Exceptionally High Yield in Glycosylation with Sialic Acid. Synthesis of a GM3 Glycoside.

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Abstract: Exceptionally high yield was obtained in the glycosylation of HO-3 of lactose derivative 1 with xanthate 2 as sialosyl donor using methylsulfenyl triflate in acetonitrile/dichloromethane at -60 °C. The yield of the sialosyl oligosaccharide was dependent on the amount of sialosyl donor used. The yields were 63, 75 and 82 % using 1.1, 1.68 and 2.0 equivalents respectively of donor and 1.0 equivalent of acceptor.

The introduction of α -sialosyl group into oligosaccharides can be achieved using various methods and strategies based on chemical and/or enzymatic approaches¹. In chemical synthesis of oligosaccharides, hexopyranosyl donors normally give yields in the range of 70-90 %, whereas sialosyl donors have been less efficient. The highest yield for the formation of a Neu5Aca(2-3)Gal unit, so far, has been reported by Hasegawa et. al.² (59 %, using 1.68 equiv. donor and 1.0 equiv. acceptor⁹).

We have recently reported³ the effect of temperature on α -selectivity and on glycal formation, in glycosylation with a Neu5Ac glycosyl xanthate³ and compared⁴ three different O-protected D-galactosides as acceptors in $\alpha(2-3)$ sialoside synthesis using methylsulfenyl triflate as promoter, and acetonitrile/dichloromethane as solvent at -70 °C. A galactoside triol protected at HO-6 was the best acceptor.

We have now investigated the $\alpha(2-3)$ sialylation of lactose derivative 1⁵, using sialosyl donor 2⁶ under the conditions optimized earlier^{3,4}.

A mixture of lactoside 1 (0.25 mmol), glycosyl donor 2, powdered molecular sieves (3 Å, 300 mg) in acetonitrile/dichloromethane (9:4, 8 mL) was stirred at room temperature for 1 h under argon, then silver triflate was added and the reaction was cooled to -60 °C. Methylsulfenyl bromide⁷ (MSB) in 1,2-dichloroethane was added dropwise during 5 min. After 1 h diisopropylamine (2.5 mmol) was injected and stirring was continued for 0.5 h, the mixture was allowed to attain 0 °C, then filtered, concentrated, and purified by silica gel chromatography. Yields⁹ and proportions of reactants are shown below.

Acceptor 1	Donor 2	AgOTf/MSB ⁷	α -Product 3 ⁸	Recovered acceptor 1
1.0	1.1	1.1	63 %	22 %
1.0	1.68	1.68	75 %	8 %
1.0	2.0	2.0	82 %	1 %



In conclusion, using sialosyl xanthate 2, activated by methylsulfenyl triflate in dichloromethane/acetonitrile at low temperature, for sialylation of 3-OH at lactose, gave yields in the same range as glycosylations with hexopyranosyl donors¹⁰.

References and Notes

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- Analytical data for 3: [a]D +14.9° (c 1.0, chloroform); ¹³C NMR (CDCl₃,75MHz) ∂ 20.5, 20.6, 20.7, 21.0 (OCOCH₃), 23.1 (NCOCH₃) 29.6 (OCH₂CH₂Br), 37.6 (C-3"), 49.6 (C-5"), 53.2 (OCH₃), 62.4, 63.4, 63.7 (C-6,6',6"), 67.0, 68.0, 68.3, 68.9 (2 C), 69.5, 72.9 (2 C), 72.9, 73.0, 73.4, 76.4, 82.2 (C-2-5, 2'-5', C-4",6"-8", OCH₂CH₂Br), 97.6 (C-2"), 101.1 (C-1), 104.4 (C-1), 165.4, 166.1, 166.6 (PhCO), 168.1 (C-1", J_C-1',H-3"_{ax} 6.1 Hz), 170.1, 170.3, 170.4, 170.7 (OCOCH₃), NCOCH₃), ¹H NMR (CDCl₃,300MHz) ∂ 2.70 (dd, 1H, J₃"e,3"a, 13.0, J₃"e,4"a 4.5 Hz, H-3"e), 4.50 (dd, 1H, J_{gem} 12.1 Hz, J₅,6 5.9 Hz, H-6 or 6'), 4.59 (d, 1H, J_{1,2} 7.9 Hz, H-1'), 4.70 (d, 1H, J_{1,2} 8.1 Hz, H-1), 4.74 (dd, 1H, J_{gem} 11.9 Hz, J₅,6 3.4 Hz, H-6 or 6'), 5.03 to 4.93 (m, 2H, H-4", H-6 or H-6'), 5.26 (dd, 1H, J_{2,3} 9.6 Hz, H-2), 5.28 (dd, 1H, J₇,8 8.0 Hz, H-7"), 5.33 (m, 1H, H-8"). On acetylation of 3, H-3, H-2' and H-4' shifted downfield as expected. Anal. Calc. for C₅₅H₆₄B₁NO₂₆: C, 53.5; H, 5.2. Found: C, 53.5; H, 5.5.
- 9. Yields based on the acceptor.
- 10. The corresponding per-O-benzoylated analogue of 2 (reference 3) proved less efficient in these glycosylations. When 1.1.equiv. of this analogue was condensed with 1.0 equiv. of lactoside 1, the resulting α (2-3)sialoside was isolated in 45 % yields and 31 % of 1 was recovered.

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