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Synthesis of 2-Aryl-4-cyano-1,3-oxazole-5-sulfonyl Chlorides and *N*-Substituted Sulfonamides

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Abstract–Oxidative chlorination of 2-aryl-5-benzylsulfanyl-1,3-oxazole-4-carbonitrile results in the previously unknown 4-cyano-1,3-oxazole-5-sulfonyl chlorides and *N*-substituted sulfonamides.

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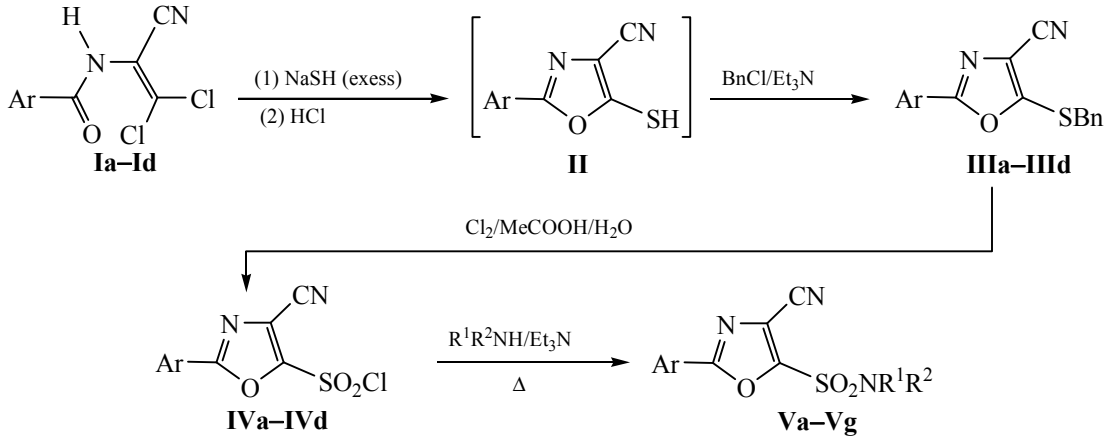
The 1,3-oxazole fragment is a component of many natural and synthetic products with various biological activity [1–7]. Therefore, the functionalization of oxazole ring is one of the main synthetic approaches to the new compounds in order to study their biological effects. In this work we attempt to synthesize the new 1,3-oxazole-5-sulfonyl chloride and *N*-substituted sulfonamides functionalized with the nitrile group in the 4 position. There are no published data on the synthesis of such compounds.

The available 2-acylamino-3,3-dichloroacrylonitriles **I** [8] were chosen as the starting materials. By the action of an excess of sodium hydrogen sulfide they underwent cyclization into the substituted 5-mercaptooxazoles [9]. The latter were immediately converted into the alkylation products **III** without isolation in the individual state (Scheme 1).

Compounds **IIIa**–**IIId** are stable colorless crystalline substances. Their oxidative chlorination proceeds in aqueous acetic acid at 0°C to give 2-aryl-4-cyano-1,3-oxazole-5-sulfonyl chlorides **IVa**–**IVd** (55–75%) along with 2-aryl-4-cyano-5-chloro-1,3-oxazoles (~15–20%). This is confirmed by the elemental analysis, ^{1}H NMR spectra, and GC-MS data.

The crystallization of this mixture (after short-time heating in hexane or cyclohexane) leads to the partial

Scheme 1.



Ia–Id **II** **IIIa–IIId** **IVa–IVd** **Va–Vg**

Ar = Ph (**Ia, IIIa–Va, Vd**), 4-MeC_6H_4 (**Ib, IIIb–Vb, Ve**), 4-ClC_6H_4 (**Ic, IIIc–Vc, Vf**), 4-MeOC_6H_4 (**Id, IIId**), 4-MeO-3,5-$Cl_2C_6H_2$ (**IVd, Vg**), R^1R^2N = $(CH_2)_5N$ (**Va–Vc**), $O(CH_2)_4N$ (**Vd–Vg**).

