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SYNTHESIS AND TAUTOMERISM OF 2-[3(5)-ARYL(METHYL)PYRAZOL-4-YL]-1-BENZIMIDAZOLES

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An efficient method has been developed for the synthesis of 2-[3(5)-aryl(methyl)pyrazol-4-yl]-1H-benzimidazoles by cyclocondensation of 2-acylmethyl-1H-benzimidazoles benzoylhydrazones with DMF dimethylacetal. The tautomerism of the compounds obtained via migrations of a proton between the pyrazole nitrogen atoms has been studied by ^{1}H NMR. The more stable tautomers have electron acceptor aryl substituents placed at position 3 of the pyrazole ring and electron donor aryl substituents or a methyl at position 5.

Keywords: benzimidazoles, DMF dimethylacetal, hydrazones, pyrazoles, tautomerism.

The tautomerism of pyrazole compounds due to the migrations of a proton between the nitrogen ring atoms has been systematically studied [1-3] since it depends unpredictable of the nature and position of the ring substituent. It influences the selectivity of a series of chemical reactions and has to be taken into account when determining the structure and chemical purity of the corresponding substrates by spectroscopic methods. The effect on it of the electronic effects of the two aryl substituents at positions 3 (or 5) and 4 of the heterocycle has not been studied up to this time. It is possible that such a situation is due to the absence of samples and methods suitable for carrying out a reliable investigation. Thus, starting from 2-phenacylbenzimidazole **1** *via* its formylation product **2** and subsequent reaction with hydrazine, we have obtained the pyrazole **3a** which, according to ^{1}H NMR data exists in solution in equilibrium with its tautomeric form **3'a** [4]. The signals of the pyrazole ring aromatic proton for both tautomers are seen separately and would seem suitable and unproblematic for qualitative and quantitative determination of the composition of the equilibrium. However, the hoped for assignment of signals to a specific tautomer is complicated by the lack of a sample for comparison. In addition, the method itself is limited for the preparation of a broad series of compounds for a number of reasons, in particular the poor selectivity in the final stage reaction. Hence we set ourselves the task of overcoming the problem by preparing a series of compounds of type **3** and studying their tautomeric behaviour.

Routes for an efficient synthetic method were not obvious and we therefore chose a method of trial and error in the reactions of 2-phenacylbenzimidazole **1** and its hydrazones. Hence we tried a possible synthetic route analogous to the known method of preparing 2-(4-pyrazolyl)benzimidazoles [5] based on the cyclocondensation of compound **1** with aroylhydrazines. However, the corresponding reaction with formylhydrazine occurs to give a mixture of products, from which we isolated only 1-(3-pyrazolyl)-benzimidazole **4**. The result of the reaction is unexpected. However, the structure of the product is not in doubt because we had obtained it before by refluxing 2-phenacylbenzimidazole hydrazone **5** in DMF [6].

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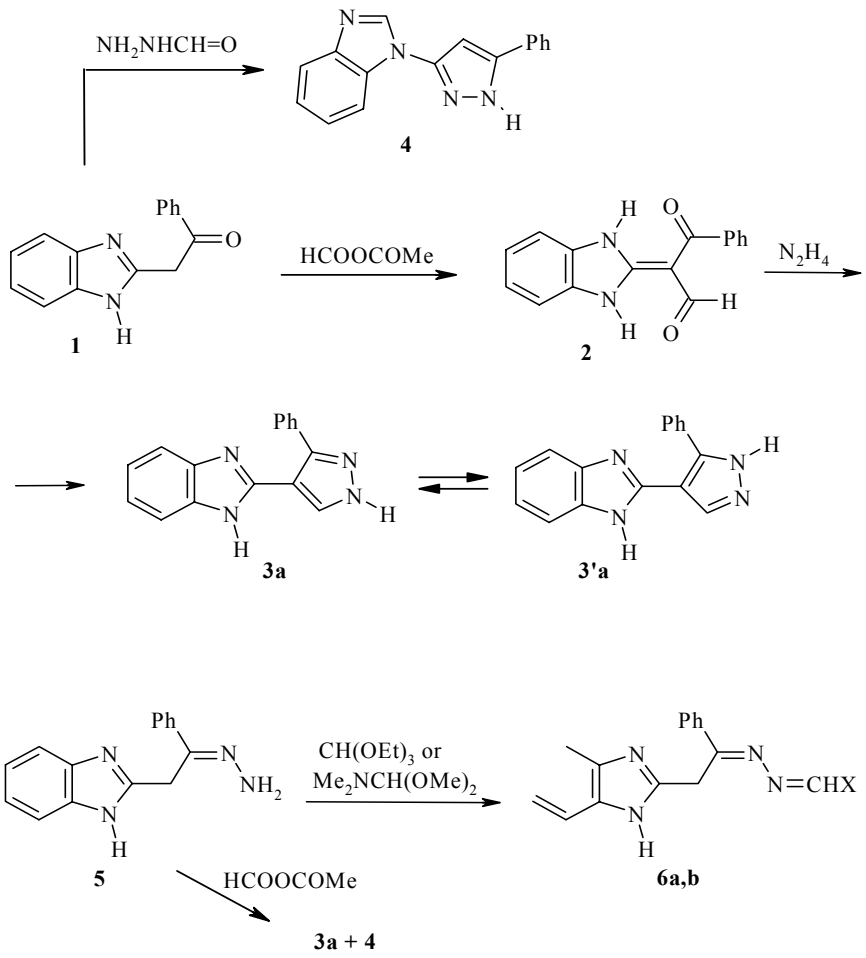


