

INVESTIGATION OF SYNTHETIC REACTION OF AZOMETHINES FROM GLUCOSAMINE AND SUBSTITUTED BENZALDEHYDES

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Abstract. Reaction of α -D-glucosamine hydrochloride with different substituted benzaldehyde has been investigated in the presence of various inorganic and organic bases. Based on obtained results, the general synthetic method for azomethines of α -D-glucosamine hydrochloride and substituted benzaldehyde proposed.

1. Introduction

D-Glucosamine, one amino monosaccharide, is a component of chitin, a natural mucopolysaccharide [1]. As an amine, so glucosamine are able to form azomethines and imines with aromatic aldehydes and aliphatic ketones. Some azomethines and imines have been synthesized in the first years of previous century [2–5]. One first azomethine deriving from glucosamines and salicylaldehyde have been prepared in water medium by Irvine and Hynd in 1913 [2]. These conversions have been performed by reaction of glucosamine hydrochloride with salicylaldehyde in water solution of sodium bicarbonate, with formation of product which was insoluble in water. In the other hand, azomethines deriving from salicylaldehyde and 4-anisaldehyde have been used as protected groups for amino groups in some conversion reaction of saccharide which have that group.

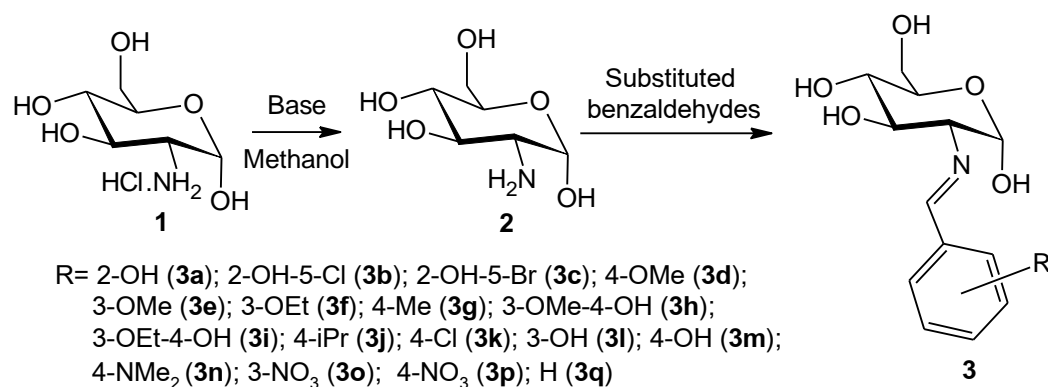
Imines and azomethines (or Schiff's bases), compounds dating back to the early days of synthetic organic chemistry, are easily generated by condensation of carbonyl groups and primary amines. The process takes place with the intermediacy of a carbinolamine that undergoes further dehydration to give a double carbon–nitrogen bond [6]. In carbohydrate chemistry, a large number of imines has been reported, both by reaction of sugar aldehydes with amines and by reaction of aminosugars with aldehydes. Such inherently chiral imines have been employed in asymmetric syntheses serving the carbohydrate fragment as a chiral inductor. Therefore, Kunz *et al* [7] have applied Schiff bases from *O*-protected glycosylamines to asymmetric versions of Strecker [8], Ugi [9], Mannich [10] tandem Mannich-Michael [11], hetero-Diels–Alder [12], and organometallics addition reactions.8 Likewise, Georg *et al.* have employed such sugar imines in the Staudinger reaction [13]. As mentioned above, these Schiff bases can easily be prepared by condensation of protected glycosylamines with the corresponding aldehyde [9,15,16]. Ugi and associates have also used a thiosugar-derived glycosylimine in the stereoselective synthesis of α -amino acids and peptides [17]. Finally, sugar imines have been postulated as intermediates in the formation of glycosylamines [18,19] and in their mutarotation reactions [20].

To contribute to these researches of azomethines from α -D-glucosamines, in this paper, we performed the investigation of the synthetic reaction of azomethines from glucosamine hydrochloride and different substituted benzaldehydes for finding optimum synthetic routes.

