Synthesis of 3,5-disubstituted 4-aminoisoxazoles by cyclization of *O*-(β-oxoalkyl)-substituted α-hydroxyimino nitriles

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4-Amino-5-benzoyl(acetyl)isoxazole-3-carboxamides were prepared by cyclization of α-hydroxyimino nitriles *O*-alkylated with bromoacetophenones (bromoacetone). The purity of the target 4-aminoisoxazoles can be substantially increased by treating *O*-alkylated oximes with $LiClO_4$ before cyclization.

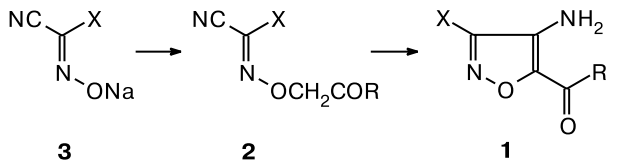
Key words: 2-(2-aryl-2-oxoethoxyimino)cyanoacetamides, 4-amino-5-benzoylisoxazole-3-carboxamides.

Procedures for the preparation of 4-aminoisoxazoles are much less developed than methods for the synthesis of 3-amino- and 5-aminoisoxazoles.[1,2] However, 4-aminoisoxazoles bearing an ester, amide, or acyl group at position 3 or 5 of the ring can be used to prepare difficultly accessible fused systems, such as isoxazolopyrimidines, isoxazolopyridines, *etc*.[1,3,4] Derivatives of these fused systems, as well as 4-aminoisoxazoles by themselves, can exhibit biological activity.[5—7] Hence, the development of new efficient methods for the synthesis of these compounds is of considerable importance. Earlier, functionalized 4-aminoisoxazoles **1** have been synthesized by the Hofmann reaction[3,8] and cyclization of *O*-acylated nitroacetophenone oximes[9,10] followed by reduction of the resulting nitroisoxazoles.[9—11] However, these procedures involve many steps and give products in low total yields, which complicates their use in the synthesis of bicyclic systems. More recently, a new procedure has been developed[3] for the synthesis of 4-aminoisoxazoles **1** by cyclization of *O*-alkylated α-hydroxyimino nitriles **2** with a large (30-fold or larger) excess of LiOH. This method has been used in subsequent studies.[4,12]

The aim of the present study was to examine the possibilities of this cyclization for preparing 4-aminoisoxazole-3-carboxamides bearing a functional substituent at position 5. We used various bases in cyclization of *O*-(β-oxoalkyl)-α-hydroxyimino nitriles **2** (Scheme 1).

The reactions with the use of aliphatic amines (triethylamine, benzylamine, or piperidine) as bases (by analogy with the reactions described in the study[3]) produced aminoisoxazoles **1** in low yields. It should be noted that isolation of the products was substantially complicated (only preparative chromatography was used), because the reaction mixtures contained large amounts of impurities.

Scheme 1



3 **2** **1**

1, **2**	X	R	**1**, **2**	X	R
a	EtOOC	4-BrC_6H_4	**h**	CONHPh	Me
b	$CONH_2$	4-BrC_6H_4	**i**	Ph	4-BrC_6H_4
c	CONHPh	4-BrC_6H_4	**1j**	COOH	4-BrC_6H_4
d	CONHPh	Ph	**2j**	Ph	OEt
e	(4-FC_6H_4)NHCO	Ph	**2k**	Ph	NHPh
f	MeNHCO	Ph	**2l**	PhNHCO	NH_2
g	$CONHCH_2Ph$	Ph			

3	X	**3**	X
a	EtOOC	**e**	MeNHCO
b	$CONH_2$	**f**	$CONHCH_2Ph$
c	CONHPh	**g**	Ph
d	(4-FC_6H_4)NHCO		

The use of stronger bases, such as LiOH, KOH, or EtONa, in cyclization proved to be more efficient. The best results were obtained with the use of LiOH. It should be noted that cyclization in aqueous alcohol is most convenient from the preparative viewpoint, because the reaction product can be separated by simple filtration. However, the reactions even with the use of LiOH afforded 4-aminoisoxazoles **1**, which were substantially contaminated (in the presence of an aryl substituent in the amide fragment (**2c—e**), the percentage of the impurity was as high as 20%). We had to purify the product by fractional crystallization. Since the use of LiOH had a positive effect on the yields of 4-aminoisoxazoles, we expected that successive treatment of *O*-alkylated oximes with a lithium salt

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 5, pp. 1159—1165, May, 2005.

