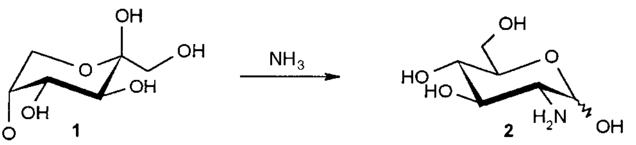
The Heyns Rearrangement Revisited: An Exceptionally Simple Two-Step Chemical Synthesis of D-Lactosamine from Lactulose[**]

Tanja M. Wrodnigg and Arnold E. Stütz*

Dedicated to Professor Robin Ferrier
on the occasion of his 60th birthday

In the 1950s, Heyns and Koch reported the formation of D-glucosamine (**2**) from the reaction of D-fructose (**1**) with ammonia (Scheme 1).[1] Yields of isolated product for this reaction were found to be around 10% with rare exceptions of 30% depending on the reaction conditions employed.[2] From the reaction of D-fructose with primary or secondary aliphatic amines, N-substituted D-glucosamine derivatives were subsequently obtained by Carson[3] as well as the Heyns group. The latter workers as well as Anet[4] also examined the reactivities of the other ketohexoses[5] and the condensation products of D-fructose with aromatic amines[6] and amino acids.[7] In all reported cases, yields rarely exceeded the 20% mark.

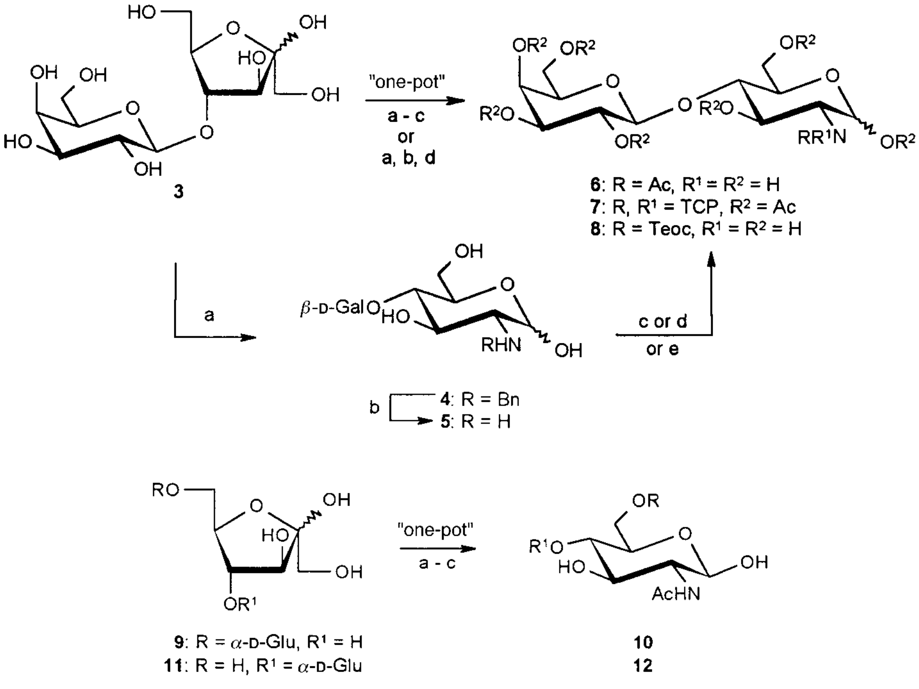


Scheme 1. Heyns rearrangement of D-fructose (**1**).

Apart from these studies with simple ketoses, preparatively useful applications of the Heyns rearrangement have not been reported to date. We focussed our attention on this interesting and versatile reaction in the context of a demand for multigramm quantities of various glycosylated *N*-acetyl-D-glucosamine derivatives, for example, *N*-acetyl-D-lactosamine (**6**, Scheme 2), which is a constituent of the sialyl Lewis^X epitope,[8] a cell-type specific oligosaccharide. Disaccharides such as **6** have been available by either multistep chemical syntheses,[9] with the inherent need for protecting group manipulations, or by enzymatic methods.[10] The best chemical syntheses, in terms of yields of isolated product as well as scale-up potential, start from lactose and allow access to **6** (Scheme 2) and/or suitable derivatives thereof in seven to nine steps and overall yields ranging from 10 to, at most, 30%.[11] Enzyme-catalyzed syntheses have employed D-galactosidases from various sources,[10, 12–14] or D-galactosyl transferases[15, 16] as components of multienzyme systems which serve co-factor recycling.

The Heyns rearrangement of lactulose (**3**) (Scheme 2) was achieved by reaction with commercial grade benzylamine followed by treatment of the resulting crude material with glacial acetic acid in methanol to give *N*-benzyl-D-lactosamine (**4**) in 65–70% yield. A small proportion of the corresponding D-mannosamine derivative was also formed, as was shown by NMR spectroscopy. The *N*-benzyl group in **4** was removed by conventional catalytic hydrogenation over palladium hydroxide in methanol. Subsequent addition of acetic anhydride to the reaction mixture containing **5** led to **6**. Overall yields for this three-step procedure were found to range between 38 and 45%. Changing the solvent in the hydrogenation step from methanol to dilute aqueous HCl allowed access to free D-lactosamine hydrochloride.

