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Synthesis of Novel Isoxazolinyl Substituted Imidazo[1,2-a]pyridine *C*-Nucleoside Analogs

Shifeng Pan, Guoping Wang, Raymond F. Schinazi† and Kang Zhao*

Department of Chemistry, 29 Washington Place, New York University, New York, NY 10003, USA
† Research Center for AIDS and HIV Infections, Veterans Affairs Medical Center, Decatur, GA 30033, and Laboratory of Biochemical Pharmacology, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA 30322

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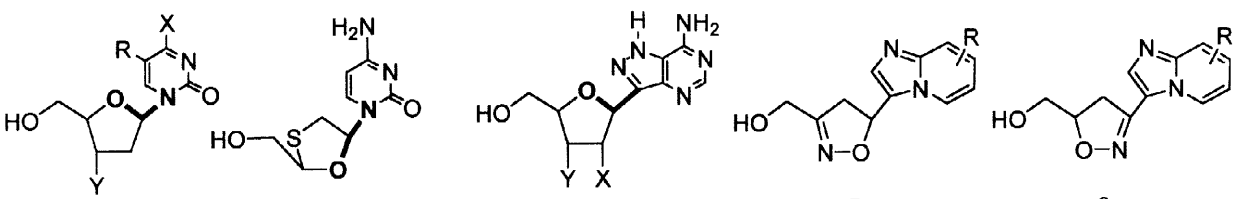
Abstract: Isoxazoline rings have been successfully connected to imidazo[1,2-a]pyridine derivatives *via* carbon-carbon bonds for the synthesis of new *C*-nucleoside analogs **7** and **8**. These two isomers, possessing altered positions of nitrogen and oxygen atoms, can be formed through dipolar cycloaddition reactions of the appropriate olefins and nitrile oxides.

The design of novel "ribose" rings has been an important strategy in the discovery of effective anticancer and antiviral agents.[1,2] Remarkable progress has been made in the field of *N*-nucleoside chemistry in which the bases of nucleosides are connected with "ribose" rings *via* carbon-nitrogen bonds **1-3** (Figure **I**).[1] A variety of structurally diversified antiviral agents result from coupling nucleoside bases with modified ribose rings (**1**, AZT; **2**, ddC), with other heterocycles (**3**, 3TC), and even with acyclic structures such as acyclovir.[3] A key element for the success in this field is the development of coupling chemistry that allows for the efficient formation of carbon-nitrogen bonds at the final stages of synthetic sequences. Therefore, a large number of *N*-analogs can be prepared from any modified "ribose" ring by its connection with a set of available nucleoside bases, and the most effective molecule can be selected by biological evaluation of this class of compounds.

Figure I



1: R=Me, X=OH, Y=N_3
2: R=H, X=NH_2, Y=H

3

4: X=Y=OH
5: X=H, Y=OH
6: X=OH, Y=H

7

8

Several naturally occurring *C*-nucleosides exhibit a wide range of biological activity, but the development of synthetic analogs has not proved fruitful for finding agents with improved activity.[4] *C*-nucleoside analogs are difficult to prepare since carbon-carbon bonds are needed to bridge nucleoside bases

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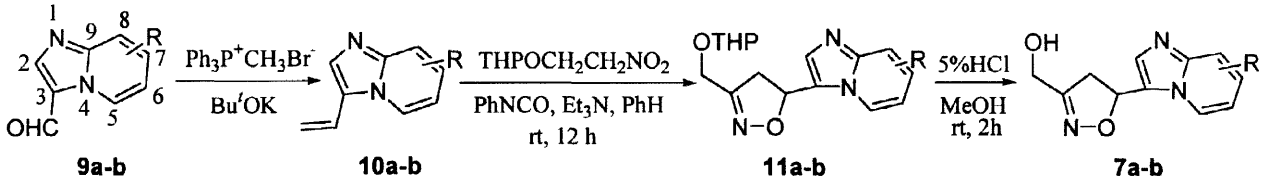
and ribose rings (for example, **4**). Although enormous efforts have been made in the construction of a variety of *C*-nucleoside bases, the modification of ribose rings is not as extensive as that for *N*-nucleosides. For example, there are only a limited number of cases in which the ribose rings of *C*-nucleosides (**5**-**6**) have been changed by removing the 2'- or 3'-hydroxyl groups.[4] Furthermore, the use of non-ribose heterocyclic structures such as dioxolanes has been rarely reported.[5] Herein, we report the preliminary results on the design and preparation of two new groups of *C*-nucleosides **7** and **8** ($C_3O^cN^d$-2H and $C_3N^cO^d$-2H),[1d] in which the ribose ring structure is replaced with a hydroxymethyl isoxazoline.

An excellent method for the construction of isoxazoline rings is the 1,3-dipolar cycloaddition between nitrile oxides and alkenes.[6] Our strategy for the synthesis of compounds **7** and **8** is outlined in Schemes **I** and **II**, respectively. The substituted imidazo[1,2-a]pyridines were initially selected as the core structure of nucleoside bases to investigate the feasibility of using cycloaddition method for *C*-nucleosides synthesis. The starting materials **9** can be readily prepared. Moreover, it has been reported that several corresponding *C*-nucleoside analogs have shown interesting activities against varicella-zoster virus (VZV), cytomegalovirus (CMV) and/or herpes simplex virus (HSV).[7]

Scheme I. Synthesis of $C_3O^cN^d$-2H *C*-Nucleosides **7**: **a**, R = 7-Me; **b**, R = 8-Me.