1066-5285/05/5405-1189

Table 1. Yields, melting points, and elemental analysis data for compounds **2a—l** and **4a,b**

Compound	R	X	Yield (%)	M.p./°C (solvent)	R_f*	Found / Calculated (%)			Molecular formula
						C	H	N	
2a	COOEt	4-BrC_6H_4	54	118—122 (EtOH)	0.81	45.9 46.0	3.40 3.25	9.0 8.3	$C_{13}H_{11}BrN_2O_4$
2b	$CONH_2$	4-BrC_6H_4	78	199—202 (DMF)	0.10	42.7 42.6	2.85 2.60	13.9 13.9	$C_{11}H_8BrN_3O_3$
2c	CONHPh	4-BrC_6H_4	82	194—197 (EtOH)	0.54	52.4 52.8	3.40 3.11	10.7 10.9	$C_{17}H_{12}BrN_3O_3$
2d	CONHPh	Ph	85	161—163 (EtOH)	0.51	66.9 66.4	4.20 4.23	13.3 13.7	$C_{17}H_{13}N_3O_3$
2e	CONH-4-FC_6H_4	Ph	74	142—144 (MeOH)	0.49	62.6 62.8	3.70 3.69	12.4 12.9	$C_{17}H_{12}FN_3O_3$
2f	CONHMe	Ph	61	162—164 (Pr^iOH)	0.25	58.7 58.8	4.50 4.49	16.8 17.1	$C_{12}H_{11}N_3O_3$
2g	CONHBn	Ph	82	107—109 (EtOH)	0.42	67.7 67.3	4.80 4.67	12.9 13.1	$C_{18}H_{15}N_3O_3$
2h	CONHPh	Me	59	132—134 (DMF—H_2O)	0.28	58.5 58.8	4.70 4.49	16.7 17.1	$C_{12}H_{11}N_3O_3$
2i	Ph	4-BrC_6H_4	71	108—110 ($PhCH_3$)	0.46	56.3 56.0	3.10 3.20	8.0 8.2	$C_{16}H_{11}BrN_2O_2$
2j	Ph	OEt	89	57—60 ($PhCH_3$)	0.80	62.0 62.1	4.90 5.17	12.4 12.1	$C_{12}H_{12}N_2O_3$
2k	Ph	NHPh	82	117—119 (Pr^iOH)	0.62	69.2 68.8	4.80 4.67	14.7 15.1	$C_{16}H_{13}N_3O_2$
2l	CONHPh	NH_2	85	212—215 (DMF)	0.24	53.9 53.7	4.05 4.1	22.4 22.8	$C_{11}H_{10}N_4O_3$
4a	—	COOH	45	182—184 (H_2O)	0.34—0.8	54.5 54.1	4.30 4.50	12.1 12.6	$C_{10}H_{10}N_2O_4$
4b	—	CONHPh	67	90—92 (BuOAc)	0.67	64.50 64.65	5.50 5.05	13.7 14.1	$C_{16}H_{15}N_3O_3$

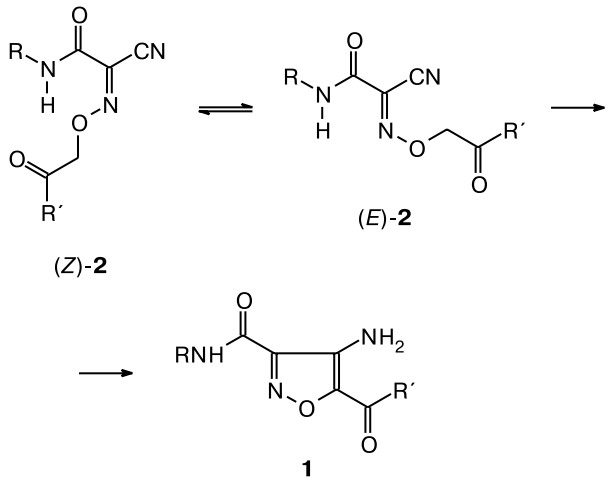
* The following systems were used: benzene (for **2i**); benzene—EtOAc, 10 : 1 (for **2a—h,j,k**); benzene—EtOAc, 1 : 1 (for **2l**, **4b**); EtOAc—EtOH, 5 : 1 (for **4a**).

and a base would facilitate the reaction. We chose perchlorate as the lithium salt, because lithium perchlorate, unlike other lithium salts, is readily soluble in organic solvents. Actually, aminoisoxazole **1d** was isolated in analytically pure form by simple filtration of the reaction mixture, which was prepared by the addition of an acetonitrile solution of *O*-alkylated oxime **2d** and an equimolar amount of $LiClO_4$ (the solution was allowed to stand for 14 h) to an aqueous LiOH solution.

This procedure has been successfully used to synthesize a series of 4-aminoisoxazoles bearing the benzoyl, bromobenzoyl, or acetonyl group at position 5 of the isoxazole ring (Tables 1 and 2).

