

Chemistry

SYNTHESIS OF NEW DERIVATIVES OF 5-OXOTETRAHYDROFURAN

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New derivatives of 5-oxotetrahydrofuran were synthesized by efficient and convenient reactions from 2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetyl chloride.

Keywords: 5-oxotetrahydrofuran, isothiocyanate, potassium thiocyanate, hydrazide, antibacterial activity.

Introduction. Saturated γ -lactones are of interest due to their biological activity. These include Artemisinin and Santonin[1–4] and many compounds such as pilocarpine, a cholinergic drug [5–7].

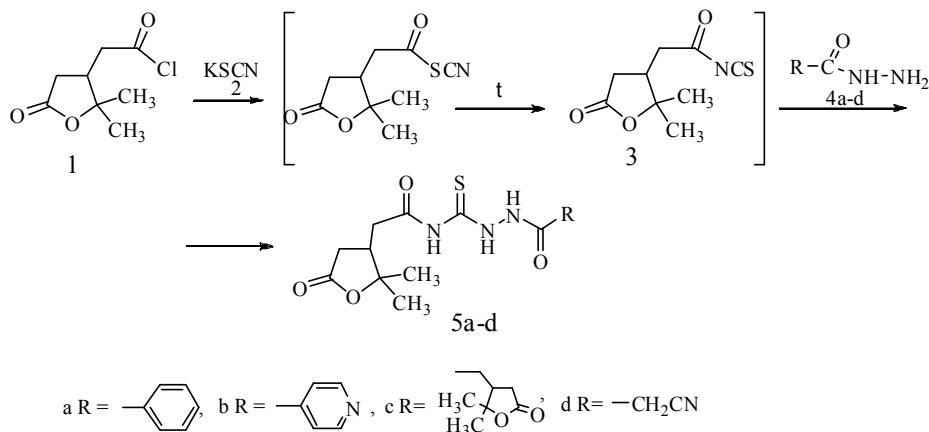
It is known that thioureide derivatives have valuable pharmacological properties and find use as antiepileptic [8], antidiabetic [9], anticancer [10], antitubercular [11] and as other therapeutically active agents [12]. They are also starting synthons in preparation of many sulfur-containing heterocycles. Hence, the introduction into the saturated γ -lactones of sulfur-containing fragments may lead to an increase in basic or the appearance of novel, biological properties.

We have previously developed [13] convenient methods for preparation of 5-oxotetrahydrofuran derivatives starting from available 2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetyl chloride (**1**) [14]. Continuing our studies on chemistry of saturated γ -lactones [9, 15], we studied the interaction of compound **1** with various hydrazides.

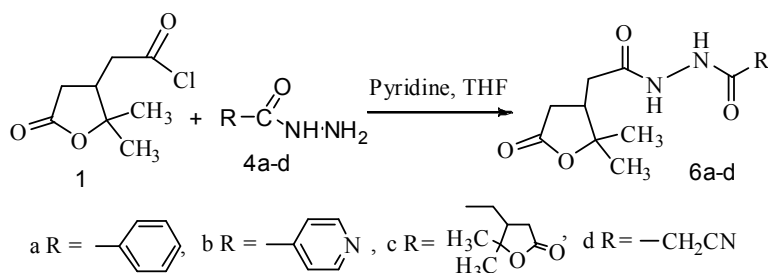
The reaction of 2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetyl isothiocyanate (**3**) with hydrazides was studied, by the method reported in [13], having an aim to synthesize 5-oxotetrahydrofuran derivatives, containing carbamothioyl fragments, and to find biologically active compounds among the synthesized structures.

Materials and Methods. Synthesis of the starting isothiocyanate **3** was carried out *in situ* by heating compound **1** with potassium thiocyanate (**2**) in acetone. Further reactions of isothiocyanate **3** with benzohydrazide (**4 a**), isonicotino-hydrazide (**4 b**), 2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetohydrazide (**4 c**), 2-cyanoacetohydrazide (**4 d**) gave the thiosemicarbazide derivatives **5 a–d**. The overall yield of this one-pot two steps synthesis is 90–94% (Scheme 1).

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Scheme 1. Synthesis of compounds **5 a–d**.

