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Cyclopropenium Cation Promoted Dehydrative Glycosylations Using 2-Deoxy- and 2,6-Dideoxy-Sugar Donors

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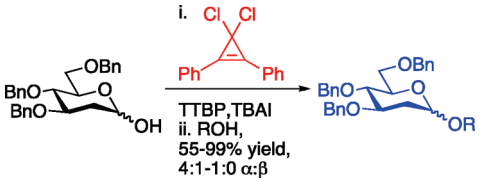
ABSTRACT



Dehydrative glycosylation reactions using 2-deoxy- and 2,6-dideoxy-sugar donors promoted by a combination of 3,3-dichloro-1,2-diphenylcyclopropene and tetrabutylammonium iodide (TBAI) are described. The reactions are α-selective and proceed under mild conditions at room temperature without the need for special dehydrating agents. The reaction is shown to be effective with a number of glycosyl acceptors, including those possessing acid and base sensitive functionality.

In many natural products the presence of deoxy-sugars is often essential for biological activity.[1] Additionally, changing these sugars through glycorandomization can dramatically alter the biological profile of a natural product.[2] As a consequence, there has been a significant amount of effort directed at developing efficient methods to synthesize deoxy-sugar containing oligosaccharides over the past few decades.[3,4] The most conceptually straightforward of these approaches rely on so-called "direct" glycosylation reactions which utilize fully functionalized glycosyl donors. While a number of elegant direct glycosylation reactions using deoxy-sugar donors have been developed, most require the use of unstable activated deoxy-sugar donors, rendering them very technically challenging for nonspecialists.[5] In this communication, we describe an operationally simple method for dehydrative glycosylation reactions using deoxy-sugar donors that is tolerant of acid and base sensitive functional groups.

Dehydrative glycosylation reactions use promoters to activate lactols in situ. This approach has advantages over other methods in that it does not require the synthesis and isolation of highly unstable activated sugar donors.[6] Despite the methods advantages, this approach has found limited application in the synthesis of deoxy-sugars,[7] in part because homocoupling reactions can be problematic.[8] While Mitsunobu glycosylations have been reported using deoxy-sugar donors,[9] they are only effective using acidic

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acceptors such as phenols or carboxylic acids. Attempts to extend this reaction to aliphatic acceptors requires the use of toxic mercury salts to drive the reaction.[10] Thus, there is still a need for a general promoter system for dehydrative glycosylations using deoxy-sugar donors. Here we report our initial efforts toward achieving this aim using armed 2-deoxy-sugar donors.

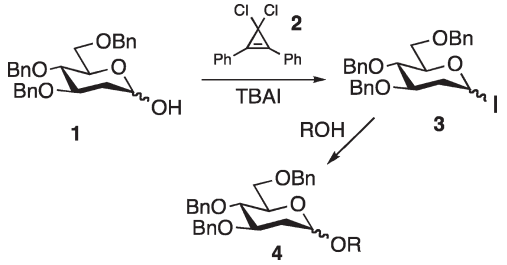

Figure 1. Cyclopropenium/TBAI promoted dehydrative glycosylation with deoxy-sugars.

We envisioned that a method that would promote the in situ conversion of a lactol to a highly reactive species, such as a glycosyl iodide,[11] would present an attractive solution to this problem. For this approach to be practical, the conversion of the lactol to the halide would have to be rapid in order to suppress homocoupling. Recently there has been a report of a novel system for the rapid conversion of alcohols into alkyl chlorides based on cyclopropenium cation activation.[12] The operational simplicity of this method made it appealing to us as a potential promoter for dehydrative glycosylation reactions. While glycosyl chlorides are not efficient glycosyl donors in the absence of heavy metal promoters, it is well established that an excess of iodide salt can transform the chloride into the much more reactive glycosyl iodide.[13] Thus, conducting the reaction in the presence of a soluble source of iodide, such as tetrabutylammonium iodide (TBAI) could potentially lead to the formation of a glycosyl iodide such as **3** (Figure 1). This species could be trapped in situ with an appropriate acceptor to form a new glycosidic linkage. Importantly, in the presence of excess halide, glycosyl iodides exist in equilibrium between the thermodynamically favored α-iodide and the much more reactive β-iodide.[14] Under these conditions, the β-iodide reacts preferentially leading to formation of α-glycosides via S_N2 displacement.[15]

