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Note

Improved synthesis of 1,3,4,6-tetra-*O*-acetyl-2-azido-2-deoxy-α-D-mannopyranose

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Abstract—By improved (anhydrous) work-up conditions of a triflate displacement reaction, the yield in the preparation of the versatile synthetic intermediate 1,3,4,6-tetra-*O*-acetyl-2-azido-2-deoxy-α-D-mannopyranose has been significantly enhanced. This important precursor is now available in three efficient steps from D-glucose.
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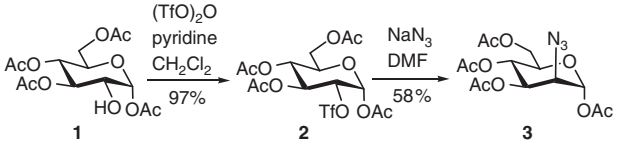
Mannosamine, that is, 2-amino-2-deoxy-mannose, is a motif in bacterial polysaccharides, that is usually found as the acetamido derivative.[1,2] This is a precursor in the biosynthesis of *N*-acetyl-neuraminic acid[3] and has been recognized as a strong ligand for the natural killer cell activating protein NKR-P1.[4] Thus, mannosamine or analogues thereof are important synthetic precursors for various biologically relevant oligosaccharides. However, there is no native glycan built from ManNAc residues and hence no cheap commercial source of mannosamine. As a synthetic intermediate, the corresponding azido derivative has been used extensively. This is most often synthesized either by an azidonitration reaction on glucal derivatives[5] or by displacement reactions at C-2 on glucose derivatives,[6] but so far there has been no optimal pathway for the simple formation of 2-azido-2-deoxy-mannose in large scale, the azidonitration reaction being limited by the low mannose/glucose ratio obtained. An obvious way would be displacement by azide ion of the 2-*O*-triflate derivative of 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose, a crystalline compound easily obtained on a large scale in a one-pot reaction from D-glucose,[7] but so far this reaction has given very low yield, with a recently published one of 7%.[8] We now show that with a careful work-up procedure following the displacement reaction, the yield can be raised to an acceptable 56% (over two steps).

Forming the 2-*O*-triflate of **1** using standard conditions[7,9] was no problem and the intermediate **2** was formed in an almost quantitative amount (Scheme 1). When attempting the displacement reaction using sodium azide in DMF at elevated temperature, the desired product was also formed in very high yield according to TLC. No other major spots were detected, but the product decomposed considerably during work-up. However, once purified, the 2-azido compound **3** was reasonably stable. No major side product could be isolated, making it difficult to speculate on the reasons for the instability and the breakdown mechanism. However, the same reaction starting from the mannose derivative 1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranose, to give the corresponding 2-azido glucose compound, is not beset by similar decomposition during work-up, but the product could be isolated in a high 84% yield.[9] Many



Scheme 1.

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various work-up methodologies were tried without much improvement, but slightly better yields were obtained when non-aqueous conditions were employed. Thus, efforts were made to perform the work-up excluding water to as high degree as possible. Dried solvents were used and, perhaps most importantly, the silica gel used for chromatography was dried extensively before use. When these precautions and conditions were applied to the work-up procedure, much less decomposition was observed, and the product **3** could be isolated in about 60% yield. Even when performing the reaction on a larger scale, a 60% yield was reproducibly obtained. Although there might be room for further improvements in the work-up procedure (as indicated by TLC), perhaps based on investigations of the decomposition mechanism, still, with these simple work-up alterations and precautions discussed, the yield in the reaction is now quite acceptable and the important synthetic building block **3** is easily available in large amounts from D-glucose in an efficient three-step synthesis including only one chromatographic purification step.

1. Experimental

1.1. General

TLC was carried out on Merck precoated 60 F_{254} plates using 8% H_2SO_4 for visualization. Column chromatography was performed on silica gel (0.040–0.063 mm, Amicon), which was first poured into a glass vessel and heated over an open flame until all water had been boiled away (approx. 15 min for 220 g silica gel) and then put in an oven at 150 °C overnight. The silica gel was then allowed to cool under an argon atmosphere before being used. NMR spectra were recorded in $CDCl_3$ (internal Me_4Si, $\delta = 0.00$) at 25 °C on a Varian 300 MHz or 400 MHz instrument. Organic solutions were concentrated at 40 °C under reduced pressure.

1.2. 1,3,4,6-Tetra-*O*-acetyl-2-*O*-trifluoromethylsulfonyl-α-D-glucopyranose (2)

Pyridine (0.542 mL, 6.71 mmol) was added to a solution of compound **1** (1.0 g, 2.87 mmol) in dry CH_2Cl_2 (20 mL). The mixture was cooled to −20 °C and a solution of trifluoromethanesulfonic anhydride (0.565 mL, 3.44 mmol) in CH_2Cl_2 (5 mL) was added over 30 min. The reaction mixture was stirred for an additional 30 min at −20 °C, then diluted with CH_2Cl_2 and washed with water, saturated $NaHCO_3$ and water. Filtration through a silica plug followed by concentration gave **2**, which can be used in the subsequent reaction without further purification. To obtain a yield, the residue was put on to a short silica gel column and eluted (toluene–EtOAc 10:1→1:1) to yield **2** (1.33 g, 2.77 mmol, 97%). $[\alpha]_D$ +101 (*c* 1.0, $CHCl_3$), lit.[8]: +99.6. NMR data were in agreement with those reported earlier.[8]

1.3. 1,3,4,6-Tetra-*O*-acetyl-2-azido-2-deoxy-α-D-mannopyranose (3)

A mixture of compound **2** (1.578 g, 3.29 mmol) and NaN_3 (408 mg, 6.28 mmol) in dry DMF (20 mL) was stirred under argon at 60 °C for 30 min. Most of the DMF was then removed under reduced pressure and the residue transferred to a dried glass column containing a slurry of pre-heated silica in dry toluene. The remaining DMF was eluted with dry toluene and then a gradient of toluene and dry EtOAc was used to elute product **3** (707 mg, 1.90 mmol, 58%). NMR data were in agreement with those reported earlier.[6]

Acknowledgements

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