Novel Dehydrative Glycosylation by Using Acid Anhydride and $TMSClO_4$

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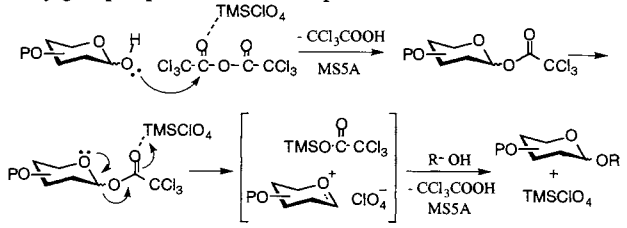
Novel dehydrative glycosylation with 1-hydroxy sugars as glycosyl donors was achieved. Combination of trifluoroacetic anhydride or trichloroacetic anhydride as dehydrating agents with $TMSClO_4$ as a Lewis acid afforded desired glycosides in good yields. t-Butyldiphenylsilyl and trichloroethoxycarbonyl groups at the 6-position of donors enhance α-selectivity of the glycosylation.

Synthesis of oligosaccharides and glycoconjugates has been of great importance for elucidation of their biological functions. Various methods have been reported[1] for glycosylation which is the key reaction for the synthesis of oligosaccharides and their derivatives. A glycosidic bond is generally constructed with a glycosyl donor which has a particular leaving group on its anomeric position. Direct formation of a glycosidic bond from a 1-hydroxy sugar has obvious advantage, since the reaction step for introduction of a leaving group is not required. Hydrolysis of donor, which is the major side reaction of glycosylation reaction, can be avoided in principle. In recent years, dehydrative glycosylation has, therefore, been extensively studied,[2] but successful α-selective glycosylation has not been reported yet. In the present study, we describe a novel α-selective dehydrative glycosylation by using acid anhydrides and a Lewis acid.

Several glycosylation methods by using 1-*O*-acyl sugars as glycosyl donors and Lewis acids as promoters have been already reported.[3] Lewis acid-catalyzed acylation of hydroxy groups was also described.[4] We anticipated that a 1-*O*-acyl sugar which was formed in situ from a 1-hydroxy sugar with an acid anhydride and a Lewis acid catalysis would be activated by the same Lewis acid and reacts with a glycosyl acceptor, if available in the mixture, to give a glycoside. The critical reaction step in this approach would thus be selective acylation of the 1-hydroxy group of the donor in the presence of the free hydroxy group of the acceptor. Since anomeric hydroxy groups generally show higher reactivity than usual hydroxy groups, selective acylation at 1-position was expected to be possible provided that no primary hydroxy group is present in the acceptor.



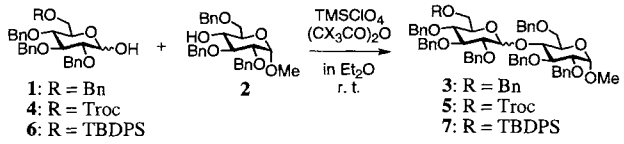
Trifluoroacetic anhydride [$(CF_3CO)_2O$] or trichloroacetic anhydride [$(CCl_3CO)_2O$] was used as dehydrating agents and $TMSClO_4$ prepared in situ from TMSCl and $AgClO_4$ as a Lewis acid.[5] All the reactions were carried out in diethyl ether in order to utilize its α-directing solvent effect. Since diethyl ether suppresses Lewis acidity, the reaction was carried out at room temperature without Lewis acid catalyzed anomerization of the product.

Glycosylation was first examined by the use of 2,3,4,6-tetra-*O*-benzyl glucose **1** as a donor and a glucose derivative **2** with a free 4-hydroxy group as an acceptor. The results are summarized in Table 1.[6] When catalytic amount of $TMSClO_4$ was used in the absence of Molecular Sieves (MS), the desired disaccharide **3** was obtained but only in 19% yield (entry 1). This result suggests that CCl_3COOH formed on 1-*O*-acylation inactivated the Lewis acid and inhibited further reaction. We then tested several MS to remove the acid from the reaction mixture. In the presence of MS 3A and 4A, the disaccharide **3** was not formed (entry 2, 3). These MS 3A and 4A seem to have no ability to remove CCl_3COOH. On the other hand, addition of MS 5A dramatically enhanced the desired glycosylation reaction (entry 4): the reaction proceeded smoothly by using a catalytic amount of $TMSClO_4$ (0.2 eq.) to give **3** in 91% yield (α:β = 82:18, entry 4).

Previously, we found that α-selectivity of glycosylation was improved by the influence of the trichloroethoxycarbonyl (Troc) function introduced at the 6-position of the donor.[7] α-Selective glycosylation was then investigated by the use of the 6-*O*-Troc glucose derivative **4** with the same acceptor **2**. Because of the lower reactivity of the 6-*O*-Troc donor than the corresponding 6-*O*-Bn donor, 0.5 equivalents of $TMSClO_4$ was required for a facile reation. The α-selectivity was improved to a great extent (α:β = 94:6). But the yield of the desired disaccharide was not satisfactory even with higher amont of the promoter (entry 5). The major side reaction in this case was 4-*O*-acylation of the acceptor **2** owing to the low reactivity of **4** with $(CCl_3CO)_2O$. When more reactive $(CF_3CO)_2O$ was used as a dehydrative agent,[8] the yield of the disaccharide **5** was improved (entry 6). Even in this case the undesired 4-*O*-acylated acceptor was still formed.