The factors responsible for the efficiency of lithium salts remain unclear. It is known[13] that oximes can exist as isomeric *Z* and *E* forms, whose interconversion is catalyzed, in particular, by traces of acids. Evidently, only the (*E*) form of *O*-alkylated oxime containing closely-spaced reaction centers can undergo cyclization to give aminoisoxazole (Scheme 2).

Scheme 2



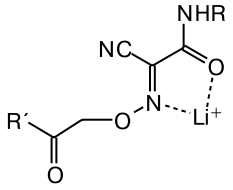
In our opinion, compounds **2** (in the absence of lithium salts) exist predominantly in the (*Z*) form, which is able

Table 2. Yields, melting points, and elemental analysis data for compounds **1a—j**

Compound	R	X	Yield (%)	M.p./°C (solvent)	R_f*	Found / Calculated (%)			Molecular formula
						C	H	N	
1a	COOEt	4-BrC_6H_4	18	150—152 ($PhCH_3$)	0.84	45.9 46.0	3.30 3.25	8.7 8.3	$C_{13}H_{11}BrN_2O_4$
1b	$CONH_2$	4-BrC_6H_4	53	228—230 (DMF)	0.25	43.0 42.6	2.80 2.60	13.7 13.6	$C_{11}H_8BrN_3O_3$
1c	CONHPh	4-BrC_6H_4	55	235—238 (EtOH)	0.80	52.7 52.8	3.00 3.11	10.4 10.9	$C_{17}H_{12}BrN_3O_3$
1d	CONHPh	Ph	42	175—177 (EtOH)	0.76	66.1 66.4	4.10 4.23	13.2 13.7	$C_{17}H_{13}N_3O_3$
1e	CONH-4-FC_6H_4	Ph	38	196—198 (EtOH)	0.76	62.5 62.8	3.90 3.69	12.5 12.9	$C_{17}H_{12}FN_3O_3$
1f	CONHMe	Ph	61	175—178 (EtOH)	0.50	58.5 58.8	4.10 4.49	16.5 17.1	$C_{12}H_{11}N_3O_3$
1g	CONHBn	Ph	68	167—170 (EtOH)	0.67	67.8 67.3	4.20 4.67	13.8 13.1	$C_{18}H_{15}N_3O_3$
1h	CONHPh	Me	41	179—182 (EtOH)	0.67	58.7 58.8	4.90 4.49	16.9 17.1	$C_{12}H_{11}N_3O_3$
1i	Ph	4-BrC_6H_4	72	185—187 ($PhCH_3$)	0.65	56.1 56.0	2.90 3.20	7.9 8.2	$C_{16}H_{11}BrN_2O_2$
1j	COOH	4-BrC_6H_4	40	200—205 (H_2O)	0.05—0.3	42.3 42.4	2.60 2.25	8.2 9.0	$C_{11}H_7BrN_2O_4$

* The following systems were used: benzene (for **1i**); benzene—EtOAc, 10 : 1 (for **1a—h**); EtOAc—EtOH, 5 : 1 (for **1j**).

to form an intramolecular hydrogen bond. The most probable mechanism of the influence of the lithium cation involves isomerization of the (*Z*) form of oximes **2** to give the (*E*) form necessary for cyclization. Apparently, the formation of a chelated complex of the (*E*) form of oxime with the lithium cation is the driving force for this transformation.



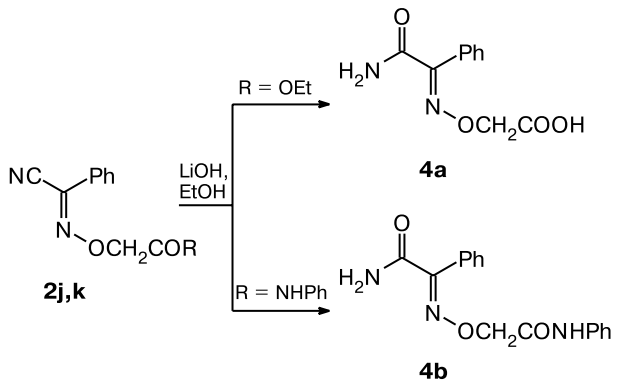
(*E*)-**2d** · Li^+

However, the available experimental data are insufficient to support this hypothesis. It is known[14] that the signal for the carbon atom of the nitrile group located in the *trans* position with respect to the N—O bond is observed at lower field than the signal for the CN group of the *cis* isomer, although the difference is small (0.2—0.3 ppm).[15] Since both the ^1H and ^{13}C NMR spectra of compounds **2** show one set of signals and contain no signals of the minor isomer, it is impossible to determine the configuration of the only isomer from the ^{13}C NMR spectrum. The determination of the structure of the complex of *O*-alkylated oxime with lithium is an even more complex problem, because the corresponding data are lacking in the literature.

