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SYNTHESIS OF 2-METHYL-1-[(5-METHYLFURAN-2-YL)-METHYL]- AND 2-METHYL-1-[(5-METHYLPYRROL-2-YL)-METHYL]-1*H*-BENZIMIDAZOLES

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A method for the synthesis of 2-methyl-1-[(5-methylfuran-2-yl)methyl]-1H-benzimidazoles based on the intramolecular cyclization of vicinal N-[(5-methylfuran-2-yl)methyl]aminoanilides has been developed. A study was carried out on the protolytic opening of the furan ring leading to the formation of a diketone fragment, which was then used for the formation of N-substituted pyrrole ring by the Paal–Knorr method. The effect of the nature of the amine on the cyclization was demonstrated.

Keywords: 1,2-disubstituted benzimidazoles, furan, *N*-substituted pyrroles, cyclization, ring opening.

Benzimidazole derivatives have long held interest in medicinal chemistry. Some of these compounds display antihistaminic [1] and antibacterial activity [1, 2] and may act as selective antagonists of the neuropeptide YY1 receptor [3] and hCRTh2 receptors as well as factor Xa inhibitor [5]. An important feature of benzimidazole derivatives is their pronounced activity toward the human immunodeficiency virus (HIV), viruses responsible for herpes and influenza, the human cytomegalovirus [1, 6-12], and virus which causes hepatitis B [13]. Some benzimidazoles display cytostatic, local anesthetic, hypotensive, and antipyretic activity [1, 14].

1,2-Disubstituted benzimidazoles are quite significant in this compound group. The presently available methods for the synthesis of these compounds fall into the following groups: 1) *N*-alkylation of the prepared 2-substituted benzimidazole system in the presence of strong base [8, 9, 15, 16], 2) *N*-alkylation of *ortho*-nitroanilides with the subsequent reductive cyclization [9, 17], and 3) cyclocondensation of *N*-substituted *ortho*-aminoanilides [18]. 1,2-Disubstituted benzimidazoles may also be obtained by the condensation of *N*-substituted *ortho*-phenylenediamines with aldehydes in the presence of various acid catalysts [19-27].

We became interested in benzimidazoles containing a furfuryl fragment at position 1. Many methods have been reported for the synthesis of 1-(furan-2-yl)methylbenzimidazoles: 1) reaction of furfural with *ortho*-phenylenediamine using various catalysts [28-36], 2) reaction of furfural with *ortho*-nitroaniline [37], and 3) *N*-alkylation of the prepared benzimidazole system with furfuryl alcohol [38].

However, the furylbenzimidazoles described in the literature do not include compounds with the 5-methylfurfuryl fragment at position 1. Interest in the synthesis of such structures is related to the ability of

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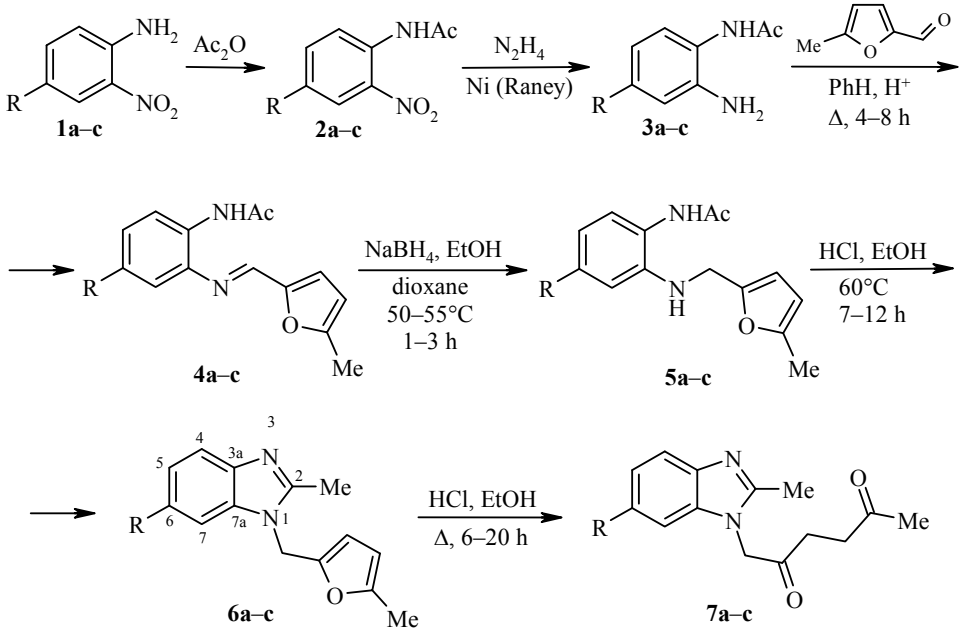
dialkylfuran to undergo recyclization to give other heterocycles [39, 40], which allows the introduction of heterocyclic fragments at position 1 of the benzimidazole system. The introduction of such fragments at this site is difficult by other methods.

In our opinion, the most suitable method for the synthesis of 1-(5-methylfurfuryl)benzimidazoles is the acid-catalyzed intramolecular cyclization of vicinal *N*-furfurylaminoanilides similar to the approach reported by Beaulieu et al. [27]. In the present work, results are given on the synthesis of 2-methyl-1-[(5-methylfuran-2-yl)-methyl]-1*H*-benzimidazoles and a study of the acid-catalyzed opening of the furan fragment and its cyclization to give a pyrrole ring.

