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Synthesis of New Unsaturated Derivatives of Functionally Substituted 2-Imino-2,5-dihydrofurans

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Abstract—5,5-Substituted 2-imino-4-methyl-2,5-dihydrofuran-3-carbonitriles reacted with aromatic aldehydes to give the corresponding 5,5-substituted 2-imino-4-(2-R-vinyl)-2,5-dihydrofuran-3-carbonitriles. The latter were converted into hydrochlorides which were hydrolyzed to 3-cyano-4-(2-R-vinyl)-2,5-dihydrofuran-2-ones whose condensation with malononitrile afforded dicyanomethylidene derivatives.

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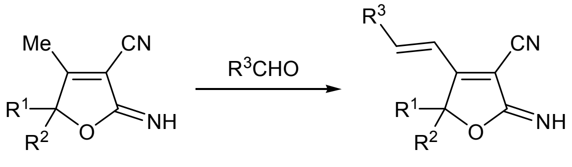
It is known that compounds containing an unsaturated lactone ring exhibit a broad spectrum of biological activity [1–3]. On the other hand, biological activity of *γ*-lactones also depends on the nature of substituents in the lactone ring. We previously reported on the lability of hydrogen atoms in the methyl group at the endocyclic double bond of Δ^3-butenolides in cyanoethylation [4] and condensation with various aromatic aldehydes [5, 6].

In continuation of our studies in the field of synthesis of new functionally substituted 2,5-dihydrofurans, the present article reports on the reaction of 2-imino-4-methyl-2,5-dihydrofuran-3-carbonitriles with aromatic aldehydes. The condensation involved labile hydrogen atoms in the methyl group in position *4* of the ring. Optimal conditions for this reaction were found. The best results were obtained at a reactant ratio of 1 : 1 in an alcoholic solution of sodium hydroxide. The products were the corresponding 4-styryl- and 4-(2-furylvinyl)-2-imino-2,5-dihydrofuran-3-carbonitriles **Ia**–**Id** and **IIa**–**IId** (Scheme 1).

Scheme 1.

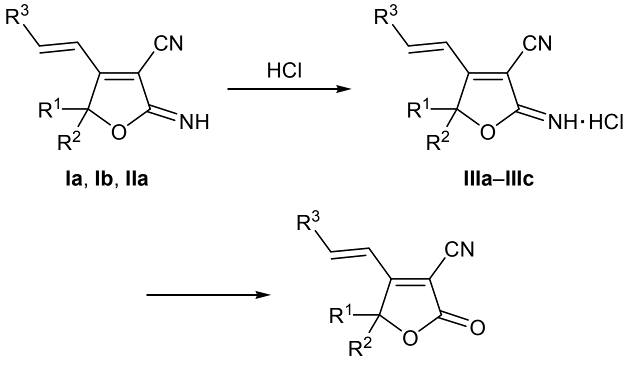


Ia–**Id**, **IIa**–**IId**

$R^1R^2 = (CH_2)_5$ (**a**); $R^1 = R^2 = Me$ (**b**); $R^1 = Me$, $R^2 = Et$ (**c**), Ph (**d**); **I**, $R^3 = Ph$; **II**, R = 2-furyl.

2-Imino derivatives **Ia**–**Id** and **IIa**–**IId** are reactive compounds. They readily form salts with acids. By passing gaseous hydrogen chloride through solutions of compounds **Ia**, **Ib**, and **IIa** in benzene we obtained the corresponding hydrochlorides **IIIa**–**IIIc** in quantitative yield (Scheme 2). Hydrochlorides **IIIa**–**IIIc** readily underwent hydrolysis in water at 70–80°C (reaction time 3 h) to give lactones **IVa**–**IVc**.

Scheme 2.



Ia, **Ib**, **IIa** **IIIa**–**IIIc** **IVa**–**IVc**

$R^1R^2 = (CH_2)_5$, $R^3 = Ph$ (**a**), 2-furyl (**b**); $R^1 = R^2 = Me$, $R^3 = Ph$ (**d**).

