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REACTION OF 5-(2-FURYL)-1-METHYL-1*H*- AND 1-METHYL-5-(2-THIENYL)-1*H*-IMIDAZOLES WITH ELECTROPHILIC REAGENTS

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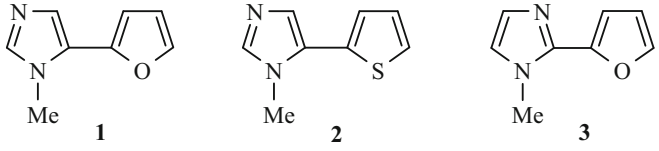
5-(2-Furyl)-1-methyl-1H- and 1-methyl-5-(2-thienyl)-1H-imidazoles were synthesized. The electron-withdrawing effect of the 5- and 2-imidazole substituents on the furan ring was studied by ^{1}H NMR spectroscopy and quantum-chemical calculations. Some electrophilic substitution reactions were investigated (nitration, bromination, sulfonation, hydroxymethylation, formylation, and acylation). In some cases, depending on the reaction conditions, both the furan and thiophene ring and the imidazole fragment undergo electrophilic attack.

Keywords: 1-methyl-5-(2-thienyl)-1H-imidazole, 5-(2-furyl)-1-methyl-1H-imidazole, quantum-chemical calculations, directing effect of substituents, electrophilic substitution.

The mutual effect of heterocyclic radicals in bihetaryls is an interesting and nevertheless inadequately studied field from the standpoint both of structure and reactivity. In the light of the foregoing our attention was attracted to derivatives of 5-(2-furyl)- (**1**) and 5-(2-thienyl)imidazole (**2**). On account of the presence of the two pharmacophoric heterocyclic fragments these compounds can be expected to exhibit various types of biological activity. In addition, the mutual effect of the heterocycles on each other should be reflected in their reactivity. It is known that the imidazole ring, which is inert to electrophiles in an acidic medium, enters fairly readily into



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electrophilic substitution under neutral conditions [1]. For this reason, whereas it is not difficult to predict the direction of electrophilic attack on the furan or thiophene ring in an acidic medium, the situation is more complicated for neutral conditions.

Methods of synthesis and the products of the methylation of 4(5)-(2-furyl)imidazole were studied earlier [2]. Here it was possible to isolate the corresponding 5-(2-furyl)-1-methylimidazole (**1**) and, later, 1-methyl-5-(2-thienyl)imidazole (**2**) in chromatographically pure form.

It seemed interesting to investigate the behavior of the undescribed bihetaryls **1** and **2** in certain electrophilic substitution reactions and to compare them with the chemical characteristics of 2-(2-furyl)-1-methylimidazole **3** [3]. It was shown that the effect of the 2-imidazolyl substituent on five-membered heterocycles with one heteroatom leads to a general decrease of electron density [4]. At the same time, there is a sharp decrease in the acidophobic characteristics of these heterocycles, which makes it possible to realize the reaction over a wider range of conditions, including media with high acidity, elevated temperature, etc. Consequently, in the present case it would be logical to compare the effect of the 5-imidazolyl radical on the five-membered heterocycles. In so far as the effect of the 2-imidazolyl group is connected with the conjugation of the hetaryl ring with the C=N bond of the azole, which is not so in the case of the 5-imidazolyl substituent, it would be reasonable to assume that mentioned influence is weakened as a result of the conjugation chain elongation.

The calculated data on the charges at the carbon atoms of the furan substituent in the 2-(2-furyl)- and 5-(2-furyl)imidazoles agree with the relative values of the chemical shifts of the corresponding protons in the ^{1}H NMR spectra (Table 1).

On the basis of the data shown in the table it can be concluded that the deshielding effect of the 5-imidazolyl substituent is somewhat lower than in the 2-isomer, and higher reactivity must therefore be expected in compound **1**. In order to confirm this conclusion, 5-(2-furyl)-1-methyl-1H- (**1**) and 1-methyl-5-(2-thienyl)-1H-imidazole (**2**) were investigated in reactions with electrophilic reagents: acetyl nitrate, bromine in dichloroethane, sulfuric acid, urotropine and acetic or benzoic acids in PPA, formalin in an acidic medium, and the Vilsmeier reagent.

