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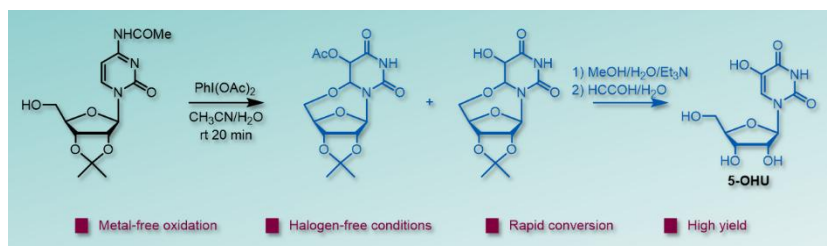
Hypervalent Iodine-Mediated Preparation of 5-Hydroxyuridine from 2',3'-O-isopropylidene N4-Acetylcytidine

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Abstract Whereas BAIB-TEMPO oxidation of 2',3'-O-TBDMS-N4-acetylcytidine results in the expected 5'-carboxylic acid nucleoside, its 2',3'-O-isopropylidene analogue reacts in a radically different way. We have demonstrated here that hypervalent iodine(III) in water triggers an unprecedented oxidative cyclization leading to a mixture of C5-substituted O6,5'-cyclo 5,6-dihydro uridines. This mixture of cyclouridines can be opened under basic conditions and, after deprotection, yields 5-hydroxyuridine, an important post-transcriptional modification of uridine at the wobble position (U34) of bacterial tRNA. NMR experimental values and calculations were performed to provide further insight on the specific reactivity of 2',3'-O-isopropylidene N4-acetylcytidine.

Key words Hypervalent iodine, nucleoside, cyclouridine, oxidative cyclization, 5-hydroxyuridine

Introduction

5-Hydroxyuridine (5-OHU) is a major RNA lesion affecting ribosomal translation that can be generated from pyrimidines by the action of reactive oxygen species and free radicals.¹ Interestingly, 5-OHU is also involved in the formation of 5-oxoalkylated modifications of the wobble position of bacterial tRNA that are believed to play key roles in the translational machinery.² From a synthetic point of view, the most common method to synthesize 5-OHU involves treating uridine with a halogenation reagent in basic aqueous media.³ Based on their work on uridine 5'-diphosphate, Eaton and Hutchinson suggested that 5-hydroxy pyrimidine nucleoside was generated from a bromohydrin intermediate in which the bromine atom at C5 position was subsequently substituted by a hydroxyl group, followed by the elimination of a water molecule.⁴ It is worth noting that, due to the presence of the 5'-diphosphate group, this proposed mechanism eliminates the possibility of the formation of an O6,5'-cyclouridine intermediate usually generated by anchimeric assistance of the 5'-hydroxyl function.^{5,6} These authors also demonstrated that the corresponding 5-bromopyrimidine nucleoside was not an intermediate in the reaction and that when performed on a cytidine analogue, deamination occurred to give 5-OHU as the major product, although in modest yield (34%).⁷ The scope of

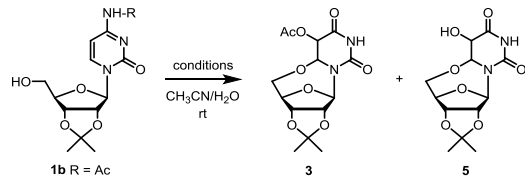
enzymatic reactions known to modify cytosine by deamination, methylation or oxidation is such that researchers see cytosine as a genomic "wild card" able to impact coding sequences and genetic expression.⁸ To the best of our knowledge, the only mention of oxidative transformation of cytosine to 5-acetoxycytidine was reported by Maki and co-workers in 1984.⁹ First, the treatment of 2',3'-O-isopropylidene N4-benzoylcytidine **1a** with lead tetraacetate generated a mixture of 5'-O,6-cyclo-2',3'-O-isopropylidene N4-benzoylcytidine **2** (15%) and 5-acetoxy-5'-O,6-cyclo-5,6-dihydro-2',3'-O-isopropylidene uridine **3** (50%), by oxidative cyclization (Scheme 1a). Heating **3** in dimethylformamide for an unspecified time gave 5-acetoxy-2',3'-O-isopropylidene uridine **4**, although the obtained yield was not reported. In the course of our study dedicated to the synthesis of C-5'-acyl-modified nucleosides,¹⁰ we had to prepare several 5'-carboxylic acid nucleosides¹¹ following the efficient 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)-[bis(acetoxy)-iodo]benzene (BAIB) method described by Epp and Widlanski.¹² C-5'-oxidation proceeded smoothly for all studied pyrimidine nucleosides, except for the cytidine protected by N4-acetyl-2',3'-O-isopropylidene groups, which led to a complex mixture of compounds. This observation was all the more surprising since, under the same conditions, N4-acetylcytidine 2',3'-O-protected by silyl groups gave the expected 5'-carboxylic acid cytidine. We have now demonstrated that in the case of 2',3'-O-isopropylidene N4-acetylcytidine, a mixture of two non-chromogenic cyclouridines **3** and **5** is formed during the hypervalent iodine-mediated reaction and that both compounds can be readily converted to 5-OHU (Scheme 1b). Here are the results of our investigations.

