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Nucleosides and Nucleotides. 189. Investigation of the Stereoselective Coupling of Thymine with *meso*-Thiolane-3,4-diol-1-oxide Derivatives via the Pummerer Reaction

Takashi Naka, Naozumi Nishizono, Noriaki Minakawa and Akira Matsuda*

Graduate School of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan.

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***Abstract*:** We investigated the stereoselective coupling of thymine with sulfoxides derived from *meso*-thiolane-3,4-diol via the Pummerer reaction. The introduction of 2,4-dimethoxybenzoyl groups to the hydroxyl groups of *meso*-thiolane-3,4-diol-1-oxide was effective to afford (2*R**, 3*R**, 4*S**)-1-[3,4-di-*O*-(2,4-dimethoxybenzoyl)thiolane-3,4-diol-2-yl]thymine stereoselectively. © 1999 Elsevier Science Ltd. All rights reserved.

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There has been increasing interest in the synthesis of 4'-thionucleosides because of their antiviral and antitumor activities.[1] The methods used to synthesize this class of compounds mainly consist of classical thioglycosidation of the corresponding thiosugar and a nucleobase. However, the stereocontrol in such thioglycosidation is not satisfactory even with the assistance of the neighboring *C*-2 acetyl group.[2] Although numerous studies have been conducted on the synthesis of 4'-thionucleoside derivatives, little attention has been paid to the stereoselectivity of the resulting 4'-thionucleosides.[3] Furthermore, there has been no systematic studies on the correlation between stereoselectivity and the neighboring group effect of an adjacent acyloxy group.

On the other hand, we previously reported a synthesis of thietane nucleosides by the Pummerer reaction in which β-nucleoside was obtained exclusively with participation of neighboring group.[4] Accordingly, we sought to develop the stereoselective coupling of a nucleobase and a five-membered thiosugar via the Pummerer reaction, which has been recognized as an alternative method for synthesizing 4'-thionucleosides.[4,5] In this report, we describe the stereoselective coupling of thymine with *meso*-thiolane-3,4-diol-1-oxide derivatives, which may be useful in the β-selective synthesis of 4'-thioribonucleosides.

It is well known that adjacent acyloxy groups, including acetyl groups, are effective as neighboring groups for the glycosidation of ribofuranose derivatives to give β-ribonucleosides. To better understand the differences between furanose and thiofuranose derivatives, computational studies of four model carbonium cation intermediates were performed.[6] The resulting bond lengths (Å), bond angles, and net atom charges are

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* Author to whom reprint requests should be addressed. Phone: +81-11-706-3228. Fax: +81-11-706-4980.
E-mail: matuda@pharm.hokudai.ac.jp

