Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry 11 (2003) 3073–3076

BIOORGANIC & MEDICINAL CHEMISTRY

Glycosylation of Sialyl Acetates with a Novel Catalyst Combination: Bismuth Triflate and $BF_3{\cdot}OEt_2$ System

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Received 7 February 2003; accepted 14 April 2003

Abstract—A combined system of bismuth triflate [$Bi(OTf)_3$] and boron trifluoride etherate ($BF_3{\cdot}OEt_2$) in dichloromethane is an efficient promoter for the glycosylation of *N*-acetylneuraminic acid derivatives. The co-existence of two acid catalysts such as $Bi(OTf)_3$–$BF_3{\cdot}OEt_2$ or $Bi(OTf)_3$–PPA is confirmed to be essential for obtaining high yields of glycosylation products with *p*-nitrobenzyl alcohol, which also turned to be superior to those reported previously.

Introduction

N-Acetylneuraminic acid (sialic acid) residues are often located at the non-reducing end of glycoconjugates and play important roles in a variety of biochemical and biological processes.[1] Consequently the development of an efficient method of *O*-sialylation has been a challenging task in the field of sialic acid chemistry.[2] Various Lewis acids such as $BF_3{\cdot}OEt_2$, AgOTf, $AgClO_4$, TMSOTf, $FeCl_3$ and so on have been used for the formation of a glycosidic linkage starting from appropriate precursors.[3] Increasing numbers of studies have dealt with milder glycosylation conditions by using triflates of rare earth elements and others. Nevertheless, the development in this area depends upon a better Lewis acid promoter of less toxicity, ready availability and easy handling. Recently, bismuth compounds have become attractive candidates for use as a versatile reagent in organic synthesis.[4] The main advantages of bismuth compounds are (i) their low toxicity with adequate activities; (ii) their low cost relative to most other known catalysts; (iii) fairly insensitive nature to water; and (iv) their easy removal by filtration, thus simplifying the purification procedure. In particular, Bismuth (III) trifluoromethanesulfonate [$Bi(OTf)_3$], in which the Lewis acidity of bismuth is amplified by three strongly electron-withdrawing groups, was shown to be a powerful Lewis acid catalyst. Bismuth triflate is not commercially available so far, but is easily prepared in a large quantity from the inexpensive reagent triphenylbismuth as described in the Experimental.[5] This reagent has been used in previous studies for Friedel–Crafts acylation of aromatic compounds,[6] sulfonylation of arenes,[7] Diels–Alder reaction,[8] the aza-Diels–Alder reaction,[9] ene reaction,[10] and also for mild and selective acylation of alcohols.[11] However, to the best of our knowledge, no application to the glycosylation reactions of sialic acids has been reported so far. Herein, we present our preliminary results on the use of $Bi(OTf)_3$ in combination with boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) as an efficient catalyst for the glycosylation of some sialic acid derivatives.

Results and Discussion

As mentioned above, some metal triflates have been successfully employed in the glycosylation of glycosyl acetates and others.[3] In these instances, however, some activation of glycosyl acceptor is necessary (e.g., as a silyl ether) in the presence of a catalytic amount of metal triflate derived from Sc or Yb.[12] We intended the direct use of the acetate **1** and a free alcohol in the presence of various metal triflates including $Bi(OTf)_3$. Due

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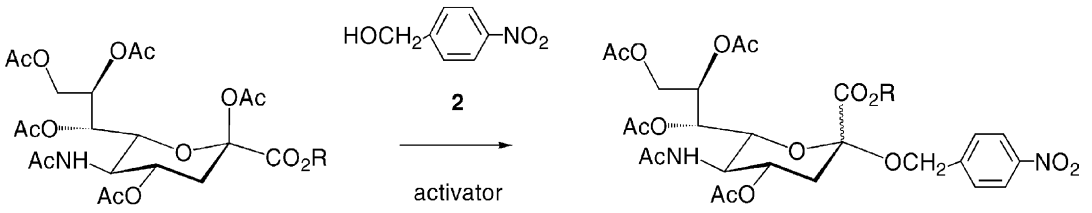
doi:10.1016/S0968-0896(03)00277-3



Scheme 1.

to its availability in large quantity with long shelf-life, $Bi(OTf)_3$ has been regarded as the most suitable catalyst for the manipulation of common sugar derivatives. We, thus, started our investigation on the glycosylation of **1a** and *p*-nitrobenzyl alcohol **2**, which is often used in biochemical studies as a hydrogen-sensitive linker[13] (Scheme 1).

