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Sugar-derived cyclic imines: one-pot synthesis and direct functionalization

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ABSTRACT

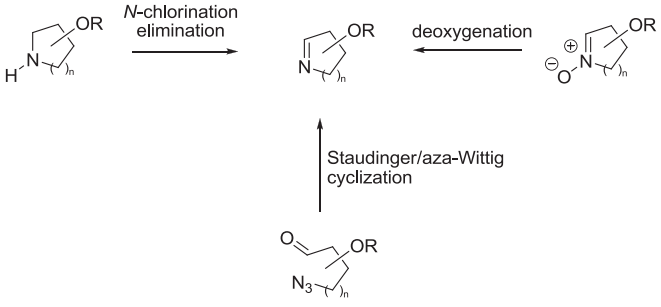
A simple method for the synthesis of sugar-derived imines by a Schwartz's reagent reduction of easily available sugar lactams has been described. A direct addition of nucleophiles to the generated in situ cyclic imines and subsequent deprotection of hydroxyl function allows to convert sugar lactams in polyhydroxylated pyrrolidines and piperidines.

1. Introduction

Cyclic imines have a broad utility for the synthesis of various pharmaceutical and agrochemical intermediates.[1–6] Principally, the sugar-derived imines are attractive building blocks for the stereocontrolled synthesis of natural products owing to the diversity of sugar sources, enantiomeric purity and high stereoselectivity of their transformations.[7–13]

A common method for the synthesis of cyclic imines relies on N-chlorination of the corresponding cyclic amines followed by an elimination (Scheme 1).[11,14] An alternative strategy utilizes a Staudinger/aza-Wittig cyclization.[14a,15] Cyclic imines can be also obtained through deoxygenation of the corresponding nitrones by treatment with phosphines[16] at elevated temperature.

Unfortunately, all of these methods suffer from some drawbacks, which tends to diminish their overall synthetic value. The treatment of α-substituted *N*-chloroamines with base usually leads to a mixture of regioisomeric imines. To a certain extent, the course of elimination can be controlled by the choice of base; for example, the use of DBU at room temperature leads to cyclic ketimines,[11,14] while a treatment of *N*-chloroamine with sterically hindered bases (e.g., LiTMP) at low temperature (−78 °C) provides kinetic aldimines.[11,14] Nevertheless, in many cases such aldimines are still accompanied by their regioisomeric forms, which cannot be easily removed using chromatographic methods due to the limited stability of imines.



Scheme 1.

The use of nitrones as precursor of imines avoids the limited regioselectivity problem and the phosphine-mediated deoxygenation of nitrones is an effective way to get the corresponding imines. However, in many cases resultant product contains phosphine (or its oxide) contamination, which must be removed before further imine transformations, particularly those catalyzed by the transition metals. Additionally, although five-membered cyclic nitrones are readily available, their six- or larger membered congeners are less accessible due to their complicated synthesis and lower stability.[17] The third approach based on Staudinger/aza-Wittig cyclization usually requires multiple-step synthesis of starting materials.[15]

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Bearing in mind these drawbacks, we considered other potential precursors of cyclic imines and our attention was focused on lactam derivatives. Although the amides are one of the most important classes of the organic molecules, due to their widespread presence in nature, their chemistry is rather limited. In fact, it is mostly concentrated on the formation of the amide bond and not on its further transformations, which is the result of a high stability of the amide bond. For example, the reduction of amides usually requires quite harsh conditions. Thus, the most common approaches to their reduction employ nucleophilic metallic hydride donors, such as aluminum and boron reagents.[18] Although such reagents are suitable for the synthesis of amines, their use to access imines can be problematic due to the intrinsic high reactivity of the hydrides needed to effect the reduction.[18]

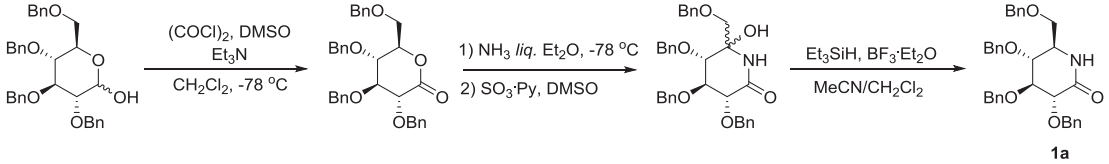
Recently, several examples of the reduction of secondary amides to the corresponding imines were reported. Charette et al.[19] demonstrated a chemoselective activation of secondary amide with Tf_2O in the presence of 2-fluoropyridine followed by the reduction to aldimines using triethylsilane. The same group also reported a general and chemoselective method based on an activation/addition sequence applicable to secondary amides and allowing the controlled isolation of structurally diverse ketones and ketimines.[20]

Alternatively, the use of stoichiometric or excess amounts of Schwartz's reagent ($Cp_2Zr(H)Cl$) can lead to the formation of a variety of aldehydes or imines with a great functional group tolerance.[21] It has been also demonstrated that this protocol works for simple 2-pyrrolidinones.[21d]

Inspired by these reports, we focused our attention on sugar lactams and considered them as promising precursors of the corresponding sugar-derived cyclic imines.