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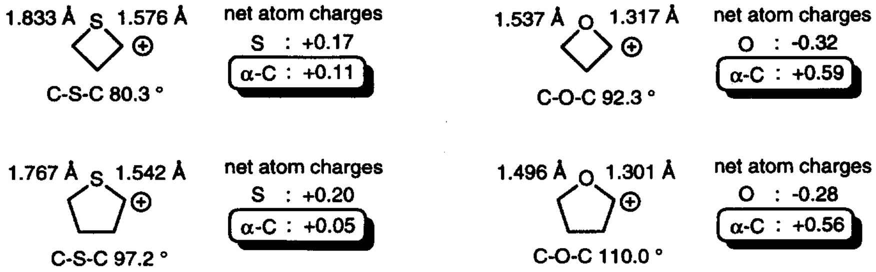
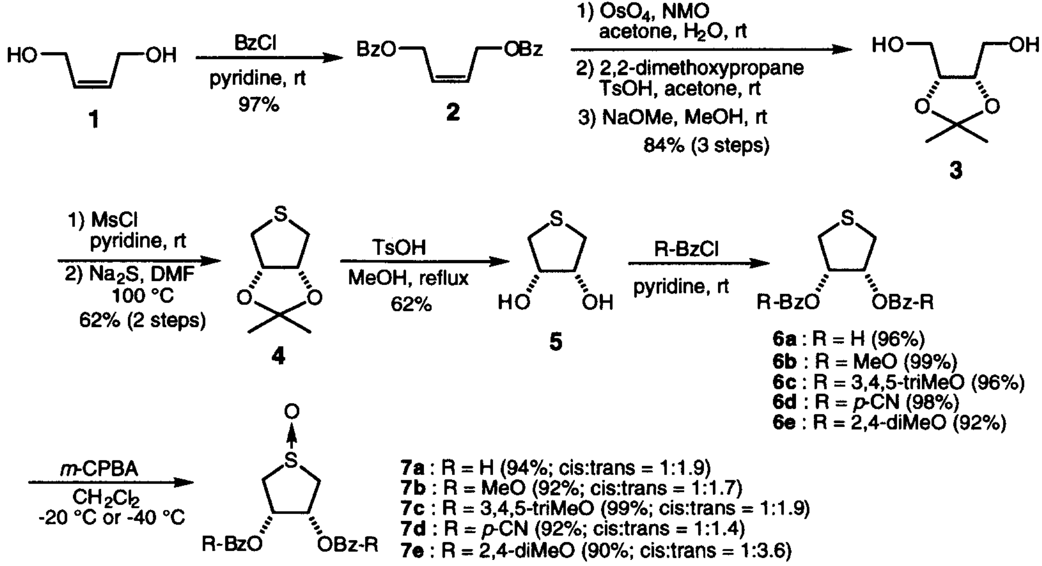


Figure 1. Geometrical values and net atom charges of model carbocation intermediates.

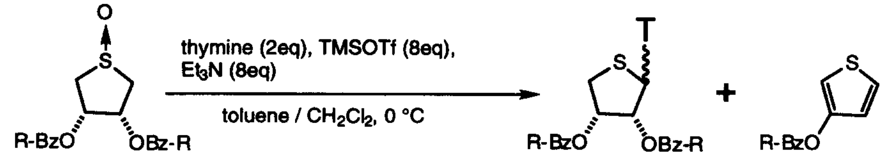
given in Figure 1. As can be seen from these results, the structures of the thiocarbonium cation and oxocarbonium cation intermediates are considerably different. Furthermore, the net atom charges at the α-position are quite different between oxo- and thiocarbonium cation intermediates. These results agree well with previous results,[2] implying that thiocarbonium cation intermediates are less susceptible to neighboring group effects than those of oxocarbonium cation, and that an acetyl group would not be efficient as a neighboring group.

Scheme 1



Based on these considerations, we investigated the stereoselective coupling of thymine and *meso*-thiolane-3,4-diol-1-oxides with various substituted benzoyl groups. Since **6** is a *meso* compound, only stereoisomers, i.e., α and β isomers, can be detected in the ^{1}H-NMR spectrum after the Pummerer reaction. The sulfoxides were prepared from *cis*-2-butene-1,4-diol (**1**) as shown in Scheme 1. After protection of the hydroxyl groups of **1** with a benzoyl group, **2** was treated with osmium tetroxide, and the resulting diol was protected with an isopropylidene group, followed by deprotection of the benzoyl groups to gave **3** in 84% yield from **2**. Reaction of **3** with methanesulfonyl chloride in pyridine gave dimesylate, which was treated with sodium sulfide in DMF to give tetrahydrothiophene derivative **4** in 62% yield. The isopropylidene group of **4** was removed by acidic conditions, and various benzoyl groups were then introduced to the hydroxyl groups to give **6a-e** in good yields. Oxidation of **6a-e** by mCPBA in dichloromethane gave the desired sulfoxides **7a-e** as diastereomeric mixtures. Among **7a-e**, each diastereomer of **7b** was easily separable by silica gel chromatography, and the geometry of the diastereomers was determined using Eu(dpm)$_3$ as a shift reagent.[7] For the geometries of the compounds other than **7b**, we speculated that the major isomer has a *trans*-geometry due to steric hindrance of the acyloxy substituents, as in **7b**.