The following reaction sequence was used to obtain 1-[(5-methylfuran-2-yl)methyl]benzimidazoles **6** from the corresponding *ortho*-nitroanilines **1**.



a R = H, **b** R = Me, **c** R = OMe

Azomethines **4a-c**, obtained by the condensation of *ortho*-aminoanilides **3a-c** with 5-methylfurfural, smoothly undergo reduction of the C=N bond by the action of $NaBH_4$ to give *N*-furfurylamines **5a-c** in yields from 67 to 77% (Table 1). The ^{1}H NMR spectra of amines **5a-c** show signals for the protons of the methylene group adjacent to the amino group as doublets with coupling constants 5.0-5.1 Hz and the signal for the amino group proton as a triplet with the same coupling constant at δ 5.27-5.41 ppm (Table 2). The signal for the proton of the amide group is found at 8.97-9.14 ppm. The ^{13}C NMR spectra show a characteristic signal for the carbon atom of the amide carbonyl group at 168.6-168.8 ppm (Table 2).

The intramolecular cyclization of amines **5a-c** leading to benzimidazoles proceeds at 60°C in ethanol solution saturated with dry gaseous hydrogen chloride (10% concentration). The yields of 1-furfuryl-benzimidazoles **6a-c** were 84-89% (Table 1). In the contrast to aminoanilides **5a-c**, the IR spectra of furfurylbenzimidazoles **6a-c** (Table 2) lack absorption bands for the stretching vibrations of the secondary amino group at 3369-3372 cm^{-1}, amide group at 3223-3240 cm^{-1} (NH) and 1641-1649 cm^{-1} (C=O). Evidence for the cyclization lies in the disappearance of the signals for the protons of the amide and amino groups in the ^{1}H NMR spectra and change in the multiplicity of the signals of the methylene group protons, which appear as a singlet with 2H intensity at 5.31-5.37 ppm, and the lack of a signal for the carbon atom of the amide carbonyl group in the ^{13}C NMR spectra of benzimidazoles **6a-c** (Table 2).

TABLE 1. Physicochemical Characteristics of Compounds **5-7 a-c** and **9a-g**

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C	Yield, %
		C	H	N		
5a	$C_{14}H_{16}N_2O_2$	68.85 / 68.83	6.54 / 6.60	11.41 / 11.47	91-92	67
5b	$C_{15}H_{18}N_2O_2$	69.69 / 69.74	7.00 / 7.02	10.76 / 10.84	97-99	73
5c	$C_{15}H_{18}N_2O_3$	65.62 / 65.68	6.53 / 6.61	10.13 / 10.21	101-102	77
6a	$C_{14}H_{14}N_2O$	74.36 / 74.31	6.29 / 6.24	12.29 / 12.38	93-94	84
6b	$C_{15}H_{16}N_2O$	75.01 / 74.97	6.66 / 6.71	11.59 / 11.66	94-95	88
6c	$C_{15}H_{16}N_2O_2$	70.24 / 70.29	6.24 / 6.29	11.01 / 10.93	97-98	89
7a	$C_{14}H_{16}N_2O_2$	68.78 / 68.83	6.57 / 6.60	11.53 / 11.47	65-67	59
7b	$C_{15}H_{18}N_2O_2$	69.79 / 69.74	6.98 / 7.02	10.80 / 10.84	103-104	67
7c	$C_{15}H_{18}N_2O_3$	65.61 / 65.68	6.63 / 6.61	10.15 / 10.21	141-142	64
9a	$C_{20}H_{21}N_3O$	75.24 / 75.21	6.59 / 6.63	13.11 / 13.16	113-114	61
9b	$C_{20}H_{21}N_3O_2$	71.56 / 71.62	6.33 / 6.31	12.46 / 12.53	135-136	64
9c	$C_{22}H_{23}N_3O$	76.55 / 76.49	6.66 / 6.71	12.12 / 12.16	127-128	71
9d	$C_{21}H_{20}FN_3$	75.59 / 75.65	6.08 / 6.05	12.53 / 12.60	69-70	72
9e	$C_{22}H_{23}N_3O_2$	73.04 / 73.11	6.43 / 6.41	11.70 / 11.63	87-88	63
9f	$C_{20}H_{20}N_4$	76.00 / 75.92	6.35 / 6.37	17.62 / 17.71	112-113	83
9g	$C_{22}H_{23}N_3$	80.15 / 80.21	7.07 / 7.04	12.69 / 12.76	85-86	73

Protolytic opening of the furan ring to give the corresponding diketones **7a-c** occurs upon heating of furfurylbenzimidazoles **6a-c** in 20% ethanolic hydrogen chloride solution at reflux for 6-20 h (Tables 1 and 2). We would like to note that the opening of the furan ring and formation of a diketone is an equilibrium process. This behavior was already reported in our previous study on the recyclization of furylmethane derivatives of 3-aminothienyl[2,3-*b*]pyridine [41]. The desired diketones **7a-c** were isolated from the reaction mixture by column chromatography.

The IR spectra of diketones **7a-c** contain strong carbonyl group absorption bands at 1697-1705 cm^{-1} (Table 2), while the ^{13}C NMR spectra of these compounds show signals for the carbon atoms of the two ketone groups at 203.1-203.8 and 206.4-207.2 ppm. The ^{1}H NMR spectra lack signals for furan ring protons but show a multiplet with 4H intensity at 2.73-2.84 ppm, corresponding to the signal of the two methylene group protons of the $COCH_2CH_2CO$ fragment.

Diketones **7a-c** are convenient precursors for the Paal–Knorr pyrrole synthesis. However, attempts to carry out this reaction under the normal conditions entailing heating in acetic acid at reflux were unsuccessful, leading to decomposition of the starting compounds and the formation of unseparable mixture of products.

The reaction of diketones **7a-c** with primary aromatic and aliphatic amines was carried out by refluxing in toluene in the presence of $Ti(OPr\text{-}i)_4$ and triethylamine to give smooth closure of the pyrrole ring (Table 3). The yields of the desired 1-pyrrolylmethylbenzimidazoles **9a-g** were from 61 to 83% (Tables 1 and 2).

