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ACYLATION OF 5-PHENYL-2-(FUR-2-YL)OXAZOLE

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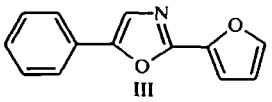
The ability of 5-phenyl-2-(fur-2-yl)oxazole to undergo acetylation and formylation is considered. It was established by x-ray structure analysis that electrophilic substitution proceeds at the position 5 of the furan ring. The direction of the reactions is analyzed from positions of the energy preference of transition states.

Derivatives of 2,5-disubstituted oxazole with aromatic and heteroaromatic radicals present great interest as organic luminophores and biologically active substances [1]. One of the possible paths for the synthesis of compounds with new properties is the modification of their structure by the introduction and conversion of functional groups. Acetylation and formylation reactions are very promising for that.

It is known that 2,5-diphenyloxazole (I) does not undergo the Vilsmeier–Haack reaction, and the Friedel–Crafts acylation with acetyl chloride proceeds at the para position of the 5-phenyl radical, but only under drastic conditions — with the sixfold excess of $AlCl_3$ by boiling for 7 h in carbon disulfide [2], or in the melt with the threefold excess of $AlCl_3$ at 110-120°C for 3 h, with the yield of 30% [3]. Such a low reactivity for compound (I) is associated with the electron-acceptor influence of the oxazole ring, the deactivating action of which is strengthened significantly by the complex formation of the nitrogen atom of the oxazole ring with the catalyst. In contrast to 2,5-diphenyloxazole, 5-phenyl-2-(thien-2-yl)oxazole (II) is successfully formylated with a good yield of 60% under drastic conditions — the 1:6:12 ratio of (II)–$POCl_3$–DMF at 100-105°C for 50 h [4]. The acetylation of compound (II) also proceeds in the melt using the 1:1.1:3 ratio of (II)–AcCl–$AlCl_3$ at 100-110°C for 20 min with the yield of 74% [4]. The electrophilic reagent is directed to the position 5 of the thiophene nucleus.

In the continuation of these investigations, we studied the ability of 5-phenyl-2-(fur-2-yl)oxazole (III) to undergo acetylation and formylation.



III

It is known that furan undergoes electrophilic substitution reaction more readily than thiophene [4]. Therefore, higher reactivity was also expected in the case of its phenyloxazole derivative (III) by comparison with the thiophene-containing analog (II). However, the acylation with acetyl chloride in trichloroethylene, hexane, or nitrobenzene using $AlCl_3$ or $SnCl_4$ as the catalyst leads to the formation of only insignificant amounts of the acetyl derivative. In the case of trichloroethylene and hexane, the temperature was varied up to the boiling temperature of the solvents, and, for nitrobenzene, up to 120°C (strong resinification). When the reaction was carried out under conditions analogous to those of the acetylation of the compounds (I) and (II), namely the 1:1.4:3 ratio of (III)–AcCl–$AlCl_3$ using the melt at 100-110°C for 15 min, the yield of the object compound (IV) comprised 16%. The ratio of the acetylated compound (IV) and the initial compound (III) in the reaction mixture thereby comprises 0.55:1. The increase in the duration of the reaction to 30 min and the temperature to 125°C increases the ratio of (IV)–(III) to 7:1. Further heating leads to significant resinification.

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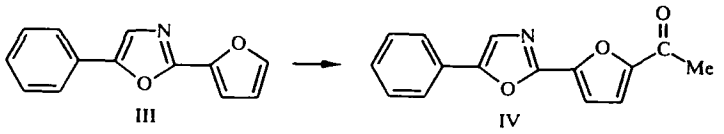
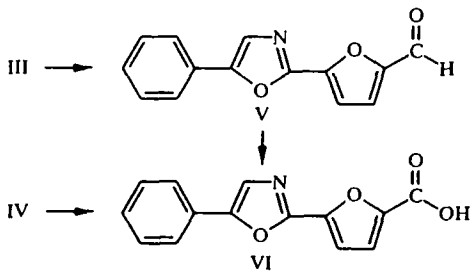


