ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

# Reagent Controlled $\beta$-Specific Dehydrative Glycosylation Reactions with 2-Deoxy-Sugars

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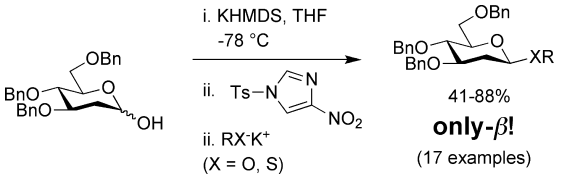
**Received July 2, 2013**

## ABSTRACT




***N*-Sulfonyl imidazoles activate 2-deoxy-sugar hemiacetals for glycosylation presumably by converting them into glycosyl sulfonates in situ. By matching the leaving group ability of the sulfonate with the reactivity of the donor, it is possible to obtain $\beta$-specific glycosylation reactions. The reaction serves as proof of the principle that, by choosing promoters that can modulate the reactivity of active intermediates, it is possible to place glycosylation reactions entirely under reagent control.**

Despite numerous advances over the past several years, the synthesis of stereodefined oligosaccharides remains a nontrivial operation.[1] This is due in large part to the fact that most methods for diastereoselective chemical glycosylation rely on substrate control.[2] In cases where neighboring group participation or conformational locking cannot be used to control selectivity, extensive optimization of both the donor and acceptor is often necessary to obtain a "matched" coupling pair.[3] This is especially true when trying to synthesize "difficult" glycosidic linkages, such as $\beta$-linked 2-deoxy-sugars. In principle, these challenges could be circumvented if the stereoselectivity of the reaction was placed under reagent control, where the stereochemical outcome of the glycosylation reaction is dictated entirely by the promoter. Here, we describe such an approach for the stereospecific construction of $\beta$-linked 2-deoxy-sugars (as opposed to stereoselective construction, which still affords diastereomeric mixtures).

$\beta$-Linked 2-deoxy-sugars play an important role in modulating the biological activity of many natural products, such as landomycin,[4] mithramycin,[5] and digitoxin.[6] This has led to the realization that it is possible to dramatically alter the pharmacokinetics of a natural product through changing the composition of its glycosides.[7] A significant hurdle to the broader application of this technology to drug discovery is the fact that $\beta$-linked 2-deoxy-sugars are generally considered to be one of the most difficult glycosidic bonds to synthesize.[8,9] A number of methods for the direct synthesis

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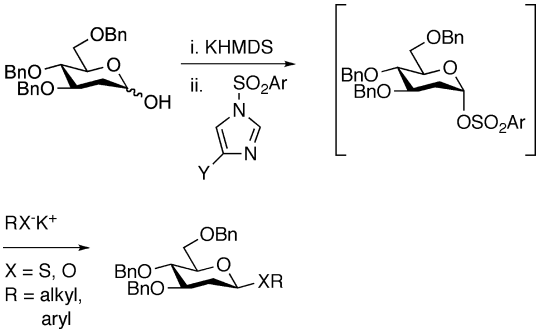
10.1021/ol4018547 

of various 2-deoxy-sugars have been described.[10] However, with the exception of Gervay-Hague's glycosyl iodides and Zhu's umpolung approach,[10d,f] little attempt has been made to elucidate the origins of the stereoselectivity in these reactions. In addition, this selectivity does not always translate well between different systems,[11] and many activated 2-deoxy-sugars are extremely unstable, requiring specialized media for their purification.[10e] As a result, many groups have developed indirect approaches to the construction of 2-deoxy-sugars through the use of either temporary directing groups[12] or de novo synthesis.[13] These latter approaches necessarily introduce additional steps, decreasing the overall efficiency of the synthesis.

