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Preliminary communication

A new, facile synthesis of 2-amino-(pento- and hexo-furano)oxazoline derivatives*

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Many syntheses of purine and pyrimidine nucleosides *via* oxazoline intermediates have been reported[1–12] since 1970. Our interest in further exploring the use of carbohydrate-oxazoline derivatives as intermediates in the synthesis of nucleosides and nucleotides has led us to investigate methods for the more efficient preparation of these compounds. We have focused on the reaction of glycosylamines with cyanamide as a new, facile method for the preparation of 2-aminoglyco-oxazolines. This general approach is appealing, because it potentially provides nucleosides and nucleotides[13] without employing conventional protection and deprotection schemes, maintaining strictly anhydrous conditions, or using exotic catalysts[14,15]. Furthermore, we find that the use of di-^{15}N-labeled cyanamide produces the di-^{15}N-labeled 2-aminoglyco-oxazoline. This reaction affords a direct and efficient route to di-^{15}N-labeled anhydronucleosides.

We now report a new procedure for the facile synthesis, in 80–90% yield, of 2-aminoglycofurano-oxazoline derivatives that involves treatment of either unprotected or *O*-isopropylidenated glycosylamines with cyanamide in methanol for 1–2 days at room temperature. Included in the study were α-D-arabinopyranosylamine (**1**), and examples in the D-ribose, D-xylose, D-glucose, and L-sorbose series, and their di-^{15}N-labeled derivatives. The structures and purity, both of unlabeled and labeled compounds, were established by comparison with authentic samples of the three 2-aminoglyco-oxazolines[2,5] known, and were further characterized by ^{1}H-, ^{13}C-, and ^{15}N-n.m.r. spectroscopy.

Previously[1–4], 2-amino-(1,2-dideoxy-β-D-arabinofurano)[1,2-*d*]-2-oxazoline (**3**) had been prepared by heating unprotected D-arabinose in aqueous (or methanolic) solution with cyanamide (**2**) in the presence of a basic catalyst (*e.g.*, $KHCO_3$) for several hours, con-

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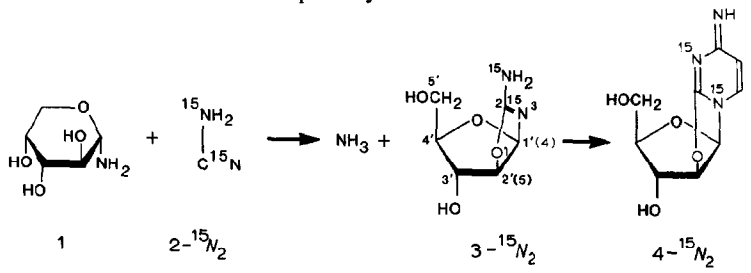
ditions that generate considerable proportions of such cyanamide polymerization products as dicyandiamide. Hsi[4] found that these by-products can be quite difficult to separate completely from 3. This is especially troublesome if a high yield of chromatographically pure, labeled 3 is needed for subsequent syntheses.



We have also obtained results[13] that indicate a somewhat limited stability of 2-aminoglyco-oxazoline derivatives on heating in aqueous solution under basic conditions. Our synthesis has the advantage of not requiring either heat or a basic catalyst. Glycosylamines appear to be inherently more reactive than free aldoses in reactions with cyanamide. Methanol is the solvent of choice for our synthesis, because hydrolysis of the glycosylamine is minimized, and this solvent is readily removed, along with the volatile by-product, ammonia.

The ultimate disposition of the nitrogen atom in the reaction was probed by using cyanamide-$^{15}N_2$. Nucleophilic attack by the nitrogen atom of the glycosylamine on cyanamide-$^{15}N_2$ would have yielded a mono-^{15}N-labeled 2-aminoglyco-oxazoline. Alternatively, if cyanamide-$^{15}N_2$ attacks an imonium-ion intermediate derived from the glycosylamine, a di-^{15}N-labeled 2-aminoglyco-oxazoline (3-$^{15}N_2$) would result. The spectra shown in Figs. 1 and 2 are entirely consistent with quantitative incorporation of *both* of the ^{15}N-labels of

