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Synthesis of Aldehydes and Ketones of 1-Methyl-2-(5-methyl-2-hetaryl)-1*H*-benzimidazole Series

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Abstract—1-Methyl-2-(5-methyl-2-furyl)-1*H*- and 1-methyl-2-(5-methyl-2-thienyl)-1*H*-benzimidazoles were synthesized by Weidenhagen reaction followed by *N*-methylation. The obtained 1*H*-benzimidazoles were formylated with hexamethylenetetramine in polyphosphoric acid and acylated with carboxylic acids in polyphosphoric acid.

Keywords: furyl(thienyl)-substituted 1*H*-benzimidazoles, *N*-methylation, electrophilic substitution reaction, acylation, formylation

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Synthesis of new benzimidazole derivatives is promising for the search of bioactive compounds. We have shown previously [1, 2] that some 5-substituted hetarylbenzimidazole derivatives possess fungicidal properties. In [3] a reaction was studied of 1-methyl-2-(5-methyl-2-furyl)-1*H*- (**I**) and 1-methyl-2-(5-methyl-2-thienyl)-1*H*-benzimidazoles (**II**) with some electrophilic reagents like acetyl nitrate, bromine, and sulfuric acid.

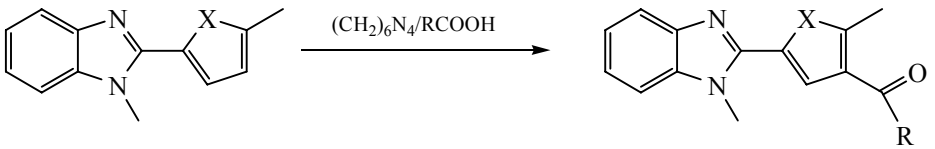
The aim of this work was the synthesis of new derivatives of **I** and **II** by reacting with such electrophilic reagents as hexamethylenetetramine and carboxylic acids, as well as the study of fungicidal activity of the obtained aldehydes and ketones.

Since the electrophilic substitution reactions of 2-hetarylbenzimidazole occur in rigid conditions, it was of interest to examine the influence of the 5-positioned methyl group on the relative reactivity of five-membered ring and the substituent orientation. Compounds **I** and **II** as well as previously studied hetarylbenzimidazoles [4] were proved inert towards the action of the Vilsmeier reagent. However, they were easily formylated with hexamethylenetetramine at 70–80°C in polyphosphoric acid medium to produce 4-formyl derivatives **III** and **IV** in yields of 67 and 72%, respectively. Interestingly, in contrast to compounds with an aldehyde group in position 5 of hetaryl ring the 4-substituted derivatives exhibit virtually no fluorescence presumably due to the absence of conjugation with the hetarylbenzimidazole molecule (Scheme 1).

Acetylation of **I** and **II** was carried out by the method described in [5] by the action of acetic acid at 110–120°C in polyphosphoric acid which serves both as a solvent and a catalyst. The formation of methyl ketones **V** and **VI** proceeded difficultly and non-selectively accompanied by further acetylation of $COCH_3$ group in monoketones. Compounds **V** and **VI** were obtained in yields of 33 and 27%, respectively (Table 1).

Aromatic carboxylic acids were also used as acylating agents. As a result, 4-benzoyl derivatives **VII**

Scheme 1.



X = O (**I**), S (**II**); X = O, R = H (**III**), Me (**V**), Ph (**VII**), *o*-ClC_6H_4 (**IX**); X = S, R = H (**IV**), Me (**VI**), Ph (**VIII**), *o*-ClC_6H_4 (**X**).

