Synthesis of new derivatives of 2-imino-2,5-dihydrofurans

**Abstract:** New N-substituted 2-imino-2,5-dihydrofurans were synthesized by using several efficient approaches starting from readily available 2-imino-2,5-dihydrofurans. All new compounds were characterized by NMR and IR spectral data and elemental analysis.

**Keywords:** acidic hydrolysis; dimethyl sulfate; iminolactone; lactone; methyl iodide; N-nucleophile.

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**Introduction**

The 2-imino-2,5-dihydrofuran structure is related to 2-oxo-2,5-dihydrofuran fragment which constitutes a part of many natural molecules, in particular, ascorbic, penicillic and tetronic acids. Introduction of aromatic substituents into iminodihydrofuran molecules may be promising from the viewpoint of improving their biological activity (Avetisyan et al., 2011a,b) and other parameters, e.g., luminescent properties which are important for creation of optoelectronic materials (Hates et al., 2000).

Synthesis of new derivatives of 2-imino-2,5-dihydrofurans (Villemin and Liao, 2001, 2003; Avetissyan and Karapetyan, 2009; Avetisyan et al., 2009a,b, 2010, Avetisyan and Karapetyan, 2010; Cheikh et al., 2011) has been of continuous interest in the development of efficient and convenient methods for preparation of various 2,5-dihydrofuran derivatives and in their synthetic applications.

To determine new synthetic capabilities of 2-imino-2,5-dihydrofuran-3-carboxamides 1a–d (Avetissyan and Karapetyan, 2009), we studied the interaction of iminolactones with primary amines which is known in coumarin series (Houben and Pfankuch, 1926; Schiemenz, 1962). Formation of salts 2a–d leads to a significant increase in electrophilicity of the carbon atom of the imino group, and this atom then easily undergoes addition with an amine molecule. The intermediate formed is stabilized by the splitting off of the ammonium salt with the formation of N-substituted 2-imino-2,5-dihydrofurans 3a–p.

N-Substituted 2-imino-2,5-dihydrofurans 3a–t were also obtained by reaction of 2-imino-2,5-dihydrofuran-3-carboxamides 1a–d with hydrochlorides of primary amines – benzaminium chloride, 4-methylbenzaminium chloride, 2-methylbenzaminium, phenylmethanaminium chloride, methanaminium chloride in ethanol (Scheme 1, route B). In this case, an equilibrium is apparently established between the base and the salt forms of 2-imino-2,5-dihydrofuran and amine, which leads to their mutual activation.

Formation of N-substituted 2-imino-2,5-dihydrofurans also takes place in the presence of sodium methoxide in methanol. Satisfactory results were obtained by route C only with aromatic amines, such as aniline, p-toluclidine and o-toluclidine. Compounds 3a–l were isolated after acidification of the solution.

2-(Methylimino)-2,5-dihydrofurans 3q–t were also obtained by reaction of 2-imino-2,5-dihydrofuran-3-carboxamides 1a–d with dimethyl sulfate in the presence of sodium carbonate (route D).

**Results and discussion**

The presence in these structures of the “iminolactone” ring, which may be regarded as a cyclic iminoester, led to the assumption that for these compounds there are possible transformations that resemble the reactions of iminoesters with N-nucleophiles (Roger and Neilson, 1961). However, interaction of 2-imino-2,5-dihydrofuran-3-carboxamides 1a–d with primary amines – aniline, p-toluclidine, o-toluclidine, phenylmethanamine in alcohols did not produce satisfactory results. By using instead of iminolactones 1a–d their hydrochlorides 2a–d, we obtained N-substituted 2-imino-2,5-dihydrofurans 3a–p in high yields (Scheme 1, route A).

