound was obtained as a pale yellow solid; yield 82%; mp 131–132°C; R_f = 0.58; IR: 1580, 1600, 1690, 1775, 3250, 3270 cm^{-1}; ^1H NMR: δ_H 1.22 (t, 6H, *J* = 7 Hz); 1.35 and 1.50 (2s, 6H), 2.30–2.90 (m, 5H), 3.45 (q, 4H, *J* = 7 Hz), 10.18 (s, 1H). ^{13}C NMR: δ_C 15.00, 24.11, 33.8, 38.50, 40.2, 49.9, 87.64, 177.2, 178.11, 189.5. Anal. Calcd for $C_{13}H_{22}N_2O_3S$: C, 54.52; H, 7.74; N, 9.78. Found: C, 54.58; H, 7.79; N, 9.82.

General procedure for 6a–d

To a precooled (0–5°C) solution of amine **4a–d** (4.4 mmol) in anhydrous acetone (10 mL), compound **1** (0.41 g, 2.2 mmol) was added. The mixture was stirred at room temperature for 30 min and heated under reflux for an additional 1 h. The solvent was removed under reduced pressure and water was added to the residue. The precipitate solid was filtered, washed with water and crystallized from ethanol.

2-(2,2-Dimethyl-5-oxotetrahydrofuran-3-yl)-*N*-phenylacetamide (6a) This compound was obtained as a pale yellow solid; yield 82%; mp 135–136°C; R_f = 0.56; IR: 1600, 1690, 1775, 3250 cm^{-1}; ^1H NMR: δ_H 1.35 and 1.50 (2s, 6H), 2.25–2.90 (m, 5H), 6.9–8.1 (m, 5H), 9.75 (s, 1H); ^{13}C NMR: δ_C 24.1, 33.8, 38.5, 40.2, 9.6, 123.6, 126.4, 131.0, 140.1, 175.2, 178.1. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.08; H, 6.98; N, 5.72.



6a: $R^1 = H$, $R^2 = C_6H_5$; **6b:** $R^1 = H$, $R^2 = CH_2C_6H_5$;
6c: $R^1 = H$, $R^2 = C_6H_{11}$; **6d:** $R^1 = R^2 = C_2H_5$.

Scheme 2 Synthesis of **6a-d**.

***N*-Benzyl-2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetamide (6b)** This compound was obtained as a pale yellow solid; yield 85%; mp 167–169°C; R_f = 0.58; IR: 1600, 1690, 1775, 3250 cm^{-1}; ^1H NMR: δ_H 1.35 and 1.50 (2s, 6H), 2.25–2.90 (m, 5H), 4.46 (d, 2H, *J* = 6.0 Hz), 6.9–8.0 (m, 5H), 9.88 (t, 1H, *J* = 6.0 Hz); ^{13}C NMR: δ_C 24.1, 33.8, 38.2, 40.5, 46.0, 87.6, 128.8, 128.90, 130.6, 143.6, 174.2, 178.1. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.99; H, 7.42; N, 5.48.

***N*-Cyclohexyl-2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetamide (6c)** This compound was obtained as a pale yellow solid; yield 85%; mp 142–143°C; R_f = 0.57; IR: 1600, 1690, 1775, 3250 cm^{-1}; ^1H NMR: δ_H 1.35 and 1.50 (s, 6H), 1.58–1.95 (m, 10H), 2.25–2.90 (m, 5H), 3.45–3.60 (m, 1H), 7.50 (d, 1H, *J* = 8 Hz); ^{13}C NMR: δ_C 24.1, 24.9, 30.0, 33.8, 35.8, 38.4, 40.8, 49.4, 87.6, 174.3, 178.1. Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.39; H, 9.18; N, 5.59.

2-(2,2-Dimethyl-5-oxotetrahydrofuran-3-yl)-*N,N*-diethylacetamide (6d) This compound was obtained as a light brown solid; yield 81%; mp 144–145°C; R_f = 0.58; IR: 1600, 1690, 1775, 3250 cm^{-1}; ^1H NMR: δ_H 1.22 (t, 6H, *J* = 7 Hz), 1.35 and 1.50 (2s, 6H), 2.30–2.90 (m, 5H), 3.45 (q, 4H, *J* = 7 Hz); ^{13}C NMR: δ_C 15.0, 24.1, 33.8, 38.5, 40.2, 49.9, 87.6, 177.2, 178.1. Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.44; H, 9.34; N, 69.19.

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