Nitration of the hetarylimidazoles **1** and **2** with nitric acid (d = 1.51 g/cm^3) in acetic anhydride or in PPA, in contrast to compound **3**, gives a complex mixture of difficultly separable substances. It was, however, possible to realize a selective reaction as in the case of thiophenes nitration by the action of a complex of copper nitrate and acetic anhydride under mild conditions [5]. The optimum ratio of substrate to nitrating agent is 1:1.2 for mononitration and 1:3 for dinitration. It was established that the direction of nitration of the hetarylimidazoles **1** and **2** by the copper nitrate–acetic anhydride system differs substantially. In the first case the product of furan ring mononitration **1a** is formed. In the case of compound **2**, however, a mixture of compound **2a** with mononitro-substituted thiophene ring and the dinitro derivative **2b** substituted both in the thiophene and in the azole ring is formed. Unfortunately, because of the identical chromatographic mobility, the nitration products **2a** and **2b** could not be separated. However, it is not difficult to identify them in the ^{1}H NMR spectrum thanks to characteristic signals intrinsic for each of the nitro derivatives presence.

TABLE 1. Chemical Shifts of the Protons in the ^{1}H NMR Spectra and the Charges at the Carbon Atoms of the Furyl Groups in Compounds **1** and **3**

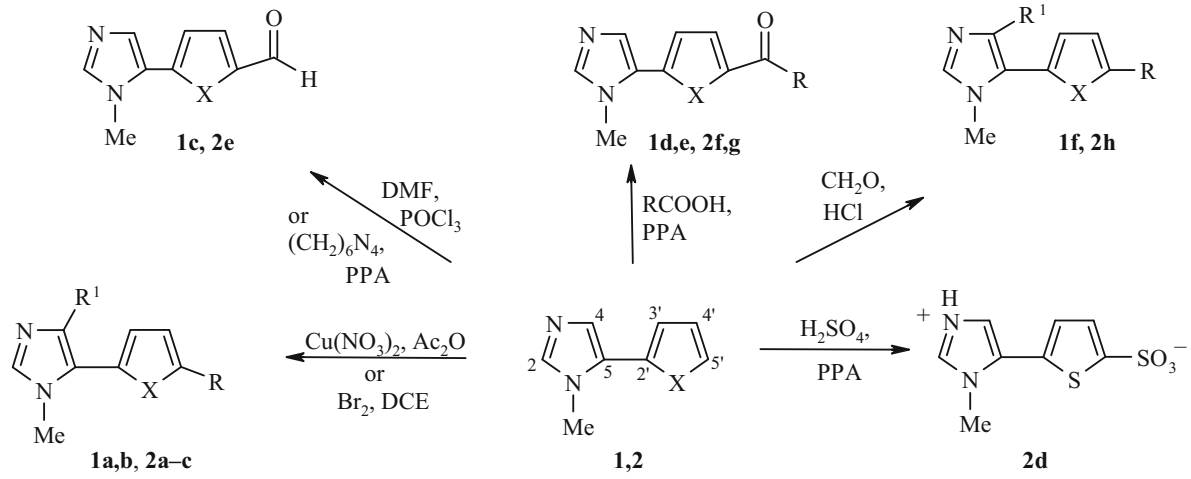
Compound	Chemical shifts, δ, ppm*			Charges, q*[2]		
	H-3	H-4	H-5	C-3	C-4	C-5
1	6.60	6.43	7.36	–0.14	–0.15	0.14
3	6.81	6.48	7.46	–0.13	–0.15	0.15

*Recorded in $CDCl_3$.

*[2]Calculated by the B3LYP/6-311G method.

