Chemistry of Heterocyclic Compounds, Vol. 46, No. 12, 2011

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

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

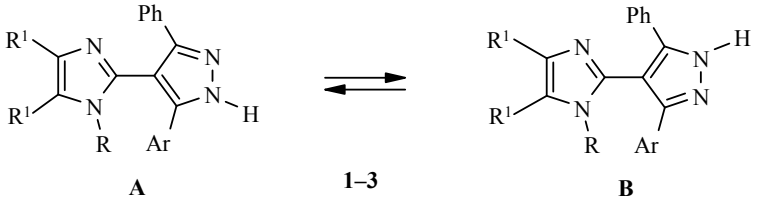
The cyclocondensation of 1-methyl-2-phenacyl-1H-benzimidazole with aroylhydrazines yields 2-(3,5-diaryl-1H-pyrazol-4-yl)-1-methyl-1H-benzimidazoles. The ^{1}H NMR spectra indicate that these products display tautomerism. The more stable tautomers have structures containing electron-donor aryl substituents at C-5 and electron-withdrawing aryl substituents at C-3 of the pyrazole ring.

Keywords: aroylhydrazines, benzimidazoles, pyrazoles, tautomerism.

The tautomerism of pyrazole and its derivatives has long been known [1] but is still under investigation [2-11] since this phenomenon is an inherent characteristic for many compounds, including recently synthesized derivatives. This feature reveals subtle structural aspects related to intramolecular and solvation interactions. Increasingly advanced methods are revealing new correlations concerning this tautomerism.

We have developed a method for the formation of the pyrazole ring, in which well-known aroylhydrazines are used for the first time as a 1,3-N,N,C-nucleophile-electrophile. Thus, the cyclocondensation of these hydrazines with 2-phenacyl-1H-benzimidazole leads to 2-(3,5-diaryl-1H-pyrazol-4-yl)-1H-benzimidazoles of **1** type. The ^{1}H NMR spectra of benzimidazoles **1** have some double signals due to proton migration between the pyrazole ring nitrogen atoms, leading to the formation of tautomers **A** and **B** [12, 13] (Scheme 1). Similarly, 2-(3,5-diaryl-1H-pyrazol-4-yl)-1H-imidazoles of **2** type are obtained from the aroylhydrazones of 2-phenacyl-1H-imidazole. In contrast, no signal doubling is noted in the spectra of imidazoles **2** in most cases [14].

Scheme 1



1 R = H, $R^1 + R^1$ = CH=CH–CH=CH; **2** R = R^1 = H; **3** R = Me, $R^1 + R^1$ = CH=CH–CH=CH

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

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

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1800-1805, December, 2010. Original article submitted May 28, 2010. Submitted after revision October 15, 2010.

TABLE 1. Characteristics of Synthesized Compounds*

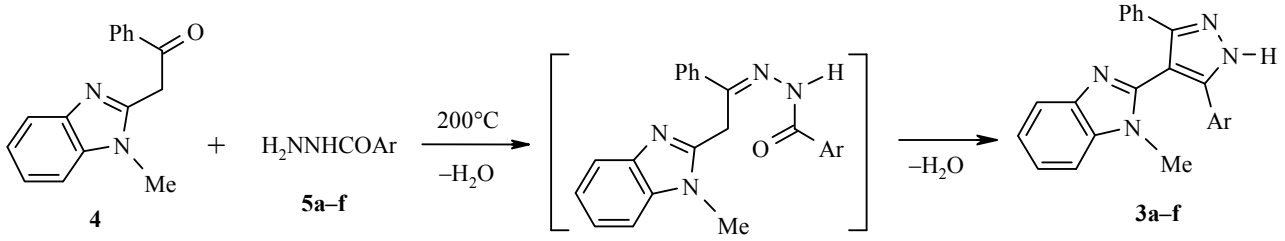
Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3a	$C_{23}H_{18}N_4$	78.75 / 78.83	5.07 / 5.18	15.85 / 15.99	279-280	69
3b	$C_{24}H_{20}N_4O$	75.57 / 75.77	5.24 / 5.30	14.58 / 14.73	242-245	71
3c	$C_{23}H_{17}N_5O_2$	69.75 / 69.86	4.18 / 4.33	17.63 / 17.71	265.0-266.5	70
3d	$C_{22}H_{17}N_5$	75.07 / 75.19	4.64 / 4.88	19.78 / 19.93	223.0-24.5	72
3e	$C_{26}H_{24}N_4O_3 \cdot H_2O$	68.33 / 68.11	5.45 / 5.72	12.38 / 12.22	142-145	51
3f	$C_{23}H_{17}ClN_4$	71.58 / 71.78	4.38 / 4.45	14.47 / 14.56	220-222	67