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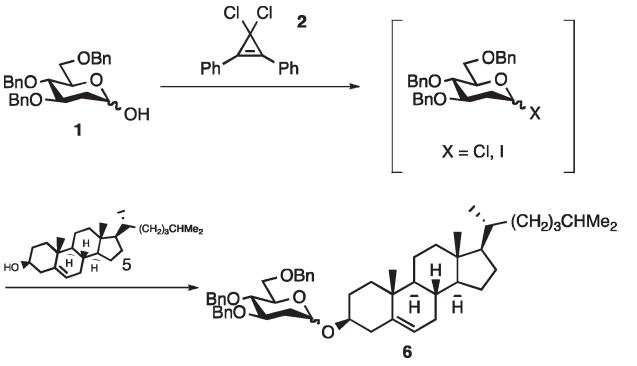
Table 1. Reaction Optimization[a]



entry	2 (equiv)	TBAI (equiv)	DIPEA (equiv)	t	solvent	additive	% yield	α/β
1	1.5	1	2	rt	CH_2Cl_2	–	72	4:1
2	1.5	0	2	rt	CH_2Cl_2	–	13	4:1
3	**1.5**	**5**	**2**	**rt**	**CH_2Cl_2**	–	**82**	**4.3:1**
4	1.5	10	2	rt	CH_2Cl_2	–	72	4:1
5	0.76	5	2	rt	CH_2Cl_2	–	64	4:1
6	1.5	5	0	rt	CH_2Cl_2	–	46	6:1
7	1.5	5	2	40 °C	CH_2Cl_2	–	23	2.2:1
8	1.5	5	2	rt	CH_2Cl_2	3AMS	13	ND
9	1.5	5	2	rt	CH_2Cl_2	AW300MS	–	ND
10	1.5	5	2	rt	CH_2Cl_2	AgOTf	55	1.6:1
11	1.5	5	2	rt	MeCN	–	–	ND
12	**1.5**	**5**	**0**	**rt**	**CH_2Cl_2**	**TTBP**	**80**	**4:1**

[a] TBAI = tetrabutylammonium iodide, DIPEA = *N*,*N*-diisopropylethylamine, TTBP = 2,4,6-tri-*tert*-butylpyrimidine, AW300MS = acid washed 3 Å molecular sieves, ND = not determined.

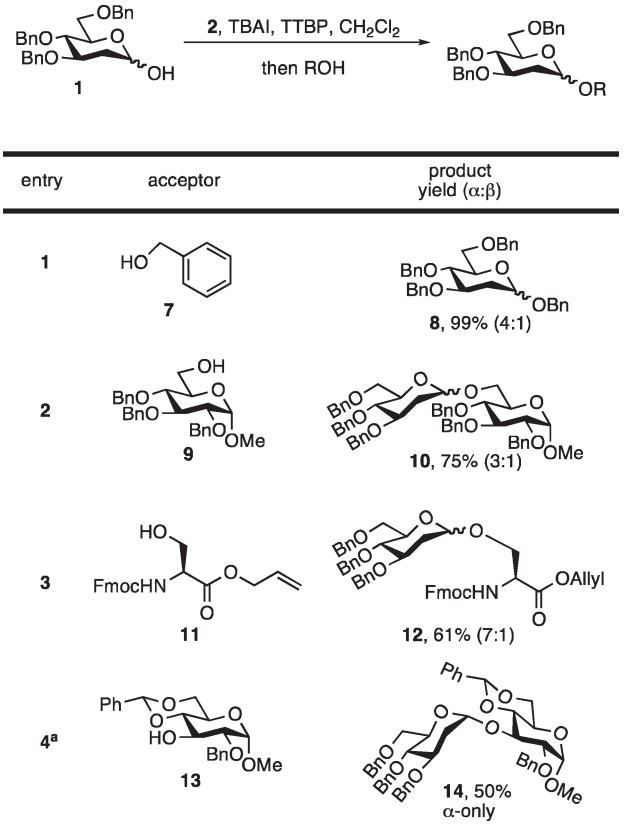
Preliminary reaction screening used cholesterol (**5**) as a model small molecule acceptor (Table 1). As anticipated activation of lactol **1** with **2** in the presence of TBAI and *N*,*N*-diisopropylethylamine (DIPEA), followed by in situ trapping with **5**, led to clean formation of glycoconjugate **6** in good yield (72%) and 4:1 α:β selectivity (Table 1, entry 1). A control reaction, run in the absence of TBAI, led to the formation of the desired product in a much lower yield (13%, Table 1, entry 2). Investigations into the reaction of **1** with **2** in the absence of an acceptor and TBAI revealed that the corresponding glycosyl chloride was being formed in quantitative yields in less than 15 min. As expected, this species was not reacting efficiently with **5**. Increasing the amount of TBAI in the reaction to 5 equiv led to a further increase in yield to 82% (Table 1, entry 3), while additional equivalents of TBAI did not have an impact on the course of the reaction (Table 1, entry 4). Further attempts to improve the reaction through varying stoichiometry, additives, the use of acetonitrile,[16] or heating all had a detrimental effect on the course of the reaction (Table 1, entries 5–11). Finally, although substitution of DIPEA with the hindered base tri-*tert*-butylpyrimidine (TTBP) led to the suppression of elimination byproducts, it did not have additional effects on the reaction (Table 1, entry 12).