Since the syntheses of 4-amino-3-phenylisoxazole-5-carboxylic acid and its derivatives described earlier[9,10] involve many steps, we attempted to prepare these compounds according to Scheme 1. Sodium salts of hydroximino nitriles **3** are smoothly alkylated with chloroacetic acid derivatives. However, we failed to synthesize the corresponding 4-aminoisoxazoles from compounds **2j—l**.

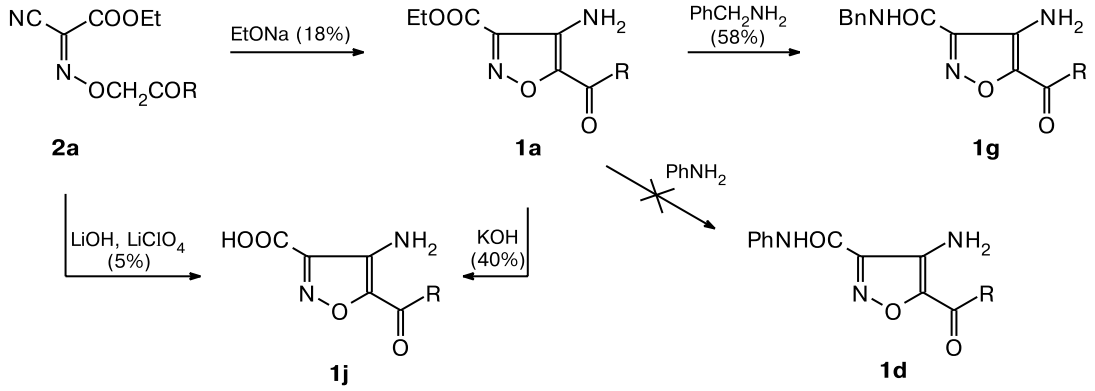
O-Alkylated nitriles **2j—l** are absolutely inert to triethylamine. Under the conditions found in the present study (LiOH, $LiClO_4$ in aqueous acetonitrile), the nitrile group in compounds **2j** and **2k** is hydrolyzed to the amide group giving rise to compounds **4a** and **4b**, respectively. Compounds **2j,k** did not react with EtONa at room temperature, whereas heating led to deep resinification giving rise to unidentified compounds (Scheme 3). Presumably,

Scheme 3



R = OEt (**2j**), NHPh (**2k**)

Scheme 4



R = 4-BrC_6H_4

compounds **2j—l** do not undergo cyclization due to the fact that the methylene group in amides has much lower acidity compared to this group in ketones, with the result that the nucleophilic attack of the base on the nitrile group of compounds **2** is the main reaction pathway.

We examined the possibility of synthesizing 4-amino-5-(4-bromobenzoyl)isoxazole-3-carboxamides from ester **1a** or acid **1j** (Scheme 4). However, this procedure proved to be inefficient. Under the standard conditions (LiOH), cyclization affords (after acidification to pH 1) only amino acid **1j**, the yield being low (5%). We succeeded in preparing amino ester **1a**, although in moderate yield (18%), by the reaction of ester **2a** with sodium ethoxide in anhydrous ethanol. Alkaline saponification of amino ester **1a** affords amino acid **1j** also in moderate yield (40%). Low yields of amino ester **1a** produced by alkaline saponification are, apparently, attributed to the fact that the isoxazole ring can be opened under the action of bases.[16,17]

The reactions of ester **1a** with amines (ammonia or benzylamine) produced the corresponding amides **1b,c**, although the reactions were accompanied by noticeable resinification, whereas the reactions of anilines with ester **1a** did not afford anilides. Earlier, it has been found that 4-amino-3-phenylisoxazole-5-carboxamides can be synthesized only by the reaction of the *N*-hydroxysuccinimide derivative of the acid with amines[18] (the reaction of isoxazolooxazine, which was prepared by the reaction of phosgen, with amines produces exclusively 4-ureidoisoxazole-5-carboxylic acid derivatives rather than amides[18]).

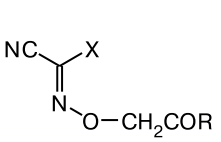
Therefore, since hydroxyiminoacetonitriles **3** are readily accessible, whereas acid **1j** or its esters are synthesized in low yields, it is more convenient to synthesize amines **1** from oximes **3**.