As part of an ongoing program aimed at developing selective methods for 2-deoxy-sugar synthesis,[14] we chose to examine the in situ generation of different glycosyl sulfonates for $\beta$-selective glycosylations. While glycosyl triflates can undergo $S_N2$-like reactions to afford $\beta$-linked products with certain substrates,[15] Crich has shown that 2-deoxy glycosyl triflates are generally very unstable.[16] Furthermore, Woerpel has demonstrated that, even in examples where 2-deoxy-sugar triflates are not subject to decomposition, they only undergo $\beta$-selective reactions when strong carbon nucleophiles are employed as acceptors.[17] In principle, a more stable sulfonate should possess greater covalent character, permitting direct $S_N2$ displacement to afford the product as a single diastereomer. While the reactivity of different sulfonates has been reported to span several orders of magnitude,[18] little work has been done on glycosyl sulfonates other than triflates since the seminal studies of the Schuerch and Koto groups over three decades ago.[19] This is due to the fact that many of these procedures required the isolation of highly unstable species. Additionally, those procedures for in situ generation of sulfonates often led to nonselective reactions. The lack of selectivity is presumably due to the presence of several other nucleophilic ions in solution, which could scramble the stereochemistry of the anomeric leaving group.[20]

**Scheme 1.** *N*-Sulfonylimidazoles for $\beta$-Selective Glycosylations




To address these issues we chose to examine the use of *N*-sulfonyl imidazoles as reagents for converting hemiacetals into glycosyl sulfonates in situ (Scheme 1). These species have been shown to promote sulfonate ester formation[21] and nucleotide coupling[22] without the generation of nucleophilic byproducts. Importantly, the synthesis of *N*-sulfonyl imidazoles is trivial,[23] which would permit the rapid synthesis of a large library of compounds to tune reactivity.

Our initial investigations focused on thiol nucleophiles owing to both their increased reactivity and the fact that thioglycoside linkages are useful, nonhydrolyzable carbohydrate mimetics.[24] To this end, deprotonation of **1** with KHMDS in THF at low temperature[25] was followed first by addition of *N*-tosylimidazole (TsIm) and then the nucleophile. The selectivity in the reaction was dependent on the amount of time **1** was allowed to react with the TsIm (Table 1, entries 1−3). Longer reaction times generally led to higher

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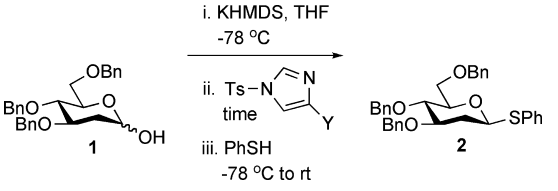
selectivity. We attribute the change in selectivity to the rapid formation of a mixture of glycosyl tosylates followed by equilibration to the more stable α-anomer. In order to improve the yield of the reaction, we next examined the more reactive leaving group found in tosyl 4-nitroimidazole ($TsImNO_2$). Not only did this reagent improve the yield of the reaction, but we observed a dramatic increase in selectivity from 5:1 $\beta$:α to all $\beta$ (Table 1, entry 4). Finally, the use of a slight excess of the activated donor led to a further increase in yield without compromising selectivity (88%, $\beta$ only, Table 1, entry 5).

**Table 1.** Reaction Optimization with Sulfur Nucleophiles




| entry | PhSH (equiv) | Y | time (min) | yield (%) | α:$\beta$ |
|---|---|---|---|---|---|
| 1 | 1 | H | 0 | 40 | 1:1 |
| 2 | 1 | H | 30 | 40 | 1:2 |
| 3 | 1 | H | 65 | 40 | 1:5 |
| 4 | 1 | $NO_2$ | 60 | 62 | $\beta$ only |
| **5** | **0.67** | **$NO_2$** | **60** | **88** | ***β* only** |
| 6[a] | 0.67 | $NO_2$ | 60 | 77 | $\beta$ only |

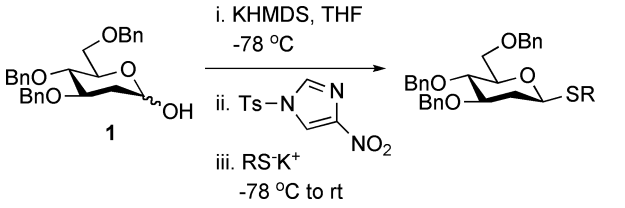
[a] An equivalent of potassium imidazolide was added to the reaction.

