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Synthesis and Properties of 2-Substituted 5-Chloro-1,3-oxazole-4-carboxamides

A. N. Kornienko, S. G. Pil'o, V. M. Prokopenko, and V. S. Brovarets

Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, ul. Murmanskaya 1, Kyiv, 02660 Ukraine
e-mail: brovarets@bpci.kiev.ua

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Abstract—Chlorination of 2-aryl-5-benzylsulfanyl-1,3-oxazole-4-carbonitrile in aqueous acetic acid at 50–60°C afforded new 2-aryl-5-chloro-1,3-oxazole-4-carboxamides. The reactivity of the chlorine atom with respect to the N-, O-, and S-nucleophiles was investigated.

Keywords: 1,3-oxazole-4-carboxamides, functionalization, reactivity, nucleophiles

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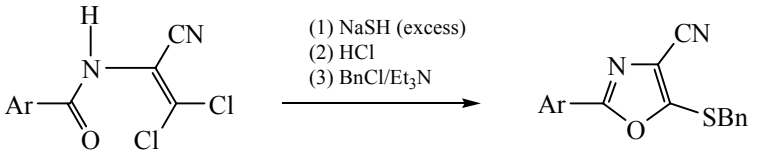
In recent decades a significant amount of natural (*Dendroamide A*, *Nostocyclamide*, *Madumycin II*, *Thiangazole*, *Tantazol*) [1–3] and synthetic [4–7] compounds containing 1,3-oxazole-4-carboxamide moiety and possessing diverse biological activity were found.

The functionalization of the oxazole fragment is one of the most efficient approaches to obtain potentially bioactive substances [8–13]. It has been shown previously [13] that oxidative chlorination of 2-aryl-5-benzylsulfanyl-1,3-oxazole-4-carbonitriles **II**, obtained from available 1-acylamino-2,2-dichloroacrylonitriles **I** [14] afforded target 2-aryl-4-cyano-1,3-oxazole-5-sulfonyl chlorides along with small amounts of their 5-chloro derivatives. It was also observed that the content of the chlorinated product increased as the reaction temperature increased or when crystallization of sulfonyl chlorides was performed (Scheme 1).

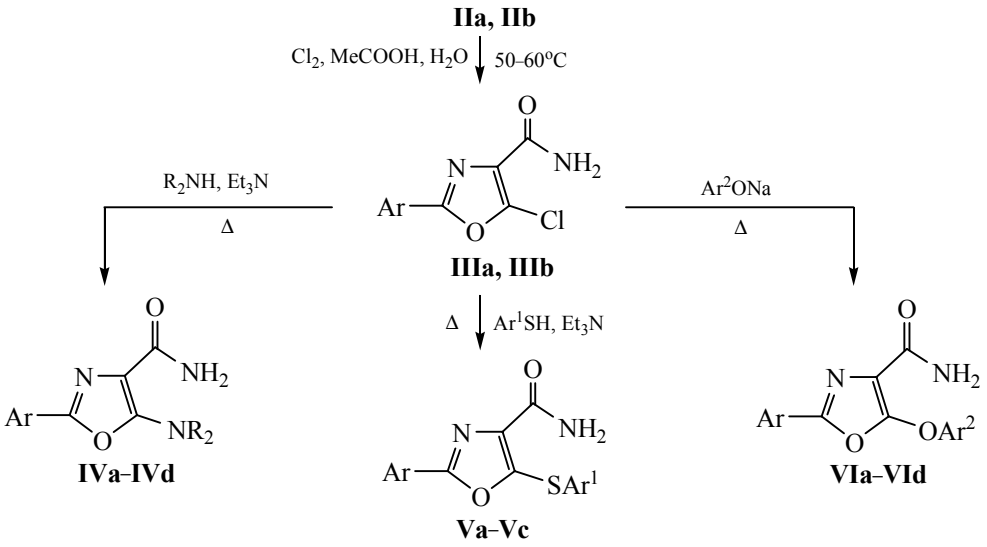
The present work was aimed to develop a preparative method for the synthesis of 5-chloro-1,3-oxazole derivatives in order to use them for obtaining new representatives of oxazole series. The chlorination of oxazoles **IIa** and **IIb** was performed in aqueous acetic acid at 50–60°C for 0.5 h. Under these optimal conditions the chlorination occurred at the position 5 of the oxazole moiety. In addition, the hydrolysis of the nitrile group into an amide proceeded to form 2-aryl-5-chloro-1,3-oxazole-4-carboxamides **IIIa** and **IIIb** with 60–64% yields. Product **IIIa** has been obtained previously in [15] by a multistage synthesis. The study of its chemical properties consisted only in the functionalization of the oxazole ring at the position 4. We found that the chlorine atom in oxazoles **IIIa** and **IIIb** is labile and could be replaced by a variety of nucleophiles. Reaction of compounds **IIIa** and **IIIb** with amines or thiophenols in the presence of triethylamine in dioxane under reflux afforded substituted 2-aryl-5-amino-1,3-oxazole-4-carboxamides **IVa**–**IVd** or 2-aryl-5-arylsulfanyl-1,3-oxazole-4-carboxamides **Va**–**Vc** with 75–80 and 74–85% yields, respectively. Oxazoles **IIIa** and **IIIb** reacted with sodium phenolate to form 2-aryl-5-aryloxy-1,3-oxazole-4-carboxamides **VIa**–**VId** with 68–72% yields. Compounds **IV**–**VI** were prepared by us for the first time (Scheme 2).

