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CHEMISTRY OF 2-HETARYLBENZIMIDAZOLES. 10*. SYNTHESIS AND PROPERTIES OF 2-(3'-FURYL)-1-METHYL-1H-BENZIMIDAZOLE

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A study was carried out on the electrophilic substitution reactions such as chloromethylation, bromination, sulfonation, nitration, and acylation of 2-(3'-furyl)-1-methyl-1H-benzimidazole in acid media. All these reactions proceed at $C_{(2)}$ and $C_{(5)}$ of the furan ring. Quantum-chemical calculations of the three-dimensional structure of such heterocyclic systems are given.

Keywords: 2-(3'-furyl)-1-methyl-1H-benzimidazole, quantum-chemical calculations, substituent orientation, electrophilic substitution reactions.

In previous work [2], we have shown that a furan ring in π-conjugation with the benzimidazole system is deactivated and loses its acidophobic properties such that electrophilic substitution in 2-(2'-furyl)-1-methyl-1H-benzimidazole (**1**) proceeds smoothly but requires rather vigorous conditions.

In the present work, we studied some electrophilic substitution reactions of 2-(3'-furyl)-1-methyl-1H-benzimidazole (**2**), in which the furan ring may be extruded from conjugation with the benzimidazole system under the reaction conditions. Benzimidazole **2** was obtained by the methyl iodide methylation of 2-(3'-furyl)-1H-benzimidazole (**3**), which, in turn, was prepared from *o*-phenylenediamine and 3-furaldehyde [3]. Reactions were carried out with benzimidazole **2** and the following electrophilic reagents: paraformaldehyde and concentrated hydrochloric acid, acetyl nitrate, a mixture of sulfuric and polyphosphoric acids, bromine in dichloroethane, acetic acid, and methanol, hexamethylenetetramine in polyphosphoric acid, and carboxylic acids in the presence of polyphosphoric acid.

Benzimidazole **2** proved less stable toward vigorous conditions than benzimidazole **1**. Thus, for example, carrying out the chloromethylation and nitration reactions using acetyl nitrate led to significant tar formation such that separation and identification of the desired products proved impossible in the case of chloromethylation, while nitrofuran **6a** was obtained in low yield. In contrast, the sulfonation of **2** proceeded smoothly at $C_{(5')}$ of the furan ring and sulfonic acid **6b** was obtained in high yield (see Scheme 1).

About 50% of starting **2** was recovered in the bromination of this compound in dichloroethane using an equimolar amount of Br_2. ^{1}H NMR spectroscopy indicated that the bromination product was 2',5'-dibromo derivative **4**, which is obtained quantitatively under the same conditions when two equivalents of bromine are used. A similar result was obtained when the reaction was carried out in acetic acid. Such behavior of the furan

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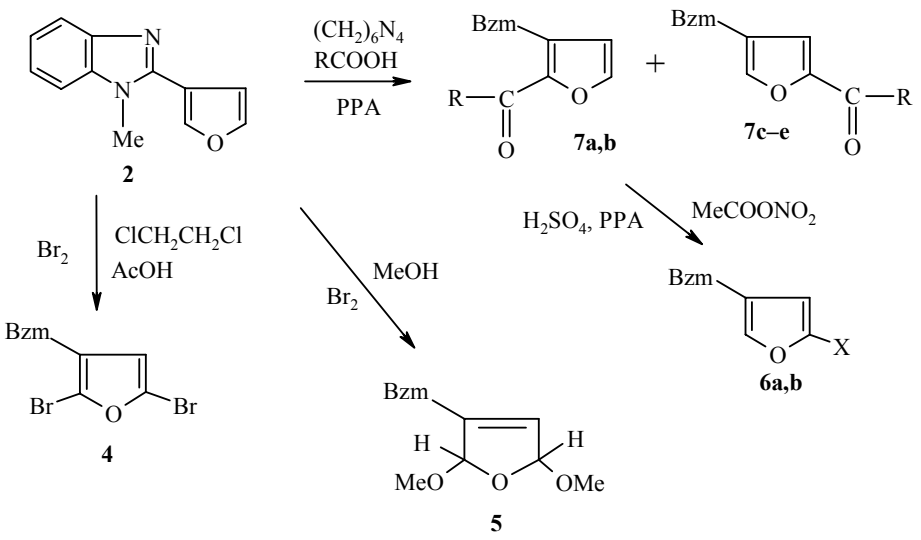
Scheme 1



