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SYNTHESIS AND ISOMERISM OF 2-(3,5-DIARYL-1H-PYRAZOL-4-YL)-1H-BENZIMIDAZOLES

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2-(3,5-Diaryl-1H-pyrazol-4-yl)-1H-benzimidazoles have been obtained by the cyclocondensation of 2-phenacyl-1H-benzimidazoles with 4-nitro- and 4-methoxybenzoylhydrazines. The reaction mechanism and the isomerism of the obtained products are discussed. According to the data of ^{1}H NMR spectroscopy the stabilized isomer is that in which the electron-withdrawing aryl substituent is located in position 3 and the electron-donating substituent in position 5 of the pyrazole ring.

Keywords: aroylhydrazines, aroylhydrazones, benzimidazoles, pyrazoles, tautomerism.

It was found previously [1] that acylhydrazones of β-dicarbonyl compounds are cyclized into pyrazoles as a result of condensation of the carbonyl group of the acylhydrazone fragment and an activated methylene group, when a methyl or phenyl substituent is present on the nitrogen atom next to the carbonyl group of the hydrazone fragment. Later [2] we showed that aroylhydrazones of 2-phenacyl-1H-benzimidazole in the absence of such substituents also undergo an analogous cyclocondensation with the formation of 2-(3-aryl-5-phenyl-1H-pyrazol-4-yl)-1H-benzimidazoles on heating to 200°C. In this case it is possible to combine the preparation of the hydrazones and their cyclocondensation in one process, however the reaction proceeds only with benzoylhydrazine and with its derivatives containing electron-withdrawing substituents in the benzene ring. Up to the present time we have produced new experimental data which indicate the broader possibilities of this reaction and enable elucidation of its mechanism.

We have found that the interaction of a series of 2-phenacyl-1H-benzimidazoles **1a-e** with 4-nitrobenzoylhydrazine **2a**, proceeding through hydrazones **3a-e** and their subsequent cyclocondensation, leads to 2-[5-aryl-3-(4-nitrophenyl)-1H-pyrazol-4-yl]-1H-benzimidazoles **4a-e**. Derivatives **4a,c,d** with various aryl substituents in positions 3 and 5 of the pyrazole ring therefore exist in DMSO-d_6 solution in equilibrium with the tautomeric forms **4'a,c,d**.

The reaction occurs smoothly on heating in DMSO at 150°C for 1 h with triethylamine hydrochloride as catalyst.

4-Methoxybenzoylhydrazine **2b**, the electrophilicity of the carbonyl group of which is reduced due to the electron-donating effect of the MeO group, reacts under more rigid conditions. The interaction of reactants **1a** and **2b** occurs at 200°C, in the presence of a small amount of diglyme preventing crystallization of

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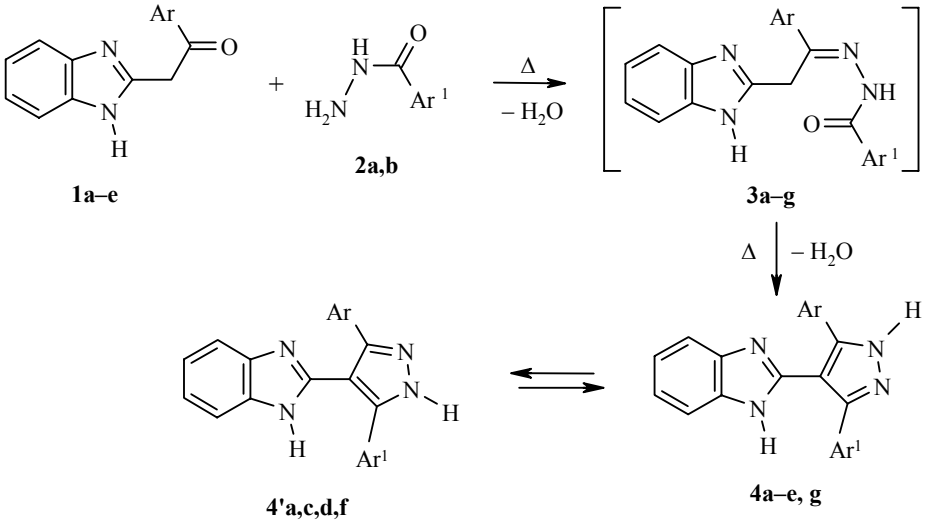
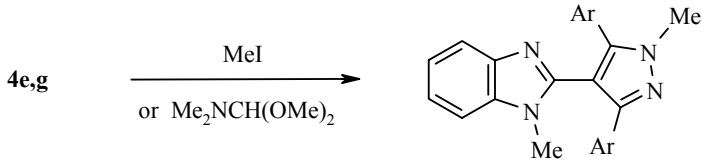
hydrazone **3f**, and is complete after 5 h with the formation exclusively of product **4'f**. The analogous cyclocondensation involving reactant **1b** is complicated by side reactions. In this case it is far more convenient to carry out the reaction in two stages. First hydrazone **3g** is obtained, which is then cyclized in boiling ethylene glycol, and is complete after 5 h with the formation of product **4g**.



