



# Synthesis of a $^{13}\text{C}$ , $^{15}\text{N}$ labeled imidazole and characterization of the 2,5-endoperoxide and its decomposition<sup>†</sup>

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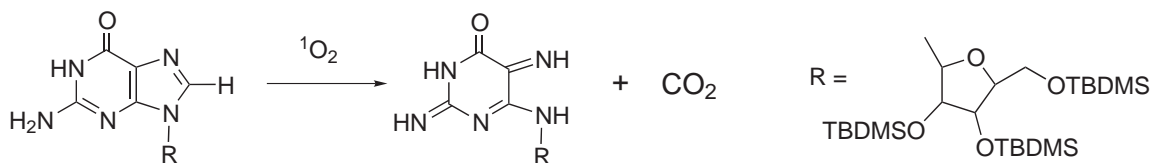
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## Abstract

A synthesis of  $^{13}\text{C}$ ,  $^{15}\text{N}$  labeled imidazoles was developed which allows the direct detection of a transient 2,5-endoperoxide at  $-100^\circ\text{C}$ . The endoperoxide was thoroughly characterized by  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{15}\text{N}$  NMR. Upon warming, the endoperoxide decomposes via a series of transient intermediates to  $^{13}\text{CO}_2$  and 1,2-diphenyl-ethanediimine. © 2000 Elsevier Science Ltd. All rights reserved.

**Keywords:**  $^{13}\text{C}$ ,  $^{15}\text{N}$  labeled imidazoles; singlet oxygen; endoperoxide; carbon dioxide.

In a study of the mechanism of photosensitized oxidation of guanosine, we found that the 8-C of guanosine is oxidized to form  $\text{CO}_2$  (Scheme 1). Only the 5-membered imidazole ring was cleaved, leaving the 6-membered ring intact.<sup>1</sup> Because of the structural similarity of imidazole and guanosine, we looked for reports of  $\text{CO}_2$  formation in the photosensitized oxidation of imidazoles but found none.<sup>2–9</sup>



Scheme 1.  $\text{CO}_2$  formation in photosensitized oxidation of a guanosine derivative

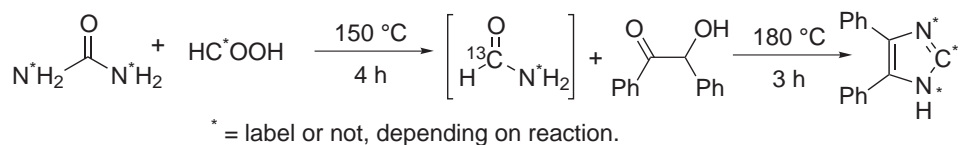
We were also able to detect several transient intermediates in the photosensitized oxidation of an 8- $^{13}\text{C}$  labeled guanosine derivative by low temperature NMR. For unlabeled 4,5-diphenylim-

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<sup>†</sup> Dedicated to Professor Harry Wasserman on the occasion of his 80th birthday.

imidazole, no transient intermediates could be detected other than the endoperoxide. In order to characterize possible transient species, we have prepared 2-<sup>13</sup>C-1,3-<sup>15</sup>N-4,5-diphenylimidazole and now report characterization of the 2,5-endoperoxide and some of its decomposition products.

In order to synthesize the <sup>13</sup>C, <sup>15</sup>N labeled imidazole, we evaluated various synthetic routes.<sup>10–18</sup> Most of the methods are not suitable because of lack of availability of labeled starting material. We chose a procedure reported by Bakibaev et al.<sup>18</sup> and Novelli.<sup>17</sup> A mixture of <sup>15</sup>N-urea and <sup>13</sup>C-formic acid was heated at 150°C for 4 hours. Benzoin was then introduced and the reaction mixture heated at 180°C for 3 hours. The product was suspended in water. After filtration, the powder was resuspended in 5% HCl and heated to 80–90°C. The filtrate was treated with an excess of NH<sub>3</sub> to give pure 4,5-diphenylimidazole in 80% yield (Scheme 2). This method should also be applicable to the synthesis of other <sup>13</sup>C and <sup>15</sup>N labeled imidazoles.



