A Facile Synthesis of 5′-O,6-Cyclo-5,5-dihalogeno-5,6-dihydropyrimidine Nucleosides

Magochi Sako, Takao Saito, Keiji Kameyama, Kosaku Hirota, Yoshifumi Maki*

Gifu Pharmaceutical University, 6-1, Mitahora-higashi 5 Chome, Gifu 502, Japan

Treatment of 2′,3′-O-isopropylidenepyrimidine nucleosides (1) uridine and cytidine) with excess N-halogenosuccinimides in an aprotic solvent at ambient temperature results in the exclusive formation of the corresponding 5′-O,6-cyclo-5,5-dihalogeno-5,6-dihydropyridendepyrimidine nucleosides 2.

Cyclonucleosides can be utilized as key intermediates in the synthesis of partially modified nucleosides and nucleotides possessing biological activities and as a tool for conformational studies of naturally occurring nucleosides and nucleotides. Along this line, various types of the cyclonucleosides have been synthesized.1

We now report here a facile synthesis of hitherto unknown 5′-O,6-cyclo-5,5-dihalogeno-5,6-dihydropyrimidine nucleosides 2, which contain convertible functional groups in the molecule, starting from the readily available 2′,3′-O-isopropylidenepyrimidine nucleosides 1. The unique feature of this method is that the reaction involves dehalogenation accompanying intramolecular 5′-O,6-cyclization.

![Diagram](image-url)

Table. 5′-O,6-Cyclo-5,5-dihalogeno-5,6-dihydro-2′,3′-O-isopropylidenepyrimidine Nucleosides 2

<table>
<thead>
<tr>
<th>2</th>
<th>R</th>
<th>X</th>
<th>Reaction Time (h)</th>
<th>Yield* (%)</th>
<th>m.p. (C) (solvent)</th>
<th>Molecular Formula</th>
<th>1H-NMR (DMSO-d6/TMS)* δ, J (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>OH</td>
<td>Br</td>
<td>5</td>
<td>89</td>
<td>220-230 (EtOH)</td>
<td>C₂,H₁₄Br₂N₂O₆ (442.1)</td>
<td>3.84, 4.40 (2d, 2H, each J = 13, C₅-H); 4.56 (brs, 1H, C₅-H); 4.80, 4.94 (2d, 2H, each J = 6, C₆-H and C₇-H); 5.32 (s, 1H, C₈-H); 6.15 (s, 1H, C₉-H)</td>
</tr>
<tr>
<td>b</td>
<td>OH</td>
<td>Cl</td>
<td>48</td>
<td>90</td>
<td>248 (dec.) (EtOAc)</td>
<td>C₂,H₁₄Cl₂N₂O₆ (353.2)</td>
<td>3.84, 4.43 (2d, 2H, each J = 13.5, C₅-H); 4.56 (brs, 1H, C₆-H); 4.73, 4.94 (2d, 2H, each J = 6, C₆-H and C₇-H); 5.65 (s, 1H, C₈-H); 6.15 (s, 1H, C₉-H)</td>
</tr>
<tr>
<td>c</td>
<td>NH₂</td>
<td>Br</td>
<td>2</td>
<td>86</td>
<td>196-198 (EtOAc)</td>
<td>C₂,H₁₄Br₂N₂O₅ (441.1)</td>
<td>3.86, 4.40 (2d, 2H, each J = 13, C₅-H); 4.56 (brs, 1H, C₆-H); 4.76, 4.91 (2d, 2H, each J = 6, C₆-H and C₇-H); 4.93 (s, 1H, C₈-H); 6.21 (s, 1H, C₉-H)</td>
</tr>
<tr>
<td>d</td>
<td>NHCO₂H₂</td>
<td>Br</td>
<td>1</td>
<td>96</td>
<td>206-207 (EtOAc)</td>
<td>C₂,H₁₄Br₂N₂O₆ (545.2)</td>
<td>3.90, 4.41 (2d, 2H, each J = 12, C₅-H); 4.59 (brs, 1H, C₆-H); 4.80, 4.94 (2d, 2H, each J = 6, C₆-H and C₇-H); 5.33 (s, 1H, C₈-H); 6.18 (s, 1H, C₉-H)</td>
</tr>
</tbody>
</table>

* Yield of isolated product based on 1
b Uncorrected, measured on a Yanagimoto micro hot-stage apparatus.

c Satisfactory microanalyses obtained. C ± 0.27, H ± 0.19, N ± 0.05.

We refer to a Hitachi R-24B (60 MHz) spectrometer.

