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RECYCLIZATION ON ACYLATION OF 1-METHYL-2-PHENACYL-1H-BENZIMIDAZOLE PHENYLHYDRAZONE

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Interaction of 1-methyl-2-phenacyl-1H-benzimidazole phenylhydrazone with acylating agents initiates a recyclization process with the formation of previously unknown 5-(2-acylamino-N-methylanilino)-1,3-diphenyl-1H-pyrazoles.

Keywords: acylating agents, benzimidazoles, hydrazones, pyrazoles, recyclization.

We showed previously that the acylation of alkyl-, aryl-, and aroylhydrazones of 2-phenacyl- and 2-acetonyl-1H-benzimidazoles with aroyl chlorides and anhydrides of carboxylic acids readily initiates a recyclization process with the formation of pyrazole derivatives. In particular, by the action on the phenylhydrazone of 2-phenacyl-1H-benzimidazole (**1a**) of the acid chloride of *p*-nitrophenylbenzoic acid (**2a**) or trifluoroacetic acid anhydride (**2b**), the 5-(2-acylaminoanilino)pyrazoles **3a**,**b** were obtained [1-3]. It was proposed that recyclization begins with the formation of either acylbenzimidazolium salts of type **A** [3], or N-acylbenzimidazoles of type **B** [1], and then proceeds through spiranes **C** (R=H). In the present work, to make more precise the initial stage of the mechanism of the reaction being considered we studied the behavior under acylating conditions of the phenylhydrazone of 1-methyl-2-phenacyl-1H-benzimidazole (**1b**), since a substituent is already present at the nitrogen atom of the heterocycle and the formation of intermediates of type **B** is impossible for it.

We found that compound **1b** under the action of acylating agents **2a**,**b** is readily recyclized with the formation of 5-(2-acylamino-N-methylanilino)pyrazoles **3c**,**d**. The structure of compound **3d** was confirmed by hydrazinolysis by means of which the trifluoroacetyl group is removed and amino compound **4** is formed.

According to new data obtained by us the initiation of recyclization of compounds of type **1** by acylating agents is a more general reaction than we supposed earlier, and is caused, extremely probably, by the regioselective formation of N-acylbenzimidazolium salts **A**, in which the carbon atom in position 2 of the heterocycle possesses enhanced electrophilicity and readily undergoes intramolecular attack by the amino group of the hydrazone fragment. Spiranes **C** formed in this way are converted into the final products by opening of

