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SYNTHESIS AND METHYLATION PRODUCTS OF 4(5)-(2-FURYL)IMIDAZOLE

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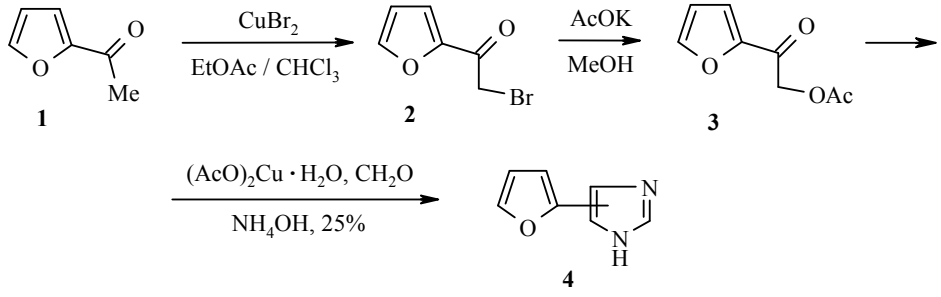
Bromination of 2-acetylfuran with copper(II) bromide in a mixture of ethyl acetate and chloroform leads selectively to furacyl bromide, the nucleophilic substitution of bromine in which by OAc and subsequent use of the Weidenhagen reaction enabled the synthesis of 4(5)-(2-furyl)imidazole. On N-methylation of this imidazole in KOH–acetone 2 isomers are formed, the 1-methyl-4- and 1-methyl-5-(2-furyl)imidazoles. It was established that, unlike alkylation of 4(5)-phenylimidazole, the main product of the reaction is 1-methyl-5-(2-furyl)imidazole.

Keywords: 2-acetylfuran, copper diacetate, methyl iodide, furacyl bromide, 4(5)-(2-furyl)imidazole, methylation.

There is very little information in the literature on 4(5)-furyl-substituted imidazoles, which is caused, in our opinion, by the difficult availability of furacyl bromide and the negative result of condensing it with formamide. We have developed a preparative method of obtaining furacyl bromide 2 selectively as a result of the reaction of 2-acetylfuran (1) with copper(II) bromide. This enabled the synthesis of 4(5)-(2-furyl)imidazole **4** by the Weidenhagen [1] method by the following scheme.



On methylating compound **4** with methyl iodide in KOH–acetone [2], in difference to the previously studied alkylation of 2-(2-furyl)imidazole [3], the formation of isomers is possible as a result of the asymmetry of the imidazole anion.

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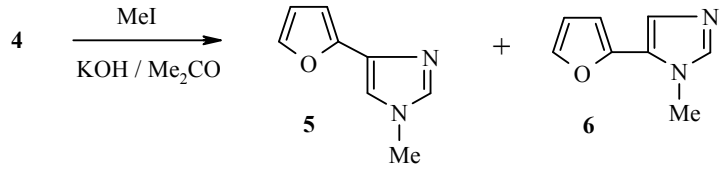
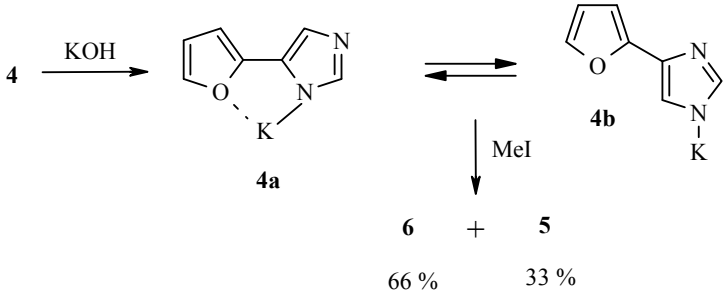


As was expected a spectroscopic ^{1}H NMR investigation of the reaction product clearly detected the presence of the two structural isomers **5** and **6**, which was expressed in the sharp increase in the multiplicity of the proton signals in the aromatic region and the appearance of two singlets at high field for the protons of methyl groups. Regretably the indicated isomers were not successfully separated due to their identical chromatographic mobility. However their identification in the ^{1}H NMR spectrum was not difficult due to the presence of specific features inherent to each of them. The ratio of isomers in the obtained mixture was established by comparing the integral intensity of the signals of the methyl group protons. In difference to the previously described methylation of 4(5)-phenylimidazole [4], where mainly 1-methyl-4-phenylimidazole is formed, 4-(2-furyl)-1-methylimidazole **5** is the minor isomer in the reaction mixture. The main product of methylation is compound **6**, and the ratio of isomers is 2:1 in favor of the latter. Assignment of the signal of methyl group protons to one or other isomer was carried out on the basis of chemical shift values. Of the two signals at 3.75 and 3.67 ppm the latter was assigned to 5-(2-furyl)-1-methylimidazole since in this isomer the methyl group is shielded additionally by the furan ring, which leads to its displacement towards high field.