Only the furan ring of furylimidazole **3** is brominated in the presence of acids [3]. Under these conditions compound **1** forms a tar, and the hetarylimidazoles **1** and **2** were therefore brominated under neutral conditions. The first of them is brominated in dichloroethane even at low temperature (from –10 to –15°C) with the formation of the monobromo derivative **1b**. The bromination of compound **2** at 0°C leads to the 4-bromo-5-(5-bromo-2-thienyl)-1-methylimidazole hydrobromide (**2c**) with the 70% yield.

As known, thanks to its characteristic acidophobic character, furan is sulfonated best of all with the such mild reagent as the adduct of sulfur trioxide with pyridine [6]. Taking this into account we first tried to extend the method to the hetarylimidazoles **1** and **2**. It was found that, as also in the case of compound **3**, sulfonation with pyridine–sulfur trioxide does not give a positive result. All compounds were therefore sulfonated with sulfuric acid (d = 1.84 g/cm^3) in PPA at 70–80°C.



1 X = O, **1 a** R = NO_2, R^1 = H, **b** R = Br, R^1 = H, **d** R = Me, **e** R = Ph, **f** R = CH_2OH, R^1 = H; **2** X = S,
2 a R = NO_2, R^1 = H, **b** R = NO_2, R^1 = NO_2, **c** R = Br, R^1 = Br, **f** R = Me, **g** R = Ph, **h** R = H, R^1 = CH_2OH

It was not possible to isolate and identify the sulfonic acid based on the 5-(2-furyl)imidazole **1** since its very high solubility in water. At the same time the 5'-sulfonic acid (**2d**), obtained with a yield of 49%, probably exists in the form of an inner salt, since the ^{1}H NMR spectrum recorded in DMSO-d_6 does not contain a signal for the OH group, which does appear in CF_3COOH at 12.28 ppm.

During the Vilsmeier formylation of compound **3** at 95°C, the 5'-formyl derivative is formed with 32% yield. About 50% of the starting compound is recovered [3]. Compound **1** reacts considerably more readily with DMF–$POCl_3$. The thiophene analog **2** was inert to the Vilsmeier reagent. However, by using urotropine as formylating reagent in PPA at 70–80°C we obtained the aldehyde (**2e**) with 80% yield.

Like compound **3**, the hetarylimidazoles **1** and **2** are acylated by carboxylic acids in PPA, but under significantly milder conditions at 70–80°C. The ketones **1d**,**e** and **2f**,**g** are formed in 40–63% yields.

The hydroxymethylation of compound **3** at position 5 of the furan ring was described in [3]. It takes place very slowly, and the yield of the hydroxymethyl derivative after boiling (16 h) in formalin solution is only 11%. Under analogous conditions, compounds **1** and **2** react more readily and with high yields. Thus, the furylimidazole **1** gives the 5-hydroxymethyl derivative **1f** in a 53% yield after 4 h, while the thienylimidazole **2** forms the 4-hydroxymethyl derivative **2h** in a 85% yield after 5 h. The last result can be explained by the fact that the reactivity of the imidazole system and of the thiophene ring under neutral conditions is comparable.

Summarizing the data on the electrophilic substitution reactions in the series of 5-(2-hetaryl)imidazoles, it can be stated that they actually take place more readily than for the previously studied 2-(2-hetaryl)imidazoles. In acidic media the hetaryl substituent mostly undergoes electrophilic attack. Under neutral conditions, the reactivity of the imidazole and hetaryl ring becomes comparable, and both the hetaryl and the imidazole rings undergo substitution.

