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Short Report

Synthesis of New Bis-Iminodihydrofurans

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A new synthetic pathway to new bis-iminodihydrofurans is proposed, which involves the synthesis of *N*-substituted iminodihydrofurans from reaction of iminodihydrofurans with 2-cyanoacetohydrazide and their condensation with tertiary α-hydroxyketones. This sequence of reactions opens the new approach to the synthesis of novel polyheteroconjugated systems consisting from iminodihydrofuran rings. The methodology is simple, rapid and inexpensive affording high yields of the potentially bioactive products.

Keywords: iminodihydrofurans, 2-cyanoacetohydrazide, *N*-substituted iminodihydrofurans, tertiary α-hydroxyketones, bis-iminodihydrofurans

Introduction

2-Oxo-2,5-dihydrofuran subunit has been found both in several bioactive natural (ascorbic, penicillic and tetronic acids), synthetic products[1-11] and in a number of drugs with diverse biological activities, such as antifungal, antibacterial and anti-inflammatory.[1,2,12-14]

The 2-imino-2,5-dihydrofuran structure is related to 2-oxo-2,5-dihydrofuran fragment. The synthesis, structure and reactivity of 2-imino-2,5-dihydrofurans have been studied intensively in the last decade.[15-28] Many of these compounds have antibacterial activity.[29,30] On the other hand, *N*-substituted derivatives of iminodihydrofurans have not been studied extensively.[31,32]

In continuation of our current studies on the chemistry of iminodihydrofurans (**1a**,**b**),[17] we studied their interaction with 2-cyanoacetohydrazide, which was known in coumarine series.[33] Synthesized *N*-substituted iminodihydrofurans condensed with tertiary α-hydroxyketones to give bis-iminodihydrofurans. In the literature, bis-iminodihydrofurans have been the subject of some reports.[22,34-36]

Results and Discussion

The simple and easy synthesis of a new series of bis-iminodihydrofurans **5a**-**e** begins with the preparation of *N*-substituted iminodihydrofurans **3a**,**b**. The latter were easily obtained by interaction of iminodihydrofurans **1a**,**b** with 2-cyanoacetohydrazide (**2**) at room temperature, in glacial acetic acid. Compounds **3a**,**b** exist as two (*E* and *Z)* stereoisomer types (Scheme 1).

Next, bis-iminodihydrofuran compounds **5a**-**e** were obtained, in cascade reaction, from tertiary α-hydroxyketones **4a**-**d** and *N*-substituted iminodihydrofuran derivatives **3a**,**b** in the presence of a catalytic amount of sodium methoxide in methanol. It has been used a method involving the condensation of tertiary α-hydroxyketones with *N*-(alkyl)-2-cyanoacetamides.[17]

The cyclization between the hydroxyl group of compounds **4a**-**e** and the cyano group of compounds **3a**,**b** followed by a Knoevenagel condensation afforded the bis-iminolactones **5a**-**e** in good yields (90-96%, Scheme 2). The ease of ring formation was due to the presence of a gem-dialkyl producing a Thorpe-Ingold conformational effect,[37,38] which states that alkyl substitution on a central methylene causes compression of the internal angle, that leads to an easier ring formation. The suggested mechanism is described in literature.[17]

The structures of the products were determined from their elemental analyses and spectroscopic data. Compounds **4b** and **5b** have asymmetric carbon atom. The specific rotation were measured for these compounds. They are optically inactive compounds.

Conclusions

We have developed a mild and efficient, environmentally friendly strategy for synthesis of potentially bioactive bis-iminodihydrofurans from readily available starting

