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Synthesis and Some Transformations of 2-(2-Thienyl)naphtho[1,2-*d*]oxazole

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Abstract—Condensation of 1-amino-2-hydroxynaphthalene with thenoyl chloride in 1-methyl-2-pyrrolidinone medium afforded 2-(2-thienyl)naphtho[1,2-*d*]oxazole. The latter was brought into electrophilic substitution reactions like nitration, bromination, sulfonation, formylation, and acylation. The reactions proceeded via electrophilic attack at the 5-position of the thiophene ring, but the nitration and bromination occurred involving both the thiophene and naphthalene fragments.

Keywords: naphthooxazoles, reactivity, electrophilic substitution, bihetaryl compounds

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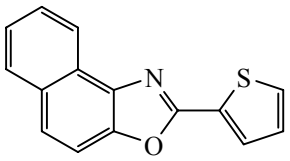
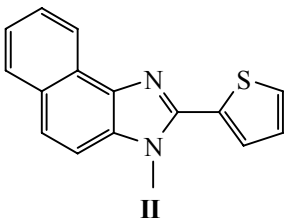
Mutual influence of heterocyclic scaffolds in bihetaryl compounds is an interesting and still insufficiently explored problem. Data on the reactivity of compounds in which naphthooxazole and π- excessive thiophene rings are linked to each other by a single bond are scarce. Sometimes the reactivity of these substances is quite unexpected. Thus, for example, the formylation of 2-(2-thienyl)oxazole occurred involving oxazole ring, although thiophene ring is more π-excessive [1].

The aim of this work was the synthesis of 2-(2-thienyl)naphtho[1,2-d]oxazole **I** and the study of its relative reactivity in comparison with naphthoimidazole analog **II** [2].

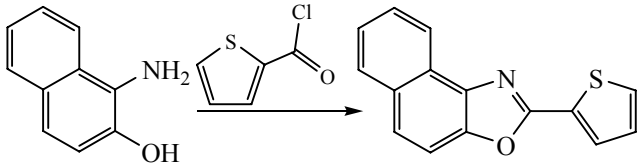


I



II

Compound **I** we obtained for the first time via condensation of 1-amino-2-hydroxynaphthalene with thenoyl chloride in 1-methyl-2-pyrrolidinone medium in 63% yield. 2-(2-Thienyl)naphtho[1,2-*d*]oxazole **I** obtained was brought into electrophilic substitution reactions like nitration, bromination, sulfonation, formylation, and acylation (Table 1).



The comparison of chemical shifts of the protons of 2-thienyl group of compounds **I**, **II** [2] shows that their H^4 protons are the most shielded (7.19 and 7.20 ppm). This insensitivity of the protons in the *meta*-position relative to the substituent is typical for all π-conjugated systems. The protons H^5 (7.53 and 7.51 ppm) and H^3 (7.93 and 7.57 ppm) are deshielded. Therefore, ^{1}H NMR spectroscopy data show a clear correlation between the downfield shift of the protons H^3 of the thiophene ring caused primarily by the inductive effect and electron-acceptor effect of naphthooxazole or naphthoimidazole moieties, which is lower in the latter case. So, a decrease in the relative reactivity of the thiophene ring in compound **I** is expectable.

The reactions performed confirm this assumption. For example, the nitration of **I** with $Cu(NO_3)_2$ in the presence of acetic anhydride did not occur, while the nitration of compound **II** under these conditions proceeded involving the naphthalene ring to afford a 5-

Table 1. Melting points, elemental analysis data, and yields of the compounds obtained

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
I	63	131–132	71.35	3.77	5.83	$C_{15}H_9NOS$	71.69	6.31	5.57
IIIa	67	179–180	53.03	1.95	12.44	$C_{15}H_7N_3O_5S$	52.79	2.07	12.31
IIIb	42	180–181	54.89	2.57	Br 23.93	$C_{15}H_8BrNOS$	54.56	2.44	Br 24.20
IIIc	53	203–204	43.79	2.03	Br 38.78	$C_{15}H_7Br_2NOS$	44.04	1.72	Br 39.06
IIId	23	203–204	69.17	3.49	4.88	$C_{16}H_9NO_2S$	69.80	3.25	5.01
IIIe	18	166–167	69.37	4.03	5.0.9	$C_{17}H_{11}NO_2S$	69.61	3.78	4.77
IIIf	37	154–155	74.69	3.37	4.28	$C_{22}H_{13}NO_2S$	74.35	3.69	3.94