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

Comp. no.	Yield, %	mp, °C (solvent for recrystallization)	Found, %			Formula	Calculated, %		
			Cl	N	S		Cl	N	S
IIIa	74[a]	108–110 (EtOH)	–	9.45	10.99	$C_{17}H_{12}N_2OS$	–	9.58	10.97
IIIb	78[a]	112–114 (EtOH)	–	9.10	10.50	$C_{18}H_{14}N_2OS$	–	9.14	10.47
IIIc	75[a]	118–120 (EtOH)	10.92	8.51	9.80	$C_{17}H_{11}ClN_2OS$	10.85	8.57	9.81
IIId	75[a]	105–107 (EtOH)	–	8.72	9.92	$C_{18}H_{14}N_2O_2S$	–	8.69	9.95
Va	70	126–128 (EtOH)	–	13.19	10.09	$C_{15}H_{15}N_3O_3S$	–	13.24	10.10
Vb	70	188–190 (EtOH)	–	12.74	9.69	$C_{16}H_{17}N_3O_3S$	–	12.68	9.68
Vc	70	173–175 (EtOH)	10.15	11.82	9.13	$C_{15}H_{14}ClN_3O_3S$	10.08	11.94	9.11
Vd	72	118–120 (EtOH)	–	12.25	10.10	$C_{14}H_{13}N_3O_4S$	–	13.16	10.04
Ve	75	200–202 (EtOH)	–	12.51	9.67	$C_{15}H_{15}N_3O_4S$	–	12.60	9.62
Vf	75	170–172 (EtOH)	10.09	11.80	9.09	$C_{14}H_{12}ClN_3O_4S$	10.02	11.88	9.06
Vg	70	178–180 (EtOH)	16.99	10.01	7.69	$C_{15}H_{13}Cl_2N_3O_5S$	16.95	10.05	7.67
VIa	68	103–105 (toluene)	–	6.44	14.82	$C_{25}H_{22}N_2OS_2$	–	6.51	14.89
VIb	65	115–117 (toluene)	7.92	6.16	14.23	$C_{24}H_{19}ClN_2OS_2$	7.86	6.21	14.22

[a] Yield by the method *a*.

elimination of SO_2 from products **IV** and to an increase (up to 60%) of the 5-chlorooxazole content. Therefore, sulfonyl chlorides **IV** were used without further purification. In the case of compound **IIId** 4-methoxyphenyl substituent also undergoes chlorination to form 4-cyano-2-(3,5-dichloro-4-methoxyphenyl)-1,3-oxazole-5-sulfonyl chloride **IVd**.

The reactions of sulfonyl chlorides **IVa**–**IVd** with piperidine and morpholine occur in a boiling anhydrous dioxane in the presence of triethylamine to give the sulfonamides **IVa**–**IVd** in yields of 65–75%.

The elemental analysis data of the synthesized compounds are given in Table 1. Their structure was confirmed by the IR, ^{1}H and ^{13}C NMR, and GC-MS spectra.

The IR spectra of oxazoles **III**, **V** contain the absorption bands at 2232–2251 cm^{-1} belonging to the cyano moiety. In the spectra of sulfonamides **V** there are also additional characteristic absorption bands at 1160–1165 and 1372–1374 cm^{-1} corresponding to the symmetric and asymmetric vibrations of the SO_2 group. The ^{1}H and ^{13}C NMR spectra of compounds **III**, **V** contain all the relevant signals (Table 2). In the GC-MS spectra of sulfonamides **Va**–**Vd** there are no molecular ion peaks, but there are peaks of the fragments $[M - SO_2]^+$, which is characteristic of such systems [10].

An alternative approach for obtaining 2-aryl-5-benzylsulfanyl-1,3-oxazole-4-carbonitriles **III** includes the substitution of the chlorine atoms in compounds **I** by the benzylthiol fragments followed by the reaction of compounds **VI** with silver carbonate, resulting in the cyclic product **III** (Scheme 2). Their structure is unambiguous, since this reaction is well studied [11, 12]. The spectral data of **III** obtained according to the Schemes 1 and 2 are identical. However, a disadvantage of this approach is a lower yield of the reaction products.

Since substituted 1,3-oxazole-5-sulfonyl amides possess diverse biological activity [13–16], it is advisable to search for bioactive agents among the synthesized 2-aryl-4-cyano-1,3-oxazole-5-sulfonamides **Va**–**Vd** that will be reported elswhere.

EXPERIMENTAL

The IR spectra were recorded on a Vertex 70 spectrometer from KBr pellets. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance DRX-500 instrument (500 and 125 MHz, respectively) relative to internal TMS. The GC-MS spectra were taken on an Agilent 1100 Series high-performance liquid chromatograph equipped with a diode array with an Agilent LC\MSD SL mass selective detector. The parameters of the GC-MS (APCI) analysis are as