Scheme 1.



Ia, Ib **IIa, IIb**

Scheme 2.



Ar = Ph (**Ia**, **IIa**, **IIIa**, **IVa**, **IVc**, **Va**, **VIa**, **VIc**), 4-MeC_6H_4 (**Ib**, **IIb**, **IIIb**, **IVb**, **IVd**, **Vb**, **Vc**, **VIb**, **VId**); Ar^1 = 4-MeC_6H_4 (**Va**, **Vb**), 4-ClC_6H_4 (**Vc**); Ar^2 = Ph (**VIa**, **VIb**), 4-MeC_6H_4 (**VIc**, **VId**); R^2NH = $(CH_2)_5NH$ (**IVa**, **IVb**), $O(CH_2)_4NH$ (**IVc**, **IVc**).

Composition and structure of derivatives **III–VI** were confirmed by elemental analysis, IR, ^1H NMR spectroscopy, and chromatography-mass spectrometry data (Tables 1, 2). The formation of 5-chloro-1,3-oxazole-4-carboxamides **IIIa** and **IIIb** was indicated by the disappearance of the absorption band of nitrile group at 2232–2241 cm^{-1} in the IR spectra [13] and by the appearance of the absorption bands at 1688–1691 and 3129–3475 cm^{-1} belonging to C=O and N–H groups, respectively. The ^1H NMR spectra of the

Table 1. Yields, melting points, and elemental analysis data of compounds **III–VI**

Comp. no.	Yield, %	mp, °C	Found, %				Formula	Calculated, %			
			C	H	N	Cl(S)		C	H	N	Cl(S)
IIIa	60	187–188 (MeCN) 183 [15]	54.10	3.28	12.30	15.99	$C_{10}H_7ClN_2O_2$	53.95	3.17	12.58	15.92
IIIb	64	181–182 (MeCN)	56.75	3.71	11.65	15.09	$C_{11}H_9ClN_2O_2$	55.83	3.83	11.84	14.98
IVa	75	175–176 (EtOH)	66.55	6.57	15.28	–	$C_{15}H_{17}N_3O_2$	66.40	6.32	15.49	–
IVb	79	174–175 (EtOH)	67.53	6.93	14.57	–	$C_{16}H_{19}N_3O_2$	67.35	6.71	14.73	–
IVc	79	156–157 (EtOH)	61.78	5.67	15.26	–	$C_{14}H_{15}N_3O_3$	61.53	5.53	15.38	–
IVd	80	169–170 (EtOH)	63.50	6.03	14.41	–	$C_{15}H_{17}N_3O_3$	62.71	5.96	14.62	–
Va	74	165–166 (EtOH)	65.94	4.71	8.87	(10.37)	$C_{17}H_{14}N_2O_2S$	65.79	4.55	9.03	(10.33)
Vb	85	172–174 (EtOH)	66.83	5.14	8.43	(9.81)	$C_{18}H_{16}N_2O_2S$	66.65	4.97	8.64	(9.88)
Vc	85	202–203 (EtOH)	59.43	4.00	7.96	10.19 (9.35)	$C_{17}H_{13}ClN_2O_2S$	59.22	3.80	8.12	10.28 (9.30)
VIa	70	210–211 (MeCN)	68.65	4.43	9.72	–	$C_{16}H_{12}N_2O_3$	68.57	4.32	9.99	–
VIb	72	211–212 (MeCN)	69.57	4.81	9.31	–	$C_{17}H_{14}N_2O_3$	69.38	4.79	9.52	–
VIc	68	211–212 (MeCN)	69.55	4.98	9.33	–	$C_{17}H_{14}N_2O_3$	69.38	4.79	9.52	–
VId	72	216–218 (MeCN)	70.28	5.57	8.89	–	$C_{18}H_{16}N_2O_3$	70.12	5.23	9.09	–