Results

Early studies showed that under standard oxidation conditions (BAIB 2.2 eq, TEMPO 0.2 eq, acetonitrile-water (1:1)), 2',3'-O-isopropylideneuridine was oxidized to 5'-COOH as described in 80% yield. Under the same conditions, 2',3'-O-isopropylidene-N4-acetylcytidine led mainly to a mixture of UV-inactive compounds that could only be detected by vanillin staining, with only traces of the expected carboxylic acid derivative. This

^a The coupling constant cannot be determined since H2' and H3' are accidentally isochronic.

Table 2. Optimization of reaction conditions for the synthesis of cyclodihydrouridines **3** and **5**



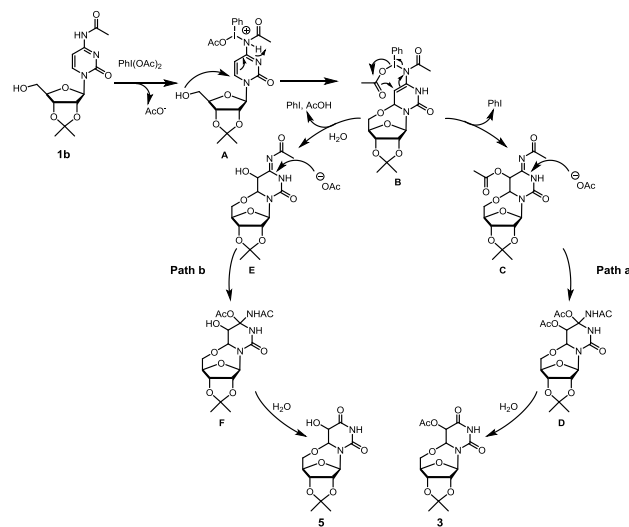
Entry	R	Oxidant (eq)	Additives (eq)	Time (h)	3 (%)	5 (%)
1	Ac	PhI(OAc) ₂ (2)	TEMPO (0.2)	3	47	4
2	Ac	PhI(OAc) ₂ (2)	TEMPO (0.2) + NaHCO ₃ (2)	3	10	5
3	Ac	PhI(OAc) ₂ (2)	-	3	70	8
4	Ac	PhI(OAc) ₂ (2)	-	12	71	11
5	Ac	PhI(OAc) ₂ (1.5)	-	3	67	11
6	Ac	PhI(OAc) ₂ (5)	-	3	34	6
7 ^a	Ac	PhI(OAc) ₂ (2)	-	3	37	5
8 ^b	Ac	PhI(OAc) ₂ (2)	-	3	47	16
9	Ac	PhI(OCF ₃) ₂ (2)	-	3	9	55
10	Bz	PhI(OAc) ₂ (2)	-	3	18	2

^a acetonitrile only; ^b water only

To gain more insight about the mechanism of formation of compounds **3** and **5**, we protected the 5'-hydroxyl group of **1b** with a benzoyl group and subjected the resulting compound to 2 equivalents of BAIB. As expected, no reaction occurred after 24 h and the starting material was fully recovered, confirming the crucial role of the 5'-hydroxyl group in the cyclization. Similarly, in the presence of BAIB alone, 2',3'-*O*-isopropylidene uridine also failed to react, suggesting the necessary involvement of the NH-Ac function.

Based on the above-mentioned experiments, we propose a possible reaction mechanism for the formation of cyclouridines **3** and **5** (Scheme 2). In line with the mechanistic proposal made by Suryavanshi and co-workers¹⁴ for the formation of α -acyloxyketones from benzylamine, the reaction between **1b** and iodobenzene diacetate would generate an ammonium intermediate **A** that would trigger the cyclization via an attack of the 5'-hydroxyl group at position C6 to give the common intermediate **B**. In path a, intramolecular acetylation at position C5 generates imine species **C** by removal of iodobenzene. **C** is then attacked at the α -position of the imine by an acetate anion to form a hemiaminal ether intermediate **D**, which is hydrolyzed in water to yield compound **3**. In path b, **B** is directly

attacked by water at position C6, triggering the removal of iodobenzene and acetic acid to form imine **E**, which undergoes the same reaction sequence as **D** to give compound **5**.



