A new method for the synthesis of nitriles enriched with the ^{15}N isotope

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A new synthetic method for the preparation of ^{15}N-labeled nitriles from nonlabeled nitriles is proposed.

Key words: ^{15}N isotope; nitriles; amidoximes.

Nitriles containing the ^{15}N isotope are used in biological and medical studies and for studying reaction mechanisms.[1] There exists a method for obtaining labeled nitriles by treating esters with ^{15}N-containing ammonia followed by dehydration of the amides formed.[2] This method requires a large excess of the ester or a large consumption of $^{15}NH_3$. Furthermore, this method affords high yields only for nitriles that are readily distilled off from the reaction mixture at the dehydration stage, but is of little use for synthesizing heterocyclic nitriles which generally have high boiling points.

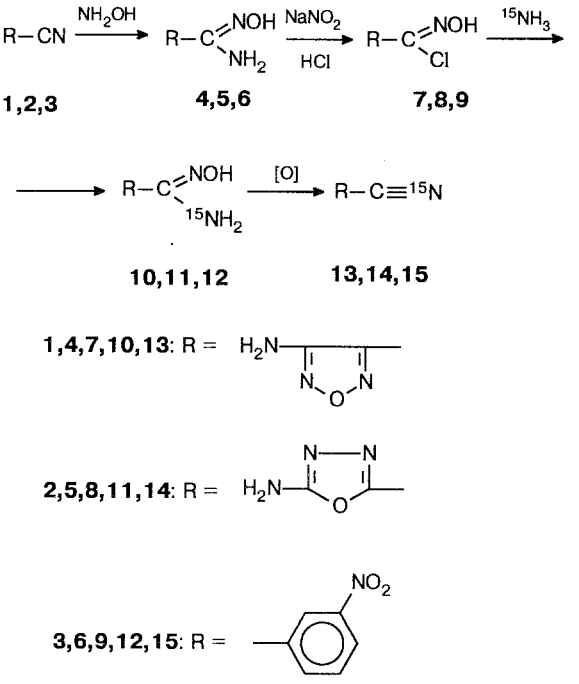
This communication describes a new synthetic method which is not subject to the above drawbacks. Normal nitriles containing no ^{15}N isotope are used as the starting compounds. The synthesis is performed according to Scheme 1.

At the first stage, nitriles **1,2,3** are treated with hydroxylamine by the known procedure[3] under mild conditions to give amidoximes **4,5,6**, which are treated with hydrochloric acid and $NaNO_2$ (*cf.* Ref. 4) to afford hydroximoyl chlorides **7,8,9**. The reaction of compound **7** with $^{15}NH_3$ in ether gave amidoxime **10** in 90.6 % yield. The reaction of compounds **8** and **9** with $^{15}NH_3$ was performed in ethanol to give compounds **11** and **12** in 79—81 % yields. It should be noted that a small excess of $^{15}NH_3$ (1.5—2 mol) was used in all cases.

Only two examples of obtaining nitriles from amidoximes are known, where I_2 (*cf.* Ref. 5) or Pb_3O_4 in glacial acetic acid[6] were used. We studied the action of I_2, Pb_3O_4, dibromoisocyanurate (DBI), and potassium permanganate as oxidants.

It was found that no nitriles are formed from amidoximes when they are oxidized with I_2. The oxidation of amidoxime **10** with DBI was performed in dry acetonitrile at 0—20 °C. When one equiv. of DBI was used, nitrile **13** was formed in 50 % yield, and some amount of the original amidoxime **10** was returned. The use of DBI in greater amounts resulted in side products, while the yield of **13** decreased markedly. Nitrile **13** obtained in this way contained ~100 % of the label.

Scheme 1



The oxidation of amidoxime **10** with potassium permanganate was conducted in a two-phase water—CH_2Cl_2 system in the presence of tetrabutylammonium bromide. The yield of nitrile **13** containing ~100 % of the label was 30 % at room temperature.

A higher yield of ^{15}N-labeled nitrile **13** (75 %) was obtained by treatment of amidoxime **10** with Pb_3O_4 in glacial acetic acid at 70 °C. As in the case of oxidation with DBI or $KMnO_4$, the reaction resulted in ~100%-labeled nitrile **13**.

Since Pb_3O_4 in acetic acid was the most successful in the oxidation of compound **10**, this method was further used to oxidate labeled amidoximes **11** and **12**. The reaction was performed at 20 °C to giye nitriles **14** and **15** in 59 and 70 % yields, respectively.

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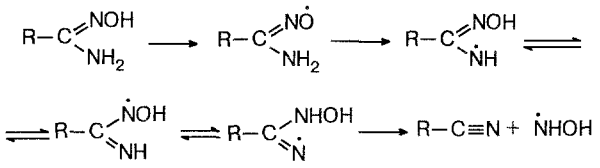
Thus, the method elaborated by us makes it possible to obtain ^{15}N-labeled nitriles in high overall yields (60—65 %) using a relatively small excess of $^{15}NH_3$. As was noted above, the resulting nitriles contain ~100 % of the label.