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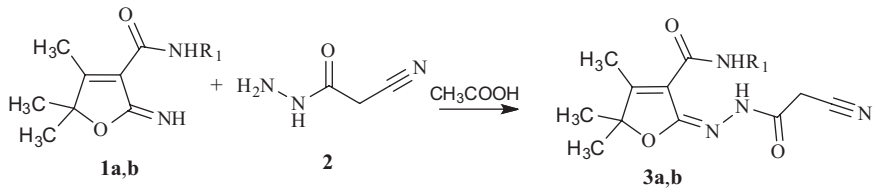
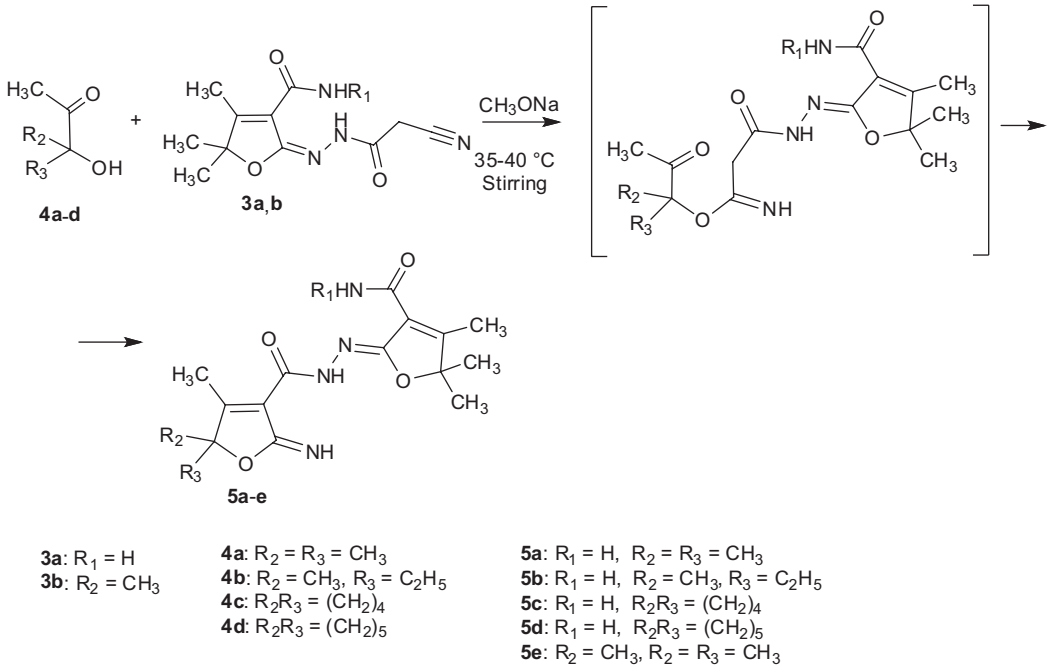


Scheme 1. Preparation of *N*-substituted iminodihydrofurans **3a**,**b**.



Scheme 2. Preparation of bis-iminodihydrofurans **5a-e**.

materials. This sequence of reactions opens a new approach to the synthesis of a novel polyheteroconjugated systems consisting from iminodihydrofuran rings. The methodology is simple, rapid and inexpensive affording high yields of the cyclized products with operational simplicity.

Experimental

All solvents were dried by standard methods. Melting points were measured on an Electrothermal 9100 apparatus (Bibby Scientific Limited, Staffordshire, UK). Elemental analyses for C, H and N were obtained using a Heraeus CHN-O-Rapid analyzer (Heraeus Holding GmbH, Hanau, Germany). Infrared (IR) spectra were recorded on a Specord 75 IR spectrometer (Analytik Jena AG, Jena, Germany). Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were recorded at 300 MHz on a Varian Mercury 300 VX spectrometer (Palo Alto, CA, USA) with dimethyl sulfoxide (DMSO)-d_6 and DMSO-d_6:carbon tetrachloride (CCl_4), 1:3 (v/v) as solvent and tetramethylsilane (TMS) as internal standard. Monitoring of the reaction course and the purity of the products was carried out by thin layer chromatography (TLC), on silufol UV254 plates, eluent acetone:benzene 1:2 (v/v) and visualized using iodine vapor. Specific optical rotation was decided on a Polartronic H532 polarimeter (Schmidt + Haensch GmbH & Co., Berlin, Germany). Tertiary α-hydoxy ketones were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used without further purification.

The starting compounds **1a**,**b** and **2** were synthesized by using a published procedure.[17,39]

General procedure for synthesis of compounds **3a**,**b**

To a well-stirred warm (40-50 °C) 10 mmol solution of 2-imino-2,5-dihydrofuran (**1a**,**b**) in 10 mL glacial acetic acid was added 2-cyanoacetohydrazide (**2**) (1 g, 10 mmol). The reaction mixture was stirred at room temperature for 2 h. The product, which precipitated in the course of the

reaction, was filtered and washed with water. Purification was performed by recrystallization.

