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Synthesis of novel dihydrooxazine and oxazoline based sugar hybrids from sugar azides ☆

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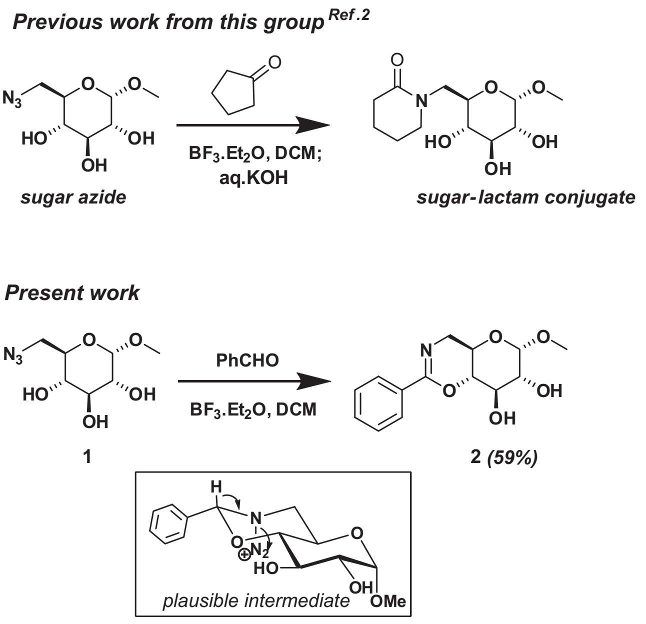
ABSTRACT

A convenient one-step method for the synthesis of novel dihydrooxazine and oxazoline based sugar hybrids is reported starting from the readily accessible sugar azides and aldehydes. We have used Aubé's protocol to achieve this transformation. The resulting glycoconjugates could be used to increase the diversity on the sugar backbone and may find applications as potential glycomimetics and in drug discovery.

Construction of sugar-based hybrids with biologically interesting scaffolds is an attractive area of research due to their widespread applications, especially in the area of drug discovery.[1] Recently, we have reported the synthesis of sugar-lactam conjugates using the Aubé reaction conditions starting from readily accessible sugar azides and cyclic ketones (Scheme 1).[2] Replacing cyclic ketones with aromatic aldehydes under the Aubé reaction conditions resulted in dihydrooxazine or oxazoline-based sugar hybrids in good to moderate yields. This observation is in line with Aube's group reports for the synthesis of dihydrooxazines/oxazolines using azido alcohols.[3] The oxazoline and dihydrooxazine heterocycles appear in numerous biologically active compounds which include natural products and synthetic drugs.[4,5] These compounds are also valuable synthetic intermediates[6] and they are often used as protecting groups.[7] Combining these important classes of compounds with sugars is always interesting and rewarding. The scope of the method with various substrates was tested and the results are disclosed in this Letter.

Initially, we have chosen readily accessible sugar azide **1**[8] to check the feasibility of the planned synthesis. The reaction was carried out with benzaldehyde in the presence of $BF_3{\cdot}Et_2O$ in dichloromethane solvent to furnish the dihydrooxazine-based glucose hybrid **2** in 59% isolated yield.[9] Compound **2** was characterized



Scheme 1. Strategy to access proposed sugar hybrids.

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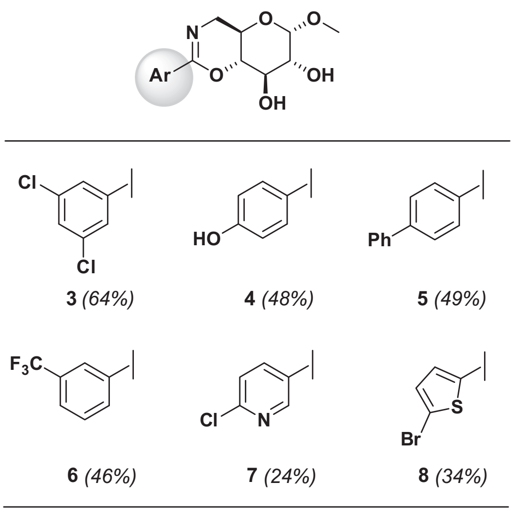
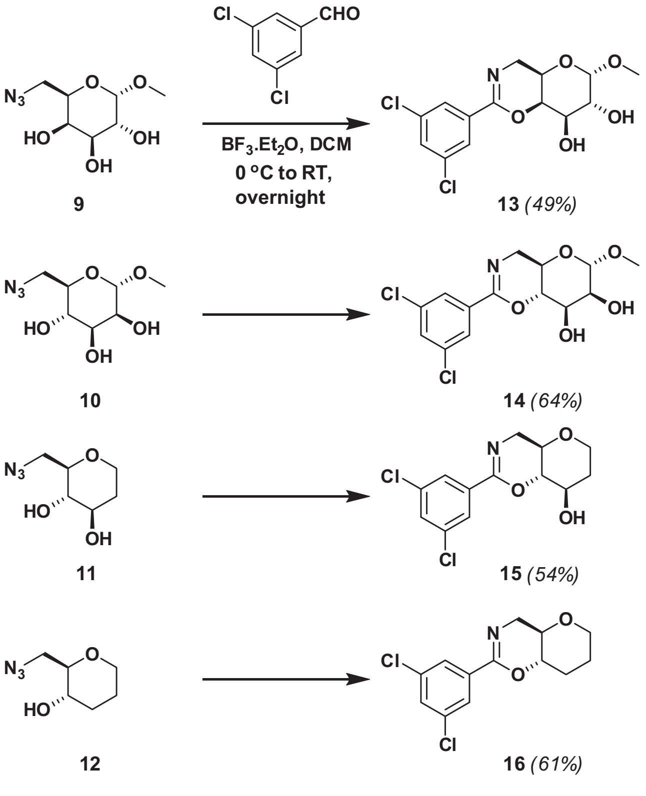


