Competitive formation of 4-aminoisoxazoles and 5-aminooxazoles in the cyclization reactions of *O*-alkylated hydroxyimino nitriles

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Base-catalyzed cyclization of *O*-alkylated α-hydroxyimino nitriles gave mixtures of 4-aminoisoxazoles and 5-aminooxazoles, their ratio depending on the substituent structures and the reaction conditions. The formation mechanism of 5-aminooxazoles in this reaction is discussed.

Key words: 4-aminoisoxazoles, 5-aminooxazoles, X-ray diffraction analysis.

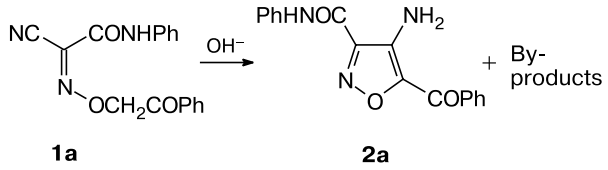
4-Aminoisoxazoles (AIA) with functional (oxo, ester, and carbamoyl) substituents in positions 3 and/or 5 of the ring are precursors for a number of fused heterocyclic systems (isoxazolopyrimidines, isoxazolopyridines, isoxazolodiazepines, *etc.*), which are of considerable interest as biologically active compounds.[1—6]

Earlier, such AIA have been synthesized in two ways. The first, six-step way involves intramolecular cyclization of *O*-acylated oximes of nitromethyl ketones into 4-nitroisoxazoles[7,8] followed by hydrogenation of the latter to AIA.[7,9] According to the second way, AIA are directly obtained by cyclization of *O*-alkylated hydroxyimino nitriles.[10] However, cyclization under the conditions cited in Ref. 10 (action of a 20—50-fold excess of LiOH on *O*-alkylated hydroxyimino nitriles) gave mixtures of the target AIA with unidentified compounds and chromatographic separation was often needed. Although we have recently demonstrated[11] that the use of lithium perchlorate allows one to minimize side processes and obtain the target AIA in the pure state, identification of by-products would elucidate the character of occurring reactions and facilitate a search for the most favorable conditions for the formation of AIA.

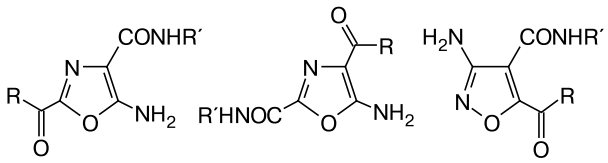
Using column chromatography, we isolated a by-product of the cyclization of oxime **1a** (Scheme 1) but failed to identify its structure by ^{1}H and ^{13}C NMR and IR spectroscopy and mass spectrometry.

It turned out that this compound is structurally isomeric to aminoisoxazole **2a**, has the same molecular formula, produces a molecular ion with the same *m*/*z* ratio, and contains identical functional groups. However, our spectroscopic data were insufficient for making an unambiguous choice between the structures of 5-aminooxazoles **3** and **4** or 3-aminoisoxazoles **5**. When comparing the ^{13}C NMR spectra recorded by us with the published ^{13}C NMR spectra of various isomeric aminooxazoles (3, 4, or 5)[12—17] and 3-aminoisoxazoles,[18,19] as well as with the ^{13}C NMR spectra predicted for these structures by the ACD Labs CNMR and ChemDraw Ultra 9.0 calculations, we found that 5-aminooxazole structures **3** or **4** are preferred to 3-aminoisoxazoles **5**. However, no obvious mechanism of formation for any of compounds **3**—**5** was available; nor was the experimental ^{13}C NMR spectrum in full agreement with the expected one.

Scheme 1



1a **2a**



3 **4** **5**

The structure of the by-product was determined by X-ray diffraction analysis and formulated as previously unknown 5-amino-2-benzoyloxazole-4-carboxanilide (**3a**) (R = R′ = Ph).