Physical and spectral data for the synthesized compounds **3a**,**b**

2-(2-(2-Cyanoacetyl)hydrazono)-4,5,5-trimethyl-2,5-dihydrofuran-3-carboxamide (**3a**)

White solid; mp: 237-238 °C (from water); yield (2.4 g, 96%); IR ν / cm^{-1} 1620, 1640, 1680, 1685, 2220, 3250, 3280; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.48 (s, 1.8H) and 1.52 (s, 4.2H, 2CH_3), 2.32 (s, 0.9H) and 2.36 (s, 2.1H, CH_3), 3.62 (s, 1.4H) and 3.92 (s, 0.6H, CH_2), 7.34 (bs, 1H), 7.43 (bs, 0.3H) and 8.18 (bs, 0.7H, NH_2), 9.96 (s, 0.3H) and 10.64 (s, 0.7H, NH); anal. calcd. for $C_{11}H_{14}N_4O_3$ (250.26): C, 52.79; H, 5.64; N, 22.39%; found: C, 52.89; H, 5.88; N, 22.51%.

2-(2-(2-Cyanoacetyl)hydrazono)-*N*-4,5,5-tetramethyl-2,5-dihydrofuran-3-carboxamide (**3b**)

White solid; mp: 268-269 °C (from water); yield (2.51 g, 95%); IR ν / cm^{-1} 1620, 1644, 1680, 1690, 2225, 3250, 3275; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.48 (s, 1.8H) and 1.52 (s, 4.2H, 2CH_3), 2.32 (s, 0.9H) and 2.36 (s, 2.1H, CH_3), 2.75 (d, 3.3H) and 2.82 (d, 0.7H, *J* 4.9 Hz, NCH_3), 3.62 (s, 1.4H) and 3.92 (s, 0.6H, CH_2), 8.62 (bs, 0.3H) and 8.88 (bs, 0.7H, NH), 9.98 (s, 0.3H) and 10.68 (s, 0.7H, NH); anal. calcd. for $C_{12}H_{16}N_4O_3$ (264.28): C, 54.53; H, 6.10; N, 21.19%; found: C, 54.65; H, 6.24; N, 21.29%.

General procedure for the synthesis of compounds **5a-d**

A mixture of the appropriate tertiary α-hydroxyketones **4a-d** (5 mmol) and 2-(2-(2-cyanoacetyl)hydrazono)-4,5,5-trimethyl-2,5-dihydrofuran-3-carboxamide **3a** (1.25 g, 5 mmol) with a solution of sodium methoxide (0.115 g, 0.5 mmol) in absolute methanol (15 mL) was stirred at 35-40 °C for 5h. After solvent evaporation, water was poured onto the residue, the resulting precipitate was filtered and washed with water.

2-(2-(2-Imino-4,5,5-trimethyl-2,5-dihydrofuran-3-carbonyl) hydrazono)-4,5,5-trimethyl-2,5-dihydrofuran-3-carboxamide (**5a**)

White solid; mp: 303-305 °C (from ethanol); yield (1.5 g, 90%); IR ν / cm^{-1} 1620, 1644, 1680, 1690, 3255, 3275; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.45 (s, 6H, 2CH_3), 1.51 (s, 6H, 2CH_3), 2.36 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.36 (bs, 1H) and 8.26 (bs, 1H, NH_2), 7.39 (s, 1H, NH), 12.25 (s, 1H, NH); anal. calcd. for $C_{16}H_{22}N_4O_4$ (334.38): C, 57.47; H, 6.63; N, 16.76%; found: C, 57.58; H, 6.75; N, 16.89%.