TABLE 2. Spectral Characteristics of Compounds **5-7 a-c** and **9a-g**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	^{3}C NMR spectrum, δ, ppm	Mass spectrum, *m/z* (I_{rel}, %)
1	2	3	4	5
5a	3369, 3240, 1649, 1602, 1534, 1507, 1443, 1368, 1303, 1218, 1128, 1023, 932, 784, 750, 739	2.04 (3H, s, $COCH_3$); 2.23 (3H, s, CH_3); 4.22 (2H, d, *J* = 5.1, $NHC\underline{H}_2$); 5.40 (1H, t, *J* = 5.1, $N\underline{H}CH_2$); 5.97 (1H, d, *J* = 3.0, H-4 Fur); 6.17 (1H, d, *J* = 3.0, H-3 Fur); 6.53–6.54 (1H, m, H Ar); 6.71 (1H, d, *J* = 8.1, H Ar); 6.93-7.06 (1H, m, H Ar); 7.15 (1H, d, *J* = 7.3, H Ar); 9.14 (1H, s, NHCO)	13.3; 23.2; 43.6; 106.3; 107.7; 111.2; 116.0; 123.9; 125.9; 126.1; 142.0; 150.5; 151.2; 168.6	245 $[M+H]^+$ (10), 244 $[M]^+$ (80), 226 (12), 199 (21), 186 (10), 150 (26), 133 (12), 132 (13), 119 (21), 108 (25), 107 (14), 96 (16), 95 (100), 80 (16), 67 (10), 52 (10), 43 (26)
5b	3377, 3223, 1641, 1610, 1574, 1534, 1520, 1425, 1369, 1322, 1276, 1214, 1175, 1138, 1019, 944, 832, 795, 785	2.00 (3H, s, $COCH_3$); 2.18 (3H, s, CH_3); 2.22 (3H, s, CH_3); 4.19 (2H, d, *J* = 5.0, $NHC\underline{H}_2$); 5.27 (1H, t, *J* = 5.0, $N\underline{H}CH_2$); 5.97 (1H, d, *J* = 2.9, H-4 Fur); 6.16 (1H, d, *J* = 2.9, H-3 Fur); 6.38 (1H, d, *J* = 8.1, H Ar); 6.53 (1H, s, H Ar); 6.97 (1H, d, *J* = 8.1, H Ar); 9.05 (1H, s, NHCO)	13.3; 20.5; 21.2; 43.3; 106.3 (2C); 107.7; 111.8; 116.7; 125.9; 135.2; 141.9; 150.4; 151.3; 168.6	259 $[M+H]^+$ (18), 258 $[M]^+$ (52), 256 (60), 241 (30), 214 (17), 213 (73), 199 (13), 171 (12), 164 (30), 147 (10), 146 (23), 145 (11), 133 (58), 132 (12), 122 (10), 121 (21), 106 (12), 104 (10), 96 (12), 95 (100), 79 (14), 78 (12), 77 (15), 51 (12), 43 (26)
5c	3373, 3232, 1650, 1610, 1558, 1533, 1517, 1436, 1365, 1325, 1283, 1215, 1141, 1029, 943, 841, 791, 765	2.00 (3H, s, $COCH_3$); 2.22 (3H, s, CH_3); 3.67 (3H, s, OCH_3); 4.21 (2H, d, *J* = 5.0, $NHC\underline{H}_2$); 5.41 (1H, t, *J* = 5.0, $N\underline{H}CH_2$); 5.98 (1H, d, *J* = 3.0, H-4 Fur); 6.13 (1H, d, *J* = 3.0, H-3 Fur); 6.16–6.19 (1H, m, H Ar),6.24 (1H, d, *J* = 2.2, H Ar); 6.94 (1H, d, *J* = 8.8, H Ar); 8.97 (1H, s, NHCO)	13.3; 23.1; 44.0; 54.9; 97.5; 100.4; 106.3; 107.8; 117.1; 127.2; 143.7; 150.5; 151.2; 158.2; 168.8	274 $[M]^+$ (70), 272 (21), 257 (12), 256 (14), 230 (15), 229 (35), 215 (21), 180 (25), 179 (66), 162 (11), 138 (15), 137 (40), 96 (41), 95 (100), 94 (11), 91 (10), 65 (10), 43 (69)
6a	1614, 1566, 1516, 1453, 1400, 1327, 1285, 1232, 1214, 1156, 1143, 1014, 937, 794, 759, 741	2.16 (3H, s, CH_3); 2.62 (3H, s, CH_3); 5.37 (2H, s, CH_2); 5.99 (1H, d, *J* = 3.0, H-4 Fur); 6.39 (1H, d, *J* = 3.0, H-3 Fur); 7.07-7.23 (2H, m, H-5,6); 7.53 (1H, d, *J* = 7.3, H-7); 7.58 (1H, d, *J* = 8.1, H-4)	13.2 (2-CH_3); 13.6; 42.6 (NCH_2); 106.5; 109.5; 110.0 (C-7); 118.2 (C-4); 121.3 (C-6); 121.5 (C-5); 135.0 (C-7a); 142.2 (C-3a); 148.0; 151.6; 151.8 (C-2)	226 $[M]^+$ (78), 145 (13), 133 (10), 132 (63), 131 (22), 97 (12), 90 (54), 78 (13), 76 (21), 67 (44), 66 (15), 65 (17), 64 (16), 63 (31), 55 (22), 53 (19), 52 (23), 51 (57), 50 (28), 43 (33)
6b	1618, 1572, 1524, 1453, 1449, 1396, 1338, 1279, 1230, 1192, 1020, 994, 854, 807, 783, 734	2.17 (3H, s, CH_3); 2.41 (3H, s, CH_3); 2.57 (3H, s, CH_3); 5.31 (2H, s, CH_2); 6.00 (1H, d, *J* = 3.0, 4-H Fur); 6.35 (1H, d, *J* = 3.0, H-3 Fur); 6.95 (1H, d, *J* = 8.1, H-5); 7.32 (1H, s, H-7); 7.37–7.40 (1H, m, H-4)	13.2 (2-CH_3); 13.6; 21.4 (6-CH_3); 42.5 (NCH_2); 106.5; 109.4; 109.8 (C-7); 117.8 (C-4); 122.6 (C-5); 130.7 (C-6); 135.2 (C-7a); 140.3 (C-3a); 148.1; 151.0 (C-2); 151.7	240 $[M]^+$ (55), 147 (10), 146 (47), 145 (21), 96 (35), 95 (100), 91 (10), 79 (12), 67 (17), 65 (17), 55 (10), 53 (11), 51 (25), 43 (33)

