Synthesis of α-*C*-Glycosides by Samarium Diiodide Mediated Coupling of Glycosyl Pyridyl Sulfones with Alkenes

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Abstract: A mild method for the synthesis of α-*C*-glycosides by the samarium diiodide mediated coupling reactions of glycosyl 2-pyridyl sulfones with different α,β-unsaturated carbonyl compounds has been developed. This method allows the use of less amount of substrates.

Key words: *C*-glycosides, samarium diiodide, glycosyl 2-pyridyl sulfones, coupling reaction

C-Glycosides as stabilized isosteres of *O*-glycosides play an important role in pharmaceutical or biological research. They exist in some biologically active natural products, and they have also been used as useful chiral building blocks for the synthesis of complex molecules.[1] Toward the synthesis of *C*-glycosides, a variety of synthetic methods have been developed.[2] Among the *C*-glycosides, the *C*-alkyl glycosides are very important, and their synthesis has drawn much attention in recent years. For instance, the preparation of *C*-alkyl glycosides was achieved by the coupling of glycosyl donors with nucleophiles[3] or the Ni-catalyzed Negishi cross-coupling reaction.[4] In particular, radical chemistry was used for the formation of *C*-alkyl glycosides by the coupling of glycosyl anomeric carbons and alkenes,[5] but usually a significant excess (6–20 equiv) of alkenes was needed. Very recently, the Gagné group developed efficient methods for the synthesis of *C*-alkyl glycosides by the reductive coupling of glycosyl bromides with 2 equivalents of alkenes.[6] Although the methods were well-behaved for acetate- or benzoate-protected glycosyl bromides, they were not well-applied to the benzyl-protected glycosyl halide substrates.

In order to overcome some shortages of coupling reactions of glycosyl anomeric radicals with alkenes, we postulated that SmI_2 would be competent for it. Since SmI_2 was pioneered by Kagan, it has become one of the most important reagents in organic chemistry.[7] SmI_2 is commercially available and easy to handle. In fact, this reagent has been employed for the stereoselective synthesis of *C*-glycosides.[8] In the SmI_2-mediated synthesis of *C*-glycosides, more reactive glycosyl 2-pyridyl sulfones were used. The glycosyl anomeric radical induced by SmI_2 could be further reduced by SmI_2 to form glycosyl anomeric samarium(III) species, which would couple with carbonyl substrates to afford 1,2-*trans*-*C*-glycosides under Barbier conditions, that is to say, to obtain α-*C*-glycosides, the C2-substituents have to be axially oriented just like in the mannopyranoside case. Moreover, a few examples have shown that the anomeric radical induced by SmI_2 can be trapped by the intramolecular alkene or alkyne to produce α-*C*-glycosides.[9] Although the reactions of glycosyl anomeric samarium(III) with carbonyl substrates have been successfully realized, and some examples of intramolecular anomeric radical addition to alkenes have been reported, the SmI_2-mediated intermolecular coupling reaction of glycosyl pyridyl sulfones with alkenes for the synthesis of α-*C*-glycosides has never been disclosed.

In this work, we tried to prepare α-*C*-glycosides by the SmI_2-induced reductive coupling of glycosyl 2-pyridyl sulfones with α,β-unsaturated esters, amides, and acids. It seemed to be difficult, because glycosyl anomeric radical could dimerize and also abstract a hydrogen atom from the solvent. Meanwhile, anomeric radicals could be reduced by SmI_2 to form glycosyl anomeric samarium(III) which would tend to elimination.[10] Moreover, α,β-unsaturated esters, amides, and acids could probably be reduced by SmI_2.[11] In spite of these difficulties, we decided to tackle this problem. First, the coupling of glucosyl 2-pyridyl sulfone **1** with 1.2 equivalents of methyl acrylate was induced by 0.1 M SmI_2 in THF at room temperature under Barbier conditions (Table 1). The α-*C*-glycoside **2** was isolated in only 10% yield when SmI_2 in THF was added dropwise in less than 10 s (Table 1, entry 1), 1-deoxy-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose and glucal were produced as the major byproducts. However, the *C*-glycoside **2** was obtained in 26% yield when SmI_2 was added at a speed of 1.5 mL/h by a syringe pump (Table 1, entry 2), meaning that it is favorable for the reaction when the addition of SmI_2 is slow enough. To improve the reductive ability of SmI_2, HMPA[9a,10,12] as a generally utilized co-solvent was used, encouragingly leading to an increased yield (34%) of the desired *C*-glucoside product **2** (Table 1, entry 3). In an effort to avoid the use of toxic HMPA, when a catalytic amount of NiI_2[8e,13] (1%) was added instead of HMPA, compound **2** was obtained in 39% yield (Table 1, entry 4). Since proton sources have a considerable impact on the efficiency of SmI_2-mediated reactions,[14] several proton sources were tested for the re-

