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A Novel One-Step Method for the Synthesis of C-5-Substituted O^6,5′-Cyclopyrimidine Nucleoside Analogues in Ammonia Water

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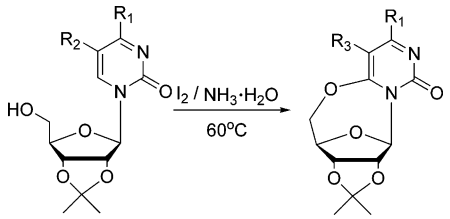
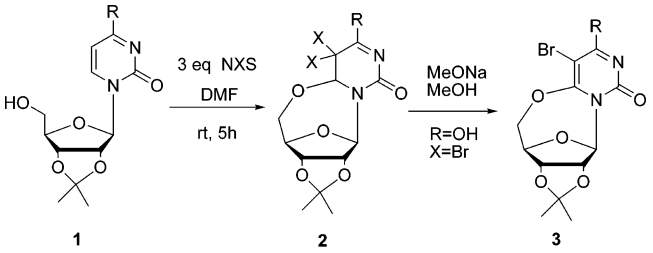


A novel one-step method for preparing C-5-substituted O^6,5′-cyclopyrimidine nucleoside analogues is reported. This method employs molecular iodine to mediate the cyclization from the 5′-*O*-hydroxyl group of the sugar ring and C-6 at the position of the nitrogen base in ammonia water under mild conditions without any other aprotic organic solvent.

Cyclic analogues of nucleosides are compounds in which the additional cycle is formed between the sugar ring and the nitrogen base. First discovered by Todd and co-workers, these compounds have received more and more attention.[1] Cyclonucleosides have served as useful synthetic intermediates[2] and in the introduction of a variety of functionalities into the heterocyclic and carbohydrate moieties of nucleosides.[3,4] They are expected to have a potential biological impact especially toward enzymatic repair processes.[5] Cyclonucleosides are also important in connection with nucleoside configurational studies.[6] The shaping of the *O*-bridge between the hydroxymethyl group and position 6 of pyrimidine makes the nucleoside a conformationally fixed one.[7] Their rigid structures facilitate interpretation of physical properties with respect to structural characteristics. Some of these have been used to examine the relationship between the circular dichroism (CD) spectra and the *N*-glycosyl conformation.

SCHEME 1



There are some reports about the synthesis of a number of O^6,5′-cyclonucleosides.[8−13] For example, the 2′,3′-*O*-isopropylidenpyrimidine nucleoside **1** with excess *N*-halogenosuccinimides (NBS, NIS) in an aprotic solvent (such as DMF, DMSO)[14] will be converted into a 5,6-saturated cyclonucleosides **2** intermediate which presumably converted to O^6,5′-cyclonucleoside **3** by the loss of hydrogen halide (Scheme 1). This method includes two steps and need organic solvent and strong base. So convenient and simple method for the synthesis of O^6,5′-cyclonucleosides is more desirable. Herein, we report a one-step method for the synthesis of C-5-substituted O^6,5′-cyclopyrimidine nucleoside analogues under mild conditions. Compared to the old methods, this method is easy to operate and low toxic by using molecular iodine to mediate the cyclization in ammonium water.

We initially attempted to obtain 2′,3′-*O*-isopropylidene-5-iodouridine by the reaction between molecular iodine and 2′,3′-*O*-isopropylideneuridine in ammonia water. However, two products were shown by TLC analysis of the reaction mixture after 30 min at 60 °C (Scheme 2). One was confirmed as **1c** by NMR. We first expected the other product as 2′,3′-*O*-isopropylidene-O^6,5′-cyclouridine **3f** which was obtained by treatment of 2′,3′-*O*-isopropylidene-5-halogenouridine in alkaline media as described by Honjo et al. and others.[4,12,15] However, the ^{1}H NMR spectrum showed clearly the signals corresponding to the vinylic protons (5: δ 5.64 and 7.80 ppm) disappeared and two methine proton signals at δ 4.022 and 4.668 (2d, 2H, each J = 12.4 Hz, C5′-H) which are characteristic of the O^6,5′-cyclopy-

