Glycosyl *N*-Tosyl Benzimidate as a New Building Block for Chemical Glycosylation

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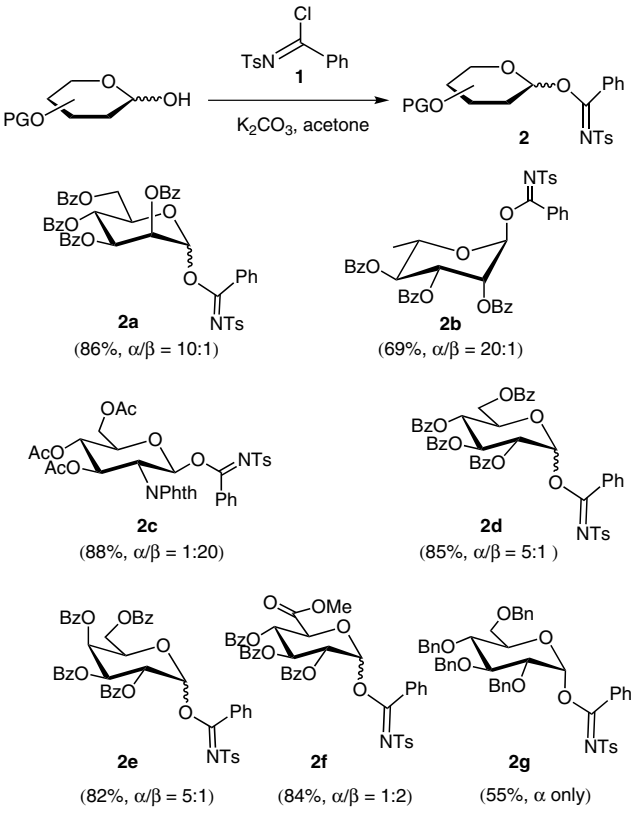
Abstract: Seven novel glycosyl *N*-tosyl benzimidates were prepared by the reactions of the corresponding hemiacetals with imidoyl chloride in 55–88% yields, which were smoothly converted to glycosides, upon treatment with alcohols and catalytic TMSOTf, in 57–99% yields.

Key words: glycosylation, glycosyl *N*-tosyl benzimidate, glycosyl donor, oligosaccarides synthesis, saponins synthesis

Chemical glycosylation[1] plays a significant role in the synthesis of oligosaccharides and glycoconjugates, which are implicated in various intracellular and extracellular recognition events.[2] In general, glycosidic linkages are constructed by the coupling of glycosyl donors, bearing activated anomeric leaving group and glycosyl acceptors which possess one or more free hydroxyl groups in the presence of appropriate promotors. The glycosyl donor has a profound influence on the stereoselectivity of glycosylation so that a myriad of donors have been developed.[1] Firstly introduced by Sinaÿ,[3a] glycosyl acetimidates had been further developed by Schmidt and co-workers with the introduction of trichloroacetimidates in 1980.[3b] Glycosyl trichloroacetimidates[3c,d] have become one of a plethora of powerful glycosyl donors due to their ease of preparation, relative stabilities, mild activation conditions, and wide substrate scopes. Recently, glycosyl *N*-phenyl-trifluoroacetimidates[4] were reported by Yu's group,[4a] which not only possess reactivity similar to glycosyl trichloroacetimidate,[3] but also display unique reaction modes including capabilities of enabling α-selective sialylation of alcohols,[5] glycosylation of primary amide of amino acids or peptides,[6] and glycosylation of hydroxamic acid,[7] for which glycosyl trichloroacetimidates[3] either failed to work or were inferior to the corresponding *N*-phenyl trifluoroacetimidate donors.[4b] More recently, studies on *N*-aryl-*O*-glucopyranosyl haloacetimidates[8] as glycosyl donors have also been reported by Schmidt's group. Although the value and power of glycosyl tricholoacetimidates,[3] trifluoroacetimidates,[4] and other glycosyl donors[1a] are unquestionable, there is still a demand of developing novel glycosyl donors and exploring their applications in the synthesis of structurally diverse glycoconjugates and oligosaccharides, as no general glycosylation available yet for all synthetic targets. Herein, we describe the preparation of glycosyl *N*-tosyl benzimidates and their applications in glycosylation.