Scheme 2. Syntheses of <sup>13</sup>C, <sup>15</sup>N isotope labeled 4,5-diphenylimidazole

This synthetic method is versatile and selective. We prepared 1,3-<sup>15</sup>N-4,5-diphenylimidazole, 2-<sup>13</sup>C-4,5-diphenylimidazole, and 2-<sup>13</sup>C-1,3-<sup>15</sup>N-4,5-diphenylimidazole, respectively. In all three cases, the incorporation of isotope into imidazole is almost 100%. The structures of labeled imidazoles were confirmed by <sup>1</sup>H NMR, <sup>13</sup>C NMR, and high resolution MS. We also observed splitting of the <sup>1</sup>H peak by <sup>13</sup>C and <sup>15</sup>N, and of the <sup>13</sup>C peak by <sup>1</sup>H and <sup>15</sup>N (Table 1). Splitting of the <sup>15</sup>N peak by <sup>1</sup>H and <sup>13</sup>C was not observed in the imidazole, but was detected in the products. These magnetic interactions are very useful in the identification of the transient intermediates.

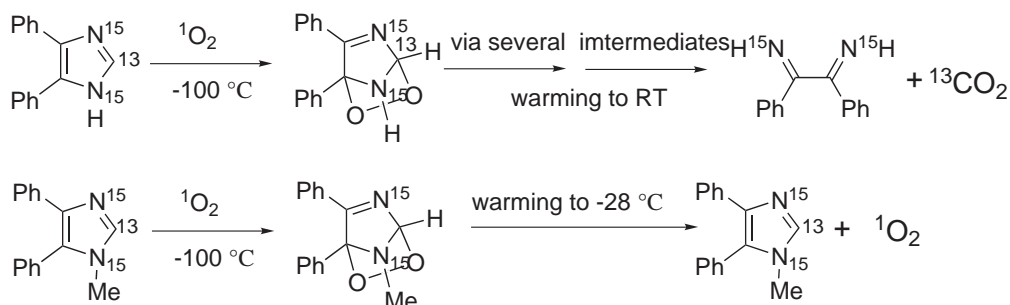
Table 1  
<sup>1</sup>H/<sup>13</sup>C/<sup>15</sup>N couplings (Hz) in 2-<sup>13</sup>C-1,3-<sup>15</sup>N-diphenylimidazole and 2,5-endoperoxide

	$J_{1\text{H}-1\text{N}}$	$J_{1\text{N}-1\text{H}}$	$J_{2\text{C}-2\text{H}}$	$J_{2\text{H}-2\text{C}}$	$J_{2\text{C}-\text{N}}$	$J_{\text{N}-2\text{C}}$	$J_{2\text{H}-\text{N}}$
<sup>13</sup> C, <sup>15</sup> N imidazole	96.4	n/a	207.1	207.0	5.0	n/a	10.3
2,5-Endoperoxide	69.7	70.0	193.5	194.5	4.9, 5.1	n/a	4.9, 5.3

The synthesis of labeled imidazole also provides some information on the mechanism of the hydroamination of ketone by urea in formic acid. It was reported that the thermal dissociation of methylurea involves two paths: the formation of methylamine and isocyanic acid, and the formation of ammonia and methylisocyanate.<sup>12</sup> Bakibaev et al.<sup>18</sup> suggested that the formamide is formed from the isocyanic acid and not from formic acid. Our observation that the <sup>13</sup>C of the formic acid is totally incorporated into imidazole indicates that <sup>13</sup>C formamide is formed from ammonia and formic acid, and reacts with benzoin to give 4,5-diphenylimidazole. The second nitrogen presumably comes either from formamide or ammonia, which is present in the reaction mixture (odor).