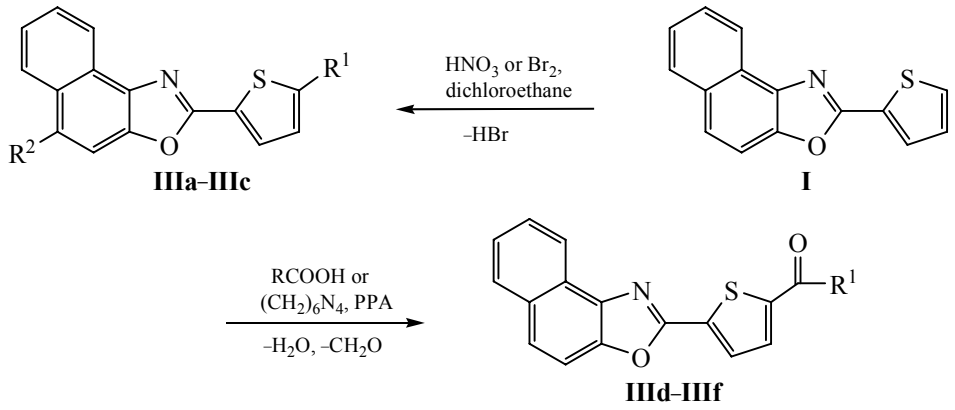
nitro derivative [2]. Refluxing of compound **I** in diluted nitric acid (d = 1.32 g cm^{-3}) resulted in 5,5-dinitro derivative **IIIa**.

The bromination of naphthooxazole **I** with 1 equiv of bromine under reflux in dichloromethane occurred involving thiophene ring to afford 5-bromo derivative **IIIb** in 42% yield; additionally, 37% of **I** was recovered. When 3 equiv of bromine was used, both the thiophene and naphthalene moieties undergo bromination to give a mixture of mono- (**IIIb**) and dibromo derivatives (**IIIc**) isolated by column chromatography. Compound **II** yielded analogous dibromo derivative already at –5°C [2], while compound **I** does not undergo conversion under these conditions (Scheme 1).

As in the case of compound **II**, we failed to isolated any sulfo derivative of 2-(2- thienyl)naphtho[1,2-*d*] oxazole **I**. According to TLC, the reaction of **I** with sulfuric acid in polyphosphoric acid (PPA) proceeds, but the sulfonic acid obtained undergoes desulfonation when the reaction is quenched with water. Apparently, in this case the sulfonic acid can exist only as a zwitterion, whose stability depends on the basicity of naphthooxazole fragment, and it is known to be the lowest among the azoles [3].

Since formylation of compound **I** with the Vilsmeier reagent had failed, in this work we performed formylation by heating a mixture of **I** with hexamethylenetetramine in polyphosphoric acid medium at 90–100°C, a procedure previously successfully used for the formylation of 2-(2-hetaryl)benzimidazoles. Compared with naphthoimidazole **II** affording 5-formyl derivative in 75% yield [2], the corresponding 2-(5-formyl-2-thienyl)naphtho[1,2-*d*]oxazole **IIId** was obtained in ~23% yield along with recovered compound **I** and unidentified impurity (64%, Table 2).

Scheme 1.



$R^1 = R^2 = NO_2$ (**a**); R^1 = Br, R^2 = H (**b**); $R^1 = R^2$ = Br (**c**); R^1 = H (**d**); R^1 = Me (**e**); R^1 = Ph (**f**).