TABLE 2. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (alcohol)*	IR spectrum, ν, cm^{-1}	Yield, %
		C	H	N			
1a	$C_8H_7N_3O_3$	50.07 / 49.75	3.37 / 3.65	22.03 / 21.75	129–130	1360 sym. (NO_2) 1545 asym. (NO_2)	52
1b	$C_8H_7BrN_2O$	42.65 / 42.32	2.88 / 3.11	12.55 / 12.34	82–83	–	66
1c	$C_9H_8N_2O_2$	61.12 / 61.36	4.71 / 4.58	16.22 / 15.90	126–127	1670 (C=O)	67
1d	$C_{10}H_{10}N_2O_2$	62.88 / 63.15	5.53 / 5.30	15.05 / 14.73	120–121	1680 (C=O)	45
1e	$C_{15}H_{12}N_2O_2$	71.54 / 71.42	5.03 / 4.79	10.78 / 11.10	128–129	1670 (C=O)	63
1f	$C_9H_{10}N_2O_2$	60.92 / 60.67	5.33 / 5.66	16.04 / 15.72	164–165	1130 (OH)	53
2	$C_8H_8N_2S$	58.72 / 58.51	5.07 / 4.91	16.94 / 17.06	98–100	–	
2a+2b*[2]	$C_8H_7N_3O_2S$ $C_8H_6N_4O_4S$	–	–	–	–	1380 sym. (NO_2), 1560 asym. (NO_2)	78
2c*[3]	$C_8H_7Br_3N_2S$	24.15 / 23.85	2.07 / 1.75	–	198–199	–	70
2d	$C_8H_8N_2O_3S_2$	39.56 / 39.33	3.47 / 3.30	11.22 / 11.47	276–277	1260 (SO_2)	49
2e	$C_9H_8N_2OS$	55.88 / 56.23	3.92 / 4.19	14.66 / 14.57	157–159	1650 (C=O)	80
2f	$C_{10}H_{10}N_2OS$	58.46 / 58.23	5.17 / 4.89	13.66 / 13.58	115–116	1650 (C=O)	52
2g	$C_{15}H_{12}N_2OS$	67.28 / 67.14	4.42 / 4.51	10.72 / 10.44	144–145	1660 (C=O)	40
2h	$C_9H_{10}N_2OS$	55.79 / 55.65	4.88 / 5.19	14.67 / 14.42	178–180	1140 (OH)	85

*Compound **2d** was crystallized from water, **1c** from hexane.
*[2]According to the ^{1}H NMR spectrum, the ratio of the compounds **2a**:**2b** was 2:1.
*[3]Found, %: Br 59.78. Calculated, %: Br 59.49.

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 spectrometer in chloroform (compounds **1a**,**c**–**f**, **2a**+**2b**, **2e**–**h**) and vaseline oil (compound **2d**). The ^{1}H NMR spectra were recorded on a Bruker-250 instrument (250 MHz, compounds **1a**,**c**, **2a**+**b**, **2c**,**e**–**h**) and a Varian Unity-300 instrument (300 MHz, compounds **1b**,**d**–**f**, **2d**) in the Fourier pulse regime. The residual signals of the protons of deuterated solvents $CDCl_3$ and DMSO-d_6 (δ 7.26 and 2.50 ppm respectively) were used as internal standard. Elemental analysis was performed on a Perkin-Elmer 2400 analyzer. The melting points were determined by capillary method on a melting point apparatus. The reactions and the individuality of the products were monitored by TLC on plates with aluminum oxide Brockmann II (development with iodine vapor) or on Silufol UV-254 plates in CH_2Cl_2.

5-(2-Furyl)-1-methyl-1H-imidazole (**1**) and 1-methyl-5-(2-thienyl)-1H-imidazole (**2**) were obtained by the method described in [2].

1-Methyl-5-(5-nitro-2-furyl)-1H-imidazole (1a). Preparation of the nitration mixture: Acetic anhydride (40 ml) was added with strong cooling in small portions to $Cu(NO_3)_2 \cdot 3H_2O$ (16.9 g, 70 mmol) while ensuring that the temperature of the reaction mixture did not rise above 30–40°C. At the end of the exothermic reaction the mixture was kept at room temperature for 24 h, after which the precipitated copper(II) acetate was filtered off. The obtained mixture was kept at 5–10°C for not more than 10 days.

