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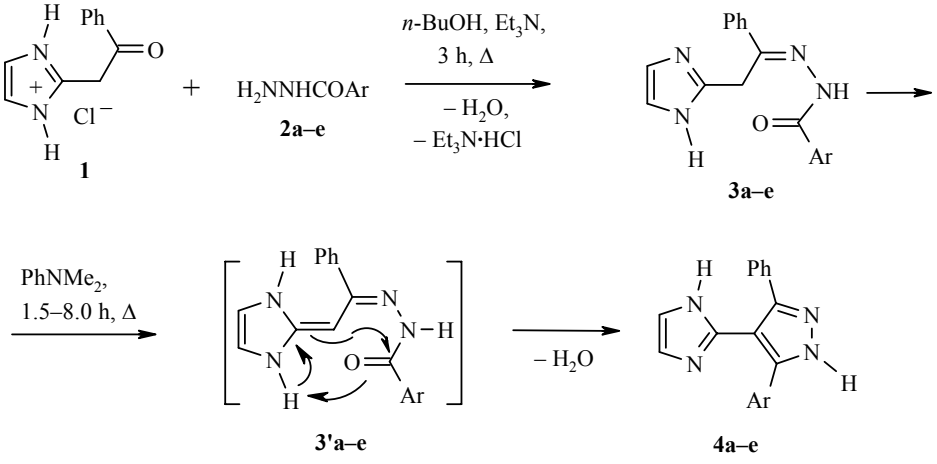
SYNTHESIS OF 3,5-DIARYL-4-(1H-IMIDAZOL-2-YL)-1H-PYRAZOLES FROM 2-PHENACYL-1H-IMIDAZOLE

I. B. Dzvinchuk[1]*, A. M. Nesterenko[1], and M. O. Lozinskii[1]

A method of synthesis is proposed for previously unknown 3,5-diaryl-4-(1H-imidazol-2-yl)-1H-pyrazoles based on the thermal intramolecular cyclocondensation of aroylhydrazones of 2-phenacyl-1H-imidazole.

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

Previously we showed that the interaction of 2-phenacyl-1H-benzimidazoles with aroylhydrazines at increased temperatures proceeds through the corresponding aroylhydrazones, which are then cyclized into 2-(3,5-diaryl-1H-pyrazol-4-yl)-1H-benzimidazoles [1, 2]. Probably this reaction has a more general character, and in the present study we used it for the synthesis of previously unknown derivatives of pyrazole with an imidazole substituent.



2, 3, 3', 4 a Ar = Ph, **b** Ar = 4-$MeOC_6H_4$, **c** Ar = 4-$O_2NC_6H_4$, **d** Ar = 3-pyridyl, **e** Ar = 4-pyridyl

* To whom correspondence should be addressed, e-mail: Rostov@bpci.kiev.ua.

[1] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kiev 02094, Ukraine.

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We found that the interaction of the hydrochloride of 2-phenacyl-1H-imidazole **1** with aroylhydrazines **2a-e** leads smoothly to the corresponding aroylhydrazones **3a-e**, which on boiling in N,N-dimethylaniline is cyclized with the formation of 3,5-diaryl-4-(1H-imidazol-2-yl)-1H-pyrazoles **4a-e**.

The first stage of the synthesis, proceeding on boiling in 1-butanol in the presence of triethylamine (to bind the hydrogen chloride) gives aroylhydrazones in 78-86% yield. The second stage in the majority of examples proceeds during 1.5 h and leads to the desired product **4a,c-e** in 75-90% yield. The exception was the cyclization of the anisoylhydrazone **3b** which, judging by TLC data, was not complete even after heating for 8 h. A further increase in reaction time was undesirable due to resinification, and product **4b** was isolated by us in a yield of only 34%.

The composition and structure of the synthesized compounds were confirmed by data of elemental analysis (Table 1) and of ^{1}H NMR spectra (Table 2).

According to data of ^{1}H NMR spectra, tautomerism is characteristic for compounds **4**, and is caused by the migration of proton between the nitrogen atoms in both heterocycles. For compounds **4a,c-e** the separate tautomers **A** and **B** (see Scheme to Table 3) are not fixed due to their rapid interconversion. On the other hand in the spectrum of compound **4b,** containing the most electron-donating substituent Ar = 4-$MeOC_6H_4$, doubling was observed of the doublet signal of its H-3,5 protons, while doublets at 6.86 and 6.94 ppm are converted into one doublet at 6.91 ppm after acceleration of the exchange processes by the addition of acetic acid to the sample being investigated (Fig. 1). With the aid of quantum-chemical calculations for tautomers **A** and **B** of this compound in DMSO we calculated the enthalpy of formation (76.91 and 78.78 kcal/mol) and the charge distribution. From these values a tendency became apparent towards the greater stability of tautomer **A** in which the substituent 4-$MeOC_6H_4$ is found at position 5, and the lowest electron surplus appears in it. Consequently the more low field of the two doublets in the spectrum of compound **4b** is assigned to tautomer **A**, the content of which is about 60% judging by the integral intensity of the signals of each of the tautomers.