*The reaction time of the synthesis is 30 min for **3a**,**c-e** and 50 min for **3b**,**f**.

This heterocyclization is probably a general reaction and the tautomerism of its products depends on the nature of the hetaryl substituent at C-4 of the pyrazole ring. Previously unreported 4-hetarylpyrazoles **3**, in which the hetaryl moiety is a 1-methyl-1H-benzimidazol-2-yl group, were synthesized in the present work in order to test this hypothesis.

Fusing 1-methyl-2-phenacyl-1H-benzimidazoles (**4**) and aroylhydrazines **5a-f** at 200°C gave 2-(3,5-diaryl-1H-pyrazol-4-yl)-1-methyl-1H-benzimidazoles **3a-f** in 51-78% yield **(**Scheme 2).

Scheme 2



3, 5 a Ar = Ph, **b** Ar = C_6H_4OMe-*p*, **c** Ar = $C_6H_4NO_2$-*p*, **d** Ar = 4-pyridyl,
e Ar = $C_6H_2(OMe)_3$-*m*,*m*',*p*, **f** Ar = C_6H_4Cl-*o*

This reaction proceeds using benzoic acid as the catalyst. The reaction without catalyst is accompanied by disproportionation of the aroylhydrazines, leading to 1,2-diaroylhydrazines and complicating isolation of the desired products. The reaction time (30-50 min) depends on the reactivity of the carbonyl group of the starting aroylhydrazine. The reaction course is readily monitored relative to the release of water vapor.

The composition and structure of the resultant products **3** were supported by their elemental analysis (Table 1) and the ^{1}H NMR spectral data (Table 2).

^{1}H NMR spectroscopy indicates that benzimidazoles **3b-d**,**f** exist in DMSO-d_6 as an equilibrium mixture of tautomers **A** and **B** (Scheme 1), which is seen in a doubling of the signals of some of the protons (see Table 2). The spectra of benzimidazoles **3a**,**e** do not show doubled signals, which, however does not exclude the existence of the product **3e** in different tautomeric forms. In the case of product **3a**, where Ar = Ph, forms **A** and **B** are identical: **A** ≡ **B**. In order to study the tautomerism of benzimidazoles **3a-f**, we used benzimidazoles **6a** and **6b** (see Fig. 1), which differ in the substitution of the pyrazole ring, as reference compounds. These structural analogs have an NMe group instead of an NH group as well as two 4-methoxyphenyl (**6a**) or two 4-nitrophenyl substituents (**6b**).

