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CHEMISTRY OF HETERO ANALOGS OF ISOFLAVONES 25.* SYNTHESIS OF 2-ALKYL-3-(2-BENZIMIDAZOLYL)-CHROMONES

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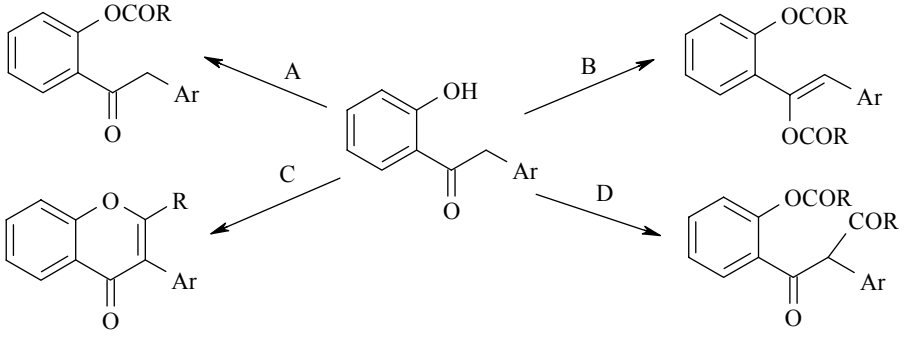
2-Alkyl-3-(1-methyl-2-benzimidazolyl)-7-acyloxychromones were synthesized by the reaction of substituted or unsubstituted 2-(2,4-dihydroxyphenacyl)-1-methylbenzimidazoles with the acid chlorides and anhydrides of carboxylic acids. The products were converted into 2-alkyl-7-hydroxychromones as a result of acid hydrolysis.

Keywords: 2-alkylchromone, acid chlorides, acid anhydrides, hetero analogs of isoflavones, Kostanetskii–Robinson reaction.

One of the most convenient methods for the synthesis of 3-(het)arylchromones is the reaction of α-(het)aryl-2-hydroxyacetophenones with the anhydrides and acid chlorides of carboxylic acids in the presence of salts of the same acid or organic base (pyridine, triethylamine) (the Kostanetskii–Robinson method) and also the reaction with carboxylic esters in the presence of metal alcoholates (the Claisen reaction). However, in spite of the profusion of reagents that can be used in the Kostanetskii–Robinson reaction currently only acetic and trifluoroacetic anhydrides and ethoxalyl chloride have been used. This can be explained by the fact that the formation of 2-alkylchromones in this reaction is not the only possible direction for the reaction.



* For Communication 24 see [1].

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Thus, depending on the reaction conditions, the reaction of α-(het)aryl-2-hydroxyacetophenones with carboxylic acid chlorides or anhydrides can take place in several alternative directions with the formation of: A) 2-acyloxydeoxybenzoins; B) 1,2′-diacyloxystilbenes [2]; C) 2-alkylchromones; D) α-acyl-2-acyloxydeoxybenzoins [3]. On the other hand, the reaction of α-hetaryl-2,4-dihydroxyacetophenones with acetic anhydride in pyridine leads only to the formation of 7-acetoxy-2-alkyl-3-hetarylchromones [4].

The aim of the present work was to study the reaction of α-hetaryl-2,4-dihydroxyacetophenones with the acid chlorides and anhydrides of carboxylic acids and subsequent branching (and, accordingly, increase in size) of the alkyl substituent – propionic, isobutyric, and pivalic acids. As model α-hetaryl-2-hydroxyacetophenone we used 2-(2,4-dihydroxyphenacyl)-1-methylbenzimidazole (**1a**) [5], which is distinguished by considerable activity in the α-methylene unit, and its ethyl homolog 2-(5-ethyl-2,4-dihydroxyphenacyl)-1-methylbenzimidazole (**1b**) [6].

The acylation of compounds **1a**,**b** was conducted in pyridine at room temperature. 7-Acyloxy-2-alkylchromones **2a**,**b**-**4a**,**b** were produced as a result of the reaction, but partial saponification of the 7-acyloxy group occurred during the isolation of compounds **2a**,**b** and **3a**,**b** from the reaction mixture. For this reason the reaction mixture was subjected to acid hydrolysis without identification of the 7-O-acyl derivative, and as a result the 2-alkyl-7-hydroxychromones **5a**,**b** and **6a**,**b** were isolated (Table 1).

It is interesting that in the case of 7-hydroxy-2-isopropylchromones **6a**,**b** the signals of the methyl groups appear in the form of two doublets, demonstrating that they are diastereotopic. This may result from the impossibility of rotation about the $C_{(3)}$–benzimidazole bond on account of the closely located bulky isopropyl group and the benzimidazole ring, as was observed in the case of the benzodioxane analogs of isoflavones [7, 8]. In order to define this effect more precisely we synthesized its analog **3c** unsubstituted at the benzimidazole NH group. In this compound the signals of the methyl groups in the ^{1}H NMR spectrum represent a doublet, demonstrating their equivalence.

