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Synthesis and Reactivity of 2-(2-Thienyl)oxazolo[4,5-*b*]pyridine

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Abstract—Condensation of 2-amino-3-hydroxypyridine with thenoyl chloride in 1-methyl-2-pyrrolidon afforded 2-(2-thienyl)oxazolo[4,5-*b*]pyridine. Reactivity of the latter towards electrophilic substitution (nitration, bromination, formylation, acylation) was studied. It is shown that the reaction occurred exclusively at the position *5* of the thiophene ring. Nucleophilic substitution of pyridine ring was performed. Quaternization of 2-(2-thienyl)oxazolo[4,5-*b*]pyridine with methyl iodide in benzene was carried out. Chichibabin amination with an excess of sodium amide in xylene failed.

Keywords: 2-amino-3-hydroxypyridine, thenoyl chloride, 2-(2-thienyl)oxazolo[4,5-*b*]pyridine, electrophilic substitution, nucleophilic substitution, Chichibabin amination

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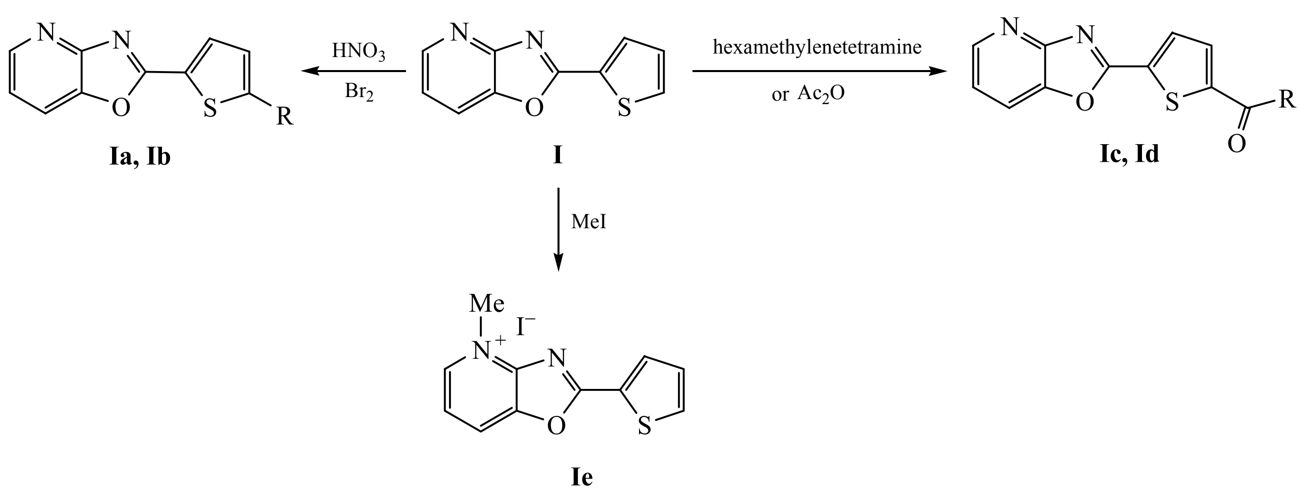
Scarce data was published on the synthesis and reactivity of oxazolo[4,5-*b*]pyridine containing thiophene moiety. At the same time, bi-heterocyclic compounds of this type are of interest as potential biologically active substances and organic phosphors. Previously we developed an approach to the synthesis of 2-(2-thienyl)benzoxazole and studied its reactivity [1].

The aim of this work was to develop or to select a convenient method for the synthesis of 2-(2-thienyl) oxazolo[4,5-*b*]pyridine **I** and to study its reactivity towards electrophilic and nucleophilic reagents.

Compound **I** was first obtained by condensation of 2-amino-3-hydroxypyridine with thenoyl chloride in 1-methyl-2-pyrrolidone in 63% yield. Next, it was introduced into the reactions with nucleophiles and electrophiles like a mixture of nitric acid and polyphosphoric acids, bromine, or sulfuric acid, sodium benzenesulfonate, hexamine, acetic anhydride and benzoic acid, methyl iodide and sodium amide.

Scheme 1.



R = NO_2 (**a**), Br (**b**), H (**c**), Me (**d**).

