Organocatalytic Conversion of Ribose and Other Protected Carbohydrate Derivatives into 2-Deoxy-lactones

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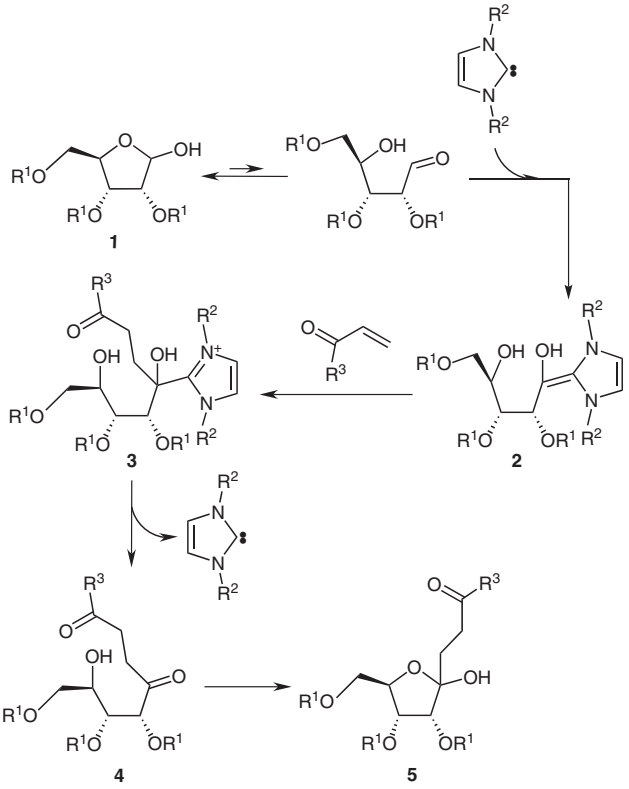
Abstract: We report the simultaneous reduction of the 2-position and oxidation of the anomeric position in several protected furanosyl and pyranosyl sugar derivatives, mediated through NHC catalysis. This reaction allows the one-step access to highly valuable 2-deoxy-sugars from abundant 2-oxygenated sugar derivatives.

Key words: carbenes, deoxygenation, green chemistry, isomerization, umpolung

In our continued interest to develop efficient reactions for the economic derivatization and functionalization of carbohydrates[1–3] we asked the question whether a N-heterocyclic carbene (NHC) catalyst can be used to directly functionalize the aldehyde functionality masked at the anomeric center in sugars as a hemiacetal. NHC catalysis is rich, but has not, to the best of our knowledge, yet been applied to the derivatization of sugars.[4–8] We envisioned that reaction of a NHC and a suitable carbohydrate would lead to a Breslow intermediate **2**[9] which could engage in different pathways, depending on protecting groups used [in particular at the C(2)–OH of the sugar] and additional reagents submitted to the reaction mixture. For example, reaction of the Breslow intermediate **2** with α,β-unsaturated ketones could lead to highly valuable products such as **5** derived from Stetter reactions at the anomeric center (pathway A, exemplified for a protected furanosyl ribose in Scheme 1). However, instead of reacting with electrophiles, the Breslow intermediate **2** could also collapse through β-elimination of an oxgygen leaving group at the C(2) position of the sugar (Scheme 2, pathway B). Also this reaction would lead to highly valuable 2-deoxy-carbohydrate-lactones, which are usually accessed from 2-oxygenated carbohydrates through multistep transformations involving oxidation of the anomeric position and radical deoxygenation of the 2-position in addition to elaborate protecting-group manipulations to allow for the desired chemoselectivity.[10] Such reactivity (pathway B) would have precedent in very elegant work independently performed by Bode[11] and Rovis[12] who have shown that reactions of aldehydes containing leaving groups such as epoxides, aziridines, and halogens or even activated carbon atoms in their α-positions undergo NHC-catalyzed redox transfer and provide esters through subsequent intermolecular reaction with alcohols. Recently, Gravel has applied this principle to the synthesis of lactams, demonstration that amides, carbamates, sulfonamides, and benzylamines can act as suitable leaving groups as well.[13] We report here our studies demonstrating that pathway B can be exploited synthetically with several different carbohydrates in moderate to good yields.