The structures of the resulting compounds were confirmed by ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis (Tables 1—5). It is known[19] that alkylation of oximes generally affords mixtures of *N*- and *O*-alkylation products, the presence of electron-withdrawing substituents in the oxime molecule suppressing *N*-alkylation.[20] We isolated the only alkylation product in high yield from the reaction mixture prepared by alkylation of oximes **3**, and this product did not show isomerism (^1H and ^{13}C NMR spectroscopic data). The structures of compounds **2** as *O*-alkylation products can be confirmed based on spectral correlations.[14] Nevertheless, the structure of the alkylation product is unambiguously supported by the fact that it is easily transformed into 4-aminoisoxazole (provided that the structures of compounds **1** were reliably established). Since 4-aminoisoxazoles **1** are completely substituted isoxazoles (contain no protons at the carbon atoms of the isoxazole ring), their structures cannot be proved by ^1H NMR spectroscopy. Hence, we measured the ^{13}C NMR spectra of these compounds. In particular, a comparison of the chemical shifts in the ^{13}C NMR spectra of compounds **1c—f** and the use of the APT technique allowed us to assign all signals for the carbon atoms in the phenyl rings and, consequently, assign the signals for the carbon atoms of the isoxazole ring: C(5) (δ 146.5—149.9), C(3) (δ 147.6—148.2), and C(4) (δ 134.99—136.0). The positions of the signals for the carbon atoms of the isoxazole ring are in satisfactory agreement with the signals for 4-amino-3-phenylisoxazole-5-carboxamide **5** described earlier[18,21] (see Table 5).

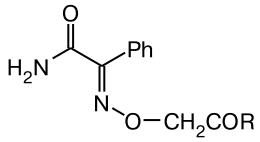
Experimental

The ^1H NMR spectra were recorded on a Bruker DRX-500 instrument operating at 500.13 MHz in DMSO-d_6. The ^{13}C NMR spectra were measured on a Bruker AM-300 instrument operating at 75.47 MHz in DMSO-d_6. The IR spectra were recorded on a Specord M-80 instrument in KBr pellets. The mass spectra were obtained on a Finnigan-MAT instrument

