Chemistry of Heterocyclic Compounds, Vol. 41, No. 2, 2005

SYNTHESIS OF 2-(3-INDOLYL)-1H-BENZIMIDAZOLES FROM 2-ACYLMETHYL-1H-BENZIMIDAZOLES

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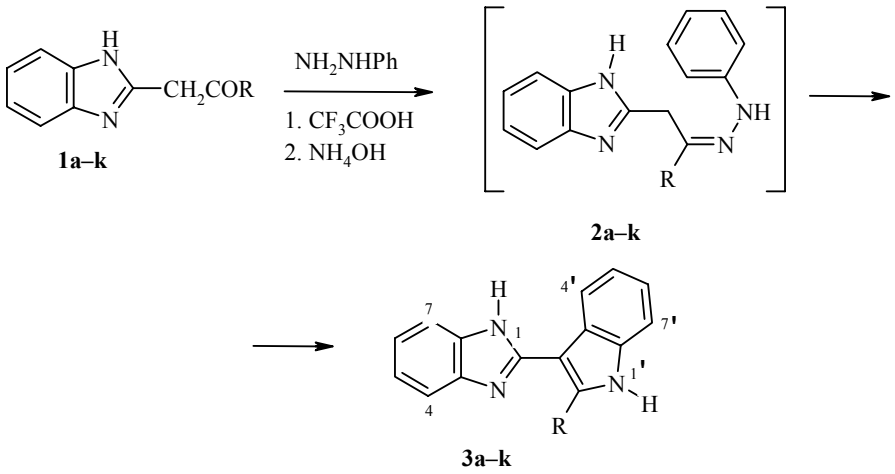
The interaction of 2-acetyl(aroyl)methyl-1H-benzimidazoles with phenylhydrazine on heating in trifluoroacetic acid proceeds by a type of Fischer reaction with the formation of 2-[2-methyl(aryl)-3-indolyl]-1H-benzimidazoles.

Keywords: benzimidazoles, indoles, phenylhydrazine, Fischer reaction.

It was shown previously that the interaction of 2-acetylmethyl-1H-benzimidazoles of type **1** with hydrazine on acid catalysis does not stop at the stage of forming the corresponding hydrazones, but is accompanied by recyclization and leads to a pyrazole compound [1]. The direction of the analogous reaction with phenylhydrazine has been studied in the present work.

We found that the interaction of reactants **1a-k** with phenylhydrazine in boiling trifluoroacetic acid does not stop at the stage of forming the corresponding phenylhydrazones **2a-k**. However, in difference to the reaction with hydrazine, the conversion is not accompanied by recyclization but proceeds selectively by a type of Fischer reaction [2] and leads to 2-(3-indolyl)-1H-benzimidazoles **3a-k**.



1a–k **2a–k** **3a–k**

1-3 a R = Me, **b** R = Ph, **c** R = 4-$MeOC_6H_4$, **d** R = 3,4,5-$(MeO)_3C_6H_2$, **e** R = 4-BrC_6H_4, **f** R = 3-ClC_6H_4, **g** R = 4-ClC_6H_4, **h** R = 3-$O_2NC_6H_4$, **i** R = 4-$O_2NC_6H_4$, **k** R = 2-thienyl

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It should be mentioned that a series of 2-(3-indolyl)-1H-benzimidazoles, including compound **3a**, has already been described. They were obtained by the cyclocondensation of *o*-phenylenediamine with derivatives of 3-indolylacetic acid [5] or 3-formylindole [6].

In the new method of synthesis introduced by us an essential role is probably played by protonation, leading to the conversion of benzimidazole compounds into benzimidazolium compounds. It may assist the stage of phenylhydrazone formation. Such a conclusion results from the data on the existence of compounds **1** in solution in equilibrium with the tautomeric β-aminovinylcarbonyl forms, in which the reactivity of the carbonyl group is suppressed by the electron-donating influence of the nitrogen atoms of the benzimidazole fragment [1, 3]. In addition the isomerization of the resulting phenylhydrazones into the enehydrazine form is facilitated by protonation, and is, according to the data of [4], an imperative condition for their indolization.

The synthesized compounds **3a-k** are high melting crystalline substances. They are inclined to form simple solvates with solvents, which are decomposed on extended heating in vacuum. The 2'-methyl and 2'-(*m*-nitrophenyl) derivatives **3a,h** are yellow, the *p*-nitrophenyl derivative **3i** is orange, and the remaining compounds are colorless. Some of their physicochemical characteristics are given in Table 1.

