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SYNTHESIS OF A NEW POLYHETEROCYCLIC SYSTEM – PYRAZOLO[5',1':2,3]PYRIMIDO[1,6-*a*]BENZIMIDAZOLE

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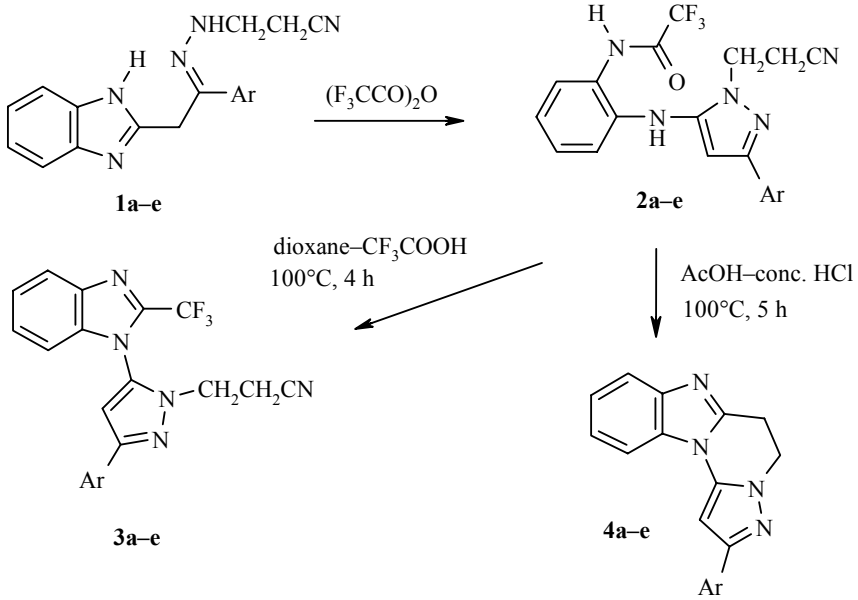
Cyanoethylhydrazones of 2-aroylmethyl-1H-benzimidazoles undergo recyclization on reaction with trifluoroacetyl anhydride to give 3-aryl-1-cyanoethyl-5-(2-trfluoroacetaminoanilino)pyrazoles. The recyclization products may be cyclized with closing of the benzimidazole ring in two ways: with formation of 1-(5-pyrazolyl)benzimidazoles or 5,6-dihydroderivatives of a new polyheterocyclic system – pyrazolo[5',1':2,3]pyrimido[1,6-a]benzimidazole.

Keywords: benzimidazoles, hydrazones, pyrimidines, trifluoroacetyl anhydride, acylation, recyclization, cyclocondensation.

We have shown previously that the reaction of hydrazones of 2-arylmethyl-1H-benzimidazoles with acylating agents is accompanied by recyclization with the formation of 5-(*o*-acylaminoanilino)pyrazoles [1-4], which on heating can be cyclized to 1-(5-pyrazolyl)-1H-benzimidazoles [1, 4, 5]. In the present work we have used these examples of molecular design to construct a new polyheterocyclic system starting from the cyanoethylhydrazones of 2-phenacyl-1H-benzimidazoles **1a-e**.



1a–e **2a–e** **3a–e** **4a–e**

1-4 a Ar = Ph, **b** Ar = 4-$MeOC_6H_4$, **c** Ar = 4-BrC_6H_4, **d** Ar = 4-ClC_6H_4, **e** Ar= 4-$O_2NC_6H_4$