Table 3. ^{1}H NMR spectroscopic data for compounds **2a—l** and **4a,b**



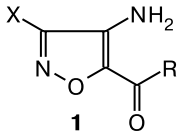
2a—l



4a,b

Compound	X	R	δ (*J*/Hz)		
			X	OCH_2 (s, 2 H)	R
2a	COOEt	4-BrC_6H_4	1.30 (t, 3 H, OCH_2Me, ^3J = 7.1); 4.35 (q, 2 H, OCH_2Me, ^3J = 7.1);	6.05	7.80 (d, 2 H, H(3), H(5), ^3J = 8.2); 7.90 (d, 2 H, H(2), H(6), ^3J = 8.2)
2b	$CONH_2$	4-BrC_6H_4	7.55, 7.80 (both s, 1 H each, $CONH_2$)	5.80	7.70 (d, 2 H, H(3), H(5), ^3J = 8.3); 7.92 (d, 2 H, H(2), H(6), ^3J = 8.2)
2c	CONHPh	4-BrC_6H_4	7.18 (t, 1 H, H(4), ^3J = 7.5); 7.35 (t, 2 H, H(3), H(5), ^3J = 7.5); 7.65 (d, 2 H, H(2), H(6), ^3J = 7.4); 10.40 (br.s, 1 H, NHCO)	5.95	7.80 (d, 2 H, H(3), H(5), ^3J = 8.3); 7.92 (d, 2 H, H(2), H(6), ^3J = 8.2)
2d	CONHPh	Ph	7.15 (t, 1 H, H(4), ^3J = 7.2); 7.35 (t, 2 H, H(3), H(5), ^3J = 7.6); 7.65 (d, 2 H, H(2), H(6), ^3J = 7.4); 10.40 (br.s, 1 H, NHCO)	6.00	7.60 (2 H, H(3), H(5), ^3J = 7.5); 7.70 (t, 1 H, H(4), ^3J = 7.5); 8.00 (d, 2 H, H(2), H(6), ^3J = 7.3)
2e	CONH-4-FC_6H_4	Ph	7.20 (t, 2 H, H(3), H(5), $^3J_{H,F} = {}^3J_{H,H}$ = 9.0); 7.65 (dd, 2 H, H(2), H(6), $^3J_{H,H}$ = 9.0, $^4J_{H,F}$ = 5.1); 10.50 (br.s, 1 H, NHCO)	6.00	7.58 (t, 2 H, H(3), H(5), ^3J = 7.5); 7.70 (t, 1 H, H(4), ^3J = 7.3); 8.00 (d, 2 H, H(2), H(6), ^3J = 7.5)
2f	CONHMe	Ph	2.70 (d, 3 H, Me, *J* = 4.7); 8.60 (br.s, 1 H, NHCO)	5.95	7.61 (t, 2 H, H(3), H(5), ^3J = 7.7); 7.74 (t, 1 H, H(4), ^3J = 7.25); 8.00 (d, 2 H, H(2), H(6), ^3J = 7.1)
2g	CONHBn	Ph	4.37 (d, 2 H, $C\underline{H}_2Ph$, *J* = 6.4); 7.20—7.35 (m, 5 H, Ph); 9.10 (br.s, 1 H, NHCO)	5.90	7.58 (t, 2 H, H(3), H(5), ^3J = 7.5); 7.68 (t, 1 H, H(4), ^3J = 7.4); 7.97 (d, 2 H, H(2), H(6), ^3J = 7.6)
2h	CONHPh	Me	7.18 (t, 1 H, H(4), ^3J = 7.5); 7.38 (t, 2 H, H(3), H(5), ^3J = 7.7); 7.80 (d, 2 H, H(2), H(6), ^3J = 7.6); 10.50 (br.s, 1 H, NHCO); 10.90 (br.s)	5.21	2.17 (s, 3 H, Me)
2i	Ph	4-BrC_6H_4	7.50—7.60 (m, 3 H, H(3), H(4), H(5)); 7.80 (d, 2 H, H(2), H(6), ^3J = 7.3)	5.70	7.72 (d, 2 H, H(3), H(5), ^3J = 8.3); 8.15 (d, 2 H, H(2), H(6), ^3J = 8.1)
2j	Ph	OEt	7.50—7.60 (m, 3 H, H(3), H(4), H(5)); 7.75 (d, 2 H, H(2),H(6), ^3J = 7.5)	5.10	1.22 (t, 3 H, OCH_2Me, ^3J = 7.1); 4.20 (q, 2 H, OCH_2Me, ^3J = 7.1)
2k	Ph	NHPh	7.50—7.60 (m, 3 H, H(3), H(4), H(5)); 7.78 (d, 2 H, H(2), H(6), ^3J = 7.4)	5.05	7.09 (t, 1 H, H(4), ^3J = 7.2); 7.31 (t, 2 H, H(3), H(5), ^3J = 7.6); 7.60 (d, 2 H, H(2), H(6), ^3J = 7.2); 10.10 (br.s, 1 H, NHCO)
2l	CONHPh	NH_2	7.18 (t, 1 H, H(4), ^3J = 7.5); 7.38 (t, 2 H, H(3), H(5), ^3J = 7.6); 7.68 (d, 2 H, H(2), H(6), ^3J = 7.5); 10.40 (br.s, 1 H, NHCO)	4.90	7.40, 7.50 (both s, 1 H each, $CONH_2$)
4a	—	OH	7.45—7.55 (m, 5 H, Ph)	4.60	7.70, 8.30 (both s, 1 H each, $CONH_2$)
4b	—	NHPh	7.45—7.50 (m, 3 H, H(3), H(4), H(5)); 7.75 (d, 2 H, H(2), H(6), ^3J = 7.2)	4.80	7.09 (t, 1 H, H(4), ^3J = 7.2); 7.31 (t, 2 H, H(3), H(5), ^3J = 7.5); 7.60 (d, 2 H, H(2), H(6), ^3J = 7.4); 8.05, 8.30 (both s, 1 H each, $CONH_2$); 9.60 (br.s, 1 H, CONH)