The tautomerism was displayed differently (Table 3) for the structural analogs of compounds **4a-e** containing 2-benzimidazole in place of the 2-imidazole fragment (Table 3). For example, only for two compounds (Ar = Ph, 4-$MeOC_6H_4$) was the doubling of the signals of substituents in the ^{1}H NMR spectrum not a characteristic, but for a different reason. The first contains phenyl substituents in positions 3 and 5 of the pyrazole ring which are displayed as equivalent due to the rapid migration of proton between the pyrazole

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3a	$C_{18}H_{16}N_4O$	70.87 / 71.04	5.42 / 5.30	18.32 / 18.41	230.5-232.0	80
3b	$C_{19}H_{18}N_4O_2$	68.07 / 68.25	5.66 / 5.43	16.52 / 16.76	230.0-231.5	81
3c	$C_{18}H_{15}N_5O_3$	61.76 / 61.89	4.58 / 4.33	19.83 / 20/05	244.5-246.0	84
3d	$C_{17}H_{15}N_5O$	66.67 / 66.87	5.08 / 4.95	22.79 / 22.94	234.5-236.0	86
3e	$C_{17}H_{15}N_5O$	66.72 / 66.87	5.12 / 4.95	22.73 / 22.94	216.0-217.5	78
4a	$C_{18}H_{14}N_4$	75.35 / 75.51	5.11 / 4.93	19.33 / 19.57	303.5-305.0	75
4b	$C_{19}H_{16}N_4O$	71.96 / 72,14	5.15 / 5.10	17.53 / 17.71	249.5-251.0	34
4c	$C_{18}H_{13}N_5O_2$	65.12 / 65.25	4.03 / 3.95	21.07 / 21.14	280.0-281.5	95
4d	$C_{17}H_{13}N_5$	70.85 / 71.07	4.68 / 4.56	24.18 / 42.37	265.0-266.5	94
4e	$C_{17}H_{13}N_5$	70.92 / 71.07	4.54 / 4.56	24.25 / 42.37	278.0-279.5	92

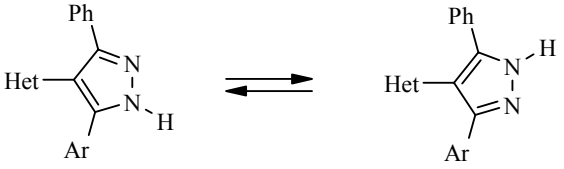
nitrogen atoms. The second compound contains a 4-methoxyphenyl substituent in position 5. It is stabilized in form **A**, forming an energetically favorable chain of conjugation with the benzimidazole fragment. These data indicate the influence of the electronic nature of the hetaryl fragment on the tautomerism of 2,5-diaryl-4-hetarylpyrazoles.

