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LETTERS TO THE EDITOR

Synthesis and Selected Transformations of 1-Methyl-(5-chloromethyl-2-furyl)-1*H*-benzimidazole Hydrochloride

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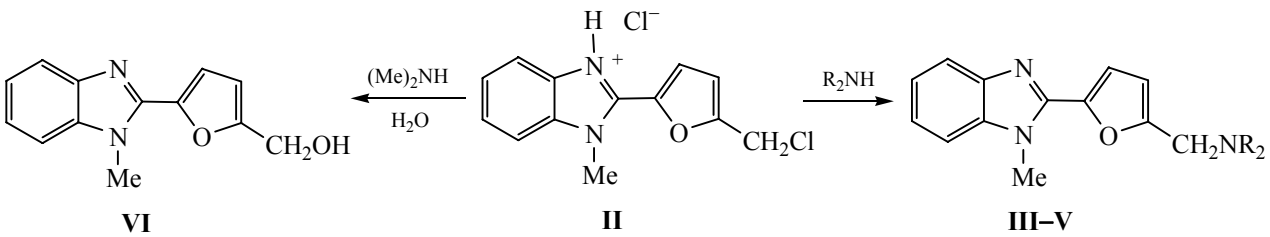
Dialkylaminomethyl-substituted furans are highly active pharmacophores [1]. In this regard, we have tried to obtain a series of the Mannich bases via reaction of 1-methyl-2-(2-furyl)-1*H*-benzimidazole **I** [2] with formaldehyde and secondary amines. However, attempt to perform this three-component reaction have failed, probably due to the low lability of the furan H^5 atom in **I**.

We have previously shown [2] that electrophilic substitution of benzimidazole **I** occur only under extremely severe conditions. Hence, in these reactions furan moiety is fairly inert. Obviously, this is due to the electron-withdrawing nature of 2-benzimidazole substituent, decreasing the electron density at C^3 and C^5 atoms, directly conjugated with the C=N bond of the imidazole ring. Therefore, we attempted synthesis of the target compounds starting from chloromethyl derivative of **I**. Chloromethylation was performed via a modified Blanc reaction [3] in the presence of paraformaldehyde in aqueous hydrochloric acid (d = 1.19 g cm^{-3}) medium, without any catalyst. The reaction mixture was autoclaved at 60–80°C during 6 h.

Compound **II** was isolated in the form of hydrochloride salt, which reacted with a piperidine or morpholine excess upon heating to give the corresponding Mannich bases **III** and **IV** with good yields. Treating of the hydrochloride **II** with aqueous solution of dimethylamine led to exchange of chlorine atom of chloromethyl group with hydroxyl group to form alcohol **VI**. The dimethylaminomethyl derivative **V** was prepared by bubbling gaseous dimethylamine through suspension of compound **II** in methanol (Scheme 1).

1-Methyl-2-(5-chloromethylfur-2-yl)-1*H*-benzimidazole hydrochloride (II). Paraformaldehyde (4.6 g, 0.052 mol) was added to solution of 7.92 g (0.04 mol) of 1-methyl-2-(2-furyl)-1*H*-benzimidazole **I** in 24 mL of aqueous hydrochloric acid (d 1.19 g cm^{-3}). The reaction mixture was incubated in autoclave at 60–70°C

Scheme 1.



VI **II** **III–V**

R_2N = piperidyl (**III**), morpholyl (**IV**), dimethylamino (**V**).

during 6 h, and then cooled to 3–5°C for 12–24 h. The formed precipitate was filtered off and recrystallized from ethanol. Yield 9.39 g (83%), mp 181–182°C. ^{1}H NMR spectrum, δ, ppm: 4.28 s (3H, NCH_3), 4.93 s (2H, CH_2), 6.95 d (1H, CH_{Fu}, *J* 3.3 Hz), 7.52 m (2H, CH_{Ar}), 7.82 m (2H, CH_{Ar}), 8.04 d (1H, CH_{Fu}, *J* 3.3 Hz). Found, %: C 55.38; H 4.43; N 10.13. $C_{13}H_{11}ClN_2O\cdot$ HCl. Calculated, %: C 55.14; H 4.27; N 9.89.

