Approaches towards the synthesis of Pyrrolidine derived Aza-sugars

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Introduction

Iminosugars or aza-sugars are compounds in which the ring oxygen of a monosaccharide has been replaced by an imino group. Many polyhydroxylated pyrimidine alkaloids have attracted considerable attention due to their ability to inhibit glycosidases. Because glycosidases are involved in several important biological processes, these polyhydroxylated alkaloids have stimulated interest in the development of specific glycosidase inhibitors such as diabetes or as antiviral, antibacterial and anticancer agents. In particulars, glycosidase inhibitors have shown potential as therapeutic agent for type II diabetes and HIV-I infection. In this direction various glycosidase inhibitors have been synthesized such as amidines, imidazoles, trizoles and tetrazoles.

Results and discussion

Due to the emerging importance of hybrid molecules, we tried to synthesize pyrrolidine analog of aza-heterocycles, which could act as glycosidase inhibitors from tri-O-benzyld-D-glucal. Two approaches were followed using the chemistry of D-glycal.

Approach-1

In this approach, 3,4,6-tri-O-benzyld-glucal was converted to tri-benzylatedallylic alcohol by the known literature procedure via two steps viz., formylation followed by NaBH₄ reduction. Compound on benzylation with benzyl bromide imprense of NaH in DMSO forms benzylated compound in 89% yield, which was characterized from its H NMR data, C NMR data and by mass spectral data. Compound on dihydroxylation with OsO₄-NMO formed a diol in 94% yields, which in its H NMR spectrum showed a singlet for anomeric proton at δ 5.36-5.39. IR spectrum of the compound showed the absorption peak for -OH group at 3408 cm⁻¹. Compound on oxidative cleavage with NaIO₄ in acetonitrile formed compound in 83% yield. Compound was directly obtained from compound by ozonolysis process.

Reagents and conditions

(a) BnBr, NaH, DMSO, rt, 5 h; (b) OsO₄-NMO, Acetone:H₂O:BuOH (1:1:0.5), Na₂S₂O₅, rt, 2.5 h; (c) NaIO₄, CH₃CN/H₂O, 0 °C to 10 °C, 2 h; (d) O₃, DCM, 15 min; (e) LiAlH₄, THF, rt, 1 h; (f) IBX, EtOAc, 80 °C, reflux, 4 h; (g) K₂CO₃, MeOH, rt, 1 h; (h) NaCNBH₃/AcOH, 0 ºC to rt; (i) MsCl, Et₃N, DCM, 2 h. (j) BnNH₂, NaH, CH₂Cl₂, 0 °C to rt.

Scheme 1

Compound 4 in its H NMR spectrum showed a peak at δ 7.78 for -OCO group. A multiplet at δ 5.15-5.17 was seen for C-5 proton. IR spectrum of compound showed a peak at 1726 cm⁻¹ for -OCHO group. Compound on hydrolysis with K₂CO₃/Methanol formed compound, which on oxidation with IBX formed compound. However, compound on LiAlH₄ reduction formed a diol in 70% yield, which was confirmed from its H NMR spectrum. IR spectrum of compound showed a peak for the hydroxy group at 3437 cm⁻¹ (Scheme1). Diol was also confirmed from its corresponding diacetate, which in its H NMR spectrum

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showed two singlets at $\delta$ 1.92 and 1.98 cm$^{-1}$ for the two $\text{–COCH}_3$ groups.

Diol 5 on oxidation with IBX in ethyl acetate forms a diketo derivative 7. Diol 5 was also oxidized by $\text{CrO}_3$/H$_2$SO$_4$ to form a diketo product 7. Compound 7 on treatment with BnNH$_2$ in presence of NaCNBH$_3$/AcOH didn’t form a cyclized aza product 8 (Scheme 1).

However, the diol 5 was mesylated with MsCl to form a dimesylated product 9 in 82 % yield, which in its $^1$H NMR spectrum showed a singlet at $\delta$ 2.96 for the mesyl group. Compound 9 on treatment with BnNH$_2$/NaH didn’t form a cyclized product 8.

The extension of this work to other six membered aza-sugars is under progress and soon will be published soon.
References
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