Synthesis of 4-aminoisoxazole-3-carboxamides using base-promoted nitrosation of *N*-substituted cyanoacetamides

V. P. Kislyi, E. B. Danilova, E. P. Zakharov, and V. V. Semenov*

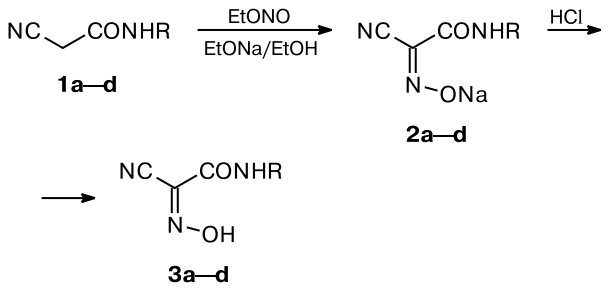
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (095) 135 5328. E-mail: vs@zelinsky.ru

The reactions of *N*-substituted cyanoacetamides with EtONO in the presence of an equimolar amount of EtONa afforded the corresponding sodium salts of hydroxyimino derivatives in 70—95% yields. The latter were transformed into 4-amino-5-(4-bromobenzoyl)isoxazole-3-carboxamides in 30—57% yields using the known method.

Key words: *N*-substituted cyanoacetamides, base-promoted nitrosation, 2-(4-bromophenyl)-2-oxoethoxyiminocyanoacetamides, 4-amino-5-(4-bromobenzoyl)isoxazole-3-carboxamides.

Base-promoted nitrosation of the α-carbon unit in nitriles (*i.e.*, the action of alkyl nitrites in the presence of bases) has previously[1] been used successfully for arylacetonitriles. However, nitrosation under acidic conditions ($NaNO_2$ in the presence of AcOH [2,3] or phosphoric acid) was mainly used for the cyanoacetic acid derivatives.[4] Base-promoted nitrosation of cyanoacetic ester (amyl nitrite, EtONa) was described[5] without indicating conditions, and only a "low yield" was mentioned.

It should be noted that the typical procedure for nitrosation of the cyanoacetic acid derivatives (ester, amide) is inappropriate for *N*-substituted amides **1b—d**, because these compounds are virtually insoluble in water.[6]

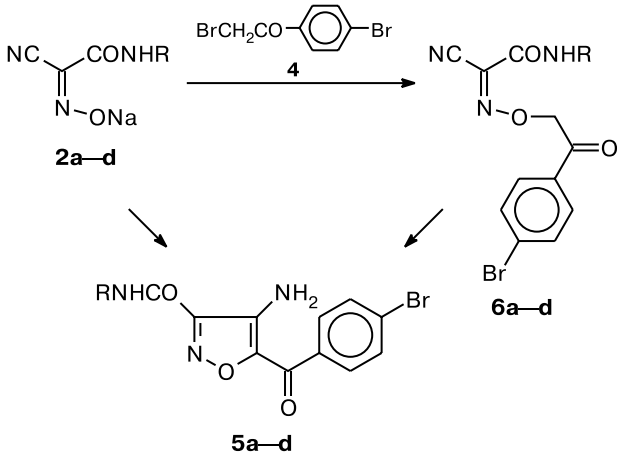


1a—d **2a—d** **3a—d**

R = Me (**a**), CH_2Ph (**b**), Ph (**c**), 2-$MeOC_6H_4$ (**d**)

We established that the addition of a solution of EtONO (in ethanol or diethyl ether) to a suspension of **1a—d** in ethanol in the presence of an equimolar amount of EtONa produces rapidly sodium salts of oximes **2a—d** in high yields. The latter can be transformed into oximes **3a—d** by acidification (Table 1).

Sodium salts of oximes treated with 4-bromophenacyl bromide (**4**) are transformed into 4-amino-5-(4-bromobenzoyl)isoxazole-3-carboxamides **5** *via* the two-step method described previously.[7] The reactions of sodium salts **2** with bromoketone **4** in DMF afford *O*-alkylated oximes **6a—c**, which are transformed into aminoisoxazoles **5a—d** under the treatment of LiOH (see Ref. 7) or KOH in water or aqueous ethanol.



2a—d **6a—d** **5a—d**

R = Me (**a**), CH_2Ph (**b**), Ph (**c**), 2-$MeOC_6H_4$ (**d**)

The presence of the aryl substituent at the amidic nitrogen atom facilitates ring closure: for instance, under the reaction conditions, *O*-substituted oxime **6d** undergoes spontaneous partial ring closure to form isoxazole **5d**.