1a–e **2a,b** **3a–g** **4'a,c,d,f** **4a–e, g**

1 a Ar = Ph, **b** Ar = 4-$MeOC_6H_4$, **c** Ar = 3,4,5-$(MeO)_3C_6H_2$, **d** Ar = 3-$O_2NC_6H_4$,
e Ar = 4-$O_2NC_6H_4$; **2 a** Ar^1 = 4-$O_2NC_6H_4$, **b** Ar^1 = 4-$MeOC_6H_4$; **3,4,4' a–e** Ar^1 = 4-$O_2NC_6H_4$,
a Ar = Ph, **b** Ar = 4-$MeOC_6H_4$, **c** Ar = 3,4,5-$(MeO)_3C_6H_2$, **d** Ar = 3-$O_2NC_6H_4$, **e** Ar = 4-$O_2NC_6H_4$;
f Ar = Ph, Ar^1 = 4-$MeOC_6H_4$; **g** Ar = Ar^1 = 4-$MeOC_6H_4$

We also carried out the methylation of product **4e** with methyl iodide, using potassium hydroxide as base, and product **4g** with the dimethylacetal of DMF, and obtained the dimethyl derivatives **5a,b**, which are convenient as comparison subjects when studying the isomerism of compounds of types **4** and **4'** by ^{1}H NMR.



4e,g **5a,b**

5 a Ar = 4-$O_2NC_6H_4$, **b** Ar = 4-$MeOC_6H_4$

The structure and composition of the synthesized compounds **3g, 4a-e,g, 4'f,** and **5a,b** were confirmed by data of elemental analysis (Table 1) and ^{1}H NMR spectra (Table 2).

Assignment of the signals in the ^{1}H NMR spectra of model compounds **5a,b** was made with the aid of NOE and COSY experiments. The protons of the nitrophenyl substituents gave doublets at 7.67, 8.18 and 7.74, 8.25 ppm, and the protons of the methoxyphenyl groups at 6.83, 7.32 and 6.93, 7.36 ppm. The spin connection between them follows from the presence of COSY spectra correlations. In both compounds the lower field signals correspond to the 5'-substituent of the pyrazole ring. This follows from the presence of a NOE

