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Efficient Sialylation with Phenyltrifluoroacetimidates as Leaving Groups

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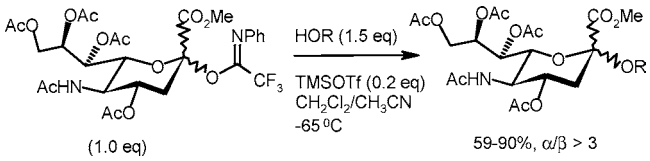
ABSTRACT



Sialylation with *N*-phenyltrifluoroacetimidates as leaving groups and a catalytic amount of TMSOTf as promoter compares favorably with the previous protocols for direct sialylation and expand in essence the scope of the Schmidt glycosylation reaction.

Sialic acids constitute a family of 2-keto-3-deoxynononic acids represented by the most abundant prototypical congener *N*-acetylneuraminic acid (Neu5Ac). Neu5Ac occurs essentially at the termini of glycoproteins and glycolipids in mammalian cellular systems frequently via a α2−3 glycosidic linkage to galactose or α2−6 linkages to galactose and *N*-acetylgalactosamine. In fact, as many as 10^7 Neu5Ac residues are bound to a single human cell forming a charged sheath of mechanical importance. These surface Neu5Ac are a significant recognition site for a variety of hormones, enzymes, viruses, and toxins, while they can also effectively block important antigenic sites and recognition markers to protect them from identification and degradation by the surrounding immune system.[1] Allured by these important biological functions, synthetic access toward sialic acid containing oligosaccharides and glycoconjugates has been a topic of intensive research.[2] However, sialylation to make the equatorial 2-α-ketosidic linkages is one of the most challenging tasks in glycosylation chemistry.[2] The electron-withdrawing C1 carboxylic function, disfavoring the oxocarbenium formation, restricts glycosidation both electronically and sterically. No neighboring C3 functionality is present to direct the stereochemical outcome of glycosylations; thus, formation of the thermodynamically more stable but unnatural β glycosidic bond prevails. In addition, an elimination to produce the 2,3-dehydro glycals can be a significant competing pathway. In fact, only limited glycosylation protocols are applicable for direct sialylation.[3] The classical Koenigs−Knorr glycosylation with 2-chloro derivatives of Neu5Ac provides good yields only when coupled with simple or primary sugar alcohols.[4] Glycosylation with 2-sulfide,[5] xanthate,[6] and phosphite[7] Neu5Ac donors has enabled the synthesis of those natural linkages of Neu5Ac in reasonable yields (commonly 30−70%).[8] And the α selectivity is ensured by the nitrile solvent effect.[2,9] It is noted that the most favorable Schmidt glycosylation protocol with trichloroacetimidate as leaving group is not suitable for sialylation.[10] Fortunately, the recent alternative with trifluo-

(1) (a) Varki, A. *Glycobiology* **1993**, *3*, 97. (b) *Biology of Sialic Acids*; Rosenberg, A., Ed.; Plenum Press: New York, London, 1995.

(2) (a) Okamoto, K.; Goto, T. *Tetrahedron* **1990**, *46*, 5835. (b) DeNinno, M. P. *Synthesis* **1991**, 583. (c) Boons, G.-J.; Demchenko, A. V. *Chem. Rev.* **2000**, *100*, 4539.

(3) Indirect sialylation mostly involves modified sialyl donors that have a participating functionality at C-3; thus, additional steps are required for installation and removal.[2c]

(4) Bromides of Neu5Ac have found limited application in sialyation, likely due to their low chemical stability.[2a]

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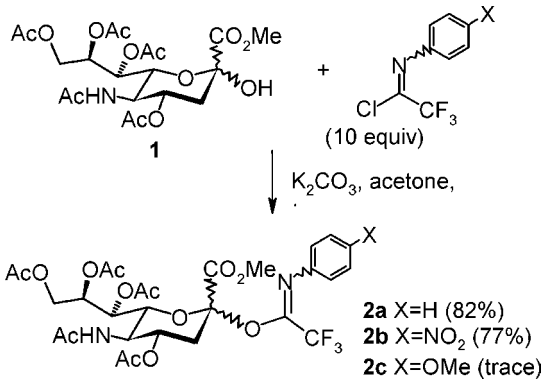
roacetimidates as leaving groups[11] compliments the Schmidt glycosylation in this respect and compares favorably with the previous direct sialylation protocols.[2] The preliminary results are herewith presented.

