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ISOMERIZATION OF 2-PHENACYL-1H-BENZIMIDAZOLE ARYLHYDRAZONES TO 1-ARYL-5-(*o*-AMINOANILINO)-3-PHENYLPYRAZOLES BY TRIFLUOROACETYLATION AND HYDRAZINOLYSIS

I. B. Dzvinchuk and M. O. Lozinskii

A convenient preparative two-stage method was developed for the isomerization of 2-phenacyl-1H-benzimidazole arylhydrazones to previously unknown 5-(o-aminoanilino)-1-aryl-3-phenylpyrazoles. The transformation scheme includes recyclization during acylation with trifluoroacetic anhydride leading to the formation of 1-aryl-3-phenyl-5-(o-trifluoroacetylaminoanilino)pyrazoles, which then undergo hydrazinolysis.

Keywords: benzimidazoles, hydrazones, pyrazoles, trifluoroacetic anhydride, hydrazinolysis, recyclization.

Recyclization is particularly attractive on account of the possibility of obtaining functionalized compounds with a mutual arrangement of structural fragments that is difficult to obtained by other methods of preparative organic chemistry [1-5]. It was interesting from this standpoint to develop a method for recyclization of 2-phenacyl-1H-benzimidazole arylhydrazones **1a-e** to the isomeric previously unknown 1-aryl-5-phenyl(*o*-aminophenyl)-3-phenylpyrazoles **2a-e**. Solution of this problem may increase the prospects for the synthesis of new pyrazole-containing compounds (Scheme 1).

It should be noted that the direct recyclization of compounds **1** to the required products is essentially intramolecular transamination, which must be subject to substantial steric and energetic hindrances. The process requires intramolecular nucleophilic attack by the not very reactive arylhydrazone fragment at position 2 of the extremely reactive benzimidazole system followed by opening of the imidazole ring on account of cleavage of the nitrogen–carbon bond. We were unable to find conditions for such direct isomerization. On heating and with acid catalysis phenylhydrazones of type **1** are transformed in a different direction and undergo Fischer indolization [6]. As we found earlier [7], the recyclization of 2-phenacyl-1H-benzimidazole phenylhydrazone (**1a**) can be initiated during acylation with benzoyl chloride, leading to the production of the N-benzoyl-substituted compound **3**, which is not however transformed into the required product when heated with hydrazine hydrate for 12 h.

We were unable to synthesize compounds **2** by using trifluoroacetic anhydride, which contains an easily removed acyl group.

The reaction of compounds **1a-e** with trifluoroacetic anhydride is accompanied by recyclization with the formation of 1-aryl-3-phenyl-5-(*o*-trifluoroacetylaminoanilino)pyrazoles **4a-e**, the hydrazinolysis of which leads to the required anilinopyrazoles **2a-e**.

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kiev, Ukraine 02094; e-mail: iochkiev@ukrpack.net. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 1002-1006, July, 2005. Original article submitted September 20, 2003.

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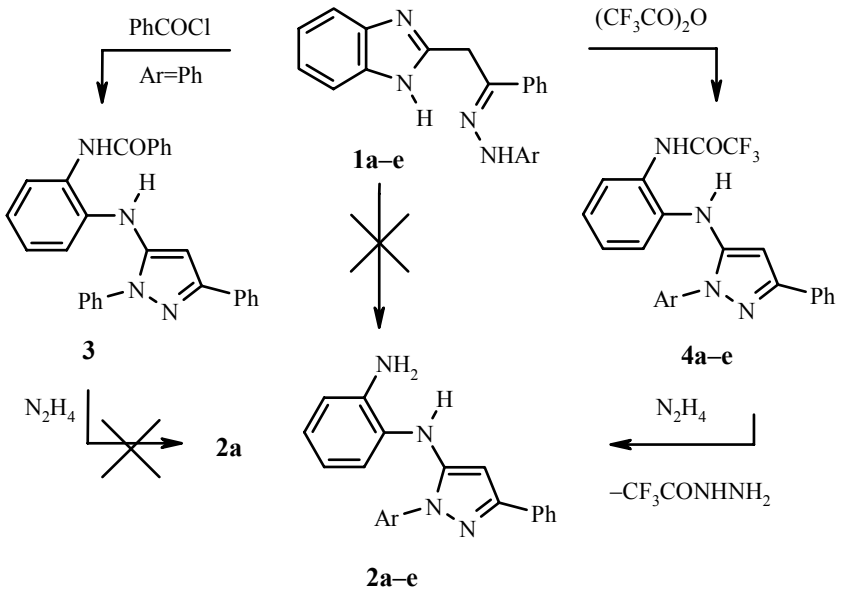
Scheme 1