correlation in the NOESY spectrum between the *ortho* protons of this aryl substituent and the signal of the 1'-Me group. Such a spectral picture is possibly caused by the fact that the electron-donating effect of the pyrazole ring nitrogen atom acts on the substituent at position 3' and the electron-withdrawing influence of the benzimidazole fragment acts on the substituent at position 5'.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3g	$C_{24}H_{22}N_4O_3$	69.32 / 69.55	5.48 / 5.35	13.38 / 13.52	243.5-245.0	86
4a	$C_{22}H_{15}N_5O_2$	69.15 / 69.28	3.75 / 3.96	18.18 / 18.36	312.0-313.5	88
4b	$C_{23}H_{17}N_5O_3$	67.07 / 67.15	4.08 / 4.16	16.86 / 17.02	304.0-305.5	81
4c	$C_{25}H_{21}N_5O_5$	63.47 / 63.69	4.36 / 4.49	14.68 / 14.85	284.0-285.5	57
4d	$C_{22}H_{14}N_6O_4 \times H_2O$	59.52 / 59.46	3.52 / 3.63	18.72 / 18.91	183.0-184.5	88
4e	$C_{22}H_{14}N_6O_4$	61.85 / 61.97	3.24 / 3.31	19.58 / 19.71	> 360.0	88
4'f	$C_{23}H_{18}N_4O$	75.27 / 75.39	4.78 / 4.95	15.18 / 15.29	259.5-261.0	92
4g	$C_{24}H_{20}N_4O_2$	72.56 / 72.71	4.94 / 5.08	13.95 / 14.13	282.0-283.5	78
5a	$C_{24}H_{18}N_6O_4$	63.27 / 63.43	4.12 / 3.99	18.24 / 18.49	259.0-260.5	72
5b	$C_{26}H_{24}N_4O_2$	73.44 / 73.57	5.53 / 5.70	13.07 / 13.20	145.0-146.5	85

On comparing the ^{1}H NMR spectra of model compounds **5a,b** and also of compounds **4a-e,g** and **4'f** the following special features of their isomerism were established.

For compounds **4d,e,g**, containing Ar and Ar^1 substituents of the same or closely similar electronic nature, a rapid migration of proton between the pyrazole ring nitrogens is characteristic, though the proton is found with practically the same probability on each of them. In this case the individual tautomers were not distinguished since the substituents Ar and Ar^1 are not different in belonging to positions 3 and 5 of the pyrazole ring and, when Ar = Ar^1, appear equivalent.

For compounds **4a,c** with substituents Ar and Ar^1 differing significantly in electronic nature, the appearance in the spectrum of individual tautomers as a doubling of the corresponding signals is characteristic. The chemical shifts and the integrated intensities of these signals permits discrimination of the tautomers and their relative content. Tautomers **4a,c**, in which the electron-withdrawing substituent occupies position 3', (80 and 75% respectively in the equilibrium mixture) are the more stable.

For compounds **4b** and **4'f**, in which one aryl substituent is 4-$MeOC_6H_4$ and the second is 4-$O_2NC_6H_4$ or Ph, the individual tautomers also did not appear. The compounds exist practically completely in the form of the isomer with location of the electron-donating aryl substituent at position 5', in which it probably forms an energetically advantageous system of conjugation with the benzimidazole fragment.

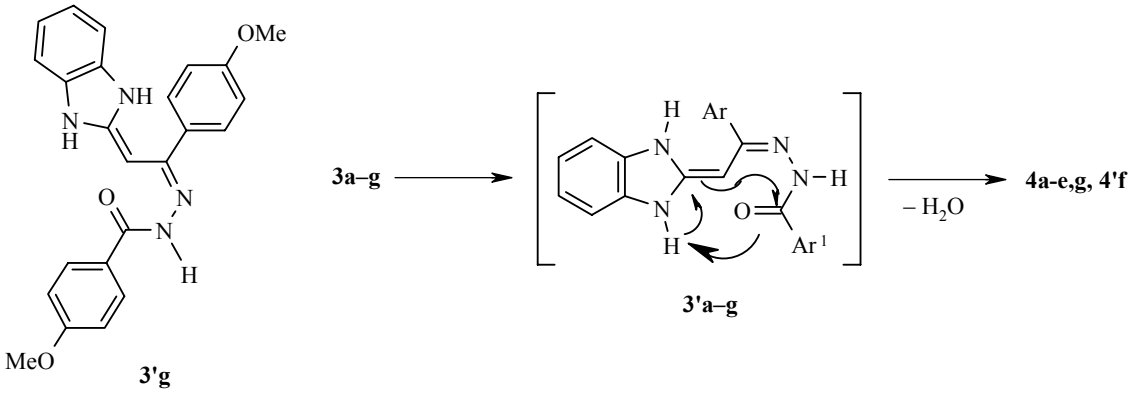
It should be mentioned that, according to data of ^{1}H NMR spectra, hydrazone **3g** contains contamination by the compound of isomeric structure (~7%). Separation of the isomers is laborious since they readily interconvert. Although we previously proposed an enehydrazine structure [2] for the analogous isomer of the benzoylhydrazone of 2-phenacyl-1H-benzimidazole, we propose an argument in favor of a heterylidene structure of type **3'** in this work. First of all, tautomerism of this type is characteristic of the initial keto compounds **1a-e**, and they exist predominantly in the heterylidene form [3, 4]. Their hydrazones [4, 5], alkyl- [6, 7], and arylhydrazones