2-(2-(5-Ethyl-2-imino-4,5-dimethyl-2,5-dihydrofuran-3-carbonyl)hydrazono)-4,5,5-trimethyl-2,5-dihydrofuran-3-carboxamide (**5b**)

White solid; mp: 309-310 °C (from ethanol); yield (1.57 g, 90%), $[\alpha]_D^{20}$ 0 (*c* 0.5, DMSO); IR ν / cm^{-1} 1622, 1645, 1680, 1685, 3254, 3278; ^{1}H NMR (300 MHz, DMSO-d_6:CCl_4, 1:3) δ 0.78 (t, 3H, *J* 4.2 Hz, CH_2CH_3), 1.42 (s, 3H, 2CH_3), 1.51 (s, 6H, 2CH_3), 1.80 (q, 2H, *J* 5.4 Hz, CH_2CH_3), 2.37 (s, 6H, 2CH_3), 7.37 (bs, 1H) and 8.28 (bs, 1H, NH_2), 7.39 (s, 1H, NH), 12.26 (s, 1H, NH); anal. calcd. for $C_{17}H_{24}N_4O_4$ (348.40): C, 58.61; H, 6.94; N, 16.08%; found: C, 58.78; H, 7.09; N, 16.27%.

2-(2-(2-Imino-4-methyl-1-oxaspiro[4.4]non-3-enecarbonyl) hydrazono)-4,5,5-trimethyl-2,5-dihydrofuran-3-carboxamide (**5c**)

White solid; mp: 281-282 °C (from ethanol); yield (1.6 g, 89%); IR ν / cm^{-1} 1625, 1640, 1680, 1685, 3250, 3275; ^{1}H NMR (300 MHz, DMSO-d_6:CCl_4, 1:3) δ 1.42 (m, 2H) and 1.58-1.85 (m, 6H, m$(CH_2)_4$), 1.45 (s, 6H, 2CH_3), 2.38 (s, 6H, 2CH_3), 7.36 (bs, 1H) and 8.25 (bs, 1H, NH_2), 7.39 (s, 1H, NH), 12.25 (s,1H, NH); anal. calcd. for $C_{18}H_{24}N_4O_4$ (360.41): C, 59.99; H, 6.71; N, 15.55%; found: C, 60.08; H, 6.85; N, 15.69%.

2-(2-(2-Imino-4-methyl-1-oxaspiro[4.5]dec-3-enecarbonyl) hydrazono)-4,5,5-trimethyl-2,5-dihydrofuran-3-carboxamide (**5d**)

White solid; mp: 274-275 °C (from ethanol); yield (1.72 g, 92%); IR ν /cm^{-1} 1620, 1642, 1684, 1691, 3254, 3280; ^{1}H NMR (300 MHz, DMSO-d_6:CCl_4, 1:3) δ 1.27 (m, 1H), 1.47(m, 2H) and 1.58-1.82 (m, 7H, $(CH_2)_5$), 1.45 (s, 6H), 2.36 (s, 3H), 2.38 (s, 3H), 7.36 (bs, 1H) and 8.25 (bs, 1H, NH_2), 7.39 (s, 1H, NH), 12.25 (s, 1H, NH); anal. calcd. for $C_{19}H_{26}N_4O_4$ (374.44): C, 60.95; H, 6.99; N, 14.96%; found: C, 61.04; H, 7.07; N, 15.14%.

2-(2-(2-Imino-4,5,5-trimethyl-2,5-dihydrofuran-3-carbonyl) hydrazono)-*N*-4,5,5-tetramethyl-2,5-dihydofuran-3-carboxamide (**5e**)

White solid; mp: 224-225 °C (from ethanol); yield (1.58 g, 91%); IR ν / cm^{-1} 1620, 1644, 1682, 1690, 3252, 3281; ^{1}H NMR (300 MHz, DMSO-d_6:CCl_4, 1:3) δ 1.45 (s, 6H, 2CH_3), 1.50 (s, 6H, 2CH_3), 2.38 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.85 (d, 3H, *J* 3.4 Hz, NCH_3), 7.39 (s, 1H, NH), 8.78 (bs, 1H, NH), 12.25 (s, 1H, NH); anal. calcd. for $C_{17}H_{24}N_4O_4$ (348.40): C, 58.61; H, 6.94; N, 16.08%; found: C, 58.66; H, 7.12; N, 16.19%.

Supplementary Information

Supplementary information is available free of charge at http://jbcs.sbq.org.br as a PDF file.

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