Chemistry of Heterocyclic Compounds, Vol. 46, No. 1, 2010

SYNTHESIS OF NEW HETEROCYCLIC DERIVATIVES OF 2-IMINO-2,5-DIHYDRO-FURANS AND SOME OF THEIR CHEMICAL TRANSFORMATIONS

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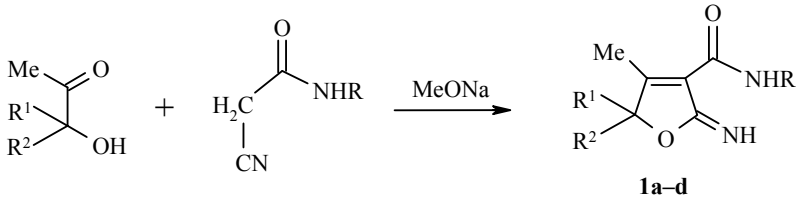
New heterocyclic derivatives of 2-imino-2,5-dihydrofurans were synthesized by the reaction of tertiary α-keto alcohols with the substituted amides of cyanoacetic acid. Some of their chemical transformations were realized.

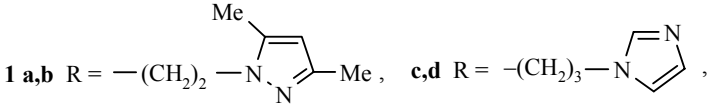
Keywords: 2,5-dihydrofuran-2-one, dicyanomethylene derivatives, 2-imino-2,5-dihydrofuran, malononitrile, tertiary α-keto alcohol.

Functionally substituted 2-imino-2,5-dihydrofurans [1] and 2,5-dihydrofuran-2-ones [2-5] are of theoretical and practical interest and are promising classes of heterocyclic compounds. Consequently their dedicated synthesis is a task of immediate interest.

In order to synthesize new functionally substituted 2-imino-2,5-dihydrofurans and 2,5-dihydrofuran-2-ones and to seek biologically active compounds among the synthesized structures and their derivatives we prepared new heterocyclic derivatives of 2-imino-2,5-dihydrofurans. For these investigations we used a method that we had developed earlier [1], involving the condensation of tertiary α-keto alcohols with the substituted



1a–d



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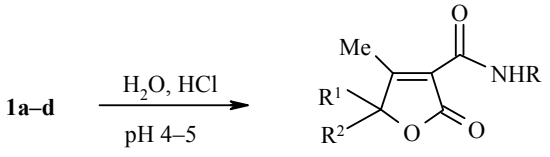
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 19-24, January, 2010. Original article submitted June 11, 2009.

TABLE 1. The Physicochemical Characteristics of Compounds **1-4**

Com-pound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f	Yield,%
		C	H	N			
1a	$C_{15}H_{22}N_4O_2$	62.21 / 62.05	7.68 / 7.64	19.36 / 19.30	114-115	0.55	90
1b	$C_{18}H_{26}N_4O_2$	65.54 / 65.43	7.99 / 7.93	16.94 / 16.95	139-140	0.54	89
1c	$C_{14}H_{20}N_4O_2$	60.88 / 60.85	7.34 / 7.29	20.32 / 20.26	121-122	0.56	94
1d	$C_{17}H_{24}N_4O_2$	64.61 / 64.53	7.55 / 7.65	17.74 / 17.71	146-147	0.52	92
2a	$C_{15}H_{21}N_3O_3$	61.95 / 61.83	7.34 / 7.26	14.54 / 14.42	128-130	0.53	72
2b	$C_{18}H_{25}N_3O_3$	65.44 / 65.23	7.69 / 7.60	12.74 / 12.68	148-150	0.53	70
2c	$C_{14}H_{19}N_3O_3$	60.69 / 60.63	6.97 / 6.91	15.19 / 15.15	50-52	0.51	72
2d	$C_{17}H_{23}N_3O_3$	64.31 / 64.33	7.41 / 7.30	13.28 / 13.24	87-89	0.52	70
3a	$C_{15}H_{22}N_4O_2 \cdot 2HCl$	49.64 / 49.59	6.68 / 6.65	15.44 / 15.42	208-212	0.53	95
3b	$C_{18}H_{26}N_4O_2 \cdot 2HCl$	53.69 / 53.60	6.95 / 6.99	13.95 / 13.89	180-185	0.54	95
3c	$C_{14}H_{20}N_4O_2 \cdot 2HCl$	48.21 / 48.15	6.44 / 6.35	16.16 / 16.04	240-245	0.54	94
3d	$C_{17}H_{24}N_4O_2 \cdot 2HCl$	52.79 / 52.45	6.34 / 6.73	14.54 / 14.39	222-226	0.51	93
4a	$C_{18}H_{21}N_5O_2$	63.79 / 63.70	6.44 / 6.24	20.74 / 20.63	186-187	0.53	90
4b	$C_{21}H_{25}N_5O_2$	66.54 / 66.47	6.79 / 6.64	18.64 / 18.46	183-184	0.54	90
4c	$C_{17}H_{19}N_5O_2$	62.79 / 62.75	5.94 / 5.88	21.64 / 21.52	182-183	0.55	94