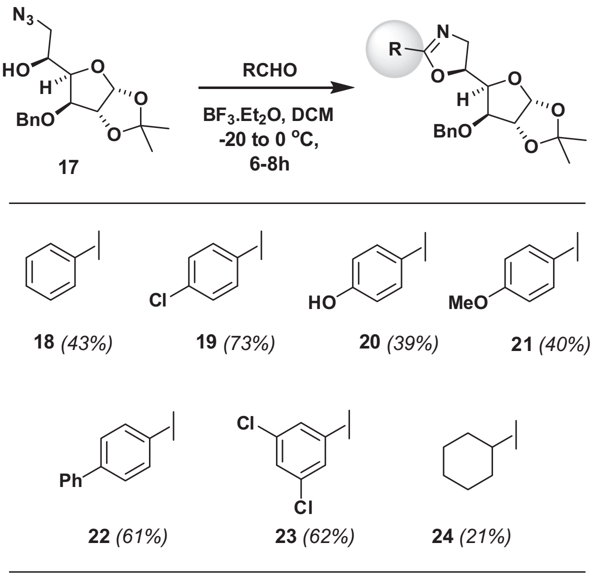
Figure 1. Products obtained from the reactions of **1** with various aldehydes.

using the spectral data (^{1}H, ^{13}C NMR, HRMS, and IR). Having this protocol in hand, azide **1** was reacted with different aromatic aldehydes and the results are outlined in Figure 1. Reaction of dichlorobenzaldehyde, *p*-hydroxy benzaldehyde, and *p*-phenyl benzaldeyhde with the sugar azide **1** under the same conditions furnished the desired products **3**, **4**, and **5** in good yields, respectively. Pharmaceutically important *m*-trifluoromethyl phenyl containing sugar hybrid **6** was also produced in 46% yield using the corresponding aldehyde.[10] In the case of heteroaryl aldehydes, products **7** and **8** were isolated in low yields compared to the aromatic ones.

By choosing the best among the examples, 3,5-dichlorobenzaldehyde was reacted with a variety of sugar azides prepared in our lab. All four sugar azides **9–12**[11] with embedded azido alcohol functions smoothly reacted under the same conditions to produce the desired products **13–16** in good yields (Scheme 2).[12] It is interesting to note that the protection of free hydroxyl groups is not required for the present method.



Scheme 2. Synthesis of dihydrooxazine based hybrids.



Scheme 3. Synthesis of oxazoline-based sugar hybrids.

To amplify the scope of this method, we have attempted the reactions with 1,2-azido alcohol embedded sugar azides to produce oxazoline-based sugar hybrids. Sugar azide **17** prepared from D-glucose was treated with a variety of aldehydes and the results are shown in Scheme 3. The benzaldehyde and all other substituted benzaldehydes gave the corresponding products **18–23** in yields ranging from 40% to 70%.[12] However, when we attempted the reaction with cyclohexylaldehyde, product **24** was formed in poor yield (21%). In all oxazoline cases, the best yields are obtained at low temperatures.

In short, we have developed an access to novel sugar hybrids based on dihydrooxazine and oxazoline frameworks starting from the readily available sugar azides using Lewis acid ($BF_3{\cdot}Et_2O$) mediated conditions. These compounds can be useful as such or may be used for further manipulations to increase the diversity of the sugar framework.

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Supplementary data

Supplementary data (general methods, experimental details and characterization data for compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.035.

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9. *Representative procedures:* (a) Dihydrooxazine-based sugar hybrid. To the mixture of 6-azido-6-deoxy-methyl-α-D-glucopyranoside **1** (150 mg, 0.68 mmol) and benzaldehyde (0.11 mL, 0.75 mmol) in dichloromethane (5 mL), $BF_3\cdot Et_2O$ (0.13 mL, 1.02 mmol) was added under argon atmosphere at 0 °C. The reaction mixture was stirred overnight at room temperature and neutralized with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3 × 20 mL), combined organic layer was washed with brine (20 mL) and dried over sodium sulfate evaporated under reduced pressure to get crude product. The crude material was purified on silica gel column chromatography (1:1 EtOAc-hexane) to afford the desired product (**2**)**.** Yield 59%; $[\alpha]_D^{24.1} = 11.8°$ (c 0.5, MeOH); IR ($CHCl_3$): 1044, 1263, 1650, and 3368 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ; 3.40–3.50 (m, 1H), 3.44 (s, 3H), 3.58 (dd, $J = 10$, 4 Hz, 1H), 3.67–3.78 (m, 2H), 3.86–3.94 (m, 2H), 4.77 (d, $J = 4$ Hz, 1H), 7.36–7.49 (m, 3H), 7.93 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 157.6, 133.7, 132.1, 129.2 (2C), 128.7 (2C), 102.0, 79.1, 73.6, 72.0, 63.1, 55.9, 48.7 (merged in solvent peaks); LC–MS = 280.1 (M+1); HRMS (ESI): m/z calculated for $C_{14}H_{18}NO_5$ $[M+H]^+$ 280.1181, found 280.1178. In case of oxazoline-based sugar hybrids, $BF_3\cdot Et_2O$ was added slowly under argon atmosphere at −20 °C and stirring continued below 0 °C for 6–8 h. See, supporting information for the details.
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11. Sugar azides are prepared using the procedures described in supporting information or cited literature in Ref. 2.
12. The analytical data (^1H, ^{13}C, IR, and MS) of all the products are in good agreement with proposed structures. All the details are included in supporting information.