6 a X = NO_2, **b** X = SO_3H; **7 a,c** R = H, **b,d** R = Me, **e** R = Ph;
Bzm = 1-methyl-2-benzimidazolyl

ring in **2** indicates the equivalence of $C_{(2)}$ and $C_{(5)}$ in this ring. The bromination of furylbenzimidazole **2** in methanol at 0°C proceeds through a well-known mechanism for furan [4] despite the presence of the imidazole substituent at $C_{(3)}$ of the furan ring to give 2,5-dimethoxydihydrofuran **5**. ^{1}H NMR spectroscopy showed that this product is a 3:1 mixture of geometric isomers, which could not be separated.

In contrast to isomer **1**, even a formyl group was introduced into isomer **2** using the Vilsmeier reagent. However, the yield of aldehydes **7a** and **7c** did not exceed 27% due to considerable tar formation. The use of hexamethylenetetramine in polyphosphoric acid proved more successful for carrying out formylation.

As expected from the overall *meta*-orienting effect of the electron-withdrawing benzimidazole group and α-directing effect of the heteroatom, the electrophilic reagent should attack the α-position most removed from the substituent at $C_{(3)}$ [5]. However, this assumption proved not entirely justified for **2** since a 3:7 mixture of isomers **7a** and **7c** is formed in the formylation reaction with attack at $C_{(2')}$ and $C_{(5')}$ of the furan ring. Similar behavior was observed in the acetylation of furylimidazole **2** by acetic acid or acetic anhydride in polyphosphoric acid. ^{1}H NMR spectroscopy showed a ~1:1 mixture of acetyl derivatives **7b** and **7d**. However, the benzoylation of **2** by benzoic acid in polyphosphoric acid proceeded smoothly in good yield to give exclusively the product of attack at $C_{(5')}$ of the furan ring. The high selectivity of the orientation in this case and also in the sulfonation is probably related to steric factors.

Unfortunately, aldehydes **7a** and **7c** and ketones **7b** and **7d** could not be separated due to identical chromatographic mobility. However, the isomers in the mixtures were identified through their ^{1}H NMR spectra. Thus, doublets for protons **H-4'** and **H-5'** at 6.8-6.9 and 7.7-7.8 ppm, respectively are characteristic for 2-acyl derivatives **7a** and **7b**, while singlets for isolated protons **H-2'** and **H-4'** at 8.1-8.2 and 7.7-7.8 ppm, respectively, are characteristic for 5-acyl isomers **7c** and **7d**.

Diminished sensitivity of the furan ring to the electron-withdrawing substituent at $C_{(3')}$ was indicated by analyzing the abovementioned anomalies in the behavior of **2** in electrophilic substitution reactions in acid media. Thus, such behavior is known to be possible when the furan ring is extruded from the π-conjugation plane with the benzimidazole system.

TABLE 1. Physicochemical Characteristics of Products **2-7**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (*i*-PrOH)	IR spectrum, ν, cm^{-1}	Yield, % (method)
		C	H	N			
2	$C_{12}H_{10}N_2O$	73.05 / 72.71	4.88 / 5.08	13.82 / 14.13	81-83		91
4	$C_{12}H_8Br_2N_2O$	40.86 / 40.48	2.53 / 2.26	8.13 / 7.87	87-89	—	42 (A), 69 (B)
5	$C_{14}H_{16}N_2O_3$	64.28 / 64.60	5.83 / 6.20	—	237-239	—	66
6a	$C_{12}H_9N_3O_3$	58.97 / 59.26	4.07 / 3.73	17.53 / 17.28	151-153	1370 (NO_2)	36
6b	$C_{12}H_{10}N_2O_4S$	52.11 / 51.79	3.41 / 3.62	9.85 / 10.07	>400*	1280 (SO_3H)	89
7a+7c	$C_{13}H_{10}N_2O_2$	69.42 / 69.02	4.53 / 4.46	12.56 / 12.38	120-122	1670 (C=O)	88
7b+7d	$C_{14}H_{12}N_2O_2$	70.36 / 69.99	4.77 / 5.03	11.83 / 11.66	105-107	1680 (C=O)	92
7e	$C_{19}H_{14}N_2O_2$	75.82 / 75.48	4.33 / 4.67	—	170-172	1680 (C=O)	89

* Recrystallized from water.