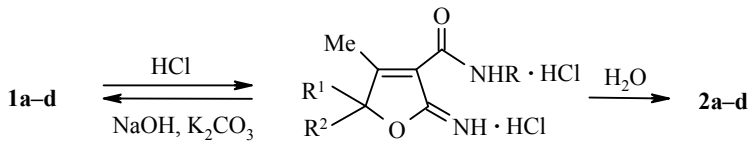
amides of cyanoacetic acid. It was established that the reaction of equimolar amounts of the tertiary α-keto alcohol and the substituted amide of cyanoacetic acid in absolute methanol at 40°C for 5 h leads to high yields of 5,5-dialkyl-2-imino-3-carbamoyl-4-methyl-2,5-dihydrofurans **1a-d**.

The synthesized 2-imino-2,5-dihydrofurans **1a-d** are easily hydrolyzed in a weakly acidic medium (pH 4-5) by heating at 85-90°C for 3 h, and this leads to the corresponding 2,5-dihydrofuran-2-ones **2a-d** (Table 1). This can be considered a method for the production of functionally substituted 2,5-dihydrofuran-2-ones.



2a–d

2-Imino-2,5-dihydrofurans **1a-d** are converted readily and with quantitative yields into the corresponding hydrochlorides **3a-d** when gaseous HCl is passed through a benzene solution. The obtained salts are titrated with a 0.1 N solution of NaOH and are easily converted into the initial 2-imino derivatives **1a-d** when treated with a solution of potash.



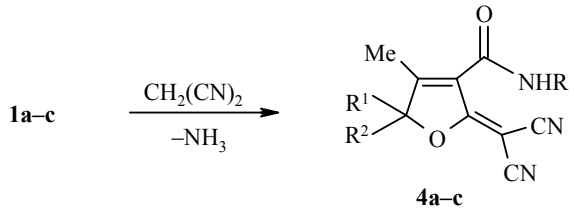
3a–d

TABLE 2. The IR Spectra of Compounds **1**, **2**, and **4**

Compound	ν, cm^{-1}
1a	3360 (NH), 3180 (NH), 1680 (C=O), 1675 (C=N), 1665 (C=N), 1625 (C=C), 1620 (C=C)
1b	3360 (NH), 3180 (NH), 1680 (C=O), 1670 (C=N), 1660 (C=N), 1628 (C=C), 1620 (C=C)
1c	3360 (NH), 3180 (NH), 1680 (C=O), 1675 (C=N), 1665 (C=N), 1625 (C=C), 1620 (C=C)
1d	3360 (NH), 3180 (NH), 1680 (C=O), 1670 (C=N), 1660 (C=N), 1628 (C=C), 1620 (C=C)
2a	3280 (NH), 1760 (C=O), 1680 (C=O), 1660 (C=N), 1625 (C=C), 1620 (C=C)
2b	3280 (NH), 1770 (C=O), 1680 (C=O), 1660 (C=N), 1625 (C=C), 1620 (C=C)
2c	3280 (NH), 1760 (C=O), 1680 (C=O), 1660 (C=N), 1625 (C=C), 1620 (C=C)
2d	3280 (NH), 1770 (C=O), 1680 (C=O), 1660 (C=N), 1625 (C=C), 1620 (C=C)
4a	3280 (NH), 2219 (CN), 1680 (C=O), 1635 (C=C), 1620 (C=C)
4b	3280 (NH), 2219 (CN), 1680 (C=O), 1635 (C=C), 1620 (C=C)
4c	3280 (NH), 2219 (CN), 1680 (C=O), 1635 (C=C), 1620 (C=C)

Hydrolysis of the hydrochlorides **3a-d** at 85-90°C for 2 h leads to 2,5-dihydrofuran-2-ones **2a-d**.