Table 1. Yields, melting points, and elemental analysis data of compounds **I**, **Ia**–**Ie**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
I	63	143–144	59.53	3.17	14.12	$C_{10}H_6N_2OS$	59.39	2.99	13.85
Ia	38	198–199	48.37	1.78	15.73	$C_{10}H_5N_3O_3S$	48.58	2.04	16.00
Ib	62	137–138	43.03	1.66	10.13	$C_{10}H_5BrN_2OS$	42.72	1.79	9.96
Ic	33	197–198	57.14	2.88	11.89	$C_{11}H_6N_2O_2S$	57.38	2.63	12.17
Id	17	126–127	58.77	3.52	11.61	$C_{12}H_8N_2O_2S$	59.01	3.30	11.47
Ie	86	247–248	38.57	2.77	7.83	$C_{11}H_9JN_2OS$	38.39	2.64	8.14

Table 2. IR and NMR ^{1}H spectral data for compounds **I**, **Ia**–**Ie**

Comp. no.	ν, cm^{-1}	δ, ppm (*J*, Hz, $CDCl_3$)
I	–	7.22 t (1H, H^4, Ht, *J* 4.5), 7.28 t (1H, H^5, Py, *J* 6.5), 7.65 d (1H, H^5, Ht, *J* 4.8), 7.83 d (1H, H^4, Py, *J* 7.8), 8.02 d (1H, H^3, Ht, *J* 3.4), 8.56 d (1H, H^6, Py, *J* 4.2)
Ia	1370 (s) 1550 (as)	7.40 d. d (1H, H^5, Py, $J_{6,5}$ 4.8, $J_{5,4}$ 5.1), 7.90 d (1H, H^4, Py, *J* 8.1), 7.92 d (1H, H^4, Ht, *J* 4.2), 7.99 d (1H, H^3, Ht, *J* 4.2), 8.66 d (1H, H^6, Py, *J* 5.7)
Ib	–	7.18 d (1H, H^4, Ht, *J* 4.2), 7.29 t (1H, H^5, Py, *J* 6.5), 7.75 d (1H, H^3, Ht, *J* 4.2), 7.83 d (1H, H^4, Py, *J* 8.1), 8.57 d (1H, H^6, Py, *J* 5.1)
Ic	1680 (C=O)	7.33 t (1H, H^5, Py, *J* 6.5), 7.82 d (1H, H^4, Ht, *J* 3.9), 7.88 d (1H, H^4, Py, *J* 8.1), 8.06 d (1H, H^3, Ht, *J* 3.9), 8.61 d (1H, H^6, Py, *J* 4.8), 10.00 s (1H, CHO)
Id	1640 (C=O)	2.65 s (3H, CH_3), 7.34 t (1H, H^5, Py, *J* 6.6), 7.80 d (1H, H^4, Ht, *J* 4.0), 7.88 d (1H, H^4, Py, *J* 8.0), 7.80 d (1H, H^3, Ht, *J* 4.0), 8.60 d (1H, H^6, Py, *J* 4.8)
Ie[a]	–	4.44 s (3H, CH_3), 7.49 t (1H, H^4, Ht, *J* 4.2), 8.01 t (1H, H^5, Py, *J* 7.8), 8.36 d (1H, H^5, Ht, *J* 4.2), 8.36 d (1H, H^3, Ht, *J* 3.3), 8.93 d (1H, H^6, Py, *J* 5.4), 8.94 d (1H, H^4, Py, *J* 7.8)

[a] ^{1}H NMR spectrum was recorded in DMSO-d_6.

Reacting 2-(2-thienyl)oxazolo[4,5-*b*]pyridine **I** with boiling dilute nitric acid (*d* 1.32 g cm^{-3}) did not lead to the formation of nitro derivative. Due to strong deactivation of thiophene moiety with protonated oxazolopyridine fragment, 5-nitro derivative **Ia** was obtained only by using fuming nitric acid (*d* 1.51 g cm^{-3}) in polyphosphoric acid at 95°C in a yield of no more than 38%. In addition, compound **Ia** was obtained by authentic synthesis via *ipso*-substitution of the bromine atom with a nitro group in 2-(5-bromo-2-thienyl)-oxazolo[4,5-*b*]pyridine **Ib**. The bromination of **I** with an excess of bromine in dichloroethane afforded exclusively 5-bromo derivative **Ib**. Carrying out the reaction in acetic or polyphosphoric acid was unsuccessful (Scheme 1).

Unlike benzimidazole analog [2] it was not possible to isolate the product of sulfonation of compound **I** due to its well solubility in water, although its formation was detected by TLC.

The formylation of five-membered π-rich heterocycles is known to be carried out with the use of Vilsmeier reagent. However, in the case of compound **I** no reaction was detected. Therefore, we used for this purpose a method based on the reaction of oxazolopyridine **I** with hexamethylenetetramine in polyphosphoric acid, which has been previously successfully used for formylation of thienylbenzoxazole [1]. As a result, aldehyde **Ib** was obtained in a yield of 33%.

