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Novel method for the preparation of hexose sugar amines using Ruthenium based complex

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ABSTRACT

A novel and convenient synthetic procedure for preparation of hexose sugar amines by reductive amination using Ruthenium based catalyst has been demonstrated. This methodology features preparation of active Ruthenium based catalyst followed by their application in reductive amination involving sugar molecules and benzyl amine thereby making it a simpler process in terms of safety and operability.

Keywords: Reductive amination of dextrose; sugar amines; glycamines; Ruthenium based complex.

INTRODUCTION

1-amino-1-deoxy sugars also known as the glycamines, have been used for several decades as a resolving agent in the synthesis of pantothenic acid [1] as a key intermediate in the synthesis of Miglitol [2] deoxynojirimycin, derivatives of deoxynojirimycin [3] and as solubilizing groups for pharmaceuticals such as theophylline [4]. Amongst the glycamines, mannamine derivatives are used in preparation of glucose dependent insulins [5]. Methyl derivative of 1-amino-1-deoxyglucitol (also known as Meglumine) is used as a drug intermediate [6]. Use of isophthalmate derivative of meglumine as a contrast medium for spinal cord radiotherapy has been reported in the literature [7]. Moreover, polyhydroxy amine-neutralized acidic polymers are also used in hair styling compositions [8]. In general the methods employed for preparation of sugar amines involves chemical reduction of oxime [9], electrolytic reduction [10], and reductive alkylation of ammonia with a sugar [11-13]. The Flint and Salzburg method [12] yielded sugar amines as oily syrups. Wayne and Adkins [13] reported glucamine synthesis by the reduction of glucose in methanolic ammonia with low yield. Holly and co-workers [14] synthesized glycamines with purity 80% by the reductive alkylation of liquid ammonia with sugars. None of these methods is suitable for preparation of sugar amines of high yield and with quantitative yield. A convenient method for synthesis of 1-amino-1-deoxy-glucitol / 1-amino-1-deoxy-galactitol in two steps using Platinum oxide based catalyst and palladium catalyst was reported by Fred Kagan et.al [1]. This method was not cost effective as it gave product with low yield (below 50%). In addition the preparation process involved hydrogenation reaction using solid catalysts, which have problems in terms of safety and operations. In parallel, Watanabe et al reported an easy and convenient method for reductive amination using Ruthenium based catalyst which has the advantage of not using hydrogen gas under pressure [15]

In this paper, we report the process for reductive amination of hexose sugars with Benzylamine using Ruthenium based complex i.e. RuCl (2-picolineamide) (p-cymene) complex (Scheme 1). The resulting benzylated sugar amines could then be hydrogenated using Pd/C as catalyst to give respective sugar amines with good yield and purity. The process was more superior in terms of operability, economics and safety aspects as compared to previous reported methods and could be used at commercial scale.

MATERIALS AND METHODS

Dextrose anhydrous was purchased from Anil pharma Ltd. Mannose was purchased from fluka & galactose was purchased from Fisher scientific. Benzyl amine was purchased from Indo amines, [$RuCl_2$(p-cymene)] from Johnson mathey, 10% Palladium carbon (50% wet, type 490) from Arroramathey, 2-picolineamide from Aldrich, formic acid from Alfa Aesar.

2.2 Analytical methods:

2.2.1 HPLC method for isolated product (1-amino-1- deoxy-glucitol / 1-amino-1- deoxy-galactitol/1-amino-1-deoxy-mannitol):

High performance liquid chromatography analysis was performed on Waters alliance 2695 high performance liquid chromatography instrument connected with 2414 refractive index detector using synergi polar RP 80A column (4.0 µm particle size, 250 X 4.6 mm length) eluted with isocratic mobile phase system 60% acetonitrile in 0.154% ammonium acetate solution at a flow rate of 0.5mL/min with column oven temperature at 40^0C and detector oven temperature 40^0C. The retention time of 1-amino-1-deoxy-1-glucitol / 1-amino-1-deoxy-1-galactitol/1-amino-1-deoxy-mannitol were found to be 8.55/8.51/8.39 min and for dimer impurity of respective product was found to be 6.62/6.47/6.69 respectively.

