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A practical method for preparation of β-glycosides of *N*-acetylglucosamine

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Abstract—A mild and efficient method for preparation of GlcNAc derivatives by reaction of glycosyl acceptors with glycosyl oxazolines has been developed. The key feature is use of $Yb(OTf)_3$ as promoter, requiring moderate reaction times and equivalence stoichiometry. We anticipate application in the preparation of a wide range of derivatives of this biologically important class of building blocks.

The 2-acetamido-2-deoxy-D-glucose moiety (GlcNAc) is found in a wide variety of biologically significant structures, including glycoproteins and lipids.[1] Accordingly, methodology for the efficient preparation of GlcNAc derivatives remains an important component of contemporary carbohydrate chemistry.[2] A seemingly attractive route involves reaction of *O*,*N*-acetyl protected glucosamines with donor nucleophiles, which (proceeding via an oxazolinium intermediate) gives mixtures of desired conjugate and varying amounts of oxazoline (e.g., **1**).[3] Means to minimize formation of oxazoline byproduct have been investigated but typically require substitution of the *N*-acetyl group for other moieties, limiting the usefulness of the process given the biological significance of GlcNAc derivatives.[4] As the oxazolines themselves are readily prepared from corresponding glucosamine hydrochlorides (Ac_2O, Py then TMSOTf) a more reliable route involves direct coupling of oxazoline with desired donor group in the presence of activators.[5] However, typical conditions often require elevated temperatures and unfavorable stoichiometries, the latter compounding purification of product by conventional means. Due to an interest in the preparation of glycosylated enediyne metabolites for screening as sequence specific DNA binders, we required an effective and reliable route for preparation of GlcNAc derivatives, and sought to develop a mild and efficient coupling strategy.

Stimulated by reports of metal halide mediated glycosylation procedures, [6] we were further guided by reports from the Danishefsky laboratories on the activating effects of lanthanide triflates for manipulating carbohydrate anomers.[7] Our reasoning was that lanthanide chelation to the oxazoline would result in anchimeric activation to suitable alkanol acceptor species. After consideration of various combinations of lanthanide halides and acid catalysts, economic analysis pointed to use of $Yb(OTf)_3$.[8] Using **1** with cyclohexanol and benzyl alcohol as test substrates, a variety of conditions were probed. In the absence of catalyst no coupled products were formed even after several days whereas with 5 mol% $Yb(OTf)_3$ products **2** were generated within hours. The importance of TfOH in the cycle is highlighted when Et_3N is added, ceasing conversion. Though >90% conversion is typically achieved within 24 h using 1 equiv of catalyst, in practise using 30 mol% gave comparable results (Scheme 1). Application to a panel of alicyclic, aromatic, and heterocyclic acceptors was effective (Chart 1) and the process was amenable to large scale (~5 g) application, workup merely requiring filtration through a silica gel plug and solvent removal. The process is also compatible with other acetylated aminosugars. As shown in Scheme 2, coupling of a protected galactose with glucosamine derived **1** produces **7**, whereas coupling with galactosamine derived **8** (Ac_2O, Py then TMSOTf) gives coupled derivative **9** in

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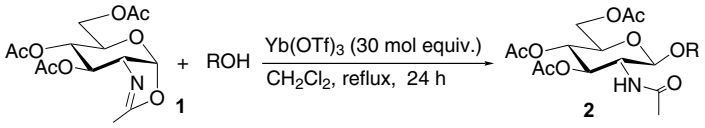


Scheme 1. Yb catalyzed preparation of β-glycosides.

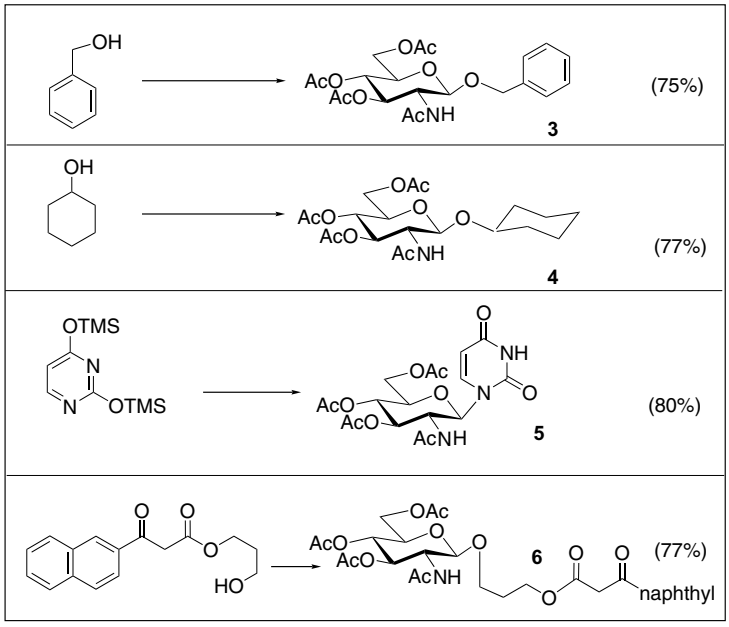
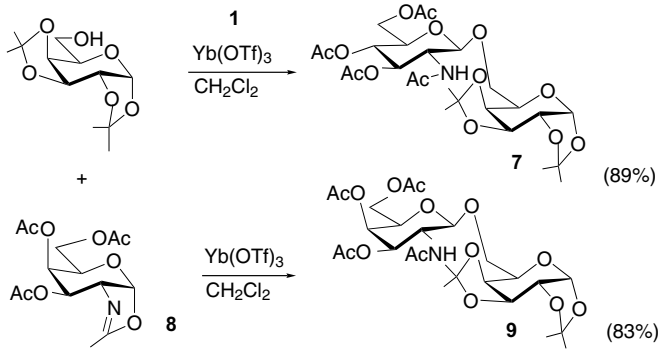