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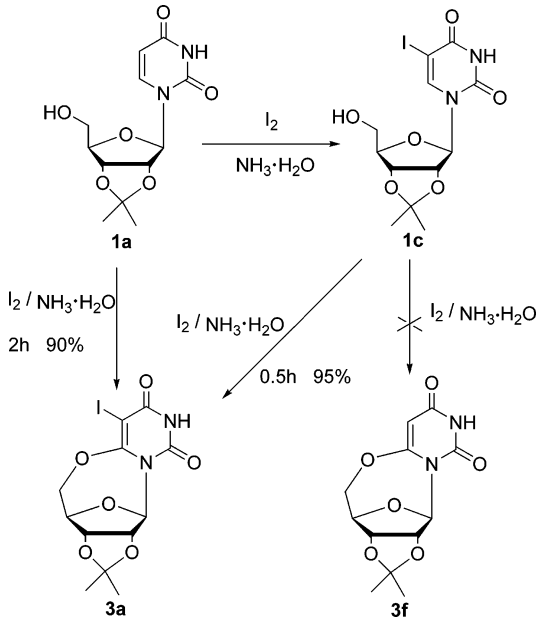
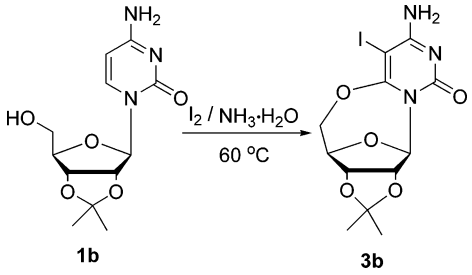
SCHEME 2



SCHEME 3



rimidine nucleosides,[16] were observed. On the other hand, the ^{13}C NMR of the signal corresponding to the carbonyl at position 5 of **1a** was shifted from δ 101.6 to 61.0 ppm for **3a** due to heavy atom effect of halogen of C-5. HMBC, HMQC, and COSY spectra also ascertained that the H-5′ signals of anhydro nucleosides contained an oxygen bridge between C-5′ and C-5-substituted aglycon. HRMS data showed that [M + Na^+] was 430.9691. So the product was proved to be **3a**. It is noteworthy that when the reaction time prolonged up to 2 h, **1c** was not detected and **3a** was obtained in 90% isolated yields. Furthermore, **3a** can also be prepared starting from **1c** under the same conditions in 95% yield within 0.5 h. On the other hand, treatment of the 2′,3′-*O* isopropylidenecytidine **1b** with $I_2/NH_3\cdot H_2O$ for 4 h at 60 °C resulted in the formation of the cyclization derivatives **3b** in good yield (Scheme 3). It could be concluded that 2′,3′-*O*-isopropylidenpyrimidine compounds could be directly converted to corresponding cyclonucleosides in ammonia water by using molecular iodine to mediate the cyclization.

The influences of reaction conditions were examined as summarized in Table 1. When ammonia water was used as a base for the reaction, excellent yield was observed (entry 1). Sodium hydroxide, potassium carbonate, and ethylamine could also be used as the bases, and lower yields were observed (entries 2−4). However, no product was obtained by employing Et_3N or 4-dimethylaminopyridine (DMAP) as the bases (entries 5 and 6). Thus, ammonia water became the best choice for the reaction. The influence of the temperature on the kinetics of the cyclization was also conducted (entries 7−11). When the temperature was 60 °C, the cyclization of nucleosides went very smoothly within 2 h to afford the best results. When the reaction temperature was lower than 60 °C, lower yields were obtained (entries 7 and 8). When the reaction temperature was higher than 60 °C, no obvious variation in yields was observed (entries 10 and 11). So the optimal reaction temperature was 60 °C. It was noteworthy that the products could also be obtained in good yield when the reaction was conducted at room temperature (entry 7) within 2 days.

