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Synthesis and Properties of 2,5-Bis(furan-2-yl)-1*H*-imidazole

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Abstract—2,5-Bis(furan-2-yl)-1*H*-imidazole was synthesized by the Weidenhagen reaction of [2-(furan-2-yl)-2-oxoethyl]acetate with furfural. Alkylation of the title compound with methyl iodide in acetone in the presence of potassium hydroxide gave a mixture of isomeric *N*-methyl derivatives, 2,5-bis(furan-2-yl)-1-methyl-1*H*-imidazole being the major one. Electrophilic substitution reactions of the latter (nitration, bromination, sulfonation, hydroxymethylation, and acylation) were studied.

Keywords: [2-(furan-2-yl)-2-oxoethyl]acetate, furfural, methyl iodide, alkylation, 2,5-bis(furan-2-yl)-1-methyl-1*H*-imidazole

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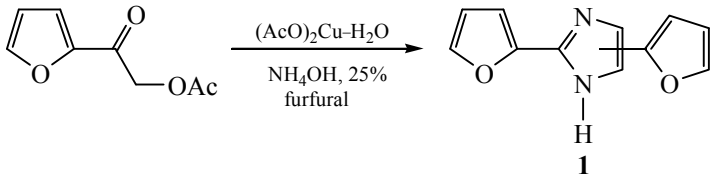
Compounds containing two or more heterocyclic fragments attract great attention due to specificity of their structure and mutual effects of these fragments on the reactivity. Of particular interest are derivatives of previously unknown 2,5-bis(furan-2-yl)imidazole. The presence of three pharmacophoric heterocyclic fragments in its molecule is expected to endow it with diverse biological activity.

In this work we studied methods of synthesis of 2,5-bis(furan-2-yl)-1*H*-imidazole (**1**) and its reactions with some electrophiles, which could lead to potential luminophores. Schubert et al. [1] synthesized 2,4(5)-bis(furan-2-yl)-1*H*-imidazole (**1**) by reaction of furoyl chloride with diazo ketone and potassium acetate, followed by condensation of the [2-(furan-2-yl)-2-oxoethyl]acetate thus obtained with formaldehyde according to Weidenhagen. We succeeded in synthesizing compound **1** in a similar way but without using explosive diazo ketone (Scheme 1).

The alkylation of 2,4(5)-bis(furan-2-yl)-1*H*-imidazole (**1**) with an equimolar amount of methyl iodide in acetone in the presence of potassium hydroxide according to the procedure described in [2] quantitatively afforded a mixture of isomeric 2,5-, and 2,4-bis(furan-2-yl)-1-methyl-1*H*-imidazoles **2** and **3** (Scheme 2). As we showed previously [3], methylation of 4(5)-(furan-2-yl)-1*H*-imidazole gives 4-(furan-2-yl)-1-methyl-1*H*-imidazole as a minor product, while the major product is 5-(furan-2-yl)-1-methyl-1*H*-imidazole; according to the ^{1}H NMR data, the isomer ratio was 1 : 2.

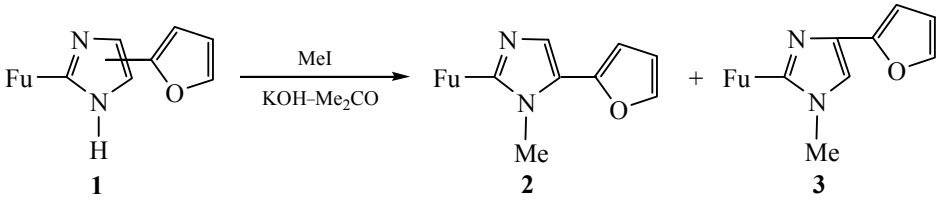
In our case, the ^{1}H NMR spectrum of the isolated product contained only traces of **3**. Protons of the furan ring in position *2* of the imidazole ring displayed a larger paramagnetic shift than those of the furan ring in the 5-position. This suggests stronger conjugation of the 2-furyl substituent with the imidazole C=N bond; therefore, the furan ring in position 5 of the imidazole ring in **2** should be expected to be more reactive toward electrophiles. In fact, the further transformations of **2** confirmed this assumption. 2,5-Bis(furan-2-yl)-1-methyl-1*H*-imidazole (**2**) was isolated by fractional crystallization and brought into reactions with such electrophiles as acetyl nitrate, bromine in 1,2-

Scheme 1.

