974 Russian Chemical Bulletin, International Edition, Vol. 59, No. 5, pp. 974—976, May, 2010

Synthesis and some chemical transformations of novel functionalized 2-imino-2,5-dihydrofurans

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Hitherto unknown functionalized 2-imino-3-(*N*-cyclohexylcarbamoyl)-2,5-dihydrofurans were synthesized by the reactions of tertiary α-hydroxy ketones with *N*-cyclohexyl(cyanoacetamide). Several reactions of thus synthesized compounds at the imino group were carried out.

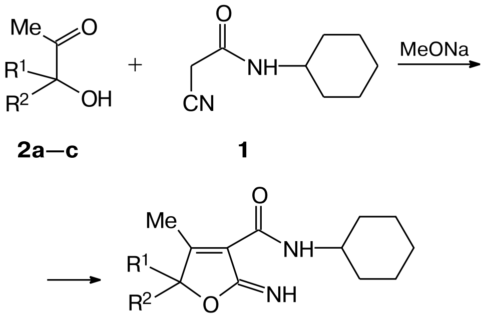
Key words: α-hydroxy ketones, imines, dihydrofuranones, malononitrile, heterocyclization.

Functionalized 2-imino-2,5-dihydrofurans[1] and 2,5-dihydrofuran-2-ones[2—5] are the promising heterocyclic compounds and of practical and scientific interest. Synthesis of these compounds is an important problem.

In continuation of our research on condensation of tertiary α-hydroxy ketones with compounds bearing the active methylene group,[1] in the present work we involved *N*-cyclohexyl(cyanoacetamide) (**1**) in the condensations with α-hydroxy ketones (Scheme 1). At an equimolar reactant ratio, the reaction of α-hydroxy ketones **2a—c** with compound **1** in MeOH in the presence of MeONa at 40 °C for 5 h resulted in 2-imino-3-(*N*-cyclohexylcarbamoyl)-4-methyl-5,5-dialkyl-2,5-dihydrofurans **3a—c** in high yields.

Hydrolysis of the resulting imino derivatives **3a—c** under weakly acidic conditions (pH 4—5) at 85—90 °C for 3 h furnished the corresponding 2,5-dihydrofuran-2-ones **4a—c** (Scheme 2).

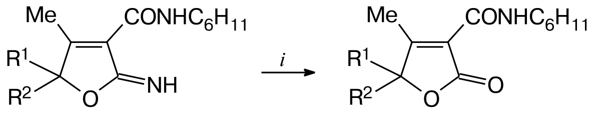
Scheme 1



2a—c **1** **3a—c**

$R^1 = R^2 = Me$ (**a**); $R^1 = Me, R^2 = Et$ (**b**); $R^1 + R^2 = (CH_2)_4$ (**c**)

Scheme 2



3a—c **4a—c**

$R^1 = R^2 = Me$ (**a**); $R^1 = Me, R^2 = Et$ (**b**); $R^1 + R^2 = (CH_2)_4$ (**c**)
i. H_2O, HCl, pH = 4—5, 85–90 °C

Bubbling of gaseous HCl through a benzene solution of 2-imino-2,5-dihydrofurans **3a—c** afforded the corresponding hydrochlorides **5a—c** in quantitative yields (Scheme 3). The resulting hydrochlorides **5a—c** can readily be converted into the starting 2-imino derivatives **3a—c** by treatment with 0.1 *M* NaOH or aqueous K_2CO_3 solution. Aqueous hydrolysis of hydrochlorides **5a—c** at 85—90 °C for 2 h resulted in 2,5-dihydrofuran-2-ones **4a—c**.

With the aim of synthesizing of dicyanomethylidene dihydrofuran derivatives bearing the chromophores, we performed the reactions of 2-iminoderivatives **3a—c** with malononitrile (Scheme 4). These reactions carried out at an equimolar reactant ratio in anhydrous EtOH at room temperature gave the corresponding 2-dicyanomethylidene-2,5-dihydrofurans **6a—c** with quantitative yields (the reactions completed when the evolution of ammonia ceased).