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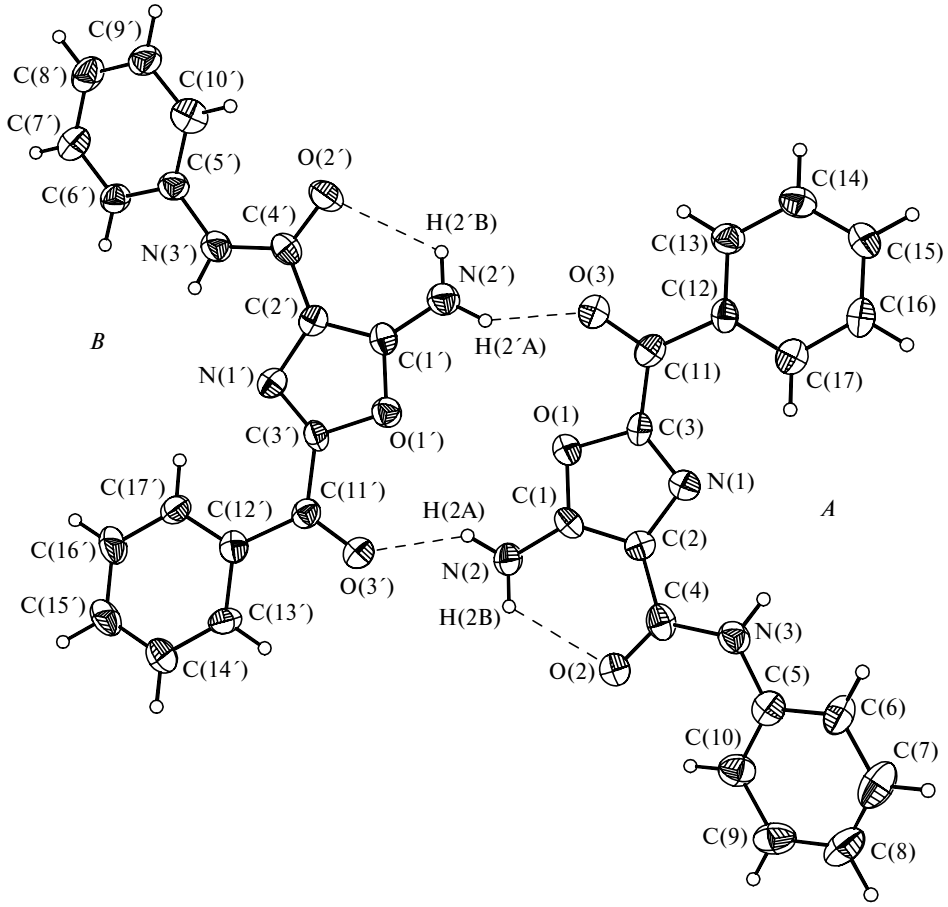


Fig. 1. General view of the molecular structure of the hydrogen-bonded dimer of compound **3a**.

Compound **3a** crystallizes in the noncentrosymmetrical space group $Pca2_1$. In the crystal, two independent molecules of anilide **3a** are united into a noncentrosymmetrical hydrogen-bonded dimer. Its general view is

Table 1. Selected bond lengths (*d*) and angles (ω) in two independent molecules of compound **3a**

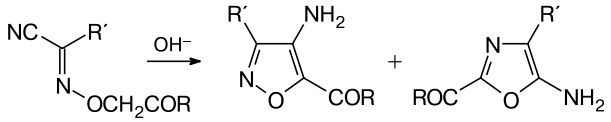
Bond	*d*/Å		Angle	ω/deg	
	A	*B*		*A*	*B*
O(1)—C(1)	1.354(4)	1.364(4)	C(1)—O(1)—C(3)	104.5(3)	104.6(3)
O(1)—C(3)	1.397(4)	1.399(4)	C(3)—N(1)—C(2)	105.3(3)	105.6(3)
O(2)—C(4)	1.238(3)	1.232(4)	C(4)—N(3)—C(5)	127.9(3)	128.9(3)
O(3)—C(11)	1.243(4)	1.227(4)	N(2)—C(1)—O(1)	119.4(3)	119.7(3)
N(1)—C(3)	1.312(4)	1.298(4)	N(2)—C(1)—C(2)	132.1(4)	132.2(4)
N(1)—C(2)	1.379(4)	1.396(4)	O(1)—C(1)—C(2)	108.5(3)	108.2(3)
N(2)—C(1)	1.340(4)	1.334(4)	C(1)—C(2)—N(1)	109.2(3)	108.6(3)
N(3)—C(4)	1.366(4)	1.367(4)	C(1)—C(2)—C(4)	122.7(3)	126.2(3)
N(3)—C(5)	1.423(4)	1.426(4)	N(1)—C(2)—C(4)	127.9(3)	125.1(3)
C(1)—C(2)	1.369(4)	1.377(4)	N(1)—C(3)—O(1)	112.5(3)	113.0(3)
C(2)—C(4)	1.451(4)	1.444(4)	N(1)—C(3)—C(11)	133.1(3)	132.5(3)
C(3)—C(11)	1.452(5)	1.455(5)	O(1)—C(3)—C(11)	114.3(3)	114.4(3)
C(11)—C(12)	1.490(5)	1.502(5)	O(2)—C(4)—N(3)	123.2(4)	124.7(3)
			O(2)—C(4)—C(2)	120.5(3)	121.1(3)
			N(3)—C(4)—C(2)	116.4(3)	114.2(3)
			O(3)—C(11)—C(3)	117.1(4)	119.4(3)
			O(3)—C(11)—C(12)	119.9(4)	119.3(3)
			C(3)—C(11)—C(12)	123.0(3)	121.3(3)

Table 2. Geometrical parameters of the hydrogen bonds in crystal structure **3a**

