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One-pot preparation and activation of glycosyl trichloroacetimidates: operationally simple glycosylation induced by combined use of solid-supported, reactivity-opposing reagents

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Abstract—By the combined use of solid-supported reactivity-opposing reagents, that is, basic PTBD and acidic Nafion®-SAC resins, sequential reactions consisting of glycosyl trichloroacetimidate formation and glycosylation can be effected in a one-pot operation starting from 1-*O*-unprotected sugars. The solid-supported reagents can be introduced into the reaction vessel either sequentially or, more conveniently, in a 'one-shot' manner in comparable yields.

Efficient methodology for the construction of glycosidic linkage plays an important role in the synthesis of biologically important carbohydrates. For this transformation, solid-supported reagents (SSRs) have recently received growing attention over soluble reagents since they allow operational simplicity and reduction of waste, as well as the safe handling of toxic, odorous, or explosive reagents.[1] Glycosylations with glycosyl sulfoxides,[2] glycosyl fluorides,[3] and glycosyl phosphite,[4] and also Fischer glycosylation[5] are representative of the methods promoted by SSRs so far reported. On the other hand, we have found, during the course of our synthetic studies of a bacterial lipopolysaccharide,[6] that glucosaminidyl trichloroacetimidate can be prepared by using basic Dowex 1-X8 resin (OH^- form) and can be activated with acidic Nafion®-TMS[7] resin (perfluorinated solid-supported sulfonic acid trimethylsilyl ester) to construct a glucosamine disaccharide, which is the essential structure for biological functions of the glycoconjugate. Inspired by this finding we undertook investigation of versatile SSRs that would allow efficient glycosylation mediated by glycosyl trichloroacetimidates, which is one of the most popular glycosyl donors.[8,9] In the present paper, we report our preliminary results regarding an efficient protocol for glycosylation catalyzed by Nafion®-H,[10] Nafion®-TMS, or Nafion®-SAC (a nanocomposite of Nafion® resin with porous silica)[11] with glycosyl trichloroacetimidates.[12] In combination with a solid-supported basic reagent that catalyzes the formation of imidates from 1-*O*-unprotected hexopyranoses, the one-pot reaction consisting of imidation and glycosylation became possible. The simultaneous presence of both cationic and anionic SSRs was proved not to interfere with the functions of each other as follows.

The glucose derivative **2** was used as a glycosyl acceptor. Glycosylation of **2** with glucosyl imidate **1** was at first examined by the action of three Nafion® reagents in CH_2Cl_2, Et_2O, CH_3CN, and CH_2Cl_2/C_6F_{14} (3:1) (Table 1). All reactions were carried out in the presence of molecular sieves 4 A at room temperature. After several experiments to explore the conditions that gave the disaccharide **3** in >50% yield using CH_2Cl_2 as a solvent, the required stoichiometry was determined to be 0.40 equiv for Nafion®-H (15 h, run 1), 0.13 equiv for Nafion®-TMS (15 h, run 5), and 0.036 equiv for Nafion®-SAC (1 h, run 9).[10] From these results, the reactivities are in the order of Nafion®-SAC ≫ Nafion®-TMS > Nafion®-H. With the corresponding soluble acidic catalyst, TMSOTf, the same reaction proceeds rapidly at a temperature even below −20 °C,[9] indicating that activation by the perfluorinated alkylsulfonic acid functionality on a solid support is apparently milder than that by soluble TMSOTf. We have also confirmed the reaction medium was neutral (pH 6–7) for all runs in

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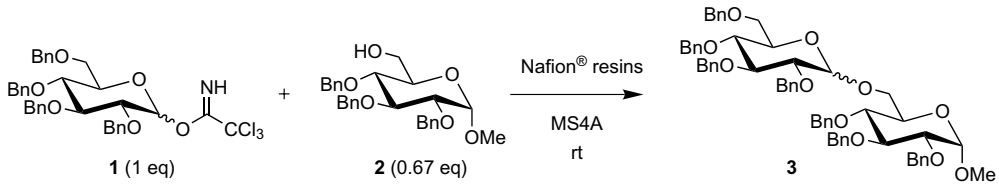
Table 1. Glycosylation of **2** by Trichloroacetimidate donor **1** with Nafion® resins[a]