TABLE 3. ^{1}H NMR Spectra of Synthesized Compounds

Compound	Chemical shifts, δ, ppm (*J*, Hz)*					
	N–CH_3 (3H, s)	H-4' (1H, d)	H-3' (1H, d)	H-4 (1H, s)	H-2 (1H, s)	Other signals
1a	3.75	7.38 ($J_{3,4}$ = 3.8)	6.81 ($J_{4,3}$ = 3.8)	7.54	7.47	–
1b	3.66	6.35 ($J_{3,4}$ = 3.5)	6.58 ($J_{4,3}$ = 3.5)	7.12	7.40	–
1c	3.74	7.28 ($J_{3,4}$ = 3.5)	6.83 ($J_{4,3}$ = 3.5)	7.48	7.41	9.55 (1H, s, CHO)
1d	3.75	7.25 ($J_{3,4}$ = 3.5)	6.78 ($J_{4,3}$ = 3.5)	7.40	7.48	2.48 (3H, s, CH_3)
1e	3.76	7.26 ($J_{3,4}$ = 3.7)	6.86 ($J_{4,3}$ = 3.7)	7.44	7.49	7.50–7.52 (3H, m, H-3",4",5"); 7.94 (2H, d, *J* = 7.0, H-2",6")
1f	3.72	6.40 ($J_{3,4}$ = 3.4)	6.58 ($J_{4,3}$ = 3.4)	7.14	7.44	4.15 (1H, s, OH); 4.93 (2H, s, SH_2)
2	3.63	6.95–7.00 (m)	7.13 ($J_{4,3}$ = 5.2)	7.02	7.36	7.20 (1H, d, $J_{4,5}$ = 3.6, H-5')
2a	3.68	7.57 ($J_{3,4}$ = 4.1)	7.24 ($J_{4,3}$ = 4.1)	7.21	7.45	–
2b	3.98	7.83 ($J_{3,4}$ = 4.4)	8.14 ($J_{4,3}$ = 4.4)	–	8.02	–
2c	3.66	7.27 ($J_{3,4}$ = 4.1)	7.35 ($J_{4,3}$ = 4.1)	–	8.33	–
2d	3.64	7.57 ($J_{3,4}$ = 3.6)	6.98 ($J_{4,3}$ = 3.6)	6.96	7.45	–
2e	3.77	7.66 ($J_{3,4}$ = 4.1)	7.33 ($J_{4,3}$ = 4.1)	7.23	7.45	9.83 (1H, s, SHO)
2f	3.69	7.58 ($J_{3,4}$ = 3.8)	7.24 ($J_{4,3}$ = 3.8)	7.17	7.42	2.48 (3H, s, SH_3)
2g	3.72	7.57 ($J_{3,4}$ = 3.8)	7.30 ($J_{4,3}$ = 3.8)	7.22	7.52	7.40–7.50 (3H, m, H-3",4",5"); 7.84 (2H, d, *J* = 8.2, H-2",6")
2h	3.66	7.00–7.05 (m)	7.17 ($J_{4,3}$ = 4.1)	–	7.37	4.30 (1H, s, OH); 4.82 (2H, s, SH_2); 7.34 (1H, d, *J* = 5.1, H-5')

*Solvents: $CDCl_3$ (compounds **1**, **1a**–**f**, **2**, **2a**,**b**,**e**–**h**) and DMSO-d_6 (compounds **2c**,**d**).

The nitration mixture (1.4 ml) was added under vigorous stirring in small portions at room temperature to a solution of compound **1** (0.74 g, 5 mmol) in freshly prepared acetic anhydride (5 ml). The reaction time was 30–40 min. Cold water (25 ml) was then added to the obtained mixture, and the mixture was neutralized with a 25% ammonia solution. The precipitate was filtered off, washed thoroughly with water, and chromatographed on a column of aluminum oxide using dichloromethane as eluent. The product was crystallized from alcohol. Yield 0.5 g.

A **mixture of 1-methyl-5-(5-nitro-2-thienyl)-1H-imidazole** (**2a**) and **1-methyl-4-nitro-5-(5-nitro-2-thienyl)-1H-imidazole** (**2b**) was obtained similarly to compound **1a**.