Bond X—H...A	*d*/Å			Angle XHA /deg
	X—H	H...A	X...A	
N(2)—H(2A)...O(3′)	0.880	2.065	2.776(3)	137.22
N(2)—H(2B)...O(2)	0.880	2.284	2.831(2)	120.29
N(2′)—H(2′A)...O(3)	0.880	2.028	2.820(2)	149.11
N(2′)—H(2′B)...O(2′)	0.880	2.429	2.959(3)	119.09

shown in Fig. 1; its selected geometrical parameters are given in Table 1. On the whole, the dimer is planar; the bond lengths and angles in its two independent molecules are virtually identical. The essential distinction between the two molecules is that the phenyl substituents at the N(3) and N(3′) atoms are rotated in opposite directions, on average, through 21°. The central part of either molecule is a planar five-membered oxazole heterocycle; its bond lengths and angles differ insignificantly from those in unsubstituted oxazole[20] and 5-benzylcarboxamido-4-methyl-2-phenyloxazole.[21] The amino group is involved in both the formation of a hydrogen-bonded dimer and intramolecular hydrogen bonding to the O atom of the carbamoyl group. The parameters of all the hydrogen bonds are listed in Table 2.

Scheme 2

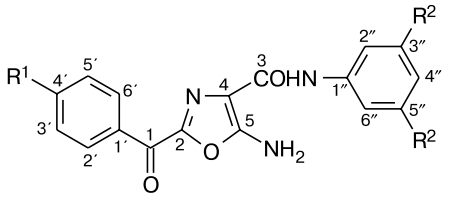


1a—h **2a—h** **3a—h**

1—3	R	R′	1—3	R	R′
a	Ph	PhNHCO	**e**	Ph	3,5-$Cl_2C_6H_3$NHCO
b	4-$MeOC_6H_4$	PhNHCO	**f**	Ph	4-$MeOC_6H_4$NHCO
c	4-BrC_6H_4	PhNHCO	**g**	Ph	MeNHCO
d	4-$NO_2C_6H_4$	PhNHCO	**h**	Ph	Ph

The ^{13}C NMR spectra were also recorded for the other 5-aminooxazoles (AOA) **3** we synthesized (Scheme 2, Table 3). The ACD Labs CNMR calculations for AOA without electron-withdrawing substituents (compound **6**) predicted the experimental spectra very accurately. However, this is not the case of AOA with electron-withdrawing substituents (compounds **3a** and **7**), which precluded the early identification of this compound as AOA from ^{13}C NMR data. This may be evidence for appreciable

Table 3. ^{13}C NMR spectra of 5-aminooxazoles **3a,c,e**, **6**, and **7**



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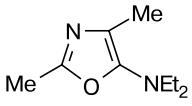
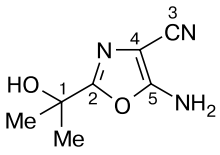


6



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Compound	δ					
	C(1)	C(2)	C(3)	C(4)	C(5)	Other C atoms
3a	175.22	144.59	160.34	107.93	159.70	122.83 (C(2″), C(6″)); 122.88 (C(4″)); 127.99 (C(3′), C(5′), C(3″), C(5″)); 129.88 (C(2′), C(6′)); 132.72 (C(4′)); 134.75 (C(1′)); 138.17 (C(1″))
3a[a]	178.7	146.2	157.5	98.5	150.1	—
3c	174.64	144.88	160.34	108.42	160.78	120.30 (C(2″), C(6″)); 123.28 (C(4″)); 127.42 (C(4′)); 128.46 (C(3′), C(5′)); 131.46 (C(3″), C(5″)); 132.32 (C(2′), C(6′)); 134.22 (C(1′)); 138.60 (C(1″))
3e	175.99	145.11	160.70	107.66	161.26	118.10 (C(2″), C(6″)); 122.14 (C(4″)); 128.47 (C(3′), C(5′)); 130.32 (C(2′), C(6′)); 133.30 (C(4′)); 133.78 (C(3″), C(5″)); 135.11 (C(1′)); 141.30 (C(1″))
6[a]	—	156.4	—	127.6	149.1	—
6[b]	—	156.0	—	127.5	149.0	—
7[a]	—	154.9	111.5	88.4	146.9	—
7[c]	—	162.1	115.6	81.8	156.8	—

[a] Calculated by the ACD CNMR method (Ver. 4.56).
[b] The data from Ref. 13.
[c] The data from Ref. 16.