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

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
3a	4.29 (2H, s, CH_2); 6.98-7.11 (2H, m, H-4,5); 7.46 (3H, m, H-3,4,5 Ph); 7.56-7.66 (3H, m, H-3,4,5 COPh); 7.96 (2H, m, H-2,6 Ph); 8.13 (2H, d, *J* = 7.2, H-2,6 COPh); 12.36 (1H, s, H-1); 13.16 (1H, s, CONH)
3b	3.86 (3H, s, OCH_3); 4.29 (2H, s, CH_2); 6.98-7.10 (2H, m, H-4,5); 7.11 (2H, d, *J* = 7.8, H-3,5 Ar); 7.46 (3H, m, H-3,4,5 Ph); 7.96 (2H, m, H-2,6 Ph); 8.12 (2H, d, *J* = 7.8, H-2,6 COPh); 12.36 (1H, s, H-1); 13.05 (1H, s, CONH)
3c	4.32 (2H, s, CH_2); 7.08 (2H, s, H-4,5); 7.48 (3H, m, H-3,4,5 Ph); 7.98 (2H, m, H-2,6 Ph); 8.36, 8.44 (2H, 2H, two d, *J* = 8.4, Ar); 12.19 (1H, s, H-1); 12.94 (1H, s, CONH)
3d	4.33 (2H, s, CH_2); 7.04 (2H, s, H-4,5); 7.47 (3H, m, H-3,4,5 Ph); 7.62 (1H, m, H-5 Ar); 7.97 (2H, m, H-2,6 Ph); 8.45 (1H, d, *J* = 5.7, H-6 Ar); 8.81 (1H, d, *J* = 2.8, H-4 Ar); 9.28 (1H, s, H-2 Ar); 12.17 (1H, s, H-1); 13.03 (1H, s, CONH)
3e	4.32 (2H, s, CH_2); 7.07 (2H, s, H-4,5); 7.48 (3H, m, H-3,4,5 Ph); 7.97 (2H, m, H-2,6 Ph); 8.03, 8.86 (2H, 2H, two d, *J* = 5.1, Ar); 12.19 (1H, s, H-1); 12.89 (1H, s, CONH)
4a	7.14 (2H, s, H-4',5'); 7.30-7.33 (6H, m, H-3,4,5 Ph); 7.42-7.44 (4H, m, H-2,6 Ph); 12.04 (1H, s, H-1'); 13.57 (1H, s, H-1)
4b	3.74 (3H, s, CH_3O); 6.86, 6.94 (0.8H, 1.2H, two d, *J* = 7.2, H-3,5 Ar); 7.13 (2H, s, H-4',5'); 7.26-7.43 (7H, m, H-2,6 Ar, 5H Ph); 12.01 (1H, s, H-1'); 13.43 (1H, s, H-1)
4b*	3.75 (3H, s, CH_3O); 6.91 (2H, d, *J* = 8.7, H-3,5 Ar); 7.14 (2H, s, H-4',5'); 7.28-7.33 (3H, m, H-3,4,5 Ph); 7.38 (2H, d, *J* = 9.0, H-2,6 Ar); 7.43 (2H, m, H-2,6 Ph); 12.13 (1H, br. s, H-1'); 13.03 (1H, br. s, H-1)
4c	7.19 (2H, s, H-4',5'); 7.36-7.38 (3H, m, H-3,4,5 Ph); 7.43-7.45 (2H, m, H-2,6 Ph); 7.67, 8.20 (2H, 2H, two d, *J* = 8.7, 4H Ar); 12.14 (1H, s, H-1'); 13.92 (1H, s, H-1)
4d	7.10, 7.22 (1H, 1H, two s, H-4',5'); 7.35 (4H, m, H-3,4,5 Ph, H-5 Ar); 7.44-7.46 (2H, m, H-2,6 Ph); 7.78 (1H, d, *J* = 8.1, H-6 Ar); 8.48 (1H, s, H-4 Ar); 8.61 (1H, s, H-2 Ar); 12.10 (1H, s, H-1'); 13.77 (1H, s, H-1)
4e	7.19 (2H, s, H-4',5'); 7.33-7.35 (5H, m, H-3,4,5 Ph, H-2,6 Ar); 8.50 (2H, m, H-3,5 Ar); 12.16 (1H, s, H-1'); 13.88 (1H, s, H-1)

*Spectrum after adding drops of acetic acid to a solution of the compound.

TABLE 3. Comparison of the Tautomeric Properties of 4-(2-Azolyl)-1H-pyrazoles in DMSO-d_6



A **B**

Ar	Composition of the equilibrium tautomeric mixture, %	
	Het = 2-imidazolyl	Het = 2-benzimidazolyl
Ph	**A** ≡ **B** = 100	**A** ≡ **B** = 100 [1]
4-$MeOC_6H_4$	**A** = 60, **B** = 40	**A** = 100, **B** = 0 [2]
4-$O_2NC_6H_4$	**A** ≡ **B** = 100	**A** = 20, **B** = 80 [1, 2]
3-Pyridyl	**A** ≡ **B** = 100	**A** = 31, **B** = 69 [1]
4-Pyridyl	**A** ≡ **B** = 100	**A** = 21, **B** = 79 [1]

The molecular diagram of the electronic structure of benzimidazole [3] demonstrates the pulling out of electron density from the imidazole ring into the *o*-phenylene fragment. It follows that the imidazole substituent is surpassed by benzimidazole in electron-withdrawing properties and surpasses it in basicity (p*K*a of imidazole and of benzimidazole, for example, are 6.95 and 5.53 respectively [4]). It is notable that for all the

