Ferrier Glycosylation Reaction Catalyzed by $Bi(OTf)_3$–Montmorillonite K-10: Efficient Synthesis of 3,4-Unsaturated Sialic Acid Derivatives

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Received 7 December 2007

Abstract: The reaction of the 4,5-oxazoline derivative of sialic acid with various alcohols was effectively promoted by a catalytic amount of montmorillonite K-10 clay supported $Bi(OTf)_3$ to produce a variety of 3,4-unsaturated sialic acids via the Ferrier glycosylation reaction in moderate yields.

Key words: Ferrier glycosylation reaction, 3,4-unsaturated sialic acid, $Bi(OTf)_3$–montmorillonite K-10, 4,5-oxazoline derivative of sialic acid, sialidase inhibitor

N-Acetylneuraminic acid (Neu5Ac, **1**) and its various analogues are critical components of cell surface glycoconjugates involved in cellular recognition processes.[1] Various 2-deoxy-2,3-didehydro-*N*-acetylneuraminic acid (Neu5Ac2en, **2**) analogues have been synthesized as competitive influenza sialidase inhibitors.[2] Among them, 2,3-didehydro-2,4-dideoxy-4-guanidinyl-*N*-acetylneuraminic acid (zanamivir, **3**)[3] in Figure 1 has been approved for human use as a specific sialidase inhibitor for anti-influenza drugs. Human parainfluenza virus type 1 (hPIV-1) is a serious pathogen causing upper and lower respiratory disease in infants and young children;[4] however, there are no known effective inhibitors of hPIV-1 infection.

Lewis acid catalyzed allylic rearrangement of acyloxy glycals is a well-known Ferrier reaction[5] and is widely employed to obtain 2,3-unsaturated glycosides (Scheme 1), which are versatile chiral intermediates in the synthesis of several biologically active natural products.[6]

Due to its great significance in the area of carbohydrate chemistry, there has been growing interest in the development of the Ferrier reaction by using a variety of catalysts.

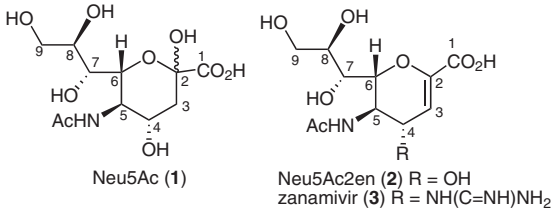
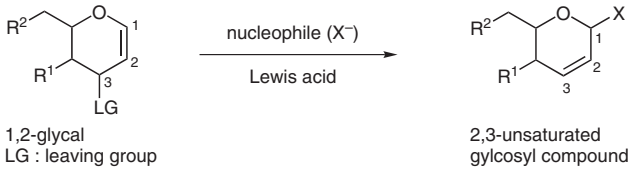


Figure 1 Structures of compounds **1**–**3**.

SYNLETT 2008, No. 7, pp 1027–1030
Advanced online publication: 28.03.2008
DOI: 10.1055/s-2008-1072649; Art ID: U12207ST



Scheme 1

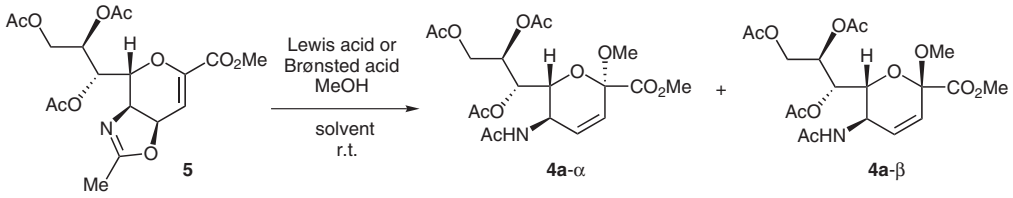
Despite their usefulness, strong Lewis acid catalysts, such as $BF_3{\cdot}OEt_2$[7] and $SnCl_4$[8] are generally employed to obtain 2,3-unsaturated glycosides. Other reagents, such as the clay catalyst montmorillonite K-10,[9] bismuth(III) trifluoromethane sulfonate (bismuth triflate) [$Bi(OTf)_3$],[10] $Bi(OTf)_3$–SiO_2,[10] DDQ,[11] *N*-iodosuccinimide,[12] and lanthanide triflates such as $Yb(OTf)_3$[13] and $Sc(OTf)_4$[14] are known to bring about the Ferrier glycosylation reaction under mild conditions. Bismuth triflate was also found to be a mild and effective promoter of glycosylation.[15] Recently, glycal derivatives as glycosyl donors have been utilized in π-allylpalladium strategies for the stereoselective synthesis of *O*-glycosides.[16]