TABLE 2. Parameters of ^{1}H NMR Spectra of the Synthesized Compounds

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
3g and **3'g**	3.81, 3.88 (3H, 3H, two s, CH_3O); 4.49 (2H, s, CH_2); 7.03 (2H, d, *J* = 8.7, H-3,5 Ar); 7.16-7.23 (4H, m, H-3,5 COAr, H-5,6); 7.51-7.54, 7.62-7.65 (1H, 1H, two m, H-7,4); 7.95, 8.18 (2H, 2H, two d, *J* = 7.5, H-2,6 Ar, H-2,6 COAr); 12.71, 12.78 (1H, 1H, two s, H-1, NHCO) and 3.76, 3.77 (3H, 3H, two s, CH_3O); 5.44 (1H, s, =CH–C=N), 6.94 (2H, d, *J* = 8.7, H-3,5 Ar); 7.41-7.44 (2H, m, H-4,7); 10.40, 10.48, 12.10 (1H, 1H, 1H, three s, H-1,3, NHCO), remaining signals are overlapped by the signals of **3g**
4a	7.20-7.23 (2H, m, H-4,5); 7.28-7.30 (1H, m, H-4 Ph); 7.38-7.48 (5H, m, H-2,3,5,6 Ph, H-7); 7.71-7.75 (3H, m, H-4, H-2,6 NC_6H_4); 8.17, 8.25 (1.60H, 0.40H, two d, *J* = 8.4, H-3,5 NC_6H_4); 12.59 (1H, s, H-1); 14.07 (1H, s, H-1')
4b	3.73 (3H, s, CH_3O); 6.94 (2H, d, *J* = 8.1, H-3,5 OC_6H_4); 7.21-7.24 (2H, m, H-4,5); 7.41-7.44 (3H, m, H-7, H-2,6 OC_6H_4); 7.71-7.74 (3H, m, H-4, H-2,6 NC_6H_4); 8.18 (2H, d, *J* = 8.1, H-3,5 NC_6H_4); 12.56 (1H, s, H-1); 13.93 (1H, s, H-1')
4c	3.48, 3.55, 3.63 (0.45H, 5.55H, 3H, three s, $3CH_3O$); 6.85, 6.92 (0.30H, 1.70H, two s, C_6H_2); 7.22-7.25 (2H, m, H-4,5); 7.43-7.46 (1H, m, H-7); 7.70-7.77 (3H, m, H-4, H-2,6 NC_6H_4); 8.20, 8.25 (1.70H, 0.30H, d, *J* = 7.5, m, H-2,6 NC_6H_4); 12.62 (1H, s, H-1); 14.04 (1H, s, H-1')
4d	7.21-7.26 (2H, m, H-4,5); 7.43-7.45 (1H, m, H-7); 7.63-7.76 (4H, m, H-4, H-5 3-NC_6H_4, H-2,6 4-NC_6H_4); 7.88 (1H, d, *J* = 7.5, H-6 3-NC_6H_4); 8.18-8.25 (3H, m, H-4 3-NC_6H_4, H-3,5 4-NC_6H_4); 8.51 (1H, br. s, H-2 3-NC_6H_4); 12.61 (1H, s, H-1); 14.35 (1H, s, H-1')
4e	7.22-7.25 (2H, m, H-4,5); 7.43-7.46 (1H, m, H-7); 7.73-7.76 (5H, m, H-4, 2H-2,6 NC_6H_4); 8.23-8.25 (4H, m, 2H-3,5 NC_6H_4); 12.64 (1H, s, H-1); 14.40 (1H, s, H-1')
4'f	3.71 (3H, s, CH_3O); 6.89 (2H, d, *J* = 8.7, H-3,5Ar); 7.17-7.22 (2H, m, H-4,5); 7.29 (2H, d, *J* = 8.7, H-2,6 Ar); 7.31-7.34 (1H, m, H-7); 7.40-7.48 (5H, m, C_6H_5); 7.67-7.70 (1H, m, H-4); 12.48 (1H, s, H-1); 13.61 (1H, s, H-1')
4g	3.70 (6H, s, CH_3O); 6.85-6.89 (4H, m, 2H-3,5 Ar); 7.18-7.21 (2H, m, H-4,5); 7.38-7.41 (5H, m, 2H-2,6 Ar, H-7); 7.67-7.69 (1H, m, H-4); 12.45 (1H, s, H-1); 13.46 (1H, s, H-1')
5a	3.34 (3H, s, 1-CH_3); 4.03 (3H, s, 1'-CH_3); 7.21-7.29 (2H, m, H-4,5); 7.48 (1H, d, *J* = 7.2, H-7); 7.66-7.68 (3H, m, H-4, H-2,6 3-Ar); 7.74 (2H, d, *J* = 8.7, H-2,6 5-Ar); 8.18 (2H, d, *J* = 8.7, H-3,5 3-Ar); 8.25 (2H, d, *J* = 8.7, H-3,5 5-Ar)
5b	3.26 (3H, s, 1-CH_3); 3.69 (3H, s, 3-CH_3O Ar); 3.72 (3H, s, 5-CH_3O NC_6H_4); 3.89 (3H, s, 1'-CH_3); 6.83 (2H, d, *J* = 8.0, H-3,5 3-Ar); 6.93 (2H, d, *J* = 8.0, H-3,5 5-Ar); 7.20-7.22 (2H, m, H-4,5); 7.32 (2H, d, *J* = 8.0, H-2,6 3-Ar); 7.36 (2H, d, *J* = 8.0, H-2,6 5-Ar); 7.44-7.46 (1H, m, H-7); 7.64-7.66 (1H, m, H-4)