III IV

Consequently, compound (III) was found to be less reactive than (II) under the conditions of the Friedel–Crafts reaction applied. This is probably caused by the better conduction of electronic effects by the furan ring in comparison with the thiophene ring ([5], p. 120). As a result of this, the electron-acceptor influence of the phenyloxazole residue, significantly strengthened by complex formation with the catalyst, exerts greater deactivating action in the furan derivative. If such an assumption is followed, then it is necessary to perform the reaction under conditions giving the maximal decrease in the probability of complex formation. In fact, when compound (III) is boiled in acetic anhydride with a catalytic amount of magnesium perchlorate for 3.5 h, the acetyl derivative (IV) is formed with the yield of 60%. The initial compound was thereby isolated with the yield of 21%. However, the increase in the duration of the reaction only leads to strong resinification of the reaction mixture. It is interesting to note that the thiophene-containing analog (II) does not react under the conditions indicated. Independently of the method of acetylation, substitution proceeds at the position 5 of the furan ring; this was confirmed by the x-ray structure analysis of the compound (IV) (Fig. 1, Table 1).

The formylation of compound (III) goes through significantly faster than that of (II) (in 3 h instead of 50 h) and with better yield (88% against 60%). The reaction has the same direction as in the case of the acetylation, since the same carboxylic acid (VI) was obtained from the formyl derivative (V) and the ketone (IV).



Therefore, under conditions lowering the probability of complex formation at the nitrogen atom of the oxazole ring, the furan-containing derivative (III) is more reactive than the thiophene analog. The higher reactivity and higher positional selectivity of the furan ring by comparison with the thiophene ring are associated ([5], p. 201) with the possible 2,5-addition mechanism for the reaction. However, the influence of the conditions of acylation of the compounds (II) and (III) on their relative reactivity indicates that such a scheme is hardly realized in the given case, and the classical S_E2Ar mechanism, going through the stage of σ-complex formation ([5], p. 164), probably takes place.

Of interest was analyzing the observed direction of the electrophilic substitution reactions since the problem of the causes of the positional selectivity in the furan ring has not been solved definitely ([5], p. 203). Different quantum-chemical methods of calculation show that the electron density in the α-positions of the heterocycle is lower that that in the β-positions ([5], p. 62, and [6]). That is confirmed by experimental ^{13}C NMR data ([5], pp. 61-62). Nevertheless, electrophilic substitution in the furan nucleus goes through with very high selectivity just in the α-position, which can probably be explained by the higher thermodynamic stability of the intermediate σ-complex formed at the α-position (owing to its higher resonance stabilization) by comparison with the β-isomer ([7], pp. 109-110, and [8]). Energy calculations which we conducted by the MNDO method showed that the heats of formation of model forms of furan protonated at the positions 1, 2, and 3 comprise 193.45, 169.84, and 175.34 kcal/mole correspondingly. Such differences in the energies are sufficient for the practical formation of only the α-isomer exclusively. The electron-acceptor substituent, which is the phenyloxazole residue or its complex with the catalyst in the case of compound (III), at the position 2 of the furan ring does not usually influence the orientation of the substitution, which is directed to the free position 5 ([7], p. 118). The only exceptions comprise some special cases, for example, 2-carbonyl-containing derivatives of furan which can give the 4-isomer together with the 5-substituted compound under conditions of complex formation with the catalyst ($AlCl_3$) [8]. Therefore, the preferableness of substitution at the position 5 of the furan ring for compound (III) (by comparison with the positions 3 and 4) seems fully well-founded.

TABLE 1. Atomic Coordinates ($\times 10^4$) and Thermal Corrections (equivalent for nonhydrogen and isotropic for hydrogen atoms) in the Molecule of (III)