TABLE 1. Effect of Reaction Conditions on Cyclization of Nucleosides[a]

entry	base	*T* (°C)	time (h)	yield[b] (%)
1	$NH_3\cdot H_2O$	60	2	90
2	NaOH[c]	60	3	50
3	K_2CO_3[c]	60	4	52
4	$EtNH_2$	60	4	46
5	Et_3N	60	5	trace
6	DMAP[c]	60	5	trace
7	$NH_3\cdot H_2O$	25	48	83
8	$NH_3\cdot H_2O$	60	0.5	42
9	$NH_3\cdot H_2O$	60	2	90
10	$NH_3\cdot H_2O$	80	2	85
11	$NH_3\cdot H_2O$	100	2	87

[a] The reaction was conducted with **1a** (1 mmol), I_2 (761 mg, 3 mmol), and base (3 mL) at 60 °C. [b] Isolated yields based on **1a**. [c] 3 equiv of base and 5 mL of H_2O were used.

TABLE 2. Halogen Effects on Cyclization of Nucleosides[a]

entry	X_2	*T* (°C)	time (h)	yield[b] (%)
1	free	60	2	0
2[c]	free	60	2	0
3	Br_2	25	0.5	0
4	I_2	60	2	90

[a] The reaction was conducted with **1a** (1 mmol), X_2 (761 mg, 3 mmol), and NH_3 water (3 mL, 45 mmol). [b] Isolated yields based on **1a**. [c] **1c** was instead of **1a**.

To investigate the influence of iodine, we carried out the reaction without iodine under the same conditions. As shown in Table 2, **1a** or **1c** was failed to convert into cyclization counterparts **3a** in ammonia water without iodine (entries 1 and 2). The treatment of **1a** with bromine in ammonia water gave only 2′,3′-*O*-isopropylidene-5-bromouridine **1f** which was identified by comparison with an authentic sample,[17] no formation of cyclization products in this reaction was shown by TLC analysis (entry 3). That is to say, iodine was essential to the reaction. Because molecular iodine is easy to sublimate under microwave irradiation and the concentration of iodine in the solution might be low, lower yield was obtained when lower equivalents of iodine (1 or 2 equiv) were used.

In order to study the application of this method, the influence of different substituents in nucleosides bases was examined. The obtained products are shown in Table 3. As can be seen, C-5-substituted 2′,3′-*O*-isopropylidenpyrimidine nucleosides could be easily converted into the corresponding cyclonucleosides in short reaction times with good to high yields (Table 3). When starting from C-5 unsubstituted pyrimidines, the reaction led to

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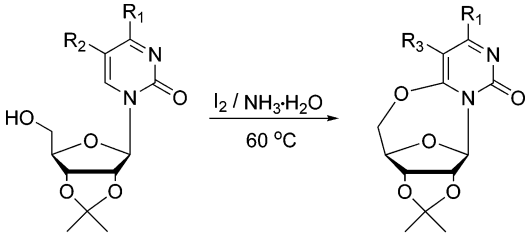
TABLE 3. Cyclization Using Different C-5-Substituted Nucleosides[a]

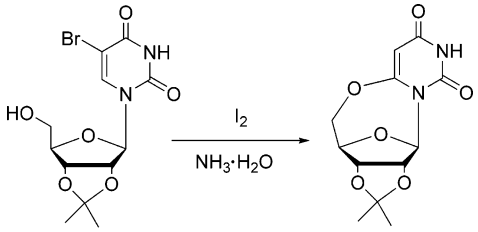


1 3

entry	R_1	R_2	R_3	product	time (h)	yield[b] (%)
1	OH	H	I	**3a**	2	83
2	OH	I	I	**3a**	0.5	90
3	NH_2	H	I	**3b**	4	80
4	NH_2	F	F	**3d**	3	75
5	NH_2	Br	Br	**3e**	4	63

[a] The reaction was conducted with substituents (1 mmol), I_2 (761 mg, 3 mmol), and NH_3 water (3 mL, 45 mmol) at 60 °C. [b] Isolated yields.