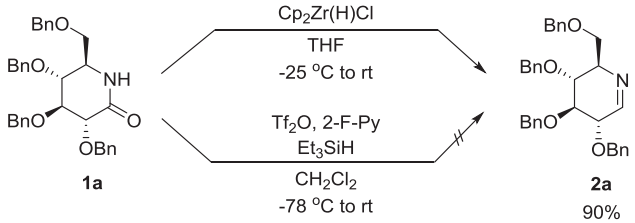
2. Results and discussion

The potential synthesis of sugar-derived cyclic imines was initially evaluated for D-*gluco*-lactam **1a**. The lactam **1a** can be readily obtained from the corresponding 2,3,4,6-*O*-tetrabenzylated glucose following Vasella's protocol (Scheme 2).[22]



Scheme 2.

Lactam **1a** was treated with 1.6 equiv $Cp_2Zr(H)Cl$ at −25 °C in THF to give desired imine **2a** in a 90% yield (Scheme 3). The progress of the reaction can be easily followed since the initial white suspension turns into a clear solution indicating the end of the reduction process. In contrast to a zirconium-mediated reaction, when the same lactam **1a** was subjected to reaction with Tf_2O in the presence of 2-fluoropyridine, followed by treatment with Et_3SiH, under the conditions developed by Charette and co-workers,[19] the imine **2a** was not detected and only starting material was recovered.



Scheme 3.

Following the reaction sequence presented in Scheme 2, lactams **1b**–**f** were synthesized starting from commercially available benzylated sugars and submitted to the reduction using the same protocol as in **1a**. With the exception of the 2,3,4,5-*O*-tetrabenzylated mannose, all other sugars gave corresponding lactams as a single C-5 isomers (**1c**–**f**), which was corroborated by the ^1H NMR analysis. Only in the case of mannose derivative, the final reduction (Scheme 2) provided lactam **1b** along with its C6-epimer (**6-*epi*-1b**) in a ratio 3:2. The same outcome was observed by Overkleeft.[23] The lack of the selectivity in this single case was rationalized considering the unfavorable stereoelectronic features of the transition states of the hydride addition step resulting in the formation of epimeric products.[23] Epimeric lactams **1b** and **6-*epi*-1b** were separated by the chromatography on silica gel.

Bearing in mind the limited stability of the imines, initially cyclic imines **2a**–**f** were isolated and purified by chromatography on Florisil. Nevertheless, the yields varied from moderate to good (Table 1). We ascribed that to the general instability of imines during the isolation and purification operations rather than to the moderate efficiency of the reduction itself. To prove it, the trapping experiments were performed where the crude imine was directly treated with a nucleophile. We expected such a one-pot protocol to be even more attractive since it should provide directly functionalized sugar-derived cyclic amines.

As previously described, lactam **1a** was treated with slight excess of $Cp_2Zr(H)Cl$ in THF at −25 °C to afford imine **2a**. When the reaction mixture became clear (ca. 30 min), allyltributylstannane (3 equiv) and $Yb(OTf)_3$ (1 equiv) were added directly to the solution of the crude imine **2a** to afford a mixture of diastereomeric homoallylic amines **3a**/**4a** in a ratio 89:11 and in overall yield 84% after two steps. The presented one-pot protocol proved to be efficient also for other lactams (**1b**–**f**) leading to the corresponding amines **3b**–**f** in good yield and with moderate to good stereoselectivity (Table 2).

The stereochemical assignment at the newly generated stereochemical center (C-2) for all products was firmly established by NOE experiments. In case of six-membered imines addition of allyltributyltin proceeded *syn* to the BnO substituent at the C-3 position. This is a result of conformational control of the process, according to Woerpel's model.[24] On the other hand, for the five-membered imines the nucleophile addition is controlled by steric effects leading to the product with *anti*-arrangement of the BnO at the C-3 position and allyl group at the C-2 position (Fig. 1).[8,11,14a,14b]

Subsequently, other types of nucleophiles were examined with the one-pot reduction/nucleophilic addition protocol (Table 3). Lactams **1a** and **1f** were selected as a model compounds for this part of the study. As shown in Table 3 the corresponding cyclic amines were obtained in a moderate to good yield (after two steps) and with good selectivity. It is particularly interesting that cyclic imines react smoothly with silylated enol ethers to provide β-aminoketones (entries 3,6). To the best of own knowledge such transformation has not been reported so far.