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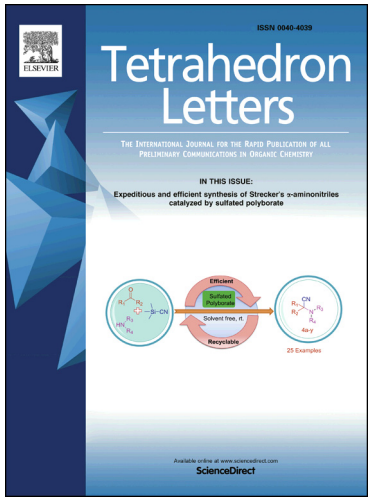

Rapid and Efficient Conversion of Sialyl Thioglycosides to Sialyl Esters via NIS/BF_3OEt_2-Promoted Glycosylation

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Rapid and Efficient Conversion of Sialyl Thioglycosides to Sialyl Esters via NIS/BF_3OEt_2-Promoted Glycosylation

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Abstract:

A rapid and efficient one-step conversion of sialyl thioglycosides to sialyl esters was disclosed. Under the promotion of NIS and BF_3OEt_2, the glycosylation of per-acetylated sialyl thioglycoside with a set of carboxylic acids provided β-sialyl esters as the major products in good to excellent yields within 5 minutes. Compared with the long-chain alkyl-, aryl- and α,β-unsaturated acids, complete β-selectivities were observed when the short-chain alkyl acids were selected as the coupling partners. The resultant β-selectivity for the glycosylation of the per-acetylated sialyl thioglycoside with acetic acid was compromised when the 5-*N*,4-*O*-oxazolidinone protected sialyl thioglycoside was employed as the coupling partner.

Keywords:

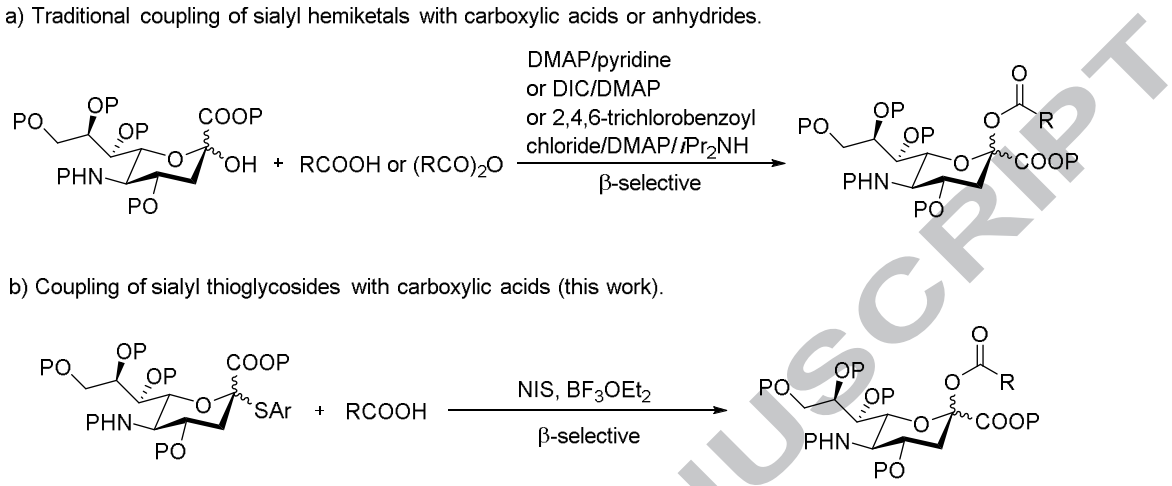
Glycosylation; Sialyl esters; Sialyl thioglycosides; Synthetic methods

Sialic acids are a large family of keto acid sugars that mostly locate at the terminal end of cell surface glycolipids and glycoproteins of vertebrates or serve as essential component of

polysialic acids of mammalian tissues and pathogenic bacteria.[1] Owing to their outmost position on the cell surface carbohydrates and the highly functionalized nature with negative charge under physiological condition, sialic acids are involved in a variety of biological processes such as cell adhesion, cell signaling, cell differentiation, neural network maturing, pathogen recognition, viral infection, cancer growth and metastasis.[2]