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TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
1a	$C_{18}H_{17}N_5$	71.22 71.27	5.37 5.65	22.95 23.09	162-163	94
1b	$C_{19}H_{19}N_5O$	68.33 68.45	5.57 5.74	20.95 21.01	122-123	83
1c	$C_{18}H_{16}BrN_5$	56.45 56.56	4.14 4.22	18.37 18.32	183.5-185	93
1d	$C_{18}H_{16}ClN_5$	63.88 64.00	4.85 4.77	20.84 20.73	171-172	91
1e	$C_{18}H_{16}N_6O_2$	61.97 62.06	4.49 4.63	24.03 24.12	196-198	37
2a	$C_{20}H_{16}F_3N_5O$	60.12 60.15	4.18 4.04	17.47 17.54	152-153.5	83
2b	$C_{21}H_{18}F_3N_5O_2$	58.61 58.74	4.17 4.23	16.22 16.31	87-88.5	71
2c	$C_{20}H_{15}BrF_3N_5O$	50.19 50.23	3.07 3.16	14.56 14.64	161-162.5	81
2d	$C_{20}H_{15}ClF_3N_5O$	55.32 55.37	3.36 3.49	16.09 16.14	158-159.5	71
2e	$C_{20}H_{15}F_3N_6O_3$	54.08 54.06	3.62 3.40	18.79 18.91	186-187.5	90
3a	$C_{20}H_{14}F_3N_5$	62.87 62.99	3.58 3.70	18.29 18.36	121-122.5	87
3b	$C_{21}H_{16}F_3N_5O$	61.25 61.31	3.79 3.92	16.93 17.02	120-121.5	86
3c	$C_{20}H_{13}BrF_3N_5$	52.04 52.19	2.66 2.85	15.12 15.22	105-106.5	78
3d	$C_{20}H_{13}ClF_3N_5$	57.79 57.77	3.01 3.15	16.72 16.84	102-103	78
3e	$C_{20}H_{13}F_3N_6O_2$	56.22 56.34	3.18 3.07	19.64 19.71	146.5-148	82
4a	$C_{18}H_{14}N_4$	75.63 75.51	4.97 4.93	19.49 19.57	217-218.5	90
4b	$C_{19}H_{16}N_4O$	72.21 72.14	5.03 5.10	17.63 17.71	189-190	90
4c	$C_{18}H_{13}BrN_4$	59.23 59.19	3.51 3.59	15.28 15.34	257.5-259	88
4d	$C_{18}H_{13}ClN_4$	67.43 67.40	4.11 4.08	17.43 17.47	233-234.5	86
4e	$C_{18}H_{13}N_5O_2$	65.32 65.25	3.78 3.95	21.03 21.14	301-302	95

It was established that interaction of compounds **1a-e** with trifluoroacetic anhydride was accompanied by recyclization with formation of the expected 3-aryl-1-cyanoethyl-5-(trifluoroacetylaminoanilino)pyrazoles **2a-e**. The latter can cyclize with closing of the benzimidazole ring in two ways. On heating with trifluoroacetic acid in dioxane a reaction proceeds with participation of the trifluoroacetyl group to form the 1-(5-pyrazolyl)-2-trifluoromethyl-1H-benzimidazoles **3a-e**. On heating with a mixture of acetic and hydrochloric acids the trifluoroacetyl group is removed as a result of hydrolysis and cyclization occurs with participation of the cyanoethyl group and simultaneous closing of the benzimidazole and pyrimidine rings to give compounds of the previously unknown pyrazolo[5',1':2,3]pyrimido[1,6-*a*]benzimidazole system, **4a-e**.