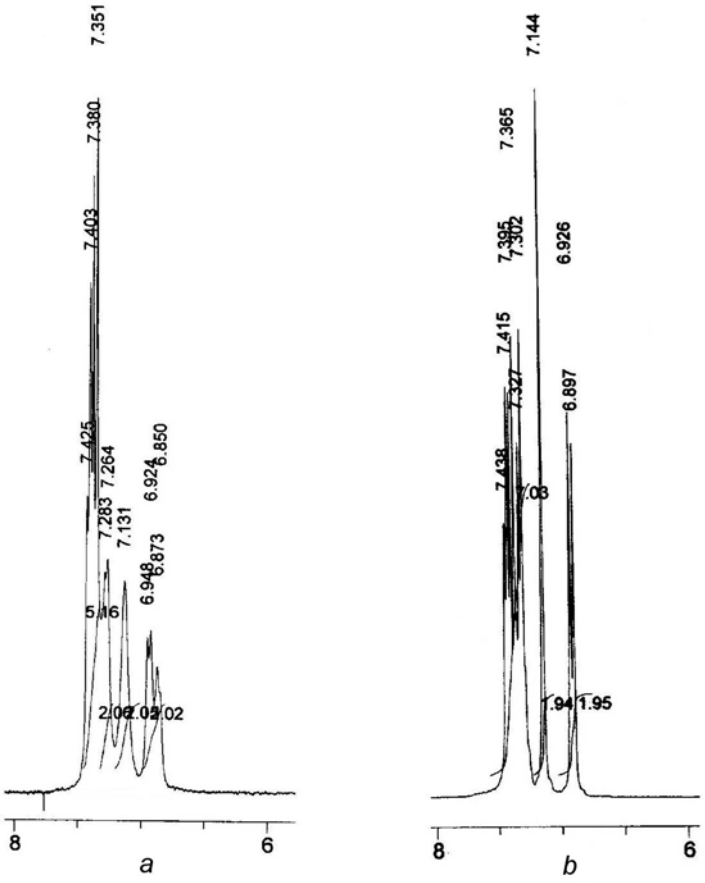


Fig. 1. Fragment of the ^{1}H NMR spectrum of compound **4b**: *a* – reflecting absorption of aromatic protons; *b* – the same after adding drops of acetic acid to the solution.

pyrazolylbenzimidazoles mentioned above inhibited migration of protons between the nitrogen atoms of the benzimidazole ring was observed, which is reflected in the ^{1}H NMR spectra by the split resonance of its H-4 and H-7 protons [1, 2]. On the other hand, for the large portion of compounds of type **4** such migrations in the imidazole fragment are accelerated, and its aromatic protons resonate in the range 7.13-7.19 ppm as a generall narrow multiplet. In compounds **4a-e** the low sensitivity of substituents Ar towards discrimination of positions 3 and 5 of the pyrazole ring is therefore possibly caused by the weak resonance component of the electron-withdrawing properties of the 2-imidazolyl fragment, and also its increased basicity, which probably aids acceleration of the exchange processes. In such a case the exception of the 4-$MeOC_6H_4$ substituent is in agreement with the fact that it, unlike other substituents, forms the energetically most favorable conjugation system with the imidazole fragment.

It is characteristic that the formation of compounds **4a-e** (especially 4-methoxyphenyl-substituted **4b**) occurs with significantly more difficulty than their benzimidazolyl analogs. This is also probably linked with the weakly expressed electron-withdrawing properties of the 2-imidazolyl fragment, and consequently with the

reduced acidity of the methylene group of hydrazines of type **3**. This hinders their isomerization into imidazolidines of form **3'**, through which, in our opinion [2], subsequent cyclization with the formation of the pyrazole ring is effected.

