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Interaction of 2-Aryl-4-cyano-1,3-oxazole-5-sulfonyl Chlorides with Amidines

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Abstract—Reaction of 4-cyano-1,3-oxazole-5-sulfonyl chlorides with amidines results in new 7-amino-1,3-oxazolo[5,4-*d*]pyrimidines. Their structure was confirmed by spectral methods and X-ray diffraction analysis.

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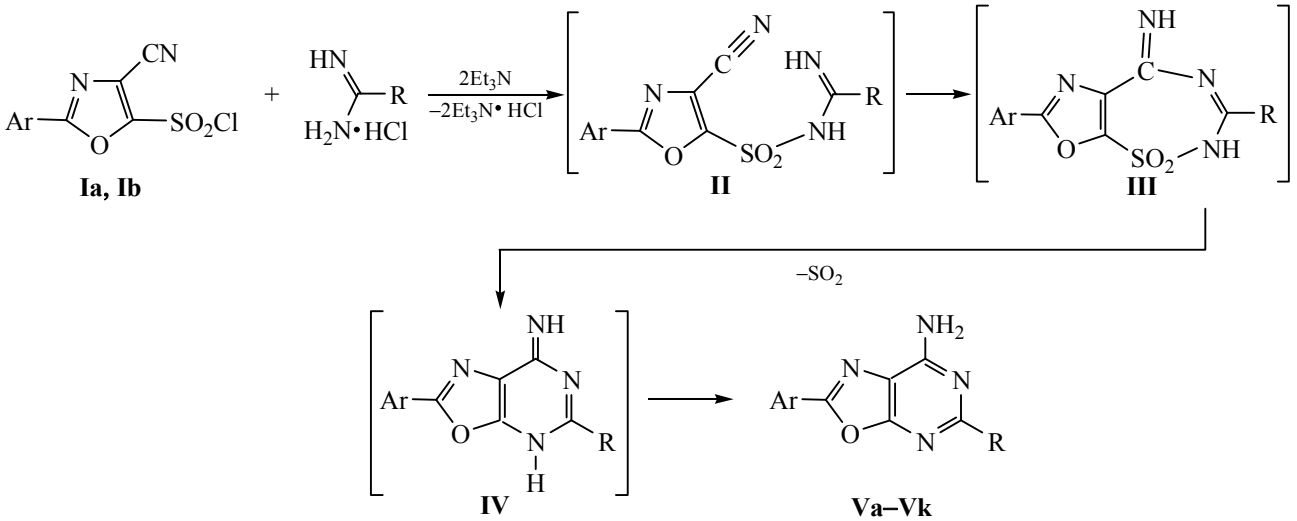
Recently, we have synthesized 4-cyano-1,3-oxazole-5-sulfonyl chlorides **I** [1], which react with piperidine or morpholine in dioxane in the presence of triethylamine at reflux to afford the corresponding sulfonamides. In this work it is shown that amidines interact originally with compounds **I** to form 7-amino-1,3-oxazolo[5,4-*d*] pyrimidines **V** in 44-60% yields (Table 1).

Synthesis of products **Va**–**Vk** includes several steps: the initial formation of intermediates **II**, the intramolecular cyclization **II** → **III**, the transformation of the seven-membered ring to the six-membered ring due to the elimination of sulfur dioxide **III** → **IV,** and the subsequent tautomerization **IV** → **V**. Also it is not improbable that sulfonamides **II** react with another molecule of amidine at the C^5 atom of the ring or the cyano group followed by the closure of the pyrimidine ring by the nucleophilic substitution of the sulfonylamide fragment. However, the fact that 4-cyano-1,3-oxazoles containing sulfamide [1] or arylsulfonyl [2] groups at the atom C^5 do not react with amidines is an indirect confirmation of the proposed scheme involveing an intermediate formation of the seven-membered structure **III**. It is noteworthy that desulfurization of the products proceeds under mild conditions (at 20°C).



R = Ph (**Va, Vh**), 4-MeC_6H_4 (**Vb**), 4-EtC_6H_4 (**Vc, Vi**), 4-$MeOC_6H_4$ (**Vd, Vj**), 4-FC_6H_4 (**Ve, Vk**), 4-MeC_6H_4S (**Vf**), Me (**Vg**); Ar = Ph (**Ia, Va–Vg**), 4-MeC_6H_4 (**Ib, Vh–Vk**).