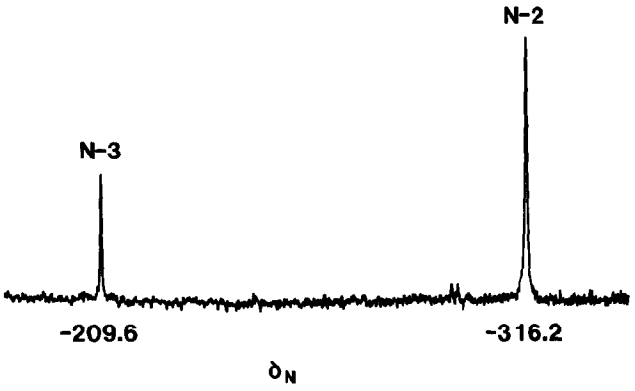


Fig. 1. Proton-decoupled, ^{15}N-n.m.r. spectrum (3,433 scans) of 2-amino-(1,2-dideoxy-β-D-arabinofurano)-[1,2-*d*]-2-oxazoline-$^{15}N_2$ (3-$^{15}N_2$) in dimethyl sulfoxide-d_6 solution (60 mM) at 40.5 MHz and 298 K. [The ^{15}N chemical-shifts are given in p.p.m. upfield from the nitrate ^{15}N signal of saturated aqueous $NH_4{}^{15}NO_3$ in an external, reference, capillary tube.]

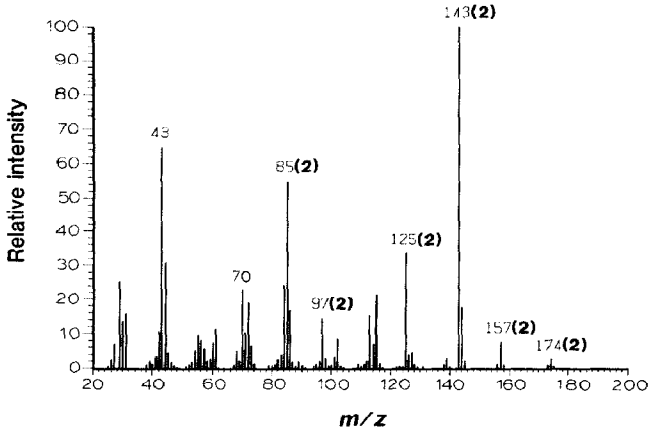


Fig. 2. Electron-impact, mass spectrum of 2-amino-(1,2-dideoxy-β-D-arabinofurano)[1,2-*d*]-2-oxazoline (**3**). [The mass shifts for the ^{15}N-labeled derivative (**3**-$^{15}N_2$) are shown in parentheses.]

the cyanamide-$^{15}N_2$ into **3**-$^{15}N_2$, indicating that it was the nitrogen atom of the glycosylamine that was lost. The observation of two singlets, at −209.6 and −316.2 p.p.m., in the proton-decoupled, ^{15}N-n.m.r. spectrum (see Fig. 1) of **3**-$^{15}N_2$ is consistent with the presence of two nitrogen-15 atoms in very different chemical environments. In addition, we have obtained[13] other ^{15}N-n.m.r. results that indicate that a single tautomer having an endocyclic, double bond preponderates in the equilibrium.

The electron-impact, mass spectrum (see Fig. 2) of **3**-$^{15}N_2$ contains a molecular ion at *m/z* 176 (3.8%). The observation of an $[M - CH_2OH]^+$ fragment provides additional support for the assignment of a furanoid structure to **3**-$^{15}N_2$, a feature that we confirmed by ^{1}H-n.m.r. spectroscopy at 400 MHz. The extent of incorporation of ^{15}N, calculated from the relative abundances of the $[M - CH_2OH]^+$ fragments, was found to be consistent with complete incorporation of both of the ^{15}N labels from the original cyanamide-$^{15}N_2$ (96.7 atom%).

Our results demonstrate the utility of ^{15}N-n.m.r. spectroscopy in the study of relevant reaction-mechanisms and tautomeric equilibria. The use of glycosylamine intermediates in the synthesis both of unlabeled and di-^{15}N-labeled pentose- and hexose-derived 2-amino-oxazolines provides an efficient pathway for the synthesis both of unlabeled and labeled pyrimidine anhydronucleosides, as, for example, the conversion of **3** into **4** already demonstrated[1,4].

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