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SYNTHESIS OF NUCLEOSIDES FROM 1-HYDROXYSUGARS USING 2-CHLOROBENZOXAZOLIUM SALT

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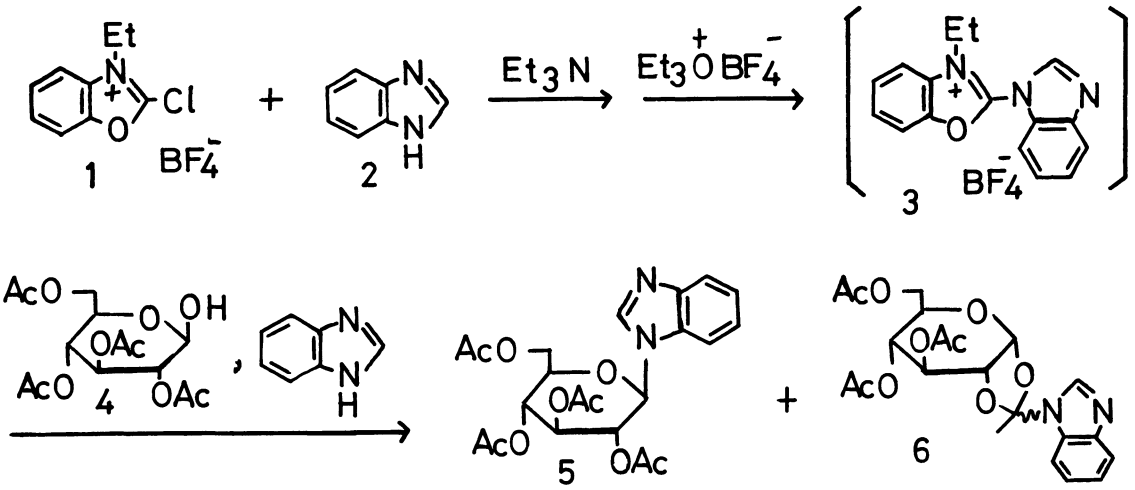
A novel method for the preparation of trans nucleosides was developed by the use of 2-chloro-3-ethylbenzoxazolium tetrafluoroborate as a condensing reagent. Several trans nucleosides were prepared from 1-hydroxysugars and heterocycles in good yields under mild conditions.

In the preceding communication,[1] we have reported that various kinds of alcohols smoothly react with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (1) in the presence of triethylamine and tetraethylammonium chloride to afford the corresponding alkyl chlorides in good yields. This reaction was also successfully applied to the transformation of 1-hydroxysugars into the corresponding glycosyl chlorides.

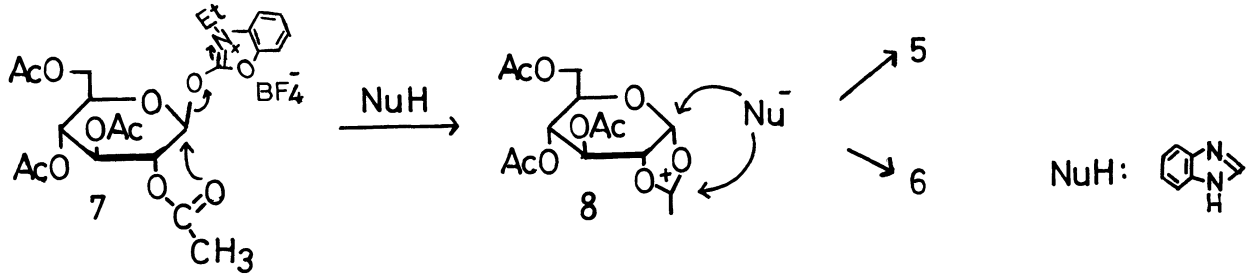
Now we wish to report a convenient method for the preparation of nucleosides from 1-hydroxysugars and heterocycles utilizing the benzoxazolium salt 1.

The following is a typical procedure for the preparation of nucleosides by the present method; To a stirred suspension of 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (1.5 mmol) and benzimidazole (1.5 mmol) in 1,2-dichloroethane (3 ml), was added a 1,2-dichloroethane (2 ml) solution of triethylamine (1.5 mmol) at -23°C under an argon atmosphere, and the resulting mixture was heated for 5 h at 60°C. The cooled reaction mixture was treated with a 1,2-dichloroethane (2 ml) solution of triethyloxonium tetrafluoroborate (1.5 mmol) and stirred overnight in order to remove the resulting chloride ion as ethyl chloride.[2] To this mixture was added a solution of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranose (1.0 mmol) and benzimidazole (1.0 mmol) in 1,2-dichloroethane (3 ml) and 1,2-dimethoxyethane (4 ml), and the

resulting mixture was heated for 10 h at 60°C. After evaporation of the solvent under reduced pressure, the residue was directly chromatographed on silica gel to give 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylbenzimidazole (5) in 73% yield along with a trace of 3,4,6-tri-O-acetyl-1,2-[1'-(1-benzimidazoyl)ethylidene]-α-D-glucopyranose (6).[3]