The data of the high resolution (300 MHz) ^{1}H NMR spectra of indolylbenzimidazoles **3a-k** are given in Table 2. A singlet for the proton of the NH group of the benzimidazole fragment appeared at the lowest field. In addition a singlet for the NH group proton of the indole substituent was also displayed at somewhat higher field, in difference to the earlier work of [5, 6]. The first signal was broadened somewhat, which indicates the restrained migration of proton between the nitrogen atoms of the benzimidazole residue. As a result of this the aromatic protons in positions 4 and 7 resonate separately, being displayed as broad signals. An analogous phenomenon was observed previously for the structural analogs of compound **3**, the 2-(4-pyrazolyl)-1H-benzimidazoles [7]. This is evidently caused by steric hindrance which may exert pressure on the substituent in position 2 of the benzimidazole ring. It is characteristic that the resonance of the proton in position 4 of an unsubstituted indole is observed at 7.55 ppm [8], but in the indole fragment of compounds **3a-k** at 7.73-8.06 ppm. Evidently such a displacement of the signal towards low field is caused by the deshielding influence of the benzimidazole residue of the molecule.

TABLE 1. Characteristics of the Synthesized Compounds **3a-k**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3a	$C_{16}H_{13}N_3$	77.68 / 77.71	5.63 / 5.30	16.87 / 16.99	298-290.5*	65
3b	$C_{21}H_{15}N_3$	81.36 / 81.53	4.75 / 4.89	13.45 / 13.58	234.5-236	80
3c	$C_{22}H_{17}N_3O$	77.68 / 77.86	4.92 / 5.05	12.32 / 12.38	223-224	86
3d	$C_{24}H_{21}N_3O_3$	72.06 / 72.17	5.18 / 5.30	10.36 / 10.52	200-201.5	60
3e	$C_{21}H_{14}BrN_3$	64.87 / 64.96	3.46 / 3.63	10.69 / 10.82	245-246.5	75
3f	$C_{21}H_{14}ClN_3$	73.24 / 73.36	4.05 / 4.10	12.09 / 12.22	281-282.5	75
3g	$C_{21}H_{14}ClN_3$	73.29 / 73.36	4.02 / 4.10	12.15 / 12.22	253.5-255	73
3h	$C_{21}H_{14}N_4O_2$	71.12 / 71.18	3.86 / 3.98	15.75 / 15.81	290-291.5	85
3i	$C_{21}H_{14}N_4O_2$	71.06 / 71.18	3.87 / 3.98	15.68 / 15.81	357-358	90
3k	$C_{19}H_{13}N_3S$	72.23 / 72.36	4.11 / 4.15	13.19 / 13.32	201-203	84

* Lit. mp 279-280°C [6].

