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# A new general synthesis of isomeric nucleosides

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**Abstract**—An efficient new method for the synthesis of isonucleosides is described. The key step in the synthesis was the direct coupling of purine and pyrimidine bases with the cyclic sulfate of a carbohydrate intermediate. This reaction proceeded with high regiospecificity and stereospecificity. 

Isomeric nucleosides (or isonucleosides) as potential antiviral agents have been the subject of intense interest in our laboratory for a number of years.[1–4] Included within this family are those compounds where the base is transposed from the natural 1′-position to the isomeric 2′-position (Fig. 1). For example, 4(*S*)-(6-amino-9*H*-purin-9-yl)-tetrahydro-1(*S*)-furanmethanol [**1a**, B = adenine] is an isomeric dideoxynucleoside synthesized in our laboratory.[1] It has potent anti-HIV activity against HIV-1 and HIV-2.[4] In addition, it has been reported that isodeoxynucleoside (**1b**), having guanine as a nucleobase, had significant activities against HSV-1 and HSV-2.[5]

While some approaches have been reported for the synthesis of isodideoxynucleosides (**1a**, B = purine and pyrimidine bases), there is no general method available for the synthesis of both purine and pyrimidine isodeoxynucleosides (**1b**) from a readily available carbohydrate precursor by direct coupling.

In addition, the methods reported earlier[1,6–10] for the synthesis of isonucleosides suffered from the following drawbacks: (1) the relatively large number of synthetic steps involved that make the syntheses cumbersome and that reduce the overall yield of the desired product; (2) the lack of a general method for the synthesis of pyrimidine isonucleosides in which the pyrimidine base can be condensed directly and in good yields to give the N-1 alkylated products; (3) our previous attempt[11] to couple nucleobases directly with the cyclic sulfite **3** had limitations because of low yields and generality; for the pyrimidine bases, the coupling reactions did not occur at all.

To overcome these and related difficulties, we developed a new approach to isonucleosides that utilized a cyclic sulfate derivative **4** of a carbohydrate as a key intermediate (Scheme 1). When treated with purine and pyrimidine bases, this cyclic sulfate underwent direct coupling with regiospecificity, stereospecificity and good overall yields.

Cyclic sulfate **4** was synthesized from cyclic sulfite **3**[11] by oxidation[12] with $RuCl_3/NaIO_4$ under conditions of phase transfer catalysis. Compound **4**, the key precursor, was condensed with purine and pyrimidine bases to produce isonucleosides. For the synthesis of purine nucleosides, the adenine base was deprotonated with DBU in $CH_3CN$ to give the adenylate anion, which reacted with the intermediate **4** at C-2 position exclusively and with the inversion of configuration to give the adenine derivative **5a**. Treatment of **5a** with 2% aqueous HCl in MeOH[13] at 65°C gives the unprotected

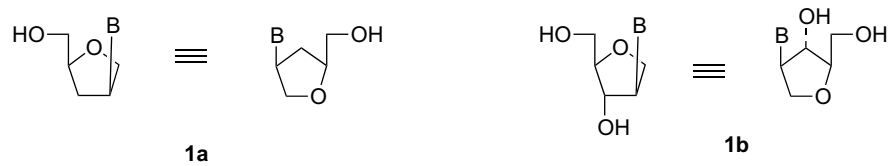


**Figure 1.**

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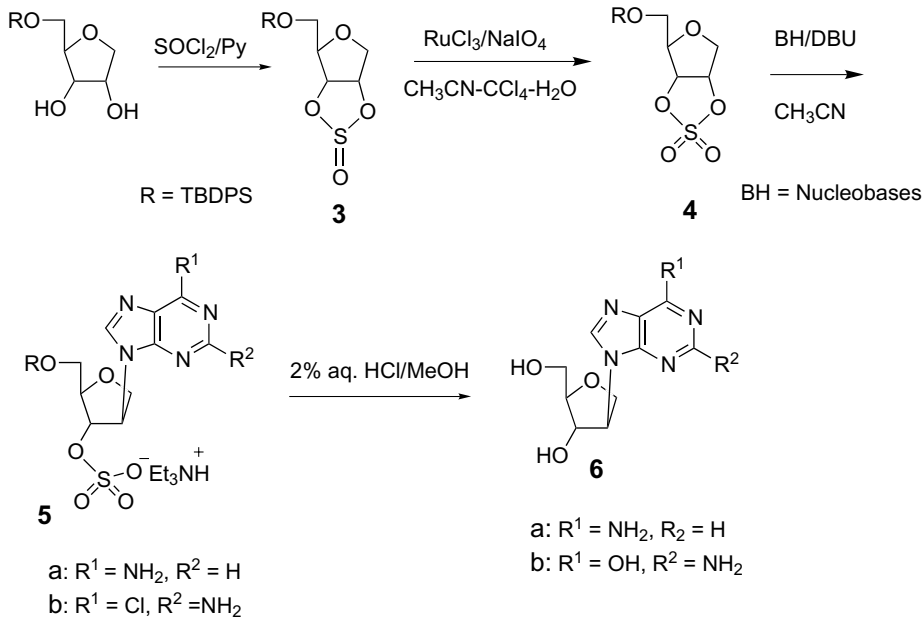
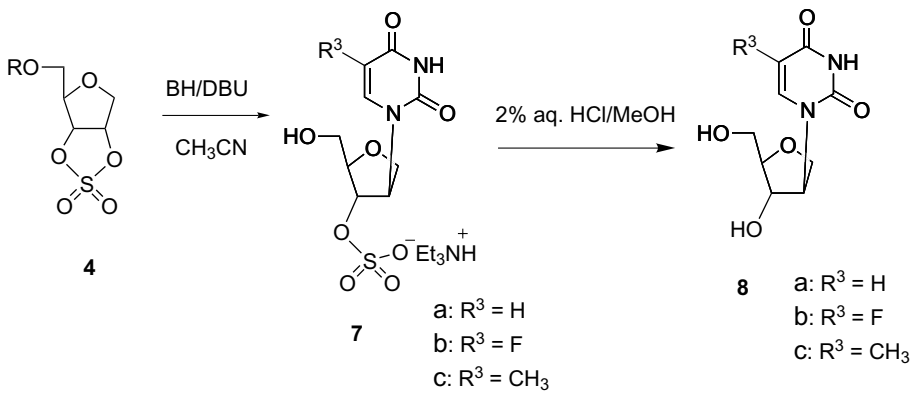



