Tetrahedron Letters 57 (2016) 2595–2597

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of lactosamine from lactulose: scalable approach for the Heyns rearrangement

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ARTICLE INFO

Article history:
Received 18 March 2016
Revised 22 April 2016
Accepted 27 April 2016
Available online 6 May 2016

Keywords:
Heyns rearrangement
Scale up
Lactosamine

ABSTRACT

A scalable approach for the preparation of lactosamine hydrochloride from lactulose is described. The reported procedure is based on the preparation of a new dibenzylamino derivative of lactosamine hydrochloride. Lactosamine hydrochloride was prepared in a two-pot reaction sequence from commercially available lactulose.

Introduction

Lactosamine is one of the most important building blocks of biologically relevant oligosaccharides and is a basic structural element of Lewis type, α-gal type, and human milk oligosaccharides. Furthermore, it forms the backbone of several cell surface glycans such as sialylated glycans or keratin sulfates.[1] Due to the biological importance of lactosamine several biological and chemical syntheses have been developed for the preparation of lactosamine and its derivatives. The enzymatic synthesis is generally based on the transfer of a galactose unit onto glucosamine by glycosyl hydrolase or transferase enzymes.[2]

The chemical synthesis of lactosamine was achieved by the glycosylation of a suitably protected glucosamine acceptor with a galactose donor,[3] however, this is labor and time consuming. Another possibility is to convert commonly available lactose into lactosamine,[4] but this reaction path is similarly tedious as the previous one. The shortest route starts from lactulose (**1**) employing the Heyns rearrangement which was first reported in 1952 by Kurt Heyns.[5] With rearrangement, ketoses can be transformed into 2-deoxy-2amino aldoses by reacting with an amine. The reaction was further studied and different *N*-substituted glucosamine derivatives were prepared from fructose and different amines by both Carson and co-workers and by the Heyns group.[6]

The procedure was revisited in 1999 by Stütz and co-workers[7] and later improved by the same group.[8] The crucial improvement in their procedure was the use of benzylamine for the rearrangement which resulted in reduced formation of the *manno* epimer (Scheme 1). As the first step of the reaction cascade a ketosyl amine (**2**) was prepared and isolated. The isolated ketosyl amine was treated with acid under anhydrous condition affording the lactosamine derivative (**3**).

The bottleneck of the reaction pathway is the isolation of the ketosylamine (**2**). The excess of benzylamine has to be removed from the reaction mixture and the only way to achieve this is the precipitation of compound **2**.[9] To date the only solvent found to be suitable for this precipitation is Et_2O. Recently, a practical protocol for this reaction pathway has been published, but did not manage to overcome the isolation problem of the ketosylamine.[10] This fact makes the procedure non-scalable beyond lab scale. In this manuscript we describe a scalable procedure for the preparation of lactosamine from lactulose via the Heyns rearrangement.

Due to the hydrolytic instability of glycosylamines it remains difficult to isolate these compounds, and as a consequence we tried to avoid this. It became clear upon deeper understanding of the reaction that only trace acid was required for the rearrangement. Furthermore, when the acid was added at the beginning of the reaction, this led to a new product which had not been identified before in the reaction mixture.

Treatment of lactulose with benzylamine in the presence of acid led to the formation of compound **5** (Scheme 2) which was isolated by crystallization from the crude reaction mixture making the whole procedure scalable. The rearrangement could be catalyzed with a wide range of Brønsted and Lewis acids.[11] Furthermore,

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http://dx.doi.org/10.1016/j.tetlet.2016.04.119
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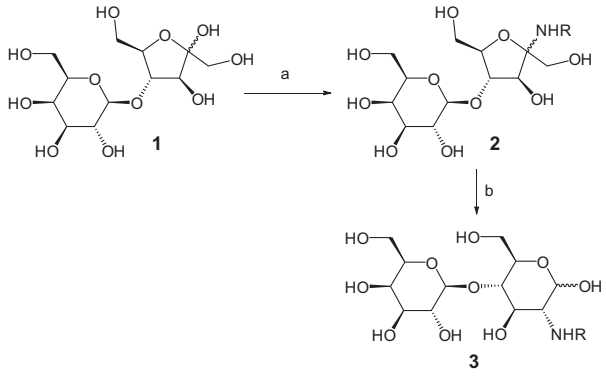
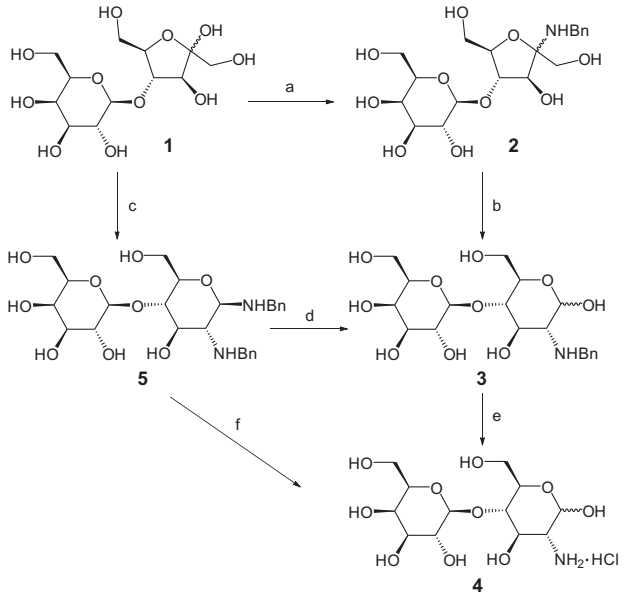