Methylation of 2-imino-2,5-dihydrofurans **3a—c** with dimethyl sulfate in the presence of Na_2CO_3 at room

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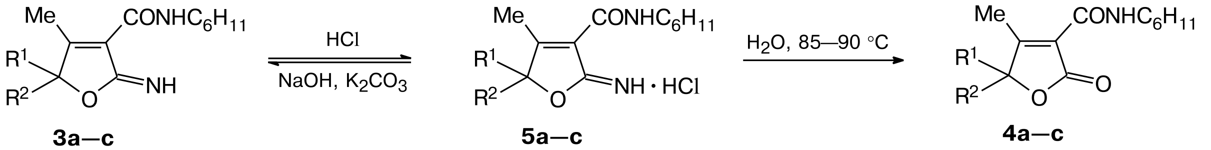
† Deceased.

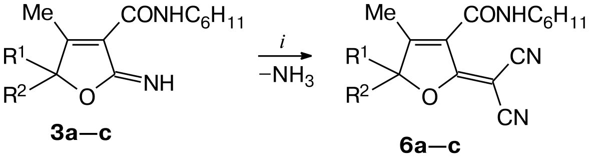
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 5, pp. 953—955, May, 2010.

Scheme 3



$R^1 = R^2 =$ Me (**a**); $R^1 =$ Me, $R^2 =$ Et (**b**); $R^1 + R^2 = (CH_2)_4$ (**c**)

Scheme 4

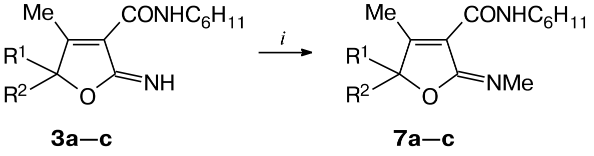


$R^1 = R^2 =$ Me (**a**); $R^1 =$ Me, $R^2 =$ Et (**b**); $R^1 + R^2 = (CH_2)_4$ (**c**)
i. $CH_2(CN)_2$

temperature furnished the corresponding 2-(*N*-methylimino)-2,5-dihydrofurans **7a—c** (Scheme 5).

The structures of the synthesized compounds were established based on the data from IR and ^{1}H NMR spectroscopy and confirmed by elemental analysis. The performed chemical reactions of compounds **3a—c** confirmed that compounds **3a—c** are actually iminodihydrofurans but not isomeric pyrrolinones.[6]

Scheme 5



$R^1 = R^2 =$ Me (**a**); $R^1 =$ Me, $R^2 =$ Et (**b**); $R^1 + R^2 = (CH_2)_4$ (**c**)
i. Me_2SO_4

Experimental

The IR spectra (in Nujol) were recorded on a Specord 571R spectrophotometer. The ^{1}H NMR spectra were obtained on a Mercury-300 Varian instrument at 300 MHz in a DMSO-d_6—CCl_4 (1 : 3) mixture. The individuality of the synthesized compounds was monitored by TLC on precoated plates Silufol UV-254 using a 1 : 2 acetone—benzene mixture as the eluent, the spots were visualized by iodine vapors. The tertiary α-hydroxy ketones **2a—c** were synthesized by the known procedure,[7] *N*-cyclohexyl(cyanoacetamide) (**1**) was prepared by the reaction of ethyl cyanoacetate with cyclohexylamine.[6]

5,5-Dialkyl-3-(*N*-cyclohexylcarbamoyl)-2-imino-4-methyl-2,5-dihydrofurans 3a—c (general procedure). To a solution of MeONa in anhydrous MeOH (1 mmol Na in 20 mL of MeOH), the tertiary α-hydroxy ketone **2** (10 mmol) and *N*-cyclohexyl(cyanoacetamide) (**1**) (10 mmol) were added. The reaction mixture was heated at 40 °C for 5 h, and the solvent was removed *in vacuo*. Water was added to the residue, the precipitate that formed was filtered off, washed with water, and recrystallized from EtOH.