Atom	x	y	z	U, Å^2 × 10^3
O(1)	4597(1)	2195(2)	6431(1)	44(1)
O(2)	4552(1)	2059(2)	8823(1)	46(1)
O(3)	4215(2)	1841(2)	10566(1)	68(1)
N	3273(2)	850(2)	7142(1)	50(1)
C(1)	4249(2)	1783(3)	7228(1)	42(1)
C(2)	3742(2)	1413(3)	5781(1)	39(1)
C(3)	2951(2)	619(3)	6218(1)	48(1)
C(4)	4991(2)	2353(3)	8051(1)	45(1)
C(5)	6083(2)	3095(3)	8242(2)	60(1)
C(6)	6364(2)	3231(3)	9188(2)	57(1)
C(7)	5417(2)	2604(3)	9526(1)	46(1)
C(8)	3846(2)	1585(3)	4837(1)	39(1)
C(9)	4730(2)	2620(3)	4550(2)	47(1)
C(10)	4776(2)	2770(3)	3638(2)	54(1)
C(11)	3960(2)	1898(3)	3002(2)	55(1)
C(12)	3093(2)	848(3)	3279(2)	55(1)
C(13)	3034(2)	694(3)	4185(2)	49(1)
C(14)	5170(2)	2405(3)	10434(1)	52(1)
C(15)	6134(3)	2891(5)	11195(2)	69(1)
H(3)	2232(17)	-46(28)	5983(13)	54(6)
H(5)	6532(20)	3411(29)	7794(14)	63(6)
H(6)	7072(19)	3713(28)	9525(14)	60(6)
H(9)	5318(18)	3194(27)	4976(14)	56(6)
H(10)	5397(20)	3512(30)	3449(14)	65(7)
H(11)	3979(18)	2017(27)	2373(16)	61(6)
H(12)	2520(20)	233(31)	2836(15)	72(7)
H(13)	2444(18)	-23(31)	4358(13)	62(7)
H(15A)	5755(45)	2726(94)	11757(36)	72(15)
H(15B)	6530(46)	4149(69)	11073(29)	57(14)
H(15C)	6762(51)	1998(80)	11189(37)	70(17)
H(15D)	6838(47)	3176(96)	10986(31)	58(15)
H(15E)	6253(49)	1783(71)	11636(38)	69(15)
H(15F)	5848(46)	3954(78)	11563(36)	74(16)

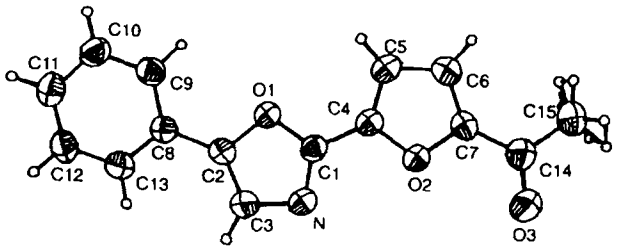


Fig. 1. Structure and numeration of atoms of the molecule of (III).

However, the acylation could also not be directed at the furan ring. Thus, for example, when 2-(fur-2-yl)oxazole is formylated, brominated, and nitrated under conditions excluding protonation or complex formation, attack at the free position 5 of the oxazole ring is also observed together with substitution at position 5 of the furan ring [9]. Moreover, the substitution in 2,5-diphenyloxazole (I) proceeds at the para-position of the 5-phenyl radical, the most distant from the nitrogen atom. Such a reaction direction agrees with the calculated energies for different protonated forms of compound (I) (Table 2). If the unreactive transition state, formed with the participation of the nitrogen atom, is excluded from consideration, then the isomer protonated at the para-position of the 5-phenyl ring and position 4 of the oxazole ring possesses minimal energy, whereby the last is shown to be even more favorable. Nevertheless, the substitution in the oxazole ring in the conditions of the acetylation reaction does not occur according to the steric conditions since it actually represents an analog of the ortho-position of phenyl,

TABLE 2. Calculated Heats of Formation (ΔH_{form}) of the Molecules (I) and (III) Protonated at Different Positions of the 2-Phenyl (2-Ph) or 2-(Fur-2-yl) (2-Fu), 5-Phenyl (5-Ph), and Oxazole (Ox) Rings

Compound	ΔH_{form}, kcal/mole (s, %)			
	2-Ph (2-Fu)			
	p- (5-)	*m*- (4-)	*o*- (3-)	(1-)
I	-3145,54	-3137,64	-3143,89	—
III	-2801,22	-2786,40	-2799,06	-2771,97

Compound	5-Ph			Ox	
	p-	*m*-	*o*-	4-	N
I	-3151,33	-3136,38	-3149,90	-3152,78	-3170,83
III	-2795,51	-2781,02	-2794,05	-2795,76	-2815,34

and the only reaction product is the 5-(4-acetylphenyl) derivative. Taking attention of these data, as well as the high conductivity of electronic influences by the furan ring, the competing substitution can also be proposed in the 5-phenyl portion in compound (III). However, the quantum-chemical calculations performed (Table 2) indicate the energy preferableness of the transition state just with the participation of the free α-position of the furan ring.

