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RECYCLIZATION ON CONDENSATION OF ALKYLHYDRAZONES OF 2-PHENACYL-1H-BENZIMIDAZOLE WITH ACYLATING AGENTS

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Cyanoethyl-, ethyl-, and methylhydrazones of 2-phenacyl-1H-benzimidazole undergo recyclization on condensation with aroyl chlorides or dimethylformamide with the formation of 5-(o-aroyl-aminoanilino)pyrazoles or 1-(5-pyrazolyl)-1H-benzimidazoles. The reaction with aroyl chlorides occurs selectively only with the corresponding cyanoethylhydrazone.

Keywords: benzimidazoles, hydrazones, pyrazoles, acylation, condensation, recyclization, selectivity.

Recyclization is aesthetically attractive and often unique in the possible preparation of functionalized compounds with mutually disposed structural fragments, which are difficult to obtain using other preparative methods [1, 2]. It was shown previously that the direction of the reaction of hydrazones of 2-phenacyl-1H-benzimidazole (**1a,b**) with acylating agents depends on the nature of the agent and the conditions used. For example, the condensation of phenylhydrazone **1a** with benzoyl chloride in pyridine is accompanied by recyclization with the formation of 5-(*o*-benzoylaminoanilino)pyrazole **2** [3,4]. Under the same conditions hydrazone **1b**, unsubstituted at the hydrazone amino group, reacts with retention of the initial heterocycle and gives the product of cyclocondensation, 2-(4-pyrazolyl)-1H-benzimidazole (**3**) [5]. Recyclization of this hydrazone occurs in boiling dimethylformamide on acid catalysis, is accompanied by condensation with the solvent used, and gives 1-(3-pyrazolyl)-1H-benzimidazole (**4**) [6, 7] (Scheme 1). Proceeding from these data it is difficult to predict the possibility of the occurrence of analogous recyclizations on condensing acylating agents with alkylhydrazones of 2-phenacyl-1H-benzimidazole (**1c-e**).

It was found that recyclization of cyanoethylhydrazone **1c**, like phenylhydrazone **1a**, occurs on condensation with aroyl chlorides **5a-f** in pyridine at 100°C. The process is fairly selective and gives the corresponding 5-(*o*-aroylaminoanilino)pyrazoles **6a-f** in good yield. On the other hand, ethyl- and methylhydrazones **1d,e** under these conditions give mixtures of products separable with difficulty. Only on interaction with 4-nitrobenzoyl chloride **5a** was the product with analogous recyclization structure **7a,b** isolated in low yield.

Differences in the selectivity of conversion of the cyanoethylhydrazone and other alkyl hydrazones, like the different behavior of phenylhydrazone **1a** and hydrazone **1b** under analogous conditions mentioned above, indicate that the direction of reaction towards recyclization is favored by structural factors which provide a reduction in the nucleophilicity of the hydrazone amino group of the initial compounds. However the opposite rule was found previously. Phenylhydrazone **1a** is recyclized on aroylation more selectively than the corresponding 4-nitrophenylhydrazone [4]. Probably recyclization is favored by certain intermediate values of