In order to design new hPIV-1 sialidase inhibitors, 3,4-unsaturated sialic acid derivatives are a promising candidate as transition-state analogue for the enzyme reaction.[17] Compound **7** was found to be a weak inhibitor against sialidase from influenza virus.[18] In keeping with our interest in the development of new inhibitors against hPIV-1 sialidase,[1,9] we present our preliminary results on the interesting use of $Bi(OTf)_3$–montmorillonite K-10[20] as an efficient catalyst for the synthesis of 3,4-unsaturated sialic acid derivative **4** via the Ferrier glycosylation reaction starting from sialic acid 4,5-oxazoline derivative **5**. To the best of our knowledge, this is the first report on $Bi(OTf)_3$–montmorillonite K-10 mediated Ferrier glycosylation reaction of sialic acid derivatives.

Our synthesis of **4** commenced with construction of the oxazoline derivative **5**[21] starting from Neu5Ac in 76% yield in three steps (Scheme 2).

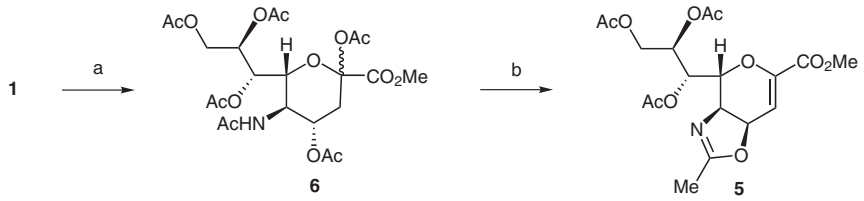
We first investigated the Ferrier glycosylation reaction to construct methyl ketoside of 3,4-unsaturated sialic acid derivatives **4a**. Thus, different reaction conditions, including promoters and solvents, were examined. These results are summarized in Table 1. The reaction between **5** and MeOH as a glycosyl acceptor using IR120 (H^+) as Brønsted acid at room temperature gave the 3,4-unsaturated glycoside **4a** in 31% yield as an anomeric mixture with the

Table 1 Ferrier Glycosylation Reaction of 4,5-Oxazoline Derivative of Sialic Acid **5**



Entry	Brønsted or Lewis acid	Solvent	Time (h)	Yield (%)[a] (α/β ratio)[b]
1	IR120 (H^+)	–	20	31 (6:94)
2	TMSOTf (1.0 equiv)	MeCN	4	56 (15:85)
3	$Hf(OTf)_4$ (1.0 equiv)	MeCN	22	42 (21:79)
4	$Sc(OTf)_3$ (20% w/w)	MeCN	17	45 (17:83)
5	$Zn(OTf)_2$ (1.0 equiv)	MeCN	22	45 (19:81)
6	$Yb(OTf)_3$ (0.2 equiv)	MeCN	17	51 (12:88)
7	$InCl_3$ (0.7 equiv)	MeCN	14	69 (6:94)
8	$BF_3{\cdot}OEt_2$ (0.8 equiv)	MeCN	39	51 (41:59)
9	$BF_3{\cdot}OEt_2$ (0.8 equiv)	CH_2Cl_2	17	64 (16:84)
10	$BF_3{\cdot}OEt_2$ (0.8 equiv)	CPME	12	60 (17:83)
11	$Bi(OTf)_3$ (0.2 equiv)	MeCN	14	50 (23:77)
12	Montmorillonite K-10 (30% w/w)	MeCN	40	63 (13:87)
13	$Bi(OTf)_3$–Montmorillonite K-10[c] (40% w/w)	MeCN	20	95 (7:93)
14	$Bi(OTf)_3$–Montmorillonite K-10[c] (40% w/w)	CH_2Cl_2	20	73 (8:92)
15	$Bi(OTf)_3$–Montmorillonite K-10[c] (40% w/w)	Et_2O	22	47 (9:91)

[a] Isolated yields after column chromatography.
[b] The anomeric ratio was determined on the basis of the integrated ratios of the hydrogens of methyl carboxylates of **4a** in the NMR spectra at 500 MHz.
[c] $Bi(OTf)_3$–Montmorillonite K-10 loading of 20% w/w of $Bi(OTf)_3$.