3-(*N*-Cyclohexylcarbamoyl)-2-imino-4,5,5-trimethyl-2,5-dihydrofuran (3a). The yield was 92%, m.p. 57—58 °C. ^{1}H NMR, δ: 1.42 (s, 6 H, 2 CH_3); 1.58—1.95 (m, 10 H, C_6H_{11}); 2.34 (s, 3 H, CH_3); 3.71 (m, 1 H, NH—C$\underline{H}$); 7.25 (s, 1 H, =NH); 9.24 (d, 1 H, NH, J = 7.9 Hz). IR, ν/cm^{-1}: 3360 (NH), 3180 (NH), 1680 (C=O), 1670 (C=N), 1620 (C=C). Found (%): C, 67.34; H, 8.97; N, 11.34. $C_{14}H_{22}N_2O_2$. Calculated (%): C, 67.17; H, 8.86; N, 11.19.

3-(*N*-Cyclohexylcarbamoyl)-5-ethyl-2-imino-4,5-dimethyl-2,5-dihydrofuran (3b). The yield was 98%, m.p. 55—57 °C. ^{1}H NMR, δ: 0.95 (t, 3 H, $CH_2C\underline{H}_3$, J = 8.5 Hz); 1.45 (s, 3 H, CH_3); 1.58—1.90 (m, 10 H, C_6H_{11}); 1.95 (q, 2 H, $C\underline{H}_2CH_3$, J = 8.5 Hz); 2.33 (s, 3 H, CH_3); 3.71 (m, 1 H, NH—C$\underline{H}$); 7.25 (s, 1 H, =NH); 9.24 (d, 1 H, NH, J = 7.9 Hz). IR, ν/cm^{-1}: 3360 (NH), 3180 (NH), 1680 (C=O), 1670 (C=N), 1620 (C=C). Found (%): C, 68.34; H, 9.29; N, 10.74. $C_{15}H_{24}N_2O_2$. Calculated (%): C, 68.15; H, 9.15; N, 10.60.

3-(*N*-Cyclohexylcarbamoyl)-2-imino-4-methyl-1-oxaspiro[4.4]non-3-ene (3c). The yield was 95%, m.p. 180—182 °C. ^{1}H NMR, δ: 1.19—1.49 (m, 4 H, C_6H_{11}); 1.58—1.95 (m, 14 H, C_5H_9, C_6H_{11}); 2.33 (s, 3 H, CH_3); 3.72 (m, 1 H, NH—C$\underline{H}$); 7.23 (s, 1 H, =NH); 9.35 (d, 1 H, NH, J = 7.9 Hz). IR, ν/cm^{-1}: 3360 (NH), 3180 (NH), 1680 (C=O), 1670 (C=N), 1620 (C=C). Found (%): C, 69.74; H, 8.94; N, 10.37. $C_{16}H_{24}N_2O_2$. Calculated (%): C, 69.53; H, 8.75; N, 10.14.

5,5-Dialkyl-3-(*N*-cyclohexylcarbamoyl)-4-methyl-2,5-dihydrofuran-2-ones 4a—c (general procedure). A mixture of 2-imino-2,5-dihydrofuran **3** (1.5 mmol) and water (5 mL) was acidified to pH 4—5 with HCl and heated at 85—90 °C for 3 h. The reaction mixture was cooled, extracted with diethyl ether (3×5 mL), the combined organic layer was dried with $MgSO_4$, the solvent was removed *in vacuo*, and the residue was recrystallized from hexanes.

3-(*N*-Cyclohexylcarbamoyl)-4,5,5-trimethyl-2,5-dihydrofuran-2-one (4a). The yield was 76%, m.p. 90—91 °C. ^{1}H NMR, δ: 1.42 (s, 6 H, 2 CH_3); 1.58—1.95 (m, 10 H, C_6H_{11}); 2.33 (s, 3 H, CH_3); 3.71 (m, 1 H, NH—C$\underline{H}$); 9.24 (d, 1 H, NH, J = 7.9 Hz). IR, ν/cm^{-1}: 3280 (NH), 1780 (C=O), 1680 (C=O), 1620 (C=C). Found (%): C, 67.03; H, 8.59; N, 5.74. $C_{14}H_{21}NO_3$. Calculated (%): C, 66.91; H, 8.42; N, 5.57.

