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Features of Reaction of Aromatic Nitro-Substituted Aldehydes with Ketones on the Matrix of 2(1*H*)-Pyridone

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Abstract—Condensation of nitrobenzaldehydes with 3-acetyl-4,6-dimethyl-2(1*H*)-pyridone gives rise to chalcones with high yield. Condensation of the close analogs of 3-acetyl-4,6-dimethyl-2(1*H*)-pyridone containing ethyl and benzyl radical was established to give stable products of aldol condensation, the corresponding alcohols, under the same conditions.

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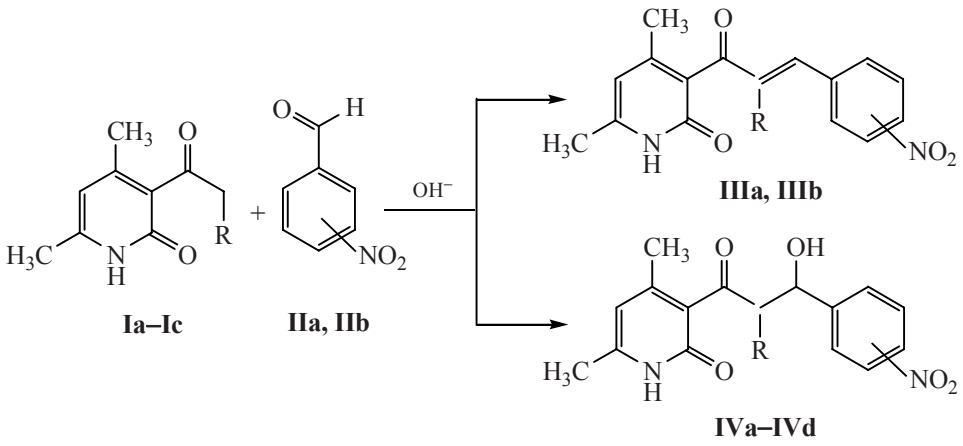
Chalcones, 1,3-diarylpropen-1-one, present an important class of natural compounds. Synthetic chalcones and their analogs are of great interest since they possess many pharmacological properties, display antiinflammatory [1], antibacterial [2], antimalarial [3], antitubeculous [4] and antineoplastic [5] activities. Comparative simplicity of the synthesis of chalcones and their analogs by condensation of aromatic and heteroaromatic aldehydes and ketones catalyzed with bases makes them widely available. It is known that reaction with benzaldehydes containing electron-withdrawing substituents proceeds very rapidly. There were reported in literature about the synthesis of the various nitro-substituted chalcones and about their cytotoxic [6] and antileishmaniasis [7] properties. The nitro-substituted chalcones are potential radioprotectors [8] and nonlinear optics materials [9]. In addition, they are the starting materials for the synthesis of biologically active compounds [10].

Aiming at the synthesis of the new potential pharmacologically active compounds, we studied condensation of heteroaromatic ketones on the matrix of 2(1*H*)-pyridone with nitro-substituted benzaldehydes. We have reported earlier that condensation of 3-acetyl-4,6-dimethyl-2(1*H*)-pyridone **Ia** and its analogs, 4,6-dimethyl-3-(1-oxopropyl)-2(1*H*)-pyridone **Ib** and 4,6-dimethyl-3-(phenacetyl)-2(1*H*)-pyridone **Ic,** with various aromatic and heteroaromatic aldehydes containing both electron-releasing and electron-withdrawing substituents result in chalcones [11]. We supposed that the condensation of ketones **Ia–Ic** with nitrobezaldehydes gives rise also to chalcones. However, the nitro-substituted chalcones were found in this work to be formed only in the reaction with pyridone **Ia**. Reaction proceeds at 35ºC for 16 h. The reaction progress was monitored by TLC method. After the initial pyridone spot disappearance the target chalcones **IIIa** and **IIIb** were isolated with yields near 60%. Ketones **Ib** and **Ic** do not form chalcones expected under the similar conditions. The new compound 3-[3-hydroxy-2-methyl-3-(3-nitrophenyl)-1-oxopropyl]-4,6-dimethyl-2(1*H*)-pyridone **IVa** was obtained in the reaction of compound **Ib** with 3-nitrobenzaldehyde. The chalcone admixture was not found in the reaction mixture. The reaction time or temperature increasing to 24 h or 45ºC respectively does not result in change of the reaction product composition, but the reaction mixture darkens, and purity and yield of the end pro-duct decrease accordingly. Similarly the corresponding stable alcohols (compounds **IVb–IVd**) were obtained as a result of the reaction of ketones **Ib** and **Ic** with 3- and 4-nitrobenzaldehydes. A necessary time for the condensation of compound **Ic** is 36 h at 35ºC. Chalcones and alcohols isolation and purification methods are identical. Structure of all the compounds is proved by NMR spectroscopy and elemental analysis methods. Structure of the new compounds **IVa–IVd** was additionally confirmed by means of the double resonance method. Finally, it was established that the presence of