2.2.2 HPLC method for monitoring the reaction towards the formation of N-benzyl-1-amino-1- deoxy-glucitol / N-benzyl-1-amino-1- deoxy-galactitol/ N-benzyl-1-amino-1- deoxy-mannitol:

High performance liquid chromatography analysis was performed on Waters alliance 2695 high performance liquid chromatography instrument connected with 2414 refractive index detector using Insertil amino column (5.0 µm particle size, 250 X 4.6 mm length) eluted with isocratic mobile phase system containing 25:75 v/v 0.272% potassium di hydrogen phosphate pH 6.5 and acetonitrile at a flow rate of 1.0 mL/min with column oven temperature at 40^0C and detector oven temperature 40^0C. The retention time of N- benzylated-1-amino-1-deoxy-1-glucitol / N- benzylated-1-amino-1-deoxy-1-galactitol were found to be 22.34 min, for Dextrose / Galactose/mannose were found to be 13.23 and N- benzylated-1-imino-1-deoxy-1-glucitol / N- benzylated-1-amino-1-deoxy-1-galactitol/ N-benzyl-1-amino-1- deoxy-mannitol were found to be 4.51 min respectively.

2.2.3 HPLC method for monitoring the reaction towards the formation of 1-amino-1- deoxy-glucitol / 1-amino-1- deoxy-galactitol/ 1-amino-1- deoxy-mannitol:

High performance liquid chromatography analysis was performed on Waters alliance 2695 High performance liquid chromatography instrument connected with 2414 refractive index detector using synergi polar RP 80A column (4.0 µm particle size, 250 X 4.6 mm length) eluted with isocratic mobile phase system 60% acetonitrile in 0.154% ammonium acetate solution at a flow rate of 0.5mL/min with column oven temperature at 40^0C and detector oven temperature 40^0C. The retention time of 1-amino-1-deoxy-1-glucitol / 1-amino-1-deoxy-1-galactitol/ 1-amino-1-deoxy-mannitol were found to be 6.5 min, N- benzylated-1-imino-1-deoxy-1-glucitol / N- benzylated-1-amino-1-deoxy-1-galactitol/ N-benzyl-1-amino-1- deoxy-mannitol were found to be 7.40 min and for dimer impurity of respective product was found to be 5.64 respectively.

2.2.4 NMR spectroscopy

The ^{1}H NMR and ^{13}C NMR spectra were recorded in D_2O on a Bruker Avance 300 spectrometer. The chemical shifts are reported in δ ppm relative to TMS (δ 0.00) and DMSO and D_2O as internal standards respectively.

2.2.5 Mass spectrometry

Electron Spray Ionization-Mass spectra (ESI-MS) of isolated compounds were measured using Agilent 1100 LC/MSD Trap SL instrument.

2.3 General procedure for preparation of RuCl (2-picolineamide) (p-cymene) complex [15]:
$[RuCl_2(p\text{-cymene})]_2$ complex (200mg, 0.327mmol), 2-picolineamide (80mg, 0.653mmol) and sodium ethoxide (44.4mg, 0.653mmol) were added in a schlenk tube and was subjected to argon replacement. A 7 ml of dehydrated methanol was added and stirred under argon gas atmosphere for 24 h. The reaction mixture was distilled off under reduced vacuum at ambient temperature to obtain crude Ru complex. To this, was added, 50ml of acetone, stirred for 5 minutes and filtered. The filtrate was distilled off under reduced vacuum at ambient temperature to obtain RuCl (2-picolineamide) (p-cymene) complex. The complex was then dissolved in 10 ml of methanol and used in below experiments.

2.4 Preparation of N-benzyl-1-amino -1-deoxy glucitol
1 g of dextrose anhydrous was added to 20 ml of methanol in a schlenk tube. To this, was added 0.73ml of benzyl amine (1.2 eq). The reaction mixture was cooled to 5 – 10 ^oC and Ru complex in methanol was added. The reaction mixture was stirred at ambient temperature for 10-15 hrs. The progress of reaction was monitored by HPLC. After completion of the reaction, the reaction mixture was cooled to 5-10 ^oC, stirred for 30 minutes, filtered and washed with methanol to obtain a solid material. The material was dried under vacuum at 50 ^oC for 10 h to obtain N-benzyl-1-amino-1-deoxy-glucitol (purity by HPLC 98.01% with 80 % w/w yield); ^{1}HNMR (300MHz, D_2O)(2a) δ 3.59- 3.91 (8H, m), 2.64 – 2.78 (2H, m), 7.41-7.43(5H, m); ESI-MS; *m/z* 272$[M+H]^+$; Melting point observed 138.5^{0}C and reported M.R 138-139^{0}C.

