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2-(Fur-2-yl)naphtho[2,1-*d*]oxazole. Synthesis and Some Transformations

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Abstract—The condensation of 1-hydroxy-2-aminonapnthalene with furoyl chloride in 1-methyl-2-pyrrolidone medium afforded 2-(fur-2-yl)naphtho[2,1-*d*]oxazole. It was involved in reactions of electrophylic substitution like nitration, bromination, sulfonation, formylation, and acylation. In all cases the substituent enters in position 2 of the furan ring.

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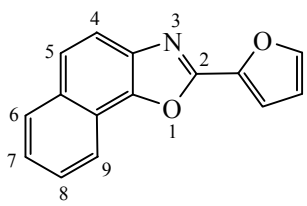
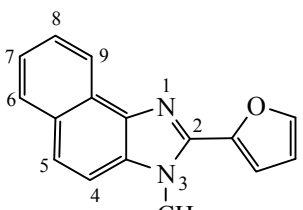
Despite the intense development of chemistry of heterocyclic compounds within several recent decades the properties of systems containing heterocyclic fragments bound with one another by a simple bond in some cases were poorly studied. It concerns also the 2-furyl-substituted derivatives of napntho[2,1-*d*]oxazole. The investigation of such compounds is interesting because it permits the observation of peculiarities of chemical behavior of heterocyclic systems containing several reactive centers in one molecule. Note also that oxazole derivatives are used as pharmaceuticals and pesticides. Besides, mutual effect of naphthooxazole ring and furan substituent can be reflected in its reactivity.

No data on the furan-containing derivatives of naphtho[2,1-*d*]oxazole **I** were reported. In connection with that we decided to develop or find a convenient method of its synthesis, investigate its relative reactivity, and compare it with previously studied naphtho-[1,2-*d*]imidazole analog **II** [1, 2].

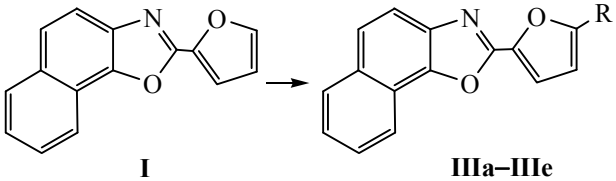


I



II

2-(2'-Furyl)naphtho[2,1-*d*]oxazole **I** we prepared for the first time by condensation of 1-hydroxy-2-amino-naphthalene with furoyl chloride in 1-methyl-2-pyrrolidone medium in 56% yield and subjected this compound to some reactions of electrophilic substitution like nitration, sulfonation, formylation. and acylation.



I **IIIa–IIIe**

R = NO_2 (**a**), Br (**b**), C(O)H (**c**), C(O)Me (**d**), C(O)Ph (**e**).

Main directions of investigation of compounds of the furan series and its isologs by NMR spectroscopy are based on the comparison of chemical shifts and coupling constants. In our work it was the main method of establishing the place of introduction of substituent while studying the electrophilic substitution reactions. On the basis of such comparison while considering bis-hetaryl compound it was possible to evaluate the effect of various heterocyclic substituents in the system. For example, the analysis of the ^1H NMR data for compounds **I** and **II** shows that signals of H^3 protons of the furan ring are located at 7.31 and 7.15 ppm which is caused first of all by the inductive effect and the degree of electron-acceptor influence of naphthooxazole or imidazole substituents. It turned out that in the first case this effect was more expressed. Besides, it was found recently [1] that in compound **II** the position 5 of naphthoimidazole fragment is the reactive center with respect to the nitration and bromination. In compound **I** the positions 4 and 5 are

Table 1. Melting points, elemental analysis data, and yields of obtained compounds[a]

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
I	56	119–120	76.33	4.15	6.23	$C_{15}H_9NO_2$	76.59	3.86	5.59
IIIa	78	181–182	64.58	3.12	9.88	$C_{15}H_8N_2O_4$	64.29	2.88	10.01
IIIb	78	134–135	57.59	2.27	25.79 Br	$C_{15}H_8BrN_2O_4$	57.35	2.57	25.44 Br
IIIc	50	141–142	73.32	3.77	5.54	$C_{16}H_9NO_3$	73.00	3.45	5.32
IIId	69	184–185	73.41	4.17	4.79	$C_{17}H_{11}NO_3$	73.64	4.00	5.05
IIIe	37	154–155	77.56	4.07	4.28	$C_{22}H_{13}NO_3$	77.87	3.86	4.13

[a] Elemental analysis data (C,H,N) correspond to the calculated values within the limits of ±0.34%.

deshielded almost equally (chemical shifts of the corresponding protons are 7.92 and 7.78 ppm). Therefore on the basis of the above-presented data a decrease in the relative reactivity of the furan ring as well as of naphthooxazole fragment must be expected.