4-Substituted 2-imino-2,5-dihydrofuran-3-carbonitriles **Ia**, **Ib**, **IIa**, and **IIb** were brought into reaction with malononitrile. Under the optimal conditions (equimolar amounts of the reactants, room tempera-

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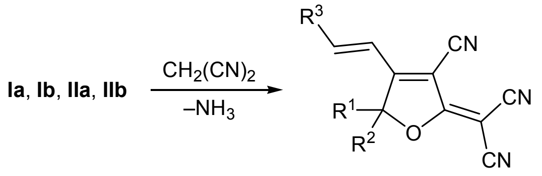
[†] Deceased.

ture), the corresponding 2-dicyanomethylidene derivatives **Va–Vd** were obtained in good yields (Scheme 3).

Scheme 3.



Va–Vd

$R^1R^2 = (CH_2)_5$, R^3 = Ph (**a**), 2-furyl (**b**); $R^1 = R^2$ = Me, R^3 = Ph (**c**), 2-furyl (**d**).

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Varian Mercury-300 spectrometer at 300 MHz using $CDCl_3$ as solvent and hexamethyldisiloxane as internal reference.

5,5-Substituted 2-imino-4-(2-*R*-vinyl)-2,5-dihydrofuran-3-carbonitriles Ia–Id and IIa–IId (*general procedure*). The corresponding 5,5-substituted 2-imino-4-methyl-2,5-dihydrofuran-3-carbonitrile, 5 mmol, and aldehyde, 5 mmol, were added to a solution of 0.01 g of sodium hydroxide in 20 ml of anhydrous ethanol. The mixture was heated for 4 h under reflux. The solvent was distilled off, the residue was treated with ice water, and the precipitate was filtered off, washed with water, dried, and recrystallized from diethyl ether–petroleum ether (1 : 4).

2-Imino-5,5-pentamethylene-4-(2-phenylvinyl)-2,5-dihydrofuran-3-carbonitrile (Ia). Yield 87%, mp 164–166°C. IR spectrum, ν, cm^{-1}: 3280, 3050, 2965, 2230, 1665, 1600, 1490, 1445, 1380, 1365, 1290, 1245, 1136, 1098, 985, 905, 865, 850, 765, 695. ^{1}H NMR spectrum, δ, ppm: 1.22–1.28 m (2H, CH_2), 1.50–1.63 m (2H, CH_2), 1.67–1.90 m (6H, CH_2), 6.15 d and 6.32 d (1H each, CH=CH, J = 16 Hz), 7.10–7.28 m (5H, H_{arom}), 10.8 s (1H, NH), Found, %: C 77.82; H 6.15; N 10.12. $C_{18}H_{18}N_2O$. Calculated, %: C 77.69; H 6.47; N 10.07.

2-Imino-5,5-dimethyl-4-(2-phenylvinyl)-2,5-dihydrofuran-3-carbonitrile (Ib). Yield 72%, mp 107–108°C. IR spectrum, ν, cm^{-1}: 3282, 3053, 2913, 2850, 2229, 1660, 1610, 1494, 1450, 1380, 1345, 1255, 1136, 1092, 985, 904, 832, 596. ^{1}H NMR spectrum, δ, ppm: 1.62 s (6H, CH_3), 6.18 d and 6.52 d (1H each, CH=CH, J = 16.1 Hz), 7.25–7.35 m (5H, H_{arom}), 10.50 s (1H, NH). Found, %: C 75.53; H 5.68; N 11.46. $C_{15}H_{14}N_2O$. Calculated, %: C 75.63; H 5.88; N 11.76.