2. Results and discussion

Reaction of α -D-glucosamine hydrochloride with substituted salicylaldehydes have been performed using different synthetic methods, depending on the nature of substituents in benzene ring (Scheme 1). In the case of salicylaldehyde (R=H), reaction was carried out by Irvine's method [2], using water as solvent and sodium bicarbonate as catalyst. We found that if the usage of Irvine's method for synthesis of azomethines having other substituents than hydroxy group, the reaction does not take place. It seems that almost benzaldehydes are insoluble in water, even liquid benzaldehydes, such as 4-methyl-, 4-isopropyl-, 3-methoxy-, 3-ethoxybenzaldehydes and benzaldehyde. Therefore, in case of substituted salicylaldehydes having chloro and bromo groups and vanillin, the reaction of these benzaldehydes with α -D-glucosamine hydrochloride must be carry out in absolute methanol together with the elimination of NaCl salt before the addition benzaldehyde to the reaction mixture. The product usually appear after 15–20 min refluxing. For other substituted benzaldehydes, we also used this synthetic method.

Irvine [2] and other authors [21] had used sodium bicarbonate for conversion of α -D-glucosamine hydrochloride into α -D-glucosamine base, whereas, another authors [3,22,23] had used NaOH for elimination HCl. For finding the most suitable basic conditions in this conversion, we have investigated the role of some inorganic bases (such as NaOH, NaHCO₃ and Na₂CO₃) and organic bases (such as triethylamine, DABCO, pyridine and piperidine) in synthetic reaction of azomethines from α -D-glucosamine hydrochloride using methanol as solvent.



Scheme 1. Reaction of α -D-glucosamine substituted benzaldehydes.

We found that, except azomethines of α -D-glucosamine with substituted salicylaldehydes **3a-c** are thermal stable, almost other remained azomethines, if formed, are thermal unstable, so the recrystallization of these azomethines lead to decrease the reaction yield, or to decompose the formed product, even some azomethines **3** become black in air. In case of azomethines of α -D-glucosamine with substituted salicylaldehydes **3a-c**, intramolecular hydrogen bond between nitrogen atom of azomethine bond and hydroxyl group on carbon C-1 of monosaccharide component through lone-pair electron on this nitrogen atom make azomethine molecule to be stable [3]. Other azomethine molecules, no having this intramolecular hydrogen bond, prove to be more unstable, decomposed easily by heat or by air oxygen.

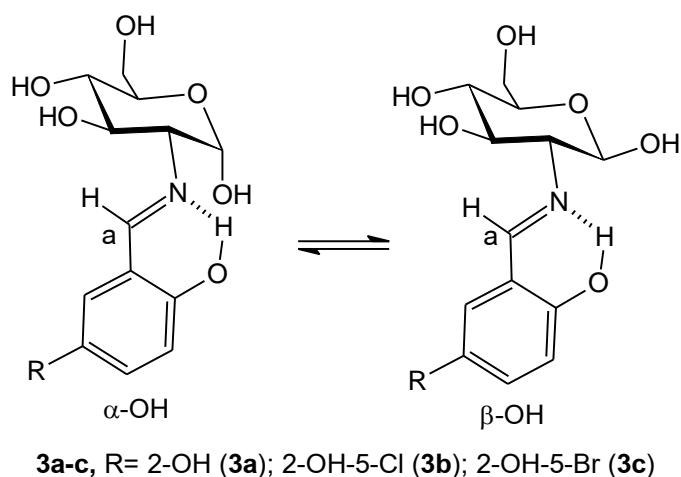


Figure 1. Intramolecular hydrogen bond in substituted salicylidene α -D-glucosamines **3a-c**.

Table 1. Results of investigation in reaction of α -D-glucosamine hydrochloride **1** and salicylaldehyde in absolute methanol

Entry	Base	Results
1	NaOH	Yellow precipitate appeared, yield 0,66 gr. of solid
2	NaHCO ₃	Solvent evaporated, yellow solid appeared
3	Na ₂ CO ₃	Solvent evaporated, yellow solid appeared, then became black tar.
4	Triethylamine	Nothing
5	Piperidine	Nothing
6	DABCO	Nothing

Table 2. Azomethines of α -D-glucosamine and substituted benzaldehydes **3a-p**

Entry	R	mp, °C	Colour	Yield, %	IR (cm ⁻¹) $\nu_{C=N}$
3a	2-OH	131–132	Yellow	93	1627
3b	2-OH-5-Cl	90–91	Yellow	75	
3c	2-OH-5-Br	105–106	Yellow	75	
3d	4-OMe	166–167	White	78	1639
3e	3-OMe	-	-	No reaction	
3f	3-OEt	-	-	No reaction	
3g	4-Me	188–190	White	80	1644