To determine if the lower selectivity observed with TsIm was due to the presence of imidazole interfering with the reaction, we repeated the reaction using $TsImNO_2$ in the presence of an equivalent of potassium imidazolide (Table 1, entry 6). No change in selectivity was observed, indicating that imidazole was only acting as a leaving group. While the origins of the change in selectivity are unclear at this point, we attribute the lower selectivity with TsIm to incomplete conversion of the donor to the glycosyl sulfonate prior to the addition of the acceptor. If the acceptor is present before the sulfonate can equilibrate to the more stable α configuration,[19] $\beta$-sulfonates will be present and react to reduce selectivity.

The scope of the reaction was next examined with several thiol acceptors (Table 2).[24e] For aliphatic thiol acceptors we found it necessary to use the potassium salt to obtain useful yields. Yields were generally moderate-to-good, with the secondary galactose derived thiol **4** providing the highest yield. In the case of primary thiol **6** the reaction was accompanied by significant amounts of disulfide bond formation, despite efforts to rigorously exclude oxygen from the reaction. In every single case, however, the reaction provided the product as a single $\beta$-anomer, as determined by $^1$H NMR.

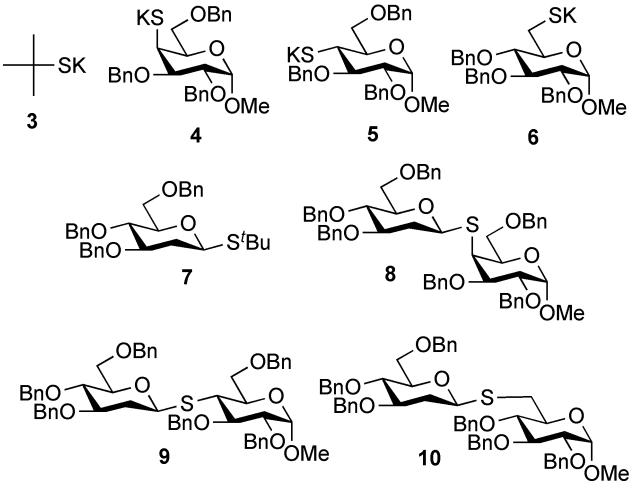
Having established that the reaction was effective with thiolates, we turned our attention to phenoxide nucleophiles,

**Table 2.** Scope with Thiol Acceptors




| entry | $RS^-K^+$ | product | yield (%) | α:$\beta$ |
|---|---|---|---|---|
| 1 | **3** | **7** | 41 | $\beta$ only |
| 2 | **4** | **8** | 80 | $\beta$ only |
| 3 | **5** | **9** | 45 | $\beta$ only |
| 4 | **6** | **10** | 50 | $\beta$ only |

**Acceptors and Products**

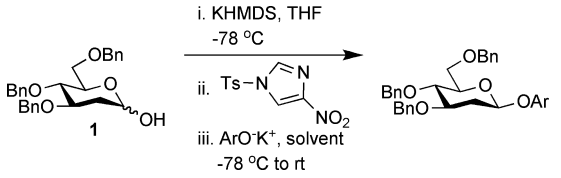



since aryloxy glycosides are important structural motifs in many natural products.[7] The reaction of **1** with $TsImNO_2$, followed by the addition of the potassium salt of 2-naphthol (prepared by treating the acceptor with KHMDS), provided the desired product as a single anomer as determined by $^1$H NMR (Table 3, entry 1).[26] Rationalizing that a solvent which could better coordinate the counterion could provide the product in enhanced yield, we next examined the use of diglyme as an additive. Pleasingly, this led to an increase in the yield, affording the product in 76% yield as a single $\beta$-anomer (Table 3, entry 2). Under these conditions we did not observe any glycal formation, indicating that elimination of the active leaving group was not a competitive pathway. Other phenolic acceptors reacted in moderate-to-good yield, with electron-rich phenols providing the best yields.