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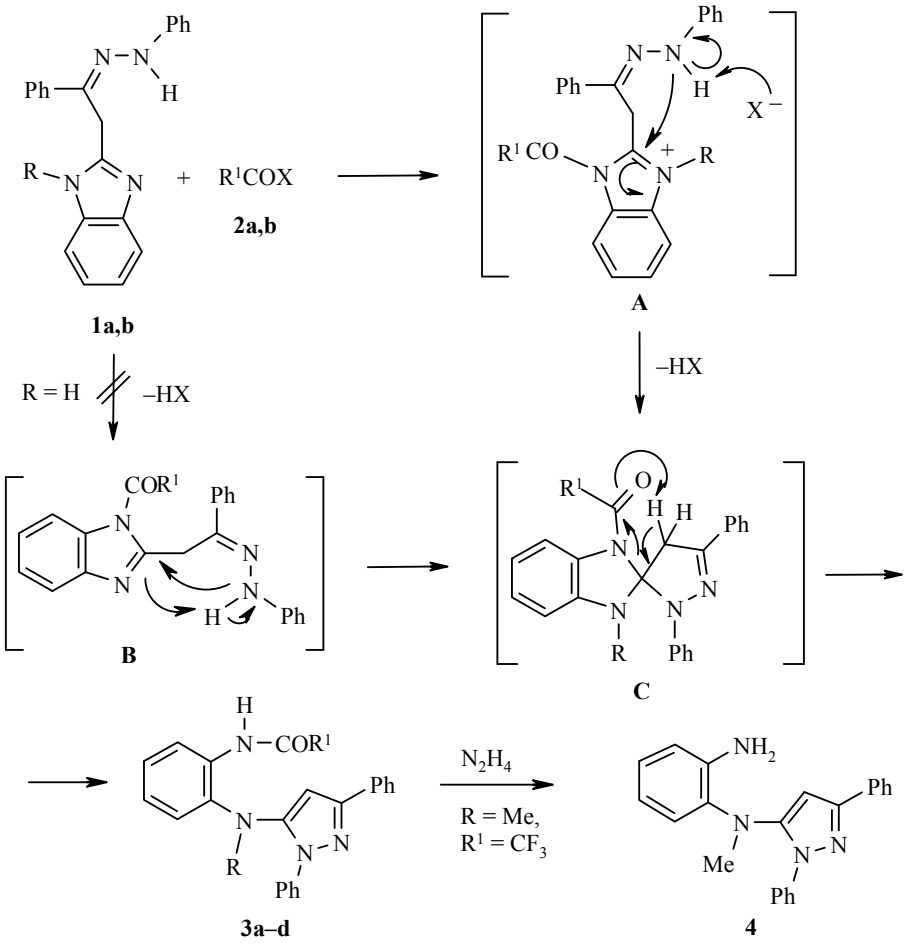
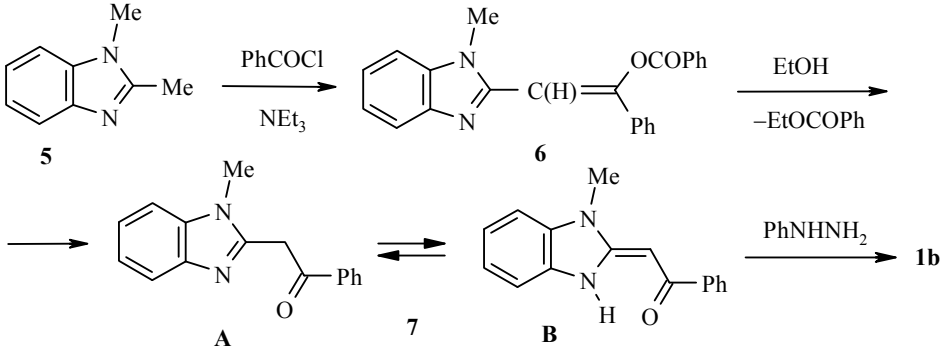
the imidazole and aromatization of the pyrazole rings. Overall the process may be represented as an intramolecular transamination at atom C(2) of the benzimidazole fragment leading to cleavage of the C(2)–N ring bond, which contains the readily-leaving acylated amino group.



1 a R = H, **b** R = Me; **2 a** $R^1 = C_6H_4NO_2$-*p*, X = Cl, **b** $R^1 = CF_3$, X = $OCOCF_3$; **3 a** R = H, $R^1 = C_6H_4NO_2$-*p*, **b** R = H, $R^1 = CF_3$, **c** R = Me, $R^1 = C_6H_4NO_2$-*p*, **d** R = Me, $R^1 = CF_3$

The initial hydrazone **1b** was synthesized by acylating 1,2-dimethylbenzimidazole (**5**) with benzoyl chloride, with subsequent deacylation of the C,O-diacylated product **6** on alcoholysis and then, by condensation of the resulting 1-methyl-2-phenacyl-1H-benzimidazole (**7**) with phenylhydrazine.



We note that compound **7** was obtained previously by acylation of compound **5** with ethyl benzoate, and also by the cyclocondensation of N-methyl-*o*-phenylenediamine with (β,β-dimethylthio)vinyl phenyl ketone in yields not exceeding 41% [4, 5]. It was obtained by our scheme for the first time in 88% overall yield. However such a synthetic scheme is not original. 2-Phenacylbenzothiazole was obtained previously in an analogous manner from 2-methylbenzothiazole [6].