The reaction between **1a** and the 1.5 molar equivalent of **2** using 2.0 molar equivalent of $Bi(OTf)_3$ in CH_2Cl_2 at room temperature gave the expected corresponding glycosides **3a** in 23% yield as an anomeric mixture with β-anomer as the major product (Table 1; entry 1). The reaction using 2.0 molar equivalent of $BF_3{\cdot}OEt_2$ instead of $Bi(OTf)_3$ afforded **3a** in a slightly lower yield of 18% (entry 2). Interestingly, the combined use of each 2.0 molar equivalent of $Bi(OTf)_3$ and $BF_3{\cdot}OEt_2$ as a mixed activating system significantly improved the glycosylation yield (50%) (entry 3). This synergetic enhancement by the addition of $BF_3{\cdot}OEt_2$ to $Bi(OTf)_3$ was tentatively understood by the formation of a BF_3–ROH complex, which might activate **1** under the influence of $Bi(OTf)_3$.[14]

Table 1. The glycosylation of **1** with **2**[a]

Entry	Glycosyl donor **1**	Activators	Solvent/ temp.	Product	Yield (%) (α/β)[g]
1	**1a**	$Bi(OTf)_3$[b]	CH_2Cl_2/rt	**3a**	23 (27:73)
2	**1a**	$BF_3{\cdot}OEt_2$[b]	CH_2Cl_2/rt	**3a**	18 (β)
3	**1a**	$Bi(OTf)_3$, $BF_3{\cdot}OEt_2$[c]	CH_2Cl_2/rt	**3a**	50 (27:73)
4	**1a**	$Bi(OTf)_3$, $BF_3{\cdot}OEt_2$[d]	CH_2Cl_2/rt	**3a**	70 (19:81)
5	**1a**	$Bi(OTf)_3$, PPA[e]	CH_2Cl_2/rt	**3a**	65 (32:68)
6	**1a**	PPA[b]	CH_2Cl_2/rt	**3a**	8 (33:67)
7	**1a**	$BiCl_3$, $BF_3{\cdot}OEt_2$[c]	CH_2Cl_2/rt	**3a**	36 (β)
8	**1a**	$Sc(OTf)_3$[b]	CH_2Cl_2/rt	**3a**	15 (β)
9	**1a**	$Yb(OTf)_3$[b]	CH_2Cl_2/rt	**3a**	2 (β)
10	**1a**	$Zn(OTf)_2$, TMSCl[f]	CH_2Cl_2/rt	**3a**	24 (20:80)
11	**1a**	$Bi(OTf)_3$, $BF_3{\cdot}OEt_2$[c]	CH_3CN/−40 °C	**3a**	18 (78:22)
12	**1a**	$Bi(OTf)_3$, $BF_3{\cdot}OEt_2$[c]	CH_3CN/rt	**3a**	27 (57:43)
13	**1b**	$Bi(OTf)_3$, $BF_3{\cdot}OEt_2$[c]	CH_2Cl_2/rt	**3b**	48 (β)

[a]Reaction time was 15 h. Powered 4 Å molecular sieves were used in all cases.
[b]With respect to **1**, 1.5 equiv of **2** and 2.0 equiv of the activator were used.
[c]With respect to **1**, 1.5 equiv of **2** and 2.0 equiv of the activator and 2.0 equiv of $BF_3{\cdot}OEt_2$ were used.
[d]With respect to **1**, 1.5 equiv of **2** and 0.5 equiv of $Bi(OTf)_3$ and 2.0 equiv of $BF_3{\cdot}OEt_2$ were used. Ultrasound sonic mixing (10 h) was used.
[e]With respect to **1**, 1.5 equiv of **2** and 2.0 equiv of $Bi(OTf)_3$ and 2.0 equiv of PPA were used. Ultrasound sonic mixing (5 h) was used.
[f]With respect to **1**, 1.5 equiv of **2** and 2.0 equiv of $Zn(OTf)_2$ and 2.0 equiv of TMSCl were used.
[g]Isolated yields. The stereochemistry of **3a,b** was confirmed by ^1H NMR (270 MHz) measurement according to the emphirical rules.[19] The anomeric ratios were determined on the basis of the integration ratios of the $3H_{eq}$ signals of the glycosides in ^1H NMR analysis.