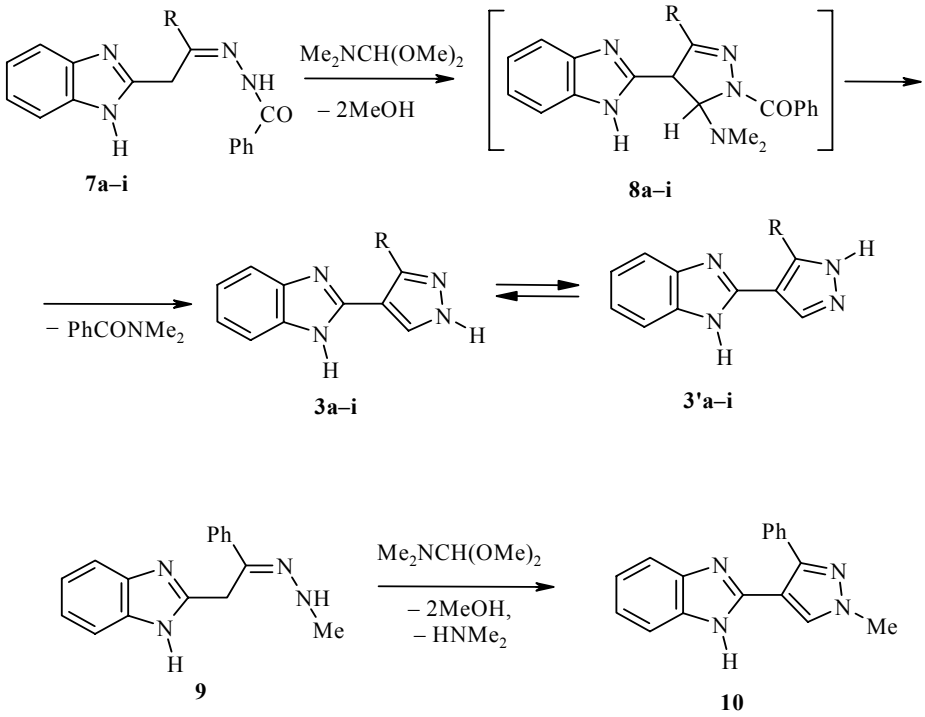
6 a X = OEt, **b** X = NMe_2

We have also investigated the report in [7] of a method of synthesis of pyrazoles based on the reaction of 2-phenacylazaheterocycle hydrazones with carboxylic anhydrides. However, the corresponding reaction of hydrazone **5** with acetoformic anhydride is complicated by the formation of compound **4** (by TLC analysis) and the target product **3a** could only be separated as the hydrochloride salt in 65% yield.

The intention of preparing compound **3a** by the reaction of hydrazone **5** with ethyl orthoformate or with DMF dimethylacetal was not realized. The reaction takes place at the hydrazone amino group to give compounds **6a,b**. In all attempts to carry out a selective subsequent intramolecular cyclization at the methylene group we did not achieve the hoped for results.

The synthetic problem was resolved *via* cyclocondensation of the 2-acylmethyl-1H-benzimidazoles **7a-i** using DMF dimethylacetal. The reaction possibly occurs via intermediate formation of a compound of type **8** and then to the target pyrazoles **3a-i** through loss of N,N-dimethylbenzamide. The process was carried out in dioxane at 80°C and is complete after 40 min without significant complication by side reactions. Dimethylbenzamide was observed in the reaction mixture by TLC but does not hinder the separation of the pyrazoles in high yields (75-99%) because of its increased solubility.