Both the alkylation of sodium salts of oximes and the reactions with H-forms of oximes in the presence of tri-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 594—596, March, 2004.

Table 1. Yields, melting points, and data of IR and ^{1}H NMR spectra of hydroxyimino derivatives **2a—d** and **3a—d**

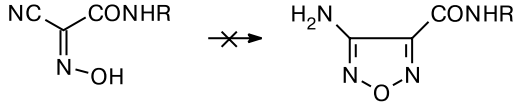
Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Empirical formula	IR		^{1}H NMR (δ, *J*/Hz)
			C	H	N		CN	CO	
2a	95	310—312 (decomp.)	32.2 32.6	2.7 2.8	28.2 28.0	$C_4H_4N_3O_2Na$	2216	1636, 1560	2.8 (d, 3 H, MeNH, *J* = 4.2); 7.4 (br.s, 1 H, NHCO)
2b	83	245—247 (decomp.)	53.3 53.0	3.6 3.7	18.7 18.9	$C_{10}H_8N_3O_2Na$	2215	1650, 1550	4.45 (d, 2 H, PhCH$_2$, *J* = 6.4); 7.2—7.4 (m, 5 H, Ph); 8.00 (1 H, NHCO)
2c	85	222—225 (decomp.)	51.2 51.7	2.8 2.9	19.9 19.2	$C_9H_6N_3O_2Na$	2196	1668, 1604, 1548	7.1—7.7 (m, 5 H, Ph); 10.3 (s, 1 H, NHCO)
2d	70	203—205 (decomp.)	49.8 49.5	3.3 3.7	17.4 17.2	$C_{10}H_8N_3O_3Na$	2200	1670, 1550	3.9 (s, 3 H, OMe); 6.9 (m, 3 H, PhOMe); 8.4 (m, 1 H, PhOMe); 9.6 (br.s, 1 H, NH)
3a	75	208—211*	37.8 37.3	3.4 4.1	33.1 32.9	$C_4H_5N_3O_2$	2244 w	1664, 1552	2.7 (d, 3 H, MeNH, *J* = 4.3); 8.3 (br.s, 1 H, NH); 14.4 (br.s, 1 H, OH)
3b	89	149—152	59.1 59.5	4.4 4.5	20.7 20.6	$C_{10}H_9N_3O_2$	2242 w	1660, 1550	4.4 (d, 2 H, PhCH$_2$, *J* = 6.3); 7.2—7.4 (m, 5 H, Ph); 9.0 (1 H, NHCO); 14.5 (br.s, 1 H, NOH)
3c	85	229—232	57.1 57.6	3.7 3.9	22.2 22.0	$C_9H_7N_3O_2$	2240 w	1660, 1600, 1548	7.2—7.7 (m, 5 H, Ph); 10.3 (s, 1 H, NHCO); 14.5 (br.s, 1 H, NOH)
3d	79	172—174	54.8 54.3	4.1 4.0	19.2 18.7	$C_{10}H_9N_3O_3$	2245 w	1665, 1550	3.9 (s, 3 H, OMe); 6.9 (m, 3 H, PhOMe); 8.4 (m, 1 H, PhOMe); 9.05 (br.s, 1 H, NH); 14.7 (br.s, 1 H, NOH)

* Ref. 6: 212 °C.

ethylamine have been described.[7] We attempted to reproduce the latter procedure and observed the formation of a complex mixture of products containing only insignificant amounts of compounds **5**, and, hence, their isolation was very difficult. The data obtained allow one to conclude that these are precisely the sodium salts of oximes, which are primarily formed by base-promoted nitrosation, that should reasonably be used instead of oximes themselves in the syntheses of 4-aminoisoxazoles.