(16) CH_2Cl_2 and acetonitrile have been established to be the optimal solvents for conversion of alcohols into halides using **2**; see ref 12a.

This latter base was utilized for studying the scope of the reaction in anticipation of using base sensitive acceptors.

Of particular note is the loss of selectivity observed when silver(I) triflate was used to promote the reaction (1.6:1, Table 1, entry 10).[17] The silver salt is expected to promote glycosylation through formation of an oxocarbenium cation. The change in selectivity between our conditions (Table 1, entries 3 and 12) and those in entry 10 indicates that the reactions are proceeding through different mechanisms. This observation, coupled with the low yields obtained in the absence of TBAI, lends further support to our proposal that the reaction proceeds through the formation of a glycosyl iodide, followed by direct displacement by the nucleophile.

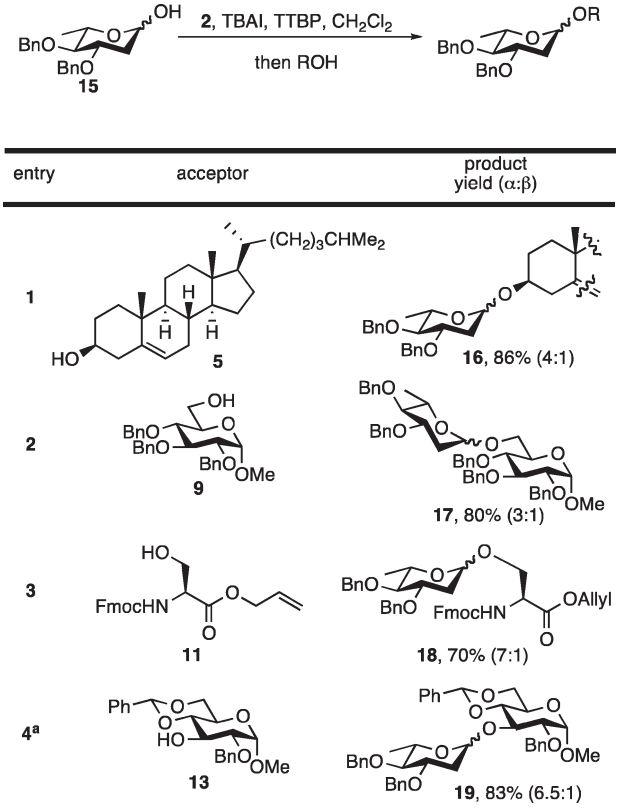
Table 2. Scope of the Reaction with D-2-Deoxy Donor **1**



[a] 3 equiv donor used.

Having established conditions for the reaction, we examined its scope with different acceptors (Table 2). The reaction using 2-deoxy-sugar **1** proceeded smoothly with benzylic and primary alcohols (Table 2, entries 1 and 2). The use of amino acid **11** as an acceptor led to a slight decrease in the yield; however, the product was formed with higher α-selectivity (Table 2, entry 3). Finally, the more hindered acceptor **13** was less efficient in the reaction, initially providing the desired product in low (27%−34%) yield. The yield could be improved by using a larger excess of donor (3 equiv, Table 2, entry 4). Pleasingly, although the reaction was more sluggish than other examples, the product was formed as a single diastereomer. The increase in selectivity observed with acceptors **11** and **13** could be a result of the lower reactivity of these species leading them to react preferentially (**11**), or exclusively (**13**) with the more electrophilic β-anomer of **3** (Figure 1).[15]

Table 3. Scope of the Reaction with L-2,6-Dideoxy Donor **15**



[a] 3 equiv donor used.

2,6-Dideoxy-sugars, which are commonly found in natural products, are more reactive than 2-deoxy-sugars because they contain one less stabilizing oxygen moiety. This increased reactivity can occasionally lead to problems with glycosylation reactions.[18] This proved not to be a concern under our conditions, as 2,6-dideoxy donor **15** reacted smoothly with a number of substrates. In all cases examined the reaction with donor **15** proceeded in higher yield than donor **1** (Table 3). Notably, the α-product was still favored despite changing the configuration of the donor from a D-sugar to an L-sugar.

