

Synthesis of 4- and 5- nitro-substituted heteroaryl cinnamoyl derivatives

Marin Marinov, Iliana Nikolova, Petja Marinova, Neyko Stoyanov, Plamen Penchev, Krasimir Ivanov

Synthesis of 4- and 5- nitro-substituted heteroaryl cinnamoyl derivatives: The aim of this study is the synthesis and structural characterization of 4- and 5- nitro-substituted heteroaryl cinnamoyl derivatives. The target compounds were obtained by a reaction of the corresponding 4- and 5- nitro-substituted 2-acetyl-1,3-indandione with various heteroaryl aldehydes. The interest in these compounds was determined by both their potential biological activity and the possibility of their use as ligands for preparation of a number of complexes.

Key words: synthesis, indandione, nitro-substituted heteroaryl cinnamoyl derivatives.

INTRODUCTION

In the condensation of the 4- and 5-nitro-substituted 2-acetyl-1,3-indandione with heteroaryl aldehydes in the presence of alkaline or acidic catalysts, the corresponding cinnamoyl derivatives are obtained that possess anticoagulant activity, compared with that of 2-acetyl-1,3-indandione. It has been proven that some of the sodium salts of the cinnamoyl-indandione possess anticoagulant activity. Different derivatives of 2-acyl-1,3-indandione manifest as anticoagulant agents and as such they are widely used in medicine and in fighting rodents [1-3]. Certain 2-acyl-1,3-indandiones have impact on *Mycobacterium tuberculosis* [4-6]. A number of complexes were obtained [7-10]. 2-Acyl-1,3-indandiones are prepared from dialkyl phthalate with the corresponding methyl ketones in the presence of CH_3ONa [11, 12]. Literature reveals a number of examples which show that the replacement of saturated with unsaturated radical very often increases the physiological effect or it is very specific [13, 14].

RESULTS AND DISCUSSION

In order to obtain the corresponding 4- and 5-nitro-substituted heteroaryl cinnamoyl derivatives, we synthesized the corresponding 4- and 5- nitro-substituted 2-acyl-1,3-indandiones by two different methods: Mosher and Meier [15] and Rotberg and Oshkaya [16]. We found that the result of the second method is much better. Enchev et al. [17, 18] demonstrated that energetically the most advantageous to 2-acetyl-1,3-indandione is not the keto form (I), but the corresponding enol form (II), which a priori can be taken for the energetically advantageous forms of 4- and 5- nitro-substituted 2-acyl-1,3-indandiones (III) (Figure 1).

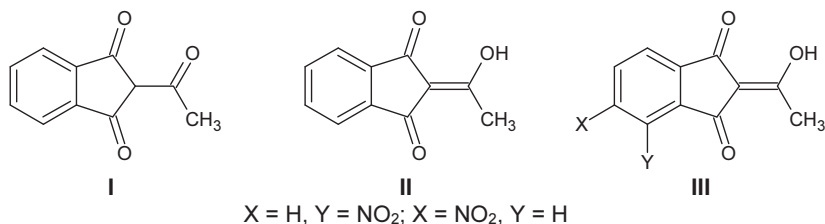
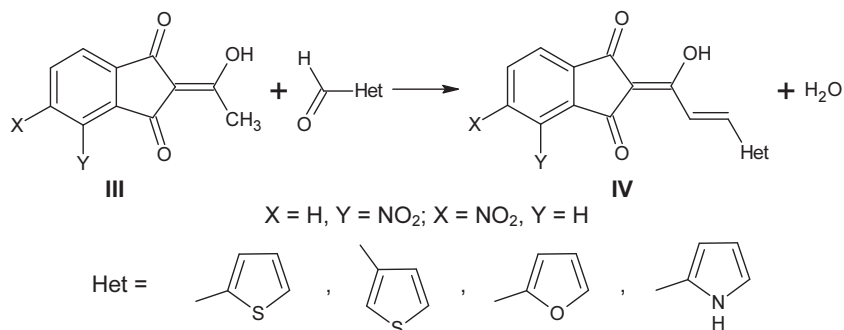


Figure 1

In the absence of the catalysts 4- and 5- nitro-substituted 2-acyl-1,3-indandiones (III) do not react with heteroaryl aldehydes, but in the presence of alkaline or acidic catalysts such as diethylamine, piperidine, pyrrolidine, acetic acid, the reaction proceeds relatively easy. The highest results are obtained with the cinnamoyl derivatives (IV) with pyrrolidine catalyst. The reaction proceeds in accordance with Scheme 1.



