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SYNTHESIS OF 1-AMINO AND 1-NITROSO DERIVATIVES OF 2',3'-DIHYDRO-2*H*,5*H*-SPIRO[IMIDAZOLIDINE-4,1'-INDENE]-2,5-DIONE

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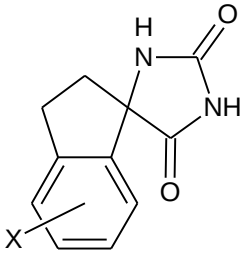
Abstract: *This article describes the synthesis of 1-amino-2',3'-dihydro-2H,5H-spiro[imidazolidine-4,1'-indene]-2,5-dione and 1-nitroso-2',3'-dihydro-2H,5H-spiro[imidazolidine-4,1'-indene]-2,5-dione. These compounds were prepared by the interaction of 2',3'-dihydro-2H,5H-spiro[imidazolidine-4,1'-indene]-2,5-dione with hydrazine hydrate and sodium nitrite. The products obtained were characterized by physicochemical parameters, elemental analysis, IR and NMR spectral data.*

Keywords: *Synthesis, 2',3'-Dihydro-2H,5H-spiro[imidazolidine-4,1'-indene]-2,5-dione, 1-Amino-2',3'-dihydro-2H,5H-spiro[imidazolidine-4,1'-indene]-2,5-dione, 1-Nitroso-2',3'-dihydro-2H,5H-spiro[imidazolidine-4,1'-indene]-2,5-dione*

INTRODUCTION

The synthesis of 2',3'-dihydro-2*H*,5*H*-spiro[imidazolidine-4,1'-indene]-2,5-dione and its derivatives is mainly due to their application as therapeutic agents (Sarges, R., 1978). Various examples of such compounds (Fig. 1) have been reported as aldose reductase inhibitors (Sarges, R., et *al*., 1988).



X = H; 6-F; 5-OMe; 6-OMe; 5,6-$(OMe)_2$; 5,6,7-$(OMe)_3$; 5,6-OCH_2O; 6-OH

Fig. 1. Structures of 2',3'-dihydro-2*H*,5*H*-spiro[imidazolidine-4,1'-indene]-2,5-dione and its derivatives

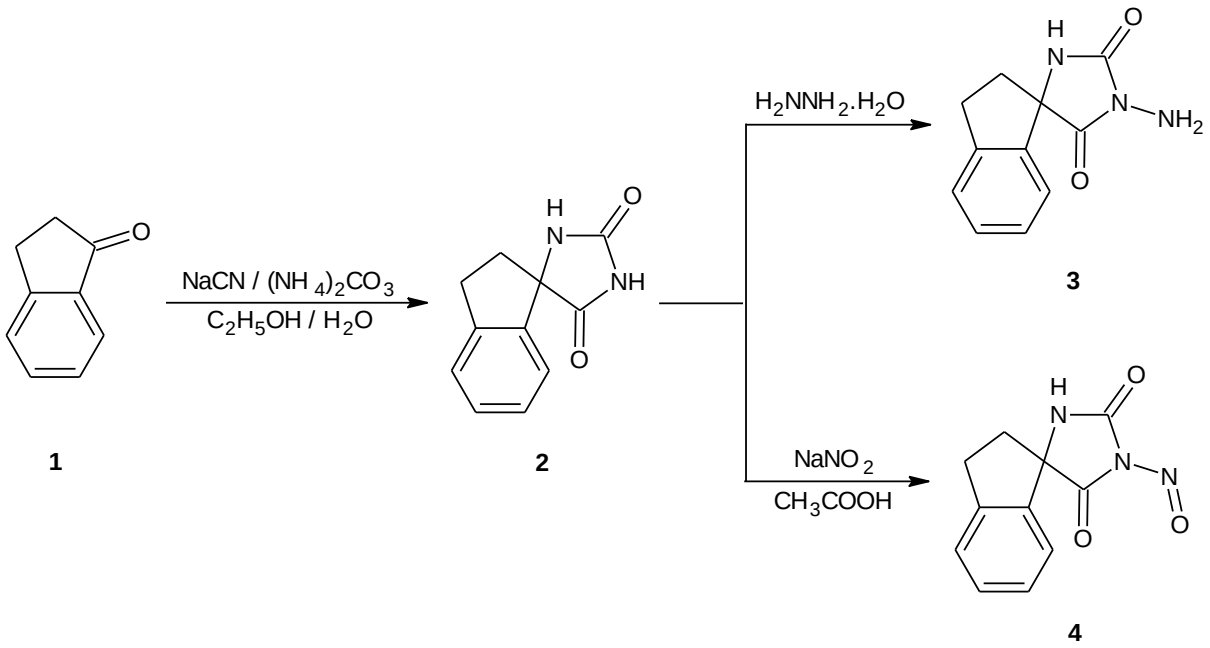
The aim of the current study is to present the synthesis of two 2',3'-dihydro-2*H*,5*H*-spiro[imidazolidine-4,1'-indene]-2,5-dione derivatives, namely 1-amino-2',3'-dihydro-2*H*,5*H*-spiro[imidazolidine-4,1'-indene]-2,5-dione and 1-nitroso-2',3'-dihydro-2*H*,5*H*-spiro[imidazolidine-4,1'-indene]-2,5-dione. Physicochemical parameters, elemental analysis, IR and NMR spectral data of the products obtained are also given.

