Synthesis and structural studies of Glucosylimino-1,2,4,5-Tetrazine

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ABSTRACT

Series of 3-tetra-O-acetyl-β-D-glucopyranosylimino, 6 substituted -1,2,4,5-tetrazine (IV) have been synthesized by the reaction of aryl dihydroformazanes (III) and tetra-O-acetyl-β-D-glucosylimino-isocyanodichloride in refluxing chloroform medium. The aryl dihydroformazans (III) were prepared by the interaction of acid hydrazides (I) and hydrazine hydrate (II) in refluxing ethanol medium in 1:1 proportion. The structures of tetrazines (IV) were confirmed on the basis of elemental analysis and IR, PMR, 13C and mass spectral analysis.

Keywords: Tetrazine, isocynodichloride, dihydroformazans.

INTRODUCTION

Natural products show a broad spectrum of biological activities with a high potential for medicinal applications. Carbohydrates are also structurally important component of such numerous biologically active natural products. Some of its N and S linked sugar derivatives are exhibiting antifungal [1], antitumor [2], anticancer [3], antiviral [4], antimalarial activity [5] and antilukemic activity [6]. Recently, ortho carbonyl glycosides used for the treatment of cancer by boron neutron capture therapy [7].

Various routes [8-16] have been reported in the literature for the synthesis of different 1,2,4,5-tetrazines. Majority of them [17-18] are 3-6-symmetrically disubstituted tetrazines obtained from the treatment of nitrile derivatives with hydrazines or aldehyde with substituted hydrazines. Tetrazines possess a wide range of antiviral and antitumor properties and have been widely used as pesticides and herbicides [19]. Recently, new 1,2,4,5-tetrazines have been successfully synthesized by using N-aryl isocynodichloride [20-21].

Such significant and diversified pharmaceutical values of glycosides have focused our interest on the studies towards the monosaccharide moiety. Our present work relates to synthesis of several N-linked glucose derivatives via one of the most powerful intermediate glucosylimino isocyanodichloride. The glucosylimino isocyanodichloride was firstly synthesized in this laboratory.

In our research interest we explored the application of glucosyl isothiocynate and its dichloro derivative in the synthesis of heterocyclic system with glucosidic base [22]. Here we explored the route for the synthesis of tetrazine molecules by using glucosylimino isocynodichloride as one of the reagent for the synthesis of heterocyclic system.
Reaction scheme