Table 1. Yields, melting points and data of elemental analyses for compounds **V**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
Va	54	251–252	70.95	4.25	19.40	$C_{17}H_{12}N_4O$	70.82	4.20	19.43
Vb	56	262–264	71.48	4.67	18.59	$C_{18}H_{14}N_4O$	71.51	4.67	18.53
Vc	60	225–226	72.10	5.02	17.82	$C_{19}H_{16}N_4O$	72.14	5.10	17.71
Vd	60	244–245	67.89	4.42	17.68	$C_{18}H_{14}N_4O_2$	67.92	4.43	17.60
Ve	50	266–267	66.72	3.67	18.18	$C_{17}H_{11}FN_4O$	66.66	3.62	18.29
Vf	50	254–255	64.67	4.24	16.70	$C_{18}H_{14}N_4OS$[a]	64.65	4.22	16.75
Vg	44	227–229	63.75	4.48	24.77	$C_{12}H_{10}N_4O$	63.71	4.46	24.76
Vh	50	303–304	71.50	4.68	18.67	$C_{18}H_{14}N_4O$	71.51	4.67	18.53
Vi	52	266–267	72.74	5.53	16.89	$C_{20}H_{18}N_4O$	72.71	5.49	16.96
Vj	52	301–303	68.62	4.80	16.91	$C_{19}H_{16}N_4O_2$	68.66	4.85	16.86
Vk	50	299–301	67.40	4.01	17.87	$C_{18}H_{13}FN_4O$	67.49	4.09	17.79

[a] Found, %: S 9.68. Calculated, %: S 9.59.

The target products were isolated in satisfactory yields. This direction of the reaction is apparently due to the formation of a thermodynamically stable pyrimidine ring. It should also be noted that this contraction of the heterocyclic fragment due to sulfur dioxide liberation is well known [3, 4]. However, such transformations are carried out under rigid conditions.

The IR spectra of compounds **Va**–**Vk** (Table 2) contain the absorption bands of the stretching vibrations of NH_2-groups at 3314–3378 and 3208–3220 cm^{-1} and the signals of 7-aminooxazolo-[5,4-*d*]-pyrimidines moiety [5]. In the ^1H NMR spectra along with the signals of the protons of aromatic rings and substituents there is a broad singlet of NH_2-group at 7.66–7.87 ppm.

To establish unambiguously the structure of compounds **V** and to consider their spatial structure we carried out XRD analysis of compound **Ve** (see figure).

Values of the bond lengths and bond angles of the central bicyclic moiety are within the expected range and are consistent with the structural formula of the compound. Thus, the bonds themselves are delocalized and have values typical of delocalized structures previously studied, for example, for the related compound containing a similar moiety [6]. The central bicycle is flat, the atoms are out-of-plane only by 0.0044 Å. Phenyl rings C^6–C^{11} and C^{12}–C^{17} are turned relative to the bicycle by 8.95(8) and 4.99(6)°, respectively. The bond length C^4–N^3 is strongly reduced compared to the value characteristic of the single C–N bonds [1.338(2) Å]. The sum of bond angles at the nitrogen atom of the amino group is 360(2)°, indicating the coupling of the lone electron pair of the nitrogen atom N^3 with the π-system of heterocycle. In the crystal the formation is observed of weak intermolecular hydrogen bonds N^3–$H^2\cdots N^{4\#1}$ and N^3–$H^1\cdots N^{2\#2}$ with the following parameters: N^3–H^2 0.93(2), $N^3\cdots N^{4\#1}$ 3.148(3), N^3–$H^2\cdots N^{4\#1}$ 152.3(17)° и N^3–H^1 0.88(2), $N^3\cdot\cdot N^{2\#2}$ 3.059(2), N^3–$H^1\cdots N^{2\#2}$ 144.7(19)°, respectively, (symbols #1 and #2 denote the atoms that are connected with the basic operations of symmetry *–x + 1, y, –z + 0.5* и *x, –y, z* – 0.5, respectively).

As compounds **V** are structural analogs of purine bases and among them substances with diverse biological activities were found [7–12], the developed approach to the synthesis of 7-amino-1,3-oxazolo[5,4-*d*]pyrimidines, which well supplements the well-known methods for their preparation [5, 9, 13, 14], deserves further studying, as will be discussed in subsequent reports.

EXPERIMENTAL

The IR spectra were recorded on a Vertex 70 instrument from KBr pellets. The ^1H and ^{13}C NMR spectra were obtained on a Bruker Avance DRX-500

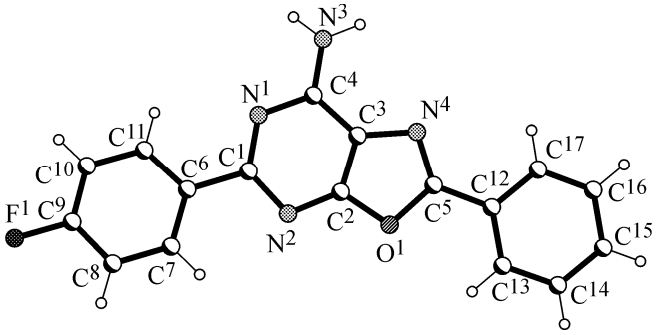
Table 2. Spectral data of compounds **V**