R = H (**Ia**), R = CH_3 (**Ib**), R = C_6H_5 (**Ic**); 3-NO_2 (**IIa**), 4-NO_2 (**IIb**); R = H, 3-NO_2 (**IIIa**), R = H, 4-NO_2 (**IIIb**); R = CH_3, 3-NO_2 (**IVa**); R = CH_3, 4-NO_2 (**IVb**); R = C_6H_5, 3-NO_2 (**IVc**); R = C_6H_5, 4-NO_2 (**IVd**).

3- or 4-nitrogroup in the molecule and the change of ketone **Ia** methyl radical with ethyl **Ib** or benzyl **Ic** complicates the chalcones formation and reaction stops, when aldol condensation product formed.

The reaction duration, melting points, elemental analysis data and reaction product yields are given in Table 1.

Nitrochalcones **IIIa–IIIb** have yellow color caused by the conjugation of π-electrons of the double bond and aromatic rings. Melting points for compounds **IIIa–IIIb** are very high and exceed sufficiently those for the analogs not contained nitro-group [11]. Alcohols **IVa–IVd** have the lower melting points and, as one would expect, have not yellow color.

Comparison of the ^{1}H NMR spectra obtained for chalcones **IIIa** and **IIIb** and for the analog described in [11] not containing nitro-group shows that signals of the protons at the interring double bond is shifted downfield by 0.1–0.2 ppm, when withdrawing substituent is incorporated into the aromatic ring. Therewith, the signals of the aromatic ring protons in the aldehyde part are shifted downfield by 1 ppm approximately, whereas signals of the pyridone fragment protons are registered at the similar values practically.

The ^{1}H NMR spectra of compounds **IVa–IVd** correspond to the presented structures. In the spectra a doublet characteristic for the interring methyl radical was observed at 0.8–0.9 ppm. Signal of hydroxyl group is represented as a doublet at 6 ppm. Characteristic multiplet of the interring fragment protons at C^2 and C^3 atoms was found in the range 3.5–5 ppm. When passing from chalcones **IIIa** and **IIIb** to alcohols **IVa–IVd**, the signal position of the pyridone fragment protons is changed not essentially. The ^{1}H NMR parameters for compounds obtained are given in Table 2.

Table 1. Reaction time, melting points, elemental analysis data and yield of compounds obtained

Comp. no.	Yield, %	Reaction time, h	mp, °C (DMF)	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
IIIa	68	16	298–300	64.56	4.80	9.34	$C_{16}H_{14}N_2O_4$	64.42	4.73	9.39
IIIb	58	16	>350	64.48	4.74	9.41	$C_{16}H_{14}N_2O_4$	64.42	4.73	9.39
IVa	51	16	208–209	61.94	5.59	8.59	$C_{17}H_{18}N_2O_5$	61.81	5.49	8.48
IVb	67	16	220–222	61.88	5.45	8.41	$C_{17}H_{18}N_2O_5$	61.81	5.49	8.48
IVc	38	36	228–229	67.49	5.29	7.19	$C_{22}H_{20}N_2O_5$	67.34	5.14	7.14
IVd	48	36	231–234	67.43	5.19	7.25	$C_{22}H_{20}N_2O_5$	67.34	5.14	7.14