Table 1. Yields, melting points, and elemental analysis data for compounds **III–X**

Comp. no.	Yield, %	Mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
III	67	175–176	70.26	5.19	11.85	$C_{14}H_{12}N_2O_2$	69.99	5.03	11.66
IV	72	181–182	65.83	4.92	10.62	$C_{14}H_{12}N_2OS$	65.60	4.72	10.93
V	33	177–178	71.13	5.62	10.88	$C_{15}H_{14}N_2O_2$	70.85	5.55	11.02
VI	27	171–172	66.81	5.13	10.58	$C_{15}H_{14}N_2OS$	66.64	5.22	10.36
VII	81	139–140	76.16	4.88	9.12	$C_{20}H_{16}N_2O_2$	75.93	5.10	8.85
VIII	69	110–111	71.97	5.07	8.25	$C_{20}H_{16}N_2OS$	72.26	4.85	8.43
IX	80	174–175	68.63	4.17	7.78	$C_{20}H_{15}ClN_2O_2$	68.48	4.31	7.99
X	75	146–147	65.72	3.92	7.88	$C_{20}H_{15}ClN_2OS$	65.48	4.12	7.64

Table 2. IR and ^{1}H NMR spectral data for compounds **III–X**

Comp. no.	ν(C=O), cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
III	1690 (C=O)	2.48 s (3H, CH_3), 3.80 s (3H, NCH_3), 7.63 s (1H, H^3, Ht), 7.38 m (4H, $H^{4–7}$, Ar), 9.65 s (1H, CHO)
IV	1680 (C=O)	2.51 s (3H, CH_3), 3.85 s (3H, NCH_3), 7.98 s (1H, H^3, Ht), 7.40 m (4H, $H^{4–7}$, Ar), 9.75 s (1H, CHO)
V	1685 (C=O)	2.32 s (3H, $COCH_3$), 2.45 s (3H, CH_3), 3.89 s (3H, NCH_3), 7.35 m (4H, $H^{4–7}$, Ar), 7.58 s (1H, H^3, Ht)
VI	1680 (C=O)	2.33 s (3H, $COCH_3$), 2.53 s (3H, CH_3), 3.80 s (3H, NCH_3), 7.33 m (4H, $H^{4–7}$, Ar), 7.88 s (1H, H^3, Ht)
VII	1655 (C=O)	2.51 s (3H, CH_3), 3.85 s (3H, NCH_3), 7.38 m (4H, $H^{4–7}$, Ar), 7.53 m (3H,$H^{3'–5'}$, Ar), 7.63 s (1H, H^3, Ht), 7.79 d (2H, $H^{2',6'}$, Ar, *J* 7.2)
VIII	1665 (C=O)	2.53 s (3H, CH_3), 3.90 s (3H, NCH_3), 7.40 m (4H, $H^{4–7}$, Ar), 7.54 m (3H,$H^{3'–5'}$, Ar), 7.83 s (1H, H^3, Ht), 7.77 d (2H, $H^{2',6'}$, Ar, *J* 7.5)
IX	1670 (C=O)	2.55 s (3H, CH_3), 3.95 s (3H, NCH_3), 7.42 m (4H, $H^{4–7}$, Ar), 7.58 m (2H,$H^{4',5'}$, Ar), 7.65 s (1H, H^3, Ht), 7.82 d (1H, $H^{6'}$, Ar, *J* 8.0), 7.90 d (1H, $H^{3'}$, Ar, *J* 7.5)
X	1680 (C=O)	2.56 s (3H, CH_3), 3.93 s (3H, NCH_3), 7.45 m (4H, $H^{4–7}$, Ar), 7.61 m (2H,$H^{4',5'}$, Ar), 7.80 s (1H, H^3, Ht), 7.84 d (1H, $H^{6'}$, Ar, *J* 8.1), 7.92 d (1H, $H^{3'}$, Ar, *J* 7.7)

and **VIII** were obtained in yields of 81 and 69%, respectively. In order to study the effect of various substituents (Cl, NO_2, NH_2, OCH_3) in the acylating agent on the acylation process we performed reactions of hetarylbenzimidazoles **I** and **II** with *ortho*-substituted nitro-, amino-, and methoxybenzoic acids in polyphosphoric acid. Unfortunately, all the reactions failed. At the same time, the acylation with *o*-chlorobenzoic acid led to the formation of the corresponding ketones **IX** and **X** in yields of 80 and 75%, respectively.

Hence, the acylation of 5-methyl-2-hetarylbenzimidazoles occurred in the position 4 of the hetaryl ring due to the mutual orientation of the methyl group and electron-withdrawing benzimidazole moiety.