The result and selectivity of the given reaction is difficult to predict since we previously found that such an electrophilic reagent as trifluoroacetic anhydride reacts with benzoylhydrazones of type **7** by a different route. Thus compound **7a** undergoes recyclization to form a pyrazole ring by opening of the benzimidazole [8] but compound **7i** undergoes polycyclocondensation to give [1,3,4]oxadiazolo[2',3':2,3]pyrimido[1,6-*a*]-



3, **3'**, **7 a** R = Ph, **b** R = 4-$MeOC_6H_4$, **c** R = 4-MeC_6H_4, **d** R = 3,4,5-$(MeO)_3C_6H_2$, **e** R = 3-ClC_6H_4, **f** R = 3-$O_2NC_6H_4$, **g** R = 4-$O_2NC_6H_4$ (g), **h** R = 2-furyl, **i** R = Me

benzimidazole [9]. None the less the synthetic method we have developed for type **3** pyrazoles is quite efficient and likely to have a broader applicability. In particular it was found that 2-phenacylbenzimidazole methylhydrazone **9** also readily gives the 1-methyl-3-phenyl-substituted pyrazole **10** which has an obvious structural similarity to tautomer **3a** and was used by us as a model compound for studying the tautomerism of type **3** compounds in DMSO-d_6.

The physicochemical parameters for the novel compounds are given in Table 1 and ^{1}H NMR spectral data in Table 2.

In the ^{1}H NMR spectrum of compound **10** the pyrazole ring 5 proton resonates at 8.25 ppm. Hence the singlets in compound **3a** at 8.31 and 8.08 ppm correspond to the tautomers **3a** and **3a'**. The signal assigned to tautomer **3'a** appears at higher field, apparently quite consistently. In fact, in this structure the nitrogen atom at position 1 of the pyrazole ring has a significant electron donor effect on position 3 of the ring. In tautomer **3a** such an effect is possible but is less efficient since the chain of conjugation is one multiple bond longer. In the spectra of the remaining compounds **3a-i** the signals for the pyrazole aromatic ring proton appear, respectively, in the range 8.27-8.46 and 8.03-8.19 ppm. Some shift of both signals occurs to low field with strengthening of the electron acceptor properties of the R substituent and is fully as expected. The quantitative composition of the tautomeric mixture can be determined from the ratio of integrated intensities of the signals mentioned. In some examples the signal for the pyrazole 3 proton is obscured by the signals for the R substituent (compounds **3e-h**). However, this situation does not hinder a study of the tautomerism since many other signals are doubled and have the same integrated intensity ratios. Thus the proton on the pyrazole ring nitrogen atom, in some cases the proton at position 1 of the benzimidazole ring, or the separate protons of the aromatic R substituent, and also methyl group of compound **3i** resonate as two signals which correspond to the two tautomers and are well separated with no other signal overlap in the majority of cases.

TABLE 1. Parameters for the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3b	$C_{17}H_{14}N_4O$	70.27 / 70.33	4.72 / 4.86	19.24 / 19.30	220.5-222	91
3c	$C_{17}H_{14}N_4$	74.36 / 74.43	5.03 / 5.14	20.28 / 20.42	163.5-165	96
3d	$C_{19}H_{18}N_4O_3$	65.06 / 65.13	5.12 / 5.18	15.81 / 15.99	155-158	75
3e	$C_{16}H_{11}ClN_4$	65.11 / 65.20	3.93 / 3.76	18.87 / 19.01	152.5-155	77
3f	$C_{16}H_{11}N_5O_2$	62.89 / 62.95	3.78 / 3.63	22.85 / 22.94	158-162	75
3g	$C_{16}H_{11}N_5O_2$	62.97 / 62.95	3.71 / 3.63	22.95 / 22.94	273.5-275	99
3h	$C_{14}H_{10}N_4O$	67.15 / 67.19	3.98 / 4.03	22.33 / 22.39	218.5-220	98
3i	$C_{11}H_{10}N_4$	66.59 / 66.65	5.02 / 5.08	28.17 / 28.26	248.5-250	82
6a	$C_{18}H_{18}N_4O$	70.42 / 70.57	5.86 / 5.92	18.15 / 18.29	180-182	89
6b	$C_{18}H_{19}N_5$	70.74 / 70.80	6.32 / 6.27	22.87 / 22.93	234-235.5	79
10	$C_{17}H_{14}N_4$	74.39 / 74.43	5.09 / 5.14	20.35 / 20.42	247-248.5	98