Table 4. Yields, melting points, and elemental analysis data for compounds **1b,d—f**, **2b,d—f**, and **3a—c,e**

Compound	M.p./°C (solvent)	R_f*	Yield** (%)	Found / Calculated (%)			Molecular formula
				C	H	N	
1b	182—185 (EtOH)	0.41	87	63.56 / 64.01	4.58 / 4.38	12.98 / 12.57	$C_{18}H_{15}N_3O_4$
1d	196—200 (EtOH)	0.30	82	57.58 / 57.96	3.12 / 3.43	16.06 / 15.90	$C_{17}H_{12}N_4O_5$
1e	186—190 (EtOH)	0.61	93	53.99 / 54.35	3.10 / 2.97	10.12 / 10.76	$C_{17}H_{11}Cl_2N_3O_3$
1f	161—163 (MeOH)	0.42	91	64.20 / 64.09	4.99 / 4.48	12.53 / 12.46	$C_{18}H_{15}N_3O_4$
2b	236—238 (EtOH)	0.63	27	64.57 / 64.19	4.82 / 4.48	12.21 / 12.46	$C_{18}H_{15}N_3O_4$
2d	257—259 (DMF—EtOH)	0.69	6	58.22 / 57.87	3.45 / 3.58	15.27 / 15.67	$C_{17}H_{12}N_4O_5$
2e	232—234 (EtOH—H_2O)	0.79	32	54.43 / 54.33	3.09 / 2.92	11.84 / 11.53	$C_{17}H_{11}Cl_2N_3O_3$
2f	164—169 (EtOH)	0.60	51	63.80 / 64.09	4.82 / 4.48	12.70 / 12.46	$C_{18}H_{15}N_3O_4$
3a	197—200 (AcOH)	0.16	13	66.70 / 66.44	4.87 / 4.26	13.08 / 13.67	$C_{17}H_{13}N_3O_3$
3b	205—207 (AcOH)	0.13	30	64.41 / 64.09	4.89 / 4.48	12.95 / 12.46	$C_{18}H_{15}N_3O_4$
3c	230—232 (EtOH)	0.18	22	52.76 / 52.87	3.84 / 3.13	10.95 / 10.88	$C_{17}H_{12}BrN_3O_3$
3e	234—236 (EtOH)	0.20	18	53.96 / 54.11	3.01 / 2.92	10.66 / 10.97	$C_{17}H_{11}Cl_2N_3O_3$

* In benzene—AcOEt (10 : 1).

** The yields of compounds **2** obtained according to procedure *A* and the yields of compounds **3** obtained according to procedure *B*.

redistribution of the electron density in the oxazole ring which simultaneously bears strong electron donors and strong electron acceptors. Selected physicochemical characteristics and ^{1}H NMR spectra of the compounds obtained are given in Tables 4 and 5.

It should be noted that the mechanism of formation of by-products identified as 5-aminooxazoles is still unclear. Nor do the experimental ratios of products **2** and **3** agree well under different synthetic conditions.

We studied the influence of the reaction conditions on the ratio of products **2a** and **3a** in the cyclization of oxime **1a** (Table 6). The cyclization in the presence of weak bases was slow and poorly selective. Although the ratio **2a** : **3a** was favorable for the synthesis of AOA, product **3a** was very difficult to separate from the nonconsumed starting compound **1a**; on the whole, this method proved to be preparatively unsuitable. The complete conversion of the starting oxyimino nitrile was reached with strong bases and the content of isoxazole was increased, especially with LiOH. In the case of preliminary coordination with a metal salt followed by treatment of the resulting complex with a base, the highest yields of both AIA **2** ($LiClO_4$, LiOH; see Experimental, method *A*) and AOA **3** (KBr, KOH; see Experimental, method *B*) were attained.

The cyclization of some *O*-alkylated oximes **1** was carried out under the conditions that were most favorable for the formation of AIA **2** or AOA **3** (Table 7). It was found that the yield of AOA **3** increases sharply when the ketone part of the starting molecule contains both electron-donating (MeO group) and weak electron-withdrawing substituents (Br atom). The formation of AOA **3d** from compound **1d** was precluded by the presence of a strong electron-withdrawing substituent (NO_2 group) in its ketone part, and the cyclization gave AIA **2d** and ethyl *p*-nitrobenzoate (**8**) (Scheme 3).

Scheme 3

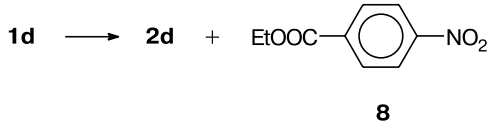

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Table 5. ^{1}H NMR spectra of compounds **1b,d—f**, **2b,d—f**, and **3a—c,e**