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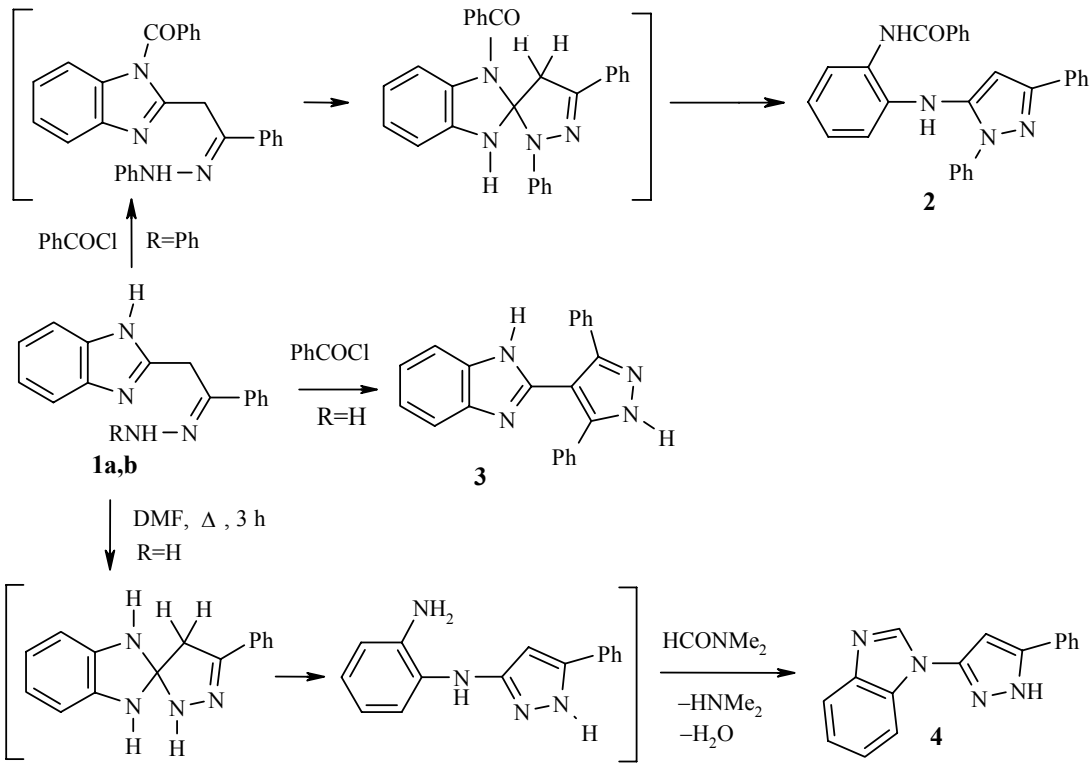
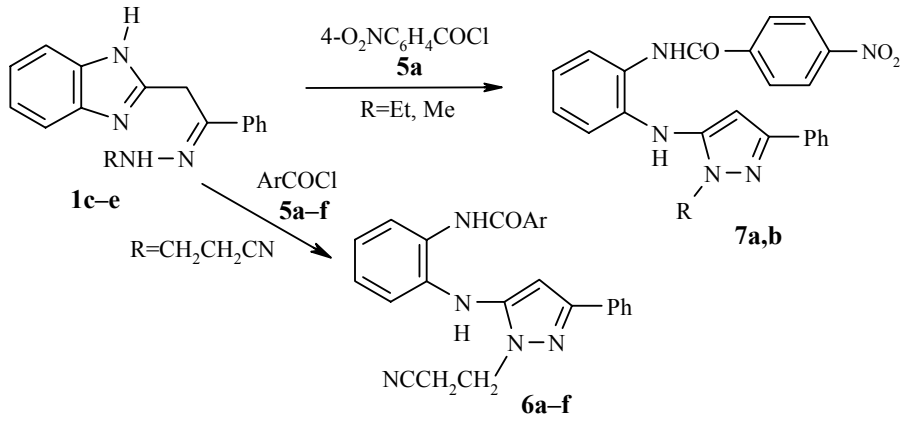
Scheme 1



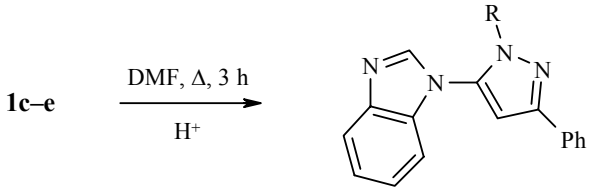
1 a R = Ph, **b** R = H

nucleophilicity for the hydrazone amino group, which aid direction of the attack of the acylating agent to the nitrogen atom of the benzimidazole ring, and not to the hydrazone fragment or the active methylene group of the polyfunctional subjects investigated. In accordance with the recyclization scheme presented above (for an analysis see [4]) conversion must begin with just a regioselective acylation and then proceeds spontaneously at an adequate nucleophilicity of the hydrazone amino group.