I. Preparation of 3-Tetra-O-acetyl-β-D-glucopyranosylimino, 6(4-nitrophenyl) 1,2,4,5-tetrazine (IVa).
3-tetra-O-acetyl-β-D-glucopyranosylimino,6(4-nitrophenyl) 1,2,4,5-tetrazine (IVa) was prepared by refluxing 4-nitrophenyl dihydroformazan (0.001mole) with glucosylimino isocyanodichloride (0.001mole) in chloroform medium for 4 hours. After completion of reaction, the reaction mixture was cooled; the solvent was distilled off to obtained pale yellow solid residue (IVa). It was recrystallized from ethanol (70%). m.p.132°C, yield 81%. 4a. IR: NH 3350 cm⁻¹, C=O 1715 cm⁻¹, -N-N- 1280 cm⁻¹, C-N 1160 cm⁻¹, C=C 1560 cm⁻¹, CH₂ bend.1400 cm⁻¹. ¹H NMR: 12H singlet 2.31 δ ppm acetyl group, 1H doublet 6.33 δ ppm β anomeric proton, 4H d-d 7.6-8.2 δ ppm aromatic ring, glucosyl ring protons 4.1-5.46 ppm, 2H 2.03-2.066 ppm -NH- proton, 1H singlet 7.26 ppm -NH- proton. Mass: (m/e) (M-1)⁺ 551. ¹³CNMR:-CDCl₃, 77.06-77.38 ppm, 4CH₃, 20.48-20.91 ppm, glucosyl ring carbon C₆ 61.43 ppm, C₅ 76.74 δ ppm, C₄ 69.16 ppm, C₃ 69.16 ppm, C₂ 67.84 ppm, β anomeric carbon C₁ 89.05 δ ppm, C₂ and C₅ of aromatic ring 1298 ppm, C₃ and C₄ of aromatic ring 1236 ppm, C₃ of aromatic ring 151 δ ppm, carbon from tetrazine ring 168.82 δ ppm carbon from (C=N) 168.44-170.71 δ ppm. (Found: C 47.63; H 4.32; N 14.86; Calc.for C₃₂H₂₆N₁₁O₁₁):
C 48.00; H 4.76; N 15.27. 4b. m.p.103°C, yield 76%. IR: NH 3345cm⁻¹, C=O 1720cm⁻¹, -N=N- 1290cm⁻¹, C=O 1725cm⁻¹, -N=N- 1280cm⁻¹, C=O 1560cm⁻¹, C=O 1720cm⁻¹. 4H singlet 7.26ppm -NH- proton. Mass: (m/e) (M) 521. 1H NMR: CDCl₃ 77.06-77.38ppm, 4CH₃ 20.48-20.91ppm, glucosyl ring carbon C₆ 61.43ppm, C₇ 76.74ppm, C₇ 69.16ppm, C₈ 67.84ppm, β anomeric carbon C₁ 89.05ppm, C₆ and C₈ of aromatic ring 128.56ppm, C₃ and C₈ of aromatic ring 128.00ppm, C₅ of aromatic ring 126.15ppm, carbon of CH₄ 30.06ppm, carbon of tetrazine ring 168.82ppm, carbon from C=6 168.44-170.71ppm. (Found: C 47.63; H 4.32; N 14.86; Calc.for C₂₂H₂₃N₅O₁₄: C 48.00; H 4.76; N 15.27). 4d. m.p.126°C, yield 77%. IR: NH 3350cm⁻¹, C=O 1725cm⁻¹, -N=N- 1280cm⁻¹, C=O 1560cm⁻¹, CH₂ bend.1400cm⁻¹. 1H NMR: CDCl₃ 77.06-77.38ppm, 4CH₃ 20.48-20.91ppm, glucosyl ring carbon C₆ 61.43ppm, C₇ 76.74ppm, C₇ 69.16ppm, C₈ 67.84ppm, β anomeric carbon C₁ 89.05ppm, C₆ and C₈ of aromatic ring 129ppm, C₅ and C₈ of aromatic ring 123ppm, C₆ of aromatic ring 151ppm, carbon from tetrazine ring 168.82ppm carbon from C=6 168.44-170.71ppm. (Found: C 47.63; H 4.32; N 14.86; Calc.for C₂₂H₂₃N₅O₁₄: C 48.00; H 4.76; N 15.27). 4e. m.p.132°C, yield 81%. IR: NH 3350cm⁻¹, C=N 1150cm⁻¹, CH bend.1400cm⁻¹. 1H NMR: CDCl₃ 77.06-77.38ppm, 4CH₃ 20.48-20.91ppm, glucosyl ring carbon C₆ 61.43ppm, C₇ 76.74ppm, C₇ 69.16ppm, C₈ 67.84ppm, β anomeric carbon C₁ 89.05ppm, C₆ and C₈ of aromatic ring 129ppm, C₅ and C₈ of aromatic ring 123ppm, C₆ of aromatic ring 151ppm, carbon from tetrazine ring 168.82ppm carbon from C=6 168.44-170.71ppm. (Found: C 47.63; H 4.32; N 14.86; Calc.for C₂₂H₂₃N₅O₁₄: C 48.00; H 4.76; N 15.27). 2. Preparation of 3-β-D-glucopyranosylimino, 6-(4-nitrophenyl) 1, 2, 4, 5-tetrazine (Va). 3-β-D-Glucopyranosylamino, 6-(4-nitrophenyl)-1,2,4,5-tetrazine (Va) was prepared by stirring the 3-tetra-O-acetyl-β-D-glucopyranosylamino-6-(4-nitrophenyl)-1,2,4,5-tetrazine (IVa) in methanolic ammonia for about 24hour. 5a. m.p.136°C, yield 68%. IR: uNH 3300cm⁻¹, uC=N 1150cm⁻¹, uC=O 1560cm⁻¹. 1H NMR: CDCl₃ 76.48ppm -NH- proton. Mass: (m/e) (M) 521. 1H NMR: CDCl₃ 77.06-77.38ppm, 4CH₃ 20.48-20.91ppm, glucosyl ring carbon C₆ 61.43ppm, C₅ 76.74ppm, C₇ 69.16ppm, C₈ 67.84ppm, β anomeric carbon C₁ 89.05ppm, C₆ and C₈ of aromatic ring 129ppm, C₅ and C₈ of aromatic ring 151ppm, carbon from tetrazine ring 168.82ppm carbon from C=6 168.44-170.71ppm. (Found: C 47.63; H 4.32; N 14.86; Calc.for C₂₂H₂₃N₅O₁₄: C 48.00; H 4.76; N 15.27).
RESULTS AND DISCUSSION