Literature search reveals that *N*-tosyl benzimidoyl chloride[9] (**1**) can be readily obtained as a solid by crystallizations in a two-step reaction sequence: condensation of *p*-toluenesulfonamide and benzoyl chloride followed by chlorination with $POCl_3$. Thus, adopting the protocol for the preparation of glycosyl *N*-phenyl trifluoroacetimidate, treatment of mannosyl hemiacetal (1.0 equiv) with *N*-tosyl benzimidoyl chloride (**1**, 1.2 equiv) in the presence of K_2CO_3 in acetone smoothly afforded the imidate **2a** in excellent yield of 86%.[10] Under these conditions, rhamnosyl, 2-deoxy-2-phthaminoglucosyl, glucosyl, galactosyl, glucuronyl imidates **2b**–**g** were successfully obtained from their corresponding hemiacetals in 55–88% yield (Scheme 1).



Scheme 1 Preparation of glycosyl *N*-tosyl benzimidates

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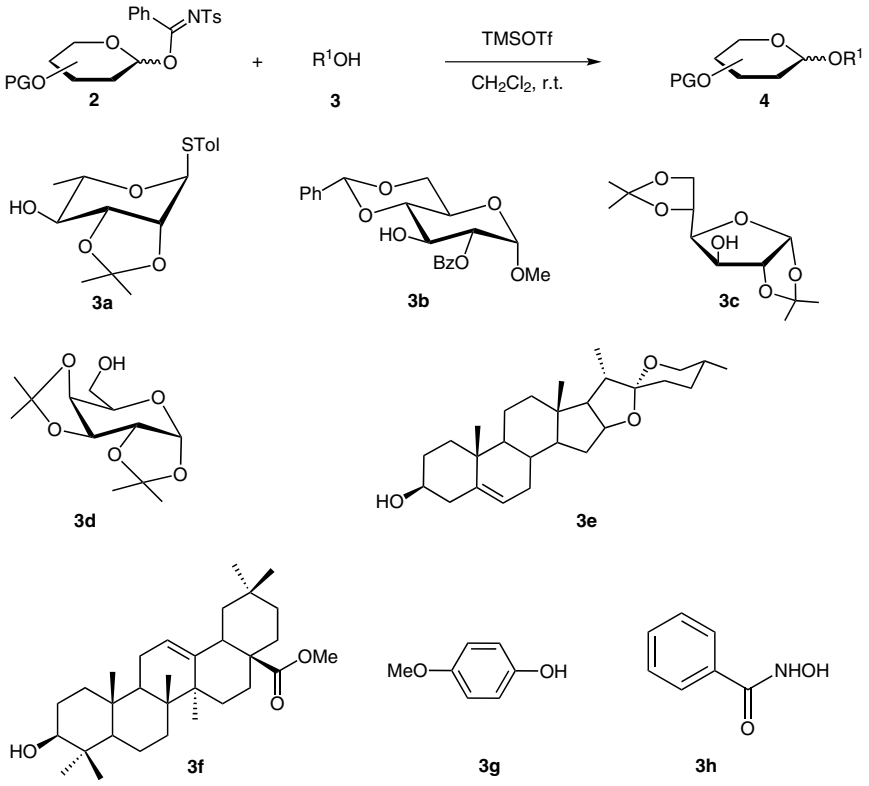
It should be noted that ^{1}H NMR spectra of glycosyl *N*-tosyl benzimidates showed that the stereoselective outcome of **2** relied on the intrinsic properties of the sugar moiety and the protecting groups used. For instance, **2a**–**c** were obtained predominantly favoring 1,2-*trans* configuration; on the other hand, **2d** and **2e** were produced at a ratio of α/β = 5:1, **2f** was obtained with β-isomer as the major product (α/β = 1:2); **2g** was isolated in 55% yield only as α isomer. In addition, all donors presented in Scheme 1 can be stored at –20 °C for several months without any degradation.

With the glycosyl *N*-tosyl benzimidates in hand, we next performed their glycosylations with various acceptors **3** (Scheme 2).

To our delight, the coupling reactions[11] proceeded smoothly with the promotion of TMSOTf in CH_2Cl_2.