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Найдено, % / Вычислено, %			mp, °C	Yield, %
		C	H	N		
1b	$C_{22}H_{20}N_4$	77.83 / 77.95	5.18 / 5.12	7.73 / 7.90	208.5-210.0	90
3c	$C_{29}H_{23}N_5O_3$	71.03 / 71.15	4.58 / 4.74	14,18 / 14.31	196.0-197.0	98
3d	$C_{24}H_{19}F_3N_4O$	66.06 / 66.05	4.53 / 4.39	12.88 / 12.84	115.0-116.5	71
4	$C_{22}H_{20}N_4$	77.47 / 77.62	6.03 / 5.92	16.33 / 16.46	123.0-124.5	70
6	$C_{23}H_{18}N_2O_2$	77.68 / 77.95	5.36 / 5.12	8.09 / 7.90	165.0-166.5	97
7	$C_{16}H_{14}N_2O$	76.63 / 76.78	5.57 / 5.64	11.03 / 11.19	150.0-151.5*	91

*Mp 150-151°C [3].

TABLE 2. Spectral Characteristics of the Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1}*	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
1b	1620, 3250	3.84 (3H, s, CH_3); 4.47 (2H, s, CH_2); 6.79 (1H, t, *J* = 7.8, H-*p* NPh); 7.10-7.28 (7H, m, H-5,6, H-*p* CPh, H-*o* and -*m* NPh); 7.32-7.36 (2H, m, H-*m* CPh); 7.48-7.52 (2H, m, H-4,7); 7.82 (2H, d, *J* = 7.8, H-*o* CPh); 9.85 (1H, s, NH)
3c	1660, 1685, 3230	3.27 (3H, s, CH_3); 6.44 (1H, s, H Het); 6.91-7.39 (10H, m, H Ar, H-*m*,*p* CPh, H-*m*,*p* NPh); 7.44 (2H, d, *J* = 8.1, H-*o* NPh); 7.63 (2H, d, *J* = 7.07, H-*o* CPh); 7.95 and 8.11 (2H and 2H, two d, *J* = 8.7, ArCO); 9.54 (1H, s, NH)
3d	1750, 3340	3.16 (3H, s, CH_3); 6.35 (1H, s, H Het); 6.98-7.34 (8H, m, H Ar, H-*m*,*p* NPh, H-*p* CPh); 7.41 (2H, d, *J* = 7.2, H-*m* CPh); 7.55 (2H, d, *J* = 7.5, H-*o* NPh); 7.77 (2H, d, *J* = 7.2, H-*o* CPh); 10.33 (1H, s, NH)
4	3365, 3465	3.01 (3H, s, CH_3); 5.02 (2H, s, NH_2, subject to deuterium exchange); 6.66 (4H, m, H Ar); 6.69 (1H, s, H Het); 7.10-7.50 (8H, m, H NPh, H-*m*,*p* CPh); 7.90 (2H, d, *J* = 7.2, H-*o* CPh)
6	1660, 1750	3.96 (3H, s, CH_3); 7.07-7.23 (3H, m, H-5,6, H-*p* Ph); 7.43 (1H, s, HetCH); 7.47-7.54 (4H, m, H-4,7, H-*m* Ph); 7.62-7.66 (2H, m, H-*m* COPh); 7.77 (1H, t, *J* = 7.2, H-*p* COPh); 7.88 (2H, d, *J* = 7.2, H-*o* Ph); 8.21 (2H, d, *J* = 7.2, H-*o* COPh)
7[*2]	1640, 3060	3.71, 3.76 (0.42H, 2.58H, two s, CH_3); 4.85 (0.28H, s, CH_2); 6.29 (0.86H, s, CHC=O); 7.15-7.21 (2H, m, H-5,6); 7.45-7.48 (3.58H, m, H-*m*,*p* Ph, H-7); 7.51-7.58 (1.28H, m, H-*m* Ph, H-4); 7.68 (0.14H, t, *J* = 7.0, H-*p* Ph); 7.98, 8.10 (1.72H, 0.28H, two d, *J* = 7.0, H-*o* Ph); 13.92 (<0.86H, br. s, NH)

* IR spectrum (CH_2Cl_2), ν, cm^{-1}: **3c** 1690, 3385, **3d** 1745, 3360.

*2 For compound **7** described previously in [4, 5] the parameters of the ^{1}H NMR spectrum in DMSO-d_6 are not given.

The composition and structure of compounds **1b**, **3c**,**d**, **4**, **6**, and **7** were confirmed by the results of elemental analysis (Table 1), and by data of IR spectra and ^{1}H NMR spectra (Table 2).