EXPOSITION

All chemicals used for the synthesis were purchased from Merck and Sigma-Aldrich. The melting points were determined with a SMP-10 digital melting point apparatus. The elemental analysis data were obtained with an automatic analyzer Carlo Erba 1106. The purity of the

compounds was checked by thin layer chromatography on Kieselgel 60 F_{254}, 0.2 mm Merck plates, eluent system (vol. ratio): benzene : ethanol = 5 : 1. The IR spectra were taken on Perkin-Elmer FTIR-1600 spectrometer in KBr discs. The NMR spectra were taken on a Bruker DRX-250 spectrometer, operating at 250.13 and 62.90 MHz for ^{1}H and ^{13}C, respectively, using the standard Bruker software. The chemical shifts were referenced to tetramethylsilane (TMS). The measurements in DMSO-d_6 solutions were carried out at ambient temperature (300 K). Typical conditions for ^{1}H NMR spectra were: pulse width 30º, 1 s relaxation delay, 16K time domain points, zero-filled to 64K, hard pulse with 90º pulse width of 11.8 μs; ^{13}C NMR spectra: pulse width 30º, 1 s relaxation delay, 16K time domain points, zero-filled to 32K, hard pulse with 90º pulse width of 6.4 μs at a power level of 3 dB below the maximum output.

The titled compounds (**3** and **4**) were synthesized following Sheme 1. The initial 2',3'-dihydro-2*H*,5*H*-spiro[imidazolidine-4,1'-indene]-2,5-dione (**2**) was obtained from 2,3-dihydro-1*H*-inden-1-one (**1**) in accordance with Nagasawa et *al*. (Nagasawa, H. T., et *al*., 1973).



1 **2** **3** **4**

Scheme 1. Synthesis of 1-amino-2',3'-dihydro-2*H*,5*H*-spiro[imidazolidine-4,1'-indene]-2,5-dione (**3**) and 1-nitroso-2',3'-dihydro-2*H*,5*H*-spiro[imidazolidine-4,1'-indene]-2,5-dione (**4**)

Synthesis of 1-amino-2',3'-dihydro-2*H*,5*H*-spiro[imidazolidine-4,1'-indene]-2,5-dione (3, Scheme 1) (Marinov, M., et *al*., 2015)

A suspension of 5.00 g (0.025 mol) of 2',3'-dihydro-2*H*,5*H*-spiro[imidazolidine-4,1'-indene]-2,5-dione (**2**, Scheme 1) and 15 ml of concentrated hydrazine hydrate was refluxed for 5 hours. After cooling down to the room temperature, the mixture was poured onto a small quantity of crushed ice. The product obtained (**3**) was filtered off and recrystallized from ethyl acetate.

Yield: 71 %; M. p. 173-174 ºC, R_f = 0.59; Anal. calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34 %; found: C, 60.67; H, 5.03; N, 19.23 %; IR (ν_{max}, KBr, cm^{-1}): 3412, 3346, 3232 (NH, NH_2), 3089 (arom.), 2951 (aliph.), 1781 (C=O), 1729 (C=O); ^{1}H NMR (δ, DMSO-d_6, ppm): 2.15-2.43 (m, 4H, aliph.), 4.79 (s, NH_2), 7.08-7.32 (m, 4H, arom.), 9.12 (s, NH); ^{13}C NMR (δ, DMSO-d_6, ppm): 25.5 (CH_2), 32.6 (CH_2), 66.6 (spiro C-atom), 123.8 (CH, arom.), 125.5 (CH, arom.), 127.5 (CH, arom.), 129.1 (CH, arom.), 160.3 (C=O), 181.1 (C=O); ^{13}C DEPT 135 (δ, DMSO-d_6, ppm): 25.5 (CH_2), 32.6 (CH_2), 123.8 (CH, arom.), 125.5 (CH, arom.), 127.5 (CH, arom.), 129.1 (CH, arom.).

Synthesis of 1-nitroso-2',3'-dihydro-2*H*,5*H*-spiro[imidazolidine-4,1'-indene]-2,5-dione (4, Scheme 1)

2',3'-Dihydro-2*H*,5*H*-spiro[imidazolidine-4,1'-indene]-2,5-dione (0.40 g, 0.002 mol) was dissolved in 25 ml of glacial acetic acid and 0.14 g (0.002 mol) of sodium nitrite were added portionwise to the solution formed. The mixture was poured into cold water. The product obtained (4) was filtered off and recrystallized from ethanol.

Yield: 84 %; M. p. 182-183 ºC, R_f = 0.66; Anal. calcd. for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17 %; found: C, 56.98; H, 3.75; N, 18.02 %; IR (ν_{max}, KBr, cm^{-1}): 3094 (NH), 3055 (arom.), 2945 (aliph.), 1768 (C=O), 1699 (C=O), 1440 (N=O); ^{1}H NMR (δ, DMSO-d_6, ppm): 2.04-2.82 (m, 4H, aliph.), 6.91-7.02 (m, 4H, arom.), 8.55 (s, NH).

CONCLUSIONS

1-Amino and 1-nitroso derivatives of 2',3'-dihydro-2*H*,5*H*-spiro[imidazolidine-4,1'-indene]-2,5-dione were successfully synthesized. Their structures were confirmed by physicochemical parameters, elemental analysis, IR and NMR spectral data.

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