TABLE 2. ^{1}H NMR Spectra of Compounds **3a-k**

Com-pound	Chemical shifts, δ, ppm (SSCC, *J*, Hz)
3a	2.72 (3H, s, CH_3); 7.05-7.11 (4H, m, H-5,6,5',6'); 7.33 (1H, m, H-7'); 7.66-7.67 (2H, m, H-4,7); 8.06 (1H, m, H-4'); 11.50 (1H, s, H*-1'); 11.95 (1H, br. s, H*-1)
3b	7.14 (4H, m, H-5,6,5',6'); 7.44-7.67 (8H, m, H-4,7,7', $5H_{Ph}$); 7.86 (1H, d, *J* = 8.7, H-4'); 11.87 (1H, s, H-1'); 12.11 (1H, br. s, H-1)
3c	3.80 (3H, s, OCH_3); 7.02 and 7.62 (2H × 2, two d, *J* = 8.7, H_{Ar}-2,3,5,6); 7.09-7.63 (4H, m, H-5,6,5',6'); 7.46-7.63 (2H, br. m, H-4,7); 7.47 (1H, d, *J* = 7.8, H-7'); 7.85 (1H, d, *J* = 7.8, H-4'); 11.87 (1H, s, H-1'); 12.04 (1H, br. s, H-1)
3d	3.71 (9H, s, $3OCH_3$); 7.12-7.27 (4H, m, H-5,6,5',6'); 7.23 (2H, s, H_{Ar}-2,6); 7.46 (1H, br. s, H-7); 7.52 (1H, d, H-7'); 7.65 (1H, s, H-4); 7.86 (1H, d, *J* = 7.8, H-4'); 11.84 (1H, s, H-1'); 12.20 (1H, br. s, H-1)
3e	7.14-7.28 (4H, m, H-5,6,5',6'); 7.53 (1H, d, *J* = 8.1, H-7'); 7.53-7.69 (6H, m, H-4,7, H_{Ar}-2,3,5,6); 7.91 (1H, d, *J* = 7.8, H-4'); 11.98 (1H, s, H-1'); 12.17 (1H, br. s, H-1)
3f	7.14-7.28 (4H, m, H-5,6,5',6'); 7.47-7.65 (6H, m, H-4,7,7', H_{Ar}-4,5,6); 7.84 (1H, s, H_{Ar}-2); 7.88 (1H, d, H-4'); 12.02 (1H, s, H-1'); 12.21 (1H, br. s, H-1)
3g	7.13-7.27 (4H, m, H-5,6,5',6'); 7.49-7.69 (7H, m, H-4,7,7', H_{Ar}-2,3,5,6); 7.89 (1H, d, *J* = 7.8, H-4'); 11.97 (1H, s, H-1'); 12.17 (1H, br. s, H-1)
3h	7.16-7.33 (4H, m, H-5,6,5',6'); 7.46 (1H, br. s, H-7); 7.56 (1H, d, *J* = 8.1, H-7'); 7.65 (1H, br. s, H-4); 7.73 (1H, t, *J* = 8.1, H_{Ar}-5); 7.94 (1H, d, *J* = 8.1, H-4'); 8.10 (1H, d, *J* = 7.8, H_{Ar}-6); 8.26 (1H, d, *J* = 7.8, H_{Ar}-4); 8.74 (1H, s, H_{Ar}-2); 12.21 (1H, s, H-1'); 12.29 (1H, br. s, H-1)
3i	7.18-7.91 (6H, m, H-4,5,6,7,5',6'); 7.47 (1H, d, *J* = 7.8, H-7'); 7.85 (1H, d, *J* = 7.8, H-4'); 7.93 and 8.31 (2H × 2, two d, H_{Ar}-2,3,5,6); 11.20 (1H, s, H-1'); 12.32 (1H, br. s, H-1)
3k	7.11-7.26 (5H, m, H-5,6,5',6', H_{Het}-3); 7.49 (1H, d, *J* = 8.1, H-7'); 7.58-7.61, (3H, m, H-4,7, H_{Het}-4); 7.73-7.75 (2H, m, H-4', H_{Het}-5); 11.92 (1H, s, H-1'); 12.41 (1H, br. s, H-1)

* Undergoes deuterium exchange.

The detected difference of phenylhydrazones **2a-k** from the corresponding hydrazones, viz. the inability to recyclize on heating in acidic media, is probably caused by the reduced nucleophilicity of the NH group of the PhNHN= fragment. It is insufficient for attack of the carbon atom in position 2 of the benzimidazole residue, after which, correctly, transformation of the initial heterocycle may result. Consequently the method developed by us previously for recyclization of arylhydrazones of type **2** into functionalized pyrazoles, based on initiating an acylation reaction [9], remains unique for the present.

The cyclocondensation of 2-acylmethyl-H-benzimidazoles with phenylhydrazine may therefore be an efficient method of synthesizing 2-(3-indolyl)-1H-benzimidazoles.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian VXR 300 (300 MHz) spectrometer 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 system benzene–ethanol, 9:1, visualizing in UV light. Before determining melting points, carrying out elemental analysis, and spectral investigations, compounds were dried in a Fischer pistol in a water-jet pump vacuum (150°C, 7 h).

2-(2-R-3-Indolyl)-1H-benzimidazoles (3a-k). A solution of the appropriate compound **1a-k** (2 mmol) and phenylhydrazine (2.4 mmol) in trifluoroacetic acid (1 ml) was kept at 80°C for 2 h. Water (2 ml) was then added, the mixture was heated with stirring to boiling, after which the heating was stopped. The solid (or oil) formed in the resulting cooled reaction mass was separated, and acetone (2 ml) and 25% aqueous ammonia

solution (1 ml) were added to it. The mixture was boiled with stirring for 2-3 min, and diluted with water (3 ml). After cooling the precipitate of product **3** was filtered off, and washed with a 1:1 mixture of water and 2-propanol.

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