Scheme 1 Hypothetical pathway A: Stetter reaction

In an intitial attempt 2,3,5-tribenzylated ribose was reacted with 0.3 equivalents of 1,3-bis-*tert*-butylimidazol-2-ylidene in THF. Disappointingly neither of the two discussed pathways occurred; instead β-elimination of the C(3)–OBn group led to the clean formation of **9** (Scheme 3). We assumed that the reported high basicity of 1,3-bis-*tert*-butylimidazol-2-ylidene [p$K_{a(DMSO)}$ = 22.7][14–16] may well be responsible for such outcome and that the utilization of a less basic carbene catalyst would suppress this competitive undesired pathway in favor of either pathway A or B.

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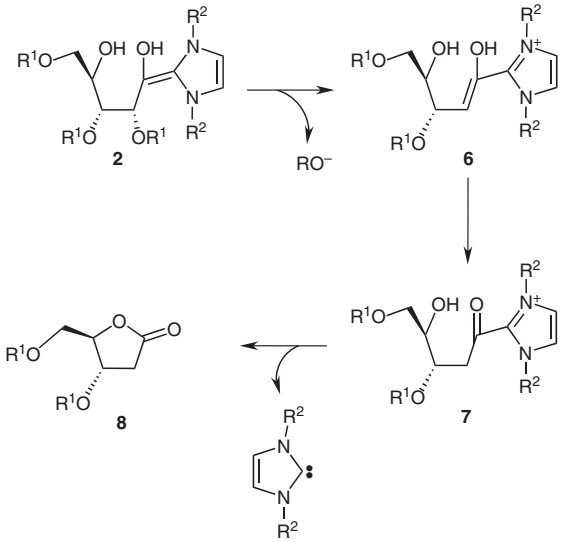


Scheme 2 Pathway B: Bode–Rovis reaction

We therefore screened reaction conditions involving the following catalysts and precatalysts (Figure 1). The reaction conditions screened are summarized in Table 1.

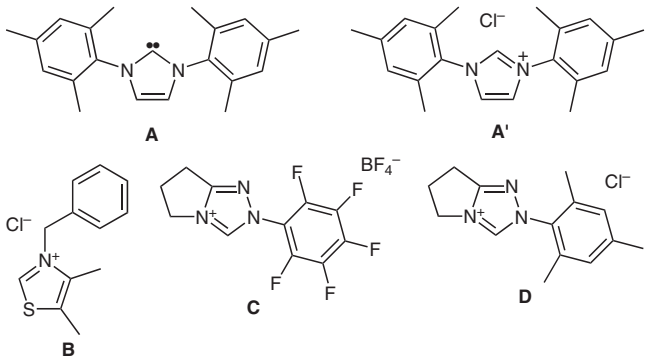
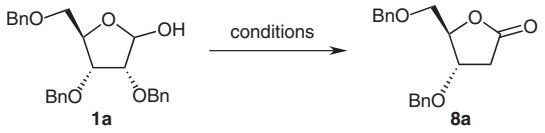


Figure 1 List of screened catalysts and precatalysts

Reaction of **1a** with catalyst **A** provided **8a** in satisfactory conversion at ambient temperature. Reaction with *in situ* generated carbene catalyst (**A′** and DBU) succeeded, however, with very low conversion (Table 1, entry 2). The catalyst generated from thiazolium **B** and either Et_3N or KO*t*-Bu resulted in no reaction (Table 1, entries 3 and 4), while **C** in the presence of either Hünig's base or KO*t*-Bu gave conversion in the range of 50% (Table 1, entries 5–7). Longer reaction times did not further improve overall conversion, suggesting catalyst deactivation. Gratifyingly, 100% conversion was observed with the catalyst derived from **D** and DBU at 50 °C (Table 1, entry 12). The use of KO*t*-Bu or Hünig's base instead of DBU resulted in either no reaction or lower conversions. Those optimized conditions allowed the isolation of **8a** in 68% yield.