To date, considerable efforts have been directed at the glycosylation of a range of sialic acid donors with alcohols for the synthesis of naturally occurring sialoglycans and congeners.[3,4] Due to the inherent challenging structure of sialic acid with electro-withdrawing carboxylic group at C-1 and without neighboring participating group at C-3, stereoselective *O*-sialylation was extensively investigated by applying various leaving groups at C-2, auxiliary groups at C-3, amino protecting groups at C-5, neighboring participating groups at C-1 as well as promoters and solvents.[3,5] However, glycosylation of sialic acid derivatives with carboxylic acids remains scarce. Traditional coupling of sialic acid derivatives with carboxylic acids mainly relied on the condensation of protected sialyl hemiketals with carboxylic acids or their activated forms (e.g., anhydrides) in the presence of DMAP/pyridine, DIC/DMAP, or 2,4,6-trichlorobenzoyl chloride/DMAP/*i*Pr_2NH, usually leading to sialyl esters with the β-anomers as the major products (Scheme 1a).[6,7] As revealed in the literature,[3,4] the stable sialyl thioglycosides were frequently utilized synthetic intermediates for the synthesis of sialic acid-containing saccharides. To convert sialyl thioglycosides into sialyl esters, a two-step sequence involving cleavage of the sialyl thioglycosides into sialyl hemiketals using NIS or NBS followed by coupling of the resulting hemiketals with carboxylic acids or their activated forms is often needed.[7] As such, development of a one-step stereoselective approach for the direct transformation of sialyl thioglycosides to sialyl esters would improve the synthetic efficiency and avoid the cumbersome purification procedures. Here, we present a rapid and efficient glycosylation approach utilizing NIS and BF_3OEt_2 as

the promoters for the direct conversion of sialyl thioglycosides to sialyl esters in a β-selective manner (Scheme 1b).

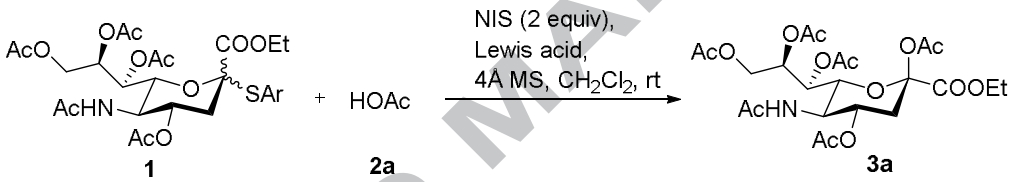


Scheme 1. Coupling strategies of sialic acid derivatives with carboxylic acids or their activated forms. P = protecting group; Ar = 5-*tert*-butyl-2-methylbenzene.

At the outset, we turned our attention to the screening of glycosylation conditions for the conversion of sialyl thioglycoside **1** that could be readily prepared by the modified literature protocols[8] to sialyl ester **3a** under the activation of NIS (2 equiv) and Lewis acids in CH_2Cl_2 at room temperature (Table 1). The anomeric configuration of the product **3a** was determined based on the long-range $^3J_{C1,H3ax}$ coupling constant and the chemical shift of the C-1.[9] Without the addition of Lewis acid, the glycosylation of **1** with acetic acid **2a** (5 equiv) led to the formation of thermodynamically more stable β-sialyl ester **3a** ($\delta_{C\text{-}1}$ = 165.8 ppm, $^3J_{C1,H3ax}$ = 0 Hz) as the single product in a moderate 60% yield, but traces of starting material **1** remained intact and a significant amount of glycal byproduct was formed (entry 1). Upon addition of 1–3 equiv of BF_3OEt_2, the glycosylation yields of β-sialyl ester **3a** were slightly improved (62–75%), in which 2 equiv of BF_3OEt_2 was found to be better (entries 2–4). Reducing the amount of acetic acid **2a** (5 equiv → 2–3 equiv) while fixing the amount of BF_3OEt_2 (2 equiv) could result in a very clean reaction and dramatically increase the yield of

3a with the β-anomer as the only product within 5 minutes (3 equiv of acetic acid, 98%, entry 5; 2 equiv of acetic acid, 80%, entry 6), which indicated that combination of suitable amounts of carboxylic acid and Lewis acid was vital for the glycosylation yield of sialyl thioglycoside with carboxylic acid. In contrast, the glycosylation employing TMSOTf or AgOTf as Lewis acid under the similar conditions led to β-sialyl ester **3a** as the sole products in moderate yields (51–62%, entries 7 and 8). Thus, glycosylation of sialyl thioglycoside **1** with acetic acid **2a** (3 equiv) promoted by NIS (2 equiv) and BF_3OEt_2 (2 equiv) for 5 minutes (entry 5) was chosen as the optimal conditions for this transformation.

Table 1. Screening of glycosylation conditions for the conversion of sialyl thioglycoside **1** to sialyl ester **3a**.