We have found that, in equilibrium solution, compounds **3a-i** contain the tautomer of type **3** in 47, 40, 43, 45, 65, 76, 76, 42, and 32% respectively. It is apparent that the content of tautomers **3a-g** increases with growth of the electron acceptor properties of the aryl fragment R (according to the σ-constant for the *m*- an *p*-substituent in the phenyl ring). The substituents R in compounds **3h-i** (2-furyl, Me) have a different steric effect on the close environment but have a clearly marked electron donor character and are able to stabilize tautomers of type **3'**.

We rationalize the observed tendency in the change of the tautomeric properties of compounds **3a-i** in the following way. The type **3** molecular system can be considered as a combination of three conjugated systems which have three interrelated and interacting points. One of these is the pyrrole type nitrogen atom which can arise from either of the two pyrazole ring nitrogen atoms (see mechanism in [5]) and have a marked electron donor effect. The second is the 2-benzimidazolyl fragment which has an electron acceptor effect. The third is the R substituent which has a changing nature and hence electronic properties. The pyrrole type nitrogen atom can have an electron donor effect on the benzimidazolyl fragment and electron acceptor substituent R in both tautomeric forms **3** and **3'** but in the latter the effect is less efficient because the chain of conjugation with substituent R is lengthened by one double bond. Hence an electron acceptor R substituent can stabilize tautomer form **3**. The benzimidazolyl fragment can have an electron acceptor effect on substituent R only in tautomer **3'**. Hence it is actually this tautomeric form which can stabilize electron donor substituents R.

Thus we have developed a preparatively convenient method for the synthesis of 2-(4-pyrazolyl)-1H-benzimidazoles containing a substituent at one of the carbon atoms of the pyrazole ring and studied their tautomerism. It was found that the more stable tautomer has electron acceptor aryl substituents at position 3 of the pyrazole ring but electron donor aryl or a methyl group at position 5.