This sequence, which can be performed conveniently as a one-pot procedure, does not require any protecting group manipulations or elaborate chromatographic separation and is well suited for scaling-up. A wide range of N-modified derivatives suitable as intermediates en route to sophisticated oligosaccharides are available in good yields by employing different acylating reagents. For example, with tetrachlorophthaloyl anhydride[17] and *N*-(2,2,2-trichloroethyl)oxycarbonyl chloride[18] the corresponding *N*-tetrachlorophthaloyl (TCP) and *N*-(2,2,2-trichloroethyl)oxycarbonyl (Teoc) protected analogues of D-lactosamine, **7** and **8**, were obtained, demonstrating the versatility of the approach.



Scheme 2. a) $BnNH_2$, 40°C, then AcOH/MeOH; b) H_2,$Pd(OH)_2$/C, MeOH; c) MeOH, Ac_2O, $NaHCO_3$; d) tetrachlorophthaloyl anhydride, NEt_3, MeOH, then Ac_2O, pyridine; e) (trichloroethyl)oxycarbonyl chloride, $NaHCO_3$, H_2O.

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[*] Prof. Dr. A. E. Stütz, Dipl.-Ing. T. M. Wrodnigg
Institut für Organische Chemie der Technischen Universität
Stremayrgasse 16, A-8010 Graz (Austria)
Fax: (+43)316-873-8740
E-mail: stuetz@orgc.tu-graz.ac.at

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Other O-glycosylated ketoses reacted accordingly. By quenching at the point of maximum aldosamine content, the formation of undesired side products, such as 1-aminodeoxy-D-fructose derivatives could be reduced to a minimum. As in the case of **4**, unoptimized yields of O-glycosylated free D-glucosamine derivatives obtained in the two-step approach based on benzylamine ranged between 40 and 70%. Consequently, N-acylated derivatives, for example, *N*-acetyl-6-*O*-(α-D-glucopyranosyl)-D-glucosamine (**10**) (40%) and *N*-acetylmaltosamine (**12**) (33%) could be prepared from isomaltulose (**9**) and maltulose (**11**), respectively, in satisfactory overall yields.

Generally, yields are superior to those obtained with unsubstituted D-fructose which can be rationalized by considering the destabilizing effects caused by unfavorable interactions of the large glycosyl residues at O-4 with other polar functional groups, particularly 5-OH, around the ketopyranose ring. This clearly contributes considerably to the driving force of the rearrangement reaction. The most telling example in this context is the ring enlargement of the highly crowded ketofuranose ring in isomaltulose (**9**) to the distinctly more relaxed 2-aminodeoxyaldopyranose chair in compound **10**.

Experimental Section

A mixture of the *O*-glycosyl-D-fructose (100 mmol) and benzylamine (700 mmol) was stirred at 40°C until TLC ($CHCl_3$/MeOH/NH_4OH, 2:4:1) indicated that the starting material was largely converted into a slightly less polar main product. Conventional removal[2] of excess amine gave a crude material which was dissolved in MeOH/glacial acetic acid (25:1) and the mixture was kept for 12 h at 25°C. $Pd(OH)_2$/C (20%, 2 g) was added and the reaction mixture containing the 2-benzylaminodeoxyaldose was stirred under an atmosphere of H_2 at ambient pressure. After removal of the catalyst by filtration, excess Ac_2O and solid $NaHCO_3$ was added to the filtrate containing the free 2-aminodeoxy disaccharide. After 1 h, the reaction mixture was concentrated under reduced pressure. N-Acylated products were purified by filtration over a plug of silica gel (Merck 60) by employing a mixture of $CHCl_3$/MeOH/NH_4OH (8:4:1). Compound **6** was NMR spectroscopically identical with a commercial sample (Sigma, A 7791). The NMR spectra (300 MHz) of compounds **10** and **12** in D_2O matched previously reported data.[19]

7: Compound **7** was prepared from **5** · HCl following the established procedure.[17] ^{13}C NMR (50.9 MHz, $CDCl_3$, 25°C): $\delta = 162.4$, 140.5, 129.8, 126.5 (TCP), 100.9 (C-1′), 90.3 (C-1), 76.5 (C-4), 71.1, 71.0, 70.8, 69.2, 67.2, 67.7 (C-3, C-5, C-2′, C-3′, C-4′, C-5′), 60.8, 60.6 (C-6, C-6′), 53.5 (C-2), signals of *N*,*O*-acetyl groups were in the expected regions.

8: To a 5% aqueous solution of intermediate **5** · HCl containing excess sodium bicarbonate, 1.5 equivalents of (trichloroethyl)oxycarbonyl chloride[18] were added and the mixture was stirred at 22°C until all starting material had reacted. Conventional work-up[18] and purification on silica gel ($CHCl_3$/MeOH/NH_4OH conc. 300:100:2) gave compound **8**: $[\alpha] = +18$ ($c = 2.7$ in MeOH); ^{13}C NMR (50.9 MHz, CD_3OD, 25°C): $\delta = 157.0$ (C=O), 105.1 (C-1′), 97.2 (CCl_3), 92.6 (C-1), 81.2 (C-4), 77.2 (C-5′), 75.7 (CH_2), 74.8 (C-3′), 72.7 (C-2′), 71.6, 71.3 (C-3, C-5), 70.4 (C-4′), 62.7 (C-6′), 61.9 (C-6), 57.5 (C-2).

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