Table 2. Spectral data of compounds **III**–**VI**

Comp. no.	IR spectrum, ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm	Mass spectrum, *m*/*z*
IIIa	1405, 1605; 1691 (C=O); 3129, 3456 (NH_2)	7.59 m, 8.00 m ($5H_{Ar}$), 7.72 s, 7.77 s (2H, NH_2)	223 $[M + 1]^+$
IIIb	1408, 1498, 1600; 1688 (C=O); 3146, 3467 (NH_2)	2.38 s (3H, CH_3), 7.37 d and 7.85 d ($4H_{Ar}$, *J* 8.0 Hz), 7.70 br.s (2H, NH_2)	237 $[M + 1]^+$
IVa	1275, 1448, 1578; 1661 (C=O); 2859, 2942; 3149, 3460 (NH_2)	1.62 br.s (6H, CH_2, piperidine), 3.70 br.s (4H, CH_2, piperidine), 6.98 s, 7.12 s (2H, NH_2), 7.49 m and 7.88 m ($5H_{Ar}$)	272 $[M + 1]^+$
IVb	1267, 1450, 1577; 1661 (C=O); 2856, 2940; 3144, 3465 (NH_2)	1.60 br.s (6H, CH_2, piperidine), 2.36 s (3H, CH_3), 3.65 br.s (4H, CH_2, piperidine), 6.98 s and 7.13 s (2H, NH_2), 7.32 d and 7.76 d ($4H_{Ar}$, *J* 7.6 Hz)	286 $[M + 1]^+$
IVc	1257, 1445, 1580; 1692 (C=O); 2864, 2953; 3150, 3467 (NH_2)	3.73 br.s (8H, $4CH_2$, morpholine), 7.09 s and 7.20 s (2H, NH_2), 7.50 m and 7.90 m ($5H_{Ar}$)	274 $[M + 1]^+$
IVd	1257, 1448, 1579; 1646 (C=O); 2840, 2966; 3165, 3432 (NH_2)	2.35 s (3H, CH_3), 3.70 br.s (8H, $4CH_2$, morpholine), 7.08 s and 7.20 s (2H, NH_2), 7.32 d and 7.79 d ($4H_{Ar}$, *J* 7.6 Hz)	288 $[M + 1]^+$
Va	1384, 1488, 1609; 1684 (C=O); 3108, 3462 (NH_2)	2.33 s (3H, CH_3), 7.27 d and 7.46 d ($4H_{Ar}$, *J* 8 Hz), 7.49 m and 7.88 m ($5H_{Ar}$), 7.65 s, 7.71 s (2H, NH_2)	311 $[M + 1]^+$
Vb	1382, 1495, 1612; 1686 (C=O); 3118, 3463 (NH_2)	2.31 s (3H, CH_3), 2.34 s (3H, CH_3), 7.25 d and 7.44 d ($4H_{Ar}$, *J* 8 Hz), 7.33 d and 7.73 d ($4H_{Ar}$, *J* 8 Hz), 7.64 s and 7.67 s (2H, NH_2)	325 $[M + 1]^+$
Vc	1386, 1475; 1686 (C=O); 3142, 3446 (NH_2)	2.36 s (3H, CH_3), 7.35–7.80 m (10H, $8H_{Ar}$, NH_2)	346 $[M + 1]^+$
VIa	1231, 1490, 1644; 1691 (C=O); 3139, 3466 (NH_2)	7.24–7.94 m (12H, $10H_{Ar}$, NH_2)	281 $[M + 1]^+$
VIb	1441, 1629; 1715 (C=O); 3254, 3465 (NH_2)	2.37 s (3H, CH_3), 7.22–7.75 m (11H, $9H_{Ar}$, NH_2)	295 $[M + 1]^+$
VIc	1218, 1439, 1627; 1718 (C=O); 3184, 3444 (NH_2)	2.33 s (3H, CH_3), 7.10 d, 7.23 d ($4H_{Ar}$, *J* 8 Hz), 7.53 m and 7.85 m ($5H_{Ar}$), 7.76 br.s (2H, NH_2)	295 $[M + 1]^+$
VId	1218, 1442, 1630; 1712 (C=O); 3247, 3475 (NH_2)	2.33 s (3H, CH_3), 2.37 s (3H, CH_3), 7.08 d and 7.23 d ($4H_{Ar}$, *J* 8 Hz), 7.33 d and 7.74 d ($4H_{Ar}$, *J* 8 Hz), 7.68 br.s (2H, NH_2)	309 $[M + 1]^+$

