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Stereoselective glycosylation of *exo*-glycals by microwave-assisted Ferrier rearrangement

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Abstract—*exo*-Glycosyl carbonates were shown to be efficient glycosyl donors in microwave-assisted glycosylation. In these reactions α-glycosyl additions occurred with excellent stereoselectivity and were complete in 4–8 min with 75–92% yield. Interestingly *exo*-glycals were found to have higher activity than *endo*-glycals and common glycosides, the reactions of which can be improved by the addition of Lewis acid to result in a higher yield and enhanced stereoselectivity.

Glycals are unsaturated sugars with a double bond at the anomeric center. They are categorized as *endo*- and *exo*-glycals according to the double bond located inside or outside the sugar ring, respectively. *endo*-Glycals have been extensively investigated and numerous applications were developed for various synthetic purposes. Especially the method of 'glycal assembly', utilizing *endo*-glycals as both glycosyl donors and acceptors, has carried out various glycosylation reactions in an iterative fashion with minimal protecting group manipulation.[1] A number of complex oligosaccharides, glycosylated natural products and tumor-associated carbohydrate antigens have been successfully prepared by Danishefsky et al. starting from *endo*-glycals.[2–6]

Furthermore, *exo*-glycals have been shown great promise in the synthesis of *C*-glycosides, ketoses, and ketosides, and *N*-glycosides.[7] In particular, we recently established an expeditious two-step method to prepare *exo*-glycals in a good overall yield starting from sugar lactones.[8,9] The procedure is not only suitable for various monosaccharyl precursors including *gluco*-, *galacto*-, *manno*-, and *fuco*-types, but also applicable to generate *exo*-glycals with different substituents.[10] Among them compounds **1** and **2** (Fig. 1) were found to be highly reactive in Lewis acid-catalyzed glycosylation to afford various glycosides with exclusive α-configuration.[11] The enhanced activity was owing to allylic rearrangement, commonly known as the Ferrier reaction. In search of a better promoter for glycosidic bond formation, carbonates **3** and **4** are considered as better glycosyl donors because the decarboxylation occurs to release carbon dioxide during the heating process, as an extra driving force to increase further the reactivity. The strategy was previously used in the inter-[12,13] and intra-molecular[14,15] glycosidations. The carbonate is able to serve as a good leaving group, as well as a linker to connect the donor and acceptor (in the latter case). Herein we report the microwave-induced glycosylation of *exo*-glycals. The microwave method was found to be superior to the traditional heating, representing a coherent conclusion with the previous reports.[16] Despite a growing interest in the studies of microwave-assisted reactions in organic synthesis since 1986,[17] their application in carbohydrate chemistry is rather restricted.[18–20]

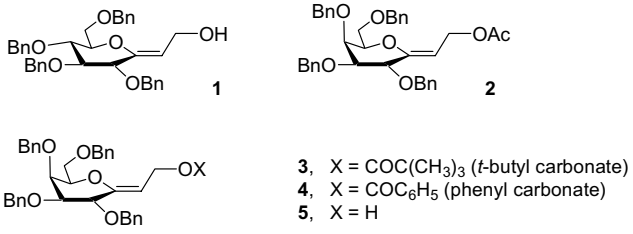

Figure 1. Structures of compounds **1**–**5**.

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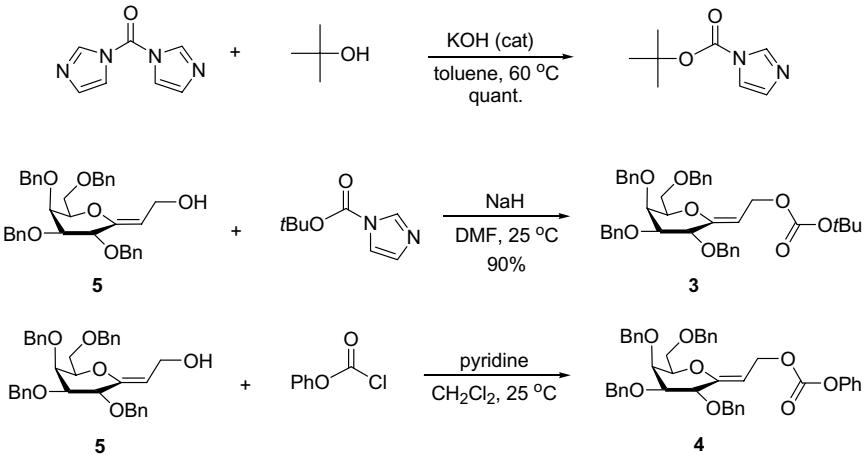
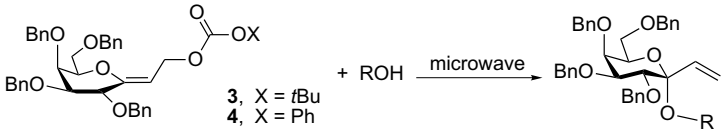


