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# A Facile Preparative Method of C-Nucleosides

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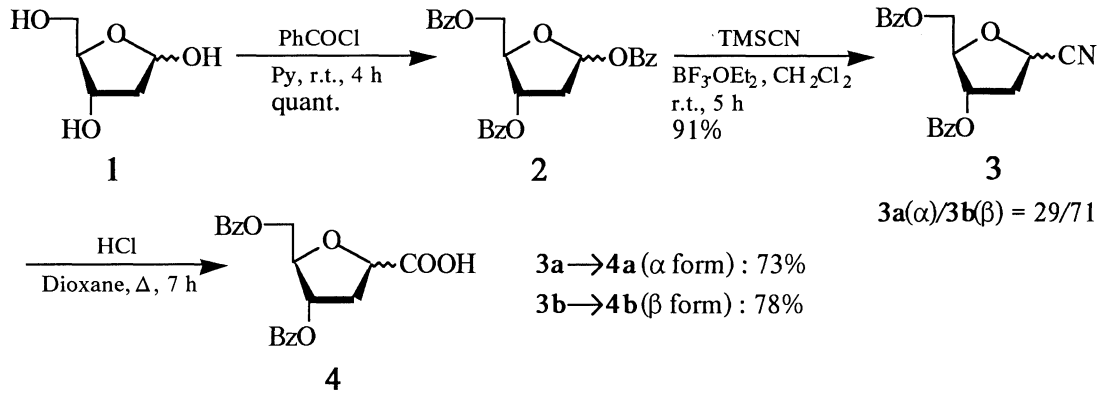
Facile and general preparative method of C-nucleosides has been achieved via 4 steps starting from 2-deoxy-D-ribose. The essential step in this method is the use of radical coupling reaction of 2-deoxy-D-ribofuranosyl radical derivative and some heteroaromatic bases.

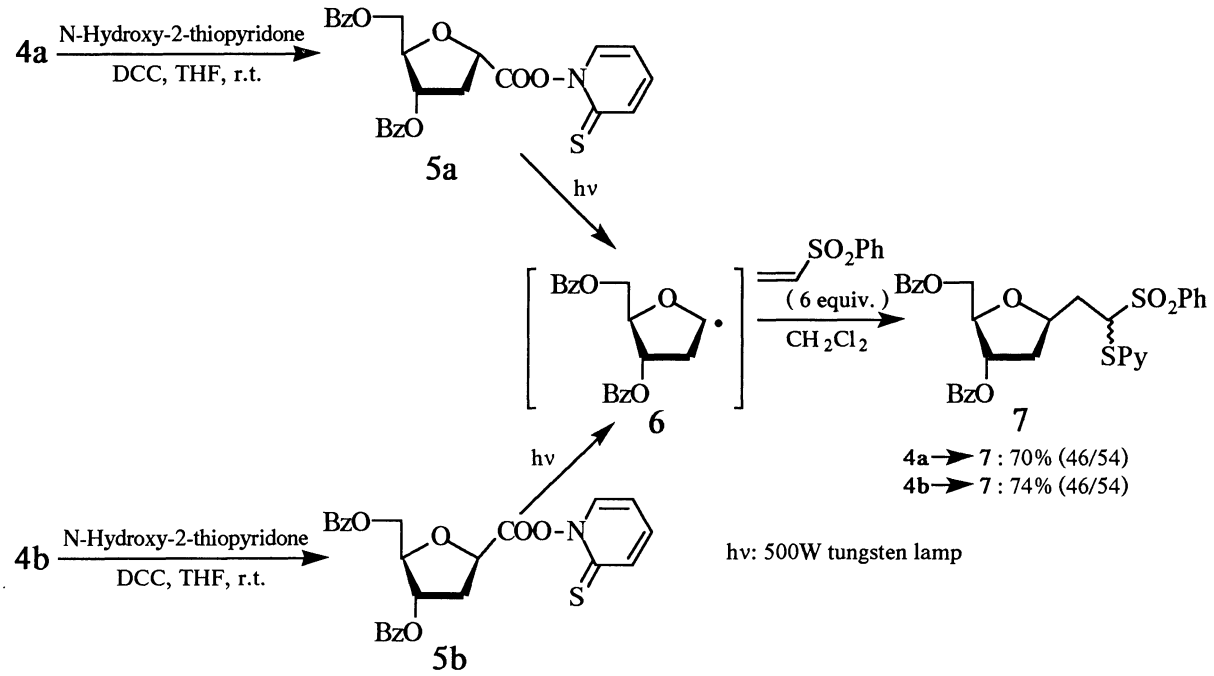
Study on nucleosides has become very attractive and important due to their high antitumor or antivirus activities.[1] Especially natural C-nucleosides such as showdomycin, pyrazomycin, oxazinomycin, formycin, and pyrrolosine, are well known to have potent antimicrobial and antitumor activities.[2] Therefore, the studies on the preparation of new type C-nucleosides have been extensively carried out.[3] However, the preparation of these C-nucleosides with previous known methods requires many steps and has much limitation to prepare many types of C-nucleosides.