Therefore, the experimentally observed direction of electrophilic substitution in compound (III) is in good agreement with the energies of model transition states calculated by the MNDO method.

EXPERIMENTAL

The IR spectra were measured on the Specord IR-75 spectrometer using tablets of KBr. Semiempirical quantum-chemical calculations were carried out by the MNDO method [10] with complete optimization of geometry.

X-Ray Structure Investigation. Crystals of compound (IV) for x-ray diffraction analysis were obtained by crystallization from toluene and had needle-shaped appearance. The basic crystallographic data are as follows: $C_{15}H_{11}NO_3$, M_r = 253.25, monoclinic, space group $P2_{1/a}$, a = 11.553(2) Å, b = 7.2416(14) Å, c = 15.075(3) Å, β = 100.10(2)°, V = 1241.7(4) Å^3, Z = 4, d_{calc} = 1.55 g/cm^3, F_{000} = 528. The x-ray diffraction analysis was performed on the Siemens P3/PC automatic four-circle diffractometer with molybdenum emission using a graphite monochromator with the angular range of 5° < 2θ < 55°. The method of $2\theta/\theta$-scanning was utilized to measure 1192 reflections, of which 1115 were independent, utilized for the interpretation and specification of structure. In the specification of the structure, a correction for extinction was introduced. The structure was determined by the direct method and specified according to the F_{hkl}^2 by the full-matrix MLS with the anisotropic approximation for nonhydrogen atoms, and with the isotropic approximation for hydrogen atoms. Disordered hydrogen atoms of the methyl group were found by the difference synthesis, and were specified using the isotropic approximation without the imposition of geometrical limitations. The final indicators of confidence for the structure are as follows: R_1 = 0.0282, ωR_2 = 0.0721 from observed ($I > 2\sigma_I$) reflections (0.0296 and 0.0758 correspondingly from the entire body of reflections), S = 1.028, N/M = 1110/229, $(\Delta\rho)_{min}$ and $(\Delta\rho)_{max}$ are −0.124 and 0.092 e/Å^3. Specification of the structure was carried out using the SHELXL program, and the structure interpretation and shaping of the results were carried out using the SHELXTL PLUS program complex [12].

The monitoring of the course of reactions and the purity of the compounds obtained was accomplished using TLC on plates of Silufol UV-254 with the 15:1 mixture of $CHCl_3$–EtOH as the eluent, as well as the Milikhrom-2 chromatograph (Nauchpribor, Orel, Russia: the column KAKh-3 of 2 × 64 mm, the sorbent Silasorb 600 Lachema 5.0 μm, and the 2:3 mixture of CCl_4–$CHCl_3$ as the eluent). Operation by the instrument and treatment of chromatograms were performed on a PC using the original program MS-4, which can be obtained in a paper from the authors.

5-Phenyl-2-(fur-2-yl)oxazole (III) was synthesized according to the method of [11].

5-Phenyl-2-(5-acetylfur-2-yl)oxazole (IV). A. The mixture of 2.10 g (10 mmole) of 5-phenyl-2-(fur-2-yl)oxazole (III) and 4.50 g (34 mmole) of anhydrous $AlCl_3$ is heated to melting prior to the dropwise addition of 1.2 ml (15 mmole) of acetyl

chloride at 125°C. The reaction mass is stirred at this temperature for 30 min, and the hot melt is poured into 100 ml of water acidified with HCl. The residue is filtered off, chromatographed on a column of continuous action (the adsorbent Silochrome type S-120 and the eluent hexane), and recrystallized from heptane. The yield is 1.3 g (51%). The mp is 137-138.5°C. Found, %: N 6.06. $C_{15}H_{11}NO_3$. Calculated, %: N 5.53.

