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Anodic Coupling Reactions and the Synthesis of C-Glycosides

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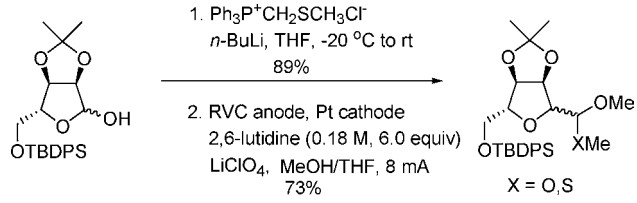
ABSTRACT



A convenient, two-step procedure has been developed for converting sugar derivatives into C-glycosides containing a masked aldehyde functional group. The chemistry takes advantage of an anodic coupling reaction between an electron-rich olefin and an alcohol. The sequence works for the formation of both furanose and pyranose derivatives if less polarized vinyl sulfide derived radical cation intermediates are used. With more polarized enol ether derived radical cations, the cyclizations work best for the formation of furanose derivatives where the rate of five-membered ring formation precludes elimination reactions triggered by the radical cation.

In connection with efforts to assemble molecular libraries that can be monitored in "real-time" for their binding to biological receptors, we have been developing techniques for locating molecules next to individually addressable electrodes in a microelectrode array.[1] This is accomplished by coating the arrays with a functionalized porous reaction layer[2] and then using the electrodes in the arrays to make chemical reagents and catalysts that trigger chemical reactions on the surface of the array. The reactions are used to couple substrates in the solution above the array to functional groups on the porous reaction layer proximal to the electrodes. To date, "site-selective" esterification reactions,[1] Heck reactions,[3] Suzuki reactions,[4] click-reactions,[5] hetero-Michael reactions,[1] reductive amination reactions,[6] and Diels−Alder reactions[7] have all been used for this purpose. The chemistry has led to a variety of substrates being placed on the arrays and the completion of initial experiments probing the utility of the arrays as analytical tools.[1,8] Because of the key role carbohydrates play in many biological contexts, these efforts are now being extended to the placement of sugars and glycopeptides on a microelectrode array.

One of the first steps in achieving this aim is to synthesize sugar derivatives that can be used to capitalize on the synthetic methodology mentioned above. To this end, C-glycosides like **1** and **2** (Figure 1) appear ideal.

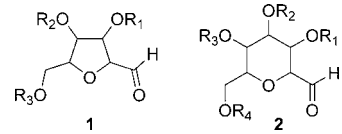


Figure 1. C-Glycoside targets.

C-Glycosides such as **1** and **2** have been used in the synthesis of bioactive sugar derivatives,[9] and the aldehyde

(1) For an example, see: Stuart, M.; Maurer, K.; Moeller, K. D. *Bioconjugate Chem.* **2008**, *19*, 1514.

(2) For the development of a new reaction layer, see: Hu, L.; Bartles, J. L.; Bartles, J. W.; Maurer, K.; Moeller, K. D. *J. Am. Chem. Soc.* **2009**, *131*, 16638.

(3) (a) Tian, J.; Maurer, K.; Tesfu, E.; Moeller, K. D. *J. Am. Chem. Soc.* **2005**, *127*, 1392. (b) Tang, R.; Chen, C.; Moeller, K. D. *Synthesis* **2007**, 3411.

(4) Hu, L.; Maurer, K.; Moeller, K. D. *Org. Lett.* **2009**, *11*, 1273.

(5) Bartles, J. L.; Lu, P.; Walker, A.; Maurer, K.; Moeller, K. D. *Chem. Commun.* **2009**, 5573.

(6) Tesfu, E.; Maurer, K.; Moeller, K. D. *J. Am. Chem. Soc.* **2006**, *128*, 70.

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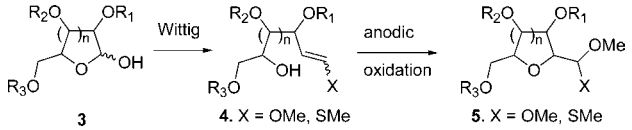
group bound to the former anomeric carbon can be readily converted into a wide variety of substrates for microelectrode-array reactions.

Previous syntheses of C-glycosides such as **1** or **2** involved either an initial conversion of a sugar to a cyano derivative followed by reduction and hydrolysis[10] or longer multistep routes.[11] As a complementary alternative, it is tempting to suggest that C-glycosides can be rapidly assembled from existing sugar derivatives by taking advantage of a Wittig reaction—anodic oxidation sequence such as the one illustrated in Scheme 1.[12,13] But are anodic coupling reactions

Scheme 1

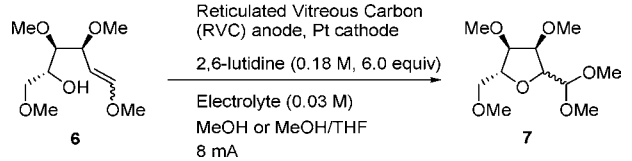


and the highly reactive radical cation intermediates generated really compatible with such highly functionalized substrates?