Treatment of 2′,3′-O-isopropylidenepyridine (1a) with 3 equivalents of N-bromosuccinimide (NBS) in dry N,N-dimethylformamide at ambient temperature for 5 h led to the formation of 5′-O,6-cyclo-5,5-dibromo-5,6-dihydro-2′,3′-O-isopropylidenepyridine (2a) in a high yield. No formation of other products in this reactions was shown by TLC analysis of the reaction mixture. The structure of 2a was determined from microanalytical and spectral data and by its chemical conversion. For example, no characteristic UV absorption of the uracil ring was observed. The 1H-NMR spectrum of 2a showed two methine proton signals at 3.84 and 4.40 (2d, 2H, each J = 13 Hz, C₅-H),
which are characteristic of the 5'-O,6-cyclopymidine nucleosides, and a methine proton signal at δ 5.32 (s, C6-H) in addition to signals assignable to an imide proton δ 11.33 (br) and protons in the protected sugar portion. On treatment of 2a with sodium methoxide under a mild conditions, 5-bromo-5'-O,6-cyclo-2',3'-O-isopropylideneuridine (3) was obtained almost quantitatively. Reduction of 2a with zinc-acetic acid gave 1a in a high yield, along with a trace amount of 5-bromo-2',3'-O-isopropylideneuridine (4) which was identified by comparison with an authentic sample.

Analogous cyclization was also observed in the reaction of 2',3'-O-isopropylidene protected cytidine derivatives 1b and 1c with N-chlorosuccinimide (NCS) and NBS, respectively.

The results of these reactions are summarized in the Table.

N,N-Dimethylacetamide or acetonitrile also can be used as solvent, whereas the employment of the protic solvent such as alcohols in this reaction causes deprotection of the sugar moiety.

In contrast to the above results, bromination of unprotected uridine under the conditions analogous to the case of 1a gave only a small amount of the corresponding pyrimidine cyclo-nucleoside (5) even after the prolonged reaction time; 5-bromo-uridine was obtained as a main product.

These observations clearly indicate that the 2',3'-O-isopropylidene protection in the ribofuranosyl ring and the use of an aprotic solvent are requisite for the 5'-O,6-cyclization described here.

When the bromination of 1a was carried out by using one equivalent of NBS, 4 was obtained in 85% yield, together with a trace amount of 2a. The product 4 was easily converted into 2a under the same conditions using excess NBS described above. These facts indicate that 4 is an intermediate for the formation of 2a in the reaction of 1a with excess NBS. An analogous reaction sequence has been proposed for the formation of 2'-O,6'-5',5'-dicyclo-(β-D-arabinofuranosyl)-5,5'-dibromo-5,6-dihydrothiourea in the reaction of 2'-O,6-cyclouridine with bromine or NBS.

Application of this procedure to the 5'-O,6-cyclization of 2',3'-O-isopropylidene protected 5'-hydroxyuridine and pseudouridine allowed the formation of 5'-O,6-cyclo-5'-hydroxy-2',3'-O-isopropylideneuridine (6) and 5-bromo-5'-O,6-cyclo-5,6-dihydro-2',3'-O-isopropylidene псевдуренид (7).

5'-O,6-Cyclo-5,5-dihalogeno-5,6-dihydro-2',3'-O-isopropylidene-pyrimidine Nucleosides (2): General Procedure:
A solution of 2',3'-O-isopropylideneuridine nucleosides (I; ~ 2 mmol) and Na-halogenosuccinimide (~ 6 mmol) in dry DMF (10 mL) is stirred at ambient temperature until disappearance of 1 (monitored by TLC analysis). After removal of the solvent, the residue is washed with a small amount of EtOH and the solid mass is recrystallized from EtOH or EtOAc to give an analytically pure sample (Table).

5-Bromo-5'-O,6-cyclo-2',3'-O-isopropylideneuridine (3):
A solution of 5'-O,6-cyclo-5,5-dibromo-5,6-dihydro-2',3'-O-isopropylideneuridine (2a; 100 mg, ~ 0.2 mmol) and NaOMe (61 mg, ~ 1 mmol) in MeOH (20 mL) is stirred overnight at ambient temperature. The mixture is neutralized by using ion-exchange resin (Amberlite CG-120 B) and then the solvent is removed under reduced pressure. The residue is recrystallized from EtOH to give 3 as colorless crystals; yield: 80 mg (98%); m.p. 222–224 °C.

C9H13BrN2O5 calc. C 39.91 H 3.63 N 7.76 (361.2) found 40.04 3.60 7.83 MS: m/e = 364 (M+) 346.