3h	3-OMe-4-OH	-	-	No reaction
3i	3-OEt-4-OH	-	-	No reaction
3j	4-iPr	177–178	White	79 1646
3k	4-Cl	-	-	No reaction
3l	3-OH	-	-	No reaction
3m	4-OH	-	-	No reaction
3n	4-NMe ₂	-	-	No reaction
3o	3-NO ₂	-	-	No reaction
3p	4-NO ₂	-	-	No reaction
3q	H	-	-	No reaction

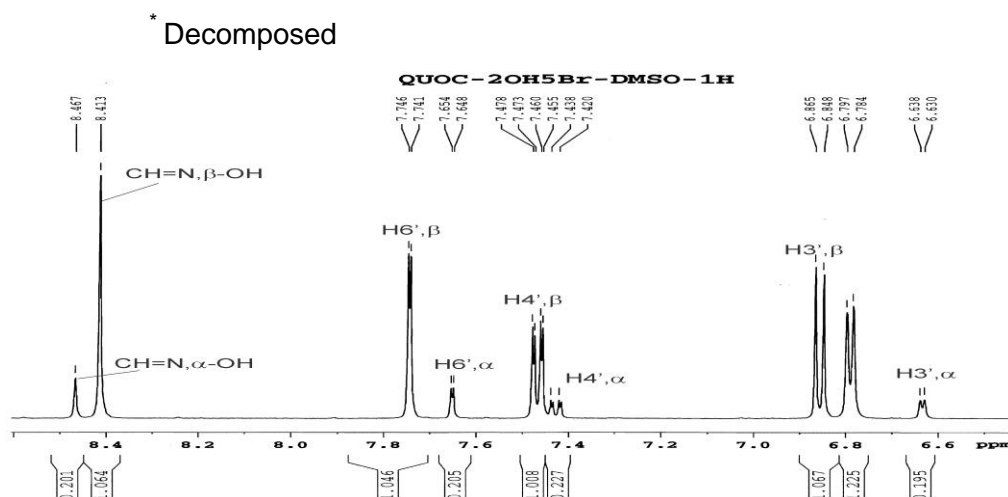


Figure 2. A part of ¹H NMR spectrum (in DMSO-*d*₆) of **3c** (Bruker 500 MHz).

IR of azomethine **3** have characteristic bands for valent vibration of C=N bond in $\nu_{C=N} = 1644\text{--}1627\text{ cm}^{-1}$, having from medium to strong intensities. Other bands, characteristic for OH and benzene ring, are present in IR spectra [2–5,10]. ¹H NMR spectrum of compound **3c** in Fig. 2, recorded in DMSO-*d*₆ solvent, showed signal regions of aromatic protons, pyranose protons, hydroxyl-proton and proton in azomethine bond. Simultaneously, its spectrum indicated that the anomer equilibrium of this compound in DMSO-*d*₆ solvent according to the Kołodziej's observation [3]. Anomer α/β ratio is 1:5,25, from ¹H NMR spectra.

3. Experimental

Melting points were determined on a STUART SMP3 apparatus (BIBBY STERILIN-UK) and uncorrected. The IR spectra were recorded on a Magna 760 FT-IR Spectrometer (NICOLET, USA) in KBr disc. The ¹H NMR (at 500.13 MHz) spectra were recorded on an AVANCE Spectrometer AV500 (BRUKER, Germany) in DMSO-*d*₆ solution in ppm compared to TMS as internal reference. α -D-Glucosamine hydrochloride have been prepared

from shrimp shells by modified Stacey-Webber's method.

General synthetic method. α -D-Glucosamine hydrochloride was suspended in suitable solvent (see Table 1). To the solution was stirred vigorously equivalent amount of appropriate base (NaOH, NaHCO₃, Na₂CO₃, triethylamine, DABCO or piperidine - see Table 1) was added. In the case of methanol solvent, NaCl precipitate was filtered off. Then appropriate substituted benzaldehyde was added, and reaction mixture was heated in reflux and stirred according to reaction conditions that represented in Table 1. The precipitate was filtered, dried in air, recrystallized from absolute ethanol of 96% ethanol. Investigation results were represented in Table 1. Synthetic results of azomethine **3** were reported in Table 2.

4. Conclusion

Reaction of α -D-glucosamine hydrochloride with different substituted benzaldehydes have been investigated in the presence of different inorganic and organic bases. Based on these obtained results, the general synthesis for azomethines from α -D-glucosamine hydrochloride have been suggested.

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