The presence of the label in the nitriles synthesized was determined using mass spectrometry. The mass spectra of the compounds obtained by us contain the following molecular ion signals: (*m/z*): 111 $[M]^+$ (**13**), 111 $[M]^+$ (**14**), and 149 $[M]^+$ (**15**), respectively.

Probably, the oxidation of amidoximes with Pb_3O_4 in acetic acid has a radical nature[7] and follows Scheme 2.

Scheme 2



A

The ESR spectrum of the reaction mixture obtained by oxidating nonlabeled compound **5** by the action of Pb_3O_4 in acetic acid contains a characteristic signal, *viz.*, an anisotropic triplet with $g = 2.0100$ and $A_{\parallel}^{N} = 12$ Oe due to splitting at the ^{14}N nuclei with the nuclear spin $I = 1$. Evidently, this signal can be attributed to radical **A**, the spin density of which is localized on the nitrogen atom not bonded with hydrogen atoms.

Experimental

IR spectra were recorded in KBr pellets on a UR-20 spectrophotometer. ^1H NMR spectra were obtained on a Tesla B-467 spectrometer, and mass spectra were obtained on a Varian MAT CH-6 spectrometer with direct insertion of samples into the source. ESR spectra were recorded at 300 and 77 K on an ERS-220 spectrometer ($\lambda = 3.2$ cm).

Synthesis of hydroximoyl chlorides

3-Amino-1,2,5-oxadiazole-4-carbohydroximoyl chloride (7) and *m*-nitrobenzhydroximoyl chloride (9) were obtained by the known procedures.[4,8]

2-Amino-1,3,4-oxadiazole-5-carbohydroximoyl chloride (8). 10 % Hydrochloric acid (20 mL) was added dropwise to a stirred suspension of amidoxime **5** (0.6 g, 4.2 mmol) until complete dissolution of the latter, then $NaNO_2$ (0.44 g, 6.3 mmol) was added in small portions at 0 °C. The mixture was stirred for 30 min. The precipitate formed was filtered off and washed with water and acetone to give 0.53 g (78 %) of compound **8**, m.p. 236 °C (dec.). Found (%): C, 21.87; H, 1.99; Cl, 21.83; N, 34.66. $C_3H_3ClN_4O_2$. Calculated (%): C, 22.15; H, 1.85; Cl, 21.85; N, 34.46. ^1H NMR [$(CD_3)_2SO$], δ: 7.56 (s, 2 H, NH_2); 13.68 (s, 1 H, NOH). MS, *m/z*: 162, 164 $[M]^+$.

Synthesis of ^{15}N-labeled amidoximes

3-Amino-1,2,5-oxadiazole-4-carbamidoxime (10). A solution of hydroximoyl chloride **7** (1 g, 6 mmol) in dry ether (200 mL) was saturated with ^{15}N-labeled ammonia (0.2 g, 12 mmol; label content 95.4 %). The mixture was kept at room temperature for one day, washed with water, and dried with $MgSO_4$. The solvent was removed, and the residue was crystallized from ethanol to give 0.8 g (90.6 %) of compound **10**, m.p. 196—199 °C (*cf.* Ref. 9: m.p. 196—199 °C). MS, *m/z*: 144 $[M]^+$.

2-Amino-1,3,4-oxadiazole-5-carbamidoxime (11). Labeled ammonia (0.046 g, 2.7 mmol) was passed through a solution of hydroximoyl chloride **8** (0.3 g, 1.8 mmol) in ethanol (20 mL). The reaction mixture was concentrated to ~5 mL. The precipitate formed was filtered off and washed with water and acetone to give 0.19 g (79 %) of product **11**, m.p. 220 °C (dec.) (*cf.* Ref. 10: m.p. 220 °C(dec.)). MS, *m/z*: 144 $[M]^+$.

***m*-Nitrobenzamidoxime (12).** Labeled ammonia (0.031 g, 1.8 mmol) was passed through a solution of hydroximoyl chloride **9** (0.2 g, 0.9 mmol) in ethanol (10 mL). The mixture was kept for 1 h at room temperature and concentrated to ~3 mL. The precipitate formed was filtered off and crystallized from ethanol to give 0.147 g (81 %) of compound **12**, m.p. 174 °C (*cf.* Ref. 3: m.p. 174 °C). MS, *m/z*: 182 $[M]^+$.

Synthesis of ^{15}N-labeled nitriles

3-Amino-1,2,5-oxadiazole-4-carbo(^{15}N)nitrile (13).