2.5 Preparation of 1-amino -1-deoxy-glucitol
1g of N-benzyl-1-amino-1-deoxy-glucitol was dissolved to the 40 ml of 1:1 methanol and demineralized water mixture. To this, was added, 0.1 g of 10% palladium carbon. Reaction mixture was hydrogenated at 50 ^oC under 10-12 kg of H_2 pressure for 24 h. The progress of reaction was monitored by HPLC. After completion of the reaction, reaction mixture was cooled to below 30 ^oC. Reaction mixture was filtered through hyflo bed. The filtration bed was then washed with 10 ml of demineralized water. The filtrate was distilled off under reduced vacuum at 40 ^oC to obtain a crude product. The crude product was stirred in isopropyl alcohol at 0-5 ^oC for 30 mins, filtered and dried under vacuum to obtain 0.4 g of 1-amino-1-deoxy-glucitol (Yield – 40 % , purity by HPLC 95-96%), M.R 127-130^{0}C, ^{1}H NMR (300MHz, D_2O)(2b) δ 2.55-2.62 (1H, m), 2.71-2.76(1H,m),3.53 – 3.57 (2H, m), 3.59-3.77 (4H, m); ESI-MS :*m/z* 182 $[M+H]^+$; M.R reported 124.5-130 ^oC.

2.6 Preparation of N-benzyl-1-amino -1-deoxy-galactitol
1 g of galactose was added to 20 ml of methanol in a schlenk tube. To this, was added 0.73ml of benzyl amine (1.2 eq). The reaction mixture was cooled to 5 – 10 ^oC and Ru complex in methanol was added. The reaction mixture was stirred at ambient temperature for 10-15 hrs. The progress of reaction was monitored by HPLC. After completion of the reaction, the reaction mixture was cooled to 5-10 ^oC, stirred for 30 minutes, filtered and washed with methanol to obtain a solid material. The material was dried under vacuum at 50 ^oC for 10 h to obtain N-benzyl-1-amino-1-deoxy-glucitol. (Yield – 80%, Purity by HPLC 99%), ^{1}HNMR (300MHz, D_2O)(2c) δ 3.10- 3.26 (2H, m), 3.49-3.52 (1H, m), 3.57-3.61(3H, m), 3.85-3.89(1H, m), 4.15-4.24(3H, m), 7.43(5H, m); ESI-MS : *m/z* 272$[M+H]^+$; M.R reported 151-157^{0}C;

2.7 Preparation of 1-amino -1-deoxy-galactitol
1g of N-benzyl-1-amino-1-deoxy-galactitol was dissolved to the 40 ml of 1:1 methanol and demineralized water mixture. To this, was added, 0.1 g of 10% palladium carbon. Reaction mixture was hydrogenated at 50 ^oC under 10-12 kg of H_2 pressure for 24 h. The progress of reaction was monitored by HPLC. After completion of the reaction, reaction mixture was cooled to below 30 ^oC. Reaction mixture was filtered through hyflo bed. The filtration bed was then washed with 10 ml of demineralized water. The filtrate was distilled off under reduced vacuum at 40 ^oC to obtain a crude product. The crude product was stirred in isopropyl alcohol at 0-5 ^oC for 30 mins, filtered and dried under vacuum to obtain 0.4 g of 1-amino-1-deoxy-galactitol. (Yield – 60%, purity by HPLC 99%), ^{1}HNMR (300MHz, D_2O) δ; 3.85-3.87(2H, m), 3.56-3.60(4H, m), 3.05-3.08(2H, m); Reported M.R. 143-145 ^oC

2.8 Preparation of N-benzyl-1-amino -1-deoxy -mannitol
1 g of mannose was added to 20 ml of methanol in a schlenk tube. To this, was added 0.73 ml of benzyl amine (1.2 eq). The reaction mixture was cooled to 5 – 10 ^oC and Ru complex in methanol was added. The reaction mixture was stirred at ambient temperature for 10-15 hrs. The progress of reaction was monitored by HPLC. After completion of the reaction, the reaction mixture was cooled to 5-10 ^oC, stirred for 30 minutes, filtered and washed with methanol to obtain a solid material. The material was dried under vacuum at 50 ^oC for 10 h to obtain N-benzyl-

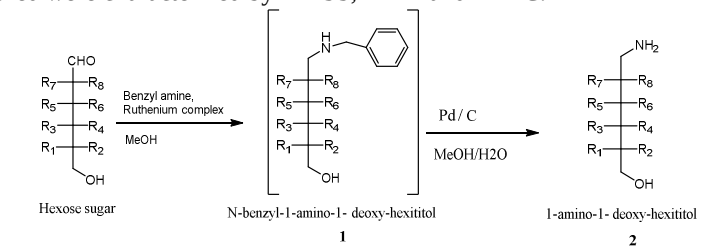
1-amino-1-deoxy-mannitol. (Yield - 80-85%, purity by HPLC 99%), ^{1}HNMR (300MHz, D_2O)(2e) δ 3.10- 3.26 (2H, m), 3.49-3.52 (1H, m), 3.64-3.87(8H, m), 2.69-2.99 (2H,m), 7.37-7.42(5H, m);ESI-MS: *m/z* 272[M+H]$^+$.

