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Exploring the glycosylation properties of a sialyl thioimidate donor

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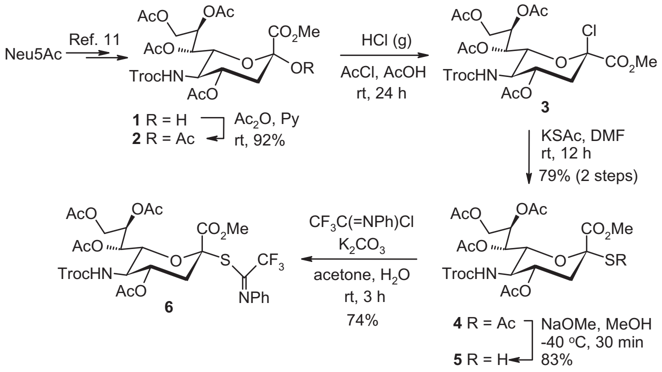
ABSTRACT

A new sialyl thioimidate donor **6** was prepared in high yields from the known sialyl hemiketal **1** over five steps. Under the action of catalytic TMSOTf, **6** exhibited excellent reactivity using a series of primary alcohols to give the desired sialylation products in high to excellent yields. Chemoselective activation of **6** in the presence of thioglycosides was also demonstrated.

Sialic acids comprise a specific class of acidic monosaccharides, and include *N*-acetylneuraminic acid (Neu5Ac), *N*-glycolylneuraminic acid and α-keto-deoxy-D-glycero-D-galactononulosonic acid.[1] Among these, Neu5Ac is the most common, and is present in a variety of glycosidic linkages, most typically α-(2,6) and α-(2,3), to galactose or in an α-(2,6) linkage to a galactosamine residue.[2] These sialylated carbohydrates are intimately involved in a wide range of biological processes such as cell recognition and communication, bacterial and viral infection, and tumour metastasis.[3] In view of their biological importance, tremendous efforts have been devoted to develop sialylation procedures,[4] and substantial progress has been achieved in this field.[5] However, a general sialylation procedure has not yet appeared, and more often than not, careful optimization of the glycosidation conditions is needed in order to achieve high yields and stereoselectivity for sialylation. Chemical sialylation remains a challenge in carbohydrate chemistry and is inherently problematic due to the unique structure of sialic acids. The electron-withdrawing carboxyl group at the anomeric centre and the lack of a participating functional group at the C-3 position of sialyl donors typically cause the sialylation reaction to proceed in low to moderate yields, with low α-selectivity and with the formation of unwanted 2,3-elimination products. Therefore, new sialylation methods and strategies are still welcome in carbohydrate chemistry.

Recently, our laboratory introduced a new class of glycosyl thioimidates, glycosyl *N*-phenyl-trifluorothioacetimidates,[6] as glycosylating agents. These thioimidates could be easily prepared from readily available glycosyl thiols in excellent yields and were effectively activated by catalytic amounts of a Lewis acid. We became curious whether similar sialyl thioimidates could also be used as new sialylating agents.[7] Hence, investigations towards the synthesis and glycosylation properties of sialyl *N*-phenyl-trifluorothioacetimidate **6** (Scheme 1) was initiated. We now wish to report that **6** can serve as a sialylating agent for primary alcohols, proceeding in high to excellent yields with fairly good α-selectivity.

Our studies commenced with the preparation of sialyl chloride **3**. It has been shown that in sialylation, protection of the C5 amino group is crucial to the success of the glycosidation reaction.[4b] We



Scheme 1. Synthesis of sialyl thioimidate **6**.

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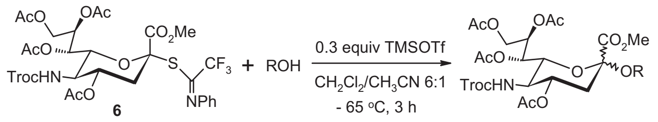
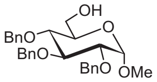
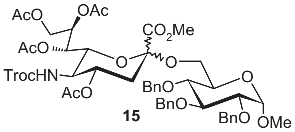
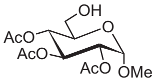
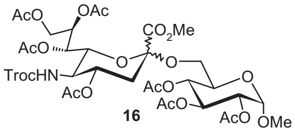
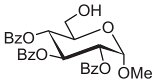
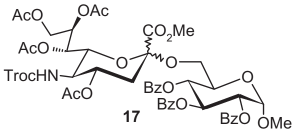
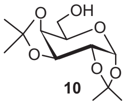
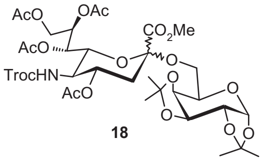
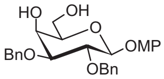
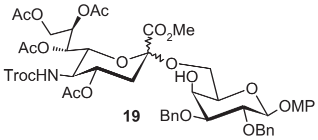
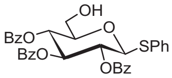
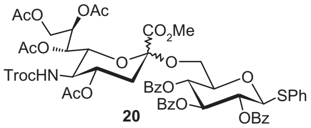
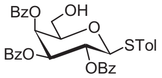
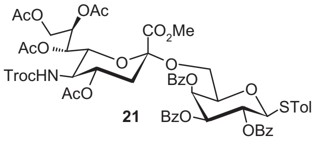
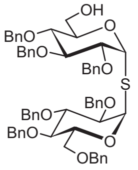
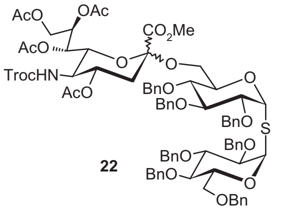
selected 2,2,2-trichloroethoxycarbonyl (Troc) group on the basis of its high stability under various reaction conditions, and more importantly, the reported high reactivity of *N*-Troc-protected sialyl donors[8] which often exhibit higher reactivity than the corresponding *N*-Ac- and *N*-TFA-protected compounds, and have thus frequently been employed to synthesize different sialyl oligosaccharides, such as sialyl Lewis X[9] and the pentasaccharide moiety of the neuritogenic ganglioside GAA-7.[10] The known *N*-Troc-protected sialyl hemiketal **1**[11] was prepared from *N*-acetylneuraminic acid following literature procedures then converted into sialyl acetate **2** in excellent yields by standard acetylation conditions. Subsequently, **2** was subjected to anomeric chlorination using anhydrous HCl in AcCl/AcOH to give sialyl chloride **3**. Without purification, **3** was treated with potassium thioacetate in DMF to produce sialyl thioacetate **4** in 79% yield over two steps. The anomeric acetyl group of **4** was subsequently removed using

Table 1
Sialylation of acceptors **7**–**14** with thioimidate **6**[a]



Entry	Acceptor	Product	Yield[b] (%)	α/β[c] ratio
1	 **7**	 **15**	86	5:1
2	 **8**	 **16**	91	3:1
3	 **9**	 **17**	96	3:1
4	 **10**	 **18**	94	5:1
5	 **11**	 **19**	92	5:1
6	 **12**	 **20**	90	2:1
7	 **13**	 **21**	87	α only
8	 **14**	 **22**	95	3:1

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[a] Reaction conditions: **6** (1.2 equiv), acceptor **7**–**14** (1.0 equiv), TMSOTf (0.3 equiv), CH_2Cl_2/CH_3CN 6:1, −65 °C under a N_2 atmosphere.

[b] Isolated yield.

[c] Determined by integration of the proton signals in the ^1H NMR spectrum after chromatographic purification.