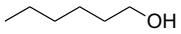
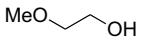
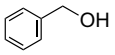
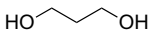
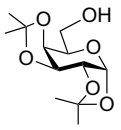
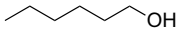
Scheme 1. Preparation of *exo*-glycosyl carbonates **3** and **4** as the glycosylation donors.

To prepare compounds **3** and **4** is straightforward. As shown in Scheme 1, the reaction of 1-(*Z*)-(2′-hydroxyethylidene)-2,3,4,6-tetra-*O*-benzyl-D-galacto-pyranoside **5** with *t*-butoxycarbonylimidazole (synthesized quantitatively by the condensation of 1,1′-carbonyldiimidazole and *t*-butanol)[21] in the presence of 1 equiv sodium hydride afforded the desired product **3** in 90% yield from **5**. Likewise compound **4** can be synthesized by a similar coupling reaction of **5** with phenyl chloroformate. However, instability made *exo*-glycal **4** less suitable for long-term storage and routine investigation.

The reaction of *exo*-glycal **3** with allyl alcohol took 20 h under the reflux condition in DMF to afford the desired product in 83% yield. A higher yield (92%) with shorter reaction time (4 min) was observed by using microwave irradiation. Table 1 demonstrates the microwave-assisted glycosylations of *exo*-glycals **3** and **4** to produce

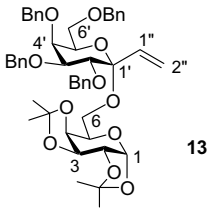
Table 1. Microwave-assisted glycosylation of *exo*-glycals **3** and **4**



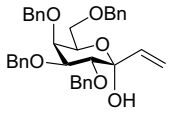
Entry	Donor	Acceptor (ROH)[a]	Time (min)	Product [yield (%)][b]
i	**3**		8	**6** (90%)
ii	**3**		8	**7** (85%)
iii	**3**		4	**8** (87%)
iv	**3**		20	**9** (75%)
v	**3**		8	**10** (85%)
vi	**3**		4	**11** (78%)
vii	**3**		4	**12** (92%)
viii	**3**		30	**13** (75%)[c]
ix	**4**		2	**6** (81%)

[a] The glycosyl additions were all under a solvent-free condition with the presence of excessive alcohol nucleophile (>30 equiv), except for the entry viii in which 3 equiv of the acceptor was dissolved in nitropropane (solvent).
[b] All the reactions were carried out at 150 °C with 200 W of microwave energy.
[c] In addition to the desired product, hydrolyzed product **14** (10%) was observed.

glycosides **6**–**13** in an open vessel. The CEM 'Discover' Focused Microwave™ Synthesis System is the instrument to provide microwave energy. Except for entry viii, all the reactions were studied under a solvent-free condition and the majority of the reactions were complete at 150 °C with 200 W of microwave energy within 4–8 min with 75–92% yield. No reaction was found for the reaction with 1,2:3,4-di-*O*-propylidene-α-D-glucopyranoside in the absence of solvent. When nitropropane was used as the reaction solvent, the desired product was obtained in 75% yield with concomitant formation of the rearranged product **14** (10% yield, resulting from the addition of water). Because the reactions were carried out without cooling, the radiation energy declined to maintain the constant temperature during the microwave process. Therefore, the same reactor with simultaneous cooling is likely to finish reaction in a shorter time.