Scheme 2. Mechanism proposal for the formation of **3** and **5**

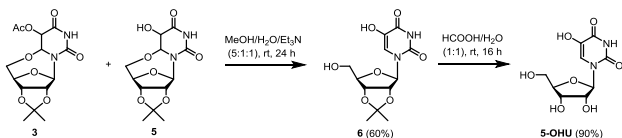
Compounds **3** and **5** proved stable for weeks when stored in powder form at room temperature, and even when heated in DMF at 80°C for several hours, no degradation or transformation was observed. This is not surprising considering the numerous pyrimidine cyclonucleosides that have already been described.¹⁵ Usually prepared by halogenation, dehalogenation or under radical conditions,^{5,6} oxidative cyclization of cytidine via hypervalent iodine has, to our knowledge, never been reported. Hypervalent iodine chemistry has gained considerable importance for the development of a wide range of organic reactions,¹⁵ but its potential in aqueous media has not yet to be fully exploited.¹⁶ The use of hypervalent iodine reagents in nucleoside chemistry is still mainly limited to glycosylation reactions.^{17,18}

To easily access to **5-OHU**, a mixture of **3** and **5** was stirred for 24 h in a MeOH/H₂O/Et₃N mixture (5:1:1), resulting in the unique formation of product **6** in 60% yield after purification on silica gel. The 2',3'-*O*-isopropylidene protecting group was then removed under acidic conditions to yield **5-OHU** in 90% yield (Scheme 3). Thus, under optimized conditions (Table 2, entry 4), **5-OHU** was obtained from **1b** in 43% yield in three steps.

However, one question remains unanswered. Indeed, when 2',3'-*O*-isopropylidene protection is replaced by 2',3'-*O*-TBDMS groups, BAIB-TEMPO conditions lead to the formation of the expected 5'-carboxylic acid cytidine without any trace of cyclonucleosides. This is also the case with the 2'-deoxy-3'-*O*-TBDMS-*N*4-acetylcytidine analogue. To gain further insight, we performed a thorough NMR analysis of the conformation of **1b** and its 2'-3'-*O*-TBDMS analogue **1c**, dissolved into a CD₃CN/D₂O mixture (9/1 v/v) in order to approximate synthesis conditions. The conformation of a nucleoside is globally defined by three factors: the base and 5'-extremity orientation as well as the sugar pucker.

The determination of the sugar geometry is usually defined according to the pseudorotation concept,¹⁹ in which the five-

membered ring shape is totally described by just two parameters: the phase angle P (0 to 360°) and the pucker amplitude ϕ_m . Most of the nucleosides and nucleotides occupy two regions of the pseudorotation wheel in particular: the North, centered around P



Scheme 3. Synthesis of 5-OHU from a mixture of nucleosides **3** and **5**

= 18° (C_3' -endo) and the South, centered around $P = 162^\circ$ (C_2' -endo), with a pucker amplitude ranging from 35 to 45°. In most mononucleos(t)ides, the sugar ring typically exists as a rapid equilibrium between these two preferred C_2' -endo and C_3' -endo conformations. Several nucleosides containing a 2',3'-*O*-isopropylidene fused ring were characterized in the solid state, and it appeared that the conformation of the ribose severely differs from the two classical C_2' -endo and C_3' -endo puckering modes. 2',3'-*O*-isopropylidene uridine for instance, crystallizes as a C_3' -exo- C_4' -endo twist (4_3T with $P = 216.3^\circ$ and $\phi_m = 23.7^\circ$).²⁰ X-ray analysis of 2',3'-*O*-isopropylidene adenosine revealed the existence of two independent structures: a C_3' -exo- C_4' -endo twist ($P = 215.3$ and $\phi_m = 31.5^\circ$) and a planar structure. 2',3'-*O*-isopropylidene guanosine crystallized as a C_3' -exo envelope (3E with $P = 196.4$ et $\phi_m = 25.7$).²¹ In solution, the $J_{1'-2'}$, $J_{2'-3'}$ and $J_{3'-4'}$ coupling constants are regularly used as indicators of sugar conformation. To get more insight in the sugar ring dynamics, coupling constants were measured at different temperatures (**Table SX**).