5-(5-Bromo-2-furyl)-1-methyl-1H-imidazole (1b). Bromine (0.8 g, 5 mmol) was added to a solution of compound **1** (0.74 g, 5 mmol) in dichloroethane (10 ml) at a temperature between –10 and –15°C. The reaction

mixture was stirred at –10°C for 30 min and washed with of a 5% ammonia solution (20 ml) and with water (2×20 ml). The dichloroethane layer was dried with anhydrous Na_2SO_4 and chromatographed on a column of aluminum oxide using dichloromethane as eluent. Yield 0.75 g.

4-Bromo-5-(5-bromo-2-thienyl)-1-methyl-1H-imidazole Hydrobromide (2c). Bromine (1.6 g, 10 mmol) was added dropwise at 0°C to a stirred solution of compound **2** (0.82 g, 5 mmol) in dichloroethane (10 ml). The reaction mixture was stirred at 0°C for 30 min, and the solvent was then evaporated under reduced pressure at room temperature. The residue was recrystallized from alcohol. Yield 1.41 g.

1-Methyl-5-(5-sulfo-2-thienyl)-1H-imidazole (2d). A mixture of compound **2 (**0.82 g, 5 mmol), sulfuric acid (d = 1.84 g/cm^3) (0.98 g, 10 mmol), and PPA (20 g) was heated at 70–80°C for 1 h. The reaction mixture was cooled and diluted with water (50 ml), and the precipitated sulfonic acid was separated. Yield 0.77 g.

5-(5-Formyl-2-furyl)-1-methyl-1H-imidazole (1c). $POCl_3$ (4.6 g, 30 mmol) was added at 0–5°C dropwise under stirring to compound **1 (**0.74 g, 5 mmol) in DMF (4.75 g, 65 mmol) . The mixture was stirred at the same temperature for 10 min and at 60°C for 30 min. After cooling, the reaction mixture was neutralized to pH 7 with a concentrated ammonia solution and extracted with chloroform (25 ml). The extract was dried with anhydrous Na_2SO_4 and chromatographed on a column of aluminum oxide using chloroform as eluent. The product was crystallized from hexane. Yield 0.59 g.

5-(5-Formyl-2-thienyl)-1-methyl-1H-imidazole (2e). A mixture of compound **2** (0.82 g, 5 mmol) and urotropine (1.4 g, 10 mmol) was stirred in PPA (15 g) at 70–80°C for 2 h. The reaction mixture was then diluted with water (50 ml) and carefully neutralized with a 25% ammonia solution under cooling. The precipitate was extracted with dichloromethane (3×15 ml), and the extract was dried over $CaCl_2$. The solvent was evaporated, and the residue was chromatographed on a column using dichloromethane as eluent. Yield 0.77 g.

5-(5-Acetyl-2-furyl)-1-methyl-1H-imidazole (1d) and **5-(5-Benzoyl-2-furyl)-1-methyl-1H-imidazole (1e)**. A mixture of compound **1** (0.74 g, 5 mmol) and acetic or benzoic acid (10 mmol) was stirred in PPA (10 g) for 2–4 h until the starting compound had disappeared according to TLC. The products (**1d**,**e**) were isolated similarly to compound **2e** with yields of 0.43 and 0.79 g respectively.

5-(5-Acetyl-2-thienyl)-1-methyl-1H-imidazole (2f) and **5-(5-Benzoyl-2-thienyl)-1-methyl-1H-imidazole (1g)**. These compounds were obtained similarly to compounds **1d**,**e** from compound **2** with yields of 0.54 and 0.54 g respectively.

5-(5-Hydroxymethyl-2-furyl)-1-methyl-1H-imidazole (1f). A drop of hydrochloric acid was added to a solution of compound **1** (0.74 g, 5 mmol) in formalin (35 ml) . The mixture was boiled for 4 h. It was then poured into cold water (100 ml) and neutralized to pH 7–8 with a 25% ammonia solution. The precipitate was filtered off and washed thoroughly with cold water. Yield 0.47 g.

4-Hydroxymethyl-5-(2-thienyl)-1-methyl-1H-imidazole (2h). The compound was obtained similarly to compound **1f** from compound (**2) (**5 mmol). Yield 0.82 g.

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