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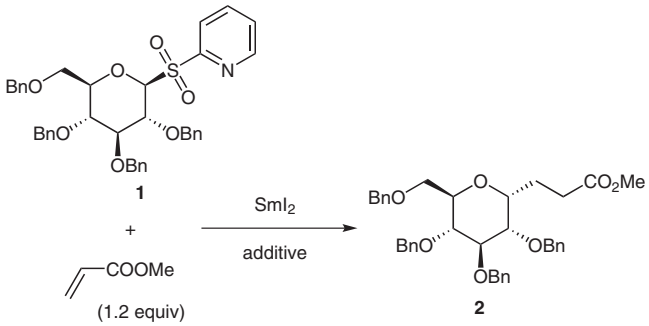
Table 1 Optimization of the Coupling Reaction of Glucosyl 2-Pyridyl Sulfone with Methyl Acrylate[a]



Entry	Additive	Product **2** (%)[b]
1	–	10[c]
2	–	26
3	HMPA (5 mol%)	34
4	NiI_2 (1 mol%)	39
5	NiI_2 (1 mol%), H_2O (2 equiv)	52
6	NiI_2 (1 mol%), MeOH (2 equiv)	55
7	NiI_2 (1 mol%), *n*-PrOH (2 equiv)	71
8	NiI_2 (1 mol%), *t*-BuOH (2 equiv)	80
9	NiI_2 (1 mol%), *i*-PrOH (2 equiv)	84
10	NiI_2 (1 mol%), *i*-PrOH (4 equiv)	84

[a] 0.1 M solution of SmI_2 was added at a speed of 1.5 mL/h by a syringe pump.
[b] Isolated yield.
[c] 0.1 M solution of SmI_2 was added in less than 10 s.

action. Fortunately, the yield of **2** was increased significantly when two equivalents of H_2O were added (Table 1, entry 5, 52%). Other solvents such as MeOH, *n*-PrOH, and *t*-BuOH also worked well and product **2** was afforded in 80% yield when two equivalents of *t*-BuOH were used (Table 1, entry 8). Interestingly, *i*-PrOH proved to be most effective, the *C*-glycoside **2** was generated in 84% yield after the addition of two equivalents of *i*-PrOH (Table 1, entry 9). The addition of more *i*-PrOH did not improve the yield (Table 1, entry 10).

Under the optimized reaction conditions, the scope of alkene substrates was examined (Table 2). The coupling reaction with acrylate derivatives such as *tert*-butyl acrylate produced the desired product **3** in good yield (Table 2, entry 1). The α,β-unsaturated amides such as acrylamide, *N*-phenylacrylamide, and 2-acrylamidoacetate reacted with glucosyl 2-pyridyl sulfone **1** under the same conditions to give the corresponding products in good or moderate yields (Table 2, entries 2–4). As anticipated, 1-(vinylsulfonyl)benzene worked well, the coupling product **8** was obtained in 62% yield, and no sulfone reduction product was isolated (Table 2, entry 6). Glycosyl propionic acids are useful synthetic intermediates, and the hydroboration–oxidation or Jones' oxidation of *C*-allyl glycosides are common approaches to produce glycosyl propionic acids.[15] The synthesis of glycosyl propionic acids from glycosyl halides was reported by Somsák's group,[16] who used a significant excess (18 equiv) of acrylic acid producing the glycosyl propionic acid in 52% yield. In our approach, the glycosyl propionic acid **7** was obtained in 47% yield when only 1.2 equivalents of acrylic acid were used (Table 2, entry 5). The optimized conditions were also applied to disubstituted alkenes.

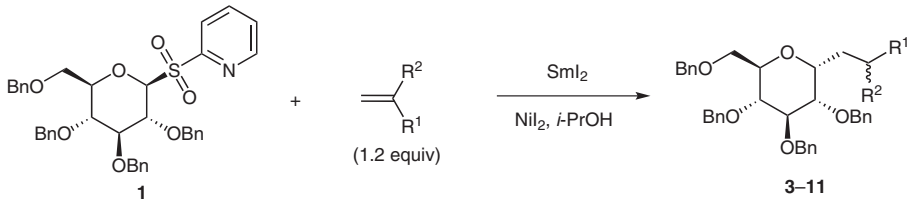
As can be seen, the coupling reaction of **1** and methyl methacrylate afforded α-*C*-glucoside **9** in 91% yield (Table 2, entry 7, dr = 3.2:1). 2-Acetamidoacrylate and methacrylamide also underwent the reaction successfully to gain **10** and **11** in 59% (dr = 1.3:1) and 68% (dr = 2.5:1) yields, respectively (Table 2, entries 8 and 9).