The mechanism of the reaction of route A is similar to acidic hydrolysis of iminolactones to lactones which is essentially known in coumarin series (Houben and Pfankuch, 1926; Schiemenz, 1962). Formation of salts 2a–d leads to a significant increase in electrophilicity of the carbon atom of the imino group, and this atom then easily undergoes addition with an amine molecule. The intermediate formed is stabilized by the splitting off of the ammonium salt with the formation of N-substituted 2-imino-2,5-dihydrofurans 3a–p.
products anhydrous acetone. The expected methylation to give compounds were allowed to react with methyl iodide in anhydrous ethanol (10 mL) was heated under reflux for 15–20 min. The precipitate was filtered, washed with water and crystallized. The products were identical to compounds 1a–d (synthesized by route A) in melting points.

Compounds 3a–t were tested for antibacterial activity at the chemotherapy laboratory, A. L. Mndzhoyan Institute of Fine Organic Chemistry, National Academy of Sciences of the Republic of Armenia. The test strains were Gram-positive Staphilococcus aureus (209p, 1, 93) and Gram-negative Shigella dysenteriae flexneri 6858, Escherichia coli 0–55. These compounds showed a moderate antibacterial activity in vitro, making it expedient to conduct further investigations in this area.

### Experimental

All solvents were dried by standard methods. Melting points were measured with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a Specord 75 IR spectrometer with samples dispersed in mineral oil. 1H NMR and 13C NMR spectra were recorded in DMSO-d6/CCl3, (1:3) solutions on a Varian Mercury-300 VX spectrometer at 300 and 75 MHz, respectively. The purity of synthesized compounds was tested by means of thin-layer chromatography (TLC) on Silufol UV-25 plates, eluent acetone/benzene (1:2), visualization with iodine vapors.

Compounds 1a–d and 2a–d were synthesized by using a published procedure (Avetissyan and Karapetyan, 2009).

### General procedures for 3a–t

**Route A** A mixture of 2a–d (2.5 mmol) and excess of an amine in anhydrous ethanol (10 mL) was heated under reflux for 15–20 min. The precipitate was filtered, washed with water and crystallized.

**Route B** A mixture of 1a–d (2.5 mmol) and excess of an amine hydrochloride in anhydrous ethanol (10 mL) was heated under reflux for 30 min. The precipitate was filtered, washed with water and crystallized. The products were identical to compounds 3a–p (synthesized by route A) in melting points.

**Route C** A mixture of 1a–d (2.5 mmol) and excess of an arylamine and sodium methoxide (0.058 g, 2.5 mmol) in anhydrous methanol (5 mL) was heated under reflux for 30 min. The mixture was cooled and acidified to pH 6 with 20% HCl. The precipitate was filtered, washed with water and crystallized. The products were identical to compounds 3a–t (synthesized by route A and by route B) in melting points.

**Route D** To a solution of 1a–d (2 mmol) in dioxane (10 mL), conc. Na2CO3 solution (10 mL) and dimethyl sulfate (0.76 g, 6 mmol) were added. The mixture was stirred at room temperature for 5 h, then water (50 mL) was added and the stirring was continued for an additional 1 h. The precipitate was filtered, washed with water and crystallized. The products were identical to compounds 3q–t (synthesized by route B) in melting points.

### Scheme 1

![Scheme 1](image)

**Scheme 2**

In continuation of our studies on the chemistry of 2-imino-2,5-dihydrofuran-3-carboxamides 1a–d, these compounds were allowed to react with methyl iodide in anhydrous acetone. The expected methylation to give products 4a,c was observed only with compounds 1a,c. Compounds 4a,c are readily hydrolyzed with aqueous hydrochloric acid (at pH 3–4) with the formation of 2,5-dihydrofuran-2-oxo-3-carboxamides 5a,c (Scheme 2). All compounds were characterized by spectroscopic methods.

### Experimental

All solvents were dried by standard methods. Melting points were measured with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a Specord 75 IR spectrometer with samples dispersed in mineral oil. 1H NMR and 13C NMR spectra were recorded in DMSO-d6/CCl3, (1:3) solutions on a Varian Mercury-300 VX spectrometer at 300 and 75 MHz, respectively. The purity of synthesized compounds was tested by means of thin-layer chromatography (TLC) on Silufol UV-25 plates, eluent acetone/benzene (1:2), visualization with iodine vapors.