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

Com-pound	Chemical shifts, δ, ppm. (*J*, Hz)
3a	7.11-7.19 (2H, m, H-5,6); 7.33-7.46 (4H, m, Ph: H-3,4,5 + H-7); 7.55-7.57 (1H, m, H-4); 7.83-7.86 (2H, d, *J* = 6.0, Ph: H-2–6); 8.08 and 8.31 (0.53 + 0.47H, two s, H-3'(5')); 12.38 and 12.43 (0.47 + 0.53H, br. s, H-1); 13.39 and 13.55 (0.47 + 0.53H, two s, H-1')
3b	3.77 and 3.81 (3H, two overlapping s, OCH_3); 6.94-6.96 and 7.03-7.06 (0.4 + 0.6H, two d, *J* = 7.2 and *J* = 7.8, 4-$CH_3OC_6H_4$: H-3,5); 7.14-7.17 (2H, m, H-5,6); 7.50-7.53 (2H, m, H-4,7); 7.63-7.86 (2H, m, 4-$CH_3OC_6H_4$: H-2,6); 8.07 and 8.31 (0.6 + 0.4H, two s, H-3'(5')); 12.48 (1H, br. s, H-1); 13.30 and 13.43 (0.4 + 0.6H, two s, H-1')
3c	2.35 (3H, s, CH_3); 7.14-7.17 (2H, m, H-5,6); 7.14-7.29 (2H, m, 4-$CH_3C_6H_4$: H-3,5); 7.51 (2H, m, H-4,7); 7.75 (2H, m, 4-$CH_3C_6H_4$: H-2,6); 8.08 and 8.31 (0.57 + 0.43H, two s, H-3'(5')); 12.39 (1H, br. s, H-1); 13.34 and 13.49 (0.43 + 0.57H, two s, H-1')
3d	3.72, 3.77 and 3.85 (9H, tree s, $3CH_3O$); 7.16-7.19 (2H, m, H-5,6); 7.52-7.55 (2H, m, H-4,7); 7.59 and 7.67 (0.45 + 0.55H, two s, $(CH_3O)_3C_6H_2$); 8.13 and 8.36 (0.55 + 0.45H, two s, H-3'(5')); 12.47 (1H, br. s, H-1); 13.34 and 13.56 (0.45 + 0.55H, two s, H-1')
3e	7.11-7.20 (2H, m, H-5,6); 7.41-7.57 (4H, m, H-4,7 + 3-ClC_6H_4: H-4,5); 7.87 (1H, m, 3-ClC_6H_4: H-6); 8.11 and 8.13 (1 + 0.35H, two overlapping s, 3-ClC_6H_4: H-2 + H-3'); 8.37 (0.65H, s, H-5'); 12.43 and 12.52 (0.65 + 0.35H, two s, H-1); 13.49 and 13.66 (0.65 + 0.35H, two s, H-1')
3f	7.14-7.22 (2H, m, H-5,6); 7.47-7.49 (1H, m, H-7); 7.57-7.59 (1H, m, H-4); 7.71-7.77 (1H, m, 3-$O_2NC_6H_4$: H-5); 8.21-8.28 (1 + 0.24H, m, 3-$O_2NC_6H_4$: H-4 + H-3'); 8.39-8.49 (1 + 0.76H, m, 3-$O_2NC_6H_4$: H-6 + H-5'); 9.13 (1H, s, 3-$O_2NC_6H_4$: H-2); 12.52 and 12.61 (0.76 + 0.24H, two s, H-1); 13.62 and 13.87 (0.76 + 0.24H, two s, H-1')
3g	7.18-7.20 (2H, m, H-5,6); 7.54-7.56 (2H, m, H-4,7); 8.26 (4 + 0.24H, m, 4-$O_2NC_6H_4$ + H-3'); 8.46 (0.76H, s, H-5'); 12.56 (1H, br.. s, H-1); 13.72 and 13.91 (0.24 + 0.76H, two s, H-1')
3h	6.60 and 6.73 (0.42 + 0.58H, two narrow m, 2-furyl: H-3); 7.19 (2H, m, H-5,6); 7.53-7.73 (3H, m, H-4,7 + 2-furyl: H-4); 7.88 (0.42H, narrow m, 2-furyl: H-2); 8.19 (0.58 + 0.58H, narrow m, 2-furyl: H-2 + H-3'); 8.40 (0.42H, s, H-5'); 12.42 and 12.58 (0.42 + 0.58H, two s, H-1); 13.44 and 13.75 (0.42 + 0.58H, two s, H-1')
3i	2.57 and 2.65 (0.32 + 0.68H, two s, CH_3); 7.10-7.17 (2H, m, H-5,6); 7.44-7.47 (1H, m, H-7); 7.57-7.59 (1H, m, H-4); 8.03 and 8.27 (0.68 + 0.32H, two s, H-3'(5')); 12.30 and 12.40 (0.32 + 0.68H, two s, H-1); 12.84 and 12.98 (0.32 + 0.68H, two s, H-1')
6a	1.23 (3H, t, *J* = 6.6, CH_3); 4.24 (2H, q, *J* = 6.6, OCH_2); 4.59 (2H, s, CCH_2); 7.04-7.13 (2H, m, H-5,6); 7.39-7.47 (5H, m, Ph: H-3,4,5 + H-4,7); 7.91 (2H, m, Ph: H-2,6); 8.49 (1H, s, OCH); 12.08 (1H, s, H-1)
6b	2.78 (6H, s, $2CH_3$); 7.08-7.11 (2H, m, H-5,6); 6.17-7.43 (6H, m, C_6H_5 + H-7); 7.53 (1H, m, H-4); 7.59 (1H, s, NCH); 12.15 (1H, s, H-1)
10	3.98 (3H, s, CH_3); 7.11-7.19 (2H, m, H-5,6); 7.32-7.40 (3H, m, Ph: H-3,4,5); 7.43-7.46 (1H, m, H-7); 7.56-7.59 (1H, m, H-4); 7.78-7.81 (2H, m, Ph: H-2–6); 8.25 (1H, s, H-5'); 12.35 (1H, s, H-1)

EXPERIMENTAL

Monitoring of the course of the reactions and purity of the compounds prepared was carried out by TLC on Silufol UV-254 plates in the solvent system benzene-ethanol (9: 1) and revealed using UV light. The ^{1}H NMR spectra of the compounds were recorded on a Varian VXR-300 instrument (300 MHz) using DMSO-d_6 and TMS as internal standard. For investigation of the pyrazole tautomerism a 0.1 M solution of the type **3** pyrazole in DMSO-d_6 was recorded twice at 3 and 24 h from the moment of preparation as a monitor of the achievement of equilibrium. The IR spectra of compounds **6a,b** were recorded on a UR-20 instrument for KBr tablets. The starting materials were prepared by known methods: **1** [10], **5** [6], **7a-i** [5, 11[, and **9** [12]. Before determination of elemental composition and spectroscopic properties the synthesized compounds were dried for 7 h in a water pump vacuum desiccator at 115°C.