TABLE 2 (continued)

1	2	3	4	5
6c	1620, 1578, 1526, 1484, 1439, 1394, 1334, 1264, 1216, 1132, 1096, 1032, 950, 865, 810, 788, 746	2.17 (3H, s, CH_3); 2.55 (3H, s, CH_3); 3.79 (3H, s, OCH_3); 5.32 (2H, s, CH_2); 6.00 (1H, d, *J* = 3.0, H-4 Fur); 6.38 (1H, d, *J* = 3.0, H-3 Fur); 6.76 (1H, dd, *J* = 8.8, *J* = 2.2, H-5); 7.14 (1H, d, *J* = 2.2, H-7); 7.38 (1H, d, *J* = 8.8, H-4)	13.2 (2-CH_3); 13.6; 42.6 (NCH_2); 55.6 (6-OCH_3); 94.2 (C-7); 106.5; 109.5 (C-5); 110.0; 118.5 (C-4); 135.6 (C-7a); 136.5 (C-3a); 148.1; 150.6; 151.7 (C-2); 155.4 (C-6)	256 $[M]^+$ (76), 163 (11), 162 (63), 120 (10), 96 (24), 95 (100), 92 (10), 77 (20), 67 (13), 63 (11), 55 (14), 52 (11), 51 (13), 43 (32)
7a	1705, 1617, 1516, 1467, 1413, 1360, 1283, 1255, 1159, 1096, 1036, 1010, 763, 737	2.10 (3H, s, $COCH_3$); 2.38 (3H, s, 2-CH_3); 2.73-2.76 (4H, m, $(CH_2)_2$); 5.30 (2H, s, NCH_2); 7.07-7.19 (2H, m, H-5,6); 7.33-7.44 (1H, m, H-7); 7.48-7.59 (1H, m, H-4)	13.2 (2-$\underline{C}H_3$); 29.4 ($CO\underline{C}H_3$); 33.1; 36.8; 51.9 (NCH_2); 109.6 (C-7); 118.1 (C-4); 121.2 (C-6); 121.4 (C-5); 135.7 (C-7a); 142.2 (C-3a); 152.3 (C-2); 203.7; 207.2	245 $[M+H]^+$ (14), 244 $[M]^+$ (59), 147 (22), 146 (81), 145 (100), 132 (27), 131 (46), 119 (11), 118 (12), 99 (75), 95 (25), 91 (14), 76 (25), 63 (15), 51 (38), 43 (49)
7b	1697, 1632, 1595, 1533, 1486, 1407, 1344, 1273, 1255, 1204, 1169, 1117, 1031, 825, 799, 633	2.10 (3H, s, $COCH_3$); 2.35 (3H, s, 6-CH_3); 2.38 (3H, s, 2-CH_3); 2.75-2.79 (4H, m, $(CH_2)_2$); 5.24 (2H, s, NCH_2); 6.95 (1H, d, *J* = 8.1, H-5); 7.17 (1H, s, H-7); 7.38 (1H, d, *J* = 8.1, H-4)	13.1 (2-CH_3); 21.3 (6-CH_3); 29.4 ($CO\underline{C}H_3$); 33.1; 36.7; 51.8 (NCH_2); 109.5 (C-7); 117.7 (C-4); 122.6 (C-5); 130.6 (C-6); 135.9 (C-7a); 140.3 (C-3a); 151.7 (C-2); 203.8; 207.1	258 $[M]^+$ (44), 160 (30), 159 (100), 146 (10), 145 (11), 99 (15), 95 (28), 91 (22), 78 (10), 55 (12), 51 (11), 43 (36)
7c	1698, 1632,1533, 1486, 1468, 1407, 1344, 1273, 1255, 1204, 1140, 1117, 1091, 1032, 825, 800, 696, 633	2.11 (3H, s, $COCH_3$); 2.39 (3H, s, 2-CH_3); 2.78–2.84 (4H, m, $(CH_2)_2$); 3.79 (3H, s, OCH_3); 5.24 (2H, s, NCH_2) 6.74 (1H, dd, *J* = 8.8, *J* = 2.2, H-5); 6.94 (1H, d, *J* = 2.2, H-7); 7.37 (1H, d, *J* = 8.8, H-4)	12.7 (2-CH_3); 28.6 ($CO\underline{C}H_3$); 32.8; 37.0; 52.1 (NCH_2); 55.1 (6-OCH_3); 93.4 (C-7); 110.1 (C-5); 118.8 (C-4); 136.6 (C-7a); 137.3 (C-3a); 151.1 (C-2); 156.2 (C-6); 203.1; 206.4	274 $[M]^+$ (76), 176 (43), 175 (100), 161 (13), 160 (21), 132 (18), 99 (15), 95 (16), 92 (14), 77 (25), 71 (15), 65 (24), 55 (10), 43 (28)
9a	1621, 1484, 1467, 1437, 1402, 1386, 1290, 1262, 1231, 1210, 1144, 1103, 1005, 936, 901, 841, 809, 756, 739	2.20 (3H, s, PyrC$\underline{H}_3$); 2.34 (3H, s, 6-CH_3); 2.40 (3H, s, 2-CH_3); 5.09 (2H, s, NC$\underline{H}_2$Pyr); 5.23 (1H, d, *J* = 3.3, H-3 Pyr); 5.39 (2H, s, NC$\underline{H}_2$Fur); 5.65 (1H, d, *J* = 3.3, H-4 Pyr); 6.23 (1H, d, *J* = 3.4, H-3 Fur); 6.40 (1H, dd, *J* = 3.4, *J* = 1.9, H-4 Fur); 6.94 (1H, d, *J* = 8.2, H-5); 7.04 (1H, s, H-7); 7.41 (1H, d, *J* = 8.2, H-4); 7.62 (1H, d, *J* = 1.9, H-5 Fur)	12.4; 13.8 (2-CH_3); 21.8 (6-CH_3); 40.5; 40.6 (N$\underline{C}H_2$Pyr); 106.2; 106.3; 107.9; 110.1 (C-7); 111.1; 118.3 (C-4); 123.0 (C-5); 126.8; 129.6; 131.1 (C-6); 136.0 (C-7a); 140.9 (C-3a); 143.4; 151.4; 151.8 (C-2)	319 $[M]^+$ (6), 175 (9), 174 (64), 94 (11), 82 (6), 81 (100), 77 (6), 53 (22), 51 (5), 40 (10)
9b	1622, 1486, 1461, 1425, 1399, 1381, 1295, 1270, 1209, 1172, 1145, 1101, 1012, 941, 898, 805, 773, 724	2.19 (3H, s, PyrC$\underline{H}_3$); 2.38 (3H, s, 2-CH_3); 3.68 (3H, s, OCH_3); 5.06 (2H, s, NC$\underline{H}_2$Pyr); 5.25 (1H, d, *J* = 3.3, H-3 Pyr); 5.39 (2H, s, NC$\underline{H}_2$Fur); 5.67 (1H, d, *J* = 3.3, H-4 Pyr); 6.17 (1H, dd, *J* = 3.4, *J* = 0.8, H-3 Fur); 6.37 (1H, dd, *J* = 3.4, *J* = 1.9, H-4 Fur); 6.73 (1H, dd, *J* = 8.7, *J* = 2.5, H-5); 6.79 (1H, d, *J* = 2.5, H-7); 7.38 (1H, d, *J* = 8.7, H-4); 7.57 (1H, d, *J* = 1.9, H-5 Fur)	12.4; 13.9 (2-CH_3); 40.5; 40.6 (N$\underline{C}H_2$Pyr); 55.9 (6-OCH_3); 94.2 (C-7); 106.4; 106.7; 107.8; 110.5 (C-5); 111.0; 119.1 (C-4); 126.6; 129.8; 136.4 (C-7a); 137.1 (C-3a); 143.3; 151.4 (2C); 155.8 (C-6)	335 $[M]^+$ (16), 175 (10), 174 (84), 94 (10), 82 (5), 81 (100), 53 (19), 43 (5)