Photosensitized oxidation of  $^{13}\text{C}$  and/or  $^{15}\text{N}$  labeled 4,5-diphenylimidazole was carried out in a 5 mm NMR tube at  $-100^\circ\text{C}$  under oxygen with ca.  $5 \times 10^{-5}$  M 2,9,16,23-tetra-*tert*-butyl-29*H*,31*H*-phthalocyanine as sensitizer and a Cermax 300w Xenon lamp as the light source. A chromium glass filter was used to cut off wavelengths below 547 nm. The starting material was dissolved in a solvent mixture of acetone- $d_6$  and fluorotrichloromethane (1:5, ca. 0.04 M). After 1 hour of photolysis, the tube was transferred to a precooled NMR probe. We detected one intermediate by NMR at  $-100^\circ\text{C}$ . This was assigned as the 2,5-endoperoxide based on the NMR spectra. In the  $^1\text{H}$  NMR, the 2C–H of the starting material (at 7.75 ppm) disappeared, and a new peak appeared at 6.92 ppm, split by the 2- $^{13}\text{C}$  and by the 1,3- $^{15}\text{N}$ . (Table 1) The NH peak (12.3 ppm at  $-80^\circ\text{C}$  for starting material) was at 5.06 ppm in the endoperoxide, split by 1- $^{15}\text{N}$ .  $^{13}\text{C}$  NMR shows the 2- $^{13}\text{C}$  peak shifted from 135.6 to 102.1 ppm. This is a tertiary carbon split by the 2-H, and also by 1,3- $^{15}\text{N}$ , which indicates that the 5-membered ring is intact. An HMQC spectrum confirmed the coupling between the 102.1 ppm carbon and the 6.92 ppm hydrogen. There are two peaks in the  $^{15}\text{N}$  NMR spectrum, at 307.0 and 111.6 ppm. The first peak is assigned to the 3- $^{15}\text{N}$  and the second to the 1- $^{15}\text{N}$  because the 111.6 ppm peak was split by a directly bonded hydrogen.

Upon warming the reaction mixture to  $-88^\circ\text{C}$ , the endoperoxide started to decompose to several other transient intermediates. We are currently working on the structure assignment of these intermediates. The final products are  $^{13}\text{CO}_2$  (124.5 ppm) and 1,2-diphenyl ethanediimine (FAB-MS: 209.1  $[\text{M}+1]^+$ ). We isolated the hydrolysis product benzil from the reaction mixture after workup) (Scheme 3). No starting material was recovered. The decomposition of the endoperoxide is triggered by the rearrangement of the 1N–H, since this peak disappeared as the endoperoxide decomposed. This observation suggested that substitution of the N–H with *N*-methyl would stabilize the endoperoxide.



Scheme 3. 2,5-Endoperoxide formation

The photosensitized oxidation of *N*-methyl-4,5-diphenylimidazole was carried out under similar conditions. The endoperoxide (2C at 105.1 ppm) is much more stable than the unmethylated derivative, and does not decompose until  $-28^\circ\text{C}$ . The decomposition of the endoperoxide regenerated the starting material as the main product (Scheme 3). Adding a methyl to the 1N position of the imidazole totally changes the reaction pathway of the endoperoxide rearrangement, which suggests that proton transfer from the N–H is much more facile than the extrusion of oxygen.<sup>7</sup>

In summary, an efficient synthesis of  $^{13}\text{C}$  monolabeled,  $^{15}\text{N}$  double labeled, and  $^{13}\text{C}$ ,  $^{15}\text{N}$  triple labeled 4,5-diphenylimidazole from readily available  $^{13}\text{C}$  formic acid and  $^{15}\text{N}$  urea was devised. The 2,5-endoperoxide from the photosensitized oxidation of the labeled imidazole was characterized. Upon warming, the endoperoxide decomposed via a series of transient intermediates to  $^{13}\text{CO}_2$  and 1,2-diphenyl-ethanediimine.

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