Run	Nafion® resins/equiv	Solvent	Time (h)	Yield (%)[b]	Selectivity (α/β)[c]
1	Nafion®-H/0.40	CH_2Cl_2	15	61	1.5:1.0
2		Et_2O	15	77	1.4:1.0
3		CH_3CN	1.5	89	1.0:2.8
4		CH_2Cl_2/C_6F_{14} (3:1)	15	79	1.2:1.0
5	Nafion®-TMS/0.13	CH_2Cl_2	15	54	1.4:1.0
6		Et_2O	15	94	1.9:1.0
7		CH_3CN	72	88	1.0:2.6
8		CH_2Cl_2/C_6F_{14} (3:1)	15	82	1.2:1.0
9	Nafion®-SAC/0.036	CH_2Cl_2	1	84	1.2:1.0
10		Et_2O	1	90	1.3:1.0
11		CH_3CN	4	75	1.0:3.5
12		CH_2Cl_2/C_6F_{14} (3:1)	1.5	86	1.2:1.0

[a] All reactions were carried out with 70 mg (0.10 mmol) of **1**.
[b] Isolated yields based on the acceptor **2**.
[c] Determined from ^{1}H NMR spectra (270 MHz).

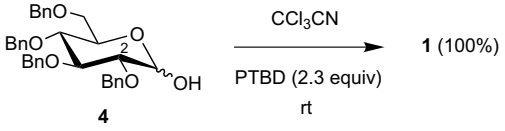
Table 1 as judged from pH indication paper, showing that the glycosylation is certainly promoted by the acidic functionality on the solid support.

Our attention next turned to the solvent effect on the glycosylation yield. Low yields were recorded when Nafion®-H or Nafion®-TMS was used in CH_2Cl_2 (runs 1 and 5) or toluene (<57% yield, data not shown), because resins are poorly swollen in these nonpolar solvents.[11] The yields were improved by using coordinative solvents, Et_2O or CH_3CN (runs 2, 3, 6, and 7). The most reactive Nafion®-SAC showed different tendencies; the disaccharide **3** was produced in good yield (84%) even in CH_2Cl_2 (run 9) and in moderate yield (75%) in CH_3CN (run 11). The lower yield is due to the inherent hygroscopicity of Nafion®-SAC, which rapidly hydrolyzes the imidate **1**. The hydrolysis competes seriously in CH_3CN wherein the rate for the glycosylation is slow. It should also be noted here that a positive effect of fluorophobicity[13] was observed for all Nafion® reagents; yields in a mixed solvent system of CH_2Cl_2–C_6F_{14} were generally higher than the reactions in CH_2Cl_2 alone (runs 1 vs 4, 5 vs 8, and 9 vs 12).

As for the stereoselectivity, glycosylation in CH_3CN (runs 3, 7, and 11) was β-predominant (α:β = 1.0:2.6–3.5) as usual, whereas only detectable α-selectivity was observed in other solvent systems such as CH_2Cl_2, Et_2O, and CH_2Cl_2/perfluorohexane. When the reaction with Nafion®-SAC was carried out in CH_3CN at −20 °C for 4 h, the β-selectivity increased to 1.0:13.3 in 66% yield (data not shown). This selectivity enhancement is comparable to the case where a soluble catalyst is used, suggesting the reaction proceeds via a kinetically favored α-nitrilium-nitrile-conjugate intermediate.[9]

Encouraged by these successful glycosylations with polymer-supported acids, we next attempted the preparation of the glucosyl imidate **1** from **4** by using solid-supported bases.[14] Among several reagents (Dowex 1-X8 OH^- form, *N*,*N*-(diisopropyl)aminomethylpolystyrene, and so on) examined, 2.3 equiv of polymer-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PTBD)[15] was found to be the most powerful to convert **4** into **1** in a quantitative yield (Scheme 1).[10] Though Dowex 1-X8 (OH^- form) is a good basic catalyst for imidation of a glucosamine derivative,[6] this is not the case for the 2-*O*-benzyl glucose **4**.