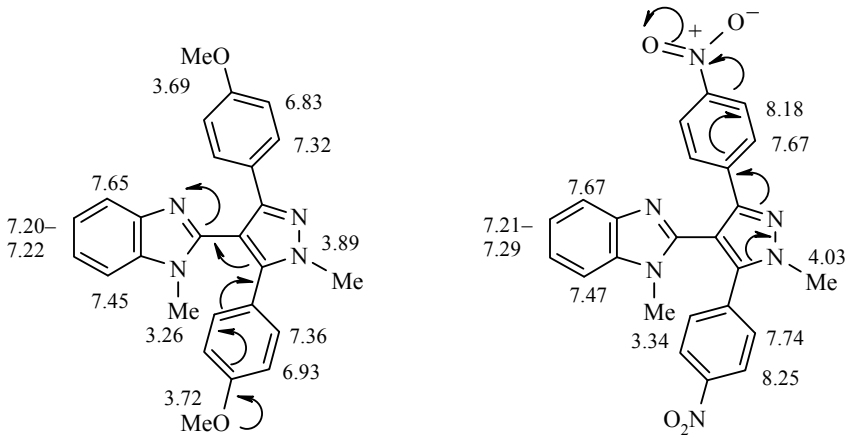


Fig. 1. Model compounds **6a**,**b** with ^{1}H NMR chemical shifts (δ, ppm). The major donor-acceptor interactions are indicated by arrows.

The synthesis and assignment of ^{1}H NMR signals of these compounds using NOE and COSY experiments were assigned in our previous work [13]. We established that the protons of the 5-Ar substituent, regardless of their electronic nature, are seen at lower field than the protons of the 3-Ar substituent. The aryl substituent at C-5 probably is subject to an overall electron-withdrawing effect of the 1-methylbenzimidazol-2-yl fragment, while the aryl substituent at C-3 is subject only to the inductive effect of this fragment and possibly the electron-donor effect of the pyrrole nitrogen atom of the pyrazole ring. These data were used to determine the tautomer composition and dependence of this composition on the nature of the aryl substituent using the chemical shifts and integral intensities in the ^{1}H NMR spectra (see Scheme 1 and Table 3). The proton migration between the nitrogen atoms in the case of a pyrazole ring with substituents possessing similar electronic properties is probably so fast that individual tautomers cannot be seen in the spectrum (benzimidazole **3e**). Tautomers **A** and **B** are seen in the spectra when there is a large difference between the aryl and phenyl substituents. The tautomers with an electron-donor substituent at C-5 and electron-withdrawing substituent at C-3 are more stable (tautomer **A** for benzimidazole **3b** and tautomers **B** for benzimidazoles **3c**,**d**).

Comparison of the tautomer data for benzimidazoles **3a-f** and their structural analogs **1a-d** and **2a-d** (Table 3) shows that an electron-donor aryl substituent stabilizes tautomer **A** (in the case of **1b**), while the introduction of a methyl group into the benzimidazolyl fragment (**3b**) or replacement of this fragment with an imidazolyl group (**2b**) markedly destabilizes tautomer **A**. In contrast, tautomers **B** are more stable in the case of electron-withdrawing Ar groups (**1c**,**d**), while introduction of a methyl group into the benzimidazolyl fragment somewhat lowers the stability of tautomers **B** (**3c**,**d**). There are no marked differences between forms **A** and **B** in the imidazolyl analogs of these compounds (**2c**,**d**) and these forms do not appear individually in the ^{1}H NMR spectra. These features are probably related to both steric and electronic factors, namely, the existence of the bulky electron-donor methyl group in benzimidazoles **3** not favorable for π-orbital overlap of the conjugation system of the benzimidazolyl fragment with the Ar substituent and the presence of the less electron-withdrawing but more basic imidazolyl fragment in imidazoles **2**.

It is interesting that the tautomeric forms for benzimidazole **3f** are not equivalent but, nevertheless, equal in energy. The tautomeric forms are seen as inequivalent since the signals of the NH group of the tautomers differ in their chemical shifts by 0.16 ppm (by 0.03-0.08 for compound **3b**,**d**), while these forms are seen to be equal in energy since integral intensity ratio of their signals is 1:1. The o-chlorophenyl substituent differs significantly from the phenyl group in its steric and deshielding effects on the proton at the pyrrolic nitrogen