Next, the molar ratio of $Bi(OTf)_3$ was surveyed. The reaction with reduced amounts of $Bi(OTf)_3$ (50 mol%) increased the yield of **3a** to 70% yield under sonication[15] (entry 4), 43% yield without the aid of sonication. We further examined other Lewis acids-solvent combinations for the reaction of **1a** and **2**. Interestingly, the reaction catalyzed by $Bi(OTf)_3$ and polyphosphoric acid (PPA) under sonication smoothly proceeded to afford **3a** in 65% yield (entry 5). The novel combination of $Bi(OTf)_3$ and PPA was also successfully applied to the rearrangement of oxime sulfonates derivatives as reported recently. In this previous study, it was suggested that $Bi(OTf)_3$ can be solvated in PPA and easily deliver TfOH, the active catalysts in this viscous solvent.[16] In contrast, the reaction using 2.0 molar equivalent of PPA afforded **3a** in a low yield of 8% (entry 6). Entry 7 showed that the use of $BiCl_3$ instead of $Bi(OTf)_3$ decreased the yield of **3a** to 36%, suggesting the involvement of a TfOH equivalent species as an activator. However, the glycosylation of **1a** with **2** using scandium (III) trifluoromethanesulfonate [$Sc(OTf)_3$] or yttrium (III) trifluoromethanesulfonate [$Yb(OTf)_3$] as a promoter was less effective, and gave **3a** in only 14 and 2% yields, respectively (entries 8 and 9). The glycosylation of **2** with **1a** in the presence of zinc triflate [$Zn(OTf)_2$] and trimethylsilyl chloride (TMSCl)[17] in dichloromethane at room temperature afforded **3a** in 24% yield (entry 10). This clearly shows the superiority of our Bi-based protocol to those of Zn-based one previously reported for some transformations of sialyl acetate.

The solvent effect was then examined briefly using dichloromethane and acetonitrile. The anomeric stereochemistry of the resulting glycoside **3a** was affected by both the identity of the solvent and the reaction temperature. Thus, relatively large amounts of α-glycosides were obtained in acetonitrile at −40 °C, as expected from the more significant solvent participation of acetonitrile than dichloromethane (entries 3, 11 and 12).[18] These results are summarized in Table 1, and in this study it turned out that, $Bi(OTf)_3$, particularly in combination with Lewis acids, such as $BF_3{\cdot}OEt_2$ or PPA, acted as an effective glycosylation promoter of sialic acid derivatives.

In conclusion, we first demonstrate here that the new reagent system $Bi(OTf)_3$ in combination with $BF_3{\cdot}OEt_2$ is a mild and effective promoter for glycosylation of sialic acid derivatives. This study showed the first example of utilization of $Bi(OTf)_3$ in glycosylation of

common sialic acid derivatives such as **1**, which also suggests the importance of the combined use of the two different types of acid catalysts in glycosylations. Application to other sugar derivatives in addition to a search for novel metal triflate superior to the present one are under active investigation in these laboratories.

Experimental

Preparation of $Bi(OTf)_3$

A solution of CF_3SO_3H (10.0 mL = 16.0 g; colorless new reagents) was added at rt to a stirred solution of Ph_3Bi (15.0 g) in dry toluene (100 mL). After an exothermic process (<45 °C) has ceased, the mixture was stirred at rt for 2 h, before being concentrated under reduced pressure (<65 °C) to form a free-flowing white solid mass of bismus triflate powder (quant), as reported.[5b] This procedure was repeated more than 10 times since its first publication, with scales ranging from 15 to 30 g of Ph_3Bi, while most colorless material was obtained at the 15-g scale reaction mentioned above. In a larger scale run, a faint yellow material was obtained. Although thermal instability had been noted by Dubac, we did not observe any decomposition during the evaporation of toluene at 65–70 °C. We also could obtain yellow powder material with excess TfOH or in the presence of Bi_2O_3 in this preparation. As an alternative solvent, we utilized dichloroethane (DCE, not dichloromethane) as a substitute for toluene, which can be evaporated much easier than toluene. The material prepared in toluene usually contains a trace of toluene as a crystalline solvent, which somewhat diminishes Lewis acidity of the triflate. In fact, in some transformations, $Bi(OTf)_3$ prepared in the presence of Bi_2O_2 in DCE solvent was most effective (e.g., acylation and sulfonylation of phenol derivatives).