Compound	δ (*J*/Hz)		
	R	NH_2, CH_2	R´
1b	3.88 (s, 3 H, OMe); 7.15 (m, 2 H, H(3), H(5)); 7.96 (d, 2 H, H(2), H(6), ^3J = 8.0)	5.94 (s, 2 H, CH_2)	7.15 (m, 1 H, H(4)); 7.36 (t, 2 H, H(3), H(5), ^3J = 8.1); 7.67 (d, 2 H, H(2), H(6), ^3J = 8.1); 10.42 (br.s, 1 H, NHCO)
1d	8.26 (d, 2 H, H(3), H(5), ^3J = 8.5); 8.39 (d, 2 H, H(2), H(6), ^3J = 8.5)	6.07 (s, 2 H, CH_2)	7.16 (t, 1 H, H(4), ^3J = 7.7); 7.37 (t, 2 H, H(3), H(5), ^3J = 7.9); 7.65 (d, 2 H, H(2), H(6), ^3J = 7.9); 10.50 (br.s, 1 H, NHCO)
1e	7.61 (t, 2 H, H(3), H(5), ^3J = 7.33); 7.75 (t, 1 H, H(4)); 8.02 (d, 2 H, H(2), H(6), ^3J = 7.33)	6.04 (s, 2 H, CH_2)	7.40 (s, 1 H, H(4)); 7.80 (s, 2 H, H(2), H(6)); 10.70 (br.s, 1 H, NHCO)
1f	7.50—7.60 (m, 2 H, H(3), H(5)); 7.70 (t, 1 H, H(4)); 8.10 (d, 2 H, H(2), H(6), ^3J = 7.3)	6.00 (s, 2 H, CH_2)	3.75 (s, 3 H, OMe); 6.92 (d, 2 H, H(3), H(5), ^3J = 9.0); 7.50—7.60 (m, 2 H, H(2), H(6)); 10.33 (br.s, 1 H, NHCO)
2b	3.90 (s, 3 H, OMe); 7.19 (m, 2 H, H(3), H(5)); 8.15 (d, 2 H, H(2), H(6), ^3J = 9.2)	6.36 (br.s, 2 H, NH_2)	7.19 (m, 1 H, H(4)); 7.40 (t, 2 H, H(3), H(5), ^3J = 7.3); 7.81 (d, 2 H, H(2), H(6), ^3J = 7.4); 10.90 (br.s, 1 H, NHCO)
2d	8.30 (d, 2 H, H(3), H(5), ^3J = 8.8); 8.44 (d, 2 H, H(2), H(6), ^3J = 8.8)	6.65 (br.s, 2 H, NH_2)	7.19 (t, 1 H, H(4), ^3J = 7.3); 7.40 (t, 2 H, H(3), H(5), ^3J = 7.3); 7.80 (d, 2 H, H(2), H(6), ^3J = 7.3); 10.90 (br.s, 1 H, NHCO)
2e	7.59—7.72 (m, 3 H, H(3)—H(5)); 8.10 (d, 2 H, H(2), H(6), ^3J = 8.1)	6.65 (br.s, 2 H, NH_2)	7.19 (s, 1 H, H(4)); 7.86 (s, 2 H, H(2), H(6)); 11.06 (br.s, 1 H, NHCO)
2f	7.60—7.70 (m, 3 H, H(3)—H(5)); 8.10 (d, 2 H, H(2), H(6), ^3J = 8.1)	6.65 (br.s, 2 H, NH_2)	3.78 (s, 3 H, OMe); 6.95 (d, 2 H, H(3), H(5), ^3J = 8.9); 7.60—7.70 (m, 2 H, H(2), H(6)); 10.33 (br.s, 1 H, NHCO)
3a	7.59 (t, 2 H, H(3), H(5), ^3J = 7.3); 7.71 (t, 1 H, H(4), ^3J = 7.0); 8.45 (d, 2 H, H(2), H(6), ^3J = 6.9)	8.03 (br.s, 2 H, NH_2)	7.08 (t, 1 H, H(4), ^3J = 7.3); 7.34 (t, 2 H, H(3), H(5), ^3J = 7.9); 7.79 (d, 2 H, H(2), H(6), ^3J = 8.5); 9.60 (br.s, 1 H, NHCO)
3b	3.90 (s, 3 H, MeO); 7.10 (m, 2 H, H(3), H(5)); 8.55 (d, 2 H, H(2), H(6), ^3J = 7.0)	8.00 (br.s, 2 H, NH_2)	7.10 (m, 1 H, H(4)); 7.35 (t, 2 H, H(3), H(5), ^3J = 7.5); 7.80 (d, 2 H, H(2), H(6), ^3J = 7.3); 9.63 (br.s, 1 H, NHCO)
3c	7.80 (d, 2 H, H(2), H(6), ^3J = 8.5); 8.40 (d, 2 H, H(3), H(5), ^3J = 8.5)	8.12 (br.s, 2 H, NH_2)	7.15 (t, 1 H, H(4), ^3J = 7.9); 7.35 (m, 2 H, H(3), H(5)); 7.80 (d, 2 H, H(2), H(6), ^3J = 8.5); 9.60 (br.s, 1 H, NHCO)
3e	7.57—7.70 (m, 3 H, H(3)—H(5)); 8.43 (d, 2 H, H(2), H(6), ^3J = 8.0)	8.20 (br.s, 2 H, NH_2)	7.26 (t, 1 H, H(4), ^4J = 1.8); 7.98 (d, 2 H, H(2), H(6), ^4J = 1.8); 10.00 (br.s, 1 H, NHCO)