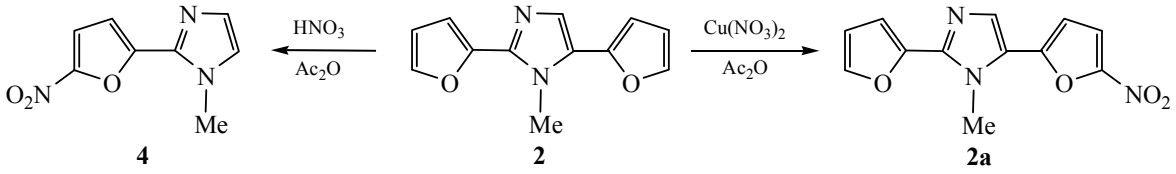


1

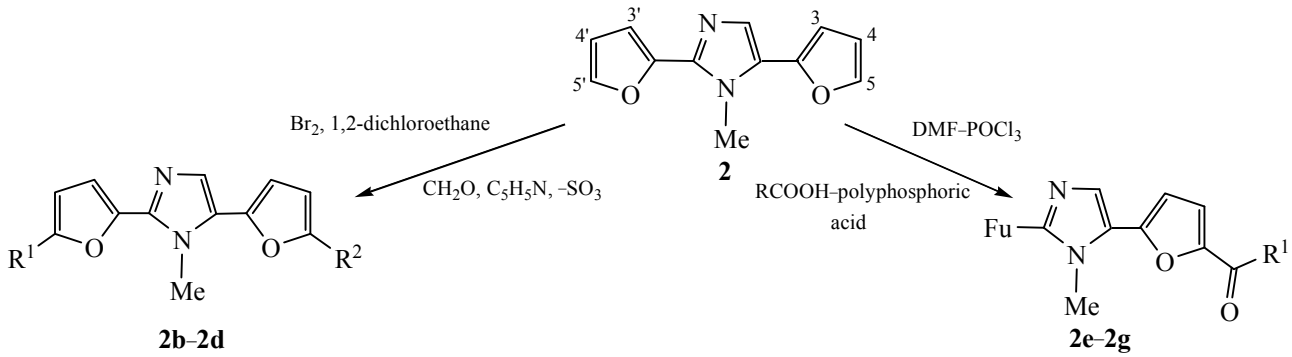
Scheme 2.



Scheme 3.



Scheme 4.



$R^1 = R^2 = Br$ (**b**); $R^1 = H$, $R^2 = SO_3H$ (**c**); $R^1 = H$, $R^2 = CH_2OH$ (**d**), H (**e**), Me (**f**), Ph (**g**).

dichloroetane, a mixture of sulfuric and polyphosphoric acids, formaldehyde, Vilsmeier reagent, and carboxylic acids in polyphosphoric acid (PPA).

The nitration of **2** with a mixture of fuming nitric aid and acetic anhydride at 0°C unexpectedly afforded 2-(5-nitrofuran-2-yl)-1-methyl-1*H*-imidazole **4** (Scheme 3). Presumably, the reactions involved complete oxidative decomposition of the furan ring on C^5, and that on C^2 underwent nitration. We succeeded in performing selective nitration of **2** according to the procedure described in [4] for the nitration of thiophenes with the copper(II) nitrate–acetic anhydride complex at 0°C. In this case, nitro group entered the furan ring on C^5, while the other furan ring in molecule **2** remained intact. The yield of 2-(furan-2-yl)-1-methyl-5-(5-nitrofuran-2-yl)-1*H*-imidazole (**2a**) was ~49%.