According to literature data in [4, 5], compound **7** exists in DMSO-d_6 as an equilibrium mixture (14:86) of phenacyl and phenacylidene tautomers **A** and **B** , but in the crystal state completely in form **B** (the absorption band of the carbonyl group, typical of aryl alkyl ketones, was missing from the IR spectrum). On the other hand, phenylhydrazone **1b** did not display an inclination to prototropic tautomerism, probably due to the fact that the electron-withdrawing properties of the azomethine grouping are far weaker than of carbonyl and do not affect substantially the increase in acidity of the neighboring methylene group.

The spectral characteristics of compounds **1b**, **3c**,**d**, and **4** are on the whole in agreement with the data given previously for their structural analogs [1, 2]. We note however, that in the IR spectra of compound **3c** the absorption of the C=O and N–H groups in KBr disks and in CH_2Cl_2 solution were different, but were practically identical for compound **3d**. For the first compound in KBr intermolecular hydrogen bonds were displayed noticeably, but for the second they were less significant. It is also notable that the absorption band of the trifluoroacetyl group is displayed in KBr for compound **3b** at 1700 [2], and for compound **3d** at 1750 cm^{-1}.

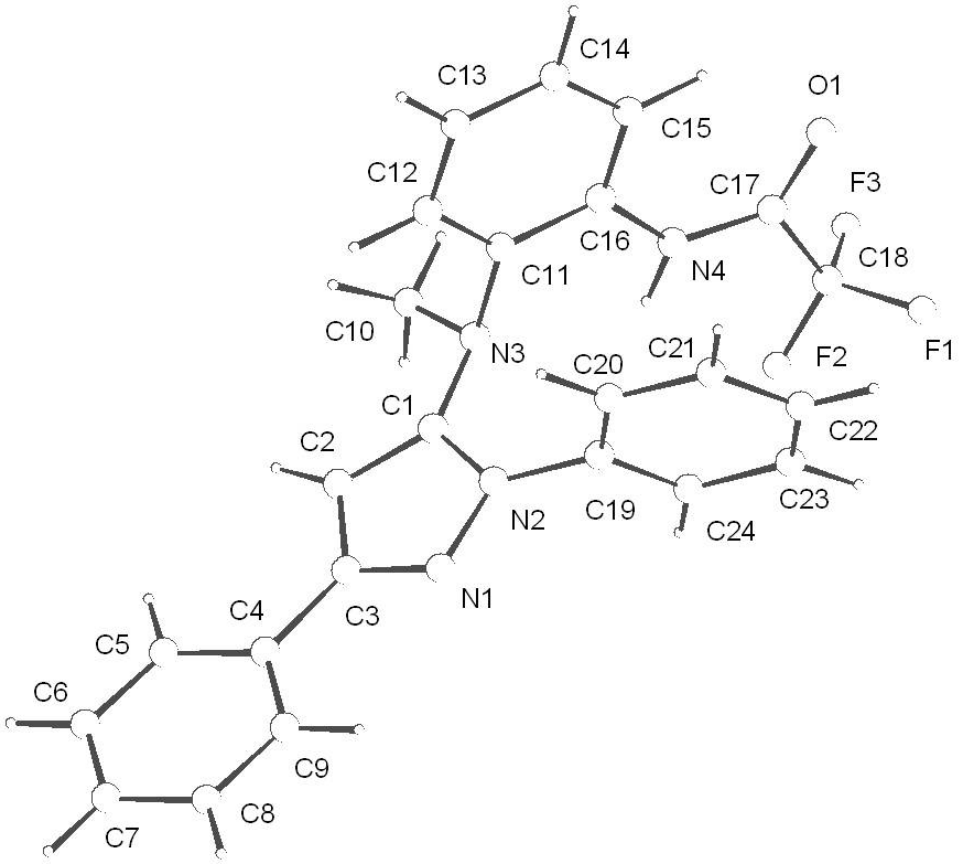


Fig. 1. General shape of the compound **3d** molecule.