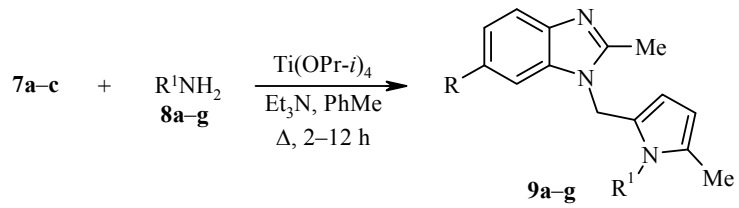
TABLE 2 (continued)

1	2	3	4	5
9c	1622, 1515, 1486, 1459, 1446, 1391, 1362, 1332, 1297, 1280, 1246, 1207, 1178, 1130, 1096, 1047, 1027, 982, 842, 829, 802, 725, 717, 621	1.87 (3H, s, PyrC$\underline{H}_3$); 2.16 (3H, s, 6-CH_3); 2.30 (3H, s, 2-CH_3); 3.77 (3H, s, OCH_3); 5.08 (2H, s, NC$\underline{H}_2$Pyr); 5.85 (1H, d, *J* = 3.3, H-3 Pyr); 6.00 (1H, d, *J* = 3.3, H-4 Pyr); 6.72 (1H, dd, *J* = 2.4, *J* = 0.6, H-7); 6.77 (1H, dd, *J* = 8.5, *J* = 2.4, H-5); 6.85 (2H, d, *J* = 8.3, H-2,6 Ar); 7.01 (2H, d, *J* = 8.3, H-3,5 Ar); 7.29 (1H, dd, *J* = 8.5, *J* = 0.6, H-4)	11.8; 12.9 (2-CH_3); 26.4 (6-CH_3); 40.5 (NCH_2); 54.9 (OCH_3); 94.0; 105.9; 108.9; 109.7 (C-7); 114.4 (2C); 118.5 (C-4); 126.9 (C-5); 129.1 (2C); 130.5 (C-6); 130.9; 136.1 (C-7a); 137.3 (C-3a); 150.5 (C-2); 155.6; 159.6	345 $[M]^+$ (10), 201 (25), 200 (99), 185 (5), 184 (6), 168 (5), 157 (6), 156 (10), 154 (11), 142 (5), 77 (10), 40 (7)
9d	1510, 1485, 1419, 1396, 1130, 1283, 1124, 1152, 842, 810, 801, 751, 723, 673, 646	1.87 (3H, s, PyrC$\underline{H}_3$); 2.16 (3H, s, 6-CH_3); 2.30 (3H, s, 2-CH_3); 5.09 (2H, s, NC$\underline{H}_2$Pyr); 5.87 (1H, d, *J* = 3.5, H-3 Pyr); 6.01 (1H, d, *J* = 3.5, H-4 Pyr); 6.37 (1H, s, H-7); 6.86 (1H, d, *J* = 8.6, H-5); 7.03-7.10 (2H, m, H-2,6 Ar); 7.14 (2H, d, *J* = 8.3, H-3,5 Ar); 7.29 (1H, d, *J* = 8.6, H-4)	12.8; 13.8 (2-CH_3); 21.7 (6-CH_3); 40.5 (NCH_2); 106.6; 109.4 (C-7); 110.1; 116.7 (2C); 118.0 (C-4); 122.7 (C-5); 127.5; 130.6 (2C); 130.9 (C-6); 134.2 (C-7a); 135.8; 140.7 (C-3a); 151.4 (C-2); 160.9; 163.3	333 $[M]^+$ (14), 189 (22), 188 (100), 186 (7), 173 (6), 172 (12), 146 (10), 95 (8), 77 (6), 32 (74)
9e	1624, 1512, 1489, 1451, 1393, 1330, 1296, 1241, 1210, 1183, 1126, 1098, 1041, 1023, 992, 843, 831, 792, 721, 717, 644	2.02 (3H, s, PyrC$\underline{H}_3$); 2.57 (3H, s, 2-CH_3); 3.83 (3H, s, 6-OCH_3); 3.90 (3H, s, ArOC$\underline{H}_3$); 5.28 (2H, s, NC$\underline{H}_2$Pyr); 5.68 (1H, d, *J* = 3.5, H-4 Pyr); 6.30 (1H, d, *J* = 3.5, H-3 Pyr); 6.82 (2H, d, *J* = 8.7, H-3,5 Ar); 6.91 (2H, d, *J* = 8.7, H-2,6 Ar); 6.94 (1H, s, H-7 Ar); 7.04 (1H, d, *J* = 8.5, H-5 Ar); 7.76 (1H, d, *J* = 8.5, H-4)	12.3; 12.9 (2-CH_3); 47.5 (NCH_2); 55.3 (6-OCH_3); 55.8; 95.9 (C-7); 104.5; 108.3 (C-5); 114.1 (2C); 117.0 (2C); 129.1 (2C); 129.6; 134.7; 135.1; 136.2 (C-7a); 138.8 (C-3a); 153.6 (C-2); 160.0 (C-6); 160.1	361 $[M]^+$ (8), 201 (18), 200 (100), 184 (5), 156 (6), 154 (7), 40 (6), 32 (91)
9f	1520, 1488, 1429, 1410, 1368, 1330, 1280, 1239, 1194, 1023, 996, 857, 809,773, 753, 709	1.92 (3H, s, PyrC$\underline{H}_3$); 2.18 (3H, s, 2-CH_3); 2.32 (3H, s, 6-CH_3); 5.17 (2H, s, NC$\underline{H}_2$Pyr); 5.94 (1H, d, *J* = 3.3, H-4 Pyr); 6.09 (1H, d, *J* = 3.3, H-3 Pyr); 6.77 (1H, s, H-7); 6.88 (1H, d, *J* = 8.0, H-5); 7.32 (1H, d, *J* = 8.0, H-4); 7.36 (1H, dd, *J* = 8.1, *J* = 4.6, H-5 Py); 7.38 (1H, d, *J* = 8.1, H-4 Py); 8.37 (1H, d, *J* = 1.6, H-2 Py); 8.58 (1H, dd, *J* = 4.6, *J* = 1.6, H-6 Py)	11.8; 13.0 (2-CH_3); 20.9 (6-CH_3); 40.2 (NCH_2); 106.7; 109.5; 109.7 (C-7); 117.9 (C-4); 122.3 (C-5); 124.0; 127.5; 130.7 (C-6); 131.0; 134.7; 135.5; 135.7 (C-7a); 140.9 (C-3a); 149.0; 149.4; 150.9 (C-2)	316 $[M]^+$ (41), 172 (10), 171 (100), 170 (12), 169 (23), 156 (35), 78 (22), 53 (31), 53 (31), 51 (19), 44 (23)
9g	1622, 1516, 1483, 1436, 1419, 1390, 1362, 1329, 1266, 1178, 1120, 1090, 1034, 824, 809, 789, 732, 623	1.90 (3H, s, PyrC$\underline{H}_3$); 2.07 (3H, s, ArC$\underline{H}_3$); 2.35 (3H, s, 6-CH_3); 2.57 (3H, s, 2-CH_3); 5.08 (2H, s, NC$\underline{H}_2$Pyr); 5.89 (1H, d, *J* = 3.4, H-4 Pyr); 6.10 (1H, d, *J* = 3.4, H-3 Pyr); 6.62 (1H, dd, *J* = 2.5, *J* = 0.6, H-7); 6.70 (1H, dd, *J* = 8.7, *J* = 2.5, H-5); 6.85 (2H, d, *J* = 8.3, H-2,6 Ar); 7.16 (2H, d, *J* = 8.3, H-3,5 Ar); 7.32 (1H, dd, *J* = 8.7, *J* = 0.6, H-4)	11.9; 12.9 (2-CH_3); 20.2 (6-CH_3); 24.2; 40.5 (NCH_2); 94.0; 105.9; 109.0; 109.7 (C-7); 118.5 (C-4); 126.8 (2C); 127.8 (2C); 129.9 (C-5); 130.7 (C-6); 135.4; 136.1; 137.3 (C-7a); 138.3 (C-3a); 150.5 (C-2); 155.6	329 $[M]^+$ (2.3), 185 (23), 184 (100), 169 (8), 168 (14), 167 (6), 154 (16), 91 (5), 65 (7), 32 (72)