2-[3(5)-Phenylpyrazol-4-yl]-1H-benzimidazole (3a). A. A solution prepared by mixing 90% formic acid (0.17 ml, 4 mmol) and acetic anhydride (0.8 ml, 8 mmol) was added to compound **1** (0.236 g, 1 mmol). The reaction mixture was stirred for 2-3 min and then held for 5 h at 20°C. Water (3 ml) was added and the product

was heated with stirring to reflux, and then evaporated to dryness using a water pump. The residue was treated with acetic acid (0.5 ml), conc. HCl (0.5 ml), and water (3 ml) and heated with stirring to reflux. After cooling, the precipitate was filtered off and washed with water and acetone. The **3a** hydrochloride obtained was mixed with acetone (1 ml) and 20% ammonia (0.5 ml) and then water (2 ml) and refluxed with stirring with evaporation of the acetone until crystallization of the product was complete. The precipitate was filtered, washed with water, and dried at 80°C. Yield 0.17 g (65%). According to TLC, mp, and ^{1}H NMR spectrum the product obtained was identical to a sample prepared by method [4].

B. A mixture of compound **7a** (0.354 g, 1 mmol), DMF dimethyl acetal (0.178 g, 1.5 mmol), and anhydrous dioxane (1 ml) was heated at 80°C for 40 min, stirring for the first 3-5 min for formation of homogeneous solution. Water was added and the product was refluxed, distilling off the solvent to a volume of 1-1.5 ml. After cooling, the precipitate was triturated to a powder, filtered, washed with water, and dried at 80°C. The product was formed in a pure state, its crystallization from ethanol-water (1: 1) occurring slowly with appreciable losses.

Compounds 3b-i were prepared similarly from the corresponding benzoylhydrazones **7b-i**. Compound **3f** was isolated as the hydrochloride salt, as in procedure A. Compound **3g** was crystallized from a ethanol–pyridine (5:1) and **3i** from pyridine–water (1:1).

1-(5-Phenylpyrazol-3-yl)-1H-benzimidazole (4). A mixture of compound **1** (0.236 g, 1 mmol), formylhydrazine (0.132 g, 2.2 mmol), triethylamine hydrochloride (0.028 mg, 0.2 mmol), and DMF (2.0 ml) was held for 4 h at 150-155°C. Water (3 ml) was added and the product was heated with stirring to reflux. After cooling, the precipitate was filtered off and crystallized from ethanol. Yield 0.18 g (69%). According to TLC, mp. and ^{1}H NMR spectrum the product obtained was identical to a sample prepared by method [6].

2-(5-Ethoxy-2-phenyl-3,4-diazapenta-2,4-dienyl)-1H-benzimidazole (6a). A mixture of compound **5** (0.25 g, 1 mmol), ethyl orthoformate (0.222 g, 1.5 mmol), and anhydrous pyridine (1.0 ml) was heated at 120°C for 2 h. Water (4 ml) was added and the product was refluxed, evaporating the solvent to 1-1.5 ml volume. The oil separated crystallized on trituration. The precipitate was filtered off, dried at 80°C, and crystallized from toluene. IR spectrum, ν, cm^{-1}: 1630 (C=N).

2-(5-Dimethylamino-2-phenyl-3,4-diazapenta-2,4-dienyl)-1H-benzimidazole (6b). A mixture of compound **5** (0.25 g, 1 mmol), anhydrous dioxane (1 ml), and DMF dimethylacetal (0.178 g, 1.5 mmol) was heated with stirring to formation of a homogeneous solution and stirred for 1 h at 95-100°C. After cooling, 2-propanol (1 ml) was added and stirred. The precipitate was filtered off, washed with 2-propanol, and dried in a water pump vacuum at 115°C. IR Spectrum, ν, cm^{-1}: 1640 (C=N).

2-[1-Methyl-3-phenylpyrazol-4-yl]-1H-benzimidazole (10). A mixture of compound **9** (0.264 g, 1 mmol), DMF dimethylacetal (0.143 g, 1.2 mmol) and anhydrous dioxane (1 ml) was heated at 80°C for 40 min. Water (1 ml) was added and the product was heated with stirring to reflux. After cooling, the precipitate was filtered off, washed with a mixture of 2-propanol and water (1:1), and crystallized from a mixture of pyridine and water (1:2).

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