To provide an initial answer for this question, a model tetramethoxyfuranose substrate was selected (Table 1). To this end, the trimethoxy sugar derivative was treated with an ylide to form methoxy enol ether **6**, and then **6** subjected to anodic electrolysis condiditons.[14] The first conditions tried (entry 1) for the electrolysis were the optimized ones developed for earlier enol ether—alcohol coupling reactions.[15] The reaction led to only a low yield of product along with recovered starting material. This was true even after 10 F (5× the stoichiometric amount) of current had been passed. The reaction could be optimized by first moving toward a more polar solvent and then taking advantage of lithium perchlorate as the electrolyte for the electrolysis. Under these conditions, an 85% isolated yield of the desired cyclic product **7** was obtained as a 1.5:1 ratio of diastereomers about the newly formed bond. The major diastereomer had the acetal group trans to the neighboring methoxy at C_3 of the ring. The formation of diastereomers was not a concern since the center generated is epimerizable following hydrolysis of the acetal. What was clear from the cyclization was that electrolysis was compatible with the highly functionalized substrate. The need for the more polar solvent and lithium perchlorate electrolyte was rationalized by considering the very polar nature of the reaction substrate. Electrolytes play a key role in defining the nature of the reaction environment surrounding an electrode.[16] A "greasy" electrolyte will exclude polar species relative to nonpolar ones. Hence with tetraethylammonium tosylate and THF present, the very polar substrate **6** might have difficulty approaching the electrode surface leading to background oxidation of the methanol solvent. As the polarity of the environment surrounding the electrode is increased, more of the substrate can reach the electrode surface and the efficiency of the reaction improves.

Support for this rationalization was gained when substrate **8** was studied (Table 2). In this case, a significant change in the oxygen—carbon balance of the substrate was made by changing from methyl to benzyl protecting groups on the oxygens. While the lithium perchlorate in methanol condi-

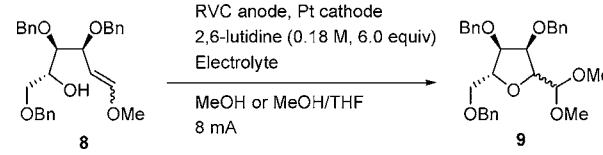
Table 1. Initial Cyclizations



entry	electrolyte	solvent (v/v)	coulomb (F)	yield (%)
1	Et_4NOTs	MeOH/THF (3:7)	10.0	22
2	Et_4NOTs	MeOH/THF (6:4)	5.5	30
3	Et_4NOTs	MeOH	5.5	40
4	**$LiClO_4$**	**MeOH**	**2.6**	**85**[a]

[a] A 1.5:1 ratio of diastereomers was formed.

Table 2. Benzyl-Protected Substrate



entry	electrolyte	solvent (v:v)	coulomb (F/mol)	yield (%)
1	$LiClO_4$	MeOH/THF (3:7)	5.5	54
2	$LiClO_4$	MeOH/THF (6:4)	3.6	60
3	**$LiClO_4$**	**MeOH**	**3.0**	**62**[a]
4	Et_4NOTs	MeOH	3.4	50

[a] A 2:1 ratio of diastereomers was formed.

(7) Bi, B.; Maurer, K.; Moeller, K. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 5872.
(8) Tesfu, E.; Roth, K.; Maurer, K.; Moeller, K. D. *Org. Lett.* **2006**, *8*, 709.
(9) Dondoni, A.; Mauer, A. *Chem. Rev.* **2000**, *100*, 4395.
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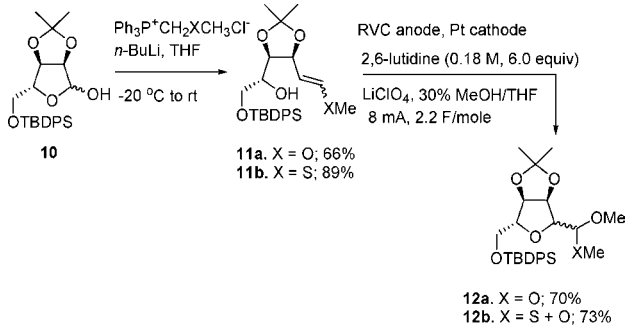
(12) For a review of anodic olefin coupling reactions, see: Moeller, K. D. *Synlett.* **2009**, *8*, 1208.
(13) For a general review of electrochemical approaches, see: Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2009**, *108*, 2265.
(14) See the Supporting Information.
(15) (a) Liu, B.; Duan, S.; Sutterer, A. C.; Moeller, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 10101. (b) Xu, H.-C.; Brandt, J. D.; Moeller, K. D. *Tetrahedron Lett.* **2008**, *49*, 3868.
(16) *Synthetic Organic Electrochemistry*, 2nd ed.; Fry, A. J., Ed.; John Wiley and Sons, Inc: New York, 1989; pp 38—42 and 113—114.