1, 2, 4 a Ar = Ph, **b** Ar = $O_2NC_6H_4$, **c** Ar = 3-ClC_6H_4, **d** Ar = 4-FC_6H_4, **e** Ar = 4-MeC_6H_4

TABLE 1. The Characteristics of the Synthesized Compounds **1c-e**, **2a-e**, and **4a-e**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
1c	$C_{21}H_{17}ClN_4$	69.78 / 69.90	4.63 / 4.75	15.47 / 15.53	225-226.5	77
1d	$C_{21}H_{17}FN_4$	73.36 / 73.24	5.05 / 4.98	16.15 / 16.27	240-242	85
1e	$C_{22}H_{20}N_4$	77.68 / 77.62	5.82 / 5.92	16.32 / 16.46	221-222.5	75
2a	$C_{21}H_{18}N_4$	77.16 / 77.28	5.67 / 5.56	17.08 / 17.16	156-157	94
2b	$C_{21}H_{17}N_5O_2$	67.83 / 67.91	4.55 / 4.61	18.69 / 18.86	170-171.5	99
2c	$C_{21}H_{17}ClN_4$	69.73 / 69.90	4.48 / 4.75	15.39 / 15.53	109-110.5	98
2d	$C_{21}H_{17}FN_4$	73.13 / 73.24	4.77 / 4.98	16.14 / 16.27	173-174.5	94
2e	$C_{22}H_{20}N_4$	77.43 / 77.62	5.75 / 5.92	16.29 / 16.46	173-175	98
4a	$C_{23}H_{17}F_3N_4O$	65.36 / 65.40	4.18 / 4.06	13.18 / 13.26	144-145	81
4b	$C_{23}H_{16}F_3N_5O_3$	59.02 / 59.10	3.49 / 3.45	14.89 / 14.98	203.5-205	92
4c	$C_{23}H_{16}ClF_3N_4O$	60.44 / 60.47	3.65 / 3.53	12.19 / 12.26	125-126.5	70
4d	$C_{23}H_{16}F_4N_4O$	62.79 / 62.75	3.72 / 3.66	12.65 / 12.72	142-143.5	80
4e	$C_{24}H_{19}F_4N_4O$	66.12 / 66.05	4.16 / 4.39	12.75 / 12.84	160-161.5	77

TABLE 2. The IR and ^{1}H NMR Spectra of Compounds **1c-e**, **2a-e**, and **4a-e**