The reaction of the 2-imino derivatives **1a-c** with malononitrile was studied in order to obtain dicyanomethylene derivatives containing chromophoric groups. The reaction takes place at room temperature when equimolar amounts of the initial reagents are mixed and leads to the formation of the corresponding 2-dicyanomethylene-2,5-dihydrofurans **4a-c** with quantitative yields. (The end of the reaction is determined by the end of the release of ammonia.)



4a–c

The structure of the synthesized compounds was proved by data from the IR and ^{1}H NMR spectra and elemental analysis (Tables 2, 3, and 1).

The obtained compounds **1a-d** – **4a-c** were tested for antibacterial activity. As shown by investigations conducted at the chemotherapy laboratory, A. L. Mndzhoyan Institute of Fine Organic Chemistry, National Academy of Sciences of the Republic of Armenia, these compounds have moderately well defined antibacterial activity *in vitro*, making it expedient to conduct further investigations in this region.

EXPERIMENTAL

The IR spectra were recorded in vaseline oil on a Specord IR-75 spectrometer. The ^{1}H NMR spectra were obtained in 1:3 DMSO-d_6–CCl_4 on a Varian Mercury 300 spectrometer (300 MHz) with TMS as internal standard. The purity of the synthesized compounds was monitored by TLC on Silufol UV-254 plates in the 1:2 acetone–benzene system with development in iodine vapor.

The physicochemical and spectral characteristics are given in Tables 1-3.

5,5-Dialkyl-3-carbamoyl-2-imino-4-methyl-2,5-dihydrofurans 1a-d. To a solution of sodium methoxide in absolute methanol (1 mmol of sodium in 20 ml of methanol), the tertiary α-keto alcohol (10 mmol) and corresponding amide of cyanoacetic acid (10 mmol) were added. The reaction mixture was heated at 40°C for 5 h. The methanol was removed at reduced pressure. Water was added to the residue, and the precipitate was filtered off, washed with water, and recrystallized from ethanol.