tions still led to the highest yield in this case, the effect of the change was not nearly as pronounced, suggesting that the less polar substrate was better able to approach the electrode surface when less polar reaction conditions were used. The yield and the current efficiency for the reactions using the benzyl protected ribose substrate were lower than those obtained with **6**. Proton NMR data for the crude reaction mixture suggested that this observation resulted from background oxidation of the benzyl protecting groups. Once again, the presence of the oxygens on the ribose backbone did not interfere with the cyclization.

Attention was next turned toward exploring the compatibility of a substrate having the oxygens differentially protected. Two such substrates were examined, one with an enol ether as the site for the initial oxidation and the second with a vinyl sulfide serving in this capacity (Scheme 2). Both

Scheme 2

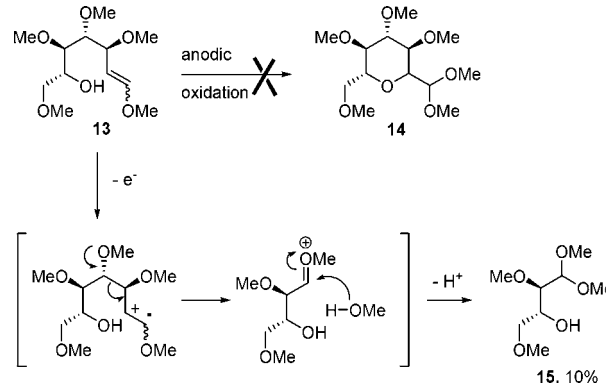


substrates were synthesized from the protected sugar using a Wittig reaction. Formation of the vinyl sulfide consistently led to higher yields of electrolysis substrate. The electrolysis of both substrates proceeded in a similar manner with both substrates benefiting from the use of $LiClO_4$ as electrolyte and 30% MeOH/THF as the solvent. With the very hydrophobic *tert*-butyldiphenylsilyl protecting group on the molecule, the reactions did benefit from the use of THF as a cosolvent. In the case of methoxy enol ether substrate **11a**, the reaction gave the product in a yield close to 100% when measured by NMR (coumarin added as an internal standard to the crude reaction material). The isolated yield was 70% with the loss of material being attributed to the instability of the acetal product. The reaction was compatible with the synthesis of multigram quantities of the product. In this case, a 2.4:1 ratio of diastereomers about the newly formed carbon−oxygen bond was formed.

In the case of the vinyl sulfide substrate **11b**, a nearly identical result was obtained with a 73% isolated yield of cyclized product being produced in a 2.5:1 ratio of diastereomers about the newly formed carbon−oxygen bond. The cyclized material was obtained as a mixture of the monothiol acetal and the dimethoxy acetal product. The thioacetal could be converted into the dimethoxy acetal using $HgCl_2$, HgO, and methanol. In our hands, this method worked better than an oxidative cleavage of the hemithioacetal.[17] Overall, the mixture of acetals was not an issue since the products will be hydrolyzed to the aldehyde for future development. Hence, the use of the vinyl sulfide proved desirable because of the higher yield associated with the substrate synthesis.

With the synthesis of furanose-derived C-glycosides in place, attention was turned to the synthesis of pyranose derivatives. Once again, the study began by examining the anodic oxidation of a polymethoxy ether substrate (Scheme 3). In this case, the anodic oxidation led to none of the

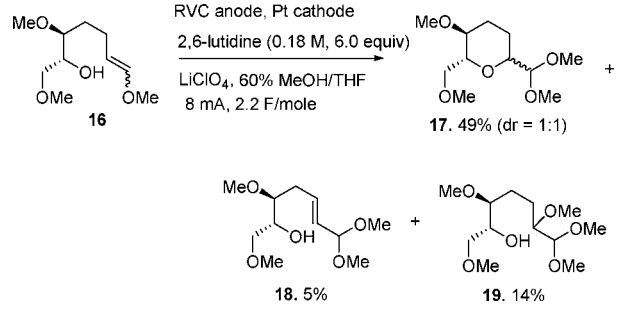
Scheme 3



desired cyclic product. Instead, a complex mixture of products was obtained out of which 10% of a product (**15**) generated by fragmentation of the initial radical cation was isolated. Presumably, product **15** arose due to the slower six-membered ring formation relative to the earlier five-membered ring formation in the furanose cases.