5-Ethyl-2-imino-5-methyl-4-(2-phenylvinyl)-2,5-dihydrofuran-3-carbonitrile (Ic). Yield 84%, mp 117–119°C. ^{1}H NMR spectrum, δ, ppm: 0.85 t (3H, $CH_2\mathbf{CH_3}$, J = 7.5 Hz), 1.45 s (3H, CH_3), 1.78–1.83 m (2H, $\mathbf{CH_2}CH_3$), 6.15 d and 6.48 d (1H each, CH=CH, J = 16.3 Hz), 7.18–7.24 m (5H, H_{arom}), 10.55 s (1H, NH). Found, %: C 76.09; H 6.45; N 11.14. $C_{16}H_{16}N_2O$. Calculated, %: C 76.19; H 6.35; N 11.11.

2-Imino-5-methyl-5-phenyl-4-(2-phenylvinyl)-2,5-dihydrofuran-3-carbonitrile (Id). Yield 80%, mp 120–122°C. IR spectrum, ν, cm^{-1}: 3280, 3052, 2910, 2848, 2230, 1660, 1615, 1492, 1450, 1385, 1342, 1250, 1135, 1090, 986, 907, 835, 595. ^{1}H NMR spectrum, δ, ppm: 1.63 s (3H, CH_3), 6.08 d and 6.35 d (1H each, CH=CH, J = 16.2 Hz), 7.12–7.35 m (5H, H_{arom}), 7.42–7.55 m (5H, H_{arom}), 10.35 s (1H, NH). Found, %: C 79.80; H 5.45; N 9.13. $C_{20}H_{16}N_2O$. Calculated, %: C 80; H 5.33; N 9.33.

4-[2-(2-Furyl)vinyl]-2-imino-5,5-pentamethylene-2,5-dihydrofuran-3-carbonitrile (IIa). Yield 88%, mp 162–163°C. ^{1}H NMR spectrum, δ, ppm: 1.20–1.25 m (2H, CH_2), 1.48–1.55 m (2H, CH_2), 1.63–1.90 m (6H, CH_2), 6.17 d and 6.33 d (1H each, CH=CH, J = 16.1 Hz), 7.60–7.75 m (3H, furan), 10.70 s (1H, NH). Found, %: C 70.62; H 6.07; N 9.72. $C_{16}H_{16}N_2O_2$. Calculated, %: C 71.64; H 5.97; N 10.45.

4-[2-(2-Furyl)vinyl]-2-imino-5,5-dimethyl-2,5-dihydrofuran-3-carbonitrile (IIb). Yield 77%, mp 123–124°C. IR spectrum, ν, cm^{-1}: 3284, 3050, 2972, 2234, 1649, 1612, 1494, 1452, 1380, 1345, 1256, 1136, 1090, 985, 835, 598. ^{1}H NMR spectrum, δ, ppm: 1.65 s (6H, CH_3), 6.25 d and 6.52 d (1H each, CH=CH, J = 16.5 Hz), 7.48–7.67 m (3H, furan), 10.50 s (1H, NH). Found, %: C 67.98; H 5.02; N 12.32. $C_{13}H_{12}N_2O_2$. Calculated, %: C 68.42; H 5.26; N 12.28.

5-Ethyl-4-[2-(2-furyl)vinyl]-2-imino-5-methyl-2,5-dihydrofuran-3-carbonitrile (IIc). Yield 86%, mp 112–114°C. ^{1}H NMR spectrum, δ, ppm: 0.86 t (3H, $CH_2\mathbf{CH_3}$, J = 7.4 Hz), 1.50 s (3H, CH_3), 1.75–1.84 m (2H, $\mathbf{CH_2}CH_3$), 6.21 d and 6.52 d (1H each, CH=CH, J = 16.3 Hz), 7.52–7.69 m (3H, furan), 10.82 s (1H, NH). Found, %: C 69.03; H 5.21; N 11.26. $C_{14}H_{14}N_2O_2$. Calculated, %: C 69.42; H 5.79; N 11.57.