With this efficient imidation method in hand, the conditions for one-pot sequential reactions consisting of imidation and glycosylation by the action of basic PTBD and acidic Nafion® resins were explored. For Nafion® resins, the most reactive Nafion®-SAC was used. Because imidation does not smoothly proceed in Et_2O, which is an efficient solvent for Nafion®-mediated glycosylation as shown in Table 1, Et_2O was added to the reaction mixture at the subsequent glycosylation stage. A typical procedure is as follows. The hexopyranosyl donor precursor (**4**–**7**, 0.056 mmol, Fig. 1) was mixed with 5 equiv of CCl_3CN and basic PTBD in CH_2Cl_2 (0.6 mL) at room temperature for 2 h. After this imidation period, Nafion®-SAC, powdered molecular sieves 4 A (300 mg), and a solution of the glycosyl acceptor **2** (0.67 equiv) in Et_2O (0.9 mL) were introduced to the reaction mixture for glycosylation. After 15 h, all insoluble materials were filtered off, and the filtrate was



Scheme 1.

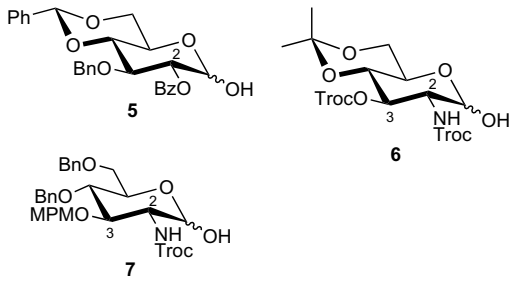


Figure 1. Donor precursors used in the one-pot glycosylations.

concentrated and the residue was purified by silica-gel chromatography.

Optimized results for one-pot reactions by sequential mixing of PTBD and Nafion®-SAC are summarized in Table 2. By the procedure, the disaccharide **3** was provided in good yield (86%, run 1). With Cs_2CO_3 instead of PTBD, the yield was poor (<70%, data not shown), probably because of the deactivation of Nafion®-SAC by the cesium cation. The glycosylation with the donor precursor **4** in run 1 was apparently α-selective, as observed in the stepwise reaction of **1** and **2** (Table 1).

This one-pot procedure was further applied to other donor precursors **5**–**7**. As can be seen from run 2 in Table 2, the 2-*O*-benzoyl donor precursor **5** gave a disaccharide in an excellent yield (93%). In contrast to the glucose derivatives **4** and **5**, for which excess amount of PTBD was practically required for complete imidation (data not shown), a lesser amount (0.67 equiv) of PTBD was found to be sufficient for imidation of glucosamine derivatives **6** and **7** (runs 3 and 4). The glycosylation of the imidate in situ formed from **6** provided a disaccharide in a moderate yield (70%, run 3). It is worthy of mention that the efficiency of Nafion®-SAC was shown again by the observation that the imidate derived from **6** was not activated by Nafion®-TMS at all. When the electron-withdrawing 3-*O*-Troc group of **6** was replaced with an electron-donating MPM group, glycosylation proceeded smoothly to give a disaccharide in 79% yield (run 4). The effect of protecting groups on glycosylation agrees well with precedent reports.[16,17] As for the stereoselectivity, all reactions were completely β-selective (runs 2–4) for donor precursors **5**–**7** bearing participating groups at the neighboring C2-position.

The one-pot procedure was extended to the glycosylation by 'one-shot mixing' of all reactants and reagents to achieve higher operational simplicity (Table 3). The reactions were effected by the concurrent introduction of PTBD and Nafion®-SAC to the mixture of the donor precursor (**4**–**7**), the glycosyl acceptor **2**, CCl_3CN, and molecular sieves 4 A in CH_2Cl_2 without Et_2O. At first, glycosylation was attempted with the donor precursor **4** (run 1). In this case, the stereoselectivity decreased (α:β = 1.2:1.0) as compared to that observed in the above sequential mixing procedure (run 1, Table 2) because of the absence of Et_2O. The yield for the disaccharide (56%) was also lower because of the undesired imidation of the acceptor **2**. This competitive imidation became a serious side process owing to the low reactivity of the 1-hydroxy group of **4** toward imidation. By contrast, with the more reactive 2-*O*-benzoyl donor precursor **5**, undesirable imidation of **2** was suppressed relatively and the disaccharide was obtained in 83% yield (run 2). The glycosylation yield with the disarmed[16] glucosamine donor derived from **6** (run 3) was comparable to that by the sequential mixing procedure (run 3, Table 2). Coupling of the glucosamine derivative **7** with **2** in the 'one-shot mixing' procedure also proceeded satisfactorily in a high yield of 89% (run 4), which was even higher than that of the same coupling with the sequential mixing procedure (run 4, Table 2). This is the most successful demonstration for 'one-shot mixing' glycosylation where the formation and the activation of the trichloroacetimidate proceed smoothly without suffering interference by undesirable side reactions.

