ISSN 1311-3321

РУСЕНСКИ УНИВЕРСИТЕТ "Ангел Кънчев"
UNIVERSITY OF RUSE "Angel Kanchev"

70 ГОДИНИ ТРАДИЦИИ и ИНОВАЦИИ
70 YEARS TRADITIONS and INNOVATIONS

НАУЧНИ ТРУДОВЕ

Том 54, серия 10.1
Химични технологии

НАУЧНЫЕ ТРУДЫ

Том 54, серия 10.1
Химические технологии

PROCEEDINGS

Volume 54, book 10.1
Chemical technologies

Русе
Ruse
2015

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

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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.*

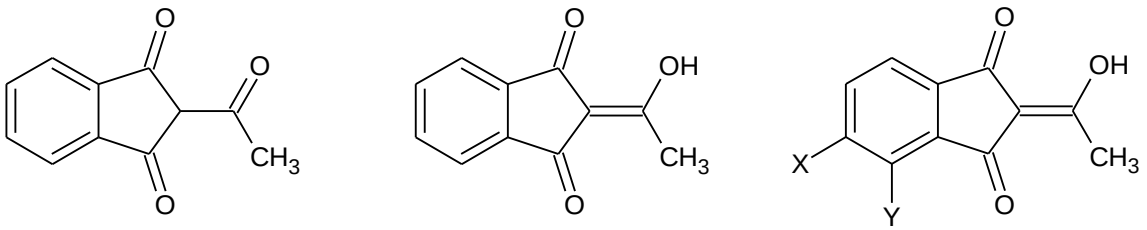
Key words: *synthesis, indandione, nitro-substituted heteroaryl cinnamoyl derivatives.*

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).

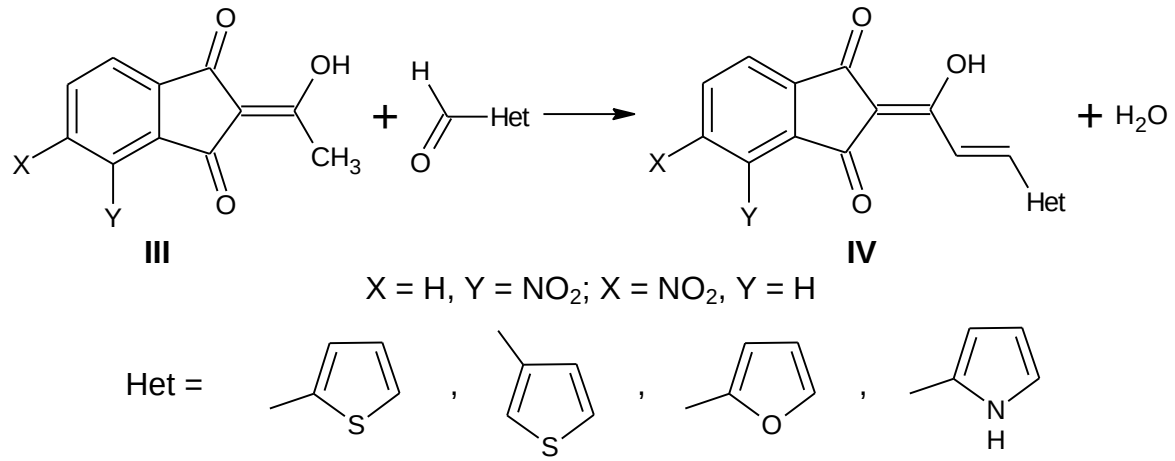


I **II** **III**

X = H, Y = NO_2; X = NO_2, Y = H

Figure 1

In the absence of the catalysts 4- and 5- nitro-subsstituted 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.

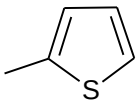
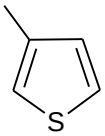
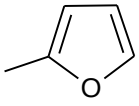
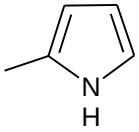
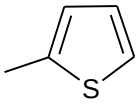
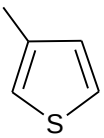