Scheme 1

As a result of that interaction, the following compounds were successfully obtained: 2-[1-hydroxy-3-(thiophen-2-yl)prop-2-en-1-ylidene]-4-nitro-1*H*-indene-1,3(2*H*)-dione (**IVa**), 2-[1-hydroxy-3-(thiophen-3-yl)prop-2-en-1-ylidene]-4-nitro-1*H*-indene-1,3(2*H*)-dione (**IVb**), 2-[3-(furan-2-yl)-1-hydroxyprop-2-en-1-ylidene]-4-nitro-1*H*-indene-1,3(2*H*)-dione (**IVc**), 2-[1-hydroxy-3-(1*H*-pyrrol-2-yl)prop-2-en-1-ylidene]-4-nitro-1*H*-indene-1,3(2*H*)-dione (**IVd**), 2-[1-hydroxy-3-(thiophen-2-yl)prop-2-en-1-ylidene]-5-nitro-1*H*-indene-1,3(2*H*)-dione (**IVe**), 2-[1-hydroxy-3-(thiophen-3-yl)prop-2-en-1-ylidene]-5-nitro-1*H*-indene-1,3(2*H*)-dione (**IVf**), 2-[3-(furan-2-yl)-1-hydroxyprop-2-en-1-ylidene]-5-nitro-1*H*-indene-1,3(2*H*)-dione (**IVg**) and 2-[1-hydroxy-3-(1*H*-pyrrol-2-yl)prop-2-en-1-ylidene]-5-nitro-1*H*-indene-1,3(2*H*)-dione (**IVh**). The possible *Z* and *E* isomers are not the subject of this study.

The physicochemical characteristics of the synthesized compounds are given in Table 1. The data of IR spectra (KBr, cm^{-1}) are listed in Table 2.

Table 1

| No | X | Y | Het | Yield, % | M. p., °C | R _f |
|------------|-----------------|-----------------|-----|----------|-----------|----------------|
| IVa | H | NO ₂ | | 42.8 | 204-205 | 0.59 |
| IVb | H | NO ₂ | | 58.1 | 206-207 | 0.62 |
| IVc | H | NO ₂ | | 60.2 | 217-218 | 0.60 |
| IVd | H | NO ₂ | | 53.9 | 188-189 | 0.71 |
| IVe | NO ₂ | H | | 45.9 | 236-237 | 0.74 |
| IVf | NO ₂ | H | | 33.6 | 192-193 | 0.68 |



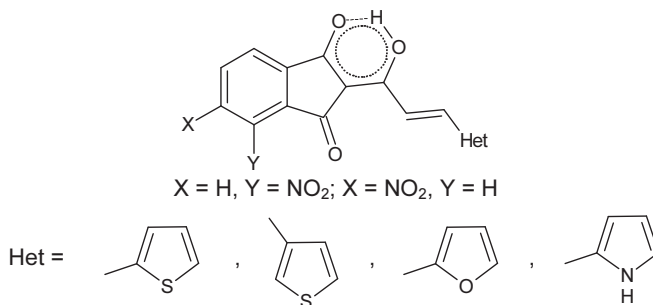
| | X | Y | Het | Yield, % | M. p., °C | R _f |
|-----|-----------------|---|---|----------|-----------|----------------|
| IVg | NO ₂ | H |  | 70.7 | 264-265 | 0.76 |
| IVh | NO ₂ | H |  | 75.2 | 156-157 | 0.69 |

Table 2

| № | IR (ν_{\max} , cm ⁻¹) | | | | | | | | | | | |
|-----|--|-------------------|----------------------|--------------------|--------------------|-------------------------|------------------------|-----------------------|-------------------|---------------------|-------------------------------|-------------------------------|
| | ν_{OH} | ν_{NH} | $\nu_{\text{arom.}}$ | $\nu_{\text{C=O}}$ | $\nu_{\text{C=C}}$ | $\nu_{\text{C=C(Het)}}$ | $\nu_{\text{as NO}_2}$ | $\nu_{\text{s NO}_2}$ | ν_{OH} | $\nu_{\text{C=CH}}$ | $\nu_{\text{2-thioph. core}}$ | $\nu_{\text{3-thioph. core}}$ |
| IVa | 3486 | | 3054 | 1699 | 1651 | 1612 | 1569 | 1532 | 1357 | 1237 | 957 | 826 |
| IVb | 3456 | | 3096 | 1704 | 1647 | 1616 | 1571 | 1538 | 1364 | 1250 | 954 | 798 |
| IVc | 3462 | | 3085 | 1703 | 1657 | 1613 | 1597 | 1531 | 1355 | 1261 | 949 | |
| IVd | 3483 | 3380 | 3071 | 1690 | 1660 | 1644 | 1613 | 1531 | 1341 | 1293 | 955 | |
| IVe | 3502 | | 3072 | 1713 | 1651 | 1607 | 1575 | 1531 | 1338 | 1267 | 962 | 836 |
| IVf | 3444 | | 3068 | 1715 | 1651 | 1602 | 1570 | 1532 | 1330 | 1266 | 954 | 800 |
| IVg | 3438 | | 3094 | 1705 | 1628 | 1598 | 1577 | 1526 | 1342 | 1266 | 941 | |
| IVh | 3492 | 3341 | 3083 | 1708 | 1649 | 1603 | 1576 | 1533 | 1340 | 1266 | 943 | |