The anomalous behavior of 4(5)-(2-furyl)imidazole in the methylation reaction clearly reflects the influence of the heteroatom, oxygen, which prevails over the steric effects of the bulky substituent. In reality, unlike the benzene ring, the furan has a hetero atom, which in its turn possesses an unshared electron pair capable of coordinating metals [5]. Evidently the imidazole anion formed under the action of potassium hydroxide has preferentially a chelate structure, which also determines the direction of the methylation reaction.



The previously undescribed 5-(2-furyl)-1-methyl-imidazole (**6**) was isolated in a spectrally pure state by fractional crystallization.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Varian Unity-300 (300 MHz) instrument in $CDCl_3$, assignment of signals was carried out relative to the signal of the residual protons of the solvent (δ 7.26 ppm). A check on the progress of reactions and the homogeneity of the synthesized compounds was effected by TLC on Al_2O_3 plates of Brockman activity grade II (visualization with iodine vapor) in CH_2Cl_2.

Furacyl Bromide (2). A solution of 2-acetylfuran (11 g, 0.1 mol) in $CHCl_3$ (100 ml) was added with boiling and stirring to a suspension of $CuBr_2$ (24.6 g, 0.11 mol) in EtOAc (100 ml). Boiling was continued for

6 h, CuBr was filtered off, the mixture of solvents was distilled off, and the residue was distilled in vacuum, bp 115-120°C (14 mm Hg) (decomp.). Yield 8.5 g (45%). Further use was possible without additional purification.

4(5)-(2-Furyl)imidazole (4). Furacyl bromide 2 (9.45 g, 0.05 mol) was poured into a solution of AcOK (6.86 g, 0.07 mol) in MeOH (100 ml) and the mixture was boiled with stirring for 2 h. The KBr was filtered off, and the filtrate added to a solution of $(AcO)_2Cu \cdot H_2O$ (100 g, 0.5 mol) in 25% NH_4OH (1200 ml) and 37% formalin (60 ml), the mixture was boiled for 1 h 30 min, the copper salt was separated, suspended in water (100 ml), and decomposed with a stream of hydrogen sulfide for 30 min. The solution obtained was acidified with conc. HCl and the CuS separated. On making the filtrate alkaline with 25% NH_4OH solution white solid compound **4** separated, which was removed and air-dried. Yield 4.3 g (32%); mp 117-118°C (water). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.44 (1H, m, H-4'); 6.59 (1H, d, *J* = 3.2, H-3'); 7.30 (1H, s, H-4(5)); 7.39 (1H, d, *J* = 0.9, H-5'); 7.68 (1H, s, H-2). Found, %: C 62.35; H 4.80; N 21.12. $C_7H_6N_2O$. Calculated, %: C 62.68; H 4.51; N 20.88.

4-(2-Furyl)-1-methylimidazole (5) and 5-(2-Furyl)-1-methylimidazole (6). Methyl iodide (8.52 g, 0.060 mol) was added dropwise to a vigorously stirred mixture of compound **4** (7.5 g, 0.056 mol), powdered KOH (4.2 g, 0.075 mol), and acetone (56 ml) at 3-5°C. At the expiry of 1 h 30 min the acetone was evaporated, the residue extracted with $CHCl_3$, the extract dried for 10 min with anhydrous Na_2SO_4, and chromatographed on a column (30×2 cm) of Al_2O_3, eluting with $CHCl_3$. Fractions contained a mixture of the 1-methyl derivatives of compounds **5** and **6**. Yield 6.71 g (81%). The ratio of isomers **5** and **6** in the mixture, according to ^{1}H NMR spectral data, was 1:2, isomer mixture mp 35-38°C. Compound **6** was isolated from the isomer mixture by fractional crystallization from petroleum ether. Yield 3.15 g (47%); mp 94-96°C (petroleum ether). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.67 (3H, s, NCH_3); 6.42-6.44 (1H, m, H-4'); 6.60 (1H, d, *J* = 3.3, H-3'); 7.10 (1H, s, H-5); 7.36 (1H, d, *J* = 1.8, H-5'); 7.42 (1H, s, H-2). Found, %: C 65.05; H 5.54; N 18.77. $C_8H_8N_2O$. Calculated, %: C 64.85; H 5.44; N 18.91.

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