The bromination of **2** in chloroform at –10 to –15°C resulted in introduction of bromine into position 5 of both furan rings with formation of dibromo derivative **2b** in 48% yield. Pyridine–sulfur trioxide is known as a mild sulfonating agent ensuring best results in the sulfonation of acidophobic furan ring. The sulfonation of **2** with pyridine sulfur trioxide in boiling 1,2-dichloroethane afforded 37% of sulfonic acid **2c**. The sulfonation selectively involved the furan ring in position *5* of imidazole (Scheme 4).

Formaldehyde is a weak electrophile; however, Stoyanov [5] described hydroxymethylation of 2-(furan-2-yl)imidazole at the 5-position of the furan ring. The reaction was very slow, and the yield was as low as 11% after refluxing for 16 h. Under analogous conditions, compound **2** was converted to hydroxymethyl derivative **2d** at the furan ring in the 5-position of imidazole (yield 49%; Scheme 4).

Stoyanov et al. [6] reported the reaction of 2-(furan-2-yl)imidazole with Vilsmeier reagent at 95°C, which produced the corresponding furancarbaldehyde in a poor yield, and about 50% of the initial compound was

Table 1. Yields, melting points, and elemental analyses of compounds **1**–**4**

Comp. no.	Yield, %	mp, °C	Found[a], %			Formula	Calculated, %		
			C	H	N		C	H	N
1	76	144–146	65.77	3.92	14.33	$C_{11}H_8N_2O_2$	60.00	4.03	14.00
2	68	113–115	67.56	4.88	13.27	$C_{12}H_{10}N_2O_2$	67.28	4.71	13.08
2a	49	188–190	59.54	3.87	17.13	$C_{12}H_9N_3O_3$	59.26	3.73	17.28
2b	48	136–138	49.57	2.32	17.55	$C_{12}H_8Br_2N_2O_2$	49.36	2.55	17.71
2c	37	350–352	49.32	3.22	9.80	$C_{12}H_{10}N_2O_5S$	48.98	3.43	9.52
2d	49	207–209	63.66	5.21	11.55	$C_{13}H_{12}N_2O_3$	63.93	4.95	11.47
2e	77	129–131	64.15	4.27	11.88	$C_{13}H_{10}N_2O_3$	64.46	4.16	11.56
2f	52	154–156	65.89	4.55	11.17	$C_{14}H_{12}N_2O_3$	65.62	4.72	10.93
2g	43	169–171	71.40	4.22	9.13	$C_{19}H_{14}N_2O_3$	71.69	4.43	8.80
4[b]	60	152–154	50.09	3.77	22.03	$C_8H_7N_3O_3$	49.75	3.65	21.75

[a] The results were consistent with the calculated values within ±0.34%.
[b] mp 153–154°C [6].

recovered from the reaction mixture. Presumably, hydrogen chloride liberated during the process reacts with the initial imidazole to give imidazolium salt which is inert toward electrophiles. Compound **2** reacted with DMF–$POCl_3$ much more readily, and the only product was aldehyde **2e** (yield 77%; Scheme 4). Like 2-(2-hetaryl)imidazoles, the acylation of **2** according to Gardner [7] with carboxylic acids or anhydrides in polyphosphoric acid occurred under considerably milder conditions (70–80°C). For example, the acetylation of 2-(2-hetaryl)imidazoles required heating to 110–120°C, and benzoylation, to 140–160°C. The acetylation of **2** with acetic acid afforded 52% of 5-(5-acetylfuran-2-yl) derivative **2f**, and 5-(5-benzoylfuran-2-yl)-2-(furan-2-yl)-1-methyl-1*H*-imidazole (**2g**) was isolated in the reaction of **2** with benzoic acid in PPA (Scheme 4).

The structure of all newly synthesized compounds was confirmed by IR and ^{1}H NMR spectra and elemental analyses (Tables 1, 2).

Thus, 2,5-bis(furan-2-yl)-1-methyl-1*H*-imidazole (**2**) reacts with electrophiles to give mainly derivatives at the furan ring in position 5 of the imidazole ring, which is likely to be determined by stronger deactivation of the furan ring in position 2 due to conjugation with the C=N bond of imidazole.

EXPERIMENTAL

The spectral studies were performed using the facilities of the Joint Center at the Platov South-Russian State Polytechnic University.