For the synthesis of compound (4a-4g) and (5a-5g) the scheme shown above were followed. The tetra-O-acetyl-β-D-glucopyranosylimino isocyanodichloride was prepared by the excess chlorination of tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate. The tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate was prepared by the known procedure. The tetra-O-acetyl-β-D-glucopyranosylimino isocyanodichloride gave negative lead plumbite test indicating the absence of C=S bond. It was charred when treated with conc. H₂SO₄ indicating the presence of glucosyl moiety. The PMR spectrum of the compound clearly indicated the signals for the acetyl protons, other glucosyl proton and doublet of β-glucopyranosyl proton. In the typical synthesis of (IVA) was synthesized by refluxing tetra-O-acetyl-β-D-glucopyranosylimino isocyanodichloride with 4-nitrophenyl dihydraformazan in 1:1 proportion for 4 hour in chloroform medium. After completion of reaction, the crude product was recrystallized from 70% of ethanol. It was charred when treated with conc. H₂SO₄ indicating the presence of glucosyl moiety. In IR, it has higher C=O stretching frequency (typically 1740) than comparable C=O (typically 1710) because of the inductive effect of ester. The IR spectra do not show the band for stretching frequency of the hydroxyl group confirming the formation of acylated glucosides. The IR spectrum displayed the band due to νNH, νC=O and νC=C groups. The PMR spectrum of the compound indicated the signals of acetyl proton, NH protons, aromatic protons and pyranosyl protons as well as doublet due to β-glucopyranosyl proton. The mass spectrum of the compound showed presence of (M-1)⁺ peak at m/e 551. Other important fragment peaks were located at 523, 413, 353, 171 etc. The elemental analysis of the product indicated the molecular formula C₂₂H₂₆N₆O₁₁.

On the basis of all the above facts the compound (IVA) was assigned structure as 3-tetra-O-acetyl-β-D-glucopyranosylimino-6(4-nitrophenyl)-1,2,4,5-tetrazine. Similarly all other compounds were prepared by extending the reaction of tetra-O-acetyl-β-D-glucopyranosylimino isocyanodichloride with other aryl dihydroformazans (IIIb-IIIg).

The compound (Va) was prepared by the deacetylation of compound (IVA) via methanolic ammonia. The product was charred on treatment with conc. H₂SO₄ indicating the presence of glucosyl ring. The IR spectrum indicated the broad band of –OH group at 3300 cm⁻¹ and the signals of carbonyl C=O band at 1740 cm⁻¹ were disappeared. Also in PMR spectra of the product the signal of acetyl protons (2.31) were absent. The PMR of the product showed the double doublet at 5.36 ppm indicating the presence of β-glucosyl ring. All the above facts favored the complete deacetylation of product (IV). The elemental analysis of product indicated the molecular formula as C₁₄H₁₈N₆O₇.

On the basis of all above fact the compound (Va) was assigned the structured of 3–β-D-glucopyranosylimino, 6(4-nitrophenyl) 1,2,4,5-tetrazine. Similarly all the other compounds were prepared (Vb-Vg) by the deacetylation of (IVb-IVg) respectively.

CONCLUSION

Here we explored the route for the synthesis of asymmetrical and symmetrical tetrazine molecules by using glucosylimino isocyanodichloride as one of the reagent for the synthesis of heterocyclic system.

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