B. The mixture of 10.55 g (50 mmole) of 5-phenyl-2-(fur-2-yl)oxazole (III), 0.65 g (2.9 mmole) of anhydrous magnesium perchlorate, and 75 ml of acetic anhydride is boiled for 3.5 h. The mixture is cooled to 20°C, poured into 0.5 liter of cold water, and neutralized with a saturated solution of Na_2CO_3. The residue which separated out is filtered off, washed with water, dried, and chromatographed on a column of continuous action (the adsorbent Al_2O_3 of activity grade 2, and the eluent hexane). After recrystallization from hexane, 2.2 g (21%) of the initial compound (III) are isolated. The eluent is then replaced by benzene prior to the isolation of the acetyl derivative (IV), which is recrystallized from heptane. The yield is 7.6 g (60%). The mp is 137-138.5°C. The IR spectrum (KBr) is characterized at 1675 cm^{-1} (C=O). Mixing tests of samples of the ketones (IV) obtained by different methods do not give depressions of the melting temperature, and their IR spectra are identical.

5-Phenyl-2-(5-formylfur-2-yl)oxazole (V). The solution of 10.55 g (50 mmole) of compound (I) in 40 ml of DMF is cooled to 10°C, and 15 ml of $POCl_3$ are added dropwise in 25 min with stirring, keeping the temperature not higher than 20°C. The mixture is stirred for 1 h at 20°C and for 3 h at 100°C; it is cooled and slowly poured onto 300 g of ice, maintaining the pH 6-7 by the addition of a saturated solution of Na_2CO_3. The resulting residue is filtered off, dried, and purified on a chromatographic column of continuous action (the adsorbent Silochrome type S-120, and the eluent hexane). The yield is 10.1 g (84%). For investigations, the product is recrystallized from ethanol and the 1:1 mixture of heptane–benzene. The mp is 115.5-117°C. The IR spectrum (KBr) is characterized at 1678 cm^{-1} (C=O). Found, %: N 5.84. $C_{14}H_9NO_3$. Calculated, %: N 5.86.

5-(5-Phenyloxazol-2-yl)furan-2-carboxylic Acid (VI). A. To the solution of 12 g (0.3 mole) of NaOH in 45 ml of water at 0-5°C are added, dropwise, 14.4 g (0.09 mole) of bromine. Then the suspension of 3.8 g (15 mmole) of the ketone (III) in 15 ml of dioxane is added in portions with intensive stirring, maintaining the temperature not higher than 12°C. The reaction mass is stirred at this temperature for 1 h prior to the addition of 0.5 g of sodium pyrosulfite and the acidification by 10% hydrochloric acid to the pH 2-3. The precipitated residue is filtered off and dried. The compound is reprecipitated from 10% aqueous NaOH, chromatographed on a column of continuous action (the adsorbent Silochrome S-120, and the eluent trichloroethylene), and recrystallized from para-xylene. The yield is 1.9 g (50%). The mp is 220.5-222°C. Found, %: N 5.47. $C_{14}H_9NO_4$. Calculated, %: N 5.49.

B. To the solution of 3.2 g (57 mmole) of KOH in 55 ml of ethanol are added 2.4 g (10 mmole) of compound (V), and the mixture is brought to boiling, maintained for 1-2 min, and poured into 500 ml of the 4% aqueous solution of KOH. The resulting residue of 2-phenyl-5-(5-hydroxymethylfur-2-yl)oxazole is separated by filtration. The yield is 0.85 g (71%). The mp is 104-105°C (from benzene). $C_{14}H_9NO_3$. The IR spectrum (KBr) is as follows: 3300 cm^{-1} (OH), 2928 cm^{-1}, and 2852 cm^{-1} ($CH_{aliphatic}$). The alkaline filtrate is acidified with 10% hydrochloric acid to the pH 2-3, and the residue is filtered off. The carboxylic acid (VI) obtained is purified by analogy with the method A. The yield is 1.1 g (79%). The mp is 220.5-222°C. Mixing tests for samples of the acids (VI) obtained by different methods do not give depressions of the melting temperature, and their IR spectra are identical. The IR spectrum (KBr) is as follows: 1625 cm^{-1} and 1675 cm^{-1} (C=O).

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