The acetylation of oxazolopyridine **I** by Dorofeenko [3] by refluxing in acetic anhydride in the presence of catalytic quantities of perchloric acid failed. 5-Acetyl derivative **Id** we prepared according to the Gardner method [4] by heating compound **I** in polyphosphoric acid with 3 equiv of acetic anhydride at 100–120°C. The attempted benzoylation of **I** was carried out similarly at 160–180°C by the action of benzoic acid, but the desired benzoylketone was not formed.

Due to the presence of the pyridine ring in the molecule compound **I** was interesting for performing a typical nucleophilic substitution reaction, like Chichibabin amination and quaternization. The quaternization of **I** was carried out in neutral conditions by boiling oxazolopyridine **I** in benzene with 3 equiv of methyl iodide for 3 h. As expected, the reaction involved the pyridine ring to give the corresponding quaternary salts in a yield of 86%.

The reaction of compound **I** with sodium amide in boiling xylene for 6 h did not lead to the formation of the amination product that is evidently due to the redistribution of π-electron density of thiophene, oxazole and pyridine rings, leading to a decrease in effective positive charge on the carbon atoms of azine and its basicity [5].

Composition and structure of the synthesized compounds were proved by elemental analysis (Table 1), IR and NMR spectroscopy data (Table 2).

EXPERIMENTAL

IR spectra were recorded on a Specord 75IR instrument from mulls in mineral oil. ^{1}H NMR spectra were registered on a Varian Unity 300 spectrometer (300 MHz, $CDCl_3$ or DMSO-d_6), internal reference TMS. The reaction progress was monitored by TLC using plates coated with Al_2O_3 (Brockmann activity II) and detecting with iodine vapor (eluent CH_2Cl_2, $CHCl_3$). Elemental analysis was performed on a Perkin Elmer 2400 analyzer. Melting points were determined on a PTP instrument by capillary method.

2-(2-Thienyl)oxazolo[4,5-*b*]pyridine (I). To a solution of 1.10 g (10 mmol) of 2-amino-3-hydroxy-pyridine in 10 mL of 1-methyl-2-pyrrolidone was added 1.76 g (12 mmol) of thenoyl chloride. The resulting mixture was refluxed for 3 h, then poured into 50 mL of water, cooled, and kept in a refrigerator for 12 h. The resulting precipitate was filtered off and recrystallized from aqueous ethanol.

2-(5-Nitro-2-thienyl)oxazolo[4,5-*b*]pyridine (Ia). To a solution of 0.202 g (1 mmol) of **I** in 5 g of polyphosphoric acid was added 0.19 g (3 mmol) of nitric acid (d 1.51 g cm^{-3}). The mixture was heated for 3 h at 90–95°C with vigorous stirring, then poured into 25 mL of water and neutralized with 25% aqueous ammonia solution. The precipitate was filtered off and recrystallized from ethanol.

2-(5-Bromo-2-thienyl)oxazolo[4,5-*b*]pyridine (Ib). To a solution of 0.202 g (1 mmol) of **I** in 10 mL of dichloroethane was added 0.48 g (3 mmol) of bromine. The mixture was refluxed for 3 h, then diluted with water and neutralized with ammonia solution. Next, the organic layer was separated and chromatographed on a column packed with alumina eluting with methylene chloride.

2-(5-Formyl-2-thienyl)oxazolo[4,5-*b*]pyridine (Ic). A mixture of 0.202 g (1 mmol) of **I**, 0.42 g (3 mmol) of hexamethylenetetramine and 5 g of polyphosphoric acid was stirred at 110–120°C for 6 h. The reaction mixture was diluted with 10 mL of water and carefully neutralized with ammonia solution. The reaction product was extracted with 10 mL of chloroform and chromatographed on a column (h 10 cm, d 2.5 cm) filled with alumina, eluting with chloroform. The compound **Ib** was crystallized from ethanol.

2-(5-Acetyl-2-thienyl)oxazolo[4,5-*b*]pyridine (Id) was prepared similarly from 0.202 g (1 mmol) of **I**, 0.31 g (3 mmol) of acetic anhydride and 5 g of polyphosphoric acid for 28 h. Compound **Id** was crystallized from methanol.

7-Methyl-2-(2-thienyl)oxazolo[4,5-*b*]pyridinium iodide (Ie). A mixture of 0.202 g (1 mmol) of **I** and 0.43 g (3 mmol) of methyl iodide in 10 mL of anhydrous benzene was refluxed for 6 h. The precipitate was filtered off and crystallized from water.

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