Compound	IR spectrum, ν, cm^{-1}, C=N, C=O and N–H	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
1	2	3
1c	1595, 3365	4.45 (2H, s, CH_2); 6.83 (1H, d, *J* = 8.1, 3-ClC_6H_4: H-4); 7.08-7.17 (2H, m, H-5,6); 7.20-7.26 (1H, m, *p*-protons C_6H_5); 7.26-7.31 (3H, m, 3-ClC_6H_4: H-2,4,5); 7.35-7.40 (2H, m, *m*-protons C_6H_5); 7.45 (1H, d, *J* = 6.9, H-7); 7.52 (1H, d, *J* = 7.2, H-4); 7.85 (2H, d, *J* = 7.5, *o*-protons C_6H_5); 10.39 (1H, s, NNH); 12.40 (1H, s, H-1)
1d	1615, 3340	4.43 (2H, s, CH_2); 7.09-7.15 (4H, m, H-5,6 and 4-FC_6H_4: H-3,5); 7.24-7.30 (3H, m, *p*-protons C_6H_5 and 4-FC_6H_4: H-2,6); 7.33-7.38 (2H, m, *m*-protons C_6H_5); 7.46 (1H, m, H-7); 7.51 (1H, m, H-4); 7.85 (2H, d, *J* = 7.8, *o*-protons C_6H_5); 10.29 (1H, s, NNH); 12.40 (1H, s, H-1)
1e	1610, 3340	2.24 (3H, s, CH_3); 4.41 (2H, s, CH_2); 7.08-7.18 (2 × 2H, 2d, *J* = 8.4, 4-$CH_3C_6H_4$); 7.09-7.16 (2H, m, H-5,6); 7.23-7.28 (1H, m, *p*-protons C_6H_5); 7.33-7.38 (2H, m, *m*-protons C_6H_5); 7.44 (1H, d, *J* = 6.9, H-7); 7.52 (1H, d, *J* = 7.2, H-4); 7.84 (2H, d, *J* = 7.8, *o*-protons C_6H_5); 10.20 (1H, s, NNH); 12.40 (1H, s, H-1)
2a	3350, 3380, 3460	4.85 (2H, s, NH_2); 6.30 (1H, s, H-4); 6.45-6.51 (1H, m, 2-$NH_2C_6H_4$: H-4); 6.67-6.71 (2H, m, 2-$NH_2C_6H_4$: H-3,5); 6.76 (1H, d, *J* = 8.1, 2-$NH_2C_6H_4$: H-6);7.06 (1H, s, NH); 7.29-7.43 (4H, m, *p*- and *m*-protons CC_6H_5 + *p*-proton NC_6H_5); 7.46-7.51 (2H, m, *m*-protons NC_6H_5); 7.73 (2H, d, *J* = 7.8, *o*-protons NC_6H_5); 7.83 (2H, d, *J* = 6.9, *o*-protons CC_6H_5)
2b	3330, 3390, 3480	4.94 (2H, s, NH_2); 6.28 (1H, s, H-4); 6.46-6.51 (1H, m, 2-$NH_2C_6H_4$: H-4); 6.72-6.78 (3H, m, 2-$NH_2C_6H_4$: H-3,5,6); 7.32-7.46 (4H, m, NH + *p*- and *m*-protons C_6H_5); 7.86 (2H, d, *J* = 7.2, *o*-protons CC_6H_5); 8.10 and 8.34 (2 × 2H, 2d, *J* = 6.9, *p*-C_6H_4)
2c	3370, 3455	4.86 (2H, s, NH_2); 6.23 (1H, s, H-4); 6.45-6.51 (1H, m, 2-$NH_2C_6H_4$: H-4); 6.70-6.77 (3H, m, 2-$NH_2C_6H_4$: H-3,5,6); 7.21 (1H, s, NH); 7.30-7.84 (9H, m, C_6H_5 + 3-ClC_6H_4)
2d	3350, 3375, 3450	4.83 (2H, s, NH_2); 6.26 (1H, s, H-4); 6.45-6.50 (1H, m, 2-$NH_2C_6H_4$: H-4); 6.67-6.72 (2H, m, 2-$NH_2C_6H_4$: H-3,5); 6.74 (1H, d, *J* = 7.8, 2-$NH_2C_6H_4$: H-6); 7.06 (1H, s, NH); 7.29-7.34 (3H, m, *p*-protons C_6H_5 + FC_6H_4: H-2,6); 7.34-7.42 (2H, m, *m*-protons C_6H_5); 7.72-7.77 (2H, m, 4-FC_6H_4: H-3,5); 7.82 (2H, m, *J* = 6.9, *o*-protons C_6H_5)
2e	3350, 3375, 3460	2.35 (3H, s, CH_3); 4.81 (2H, s, NH_2); 6.29 (1H, s, H-4); 6.45-6.50 (1H, m, 2-$NH_2C_6H_4$: H-4); 6.66-6.70 (2H, m, 2-$NH_2C_6H_4$: H-3,5); 6.75 (1H, d, *J* = 7.8, 2-$NH_2C_6H_4$: H-6); 6.95 (1H, s, NH); 7.27-7.33 (3H, m, *p*-protons C_6H_5 + $CH_3C_6H_4$: H-3,5); 7.37-7.42 (2H, m, *m*-protons C_6H_5); 7.60 (2H, d, *J* = 8.1, $CH_3C_6H_4$: H-2,6); 7.81 (2H, d, *J* = 7.2, *o*-protons C_6H_5)
4a	1700, 3200, 3280, 3600	6.60 (1H, s, H-4); 6.80 (1H, d, *J* = 7.8, 2-$CF_3CONHC_6H_4$: H-6); 6.85 (1H, m, 2-$CF_3CONHC_6H_4$: H-4); 7.12 (1H, m, 2-$CF_3CONHC_6H_4$: H-5); 7.18 (1H, d, *J* = 7.8, 2-$CF_3CONHC_6H_4$: H-3); 7.29-7.36 (2H, m, *p*-protons NC_6H_5 and CC_6H_5); 7.41-7.46 (4H, m, *m*-protons NC_6H_5 and CC_6H_5); 7.75 (2H, d, *J* = 7.5, *o*-protons NC_6H_5); 7.77 (1H, s, NH); 7.87 (2H, d, *J* = 6.9, *o*-protons C_6H_5); 10.74 (1H, s, NHCO)
4b	1700, 3315	6.72 (1H, s, H-4); 6.78 (1H, d, *J* = 8.1, 2-$CF_3CONHC_6H_4$: H-6); 6.89 (1H, m, 2-$CF_3CONHC_6H_4$: H-4); 7.14 (1H, m, 2-$CF_3CONHC_6H_4$: H-5); 7.22 (1H, d, *J* = 7.8, 2-$CF_3CONHC_6H_4$: H-3); 7.36-7.49 (3H, m, *p*- and *m*-protons C_6H_5); 7.93 (2H, d, *J* = 7.2, *o*-protons C_6H_5); 8.11 (1H, s, NHHet); 8.15 and 8.28 (2 × 2H, 2d, *J* = 9.3, 4-$NO_2C_6H_4$); 10.80 (1H, s, NHCO)
4c	1710, 3200, 3300	6.54 (1H, s, H-4); 6.84 (1H, d, *J* = 8.1, 2-$CF_3CONHC_6H_4$: H-6); 6.90 (1H, m, 2-$CF_3CONHC_6H_4$: H-4); 7.15 (1H, m, 2-$CF_3CONHC_6H_4$: H-5); 7.22 (1H, d, *J* = 7.5, 2-$CF_3CONHC_6H_4$: H-3); 7.33-7.88 (9H, m, C_6H_5 + 3-ClC_6H_4); 7.86 (1H, s, NHHet); 10.73 (1H, s, NHCO)