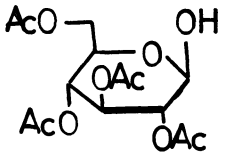
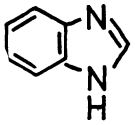
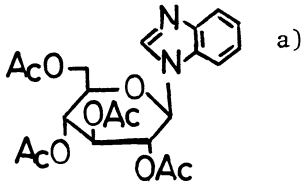
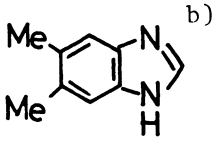
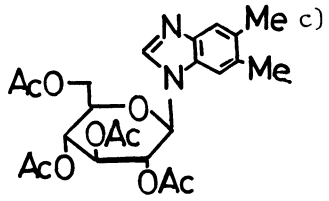
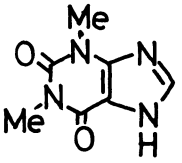
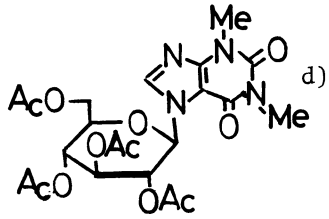
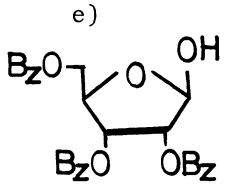
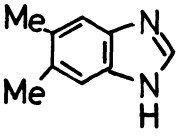
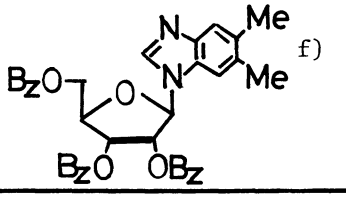
In the first stage of this reaction, a considerable amount of glucopyranose 6 was formed along with the desired nucleoside 5 (the ratio of 6 to 5 is about 2 to 1). The formation of 5 and 6 in the above reaction may be explained as follows; 2-(1-benzimidazoyl)benzoxazolium tetrafluoroborate (3), formed according to the procedure mentioned above, reacts with acetyl glucose 4 to give the intermediate 7. By the assistance of 2-acetoxy group of sugar moiety, the elimination of 3-ethyl-2-benzoxazolinone from 7 takes place easily to result in the formation of acetoxonium ion 8. This ion was then converted into glucopyranose 6 or β-nucleoside 5 by the nucleophilic attack of benzimidazole either on the electrophilic orthoester carbon or glycosidic center.



By the application of heat, the glucopyranose 6 was converted into thermodynamically stable β-nucleoside 5.

The conversion of glucopyranose 6 into β-nucleoside 5 is assumed to proceed in a similar manner to the rearrangement of orthoesters of sugars to trans glycosides.[4]

Table Synthesis of Nucleosides

Sugar	Heterocycle	Conditions Temp.	Time	Nucleoside	Yield (%)
		60°C	10h	 a)	73
	 b)	60°C	10h	 c)	86
		60°C	10h	 d)	93
 e)		60°C	10h	 f)	66

a) mp 152°C (lit.[8] mp 151-152°C). $[\alpha]_D^{19}$ -21.6° (c 2.1, chloroform) [lit.[8] $[\alpha]_D^{24.6}$ -22.8° (c 1.0, chloroform)].

b) This sample was provided from Prof. Y. Ishido of Tokyo Institute of Technology.

c) mp 170-173°C (lit.[8] 189-191°C). $[\alpha]_D^{24}$ -39° (c 1.0, chloroform) [lit.[8] -40.4° (c 1.0, chloroform)]. The NMR spectrum of this compound exhibited a similar pattern to that of glucopyranosylbenzimidazole 5 .

d) mp 166-167°C (lit.[9] 167°C). $[\alpha]_D^{22}$ -16.0° (c 1.0, chloroform) [lit.[9] $[\alpha]_{578}^{21}$ -19.0°, $[\alpha]_{546}^{21}$ -23.0° (c 1.0, chloroform)].

e) Bz=Benzoyl

f) $[\alpha]_D^{23}$ -119.1° (c 1.07, chloroform) [lit.[10] $[\alpha]_D^{20}$ -121.0° (c 1.02, chloroform)]. The product was identified by comparison of NMR spectrum and specific rotation with those reported by Fletcher et al. [J. D. Stevens and H. G. Fletcher, Jr., J. Org. Chem., 33, 1799 (1968).

Concerning the preparation of nucleosides, there are two general methods, namely, 1) the reaction of heavy metal salts of heterocycles and glycosyl halides reported by Lowy and Davoll,[5] and 2) the fusion of heterocycles with acylated sugars in the presence of acidic catalysts reported by Sato and Ishido.[6]

It is noted that, according to the present method of using 2-chlorobenzoxazolium salt 1 as a condensing reagent, trans nucleosides are produced in good yields under mild conditions without any assistance of heavy metal or acidic catalyst.

We would like to express our hearty thanks to Professor Yoshiharu Ishido of Tokyo Institute of Technology for his helpful discussion.

References and Notes

1) T. Mukaiyama, S.Shoda,and Y. Watanabe, Chem. Lett., 1977, 383.
2) J. P. Marino and R. C. Landick, Tetrahedron Lett., 1975, 4531.
3) The glucose 6 was separated by thin layer chromatography (silica gel), and purified by recrystalization from ethanol; Elemental analysis, Found:C, 56.30; H, 5.35; N, 5.79%. Calcd for $C_{21}H_{24}O_9N_2$: C, 56.24; H, 5.39; N, 6.25%. The NMR spectra of 6 shows H-2 and H-3 signals at 5.81 ($J_{1,2}$= 5.2 Hz) and 5.32 ($J_{2,3}$= 2.7 Hz), which is similar to that of tri-O-acetyl-α-D-glucopyranose 1,2-(methyl-orthoacetate).[7] The glucose 6 was converted into the corresponding tri-O-acetyl-α-D-glucopyranose 1,2-(ethylorthoacetate)[7] by the treatment with ethanol in the presence of a catalytic amount of zinc chloride.
4) H. Paulsen, Advances in Carbohydrate Chemistry and Biochemistry, 26, 127, (1971).
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