TABLE 3. The ^{1}H NMR Spectra of Compounds **1a-d** – **3a-d** and **4a-c**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
1a	1.42 (6H, s, $2CH_3$); 2.11 (3H, s, CH_3 pyrazole); 2.22 (3H, s, CH_3 pyrazole); 2.37 (3H, s, CH_3C=C); 3.59 (2H, q, *J* = 6.6, $NHC\underline{H}_2$); 4.03 (2H, t, *J* = 6.6, $NHCH_2C\underline{H}_2$); 5.65 (1H, s, H-4 pyrazole); 7.23 (1H, s, =NH); 9.55 (1H, t, *J* = 6.6, $N\underline{H}CH_2$)
1b	1.27 (1H, m), 1.47 (2H, m) and 1.58-1.82 (7H, m, C_5H_{10}); 2.12 (3H, s, CH_3 pyrazole); 2.24 (3H, s, CH_3 pyrazole); 2.33 (3H, s, $C\underline{H}_3C$=C); 3.59 (2H, q, *J* = 6.6, $NHC\underline{H}_2$); 4.03 (2H, t, *J* = 6.6, $NHCH_2C\underline{H}_2$); 5.66 (1H, s, H-4 pyrazole); 7.23 (1H, s, =NH); 9.55 (1H, t, *J* = 6.6, $N\underline{H}CH_2$)
1c	1.42 (6H, s, $2CH_3$); 1.92-2.04 (2H, m, $NHCH_2C\underline{H}_2CH_2$); 2.35 (3H, s, CH_3); 3.25 (2H, q, *J* = 6.6, $NHC\underline{H}_2$); 4.04 (2H, t, *J* = 6.6, $NHCH_2CH_2C\underline{H}_2$); 6.82 (1H, s, H-5 imidazole); 7.0 (1H, s, H-4 imidazole); 7.28 (1H, s, =NH); 7.45 (1H, s, H-2 imidazole); 9.58 (1H, t, *J* = 6.6, $N\underline{H}CH_2$)
1d	1.27 (1H, m), 1.47 (2H, m) and 1.58-1.82 (7H, m, C_5H_{10}); 1.92-2.04 (2H, m, $NHCH_2C\underline{H}_2CH_2$); 2.35 (3H, s, CH_3); 3.15 (2H, q, *J* = 6.6, $NHC\underline{H}_2$); 4.04 (2H, t, *J* = 6.6, $NHCH_2CH_2C\underline{H}_2$); 6.82 (1H, s, H-5 imidazole); 7.0 (1H, s, H-4 imidazole); 7.28 (1H, s, =NH); 7.45 (1H, s, H-2 imidazole); 9.55 (1H, s, $N\underline{H}CH_2$)
2a	1.42 (6H, s, $2CH_3$); 2.11 (3H, s, CH_3 pyrazole); 2.22 (3H, s, CH_3 pyrazole); 2.37 (3H, s, CH_3C=C); 3.59 (2H, q, *J* = 6.6, $NHC\underline{H}_2$); 4.03 (2H, t, *J* = 6.6, $NHCH_2C\underline{H}_2$); 5.65 (1H, s, H-4 pyrazole); 9.55 (1H, t, *J* = 6.6, $N\underline{H}CH_2$)
2b	1.27 (1H, m), 1.47 (2H, m) and 1.58-1.83 (7H, m, C_5H_{10}); 2.12 (3H, s, CH_3 pyrazole); 2.24 (3H, s, CH_3 pyrazole); 2.33 (3H, s, CH_3C=C); 3.59 (2H, q, *J* = 6.6, $NHC\underline{H}_2$); 4.03 (2H, t, *J* = 6.6, $NHCH_2C\underline{H}_2$); 5.65 (1H, s, H-4 pyrazole); 9.55 (1H, t, *J* = 6.6, $N\underline{H}CH_2$)
2c	1.42 (6H, s, $2CH_3$); 1.92-2.04 (2H, m, $NHCH_2C\underline{H}_2CH_2$); 2.35 (3H, s, CH_3); 3.25 (2H, q, *J* = 6.6, $NHC\underline{H}_2$); 4.04 (2H, t, *J* = 6.6, $NHCH_2CH_2C\underline{H}_2$); 6.82 (1H, s, H-5 imidazole); 7.0 (1H, s, H-4 imidazole); 7.45 (1H, s, H-2 imidazole); 9.55 (1H, t, *J* = 6.6, $N\underline{H}CH_2$)
2d	1.27 (1H, m), 1.45 (2H, m) and 1.58-1.82 (7H, m, C_5H_{10}); 1.92-2.04 (2H, m, $NHCH_2C\underline{H}_2CH_2$); 2.35 (3H, s, CH_3); 3.15 (2H, q, *J* = 6.6, $NHC\underline{H}_2$); 4.04 (2H, t, *J* = 6.6, $NHCH_2CH_2C\underline{H}_2$); 6.82 (1H, s, H-5 imidazole); 7.01 (1H, s, H-4 imidazole); 7.45 (1H, s, H-2 imidazole); 9.55 (1H, s, $N\underline{H}CH_2$)
3a	1.42 (6H, s, $2CH_3$); 2.11 (3H, s, CH_3 pyrazole); 2.22 (3H, s, CH_3 pyrazole); 2.37 (3H, s, CH_3C=C); 3.59 (2H, q, *J* = 6.6, $NHC\underline{H}_2$); 4.05 (2H, t, *J* = 6.6, $NHCH_2C\underline{H}_2$); 5.65 (1H, s, H-4 pyrazole); 9.55 (1H, t, *J* = 6.6, $N\underline{H}CH_2$); 10.34 (2H, br. s, NH·HCl); 11.25 (1H, br. s, N·HCl)
3b	1.27 (1H, m), 1.47 (2H, m) and 1.58-1.81 (7H, m, C_5H_{10}); 2.12 (3H, s, CH_3 pyrazole); 2.24 (3H, s, CH_3 pyrazole); 2.36 (3H, s, CH_3C=C); 3.58 (2H, q, *J* = 6.6, $NHC\underline{H}_2$); 4.04 (2H, t, *J* = 6.6, $NHCH_2C\underline{H}_2$); 5.65 (1H, s, H-4 pyrazole); 9.55 (1H, t, *J* = 6.6, $N\underline{H}CH_2$); 10.32 (2H, br. s, NH·HCl); 11.23 (1H, br. s, N·HCl)
3c	1.43 (6H, s, $2CH_3$); 1.92-2.04 (2H, m, $NHCH_2C\underline{H}_2CH_2$); 2.35 (3H, s, CH_3); 3.25 (2H, q, *J* = 6.6, $NHC\underline{H}_2$); 4.05 (2H, t, *J* = 6.6, $NHCH_2CH_2C\underline{H}_2$); 6.82 (1H, s, H-5 imidazole); 7.00 (1H, s, H-4 imidazole); 7.43 (1H, s, H-2 imidazole); 9.56 (1H, t, *J* = 6.6, $N\underline{H}CH_2$); 10.35 (2H, br. s, NH·HCl); 11.26 (1H, br. s, N·HCl)
3d	1.28 (1H, m), 1.49 (2H, m) and 1.58-1.82 (7H, m, C_5H_{10}); 1.92-2.04 (2H, m, $NHCH_2C\underline{H}_2CH_2$); 2.33 (3H, s, CH_3); 3.16 (2H, q, *J* = 6.6, $NHC\underline{H}_2$); 4.04 (2H, t, *J* = 6.6, $NHCH_2CH_2C\underline{H}_2$); 6.83 (1H, s, H-5 imidazole); 7.02 (1H, s, H-4 imidazole); 7.46 (1H, s, H-2 imidazole); 9.56 (1H, t, *J* = 6.6, $N\underline{H}CH_2$); 10.34 (2H, br. s, NH· HCl); 11.28 (1H, br. s, N·HCl)
4a	1.42 (6H, s, $2CH_3$); 2.11 (3H, s, CH_3 pyrazole); 2.22 (3H, s, CH_3 pyrazole); 2.38 (3H, s, CH_3C=C); 3.58 (2H, q, *J* = 6.6, $NHC\underline{H}_2$); 4.04 (2H, t, *J* = 6.6, $NHCH_2C\underline{H}_2$); 5.65 (1H, s, H-4 pyrazole); 9.66 (1H, t, *J* = 6.6, $N\underline{H}CH_2$)
4b	1.28 (1H, m), 1.48 (2H, m) and 1.59-1.84 (7H, m, C_5H_{10}); 2.14 (3H, s, CH_3 pyrazole); 2.24 (3H, s, CH_3 pyrazole); 2.34 (3H, s, CH_3C=C); 3.58 (2H, q, *J* = 6.6, $NHC\underline{H}_2$); 4.04 (2H, t, *J* = 6.6, $NHCH_2C\underline{H}_2$); 5.64 (1H, s, H-4 pyrazole); 9.58 (1H, t, *J* = 6.6, $N\underline{H}CH_2$)
4c	1.44 (6H, s, $2CH_3$); 1.96-2.08 (2H, m, $NHCH_2C\underline{H}_2CH_2$); 2.37 (3H, s, CH_3); 3.26 (2H, q, *J* = 6.6, $NHC\underline{H}_2$); 4.08 (2H, t, *J* = 6.6, $NHCH_2CH_2C\underline{H}_2$); 6.84 (1H, s, H-5 imidazole); 7.20 (1H, s, H-4 imidazole); 7.49 (1H, s, H-2 imidazole); 9.59 (1H, t, *J* = 6.6, $N\underline{H}CH_2$)