TABLE 2. ^{1}H NMR Spectra of Compounds **1a-e** – **4a-e**

Com-pound	Chemical shifts, δ, ppm, *J* (Hz)
1	2
1a	2.80 (2H, t, *J* = 6.3, CH_2CN); 3.51 (2H, dt, J_1 = 6.3, J_2 = 4.5, CH_2N); 4.23 (2H, s, CH_2); 7.12-7.15 (2H, m, H-5,6); 7.24-7.29 (1H, m, H_{Ar}-4); 7.31-7.36 (2H, m, H_{Ar}-3, 5); 7.45 (1H, d, *J* = 7.2, H-7); 7.53 (1H, d, *J* = 8.1, H-4); 7.79 (3H, m, H_{Ar}-2,6 + NH); 12.38 (1H, s, H-1)
1b	2.78 (2H, t, *J* = 6.0, CH_2CN); 3.48 (2H, dt, J_1 = 5.7, J_2 = 4.5, CH_2N); 3.75 (3H, s, OCH_3); 4.20 (2H, s, CH_2); 6.89 and 7.73 (2 × 2H, two d, *J* = 7.8, H_{Ar}-2,6 and H_{Ar}-3,5); 7.12-7.14 (2H, m, H-5,6); 7.44 (1H, d, *J* = 5.4, H-7); 7.53 (1H, d, *J* = 6.0, H-4); 7.59 (1H, t, *J* = 4.5, NH); 12.32 (1H, s, H-1)
1c	2.80 (2H, t, *J* = 6.0, CH_2CN); 3.51 (2H, dt, J_1 = 5.7, J_2 = 4.5, CH_2N); 4.22 (2H, s, CH_2); 7.12-7.14 (2H, m, H-5,6); 7.47 (2H, m, H-4,7); 7.52 and 7.73 (2 × 2H, two d, *J* = 8.4, H_{Ar}-2,6 and H_{Ar}-3,5); 7.82 (1H, t, *J* = 4.5, NH); 12.35 (1H, s, H-1)
1d	2.79 (2H, t, *J* = 6.3, CH_2CN); 3.51 (2H, dt, J_1 = 6.0, J_2 = 4.5, CH_2N); 4.21 (2H, s, CH_2); 7.12-7.14 (2H, m, 5-, H-6); 7.38 and 7.79 (2 × 2H, two d, *J* = 8.7, H_{Ar}-2,6 and H_{Ar}-3,5); 7.46 (1H, m, H-7); 7.51 (1H, m, H-4); 7.80 (1H, m, NH); 12.33 (1H, s, H-1)
1e	2.82 (2H, t, *J* = 6.6, CH_2CN); 3.51 (2H, dt, J_1 = 6.0, J_2 = 4.5, CH_2N); 4.28 (2H, s, CH_2); 7.12-7.14 (2H, m, H-5,6); 7.45 (1H, m, H-7); 7.51 (1H, m, H-4); 7.98 and 8.17 (2 × 2H, two d, *J* = 9.0, H_{Ar}-2,6 and H_{Ar}-3,5); 8.15 (1H, m, NH); 12.37 (1H, s, H-1)
2a	3.05 (2H, t, *J* = 6.9, CH_2CN); 4.26 (2H, t, *J* = 6.6, CH_2N); 6.49 (1H, s, H-4); 6.83 (1H, d, *J* = 7.5, 2-$CF_3CONHC_6H_4$: H-6); 6.89 (1H, m, 2-$CF_3CONHC_6H_4$: H-4); 7.17-7.23 (2H, m, 2-$CF_3CONHC_6H_4$:H-3,5); 7.28-7.33 (1H, m, H_{Ar}-4); 7.38-7.43 (2H, m, H_{Ar}-3,5); 7.63 (1H, s, NH); 7.81 (2H, d, *J* = 7.5, H_{Ar}-2,6); 10.75 (1H, s, NHCO)
2b	3.03 (2H, t, *J* = 6.6, CH_2CN); 3.78 (3H, s, OCH_3); 4.23 (2H, t, *J* = 6.3, CH_2N); 6.41 (1H, s, H-4); 6.82 (1H, d, *J* = 7.5, 2-$CF_3CONHC_6H_4$: H-6); 6.88 (1H, m, 2-$F_3CONHC_6H_4$: H-4); 6.96 and 7.73 (2 × 2H, two d, *J* = 8.7, H_{Ar}-3,5 and H_{Ar}-2,6); 7.17-7.22 (2H, m, 2-$CF_3CONHC_6H_4$: H-3,5); 7.61 (1H, s, NH); 10.76 (1H, s, NHCO)