Nevertheless the structure of compound **3d** is not in doubt, it was unequivocally established by us by the X-ray structural method. The general shape of the **3d** molecule and its main geometric parameters are given in Fig. 1. The central five-membered ring N(1)N(2)C(1-3) is planar to within 0.009 Å. The benzene ring C(4-9) is practically coplanar with it, while the benzene rings C(11-16) and C(19-24) are disposed orthogonally to the heterocycle (the dihedral angles are 6.2, 87.8, and 82.7^o respectively). It is interesting to note that the dihedral angle between rings C(11-16) and C(19-24), in spite of the significant steric hindrance, is only 26.5^o. The N(2)

TABLE 3. Main Bond Lengths (*l*) and Valence Angles (ω) of the Compound **3d** Molecule

Bond	*l*, Å	Angle	ω, deg
N(1)–N(2)	1.359(3)	N(2)N(1)C(3)	105.1(2)
N(1)–C(3)	1.331(4)	N(1)N(2)C(1)	111.9(2)
N(2)–C(1)	1.361(4)	C(1)N(3)C(11)	114.7(2)
N(2)–C(19)	1.429(4)	C(16)N(4)C(17)	128.4(3)
N(3)–C(1)	1.402(4)		
N(3)–C(11)	1.454(4)		
N(4)–C(1)	1.415(4)		
N(4)–C(17)	1.336(4)		

and N(4) atoms have a plane-trigonal configuration of bonds (sum of valence angles at their atoms are 359.9 and 359,8°). At the same time the N(3) atom has a pyramidal coordination (sum of valence angles is 339.8°). As a result of the effective conjugation n[N(4)]-π[C(17)=O(1)] the bond N(4)–C(17) is formally single having a length of 1.336(4), substantially shortened compared with the range 1.43-1.45 Å characteristic of a pure single N(sp^2)–C(sp^2) bond [7, 8]. The shortened interatomic distance N(4)···N(3) 2.720(4), (N(3)···H(4) 2.25(4) Å, N(3)H(4)N(4) 140(4)°) shows the possibility of forming a N(4)–H(4)···N(3) intramolecular hydrogen bond, by closing the N(3)H(4)N(4)C(16)C(11) five-membered ring.

The phenylhydrazone of 1-methyl-2-phenacyl-1H-benzimidazole is recyclized under the action of acylating agents, in spite of the presence in the initial heterocycle of a substituent at the nitrogen atom. The process probably occurs by way of the formation of the corresponding N-acylbenzimidazolium salts, which undergo an intramolecular restructuring through a spiro compound into the previously unknown 5-(2-acyl-amino-N-methylanilino)-1,3-diphenyl-1H-pyrazoles.

EXPERIMENTAL

The IR spectra were obtained on a UR-20 instrument in KBr disks and in CH_2Cl_2 solution. The ^{1}H NMR spectra of compounds were recorded on a Varian VXR-300 (300 MHz) spectrometer in DMSO-d_6, standard was TMS. 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, visualization was in UV light.

X-ray Structural Investigation of a Monocrystal with linear dimensions 0.22×0.47×0.57 mm, grown from a solution of compound **3d** in a mixture of ethanol–water, 1 : 1, was carried out at room temperature on a Bruker Apex II automatic diffractometer (MoKα radiation, λ = 0.71069 Å, θ_{max} = 26.6°, $-8 \le h \le 9$, $-30 \le k \le 29$, $-15 \le l \le 14$). In all 11891 reflections were collected (4284 independent reflections, R_{int} = 0.002). The crystals of compound 3d were monoclinic, a = 7.5700(6), b = 24.245(2), c = 11.951(1) Å, β = 99.51(2)o, V = 2163.3(3) Å^3, M = 436.4, Z = 4, d_{calc} = 1.34 g/cm^3, μ = 1.02 cm^{-1}, F(000) = 904, space group $P2_1/n$ (N 14). The structure was solved by the direct method and refined by least squares in a full-matrix anisotropic approximation using the CRYSTALS set of programs [9]. In the refinement 1997 reflections with $I > 3\sigma(I)$ were used (293 refinable parameters, number of reflections per parameter 6.8). All hydrogen atoms were made apparent from an electron density difference synthesis and are included in the refinement with fixed positions and thermal parameters. The Chebyshev weighting factor [10] was used in the refinement with parameters 1.28, 1.08, and 0.89. The final values of the divergence factors were R = 0.047 and R_w = 0.056, *GOOF* = 1.159. The residual electron density from the Fourier difference series was -0.37 and 0.64 e/Å^3. A complete set of the X-ray structural data for compound **3d** has been deposited in the Cambridge Structural Data base (deposit No. CCDC 740976).