The structures of the synthesized compounds were confirmed by the IR and ^{1}H NMR spectra (Table 2). The IR spectra of sodium salts of oximes **2a—d** contain a rather intense absorption band of the CN group, although its frequency (2216—2196 cm^{-1}) is strongly decreased compared to that of the CN group in the starting cyanoacetamides (2276—2260 cm^{-1}). At the same time, in the H-forms of oximes **3a—d** and *O*-alkylated oximes **6a—c**, the CN group has an unexpectedly low intensity at the normal frequency (2235—2245 cm^{-1}), while the intensity of the absorption band of the nitrile group in the IR spectra of some alkylated oximes **6** is close to the "noise" level. This is rather unusual. The absence of an absorption band of the CN group has already been mentioned[7] for some compounds of type **6** and is related, probably, to the noticeable conjugation of the CN group in the hydroxyiminocyanoacetamide fragment of compounds of type **6**. At the same time, the structures of compounds **6** seem doubtless, because they were confirmed by the ^{1}H NMR spectra and, in addition, oximes **6** served as the starting compounds for the synthesis of isoxazoles **5**. The ^{1}H NMR spectra of oximes **6** exhibit a narrow singlet of the CH_2CO group at 5.8—6.0 ppm. However, this signal is absent from the ^{1}H NMR spectra of isoxazoles **5**, which contain, by contrast, a noticeably broadened singlet of the amino group at 6.3—6.5 ppm.

It should be noted that hydroxyiminonitriles **3** can be used for the synthesis of 4-aminoisoxazoles and also for syntheses of aminofurazans,[8] 4-aminoisothiazoles,[9] 4-aminoimidazoles,[10] and 5-aminooxazoles.[11] When oximes **3** were heated with hydroxylamine for many hours under the conditions indicated in the study,[8] we detected



3 **7**

R = H (**3e**, **7a**), CH_2Ph (**3b**, **7b**)

Table 2. Yields, melting points, and data of elemental analyses and ^{1}H NMR spectra of isoxazoles **5a—d** and amides **6a—c**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Empirical formula	IR		^{1}H NMR (δ, *J*/Hz)		
			C	H	N		CO	Y*	X**	BrPh	Other signals
5a	72	180—182	44.4 44.5	3.1 3.2	13.0 12.9	$C_{12}H_{10}BrN_3O_3$	1720, 1660	3488, 3364	6.3 (br.s, 2 H)	7.7—8.05 (m, 4 H)	2.90 (d, 2 H, MeNH, *J* = 4.6); 8.55 (br.s, 1 H, NHCO)
5b	63	160—162	54.0 54.1	3.5 3.2	10.5 10.3	$C_{18}H_{12}BrN_3O_3$	1725, 1680	3375, 3300	6.3 (br.s, 2 H)	7.7—8.07 (m, 4 H)	4.50 (d, 2 H, CH_2Ph, *J* = 6.2); 9.20 (br.s, 1 H, NHCO); 7.2—7.4 (m, 5 H, Ph)
5c	55	205—207	52.9 52.7	3.1 3.0	10.9 10.1	$C_{17}H_{12}BrN_3O_3$	1740, 1694	3450, 3350	6.42 (br.s, 2 H)	7.7—8.07 (m, 4 H)	7.2—7.7 (m, 5 H, Ph); 10.7 (s, 1 H, NHCO)
5d	30	158—162	51.9 52.9	3.4 3.9	10.1 10.1	$C_{18}H_{14}BrN_3O_4$	1735, 1690	3455, 3310	6.38 (br.s, 2 H)	7.7—8.1 (m, 4 H)	7.1—8.3 (m, 4 H, MeOPh); 3.97 (s, 3 H, MeOPh); 9.22 (s, 1 H, NHCO)
6a	80	160—162	44.4 44.9	3.1 3.0	13.0 13.8	$C_{12}H_{10}BrN_3O_3$	1692, 1584 w	2240	5.82 (s, 2 H)	7.7—7.93 (4 H)	2.70 (d, 3 H, MeNHCO, *J* = 4.7); 8.3 (br.s, 1 H, NHCO)
6b	64	162—164	54.0 53.7	3.5 3.6	10.5 10.2	$C_{18}H_{14}BrN_3O_3$	1690, 1587 w	2240	5.82 (s, 2 H)	7.7—7.93 (4 H)	4.4 (d, 2 H, CH_2NH, *J* = 6.4); 7.2—7.3 (5 H, Ph); 8.9 (br.s, 1 H, NHCO)
6c	32	194—197	52.8 51.5	3.1 3.7	10.9 10.2	$C_{17}H_{12}BrN_3O_3$	1688, 1604 w	2235	6.0 (s, 2 H)	7.7—7.93 (m, 4 H)	7.1—7.7 (m, 5 H,Ph); 10.45 (s, NHCO)

* Y = NH (**5a—d**), CN (**6a—c**).
** X = $COCH_2$ (**5a—d**), NH_2 (**6a—c**).

no aminofurazans **7** (TLC analysis using as references authentic amides **7a**,**b** obtained from methyl aminofurazan-3-carboxylate[8]).