The resulting cinnamoyl derivatives (Figure 2) are yellow to orange colored compounds that dissolve readily in an alcoholic alkaline medium with formation of salts. With FeCl₃ in alcoholic medium the cinnamoyl derivatives are colored in red, which is a proof to chelation similar to that of 2-acetyl-1,3-indandione. In the IR-spectrum a band of -OH group was observed between 3462-3312 cm⁻¹ and bands concerning the chelating structure (1731, 1657, 1626 and 1597 cm⁻¹) and the bands between 1626 and 1657 cm⁻¹ refer to the link in the chelating cycle.


Figure 2

EXPERIMENTAL

All used chemicals were purchased from Merck and Sigma-Aldrich. The melting points were determined by a SMP-10 digital melting point apparatus. The purity of the compounds was checked by thin layer chromatography on Kieselgel 60 F₂₅₄, 0.2 mm Merck plates, eluent system (vol. ratio): CH₂Cl₂ : CH₃COCH₃ = 1 : 1. The IR spectra were registered in KBr pellets on a Bruker FT-IR VERTEX 70 Spectrometer from 4000 cm⁻¹ to 400 cm⁻¹ at resolution 2 cm⁻¹ with 25 scans.

I. Synthesis of 4- and 5- nitro-substituted 2-acetyl-1,3-indandiones

0.01 mol of 4- and 5- nitro-substituted phthalic anhydride were dissolved in 10.2 g of acetic anhydride, condensed with 1 g of acetylacetone in the presence of 3 g of triethylamine for 24 hours, then the mixture was poured onto a mixture of 150 g of ice and 50 ml of conc. HCl. The resulting precipitate was filtered off, then treated with 100 ml of 1 % NaOH. The solution was filtered and the filtrate was acidified with HCl (1 : 2) to pH ~ 1. The resulting precipitate was filtered off and dried. The dried compounds were recrystallized from 2-butanone.

II. Synthesis of 4- and 5- nitro-substituted cinnamoyl derivatives

0.005 mol of the corresponding 4- or 5- nitro-substituted 2-acetyl-1,3-indandione was heated under boiling on a water bath for 10-15 min with 0.0075 mol of the corresponding hetero aldehyde and 0.2 ml of pyrrolidine. Then 10 ml of abs. EtOH was added to the mixture and it was heated with boiling for 1-2 hours. After cooling, the separated precipitate was filtered off and recrystallized from EtOH.

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About the authors:

Marin Marinov, Assoc. Prof., PhD, Faculty of Plant Protection and Agroecology, Department of General Chemistry, Agricultural University – Plovdiv, e-mail: m_n_marinov@abv.bg

Iliana Nikolova, Assist. Prof., Department of Chemistry and Chemical Technologies, “Angel Kanchev” University of Ruse, Razgrad Branch, e-mail: inikolova@uni-ruse.bg

Petja Marinova, Chief Assist. Prof., PhD, Faculty of Chemistry, Department of General and Inorganic Chemistry with Methodology of Chemistry Education, Plovdiv University “Paisii Hilendarski”, e-mail: marinova@uni-plovdiv.bg

Neyko Stoyanov, Prof., PhD, Department of Chemistry and Chemical Technologies, “Angel Kanchev” University of Ruse, Razgrad Branch, e-mail: nstoyanov@uni-ruse.bg.

Plamen Penchev, Assoc. Prof., PhD, Faculty of Chemistry, Department of Analytical Chemistry and Computer Chemistry, Plovdiv University “Paisii Hilendarski”, e-mail: plamen@uni-plovdiv.bg

Krasimir Ivanov, Prof., DSc., Faculty of Plant Protection and Agroecology, Department of General Chemistry, Agricultural University – Plovdiv, e-mail: kivanov1@abv.bg

This paper has been reviewed