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Novel glycosylation reactions using glycosyl thioimidates of *N*-acetylneuraminic acid as sialyl donors

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Abstract—Novel sialyl donors **4** bearing a thioimidolyl moiety as the leaving group were successfully prepared from the corresponding arylthio derivatives **3** and a peracetylated chloro derivative of Neu5Ac **2** in the presence of *N*,*N*-di-isopropylethylamine with moderate yields. The reaction of **4** with various alcohols **5** was effectively activated by AgOTf as the promoter to give the corresponding *O*-sialosides **6** with good yields. Selective activation of **4a** over 4-pentenyl 2-glycoside of Neu5Ac **7** with AgOTf was also achieved.

N-Acetylneuraminic acid (sialic acid, Neu5Ac) and its various analogs play essential roles in a variety of biochemical and biological processes.[1] The development of an efficient method of O-sialylation has been a challenging task in the field of sialic acid chemistry.[2] Recent analysis has focused on the utilization of metal triflate salts as activators for milder and stereoselective O-glycosylation.[3] Recently, AgOTf or $Cu(OTf)_2$ promoted O-sialylation using *S*-benzoxazolyl and *S*-thiazolyl glycoside derivatives of Neu5Ac has been reported.[4] As part of our program aimed at the development of new O-sialylation reaction,[5] we demonstrated the utility of glycosyl thioimidates of Neu5Ac based on a variation of the remote activation concept[6] in the synthesis of *O*-sialoside.[7] Here, we report the preparation of sialyl donors bearing a thioimidolyl moiety and their application to stereoselective O-sialylation.

Synthesis of **4a–d** was achieved by pathways from **2a**, which was easily prepared from **1a** with AcCl. We succeeded in stereoselective preparation of α-sialosides **4a**,[8] **4b**,[4] **4c**, and **4d** through S_N2 displacement of the chloro group in **2** with 2-mercaptobenzothiazole **3a**, 2-mercaptobenzoxazole **3b**, 2-mercaptobenzimidazole **3c**, and 2-mercapto-5-nitro-benzimidazole **3d** in the presence of *N*,*N*-di-isopropylethylamine[9] in CH_2Cl_2 at room temperature with 95%, 58%, 49%, and 56% yields, respectively (Scheme 1). Faillard and Rothermel have reported the synthesis of **4a** using phase-transfer catalysis[10] from **2a** and **3a** with only a moderate yield of 53%. Compound **4e** was also synthesized from **2b** prepared from **1b** and **2a** with a 63% yield.

We started our investigation on the glycosylation of **4a** with *p*-nitrobenzyl alcohol **5a**[11] as an acceptor. The glycosylation reaction between **4a** and 1.5 equiv of **5a** using 2.0 equiv of AgOTf[12] in CH_2Cl_2 at room temperature gave the expected glycoside **6a**[13] with an 89% yield as an anomeric mixture with β-anomer as the major product (Table 1, entry 1). Next, glycosylations of other glycosyl donor **4b–d** with **5a** were examined. As summarized in Table 1, the reactions of **4b–d** with **5a** were activated by AgOTf as a promoter to give **6a** with 72%, 63%, and 64% yields, respectively (entries 2–4). Different reaction conditions including promoters and solvents were tested. The reaction using $Cu(OTf)_2$[14] or MeOTf[15] as promoters afforded **6a** with 48% and 36% yields, respectively (entries 6 and 7). These results show the superiority of AgOTf to $Cu(OTf)_2$ or MeOTf as promoters. The solvent effect was then examined using CH_3CN and CH_2Cl_2. A relatively large amount of α-glycosides was obtained in CH_3CN with α-anomer as the major product (α/β = 2:1), as expected from the assistance of the nitrile solvent effect,[16] compared to the use of CH_2Cl_2 (entries 5,[17] 7, 9, and 10). Encouraged by these results, we next examined the coupling of **4a** with biologically relevant acceptors, galactose derivatives **5b**, **5c**, and **5d**. The reaction of **4a** with **5b** promoted

