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SILVER ZEOLITE - EFFECTIVE CATALYST FOR THE REGIO-STEREOSELECTIVE FORMATION OF THE Neu5Acα2→6 GLYCOSYL LINKAGE - SYNTHESIS OF SEVERAL SIALOSACCHARIDES

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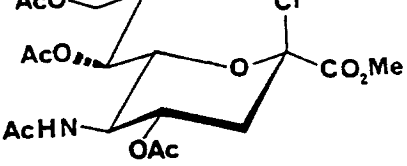
Abstract: Several sialosaccharides containing the Neu5Acα2→6 glycosyl linkage have been synthesized using Ag-zeolite as an effective catalyst for exclusive α-glycosylation.

Sialic acid[1] α-glycosidically linked to other sugars forms an important constituent of glycoprotein and glycolipid in cell membrane. Recently, new efforts[2] have been made toward the synthesis of such α-glycosides of NeuAc. Traditionally, efforts towards the synthesis of sialosaccharides have mainly entailed the implementation of methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-2-chloro-2,3,5-trideoxy-D-glycero-β-D-galacto-2-nonulopyranosate (1) in the presence of a heavy metal catalyst. However, in most cases the desired α-linked isomer was accompanied by the β-anomer. Recently Hasegawa, et al. reported that the methyl (methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-2-thio-D-glycero-α-D-galacto-2-nonulopyranoside)onate, in the presence of DMTST afforded only the α-linked sialosaccharide, but the glycosyl donor preparation is multistep and tedious. Herein, we describe the usefulness of silver zeolite as an effective catalyst to afford only α-linked sialosaccharides using chloride (1) as the glycosyl donor.



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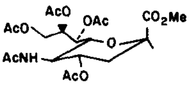
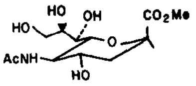
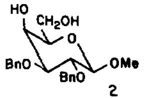
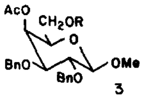
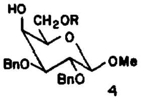
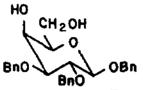
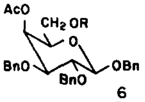
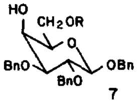
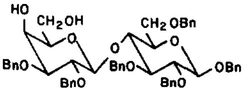
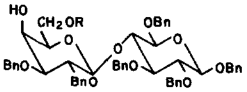
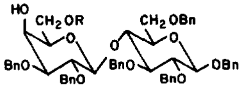
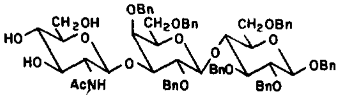
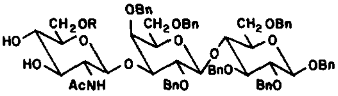
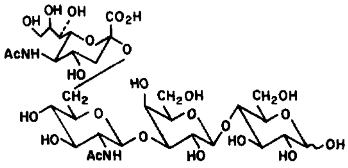
Several sialosaccharides (4,7,10 and 13) were successfully procured via the glycosylation of suitably protected glycosides (2,5,8 and 11, given in Table I) with chloride[3] 1 in the presence of silver zeolite. In general, the glycosylation reaction conditions were standardized such that 1 mmol of glycoside was combined with 1.2 meq of chloride 1 in dry dichloromethane (40 mL) in the presence of freshly prepared[4] silver zeolite (1.2 gm). The combined mixture was placed under dry nitrogen, protected from light and permitted to stir for 24 hrs at room temp. (~25°C). Both the progression and anomeric purity was monitored by thin-layer chromatography (t.l.c.) and with completion of the reaction the mixture was processed in the usual manner. In some instances, the reaction product was acetylated [Pyr/Ac_2O (2:1 v/v)] to facilitate purification, as evidenced in compounds 3 and 6. See Table I for a summary of those sialosaccharides synthesized and yields obtained therein.

^{1}H-n.m.r. investigation of product 3 resulted in the value of $\delta[H(3e)]$ = 2.60 (12.81 Hz) affirming the presence of an α-ketosidic linkage. However, it has been shown that the presence of protecting groups, such as the acetyl, will affect the chemical shift of H(3e). Zemplen transesterification[5] of 3 afforded 4 whose ^{1}H-n.m.r. spectrum showed H(3e) at δ2.69 (12.80 Hz), consistent with the findings of Dabrowski et al.[6] who reported $\delta[H(3e)] = 2.72 \pm 0.05$ for α-ketosidically linked sialosaccharides while a value of 2.32 ± 0.05 was observed for the β-ketosidically linked sialosaccharide. To support the presence of the Neu5Ac moiety at *O*-6 of the Gal*p* residue, the ^{13}C-n.m.r. spectrum of the completely deblocked Neu5Acα2→6Galpβ1→OMe was obtained with 6-C, normally present at 60 p.p.m., having undergone a downfield shift to 66.20 p.p.m. which served as a clear indication that C-6 was glycosylated. Additionally, the same spectrum clearly showed that C-4, an earlier potential site of glycosylation, resonated at 71.48 p.p.m., analogous to C-4 in unsubstituted Galpβ1→OMe, which resonates at 71.46 p.p.m.

In the area of mechanistic considerations, silver zeolite, a heterogenous catalyst, may be absorbing to the β-face of the glycosyl donor, and thereby only allow the incoming nucleophile to attack the α-face, via the steric impedence inherent to this catalyst.

In conclusion we would suggest that the use of silver zeolite provides a viable method for the stereoselective procurement of various sialosaccharides containing the Neu5Acα2→6-OR glycosyl linkage. Furthermore, we are concurrently examining the synthetic utility of silver zeolite in regard to the glycosylation of various secondary hydroxyl groups, especially the Neu5Acα2→3-OR glycosyl linkage found in many glycoconjugates.

TABLE I - PREPARATION OF SIALOSACCHARIDES, VIA SILVER ZEOLITE PROMOTION

	PRODUCT[a]	DEACETYLATED SIALOSACCHARIDE
	R = 	R = 
 2	 3	 4
 5	 6	 7
 8	 9	 10
 11	 12	 13

ALL COMPOUNDS WERE CHARACTERIZED BY 200 MHz H-N.M.R. IN THE FOURIER TRANSFORM MODE AND BY ELEMENTAL ANALYSIS

CMPD #	YIELD	$[\alpha]_D^{25}$	δ[H(3e)]	CMPD #	$[\alpha]_D^{25}$	δ[H(3e)]	δ[H(3a)]
3	65%	+2.8 (c1.0, $CHCl_3$)	2.6 (12.81 Hz)	4	+13.7 (c1.0, CH_3OH)	2.69 (12.80Hz)	1.75
6	65%	−14.2 (c0.5, $CHCl_3$)	2.6 (12.90Hz)	7	−4.2 (c1.5, CH_3OH)	2.72 (12.88Hz)	1.78
9	68%	−7.8° (0.6, $CHCl_3$)	2.50 (12.82Hz)	10	+3.9 (c0.6, CH_3OH)	2.65 (12.83Hz)	1.78
12	60%	−17° (c0.5, CHCl)	2.54 (12.83Hz)	13	−8 (24H) (c1.4, H_2O)	2.65 (11.14Hz)	1.70

Acknowledgements

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7. This publication is Part LXII of Synthetic Studies in Carbohydrates. For Part LXXI see R.K. Jain and K.L. Matta, Carbohydr. Res., (RJ1715 accepted for publication).

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