4-[2-(2-Furyl)vinyl]-2-imino-5-methyl-5-phenyl-2,5-dihydrofuran-3-carbonitrile (IId). Yield 83%, mp 105–107°C. ^{1}H NMR spectrum, δ, ppm: 1.62 s (3H, CH_3), 6.10 d and 6.38 d (1H each, CH=CH, J = 16.1 Hz), 6.95–7.15 m (5H, H_{arom}), 7.45–7.58 m (3H, furan), 10.75 s (1H, NH). Found, %: C 74.65; H 4.72; N 9.69. $C_{16}H_{19}N_2O_2$. Calculated, %: C 74.48; H 4.83; N 9.66.

5,5-Substituted 2-imino-4-(2-*R*-vinyl)-2,5-dihydrofuran-3-carbonitrile hydrochlorides IIIa–IIIc (*general procedure*). Gaseous hydrogen chloride was passed through a solution of 2.5 mmol of compound **Ia**, **Ib**, or **IIa** in benzene. The precipitate was filtered off, washed with anhydrous benzene, and dried.

2-Imino-5,5-pentamethylene-4-(2-phenylvinyl)-2,5-dihydrofuran-3-carbonitrile hydrochloride (IIIa). Yield 92%, mp 170–172°C. Found, %: C 68.32; H 6.15; Cl 11.36; N 8.63. $C_{18}H_{19}ClN_2O$. Calculated, %: C 68.68; H 6.04; Cl 11.28; N 8.90.

4-[2-(2-Furyl)vinyl]-2-imino-5,5-pentamethylene-2,5-dihydrofuran-3-carbonitrile hydrochloride (IIIb). Yield 94%, mp 208–210°C. Found, %: C 63.21; H 5.35; Cl 11.59; N 9.16. $C_{16}H_{17}ClN_2O_2$. Calculated, %: C 63.05; H 5.58; Cl 11.66; N 9.19.

2-Imino-5,5-dimethyl-4-(2-phenylvinyl)-2,5-dihydrofuran-3-carbonitrile hydrochloride (IIIc). Yield 91%, mp 145–147°C. Found, %: C 65.42; H 5.37; Cl 12.89; N 10.12. $C_{15}H_{15}ClN_2O$. Calculated, %: C 65.57; H 5.46; Cl 12.93; N 10.2.

5,5-Substituted 3-cyano-4-(2-*R*-vinyl)-2,5-dihydrofuran-2-ones IVa–IVc (*general procedure*). A mixture of 0.01 mol of compound **IIIa–IIIc** and 8 ml of water was heated for 3 h on a water bath. The precipitate was filtered off and recrystallized from aqueous ethanol (1:1).

3-Cyano-5,5-pentamethylene-4-(2-phenylvinyl)-2,5-dihydrofuran-2-one (IVa). Yield 72%, mp 220–222°C. IR spectrum, ν, cm^{-1}: 2935, 2860, 1735, 1662, 1490, 1445, 1380, 1204, 1120, 985, 945, 860, 795. ^{1}H NMR spectrum, δ, ppm: 1.18–1.23 m (2H, CH_2), 1.48–1.60 m (2H, CH_2), 1.65–1.85 m (6H, CH_2), 6.10 d and 6.28 d (1H each, CH=CH, J = 16.1 Hz), 7.18–7.32 m (5H, H_{arom}). Found, %: C 77.31; H 6.18; N 5.21. $C_{18}H_{17}NO_2$. Calculated, %: C 77.42; H 6.09; N 5.02.

3-Cyano-4-[2-(2-furyl)vinyl]-5,5-pentamethylene-2,5-dihydrofuran-2-one (IVb). Yield 75%, mp 126–128°C. ^{1}H NMR spectrum, δ, ppm: 1.20–1.26 m (2H, CH_2), 1.52–1.63 m (2H, CH_2), 1.65–1.87 m (6H, CH_2), 6.18 d and 6.4 d (1H each, CH=CH, J = 16.4 Hz), 7.58–7.65 m (3H, furan). Found, %: C 71.22; H 5.14; N 5.31. $C_{16}H_{15}NO_3$. Calculated, %: C 71.38; H 5.58; N 5.20.

