Glycosyl Sulfonylcarbamates: New Glycosyl Donors with Tunable Reactivity

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The advent of the Koenigs−Knorr method of glycosylation enabled the chemical synthesis of oligosaccharides.[1] Since that advance, the differences in regiochemistry and stereochemistry of glycosyl linkages and variations in the stereoelectronic properties of glycosyl donors and acceptors have impelled the search for milder and more selective procedures.[2] Successes in this pursuit have expanded the variety of complex, saccharide-containing natural products accessible through chemical synthesis. The method of choice for a given donor−acceptor pair, however, depends on a number of variables. One such parameter is the nature of the anomeric leaving group. A divergent synthetic strategy to generate various glycosyl donors from a single intermediate would facilitate the construction of different glycosidic linkages. In search of such a donor, we explored the glycosylation reactions of glycosyl sulfonylcarbamates.

We hypothesized that glycosyl sulfonylcarbamates could serve as glycosyl donors with a unique feature: the reactivity of these donors could be tuned by postsynthetic modification. Allyl[3] and phenyl[4] glycosylcarbamates have previously been shown to act as glycosyl donors. Likewise, we envisioned that treatment of glycosyl sulfonylcarbamates with an electrophilic promoter would result in a loss of CO_2 and sulfonamide with production of a reactive glycosyl donor (Figure 1).

A unique feature of the sulfonylcarbamate group is that it can be selectively altered by *N*-alkylation. We postulated that donors of differing reactivity could be generated through alteration of the characteristics of the resulting *N*-alkyl group.[5] This approach offers significant advantages over the current methods of reaction tuning, which involve the independent syntheses of differently functionalized glycosyl donors of varying reactivities.[6]

Glycosyl sulfonylcarbamates are readily synthesized from the reaction of a sulfonyl isocyanate with the anomeric hydroxyl group of a protected saccharide (Figure 2). The putative glycosyl donors are formed in quantitative yield as a mixture of α and β isomers. The resulting compounds can be purified by silica gel chromatography, and are extremely stable; no decomposition is observed for samples stored at room temperature for three months. Although the two anomers can be separated, methods for generating the α- or β-isomer preferentially were developed. The β-anomer can be prepared by treatment of the starting material with excess 1,4-diazabicyclo[2.2.2]octane (DABCO) in toluene followed by addition of *p*-toluenesulfonyl isocyanate (TsNCO). The resulting glycosyl *p*-toluenesulfonylcarbamate is obtained in high selectivity (1:13 α: β ratio).[4] When DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene) is used as a base, the α-isomer is favored

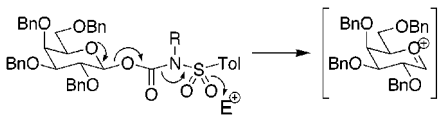

Figure 1. Proposed formation of oxonium ion upon addition of an electrophile.

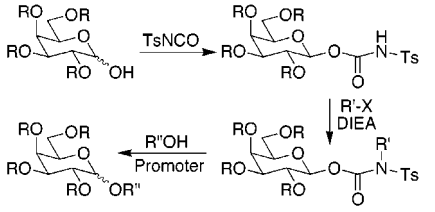

Figure 2. General scheme for the synthesis and postsynthetic reaction tuning of glycosyl sulfonylcarbamate donors.

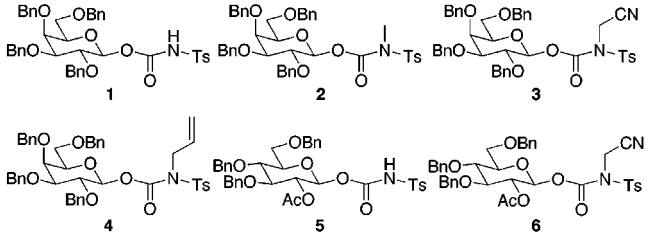

Figure 3. Donors synthesized to investigate the glycosylation reactions of glycosyl sulfonylcarbamates.

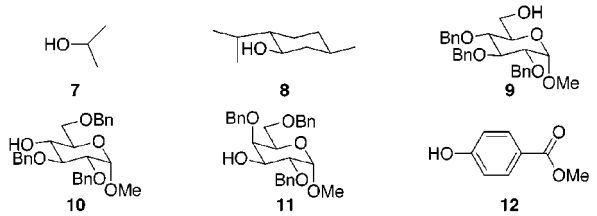

Figure 4. Acceptors used to determine the substrate specificity.

(5:1 α: β). Since the β-isomer can be produced most efficiently, it was used to explore the feasibility and scope of the proposed glycosylation reaction.

Compound **1** was tested as a glycosyl donor (Figure 3). We reasoned that **1** could be activated with Lewis acids to promote glycosylation. The most effective promoter was found to be trimethylsilyl triflate (TMSOTf). Treatment of **1** with TMSOTf results in the production of a silylated intermediate; presumably the trifluoromethanesulfonic acid that is generated activates this intermediate for glycosylation. Using these conditions, a variety of primary and secondary alcohols (Figure 4) were glycosylated in high yields, including hindered hydroxyl groups (Table 1, entries 8 and 9). As with typical glycosyl donors, however, the yields of some reactions were lower. For example, phenols were especially poor acceptors for glycosylation (entry 10). To optimize the donor reactivity for less nucleophilic acceptors, donors with alternative anomeric leaving groups were generated in a single step.