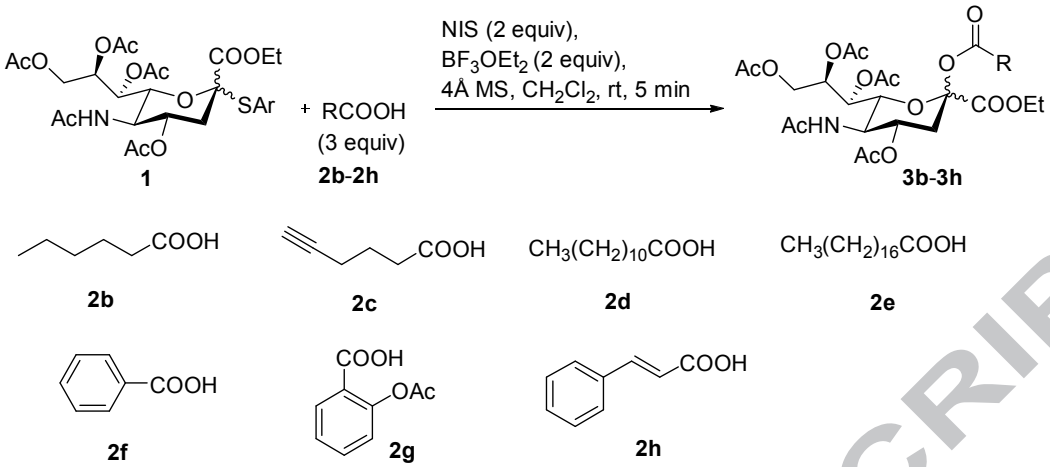


Entry	HOAc (equiv)	Lewis acid (equiv)	Yield[a] (%)	β/α[b]
1	HOAc (5)	None	60	β only
2	HOAc (5)	BF_3OEt_2 (1)	71	β only
3	HOAc (5)	BF_3OEt_2 (2)	75	β only
4	HOAc (5)	BF_3OEt_2 (3)	62	β only
5	HOAc (3)	BF_3OEt_2 (2)	98	β only
6	HOAc (2)	BF_3OEt_2 (2)	80	β only
7	HOAc (3)	TMSOTf (2)	51	β only
8	HOAc (3)	AgOTf (2)	62	β only

[a] Isolated yield.
[b] The ratio of β/α was determined by ^{1}H NMR spectroscopy.

The scope of the present method was then briefly examined with a series of carboxylic acids (Table 2). When the six-carbon alkyl carboxylic acids such as *n*-hexanoic acid **2b** and 5-hexynoic acid **2c** were used, the glycosylation with sialyl thioglycoside **1** under the optimal conditions afforded exclusively β-sialyl esters **3b** ($\delta_{C\text{-}1}$ = 165.8 ppm, $^{3}J_{C1,H3ax}$ = 0 Hz) and **3c** ($\delta_{C\text{-}1}$ = 165.7 ppm, $^{3}J_{C1,H3ax}$ = 0 Hz) in 90% and 83% yield, respectively (entries 1 and 2). In comparison to **2b** and **2c**, glycosylation of **1** with 5-hexenoic acid under the same conditions could not yield the desired sialyl ester probably due to the attack of NIS on the double bond of 5-hexenoic acid.[10] With regard to long-chain alkyl acids, high yields and good β-stereoselectivities of **3d** (84%, β : α = 5 : 1; β-anomer: $\delta_{C\text{-}1}$ = 165.8 ppm, $^{3}J_{C1,H3ax}$ = 0 Hz) and **3e** (79%, β : α = 5 : 1; β-anomer: $\delta_{C\text{-}1}$ = 165.8 ppm, $^{3}J_{C1,H3ax}$ = 0 Hz) were still observed when lauric acid **2d** bearing a 12-carbon chain or stearic acid **2e** bearing an 18-carbon chain was employed as the coupling partner, respectively (entries 3 and 4). Coupling of thioglycoside **1** with benzoic acid **2f** proceeded smoothly to provide sialyl ester **3f** in 82% yield with the β-anomer as the major product (β : α = 5 : 1; β-anomer: $\delta_{C\text{-}1}$ = 165.8 ppm, $^{3}J_{C1,H3ax}$ = 0 Hz; entry 5). Glycosylation of aspirin **2g** and α,β-unsaturated cinnamic acid **2h** with thioglycoside **1** afforded sialyl esters **3g** (65%, β : α = 3 : 1; β-anomer: $\delta_{C\text{-}1}$ = 165.7 ppm, $^{3}J_{C1,H3ax}$ = 0 Hz) and **3h** (87%, β : α = 2.5 : 1; β-anomer: $\delta_{C\text{-}1}$ = 165.9 ppm, $^{3}J_{C1,H3ax}$ = 0 Hz) in good yields and moderate β-selectivities which could be explained by the less nucleophilicity of the nucleophiles (entries 6 and 7).[11]

Table 2. Conversion of sialyl thioglycoside **1** to a series of sialyl esters **3b**-**3h** under the promotion of NIS/BF_3OEt_2.[a]



Entry	RCOOH	Yield[b] (%)	β/α[c]
1	**2b**	90	β only
2	**2c**	83	β only
3	**2d**	84	5 : 1
4	**2e**	79	5 : 1
5	**2f**	82	5 : 1
6	**2g**	65	3 : 1
7	**2h**	87	2.5 : 1

