A MILD AND RAPID GLYCOSYLATION REACTION BETWEEN PYRIMIDINE BASES AND 2-DEOXYRIBOFURANOSYL *N,N,N',N'*-TETRAMETHYLPHOSPHOROAMIDATES†

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Abstract — A trimethylsilyl triflate-mediated coupling reaction to produce protected 2'-deoxynucleosides has been developed by using *N,N,N',N'*-tetramethylphosphoroamidate as a leaving group. In this reaction, employment of a 3,4,5-trimethoxybenzoyl group as the 3-hydroxyl protective group in the sugar moiety improved the β-stereoselectivity *via* a novel 1,3-participation.

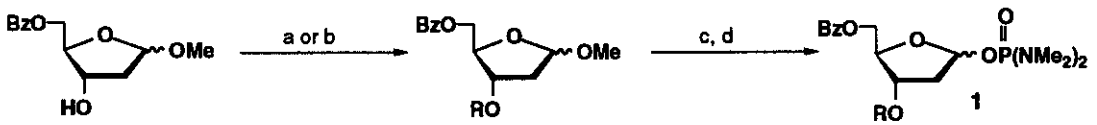
In recent years, much attention has been paid to 2'-deoxynucleosides and their analogs as significant antiviral and antibiotic agents. The condensation of nucleoside bases with appropriate sugar moieties is one of the most useful method for constructing these materials. The Vorbrüggen reaction[2] has been used most commonly to prepare modified nucleosides by reaction of silylated bases with sugar derivatives. However, it is less effective for preparing 2-deoxyribonucleosides, since desired β-anomers are produced non-stereoselectively with α-anomers in this process.[3] Intramolecular glycosylation methods have been applied to the preparation of 2'-deoxy-β-nucleosides recently,[4] in which multi-step sequences were required, and thus there still be needed a mild and high-yielding stereoselective glycosylation reaction. We have recently developed glycosyl donors having phosphorous-containing leaving groups, the glycosidation of which features mild and efficient methods for highly stereocontrolled construction of glycosidic linkages.[5,6] Applying this method to 2'-deoxyribonucleoside synthesis, we found interesting participation effects of 3-hydroxyl protective groups of sugar moiety on the stereoselectivity. Herein we wish to report a mild and direct glycosylation reaction which affords β-anomers predominantly by an aid of the protective group participation.

† Dedicated to the memory of the late Professor Yoshio Ban.

While we have devised several kinds of glycosyl donors characterized by their reactivity and stability, benzoyl-protected ribofuranosyl *N,N,N',N'*-tetramethylphosphoroamidate (**1**) was chosen as a substrate because of its high shelf-stability.[6,7] Coupling of the phosphoroamidate **1a** (R = Bz, 1.0 equiv.) and bis(trimethylsilyl)uracil (**2**, 1.5 equiv.) in CH_2Cl_2 in the presence of trimethylsilyl triflate (1.0 equiv.) at -20 °C was found to proceed to completion within 30 min., affording mixture of anomers (**3a**) in 90% yield with an only slight β-selectivity (entry 1 in Table 1). In order to improve the stereoselectivity we reinvestigated promoters (BF_3-OEt_2, $TiCl_4$, $SnCl_4$, $ZnCl_2$ and $Zn(OTf)_2$) and solvents (toluene, ether and propionitrile), but none proved to be better than the above conditions.[8]

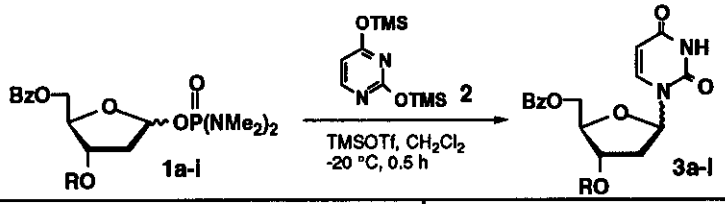
Wiesner and co-workers have pointed out 1,3-participation by the 4-methoxybenzoyl group attached to the C-3 position in their stereoselective β-glycosylation of digitoxose (2,6-dideoxy-D-*ribo*-hexopyranose).[9] Sugimura and co-workers have also reported the effects of protective groups on stereoselectivity in their synthesis of 1-(2-