13



14

Consistent with our earlier work,[11] the glycosylation reactions displayed exclusive stereoselectivity. All the reactions occurred via α-glycosyl additions, that is, the nucleophilic attack from the bottom face of the sugar ring, to result in the vinyl group at the β-position. The product structures were either rigorously determined by DEPT, NOESY and other spectroscopic spectra, or in good agreement with the reported NMR spectral data. For example, the DEPT spectra of the glycosylation product **13** indicated the C-1′ resonance appeared at δ 99.96, besides the other two quaternary carbons (δ 108.44 and 109.11) of the isopropylidene groups. The NOESY spectra of **13** (Fig. 2) exhibited the cross-peaks between H5′ (δ 4.16) and H6a (δ 3.50), as well as H2′ (δ 3.84) and H1″ (δ 5.95), which thus verified that the *C*-vinyl group is located at the β-position. In addition, the three-bond carbon–proton coupling constant $^{3}J_{C,H}$ (~1.6 Hz), related to the orientation of the H2′ and vinyl carbon (–*C*H=), also confirmed the expected stereochemical outcome.[22]

Despite the low stability, the phenyl-substituted *exo*-glycal **4** can be possibly used as the glycosyl donor providing that the compound is freshly made before the glycosylation. In the reaction with *n*-hexanol (entry ix), the formation of the desired product was finished within 2 min in 81% yield by the microwave method, in contrast to the 64% yield (plus 20% of an unknown product) obtained by the conventional heating at 100 °C for 30 min. Consistent with the previous result, this comparison clearly indicates that the microwave irradiation has the advantages of shorter reaction time and cleaner reactions.

Additionally, there are a number of factors affecting the reactivity, as shown in Table 2. The glycosylation of *exo*-glycosyl acetate **2** (entries i and ii) took a longer time than that of **3**, which echoes the previous result that *t*-butyl and phenyl carbonates have dissimilar rates. Interestingly the carbonate functionality exerts varied activity in *exo*-glycal, *endo*-glycal, and glycoside. *endo*-Glycal **15** is less reactive than analogous *exo*-glycal **3**, as indicated by the longer reaction time and incomplete reaction in entries iii, v, vi, and viii (in comparison with entries i–iv of Table 1, respectively), even though the latter molecule exhibits more steric hindrance. The formation of hydrolyzed product **21** was only observed for the microwave irradiation of *t*-butylcarbonyl 2,3,4,6-*O*-tetrabenzyl-α-D-galactoside **16**, as shown in the parallel studies of entries x and xi. The addition of Lewis acid

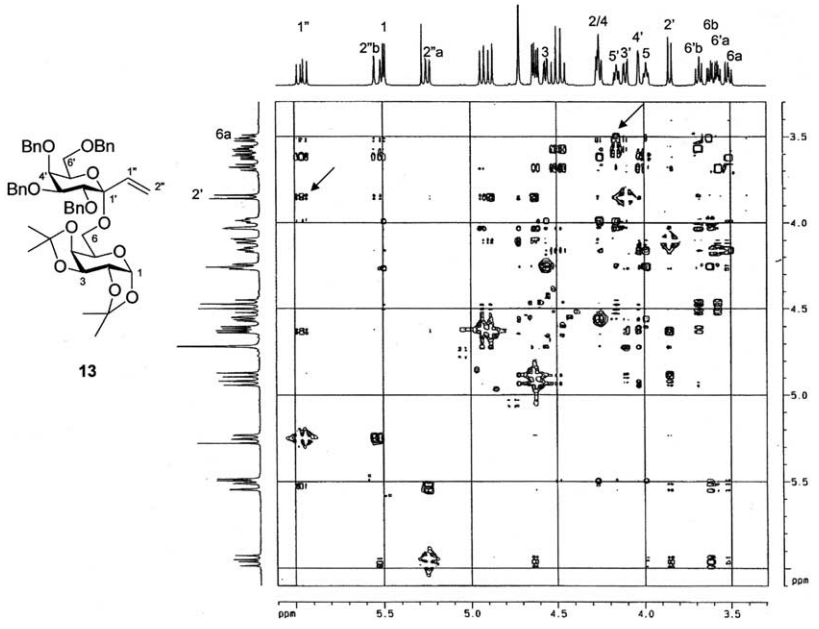
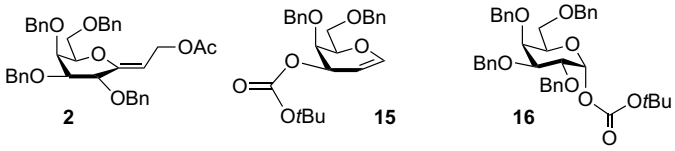
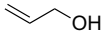
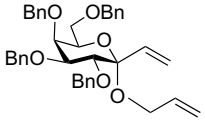
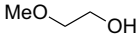
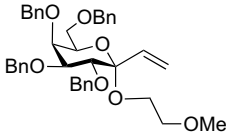
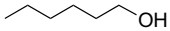
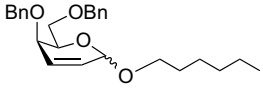
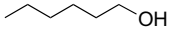
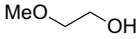
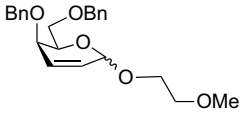
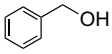
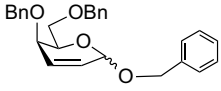
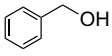
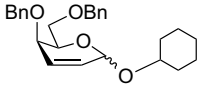
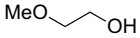
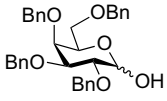
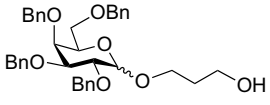