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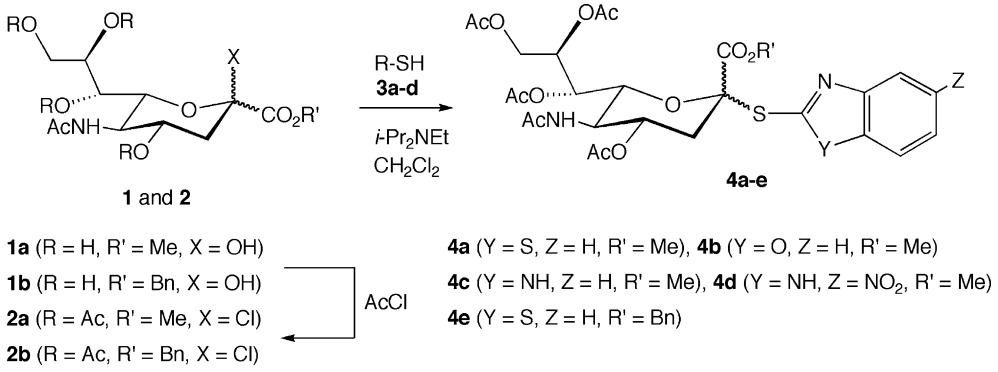
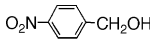
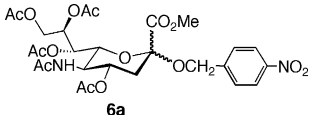
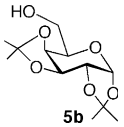
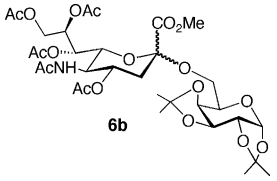
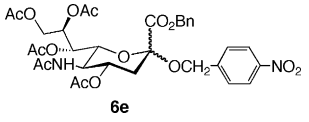
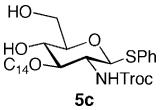
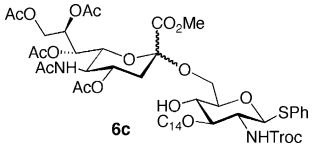
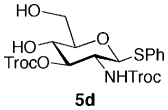
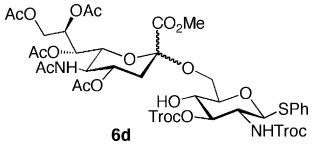


Scheme 1. Synthesis of **4**.

Table 1. Glycosylation reactions between **4a–e** and **5a–d**

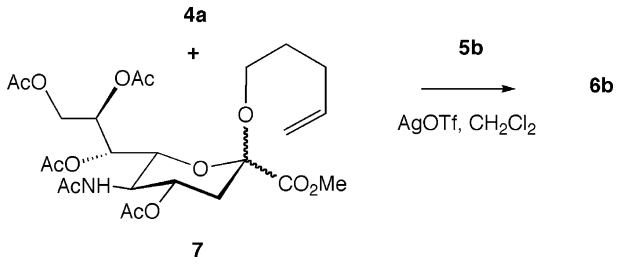
Entry	Glycosyl donor	Glycosyl acceptor	Condition[a]	Product	Yield (%) (α/β)[b]
1	**4a**	 **5a**	AgOTf, rt, CH_2Cl_2	 **6a**	89 (1:6)
2	**4b**	**5a**	AgOTf, rt, CH_2Cl_2	**6a**	72 (1:7)
3	**4c**	**5a**	AgOTf, rt, CH_2Cl_2	**6a**	63 (1:8)
4	**4d**	**5a**	AgOTf, rt, CH_2Cl_2	**6a**	64 (1:8)
5	**4a**	**5a**	AgOTf, −20 °C to 0 °C, CH_3CN	**6a**	71 (2:1)
6	**4a**	**5a**	$Cu(OTf)_2$, rt, CH_2Cl_2	**6a**	48 (1:9)
7	**4a**	**5a**	MeOTf, −20 °C to 0 °C, CH_3CN	**6a**	36 (2:1)
8	**4a**	 **5b**	AgOTf, rt, CH_2Cl_2	 **6b**	54 (1:3)
9	**4a**	**5b**	AgOTf, −20 °C to 0 °C, CH_3CN	**6b**	54 (2:1)
10	**4e**	**5a**	AgOTf, −20 °C to 0 °C, CH_3CN	 **6e**	41 (2:1)
11	**4a**	 **5c**	AgOTf, rt, CH_2Cl_2	 **6c**	33 (1:2)
12	**4a**	 **5d**	AgOTf, rt, CH_2Cl_2	 **6d**	41 (1:3)

Troc: $Cl_3CCH_2OC(O)$–, C_{14}: $CH_3(CH_2)_{12}C(O)$–

[a] With respect to **4**, 1.5 equiv of **5** and 2.0 equiv of promoter were used. Reaction time was 15 h.