3-(*N*-Cyclohexylcarbamoyl)-5-ethyl-4,5-dimethyl-2,5-dihydrofuran-2-one (4b). The yield was 72%, m.p. 58—60 °C. ^{1}H NMR, δ: 0.95 (t, 3 H, $CH_2C\underline{H}_3$, J = 8.5 Hz); 1.45 (s, 3 H, CH_3); 1.58—1.90 (m, 10 H, C_6H_{11}); 1.95 (q, 2 H, $C\underline{H}_2CH_3$, J = 8.5 Hz); 2.33 (s, 3 H, CH_3); 3.71 (m, 1 H, NH—C$\underline{H}$); 9.24 (d, 1 H, NH, J = 7.9 Hz). IR, ν/cm^{-1}: 3280 (NH), 1780 (C=O), 1680 (C=O), 1620 (C=C). Found (%): C, 67.98; H, 8.75; N, 5.34. $C_{15}H_{23}NO_3$. Calculated (%): C, 67.90; H, 8.74; N, 5.28.

3-(*N*-Cyclohexylcarbamoyl)-4-methyl-1-oxaspiro[4.4]non-3-en-2-one (4c). The yield was 80%, m.p. 115—117 °C. ^{1}H NMR, δ: 1.19—1.49 (m, 4 H, C_6H_{11}); 1.58—1.95 (m, 14 H, C_5H_9, C_6H_{11}); 2.33 (s, 3 H, CH_3); 3.72 (m, 1 H, NH—C$\underline{H}$); 9.35 (d, 1 H, NH, *J* = 7.9 Hz). IR, ν/cm^{-1}: 3280 (NH), 1780 (C=O), 1680 (C=O), 1620 (C=C). Found (%): C, 69.44; H 8.52; N 5.21. $C_{16}H_{23}NO_3$. Calculated (%): C, 69.29; H, 8.36; N, 5.05.

5,5-Dialkyl-3-(*N*-cyclohexylcarbamoyl)-2-imino-4-methyl-2,5-dihydrofuran hydrochlorides 5a—c (general procedure). Gaseous HCl was bubbled through a solution of 2-imino-2,5-dihydrofuran **3** (2 mmol) in benzene (5 mL). Precipitate that formed was filtered off and washed with diethyl ether.

3-(*N*-Cyclohexylcarbamoyl)-2-imino-4,5,5-trimethyl-2,5-dihydrofuran hydrochloride (5a). The yield was 94%, m.p. 230—234 °C. ^{1}H NMR, δ: 1.42 (s, 6 H, 2 CH_3); 1.58—1.96 (m, 10 H, C_6H_{11}); 2.33 (s, 3 H, CH_3); 3.72 (m, 1 H, NH—C$\underline{H}$); 9.24 (d, 1 H, NH, *J* = 7.9 Hz); 10.34 (br.s, 2 H, NH • HCl). Found (%): C 58.74; H, 8.23; N, 9.84. $C_{14}H_{22}N_2O_2 \cdot HCl$. Calculated (%): C, 58.63; H, 8.08; N, 9.78.

3-(*N*-Cyclohexylcarbamoyl)-5-ethyl-2-imino-4,5-dimethyl-2,5-dihydrofuran hydrochloride (5b). The yield was 95%, m.p. 178—185 °C. ^{1}H NMR, δ: 0.95 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 8.5 Hz); 1.45 (s, 3 H, CH_3); 1.58—1.90 (m, 10 H, C_6H_{11}); 1.95 (q, 2 H, $C\underline{H}_2CH_3$, *J* = 8.5 Hz); 2.33 (s, 3 H, CH_3); 3.71 (m, 1 H, NH—C$\underline{H}$); 9.24 (d, 1 H, NH, *J* = 7.9 Hz); 10.34 (br.s, 2 H, NH • HCl). Found (%): C, 59.94; H, 8.42; N, 9.34. $C_{15}H_{24}N_2O_2 \cdot HCl$. Calculated (%): C, 59.89; H, 8.38; N, 9.31.

