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.

Keywords: Sialic acid; O-Sialylation; Thioimidolyl group; Silver triflate.

N-Acetylneuraminic acid (sialic acid, Neu5Ac) and its various analogs play essential roles in a variety of biochemical and biological processes. The development of an efficient method of O-sialylation has been a challenging task in the field of sialic acid chemistry. Recent analysis has focused on the utilization of metal triflate salts as activators for milder and stereoselective O-glycosylation. Recently, AgOTf or Cu(OTf)2 promoted O-sialylation using S-benzoxazolyl and S-thiazolyl glycoside derivatives of Neu5Ac which has been reported. As part of our program aimed at the development of new O-sialylation reaction, we demonstrated the utility of glycosyl thioimidates of Neu5Ac based on a variation of the remote activation concept in the synthesis of O-sialosides. 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, 4b, and 4d through SN2 displacement of the chloro group in 2 with 2-mercaptobenzothiazole 3a, 2-mercaptobenzoxazole 3b, 2-mercaptobenzimidazole 3c, and 2-mercaptop-5-nitro-benzimidazole 3d in the presence of N,N-di-isopropylethylamine in CH2Cl2 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 from 2a and 3a with only a moderate yield of 53%. Compound 4c was also synthesized from 4b prepared from 1b and 2a with a 63% yield.

We started our investigation on the glycosylation of 4a with p-nitrobenzyl alcohol 5a as an acceptor. The glycosylation reaction between 4a and 1.5 equiv of 5a using 2.0 equiv of AgOTf in CH2Cl2 at room temperature gave the expected glycoside 6a 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 or MeOTf 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 CH3CN and CH2Cl2. A relatively large amount of α-glycosides was obtained in CH3CN with α-anomer as the major product (α/β = 2:1), as expected from the assistance of the nitrile solvent effect, compared to the use of CH2Cl2 (entries 5, 7, 9, and 10). Encouraged by these results, we next examined the coupling of 4a with bio-logically relevant acceptors, galactose derivatives 5b, 5c, and 5d. The reaction of 4a with 5b promoted...
by AgOTf in CH₂Cl₂ at room temperature gave the corresponding Neu5Ac(2–6)Gal with a 54% yield (entry 8). When CH₃CN 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 of 4b with 5b in the

attached figure and table.
presence of AgOTf in CH₂CN 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, we performed competitive glycosylation of 4a with the 4-pentenyl-2-glycoside of Neu5Ac 7. The glycosylation of 4a in the presence of 7 with 5b was carried out using AgOTf in CH₂Cl₂ 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 thiomidolyl moiety and demonstrated their utility for the synthesis of novel sialyl donors bearing a thiomidolyl moiety and demonstrated their utility in the synthesis of various sialyl donors bearing a thiomidolyl moiety and demonstrated their utility in the synthesis of various sialyl donors bearing a thiomidolyl moiety and demonstrated their utility.

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

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References and notes

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%): 1H NMR (CDCl₃): δ 1.87, 1.98, 1.99, 2.02, 2.04 (s, each 3H, NHCOCH₃, OCOCH₃), 2.29 (dd, 1H, J₅,₆ = 11.5 Hz, J₆,₇ = 13.2 Hz, H-3ax), 2.91 (dd, 1H, J₆,₇ = 4.6 Hz, H-3eq), 3.77 (s, 6H, OCH₃), 4.02 (dd, 1H, J₅,₆ = 11.5 Hz, J₆,₇ = 17 Hz, H-6), 4.15 (dd, 1H, J₅,₆ = 5.5 Hz, J₆,₇ = 12.6 Hz, H-9a), 4.37 (dd, 1H, J₉₈,₉₉ = 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 (1H, J₉₈,₉₉ = 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 C₂₇H₃₃O₁₂N₂S₂ (M⁺): 641.1475. Found: 641.1483.
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 CH₂Cl₂ (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 CH₂Cl₂. 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.
17. It was reported that sialylation of 5a (1.5 equiv) with methyl peracetylated Neu5Ac (2.0 equiv of BrOTf) and 2.0 equiv of BF₃·OEt₂, CH₂CN, rt) gave 6a in 27% yield and α/β = 57:43.²⁶