Table 2. Spectral data of compounds **III**, **V**, **VI**

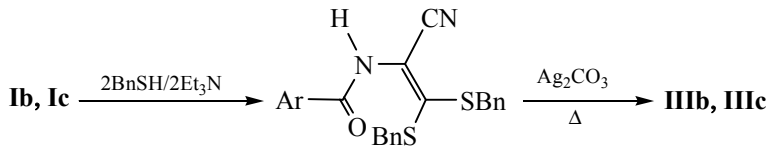
Comp. no.	IR spectrum (KBr), ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm	Mass spectrum, *m*/*z*
IIIa	2239 (C≡N)	4.41 s (2H, CH_2S), 7.33–7.96 m (10H, $2C_6H_5$)	293 $[M+1]^+$
IIIb[a]	2241 (C≡N)	2.44 s (3H, CH_3), 4.24 s (2H, CH_2S), 7.25 m (7H, C_6H_5, C_6H_2), 7.85 d (2H, C_6H_2, $^3J_{HH}$ 7.6 Hz)	307 $[M+1]^+$
IIIc	2232 (C≡N)	4.25 s (2H, CH_2S), 7.30 m (5H, C_6H_5), 7.49 d, 7.90 d (4H, C_6H_4, $^3J_{HH}$ 7.5 Hz)	327 $[M+1]^+$
IIId	2241 (C≡N)	3.86 s (3H, CH_3O), 4.38 s (2H, CH_2S), 7.14 d, 7.90 d (4H, C_6H_4, $^3J_{HH}$ 7.6 Hz), 7.31 m (5H, C_6H_5)	323 $[M+1]^+$
Va	1163, 1373 (SO_2), 2248 (C≡N)	1.76 m (6H, $3CH_{2\ piperid}$), 3.64 m (4H, $2CH_{2\ piperid}$), 7.44 m, 7.88 m (5H, C_6H_5)	253 $[M-SO_2]^+$
Vb[b]	1165, 1374 (SO_2), 2249 (C≡N)	1.64 m (6H, $3CH_{2\ piperid}$), 2.44 s (3H, CH_3), 3.66 m (4H, $2CH_{2\ piperid}$), 7.45 d, 7.96 d (4H, C_6H_4, $^3J_{HH}$ 7.5 Hz)	267 $[M-SO_2]^+$
Vc	1165, 1374 (SO_2), 2251 (C≡N)	1.63 m (6H, $3CH_{2\ piperid}$), 3.59 m (4H, $2CH_{2\ piperid}$), 7.72 d, 8.07 d (4H, C_6H_4, $^3J_{HH}$ 7.4 Hz)	287 $[M-SO_2]^+$
Vd	1164, 1373 (SO_2), 2248 (C≡N)	3.41 m (4H, $2CH_{2\ morpholin}$), 3.89 m (4H, $2CH_{2\ morpholin}$), 7.47 m, 7.89 m (5H, C_6H_5)	255 $[M-SO_2]^+$
Ve	1161, 1372 (SO_2), 2249 (C≡N)	2.43 s (3H, CH_3), 3.60 m (4H, $2CH_{2\ morpholin}$), 3.72 m (4H, $2CH_{2\ morpholin}$), 7.46 d, 7.97 d (4H, C_6H_4, $^3J_{HH}$ 7.8 Hz)	269 $[M-SO_2]^+$
Vf	1162, 1372 (SO_2), 2246 (C≡N)	3.62m (4H, $2CH_{2\ morpholin}$), 3.78 (4H, $2CH_{2\ morpholin}$), 7.50 d, 7.99 d (4H, C_6H_4, $^3J_{HH}$ 7.7 Hz)	289 $[M-SO_2]^+$
Vg	1160, 1373 (SO_2), 2245 (C≡N)	3.63 m (4H, $2CH_{2\ morpholin}$), 3.76 m (4H, $2CH_{2\ morpholin}$), 3.89 s (3H, CH_3O), 7.97 s (2H, C_6H_2)	354 $[M-SO_2]^+$
VIa	1657 (C=O), 2217 (C≡N), 3269 (N–H)	2.38 s (3H, CH_3), 4.16 s (2H, CH_2S), 4.21 s (2H, CH_2S), 7.30 m (7H, C_6H_5, C_6H_2), 7.80 d (2H, C_6H_2, $^3J_{HH}$ 8.0 Hz), 10.16 s (1H, NH)	431 $[M+1]^+$
VIb[c]	1658 (C=O), 2212 (C≡N), 3241 (N–H)	4.17 s (2H, CH_2S), 4.22 s (2H, CH_2S), 7.30 m (5H, C_6H_5), 7.62 d, 7.90 d (4H, C_6H_4, $^3J_{HH}$ 7.8 Hz), 10.35 s (1H, NH)	452 $[M+1]^+$