SCHEME 4



1f 3f

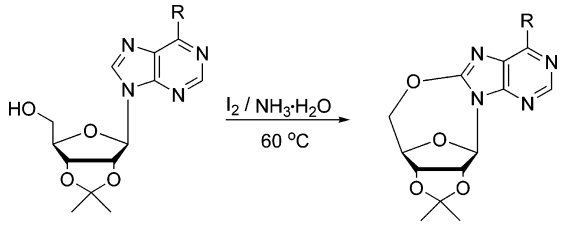
5-iodo-O^6,5′-cyclopyrimidine (entries 1 and 3). When 5-bromocytidine or 5-fluorocytidine was used, 5-bromo-*O*^{6},5′-cyclocytidine or 5-fluoro-O^6,5′-cyclocytidine was obtained (entries 4 and 5). These interesting observations showed that this synthetic pathway could lead to the preparation of various 5-substituted-*O*^{6},5′-cyclopyrimidine nucleosides. In addition, the 2′- and 3′-hydroxyl groups are protected with bis-isopropylidene, which facilitates intramolecular coupling of the 5′-hydroxyl group of the sugar moiety with pyrimidine and purine base moieties.

Unprotected nucleosides gave only a small amount of the corresponding pyrimidine cyclonucleosides even after prolonged reaction time under the same conditions as that of uridine or cytidine. The reason of this difference might be that the isopropylidene ring "forces the furanose ring into a conformation that favors the proximity of the hydroxy group to the uracil double bond".[18]

There is an interesting fact to be addressed (Scheme 4). Treatment of **1f** with iodine in ammonia water gave **3f** with loss of bromine at position 5 which is different from that described above (Table 3).

When this procedure was applied to other purine nucleosides derivatives **4** (Scheme 5), to our delight, the corresponding cyclonucleosides 2′,3′-*O*-isopropylidene-*O*^{8},5′-cycloadenosine **5a** and 2′,3′-*O*-isopropylidene-*O*^{8},5′-cycloinosine **5b** were obtained in good isolated yield (**5a**: 34%; **5b**: 30%). Moreover, its operational simplicity was efficient compared with the reported results[19,20] (two steps or more complex procedure and in 23% yield).

SCHEME 5



4 5

a: R= NH_2
b: R= OH

In summary, we have developed a novel one-step efficient synthetic method to prepare 5-substituted *O*^{6},5′-cyclopyrimidine nucleoside analogues. Compared to the old method, which usually contains two or more steps, this new method has only one step and the yield is high. This method has several advantages such as operational simplicity, low cost, and low toxicity by using molecular iodine instead of *N*-halogenosuccinimides to mediate the cyclization. Organic solvents are avoided in this method by using ammonia water both as a base and as a solvent. The advantages of this strategy make it possible to generate C-5-substituted *O*^{6},5′-cyclopyrimidine nucleosides directly and to be applied in advanced functional organic materials and medicinal chemistry. Further work is in progress in order to elucidate the mechanisms for these reactions and to determine the scope of the ring-closing reactions of the cyclonucleosides with common nucleophiles.