Table 4. ^{1}H NMR spectroscopic data for compounds **1a—j**



1

Compound	X	R	δ (*J*/Hz)		
			X	NH_2 (br.s, 2 H)	R
1a	COOEt	4-BrC_6H_4	1.45 (t, 3 H, OCH_2Me, J = 7.1); 4.50 (q, 2 H, OCH_2Me, ^3J = 7.1)	6.30	7.75 (d, 2 H, H(3), H(5), ^3J = 8.2); 8.07 (d, 2 H, H(2), H(6), ^3J = 8.2)
1b	$CONH_2$	4-BrC_6H_4	7.95, 8.25 (both s, 1 H each, $CONH_2$)	6.40	7.82 (d, 2 H, H(3), H(5), ^3J = 8.3); 8.00 (d, 2 H, H(2), H(6), ^3J = 8.3)
1c	CONHPh	4-BrC_6H_4	7.20 (t, 1 H, H(4), ^3J = 7.6); 7.40 (t, 2 H, H(3), H(5), ^3J = 7.6); 7.80 (d, 2 H, H(2), H(6), ^3J = 7.4); 10.90 (br.s, 1 H, NHCO)	6.52	7.87 (d, 2 H, H(3), H(5), ^3J = 8.4); 8.05 (d, 2 H, H(2), H(6), ^3J = 8.4)
1d	CONHPh	Ph	7.18 (t, 1 H, H(4), ^3J = 7.2); 7.38 (t, 2 H, H(3), H(5), ^3J = 7.6); 7.80 (d, 2 H, H(2), H(6), ^3J = 7.4); 10.80 (br.s, 1 H, NHCO)	6.40	7.62 (t, 2 H, H(3), H(5), ^3J = 7.5); 7.70 (t, 1 H, H(4), ^3J = 7.4); 8.10 (d, 2 H, H(2), H(6), ^3J = 7.2)
1e	CONH-4-FC_6H_4	Ph	7.27 (t, 2 H, H(3), H(5), $^3J_{H,F}$ = $^3J_{H,H}$ = 8.7); 7.80 (dd, 2 H, H(2), H(6), $^3J_{H,H}$ = 9.0, $^4J_{H,F}$ = 5.1); 11.00 (br.s, 1 H, NHCO)	6.45	7.65 (t, 2 H, H(3), H(5), ^3J = 7.5); 7.70 (t, 1 H, H(4), ^3J = 7.1); 8.10 (d, 2 H, H(2), H(6), ^3J = 7.2)
1f	CONHMe	Ph	2.80 (d, 3 H, Me, J = 4.6); 8.90 (br.s, 1 H, NHCO)	6.40	7.60 (t, 2 H, H(3), H(5), ^3J = 7.8); 7.70 (t, 1 H, H(4), ^3J = 7.8); 8.07 (d, 2 H, H(2), H(6), ^3J = 7.8)
1g	CONHBn	Ph	4.50 (d, 2 H, CH_2, J = 6.3); 7.25—7.35 (m, 5 H, Ph); 9.50 (br.s, 1 H, NHCO)	6.35	7.62 (t, 2 H, H(3), H(5), ^3J = 7.5); 7.68 (t, 1 H, H(4), ^3J = 7.3); 8.08 (d, 2 H, H(2), H(6), ^3J = 7.7)
1h	CONHPh	Me	7.14 (t, 1 H, H(4), ^3J = 7.5); 7.38 (t, 2 H, H(3), H(5), ^3J = 7.8); 7.80 (d, 2 H, H(2), H(6), ^3J = 7.5); 10.90 (br.s, 1 H, NHCO)	6.10	2.47 (s, 3 H, Me)
1i	Ph	4-BrC_6H_4	7.50—7.60 (m, 3 H, H(3), H(4), H(5)); 7.80 (d, 2 H, H(2), H(6), ^3J = 7.2)	6.25	7.72 (d, 2 H, H(3), H(5), ^3J = 8.2); 8.15 (d, 2 H, H(2), H(6), ^3J = 8.3)
1j	COOH	4-BrC_6H_4	—	6.25	7.72 (d, 2 H, H(3), H(5), ^3J = 8.5); 8.05 (2 H, H(2), H(6), ^3J = 8.4)

(EI, 70 eV). Sodium salts of α-hydroxyimino nitriles were prepared according to a procedure described earlier.[12]

Alkylation of sodium salts of oxyimino derivatives 3 with bromo ketones (synthesis of 2a—i, general procedure). A mixture of the sodium salt of oxime **3a—f** (5 mmol), the corresponding bromo ketone (6 mmol), and a solvent (DMF for **2b—e,h**, EtOH for **2a,f,g,i**; 5—10 mL) was stirred at room temperature for 8 h. Then water (5—10 mL) was added to the solution in DMF. After a time, the product was filtered off (when the reaction was carried out in EtOH, the product was filtered without dilution with water), washed on a filter with a small amount of diethyl ether, and dried *in vacuo*.

The yields and melting points of products **2a—i** are listed in Table 1. The ^{1}H NMR spectroscopic data are given in Table 3.

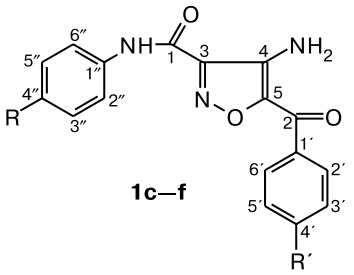
2-(Benzoylmethoxyimino)cyano-*N*-phenylacetamide (2d). Amide **2d** was prepared according to the general procedure from the K salt of hydroxyiminocyano-*N*-phenylacetamide (**3d**) (5.8 g) in a yield of 8.4 g (85%). After recrystallization from EtOH, compound **2d** was isolated in a yield of 6.7 g, m.p. 161—163 °C. The ^{1}H and ^{13}C NMR spectroscopic data are given in Tables 3 and 5, respectively. IR, ν/cm^{-1}: 3472, 3392, 3352 (NH); 1688 (C=O); 1648, 1600, 1540 (CONH). MS, m/z (I_{rel} (%)): 307 $[M]^+$ (20); 173 $[M - PhCOCH_2O]^+$ (16); 146 $[173 - CN]^+$ (14); 119 $[PhCOCH_2]^+$ (55); 105 $[PhCO]^+$ (100); 91 (42); 77 (69).