The α-directing effect of the 6-*O*-Trt group observed in our previous work was also examined. But this acid labile group proved not to survive under present reaction conditions. As the α-directing effect of the Trt group is attributed to its shielding of the β-face of the anomeric position, the t-butyldiphenylsilyl (TBDPS) group was next examined as a bulky and acid-stable protecting group. The desired disaccharide **7** was obtained in 73% yield with higher α-selectivity (α:β = 88:12, entry 7) than in the case of **3** by using an excess acceptor **2** against the 6-*O*-TBDPS donor in order to suppress the major side reaction to form 1,1'-disaccharide from **6**.

Dehydrative glycosylation was also investigated of an acceptor **8** with a reactive primary 6-hydroxy group. Considerable amount of 6-*O*-acylated compound was formed as a byproduct when the acid anhydride was added at once to a mixture of **1** and **8** (data not shown). Application of a stepwise procedure proved to be effective for this case: $(CCl_3CO)_2O$ and $TMSClO_4$ were first added to the donor solution and then acceptor **8** was added to the mixture. The desired disaccharide **9** was obtained in 53% yield by using 0.4 eq. of $TMSClO_4$ in the presence of MS 5A (see Table 2). Since MS 5A enhances both glycosylation and acylation, the reaction was carried out in the absence of MS 5A in order to suppress undesired 6-*O*-acylation. The desired **9** was



1: R = Bn
4: R = Troc
6: R = TBDPS

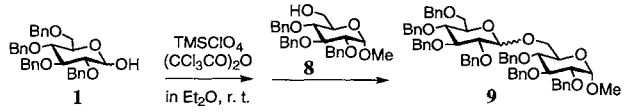
2

3: R = Bn
5: R = Troc
7: R = TBDPS

Table 1. Glycosylation with $(CX_3CO)_2O$ and $TMSClO_4$[a]

Entry	R	X	$TMSClO_4$[b]	MS[c]	Time	Yield/%	α:β[d]
1	Bzl	Cl	0.2	-	3 d	19	77:23
2			0.2	3A	3 d	trace	-
3			0.2	4A	3 d	trace	-
4			0.2	5A	8 h	91	82:18
5	Troc	Cl	0.5	5A	15 h	50	94:6
6		F	0.5	5A	4 h	60	94:6
7[e]	TBDPS	Cl	0.5	5A	6 h	73	88:12

[a] The reaction was carried out using 1.0 eq. of $(CCl_3CO)_2O$ and 0.67 eq. of the acceptor to the donor. [b] Equivalents to donor. [c] Molecular Sieves: 125 mg/ml of solvent. [d] The ratio was determined by ^{1}H-NMR. [e] The reaction was carried out by the use of 1.5 eq. of the acceptor to the donor.



1 **8** **9**

Table 2. Glycosylaton of a 6-hydroxy acceptor under the stepwise procedure[a]

Entry	$TMSClO_4$[b]	MS[c]	Time/h	Yield/%	α:β[d]
1	0.4	5A	18	53	82:18
2	1.0	5A	4	57	88:12
3	1.0	-	4	81	91: 9

[a] The reaction was carried out using 1.0 eq. of $(CCl_3CO)_2O$ and 0.67 eq. of the acceptor to the donor. [b] Equivalents to donor. [c] Molecular Sieves: 125 mg/ml of solvent. [d] The ratio was determined by ^{1}H-NMR.

thus obtained in 81% with high α-selectivity (α:β = 91:9) by employing a stoichiometric amount of $TMSClO_4$.

As described, combination of acid anhydrides and $TMSClO_4$ effectively promotes dehydrative glycosylation from the 1-hydroxy sugar **4**. Potent α-directing effect of TBDPS group at the 6-position of a donor was newly found. MS 5A enhances both acylation and glycosylation since MS 5A can trap carboxylic acids but do not absorb Lewis acids. The yields of glycosylation are generally lower than the corresponding reaction with thioglycosides. The major advantage of the present method is its simple operation without extremely careful precausion against moisture which causes serious problems in other glycosylation methods.

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5 $TMSCl$-$AgClO_4$ gave the best results among Lewis acids tested. Since $TMSClO_4$ may be explosive, concentration of the reaction mixture must be avoided. Combination of perchlorates and ether has been frequently used for α-selective glycosylation as cited in references 1 and 9.

6 A typical reaction procedure is as follows: To a suspension of glycosyl donor **1** (81 mg, 1.5 mmol), glycosyl acceptor **2** (46 mg, 1.0 mmol), and Molecular Sieves 5A (500 mg) in dry diethyl ether (4 ml) was added $AgClO_4$ (6.3 mg, 0.3 mmol), $(CCl_3CO)_2O$ (27.4 μl, 1.5 mmol), and $TMSCl$ (3.8 μl, 0.3 mmol) under N_2 atmosphere. The mixture was stirred at room temperature for 8 h. Ethyl acetate and saturated aqueous $NaHCO_3$ solution was added to the mixture and Molecular Sieves 5A was removed by filtration. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica-gel column chromatography to give an oily product as a mixture of α- and β-anomers: Yield 90 mg (91%).

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8 In the case of reactive donor, $(CF_3CO)_2O$ worked as well as $(CCl_3CO)_2O$ (data not shown).

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