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Novel Synthesis of Schiff bases Bearing Glucosamine Moiety

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Abstract

Condensation of diverse substituted benzaldehydes, with protected glucosamine in the presence of pyridine afforded the corresponding imines in good to excellent yield.

Keywords: Schiff base, aminosugar, glucosamine.

Introduction

Schiff bases are some of the most widely used organic compounds. They are used as pigments and dyes, catalysts, intermediates in organic synthesis, and as polymer stabilizers[1]. Schiff bases have also been shown to exhibit a broad range of biological activities[2,3], including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, antimicrobial[4-6] and antipyretic properties[7]. Imine or azomethine groups are present in various natural, natural-derived, and non-natural compounds[8].

Glucosamine Schiff bases, although known since 1922, have received relatively less attention in the literature. For the compounds that consist of the Schiff base and glucose sub-units, a possibility of tautomeric and anomeric equilibria has to be taken into consideration. Dziembowska et al. studied the structure of some glucosamine Schiff bases by means of *ab initio* calculations and the anomeric and tautomeric equilibria in a DMSO solution by spectroscopic methods[9]. Kunz et al. have applied Schiff bases from *O*-protected glycosylamines to asymmetric versions of Strecker[10], Ugi[11], Mannich[12] and tandem Mannich-Michael[13]. Also Schiff bases derived amino sugars with salicylaldehyde have been shown to give stable complexes with transition-metal ions such as Cu (II), Fe (III), and Co (II) and can be applied as asymmetric catalysts[14]. On the other hand Pérez et al. have reported the first detailed study on the Schiff bases formed by reaction of D-glucosamine with aliphatic ketones. The precise stereochemistry of imines has been explored by NOE experiments and DFT calculations[15].

As an extension of our works on Schiff base, now we report the synthesis of some Schiff base compounds derived from β-D-Glucosamine.

Material and Methods

Chemicals were either purchased from Merck and Fluka chemical companies. All products were characterized by comparison of their IR and/or ^{1}HNMR spectra. All yields refer to the isolated products. The purity determination of the substrates, products and reaction monitoring were accomplished by TLC on silica gel polygram SIL/UV 254 plates. FT-IR spectra were run on a Shimadzu FTIR-8300 Spectrophotometer. ^{1}H-NMR (250 MHz) and ^{13}C-NMR (62.5 MHz) were recorded on a Bruker Avance DPX instrument. Melting points were recorded on a Büchi B-545 (Swiss) apparatus in open capillary tubes.

Synthesis of 2-deoxy-2-[p-methoxybenzylidene(amino)]-D-glucopyranose (**2**): To a solution of D-(+)-glucosamine hydrochloride (**1**) (5 g, 24.0 mmol) in a freshly prepared aqueous solution of NaOH 1M (24 mL) under stirring *p*-anisaldehyde (3.4 mL, 28.0 mmol) is added. After a short time crystallization began. Then the mixture is refrigerated and after 2 hours the white precipitated product is filtered off and washed with cold water, and followed by a mixture of 1:1 EtOH–Et_2O to give desired product with yield of 70%.

Synthesis of 1, 3, 4, 6-tetra-O-acetyl-2-deoxy-2-[p-methoxybenzylidene(amino)]-β-D-glucopyranose (**3**): Intermediate product **2** (5 g, 17.0 mmol) is added successively to a cooled mixture of pyridine (27 mL) and Ac_2O (25 mL). The mixture is stirred in ice-bath for 1 hour and then at room temperature overnight.

The yellow solution is poured into 100 mL of ice-water. The precipitated white product is filtered, washed with cold water and dried to give desired product with melting point 180–182°C.

Preparation of 1, 3, 4, 6-tetra-O-acetyl-β-D-glucosamine hydrochloride (**4**): Subsequently the compound **3** (6.8 g, 14.6 mmol) is dissolved in warm acetone (30 ºC, 60 mL), and then HCl 5 M (3 mL) is added with immediate formation of a precipitate. The mixture is cooled, and after addition of Et_2O (60 mL), it is stirred for 2 hours and refrigerated overnight. The precipitated product is filtered, washed with Et_2O and dried to give compound **4**. At 200°C this compound decomposed.