Table 1



7a-e **8a-e** **9a-e**

entry	R	method[a)]	yield of **8** (%)[b)]	α:β[c)]	yield of **9** (%)[b)]
1	H	A	11	1:16	39
2	H	B	41	1:>30	22
3	*p*-MeO	B	59	1:>30	13
4	2,4-diMeO	B	70	1:>30	9
5	3,4,5-triMeO	B	50	1:>30	15
6	*p*-CN	B	22	1:14	55
7	*cis*-*p*-MeO	B	52	1:>30	13
8	*trans*-*p*-MeO	B	45	1:>30	15

a) Method A: a CH$_2$Cl$_2$ solution of **7** was added to a mixture of thymine, Et$_3$N, and TMSOTf in toluene, followed by ZnI$_2$. Method B: a mixture of thymine, Et$_3$N, and TMSOTf in toluene was added to a CH$_2$Cl$_2$ solution of **7** in the absence of ZnI$_2$.[8] b) Isolated yields. c) Determined by ^{1}H NMR.

We next examined the Pummerer reaction with thymine (Table 1). When **7a** was treated with thymine under conditions identical to those in thietane nucleoside synthesis,[4] coupling product **8a** was obtained in only 11% yield along with thiophene derivative **9a** in 39% yield (entry 1). Although the α:β ratio was satisfactory due to participation of the neighboring benzoyl group,[9] the isolated yield of **8a** was quite low, and the formation of undesirable **9a** posed a new problem in this reaction. It was considered that **9a** is formed by the elimination of benzoic acid due to coexistent excess triethylamine, followed by aromatization. This side reaction appeared to compete with the Pummerer reaction. Thus, the reaction involved an inverse addition as described in method B. Consequently, the desired **8a** was obtained in 41% yield, and the formation of **9a** was decreased to 22% yield. Moreover, the stereochemistry of the coupling product was quite β-selective (entry 2). Although this result revealed that a benzoyl group was sufficient as a neighboring group, further attempts were made with sulfoxides with an electron-donating group to suppress thiophene formation. As shown in entry 4, when **7e** was used as a reactant, the desired **8e** was obtained in 70% yield stereoselectively along with **9e** in 9% yield, as expected.[10] On the other hand, using a sulfoxide with *p*-cyanobenzoyl groups resulted in a decrease in the chemical yield and stereoselectivity of the desired compound (entry 6). Since each sulfoxide has a different diastereomeric ratio, this may contribute to these differences. Hence, the separated diastereomers were each subjected to the Pummerer reaction. As a result, both of the diastereomers gave almost the same results, which implies that the substituent on the benzoyl group influences not only neighboring group effects but also the formation of thiophene derivatives in the Pummerer reaction (entries 7 and 8).

In conclusion, we have developed an efficient and β-selective method for coupling thymine with *meso*-thiolane-3,4-diol-1-oxide using the Pummerer reaction. This method may be adapted to the synthesis of 4'-thioribonucleosides. Furhter investigations are in progress.

References and Notes

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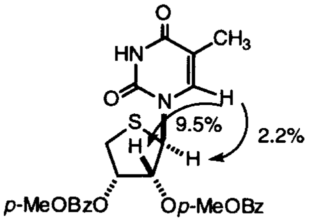
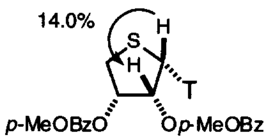
6. The optimal geometries of four model carbocation intermediates were obtained using AM1 methods. The net atom charges were calculated by RHF/6-31G* after geometry optimizations.
7. Folli, U.; Iarossi, D.; Taddei, F. *J. Chem. Soc., Perkin Trans. II*, **1974**, 933–937.
8. After several attempts, we found that the addition of ZnI_2 had no effects on the Pummerer reaction.
9. The structures of α and β isomers were confirmed by nOe experiments as shown in below after the HPLC separation.



β-isomer



α-isomer

10. Although it was thought that introduction of 2,4,6-trimethoxybenzoyl group would be more effective for the reaction, all of attempts to introduce 2,4,6-trimethoxybenzoyl group on both hydroxyl groups were failed due to steric hindrance.