The HF/6-31Y quantum-chemical calculations carried out using the GAMESS program [6] support this hypothesis. The angle of rotation of the furan ring plane is 23° when the benzimidazole fragment is protonated. On the other hand, the two heterocycles are coplanar in the neutral 2-(3'-furyl)-1-methyl-1H-benzimidazole molecule.

EXPERIMENTAL

The IR spectra of the compounds studied were taken on a Specord IR-75 spectrometer in vaseline mull. The ^1H NMR spectra were taken on a Varian Unity 300 spectrometer at 300 MHz using HMDS (δ 0.05 ppm) as the internal standard. The reaction course and purity of the products were monitored by thin-layer chromatography on Brockmann grade-II activity alumina plates with development by iodine vapor and on Silufol UV-254 plates with CH_2Cl_2 as the eluent. The yields, melting points, and spectral data of the products are given in Tables 1 and 2.

2-(3'-Furyl)-1H-benzimidazole (3). A mixture of *o*-phenylenediamine (4.32 g, 40 mmol) in 2-propanol (70 ml), copper acetate (16 g, 80 mmol) in water (200 ml), and 3-furaldehyde (3.84 g, 40 mmol) was heated for 2 h at 80-90°C. The reaction mixture was cooled. The copper salt precipitate was separated and suspended in 2-propanol (100 ml). A strong stream of hydrogen sulfide was passed through this suspension over 2 h. The mixture was heated to reflux and copper sulfide was filtered off. The filtrate was highly diluted in cold water. The precipitate formed was separated and dried to give **3** in 88% yield; mp 292-294°C.

2-(3'-Furyl)-1-methyl-1H-benzimidazole (2). A sample of powdered KOH (1.86 g, 33 mmol) and methyl iodide (4.26 g, 30 mmol) were added consecutively to a solution of **3** (5.52 g, 30 mmol) in acetone (20 ml) and stirred at room temperature for 2 h. Then, water (200 ml) was added to the reaction mixture. The precipitate formed was separated and dried at 20-30°C to give **2** in 98% yield.

2-(2',5'-Dibromo-3'-furyl)-1-methyl-1H-benzimidazole (4). A. A solution of bromine (1.6 g, 10 mmol) in dichloroethane (5 ml) was added gradually to a solution of **2** (0.99 g, 5 mmol) in dichloroethane (20 ml) at room temperature. The mixture was diluted with water and neutralized by adding ammonium

TABLE 2. ^{1}H NMR Spectra of **2** and **4-7**

Compound	Chemical shifts ($CDCl_3$), δ, ppm. (SSCC, *J*, Hz)						
	N–CH_3 (3H, s)	H-4'	H-5'	H-2' (1H, s)	H-4 arom. (1H, m)	H-5,6,7 arom. (3H, m)	others signals
2	3.88	6.98 (1H, d, $J_{4,5}$ = 2.3)	7.57 (1H, d $J_{5,4}$ = 2.3)	7.97	7.77	7.28	—
4	3.81	6.66 (1H, s)	—	—	7.78	7.32	—
cis-**5***	4.00	6.85 (1H, s)	6.12 (1H, s)	8.12	8.72	8.64	3.88 (3H, s, OCH_3); 4.22 (3H, s, OCH_3
trans-**5***	4.00	6.83 (1H, s)	6.03 (1H, s)	8.10	8.72	8.64	3.82 (3H, s, OCH_3); 4.16 (3H, s, OCH_3
6a*	3.95	7.92 (1H, s)	—	8.02	7.80	7.32	—
6b*	4.15	7.20 (1H, s)	—	8.70	8.02	7.60	7.82 (1H, d, H-7 arom., J_{67} = 4.15)
7a	3.88	6.92 (1H, d, $J_{4,5}$ = 3.2)	7.78 (1H, d, $J_{5,4}$ = 3.2)	—	7.80	7.28	10.06 (1H, s, CHO)
7b	3.66	6.86 (1H, d, $J_{4,5}$ = 3.1)	7.68 (1H, d, $J_{5,4}$ = 3.2)	—	7.80	7.18	2.53 (3H, s, $COCH_3$)
7c	3.93	7.80 (1H, s)	—	8.22	7.80	7.28	9.78 (1H, s, CHO)
7d	3.95	7.70 (1H, s)	—	8.13	7.80	7.18	2.46 (3H, s, $COCH_3$)
7e	3.93	7.76 (1H, s)	—	8.22	7.78	7.32	8.00 (2H, m, C_6H_5); 7.50 (2H, m, C_6H_5); 7.60 (1H, m, C_6H_5)