We next turned our attention to the more reactive 2,6-dideoxy-L-arabino hexopyranose donor **11** (Table 4). Again no glycal formation was observed. Interestingly, electron-rich phenols were less effective than electron-poor phenols with this substrate, representing a reversal of the trend observed in Table 3. While we can attribute the lower

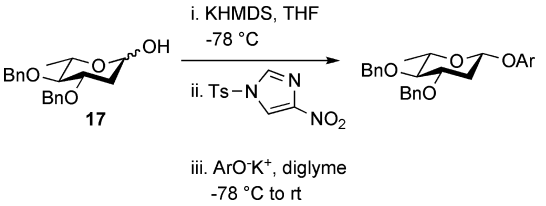
(26) No reaction was observed with neutral acceptors.

**Table 3.** Scope with Aryloxy Acceptors




| entry | $ArO^-K^+$ | solvent | product | yield (%) | α:β |
|---|---|---|---|---|---|
| 1 | 2-naphthol | THF | **11** | 43 | β only |
| 2 | 2-naphthol | diglyme | **11** | 76 | β only |
| 3 | 1-naphthol | diglyme | **12** | 70 | β only |
| 4 | PhOK | diglyme | **13** | 67 | β only |
| 5 | *o*-cresol | diglyme | **14** | 62 | β only |
| 6 | *p*-MeO-PhOK | diglyme | **15** | 74 | β only |
| 7 | *p*-$CF_3$-PhOK | diglyme | **16** | 45 | β only |

**Table 4.** Reactions with 2,6-Dideoxy-donors




| entry | $ArO^-K^+$ | product | yield (%) | α:β |
|---|---|---|---|---|
| 1 | 2-naphthol | **18** | 41 | β only |
| 2 | 1-naphthol | **19** | 53 | β only |
| 3 | PhOK | **20** | 73 | β only |
| 4 | *o*-cresol | **21** | 56 | β only |
| 5 | *p*-MeO-PhOK | **22** | 63 | β only |
| 6 | *p*-$CF_3$-PhOK | **23** | 71 | β only |

yields to be due in part to the decreased stability of the 2,6-dideoxy-sugar products, the origin of this reversal in reactivity trend is unclear at this point. Importantly however, the reactions again afforded the products exclusively as β-anomers, despite the fact that the absolute configuration of the donor had been switched from D- to L-. These observations support our hypothesis that that the $TsImNO_2$ activates the hemiacetal donors as α-glycosyl tosylates, which react through an $S_N2$-like manifold to afford β-linked products.

In conclusion, we have found that treating 2-deoxy-sugar hemiacetals with $TsImNO_2$ results in the *in situ* formation of a species that reacts with S- and O-nucleophiles to form glycoside products exclusively as β-anomers. The reaction presumably proceeds through the formation of a glycosyl tosylate, which reacts through an $S_N2$ or $S_N2$-like manifold. This is supported by the fact that no α-anomer was observed with either D- or L-sugar donors. These studies provide proof of the principle that it is possible to obtain stereospecific glycosylation reactions by matching sulfonate leaving group ability with the intrinsic reactivity of the glycosyl donor. Taken together with our cyclopropenium cation promoted α-selective glycosylation methodology,[14] these studies also demonstrate that it is possible to obtain either anomer of a glycoside starting from the same donor, simply by placing the reaction under reagent control. While it is unlikely that the tosylate leaving group will be effective with all classes of glycosyl donors (such as mannose, rhamnose, etc.), the range of reactivities of different sulfonates is such that it should be possible to match each class of donor to a proper leaving group for β-specific glycosylation reactions. Studies aimed at doing this and confirming our proposed reaction mechanism are currently under investigation in our laboratory.

**Acknowledgment.** We thank the National Science Foundation (NSF 1300334) and Tufts University for supporting this work.

**Supporting Information Available.** Experimental details and $^1H$ and $^{13}C$ NMR, and additional characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest