

Synthesis and Some Transformations of Functionally Substituted Lactones

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Received May 6, 2009

Abstract—Reactions of functionally substituted unsaturated five- and six-membered cyanolactones with α - and β -hydroxy ketones in the presence of sulfuric acid gave substituted 2-oxofuran- and 2-oxopyran-3-carboxamides. Hydrolysis of some keto amides thus obtained afforded the corresponding carboxylic acids, and reactions with hydrazines and semicarbazides led to hydrazones and semicarbazones at the side-chain oxo group.

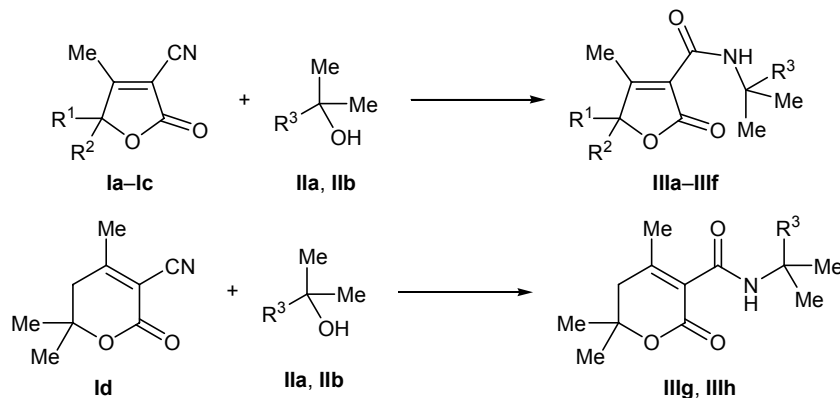
DOI: 10.1134/S1070428011060133

Unsaturated lactone fragment is a structural unit of many natural and synthetic biologically active compounds [1–4], and synthesis of the latter constitutes an important problem in contemporary organic chemistry. The present article reports on the results of our study on the Ritter reaction [5, 6] in the series of 2,5-dihydro-2-oxofuran-3-carbonitriles and 5,6-dihydro-2-oxopyran-3-carbonitriles, which gave rise to new functionally substituted derivatives.

The Ritter reaction of aldehydes with nitriles in the presence of an acid is known to give bisacylamides [7]. Under analogous conditions, ketones undergo self-condensation and subsequent transformation into acylamino ketones [8]. Afanas'eva et al. [9] showed that

pinacolone reacted with benzonitrile in the presence of trifluoromethanesulfonic acid, yielding protonated 4-*tert*-butyl-4-methyl-2,6-diphenyl-4*H*-1,3,5-oxadiazine, and that pivalophenone failed to react under similar conditions. This was rationalized by insufficient reactivity of hydroxycarbenium ions formed by protonation of ketones toward weakly nucleophilic nitriles. Luk'yanov and Borodaev [10] succeeded in developing a procedure for generation of acyloxy-carbenium ions in mixtures of ketones with nitriles and performing the Ritter reaction with ketones [11]. However, reactions of nitriles with hydroxy ketones, i.e., compounds containing both hydroxy and oxo group in a single molecule, were not reported at all.

Scheme 1.

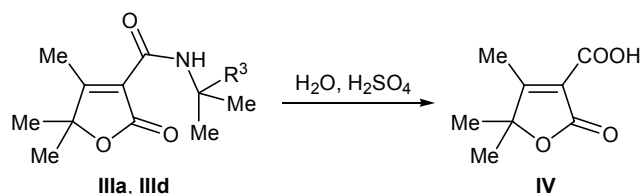


I, $R^1 = R^2 = \text{Me}$ (a); $R^1 = \text{Me}$, $R^2 = \text{Et}$ (b); $R^1 R^2 = (\text{CH}_2)_5$ (c); II, $R^3 = \text{MeC(O)CH}_2$ (a), MeC(O) (b); III, $R^1 = R^2 = \text{Me}$, $R^3 = \text{MeC(O)CH}_2$ (a), MeC(O) (d); $R^1 = \text{Me}$, $R^2 = \text{Et}$, $R^3 = \text{MeC(O)CH}_2$ (b), MeC(O) (e); $R^1 R^2 = (\text{CH}_2)_5$, $R^3 = \text{MeC(O)CH}_2$ (c, g), MeC(O) (f, h).

In the present work we examined reactions of 5,5-disubstituted 4-methyl-2-oxo-2,5-dihydrofuran-3-carbonitriles **Ia–Ic** and 4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile (**Id**) with some tertiary keto alcohols. The effects of different factors on the reaction course were studied, and optimal conditions were found. The reactions readily occurred upon mixing the initial reactants in benzene solution at 0°C in the presence of sulfuric acid, and the products were the corresponding oxo amides **IIIa–IIIh** (Scheme 1). The observed behavior of the carbonyl group is consistent with published data [11]. Elevated temperature induces tarring.

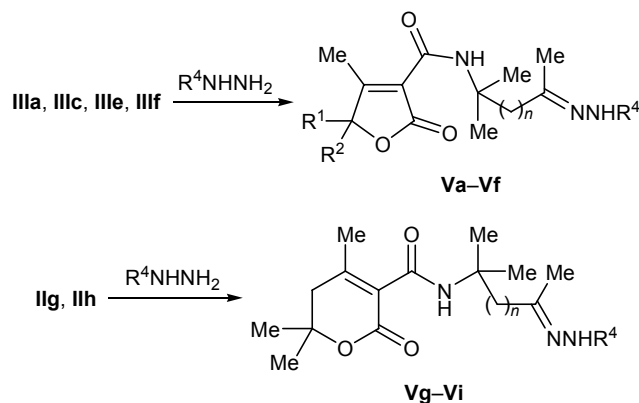
The product structure was confirmed by both spectral methods and chemical transformations. Hydrolysis of amides **IIIa** and **IIIh** with 20% sulfuric acid gave 4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-carboxylic acid (**IV**) (Scheme 2) whose physical constants coincided with those reported in [12].

Scheme 2.



The presence of an oxo group in the side chain of amides **IIIa–IIIh** makes it possible to synthesize their new derivatives which could attract some interest. Compounds **IIIa**, **IIIc**, **IIIh**, and **IIIg**–**IIIh** reacted with hydrazine hydrate, semicarbazide, and 2,4-dini-

Scheme 3.



V, $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^4 = \text{H}$ (**a**), $\text{H}_2\text{NC(O)}$ (**c**), 2,4-(O_2N) $_2$ - C_6H_3 (**e**); $\text{R}^1\text{R}^2 = (\text{CH}_2)_5$, $\text{R}^4 = \text{H}$ (**b**), $\text{H}_2\text{NC(O)}$ (**d**), 2,4-(O_2N) $_2$ - C_6H_3 (**f**); $\text{R}^4 = \text{H}$ (**g**), $\text{H}_2\text{NC(O)}$ (**h**), 2,4-(O_2N) $_2$ - C_6H_3 (**i**); $n = 1$ (**a**, **b**, **e**, **g**), 0 (**c**, **d**, **f**, **h**, **i**).

trophenylhydrazine to give the corresponding hydrazones **Va**, **Vb**, **Ve–Vg**, and **Vi** and semicarbazones **Vc**, **Vd**, and **Vh** in almost quantitative yield (Scheme 3).

EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR spectrometer. The ^1H NMR spectra were measured on a Varian Mercury-300 instrument at 300 MHz using hexamethyldisiloxane as internal reference. Thin-layer chromatography was performed on Silufol UV-254 plates.

5,5-Dialkyl-4-methyl-2-oxo-2,5-dihydrofuran-3-carboxamides IIIa–IIIh and 4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carboxamides IIg and IIIh (general procedure). Concentrated sulfuric acid, 5 ml, was added dropwise at $\sim 0^\circ\text{C}$ to a suspension of 0.01 mol of substituted 2,5-dihydro-2-oxofuran-3-carbonitrile **Ia–Ic** or 4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile (**Id**) and 0.011 mol of hydroxy ketone **IIa** or **IIb** in 15 ml of anhydrous benzene. The mixture was stirred for 5 h and poured into 100 ml of cold water ($\sim 5^\circ\text{C}$), the organic phase was separated, the aqueous phase was neutralized with a solution of sodium hydrogen carbonate, and the precipitate was filtered off, dried, and recrystallized from aqueous alcohol (1 : 1).

N-(1,1-Dimethyl-3-oxobutyl)-4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-carboxamide (IIIa). Yield 1.73 g (65%), mp $105\text{--}106^\circ\text{C}$, R_f 0.66 (acetone–benzene, 1 : 1). IR spectrum, ν , cm^{-1} : 3340 (NH), 1740 ($\text{C}=\text{O}$, lactone), 1720 ($\text{C}=\text{O}$, ketone), 1640 ($\text{C}=\text{O}$, amide). ^1H NMR spectrum, δ , ppm: 1.48 s (6H, CH_3), 2.00 s (6H, CH_3), 2.25 s (3H, CH_3), 2.32 s (2H, CH_2), 2.60 s (3H, COCH_3), 8.50 br.s (1H, NH). Found, %: C 62.71; H 7.61; N 5.52. $\text{C}_{14}\text{H}_{21}\text{NO}_4$. Calculated, %: C 62.92; H 7.87; N 5.24.

N-(1,1-Dimethyl-3-oxobutyl)-5-ethyl-4,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxamide (IIIb). Yield 1.97 g (70%), mp $111\text{--}112^\circ\text{C}$, R_f 0.65 (acetone–benzene, 1 : 1). IR spectrum, ν , cm^{-1} : 3315 (NH), 1740 ($\text{C}=\text{O}$, lactone), 1718 ($\text{C}=\text{O}$, ketone), 1638 ($\text{C}=\text{O}$, amide). Found, %: C 63.98; H 8.08; N 4.69. $\text{C}_{15}\text{H}_{23}\text{NO}_4$. Calculated, %: C 64.06; H 8.19; N 4.98.

N-(1,1-Dimethyl-3-oxobutyl)-4-methyl-2-oxo-1-oxaspiro[4.5]dec-3-ene-3-carboxamide (IIIc). Yield 2.13 g (70%), mp $139\text{--}140^\circ\text{C}$, R_f 0.63 (acetone–benzene, 1 : 1). IR spectrum, ν , cm^{-1} : 3316 (NH), 1735 ($\text{C}=\text{O}$, lactone), 1715 ($\text{C}=\text{O}$, ketone), 1640 ($\text{C}=\text{O}$, amide). ^1H NMR spectrum, δ , ppm: 1.20–1.48 m (2H,

CH₂), 1.52–1.80 m (8H, CH₂), 1.84 s (6H, CH₃), 2.1 s (3H, CH₃), 2.35 s (2H, CH₂), 2.60 s (3H, COCH₃), 8.16 br.s (1H, NH). Found, %: C 66.94; H 8.21; N 4.62. C₁₇H₂₅NO₄. Calculated, %: C 66.45; H 8.14; N 4.56.

N-(1,1-Dimethyl-3-oxopropyl)-4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-carboxamide (III_d). Yield 1.71 g (69%), mp 100–101°C, *R_f* 0.67 (acetone–benzene, 1:1). IR spectrum, ν , cm^{–1}: 3375 (NH), 1740 (C=O, lactone), 1710 (C=O, ketone), 1645 (C=O, amide). ¹H NMR spectrum, δ , ppm: 1.45 s (6H, CH₃), 2.15 s (6H, CH₃), 2.5 s (3H, CH₃), 2.75 s (3H, COCH₃), 8.40 br.s (1H, NH). Found, %: C 61.52; H 7.62; N 5.71. C₁₃H₁₉NO₄. Calculated, %: C 61.66; H 7.51; N 5.53.

N-(1,1-Dimethyl-3-oxopropyl)-5-ethyl-4,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxamide (III_e). Yield 1.82 g (71%), mp 107°C, *R_f* 0.66 (acetone–benzene, 1:1). IR spectrum, ν , cm^{–1}: 3367 (NH), 1736 (C=O, lactone), 1717 (C=O, ketone), 1640 (C=O, amide). Found, %: C 62.49; H 7.59; N 5.09. C₁₄H₂₁NO₄. Calculated, %: C 62.92; H 7.87; N 5.24.

N-(1,1-Dimethyl-3-oxopropyl)-4-methyl-2-oxo-1-oxaspiro[4.5]dec-3-ene-3-carboxamide (III_f). Yield 2.14 g (73%), mp 132–133°C, *R_f* 0.69 (acetone–benzene, 1:1). IR spectrum, ν , cm^{–1}: 3360 (NH), 1740 (C=O, lactone), 1645 (C=O, amide). ¹H NMR spectrum, δ , ppm: 1.25–1.48 m (2H, CH₂), 1.50–1.75 m (8H, CH₂), 1.85 s (6H, CH₃), 2.10 s (3H, CH₃), 2.70 s (3H, COCH₃), 8.25 br.s (1H, NH). Found, %: C 65.31; H 7.92; N 4.63. C₁₆H₂₃NO₄. Calculated, %: C 65.53; H 7.85; N 4.78.

N-(1,1-Dimethyl-3-oxobutyl)-4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carboxamide (III_g). Yield 1.81 g (64%), mp 107–108°C, *R_f* 0.66 (acetone–benzene, 1:1). IR spectrum, ν , cm^{–1}: 3320 (NH), 1745 (C=O, lactone), 1710 (C=O, ketone), 1645 (C=O, amide). ¹H NMR spectrum, δ , ppm: 1.40 s (6H, CH₃), 2.05 m (9H, CH₃), 2.66 s (3H, CH₃), 2.66 s (3H, COCH₃), 2.83 s (2H, CH₂), 8.72 br.s (1H, NH). Found, %: C 64.41; H 7.91; N 5.16. C₁₅H₂₃NO₄. Calculated, %: C 64.06; H 8.19; N 4.98.

N-(1,1-Dimethyl-3-oxopropyl)-4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carboxamide (III_h). Yield 1.95 g (76%), mp 88–89°C, *R_f* 0.68 (acetone–benzene, 1:1). IR spectrum, ν , cm^{–1}: 3340 (NH), 1745 (C=O, lactone), 1710 (C=O, ketone), 1645 (C=O, amide), 1610 (C=C). ¹H NMR spectrum, δ , ppm: 1.60 s (6H, CH₃), 2.20 m (9H, CH₃), 2.70 s (3H, COCH₃), 3.20 s (2H, CH₂), 8.61 br.s (1H, NH). Found,

%: C 63.25; H 7.73; N 5.34. C₁₄H₂₁NO₄. Calculated, %: C 62.49; H 7.87; N 5.24.

4,5,5-Trimethyl-2-oxo-2,5-dihydrofuran-3-carboxylic acid (IV). A mixture of 0.01 mol of compound III_a or III_d and 10 ml of 20% sulfuric acid was heated for 4 h at 60°C on a water bath. The mixture was cooled and poured onto 50 g of crushed ice. After 10 h, the crystalline material was filtered off, washed with water, and recrystallized from xylene. Yield 1.17 g (67%), mp 113°C [12].

Hydrazones Va, Vb, and Vg (general procedure). Compound III_a, III_c, or III_g, 0.005 mol, was dissolved in 10 ml of anhydrous ethanol, 0.5 ml of dimethylformamide and 2 ml of hydrazine hydrate were added, and the mixture was heated for 15 min under reflux and left overnight. The precipitate was filtered off and recrystallized from water.

N-(1,1-Dimethyl-3-hydrazonobutyl)-4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-carboxamide (Va). Yield 1.18 g (91%), mp 172–173°C. IR spectrum, ν , cm^{–1}: 3260, 3175 (NH); 1755 (C=O, lactone); 1640 (C=O, amide); 1620 (C=N). Found, %: C 59.70; H 8.23; N 14.43. C₁₄H₂₃N₃O₃. Calculated, %: C 59.79; H 8.19; N 14.95.

N-(1,1-Dimethyl-3-hydrazonobutyl)-4-methyl-2-oxo-1-oxaspiro[4.5]dec-3-ene-3-carboxamide (Vb). Yield 1.4 g (88%), mp 167–168°C. IR spectrum, ν , cm^{–1}: 3260, 3180 (NH); 1735 (C=O, lactone); 1640 (C=O, amide); 1620 (C=N). Found, %: C 63.71; H 8.59; N 13.31. C₁₇H₂₇N₃O₃. Calculated, %: C 63.55; H 8.41; N 13.08.

N-(1,1-Dimethyl-3-hydrazonobutyl)-4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carboxamide (Vg). Yield 1.3 g (89%), mp 165°C. IR spectrum, ν , cm^{–1}: 3260, 3185 (NH); 1750 (C=O, lactone); 1644 (C=O, amide); 1620 (C=N). Found, %: C 61.23; H 8.16; N 14.30. C₁₅H₂₅N₃O₃. Calculated, %: C 61.02; H 8.47; N 14.24.

Semicarbazones Vc, Vd, and Vh (general procedure). A mixture of 0.01 mol of amide III_d, III_f, or III_h, 1.1 g (0.01 mol) of semicarbazide hydrochloride, 2.2 g (0.02 mol) of anhydrous sodium acetate, and 10 ml of anhydrous ethanol was heated for 1 h under reflux (on a water bath). The mixture was cooled and diluted with 30 ml of water, and the precipitate was filtered off, washed with water, dried, and recrystallized from ethanol.