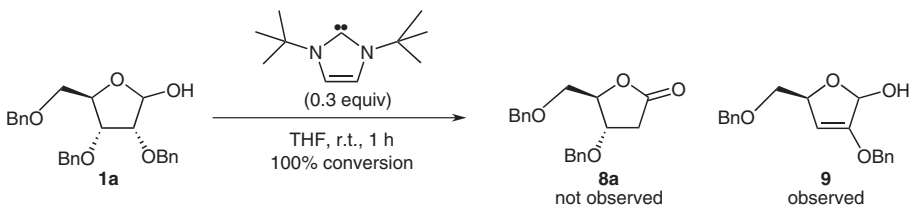
Table 1 Reaction Conditions for the Synthesis of **8a**[a]



Entry	NHC[b]	Base[d]	Solvent	Temp (°C)	Time (h)	Conv. (%)[e]
1	**A**[c]	–	THF	24	20	75
2	**A′**	DBU	PhMe	90	16	10
3	**B**	*i*-Pr_2NEt	DCE	70	24	0
4	**B**	KO*t*-Bu	PhMe	50	20	0
5	**C**	*i*-Pr_2NEt	PhMe	90	7	50
6	**C**	DBU	PhMe	90	16	40
7	**C**	*i*-Pr_2NEt	PhMe	90	24	50
8	**D**	KO*t*-Bu	PhMe	50	20	0
9	**D**	*i*-Pr_2NEt	PhMe	90	7	50
10	**D**	*i*-Pr_2NEt	PhMe	90	24	30
11	**D**	DBU	PhMe	24	16	20
12	**D**	DBU	PhMe	50	16	100 (68)[f]

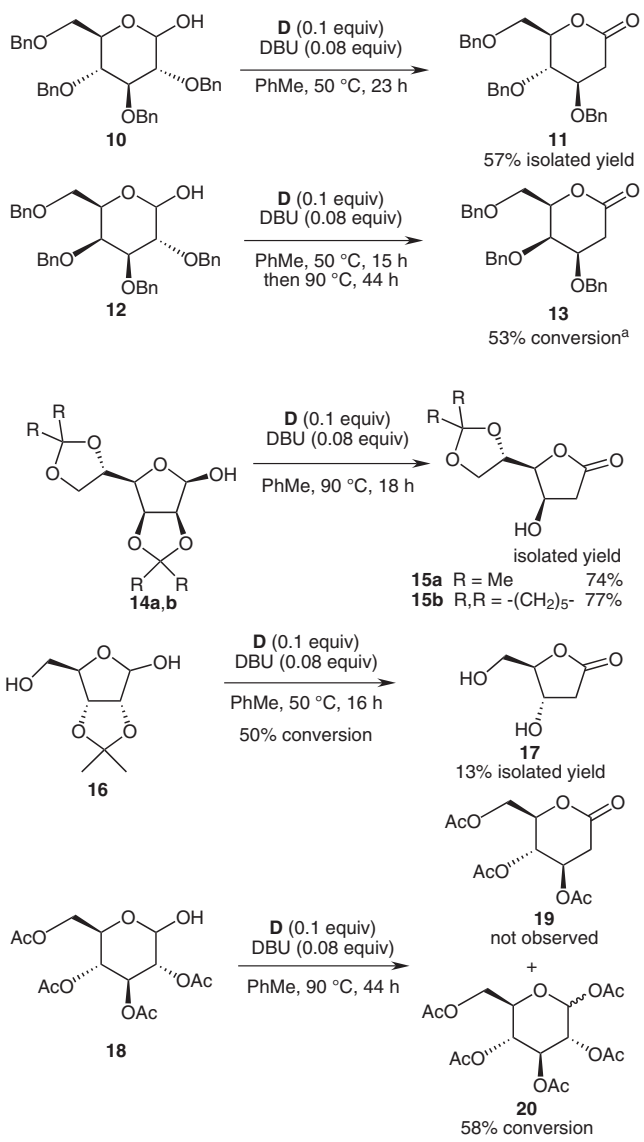
[a] Reaction conditions screened for conversion of **1a** into **8a**.
[b] 0.1 equiv.
[c] 0.3 equiv.
[d] 0.08 equiv
[e] Based on crude ^{1}H NMR, the remainder being starting material.
[f] Isolated yield of **8a** on a 400 mg scale.