Compounds 1a–d and 2a–d were synthesized by using a published procedure (Avetissyan and Karapetyan, 2009).

### General procedures for 3a–t

**Route A** A mixture of 2a–d (2.5 mmol) and excess of an amine in anhydrous ethanol (10 mL) was heated under reflux for 15–20 min. The precipitate was filtered, washed with water and crystallized.

**Route B** A mixture of 1a–d (2.5 mmol) and excess of an amine hydrochloride in anhydrous ethanol (10 mL) was heated under reflux for 30 min. The precipitate was filtered, washed with water and crystallized. The products were identical to compounds 3a–p (synthesized by route A) in melting points.

**Route C** A mixture of 1a–d (2.5 mmol) and excess of an arylamine and sodium methoxide (0.058 g, 2.5 mmol) in anhydrous methanol (5 mL) was heated under reflux for 30 min. The mixture was cooled and acidified to pH 6 with 20% HCl. The precipitate was filtered, washed with water and crystallized. The products were identical to compounds 3a–t (synthesized by route A and by route B) in melting points.

**Route D** To a solution of 1a–d (2 mmol) in dioxane (10 mL), conc. Na2CO3 solution (10 mL) and dimethyl sulfate (0.76 g, 6 mmol) were added. The mixture was stirred at room temperature for 5 h, then water (50 mL) was added and the stirring was continued for an additional 1 h. The precipitate was filtered, washed with water and crystallized. The products were identical to compounds 3q–t (synthesized by route B) in melting points.

### Scheme 2

![Scheme 2](image)
xamide (3f)
yield 90% (route A), 89% (route B), 92% (route C); mp 123 – 124

xamide (3d)
yield 95% (route B), 92% (route C); mp 189 – 190

4-Methyl-2-(phenylimino)-1-oxaspiro[4.5]dec-3-ene-3-carboxamide (3b)
This compound was obtained as a white solid; yield 92% (route A), 92% (route B), 90% (route C); mp 208–209°C (from ethanol);
\( R_f = 0.53; \) IR: 1501–1602, 1621, 1642, 1681, 3124 cm\(^{-1}\); \( \text{H NMR:} \) \( \delta \) 1.49 (m, 1H), 1.76 (m, 2H) and 2.16–2.32 (m, 4H), 2.42 (s, 3H), 6.91 (td, \( J = 4.9 \) Hz, 6.91 (td, \( J = 4.9 \) Hz), 7.05 (td, \( J = 7.4 \) Hz, 7.05 (td, \( J = 7.4 \) Hz), 7.09 (dd, \( J = 7.4 \) Hz, 7.09 (dd, \( J = 7.4 \) Hz, 7.22 (s, 3H), 2.87 (s, 3H), 6.99 (dd, \( J = 7.4 \) Hz, 7.22 (s, 3H), 2.42 (s, 3H), 7.04 (s, 4H), 6.99 (dd, \( J = 7.4 \) Hz, 7.04 (s, 4H), 6.99 (dd, \( J = 7.4 \) Hz, 7.4 Hz), 7.05 (dd, \( J = 7.4 \) Hz, 7.05 (dd, \( J = 7.4 \) Hz, 7.4 Hz), 7.26 (bs, 1H) and 8.87 (bs, 1H); \( \text{13 C NMR:} \) \( \delta \) 12.1, 21.2, 23.9, 32.4, 88.7, 119.1, 122.3, 127.8, 130.4, 149.4, 162.4, 166.5, 170.9. Anal. Calcld for \( \text{C}_8\text{H}_8\text{N}_2\text{O}_2 \): C, 71.80; H, 7.09; N, 9.85. Found: C, 71.83; H, 7.11; N, 9.86.