TABLE 2 (continued)

1	2	3
4d	1700, 3295, 3420	6.59 (1H, s, H-4); 6.79 (1H, d, J = 7.8, 2-$CF_3CONHC_6H_4$: H-6); 6.86 (1H, m, 2-$CF_3CONHC_6H_4$: H-4); 7.13 (1H, m, 2-$CF_3CONHC_6H_4$: H-5); 7.18 (1H, d, J = 7.8, 2-$CF_3CONHC_6H_4$: H-3); 7.24-7.30 and 7.76-7.80 (2 × 2H, 2m, 4-FC_6H_4); 7.43 and 7.43 (1H and 2H, 2m, *p*- and *m*-protons C_6H_5); 7.76 (1H, s, NHHet); 7.87 (2H, d, J = 7.2, *o*-protons C_6H_5); 10.73 (1H, s, NHCO)
4e	1700, 3285, 3425	2.32 (3H, s, CH_3); 6.58 (1H, s, H-4); 6.79 (1H, d, J = 7.8, 2-$CF_3CONHC_6H_4$: H-6); 6.85 (1H, m, 2-$CF_3CONHC_6H_4$: H-4); 7.13 (1H, m, 2-$CF_3CONHC_6H_4$: H-5); 7.18 (1H, d, J = 7.8, 2-$CF_3CONHC_6H_4$: H-3); 7.24-7.63 (2 × 2H, 2d, J = 8.1, 4-$CH_3C_6H_4$); 7.33 and 7.42 (1H and 2H, 2m, *p*- and *m*-protons C_6H_5); 7.67 (1H, s, NHHet); 7.87 (2H, d, J = 7.2, *o*-protons C_6H_5); 10.72 (1H, s, NHCO)

The first stage of the synthesis (recyclization initiated by acylation) takes place in dioxane at 20-25°C and is complete in 1 h. In order to obtain complete conversion of the trifluoroacetic anhydride a 1.5-fold excess above the theoretical amount is used. The reaction takes place smoothly, and the yields of compounds **4a-e** amount 70-92%.