1-Methyl-2-(5-*N*-piperidylmethylfur-2-yl)-1*H*-benzimidazole (III). Solution of 2.83 g (0.01 mol) of **II** in 10 mL of piperidine was refluxed during 0.5 h. Then the reaction mixture was poured into 100 mL of water. The precipitate was filtered off and recrystallized from methanol. Yield 2.53 g (86%), mp 95–96°C. ^{1}H NMR spectrum, δ, ppm: 1.42 m (2H, CH_{2Pip}), 1.58 m (4H, $2CH_{2Pip}$), 2.48 m (4H, $2CH_{2Pip}$), 3.63 s (2H, CH_2), 4.02 s (3H, NCH_3), 6.40 d (1H, CH_{Fu}, *J* 3.4 Hz), 7.08 d (1H, CH_{Fu}, *J* 3.4 Hz), 7.32 m (3H, CH_{Ar}), 7.77 m (1H, CH_{Ar}). Found, %: C 72.87; H 7.32; N 13.95. $C_{18}H_{21}N_3O$. Calculated, %: C 73.19; H 7.17; N 14.23.

1-Methyl-2-(5-N-morpholylmethylfur-2-yl)-1*H*-benzimidazole (IV) was prepared similarly. Yield 2.14 g (72%), mp 66–67°C. ^{1}H NMR spectrum, δ, ppm: 2.50 m (4H, $2CH_{2Morph}$), 2.68 m (4H, $2CH_{2Morph}$), 3.65 s (2H, CH_2), 4.02 s (3H, NCH_3), 6.42 d (1H, CH_{Fu}, *J* 3.6 Hz), 7.10 d (1H, CH_{Fu}, *J* 3.6 Hz), 7.33 m (3H, CH_{Ar}), 7.79 m (1H, CH_{Ar}). Found, %: C 68.43; H 6.59; N 13.88. $C_{17}H_{19}N_3O_2$. Calculated, %: C 68.67; H 6.44; N 14.13.

1-Methyl-2-(5-dimethylaminomethylfur-2-yl)-1*H*-benzimidazole (V). Gaseous dimethylamine was bubbled through suspension of 2.83 g (0.01 mol) of **II** in 20 mL of methanol during 10 min. Methanol was then evaporated, and the residue was recrystallized from benzene. Yield 1.35 g (53%), mp 72–73°C. ^{1}H NMR spectrum, δ, ppm: 3.03 s (6H, $2CH_3$), 3.60 s (2H, CH_2), 4.02 s (3H, NCH_3), 6.38 d (1H, CH_{Fu}, *J* 3.5 Hz), 7.10 d (1H, CH_{Fu}, *J* 3.5 Hz), 7.33 m (3H, CH_{Ar}), 7.80 m (1H, CH_{Ar}). Found, %: C 70.33; H 6.92; N 16.59. $C_{15}H_{17}N_3O$. Calculated, %: C 70.56; H 6.71; N 16.46.

1-Methyl-2-(5-hydroxymethylfur-2-yl)-1*H*-benzimidazole (VI). Solution of 2.83 g (0.01 mol) of compound **II** in 20 mL of water was neutralized with 15 wt % aqueous dimethylamine. White precipitate was filtered off. Yield 2.12 g (93%), mp 185–186°C. IR spectrum, ν, cm^{-1}: 3170 (OH). ^{1}H NMR spectrum, δ, ppm: 3.92 s (3H, NCH_3), 4.64 s (2H, CH_2), 5.22 s (1H, OH), 6.47 d (1H, CH_{Fu}, *J* 3.6 Hz), 7.18 d (1H, CH_{Fu}, *J* 3.6 Hz), 7.40 m (4H, CH_{Ar}). Found, %: C 68.17; H 5.43; N 12.55. $C_{13}H_{12}N_2O_2$. Calculated, %: C 68.41; H 5.30; N 12.27.

IR spectrum was registered with the Specord 75 IR instrument (liquid paraffin). ^{1}H NMR spectra (DMSO-d_6 or $CDCl_3$) were recorded with the Varian Unity 300 spectrometer (300 MHz) relative to TMS as internal reference.

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