As shown in Table 1, the glycosyl donors **2a**–**c** reacted well with secondary alcohols **3a**–**c**, primary alcohols **3d**, as well as phenol **3g** to afford the corresponding glycosides in excellent yields of 80–98% (Table 1, entries 1–3 and 5–9). Saponins containing glucosyl, galactosyl, and uronic moieties possess various bioactivities,[12] and their synthesis[13] have attracted extensive interest. Hence, glycosyl donors **2d**–**f** were subjected to the glycosylations with diosgenin (**3e**) and oleanic acid (**3f**), which generated the corresponding saponins without any problem in satisfactory yields (Table 1, entries 11, 12, 14, and 16). By comparing with those reported results using trifluoroacetimidate[4a] and trichloroacetimidate[13a] as glycosyl donors, we assume that the lower yields of **4de**, **4df**, **4ee**, and **4ff** may arise from mismatched glycosylations[14] of *N*-tosyl benzimidates with sapogenins due to the tosyl substituent, an electron-withdrawing group which can decrease the reactivities of benzimidate donors. In addition, **2e** and **2f** reacted with **3d** and **3g** to afford glycosides **4ed** and **4fg** in 99% and 96% yield, respectively (Table 1, entries 15 and 17). As expected, exposure of benzyl-protected glucosyl donor **2g** to **3d** produced the disaccharide **4gd** (Table 1, entry 18) as an anomeric isomer with a α/β ratio of 5:4 in 87% yield due to the lack of neighboring-group participation. Finally, glycosylations of **2a** and **2d** with hydroxamic acid **3h** proceeded well to afford glycosides **4ah** and **4dh** in 86% and 90% yield, respectively (Table 1, entries 4 and 13). In comparison, glycosyl trichloroacetimidates are not efficient donors when hydroxamic acids were used as acceptors.[7]

In conclusion, glycosyl *N*-tosyl benzimidates as novel donors were prepared, and their glycosylations with various acceptors proceeded smoothly in moderate to excellent yields, which suggested that glycosyl *N*-tosyl benzimidates may function as novel glycosylating agents. Another advantage of the present procedure over trichloroacetimidates and *N*-phenyl trifluoroacetimidates is that readily available solid *N*-tosyl benzimidoyl chloride can be easily handled. Further applications of *N*-tosyl benzimidates in the synthesis of oligosaccharides and glycoconjugates are under way in our laboratory.



Scheme 2 Glycosyl acceptors and their glycosylations with glycosyl *N*-tosyl benzimidates

Table 1 Glycosylations of **2** with **3**

Entry	Donor	Acceptor	Product	Yield (%)	α/β
1	**2a**	**3a**	**4aa**	80	α
2	**2a**	**3b**	**4ab**	94	α
3	**2a**	**3e**	**4ae**	92	α
4[a]	**2a**	**3h**	**4ah**	86	α
5	**2b**	**3a**	**4ba**	84	α
6	**2b**	**3c**	**4bc**	88	α
7	**2b**	**3e**	**4be**	97	α
8	**2c**	**3a**	**4ca**	95	β
9	**2c**	**3d**	**4cd**	98	β
10	**2c**	**3g**	**4cg**	93	β
11	**2d**	**3e**	**4de**	57	β
12	**2d**	**3f**	**4df**	65	β
13[a]	**2d**	**3h**	**4dh**	90	β
14	**2e**	**3e**	**4ee**	74	β
15	**2e**	**3d**	**4ed**	99	β
16	**2f**	**3f**	**4ff**	66	β
17	**2f**	**3g**	**4fg**	96	β
18	**2g**	**3d**	**4gd**	87	5:4

[a] Conditions: 1.0 equiv of TMSOTf was used in the glycosylation reaction.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are data and NMR spectra for compounds **2** and **4**.