The anomeric substituents that were employed vary in their ability to serve as a leaving group. Because of the low pK_a of the sulfonylcarbamate group, we anticipated that *N*-alkylation of **1** could produce a variety of different donors.[7] Backes et al. demonstrated in reactions of related acylsulfonamides that the electronic properties of an *N*-alkyl substituent could perturb the ability of the sulfonamide to serve as a leaving group.[5] Given

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Table 1. Results of Glycosylation Reactions with Different Glycosyl Donors and Acceptors under Various Conditions

entry	donor	acceptor	promoter	equiv	yield (α:β)
1	1	7	TfOH	0.1	no rxn
2	1	7	BF_3OEt_2	1.5	77 (2:1)
3	1	7	$Yb(OTf)_3$	1.5	64 (3:1)
4	1	7	TMSOTf	1.1	97 (3:1)
5	1	8	$Yb(OTf)_3$	1.5	58 (3:1)
6	1	8	TMSOTf	1.1	82 (6:1)
7	1	9	TMSOTf	1.1	85 (4:1)
8	1	10	TMSOTf	1.1	73 (6:1)
9	1	11	TMSOTf	1.1	82 (10:1)
10	1	12	TMSOTf	1.1	35 (3:1)
11	2	7	TfOH	0.1	88 (1.4:1)
12	2	8	TMSOTf	0.1	84 (1.7:1)
13	2	11	TMSOTf	0.1	75 (5:1)
14	3	7	TfOH	1.1	90 (1:1.5)
15	3	7	BF_3OEt_2	1.5	74 (1:1)
16	3	7	$Yb(OTf)_3$	1.5	65 (1:1)
17	3	7	TMSOTf	0.1	72 (1:1)
18	3	8	TMSOTf	0.1	89 (1.3:1)
19	3	9	TMSOTf	0.1	82 (2:1)
20	3	10	TMSOTf	0.1	53 (5:1)
21	3	11	TMSOTf	0.1	74 (4:1)
22	3	12	TMSOTf	0.1	78 (10:1)
23	4	8	TfOH	0.1	no rxn
24	4	8	TMSOTf	0.1	no rxn
25	4	8	Br_2	1.1	59 (9:1)
26	5	8	TMSOTf	1.1	84 (0:100)
27	5	9	TMSOTf	1.1	87 (0:100)
28	6	8	TMSOTf	1.1	78 (0:100)
29	6	9	TMSOTf	1.1	86 (0:100)

these observations, we hypothesized that variations in the *N*-alkyl substituent could lead to new donors with different characteristics. To explore whether glycosyl sulfonylcarbamates with different reactivities could be generated, compound **1** was treated with TMS-diazomethane to form the *N*-methyl product **2** in quantitative yield. The cyanomethylated donor, **3**, was generated by reaction with bromoacetonitrile in the presence of Hünig's base in 97% yield. In addition, allyl bromide can be used to synthesize the *N*-allyl sulfonylcarbamate **4** in 94% yield. Thus, several different potential glycosyl donors can be assembled in a divergent manner from a common intermediate.

We examined the scope of glycosylation reactions with donors **1** and **3** using a variety of different acceptors. We anticipated that the nucleophilicity of the acceptors and the electrophilicity of the donor leaving group would be important parameters in determining the efficiency of the glycosylation reaction. The data reveal such a relationship. With acceptors **7**−**11**, the less electrophilic glycosyl donor **1** afforded the highest yields. These reactions proceeded in good to excellent selectivities for the α-isomer. For example, a derivative of the galactosyl-α(1→3)-galactose epitope, which is responsible for organ rejection in xenotransplantation, was synthesized efficiently (entry 9).[8] With the phenolic acceptor **12**, however, the reaction of donor **3** is preferred (compare entries 22 and 10). Treatment of the more electrophilic donor, **3**, with a promoter afforded a good yield of the desired product as well as a marked increase in selectivity. Thus, the postsynthetic modification protocol provides a means to tune the reactivity of the donor to that of the acceptor.

The differences in reactivity of **1**−**4** also are manifested in the conditions needed to promote glycosylation. For example, compound **1** is stable to trifluoromethanesulfonic acid (Table 1, entry 1), yet compounds **2** and **3** undergo glycosylation in high yields when activated by trifluoromethanesulfonic acid (entries 11 and 14). In addition, the glycosylation reactions of **2** and **3** can be promoted with catalytic amounts of trimethylsilyl triflate (entries 12, 13, and 17−21). Unalkylated donors (e.g., **1** and **5**), however, require stoichiometric amounts of TMSOTf, presumably because the silylated intermediate is the reactive species. The *N*-allylated compound **4** does not react when subjected to TfOH or TMSOTf, unlike **2** and **3**. However, treatment with bromine promotes the reaction with higher selectivity than **2** or **3** (entries 23−25). These results demonstrate that donors with orthogonal reactivities can be generated. Such compounds could be useful for the sequential assembly of complex oligosaccharides in one pot.

To determine the reaction outcome with donors containing a C2 participating group, substrates **5** and **6** were synthesized. By incorporating a directing group at the 2-position, the β-isomer was expected to predominate. Glycosylation of **8** or **9** with **5** proceeded in high yield with complete β-selectivity (entries 26−29). Cyanomethylation of the glycosyl sulfonylcarbamate and subsequent reaction with **8** or **9** afforded the glycosides in similar yields and with similar selectivities.

We have shown that glycosyl sulfonylcarbamates are effective and selective glycosyl donors. Both α- and β-linked products can be obtained in high yield. By modifying compound **1** to generate donors with differing reactivities, the characteristics of the donor and the conditions under which it reacts can be tuned. The search for one-pot glycosylation procedures, which allow the efficient assembly of complex oligosaccharides, is ongoing.[6,9] The tunable and orthogonal nature of the donors **1**−**4** suggests that these may be useful in such venues. Postsynthetic tuning of a glycosyl donor is a concept that has been demonstrated with glycosyl sulfonylcarbamates, but we suggest this idea can be extended to alternative glycosyl donors.

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Supporting Information Available: Experimental procedures and NMR spectra for compounds **1**−**6** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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