Initially, we investigated the preparation of trifluoroacetimidates **2a**−**c** to evaluate their potential for undergoing efficient glycosylation (Scheme 1). Treatment of methyl

Scheme 1

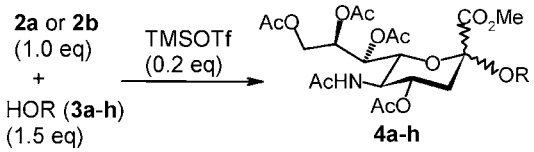


Neu5Ac tetraacetate **1**[12] with *N*-phenyltrifluoroacetimidoyl chloride (10 equiv) in the presence of K_2CO_3 (3.0 equiv) in acetone at room temperature for 3 h provided the desired sialyl imidate **2a** in 82% yield (α/β = 1:1). The reaction between **1** with *N*-(*p*-nitrophenyl)trifluoroacetimidoyl chloride was complete within 15 min, affording **2b** (77%) as predominantly the β anomer. The reaction between **1** and *N*-(*p*-methoxyphenyl)trifluoroacetimidoyl chloride led to a mixture of products in which **2c** could hardly be detected.[13]

Sialyl imidates **2a** and **2b** were purified by silica gel column chromatography and were stable to storage at 4 °C for several weeks.

The donor property of **2a** was first examined with primary sugar alcohol **3a** as an acceptor (Scheme 2). Thus, to a

Scheme 2



stirring mixture of **2a** (∼ 80 mg), **3a** (1.5 eq), and 3Å MS in CH_2Cl_2 at −30 °C under argon, was added TMSOTf (0.2 eq). TLC indicated the completion of the reaction in 1.5 h. Usual workup provided the desired coupling product **4a** in 74% yield. The dominance of the β anomer was proved by ^{1}H NMR analysis (Table 1, entry 1).[2] Replacement of CH_2Cl_2 with CH_3CN as solvent afforded **4a** (80%) with the α anomer being the major product (α/β = 3:1) (entry 2). Lower reaction temperature was found to favor the α glycosidation presumably via the intermediacy of an axial β sialyl nitrilium ion intermediate.[6b] Indeed, the coupling reaction in CH_2Cl_2/CH_3CN (1:1) at −65 °C in 1.5 h produced **4a** (79%) with an improved α/β ratio of 6.6:1 (entry 3).[14] Similar results were obtained when **2b** was used as donor (entries 4−5) or the primary sugar alcohols **3b**[15] and **3c** as acceptors (entries 6−9).

Next, a variety of the secondary alcohols (**3d**−**g**) were examined as acceptors to couple with **2a** under the fixed conditions (0.2 equiv of TMSOTf, 1:1 CH_2Cl_2/CH_3CN, 3 Å MS, Ar, −65 °C) (entries 10−13). Sialylation of triterpenoids and spirostan steroids has not been previously practiced, while sialylation of **3d** and **3e** with imidate **2a** led to the coupling products (**4d** and **4e**) in 80% and 77% yields, respectively, with α/β ratios > 3.5:1 (entries 10 and 11). For the hindered alcohol **3f**, the sialylation product **4f** could still be obtained in a satisfactory 59% yield and α/β ratio = 6.8:1 (entry 12). Regioselective sialylation of galactopyranoside 3,4-diols and 2,4,6-triols analogous to **3g** and **3h**, to produce the naturally occurring α2−3 and α2−6 linkages, has been successful with previous sialylation protocols.[5a,e,6,8] Coupling with the present

(5) For earlier reports, see: (a) Murase, T.; Ishida, H.; Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1988**, *184*, C1. (b) Kirchner, E.; Thiem, F.; Dernick, R.; Heukeshoven, J.; Thiem, J. *J. Carbohydr. Chem.* **1988**, *7*, 453. (c) Kanie, O.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1988**, *7*, 501. (d) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 1061. (e) Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1990**, *202*, 165. (e) Hasegawa, A.; Nagahama, T.; Ohki, H.; Hotta, K.; Ishida, H.; Kiso, M. *J. Carbohydr. Chem.* **1991**, *10*, 493. (f) Roy, R.; Andersson, F. O.; Letellier, M. *Tetrahedron Lett.* **1992**, *33*, 6053.