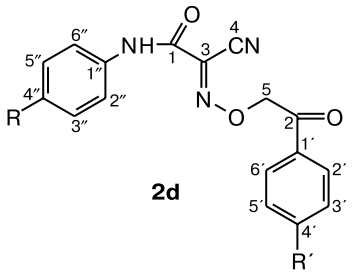
Alkylation of sodium salts of oxyimino derivatives 3 with chloroacetamides (synthesis of 2j—l, general procedure). The corresponding chloroacetamide (8 mmol) and $NaI \cdot 2H_2O$ (1.6 mmol) were added to a suspension of sodium salt **3** (12 mmol) in EtOH (10 mL) and the reaction mixture was stirred at 60 °C for 3 h. The precipitate that formed was filtered off, washed successively with water and EtOH, dried, and additionally recrystallized from AcOH.

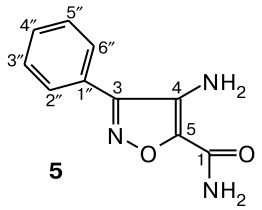
The yields, melting points, and ^{1}H NMR spectroscopic data for compounds **2j—l** are given in Table 1.

Synthesis of 4-aminoisoxazole-3-carboxamides 1a—i (general procedure). A mixture of amide **2a—i** (5 mmol),

Table 5. ^{13}C NMR spectroscopic data for compounds **1c—f**, **2d**, and **5** [18,21]*







Compound	δ (*J*/Hz)									
	C(1)	C(2)	C(3)	C(4)	C(5)	C(1′)	C(2′), C(6′)	C(3′), C(5′)	C(4′)	Other signals
1c	−157.72	−179.0	−148.24	−135.65	−146.66	−138.36	+131.89	+130.72	−127.17	137.58 (C(1″)); +128.69 (C(3″), C(5″)); +124.58 (C(4″)); +120.8 (C(2″), C(6″))
1d	−157.29	−179.7	−147.8	−134.99	−146.5	−137.68	+132.6	+128.25	+128.4	137.15 (C(1″)); +128.32 (C(3″), C(5″)); +124.2 (C(4″)); +120.5 (C(2″), C(6″))
1e	−157.7	−180.25	−148.1	−136.01	−146.9	−138.12	+133.1	+128.79	+128.73	−158.7 (C(4″), $^1J_{C,F}$ = 241.4); −133.95 (C(1″)); +122.7 (C(2″), C(6″), $^3J_{C,F}$ = 8.1); +115.4 (C(3″), C(5″), $^2J_{C,F}$ = 22.3)
1f	−159.56	−180.19	−147.7	−136.0	−146.7	−137.96	+132.99	+128.72	+128.72	+25.59 (MeNH)
2d	154.98	192.6	128.44	107.9	78.52	133.38	133.67	128.51	127.4	136.7 (C(1″)); 128.38 (C(3″), C(5″)); 124.4 (C(4″)); 120.5 (C(2″), C(6″))
5	160.0	—	155.5	132.0	142.5	—	—	—	—	—

* The plus sign of the chemical shift indicates that the signal is not inverted in the APT (Attached Proton Test) experiment, and the minus sign indicates that the signal is inverted.

$LiClO_4 \cdot 3H_2O$ (1 g), and acetonitrile (10—25 mL) was brought to boiling (complete dissolution was observed) and allowed to stand for ~14 h. Then the resulting solution was added dropwise to a solution of $LiOH \cdot H_2O$ (0.2 g) in water (10—20 mL), and the mixture was stirred for 2 h. The precipitate that formed was filtered off, washed successively on a filter with 2% HCl and water, and dried *in vacuo*. The yields and melting points of products **1a—i** are listed in Table 2. The ^1H and ^{13}C NMR spectroscopic data are given in Tables 4 and 5, respectively.

4-Amino-5-benzoylisoxazole-*N*-phenyl-3-carboxamide (1d). A solution of compound **2d** (3 g) and $LiClO_4$ (2 g) in acetonitrile (30 mL) was kept for ~14 h and then concentrated. A suspension of LiOH (0.3 g) in EtOH (20 mL) was added to the residue. The mixture was stirred for 2 h. The residue was filtered off, washed successively on a filter with 2% HCl and water, and dried *in vacuo*. The ^1H and ^{13}C NMR spectroscopic data for compound **1d** are given in Tables 4 and 5, respectively. IR, ν/cm^{-1}: 3328 (NH); 2244 (w, CN); 1688 (C=O); 1572, 1548 (CONH). MS, *m/z* (I_{rel} (%)): 307 $[M]^+$ (18); 202 $[M - PhCO]^+$ (14); 188 $[M - PhNCO]^+$ (24); 119 $[PhNCO]^+$ (18); 105 $[PhCO]^+$ (100); 93 (44); 77 (81).

This study was financially supported by the Du Pont de Nemours.

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Received June 27, 2004;
in revised form December 24, 2004