In the case of the acylation of the ketones **1a**,**b** with pivaloyl chloride 2-*tert*-butyl-7-pivaloyloxychromones **4a**,**b** were obtained; 2-*tert*-butyl-7-hydroxychromone **7b** was obtained by the acid hydrolysis of compound **4b**.

Thus, we have demonstrated the fundamental possibility of using the anhydrides and acid chlorides of higher aliphatic carboxylic acids for the synthesis of 2-substituted hetero analogs of isoflavones, and this can be used for the planned synthesis of 2-alkylchromones. As found, in spite of the considerable size of the benzimidazole residue at position 3 of the chromone system chromones containing a *tert*-butyl group can be obtained by this method.

TABLE 1. The Characteristics of 3-(2-Benzimidazolyl)chromones **3**-**7**

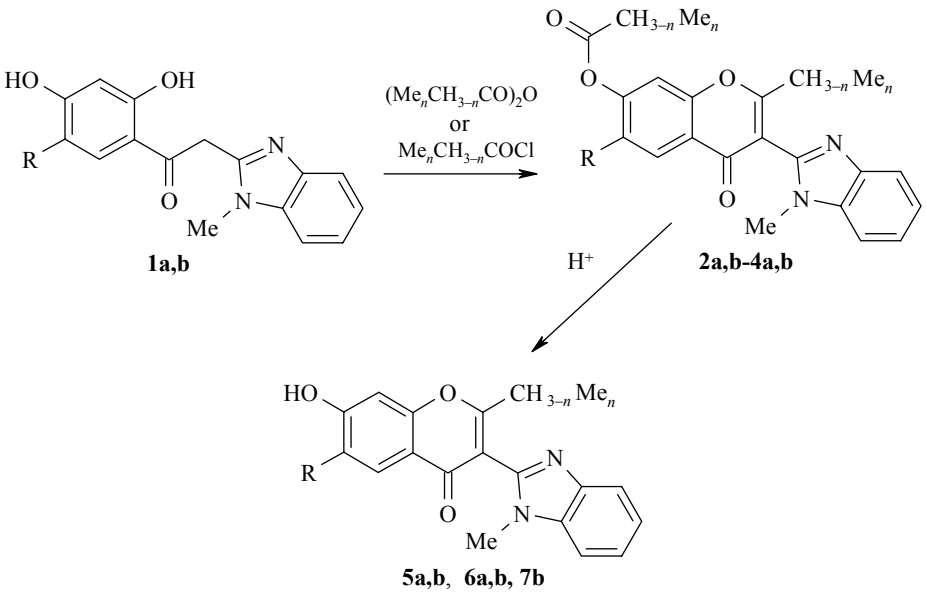
Compound	Empirical formula	Found, N % / Calculated, N %	mp, °C	Выход, %
3c	$C_{23}H_{22}N_2O_4$	6.93 / 7.17	174-176	73
4a	$C_{26}H_{28}N_2O_4$	6.80 / 6.48	138-139	65
4b	$C_{28}H_{32}N_2O_4$	6.00 / 6.08	212-214	70
5a	$C_{19}H_{16}N_2O_3$	8.66 / 8.74	289-290	65
5b	$C_{21}H_{20}N_2O_3$	8.25 / 8.04	268-270	58
6a	$C_{20}H_{18}N_2O_3$	8.16 / 8.38	299-300	56
6b	$C_{22}H_{22}N_2O_3$	7.60 / 7.73	327-328	43
7b	$C_{23}H_{24}N_2O_3$	7.59 / 7.44	334-335	75