TABLE 3. Conditions for the Cyclization of Diketones **7a-c** and Yields of Compounds **9a-g**

Diketone **7**	Amine **8**	Reaction time, h	Yield of compound **9**, %	Diketone **7**	Amine **8**	Reaction time, h	Yield of compound **9**, %
7b	**8a**	3	61 (**9a**)	**7b**	**8e**	12	83 (**9f**)
7c	**8a**	3	64 (**9b**)	**7b**	**8d**	9	73 (**9g**)
7b	**8b**	6	71 (**9c**)	**7a**	**8f**	24	–
7b	**8c**	10	72 (**9d**)	**7c**	**8f**	22	–
7c	**8b**	7	63 (**9e**)	**7b**	**8g**	12	–

Table 3 shows that the reaction time depends largely on the nature of the amine reagent. Thus, the reaction with furfurylamine proceeds in 3 h, while for aromatic amines the reaction time is from 6 to 12 hours. We should note that formation of a pyrrole ring does not occur at all when employing 4-nitroaniline (**8f**) and an aliphatic amine with a bulky substituent, namely, *tert*-butylamine (**8g**).



8 a R^1 = furfuryl, **b** R^1 = 4-$MeOC_6H_4$, **c** R^1 = 4-FC_6H_4, **d** R^1 = 4-MeC_6H_4, **e** R^1 = 3-pyridyl, **f** R^1 = 4-$O_2NC_6H_4$, **g** R^1 = *t*-Bu; **9 a** R = Me, R^1 = furfuryl; **b** R = MeO, R^1 = furfuryl; **c** R = Me, R^1 = 4-$MeOC_6H_4$; **d** R = Me, R^1 = 4-FC_6H_4; **e** R = MeO, R^1 = 4-$MeOC_6H_4$; **f** R = Me, R^1 = 3-pyridyl; **g** R = Me, R^1 = 4-MeC_6H_4

Evidence for the formation of a pyrrole ring in products **9a-g** is found in the disappearance of the carbonyl group absorption bands in the IR spectra and of the signals of the methylene group protons in the $COCH_2CH_2CO$ fragment in the ^1H NMR spectra (Table 2). At the same time, the ^1H NMR spectra show signals for the β-protons of the pyrrole ring at 5.23-6.30 ppm.

In conclusion, we have developed a method for the synthesis of new benzimidazole derivatives containing a (5-methylfuran-2-yl)methyl fragment at position 1, studied the protolytic opening of the furan ring, and found conditions for the subsequent cyclization of the diketones to provide pyrrole derivatives. Success of the pyrrole ring formation was found to depend on the nature of the amine used.

EXPERIMENTAL

The IR spectra were recorded on a Perkin-Elmer Spectrum Two spectrometer with a NPVO annex. The ^1H and ^{13}C NMR spectra were recored on a Agilent 400-MR spectrometer (400 and 100 MHz, respectively) in DMSO-d_6 with TMS as internal standard. The mass spectra were recorded on a Kratos MS-30 mass spectrometer, electron impact ionization (70 eV). Elemental analysis was carried out on a Flash EA 1112 CHN analyzer. Melting points were determined on a Stuart SMP 30 apparatus and were not corrected. TLC was carried out on Silufol UV-254 and Sorbfil (JSC "Sorbpolymer") plates, visualization was by iodine or bromine vapor. For column chromatography, silica gel KSK (JSC "Sorbpolymer", 50-100 μ) was used.

Aminoanilides **3a-c** were obtained by consecutive acylation of *o*-nitroanilines **1a-c** using acetic anhydride by a method described by Tietze and Eicher [42] and reduction of the nitro group in the resultant amides **2a-c** using Raney nickel in the presence of $NH_2NH_2 \cdot H_2O$ according to the procedure described in our previous work [43].

Compounds 4a-c (General Method). Ion exchange resin Amberlist 15 (1 g) was added to a solution of *o*-aminoanilide **3a-c** (50 mmol) and 5-methylfurfurol (5 ml, 50 mmol) in benzene (150 ml). The obtained mixture was refluxed with azeotropic removal of water for 4-8 h. After cooling, the resin was filtered off, and the filtrate was evaporated to dryness *in vacuo*. The obtained residue was recrystallized from EtOH.

***N*-(2-{[(5-Methylfuran-2-yl)methylidene]amino}phenyl)acetamide (4a)**. Yield 75%, light-yellow crystals, mp 94-95°C. IR spectrum, ν, cm^{-1}: 3248, 3105, 1678, 1622, 1549, 1522, 1443, 1367, 1301, 1278, 1027, 754. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.09 (3H, s, CH_3); 2.36 (3H, s, CH_3); 6.36 (1H, d, *J* = 3.3, H-4 Fur); 7.05-7.08 (1H, m, H Ph); 7.13 (1H, d, *J* = 3.3, H-3 Fur); 7.14-7.16 (1H, m, H Ph); 7.18-7.23 (1H, m, H Ph); 8.08 (1H, d, *J* = 7.8, H Ph); 8.32 (1H, s, CH=N); 9.31 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 14.1; 24.5; 109.8; 118.0; 120.2; 121.4; 124.5; 126.7; 133.3; 141.1; 148.1; 151.2; 157.0; 168.6. Found, %: C 69.35; H 5.77; N 11.59. $C_{14}H_{14}N_2O_2$. Calculated, %: C 69.41; H 5.82; N 11.56.