In addition to glucosyl 2-pyridyl sulfone **1**, the SmI_2-mediated reaction was extended to the coupling of galactosyl and mannosyl 2-pyridyl sulfones with methyl acrylate (Table 3). As shown, the α-*C*-glycosides were smoothly isolated in 74% and 65% yields, respectively (Table 3, entries 1 and 2). Glycosyl halides are usually used to produce anomeric radicals for the preparation of *C*-glycosides. However, when 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranosyl bromide was used, no coupling product (only oxazoline side-product) was achieved.[17] Gallagher's group[18] developed a method for the synthesis of *C*-2-amino-2-deoxyglycosides by using anomeric selenides as radical precursors, but toxic Bu_3SnH was needed. In our approach, when *N*-acetyl-glucosyl 2-pyridyl sulfone was used, the desired α-coupling product **14** was gained in 55% isolated yield when four equivalents of methyl acrylate were employed.

The anomeric configuration of the coupling product was determined by ^1H NMR analysis. The coupling constant $J_{1,2}$ = 5.6–6.0 Hz indicates that the anomeric configuration of *C*-glucosides is α type. For example, the stereochemsitry of *C*-glycosides **4**–**6**, which adopt a $^4C_1$ conformation, was established by their ^1H NMR spectra: for compound **4**, H(2) δ = 3.72 (dd, $^3J_{2,3}$ = 9.2 Hz, $^3J_{1,2}$ = 5.6 Hz); for compound **5**, H(2) δ = 3.74 (dd, $^3J_{2,3}$ = 9.6 Hz, $^3J_{1,2}$ = 5.6 Hz); for compound **6**, H(2) δ = 3.75 (dd, $^3J_{2,3}$ = 9.2 Hz, $^3J_{1,2}$ = 5.6 Hz). In order to further confirm the anomeric configuration, the *C*-glycoside **12** was deprotected by hydrogenolysis which was followed by acetylation to yield the product **15** (Scheme 1, a), its spectroscopic data coincide with those described in the literature.[19] The protective groups of *C*-glycoside **14** were also manipulated to form compound **16** (Scheme 1, b). For *C*-glycoside **16**, the α-configuration of the predominant $^4C_1$ conformation was again assigned by using ^1H NMR analysis: H(2) δ = 4.28 (td, $^3J_{2,NH}$ = 8.4 Hz, $^3J_{2,3}$ = 8.0 Hz, $^3J_{1,2}$ = 3.6 Hz). Using our method, only α-*C*-glycosides were provided, and β-isomers were not detected by the ^1H NMR analysis of the crude mixtures. Our results are different from the previous reports.[8a–g] In the previous approach, 1,2-*trans*-*C*-glycosides were obtained by the coupling reaction of glycosyl 2-pyridyl sulfones with alkyl ketones and aldehydes. That is because the C1

radicals were reduced by SmI_2 to produce glycosyl samariums that could be trapped with alkyl ketones and aldehydes, affording 1,2-*trans*-*C*-glycosides.[4a] In our procedure, the thermodynamically stable α-glycosyl radicals were trapped with alkenes to result in α-*C*-glycosides.[20]

Table 2 Coupling Reactions of Alkenes with Glucosyl 2-Pyridyl Sulfone[a]



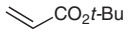
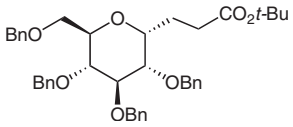
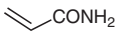
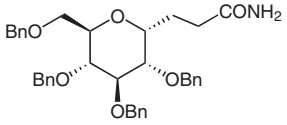
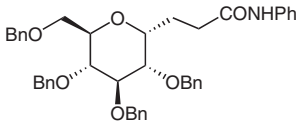
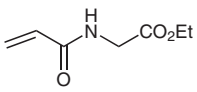
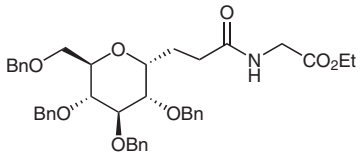
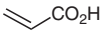
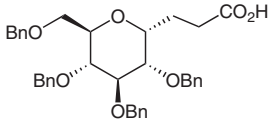
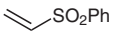
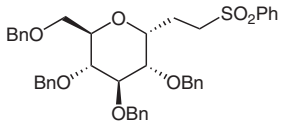
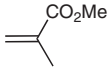
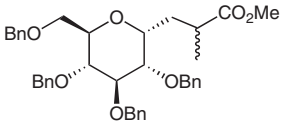
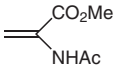
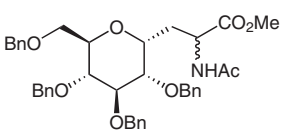
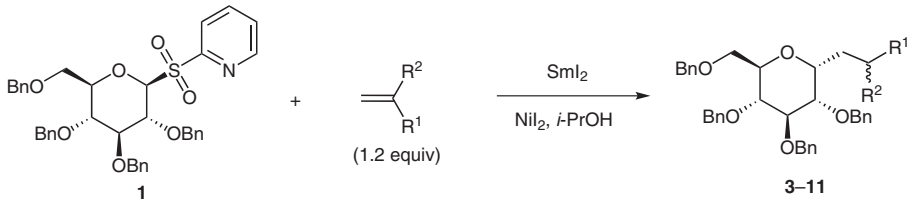
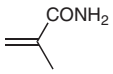
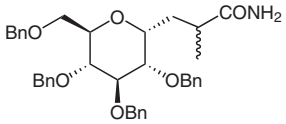
Entry	Alkene	Product	Yield (%, dr)[b,c]
1		 **3**	80
2		 **4**	80
3		 **5**	67
4		 **6**	51
5		 **7**	47
6		 **8**	62
7		 **9**	91 (3.2:1)
8		 **10**	59 (1.3:1)