Table 2. The ^{1}H NMR parameters of the synthesized compounds

Comp. no.	^{1}H NMR spectra, δ, ppm, DMSO-d_6
IIIa	2.12 s (3H, CH_3),2.21 s (3H, CH_3), 6.04 s (1H), 7.36 d (1H, *J* 16.38 Hz), 7.59 d (1H, *J* 16.38 Hz), 7.71 t (1H, *J* 8.09 Hz), 8.19 m (2H), 8.52 s (1H), 11.90 s (1H, NH)
IIIb	2.12 s (3H, CH_3), 2.22 s (3H, CH_3), 6.05 s (1H), 7.38 d (1H, *J* 16.1 Hz), 7.54 d (1H, *J* 16.1 Hz), 7.96 d (2H, *J* 8.6 Hz), 8.21 d (2H, *J* 8.6 Hz), 11.88 s (1H, NH)
IVa	0.89 d (3H, CH_3, *J* 6.54 Hz), 2.15 s (3H, CH_3), 2.18 s (3H, CH_3), 3.62 m (1H, CH), 4.75–4.85 m (1H, CH), 5.95 s (1H), 6.05 d (1H, OH, *J* 5.35 Hz), 7.52–7.59 t (1H, *J* 7.68 Hz), 7.75 d (1H, *J* 7.0 Hz), 8.08–8.16 m (2H), 11,82 s (1H, NH)
IVb	0.82 d (3H, CH_3, *J* 6.64 Hz), 2.14 s (3H, CH_3), 2.19 s (3H, CH_3), 3.50–3.62 m (1H, CH), 4.70–4.80 m (1H, CH), 5.95 s (1H), 6.05 d (1H, OH, *J* 5.19 Hz), 7.57 d (2H, *J* 8.51 Hz), 8.15 d (2H, *J* 8.51 Hz), 11,89 s (1H, NH)
IVc	2.09 s (3H, CH_3), 2.18 s (3H, CH_3), 3.33 m (1H, CH), 5.06 m (1H, CH), 5.77 d (1H, OH, *J* 6.05), 6.03 s (1H), 7.35–7.45 m (3H), 7.80–7.90 m (4H), 8.05 d (1H, *J* 8.74 Hz), 8.32 s (1H), 11.80 s (1H, NH)
IVd	2.07 s (3H, CH_3), 2.19 s (3H, CH_3), 3.29 m (1H, CH), 5.00 m (1H, CH), 5.79 d (1H, OH, *J* 5.95 Hz), 6.00 s (1H), 7.05–7.17 m (3H), 7.45–7.54 m (4H), 8.28 d (2H, *J* 8.64 Hz), 11.83 s (1H, NH)

EXPERIMENTAL

The NMR spectra were registered on a Brucker-DPX-200 device (200 MHz) in DMSO-d_6 relatively to internal TMS. The melting points were measured on a Boëtius device. In the work Aldrich commercial nitrobenzaldehydes were used. The initial compounds **Ia–Ic** were prepared by the procedure described earlier [12]. TLC was carried out on Silufol-254 plates, eluent is EtOH.

General procedure. To a solution of 0.025 mol of KOH in 20 ml of water was added 0.020 mol of pyridone **Ia-Ic** under stirring. Then to this mixture was added a solution of 0.024 mol of nitrobenzaldehyde in 30 ml of THF. The reaction mixture was kept at 35ºC for 16–36 h. After cooling the mixture was neutralized with acetic acid to pH 6 and diluted with water. The precipitate formed was filtered off, dried, refluxed in ethanol to remove admixture dissolved and then recrystalled from DMFA.

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