1 c R = CH_2CH_2CN, **d** R = Et, **e** R = Me; **5, 6 a** Ar = 4-$O_2NC_6H_4$, **b** Ar = 4-ClC_6H_4, **c** Ar = Ph, **d** Ar = 3,4-$Me_2C_6H_3$, **e** Ar = 4-$MeOC_6H_4$, **f** Ar = 2-thienyl; **7 a** R = Et, **b** R = Me

On condensation with DMF compounds **1c-e**, like hydrazone **1b**, undergo recyclization with a double heterocyclization and give 1-(5-pyrazolyl)-1H-benzimidazoles **8a-c** in satisfactory yield.



8a–c

8 a R = CH_2CH_2CN, **b** R = Et, **c** R = Me

In the analogous conversion the yield of compound **4** was significantly greater at 91% [7], but the reaction proved not to be characteristic for phenylhydrazone **1a**. Consequently enhanced nucleophilicity of the hydrazone amino group aids recyclization on condensation of compounds of type **1** with DMF. Such a result is completely in agreement with the scheme presented above for the corresponding conversion, which begins with nucleophilic attack of the hydrazone amino group at the carbon atom in position 2 of the benzimidazole system.

The structures of the new compounds were confirmed by elemental analysis (Table 1) and by ^{1}H NMR spectra (Table 2). The spectral characteristics are in agreement with the data of [3, 4, 6, 7] for compounds of analogous structure obtained previously.

TABLE 1. Characteristics of the Synthesized Compounds **1c-e**, **6a-f**, **7a,b**, and **8a-c**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
1c	$C_{18}H_{17}N_5$	71.22 / 71.26	5.37 / 5.65	22.95 / 23.09	162-163	94
1d	$C_{17}H_{18}N_4$	73.22 / 73.35	6.45 / 6.52	20.08 / 20.13	175-176	76
1e	$C_{16}H_{16}N_4$	72.59 / 72.70	5.97 / 6.10	21.15 / 21.20	182-183	89
6a	$C_{25}H_{20}N_6O_3$	66.42 / 66.36	4.63 / 4.46	18.79 / 18.58	195-196	77
6b*	$C_{25}H_{20}ClN_5O$	67.88 / 67.95	4.62 / 4.56	—	172.5-174	93
6c	$C_{25}H_{21}N_5O$	73.55 / 73.69	5.18 / 5.20	17.12 / 17.19	160-163	87
6d	$C_{27}H_{25}N_5O$	74.43 / 74.46	5.65 / 5.79	15.97 / 16.08	154-155	92
6e	$C_{26}H_{23}N_5O_2$	71.42 / 71.38	5.25 / 5.30	15.93 / 16.01	154.5-156	94
6f	$C_{23}H_{19}N_5OS$	66.74 / 66.81	4.48 / 4.63	16.87 / 16.94	182-183	95
7a	$C_{24}H_{21}N_5O_3$	67.55 / 67.43	4.85 / 4.95	16.22 / 16.39	161-162.5	45
7b	$C_{23}H_{19}N_5O_3$	66.69 / 66.82	4.51 / 4.63	16.85 / 16.94	192-193	50
8a	$C_{19}H_{15}N_5$	72.67 / 72.82	4.64 / 4.83	22.18 / 22.35	58-60	55
8b	$C_{18}H_{16}N_4$	74.95 / 74.97	5.48 / 5.59	19.51 / 19.43	97-98.5	61
8c	$C_{17}H_{14}N_4$	74.38 / 74.43	4.98 / 5.14	20.37 / 20.43	115-116.5	70

* Found, %: Cl 7.89. Calculated, %: Cl 8.02.