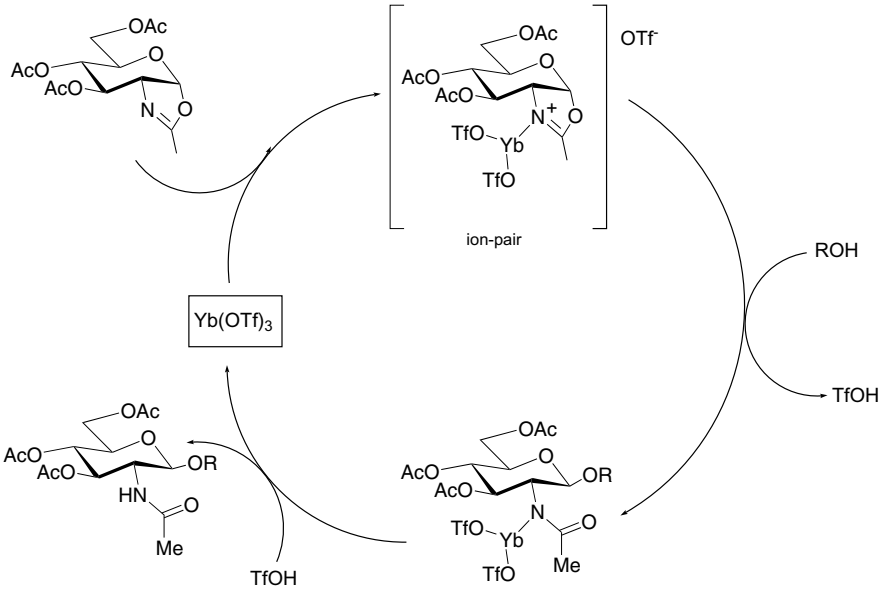
Chart 1. Yb catalyzed coupling of oxazolines with alcohol substrates.



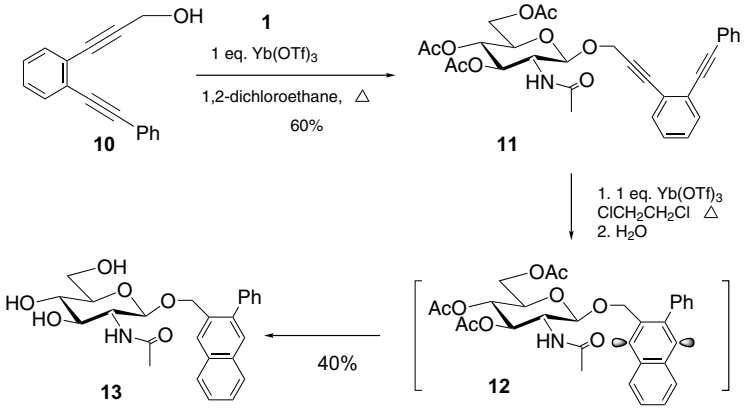
Scheme 2. Divergent routes to gal-glu and gal-gal derivatives.

good yield.[5] Analysis of the likely mechanism of the process suggests a cycle as depicted in Scheme 3, where trifluoromethanesulfonic acid is cycled and is consistent with observed effects of lanthanide loading, scavenging of byproducts, induction period, and stoichiometry on rate. Consistent with this pathway, it was evident that at elevated temperatures and stoichiometries, partial de-acetylation of product could be achieved on workup. As the liberation of a Bronsted acid might be useful for subsequent in situ product transformations, we sought to demonstrate the application of the method to preparation of library precursors where in situ unmasking of the *O*-acetyl groups is desirable.

We have been particularly interested in preparation of libraries of conjugates composed of biologically active molecules coupled to post-activated enediynes.[9,10] By screening these chemically stable hybrids against biological targets in affinity driven assays, candidates can then be identified for the study of the chemically reactive enediyne parent with the biological target. This had led to the discovery of enediyne–estrogens capable of binding to and degrading human estrogen receptor.[11] Given that the DNA binding of the enediyne antitumor antibiotic calicheamicin has been linked to its pendant aminosugar moiety,[12] methodology for the production and bioassay of aminosugar–enediyne hybrids is of



Scheme 3. Proposed mechanism for Yb catalyzed coupling.



Scheme 4. Preparation and in situ cycloaromatization of enediyne–glu hybrid.

potential significance. Accordingly, we wished to determine if the present coupling methodology could be used to prepare such an agent, and then perform controlled cycloaromatization. Enediyne **10**, available from Pd coupling methodology,[13] was subjected to coupling with **1** using 1:1 stoichiometry (Scheme 4). To achieve efficient coupling it was ultimately required to utilize a higher boiling solvent, and under these conditions, substantial quantities of the post-cyclized products derived from conjugate **11** were recovered. Following prolonged reaction (40 h) it was possible to isolate coupled, cycloaromatized and deacetylated product **13**, presumably formed via capture of diyl radical **12** and subsequent trifluoromethanesulfonic acid mediated deprotection. Especially intriguing is the mechanism of the cycloaromatization process, as attempts to deacetylate **11** in situ always resulted in cycloaromatization. Given the propensity for Yb to form alkyne complexes[14] and precedent for metal assisted Bergman cycloaromatizations,[15] it is likely that this transformation can be optimized yet further.[16] Additionally, with a glycosylated post-Bergman substrate in hand, we are now in a position to study binding characteristics and design then produce libraries of such analogs.

In summary, a facile method for preparation of GlcNAc derivatives has been developed. Reagent acceptor stoichiometry and mild conditions are attractive features, and we anticipate application in the preparation of a range of derivatives of this biologically important class of building blocks.

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