2.9 Preparation of 1-amino -1-deoxy-mannitol

1g of N-benzyl-1-amino-1-deoxy-mannitol was dissolved to the 40 ml of 1:1 methanol and demineralized water mixture. To this, was added, 0.1 g of 10% palladium carbon. Reaction mixture was hydrogenated at 50 ^{o}C under 10-12 kg of H_2 pressure for 24 h. The progress of reaction was monitored by HPLC. After completion of the reaction, reaction mixture was cooled to below 30 ^{o}C. Reaction mixture was filtered through hyflo bed. The filtration bed was then washed with 10 ml of demineralized water. The filtrate was distilled off under reduced vacuum at 40 ^{o}C to obtain a crude product. The crude product was stirred in isopropyl alcohol at 0-5 ^{o}C for 30 mins, filtered and dried under vacuum to obtain 0.4 g of 1-amino-1-deoxy-mannitol. (Yield – 70%, Purity by HPLC 94-95%), ^{1}HNMR (300MHz, D_2O)(2f) δ 2.659- 2.68 (1H, m), 2.91-2.92(1H, m), 3.57 – 3.81 (6H, m); ESI-MS: *m/z*;182[M+H].

RESULTS AND DISCUSSION

The synthetic route adopted for preparation of sugar amines are shown in Scheme 1. Ruthenium based catalysts was first prepared using $[RuCl_2$ (p-cymene)$]_2$ complex, 2-picolinamide and sodium ethoxide which are commercially available in market under inert atmosphere by using the method which is reported in literature [11]. The catalyst thus prepared was then used for reductive amination of glucose and benzylamine, without using hydrogen gas or pressure atmosphere. Benzylated intermediate was obtained in good yield and was properly characterized. The product obtained was then conveniently debenzylated using Pd/C and H_2 gas pressure to give amino sorbitol (Glucamine). In the same way other isomers such as Galactamine and Mannamine was also prepared by using Galactose and Mannose as the starting material instead of Glucose. Reductive amination of Benzyl amine with Glucose, Galactose and Mannose was carried out in methanol solvent and at ambient temperature with a reaction time of 12-15 hours. All the compounds prepared were characterized by MASS, NMR and HPLC.



Dextrose - $R_1,R_3,R_6,R_7 = H$
$R_2,R_4,R_5,R_8 = OH$

Galactose - $R_1,R_4,R_6,R_7 = H$
$R_2,R_3,R_5,R_8 = OH$

Mannose - $R_1,R_3,R_6,R_8 = H$
$R_2,R_4,R_5,R_7 = OH$

Scheme1. Synthetic route for preparation of sugar amines

In order to know the role of solvent towards the synthesis of 1-amino -1-deoxy glucitol, various solvents were screened towards the synthesis of N-benzyl-1-amino -1-deoxy glucitol (Fig 1).

A maximum conversion of > 99% was obtained when methanol and dimethyl formamide were used. Acetonitrile and 1, 4-dioxane showed 96.53 and 92.59 % conversions respectively. No conversion was observed when ethane diol was used.

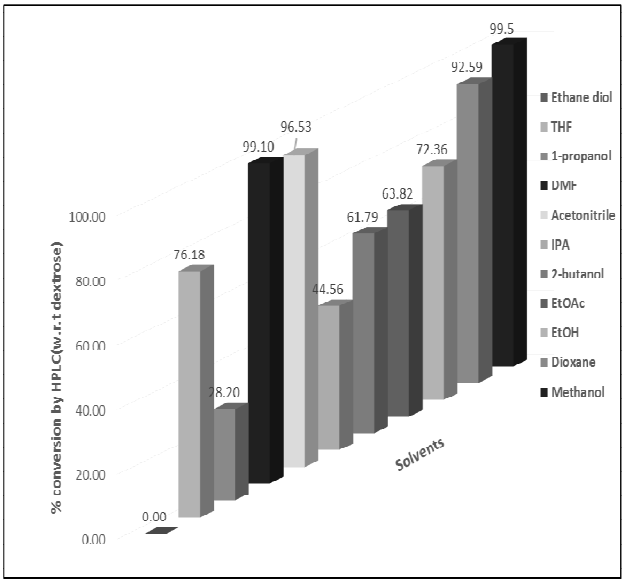


Fig 1. Screening of solvents towards synthesis of N-benzyl-1-amino -1-deoxy glucitol. Dextrose anhydrous (100mg), benzyl amine (73µl) and ruthenium complex (150 µl) in solvent (1.5ml) and stirred at 27 ^{o}C for 24hrs

CONCLUSION

Synthesis of hexose sugar amines like 1-amino-1-deoxy glucitol, 1-amino-1-deoxy galactitol and 1-amino-1-deoxy mannitol using ruthenium based complex as primary catalyst has been demonstrated. The process was convenient as the reaction doesn't require pressure reactor and is economical and operation friendly.

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