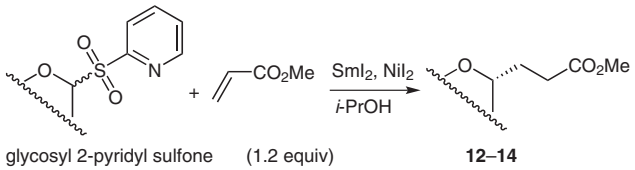
Table 2 Coupling Reactions of Alkenes with Glucosyl 2-Pyridyl Sulfone[a] (continued)

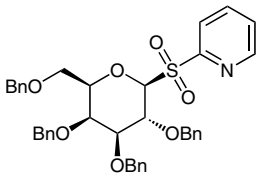
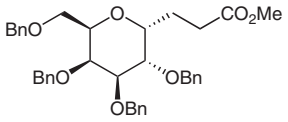
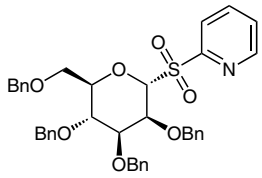
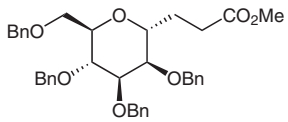
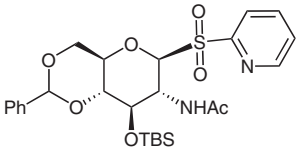
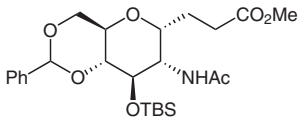


Entry	Alkene	Product	Yield (%, dr)[b,c]
9		 **11**	68 (2.5:1)

[a] Reaction conditions: NiI_2 (1 mol%), *i*-PrOH (2.0 equiv), SmI_2 (0.1 M in THF, 2.0–5.0 equiv), r.t., 0.7–1.7 h.
[b] Isolated yield.
[c] An inseparable mixture of diastereomers was observed, the dr value was determined by NMR.

Table 3 Coupling Reactions of Glycosyl 2-Pyridyl Sulfones with Methyl Acrylate[a]

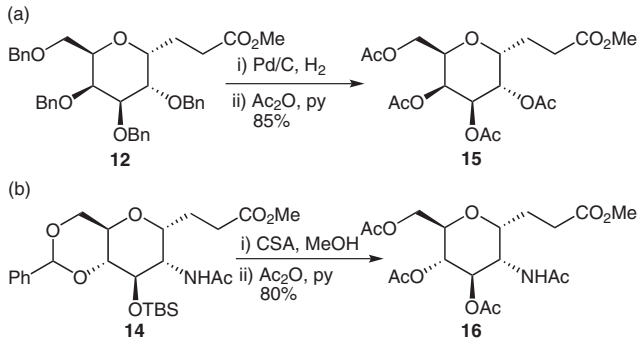


Entry	Glycosyl 2-pyridyl sulfone	Product	Yield (%)[b]
1		 **12**	74
2		 **13**	65
3		 **14**	55[c]

[a] Reaction conditions: NiI_2 (1 mol%), *i*-PrOH (2.0 equiv), SmI_2 (0.1 M in THF, 2.0–5.0 equiv), r.t., 0.7–1.7 h.
[b] Isolated yield.
[c] Methyl acrylate (4 equiv) was used.

In summary, we have developed a mild method for the synthesis of α-*C*-glycosides by the SmI_2-mediated coupling of glycosyl 2-pyridyl sulfones with α,β-unsaturated esters, amides, and acids. This approach enjoys the use of low amounts of alkene substrates. The yields of *C*-glycosides can be significantly improved by the use of *i*-PrOH as a proton source. This method can be also applied to the preparation of α-*C*-*N*-acetyl-2-amino-2-deoxyglucosides.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.



Scheme 1 The protective group manipulations of *C*-glycosides **12** and **14**

Acknowledgment

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