4,5,5-Tetramethyl-2-(phenylimino)-1-oxaspiro[4.5]dec-3-ene-3-carboxamide (3c)
This compound was obtained as a pale yellow solid; yield 92% (route A), 95% (route B), 92% (route C); mp 208–209°C (from ethanol);
\( R_f = 0.50; \) IR: 1502–1602, 1624, 1642, 1681, 3124 cm\(^{-1}\); \( \text{H NMR:} \) \( \delta \) 1.46 (s, 6H), 2.17 (s, 3H), 2.42 (s, 3H), 6.90 (td, \( J = 7.4 \) Hz, 6.90 (dd, \( J = 7.4 \) Hz, 6.99 (dd, \( J = 4.9 \) Hz, 6.99 (dd, \( J = 4.9 \) Hz), 7.04 (s, 4H), 9.86 (q, \( J = 7.6 \) Hz); \( \text{13 C NMR:} \) \( \delta \) 11.8, 20.3, 21.2, 23.9, 32.4, 41.6, 87.7, 118.3, 122.3, 130.4, 136.9, 146.4, 162.3, 166.2, 170.8. Anal. Calcld for \( \text{C}_8\text{H}_8\text{N}_2\text{O}_2 \): C, 70.46; H, 7.76; N, 8.99.

4,5,5-Tetramethyl-2-(p-tolylimino)-1-oxaspiro[4.5]dec-3-ene-3-carboxamide (3d)
This compound was obtained as a pale yellow solid; yield 91% (route A), 93% (route B), 92% (route C); mp 125–126°C (from hexane);
\( R_f = 0.51; \) IR: 1501–1602, 1621, 1642, 1680, 3254 cm\(^{-1}\); \( \text{H NMR:} \) \( \delta \) 1.27 (m, 1H), 1.47 (m, 2H) and 1.58–1.82 (m, 7H), 9.90 (q, \( J = 7.4 \) Hz, 9.90 (q, \( J = 7.4 \) Hz), 7.04 (s, 4H), 9.86 (q, \( J = 7.4 \) Hz); \( \text{13 C NMR:} \) \( \delta \) 11.8, 20.3, 21.2, 23.9, 32.4, 41.6, 87.7, 118.3, 122.3, 130.4, 136.9, 146.4, 162.3, 166.2, 170.8. Anal. Calcld for \( \text{C}_8\text{H}_8\text{N}_2\text{O}_2 \): C, 70.46; H, 7.76; N, 8.99.
2-(Benzylimino)-4,5,5-trimethyl-2,5-dihydrofuran-3-carboxamide (3m)
This compound was obtained as a white solid; yield 90% (route A), 91% (route B); mp 113–115°C (from toluene); δ = 0.57; IR: 1502–1601, 1624, 1641, 1674, 3200 cm⁻¹; ¹H NMR: δ = 1.27 (m, 1H), 1.47 (m, 2H) and 1.58–1.82 (m, 7H), 2.35 (s, 3H), 2.82 (d, 3H, J = 4.9 Hz), 2.98 (s, 3H), 7.14 (bs, 1H) and 8.99 (bs, 1H); ¹³C NMR: δ = 11.8, 21.2, 23.9, 32.4, 41.6, 42.6, 87.6, 118.3, 125.3, 127.8, 128.4, 138.4, 160.4, 166.2, 170.8. Anal. Calcd for C₇H₁₅NO₂: C, 69.76; H, 7.03; N, 11.61.