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

Compound	Chemical shifts, δ, ppm (*J*, Hz)
3a	3.29 (3H, s, NCH_3); 7.26-7.33 (8H, m, *m*-, *p*-H Ph, H-5,6); 7.39-7.41 (4H, m, *o*-H Ph); 7.51-7.54 (1H, m, H-7); 7.70-7.73 (1H, m, H-4); 13.88 (1H, s, NH)
3b	3.29 (3H, s, NCH_3); 3.69 and 3.72 (1.29H and 1.71H, two s, OCH_3); 6.83 and 6.93 (0.82H and 1.18H, two d, $J_1 = J_2 = 8.4$, *m*-H Ar); 7.25-7.38 (9H, m, *o*-, *m*-, *p*-H Ph, *o*-H Ar, H-5,6); 7.51-7.54 (1H, m, H-7); 7.70-7.72 (1H, m, H-4); 13.72 and 13.75 (0.57H and 0.43H, two s, NH)
3c	3.31 (3H, s, NCH_3); 7.26-7.38 (7H, m, H-5,6, *o*-, *m*-, *p*-H Ph); 7.54-7.56 (1H, m, H-7); 7.68-7.74 (3H, m, *o*-H Ar, H-4); 8.16 and 8.21-8.23 (1.50H and 0.50H, d, $J = 8.1$ and m, *m*-H Ar); 14.20 (1H, s, NH)
3d	3.33 (3H, s, NCH_3); 7.27-7.38 (9H, m, H-5,6, *o*-, *m*-, *p*-H Ph, *o*-H Ar); 7.55-7.58 (1H, m, H-7); 7.73-7.75 (1H, m, H-4); 8.49, 8.55-8.57 (1.46H and 0.54H, d, $J = 4.8$ and m, *m*-H Ar); 14.18 and 14.26 (0.73H and 0.27H, two s, NH)
3e	3.30 (3H, s, NCH_3); 3.46 (6H, s, *m*-OCH_3); 3.61 (3H, s, *p*-OCH_3); 6.80 (2H, s, C_6H_2); 7.25-7.35 (5H, m, H-5,6, *m*-, *p*-H Ph); 7.46 (2H, d, $J = 7.8$, *o*-H Ph); 7.52-7.55 (1H, m, H-7); 7.71-7.74 (1H, m, H-4); 13.86 (1H, s, NH)
3f	2.24, 3.26 (1.5H and 1.5H, two s, NCH_3); 7.16-7.34 (2H, m, H-5,6); 7.31-7.45 (10H, m, H-7, *o*-, *m*-, *p*-H Ph, *o*-, *m*-, *p*-H Ar); 7.58-7.60 (1H, m, H-4); 13.79, 13.95 (0.50H and 0.50H, two s, NH)

TABLE 3. Content of Tautomer **A** in Benzimidazoles **3** and Their Structural Analogs **1** and **2** in Equilibrium Mixture with Tautomer **B** from ^{1}H NMR Spectral Data

Ar	Content of **A**, %		
	3	**1**	**2** [14]
Ph (**a**)	**A** ≡ **B**	**A** ≡ **B** [12]	**A** ≡ **B**
C_6H_4OMe-*p* (**b**)	59	100 [13]	60
$C_6H_4NO_2$-*p* (**c**)	25	20 [12, 13]	—*
4-Pyridyl (**d**)	27	21 [12]	—*
$C_6H_2(OMe)_3$-*m*,*m*′,*p* (**e**)	—*	—	—
C_6H_4Cl-*o* (**f**)	50	—	—

* The ^{1}H NMR spectrum does not distinguish between tautomers **A** and **B**.

group and this difference accounts for the lower rate of tautomeric interconversions such that each tautomer is clearly seen in the spectrum.

Thus, 2-(3,5-diaryl-1H-pyrazol-4-yl)-1-methyl-1H-benzimidazoles are readily obtained in the cyclocondensation of 1-methyl-2-phenacyl-1H-benzimidazoles with aroylhydrazines. Introduction of a methyl group at the nitrogen atom of the benzimidazole fragment does not alter the preferential stabilization for the tautomers with electron-withdrawing aryl substituents at C-3 and electron-donor substituents at C-5 of the pyrazole ring but reduces the difference between substituents at these positions.

