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A NEWLY DEVISED METHOD FOR THE OXIDATIVE UNMASKING OF 1,*N*^{6}-ETHENOADENOSINES: FACILE CONVERSION OF ADENOSINE INTO 2-DEUTERATED ADENOSINE

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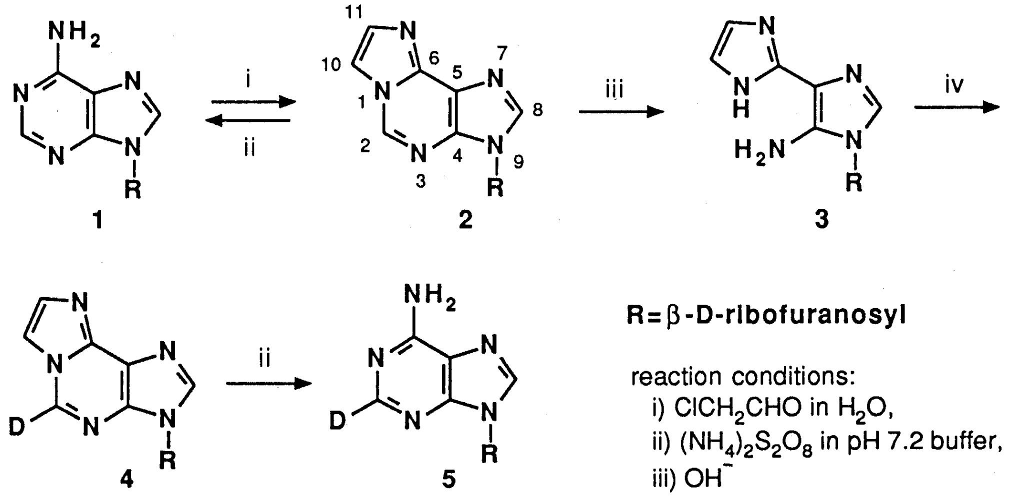
2-Deuterated adenosine (**5**) was conveniently prepared from adenosine (**1**) by applying the ring-fission and reclosure methodology of 1,*N*^{6}-ethenoadenosine (**2**) and a new oxidative unmasking method of the etheno moiety.

KEYWORDS 1,*N*^{6}-ethenoadenosine; oxidative unmasking; adenosine; 2-deuterated adenosine

1,*N*^{6}-Ethenoadenosine (**2**) has been extensively investigated from viewpoints of fluorescent probe in biochemical studies 1) and of mutagenicity of vinyl chloride and its equivalents. 2) The diverse chemical reactivities of **2** were also documented, 3) and some of them were applied to the chemical modification at the 2-position of adenosine (**1**) and its derivatives. 4,5)

Alkaline hydrolysis of **2** occurs with ease to give 3-β-D-ribofuranosyl-4-amino-5-(imidazol-2-yl)imidazole (**3**) which is recycled to 2-substituted 1,*N*^{6}-ethenoadenosines upon treatment with various reagents. 4) Unmasking of the etheno moiety is achieved by bromination using *N*-bromosuccinimide (NBS) followed by alkaline treatment. 5) Thus, Yamaji et al. have succeeded in the preparation of various 2-substituted adenosine 3',5'-cyclic phosphates by application of ring-fission and reclosure methodology to 1,*N*^{6}-ethenoadenosine 3';5'-cyclic phosphates and subsequent unmasking of the etheno moiety. 5)



R=β-D-ribofuranosyl

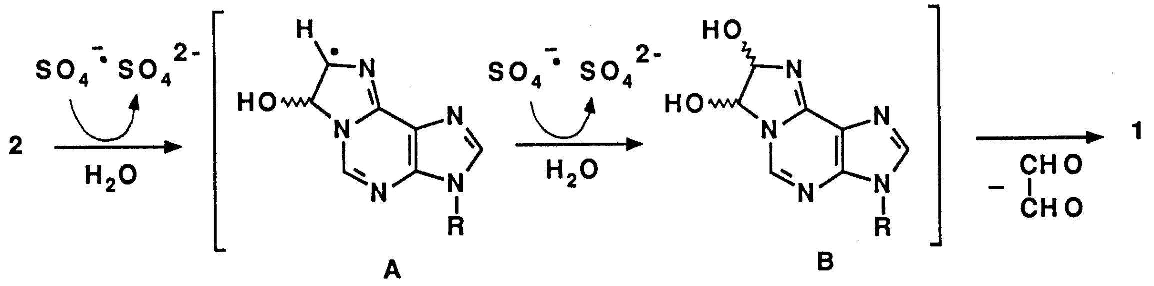
reaction conditions:
i) $ClCH_2CHO$ in H_2O,
ii) $(NH_4)_2S_2O_8$ in pH 7.2 buffer,
iii) OH^-
iv) $CD(OEt)_3$ in DMA