Comp. no.	IR spectrum (KBr), ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm	Mass-spectrum, *m*/*z*
Va	3322, 3210 (NH_2); 1637, 1592, 1392, 1316, 1275, 1130, 1048	7.50–8.37 m (10H, $2C_6H_5$), 7.83 br.s (2H, NH_2)	289 $[M + 1]^+$
Vb	3326, 3212 (NH_2); 1635, 1590, 1393, 1313, 1278, 1129, 1048	2.37 s (3H, CH_3), 7.29 d, 8.26 d (4H, C_6H_4, *J* 8.0 Hz), 7.61 m, 8.15 m (5H, C_6H_5), 7.78 br.s (2H, NH_2)	303 $[M + 1]^+$
Vc[a]	3324, 3211 (NH_2); 1637, 1588, 1395, 1312, 1276, 1130, 1048	1.23 t (3H, CH_3, *J* 7.5 Hz), 2.68 q (2H, CH_2, *J* 7.5, *J* 1.5 Hz), 7.33 d, 8.28 d (4H, C_6H_4, *J* 8.5 Hz), 7.63 m, 8.16 m (5H, C_6H_5), 7.79 br.s (2H, NH_2)	317 $[M + 1]^+$
Vd[b]	3326, 3213 (NH_2); 1634, 1607, 1395, 1304, 1253, 1131, 1048	3.84 s (3H, OCH_3), 7.04 d, 8.32 d (4H, C_6H_4, *J* 8.5 Hz), 7.63 m, 8.15 m (5H, C_6H_5), 7.75 br.s (2H, NH_2)	319 $[M + 1]^+$
Ve[c]	3326, 3213 (NH_2); 1637, 1593, 1395, 1303, 1277, 1131, 1048	7.32 m, 8.40 m (4H, C_6H_4), 7.63 m, 8.15 m (5H, C_6H_5), 7.85 br.s (2H, NH_2)	307 $[M + 1]^+$
Vf[d]	3378, 3211 (NH_2); 1626, 1599, 1346, 1307, 1276, 1133, 1045	2.38 s (3H, CH_3), 7.29 d, 7.50 d (4H, C_6H_4, *J* 8.5 Hz), 7.57 m, 8.05 m (5H, C_6H_5), 7.87 br.s (2H, NH_2)	335 $[M + 1]^+$
Vg	3314, 3220 (NH_2); 1665, 1599, 1404, 1297, 1274, 1136, 1045	2.44 s (3H, CH_3), 7.61 m, 8.10 m (5H, C_6H_5), 7.66 br.s (2H, NH_2)	227 $[M + 1]^+$
Vh	3320, 3209 (NH_2); 1638, 1593, 1391, 1316, 1273, 1129, 1048	2.43 s (3H, CH_3), 7.44 d, 8.06 d (4H, C_6H_4, *J* 8.5 Hz), 7.50 m, 8.37 m (5H, C_6H_5), 7.81 br.s (2H, NH_2)	303 $[M + 1]^+$
Vi	3322, 3208 (NH_2); 1635, 1596, 1395, 1311, 1275, 1135, 1051	1.20 t (3H, CH_3, *J* 7.5 Hz), 2.39 s (3H, CH_3), 2.66 q (2H, CH_2, *J* 7.5, *J* 1.5 Hz), 7.32–8.30 m (8H, $2C_6H_4$), 7.76 br.s (2H, NH_2)	331 $[M + 1]^+$
Vj	3323, 3209 (NH_2); 1635, 1608, 1396, 1306, 1256, 1134, 1050	2.42 s (3H, CH_3), 3.84 s (3H, OCH_3), 7.04–8.31 m (8H, $2C_6H_4$), 7.71 br.s (2H, NH_2)	333 $[M + 1]^+$
Vk	3326, 3212 (NH_2); 1637, 1594, 1395, 1304, 1235, 1131, 1050	2.42 s (3H, CH_3), 7.34–8.39 m (8H, $2C_6H_4$), 7.82 br.s (2H, NH_2)	321 $[M + 1]^+$

[a] ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 15.78, 28.53, 115.03, 126.87, 127.24, 128.26, 128.38, 129.84, 132.14, 135.49, 146.73, 156.70, 158.49, 160.19, 165.78. [b] ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 55.77, 114.22, 114.69, 126.90, 127.19, 129.82, 129.94, 130.42, 132.08, 156.65, 158.26, 160.03, 161.67, 165.81. [c] ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 115.14, 115.69, 115.86, 126.80, 127.26, 129.84, 130.53, 130.60, 132.20, 134.38, 134.40, 156.72, 158.64, 159.12, 163.15, 165.12, 165.71. [d] ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.36, 114.00, 126.57, 126.69, 127.10, 129.76, 130.32, 132.03, 135.64, 139.36, 156.46, 157.51, 165.10, 166.82.