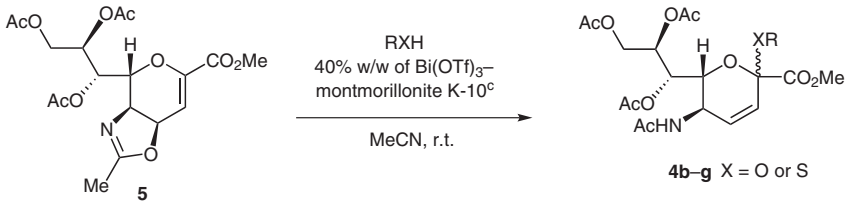


Scheme 2 *Reagents and conditions*: (a) (i) MeOH, IR120 (H^+), r.t., 15 h, quant.; (ii) Ac_2O, pyridine, r.t., 15 h, 98%; (b) TMSOTf, MeCN, 50 °C, 2 h, 78%.

β-anomer as the major product (α/β = 6:94; Table 1, entry 1).

The α/β ratio of **4a**[22] was determined by ^1H NMR analysis. Using Lewis acids TMSOTf, $Hf(OTf)_4$, $Zn(OTf)_2$, $Yb(OTf)_3$, $Sc(OTf)_3$, and $InCl_3$ as promoters in MeCN, the reaction gave **4a** in 56, 42, 45, 45, 51, and 69% yield, respectively, mainly as β-anomer (Table 1, entries 2–7). A relatively large amount of α-glycosides **4a** was obtained in MeCN in the presence of 0.8 equivalents of $BF_3{\cdot}OEt_2$ in 51% yield with an α/β ratio of 41:59, as expected from the more significant solvent participation of MeCN than CH_2Cl_2 (entries 8 and 9). The solvent effect of CPME[23] was examined. When the reaction of **5** with MeOH was carried out the using 0.8 equivalents of $BF_3{\cdot}OEt_2$ in CPME at room temperature, however, no increment of α-selectivity was observed (α/β ratio = 17:83, entry 10). When both the 0.2 equivalents of $Bi(OTf)_3$ and 30% w/w of montmorillonite K-10 were used as activators, the reactions gave **4a** in 50% and 63% yield, respectively (entries 11 and 12). Interestingly, the reaction of **5** with MeOH in the presence of 40% w/w $Bi(OTf)_3$–montmorillonite K-10 loading of 20% w/w of $Bi(OTf)_3$ in MeCN showed re-

Table 2 Ferrier Glycosylation Reaction of 4,5-Oxazoline Derivative of Sialic Acid **5**



Entry	RXH	Time (h)	Product	Yield (%)[a] (α/β ratio)[b]
1	EtOH	16	**4b**	77 (9:91)
2	*n*-PrOH	14	**4c**	44 (6:94)
3	*i*-PrOH	13	**4d**	32 (12:88)
4	*n*-BuOH	15	**4e**	50 (10:90)
5	*n*-BuOH	19	**4f**	41 (10:90)
6	$Me(CH_2)_{11}SH$	23	**4g**	40 (9:91)