Applying the optimized reaction conditions to other pentose and hexose derivatives allowed for the preparation of several C(2)-deoxy-lactones. Results are summarized in Scheme 4. Both, C(2)-benzyl ethers and C(2,3)-ketals were suitable leaving groups allowing for deoxygenation of the C(2)-position with concomitant oxidation of the anomeric C(1) in several sugar derivatives. In the case of C(2,3)-ketals (**14** and **16**) the corresponding C(3) free alcohols were isolated. In the case of **16**, the reaction proceeded with 50% conversion, as judged by ^{1}H NMR of the crude reaction mixture. The low isolated yield of **17** may



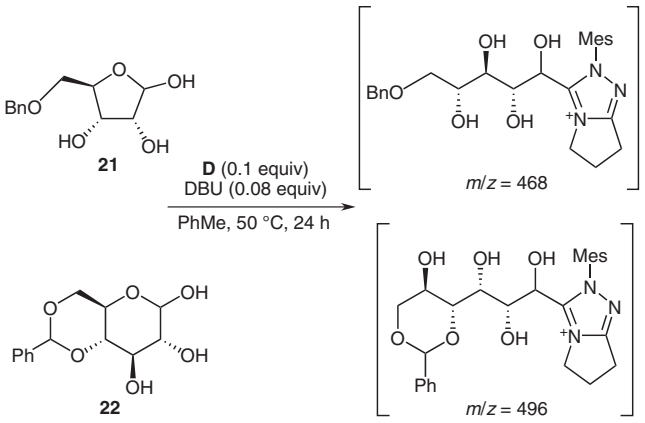
Scheme 3 Undesired β-elimination with 1,3-bis-*tert*-butylimidazol-2-ylidene

be explained by acid-catalyzed conversion into its pyranosyl derivative.[17] By contrast, acetylated sugars were not suitable substrates for this redox-transfer reaction. The known NHC-catalyzed transacetylation[18] took place instead and produced **20**, the peracetylated derivative.



Scheme 4 Redox transfer between C(1) and C(2) of pentose and hexose derivatives. [a] Separation from remaining starting material not possible.

As discussed in introduction, we were wondering if functionalization of the anomeric position would be possible if a weaker leaving group was present in the carbohydrate substrate. We therefore attempted reactions with 2-hydroxylated sugars. No reaction occurred when **21** and **22** were treated with catalytic amounts of **D** and DBU (Scheme 5). However, LC–ESMS inspection of the reaction mixture showed a new peak (m/z = 468 for the reaction of **21** and m/z = 496 for the reaction of **22**) consistent with the adduct of the carbene and the sugar. In contrast to benzyloxy- and acetal-protected alcohols in **1a**, **10**, **12**, **14**, and **16** no elimination of hydroxide occurred. Addition of methyl vinyl ketone to the reaction mixture derived from **22** did not lead to the desired Stetter product.



Scheme 5 Adduct formation observed by LC–ESMS between ribose or glucose derivatives not protected in the C(2)-position and catalyst generated from **D**

In summary, we have shown that sugars can be oxidized to the corresponding lactones with simultaneous reduction of the C(2)-position through a catalytic NHC-mediated reaction. This reaction allows for a particular efficient access to C(2)-deoxygenated lactones from carbohydrates. While a free C(1)–OH is required, the C(2)–OH group has to be protected, like for example by a benzyl ether or an acetal. The proposed Breslow intermediate could be observed by mass spectrometry with substrates containing a free C(2)–OH, however, their engagement in Stetter reactions failed.

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(17) (a) **Spectroscopic Data for Compound 17** ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.22 (dd, *J* = 17.61, 2.20 Hz, 1 H), 2.81 (dd, *J* = 17.79, 6.42 Hz, 1 H), 3.47–3.62 (m, 2 H), 4.21–4.32 (m, 2 H), 5.06 (t, *J* = 5.50 Hz, 1 H), 5.49 (d, *J* = 4.03 Hz, 1 H). (b) Compound **17** isolated from the NHC-catalyzed rearrangement was identical to that of an authentic sample purchased from Carbosynth (www.carbosynth.com; catalog number MD00127) and to spectral data reported in: Miranda, P. O.; Estévez, F.; Quintana, J.; García, C. I.; Brouard, I.; Padrón, J. I.; Pivel, J. P.; Bermejo, J. *J. Med. Chem.* **2004**, *47*, 292.
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