Representative procedure for glycosylation (Table 1; entry 3)

A solution of *N*-acetylneuraminic acid derivative (**1a**) (31 mg, 0.058 mmol) and *p*-nitrobenzyl alcohol (13 mg, 0.087 mmol) in dichloromethane (1.0 mL) in the presence of powdered 4 Å molecular sieves (0.22 g) were treated with $Bi(OTf)_3$ (79 mg, 0.12 mmol) and $BF_3{\cdot}OEt_2$ (17 mg, 0.12 mmol) and stirred for 15 h at room temperature. The precipitates were filtered off through a pad of Celite, and concentrated to give the crude product, which was purified on a preparative TLC with the solvent system of AcOEt to give the glycoside **3a** (16 mg, 50%) as a mixture of α/β anomers as a white amorphous powder. An improved yield of 70% was attained (Table 1; entry 4) when **1a** was treated with 1.5 equiv of **2** and 0.5 equiv of $Bi(OTf)_3$ and 2.0 equiv of $BF_3{\cdot}OEt_2$ under ultrasound sonic mixing for 10 h.

Selected spectral data for compound 3a (α-glycoside). Mp 76–78°C: $[\alpha]_D$ −12 (*c* 1.0, $CHCl_3$); IR (NaCl): 1745, 1666, 1523 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 1.89 (s, 3H, NAc), 2.03, 2.06, 2.12, 2.14 (s, each 3H, 4×OAc), 2.70 (dd, 1H, $J_{3eq,\ 3ax}$ = 12.4, $J_{3eq,\ 4}$ = 3.1 Hz, $3H_{3eq}$), 3.70 (3H, s, OCH_3), 4.55 and 4.93 (each 1H, d, *J* = 13.5 Hz, $PhCH_2O$), 5.14 (br d, 1H, NH), 5.39 (m, 1H, H-8), 7.52 (d, 2H, *J* = 7.8 Hz, Ph), 8.20 (d, 2H, Ph). HRMS (FAB) calcd for $C_{27}H_{35}N_2O_{15}H^+$ $(M+H)^+$: 627.2037; found 627.2031. Anal. calcd for $C_{27}H_{35}N_2O_{15}$: C, 51.76; H, 5.47; N, 4.47; Found: C, 51.54; H, 5.43; N, 4.32.

Selected spectral data for compound 3b (α-glycoside) as a white amorphous powder. Mp 64–66 °C: $[\alpha]_D$ −25 (*c* 0.75, $CHCl_3$); IR (NaCl): 1744, 1688, 1522, 762, 731 cm^{-1}; ^1H NMR (270MHz, $CDCl_3$): δ 1.89 (s, 3H, NAc), 2.03, 2.04, 2.14, 2.17 (s, each 3H, 4×OAc), 2.74 (dd, 1H, $J_{3eq,\ 3ax}$ = 13.0, $J_{3eq,\ 4}$ = 4.6 Hz, $3H_{3eq}$), 4.01–4.15 (m, 3H, H-5, 9, 9′), 4.39 and 4.86 (d, each 1H, *J* = 13.5 Hz, $PhCH_2O$), 5.31–5.35 (m, 1H, H-7), 5.37–5.43 (m, 1H, H-8), 7.31–7.34 (m, 5H, aromatic-H), 7.39 (d, 2H, *J* = 7.8 Hz, Ph), 8.12 (d, 2H, Ph). HRMS (FAB) calcd for $C_{33}H_{39}N_2O_{15}H^+$ $(M+H)^+$: 703.2350; found 703.2320. Anal. calcd for $C_{33}H_{39}N_2O_{15}$: C, 56.41; H, 5.45; N, 3.99; Found: C, 56.61; H, 5.59; N, 3.86.

Acknowledgements

We thank Prof. Shunichi Hashimoto (Hokkaido University) for helpful discussion and encouragement. This work was supported in part by a Grant-in-Aid for Scientific Research (No. 13672223) from the Ministry of Education, Science, Sports and Culture of Japan.

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