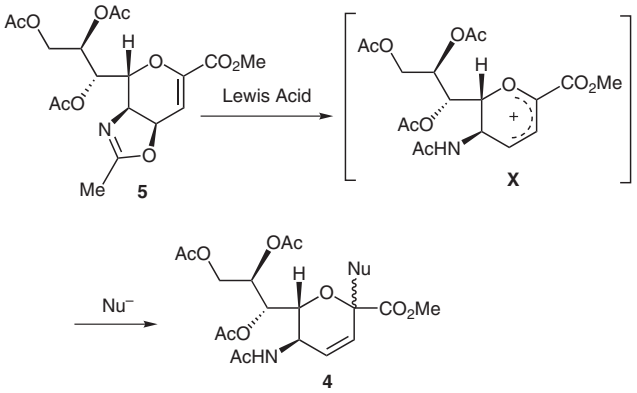
[a] Isolated yields after column chromatography.
[b] The anomeric ratio was determined on the basis of the integrated ratios of the hydrogens of methyl carboxylates of **4b**–**g** in the ^1H NMR spectra at 500 MHz.
[c] $Bi(OTf)_3$–Montmorillonite K-10 loading of 20% w/w of $Bi(OTf)_3$.

markable improvement in the glycosylation yield (95%, α/β ratio = 7:93; entry 13).[24] This synergetic enhancement by the addition of montmorillonite K-10 to $Bi(OTf)_3$ was tentatively understood by the formation of a montmorillonite K-10–ROH complex, which might activate **5** under the influence of $Bi(OTf)_3$. This result shows that it is important to use the combination of $Bi(OTf)_3$ and montmorillonite K-10 for higher yields in the Ferrier glycosylation reaction. The solvent effects were tested; however, the yields of **4a** in CH_2Cl_2 and Et_2O decreased to 73% and 47% yield, respectively (entries 14 and 15).

Next, the glycosyl donor of the propriety of **5** was evaluated by coupling with various alcohols. As summarized in Table 2, the reactions of **5** with ethyl, *n*-propyl, *i*-propyl, *n*-butyl, benzyl alcohols, and thiophenol were activated by 40% w/w of $Bi(OTf)_3$ (20%)–montmorillonite K-10 in MeCN at room temperature to give **4b**–**g** in 77%, 44%, 32%, 50%, 41%, and 40% yield, respectively, as an anomeric mixture with the β-anomer as the major product.

The possible mechanism of the Ferrier glycosylation reaction involves the intermediacy of a cyclic allylic oxonium ion **X** with which the nucleophile undergoes a subsequent addition reaction (Scheme 3).

Molecular orbital calculations using the Spartan'04 Semi-Empirical Program PM3 of the cyclic allylic oxonium ion **X** in Scheme 3 were carried out to study the origin of β-orientation. The stereostructure of the lowest energy conformation of **X** is shown in Figure 2. The pyrane ring has almost planar conformation. This conformation led us to suppose that nucleophilic attack would occur from the β-face of the donor moiety **X** to result in the predominant formation of β-glycoside, since the α-face is hindered by the acetyl group at C-7.



Scheme 3 Possible mechanism of Ferrier glycosylation reaction of **5**

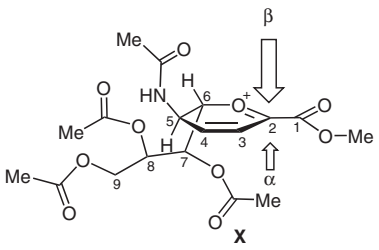
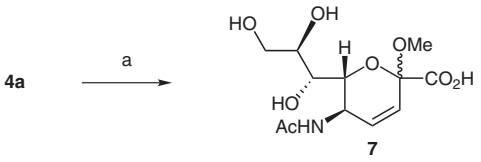


Figure 2 Optimized molecular structures of oxocarbonium ion **X** in Scheme 3

De-O-acetylation of **4a** and subsequent saponification of the resulting methyl ester gave sialidase inhibitor **7** in 92% yield in two steps (Scheme 4).

Our synthesis approach is the first example of the Ferrier glycosylation reaction for the construction of 3,4-unsaturated sialic acid derivatives. It is an important to use the combination of $Bi(OTf)_3$ and montmorillonite K-10 for



Scheme 4 *Reagents and conditions*: (a) (i) NaOMe, MeOH, r.t., 15 h, 92%; (ii) 0.1 M KOH, MeOH, r.t., 15 h, quant.

higher yields in the Ferrier glycosylation reaction. We believe that this synthesis method provides a practical route to establish novel 3,4-unsaturated sialic acid analogues. The use of inexpensive and readily accessible $Bi(OTf)_3$ with high yields makes it a useful and attractive alternative to the more expensive lanthanide triflate or stoichiometric conventional Lewis acid promoted O-glycosidation procedures.