N-[2-[(Aminocarbonyl)hydrazono]-1,1-dimethylpropyl]-4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-

carboxamide (Vc). Yield 3 g (94%), mp 145–146°C, R_f 0.73 (acetone–benzene, 1:1). IR spectrum, ν , cm^{-1} : 3250, 3180 (NH); 1730 (C=O); 1640 (C=O, amide); 1660 (NHCONH₂); 1620 (C=N). Found, %: C 54.50; H 7.42; N 18.48. $\text{C}_{14}\text{H}_{22}\text{N}_4\text{O}_4$. Calculated, %: C 54.19; H 7.097; N 18.07.

***N*-{2-[(Aminocarbonyl)hydrazono]-1,1-dimethylpropyl}-4-methyl-2-oxo-1-oxaspiro[4.5]dec-3-ene-3-carboxamide (Vd).** Yield 3.24 g (89%), mp 149–150°C, R_f 0.71 (acetone–benzene, 1:1). IR spectrum, ν , cm^{-1} : 3250, 3180 (NH); 1756 (C=O); 1665 (NHCONH₂); 1642 (C=O, amide); 1620 (C=N). Found, %: C 58.45; H 7.23; N 16.41. $\text{C}_{17}\text{H}_{26}\text{N}_4\text{O}_4$. Calculated, %: C 58.89; H 7.43; N 16.00.

***N*-{2-[(Aminocarbonyl)hydrazono]-1,1-dimethylpropyl}-4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carboxamide (Vh).** Yield 2.97 g (95%), mp 169–170°C. IR spectrum, ν , cm^{-1} : 3250, 3180 (NH); 1750 (C=O, lactone); 1670 (NHCONH₂); 1640 (C=O, amide); 1615 (C=N). Found, %: C 55.43; H 7.23; N 17.13. $\text{C}_{15}\text{H}_{24}\text{N}_4\text{O}_4$. Calculated, %: C 55.56; H 7.41; N 17.28.

2,4-Dinitrophenylhydrazones Ve, Vf, and Vi (general procedure). Concentrated sulfuric acid, 2 ml, was added to 1.98 g of 2,4-dinitrophenylhydrazine, 3 ml of water was added dropwise under stirring, and 20 ml of ethanol was then added to the warm solution. Compound **IIIa**, **IIIb**, or **IIIh**, 0.01 mol, was added to the freshly prepared solution, and the mixture was left overnight. The precipitate was filtered off and recrystallized from dioxane.

***N*-{3-[(2,4-Dinitrophenyl)hydrazono]-1,1-dimethylbutyl}-4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-carboxamide (Ve).** Yield 3.48 g (95%), mp 157–158°C. IR spectrum, ν , cm^{-1} : 3335, 3220 (NH); 1740 (C=O); 1640 (C=O, amide); 1615 (C=N). Found, %: C 53.40; H 5.82; N 15.63. $\text{C}_{20}\text{H}_{25}\text{N}_5\text{O}_7$. Calculated, %: C 53.69; H 5.59; N 15.66.

***N*-{2-[(2,4-Dinitrophenyl)hydrazono]-1,1-dimethylpropyl}-4-methyl-2-oxaspiro[4.5]dec-3-ene-**

3-carboxamide (Vf). Yield 3.76 g (93%), mp 161–162°C, R_f 0.71 (acetone–benzene, 1:1). IR spectrum, ν , cm^{-1} : 3330, 3220 (NH); 1730 (C=O); 1640 (C=O, amide); 1615 (C=N). Found, %: C 55.51; H 5.70; N 14.17. $\text{C}_{22}\text{H}_{27}\text{N}_5\text{O}_7$. Calculated, %: C 55.82; H 5.71; N 14.80.

***N*-{2-[(2,4-Dinitrophenyl)hydrazono]-1,1-dimethylpropyl}-4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carboxamide (Vi).** Yield 3.21 g (88%), mp 203–204°C. IR spectrum, ν , cm^{-1} : 3330, 3215 (NH); 1730 (C=O); 1640 (C=O, amide); 1615 (C=N). Found, %: C 53.67; H 5.41; N 15.73. $\text{C}_{20}\text{H}_{25}\text{N}_5\text{O}_7$. Calculated, %: C 53.69; H 5.59; N 15.65.

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