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SHORT COMMUNICATION

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Halide Effects on Cyclopropenium Cation Promoted Glycosylation with Deoxy Sugars: Highly α-Selective Glycosylations Using a 3,3-Dibromo-1,2-diphenylcyclopropene Promoter

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Dedicated to the memory of Professor David Y. Gin

Keywords: Carbohydrates / Diastereoselectivity / Glycosylation / Synthetic methods

A mixture of 3,3-dibromocyclopropene and TBAI promotes highly α-selective glycosylation reactions (up to >20:1) by using deoxy sugar hemiacetal donors. The reaction provides a convenient method for generating highly reactive glycosyl donors in situ from shelf-stable starting materials. Both armed and disarmed sugars undergo the reaction, and selectivity is independent of the configuration of the donor sugar.

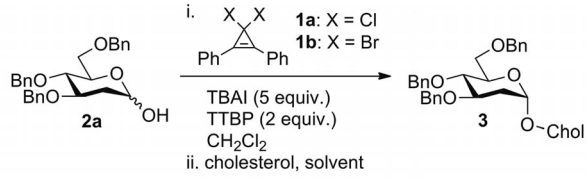
Introduction

Deoxy sugars constitute an important component of many biologically active natural products such as vancomycin, landomycin, mithramycin, and vineomycin B-2.[1–5] While changing the composition of the sugar chains on these molecules can have profound effects on their biological activity,[6] very few groups have taken advantage of this approach for drug discovery.[7,8] This is due to the difficulties associated with the stereoselective construction of oligosaccharides, especially those possessing deoxy sugar moieties.[9] In particular, the lack of oxygen at C-2 and C-6 in many deoxy sugars precludes the use of protecting group strategies normally used to control the stereochemical outcome of glycosylation reactions.[10–13] In addition, the instability of many activated deoxy sugars frequently limits their direct use in synthesis.[14] As a consequence, there is a pressing need for stereoselective direct glycosylation reactions using stable deoxy sugar donors.[15,16]

Results and Discussion

Our group has an interest in developing mild stereoselective glycosylation reactions using shelf-stable deoxy sugar donors. Recently, we introduced a new promoter system, based on cyclopropenium cation activation, for dehydrative glycosylations using deoxy sugar donors.[17,18] The reaction proceeds through the formation of a glycosyl chloride, which in the presence of an excess amount of iodide is a competent donor, presumably through the in situ formation of a reactive glycosyl iodide.[19] While the conditions tolerated a large number of functional groups, and yields were generally good, the selectivity was only moderate (Table 1 entry 1). In addition, only armed deoxy sugar donors were found to be effective in the reaction.[20] In this communica-

Table 1. Optimization of cyclopropenium cation promoted dehydrative glycosylation.



Entry	X	Solvent	Time [h]	Yield [%]	α/β
1	Cl	CH_2Cl_2	48	82	4.3:1
2	Br	CH_2Cl_2	12	82	5:1
3[a]	Br	CH_2Cl_2	12	79	2.9:1
4[b]	Br	CH_2Cl_2	12	52	3.3:1
5	Br	MeCN	12	75	5.5:1
6	Br	TBME	12	85	7.7:1
7	Br	Et_2O	12	80	10:1
8	Br	1,4-dioxane	12	79	10:1
9[c]	Br	1,4-dioxane	12	42	8.3:1

[a] No TBAI added. [b] No TTBP added. [c] Oxalyl bromide and TBAI used as a promoter. Chol = cholesterol, TBAI = tetrabutylammonium iodide, TTBP = 2,4,6-tri-*tert*-butylpyrimidine, TBME = *tert*-butyl methyl ether.

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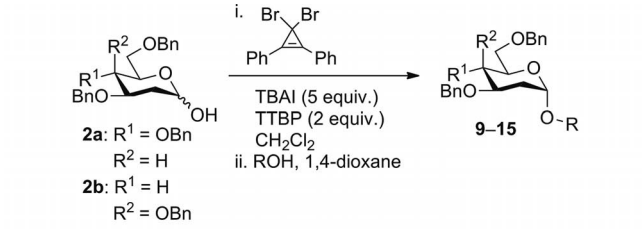
tion we report a second-generation promoter for dehydrative glycosylations, which provides very high levels of α-selectivity (up to >20:1) with both armed and disarmed sugars.