The IR spectra were recorded on a Specord 75IR spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Varian Unity 300 instrument at 300 MHz using $CDCl_3$ as solvent and tetramethylsilane as internal standard. The progress of reactions was monitored by TLC on Al_2O_3 plates (Brockmann activity grade II) using methylene chloride or chloroform as eluent; spots were visualized by treatment with iodine vapor. The elemental analyses were obtained with a Perkin Elmer 2400 analyzer. The melting points were measured in capillaries with a PTP melting point apparatus.

2,5-Bis(furan-2-yl)imidazole (1). 2-Bromo-1-(furan-2-yl)ethanone, 8.85 g (0.05 mol), was added to a solution of 6.86 g (0.07 mol) of potassium acetate in 100 mL of methanol, and the mixture was refluxed for 2 h under vigorous stirring. The precipitate of potassium bromide was filtered off, and the filtrate was added to a solution of 100 g (0.5 mol) of copper(II) acetate in 1200 mL of 25% aqueous ammonia containing 4.8 g (0.05 mol) of furfural. The mixture was refluxed for 1.5 h, the copper salt was filtered off and dispersed in 100 mL of water, and a stream of hydrogen sulfide was passed through the suspension over a period of 0.5 h. The resulting solution was acidified with concentrated aqueous HCl, copper(II) sulfide was filtered off, and the filtrate was made alkaline by adding 25% aqueous ammonia. The precipitate of **1** was filtered off and recrystallized from alcohol. Yield 7.6 g, off-white crystals.

2,5-Bis(furan-2-yl)-1-methyl-1*H*-imidazole (2). Methyl iodide, 5.68 g (0.04 mol), was added dropwise

Table 2. IR and ^{1}H NMR spectra of compounds **1**–**4**

Comp. no.	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum,[a] δ, ppm (*J*, Hz)
1	–	6.43–6.45 m (1H, 4′-H), 6.48–6.50 m (1H, 4″-H), 6.58 d (1H, 3′-H, *J* = 3.3), 6.80 d (1H, 3″-H, *J* = 3.6), 7.12 s (1H, 4-H), 7.34 d (1H, 5′-H, *J* = 1.2), 7.48 d (1H, 5″-H, *J* = 1.8)
2	–	3.69 s (3H, NCH_3), 6.42–6.44 m (1H, 4′-H), 6.47– 6.49 m (1H, 4″-H), 6.60 d (1H, 3′-H, *J* = 3.2), 6.81 d (1H, 3″-H, *J* = 3.6), 7.10 s (1H, 4-H), 7.36 d (1H, 5′-H, *J* = 0.8), 7.46 d (1H, 5″-H, *J* = 1.8)
2a	1542 [$\nu_{as}(NO_2)$], 1386 [$\nu_s(NO_2)$]	3.87 s (3H, NCH_3), 6.56–6.58 m (1H, 4″-H), 6.75 d (1H, 3′-H, *J* = 3.4), 6.85 d (1H, 3″-H, *J* = 3.2), 7.28 s (1H, 4-H), 7.37 d (1H, 4′-H, *J* = 3.4), 7.58 d (1H, 5″-H, *J* = 1.8)
2b	–	3.75 s (3H, NCH_3), 6.30 d (1H, 4′-H, *J* = 3.8), 6.39 d (1H, 4″-H, *J* = 3.6), 6.65 d (1H, 3′-H, *J* = 3.8), 6.86 d (1H, 3″-H, *J* = 3.6), 7.15 s (1H, 4-H)
2c[b]	1280 (SO_2)	3.82 s (3H, NCH_3), 6.52–6.54 d (1H, 4″-H), 6.61 d (1H, 4′-H, *J* = 3.3 Hz), 6.65 d (1H, 3′-H, *J* = 3.3 Hz), 6.84 d (1H, 3″-H, *J* = 3.8 Hz), 7.13 s (1H, 4-H), 7.50 d (1H, 5″-H, *J* = 0.8 Hz), 12.08 s (1H, SO_3H)
2d	1138 (OH)	3.70 s (3H, NCH_3), 4.28 s (1H, OH), 5.07 s (2H, CH_2), 6.45 d (1H, 4′-H, *J* = 3.5), 6.52–6.54 m (1H, 4″-H), 6.55 d (1H, 3′-H, *J* = 3.5), 6.88 d (1H, 3″-H, *J* = 3.2), 7.10 s (1H, 4-H), 7.53 d (1H, 5″-H, *J* = 1.8)
2e	1666 (C=O)	3.84 s (3H, NCH_3), 6.51–6.53 m (1H, 4″-H), 6.78 d (1H, 3′-H, *J* = 3.5), 6.84 d (1H, 3″-H, *J* = 3.2), 7.10 s (1H, 4-H), 7.18 d (1H, 4′-H, *J* = 3.5), 7.50 d (1H, 5″-H, *J* = 0.8), 9.51 s (1H, CHO)
2f	1648 (C=O)	2.55 s (3H, CH_3), 3.84 s (3H, NCH_3), 6.48–6.51 m (1H, 4″-H), 6.75 d (1H, 3′-H, *J* = 3.5), 6.82 d (1H, 3″-H, *J* = 3.6), 7.12 s (1H, 4-H), 7.22 d (1H, 4′-H, *J* = 3.5), 7.48 d (1H, 5″-H, *J* = 1.8)
2g	1685 (C=O)	3.78 s (3H, NCH_3), 6.51–6.53 m (1H, 4″-H), 6.72 d (1H, 3′-H, *J* = 3.2), 6.80 d (1H, 3″-H, *J* = 3.6), 7.15 s (1H, 4-H), 7.20 d (1H, 4′-H, *J* = 3.2), 7.50 d (1H, 5″-H, *J* = 1.8), 7.50–7.52 m (3H, *m*-H, *p*-H), 7.92 d (2H, *o*-H, *J* = 7.2)
4	1540 [$\nu_{as}(NO_2)$], 1380 [$\nu_s(NO_2)$]	4.03 s (3H, NCH_3), 7.03 s (1H, 4-H), 7.08 d (1H, 3′-H, *J* = 3.4), 7.03 s (1H, 5-H), 7.43 d (1H, 4′-H, *J* = 3.4)