In 2',3'-OH ribonucleos(t)ides undergoing a classical north-south equilibrium (with a pucker amplitude of 39°), the cisoidal $J_{2'-3'}$ coupling constant and the sum of the two transoidal couplings constants ($J_{1'-2'} + J_{3'-4'}$) are found around 5.0 and 9.5 Hz respectively. An abnormally puckered ribose is related to a lower value of $J_{2'-3'}$ associated with a higher value of $J_{1'-2'} + J_{3'-4'}$. In contrast, the reverse observation is diagnostic of a flattened sugar.¹⁹ For 2',3'-*O*-TBDMS- C^{Ac} , $J_{2'-3'}$ is found around 4.2 Hz, *i.e.* about 1 Hz below the usual value of ~5.0 Hz observed for non-constrained ribose, while the value for $J_{1'-2'} + J_{3'-4'}$ (9.3 Hz) remained quite close to the standard value. In contrast, for the 2',3'-*O*-isopropylidene nucleoside **1b**, the value for $J_{2'-3'}$ was found about 1.5 Hz above the ~5.0 Hz value, while $J_{1'-2'} + J_{3'-4'}$ dropped down to 5.3 Hz, indicating a flattening of the ribose and/or a shift of the phase angle (P) values corresponding to less usual conformations. Both compounds also showed different behavior with respect to increasing temperature. For 2',3'-*O*-TBDMS- C^{Ac} increasing the temperature results in an increase of $J_{1'-2'}$ ($\Delta J \sim +0.6$ Hz) and in a decrease of $J_{3'-4'}$ ($\Delta J \sim -0.7$ Hz). The variations observed between the two extreme temperatures suggest the existence of an equilibrium between two conformations. For compound **1b**, the coupling constants are much less temperature-dependent than for the silylated analogue **1c**, $J_{2'-3'}$ and $J_{3'-4'}$ increasing in a lesser extent ($\Delta J \sim 0.1$ and 0.3 Hz respectively) while $J_{1'-2'}$ remains unchanged (Table 3).

A graphical means of exploring the sugar conformation, in particular when a two-state equilibrium occurs, is to plot $J_{3'-4'}$ as a function of $J_{1'-2'}$.²² Vicinal coupling constants were calculated from Karplus-type equations using the Altona parametrization

defined for β -ribose.²³ Plots of $J_{3'-4'}$ versus $J_{1'-2'}$ calculated for $P = 0$ to 360° and for two values of ϕ_m , together with experimental values, are shown in Figure 2.

For 2',3'-*O*-TBDMS- C^{Ac} **1c** (Figure 2, left), the experimental points are aligned on a straight line which suggests an equilibrium between two conformations.

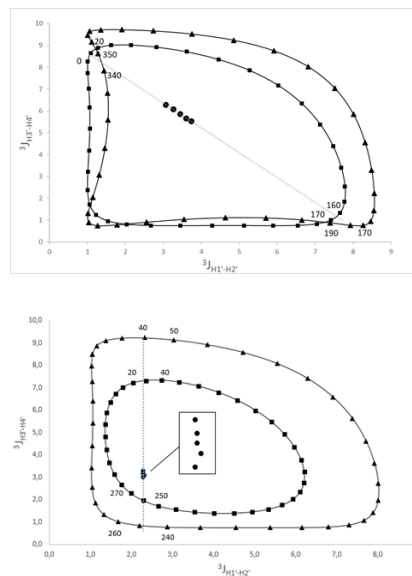


Figure 2. Plots of $J_{1'-2'}$ vs $J_{3'-4'}$. Curves represent the dependence of $J_{1'-2'}$ and $J_{3'-4'}$ calculated for P values ranging from 0 to 360° and for two values of ϕ_m using the Karplus-type equation parametrized by Altona.^[24] Dots are the experimental data. Top: for compound **1c** with $\phi_m = 35^\circ$ (■) and 45° (▲). Bottom: for compounds **1b**, with $\phi_m = 20^\circ$ (■) and 35° (▲). Relevant P values are reported on the curves.

The reverse dependence of the two experimental coupling constants with temperature (Table 3) is characteristic of a classical north-south equilibrium and the low value of $J_{1'-2'}$ as well as the position of the points on the figure indicate that the north conformer slightly prevails. Its population can be approximated at 55-63% from $10 \times {}^3J_{3'-4'}$.^[19] As the low value of ${}^3J_{2'-3'}$ (4.2 Hz) suggests an increase in pucker amplitude, theoretical curves were plotted for $\phi_m = 35^\circ$ and 45° . From the intercept of the line with the two curves, P_N and P_S were estimated to -20° to $+20^\circ$ (C_2' -exo to C_3' -endo) and 160° to 190° (C_3' -exo to C_2' -endo) respectively.