**Scheme 1.**




**Scheme 2.**

isonucleoside **6a** (60% yield from **4**).[14] Similarly, treatment of **4** with 2-amino-6-chloropurine followed by the treatment of the resulting nucleoside sulfate **5b** with 2% aqueous HCl in MeOH gave the guanine derivative **6b** (57% yield from **4**).

For the synthesis of pyrimidine isonucleosides, cyclic sulfate **4** was treated with uracil, 5-fluorouracil and thymine in a similar manner to give the nucleoside sulfates **7a**–**c** (Scheme 2). These sulfates were treated with 2% HCl in MeOH to produce the unprotected isonucleosides **8a**–**c** (46–59% from **4**).[15]

In summary, we have developed a general and efficient approach for the synthesis of isonucleosides that is superior to previously known methods on the basis of yield, regiochemistry, stereospecificity and simplicity of methodology.

## Acknowledgements

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14. **General method for the synthesis of 6**: To a suspension of purine base in anhydrous $CH_3CN$ (10–15 mL/mmol base), DBU (1.05 equiv.) was added and the suspension was stirred at room temperature for 0.5 h. To the resulting clear solution was added a solution of sulfate **4** in $CH_3CN$ (10 mL/mmol). The reaction mixture was then heated at 75°C for 2 h. The solvent was evaporated under reduced pressure and the residue was purified over silica gel column ($CH_2Cl_2$/MeOH/$Et_3N$, 30:3:1) to produce **5**. A solution of **5** in methanol (25 mL/mmol) containing 2% (v/v) of a 37% aqueous HCl solution was heated at 65°C for 20 h. The solvent was evaporated to dryness, coevaporated with ethanol and toluene. The residue was dissolved in MeOH/water (25 mL, 1:1), neutralized with 0.5N aqueous NaOH, evaporated to dryness and purified over silica gel to give **6a** and **6b** in 60 and 57% yields, respectively, from **4**.
15. **General procedure for the synthesis of 8**: To a suspension of pyrimidine base in anhydrous $CH_3CN$ (10–15 mL/mmol base), DBU (1.05 equiv.) was added and the suspension was heated under reflux for 1 h. To the resulting clear solution was added a solution of sulfate **4** in $CH_3CN$ (10 mL/mmol). The reaction mixture was then heated under reflux for 1.5 h. The solvent was evaporated under reduced pressure and the residue was purified over a silica gel column ($CH_2Cl_2$/MeOH/$Et_3N$, 60:3:1) to produce **7**. A solution of **7** in methanol (25 mL/mmol) containing 2% (v/v) of a 37% aqueous HCl solution was heated at 45°C for 20 h. The solvent was evaporated to dryness, coevaporated with ethanol and toluene. The residue was purified over silica gel to give **8a**, **8b** and **8c** in 59, 46 and 55% yields, respectively, from **4**. Data of compound **8b**: white solid (hygroscopic); $\lambda_{max}$ (MeOH) 274 nm ($\varepsilon$ 8100); $^1$H NMR (MeOH-$d_4$): 7.96 (d, $J=6.9$ Hz, 1H), 4.88 (m, 1H), 4.24 (m, 1H), 4.13 (dd, $J=6.7$, 10.7 Hz, 1H), 4.02 (dd, $J=3.1$, 10.7 Hz, 1H), 3.84 (d, $J=9.9$ Hz, 1H), 3.71–3.65 (m, 2H).