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(10) **A Typical Procedure for the Preparation of Glycosyl *N*-Tosyl Benzimidate**
To a solution of mannosyl hemiactal (500 mg, 0.84 mmol) in acetone (3 mL) was added K_2CO_3 (290 mg, 2.10 mmol, 2.50 equiv) and *N*-tosylbenzimidoyl chloride (296 mg, 1.0 mmol, 1.20 equiv) at ambient temperature. After stirring for 2 h the solid was filtered off, and the filtrate was concentrated under vacuum, and the residue was purified by silica gel chromatography (EtOAc–PE = 1:4) to give imidate **2a** as a white solid (617 mg, 0.72 mmol, 86%). $[\alpha]_D^{20} = -30.1$ (*c* 1.09 $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.2 Hz, 2 H), 8.03 (m, 4 H), 7.93 (d, *J* = 7.14 Hz, 2 H), 7.82 (m, 4 H), 7.68 (t, *J* = 7.68 Hz, 1 H), 7.59 (m, 4 H), 7.50 (t, *J* = 7.14 Hz, 1 H), 7.43 (m, 5 H), 7.35 (t, *J* = 7.74 Hz, 2 H), 7.28 (d, *J* = 8.28 Hz, 2 H), 7.20 (d, *J* = 8.28 Hz, 2 H), 6.38 (d, *J* = 1.62 Hz, 1 H), 6.20 (t, *J* = 10.44 Hz, 1 H), 5.91 (m, 2 H), 4.73 (dd, *J* = 2.16, 12.06 Hz, 1 H), 4.59 (m, 1 H), 4.47 (dd, *J* = 4.38, 12.12 Hz, 1 H), 2.34 (s, 3 H). ^{13}C NMR (150 MHz,$CDCl_3$): δ = 166.5, 166.1, 165.6, 165.4, 164.9, 143.5, 138.6, 133.9, 133.8, 133.5, 133.4, 133.3, 130.0, 129.9, 129.8, 129.5, 128.8, 128.7, 128.65, 128.6, 128.5, 127.0, 94.6, 71.8, 69.7, 68.9, 66.0, 62.5, 21.6. ESI-MS: *m/z* = 876.2 $[M + Na]^+$. HRMS: *m/z* calcd for $C_{48}H_{39}O_{12}NNaS$ $[M + Na]^+$: 876.2091; found: 876.2085.

(11) **Typical Procedure for the Glycosylation**
A solution of **2a** (100 mg, 0.12 mmol, 1.40 equiv) and **3a** (27 mg, 0.086 mmol) in anhyd CH_2Cl_2 (2 mL) was stirred for 30 min in the presence of freshly activated 5 Å MS (150 mg) under argon atmosphere. At this point, the mixture was cooled to 0 °C, then TMSOTf (1.50 μL, 0.0086 mmol, 0.1 equiv) was added. After the resulting mixture was stirred for another 2 h, Et_3N (1.20 μL, 0.0086 mmol, 0.1 equiv) was added to quench the reaction. The solid was filtered off, and the filtrate was concentrated under vacuum, the residue was applied to silica gel chromatography (EtOAc–PE = 1:9) to afford the disaccharide **4aa** (61 mg, 0.069 mmol, 80%). $[\alpha]_D^{22} = -104.5$ (*c* 0.32, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.22 Hz, 2 H), 8.07 (d, *J* = 8.28 Hz, 2 H), 8.00 (d, *J* = 8.28 Hz, 2 H), 7.89 (d, *J* = 7.74 Hz, 2 H), 7.59 (m, 2 H), 7.52 (t, *J* = 7.14 Hz, 1 H), 7.42 (m, 8 H), 7.27 (m, 2 H),

7.17 (d, *J* = 7.74 Hz, 2 H), 6.32 (t, *J* = 10.44 Hz, 1 H), 5.95 (dd, *J* = 3.30, 9.84 Hz, 1 H), 5.73 (s, 1 H), 5.69 (m, 1 H), 5.26 (s, 1 H), 4.75 (t, *J* = 12.66 Hz, 2 H), 4.49 (d, *J* = 11.04 Hz, 1 H), 4.37 (m, 2 H), 4.31 (m, 1 H), 3.61 (dd, *J* = 7.68, 9.36 Hz, 1 H), 2.35 (s, 3 H), 1.62 (s, 3 H), 1.39 (s, 3 H), 1.33 (d, *J* = 6.60 Hz, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.3, 165.8, 165.6, 165.5, 138.1, 133.5, 133.4, 132.7, 130.1, 129.9, 129.8, 129.4, 129.2, 128.7, 128.5, 128.4, 109.8, 98.4, 84.0, 82.2, 76.8, 76.7, 70.6, 70.2, 69.1, 66.6, 66.2, 62.3, 28.4, 26.7, 21.2, 17.4. ESI-MS: *m/z* = 911.8 $[M + Na]^+$. HRMS: *m/z* calcd for $C_{50}H_{48}O_{13}NaS$ $[M + Na]^+$: 911.2713; found: 911.2709.

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