Table 2. Spectral parameters of compounds obtained

Comp. no.	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)
I	–	7.19 t (1H, $H^{4'}$, *J* 4.5), 7.52 t (1H, H^7, *J* 8.2), 7.53 d (1H, $H^{5'}$, *J* 5.1), 7.64 t (1H, H^8, *J* 8.2), 7.68 d (1H, H^5, *J* 8.7), 7.78 d (1H, H^4, *J* 8.7), 7.93 d (1H, $H^{3'}$, *J* 3.9), 7.95 d (1H, H^6, *J* 7.5), 8.54 d (1H, H^9, *J* 8.1)
IIIa	1370 s (NO_2)	7.81 t (1H, H^7, *J* 8.1), 7.85 t (1H, H^8, *J* 8.1), 7.92 d (1H, $H^{4'}$, *J* 4.5), 8.02 d (1H, $H^{3'}$, *J* 4.5), 8.55 s (1H, H^4), 8.66–8.68 m (1H, H^9), 8.69 d (1H, H^6, *J* 7.5)
IIIb	1550 as (NO_2)	7.16 d (1H, $H^{4'}$, *J* 3.9), 7.50 t (1H, H^7, *J* 8.0), 7.62 t (1H, H^8, *J* 8.2), 7.65 d (1H, H^5, *J* 8.5), 7.67 d (1H, $H^{3'}$, *J* 3.9), 7.75 d (1H, H^4, *J* 8.5), 7.98 d (1H, H^6, *J* 7.5), 8.52 d (1H, H^9, *J* 8.0)
IIIc	–	7.16 d (1H, $H^{4'}$, *J* 3.9), 7.65 d (1H, $H^{3'}$, *J* 3.9), 7.66 t (1H, H^7, *J* 8.1), 7.71 t (1H, H^8, *J* 8.0), 8.04 s (1H, H^4), 8.34 d (1H, H^6, *J* 7.5), 8.53 d (1H, H^9, *J* 8.1)
IIId	–	7.58 t (1H, H^7, *J* 8.4), 7.70 t (1H, H^8, *J* 8.0), 7.72 d (1H, H^5, *J* 9.0), 7.82 d (1H, $H^{4'}$, *J* 3.9), 7.86 d (1H, H^4, *J* 9.0), 7.98 d (1H, H^6, *J* 8.0), 7.99 d (1H, $H^{3'}$, *J* 3.9), 8.56 d (1H, H^9, *J* 8.4), 10.00 s (1H, CHO)
IIIe	1680 (C=O)	2.63 s (3H, CH_3), 7.57 t (1H, H^7, *J* 8.2), 7.69 t (1H, H^8, *J* 8.1), 7.70 d (1H, H^5, *J* 9.0), 7.72 d (1H, $H^{4'}$, *J* 4.2), 7.84 d (1H, H^4, *J* 9.0), 7.92 d (1H, $H^{3'}$, *J* 4.2), 7.97 d (1H, H^6, *J* 8.0), 8.56 d (1H, H^9, *J* 8.1)
IIIf	1670 (C=O)	7.55 t (1H, H^7, *J* 8.2), 7.67 t (1H, H^8, *J* 8.1), 7.70 d (1H, H^5, *J* 9.0), 7.70–7.75 m (3H, $H^{3'',4'',5''}$), 7.72 d (1H, $H^{4'}$, *J* 4.2), 7.86 d (1H, H^4, *J* 9.0), 7.93 d (2H, $H^{2'',6''}$, *J* 7.5), 7.96 d (1H, $H^{3'}$, *J* 4.2), 7.98 d (1H, H^6, *J* 8.0), 8.57 d (1H, H^9, *J* 8.1)
	1640 (C=O)	

Acylation of compound **I** by various methods was unsuccessful. Recently compound **II** has been acylated similarly to acylation of phenols and phenyl ethers by the action of acetic acid or anhydride in polyphosphoric acid at 110–120°C [4]. Therefore we applied this method for acylation of compound **I**. Acylation of naphthooxazole **I** occurred slowly to give in 28 h ketone **IIIe** in 18% yield, while compound **II** transformed into a similar ketone in 55% yield within 6 h.

Benzoylation of thienylnaphthooxazole **I** was performed by the Gardner method by the action of benzoic acid in polyphosphoric acid medium at 160°C. Unlike compound **II**, the reaction proceeded with great difficulties to give ketone **IIIf** in 37% yield within 15 h. In addition, 47% of recovered compound **I** was obtained. For comparison, compound **II** was converted into 5-benzoyl derivative in 4–6 h in 56% yield.

In summary, it may be concluded that the reactions of electrophilic substitution of 2-(2-thienyl)naphtho-[1,2-*d*]oxazole proceeded with greater difficulty than in the case of 1-methyl-2-(2-thienyl)-1*H*-naphtho-[1,2-*d*]imidazole. The experimental data confirm higher deshielding (electron-withdrawing) effect of naphtho[1,2-*d*]oxazol-2-yl group compared with naphtho[1,2-*d*]imidazole moiety.