As a part of our study to develop the new preparative method of C-nucleosides with radical coupling reaction of anomeric radical and heteroaromatic bases,[4] here we report a facile preparative method of C-nucleosides from 2-deoxy-D-ribose by utilizing Barton's decarboxylative radical reaction.[5] The previous procedure[4] as a preliminary study required many steps to get C-nucleosides and the final deprotection was almost disappointing because the yield of free C-nucleoside was extremely low and many undesired products were formed. Here, the starting material **4a** and **4b** could be obtained from 2-deoxy-D-ribose **1** in high yields as shown in Scheme 1.[6] The key step is the use of trimethylsilyl cyanide (TMSCN) to get cyanide derivatives **3a** and **3b**, which could be easily separated by column chromatography on silica gel.



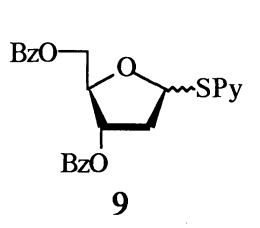

Scheme 1.

In order to examine the nucleophilic reactivity of anomeric radical **6** to electron deficient olefinic compounds (Scheme 2),[6] both thiohydroxamic acid esters **5a** and **5b**, which were prepared from **4a** and **4b** respectively, were treated with phenyl vinyl sulfone under irradiation with tungsten lamp to give the same product **7** (only β form) in the same diastereomeric ratios and in good yields, respectively. This result suggests that the anomeric

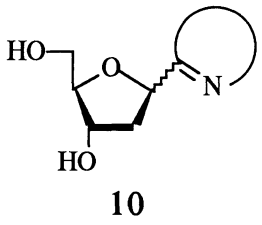



Scheme 2.

radical **6** is formed from both **5a** and **5b** in good yield under these conditions. Using the same procedure, the thiohydroxamic acid ester **5** was irradiated in the presence of heteroaromatic bases to get the corresponding C-nucleosides **8** in moderate yields as shown in Table 1.[6] The by-products were the corresponding decarboxylated compound **9** (10-30%) and 2, 2'-dipyridyl disulfide (20-66%), respectively. Especially, the yield of compound **9** increased when the benzothiazole and 5-(2-acetoxyethyl)-4-methylthiazole were used as heteroaromatic bases. The stereoselectivity depends on the used heteroaromatic bases. Thus, the major product with lepidine was β form. While, α form was major product with methyl nicotinate, methyl isonicotinate, benzothiazole, and pyrimidine.[7] The yields of **8** slighly depends on the reaction temperature as shown with lepidine. Thus the yields in Table 1 are shown under the best reaction conditions. While, the stereoselectivities with some heteroaromatic bases did not change in the range of 0 °C to 50 °C. Once **8** is obtained, it can be easily deprotected to give **10** in high yield.[6] This method could be also applied to D-ribose by the same procedure, though the yield of radical coupling reaction with heteroaromatic base was low.