General Procedure for Synthesis of Schiff Bases (**6(a-k)**): In a round bottomed flask (25 mL), to a suspension of 1, 3, 4, 6-tetra-*O*-acetyl-β-D-glucosamine hydrochloride (1.0 mmol) in

dry CH_2Cl_2 (10 mL) and pyridine (2 mL) under stirring, desired aldehyde (1.0 mmol) (**5(a-k))** is added.

After stirring for 24 hours the solution is poured into ice-water. The organic phase is separated from water, dried and concentrated. Purification is done with ethanol.

Results and Discussion

To the best of our information there are only synthetic methods for the synthesis of Schiff bases has derived from β-D-glucosamine with 4-methoxybenzaldehyde and 2-hydroxybenzaldehyde. But when the same procedure is used for other aromatic aldehydes such as 3-methoxybenzaldehyde, nitrobenzaldehydes, methyl benzaldehydes and naphtylaldehydes, no product is obtained. Because of our need to the other Schiff bases resulting from this amino sugar, we intended to examine a new procedure that is able to produce reasonable amount of products. For this purpose, we used 1, 3, 4, 6-tetra-*O*-acetyl-β-D-glucosamine hydrochloride that its synthetic procedure was explained from β-D-glucosamine under three steps by Myszka and et al[16].

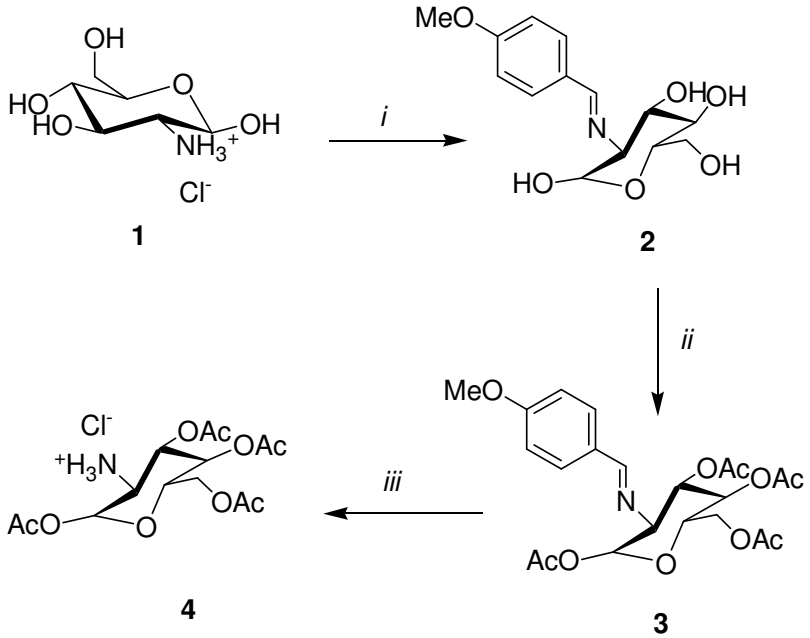
Solid form of commercially D-(+)-glucosamine is glucosamine hydrochloride (**1**), So NaOH solution is used for liberation of its amino group. After addition of *p*-methoxybenzaldehyde to free D-(+)-glucosamine, a white precipitate is produced. This imine [(2-deoxy-2-[*p*-methoxybenzylidene(amino)]-D-glucopyranose] (**2**) is identified with IR spectroscopy by presence of a sharp peak in 1645 cm^{-1} that is interrelated to C=N bond in imines and broad peak in 3200-3600 cm^{-1} for hydroxyl groups.

Acylation of hydroxyl groups of (**2**) are done by the mixture of acetic anhydride and pyridine under low temperature. This Schiff base is known as 1, 3, 4, 6-tetra-*O*-acetyl-2-deoxy-2-[*p*-methoxybenzylidene (amino) β-D-glucopyranose (**3**). IR spectrum of this compound shows the absence of OH band in 3200 cm-1 region and also the presence of a strong peak in 1755 cm^{-1} for carbonyl bonds.