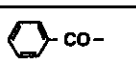
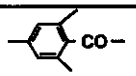
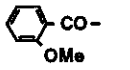
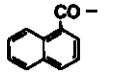
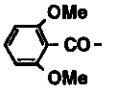
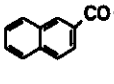
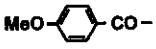
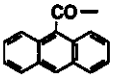
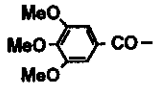
Scheme 1. Preparation of Phosphoroamidates (**1**)



(a) RCOCl, pyridine. (b) RCOOH, DCC, DMAP, CH_2Cl_2. (c) AcOH, 2N HCl. (d) BuLi, THF; $ClP(O)(NMe_2)_2$, THF-HMPA.

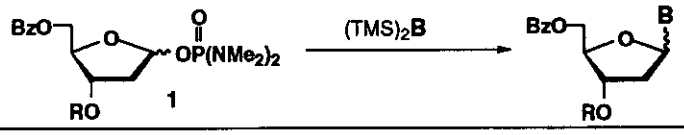
Table 1. Effect of 3-hydroxy protecting group on stereoselectivity



entry	R		yield (%)[a]	β / α ratio[b]	entry	R		yield (%)[a]	β / α ratio[b]
1		**1a**	90	1.5	6		**1f**	87	1.5
2		**1b**	89	1.9	7		**1g**	86	1.4
3		**1c**	90	1.2	8		**1h**	81	1.4
4		**1d**	77	1.5	9		**1i**	57	1.9
5		**1e**	83	2.6					

[a] Isolated total yield based on the sugar **1**. [b] Determined by 400 MHz ^1H NMR integration of the anomeric protons.

Table 2. Coupling of benzoyl and 3,4,5-trimethoxybenzoyl protected sugars (**1**) with silylated bases[a]



B (base)	**1a** (R=benzoyl) yield (%)[b]	**1a** (R=benzoyl) β / α ratio[c]	**1e** (R=3,4,5-trimethoxybenzoyl) yield (%)[b]	**1e** (R=3,4,5-trimethoxybenzoyl) β / α ratio[c]
thymine	84	1.5	87	4.9
5-trifluoromethyluracil	90	2.2	89	5.3
cytosine	90	0.9	83	1.4

[a] The reaction was carried out at -20 °C for 0.5 h using 1.5 equiv. of silylated base in the presence of 1.0 equiv. of TMSOTf. [b] Isolated total yield based on the sugar **1**. [c] Determined by 400MHz ^{1}H NMR integration of the anomeric protons.

deoxy-D-*threo*-pentfuranosyl)thymine.[10] As we were interested in this 1,3-participation, we turned our attention to the effects of 3-hydroxyl protective groups. Although the substrates (**1**) having 3-*O*-(4-nitrobenzoyl) or 3-*O*-(4-bromobenzoyl) group could not be prepared practically by our standard procedure, methoxy-substituted benzoate and sterically bulky acyl groups were introduced at C-3 position successfully (Scheme 1).

All the substrates prepared in this study were found to proceed the trimethylsilyl triflate-mediated coupling reaction in high yield with similar stereoselectivity except entry 5 (Table 1). 3,4,5-Trimethoxybenzoyl group was found to have an exceptional effect on stereoselectivity (β / α ratio = 2.6). Sterically bulky groups did not effect the stereoselectivity (entry 6-9 in Table 1). While the mechanistic basis for this 1,3-participation by the 3,4,5-trimethoxybenzoyl group is unclear, some electronic properties might play an important role in this stereochemical outcome.