Table 6. Ratio of products **2a** and **3a** in the cyclization of oxime **1a**

Substrate	Solvent	Base	*t**/h	Conversion (%)	**2a** : **3a**	Yield of **3a**** (%)
1a	EtOH	KOCN	48	25	40 : 60	7.8
1a	EtOH	$NaHCO_3$	48	40	45 : 55	9.8
1a	EtOH	K_2CO_3	6	95	79 : 21	8.6
1a	MeCN	Et_3N	4	95	65 : 35	5.9
1a	MeCN	DBU	2.5	97	60 : 40	5.8
1a	60% EtOH	LiOH	4.5	100	90 : 10	3.4
1a	60% EtOH	KOH	2	100	83 : 17	6.6
1a · $LiClO_4$	60% EtOH	LiOH	4.5	100	95 : 5	1.9
1a · KBr	60% EtOH	KOH	2	100	72 : 28	13

* The reaction duration.

** Obtained by integration of the signals in the ^{1}H NMR spectrum of the corresponding mixtures; chromatographic separation was carried out only in the last case.

Table 7. Ratio of products **2** and **3** in the cyclization of *O*-alkylated oximes **1a—h**

Compound	2 : 3		Compound	2 : 3	
	Method A^a	Method B^b		Method A^a	Method B^b
1a	95 : 5	72 : 28	**1e**	84 : 16	55 : 45
1b	49 : 51	25 : 75	**1f**	96.5 : 3.5	84.5 : 12.5
1c	83 : 17	57 : 43	**1g**	100 : 0	100 : 0
1d	—[c]	—[d]	**1h**	100 : 0	100 : 0

[a] Coordination with $LiClO_4$ followed by the action of LiOH.
[b] Coordination with KBr followed by the action of KOH.
[c] In the cyclization in aqueous 60% EtOH, the conversion of the starting compound was incomplete even with a threefold excess of the base. The cyclization in aqueous DMF in the presence of LiOH gave AIA only, although its yield was low.
[d] The cyclization in anhydrous EtOH in the presence of KOH gave a mixture of AIA **2d** and ethyl *p*-nitrobenzoate (**8**) in the ratio 5.5 : 1.

Introduction of electron-releasing substituents into the carbamoyl fragment of the starting molecule (compounds **1f,g**) suppressed the formation of AOA virtually completely, whereas introduction of electron-withdrawing substituents greatly increased the yield of AOA **3**. The general conclusion we can draw is that the ratio of AIA and AOA is more dependent on the structure of the starting oxyimino nitrile **1** than on the reaction conditions.

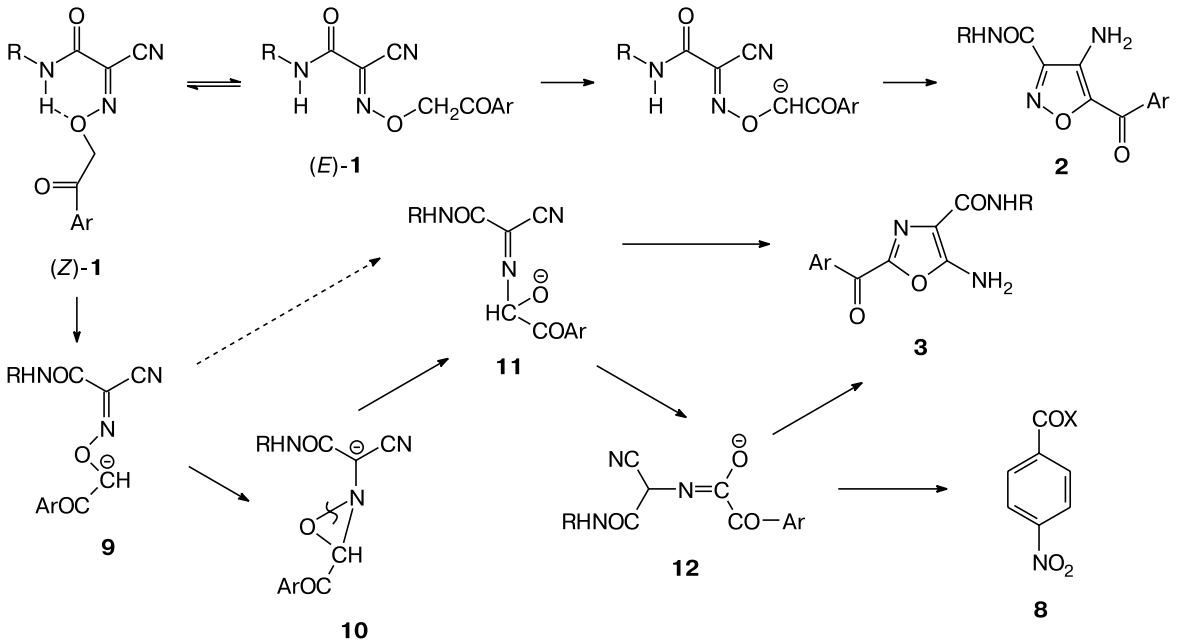
The data obtained can be interpreted in terms of the following mechanism (Scheme 4).