5,5-Dialkyl-3-carbamoyl-4-methyl-2,5-dihydrofuran-2-ones 2a-d. A mixture of 2-imino-2,5-dihydrofuran **1a-d** (1.5 mmol) and water (5 ml) was heated in the presence of hydrochloric acid (pH of medium 4-5) at 85-90°C for 3 h. The reaction mixture was cooled and extracted with ether (3×5 ml), and the extract was dried with $MgSO_4$. After distillation of the ether the residue was recrystallized from petroleum ether.

Dihydrochlorides of 5,5-Dialkyl-3-carbamoyl-2-imino-4-methyl-2,5-dihydrofurans 3a-d. Gaseous hydrogen chloride was passed through a benzene solution of 2-imino-2,5-dihydrofuran **2a-d** (2 mmol). The precipitate was filtered off, washed with ether, and dried.

Reaction of Compounds 3a-d with Potash. To an aqueous solution of the hydrochloride **3a-d** (1 mmol) we added a concentrated aqueous solution of potash to pH 7-8. The precipitate was filtered off and washed with water, and the corresponding iminolactone **1a-d** was obtained. A mixed melting test with the respective iminolactones **1a-d** did not give a melting point depression.

Hydrolysis of Compounds (3a-d). A mixture of the dihydrochloride **3a-d** (0.5 mmol) and water (5 ml) was heated at 85-90°C for 2 h. The reaction mixture was cooled and extracted with ether (3×5 ml), and the extract was dried with $MgSO_4$. The residue after distillation of the ether was recrystallized from petroleum ether. Compounds **2a-d** not differing from the previously obtained compounds in melting point were obtained.

5,5-Dialkyl-3-carbamoyl-2-dicyanomethylene-4-methyl-2,5-dihydrofurans 4a-c. A mixture of the compound **1a-c** (2.5 mmol), malononitrile (0.17 g, 2.5 mmol), and absolute ethanol (5 ml) was stirred at room temperature until the release of ammonia had stopped. Water was added to the residue after removal of the solvent, and the precipitate was filtered off, washed with water, and recrystallized from a 2:1 mixture of ethanol and water.

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