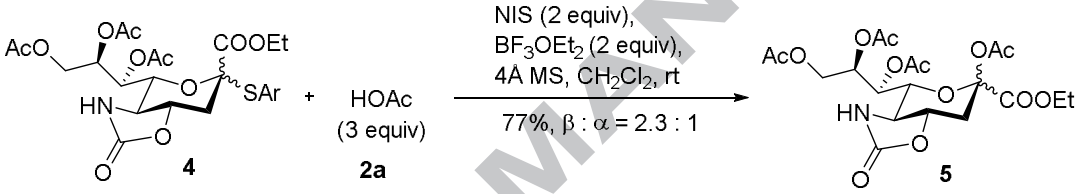
[a] For a typical procedure for this glycosylation: To a solution of compound **1** (134 mg, 0.20 mmol) and freshly activated 4Å MS in anhydrous CH_2Cl_2 at room temperature, was added *n*-hexanoic acid **2b** (75 μL, 0.60 mmol) under argon. After stirring at room temperature for 15 min, the mixture was added BF_3OEt_2 (50 μL, 0.40 mmol) and NIS (90 mg, 0.40 mmol). After stirring at room temperature for 5 min, the mixture was filtered and the filtrate was washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, respectively. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue, which was purified by silica gel column chromatography (petroleum ether/EtOAc: 1/1 → 1/2) to afford **3b** (109 mg, 90%) as a pale yellow syrup.

[b] Isolated yield.

[c] The ratio of β/α was determined by ^{1}H NMR spectroscopy.

To investigate whether the present method could be utilized for the conversion of 5-*N*,4-*O*-oxazolidinone protected sialyl thioglycoside to sialyl ester under the optimal conditions, 5-*N*,4-*O*-oxazolidinone protected sialyl thioglycoside **4**[12] was synthesized (see supporting information for details) for glycosylation with acetic acid **2a** under the promotion of NIS and

BF_3OEt_2 (Scheme 2). As expected, NIS/BF_3OEt_2-promoted glycosylation of thioglycoside 4 with acetic acid **2a** proceeded smoothly to provide sialyl ester **5** in 77% yield within 15 minutes. Also, we found that the complete β-selectivity obtained with *N*-acetyl sialyl thioglycoside **1** as donor (Table 1, entry 5) was compromised to the moderate β-selectivity (β : α = 2.3 : 1; β-anomer: $\delta_{C\text{-}1}$ = 165.4 ppm, $^3J_{C1,H3ax}$ = 0 Hz) when the glycosylation was performed with 5-*N*,4-*O*-oxazolidinone protected sialyl thioglycoside **4** as donor. The moderate β-selectivity could be explained by the resultant force of the α-directed effect of the 5-*N*,4-*O*-oxazolidinone protecting group and the β-directed effect of the optimal glycosylation conditions.



Scheme 2. Conversion of 5-*N*,4-*O*-oxazolidinone protected sialyl thioglycoside **4** to sialyl ester **5** under the promotion of NIS and BF_3OEt_2.

In summary, we have developed a rapid and efficient one-step approach for the conversion of sialyl thioglycosides to sialyl esters under the promotion of NIS and BF_3OEt_2. The complete β-selectivities for the glycosylation of per-acetylated sialyl thioglycoside with the short-chain alkyl acids were eroded by introducing the long-chain alkyl acids, aryl acid, α,β-unsaturated acid, or 5-*N*,4-*O*-oxazolidinone protected sialyl thioglycoside as the coupling partner. The present method serves as a useful tool for the direct transformation of sialyl thioglycosides to sialyl esters in the synthesis of sialoglycans.

Acknowledgements

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/

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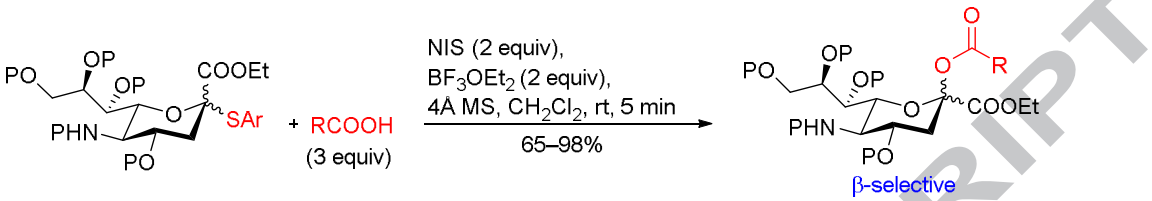
Graphical Abstract



Highlights：

- A rapid and efficient conversion of sialyl thioglycosides to sialyl esters was developed.
- NIS/BF_3OEt_2-promoted glycosylation mainly provided β-sialyl esters within 5 minutes.
- Complete β-selectivities were observed with the short-chain alkyl acids.