The second stage of the synthesis (hydrazinolysis) takes place in boiling methanol and is complete in 30 min. The trifluoroacetylhydrazine formed in the reaction has high solubility and does not interfere with the isolation of the products **2a-e**, the yields of which are close to quantitative.

The synthesized new compounds (Table 1) are perfectly stable crystalline substances, the structure of which was supported by data from the IR and ^{1}H NMR spectra (Table 2).

Thus, a new convenient method was found for the isomerization of 2-phenacyl-1H-benzimidazole arylhydrazones to 5-(2-aminoanilino)-1-aryl-3-phenylpyrazoles by the action of trifluoroacetic anhydride followed by hydrazinolysis of the obtained pyrazolylaminotrifluoroacetanilides.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer (300 MHz) in DMSO-d_6 with TMS as internal standard. The IR spectra were recorded on a UR-20 instrument in tablets with potassium bromide. The reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates in the 9:1 benzene–ethanol solvent system (with development in UV light). Compounds **1a**,**b** and **3** were obtained by the methods in [7, 8].

2-Phenacyl-1H-benzimidazole 3-Chlorophenylhydrazone (1c). A mixture of 2-phenacyl-1H-benzimidazole (10 mmol), 3-chlorophenylhydrazine hydrochloride (11 mmol), pyridine (15 mmol), and dioxane (5 ml) was heated at 95-100°C for 1.5 h. We added water (3 ml) and 2-propanol (3 ml) and stirred the mixture until crystallization began. After cooling the precipitate was filtered off, washed with 2-propanol, and dried at 115°C for 5 h under the vacuum of a water-jet pump. The product is formed in the analytically pure form.

The arylhydrazone **1d** was obtained similarly.

2-Phenacyl-1H-benzimidazole 4-Tolylhydrazone (1e). A mixture of 2-phenacyl-1H-benzimidazole (5 mmol), 4-tolylhydrazine (7 mmol), and dioxane (5 ml) was heated for 1.5 h in the presence of five drops of glacial acetic acid at 95-100°C. We added water (2.5 ml) and stirred the mixture until crystallization began. After cooling the precipitate was filtered off, washed with 2-propanol, and dried at 115°C for 5 h under the vacuum of a water-jet pump. The product is formed in the analytically pure form.

1-Aryl-3-phenyl-5-(2-trifluoroacetylaminoanilino)pyrazoles (4a-e). To a suspension of the respective compound **1a-e** (2 mmol) in anhydrous dioxane (2.0 ml) with cooling on a water bath (20-25°C) and stirring we added trifluoroacetic anhydride (0.42 g, 3 mmol) over 3-4 min. The solution was kept at 20-25°C for 1 h and was then diluted with a mixture of 1 ml of an aqueous solution (20%) of ammonia and 3 ml of water. The mixture was heated with stirring until the oil that separated had completely crystallized. If crystallization did not occur the reaction mixture was evaporated to half the volume and diluted with 2 ml of 2-propanol. After cooling the precipitate was filtered off, washed with a cold 1:1 mixture of water and 2-propanol, dried at 90°C, and recrystallized from toluene.

5-(2-Aminoanilino)-1-aryl-3-phenylpyrazoles 2a-e. To a mixture of the respective compound **4a-e** (0.3 g) in methanol (1.5 ml) heated on a bath (95-100°C) we added hydrazine hydrate (80%) (0.3 ml). The mixture was boiled for 30 min and diluted with water with stirring (1.5 ml). If the product separated as an oil, ether (0.5 ml) was added. After cooling the precipitate was filtered off, washed with a 1:1 mixture of methanol and water, and dried at 100°C for 5 h. The products were formed in the analytically pure form.

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