* ^{1}H NMR spectra was recorded in $CDCl_3$ (compounds **2**, **4**, **7a-e**) and DMSO-d_6 (compounds **5**, **6**).

hydroxide. The product was extracted with methylene chloride and subjected to chromatography on an alumina column using methylene chloride as the eluent to give 0.78 g of **4**.

B. A sample of bromine (1.6 g, 10 mmol) was added to a solution of **2** (0.99 g, 5 mmol) in acetic acid (15 ml) and the mixture was heated at reflux for 2 h. Work-up similar to method A gave 1.23 g of **4**.

2-(2',5'-Dimethoxy-2',5'-dihydro-3'-furyl)-1-methyl-1H-benzimidazole (5). A sample of bromine (0.8 g, 5 mmol) was added to a solution of **2** (0.99 g, 5 mmol) in methanol (15 ml) at 0°C. The reaction mixture was stirred at this temperature for 30 min and the precipitate formed was separated to give 0.75 g (58%) of **5**.

1-Methyl-2-(5'-nitro-3'-furyl)-1H-benzimidazole (6a). A sample of nitric acid (*d* 1.5) (5 g) was added dropwise to acetic anhydride (8 ml) at 0°C and then, **2** (0.99 g, 5 mmol) was added to the nitrating mixture obtained. The reaction mixture was maintained at 0°C for 1 h and poured onto chopped ice. Yellow crystals were separated to give 0.44 g of **6a**.

1-Methyl-2-(5'-sulfo-3'-furyl)-1H-benzimidazole (6b). A mixture of **2** (0.99 g, 5 mmol), sulfuric acid (0.98 g, 10 mmol), and polyphosphoric acid (20 g) was heated for 90 min at 110°C. The reaction mixture was cooled and diluted with water (50 ml). The sulfonic acid precipitate was filtered off. To purify this product, the precipitate was dissolved in 5% aq. alkali, heated with activated charcoal, and neutralized by adding sulfuric acid until the mixture was slightly acidic. Product **6b** was obtained as snow-white prisms.

2-[2'(5')-Formyl-3'-furyl]-1-methyl-1H-benzimidazole (7a+7c) (Mixture of Isomers). A. A sample of $POCl_3$ (3.07 g, 20 mmol) was added to a solution of **2** (0.99 g, 5 mmol) in DMF (1.46 g, 20 mmol) such that the temperature of the mixture did not rise above 20°C. The mixture was stirred for 30 min at 0°C and for 2 h at 80°C. The reaction mixture was cooled, poured into water (50 ml), and neutralized by adding ammonium hydroxide. The product was subjected to chromatography on an alumina column with chloroform as the eluent to give 0.30 g of a 25:75 mixture of **7a+7c** as indicated by ^{1}H NMR spectroscopy.

B. A solution of **2** (0.99 g, 5 mmol) and hexamethylenetetramine (2.1 g, 15 mmol) in polyphosphoric acid (20 g) was stirred for 10 h at 80-90°C. The reaction product was isolated as in method A to give 0.99 g of **7a+7c.**

2-[2'(5')-Acetyl-3'-furyl]-1-methyl-1H-benzimidazole (7b+7d) (Mixture of Isomers). A solution of **2** (0.99 g, 5 mmol) and acetic acid (0.6 g, 10 mmol) in polyphosphoric acid (20 g) was stirred for 30 h at 120°C. The reaction mixture was diluted with water (100 ml) and neutralized by adding ammonium hydroxide. The reaction product separated was extracted with methylene chloride (20 ml). The extract was dried over sodium sulfate and subjected to chromatography on an alumina column.

2-(5'-Benzoyl-3'-furyl)-1-methyl-1H-benzimidazole (7e). A solution of **2** (0.99 g, 5 mmol) and benzoic acid (3.05 g, 25 mmol) in polyphosphoric acid (20 g) was stirred for 6 h at 140°C. The reaction product was isolated as in the procedure for **7b+7d**.

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