It is quite obvious that the deprotonated *E*-form of *O*-alkylated oxime undergoes cyclization into AIA **2**. Deprotonation of the *Z*-form of oxime gives rise to anion **9**; its subsequent transformations can vary with the substituents in the starting oximes **1** and the reaction conditions.

The formation of AOA **3** can involve rearrangement of anion **9** into anion **11** or cyclization of anion **9** into oxaziridine **10** followed by its opening into anion **11**. We have no documented examples of the direct rearrangement of anion **9** into anion **11** and this (or similar) transformation seems to be unlikely. At the same time, a two-step way leading to anion **11** through intermediate oxaziridine **10** is consistent with available literature data. The formation of the oxaziridine ring by cyclization of *O*-alkylated oximes has not been exemplified in the literature; such a reaction is hardly possible because *N*-alkylated oxaziridines easily undergo opening through cleavage of the O—N bond in the presence of two acceptors in the α-position of the *N*-alkyl substituent in oxaziridine or in the presence of one acceptor under the action of bases, silica gel, or transition metal salts.[22—24] Since an adduct initially forms as deprotonated *N*-alkylated oxaziridine, prompt cleavage of its O—N bond should give anion **11** as described earlier[22] for the action of bases on oxaziridines. Thus, the addition—elimination sequence will ultimately result in rearrangement of anion **9** into anion **11**.

The formation of the oxaziridine ring *via* addition of a carbon nucleophile to the N rather than C atom of the C=N bond formally contradicts the charge balance rule

Scheme 4



since it is commonly believed that the N atom of the C=N bond is negatively charged and hence addition should occur at the C atom. However, in the presence of one or two strong acceptors at the C atom, the electron density can be substantially redistributed. Actually, AOA did not form from oxyimino nitrile **1h** containing only one electron-withdrawing group or the yield of product **3** decreased considerably when the starting reagent contained electron-releasing substituents in the carbamoyl fragment. Thus, the formation of oxaziridine **10** and its immediate opening into anion **11** become possible only in the presence of two strong acceptors at the C atom of *O*-alkylated oximes **1**.

The transformation of anion **11** into AOA **3** can occur *via* an attack of the O atom on the C atom of the cyano group and *via* a hydride shift giving rise first to anion **12** and then AOA **3**. The generated α-keto amide anion **12** could be expected to yield carboxylic acids or their esters of the type **8** through decomposition by strong bases. However, only for Ar = 4-$NO_2C_6H_4$ (see Scheme 4), the corresponding benzoate was the major reaction product, while AOA **3d** was not detected. Decomposition of other oxyimino nitriles to carboxylic acids was insignificant unless the reaction temperature was raised to 40—60 °C; however, the ratio of the products under these conditions was not particularly studied. Such a behavior of some α-keto amides **12** is not in conflict with the literature data since transformations of aryloxoacetic acid esters with electron-releasing substituents into the corresponding benzoic acids are known[25,26] to require short-time heating (5 min) with NaOH and the presence of a nitro group in the benzene ring should sharply promote this decomposition.

Thus, although *O*-alkylated oximes **1** predominantly exist in the *Z*-form stabilized by intramolecular hydrogen bonding,[11] we failed to select conditions for the synthesis of AOA **3** as sole products. Apparently, this is due to slow rearrangement of anion **9** into anion **11**, which allows a considerable part of *O*-alkylated oxime to convert into the *E*-form and then into AIA. Aminooxazoles with two electron-withdrawing substituents can be synthesized in less ambiguous and preparatively more suitable ways.[27,28]

Experimental

^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 and Bruker AM-300 instruments (500.13 and 75.47 MHz, respectively) in DMSO-d_6. IR spectra were recorded on a Specord M-80 instrument (in KBr pellets). Mass spectra were recorded on a Finnigan-MAT instrument (EI, 70 eV). Sodium salts of oximes were prepared according to a known procedure.[11] α-Bromoacetophenone, α-bromo-4-methoxyacetophenone, and α,4-dibromoacetophenone were synthesized by bromination in methanol according to a published procedure;[29] α-bromo-4-nitroacetophenone was prepared by bromination in dioxane as described earlier.[30]

Alkylation of sodium salts of oximes with bromo ketones (synthesis of compounds 1a—h, general procedure). A mixture of a sodium salt of an oxime (5 mmol) and an appropriate bromo ketone (6 mmol) was stirred in ethanol (or DMF) (5—10 mL) at ~20 °C for 4 h. The precipitate was filtered off (with DMF as the solvent, the product was precipitated by adding water (5—10 mL)), washed with a small amount of ether, and dried *in vacuo*. The yields, melting points, and ^{1}H NMR spectra of the products obtained are given in Tables 4 and 5.