We examined the reaction of compound **1** with hydrazides **4 a–d** in anhydrous tetrahydrofuran in the presence of pyridine. The use of above mentioned conditions was more effective for hydrazides, than previously reported method [13, 15]. The transformations in anhydrous tetrahydrofuran in the presence of pyridine gave the corresponding compounds **6 a–d** in higher yields (Scheme 2).

Scheme 2. Synthesis of compounds **6 a–d**.

The structures of the synthesized compounds **5**, **6 a–d** were confirmed by IR, ¹H NMR spectroscopic data.

In order to reveal the potential biological activity of the synthesized compounds, a study of compounds **5**, **6 a–d** has been carried out for their antibacterial behavior at the chemotherapy laboratory, A.L. Mndzhoyan Institute of Fine Organic Chemistry of Scientific-Technological Center of Organic and Pharmaceutical Chemistry and National Academy of Sciences of the Republic of Armenia. These compounds exhibited moderate antibacterial activity compared with the furazolidone against both Gram-positive and Gram-negative bacteria.

Hence, from 2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetyl chloride we have derived previously unknown derivatives of 5-oxotetrahydrofuran by efficient and convenient reactions according to two strategies. The methodologies are simple, rapid and inexpensive affording high yields of the products with operational simplicity. It was found that obtained products **5**, **6 a–d** have moderate antibacterial activity.

Experimental Part. IR spectra were recorded on a Specord 75 IR spectrometer. ^1H NMR spectra were recorded on a Varian Mercury-300 VX spectrometer (300 MHz) using $\text{DMSO-}d_6\text{-CCl}_4$ (1: 3). Melting points were determined using an Electrothermal 9100 apparatus. The homogeneity and the purity of the products was carried out by thin-layer chromatography on Silufol UV-254 plates, eluent acetone/benzene (1:2), visualization with iodine vapors.

The starting compound **1** was obtained by the reported method [14].

General Procedure for 5 a–d. A mixture of compounds **1** (0.41 g, 2.2 mmol) and **2** (0.42 g, 4.4 mmol) in anhydrous acetone (10 mL) is stirred at room temperature for 30 min, then treated with hydrazide **4 a–d** (4.4 mmol) and refluxed for 1 h. The solvent is removed under reduced pressure and water is poured to the residue. The precipitated solid is filtered, washed with water and crystallized.

2-(2,2-Dimethyl-5-oxotetrahydrofuran-3-yl)-N-(2-benzoylhydrazinecarbonothioyl)acetamide (5 a). Yield 0.7 g (91%). Light-yellow crystals; mp 94–96 °C (from ethanol), R_f 0.54. IR spectrum, ν , cm^{-1} : 3270 (NH), 3250 (NH), 1770 (C=O lactone), 1690 (C=O), 1680 (C=O), 1580 (C=S), 1600–1500 (H arom.). ^1H NMR spectrum, δ , ppm: 1.25 and 1.45 s (6H, 2CH₃); 2.25–2.90 m (5H, CH₂CHCH₂); 6.9–8.0 m (5H, C₆H₅); 11.19, 11.58 and 12.18 s (3H, NH).

2-(2,2-Dimethyl-5-oxotetrahydrofuran-3-yl)-N-(2-sonicotinoylhydrazinecarbonothioyl)acetamide (5 b). Yield 0.72 g (94%). Light-yellow crystals; mp 155–158 °C (from benzene), R_f 0.54. IR spectrum, ν , cm^{-1} : 3270 (NH), 3255 (NH), 1775 (C=O lactone), 1690 (C=O), 1685 (C=O), 1580 (C=S), 1600–1500 (H arom.). ^1H NMR spectrum, δ , ppm: 1.25 and 1.45 s (6H, 2CH₃); 2.25–2.90 m (5H, CH₂CHCH₂); 7.78 d (2H, $J=8.0$ Hz, H arom.); 8.72 d (2H, $J=8.0$ Hz, H arom.); 11.19, 11.58 and 12.18 s (3H, NH).