EXPERIMENTAL

IR spectra were recorded in chloroform solutions on a Specord IR-75 spectrometer. ^1H NMR spectra were taken on a Varian Unity-300 spectrometer (300 MHz) using the residual proton signals of $CDCl_3$ as internal reference (δ = 7.26 ppm). Elemental analysis was performed on a Perkin-Elmer 2400 analyzer. Melting points were determined by the capillary method on a PTP instrument. The reaction progress was monitored by TLC using plates coated with Al_2O_3 or Silufol UV-254 plates, eluting with CH_2Cl_2 and detecting with iodine vapor. Yields, melting points, elemental analysis data, and spectral characteristics of the compounds obtained are reported in Tables 1 and 2.

2-(2-Thienyl)naphtho[1,2-*d*]oxazole (I). To a solution of 1.59 g (10 mmol) of 1-amino-2-hydroxy-naphthalene in 10 mL of 1-methyl-2-pyrrolidone was added 1.44 g (10 mmol) of thenoyl chloride. The mixture was refluxed for 2 h, then cooled and poured into 50 mL of cold water. The precipitate was separated, washed thoroughly with ethanol, and recrystallized to yield colorless needles.

5-Nitro-2-(5-nitro-2-thienyl)naphtho[1,2-*d*]oxazole (IIIa). A solution of 1.26 g (5 mmol) of compound **I** in 25 mL of nitric acid (d = 1.32 g cm^{-3}) was refluxed

for 2 h. After cooling the reaction mixture was poured into 100 mL of cold water. The precipitate was filtered off, washed 2–3 times with cold water, and recrystallized from propan-2-ol to yield yellow crystals.

2-(5-Bromo-2-thienyl)naphtho[1,2-*d*]oxazole (IIIb). To a solution of 1.26 g (5 mmol) of compound **I** in 25 mL of dichloroethane was added 0.8 g (5 mmol) of bromine. The mixture was refluxed for 6 h. Then the solvent was evaporated in air. The residue was dissolved in methylene chloride and chromatographed on Al_2O_3, eluting with methylene chloride. Recrystallization from alcohol afforded needle crystals.

5-Bromo-2-(5-bromo-2-thienyl)naphtho[1,2-*d*]-oxazole (IIIc). To a solution of 1.26 g (5 mmol) of compound **I** in 25 mL of dichloroethane was added 2.4 g (15 mmol) of bromine. The mixture was refluxed for 4 h and then poured into a Petri dish. After dichloroethane evaporation the residue was dissolved in CH_2Cl_2 and chromatographed on a column filled with Al_2O_3, eluting with methylene chloride. Recrystallization from alcohol afforded needle crystals.

2-(5-Formyl-2-thienyl)naphtho[1,2-*d*]oxazole (IIId). To a mixture of 1.26 g (5 mmol) of compound **I** in 20 g of polyphosphoric acid was added 2.8 g (20 mmol) of hexamethylenetetramine. The mixture was heated for 6 h at 90–100°C with vigorous stirring. Then the reaction mixture was diluted with 50 mL of water and neutralized with ammonia under cooling. The reaction product was extracted with methylene chloride. The extract was dried over anhydrous Na_2SO_4 and chromatographed on a column filled with Al_2O_3 eluting with methylene chloride. Recrystallization from alcohol afforded yellow crystals.

2-(5-Acetyl-2-thienyl)naphtho[1,2-*d*]oxazole (IIIe). To a solution of 1.26 g (5 mmol) of compound **I** in 20 g of polyphosphoric acid was added 0.95 mL (10 mmol) of acetic anhydride. The resulting mixture was heated for 28 h at 110–120°C under stirring. The reaction mixture was poured into 100 mL of water, neutralized with ammonia solution, and then the reaction product was isolated similarly to **IIId**. Recrystallization from alcohol afforded yellow crystals.

2-(5-Benzoyl-2-thienyl)naphtho[1,2-*d*]oxazole (IIIf). A mixture of 1.26 g (5 mmol) of compound **I**, 20 g of polyphosphoric acid, and 2.44 g (20 mmol) of benzoic acid was heated at 140–150°C for 15 h. The reaction product was isolated similarly to **IIId**. Recrystallization from alcohol afforded pale brown crystals.

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