Scheme 1. The Heyns rearrangement. Reagents and conditions: (a) benzylamine, 0–40 °C, 48 h; (b) AcOH, MeOH, rt, 1 h, 38–45%.[7]

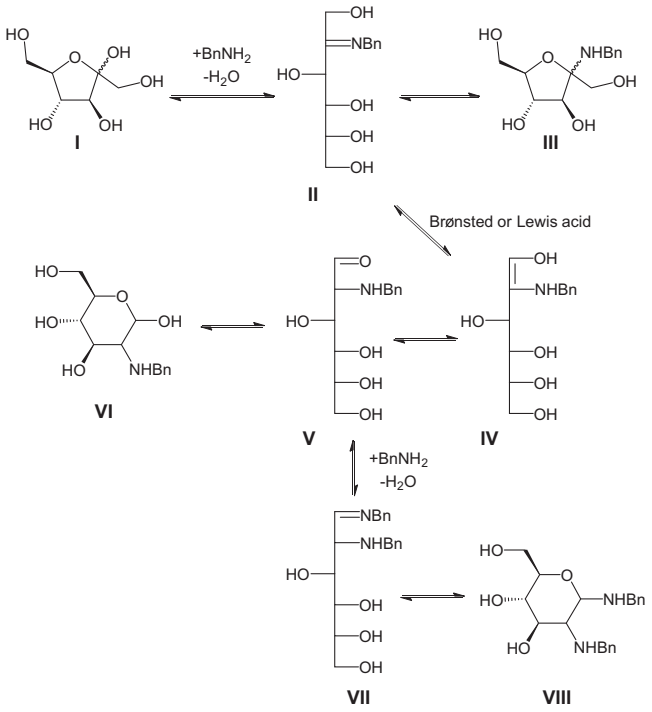
the rearrangement can be performed using different disaccharides as stating material and various substituted benzylamines as aromatic amines for the reaction.[11] Palatinose, nigerose, turanose, and maltulose were used as keto disaccharides for the rearrangement and resulted in the formation of the corresponding 1,2-dibenzylamino substituted disaccharides.[11] A similar reaction has been developed parallel to our work using fructose as a starting material and $ZnCl_2$ as a Lewis acid.[12] The synthesized compounds can be regarded as potential surfactants. Although the authors isolated the products in very high yield, we were unable to repeat this. In our case the yields were moderate and the mother liquor of the crystals contained an anomeric mixture of compound **5** and traces of the C-2 epimer of compound **5**.

Compound **5** was treated with dilute acid to hydrolyze the anomeric benzylamino residue affording compound **3** (Scheme 2). Compound **3** could be isolated if required, but more practically Pd/C was added to the reaction mixture and stirred under H_2 to afford lactosamine hydrochloride (**4**). A high isolated yield of compound **4** was achieved by using recrystallized starting material for the reaction.

The reaction proceeds via well-known intermediates (Scheme 3).[7,10] Ketosugar (**I**) reacts with benzlyamine to form



Scheme 2. Preparation of lactosamine (**4**) from lactulose (**1**) via the bisbenzyl derivative. Reagents and conditions: (a) $BnNH_2$, 0–40 °C, 48 h; (b) AcOH, MeOH, rt, 2 h, 65–70%[7] over two steps; (c) $BnNH_2$, $BnNH_3Cl$, 40 °C, 96 h, 25%; (d) HCl, H_2O, MeOH, rt, 30 min, 80%; (e) $Pd(OH)_2/C$, H_2, HCl, H_2O, MeOH, rt, 2 h 38–45% from compound **1**;[7] (f) HCl, H_2O, MeOH, then Pd/C, H_2, H_2O, MeOH, rt, 24 h, 95%.



Scheme 3. Suggested intermediates for the reaction cascade.

ketosamine (**III**) proceeding through a Schiff base intermediate (**II**). In the absence of an acid catalyst the reaction stops at this stage and the ketosamine can be isolated.[7–10] In the presence of an acid catalyst the Schiff-base intermediate (**II**) enters to the Heyns reaction cascade. The reaction proceeds through an enol intermediate (**IV**) followed by the formation of aldosamine intermediates **V** and **VI** which are in equilibrium (**VI** could be isolated if needed) but in the presence of benzylamine intermediate **V** reacts further to form **VII** and **VIII** as a final stage of the reaction path. Although all steps are reversible due to the excess of benzylamine used, the reaction cascade is pushed toward the dibenzylamino derivatives. In most cases compound **VIII** can be isolated as a crystalline compound.

In conclusion a scalable route for the preparation of lactosamine hydrochloride is presented. The reaction starts from commercially available lactulose and applies the Heyns rearrangement. A new 1,2-dibenzylamino substituted lactosamine was isolated as a crystalline intermediate allowing the possibility of avoiding ether type solvents for the whole process. The procedure has been performed on a hundred-kilogram scale under industrial conditions.

Acknowledgment

Authors thank to Glycom A/S for support.

Supplementary data

Supplementary data (experimental description, NMR spectra, HPLC chromatogram) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.04.119.

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