2c	3.05 (2H, t, *J* = 6.9, CH_2CN); 4.26 (2H, t, *J* = 6.9, CH_2N); 6.52 (1H, s, H-4); 6.84 (1H, d, *J* = 7.5, 2-$CF_3CONHC_6H_4$: H-6); 6.89 (1H, m, 2-$CF_3CONHC_6H_4$: H-4); 7.18-7.23 (2H, m, 2-$CF_3CONHC_6H_4$: H-3,5); 7.60 and 7.76 (2 × 2H, two d, *J* = 8.7, H_{Ar}-2,6 and H_{Ar}-3,5); 7.67 (1H, s, NH); 10.79 (1H, s, NHCO)
2d	3.05 (2H, t, *J* = 6.6, CH_2CN); 4.27 (2H, t, *J* = 6.6, CH_2N); 6.52 (1H, s, H-4); 6.84 (1H, d, *J* = 7.8, 2-$CF_3CONHC_6H_4$: H-6); 6.90 (1H, m, 2-$CF_3CONHC_6H_4$: H-4); 7.18-7.23 (2H, m, 2-$CF_3CONHC_6H_4$: H-3,5); 7.47 and 7.83 (2 × 2H, two d, *J* = 8.7, H_{Ar}-2,6 and H_{Ar}-3,5); 7.67 (1H, s, NH); 10.80 (1H, s, NHCO)
2e	3.08 (2H, t, *J* = 6.6, CH_2CN); 4.32 (2H, t, *J* = 6.6, CH_2N); 6.69 (1H, s, H-4); 6.87-6.95 (2H, m, 2-$CF_3CONHC_6H_4$: H-4,6); 7.20-7.25 (2H, m, 2-$CF_3CONHC_6H_4$: H-3,5); 7.75 (1H, s, NH); 8.09 and 8.28 (2 × 2H, two d, *J* = 8.7, H_{Ar}-2,6 and H_{Ar}-3,5); 10.80 (1H, s, NHCO)
3a	3.05 (2H, m, CH_2CN), 4.20 (2H, m, CH_2N), 7.33 (1H, s, H-4'), 7.38-7.60 (6H, m, H-5,6,7 + H_{Ar}-3,4,5), 7.93 (2H, d, *J* = 6.9, H_{Ar}-2,6), 8.01-8.04 (1H, m, H-4)
3b	3.04 (2H, m, CH_2CN), 3.81 (3H, s, OCH_3), 4.15 (2H, m, CH_2N), 7.04 and 7.84 (22H, two d, *J* = 8.4, H_{Ar}-3,5 and H_{Ar}-2,6), 7.22 (1H, s, H-4'), 7.45 (1H, d, *J* = 8.1, H-7), 7.55 (2H, m, H-5,6), 8.02 (1H, d, *J* = 8.1, H-4)
3c	3.06 (2H, m, CH_2CN), 4.18 (2H, m, CH_2N), 7.36 (1H, s, H-4'), 7.44-7.47 (1H, m, H-7), 7.54-7.57 (2H, m, H-5,6), 7.69 and 7.87 (2 × 2H, two d, *J* = 9.0, H_{Ar}-2,6 and H_{Ar}-3,5), 8.00-8.03 (1H, m, H-4)
3d	3.06 (2H, m, CH_2CN), 4.20 (2H, m, CH_2N), 7.37 (1H, s, H-4'), 7.45-7.48 (1H, m, H-7), 7.52-7.55 (2H, m, H-5,6), 7.57 and 7.94 (2 × 2H, two d, *J* = 8.7, H_{Ar}-2,6- and H_{Ar}-3,5), 8.01-8.04 (1H, m, H-4)
3e	3.07 (2H, m, CH_2CN), 4.26 (2H, m, CH_2N), 7.47-7.50 (1H, m, H-7), 7.56 (1H, s, H-4'), 7.56-7.58 (2H, m, H-5,6), 8.02-8.05 (1H, m, H-4), 8.19 and 8.36 (2 × 2H, two d, *J* = 9.0, H_{Ar}-2,6 and H_{Ar}-3,5)
4a	3.58 (2H, t, *J* = 5.1, CCH_2), 4.55 (2H, t, *J* = 5.4, NCH_2), 7.33-7.37 (2H, m, H-9,10), 7.40 (1H, s, H-1), 7.42-7.48 (3H, m, H_{Ar}-3,4,5), 7.73 (1H, d, *J* = 6.3, H-11), 7.97 (2H, d, *J* = 5.4, H-11), 8.07 (1H, d, *J* = 6.6, H-8)