Phenylhydrazone of 1-Methyl-2-phenacyl-1H-benzimidazolo (1b). A mixture of compound **7** (2.50 g, 10 mmol), phenylhydrazine (1.30 g, 12 mmol), 1-butanol (7.0 ml), and glacial acetic acid (3 drops) was maintained in a bath at 115-120°C for 1.5 h. The cooled mass was filtered, the solid was washed with 2-propanol, dried at 90-95°C, and product **1b** (3.08 g) was obtained in an analytically pure form.

5-[N-Methyl-2-(*p*-nitrobenzoylamino)aniline]-1,3-diphenyl-1H-pyrazole (3c). A mixture of compound **1b** (0.340 g, 1 mmol), *p*-nitrobenzoyl chloride (0.204 g, 1.1 mmol), and anhydrous pyridine (1 ml) was maintained for 2 h at 100°C, then water (2 ml) was added and the mixture heated with stirring until the product began to crystallize. The cooled mass was filtered, the solid washed with a mixture of 2-propanol–water, 1:1, the yellow solid was dried at 110°C, and product **3c** (0.480 g) was obtained in an analytically pure form.

5-[N-Methyl-2-(trifluoroacetylamino)anilino]-1,3-diphenyl-1H-pyrazole (3d). Trifluoroacetic anhydride (0.42 ml, 3 mmol) was added dropwise during 5 min to a stirred and cooled (15-20°C) suspension of compound **1b** (0.680 g, 2 mmol) in anhydrous dioxane (1 ml). The reaction mixture was maintained for 1 h at 20-25°C, then diluted with water (3 ml), made alkaline with 20% aqueous ammonia solution (1 ml), stirred, and cooled. The aqueous layer was decanted, the oily residue was stirred with water (3 ml), and boiled for 5 min, distilling off the dioxane residue. After cooling, the aqueous layer was decanted, the oily residue was dissolved in methanol (2.5 ml). Hydrazine hydrate (40%, 1.0 ml) was added dropwise to the obtained solution with stirring and cooling to 15-20°C. After 1 h the separated solid was filtered off, washed with cooled 2-propanol, dried at 70-80°C, and product **3d** (0.62 g) was obtained in an analytically pure state.

5-(2-Amino-N-methylanilino)-1,3-diphenyl-1H-pyrazole (4). A mixture of compound **3d** (0.630 g), 80% hydrazine hydrate (0.63 ml), and methanol (3 ml) was boiled for 30 min, then diluted with water (5 ml), and boiled with stirring, while distilling off the methanol. The mixture was cooled, the separated oil was triturated to a powder, which was filtered off and washed with water. After crystallization from 2-propanol, product **4** (0.345 g) was obtained.

2-(2-Benzoyloxy-2-phenylvinyl)-1-methyl-1H-benzimidazole (6). Benzoyl chloride (34.4 ml, 0.275 mol) was added in three portions to a mixture of compound **5** (18.3 g, 0.125 mol) and triethylamine (42.8 ml, 0.275 mol) in anhydrous dioxane (43 ml), each time carefully stirring the reaction mixture, and anticipating the discontinuation of the exothermic reaction. The reaction mixture was then maintained for 1 h in a bath (100°C), diluted with water (43 ml), and stirred until crystallization commenced. The cooled mass was filtered, the solid washed with water, with cooled 2-propanol, dried at 60-70°C, and product **6** (43.0 g, 97%) was obtained, having a yellow color, and ready for further conversions.

1-Methyl-2-phenacyl-1H-benzimidazole (7). Compound **6** (40.58 g) was boiled in ethanol (100 ml) for 2 h. The cooled mixture was filtered, the solid was washed with cooled ethanol, dried at 60-70°C, and product **7** (25.9 g) was obtained in an analytically pure state.

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