[a] Primed locants refer to the furan ring on C^5, and double-primed, to the furan ring on C^2.
[b] The ^{1}H NMR spectrum was recorded in trifluoroacetic acid.

with vigorous stirring to a cold (3–5°C) mixture of 7.6 g (0.038 mol) of compound **1**, 2.24 g (0.04 mol) of powdered potassium hydroxide, and 40 mL of acetone, maintaining the temperature no higher than 8°C. The mixture was kept for 1 h at that temperature and poured into 300 mL of water. The product was filtered off, dried, and subjected to fractional crystallization from hexane. Yield 5.82 g, white crystals.

2-(Furan-2-yl)-1-methyl-5-(5-nitrofuran-2-yl)-1*H*-imidazole (2a). A 100-mL Erlenmeyer flask was charged with 16.5 g (0.07 mol) of $Cu(NO_3)_2 \cdot 3H_2O$, and 40 mL of acetic anhydride was added in small portions with efficient cooling so that the temperature did not exceed 30–40°C. When the exothermic reaction ceased, the mixture was left to stand for 24 h at room temperature, and the precipitate of copper(II) acetate was filtered off. The filtrate (nitrating mixture) was stored in a refrigerator for no longer than 10 days [4]. Compound **2**, 0.21 g (1 mmol), was dissolved in 5 mL of freshly distilled acetic anhydride, and 0.56 mL of the nitrating mixture was added in portions at room temperature. The reaction time was 30–40 min. The mixture was then treated with 15 mL of cold water and neutralized with 25% aqueous ammonia. The precipitate was filtered off, thoroughly washed with water, and purified by column chromatography on aluminum oxide using methylene chloride as eluent. The product was additionally recrystallized from ethanol. Yield 0.12 g, yellow crystals.