Performed transformations confirmed this proposal. For example, while treating compound **I** with a complex of $Cu(NO_3)_2$ and acetic anhydride no reaction was observed, but compound **II** under analogous conditions gave 5,5'-dinitro compound both in the furan and the naphthalene rings. Nitro derivative of compound **I** was prepared by boiling the starting substance in the dilute nitric acid (*d* 1.32). According to ^{1}H NMR spectrum it was 5'-nitro derivative **IIIa** in the furan ring. Analogous result was obtained at the bromination of compound **I** in dichloroethane. Yield of 2-(5-bromofur-2-yl)naphtho[2,1-*d*]oxazole **IIIb** was 78%. Compound **II** formed 5,5'-dibromoderivative already at –5°C [1] while compound **I** under these conditions was recovered from the reaction.

Nowadays the formylation of five-membered p-excessive heterocycles is carried out successfully by Vilsmeier reagent, but compound **I** under these conditions returns unaltered. Therefore we treated naphtoxazole **I** with hexamethylenetetramine in polyphosphoric acid. This system we successfully used for the formylation of heterylbenzimidazoles [3]. Furylnaphthoimidazole **II** furnished the 5'-formyl derivative in 75% yield [1], while the corresponding 2-(5-formylfur-2-yl)-naphtho[2,1-*d*]oxazole **IIIc** was prepared in the yield no exceeding 50%.

According to the reported data [1] the acetylation of compound **II** was carried out by treating it with acetic anhydride at 100–110°C in polyphosphoric acid. It is interesting that we managed to carry out the acetylation of compound **I** by boiling in acetic anhydride in the bpresence of catalytic amount of anhydrone, that is, under the mild conditions of Dorofeenko reaction [4]. Probably in this case compound **I** was acetylated as a base. In this case electron-acceptor properties of naphtho[2,1-*d*]oxazole fragment are significantly lower. As known, this fragment exhibits significantly low basicity [5] which favors the reaction. Yield of 5'-acetyl derivative **IIId** was rather high (69%).

The benzoylation of furylnaphtho[2,1-*d*]oxazole **I** was carried out in polyphosphoric acid by treating with benzoic acid at 160°C. In contrast to analogous transformation of compound **II** it proceeded with great difficulty, and the yield of ketone **IIIe** was low. For comparison, compound **II** forms 5'-benzoyl derivative in 4-6 h in 70% yield while the yield of 2-(5-benzoylfur-2-yl)napntho[2,1-*d*]oxazole **IIIe** in 14 h does not exceed 37%, and 49% of starting substance **I** is recovered.

As known, acidophobic five-membered heterocycles of pyrrole type are sulfonated with the adduct of sulfur trioxide with pyridine [6]. At the same time the sulfonation of the majority of 2-hetarylimidazoles could be carried out only under the action of concentrated sulfuric acid in polyphosphoric acid medium. We failed to carry out the sulfonation of compound **I** by either procedure. It is evidently due to the fact that sulfonic acids exist as betains. The stability of the latter depends on the basicity of naphtoxazole fragment which is known to be the lowest among the azoles [5].

Together with imidazoles and thiazoles some derivatives of 2-furyloxazoles are known as antiparasite agents. Investigation of their biological activity showed that 5'-nitroderivatives exhibit high antihelminthes activity [7].