Scheme 1

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

№	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

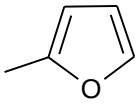
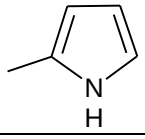
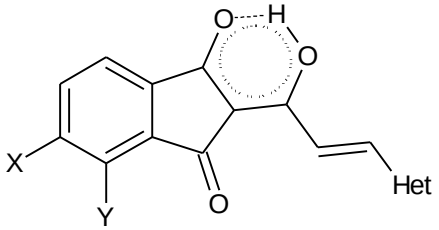
	X	Y	Het	Yield, %	M. p., °C	R_f
IVg	NO_2	H		70.7	264-265	0.76
IVh	NO_2	H		75.2	156-157	0.69

Table 2

№	IR (ν_{max}, cm^{-1})												
	ν_{OH}	ν_{NH}	$\nu_{arom.}$	$\nu_{C=O}$	$\nu_{C=O}$	$\nu_{C=C}$	$\nu_{C=C(Het)}$	$\nu_{as\ NO_2}$	$\nu_{S\ NO_2}$	ν_{OH}	$\nu_{=CH}$	$\nu_{2\text{-thioph. core}}$	$\nu_{3\text{-thioph. core}}$
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 $FeCl_3$ in alcoholic medium the cinnamoyl derivatives are colored in red, which is a proof to chelatization 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.



X = H, Y = NO_2; X = NO_2, Y = H

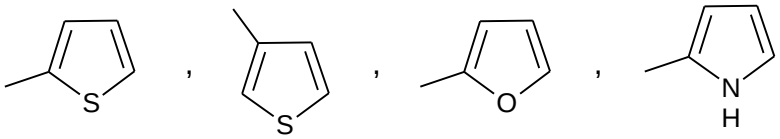
Het = 

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 F_{254}, 0.2 mm Merck plates, eluent system (vol. ratio): CH_2Cl_2 : CH_3COCH_3 = 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.

REFERENCES

[1] J. Correll, L. Coleman, S. Long, R. Willy. Proc. Soc. Exp. Biol. Med., 1952, 80 (1), 139.

[2] В. Витол, Г. Ванаг. Изв. АН Латв. ССР, 1955, 9, 111.

[3] Г. Ванаг, Б. Фалькенщейн, Л. Егорова, В. Зелмен. Изв. АН Латв. ССР, 1959, 5, 99.

[4] C. Hassal. Experientia, 1950, 6 (12), 462.

[5] A. Marshak, W. Schaefer, S. Rajagopalan. Proc. Soc. Exp. Biol. Med., 1949, 70 (4), 565.

[6] Y. Chin, H. Anderson, G. Alderton, J. Lewis. Exp. Biol. Med., 1949, 70, 158.

[7] A. Ahmedova, V. Atanasov, P. Marinova, N. Stoyanov, M. Mitewa. Cent. Eur J. Chem., 2009, 7 (3), 429.

[8] A. Ahmedova, P. Marinova, S. Ciattini, N. Stoyanov, M. Springborg, M. Mitewa. Struct. Chem., 2009, 20, 101.

[9] A. Ahmedova, G. Pavlović, D. Zhiryakova, D. Šišak, N. Stoyanov, M. Springborg, M. Mitewa. J. Mol. Str., 2010, 981, 10.

[10] A. Ahmedova, P. Marinova, G. Pavlović, M. Guncheva, N. Stoyanov, M. Mitewa. J. Iran. Chem. Soc., 2012, 9 (3), 297.

[11] E. Schverin. Ber., 1894, 27, 104.

[12] Г. Ванаг, Б. Фалькенщейн, З. Крастынь, В. Зелмен, Л. Егорова. Авт. свид. СССР, 145417 (1962); Бюлл. изобр., 1962, № 5.

[13] M. Protiva, V. Hněvsová-Seidlová, Z. Vejdělek, I. Jirkovský, Z. Votava, J. Metyšová. J. Med. Pharm. Chem., 1961, 4, 411.

[14] F. Villani, C. Ellis, C. Teichman, C. Bigos. J. Med. Pharm. Chem., 1962, 5, 373.

[15] W. Moscher, W. Meier. J. Org. Chem., 1970, 35, 2924.

[16] Ю. Ротберг, В. Ошкая. ЖОрХ, 1972, 8 (1), 84.

[17] V. Enchev, S. Bakalova, G. Ivanova, N. Stoyanov. Chem. Phys. Lett., 1999, 314, 234.

[18] V. Enchev, A. Ahmedova, G. Ivanova, N. Stoyanov, M. Mitewa. J. Mol. Str., 2001, 67, 595.

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This paper has been reviewed