1-Methyl-2-(5-nitrofuran-2-yl)-1*H*-imidazole (4). A solution of 0.42 g (2 mmol) of compound **2** in 5 mL of freshly distilled acetic anhydride was cooled to 0°C, 0.76 g (12 mmol) of nitric acid (d = 1.5 g/cm^3) was added, and the mixture was stirred for 1 h at room temperature. The mixture was then poured into 20 mL of water, neutralized with 25% aqueous ammonia, and extracted with 10 mL of chloroform. The extract was dried over anhydrous sodium sulfate, and the product

was isolated by column chromatography on aluminum oxide using chloroform as eluent. The eluate was evaporated, and the residue was recrystallized from benzene. Yield 0.23 g, yellow crystals.

2,5-Bis(5-bromofuran-2-yl)-1-methyl-1*H*-imidazole (2b). A solution of 0.63 g (3 mmol) of compound **2** in 10 mL of 1,2-dichloroethane was cooled to –10 to –15°C, 0.96 g (6 mmol) of bromine was added, and the mixture was stirred for 30 min. The mixture was then washed with 30 mL of 5% aqueous ammonia, the organic layer was separated, dried over anhydrous sodium sulfate, and evaporated, and the residue was purified by column chromatography on aluminum oxide using methylene chloride as eluent. Yield 0.53 g, off-white crystals.

5-[2-(Furan-2-yl)-1-methyl-1*H*-imidazol-5-yl]furan-2-sulfonic acid (2c). A mixture of 0.63 g (3 mmol) of compound **2** and 0.96 g (6 mmol) of pyridine sulfur trioxide in 20 mL of 1,2-dichloroethane was refluxed for 8 h. The mixture was treated with barium carbonate, the sulfonic acid salt was filtered off and dissolved in 50 mL of water on heating, and 5 mL of 10% aqueous HCl was added. After cooling, crystals of sulfonic acid **2c** were filtered off and recrystallized from aqueous ethanol. Yield 0.33 g, colorless crystals.

{5-[2-(Furan-2-yl)-1-methyl-1*H*-imidazol-5-yl]-furan-2-yl}methanol (2d). A solution of 0.63 g (3 mmol) of compound **2** in 20 mL of 40% aqueous formaldehyde was refluxed for 10 h. The mixture was evaporated under reduced pressure, and the residue was purified by column chromatography. Yield 0.36 g, colorless crystals.

5-[2-(Furan-2-yl)-1-methyl-1*H*-imidazol-5-yl]-furan-2-carbaldehyde (2e). Phosphoryl chloride, 1.54 g (10 mmol), was slowly added to a solution of 0.63 g (3 mmol) of compound **2** in 5 mL of dimethylformamide cooled to 0°C, maintaining the temperature no higher than 10–15°C. The mixture was stirred for 30 min at that temperature and for 1 h at 80°C, poured into 25 mL of water, and neutralized with an ammonia solution. The precipitate was filtered off, thoroughly washed with water, and purified by column chromatography on aluminum oxide using methylene chloride as eluent. Yield 0.56 g, yellowish crystals.

1-{5-[2-(Furan-2-yl)-1-methyl-1*H*-imidazol-5-yl]-furan-2-yl}ethanone (2f). A mixture of 0.63 g (3 mmol) of compound **2** and 0.36 g (6 mmol) of acetic acid in 10 g of polyphosphoric acid was stirred for 2 h at 70–80°C. The mixture was diluted with 30 mL of water and neutralized with a solution of ammonia. The precipitate was filtered off, thoroughly washed with water, and purified by column chromatography on aluminum oxide using methylene chloride as eluent. Yield 0.4 g, colorless crystals.

{5-[2-(Furan-2-yl)-1-methyl-1*H*-imidazol-5-yl]-furan-2-yl}phenylmethanone (2g). A mixture of 0.63 g (3 mmol) of compound **2** and 1.1 g (9 mmol) of benzoic acid in 10 g of polyphosphoric acid was stirred for 4 h at 70–80°C. The mixture was diluted with 30 mL of water and neutralized with a solution of ammonia. The precipitate was filtered off, thoroughly washed with water, and purified by column chromatography on aluminum oxide using methylene chloride as eluent. Yield 0.41 g, off-white crystals.

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