A Catalytic and α-Selective Sialylation Using Novel 5-Azido Sialyl Fluoride

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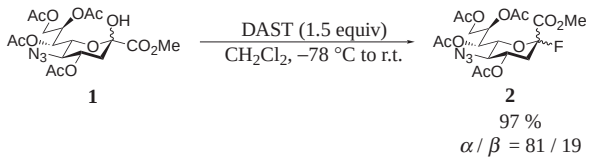
Catalytic and α-selective sialylation of several glycosyl acceptors with 5-azido sialyl fluoride **2** was successfully carried out in *n*-valeronitrile using a combined catalyst system of stannic chloride ($SnCl_4$) and silver perchlorate ($AgClO_4$) (1:2) in the coexistence of MS 5A and the corresponding sialosides were obtained in excellent yields with high α-selectivities.

N-Acetylneuraminic acid (sialic acid, Neu5Ac) which exists in several biologically active oligosaccharides[1] and glycolipids of cell membranes[2] is found at their nonreducing ends. In order to develop a study on the vital role of these glycoconjugates, it is strongly desired to establish an efficient and stereoselective method for the preparation of α-sialoside. However, it is quite tough to obtain α-sialoside in high yields because α-sialoside is less stable compared with the corresponding β-sialoside and always undesirable side reaction such as 2, 3-elimination takes place during sialylation. Further, stoichiometric amounts of activators are required in many sialylation reactions[3] since the reactivities of most sialyl donors at anomeric positions are low. As for catalytic sialylation, only a few examples in which sialyl phosphites[4] were used as donors have been reported. On the other hand, glycosyl fluoride,[5] in spite of being known as one of the most superb glycosyl donors in the synthesis of complex oligosaccharide chain, has rarely been employed as a donor in sialylation[6] nor any catalytic methods have been introduced. Recently, it was reported[7] from our laboratory that the combined catalyst system of stannic chloride ($SnCl_4$) and silver tetrakis(pentafluorophenyl)borate [$AgB(C_6F_5)_4$] (1:2) was effective in the cases of glycosylation using 'disarmed' glycosyl fluoride having phthaloyl (Phth) or 4,5-dichlorophthaloyl (DCPhth) protecting group for 2-amino function. In this communication, we would like to report catalytic and α-selective sialylation with newly prepared 5-azido sialyl fluoride **2**, a donor, by using combined catalyst system of $SnCl_4$ and $AgClO_4$ (1:2), which afforded the corresponding sialoside in excellent yield with high α-selectivity.

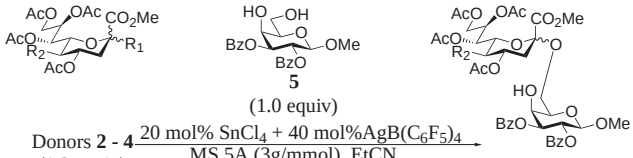
Recently, Wong[8] et al. reported that the sialic acid possessing 5-azido group, a donor, gave a good result in α-selective sialylation, in which the side reaction of 2,3-elimination was prevented. Then, novel 5-azido sialyl fluoride **2** was firstly prepared from readily available 5-azido 2-OH sialic acid **1**[9] by treating with diethylaminosulfur trifluoride (DAST)[10] (Scheme 1). According to our previously reported procedure,[7] the sialylation of glycosyl acceptor **5** with various sialyl fluorides was examined in propionitrile (EtCN) by using a combination of 0.2 equivalents of $SnCl_4$ and 0.4 equivalents of $AgB(C_6F_5)_4$ in the coexistence of MS 5A (Table 1). The reaction proceeded smoothly to afford the desired α-sialoside **6** in good yield with good α-selectivity only when 5-azido sialyl fluoride **2** was used as a sialyl donor (Entry 1). On the other hand, sialyl fluorides **3** or **4** were not activated enough to react with glycosyl acceptor under the above mentioned conditions (Entries 2 and 3). The anomeric configurations of these sialosides were determined by NMR measurement based on their chemical shifts of H'-3eq, H'-4 according to empirical rules.[11] Also, it should be noted that the sialylation using 5-azido sialyl fluoride **2** proceeded smoothly even in a catalytic manner.



1 → **2**: 97 %, α / β = 81 / 19

Scheme 1. Preparation of 5-azido sialyl fluoride **2**.

Table 1. Catalytic sialylation using various donors

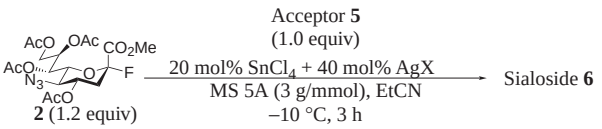


Entry	Donor	Yield / %(α / β)[a]
1	**2** : R_1 = F (α), R_2 = N_3	**6** : 82 (71 / 29)
2	**3** : R_1 = F (β), R_2 = Ac_2N	**7**: not detected
3	**4** : R_1 = F (β), R_2 = AcNH	**8** : not detected

[a]The α / β ratios were determined by ^{1}H NMR measurement according to empirical rules.