Hydrolysis of C=N bond in Schiff base (**3**) is done in the warm mixture of acetone and hydrochloric acid. This product is named 1, 3, 4, 6-tetra-*O*-acetyl-β-D-glucosamine hydrochloride (**4**) (figure-1).

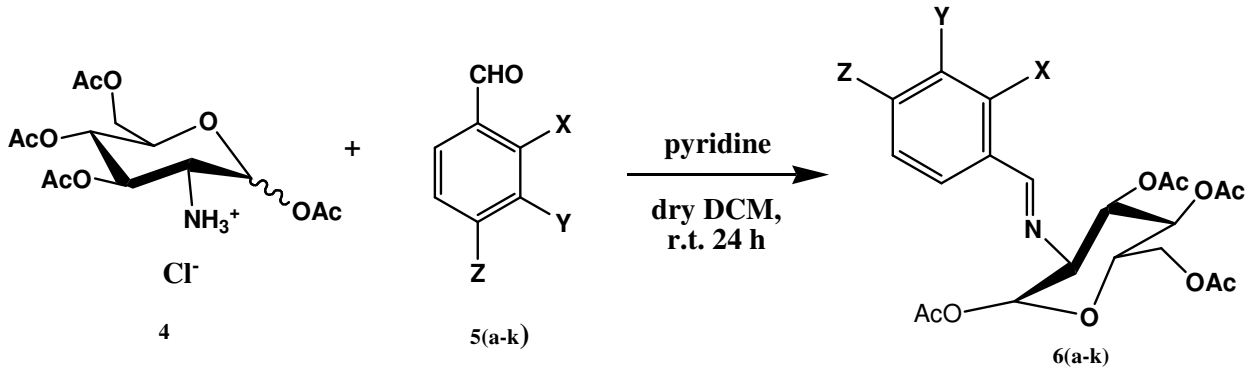
IR spectroscopy of this salt shows the elimination of imine (C=N) band and aromatic (C=C) band. This compound is decomposed after 200 ºC.

Finally, for synthesis of desired Schiff bases, to a suspension of 1, 3, 4, 6-tetra-*O*-acetyl-β-D-glucosamine hydrochloride (**4**) in dry dichloromethane and pyridine, as a base, at room temperature, different aldehydes are added discretely. Each Schiff base that is produced with this procedure is identified with its IR and NMR spectrums (figure-2).



i: p-anisaldehyde, NaOH 1M, ii: Pyrridine, Ac_2O, *iii:* acetone, HCl 5M;

Figure-1
Synthesis of *O*-acylated glucosamine hydrochloride



5a:X: Methoxy, Y: H, Z: H
5b:X: Methyl, Y: H, Z: H
5c:X: Nitro, Y: H, Z: H
5d:X: Acetyl, Y: H, Z: H
5e:X: H, Y: Methoxy, Z: H
5f:X: H, Y: Methyl, Z: H
5g:X: H, Y: Nitro, Z: H
5h:X: H, Y: H, Z: Methoxy
5i:X: H, Y: H, Z: Methoxy
5j:X: H, Y: H, Z: Nitro
5k: 2-naphtyl

Figure-2
Synthesis of different Schiff bases from different aldehydes

Conclusion

In conclusion, the procedure has been used for conversion of D-Glucosamine into the corresponding Schiff base molecules through protection of its hydroxyl groups, followed by condensation with substituted aldehydes. Handling, safety, mild reaction conditions, good to excellent yields of the products and simple recovery of the reaction products make this method useful in organic synthesis. As our major concern is on the synthesis of new azetidinones, β-lactams derived these Schiff base have been synthesized and will report in next papers.