3-(*N*-Cyclohexylcarbamoyl)-2-imino-4-methyl-1-oxaspiro[4.4]non-3-ene hydrochloride (5c). The yield was 93%, m.p. >350 °C. ^{1}H NMR, δ: 1.19—1.49 (m, 4 H, C_6H_{11}); 1.58—1.95 (m, 14 H, C_5H_9, C_6H_{11}); 2.33 (s, 3 H, CH_3); 3.72 (m, 1 H, NH—C$\underline{H}$); 7.23 (s, 1 H, =NH); 9.35 (d, 1 H, NH, *J* = 7.9 Hz); 10.44 (br.s, 2 H, NH • HCl). Found (%): C, 61.64; H, 8.24; N, 9.01. $C_{16}H_{24}N_2O_2 \cdot HCl$. Calculated (%): C, 61.43; H, 8.05; N, 8.95.

5,5-Dialkyl-3-(*N*-cyclohexylcarbamoyl)-2-dicyanomethylidene-4-methyl-2,5-dihydrofurans 6a—c (general procedure). A mixture of 2-imino-2,5-dihydrofuran **3** (2.5 mmol) and malononitrile (0.17 g, 2.5 mmol) in anhydrous EtOH (5 mL) was stirred at room temperature until evolution of ammonia ceased, and the solvent was removed *in vacuo*. To the residue water was added, the precipitate that formed was filtered off, washed with water, and recrystallized from ethanol—water (2 : 1).

3-(*N*-Cyclohexylcarbamoyl)-2-dicyanomethylidene-4,5,5-trimethyl-2,5-dihydrofuran (6a). The yield was 95%, m.p. 230—232 °C. ^{1}H NMR, δ: 1.42 (s, 6 H, 2 CH_3); 1.58—1.95 (m, 10 H, C_6H_{11}); 2.33 (s, 3 H, CH_3); 3.71 (m, 1 H, NH—C$\underline{H}$); 9.24 (d, 1 H, NH, *J* = 7.9 Hz). IR, ν/cm^{-1}: 3280 (NH), 2219 (C≡N), 1680 (C=O), 1670 (C=N), 1635 (C=C), 1620 (C=C). Found (%): C, 68.45; H, 7.39; N, 14.32. $C_{17}H_{21}N_3O_2$. Calculated (%): C, 68.20; H, 7.07; N, 14.04.

3-(*N*-Cyclohexylcarbamoyl)-2-dicyanomethylidene-5-ethyl-4,5-dimethyl-2,5-dihydrofuran (6b). The yield was 96%, m.p. 195—197 °C. ^{1}H NMR, δ: 0.95 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 8.5 Hz); 1.45 (s, 3 H, CH_3); 1.58—1.90 (m, 10 H, C_6H_{11}); 1.95 (q, 2 H, $C\underline{H}_2CH_3$, *J* = 8.5 Hz); 2.33 (s, 3 H, CH_3); 3.71 (m, 1 H, NH—C$\underline{H}$); 9.24 (d, 1 H, NH, *J* = 7.9 Hz). IR, ν/cm^{-1}: 3280 (NH), 2219 (C≡N), 1680 (C=O), 1670 (C=N), 1635 (C=C), 1620 (C=C). Found (%): C, 69.29; H, 7.51; N, 13.58. $C_{18}H_{23}N_3O_2$. Calculated (%): C, 68.98; H, 7.40; N, 13.41.

3-(*N*-Cyclohexylcarbamoyl)-2-dicyanomethylidene-4-methyl-1-oxaspiro[4.4]non-3-ene (6c). The yield was 95%, m.p. 164—166 °C. ^{1}H NMR, δ: 1.19—1.49 (m, 4 H, C_6H_{11}); 1.58—1.95 (m, 14 H, C_5H_9, C_6H_{11}); 2.33 (s, 3 H, CH_3); 3.72 (m, 1 H, NH—C$\underline{H}$); 9.34 (d, 1 H, NH, *J* = 7.9 Hz). IR, ν/cm^{-1}: 3280 (NH), 2219 (C≡N), 1680 (C=O), 1670 (C=N), 1635 (C=C), 1620 (C=C). Found (%): C, 70.36; H, 7.42; N, 12.99. $C_{19}H_{23}N_3O_2$. Calculated (%): C, 70.13; H, 7.13; N, 12.91.