Chart 1

For the extensive application of **2** to the chemical modification at the 2-position of **1**, however, a more efficient method under mild conditions for the unmasking of the etheno group seems to be requisite because the previous method (NBS-alkaline treatment) is not always satisfactory in view of its efficacy and versatility.

This paper describes a newly devised method for the unmasking of the etheno moiety in **2**, which involves oxidation with ammonium persulfate [$(NH_4)_2S_2O_8$] under mild conditions, and its application to the convenient preparation of 2-deuterated adenosine (**5**). The present methodology promises to be applicable to the chemical modification of **1** and its derivatives in a wide scope.

The 1,N^6-ethenoadenosine **2** was prepared in 90% yield by the reaction of **1** with chloroacetaldehyde according to the procedure previously reported.[6)] In order to remove the etheno moiety in **2**, some oxidants such as hydrogen peroxide, lead tetraacetate,[7)] iodosylbenzene diacetate,[7)] and $(NH_4)_2S_2O_8$ were examined under various conditions. Among them, employment of $(NH_4)_2S_2O_8$ as an oxidant resulted in the most smooth unmasking of **2** to give **1**; *i.e.*, when **2** was treated with two equimolar amounts of $(NH_4)_2S_2O_8$ in pH 7.2 phosphate buffer at 80 °C for 4h, **1** was obtained almost quantitatively. Peroxydisulfate ion ($S_2O_8^{2-}$) generates sulfate anion radical ($SO_4^{-\cdot}$), a very strong single-electron oxidant, under the conditions employed.[8)] Thus, the possible reaction sequence for the oxidative unmasking is outlined as shown in Chart 2. The electron-rich etheno moiety undergoes single-electron oxidation by $SO_4^{-\cdot}$ to give a cation radical which reacts with water to give a radical **A** (an alternative structure possessing a hydroxy group at the 11-position is also possible). Further single-electron oxidation of **A** by $SO_4^{-\cdot}$ and subsequent trapping of the resulting cation by water produce an unisolable 10,11-diol intermediate **B**. Elimination of glyoxal from **B** results in the formation of **1**.



R= β-D-ribofuranosyl

Chart 2

The hydrogen-isotope labeling of nucleic acid bases is required in nucleic acid research. Although many papers have already appeared on facile deuteration at the 8-position of **1** and its reversibility in water,[9,10)] the methods for the preparation of stable and more useful 2-deuterated adenosine **5** as a labeled adenosine are limited to only a few examples. Previous preparative methods of **5** involve the ring-fission and reclosure reactions *via* adenosine N_1-oxide,[11)] catalytic hydrogen-atom exchange of **1** using platinum catalyst-deuterium gas at both the 2- and 8-positions followed by regioselective delabeling from the 8-position by water,[12] and isotopic hydrogenolysis of 2-halogenoadenosine.[13] These methods, however, may frequently be tedious, inconvenient, or difficult to carry out and do not always guarantee the magnitude of labeling.

Upon employment of the present oxidative unmasking method, we attained the convenient preparation of **5** as follows. According to the previously reported procedure,[14] alkaline treatment of **2** gave the ring-cleavage compound **3** in 75% yield. Condensation of **3** with deuterated ethyl orthoformate [$CD(OEt)_3$, D-content: 97%][15] in *N*,*N*-dimethylacetamide at 100°C for 4h resulted in the smooth formation of 2-deuterated 1,N^6-ethenoadenosine (**4**)(D-content: 96%) in 90% yield. In a manner similar to the case of **2**, the etheno moiety in **4** was easily unmasked to give the 2-deuterated adenosine **5** (D-content: 94%) in 91% yield (58% total yield from **1**). The structure of **5** was confirmed by comparison of ^1H-NMR and mass spectral data with those of **1** and 8-deuterated adenosine. The present method for the preparation of **5** is superior to the previous methods in view of both yield and isotopic purity.

The extension of the present methodology to the facile conversion of **1** into various types of 2-substituted adenosines is in progress.

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