(6) For earlier reports, see: (a) Marra, A.; Sinaÿ, P. *Carbohydr. Res.* **1990**, *195*, 303. (b) Birberg, W.; Lönn, H. *Tetrahedron Lett.* **1991**, *32*, 7453. (c) Martichonok, V.; Whitesides, G. M. *J. Org. Chem.* **1996**, *61*, 1702.

(7) For earlier reports, see: (a) Martin, T. J.; Schmidt, R. R. *Tetrahedron Lett.* **1992**, *33*, 6123. (b) Kondo, H.; Ichikawa, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **1992**, *114*, 8746.

(8) The latest development for direct sialylation involves dehydrative coupling of C2-hemiketal sialyl donors, see: Haberman, J. M.; Gin, D. Y. *Org. Lett.* **2003**, *5*, 2539.

(9) (a) Schmidt, R. R.; Rucker, E. *Tetrahedron Lett.* **1980**, *21*, 1421. (b) Ratcliffe, A. J.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 747.

(10) (a) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21. (b) Schmidt, R. R.; Jung, K.-J. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; p 283.

(11) (a) Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2505. (b) Yu, B.; Tao, H. *J. Org. Chem.* **2002**, *67*, 9099. (c) Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Org. Lett.* **2003**, *5*, 987.

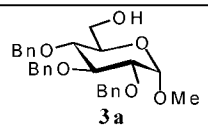
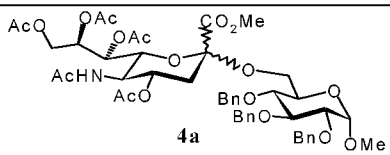
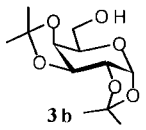
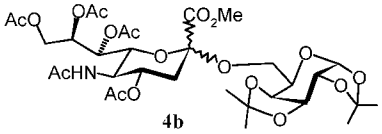
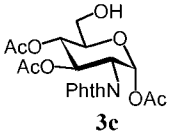
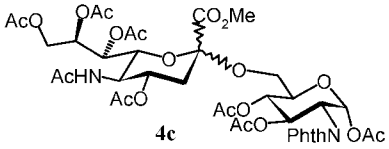
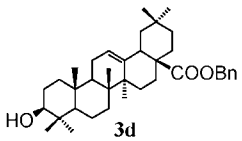
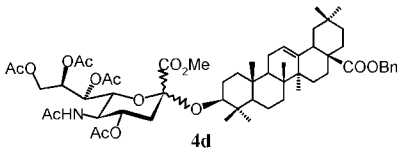
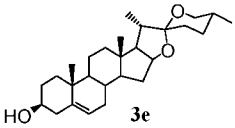
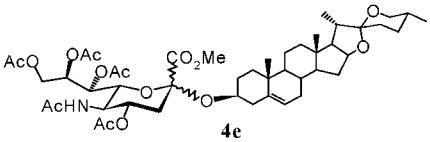
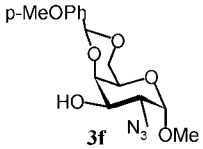
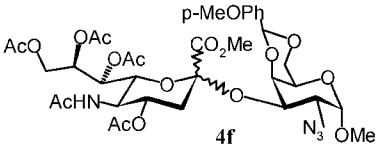
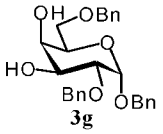
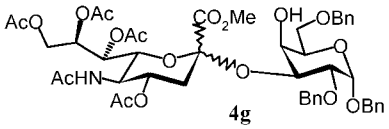
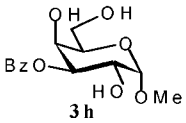
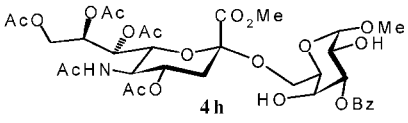
(12) Marra, A.; Sinay, P. *Carbohydr. Res.* **1989**, *190*, 317.

(13) Condensation of **1** with Cl_3CCN under similar conditions also failed, probably due to the lability of the resulting Neu5Ac 2-imidate.[10b]

(14) It was reported that sialylation of **3a** (1.5 equiv) with methyl tetra-*O*-acetyl-Neu5Ac 2-dibenzyl phosphite (0.2 equiv of TMSOTf, CH_3CN, −42 °C) provided **4a** in 80% yield and α/β = 5:1;[7b] sialylation with 2-diethyl phosphite (0.1 equiv of TMSOTf, CH_3CN, −40 °C) gave **4a** in 70% yield and α/β = 4:1;[7a] sialylation with 2-SMe (1.5 equiv of PhSeOTf, CH_3CN, −35 °C) gave **4a** in 78% yield and α/β = 4.5:1.[5e]

(15) It was reported that sialylation of **3b** (1.0 equiv) with methyl tetra-*O*-acetyl-Neu5Ac 2-SMe (PhHgOTf, 1:1 CH_3CN/$PhCH_3$, rt) gave **4b** in 24% yield and α/β = 5:1;[5b] sialylation with 2-SPhOMe-*p* (NIS/TfOH, 2:1 CH_3CN/CH_2Cl_2, −15 °C) gave **4b** in 89% yield and α/β = 2.6:1.[5g]

Table 1. Sialylation with Trifluoroacetimidate Donors **2a**,**b**

entry	donor	Acceptor	conditions[a]	product	yield[b]	α : β [c]
1	**2a**	 **3a**	A	 **4a**	74%	1:48[c]
2			B		80%	3:1
3			C		79%	6.6:1[c]
4	**2b**	**3a**	A	**4a**	83%	<1:10
5			C		63%	4:1[c]
6	**2a**	 **3b**	A	 **4b**	75%	1:2.4[c]
7			B		71%	1.6:1[c]
8			C		90%	5:1[c]
9	**2a**	 **3c**	C	 **4c**	81%	4:1[c]
10	**2a**	 **3d**	C	 **4d**	80%	3.6:1[c]
11	**2a**	 **3e**	C	 **4e**	77%	4.4:1[c]
12	**2a**	 **3f**	C	 **4f**	59%	6.8:1[c]
13	**2a**	 **3g**	C	 **4g**	81%	3:1
14	**2a**	 **3h**	C	 **4h**	61%	α

[a] Key: (A) CH_2Cl_2, −30 °C; (B) CH_3CN, −30 °C; (C) CH_2Cl_2−CH_3CN (1:1), −65 °C; all the reactions were carried out in the presence of 3 Å MS and a positive charge of argon. [b] Isolated yields, based on donor **2**. [c] Determined by ^1H NMR analysis.

trifluoroacetimidate donor **2a** gave comparable or favorable yields and α selectivity (entries 13 and 14). In all the above sialylations, the 2,3-glycal derivative was detected to be the major side product.

In summary, *N*-phenyltrifluoroacetimidates were disclosed as excellent leaving groups for direct sialylation, which compares favorably with the previous protocols for direct sialylation with respect to the coupling yields, α-selectivity,

and ease of operations. The method also employs a nontoxic catalytic amount of the promoter.

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Supporting Information Available: Experimental procedures and analytical data for new compounds. Reproductions of ^{1}H NMR spectra for compounds **2a**(α), **2a**(*β*), **2b**(*β*), **4a**(α), **4b**, **4c**, **4d**(α), **4e**(α), **4f**, **4g**(α), and **4h**(α) and ^{13}C NMR spectra for compounds **2a**(α), **2a**(*β*), **2b**(*β*), **4d**(α), **4e**(α), **4f**, **4g**(α), and **4h**(α). This material is available free of charge via the Internet at http://pubs.acs.org.

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