[a] ^{13}C NMR spectrum, δ_C, ppm: 21.64 (CH_3), 39.91 (SCH_2), 112.61 (C^4_{ox}), 118.94 (CN), 122.76 (C^5_{ox}), 127.01, 128.23, 129.09, 129.43, 130.40, 137.13, 142.99, 154.05, 164.15 (C^2_{ox}). [b] ^{13}C NMR spectrum, δ_C, ppm: 21.74 (CH_3), 22.91 ($C^4_{piperid}$), 25.21 ($C^{3,5}_{piperid}$), 46.60 ($C^{2,6}_{piperid}$), 111.35 (C^4_{ox}), 117.74 (CN), 122.15 (C^5_{ox}), 127.87, 130.57, 144.08, 151.33, 164.14 (C^2_{ox}). [c] ^{13}C NMR spectrum, δ_C, ppm: 21.55 (CH_3), 38.22 (SCH_2), 111.87 (NC<u>C</u>NH), 115.56 (CN), 128.32, 129.10, 129.40, 129.47, 129.61, 136.91, 137.22, 143.08, 149.49, 165.31 (CO).

follows: Zorbax SB-C18 column, 1.18 μm 4.6×15 mm (PN 821975-932); acetonitrile–water (95:5), 0.1% aqueous trifluoroacetic acid; eluent flow 3 ml min^{-1}, injection volume 1 μm, UV detectors 215, 254, 285 nm; scanning range *m*/*z* 80–1000. The melting points were measured on a Fisher-Johns instrument.

2-Aryl-5-benzylsulfanyl-4-cyano-1,3-oxazoles (IIIa–IIId). *a*. To a solution of 0.01 mol of the appropriate dichloroacrylonitrile **Ia–Id** in 50 ml of methanol was added 0.025 mol of sodium hydrogen sulfide. The mixture was stirred at 20–25°C for 24 h. Then methanol was removed in a vacuum. To the

Scheme 2.



VIa, VIb

Ar = 4-MeC_6H_4 (**VIa**), 4-ClC_6H_4 (**VIb**).

residue 30 ml of water was added. The solution was acidified with 5% hydrochloric acid to pH ~ 2. The precipitate was filtered off, dried, and dissolved in 30 ml of methanol. Then 0.01 mol of triethylamine and 0.011 mol of benzyl chloride were added. The mixture was boiled for 2–3 h and was left to stand at 20–25°C for 12 h. The solvent was removed in a vacuum. The residue was treated with water, and the precipitate was filtered off and recrystallized.

b. To a solution of 0.01 mol of compound **VIa** or **VIb** (obtained as described below) in 50 ml of anhydrous acetonitrile was added 0.025 mol of silver carbonate. The suspension was refluxed for 8 h and was left to stand at 20–25°C for 12 h. Then the precipitate was filtered off, and acetonitrile was removed in a vacuum. To the residue was added 50 ml of water, and the precipitate was filtered off. Compounds **IIIb**, **IIIc** were recrystallized from ethanol. Yield 50%. The mixed melting point for two samples of compounds **IIIb** and **IIIc** obtained by the *a* and *b* methods showed no depression. Their IR and ^{1}H NMR spectra were identical.

2-Aryl-4-cyano-1,3-oxazole-5-sulfonyl chloride (IVa–IVd). Through a solution of 0.01 mol of compound **III** in 30 ml of 95% acetic acid was bubbled Cl_2 under stirring for 0.5 h at 20°C. The mixture was kept for 12 h at 20–25°C and poured into ice. The precipitate was filtered off, washed with water, and dried in a vacuum desiccator over phosphorus(V) oxide. Compounds **IVa–IVd** were used without additional purification for further reactions.

2-Aryl-5-(piperidine-1-sulfonyl)-1,3-oxazole-4-carbonitrile (Va–Vc). To a solution of 0.001 mol of compounds **IVa–IVc** was added 0.0008 mol of piperidine and 0.0008 mol of Et_3N. The mixture was heated for 2 h and kept at 20–25°C for 12 h. The precipitate was filtered off, the solvent was removed in a vacuum. The residue was treated with water, filtered off, dried and, recrystallized.

2-Aryl-5-(morpholine-1-sulfonyl)-1,3-oxazole-4-carbonitriles (Vd–Vg) were prepared similarly starting from sulfonyl chlorides **IVa–IVd** and morpholine.

2-Acylamino-3,3-di(benzylsulfanyl)acrylonitriles (VIa, VIb). To a solution of 0.01 mol of dichloroacrylonitrile **Ib** or **Ic** in 30 ml of acetonitrile were added 0.02 mol of benzyl mercaptan and 0.02 mol of Et_3N. The mixture was kept for 12 h at 20–25°C. Then the precipitate was filtered off, and the solvent was removed in a vacuum. The residue was treated with water, dried, and recrystallized.

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