TABLE 2 (continued)

1	2
4b	3.62 (2H, t, J = 6.9, CCH_2), 3.81 (3H, s, OCH_3), 4.52 (2H, t, J = 6.9, NCH_2), 7.02 and 7.89 (2 × 2H, two d, J = 8.7, H_{Ar}-2,6 and H_{Ar}-3,5), 7.29 (1H, s, H-1), 7.32-7.44 (2H, m, H-9,10), 7.73 (1H, d, J = 7.5, H-11), 8.05 (1H, d, J = 7.8, H-8)
4c	3.57 (2H, t, J = 6.9, CCH_2), 4.55 (2H, t, J = 6.9, NCH_2), 7.32-7.44 (2H, m, H-9,10), 7.43 (1H, s, H-1), 7.66 and 7.91 (2 × 2H, two d, J = 8.4, H_{Ar}-3,5- and H_{Ar}-2,6), 7.73 (1H, d, J = 8.1, H-11), 8.05 (1H, d, J = 7.8, H-8)
4d	3.57 (2H, t, J = 6.9, CCH_2), 4.55 (2H, t, J = 6.9, NCH_2), 7.32-7.44 (2H, m, H-9,10), 7.40 (1H, s, H-1), 7.52 and 7.98 (2 × 2H, two d, J = 8.7, H_{Ar}-3,5 and H_{Ar}-2,6), 7.72 (1H, d, J = 8.1, H-11), 8.04 (1H, d, J = 7.8, H-8)
4e	3.59 (2H, t, J = 6.9, CCH_2), 4.60 (2H, t, J = 7.2, NCH_2), 7.32-7.445 (2H, m, H-9,10), 7.59 (1H, s, H-1), 7.72 (1H, d, J = 8.1, H-11), 8.05 (1H, d, J = 7.5, H-8), 8.19 and 8.30 (2 × 2H, two d, J = 9.3, H_{Ar}-3,5 and H_{Ar} -2,6)

The synthesized compounds are completely stable crystalline substances. The structure and composition of all the compounds have been confirmed elemental analysis (Table 1) and ^{1}H NMR spectra (Table 2). The structures of compounds **2a** and **3a** have also been confirmed by IR spectra and ^{19}F NMR spectra, and compound **4a** by mass spectroscopy.

According to the ^{1}H NMR spectra there is restricted rotation about the bond connecting the benzimidazole and pyrazole rings in compounds **3a-e** because of steric hindrance. Each of the protons of the two linked CH_2 groups appears in unexpected chemical surroundings: consequently the signals of these groups have increased multiplicity. It is known [6] that compounds of this type exist as racemic mixtures. Evidently the heterocyclic fragments of compounds **3a-e** do not lie in the same plane. This is shown clearly by the shift of the signal of proton H-7 of the benzimidazole unit to strong field (7.44-7.50 ppm) in comparison with the signal of the proton in the same position in the benzimidazole ring in compounds **4a-e** (7.72- 7.73 ppm). In compounds **4a-e** the heterocyclic system is close to coplanar and the pyrazole ring shows a maximum deshielding effect on the closest hydrogen atom of the benzimidazole fragment. In the given cases both protons of each of the mutually bonded methylene groups are chemically equivalent; and the signals of these groups appear as well expressed triplets.

Thus the cyclocondensation of 3-aryl-1-cyanoethyl-5-(tifluroacetaminoanilino)pyrazoles on heating with hydrochloric acid is a preparatively satisfactory and effective method for the synthesis of compounds of the previously unknown tetracyclic pyrazolo[5',1':2,3]pyrimido[1,6-*a*]benzimidazole system.

EXPERIMENTAL

^{1}H and ^{19}F NMR spectra of DMSO-d_6 solutions with TMS and $CFCl_3$ standards were recorded with a Varian VXR-300 (300 MHz) spectrometer. IR spectra of KBr disks were recorded with a UR-20 instrument and mass spectra with a MX-1321 machine (70 eV, 220°C). The course of reactions and the purity of the compounds synthesized were monitored by TLC on Silufol UV-254 strips with 9:1 benzene–ethanol solvent and detection with UV light.