[8-10] do not display an inclination towards such isomerism, since they contain a less acidic methylene group. In their turn acylhydrazones are distinguished by the high polarity of the hydrazone azomethine bond, and consequently in their nature they are closer to the initial keto compounds **1a-e**. Secondly, in the ^{1}H NMR spectrum of compound **3g** many signals of its isomer (both OMe, H-1,3,4,7, NHC=O, different Ar portion), were displaced towards high field. This may be caused by the electron-donating influence of the nitrogen atoms of the heterylidene fragment and permits the **3'g** configuration to be definitely probable for the minor isomer. On the other hand in the enehydrazone form the benzimidazole fragment shows an electron-withdrawing action, which must lead to a displacement of the indicated signals towards low field.

We suggest that these circumstances clarify the mechanism of the cyclocondensation being studied. Probably, the significant moment of the process is the isomerization of aroylhydrazones **3a-g** into the hetarylidene forms **3'a-g**, in which there is a nucleophilic center of the enamine type, sufficiently reactive at elevated temperatures for intramolecular attack at the carbonyl group. The increased electrophilicity of this carbonyl group assists cyclization, which is also shown in the clear difference discovered by us of the conditions of carrying out the reaction with aroylhydrazines **2a,b**.



The cyclocondensation of 2-phenacyl-1H-benzimidazoles with aroylhydrazines is therefore a fairly general method of obtaining 2-(3,5-diaryl-1H-pyrazol-4-yl)-1H-benzimidazoles, but in individual cases the synthesis is best carried out in two stages with the intermediate isolation of the aroylhydrazone.