5,5-Dialkyl-3-(*N*-cyclohexylcarbamoyl)-4-methyl-2-(*N*-methylimino)-2,5-dihydrofurans 7a—c (general procedure). To a solution of 2-imino-2,5-dihydrofuran **3** (2 mmol) in dioxane (10 mL), conc. Na_2CO_3 solution (10 mL) and dimethyl sulfate (0.76 g, 6 mmol) were added. The reaction mixture was stirred at room temperature for 5 h, then water (50 mL) was added, and the stirring was continued for 1 h. The precipitate that formed was filtered off, washed with water, and recrystallized from heptane.

3-(*N*-Cyclohexylcarbamoyl)-4,5,5-trimethyl-2-(*N*-methylimino)-2,5-dihydrofuran (7a). The yield was 76%, m.p.103—105 °C. ^{1}H NMR, δ: 1.42 (s, 6 H, 2 CH_3); 1.58—1.95 (m, 10 H, C_6H_{11}); 2.33 (s, 3 H, CH_3); 2.98 (s, 3 H, $=NCH_3$); 3.72 (m, 1 H, NH—C$\underline{H}$); 9.46 (d, 1 H, NH, *J* = 7.9 Hz). IR, ν/cm^{-1}: 3260 (NH), 1680 (C=O), 1670 (C=N), 1620 (C=C). Found (%): C, 68.44; H, 9.46; N, 10.92. $C_{15}H_{24}N_2O_2$. Calculated (%): C, 68.15; H, 9.15; N, 10.60.

3-(*N*-Cyclohexylcarbamoyl)-5-ethyl-4,5-dimethyl-2-(*N*-methylimino)-2,5-dihydrofuran (7b). The yield was 74%, m.p. 115—117 °C. ^{1}H NMR, δ: 0.95 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 8.5 Hz); 1.45 (s, 3 H, CH_3); 1.58—1.90 (m, 10 H, C_6H_{11}); 1.95 (q, 2 H, $C\underline{H}_2CH_3$, *J* = 8.5 Hz); 2.35 (s, 3 H, CH_3); 3.00 (s, 3 H, $=NCH_3$); 3.72 (m, 1 H, NH—C$\underline{H}$); 9.24 (d, 1 H, NH, *J* = 7.9 Hz). IR, ν/cm^{-1}: 3340 (NH), 1680 (C=O), 1670 (C=N), 1620 (C=C). Found (%): C, 69.47; H, 9.74; N, 10.25. $C_{16}H_{26}N_2O_2$. Calculated (%): C, 69.03; H, 9.41; N, 10.06.

3-(*N*-Cyclohexylcarbamoyl)-4-methyl-2-(*N*-methylimino)-1-oxaspiro[4.4]non-3-ene (6c). The yield was 71%, m.p. 108—110 °C. ^{1}H NMR, δ: 1.19—1.49 (m, 4 H, C_6H_{11}); 1.58—1.95 (m, 14 H, C_5H_9, C_6H_{11}); 2.33 (s, 3 H, CH_3); 2.98 (s, 3 H, $=NCH_3$); 3.72 (m, 1 H, NH—C$\underline{H}$); 9.34 (d, 1 H, NH, *J* = 7.9 Hz). IR, ν/cm^{-1}: 3280 (NH), 1680 (C=O), 1670 (C=N), 1635 (C=C), 1620 (C=C). Found (%): C, 70.44; H, 9.14; N, 9.77. $C_{17}H_{26}N_2O_2$. Calculated (%): C, 70.31; H, 9.02; N, 9.65.

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Received June, 29 2009;
in revised form January, 15 2009