1H-NMR (CDCl3): δ = 1.32, 1.45 (2 br s, each 3 H, 2-C–Me); 4.08, 4.63 (2 br d, 2 H, each J = 12 Hz, 2C6-CH); 4.86 (8 s, 1 H, C6-H); 5.00 (2 d, 2 H, each J = 6 Hz, C6—H and C3—H); 6.29 (s, 1 H, C6—H); 9.17 (br, 1 H, NH).

5'-O,6-Cyclo-5,5-dibromo-5,6-dihydrouridine (5):
A mixture of uridine (496 mg, ~ 2 mmol), N-bromosuccinimide (1.07 g, ~ 6 mmol), and dry DMF (10 mL) is stirred for 3 h at ambient temperature. After removal of the solvent under reduced pressure, the residual oil is chromatographed on silica gel (CHCl3 as eluent) to give 5-bromouridine; yield: 388 mg (60%); and 5; yield: 257 mg (32%); m.p. 155–157 °C.

C14H11BrN2O5 calc. C 38.69 H 2.51 N 6.97 (402.0) found 38.69 2.53 6.84 IR (KBr): ν = 3430, 3200, 1720, 1690 cm⁻¹.

1H-NMR (DMSO-d6): δ = 3.80, 4.50 (m, 5 H, C5—H, C6—H, and 2 C2—H); 5.28 (s, 1 H, C5—H); 6.00 (d, 1 H, J = 2 Hz, C1—H); 11.18 (s, 1 H, NH).

5'-O,5'-6-Cyclo-2',3'-O-isopropylideneuridine (6):
A mixture of 5-hydroxy-2',3'-O-isopropylideneuridine (300 mg, ~ 1 mmol), N-bromosuccinimide (200 mg, ~ 1.1 mmol), and dry DMF (5 mL) is stirred for 0.5 h at ambient temperature and then evaporated under reduced pressure. The residue is washed with EtOH (5 mL) and recrystallized from EtOH to give 6; yield 235 mg (79%); m.p. > 300 °C.

C13H14BrNO5 calc. C 38.92 H 4.73 N 9.39 (298.3) found 38.16 4.81 9.30 MS: m/e = 298 (M+) 283, 240.

1H-NMR (DMSO-d6): δ = 1.20, 1.43 (2 br s, each 3 H, 2-C–Me); 3.78, 4.58 (2 br d, 2 H, each J = 13 Hz, 2C6-CH); 4.54 (s, 1 H, C6—H); 4.83, 4.95 (2 br d, 2 H, each J = 6 Hz, C6—H and C3—H); 6.20 (s, 1 H, C6—H); 11.32 (br, 1 H, NH).

5-Bromo-5'-O,6-cyclo-5,6-dihydro-2',3'-O-isopropylidene pseudouridine (7):
A mixture of 2',3'-O-isopropylidene pseudouridine (114 mg, ~ 0.4 mmol), N-bromosuccinimide (214 mg, ~ 1.2 mmol), and dry DMF (5 mL) is stirred for 3 h at ambient temperature and then evaporated under reduced pressure. The residue is recrystallized from EtOH to give 7; yield: 90 mg (62%); m.p. 160 °C (decomp.).
C$_2$H$_1$.BrN$_2$O$_6$  

Calculated: C 39.69  H 4.16  N 7.71  

Found:  39.50  4.12  7.84  

MS:  m/z = 363 (M$^+$). 348.  

IR (KBr): $\nu = 2260, 1720$ cm$^{-1}$.  

$^1$H-NMR (DMSO-$d_6$): $\delta = 1.27, 1.44$ (2 br s, each 3H, 2 CH$_2$-Me); 3.69, 4.03 (2 d, 2H, each $J = 13$ Hz, 2 C$_6$-H); 4.48 (m, 1H, C$_2$-H); 4.55–4.80 (m, 3H, C$_4$-H, C$_2$-H, and C$_3$-H); 4.90 (d, 1H, $J = 4.5$ Hz, C$_8$-H); 8.74 (d, 1H, $J = 4.5$ Hz, N$_2$H); 11.06 (br, 1H, N$_3$H).  

Received: 2 September 1986; revised: 31 March 1987  

1. Pertinent reviews on the chemistry of the pyrimidine cyclonucleosides:  


5. Analogous results have been already observed in the reaction of unprotected 2-deoxyctydine with iodine-iodic acid; cf.: Chang, P.K. J. Org. Chem. 1965, 30, 3913.  