TABLE 2. ^{1}H NMR Spectra of Compounds **1c-e**, **6a-f**, **7a,b**, and **8a-c**

Compound	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
1c	2.80 (2H, t, *J* = 6.3, CH_2CN); 3.51 (2H, t, *J* = 6.3, CH_2N); 4.23 (2H, s, CH_2); 7.12-7.15 (2H, m, H-5,6); 7.24-7.29 (1H, m, *p*-proton C_6H_5); 7.31-7.36 (2H, m, *m*-protons C_6H_5); 7.45 (1H, d, *J* = 7.2, H-7); 7.53 (1H, d, *J* = 8.1, H-4); 7.79 (3H, m, *o*-protons C_6H_5 + NH); 12.38 (1H, s, H-1)
1d	1.19 (3H, t, *J* = 7.2, CH_3); 3.29 (2H, q, *J* = 7.8, CH_2N); 4.20 (2H, s, CH_2); 7.12-7.15 (2H, m, H-5,6); 7.21-7.26 (1H, m, *p*-proton C_6H_5); 7.30-7.35 (2H, m, *m*-protons C_6H_5); 7.47 (3H, br. s, H-4,7 + NH); 7.76 (2H, m, *o*-protons C_6H_5); 12.36 (1H, s, H-1)
1e	3.02 (3H, d, *J* = 4.2, CH_3); 4.20 (2H, s, CH_2); 7.09-7.17 (2H, m, H-5,6); 7.21-7.25 (1H, m, *p*-proton C_6H_5); 7.30-7.35 (3H, m, *m*-protons C_6H_5 + NH); 7.45 (1H, d, *J* = 8.1, H-7); 7.52 (1H, d, *J* = 7.8, H-4); 7.74 (2H, m, *o*-protons C_6H_5); 12.34 (1H, s, H-1)
6a	3.06 (2H, t, *J* = 7.0, CH_2CN); 4.31 (2H, t, *J* = 7.0, CH_2N); 6.49 (1H, s, H-4); 6.85-7.42 (7H, m, *o*-C_6H_4 + *p*- and *m*-protons C_6H_5); 7.54 (1H, s, NHHet); 7.79 (2H, d, *J* = 7.2, *o*-protons C_6H_5); 8.23, 8.36 (2 × 2H, 2d, *J* = 7.8, $C_6H_4NO_2$); 10.19 (1H, s, NHCO)
6b	3.05 (2H, t, *J* = 6.5, CH_2CN); 4.28 (2H, t, *J* = 6.5, CH_2N); 6.48 (1H, s, H-4); 6.85-7.42 (7H, m, *o*-C_6H_4 + *p*- and *m*-protons C_6H_5); 7.50 (1H, s, NHHet); 7.79 (2H, d, *J* = 8.1, *o*-protons C_6H_5); 7.59, 8.03 (2 × 2H, 2d, *J* = 8.1, C_6H_4Cl); 9.97 (1H, s, NHCO)
6c	3.06 (2H, t, *J* = 7.0, CH_2CN); 4.29 (2H, t, *J* = 7.0, CH_2N); 6.47 (1H, s, H-4); 6.86-7.61 (10H, m, *o*-C_6H_4 + *p*- and *m*-protons C_6H_5 + *p*- and *m*-protons COC_6H_5); 7.54 (1H, s, NHHet); 7.80 (2H, d, *J* = 7.2, *o*-protons C_6H_5); 8.02 (2H, d, *J* = 7.2, *o*-protons COC_6H_5); 9.90 (1H, s, NHCO)
6d	2.29 (6H, s, $2CH_3$); 3.05 (2H, t, *J* = 6.6, CH_2CN); 4.30 (2H, t, *J* = 6.6, CH_2N); 6.44 (1H, s, H-4); 6.87-7.42 (8H, m, *o*-C_6H_4 + *p*- and *m*-protons C_6H_5 + H-5 C_6H_3); 7.49 (1H, s, NHHet); 7.73 (1H, d, *J* = 7.5, H-6 C_6H_3); 7.77 (1H, s, H-2 C_6H_3); 7.79 (2H, d, *J* = 8.1, *o*-protons C_6H_5); 9.78 (1H, s, NHCO)