spectrometer (500 and 125 MHz, respectively), internal reference TMS. GC-MS spectra were recorded using a high-performance liquid chromatograph-mass spectrometer Agilent 1100 Series equipped with a diode array with a mass selective detector Agilent LC\MSD SL. Parameters of GC-MS analysis: column Zorbax SB-C18 1.18 μm 4.6×15 mm (PN 821975-932); solvent 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 *m*/*z* 80–1000. Melting points were measured on a Fisher-Johns instrument.

Single crystal X-ray diffraction analysis of compound Ve was performed at room temperature on a Bruker Smart Apex II diffractometer (λMoK_α- radiation, graphite monochromator, θ_{max} 28.1°, crystal size 0.14×0.25×0.30 mm, spherical segment $-25 \le h \le 41$, $-9 \le k \le 8$, $-16 \le l \le 17$). 11022 reflections were collected, 3379 of which were independent (*R*-factor is 0.0403). The crystals of compound **Ve** are monoclinic, $C_{17}H_{11}FN_4O$, *M* 306.3, space group *C*2/*c*, *a* 31.366(3), *b* 7.2159(5), *c* 10.9413(3) Å, β 103.406(7)°, *V* 2830.6(4) $Å^3$, Z 8, d_{calc} 1.437, μ 0.103 mm^{-1}, *F*(000) 1264. The structure was solved by the direct method and refined by the least squares method using



General view of the molecule of compound **Ve**. Main bond lengths and angles: C^1N^1 1.330(2), C^1N^2 1.354(2), C^2N^2 1.324(2), C^2C^3 1.374(3), C^3C^4 1.397(2), C^4N^1 1.357(2), C^4N^3 1.338(2), C^3N^4 1.390(2), C^5N^4 1.304(2), C^2O^1 1.373(2), C^5O^1 1.386(2) Å; $C^1N^1C^4$ 119.79(16), $N^1C^1N^2$ 127.19(17), $C^2N^2C^1$ 110.31(15), $N^2C^2C^3$ 129.29(17), $C^2C^3C^4$ 115.59(18), $N^1C^4C^3$ 117.82(17), $O^1C^2C^3$ 107.18(16), $C^2C^3N^4$ 110.50(16), $C^5N^4C^3$ 103.49(15), $N^4C^5O^1$ 114.74(16), $C^2O^1C^5$ 104.09(14), $N^2C^2O^1$ 123.53(16), $N^4C^3C^4$ 133.89(18)°.

SHELXTL program [15]. For refining 1895 reflections with $I > 2\sigma(I)$ were used {216 refined parameters, 8.8 reflections per one parameter, the weight scheme $\omega = 1/[\sigma^2(Fo^2) + (0.0517P)^2 + 0.9395P]$ was used, where $P = (Fo^2 + 2Fc^2)/3$, the ratio of the maximal (average) shift to the error in the last cycle was 0.001(0.000)}. The extinction was corrected by multiscanning method using SADABS program (T_{min}/T_{max} = 0.9857/0.9697). All non-hydrogen atoms were anisotropically refined. All CH-hydrogen atoms in the molecule were geometrically placed (*riders*). Their positions and thermal parameters were refined together with positions and thermal parameters of the carbon atoms. The hydrogen atoms at the nitrogen atoms were identified in the difference Fourier syntheses and refined isotropically. Final values of divergence factors are $R_1(F)$ 0.0503, $wR_2(F^2)$ 0.1086 for reflections with $I > 2\sigma(I)$ and $R_1(F)$ 0.1076, $wR_2(F^2)$ 0.1326, *GOF* 1.032 for all reflections. Residual electron density from the difference Fourier series after the last cycle of refinement is 0.27 and –0.21 *e* Å^{-3}.

A complete set of X-ray diffraction data for compound **Ve** was deposited in the Cambridge Structural Database (CCDC 882263).

2-Aryl-5-methyl(aryl, arylthio)-7-amino-1,3-oxazolo[5,4-*d*]pyrimidines (Va–Vk). A mixture of 0.01 mol of a 4-cyano-1,3-oxazole-5-sulfonyl chloride **I** [1], 0.01 mol of the appropriate amidine hydrochloride, and 0.02 mol of triethylamine in 50 ml of anhydrous tetrahydrofuran was stirred at 20–25°C for 48 h. The precipitate was filtered off, the solvent was removed in a vacuum. The residue was treated with water, filtered off, dried, and purified by recrystallization from acetonitrile.

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