Application of this coupling reaction to other pyrimidine nucleosides was summarized in Table 2. Protected deoxythymidine, deoxytrifluoromethyluridine and deoxycytidine were obtained in high yield. It is noteworthy that 3,4,5-trimethoxybenzoyl group enhanced β-selectivity obviously in all substrates. The reaction of silylated 5-trifluoromethyluracil and **1e** seems to be useful for the practical synthesis of 2'-deoxy-5-trifluoromethyluridine, because achievement of high yield and good β-selectivity necessitated less equivalents of silylated base (1.5 equiv.) than that in the reported procedure.[11]

Although the stereoselectivity is not necessarily satisfactory in terms of practical value, mild and high-yielding glycosylation procedure reported herein may be useful method of modified nucleoside synthesis. Moreover, this anomalous effect of 3,4,5-trimethoxybenzoyl group provides a new aspect on stereoselectivity in this type of coupling reaction.

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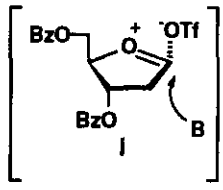
REFERENCES AND NOTES

1. Present address: Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Hokkaido 060, Japan.
2. H. Vorbrüggen, K. Krolikiewicz, and B. Bennua, *Chem. Ber.*, 1981, **114**, 1234 .
3. The S_N2 type displacement using α-anomers of the chlorosugars affords β–nucleosides selectively: H. Aoyama, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 2073; Z. Kazimierczuk, H. B. Cottam, G. R. Revankar, and R. K. Robins, *J. Am. Chem. Soc.*, 1984, **106**, 6379.
4. M. E. Jung and C. Castro, *J. Org. Chem.*, 1993, **58**, 807; K. Sujino and H. Sugimura, *Chem. Lett.*, 1993, 1187.
5. S. Hashimoto, T. Honda, and S. Ikegami, *J. Chem. Soc., Chem. Commun.*, 1989, 685; S. Hashimoto, T. Honda, and S. Ikegami, *Heterocycles*, 1990, **30**, 775; S. Hashimoto, T. Honda, and S. Ikegami, *Chem. Pharm. Bull.*, 1990, **38**, 2323; S. Hashimoto, T. Honda, and S. Ikegami, *Tetrahedron Lett.*, 1990, **31**, 4769; S. Hashimoto, T. Honda, and S. Ikegami, *Tetrahedron Lett.*, 1991, **32**, 1653.
6. S. Hashimoto, Y. Yanagiya, T. Honda, H. Harada, and S. Ikegami, *Tetrahedron Lett.*, 1992, **33**, 3523.
7. Attachment of the other phosphorous-containing leaving groups developed by us[5] was found to be difficult because of their high reactivity. Benzyl-protected ribofuranosyl *N,N,N',N'*-tetramethylphosphoroamidate was also unstable and considerable decomposition occurred during chromatographic purification.
8. $ZnCl_2$ and $Zn(OTf)_2$ as promoteres improved β-selectivity slightly ($\beta / \alpha = 2.1$), but yields were considerably low (10 - 20%). It was also found that the use of excess of TMSOTf (5 equiv.) afforded the β-anomer predominantly ($\beta / \alpha = 5.3$) in 10% yield. These results might be ascribed to the selective decomposition of the reaction intermediate such as **i** (β-ion pair) which afforded the α-anomer by the backside attack of nucleoside base (**B**).



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9. K. Wiesner, T. Y. R. Tsai, and H. Jin, *Helv. Chim. Acta*, 1985, **68**, 300.
10. H. Sugimura, K. Sujino, and K. Osumi, *Tetrahedron Lett.*, 1992, **33**, 2515.
11. Kawakami and co-workers have been reported that a large amount of silylated base was required to obtain high stereoselectivity in their synthesis of 2'-deoxy-5-trifluoromethyluridine: Kawakami, T. Ebata, K. Koseki, H. Matsushita, Y, Naoi, K. Ito, and N. Mizutani, *Heterocycles*, 1990, **31**, 569.

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