Experimental

^{1}H NMR spectra were recorded on Bruker AM-300 and Bruker DRX-500 instruments with working frequencies of 300.13 and 500.13 MHz, respectively, in a mixture of DMSO-d_6 and CCl_4 (1 : 3). IR spectra were obtained on a Specord M-80 instrument in KBr pellets.

Base-promoted nitrosation of cyanoacetamides (general procedure). A mixture of concentrated H_2SO_4 (8 mL, *d* = 1.84), ethanol (10.4 mL), and water (84 mL) was slowly added dropwise to a solution of $NaNO_2$ (21.2 g, 0.3 mol) in a mixture of ethanol (92 mL) and water (84 mL) with gradual heating (30—45 °C) and absorption of the released gas (ethyl nitrite) with ethanol (30 mL). An ethanolic solution of EtONO was rapidly added to a suspension of sodium salt of oxime **2**, which was obtained by mixing of *N*-substituted cyanoacetamide **1a—d** (0.07 mol) with a solution of sodium ethoxide (6.8 g, 0.1 mol) in ethanol (50 mL) and stirring of the resulting mixture for 1 h. The mixture was stored for 16 h (in the case of **1b—d**, complete dissolution was observed) and concentrated on a rotary evaporator. Toluene was added to the residue, and sodium salt of hydroxyiminocyanoacetamide **2** was filtered off.

The yields, melting points, and ^{1}H NMR spectra of the products are presented in Table 1.

Synthesis of hydroxyiminocyanoacetamides 3a—d (general procedure). Sodium salt of *N*-substituted isonitrosoacetamide **2** (0.05 mol) was suspended in water (30 mL), the suspension was acidified with hydrochloric acid to pH 5—6 and stirred for 30 min at ~20 °C, and the product was filtered off. The yields, melting points, and ^{1}H NMR spectra of the products are presented in Table 1.

Alkylation of sodium salts of the hydroxyimino derivatives (synthesis of 6a—d, general procedure). A mixture of 4-bromophenacyl bromide (**4**) (1.4 g, 5 mmol), the corresponding sodium salt **2a—d** (5 mmol), and a solvent (8 mL, DMF for **1a** or ethanol for **1b—d**) was stirred for 8 h at ~20 °C and left for 16 h. Then the solvent was evaporated on a rotary evaporator, and water was added to the residue. *O*-Substituted oxime was filtered off, washed with water and hexane on the filter, and dried *in vacuo*. In the case of salt **2d**, a mixture of *O*-alkylated oxime **6d** and the corresponding isoxazole **5d** (~1 : 1) was formed.

The yields, melting points, and ^{1}H NMR spectra of the products are presented in Table 2.

Synthesis of 4-aminoisoxazole-3-carboxamides 5a—d (general procedure). A suspension of compounds **6a—c** (5 mmol) or a **5d** + **6d** mixture (see above) in a solution of $LiOH \cdot H_2O$ (0.6 g) in 40 mL of water (for **6a**) or 40 mL of 50% ethanol (for **6b**,**c**) was stirred for 8 h. The product was filtered off, washed with water on the filter, and dried *in vacuo*.

The yields, melting points, and ^{1}H NMR spectra of the products are presented in Table 2.

References

1. O. Touster, in *Organic Reactions*, Ed. R. Adams, 1953, **7**, 327.
2. M. Conrad and A. Schulze, *Chem. Ber.*, 1909, **42**, 736.
3. M. Fields, D. Walz, and S. Rothchild, *J. Am. Chem. Soc.*, 1951, **73**, 1000.
4. C. O. Parker, *Tetrahedron*, 1962, **17**, 109.
5. A. Muller, *Ann. Chim. Phys.*, 1894, **1**(7), 463.
6. G. Shaw, R. W. Warrener, D. N. Butler, and R. K. Ralph, *J. Chem. Soc.*, 1959, 1648.
7. K. Gewald, P. Bellmann, and H.-J. Jaensch, *Liebigs. Ann. Chem.*, 1980, 1623.
8. G. Longo, *Gazz. Chim. Ital.*, 1931, **61**, 575.
9. K. Gewald and P. Bellman, *Liebigs. Ann. Chem.*, 1979, 1534.
10. M. R. Grimmet, *Adv. Heterocycl. Chem.*, 1970, **27**, 241.
11. J. P. Ferris and L. E. Orgel, *J. Am. Chem. Soc.*, 1966, **88**, 3829.

Received October 13, 2003;
in revised form February 11, 2004