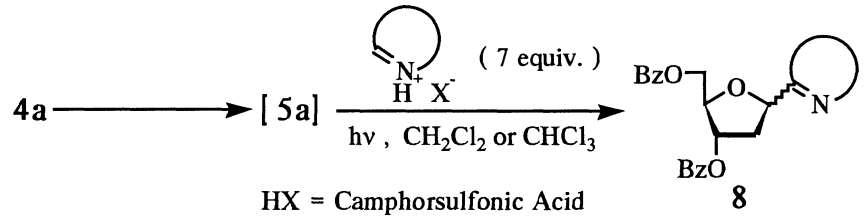

**9**

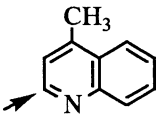
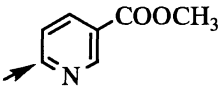
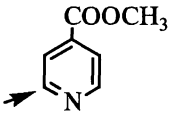
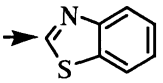
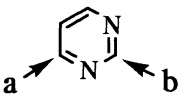
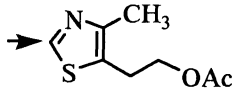



**10**

**10I**: 93%
**10IV**: 82%
**10V**: 70%

Table 1. Reaction with Heteroaromatic Bases




| Base | Temp / °C | 8 Yield / %[a] | Ratio (α/β) |
|---|---|---|---|
|  | ice bath | 54 (8I) | 14/86 |
| 〃 | 15-20 | 60 | 〃 |
| 〃 | 30-33 | 70 | 〃 |
| 〃 | 40-43 | 69 | 〃 |
| 〃 | 50-55 | 59 | 〃 |
| 〃 b) | 30-33 | 66 | 7/93 |
|  | ice bath | 45 (8II) | α only |
|  | 10-15 | 45 (8III) | α only |
|  | ice bath | 26 (8IV) | α only |
|  | 32-37 | 56 (8Va : 8Vb =71 : 29) | α only |
| 〃 b) | 33-37 | 40 (8Va : 8Vb =71 : 29) | α only |
|  | 34-37 | 30 (8VI) | α only |

a) Isolated yield. b) **4b** was used. → : C-C bond forming position

In conclusion, the key step in this procedure for the synthesis of C-nucleosides consists in radical coupling reaction of ribofuranosyl radical **6** and some heteroaromatic bases. Thus, this procedure has the great advantages such as the short synthetic route for C-nucleosides from 2-deoxy-D-ribose (4 steps), easy deprotection, and applicable to various heteroaromatic bases in principle. Further investigation on this radical coupling reaction and the biological activity of these obtained C-nucleosides are undergoing in this laboratory.

References

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2) Recent reviews; U. Hacksell and G. D. Daves, *Prog. Med. Chem.*, **22**, 1 (1985); T. Sato and R. Noyori, *Yuki Gosei Kagaku Kyokai Shi*, **38**, 862 and 947 (1980); K. A. Watanabe, *ibid.*, **45**, 212 (1987); N. Katagiri, *ibid.*, **47**, 707 (1989).

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4) H. Togo, M. Fujii, T. Ikuma, and M. Yokoyama, *Tetrahedron Lett.*, **32**, 3377 (1991).

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6) All these new compounds gave satisfactory spectroscopic and microanalytical data, and the structures were determined by both COSY and NOESY measurements.

7) The similar stereoselectivities for major products were also supported by MOPAC calculation roughly as below. MOPAC; $\Delta\Delta G^{\circ}$. ($\beta$-$\alpha$): **8I**, -0.635 kcal/mol; **8II**, 1.090 kcal/mol; **8III**, 1.194 kcal/mol; **8IV**, 0.384 kcal/mol.

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