Cyanoethylhydrazone of 2-Phenacyl-1H-benzimidazole (1a). A mixture of 2-phenacyl-1H-benzimidazole (5 mmol), cyanoethylhydrazine (7.5 mmol), 2-propanol (2.5 ml), and glacial acetic acid (1 drop) was boiled for 1 h. Water (2.5 ml) was added and the mixture was boiled with stirring until crystallization began. After cooling the precipitate was filtered off, washed with 2-propanol and water (1:1), and dried for 5 h at 80°C. The product was obtained in an analytically pure form.

Hydrazones 1b-d were prepared analogously from the corresponding 2-aroylmethylbenzimidazoles [7].

Cyanoethylhydrazone of 2-(4-Nitrophenacyl)-1H-benzimidazole (1e). A mixture of 2-(4-nitrophenacyl)-1H-benzimidazole (12 mmol) [7], cyanoethylhydrazine (28 mmol), DMSO (10 ml), and glacial acetic acid (6 drops) was stirred at 90-95°C for 5 h. The solution was kept at 15-17°C for 20 h. The precipitate was filtered off and washed with 2-propanol. The product was obtained analytically pure after drying in water pump vacuum at 115°C for 5 h.

1-Cyanoethyl-3-phenyl-5-(*o*-trifluoroacetaminoanilino)pyrazole (2a). Trifluoroacetic anhydride (6 mmol) was added dropwise, while keeping the temperature 17-20°C, to a stirred mixture of compound **1a** (4 mmol) and anhydrous dioxane (2 ml). The reaction mixture was kept at 20°C for 1 h, water (20 ml) and 20% aqueous ammonia (2 ml) were added, heated to 60°C and stirred until crystallization began. After cooling, the precipitate was filtered off, washed with water, a 1:1 mixture of water and 2-propanol, dried at 75°C and crystallized from toluene. IR spectrum, ν, cm^{-1}: 1735 (C=O), 2275 (C≡N), 3270, 3435 (N–H). ^{19}F NMR spectrum, δ, ppm: -73.32.

Pyrazoles 2b-e were obtained analogously from compounds **1b-e**. The amount of anhydrous dioxane was increased to 4 ml in the preparation of compound **2e**.

1-(1-Cyanoethyl-3-phenylpyrazol-5-yl)-2-trifluoromethyl-1H-benzimidazole (3a). A solution of compound **2a** (0.5 g) in a mixture of anhydrous dioxane (5 ml) and trifluoroacetic acid (0.5 ml) was kept at 100°C for 4 h. The solvent was evaporated at a water pump vacuum while heating to 100°C and the residue was dissolved in a minimum quantity of benzene. The solution was passed through a short column of aluminum oxide with benzene as eluant. The benzene was evaporated and the residue was crystallized from ethanol. IR spectrum, ν, cm^{-1}: 2270 (C≡N). ^{19}F NMR spectrum, δ, ppm: -60.81.

Pyrazolylbenzimidazoles 3b-e were prepared analogously from compounds **2b-e.**

5,6-Dihydro-2-phenylpyrazolo[5',1':2,3]pyrimido[1,6-*a*]benzimidazole (4a). A mixture of compound **2a** (0.5 g), acetic acid (1 ml) and concentrated hydrochloric acid (1 ml) as maintained at 100°C for 5 h. The mixture was then evaporated with stirring and heated to 140°C. The solid residue was boiled with pyridine (5 ml), the mixture was stirred and carefully diluted with 20% aqueous ammonia (2 ml) and water (3 ml). After cooling the reside was filtered off, washed with water and 2-propanol, and dried at 115°C for 5h with a water pump vacuum to give an analytically pure product. Mass spectrum, *m/z*, (I_{rel}, %): 286 M^+ (100), 258 (12), 143 (12), 101 (4).

Compounds 4b-e were made analogously from compounds **2b-e.**

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