The structures of **III–X** were confirmed by IR and ^{1}H NMR spectroscopy (Table 2).

The obtained β-aldehydes (**III**, **IV**) and ketones (**V–X**) were tested for antifungal activity towards fungal cultures *Trichophyton rubrum* and *Microsporum canis*. 1-Methyl-2-(5-methyl-4-formyl-2-thienyl)-1*H*-benzimidazole **IV** showed the highest activity and was recommended for further studies.

EXPERIMENTAL

IR spectra were recorded on a Specord 75IR spectrometer from mulls in mineral oil. ^{1}H NMR spectra were registered on a FX-90Q instrument (90 MHz), internal reference TMS. The reaction progress was monitored by TLC using plates coated

with Al_2O_3 (II Brockmann activity) and detecting with iodine vapor (eluent CH_2Cl_2, $CHCl_3$). Elemental analysis was performed on a Perkin Elmer 2400 analyzer. Melting points were determined on a PTP instrument by capillary method. Physicochemical and spectral data of compounds obtained are shown in Tables 1 and 2.

1-Methyl-2-[5-methyl-2-furyl(thienyl)]-1*H*-benzimidazoles **I** and **II** were prepared by the Weidenhagen method followed by *N*-methylation as described in [3].

1-Methyl-2-(5-methyl-4-formyl-2-furyl)-1*H*-benzimidazole (III). A mixture of 2.12 g (0.01 mol) of **I** and 2.8 g (0.02 mol) of methenamine in 40 g of polyphosphoric acid was stirred at 70–80°C for 4 h. Next, 100 mL of water was added, and the reaction mixture was neutralized with ammonia solution. The reaction product was extracted with chloroform and chromatographed on a column (*h* 20 cm, *d* 2.5 cm) filled with 70 g of Al_2O_3, eluting with chloroform. Yield 1.6 g.

1-Methyl-2-(5-methyl-4-formyl-2-thienyl)-1*H*-benzimidazole (IV) was obtained similarly from 2.28 g (0.01 mol) of compound **II** and 2.8 g (0.02 mol) of methenamine. Yield 1.84 g.

1-Methyl-2-(5-methyl-4-acetyl-2-furyl)-1*H*-benzimidazole (V). A mixture of 2.12 g (0.01 mol) of **I** and 1.8 g (0.03 mol) of glacial acetic acid in 40 g of polyphosphoric acid was mixed at 110–120°C for 12 h. The reaction product was isolated by column chromatography. Yield 0.84 g.

1-Methyl-2-(5-methyl-4-acetyl-2-thienyl)-1*H*-benzimidazole (VI) was obtained similarly from 2.28 g (0.01 mol) of compound **II** and 1.8 g (0.03 mol) of acetic acid. Yield 0.73 g.

1-Methyl-2-(5-methyl-4-benzoyl-2-furyl)-1*H*-benzimidazole (VII) was obtained similarly from 2.12 g (0.01 mol) of compounds **I** and 3.66 g (0.03 mol) of benzoic acid; the reaction temperature 150–160°C. Yield 2.56 g.

1-Methyl-2-(5-methyl-4-benzoyl-2-thienyl)-1*H*-benzimidazole (VIII) was obtained similarly from 2.28 g (0.01 mol) of compound **II** and 3.66 g (0.03 mol) of benzoic acid. Yield 2.29 g.

1-Methyl-2-(5-methyl-4-*o*-chlorobenzoyl-2-furyl)-1*H*-benzimidazole (IX) was obtained similarly from 2.12 g (0.01 mol) of compound **I** and 3.13 g (0.02 mol) of *o*-chlorobenzoic acid. Yield 2.8 g.

1-Methyl-2-(5-methyl-4-*o*-chlorobenzoyl-2-thienyl)-1*H*-benzimidazole (X) was obtained similarly from 2.28 g (0.01 mol) of compound **II** and 3.13 g (0.02 mol) of *o*-chlorobenzoic acid. Yield 2.74 g.

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