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this approach robust in the research laboratory environment.

CH2OH

-н

-OH

-OH

сн₂он

D-fructose

RNH,

HO

H-

H

Ċ=O

н

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# Lactosamine from lactulose via the Heyns rearrangement: a practical protocol

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#### ARTICLE INFO

#### ABSTRACT

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2-Deoxy-2-amino sugars are undoubtedly important in living organisms and widely distributed as subunits in glycoconjugates such as glycosaminoglycans and peptidoglycans.<sup>1</sup> While N-acety-lated glucosamine is a readily accessible bulk chemical, generally produced by hydrolysis of the second most abundant biopolymer in the world, chitin,<sup>2</sup> *N*-acetyl lactosamine is a common disaccharide epitope in complex glycans such as in the Lewis x family, but is rather expensive.

Many alternative routes for the preparation of 2-deoxy-2-amino sugars have been described, including the slightly hazardous but well-applied azidonitration<sup>3</sup> and azidoselenation<sup>4,5</sup> of glycals. Recent achievements in the preparation and use of 2-deoxy-2-amino sugars have been thoroughly reviewed.<sup>6,7</sup>

Possibly the oldest, and maybe the easiest way to access 2deoxy-2-amino sugars is via the Heyns rearrangement (Scheme 1).

As summarised earlier,<sup>8</sup> the observation that ketoses react with amines to afford ketosyl amines, followed by isomerisation into the corresponding 2-amino-2-deoxy-1-aldoses, was first reported by Fischer et al.<sup>9</sup> This type of reaction was further investigated by Heyns and Koch in 1952.<sup>10</sup> They found that p-fructose reacts with ammonia to form p-glucosamine. Subsequently, it was demonstrated that numerous organic amines react in a similar fashion.<sup>11,12</sup> The major drawback of this reaction sequence is the generally low to moderate isolated yields (about 20%). Competing Amadori rearrangement, especially when using primary amines, and the ease of hydrolysis of the initial condensation product are possibly the major factors accounting for this.

Thus, only very few studies have included the Heyns rearrangement.<sup>13</sup> In 1999, Wrodnigg and Stütz revisited this neglected reaction by focusing on benzylamine as the nitrogen source, producing *N*-acetyl-p-lactosamine in 38–45% yield with respect to lactulose using a 'one-pot' protocol.<sup>14</sup> This study was followed up by applying their elaborated methodology to a range of ketuloses producing various N-substituted sugar amine derivatives.<sup>8,15</sup>

The Heyns rearrangement is possibly one of the oldest, easiest and most economic ways to synthesise 2-

deoxy-2-amino sugars. Initially reported yields were disappointingly low, but in the late 90s Wrodnigg

and Stütz discovered modified reaction conditions that gave substantially increased yields, making the

reaction viable on preparative scale. Requiring larger amounts of N-acetyl lactosamine, we utilised the

reported reaction conditions and found that additional modifications, especially in the work-up procedure—for example employing rapid filtration of crude diethyl ether precipitates, were necessary to make

> To our knowledge two companies are producing lactosamine on industrial scale in 300 kg batches, and giving the prospect of access to a variety of rare and expensive sugar derivatives. However, despite the apparent ease of the protocol this development seemed to have difficulties in entering the carbohydrate community.

> To our knowledge, only one research paper<sup>16</sup> on orthogonally protected Lewis x derivatives, and a patent<sup>17</sup> on novel lactosamine derivatives have utilised the Heyns rearrangement for lactosamine.

cat H<sup>1</sup>

СНОН

-н

-OH

-ОН

ĊH₂OH

H-

H

-NH-R

CHO

-н

-OH

-он

CH2OH

H-

H-

H-

HO

-NH-R

CH2OH

-н

⊢он

⊢он

сн₂он

=N-R



Scheme 1. Heyns rearrangement of D-fructose shown with intermediate steps.





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Scheme 2. Reagents and conditions: (i) BnNH<sub>2</sub>, 40 °C, 3 d; (ii) MeOH, glacial AcOH, rt, 2 h; (iii) HCl, pH 1-2, Pd(OH)<sub>2</sub>/C, H<sub>2</sub>, 6 bar, 40 °C, 60%; (iv) MeOH, NaOMe, Ac<sub>2</sub>O, 40 °C, 82%; (v) Ac<sub>2</sub>O, pyridine, rt, overnight, 67%.

Previously, in 1996, the Cytel Corporation submitted a patent application on sialyl Lewis x analogues detailing Heyns rearrangement reaction conditions producing successfully the desired derivatives, but encountering similar problems linked to the intermediate work-up procedures as we experienced when we started our investigations.<sup>18</sup> Requiring larger amounts of N-acetyl lactosamine,<sup>19</sup> we set out to utilise the reported reaction conditions and found, after numerous unsuccessful attempts, that additional modifications, especially in the work-up procedure, were necessary to provide the desired product in acceptable yields. This communication discusses the additional details of this practical protocol.

Lactulose (1) (25 g) was reacted with excess benzylamine to produce ketosyl amine **2** as previously described,<sup>15</sup> monitoring the reaction progress by TLC. Ketosyl amine 2 was produced as the major product while some unreacted lactulose remained (Scheme 2). NMR sampling can be used to follow the reaction. The crude mixture was then precipitated from diethyl ether at 4 °C without the reported addition of methanol.<sup>8,16</sup> Possibly due to the large amount of benzylamine, the precipitate showed a tendency to convert into a syrup-like mass as described in one of the patents.<sup>18</sup> This could be avoided by rapid suction filtration using a small amount of cold diethyl ether (4 °C) to wash out excess benzylamine. The rearrangement reaction was then carried out with the crude yellow solid 2 (35 g) using glacial acetic acid in methanol at room temperature. During this step, N-benzyl lactosamine 3 was formed within a short time (2 h). Isolation of this crude material **3**. still containing some unreacted lactulose 1 and remaining benzylamine, was difficult, as the material refused to solidify after slow addition to diethyl ether and subsequent cooling. However, using a similar work-up procedure as applied for the first reaction provided crude solid 3 (ca. 40 g). It turned out to be advantageous not to allow the precipitation of 3 from diethyl ether in a refrigerator because, after extended times, the semi-crystalline material started to convert into a syrup-like mass that could not be filtered. The best way was to filter the precipitate immediately. Although the hydrogenolysis can be carried out at ambient pressure, application of 6 bar hydrogen pressure increased the overall efficiency of the reaction. According to our results, the reaction times seem to depend on the quality of the catalyst. At this point, it was also possible to remove remaining lactulose **1** from the reaction mixture by cation exchange chromatography giving p-lactosamine hydrochloride **4** in an overall 60% yield starting from (**1**). However, it was found that this extra purification step did not increase significantly the overall yield.

N-acetylation was achieved by adding sodium methoxide and subsequently acetic anhydride to the crude material **4** providing crude 5 (yield, 82%). The crude *N*-acetyl lactosamine 5 was then peracetylated using acetic anhydride in pyridine to form amino sugar 6 (Scheme 2). After this step, the material was purified by flash column chromatography providing the target compound **6** as an anomeric mixture in a total yield of 48% on a 25 g scale with respect to the starting material 1.

In summary, we improved the protocol for the Heyns rearrangement giving straightforward access to N-acetyl lactosamine from lactulose. Similar to the previously reported procedures the same material can be prepared without chromatography and other Nprotecting groups can be used.

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# Supplementary data

Supplementary data (a detailed experimental description and selected NMR spectra are reproduced and compiled) associated with this article can be found, in the online version, at http:// dx.doi.org/10.1016/j.tetlet.2013.05.086.

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