Synthesis of 4-aminoisoxazoles 2a—h (general procedure *A*). A mixture of compound **1a—h** (5 mmol) and $LiClO_4 \cdot 3H_2O$ (1 g) was refluxed in MeCN (10—25 mL) for 5 min to complete homogenization and left at ~20 °C for ~14 h. The resulting solution was concentrated and the residue was suspended in 60% ethanol (10—20 mL). Cyclization was carried out by adding dropwise aqueous 5% LiOH with stirring for 20 min (TLC monitoring until the starting *O*-alkylated hydroxyimino nitrile was completely consumed). The precipitate of the product was filtered off, washed with 2% HCl and water, and recrystallized (see Table 4). The yields, melting points, and ^{1}H NMR spectra of the compounds obtained are given in Tables 4 and 5.

Synthesis of 5-amino-2-benzoyloxazole-4-carboxamides 3a—e (general procedure *B*). A mixture of *O*-alkylated oximes **1a—e** (5 mmol) and KBr (2 g) in aqueous 60% ethanol (4 mL) was allowed to stand in an open beaker for ~14 h. The moist precipitate that formed was suspended in aqueous 60% ethanol (15—25 mL) and then aqueous 10% KOH (0.6 g) was added dropwise to the stirred suspension. After 2 h, the precipitate was filtered off, washed with 2% HCl and water, and dried. The resulting mixture of 4-aminoisoxazole and 5-aminooxazole was dissolved in MeCN (25 mL) and concentrated on a rotary evaporator with an equal amount (w/w) of silica gel. The resulting powder was applied to a column and separated by chromatography with benzene (for 4-aminoisoxazole) and benzene—AcOEt (from 10 : 1 to 2 : 1; for 5-aminooxazole) as eluents. The yields, melting points, and ^{1}H and ^{13}C NMR spectra of the products obtained are given in Tables 3—5.

***N*-Phenyl-4-amino-5-benzoylisoxazole-3-carboxamide (2a) and *N*-phenyl-5-amino-2-benzoyloxazole-4-carboxamide (3a)** were obtained in the ratio 72 : 28 from *N*-phenyl-2-(benzoylmethoxyimino)cyanoacetamide (**1a**) (2 g, 6.5 mmol) and KBr (2.5 g) according to general procedure *B*. The total yield of their mixture was 918 mg. Separation by column chromatography gave compounds **2a** (597 mg) and **3a** (218 mg).

Compound 2a. For m.p. and ^{1}H NMR data, see Tables 4 and 5, respectively. MS, *m/z*: 307 (18), 202 (14), 188 (24), 119 (18), 105 (100), 93 (44), 77 (81). IR, ν/cm^{-1}: 3472, 3392, 3352, 1688, 1648, 1600, 1540, 1504.

Compound 3a. For m.p. and ^{1}H NMR data, see Tables 4 and 5, respectively. MS, *m/z*: 307 (20), 202 (2), 149 (4), 119 (7), 105 (100), 93 (25), 77 (51). IR, ν/cm^{-1}: 3440, 3400, 3264, 1664, 1632, 1600, 1548, 1516.

X-ray diffraction analysis of compound 3a. Light yellow needle-like crystals are orthorhombic, $C_{17}H_{13}N_3O_3$ (M = 307.30); at 120 K, a = 12.090(4) Å, b = 32.174(11) Å, c = 7.424(3) Å, α = 90.00°, β = 90.00°, γ = 90.00°, V = 2887.8(18) Å^3, space group $Pca2_1$, Z = 8, d_{calc} = 1.414 g cm^{-3}. An experimental array of 25 443 reflections was collected from a single crystal (0.7×0.02×0.01 mm) on a Bruker SMART 1000 CCD diffractometer at 120 K (Mo-Kα radiation, λ = 0.71073 Å, $2\theta_{max}$ = 54°). After the averaging of equivalent reflections,

6277 independent reflections (R_{int} = 0.061) were used in structure determination and refinement. The structure was solved by the direct method; all atoms were located from the electron density difference maps and refined on F^2_{hkl} in the anisotropic approximation. Hydrogen atoms were located geometrically and refined in the rider model. Final residuals were R_1 = 0.0515 (on F_{hkl} for 2844 reflections with $I > 2\sigma(I)$) and wR_2 = 0.0673 (on F^2_{hkl} for all reflections); GOOF 0.935, 415 parameters refined. All calculations were performed with the SHELXTL PLUS 5 program package.[31] The general view of the structure is shown in Fig. 1. Selected geometrical parameters are given in Tables 1 and 2.

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