2-Benzylinomino-N,4,5,5-tetramethyl-2,5-dihydrofuran-3-carboxamide (3n)
This compound was obtained as a pale yellow solid; yield 85% (route A), 87% (route B); mp 135–136°C (from ethanol); δ = 0.56; IR: 1502–1604, 1624, 1640, 1681, 3230 cm⁻¹; ¹H NMR: δ = 1.27 (m, 1H), 1.46 (s, 6H), 2.35 (s, 3H), 2.82 (d, 3H, J = 4.9 Hz), 4.51 (s, 2H), 7.17 (m, 1H) and 7.25–7.28 (m, 4H), 7.16 (bs, 1H) and 8.99 (bs, 1H); ¹³C NMR: δ = 11.8, 24.2, 41.5, 42.6, 87.6, 118.3, 125.3, 127.8, 128.4, 138.4, 160.4, 166.2, 170.8. Anal. Calcd for C₁₄H₂₂NO₂: C, 72.46; H, 7.43; N, 9.39.

N,4-Dimethyl-2-(benzylimino)-1-oxaspiro[4.5]dec-3-ene-3-carboxamide (3t)
This compound was obtained as a white solid; yield 88% (route B), 93% (route D); mp 118–120°C (from ethanol); δ = 0.51; IR: 1620, 1640, 1680, 3270 cm⁻¹; ¹H NMR: δ = 1.27 (m, 1H), 1.47 (m, 2H) and 1.58–1.82 (m, 7H), 2.35 (s, 3H), 2.82 (d, 3H, J = 4.9 Hz), 2.98 (s, 3H), 9.88 (q, 1H, J = 7.6 Hz); ¹³C NMR: δ = 12.0, 12.5, 21.2, 23.9, 32.4, 41.6, 87.7, 118.9, 162.3, 166.3, 170.9. Anal. Calcd for C₁₄H₁₈NO₂: C, 66.07; H, 8.53; N, 11.85. Found: C, 66.09; H, 7.42; N, 11.61.

General procedure for 4a,c
A mixture of 2a,c (2.5 mmol) and methyl iodide (0.2 mL, 3.75 mmol) in anhydrous acetone (10 mL) was stirred at room temperature for 20 h. The precipitated solid was filtered, washed with acetone and crystallized from ethanol or hexane.

N-(3-Carbamoyl-4-methyl-1-oxaspiro[4.5]dec-3-ene-3-carboxamide (5a)
This compound was obtained as a white solid; yield 71%; mp 264–266°C (from ethanol); δ = 0.57; IR: 1620, 1640, 1680, 3160, 3300 cm⁻¹; ¹H NMR: δ = 1.42 (s, 6H), 2.35 (s, 3H), 2.98 (d, 3H, J = 4.9 Hz), 7.14 (bs, 1H) and 8.99 (bs, 1H), 10.70 (bs, 1H). Anal. Calcd for C₆H₁₄NO₂: C, 34.86; H, 4.88; N, 9.03. Found: C, 34.88; H, 4.89; N, 9.04.

General procedure for 5a,c
A solution of 4a,c (2.5 mmol) in 10 mL of a mixture of ethanol/water/ 31% hydrochloric acid (30:1:v/v/v) was heated under reflux with vigorous stirring for 1 h, then cooled and extracted with diethyl ether (3×10 mL). The extract was dried with magnesium sulfate, concentrated and the residue was crystalized using a solvent indicated below.

N,4,5,5-Tetramethyl-2-(benzylimino)-2,5-dihydrofuran-3-carboxamide (3s)
This compound was obtained as a pale yellow solid; yield 89% (route B), 92% (route D); mp 207–208°C (from benzene); δ = 0.52; IR: 1621, 1645, 1678, 3128, 3264 cm⁻¹; ¹H NMR: δ = 1.27 (m, 1H), 1.47 (m, 2H) and 1.58–1.82 (m, 7H), 2.35 (s, 3H), 2.99 (s, 3H); 7.14 (bs, 1H) and 8.84 (bs, 1H); ¹³C NMR: δ = 12.1, 12.5, 21.2, 23.9, 32.4, 88.7, 119.1, 162.4, 166.4, 170.9. Anal. Calcd for C₁₈H₂₂NO₂: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.85; H, 8.18; N, 12.61.

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This compound was obtained as a white solid; yield 84%; mp 125–126°C (from octane) (Avetisyan et al., 1971).
References