The effects of the slower six-membered ring cyclization were also seen when a substrate lacking the C_3 and C_4 methoxy groups was oxidized (Scheme 4). In this example,

Scheme 4



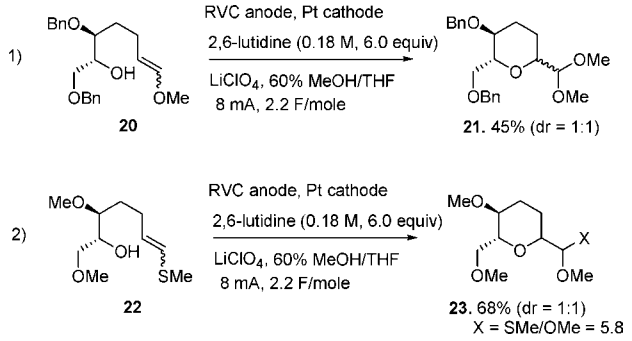
there was no ether substituent to trigger the fragmentation. However, the yield of the cyclization was still low, this time

(17) For alternative methods, see: Saito, I.; Takayama, M.; Sakurai, T. *J. Am. Chem. Soc.* **1994**, *116*, 2653. (b) Yoshida, J.; Isoe, S. *Chem. Lett.* **1987**, *16*, 631. (c) Yoshida, J.; Sugawara, M.; Tatsumi, M.; Kise, N. *J. Org. Chem.* **1998**, *63*, 5950.

due to the elimination and methanol trapping pathways that are more traditional side reactions for an anodically generated radical cation. Attempts to optimize the yield of the cyclization using the same set of conditions shown in Tables 1 and 2 led to a decrease in the yield of the cyclized product and the overall mass balance of the reaction. In some ways, the low yield of the cyclization was not a surprise. The yields obtained for previous anodic cyclizations coupling enol ether radical cations and alcohols leading to tetrahydropyran rings benefited from the use of Et_4NOTs as the electrolyte and were sensitive to substituents on the tether connecting the reactive groups.[15a] Presumably for these cyclizations, the use of the Et_4NOTs excludes methanol from the region surrounding the electrode providing more time for the cyclization. With the more polar substrates used in the current study, this approach proved problematic due to the lower efficiency of the desired oxidation. What was needed was either a method for making a less polar substrate so that Et_4NOTs could be used as the electrolyte or a method for accelerating the cyclization.

An attempt to improve the cyclization using larger hydrocarbon protecting groups was not successful (Scheme 5, eq 1). The reaction behaved in a fashion identical to the

Scheme 5

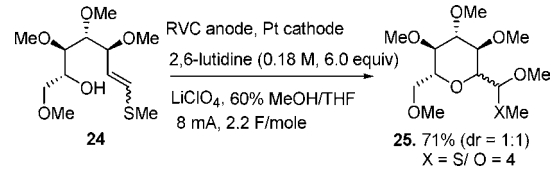


oxidation of **16**. While still larger groups might help in this regard, the overall approach was abandoned because of the limitations it placed on substrate generality.

Instead, a strategy to increase the rate of the cyclization was pursued. Since the trapping of radical cation intermediates by heteroatoms is accelerated by the use of less polarized radical cations,[18,19] a substrate having a vinyl sulfide as a site for the initial oxidation was synthesized. The anodic oxidation of this substrate led cleanly to the cyclized material (Scheme 5, eq 2). A 68% yield of the desired product was obtained as a mixture of acetal products. Once again, this mixture was not important since carrying the product forward involves hydrolysis of the acetal.

The success of this reaction turned our attention back to the fully substituted sugar derivative. Did the use of the vinyl sulfide derived radical cation accelerate the cyclizaton to a point where the fragmentation could be avoided? To our delight, the answer to this question is yes (Scheme 6).

Scheme 6



When the fully methoxylated pyranose was converted into a vinyl sulfide and then oxidized at an RVC anode, a 71% isolated yield of the cyclized product was obtained. Only a trace amount of fragmentation product **15** was observed.

In conclusion, a two-step Wittig reaction−anodic coupling reaction strategy provides a very rapid, convenient method for converting protected furanose and pyranose sugars into C-glycosides. Currently, work to expand this chemistry to include transformations involving sugar oligomers and efforts to place and monitor the behavior of sugars site-selectively on microelectrode arrays are underway.

Acknowledgment. We thank the National Science Foundation (CHE-0809142) for their generous support of this work.

Supporting Information Available: Sample experimental procedure for the oxidation reaction along with characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc.* **2010**, *132*, 2839.