9a-b **10a-b** **11a-b** **7a-b**

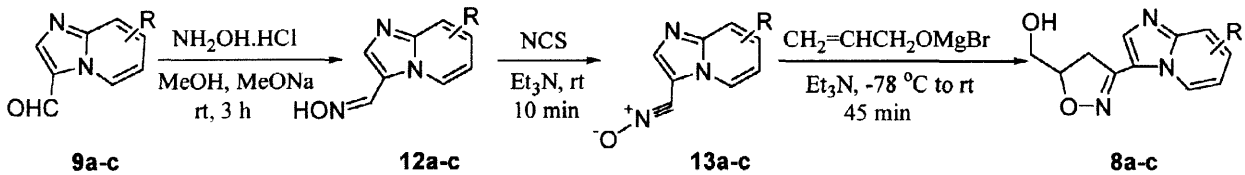
The facile synthesis of *C*-nucleosides **7** can be achieved in three steps from readily available substituted 3-fomylimidazo[1,2-a]pyridines **9** (Scheme **I**), prepared according to literature procedures.[8] For example, compound **9a** (R = 7-Me) reacted with methyltriphenylphosphonium bromide and potassium *tert*-butoxide in dry THF to give the corresponding 3-vinylimidazo[1,2-a]pyridine derivative **10a** in 90% yield. Cycloadduct **11a** was produced in 75% yield by coupling of vinyl base **10a** with the nitrile oxide, which resulted from the Et_3N-promoted reaction of phenyl isocyanate and $THPOCH_2CH_2NO_2$. The desired *C*-nucleoside analog **7a** (R = 7-Me) was obtained by the hydrolysis of **11a** in 92% yield. The related analog **7b** (R = 8-Me) was prepared in a similar way from compound **9b** in 74% overall yield as a single regioisomer.

The regiochemistry of the final product **7** was determined by analysis of NMR spectroscopic data. One proton of the presumed isomer **7** is connected to the oxygen-substituted carbon and expected to give downfield peaks corresponding to a single proton. The methylene group in the isoxazole ring is expected to show upfield proton peaks. The ^1H NMR spectrum of compound **7**, indeed, showed one-proton peak at 6.0 ppm and two-proton peaks at 3.5 ppm. This assignment of regiochemistry is consistent with literature reports in which the oxygen atom of nitrile oxide usually connects to the more hindered position of mono-substituted

alkenes. Finally, both ^{1}H and ^{13}C NMR spectra of products **7** correlated well with the related isoxazoline derivatives.[9]

Nucleoside analogs **8a-c** were also prepared from the corresponding aldehydes **9a-c**, respectively (Scheme **II**). The reaction of compound **9a** with hydroxylamine in methanol gave oxime **12a**, which was oxidized to intermediate **13a** by using an excess amount of NCS in CH_2Cl_2 in the presence of Et_3N (0.1 eq). Nitrile oxide **13a** was not isolated, and upon reaction with five equivalents of 2-propenyloxymagnesium bromide, the corresponding *C*-nucleoside **8a** (R = 7-Me) was produced in 61% yield. Using this approach, analogs **8b** (R = 8-Me) and **8c** (R = 5-Me) were also prepared in 52 and 46% overall yields. This desired regioisomer showed multiple peaks from one proton at 4.8 ppm, which is attached to the oxygen-substituted carbon atom, and two protons from the ring methylene group at 3.5 ppm.[9] It is worthwhile noting that the use of 2-propenyloxymagnesium bromide improved the results of 1,3-dipolar cycloaddition reactions, as reported,[10] while the reaction of **13** with allyl alcohol produced no desired cycloadducts.

Scheme II. Synthesis of $C_3N^cO^d$-2H *C*-Nucleosides **8**: **a**, R = 7-Me; **b**, R = 8-Me; **c**, R = 5-Me.



This work reports the synthesis of new *C*-nucleoside analogs **7-8** that use hydroxymethyl substituted isoxazoline rings for the replacement of the corresponding ribose rings. The synthesis of compounds **7a-b** and **8a-c** was achieved from readily available starting materials **9** *via* cycloaddition methods in several simple steps. Although one of analogs shows only weak anti-HIV-1 activity (**8c**, EC_{50} = 59.5 μM),[11] compounds **7** and **8** were the first examples of this class of *C*-nucleosides to be potentially prepared from a variety of available nucleoside bases.

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9. NMR data for selected compounds: (a) **7b**, ^{1}H NMR (200 MHz, CD_3OD) δ 8.15 (d, J = 6.9 Hz, 1H), 7.61 (s, 1H), 7.12 (d, J = 6.8 Hz, 1H), 6.87 (t, J = 6.9 Hz, 1H), 6.03 (t, J = 9.7 Hz, 1H), 4.81 (s, 1H), 4.42 (s, 2H), 3.52 (d, J = 9.5 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (50 MHz, CD_3OD) δ 131.6, 126.4, 124.3, 114.6, 74.7, 58.3, 39.5, 17.4. (b) **8b**, ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.00 (d, J = 6.9 Hz, 1H), 7.81 (s, 1H), 7.16 (d, J = 7.0 Hz, 1H), 6.90 (t, J = 6.9 Hz, 1H), 4.82 (m, 1H), 3.90 (dd, J = 3.6, 12.2 Hz, 1H), 3.73 (dd, J = 4.6, 12.1 Hz, 1H), 3.51 (d, J = 4.4 Hz, 1H), 3.47 (d, J = 2.9 Hz, 1H), 3.32 (bs, 1H), 2.63 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 136.6, 127.0, 126.5, 114.5, 80.4, 78.2, 63.9, 38.1, 17.5.
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