Next, in order to improve both yield and α-selectivity of the sialylation using 5-azido sialyl fluoride **2**, the effect of silver salts was examined (Table 2). It was found then that a catalyst[12] generated from $SnCl_4$ and $AgClO_4$ gave the best result although the role of counter anions was not clear so far (Entry 6). Next, several other solvents were screened and effects of the solvent on both reactivity and stereoselectivity in the present sialylation are shown in Table 3. Good α-selectivities were observed in all

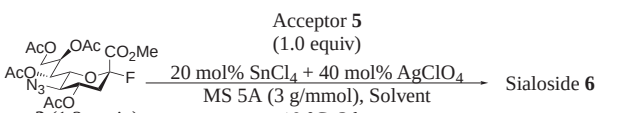
Table 2. Effect of silver salt



Entry	AgX	Yield / % (α / β)[a]	Entry	AgX	Yield / % (α / β)[a]
1	$AgB(C_6F_5)_4$	82 (71 / 29)	5	$AgNTf_2$	59 (74 / 26)
2	AgOTf	74 (81 / 19)	6	$AgClO_4$	91 (82 / 18)
3	$AgSbF_6$	89 (71 / 29)	7	None	74 (73 / 27)
4	$AgPF_6$	46 (74 / 26)			

[a]The α / β ratios were determined by HPLC analysis.

Table 3. Effect of solvent



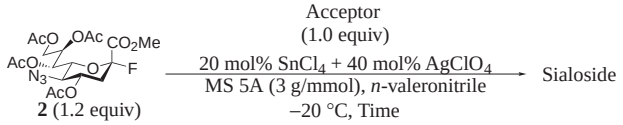
Entry	Solvent	Yield / % (α / β)[a]	Entry	Solvent	Yield / % (α / β)[a]
1	MeCN	95 (71 / 29)	7[d]	*n*-valeronitrile	17 (91 / 9)[13]
2	EtCN	91 (82 / 18)	8	hexanenitrile	89 (86 / 14)
3	*n*-PrCN	90 (84 / 16)	9	^{i}-PrCN	77 (86 / 14)
4	*n*-valeronitrile	94 (86 / 14)	10	CH_2Cl_2	trace
5[b]	*n*-valeronitrile	53 (88 / 12)	11	Et_2O	no reaction
6[b,c]	*n*-valeronitrile	93 (89 / 11)	12	toluene	not detected

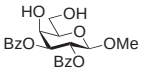
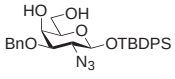
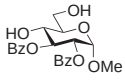
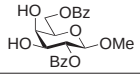
[a]The α / β ratios were determined by HPLC analysis. [b]The reaction was carried out at – 20 °C. [c]The reaction time was 9 h. [d]The reaction was carried out at – 30 °C.

nitriles examined and the selectivity increased when their carbon chains were longer. In contrast, CH_2Cl_2, Et_2O and toluene were not effective. The optimized reaction conditions were determined in Entry 6 (20 mol% $SnCl_4$ + 40 mol% $AgClO_4$, *n*-valeronitrile, $-20\,^{\circ}C$, 9 h, 93%, $\alpha/\beta = 89/11$). When the sialylation was carried out by using other Lewis acids such as $SnCl_2$, $TiCl_4$ or $AlCl_3$, only a trace amount of sialoside was obtained.

Finally, glycosyl acceptors **5**, **9** and **11** that are frequently found in biologically active saccharides and unnatural glycosyl acceptor **10** were tried in order to extend the scope of the present sialylation (Table 4). In the cases of using the glycosyl acceptors **5**, **9** and **10** having primary hydroxyl group at C-6 position, the desired sialosides were obtained in high yields with high stereoselectivities. When the glycosyl acceptor **11** having secondary hydroxyl group at C-3 and C-4 positions was used, however, the sialylation proceeded slowly and both yield and α-selectivity of the desired sialoside were low probably because of its steric hindrance.

Table 4. The sialylation of various acceptors



Entry	Acceptor		Time /h	Yield / % (α / β)[a]
1		**5**	9	93 (89 / 11)
2		**9**	24	90 (89 / 11)[b]
3		**10**	5	99 (82 / 18)[b]
4[c, d]		**11**	24	36 (55 / 45)[b]

[a]The α / β ratios were determined by HPLC analysis. [b]The α / β ratios were determined by ^{1}H NMR measurement according to empirical rules. [c]The reaction was carried out at –10 °C. [d]2.0 equiv of **2** was used.

It is noted that catalytic and α-selective sialylation with novel 5-azido sialyl fluoride **2** was successfully achieved in *n*-valeronitrile by using the combined catalyst system of stannic chloride ($SnCl_4$) and silver perchlorate ($AgClO_4$) (1:2) in the coexistence of MS 5A. This is the first example of a catalytic sialylation of glycosyl acceptors with sialyl fluoride which affords the corresponding sialosides in excellent yields with high α-selectivities. The azido group of α-sialoside **6** was easily converted to 5-NHAc group in 83% yield by successive reduction with AcSH.[14]

Further studies on sialylation of glycosyl acceptor having alkylthio group at anomeric position and one-pot sequential synthesis of trisaccharide are now in progress.

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References and Notes

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13 The high α-selectivities were also observed when the glycosylations were carried out in *n*-valeronitrile using 120 mol% $SnCl_4$ + 240 mol% $AgClO_4$ at $-30\,^{\circ}C$ (3 h, 83%, $\alpha/\beta = 92/8$) and $-40\,^{\circ}C$ (3 h, 77%, $\alpha/\beta = 94/6$), respectively.
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