Experimental Section

Typical Experimental Procedure for the Cyclization Reaction of Nucleosides with Iodine in Ammonia Water. 5-Iodo-2′,3′-*O*-isopropylidene-*O*^{6},5′-cyclouridine (3a). 2′,3′-*O*-isopropylideneuridine **1a** (1 mmol) and ammonia water (3 mL, 45 mmol) were put in a 10 mL glass vial equipped with a small magnetic stirring bar. To this was added I_2 (761 mg, 3 mmol) at 60 °C under empty balloon. After 2 h of stirring at the same temperature, the mixture was quenched with H_2O and satd aq Na_2SO_3, and was extracted with Et_2O (3 × 20 mL). The organic layer was washed with brine and dried over Na_2SO_4 to provide crude product which was purified with flash column chromatography on silica gel to give pure **3a**. Yield: 83%. White solid. Mp: 186−190 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.70 (s, 1H, NH), 6.25 (s, 1H, H-1′), 4.99 (d, J = 5.6 Hz, 1H, H-2′), 4.91 (d, J = 5.6 Hz, 1H, H-3′), 4.67 (d, J = 12.4 Hz, 1H, H-5′), 4.63 (s, 1H, H-4′), 4.01 (d, J = 12.4 Hz, 1H, H-5′), 1.42 (s, 3H, CH_3), 1.28 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz): 161.1 (C, C-4), 160.2 (C, C-6), 149.5 (C, C-2), 111.6 [C, $C(CH_3)_2$], 89.6 (CH, C-1′), 84.5 (CH, C-3′), 83.6 (CH, C-4′), 81.8 (CH, C-2′), 76.9 (CH_2, C-5′), 61.0 (C, C-5), 26.0 (CH_3, CCH_3), 24.4 (CH_3, CCH_3). HRMS: calcd for $C_{12}H_{13}IN_2NaO_6$ [M + Na$^+$] 430.9716, found 430.9691.

Preparation of 2′,3′-*O*-Isopropylidene-*O*^{8}-5′-cyclopurine Nucleosides 5. 2′,3′-*O*-Isopropylidenepurine nucleosides **4** (1 mmol) and ammonia water (3 mL, 45 mmol) were put in a 10 mL glass vial equipped with a small magnetic stirring bar. To this was added I_2 (761 mg, 3 mmol) at 60 °C under empty balloon. After 8 h of stirring at the same temperature, the mixture was quenched with H_2O and satd aq Na_2SO_3. The product was purified by flash column chromatography on silica gel to give pure **5**.

2′,3′-*O*-Isopropylidene-*O*^{8},5′-Cycloadenosine (5a). Yield: 34%. White solid. Mp: 226−227 °C; ^{1}H NMR (DMSO-d_6, 400 MHz):

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δ 8.11 (s, 1H), 7.10 (s, 2H), 6.03 (s, 1H), 5.10 (d, J = 5.6 Hz, 1H), 4.90 (d, J = 5.6 Hz, 1H), 4.75 (s, 1H), 4.64 (d, J = 12.4 Hz, 1H), 4.13 (d, J = 12.4 Hz, 1H), 1.46 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): 154.8, 153.1, 152.0, 147.6, 114.4, 111.9, 85.8, 85.2, 84.8, 80.9, 74.3, 25.9, 24.3.

2′,3′-*O*-Isopropylidene-*O*^{8},5′-cycloinosine (5b). Yield: 30%. White solid. Mp: 166−168 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.40 (s, 1H), 8.05 (s, 1H), 5.99 (s, 1H), 5.09 (d, J = 5.6 Hz, 1H), 4.92 (d, J = 5.6 Hz, 1H), 4.75 (s, 1H), 4.62 (dd, J = 13.2 Hz, 1.6 Hz, 1H), 4.11 (d, J = 13.2 Hz, 1H), 1.46 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): 155.8, 152.4, 145.9, 145.8, 119.5, 111.9, 86.3, 85.4, 84.8, 80.9, 74.2, 25.9, 24.3. HRMS: calcd for $C_{13}H_{14}N_4NaO_5$ [M + Na$^+$] 329.0862, found 329.0858.

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Supporting Information Available: Experimental details, characterization data, and NMR spectra for compounds **1c**,**f**, **3a**,**b**,**d**−**f**, and **5a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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