In an effort to improve the reaction and understand the basis of the selectivity, we used NMR spectroscopy to identify key intermediates.[17] Through these studies we found that while **1a** quickly converts hemiacetal donors to the corresponding glycosyl chlorides, these latter species react very slowly with the excess amount of tetrabutylammonium iodide (TBAI) to generate glycosyl iodides. Rationalizing that a more reactive glycosyl halide would undergo faster exchange with the iodide,[21] we next examined the use of dibromocyclopropene **1b** as a promoter. To this end, we treated hemiacetal **2a** with **1b** in the presence of TBAI, followed by the addition of cholesterol as an acceptor (Table 1, entry 2). Under these conditions we observed a slight increase in the selectivity of the reaction, accompanied by a significant decrease in reaction time. Further studies showed that both TBAI and base were essential for the efficacy of the reaction (Table 1, entries 3 and 4). To further enhance the selectivity of the reaction, we next examined the effects of several solvents. Acetonitrile, which in certain cases has been shown to promote β-selectivity,[22] led to a modest increase in α-selectivity (Table 1, entry 5). Further increases in selectivity were observed with ethereal solvents (Table 1 entries 6–8), with 1,4-dioxane and diethyl ether affording optimal selectivity.[23] Finally, to assess the necessity of the dibromocyclopropene promoter, we examined the use of oxalyl bromide and TBAI as a promoter system. Under these conditions, the reaction afforded the desired product with good selectivity; however, the yield was significantly attenuated (Table 1 entry 9).

We next sought to examine the scope of the reaction. For these studies, we chose to use 1,4-dioxane as a cosolvent, owing to the limited solubility of many acceptors in diethyl ether. Pleasingly, we found that in most cases both 2-deoxyglucose and 2-deoxygalactose donors provided the products in good yield and excellent selectivity (Table 2). The exception was when diosgenin (**8**) was used as an acceptor (Table 2, entry 4). In this case, both the yield and the selectivity of product **12** were diminished. This was surprising, considering that the structure of this acceptor closely resembles cholesterol. While the lower yield may be due to sensitivity of the spiroketal, we have yet to find a satisfying rationale to explain the loss of selectivity. Importantly, both glucose- and galactose-derived sugars afforded the product with similar levels of yield and selectivity, indicating that changing the configuration of the pyranose substituents did not affect the outcome of the reaction.

We next turned our attention to 2,6-dideoxy sugars. These molecules are important components in many natural products; however, glycosidic linkages between 2,6-dideoxy sugars are extremely labile due to the lack of two stabilizing oxygen atoms. While dichlorocyclopropene activation was compatible with these species, we were concerned that the 2,6-dideoxyglycosyl bromides that we were generating in situ could decompose in the presence of base. In addition, there was also a possibility that the selectivity of the reaction would suffer, due to the higher reactivity of the glycosyl bromide intermediate. Pleasingly, this proved not to be the case, as 2,6-dideoxy donor **16** reacted under our conditions to provide most products in good yield and excellent selectivity (Table 3). The one exception was with acceptor **8**, which again led to lower selectivity than other substrates (Table 3, entry 5).

Table 2. Scope of reaction with 2-deoxy sugars.



Entry	Donor	Acceptor	Product	Yield [%]	α/β
1	**2a**	**5**	**9**	74	α only
2	**2a**	**6**	**10**	58	9.7:1
3	**2a**	**7**	**11**	98	8:1
4	**2a**	**8**	**12**	52	6:1
5	**2b**	**4**	**13**	65	11.1:1
6	**2b**	**5**	**14**	92	12.6:1
7	**2b**	**6**	**15**	50	α only

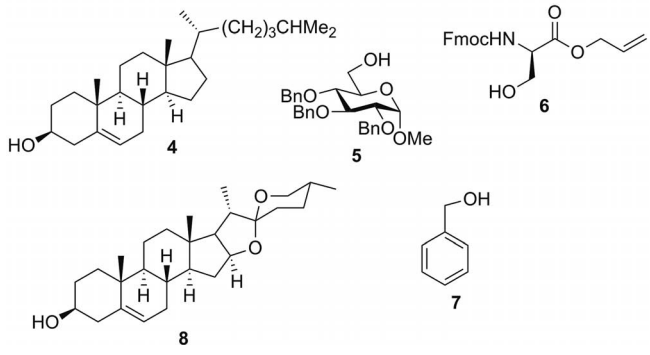
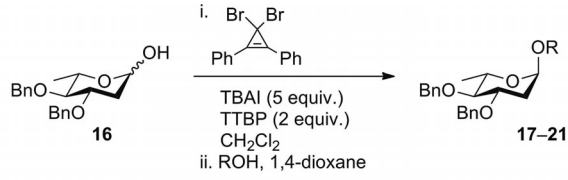


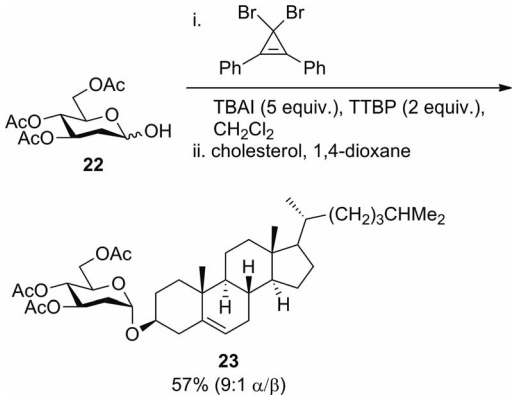
Table 3. Dehydrative glycosylations of 2,6-dideoxy sugars promoted by **1b**.