Fischer direct glycosylation[5] of **2** with **4** was sluggish even with a large amount of Nafion®-SAC (0.21 equiv), and less than 50% of disaccharide **3** was formed after 15 h in various solvents (data not shown). This fact indicates that the one-pot reaction by the 'one-shot-mixing' procedure proceeds via the in situ-formed

Table 2. Trichloroacetimidation followed by glycosylation in one-pot by sequential addition of PTBD and Nafion®-SAC[a]

glycosyl donor precursor **4-7** (1.0 equiv) → 1) CCl_3CN (5 equiv), PTBD, CH_2Cl_2, rt, 2 h; 2) **2** (0.67 equiv), Nafion®-SAC, MS4A, Et_2O, rt, 15 h → disaccharides

Run	Donor precursor	PTBD (equiv)	Nafion®-SAC (equiv)	Yield (%)[b]	Selectivity (α/β)[c]
1	**4**	1.4	0.036	86	2.1:1.0
2	**5**	1.5	0.021	93	0:1.0
3	**6**	0.67	0.039	70	0:1.0
4	**7**	0.67	0.054	79	0:1.0

[a] For experimental procedures, see text.
[b] Isolated yields based on the acceptor **2**.
[c] Determined from ^{1}H NMR spectra (270 MHz).

Table 3. Trichloroacetimidation followed by glycosylation in one-pot by 'one-shot' addition of PTBD and Nafion®-SAC[a]

glycosyl donor precursor **4-7** (1.0 equiv) → **2** (0.67 equiv), CCl_3CN (5 equiv), PTBD, Nafion®-SAC, MS4A, CH_2Cl_2, rt, 15 h → disaccharides

Run	Donor precursor	PTBD (equiv)	Nafion®-SAC (equiv)	Yield (%)[b]	Selectivity (α/β)[c]
1	**4**	1.3	0.036	56	1.2:1.0
2	**5**	1.1	0.018	83	0:1.0
3	**6**	0.67	0.054	71	0:1.0
4	**7**	0.87	0.023	89	0:1.0

[a] All reactions were carried out with 0.056 mmol of a glycosyl donor.
[b] Isolated yields based on the acceptor **2**.
[c] Determined from ^{1}H NMR spectra (270 MHz).

glycosyl imidate intermediates as expected. In all runs, trehalose-type dimeric products, which are often observed as undesirable side products in Fischer and other dehydrative glycosylations,[18] were not detected at all. This is another merit of the present glycosylation procedure starting from 1-*O*-unprotected sugars.

This work provides a new simple one-pot procedure for imidate-mediated glycosylation starting from reducing sugars as sources of glycosyl donors. The procedure is based on the characteristic of SSRs, which do not interact or interfere with each other's functions.[19] Thus, in the stepwise protocol the basic reagent, PTBD, which catalyzes the formation of the imidates, does not need to be removed prior to glycosylation. PTBD did not inhibit the function of the acidic Nafion®-SAC added to the mixture and the desired glycosides were formed in satisfactory yields.

The same glycosylation was effected by a more convenient, complete one-pot procedure where all the reaction partners were mixed in 'one-shot': the same series of reactions occurred as in the stepwise protocol and the desired glycosides were formed in fair to good yields. In some cases, the yields were not satisfactory because of undesired imidation of the acceptor and/or decomposition of the imidates in the presence of acidic and hygroscopic Nafion®-SAC. But in other cases, an even higher yield was obtained than that with the corresponding stepwise protocol. Since we have already found the 'one-shot mixing' procedure is also effective for the construction of 1,4-glycosides,[20] this technology is expected to become a practical choice for synthetic glycochemistry.

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