6e	3.05 (2H, t, *J* = 6.5, CH_2CN); 3.83 (3H, s, OCH_3); 4.28 (2H, t, *J* = 6.5, CH_2N); 6.44 (1H, s, H-4); 6.85-7.41 (9H, m, *o*-C_6H_4 + *p*- and *m*-protons C_6H_5 + H-3,5 $C_6H_4OCH_3$); 7.46 (1H, s, NHHet); 7.79 (2H, d, *J* = 7.8, *o*-protons C_6H_5); 7.99 (2H, d, *J* = 8.7, H-2,6 $C_6H_4OCH_3$); 9.74 (1H, s, NHCO)
6f	3.05 (2H, t, *J* = 6.5, CH_2CN); 4.28 (2H, t, *J* = 6.5, CH_2N); 6.47 (1H, s, H-4); 6.85-7.42 (8H, m, *o*-C_6H_4 + *p*- and *m*-protons C_6H_5 + H-4 thienyl); 7.53 (1H, s, NHHet); 7.80 (2H, d, *J* = 7.8, *o*-protons C_6H_5); 7.83 (1H, d, *J* = 4.8, H-5 thienyl); 7.99 (1H, d, *J* = 3.3, H-3 thienyl); 9.90 (1H, s, NHCO)
7a	1.30 (3H, t, *J* = 7.0, CH_3); 4.02 (2H, q, *J* = 7.0, CH_2N); 6.45 (1H, s, H-4); 6.76 (1H, d, *J* = 8.4, H-6 *o*-C_6H_4); 6.87, 7.15 (2H, 2m, H-5,4 *o*-C_6H_4); 7.25-7.40 (4H, m, H-3 *o*-C_6H_4 + *p*- and *m*-protons C_6H_5); 7.44 (1H, s, NHHet); 7.78 (2H, d, *J* = 7.5, *o*-protons C_6H_5); 8.24, 8.35 (2 × 2H, 2d, *J* = 8.4, $C_6H_4NO_2$); 10.19 (1H, s, NH)
7b	3.67 (3H, s, CH_3); 6.46 (1H, s, H-4); 6.78 (1H, d, *J* = 8.1, H-6 *o*-C_6H_4); 6.88, 7.16 (2H, 2m, H-5,4 *o*-C_6H_4); 7.25-7.40 (4H, m, H-3 *o*-C_6H_4 + *p*- and *m*-protons C_6H_5); 7.54 (1H, s, NHHet); 7.77 (2H, d, *J* = 7.2, *o*-protons C_6H_5); 8.24, 8.36 (2 × 2H, 2d, *J* = 8.7, $C_6H_4NO_2$); 10.21 (1H, s, NH)
8a	3.06 (2H, br. s, CH_2CN); 4.20 (2H, br. s, CH_2N); 7.21 (1H, s, H-4'); 7.39-7.48 (6H, m, H-5,6,7 + *p*- and *m*-protons C_6H_5); 7.85 (1H, br. s, H-4); 7.93 (2H, d, *J* = 6.0, *o*-protons C_6H_5); 8.54 (1H, s, H-2)
8b	1.27 (3H, t, *J* = 7.0, CH_3); 3.93 (2H, q, *J* = 7.0, CH_2N); 7.16 (1H, s, H-4'); 7.35-7.48 (6H, m, H-5,6,7 + *p*- and *m*-protons C_6H_5); 7.82-7.85 (1H, m, H-4); 7.90 (2H, d, *J* = 6.9, *o*-protons C_6H_5); 8.59 (1H, s, H-2)
8c	3.71 (3H, s, CH_3); 7.16 (1H, s, H-4'); 7.36-7.48 (6H, m, H-5,6,7 + *p*- and *m*-protons C_6H_5); 7.82-7.85 (1H, m, H-4); 7.89 (2H, d, *J* = 8.4, *o*-protons C_6H_5); 8.60 (1H, s, H-2)