2-(2,2-Dimethyl-5-oxotetrahydrofuran-3-yl)-N-(2-(2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetyl)hydrazinecarbonothioyl)acetamide (5 c). Yield 0.79 g (90%). Light-yellow crystals; mp 116–118 °C (from ethanol), R_f 0.51. IR spectrum, ν , cm^{-1} : 3270 (NH), 3250 (NH), 1760 (C=O lactone), 1690 (C=O), 1680 (C=O), 1580 (C=S). ^1H NMR spectrum, δ , ppm: 1.25 and 1.45 s (12H, 2CH₃); 2.25–2.90 m (10H, 2(CH₂CH–CH₂)); 11.19, 11.58 and 12.18 s (3H, NH).

2-(2,2-Dimethyl-5-oxotetrahydrofuran-3-yl)-N-(2-(2-cyanoacetyl)hydrozinecarbonothioyl)acetamide (5 d). Yield 0.64 g (93%). Yellow crystals; mp 221–222 °C (from methanol), R_f 0.54. IR spectrum, ν , cm^{-1} : 3260 (NH), 3245 (NH), 2250 (CN), 1765 (C=O lactone), 1690 (C=O), 1680 (C=O), 1580 (C=S). ^1H NMR spectrum, δ , ppm: 1.25 and 1.45 s (6H, 2CH₃); 2.25–2.90 m (5H, CH₂CHCH₂); 3.70 s (2H, CH₂); 11.15, 11.56 and 12.35 s (3H, NH).

General Procedure for 6 a–d. To a solution of hydrazide **4 a–d** (2.2 mmol) in anhydrous THF (10 mL), compound **1** (0.41 g, 2.2 mmol) and pyridine (0.18 mL, 2.2 mmol) are added. The mixture is refluxed for 1 h. The solvent is removed under reduced pressure and water is poured to the residue. The precipitate solid is filtered, washed with water and crystallized.

N'-(2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetyl)benzohydrazide (6 a). Yield 0.6 g (94%). White crystals; mp 185–186 °C (from toluene), R_f 0.55. IR spectrum, ν , cm^{-1} : 3250 (NH), 1775 (C=O lactone), 1690 (C=O), 1680 (C=O), 1600–1500 (H arom.). ^1H NMR spectrum, δ , ppm: 1.25 and 1.45 s (6H, 2CH₃); 2.25–2.90 m (5H, CH₂CHCH₂); 6.9–8.0 m (5H, C₆H₅); 11.20 and 11.62 s (2H, NH).

N'-(2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetyl)isonicotinohydrazide (6 b). Yield 0.58 g (91%). Pale yellow crystals; mp 170–171°C (from ethanol), R_f 0.55. IR spectrum, ν , cm^{-1} : 3255 (NH), 1775 (C=O lactone), 1690 (C=O), 1685 (C=O), 1600–1500 (H arom.). 1H NMR spectrum, δ , ppm: 1.25 and 1.45 s (6H, 2CH₃); 2.25–2.90 m (5H, CH₂CHCH₂); 7.78 d (2H, J = 8.0 Hz, H arom.); 8.72 d (2H, J = 8.0 Hz, H arom.); 11.10 and 11.55 s (2H, NH).

2-(2,2-Dimethyl-5-oxotetrahydrofuran-3-yl)-N'-(2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetyl)acetohydrazide (6 c). Yield 0.66 g (88%). Pale yellow crystals; mp 169–171°C (from ethanol), R_f 0.51. IR spectrum, ν , cm^{-1} : 3250 (NH), 1760 (C=O lactone), 1690 (C=O), 1680 (C=O). 1H NMR spectrum, δ , ppm: 1.25 and 1.45 s (12H, 2CH₃); 2.25–2.90 m (10H, 2(CH₂CHCH₂)); 10.76 and 11.20 s (2H, NH).

2-Cyano-N'-(2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetyl)acetohydrazide (6 d). Yield 0.51 g (92%). Pale yellow crystals; mp 209–211°C (from benzene), R_f 0.5. IR spectrum, ν , cm^{-1} : 3245 (NH), 2250 (CN), 1765 (C=O lactone), 1690 (C=O), 1680 (C=O). 1H NMR spectrum, δ , ppm: 1.25 and 1.45 s (6H, 2CH₃); 2.25–2.90 m (5H, CH₂CHCH₂); 3.70 s (2H, CH₂); 11.10 and 11.55 s (2H, NH).

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