Entry	Acceptor	Product	Yield [%]	α/β
1	**4**	**17**	69	α only
2	**5**	**18**	65	20:1
3	**6**	**19**	55	α only
4	**7**	**20**	83	20:1
5	**8**	**21**	53	6:1

Having established that this new promoter was indeed superior to our previously reported one, we turned out at-

tention to disarmed donors.[24] When dichlorocyclopropene **1a** was used as a promoter, disarmed donors did not undergo glycosylation reactions. We attributed this to the disarmed 2-deoxyglycosyl chloride intermediate being too stable to undergo exchange with iodide to generate a reactive species. Reasoning that the more reactive species generated by **1b** could potentially undergo glycosylation, we chose to examine the reaction between **22** and **4** (Scheme 1). Using **1b** as a promoter, glycosylation between these two species proceeded efficiently to afford **23** with good selectivity. While the yield of this reaction was somewhat lower than that observed with armed **2a**, this result indicates that other classes of glycosyl donors could be amenable to dehydrative glycosylation using cyclopropenium cation promoters.



Scheme 1. Glycosylation with disarmed donor **22**.

Our working hypothesis for the mechanism of the reaction involves conversion of the hemiacetal into the corresponding glycosyl bromide. The α and β anomers are expected to be in equilibrium, and the β anomer is anticipated to react at a faster rate leading to the preferential formation of the α-product.[19,21,25] In the presence of an excess amount of TBAI, both of these species will be in equilibrium with the corresponding glycosyl iodides. The α and β anomers of these species will also be in equilibrium with each other and react through an S_N2-like manifold. The increase in selectivity observed with the iodide is most likely due to the fact that the β-iodide is much more reactive then other species in solution, leading to Curtin–Hammett scenario.[26] Selectivity is still moderate when the reaction is conducted in CH_2Cl_2, however, as the α-iodide is a potent electrophile in its own right.[27]

Conclusions

In conclusion we have demonstrated that a combination of 3,3-dibromo-1,2-diphenylcyclopropene and TBAI is a highly efficient promoter of dehydrative glycosylations with deoxy sugars. The reaction tolerates a broad range of functional groups, and in the presence of 1,4-dioxane, the selectivity of the reaction ranges from good to excellent. Importantly, preliminary evidence shows that this reagent combination can promote glycosylations using disarmed donors with no appreciable loss in selectivity. To the best of our knowledge this is the first example of a dehydrative glycosylation between a disarmed 2-deoxy sugar donor and a complex aliphatic acceptor.[28–30] In addition, it demonstrates that the diastereoselectivity of these glycosylations can be enhanced through fine-tuning of the cyclopropenium cation promoter. In principle, this promoter system should be applicable to glycosylation reactions using other classes of monosaccharides, perhaps with further tuning of the cyclopropene. This avenue of investigation and studies directed at determining the exact mechanism of the reaction are currently under investigation in our laboratory.

Experimental Section

Typical Glycosylation Procedure: A solution of diphenylcyclopropenone (0.75 mmol) and TBAI (0.75 mmol) in CH_2Cl_2 (5 mL) was treated dropwise with a solution of oxalyl bromide (2.0 M in CH_2Cl_2, 0.375 mL) and allowed to stir at room temperature for 5 min. Once gas evolution ceased, the resulting dark-brown solution was treated with the hemiacetal donor (0.75 mmol) and TTBP (1.5 mmol) in CH_2Cl_2 (4 mL). After stirring for 15 min, the acceptor (0.25 mmol) in 1,4-dioxane (4 mL) was added to the reaction. Following consumption of the acceptor, the reaction was concentrated in vacuo. Flash column chromatography afforded the desired product.

Supporting Information (see footnote on the first page of this article): Experimental details and copies of the NMR spectra.

Acknowledgments

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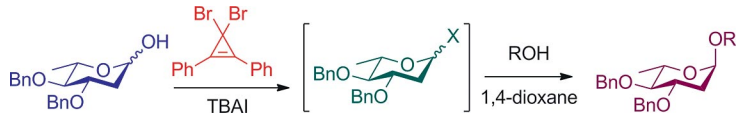
Glycosylation



α-Selective dehydrative glycosylations are achieved by using a cyclopropenium cation promoter system. The conditions permit glycosylations using 2-deoxy sugar donors without the need to isolate highly reactive intermediates. Yields and selectivity (up to >20:1) are good, and the reaction tolerates a range of substrates, including disarmed donors.

Keywords: Carbohydrates / Diastereoselectivity / Glycosylation / Synthetic methods