Crystallographic data for 2',3'-*O*-isopropylidene analogues revealed that 2',3'-cyclization leads to a reduced pucker amplitude for the ribose ring, with ϕ_m ranging between 20 and 35 degrees for solid-state non-planar structures.^[20-21] Curves of $J_{3'-4'}$ against $J_{1'-2'}$ for **1b** were therefore built for these two ϕ_m values (Figure 2, right). The position of the data points in the lower left part of the graph indicates a predominance of a South/West conformation. The experimental points are clustered in a shorter area, suggesting a much lower flexibility compared to the 2',3'-*O*-TBDMS analogue **1c**, but since it was nevertheless possible to fit a straight line through the experimental data, we concluded that compound **1b** was still involved in a two-state equilibrium. From the intersection of this straight line with the two curves, it emerges that the compound mainly adopts a West-type conformation ($240^\circ < P_W < 270^\circ$) in equilibrium with a less favorable North-type

conformation ($20^\circ < \text{P}_N < 50^\circ$). Orientation of the 5' extremity was then assessed, from analysis of the coupling constants implying protons H5' and H5'' after stereospecific assignment of the latter (see Supporting Information). The γ torsion angle about the C₄-C_{5'} bond (O₅-C₅-C₄-C_{3'}) usually adopts three main staggered conformations g^+ (60°), t (180°) and g^- (-60°). The populations of each rotamer was estimated from the experimental coupling constants $^3J_{\text{H}4'-\text{H}5'}$ and $^3J_{\text{H}4''-\text{H}5''}$ as follow: 80 % of g^+ , 18% of t and 2% of g^- for 2',3'-*O*-TBDMS-C^A **1c**; 53 % of g^+ , 35% of t and 12% of g^- for **1b**. The g^+ conformation, which is found in the rigid cyclized dihydro compounds, is the one that brings the 5'-O extremity closer to the base. Nevertheless, this conformation is much more represented in the silylated compound than in the isopropylidene analogue **1b**, which is nevertheless the only one capable of forming the 5'-O-C6 bridge. In both compounds, the 5'-O extremity is flexible enough to adopt any of the three staggered conformations which is probably more important than the ability of the 5'-OH to pre-organize into the final g^+ conformation.

Finally, orientation of the base relative to the sugar and defined by the χ torsion angle (O4'-C1'-N1-C2) was also considered using the three-bond heteronuclear couplings between H_{1'} and the carbons C₂ and C₆ (see Supporting Information), and showed as expected the prevalence of the *anti* conformation for both **1b** and **1c**. It is very likely that the conformational constraints induced by the isopropylidene group at the 2'-*O*- and 3'-*O* positions are responsible for the difference in chemical reactivity between this compound and the 2',3'-*O*-TBDMS analogue. The creation of a bond between the base and the 5' extremity implies that the O5' and C6 atoms can be close enough in space for the bond to be formed. The conformational study showed that the most important difference between **1c** and **1b** is the sugar pucker, the dioxolane ring fused at the 2'-*O* and 3'-*O* positions pushing the ribose towards a more rigid and preferred West conformation. Whatever the 2'-3' protecting group - isopropylidene or TBDMS - in both cases, the base and 5'-OH preferentially adopt the ideal conformation where 5'-OH points in the C1'-C2' direction and C6 points in the O4'-C4' direction. This might explain the observed stereoselectivity at C6 in anhydro (ou dihydro?) compound **3**. Interestingly, the g^+ conformation is more favored in the silylated compound **1c** than in the isopropylidene analogue **1b**, yet only the latter led to the formation of an anhydro nucleoside. Moreover, it is well known that the sugar conformation directly affects the base and the 5' extremity's orientations. This suggests that although in both compounds the base and the 5' extremity are able to place themselves in the right position, in **1c** where a standard north-south equilibrium takes place, O5' and C6 are probably too far apart while in **1b** the north-west equilibrium would bring these atoms close enough to allow bonding.

Conclusion

In summary, we have developed an efficient and unprecedented metal-free and halogen-free method for the synthesis of 5-hydroxuridine. Its access involves sequential oxidation mediated by hypervalent iodine(III) followed by mild deprotection reaction conditions. An in-depth NMR study showed that the presence of the 2',3'-*O*-isopropylidene moiety

had a major influence on the sugar puckering, which was crucial for promoting oxidative cyclization. In addition to providing a rapid access to 5-OHU, a major RNA lesion, these results also extend the use of hypervalent iodine(II) in aqueous media.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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