***a*. Oxidation of amidoxime 10 with DBI.** DBI (0.29 g, 0.7 mmol) was added at 0 °C to a stirred solution of amidoxime **10** (0.1 g, 0.7 mmol) in dry acetonitrile (3 mL). The mixture was kept for one day at room temperature. The acetonitrile was distilled off, and the residue was extracted with ether, washed with dilute sodium bisulfite and water, and dried with $MgSO_4$. The solvent was removed, and the residue was purified by TLC (silica gel, ethyl acetate—hexane, 1:2) to give 0.04 g (50 %) of compound **13**, m.p. 83—84 °C (*cf.* Ref. 6: m.p. 83—84 °C). MS, *m/z*: 111 $[M]^+$.

***b*. Oxidation of amidoxime 10 with potassium permanganate.** A solution of amidoxime **10** (0.1 g, 0.7 mmol) in CH_2Cl_2 (5 mL), $KMnO_4$ (0.5 g), and tetrabutylammonium bromide (0.1 g) in water (5 mL) was stirred for 10 h at room temperature. The organic layer was separated, the aqueous phase was extracted with methylene dichloride, and the combined extract was dried with $MgSO_4$. The solvent was removed, and the residue was purified by TLC (silica gel, ethyl acetate—hexane, 1:2) to give 0.024 g (30 %) of compound **13**, m.p. 83—84 °C. MS, *m/z*: 111 $[M]^+$.

***c*. Oxidation of amidoxime 10 with Pb_3O_4 in acetic acid.** Red lead (17.8 g) was added in 5—8 g portions at ≤ 25 °C for 10 min to a vigorously stirred solution of amidoxime **10** (11.44 g, 0.08 mol) in glacial acetic acid (50 mL). Stirring was continued at 60—70 °C until complete dissolution of the red lead (~1.5 h). The reaction mixture was poured into water (300 mL), and the product was extracted with ether. The extract was washed with 10 % $NaHCO_3$ and dried with $MgSO_4$, then the solvent was distilled off, and the residue was crystallized from ethanol to give 6.6 g (75 %) of compound **13**, m.p. 83—84 °C. MS, *m/z*: 111 $[M]^+$.

2-Amino-1,3,4-oxadiazole-5-carbo(^{15}N)nitrile (14). Red lead (0.47 g) was added portionwise at ≤ 25 °C to a vigorously stirred solution of ^{15}N-labeled amidoxime **11** (0.3 g, 2 mmol) in 30 mL of glacial acetic acid. The mixture was stirred for

2.5 h and then poured into water (~100 mL). The product was extracted with ethyl acetate, and the extract was washed with 10 % $NaHCO_3$, dried with $MgSO_4$, and concentrated to give 0.136 g (59 %) **14**, m.p. 189—190 °C (*cf.* Ref. 10: m.p. 189—190 °C). MS, *m/z*: 111 $[M]^+$.

***m*-Nitrobenzo(^{15}N)nitrile (15).** Red lead (0.24 g) was added portionwise at ≤ 25 °C to a vigorously stirred solution of ^{15}N-labeled amidoxime **12** (0.2 g, 1 mmol) in acetic acid (10 mL). The mixture was stirred for 1.5 h and poured into water (~30 mL). The product was extracted with ether; the extract was washed with 10 % $NaHCO_3$, dried with $MgSO_4$, and concentrated to give 0.114 g (70 %) **15**, m.p. 118 °C (*cf.* Ref. 11: m.p. 118 °C). MS, *m/z*: 149 $[M]^+$.

References

1. J. L. Hicks, R. W. Sheencan, and J. D. Harfman, *J. Label. Compound Radiopharm.*, 1991, **29**, 415.
2. V. N. Yarovenko, V. K. Taralashvili, I. V. Zavarzin, and M. M. Krayushkin, *Tetrahedron,* 1990, **46**, 3941.
3. F. Eloy and R. Lenaers, *Chem. Rev.*, 1962, **62**, 155.
4. M. Kocevar, L. Polanc, and M. Sollner, *Synth. Comm.*, 1988, **18**, 1427.
5. F. Eloy and R. Lenaers, *Chem. Rev.*, 1962, **62**, 167.
6. V. Andrianov and A. Eremeev, *Khim. Geterotsikl. Soedin.*, 1994, in press [*Chem. Heterocycl. Compd.* (Engl. Transl.)].
7. N. Ooi and D. Wilson, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1792.
8. A. Werner, *Ber.*, 1894, **27**, 2847.
9. T. Ichikawa, T. Kato, and T. Takenishi, *J. Heterocycl. Chem.*, 1965, **2**, 253.
10. F. M. Stoyanovich, E. P. Zakharov, O. V. Lysenko, V. N. Yarovenko, and M. M. Krayushkin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 243 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, **40**, 225 (Engl. Transl.)].
11. B. M. Bogoslovskii, *Zh. Obshch. Khim.*, 1938, **8**, 1784 (in Russian).

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