TABLE 2. The ^{1}H NMR Spectra of 3-(2-Benzimidazolyl)chromones **3-7**

Com-pound	Chemical shifts (DMSO-d_6); δ, ppm (*J*, Hz)						
	Chromone residue					Het*	
	2-R	H-5 (1H)	6-R	7-R	H-8 (1H)	H-4 and H-7 (2H, m)	H-5 and H-6 (2H, m)
3c	1.32 (6H, d, *J* = 7.2); 3.83 (1H, m)	8.20 (d, *J* = 8.5)	7.34 (1H, dd, *J* = 8.5, *J* = 2.0)	1.32 (6H, 2d, *J* = 7.2) 2.90 (1H, m)	7.66 (d, *J* = 2.0)	7.69, 7.59	7.21
4a	1.18 (9H, s)	8.10 (d, *J* = 8.5)	7.30 (m)	1.36 (9H, s)	7.68 (d, *J* = 2.0)	7.66, 7.60	7.30
4b	1.18 (9H, s)	7.95 (s)	1.15 (3H, t, *J* = 7.0); 2.61 (2H, q, *J* = 7.0)	1.37 (9H, s)	6.96 (s)	7.61	7.28
5a	1.20 (3H, t, *J* = 7.0); 2.60 (2H, q, *J* = 7.0)	7.94 (d, *J* = 8.5)	6.97 (dd, *J* = 8.5, *J* = 2.0)	10.97 (1H, s)	6.94 (d, *J* = 2.0)	7.63	7.30
5b	1.20 (6H, m); 2.68 (4H, m)	7.81 (s)	—*[2]	10.90 (1H, s)	6.98 (s)	7.65	7.30
6a	1.15, 1.19 (6H, 2d, *J* = 7.2); 2.88 (1H, m)	7.90 (d, *J* = 8.5)	6.97 (1H, dd, *J* = 8.5, *J* = 2.0)	10.96 (1H, s)	6.95 (d, *J* = 2.0)	7.63	7.28
6b	1.18 (6H, d, *J* = 7.2); 2.91 (1H, m)	7.79 (s)	1.20 (3H, t, *J* = 7.0); 2.67 (2H, q, *J* = 7.0)	10.86 (1H, s)	6.97 (s)	7.64	7.28
7b	1.18 (9H, s)	7.78 (s)	1.20 (3H, t, *J* = 7.0); 2.71 (2H, q, *J* = 7.0)	10.86 (1H, s)	7.01 (s)	7.68	7.30

* The N–CH_3 signal (3H, s) is observed in the region of 3.62-3.64 ppm, the NH group (1H, s) of compound **3c** at 12.60 ppm.

*[2] Superimposed on the signals of the 2-Et group.



1a–6a R = H, **1b-7b** R = Et, **2a,b, 5a,b** *n* = 1, **3a,b, 6a,b** *n* = 2, **4a,b, 7b** *n* = 3

EXPERIMENTAL

The reactions were monitored and the purity of the compounds was assessed by TLC on Silufol UV-254 and Merck 60 F_{254} plates. Chloroform–methanol (9:1, 95:5) and hexane–ethyl acetate (1:2) mixtures were used as eluent. The ^{1}H NMR spectra were measured on a Varian VXR 300 instrument (300 MHz) with TMS as internal standard. The spectral data are given in Table 2.

Production of 2-Alkyl-3-(1-methyl-2-benzimidazolyl)-7-hydroxychromones 5a,b and 6a,b (General Method). A mixture of the initial ketone **1a**,**b** (10 mmol) and propionic or isobutyric anhydride (50-60 mmol) in absolute pyridine (25 ml) was kept at room temperature for 72 h. The reaction mixture was poured onto ice, and the precipitate after solidification was filtered off. The residue, representing a mixture of the respective 7-acyloxy-2-alkylchromone **2a**,**b** and **3a**,**b** and 2-alkyl-7-hydroxychromone **5a**,**b** and **6a**,**b**, was transferred to ethanol (50-70 ml) containing HCl (2-3 ml) and boiled for 20-30 h. The reaction mixture was neutralized with dilute sodium hydroxide solution and diluted with water, and the precipitated 7-hydroxychromone was filtered off. Compounds **5a**,**b** were crystallized from a mixture of DMF and water, and compounds **6a**,**b** from 2-propanol.

3-(1H-Benzimidazol-2-yl)-2-isopropyl-4-oxo-4H-chromen-7-yl 2-Methylpropionate (3c). This compound was obtained similarly to compounds **3a**,**b** from compound **1c** (10 mmol) [5] and isobutyraldehyde (60 mmol). The product was crystallized from acetonitrile.

2-*tert*-Butyl-3-(1-methyl-1H-benzimidazol-2-yl)-4-oxo-4H-chromen-7-yl Pivalate (4a) and 2-*tert*-Butyl-3-(1-methyl-1H-benzimidazol-2-yl)-6-ethyl-4-oxo-4H-chromen-7-yl Pivalate (4b). These compounds were obtained similarly to compounds **3a**,**b** with a 5-6-fold excess of pivaloyl chloride. The reaction mixture was poured onto ice, and after the mixture had set the precipitate was filtered off and crystallized from heptane or hexane.

2-*tert*-Buty`l-7-hydroxy-3-(1-methyl-1H-benzimidazol-2-yl)-6-ethyl-4H-chromen-4-one (7b). Pivaloyl derivative **4b** (1 g) was dissolved in alcohol (30 ml) and HCl (1 ml) and heated for 20-30 h; after neutralization with dilute sodium hydroxide solution the precipitate was filtered off and crystallized from aqueous ethanol.

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