EXPERIMENTAL

The ^{1}H NMR spectra of these compounds were taken on a Varian VXR-300 spectrometer at 300 MHz in DMSO-d_6 with TMS as the internal standard. Monitoring of the course of the reactions and purity of the products was carried out by thin-layer chromatography on Silufol UV-254 plates using benzene–ethanol, 9:1, as the eluent and development with UV light.

2-(3,5-Diphenyl-1H-pyrazol-4-yl)-1-methyl-1H-benzimidazole (3a). A mixture of benzimidazole **4** (0.250 g, 1 mmol), aroylhydrazine **5a** (0.136 g, 1 mmol), and benzoic acid (0.030 g, 0.25 mmol) was fused on a bath at 195-200°C for 30 min. The cooled melt was dissolved in 1.5 ml pyridine heated to reflux. The solution was diluted by carefully adding water with stirring until the onset of crystallization was observed. The cooled mass was filtered. The precipitate was washed with cold 2-propanol and dried in vacuum at a water pump at 115°C to give 0.241 g analytically pure **3a**.

Products **3b-f** were obtained analogously from benzimidazole **4** and aroylhydrazines **5b-f**. The reaction times are given in Table 1.

REFERENCES

1. J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, *The Tautomerism of Heterocycles*, Academic Press, New York (1976).
2. A. Hadhiri, H. W. Lerner, M. Wagner, and J. W. Bats, *Acta Crystallogr.*, **E58**, 1378 (2002).
3. M. A. P. Martins, R. F. Blanko, C. M. P. Pereira, P. Beck, S. Brondani, W. Cunico, N. E. K. Zimmermann, H. G. Bonacorso, and N. Zanatta, *J. Fluorine Chem.*, **118**, 69 (2002).
4. A. F. C. Flores, S. Brondani, N. Zanatta, A. Rosa, and M. A. P. Martins, *Tetrahedron Lett.*, **43**, 8701 (2002).
5. M. Yaronczyk, J. C. Dobrovolski, and A. P. Mazurek, *J. Mol. Struct.*, **672**, Nos. 1-3, 17 (2004).
6. M. Yaronczyk, J. C. Dobrovolski, and A. P. Mazurek, *Theochem.*, **673**, 17 (2004).
7. M. A. P. Martins, C. M. P. Pereira, N. E. K. Zimmermann, W. Cunico, S. Moura, P. Beck, N. Zanatta, and H. G. Bonacorsco, *J. Fluorine Chem.*, **123**, 261 (2003).
8. P. F. Chmutova, E. Z. Ismailova, and G. A. Shamov, *Zh. Obshch. Khim.*, **76**, 1166 (2006).
9. I. Alkota, J. Elguero, and J. Liebmann, *Struct. Chem.*, **17**, 439 (2006).
10. S. Trofimenko, G. P. A. Yap, F. A. Jove, R. M. Claramunt, M. A. Garsia, M. D. Santa Maria, I. Alkorta, and J. Elguero, *Tetrahedron*, **63**, 8104 (2007).
11. A. Levai, A. M. S. Silva, J. A. S. Cavaleiro, J. Elguero, I. Alkorta, and J. Jeko, *Austral. J. Chem.*, **60**, 905 (2007).
12. I. B. Dzvinchuk, A. V. Vypirailenko, V. V. Pirozhenko, and M. O. Lozinskii, *Khim. Geterotsikl. Soedin.*, 1512 (1999). [*Chem. Heterocycl. Comp.*, **35**, 1319 (1999)].
13. I. B. Dzvinchuk, A. V. Turov, and M. O. Lozinskii, *Khim. Geterotsikl. Soedin.*, 1651 (2009) [*Chem. Heterocycl. Comp.*, **45**, 1325 (2009)].
14. I. B. Dzvinchuk, A. M. Nesterenko, and M. O. Lozinskii, *Khim. Geterotsikl. Soedin.*, 77 (2010) [*Chem. Heterocycl. Comp.*, **46**, 66 (2010)].