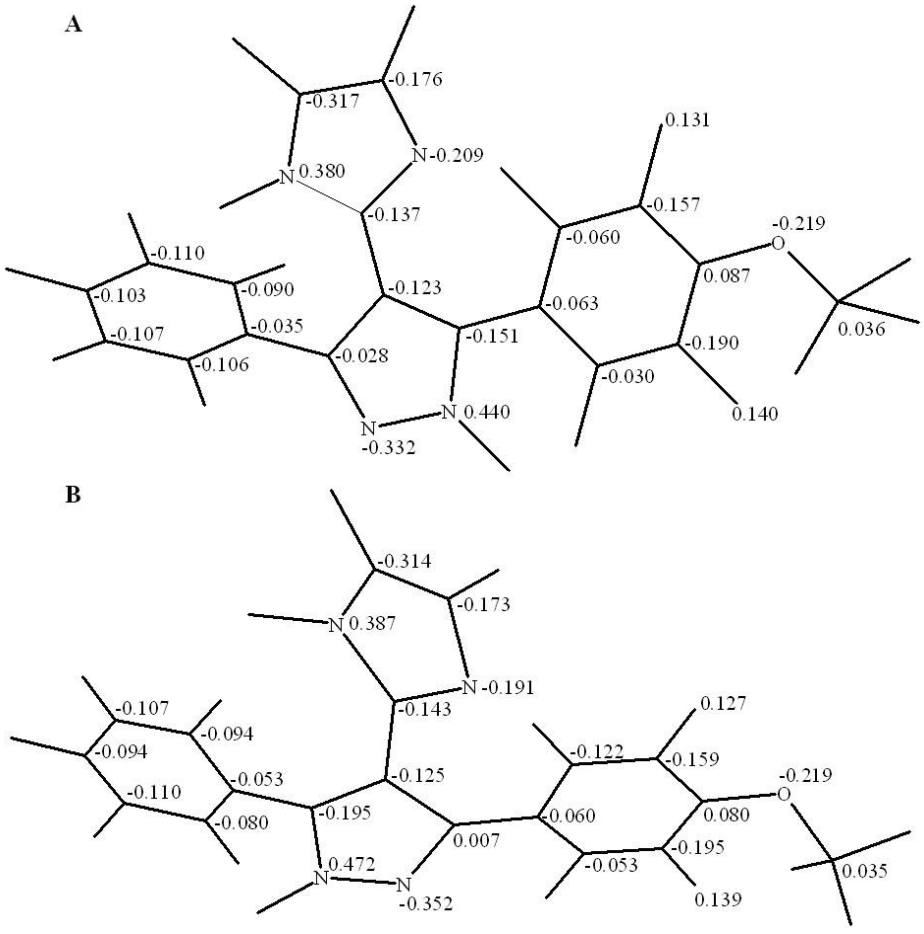


Fig. 2. Charge distribution and enthalpy of formation of tautomers **A** (ΔH_0 = 76.91 kcal/mol) and **B** (ΔH_0 = 78.78 kcal/mol) of compound **4b** in DMSO, according to data of quantum-chemical calculation.

We note that 4-(1H-imidazol-2-yl)-1H-pyrazoles containing only one aryl substituent in the pyrazole ring have been described previously [5]. However condensation of 2-phenacyl-1H-imidazoles with triethyl orthoformate accompanied by cyclocondensation of the obtained β-ethoxyvinyl ketones with hydrazine, was used for their synthesis.

The thermal intramolecular cyclization of aroylhydrazones of 2-phenacyl-1H-imidazoles may therefore be considered as a new method of synthesis of 4-(1H-midazol-2-yl)-1H-pyrazoles, which permits the preparation of previously unknown 3,5-diaryl derivatives.

EXPERIMENTAL

A check on the progress of reactions and on 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. The ^{1}H

NMR spectra of compounds were recorded on a Varian VXR-300 (300 MHz) spectrometer in DMSO-d_6, standard was TMS. Quantum-chemical calculations were carried out using the MOPAC2007 program in the semiempirical PM3 approximation allowing for the effect of solvent [6].

Benzoylhydrazone of 2-Phenacyl-1H-imidazole (3a). A mixture of compound **1** [7] (1.115 g, 5 mmol), benzoylhydrazine (**2a**) (0.68 g, 5 mmol), triethylamine (1.0 ml, 7 mmol), and 1-butanol (5.0 ml) was maintained at 115-120°C in an oil bath for 3 h. The reaction mixture was diluted with water (2.0 ml) with stirring and after cooling the separated product **3a** was filtered off, washed with 2-propanol, with water, and once again with 2-propanol. The product was ready for further conversion, an analytical sample was obtained by crystallization from a mixture of pyridine–water, 2:1.

Hydrazones 3b-e were obtained analogously from compound **1** and aroylhydrazines **2b-e**.

4-(1H-Imidazol-2-yl)-3,5-diphenyl-1H-pyrazole (4a). A mixture of compound **3a** (1.0 g) and N,N-dimethylaniline (3.0 ml) was heated in an oil bath at 220-230°C for 1.5 h. The hot mixture was diluted with toluene (3.0 ml) with stirring. The cooled mass was filtered, the solid was washed with toluene, and with a small quantity of cold 2-propanol. Product **4a** was obtained in an analytically pure state.

Compounds **4b-e** were obtained analogously from hydrazones **3b-e**. In the synthesis of **4b** heating was continued for 8 h, and the product was recrystallized from a mixture of acetic acid–water, 1:1, and a mixture of ethanol–water, 3:1, with addition of 20% aqueous ammonia solution (0.5 ml).

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