[b] Isolated yields. The stereochemistry of **6** was confirmed by ^1H NMR (500 MHz) spectral comparison of the chemical shifts of $3H_{eq}$ signals of the glycosides. The anomeric ratios were determined on the basis of the integration ratios of the $3H_{eq}$ signals of the glycosides in ^1H NMR spectroscopy.

by AgOTf in CH_2Cl_2 at room temperature gave the corresponding Neu5Ac(2–6)Gal **6b** with a 54% yield (entry 8). When CH_3CN was used as the solvent at −40 °C, an increase of α-selectivity was observed with α-anomer as the major product (54%, α/β = 2:1) (entry 9). It should be noted that no glycosylation[4] of **4b** with **5b** in the



Scheme 2. Selective activation of **4a** in the presence of *O*-pentyl glycoside of Neu5Ac **7**.

presence of AgOTf in CH_3CN was observed. The glycosylation of **4a** with **5c** afforded the resulting (2–6)sialoside **6c** with a moderate yield of 33% (entry 11). Coupling of **4a** with **5d** gave **6d** with a 41% yield (entry 12).

To evaluate the applicability of **4a** to the armed–disarmed like coupling reaction,[18] we performed competitive glycosylation of **4a** with the 4-pentenyl 2-glycoside of Neu5Ac **7**.[19] The glycosylation of **4a** in the presence of **7** with **5b** was carried out using AgOTf in CH_2Cl_2 at room temperature to give **6b** with a 43% yield (α/β = 1:6) together with the recovery of 89% of **7** (Scheme 2). The selective activation of **4a** over **7** was achieved in the presence of AgOTf.

In summary, we have developed an efficient method for the preparation of novel sialyl donors bearing a thioimidolyl moiety and demonstrated their utility toward synthesizing various α-sialosides. We are currently applying this methodology to the synthesis of other oligosaccharides.

Acknowledgment

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8. Experimental data of **4a**: *N*,*N*-di-isopropylethylamine (0.529 g, 4.1 mmol) was added to a solution of **2a** (1.67 g, 3.28 mmol) and **3a** (0.457 g, 2.73 mmol) in dry dichloromethane (20 ml) under an atmosphere of argon. The reaction mixture was stirred for 16 h at room temperature. Upon completion, the mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel (AcOEt) to afford **4a** (1.66 g, 95%): ^{1}H NMR ($CDCl_3$) δ: 1.87, 1.98, 1.99, 2.02, 2.04 (s, each 3H, $NHCOCH_3$, $OCOCH_3$), 2.29 (dd, 1H, $J_{3ax,4}$ = 11.5 Hz, $J_{3ax,3eq}$ = 13.2 Hz, H-3ax), 2.91 (dd, 1H, $J_{3eq,4}$ = 4.6 Hz, H-3eq), 3.77 (s, 3H, OCH_3), 4.02 (ddd, 1H, $J_{5,4} = J_{5,6} = J_{5,NH}$ = 10.3 Hz, H-5), 4.13 (dd, 1H, $J_{6,7}$ = 1.7 Hz, H-6), 4.15 (dd, 1H, $J_{9a,8}$ = 5.5 Hz, $J_{9a,9b}$ = 12.6 Hz, H-9a), 4.37 (dd, 1H, $J_{9b,8}$ = 2.3 Hz, H-9b), 4.89–4.94 (m, 1H, H-4), 5.18–5.20 (m, 1H, NH), 5.28–5.37 (m, 1H, H-8), 5.29 (d, 1H, $J_{7,8}$ = 7.5 Hz, H-7), 7.42–7.51 (m, 2H, aromatic-H), 7.89, 8.05 (d, each 1H, *J* = 7.5 Hz, aromatic-H). Positive FAB-MS *m*/*z* 641 $[M+H]^+$. HR-FAB-MS Calcd for $C_{27}H_{33}O_{12}N_2S_2$ $(M+H)^+$: 641.1475. Found: 641.1483.
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13. Representative procedure for glycosylation (Table 1, entry 1): A mixture of the glycosyl donor **4a** (46 mg, 0.072 mmol), glycosyl acceptor **5a** (16 mg, 0.108 mmol), and 4 Å molecular sieves (0.25 g) in CH_2Cl_2 (2.0 ml) was stirred under argon for 1 h. Freshly conditioned AgOTf (37 mg, 0.144 mmol) was added and the reaction mixture was stirred for 17 h at room temperature and then diluted with CH_2Cl_2. The precipitates were filtered off through a pad of Celite and concentrated to give the crude product, which was purified on a preparative-TLC with a solvent system of AcOEt to give the glycoside **6a** (40 mg, 70%) as a mixture of α/β anomers.
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17. It was reported that sialylation of **5a** (1.5 equiv) with methyl peracetylated Neu5Ac (2.0 equiv of $Bi(OTf)_3$ and 2.0 equiv of $BF_3{\cdot}OEt_2$, CH_3CN, rt) gave **6a** in 27% yield and α/β = 57:43.[5b]
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