The recyclization of alkylhydrazones of 2-phenacyl-1H-benzimidazoles, in difference to the corresponding phenylhydrazone and hydrazone, may therefore occur on condensation both with aroyl chlorides and with DMF. The reaction leads to the formation of previously unknown compounds of the pyrazole series, which are of interest in the search for new useful substances.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian VXR 300 (300 MHz) instrument in DMSO-d_6. A check on the progress of reactions and the purity of the compounds synthesized was carried out by TLC on Silufol UV 254 plates in the solvent system benzene–ethanol, 9:1 (visualization in UV light). The initial hydrazones **1c-e** were obtained by the standard method from 2-phenacyl-1H-benzimidazole [8] and the appropriate alkylhydrazine. Cyanoethylhydrazine was obtained by the method of [9].

Cyanoethylhydrazone of 2-Phenacyl-1H-benzimidazole (1c). A mixture of 2-phenacyl-1H-benzimidazole (20 mmol), cyanoethylhydrazine (30 mmol), 2-propanol (10 ml), and glacial acetic acid (5 drops) was boiled for 1 h. Water (10 ml) was added and the mixture boiled with stirring until crystallization began. After cooling, the solid was filtered off, washed with aqueous 2-propanol, 1:1, and dried for 5 h at 80°C. The product was obtained in analytically pure form.

Compounds **1d,e** were obtained analogously.

1-Cyanoethyl-5-[2-(4-nitrobenzoylamino)anilino]-3-phenylpyrazole (6a). A mixture of compound **1c** (1 mmol) and acid chloride **5a** (1 mmol) in dry pyridine (1 ml) was kept for 1 h at 95-100°C. Water (4 ml) and 2-propanol (1 ml) were added, and the mixture stirred until crystallization. After cooling, the solid was filtered off, washed with 2-propanol, and recrystallized from ethyl acetate–acetone, 5:1.

Compounds **6b-f** were obtained analogously, but using the appropriate acid chloride **5b-f** (1.1 mmol) and recrystallizing the products from 2-propanol–methyl ethyl ketone, 3:1.

1-Ethyl-[2-(4-nitrobenzoylamino)anilino]-3-phenylpyrazole (7a). A mixture of compound **1c** (1 mmol) and acid chloride **5a** (1 mmol) in dry pyridine (1 ml) was kept for 1 h at 95-100°C, then diluted with water (4 ml). The oily layer was separated and dissolved in 2-propanol (2 ml). Water (2 ml) and conc. hydrochloric acid (0.5 ml) were added. The mixture was heated to 50°C, and left to cool slowly to 15°C. After cooling the salt of the product was filtered off, and washed with 2-propanol. The salt was converted into the base by treatment with conc. aqueous ammonia solution (1 ml) in acetone (5 ml). The mixture obtained was diluted with water (5 ml), and boiled until complete evaporation of the acetone. The residue was dried and recrystallized from toluene.

Compound **7a** was obtained analogously.

1-(1-Alkyl-3-phenyl-5-pyrazolyl)-1H-benzimidazoles (8a-c). A mixture of the appropriate compound **1c-e** (2 mmol), DMF (2 ml), and trifluoroacetic acid (3 mmol) was boiled for 3 h. Isolation of each of the desired products was carried out in the following way.

Compound 8a. An oil was precipitated from the reaction mixture with an excess of water. The oil was separated, dissolved in benzene (5 ml), and passed through a column of neutral aluminum oxide, eluting with benzene. The fraction after passing of the yellow layer was taken. The benzene was evaporated, the residue dried for 3 h in the vacuum of a water-jet pump at 100°C, left overnight at 20°C, and triturated to a powder.

Compound 8b. An oil was precipitated from the reaction mixture with an excess of water. The oil was separated and dissolved in ethanol (3 ml). Picric acid (2 mmol) and ethanol (3 ml) were added, and the mixture boiled with stirring for 5 min. After cooling, the solid was filtered off, and washed with ethanol. After crystallization from a mixture of ethanol–acetone, 4:1, the picrate of the product was obtained (mp 166-167°C), from which the free base was isolated by passing through a column of alkaline aluminum oxide (eluent methylene chloride). The solvent was evaporated, the residue was dried for 3 h at 100°C in the vacuum of a water-jet pump, water (8 ml) was poured in and the mixture maintained at 75-80°C until crystallization was complete., The solid was recrystallized from aqueous ethanol, 1:1.

Compound 8c. Water (3 ml) and conc. aqueous ammonia solution (1 ml) were added, and the mixture was stirred until crystallization of the precipitated oil. The solid was triturated, filtered off, washed with water, dried at 80°C, then recrystallized from 2-propanol.

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