Table 2. Parameters of the IR and ^{1}H NMR spectra of obtained compounds

Comp. no.	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz, $CDCl_3$)
I	–	6.62–6.64 m (1H, $H^{4'}$), 7.31 d (1H, $H^{3'}$, *J* 3.6), 7.52 t (1H, H^7, arom., *J* 8.2), 7.63 t (1H, H^8, arom., *J* 7.8), 7.67 d (1H, $H^{5'}$, *J* 1.5), 7.78 d (1H, H^5, arom., *J* 8.7), 7.82 d (1H, H^4, arom., *J* 8.7), 7.96 d (1H, H^6, arom., *J* 8.4), 8.27 d (1H, H^9, arom., *J* 8.1)
IIIa	1370 s 1550 as	7.45 d (1H, $H^{3'}$, *J* 3.9), 7.48 d (1H, $H^{4'}$, *J* 3.9), 7.62 t (1H, H^7, arom., *J* 8.1), 7.67 t (1H, H^8, arom., *J* 8.1), 7.80 d (1H, H^5, arom., *J* 8.7), 7.84 d (1H, H^4, arom., *J* 8.7), 7.96 d (1H, H^6, arom., *J* 8.4), 8.29 d (1H, H^9, arom., *J* 8.1)
IIIb	–	6.56 d (1H, $H^{4'}$, *J* 3.6), 7.24 d (1H, $H^{3'}$, *J* 3.6), 7.53 t (1H, H^7, arom., *J* 8.1), 7.63 t (1H, H^8, arom., *J* 8.1), 7.78 d (1H, H^5, arom., *J* 8.7), 7.81 d (1H, H^4, arom., *J* 8.7), 7.96 d (1H, H^6, arom., *J* 8.4), 8.27 d (1H, H^9, arom., *J* 8.1)
IIIc	1680 (C=O)	7.41 d (1H, $H^{3'}$, *J* 3.6), 7.43 d (1H, $H^{4'}$, *J* 3.6), 7.57 t (1H, H^7, arom., *J* 8.1), 7.67 d (1H, H^8, arom., *J* 8.1), 7.83 d (1H, H^5, arom., *J* 8.7), 7.84 d (1H, H^4, arom., *J* 8.7), 7.98 d (1H, H^6, arom., *J* 8.4), 8.32 d (1H, H^9, arom., *J* 8.1), 9.86 s (1H, CHO)
IIId	1670 (C=O)	2.64 s (3H, CH_3), 7.34 d (1H, $H^{3'}$, *J* 3.6), 7.38 t (1H, $H^{4'}$, *J* 3.6), 7.57 t (1H, H^7, arom., *J* 8.1), 7.66 t (1H, H^8, arom., *J* 8.1), 7.83 d (1H, H^5, arom., *J* 8.7), 7.84 d (1H, H^4, arom., *J* 8.7), 7.98 d (1H, H^6, arom., *J* 8.4), 8.32 d (1H, H^9, arom., *J* 8.1)
IIIe	–	7.37 d (1H, $H^{3'}$, *J* 3.5), 7.40 d (1H, $H^{4'}$, *J* 3.5), 7.54 t (3H, $H^{3,4,5}$, arom., *J* 7.7), 7.58 t (1H, H^7, arom., *J* 8.1), 7.68 t (1H, H^8, arom., *J* 8.1), 7.83 d (1H, H^5, arom., *J* 8.6), 7.85 d (1H, H^4, arom., *J* 8.6), 7.98 d (1H, H^6, arom., *J* 8.3), 8.12 d (2H, $H^{2,6}$, arom., *J* 7.8), 8.32 d (1H, H^9, arom., *J* 8.1)

EXPERIMENTAL

^{1}H NMR spectra were taken on a Varian Unity 300 spectrometer (300 MHz) in $CDCl_3$, internal reference TMS. Elemental analysis was carried out on a Perkin Elmer 2400 analyzer. Melting points were measured in capillary on a PTP device. Yields and properties of compounds are listed in tables 1 and 2.

2-(Fur-2-yl)naphtha[2,1-*d*]oxazole (I). To a solution of 1.59 g of 1-hydroxy-2-aminonaphthalene in 10 ml of 1-methyl-2-pyrrolidone 1.31 g of furoyl chloride was added. Reaction mixture was boiled for 2 h, cooled and poured in 50 ml of cold water. The obtained precipitate was filtered off, thoroughly washed with cold water, and crystallized from ethanol.

2-(5-Nitrofur-2-yl)naphtho[2,1-*d*]oxazole (IIIa). A solution of 1.18 g of compound **I** in 25 ml of nitric acid (*d* 1.35) was boiled for 2 h. The reaction mixture was cooled and poured in 100 ml of cold water. The obtained precipitate was filtered off, washed 2-3 times with small amounts of cold water, and crystallized from ethanol.

2-(5-Bromofur-2-yl)naphtho[2,1-*d*]oxazole (IIIb). To a solution of 1.18 g of compound **I** in 25 ml of dichloroethane 1.6 g of bromine was added, and the resulting mixture was refluxed for 4 h. After that it was evaporated in air, the residue was dissolved in methylene chloride and chromatographed on a 15×2.5 cm column fllled with Al_2O_3, elution with methylene chloride. The product was crystallized from ethanol.

2-(5-Formylfur-2-yl)naphtho [2,1-*d*]oxazole (IIIc). To a mixture of 1.18 g of compound **I** and 20 g of polyphosphoric acid 2.8 g of hexamethylenetetramine was added, and the resulting mixture was heated at 80–90°C with intense stirring for 5 h. After that the reaction mixture was diluted with 50 ml of water and neutralized with ammonia. The reaction product was extracted with methylene chloride and chromatographed on a column filled with aluminum oxide. After that the solvent was removed and the residue was crystallized from ethanol.

2-(5-Acetylfur-2-yl)naphtho[2,1-*d*]oxazole (IIId). To a solution of 1.18 g of compound **I** in 15 ml of acetic anhydride the catalytic amount of magnesium perchlorate (0.005 g) was added, and the resulting mixture was boiled for 1.5 h. After that the reaction mixture was decomposed with 25 ml of water and neutralized with concentrated ammonia. The reaction product was extracted with methylene chloride and chromatographed on a column packed with Al_2O_3, elution with methylene chloride. The solvent was evaporated, and the residue was crystallized from ethanol.

2-(5-Benzoylfur-2-yl)naphtho[2,1-*d*]oxazole (IIIe). A mixture of 1.18 g of compound **I,** 20 g of polyphosphoric acid, and 1.8 g of benzoic acid was heated with stirring at 150–160°C for 15 h. The reaction product was isolated analogously to the acetyl derivative **Id** and crystallized from 2-propanol.

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