3-Cyano-5,5-dimethyl-4-(2-phenylvinyl)-2,5-dihydrofuran-2-one (IVc). Yield 68%, mp 175–177°C; published data [6]: mp 176–178°C. ^{1}H NMR spectrum, δ, ppm: 1.60 s (6H, CH_3), 6.15 d and 6.30 d (1H each, CH=CH, J = 16.1 Hz), 7.32–7.40 m (5H, H_{arom}). Found, %: C 75.71; H 5.88; N 5.71. $C_{15}H_{13}NO_2$. Calculated, %: C 75.31; H 5.44; N 5.86.

2-[3-Cyano-4-(2-*R*-vinyl)-2,5-dihydrofuran-2-ylidene]malononitriles Va–Vd (*general procedure*). A mixture of 0.01 mol of compound **Ia**, **Ib**, **IIa**, or **IIb** and 0.66 g (0.01 mol) of malononitrile in 10 ml of anhydrous ethanol was kept for 20 h at room temperature. The solvent was partially distilled off under reduced pressure, and the precipitate was filtered off and recrystallized from ethanol–water (2:1).

2-[3-Cyano-5,5-pentamethylene-4-(2-phenylvinyl)-2,5-dihydrofuran-2-ylidene]malononitrile (Va). Yield 74%, mp 224–226°C. ^{1}H NMR spectrum, δ, ppm: 1.22–1.28 m (2H, CH_2), 1.45–1.54 m (2H, CH_2), 1.62–1.80 m (6H, CH_2), 6.20 d and 6.45 d (1H each, CH=CH, J = 16.3 Hz), 7.15–7.40 m (5H, H_{arom}). Found, %: C 77.16; H 5.29; N 12.64. $C_{21}H_{17}N_3O$. Calculated, %: C 77.86; H 5.19; N 12.84.

2-{3-Cyano-4-[2-(2-furyl)vinyl]-5,5-pentamethylene-2,5-dihydrofuran-2-ylidene}malononitrile (Vb). Yield 72%, mp 315–317°C. ^{1}H NMR spectrum, δ, ppm: 1.25–1.30 m (2H, CH_2), 1.40–1.52 m (2H, CH_2), 1.60–1.76 m (6H, CH_2), 6.20 d and 6.45 d (1H each, CH=CH, J = 16.2 Hz), 7.50–7.70 m (3H, furan). Found, %: C 71.12; H 4.21; N 13.08. $C_{19}H_{15}N_3O_2$. Calculated, %: C 71.92; H 4.73; N 13.25.

2-[3-Cyano-5,5-dimethyl-4-(2-phenylvinyl)-2,5-dihydrofuran-2-ylidene]malononitrile (Vc). Yield 70%, mp 238–240°C. IR spectrum, ν, cm^{-1}: 3285, 3056, 2975, 2237, 1650, 1615, 1495, 1453, 1382, 1350, 1255, 1135, 1092, 985, 832, 596. ^{1}H NMR spectrum, δ, ppm: 1.67 s (6H, CH_3), 6.30 d and 6.48 d (1H each, CH=CH, J = 16.5 Hz), 7.30–7.50 m (5H, H_{arom}). Found, %: C 75.01; H 4.32; N 14.74. $C_{18}H_{13}N_3O$. Calculated, %: C 75.26; H 4.53; N 14.63.

2-{3-Cyano-4-[2-(2-furyl)vinyl]-5,5-dimethyl-2,5-dihydrofuran-2-ylidene}malononitrile (Vd). Yield 76%, mp 247–248°C; published data [7]: mp 245–246°C. ^{1}H NMR spectrum, δ, ppm: 1.62 s (6H, CH_3), 6.18 d and 6.48 d (1H each, CH=CH, $J = 16.3$ Hz), 7.62–7.75 m (3H, furan). Found, %: C 69.39; H 3.38; N 15.25. $C_{16}H_{11}N_3O_2$. Calculated, %: C 69.31; H 3.97; N 15.16.

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