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References

1. Dhar D.N. and Taploo C.L., Scheiff bases and their applications, *J. Sci. Ind. Res*., **41**, 501-506 **(1982)**

2. Kokila P., Sarju P., Rinku P. and Rekha P., A simple and efficient procedure for synthesis of biologically active 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole -2-aryl-thiazolidine -4-one derivatives, *Res. J. chem. sci.,* **1(1)**, 18-24 **(2011)**

3. Prasad K.R. and Kumar J.V.S., Synthesis and Characterisation of New Mesogenic 4-n-Alkoxy Benzaldehyde Semicarbazones, *Res. J. chem. sci.,* **1(7),** 89-91 **(2011)**

4. Elemike E.E., Oviawe A.P. and Otuokere I.E., Potentiation of the Antimicrobial Activity of 4-Benzylimino-2, 3-Dimethyl-1-Phenylpyrazal-5-One by Metal Chelation, *Res. J. chem. sci.,* **1(8),** 6-11 **(2011)**

5. Gupta Y.K., Agarwal S.C., Madnawat S.P. and Narain R., Synthesis, Characterization and Antimicrobial Studies of Some Transition Metal Complexes of Schiff Bases, *Res. J. chem. sci.,* **2(4),** 68-71 **(2012)**

6. Nagajothi A., Kiruthika A., Chitra S. and Parameswari K., Fe(III) Complexes with Schiff base Ligands: Synthesis, Characterization, Antimicrobial Studies, *Res. J. Chem. Sci.,* **3(2),** 35-43 **(2013)**

7. Przybylski P., Huczynski A., Pyta K., Brzezinski B. and Bartl F., Biological Properties of Schiff Bases and Azo Derivatives of Phenols, *Curr. Org. Chem.*, **13**, 124-148 **(2009)**

8. Da Silva C.M., Da Silva D.L. and Modolo L.V., Schiff bases: A short review of their antimicrobial activities, *J. Adv. Res*., **2**, 1-8 **(2011)**

9. Kołodziej B., Grech E., Schilf W., Kamienski B., Makowski M., Rozwadowski Z. and Dziembowska T., Anomeric and tautomeric equilibria in d-2-glucosamine Schiff bases, *J. Mol. Struc*t., **844**, 32-37 **(2007)**

10. Kunz H., Pfrengle W., Rück K. and Sager W., Stereoselective Synthesis of L-Amino Acids via Strecker and Ugi Reaktions on Carbohydrate Templates, *Synthesis*, 1039-1042 **(1991)**

11. (a) Kunz H. and Pfrengle W., Asymmetric synthesis on carbohydrate templates: stereoselective Ugi-synthesis of .alpha.-amino acid derivatives, *J. Am. Chem. Soc*., **110**, 651-652 **(1988)** (b) Kunz, H. Pfrengle, W., Carbohydrates as chiral templates: asymmetric ugi-synthesis of alpha-amino acids using galactosylamines as the chiral matrices, *Tetrahedron,* **44**, 5487-5494 **(1988)**

12. (a) Kunz H., Burgard A. and Schanzenbach D., Asymmetric Mannich Synthesis of β-Amino Acids with Two New Stereogenic Centers at the α and β Positions, *Angew. Chem., Int. Ed*., **36**, 386-387. **(1997)** (b) Allef P. and Kunz H., Glycosylation-induced asymmetric synthesis: β-amino acid esters via Mannich reactions, *Tetrahedron: Asymmetry*, **11**, 375-378 **(2000)**

13. Kunz H. and Pfrengle W., Carbohydrates as Chiral Templates: Stereoselective Tandem Mannich-Michael Reactions for the Synthesis of Piperidine Alkaloids, *Angew. Chem., Int. Ed. Engl*., **28**, 1067-1068 **(1989)**

14. Pérez E.M.S., Avalos M., Babiano R., Cintas P., Light M.E., Jiménez J.L., Palacios J.C. and Sancho A., Schiff bases from d-glucosamine and aliphatic ketones, *Carbohydr. Res*., **345**, 23-32 **(2010)**

15. Costamagna J., Lillo L.E., Matsuhiro B., Noseda M.D. and Villagran M., Ni(II) complexes with Schiff bases derived from amino sugars, *Carbohyd. Res*., **338**, 1535-1542 **(2003)**

16. Myszka H., Bednarczyk D., Najder M. and Kaca W., Synthesis and induction of apoptosis in B cell chronic leukemia by diosgenyl 2-amino-2-deoxy-β-D-glucopyranoside hydrochloride and its derivatives, *Carbohyd. Res.,* **338**, 133-141 **(2003)**