EXPERIMENTAL

A check on the progress of reactions and the purity of the synthesized compounds was carried out by TLC on Silufol UV-254 plates in the solvent system benzene–ethanol, 9 : 1, visualizing with UV light. Before carrying out elemental analysis and spectral investigations compounds **4a-e,g, 4'f**, and **5a** were dried for 3 h at 150°C, and **5b** for 6 h at 115°C in a water-jet pump vacuum. The ^{1}H NMR spectra of compounds were recorded on a Varian VXR-300 spectrometer (300 MHz) in DMSO-d_6, standard was TMS. The NOE and COSY experiments were carried out on a Varian Mercury 400 spectrometer (400 MHz).

4-Methoxybenzoylhydrazone of 2-(4-Methoxyphenacyl)-1H-benzimidazole (3g). A mixture of compound **1b** (1.065 g, 4 mmol) and hydrazide **2b** (0.664 g, 4 mmol), 1-butanol (4 ml) and glacial acetic acid (4 drops) was maintained at 120°C for 3 h. The cooled mass was filtered, the solid product **3g** was washed with 2-propanol, and crystallized from a mixture of pyridine–water, 2, 1.

2-[3-(4-Nitrophenyl)-5-phenyl-1H-pyrazol-4-yl]-1H-benzimidazole (4a). A mixture of compound **1a** (0.236 g, 1 mmol), hydrazide **2a** (0.199 g, 1.1 mmol), triethylamine hydrochloride (0.028 g, 0.2 mmol), and DMSO (2 ml) was maintained at 145-150°C for 1 h. The reaction mixture was cooled to 100°C, diluted with water (1.0 ml), and heated with stirring until crystallization began. The cooled mixture was filtered, the solid product **4a** was washed with a 2-propanol–water, 1:1 mixture, and crystallized from a pyridine–water, 2:1 mixture.

Products 4b-e were obtained from compounds **1b-e** and **2a** analogously. On isolating compound **4c** the reaction mixture was diluted with water (3 ml). Compound **4e** was crystallized from a mixture of DMF–water, 2:1.

2-[5-(4-Methoxyphenyl)-3-phenyl-1H-pyrazol-4-yl]-1H-benzimidazole (4'f). A mixture of compound **1a** (2.36 g, 10 mmol), hydrazide **2b** (1.80 g, 11 mmol), and diglyme (2.0 ml) was heated using an oil bath at 200-205°C for 5 h. After cooling, the reaction mixture was diluted with ethanol (5 ml), warmed with stirring until crystallization began, and diluted with water (5 ml). The cooled mass was filtered, product **4'f** was washed with an ethanol–water 2:1 mixture, and after drying was obtained in an analytically pure state.

2-[3,5-Bis(4-methoxyphenyl)-1H-pyrazol-4-yl]-1H-benzimidazole (4g). A mixture of hydrazone **3g** (0.414 g, 1 mmol) and ethylene glycol (2.0 ml) was boiled for 5 h. The cooled mass was filtered, the solid product **4g** was washed with a 2-propanol–water, 1:1 mixture, and recrystallized from a DMF–H_2O, 2:1 mixture.

1-Methyl-2-[1-methyl-3,5-bis(4-nitrophenyl)-1H-pyrazol-4-yl]-1H-benzimidazole (5a). Methyl iodide (0.312 ml, 5 mmol) was added dropwise during 15 min with stirring by a magnetic stirrer to a mixture of compound **4e** (0.426 g, 1 mmol), finely powdered potassium hydroxide (0.56 g, 10 mmol), and DMSO (3 ml) at 15-20°C. The mixture was stirred for a further 30 min and diluted with water (5 ml). The resulting solid product **5a** was filtered off, washed with a mixture of 2-propanol–water, 1:1, and crystallized from DMF–water, 3:1.

2-[3,5-Bis(4-methoxyphenyl)-1-methyl-1H-pyrazol-4-yl]-1-methyl-1H-benzimidazole (5b). A mixture of compound **4g** (0.396 g, 1 mmol), DMF dimethylacetal (1.5 ml), and anhydrous dioxane (2.5 ml) was maintained at 105°C for 10 h. The reaction mixture was carefully diluted with water (4 ml) with stirring. The cooled mass was filtered, the solid product **5b** was dried, and obtained in analytically pure form.

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