The increased yield is most notable in the case of the hindered acceptor **13**. Whereas the reaction of **13** with **1** proceeded in moderate yield (50% Table 2, entry 4), the use of donor **15** in the reaction provided the desired product in 83% yield (Table 3, entry 4), albeit with slightly lower selectivity. The reduction in selectivity in this reaction is presumably a consequence of the higher reactivity of the

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2,6-dideoxy-sugars. Since both the α- and β-iodides generated from **15** are anticipated to be more electrophilic than the corresponding iodides generated from **1**, it is possible that the α-iodide can react with **13** to a limited extent, leading to some β-product.

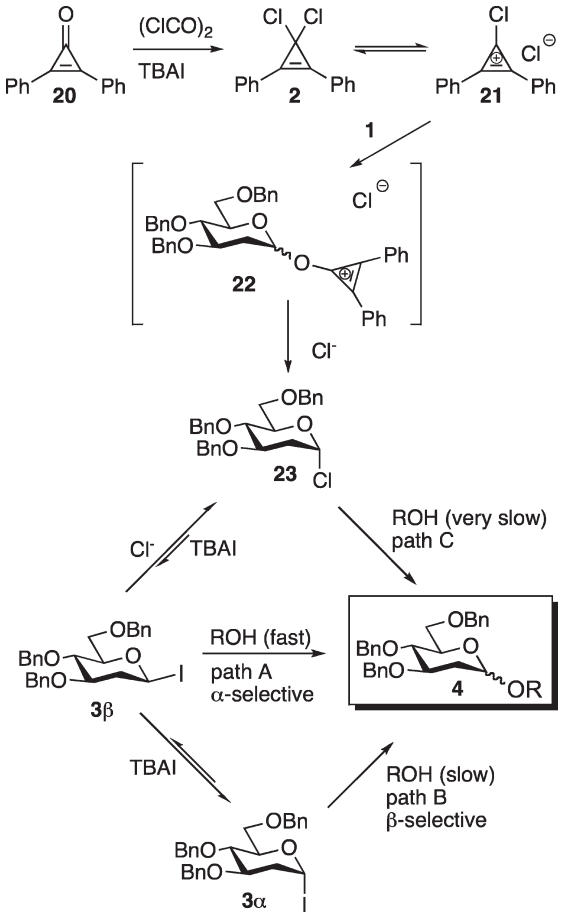

Figure 2. Proposed reaction mechanism.

A mechanistic proposal for the reaction is shown in Figure 2. Prior to addition of the lactol, cyclopropene **2** is generated in situ from diphenylcyclopropenone. This species is in equilibrium with **21**, which rapidly converts lactol **1** into α-chloride **23**, possibly through the intermediacy of **22**.[19,20] NMR experiments demonstrate that in the presence of TBAI this species exists in equilibrium with >10% of another species, possibly iodide **3α** or ***3β*** (see Supporting Information). These latter two species are presumably the reactive donors, as chloride **23** is not a good donor under these conditions (Table 1, entry 2). Excess iodide in the reaction will promote an equilibrium between the more stable **3α** and the more reactive ***3β***. The observed α-selectivity of the products arises through preferential reaction of the acceptors with ***3β*** via an S_N2-like pathway (path A).[21] As discussed above, stereochemical outcome of the reaction will depend on the reactivity of the acceptor, with less reactive acceptors affording the higher levels of selectivity.

In conclusion we have developed a new promoter system for dehydrative glycosylation reactions. The system tolerates acid and base sensitive substrates, and reactions work especially well with armed 2,6-dideoxy donor species.[22] The reaction compares favorably with previously reported dehydrative glycosylation reactions in that homocoupling of the donor sugar is not observed. Additionally, unlike previously reported Mitsunobu coupling approaches to deoxy-sugars, the system permits glycosylations with aliphatic acceptors. Moreover, to the best of our knowledge this is the first example where cyclopropenium cation activation has been used to promote intermolecular coupling between complex molecules. Finally, since the reaction uses stable lactols as donors, special precautions are not necessary to purify donors or carry out the reaction. Attempts to further improve the scope (including extending the methodology to disarmed donors) and selectivity of the reaction are currently under investigation in our laboratory.

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Note Added after ASAP Publication. Errors in Table 1 were corrected in the version reposted May 27, 2011.

Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) NMR experiments have shown that **1** is converted into **23** in less than 15 min; see Supporting Information.

(20) One referee raised the possibility that oxalyl chloride/TBAI could be an effective promoter in the absence of the cyclopropenone. Preliminary data indicate that this may be the case; however the reaction is not as efficient as when the dichlorocyclopropene is used as the promoter.

(21) The fact that both D- and L-donors afford α-products is evidence against the formation of oxocarbenium cation intermediates, which would be expected to lead to "matched" and "mismatched" products. See: Spijker, N. M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 180.

(22) At present, the reaction does not work well with disarmed donors, including fully substituted pyranoses.