We are currently applying this methodology to the development of new hPIV-1 inhibitors.

Acknowledgment

We thank Dr. Kimio Furuhata (Kitazato University) for helpful discussion and encouragement. This work was financially supported in part by a Grant-in-Aid for Scientific Research No. 19590103 from the Ministry of Education, Science, Sports, and Culture of Japan. The authors thank Dr. Yasuhiro Torisawa (Takasaki University of Health and Welfare) for the generous gift of $Bi(OTf)_3$. The authors thank JAPAN FOOD & LIQUOR ALLIANCE INC. (Kyoto, Japan) for the generous gift of Neu5Ac.

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(22) The α-methyl ketoside of 5-acetamido-3,4,5-trideoxy-D-manno-non-3-en-2-ulosonic acid (**4a**), and its β-epimer were synthesized from 3-acetamido-4,5,6,7-tetra-*O*-acetyl-2,3-dideoxy-D-manno-heptose, and methyl 2-methoxy-2-dimethylphosphono acetate in 29% yield over five steps.[18]

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(24) **Typical Procedure**
To a stirred mixture of **5** (50 mg, 0.12 mmol) and MeOH (0.1 mL) in MeCN (1.0 mL) was added 40% w/w $Bi(OTf)_3$–montmorillonite K-10 loading of 20% w/w of $Bi(OTf)_3$ (15 mg) at ambient temperature. The mixture was stirred for 20 h at r.t. The reaction suspension was filtered and the filtrate was evaporated under vacuum. The residue was purified by column chromatography on silica gel with CH_2Cl_2–MeOH (10:1) to give **4a** (51 mg, 95%).
Compound **4a**-α: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.99 (s, 3 H, CH_3CONH), 2.05, 2.12, 2.14 (s, each 3 H, CH_3CO), 3.34 (s, 3 H, CH_3O), 3.78 (s, 3 H, CH_3COO), 4.24 (dd, 1 H, $J_{9a,9b}$ = 12.4 Hz, $J_{8,9a}$ = 5.9 Hz, H-9a), 4.26 (dd, 1 H, $J_{5,6}$ = 9.8 Hz, $J_{6,7}$ = 2.1 Hz, H-6), 4.48 (dd, 1 H, $J_{8,9b}$ = 2.4 Hz, H-9b), 4.52 (dddd, $J_{5,NH}$ = 9.2 Hz, $J_{4,5}$ = 2.6 Hz, $J_{3,5}$ = 1.9 Hz, H-5), 5.35 (dd, 1 H, $J_{7,8}$ = 6.1 Hz, H-7), 5.44 (ddd, 1 H, H-8), 5.59 (d, 1 H, CH_3CONH), 5.78 (dd, 1 H, $J_{3,4}$ = 10.1 Hz, H-4), 6.07 (dd, 1 H, H-3). MS–FAB (NBA): *m/z* = 446 $[M + H]^+$, 468 $[M + Na]^+$. HRMS–FAB: *m/z* calcd for $C_{19}H_{28}NO_{11}$: 446.1662; found: 446.1613.
Compound **4a**-β: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.99 (s, 3 H, CH_3CONH), 2.04, 2.10, 2.16 (s, each 3 H, CH_3CO), 3.29 (s, 3 H, CH_3O), 3.82 (s, 3 H, CH_3COO), 4.05 (dd, 1 H, $J_{5,6}$ = 10.2 Hz, $J_{6,7}$ = 2.3 Hz, H-6), 4.24 (dd, 1 H, $J_{9a,9b}$ = 12.5 Hz, $J_{9a,8}$ = 6.3 Hz, H-9a), 4.63 (dd, 1 H, $J_{8,9b}$ = 2.3 Hz, H-9b), 4.64 (m, 1 H, H-5), 5.35 (ddd, 1 H, $J_{7,8}$ = 5.6 Hz, H-8), 5.40 (dd, 1 H, H-7), 5.51 (d, 1 H, CH_3CONH), 5.91 (s, 2 H, H-3 and H-4).