obtained compounds contained two signals (**IIIa**, **IVa**–**IVd**, **Va**, **Vb**) or one broadened signal (**IIIb**, **VIc**, **VId**) of the NH_2 protons at 6.64–7.77 ppm. In the spectra of **Vc**, **VIa**, **VIb** these signals overlapped with the signals of aromatic protons. Mass spectra of compounds **III**–**VI** contained the peaks of molecular ions $[M + 1]^+$.

In summary, a new method for the synthesis of 2-aryl-5-chloro-1,3-oxazole-4-carboxamides based on chlorination of the available 2-aryl-5-benzylsulfanyl-1,3-oxazole-4-carbonitriles was developed. It was found that the chlorine atom in the resulting product is labile, which was used for preparation of new 5-amino-, 5-aryloxy- and 5-arylsulfanyl derived 1,3-oxazole-4-carboxamides.

EXPERIMENTAL

IR spectra were recorded on a Vertex 70 spectrometer from KBr pellets. The ^1H NMR spectra were taken on a Bruker AVANCE DRX-500 spectrometer (500 MHz), internal reference TMS. GC-MS spectra were registered on a HPLC Agilent 1100 Series liquid chromatography-mass spectrometry system equipped with a diode array with a mass selective detector

Agilent LC\MSD SL [Zorbax SB-C18 column, 1.18 μm 4.6Ч15 mm (PN 821975-932); eluent acetonitrile–water (95 : 5), 0.1% aqueous trifluoroacetic acid; eluent flow 3 mL min^{-1}; injection volume 1 μL; UV detecting at 215, 254, 285 nm; chemical ionization at atmospheric pressure (APCI), scan range of *m*/*z* 80–1000]. Melting points were measured on a Fisher-Johns instrument. The reaction progress and individuality of the obtained compounds were monitored by TLC on Silufol UV-254 plates, eluting with a chloroform–methanol mixture (9 : 1) and detecting with UV irradiation. Elemental analysis was performed in the Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine.

2-Aryl-5-chloro-1,3-oxazole-4-carboxamides (IIIa, IIIb). Gaseous Cl_2 was bubbled through a solution of 0.01 mol of compound **IIa** or **IIb** in 50 mL of 95% acetic acid at 50–60°C with stirring for 0.5 h. Then the reaction mixture was maintained at 20–25°C for 12 h and treated with water. The formed precipitate was filtered off, dried, and purified by recrystallization.

2-Aryl-5-piperidino(morpholino)-1,3-oxazole-4-carboxamides (IVa–IVd). To a solution of 0.01 mol of compound **IIIa** or **IIIb** in 25 mL of anhydrous dioxane were added 0.01 mol of triethylamine and 0.01 mol of piperidine or morpholine. The mixture was refluxed for 2 h and maintained at 20–25°C for 12 h. Then the solvent was removed in a vacuum. The residue was treated with water, filtered off, dried, and recrystallized.

2-Aryl-5-arylsulfanyl-1,3-oxazole-4-carboxamides (Va–Vc). To a solution of 0.01 mol of compound **IIIa** or **IIIb** in 25 mL of anhydrous dioxane was added 0.01 mol of triethylamine and 0.01 mole of the corresponding thiophenol. The mixture was refluxed for 6 h, then cooled to 20–25°C, and evaporated. The residue was treated with water, filtered off, dried, and recrystallized.

2-Aryl-5-aryloxy-1,3-oxazole-4-carboxamides (VIa–VId). A mixture of 0.01 mol of compound **IIIa** or **IIIb** and 0.01 mol of the corresponding sodium phenolate in 25 mL of anhydrous dioxane was refluxed for 6 h, and then cooled to 20–25°C. The solvent was removed in a vacuum. The residue was treated with water, filtered off, dried, and recrystallized.

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