Figure 2. NOESY spectra of product **13**. The arrows designate the cross-peaks between H5′ and H6a, as well as H2′ and H1″.

Table 2. Glycosylation reactions of carbonate donors **2**, **15**, and **16**



Entry	Substrate	Nucleophile	Time (min)	Product[a,b] [yield (%), α/β ratio]
i	**2**		10	 **12** (80%)
ii	**2**		30	 **7** (80%)
iii	**15**		30	 **17** (50%, 5/1)[c]
iv	**15**		2 (With $InCl_3$)	**17** (91%, 7/1)
v	**15**		40	 **18** (74%, 4/1)[c]
vi	**15**		30	 **19** (70%, 7/1)[c]
vii	**15**		2 (With $InCl_3$)	**19** (75%, 13/1)
viii	**15**		30	 **20** (25%, 7/1)[c]
ix	**15**		2 (With $InCl_3$)	**20** (85%, 11/1)
x	**16**		30	 **21** (90%)
xi	**16**	—[d]	20	**21** (93%)
xii	**16**		4 (With $InCl_3$)	 **22** (85%, 5/1)

[a] All reactions were carried out at 150 °C with 200 W of microwave energy in a solvent-free condition with the alcohol acceptor in excess (>30 equiv), except for entry xi.
[b] The α/β ratio was determined on the basis of ^1H NMR integration.
[c] The reactions of entries iii, v, and viii were not complete with the remaining starting materials of 40%, 20%, and 70%, respectively.
[d] DMF was the solvent.

will enhance the glycosylation activity. In the presence of $InCl_3$ (0.2 equiv), for instance, the reaction of *endo*-glycal **15** with *n*-hexanol (entry vi) was complete in 2 min to produce the desired glycoside (91%).[19] Similar improvements in the yield, reaction time and stereoselectivity were made in the case of benzyl alcohol (entry vii)

and cyclohexanol (entry ix).[23] This approach was also effective to the glycosyl addition of galactoside **16** (entry xii). As a consequence, the presence of Lewis acid is complementary to microwave-assisted glycosylation.

In summary, this report not only demonstrates the high efficiency of the microwave-induced glycosylation of *exo*-glycals, but also compares the activity among *exo*-glycals, *endo*-glycals and general glycosides. Further investigation to understand the basis underlying the rate difference is in progress and will be published in due course.

Acknowledgements

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23. The stereochemistry of compounds **17**–**20** was determined by the integration of the ^{1}H NMR spectra. In order for clear assignment, the α-form (major) of **20** was hydrogenated to saturate the double bond at 25 °C over Pd/C in EtOAc containing Et_3N. The resulting product **23** has the anomeric H1 resonance at δ 5.02. The small $J_{1,2}$ value (3.0 Hz) confirms the α-configuration.