***N*-(4-Methyl-2-{[(5-methylfuran-2-yl)methylidene]amino}phenyl)acetamide (4b)**. Yield 77%, light-yellow crystals, mp 153-154°C. IR spectrum, ν, cm^{-1}: 3245, 3110, 1677, 1625, 1541, 1519, 1444, 1363, 1302, 1264, 1114, 1028, 959, 797. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.06 (3H, s, CH_3); 2.24 (3H, s, CH_3); 2.38 (3H, s, CH_3); 6.41 (1H, d, *J* = 3.0, H-4 Fur); 6.75 (1H, d, *J* = 8.6, H Ph); 6.82 (1H, s, H Ph); 7.05 (1H, d, *J* = 3.0, H-3 Fur); 7.88 (1H, d, *J* = 8.6, H Ph); 8.36 (1H, s, CH=N); 9.00 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 14.1; 24.3; 26.8; 109.7; 111.9; 120.1; 122.6; 123.5; 126.7; 143.2; 148.6; 151.2; 156.4; 157.0; 168.5. Found, %: C 70.22; H 6.24; N 11.00. $C_{15}H_{16}N_2O_2$. Calculated, %: C 70.29; H 6.29; N 10.93.

***N*-(4-Methoxy-2-{[(5-methylfuran-2-yl)methylidene]amino}phenyl)acetamide (4c)**. Yield 75%, light-yellow crystals, mp 178-179°C. IR spectrum, ν, cm^{-1}: 3242, 3107, 1678, 1623, 1574, 1521, 1443, 1355, 1302, 1242, 1153, 1121, 1025, 948, 799. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.03 (3H, s, CH_3); 2.39 (3H, s, CH_3); 3.75 (3H, s, OCH_3); 6.36 (1H, d, *J* = 3.3, H-4 Fur); 6.73 (1H, d, *J* = 8.5, H Ph); 6.78 (1H, s, H Ph); 7.12 (1H, d, *J* = 3.3, H-3 Fur); 7.83 (1H, d, *J* = 8.5, H Ph); 8.34 (1H, s, CH=N); 8.99 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 14.1; 24.3; 55.8; 103.6; 109.8; 112.0; 120.1; 123.6; 126.3; 143.2; 148.6; 151.2; 156.6; 156.9; 168.3. Found, %: C 66.09; H 5.89; N 10.22. $C_{15}H_{16}N_2O_3$. Calculated, %: C 66.16; H 5.92; N 10.29.

Synthesis of *N*-2-(4-R-2-{[(5-Methylfuran-2-yl)methyl]amino}phenyl)acetamides 5a-c by Reduction of Azomethines 4a-c (General Method). $NaBH_4$ (4.44 g, 120 mmol) was added portionwise to a solution of compound **4a-c** (40 mmol) in a mixture of dioxane (70 ml) and EtOH (20 ml). The reaction mixture was stirred at 50-55°C until the complete dissolution of the starting azomethine (1-3 h). The cooled reaction mixture was poured into ice water (300 ml) and stirred until crystalline precipitate was formed. The precipitate was filtered off, washed with water, dried, and recrystallized from EtOAc–petroleum ether to give amines **5a-c** as white powders.

Synthesis of 6-R-2-Methyl-1-[(5-methylfuran-2-yl)methyl]benzimidazoles 6a-c (General Method). A 10% solution of dry HCl in MeOH (20 ml) was added to a solution of compound **5a-c** (25 mmol) in EtOH (70 ml). The obtained mixture was maintained for 7-12 h at 60°C until complete disappearance of the starting amine **5a-c** as determined by TLC (eluent EtOAc). The cooled reaction mixture was poured into cold water (200 ml) and neutralized by addition of $NaHCO_3$ to pH 6-7. The presipitate formed was filtered off, washed with water, dried, and recrystallized from EtOAc–petroleum ether to give benzimidazoles **6a-c** as white powders

Synthesis of 1-(6-R-2-Methyl-1*H*-benzimidazol-1-yl)hexane-2,5-diones 7a-c (General Method). A solution of compound **6a-c** (20 mmol) in a mixture of EtOH (20 ml) and 20% solution of dry HCl in EtOH (35 ml) was heated at reflux for 6-20 h. The cooled reaction mixture was poured into cold water (200 ml) and neutralized by addition of $NaHCO_3$ to pH 6-7. The presipitate formed was filtered off, washed with water, dried, and subjected to column chromatography (eluent PhH–2-PrOH, 8:3) to give diketones **7a-c** as white powders.

Synthesis of 6-R-2-Methyl-1-{[1-R^1-5-methylpyrrol-2-yl]methyl}-1*H*-benzimidazoles 9a-g (General Method). $Ti(OPr\text{-}i)_4$ (2.46 ml, 2.1 mmol) was added dropwise to a solution of diketone **7a-c** (2.0 mmol), amine **8a-g** (2.1 mmol), and freshly distilled Et_3N (1.08 ml, 2.1 mmol) in PhMe (20 ml). The obtained mixture was heated at reflux for 3-12 h until the dissapearance of diketone **7a-c** as determined by TLC

(eluent EtOAc). After the completion of the reaction, the reaction mixture was cooled, 10% NaOH solution (30 ml) was added and filtrated at reduced pressure. The organic layer of the filtrate was separated, and the aqueous layer was extracted with PhMe (2×10 ml). The combined organic phase was dried over Na_2SO_4 and evaporated *in vacuo* to 1/4 of the original volume. Petroleum ether was added to the residue, and the mixture was left to crystallize. The crystals were filtered off, dried, and recrystallized form EtOAc–petroleum ether, to give products **9a-g** as white powders.

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