

Simple and Eco-friendly Synthesis of Glycosides bearing triazolo[3,4-b][1,3,4]thiadiazole moiety linked through N atoms

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Abstract: There is a vast variety of naturally occurring glycosides which have marked pharmacological properties. These glycosides have widely diversified functional groups modifications which result in influencing pharmacological performance of corresponding glycosides. The 3,6-disubstituted-s-triazolo[3,4-b][1,3,4]thiadiazoles were glucosidated with 2,3,4,6-tetra-O-acetyl α -D-glucopyranosyl bromide using simple methodologies. The compounds obtained in good yield in a 80-90 minutes.

Keywords: anti helminthic, anti hypertensive, thiosemicarbozes, triazoles, thiadiazoles

I. Introduction

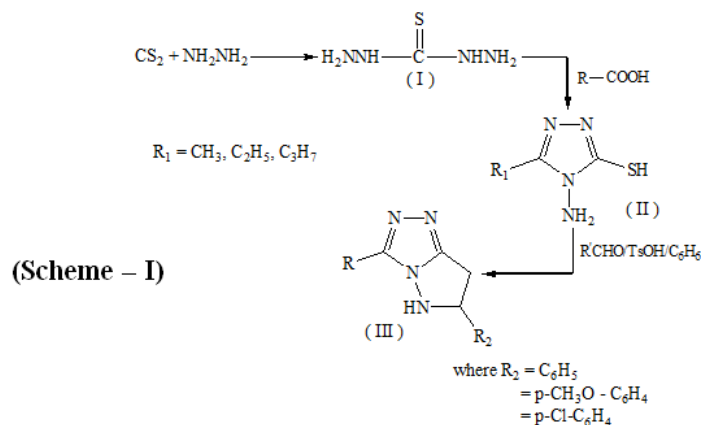
The N-heterocycles are known for their potent biological activities. Among them the 1,2,4-triazoles and N-bridged heterocyclic have received a considerable attention due to their strong pharmacological properties [1-5]. A triazolo nucleus appear to be very important for its biological potency. Likewise in various heterocyclic products a 1,3,4-thiadiazole ring also possesses a diverse biological activities due to -N-C=S linkage, the importance of which has been well stressed in many pesticides. Further 2-amino-1,3,4-thiazoles may be viewed as cyclic analogue of thiosemicarbazone, the physiological properties of which have been well established. The triazolo[3,4-b][1,3,4]-thiadiazoles, thiosemicarbazide [6] and biguanides [7] which possess diverse biological activities such as antimicrobial, bacteriocidal, anti-inflammatory, antiviral, anti-hypertensive, anti-helminthic and analgesic [8-25].

The glycosides are found in a wide variety of natural products. The carbohydrate moiety in these glycosides is generally a mono or disaccharide and less frequently a higher oligosaccharide. These glycosides are attached to aglycan part through C-1 of carbohydrate and N-part of amine. Numerous glycosides are used as drugs and have a wider therapeutic applications [26-29]. Most of these glycosides are optically active.

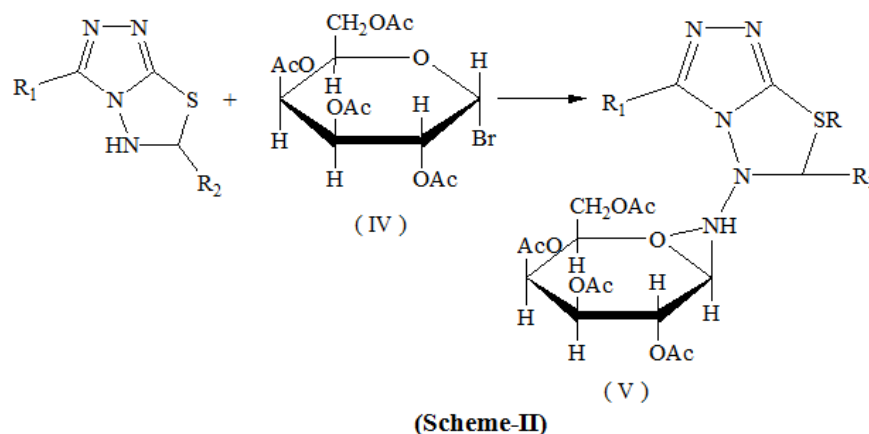
II. Results and Discussion

The series of glycosides bearing triazolo[3,4-b][1,3,4]thiadiazole moiety linked through N atoms was synthesized. The N-glycosides were condensed with mercapto amino triazoles in a microwave oven in presence of DMF and TsOH.

General scheme involves glucosidation of 3,6-disubstituted-s-triazolo[3,4-b][1,3,4]-thiadiazoles with 2,3,4,6-tetra-O-acetyl α -D-glucopyranosyl bromide having N-glycoside linkage. A mixture of hydrazine hydrate, water and CS₂, on refluxing yielded thiocarbohydrazide (I). This on heating with carboxylic acid gave 4-aminomercapto-3-alkyl-s-triazole (II). The (II) on treatment with aromatic aldehyde in dry benzene using Dean-Stark apparatus and catalytic amount of TsOH yielded 3,6-disubstituted-s-triazolo[3,4-b][1,3,4]-thiadiazoles (Scheme - I).



3,6-Disubstituted-s-triazole [3,4-6][1,3,4]-thiadiazoles (2) on treatment with 2,3,4,6-tetra-o-acetyl- α -D-glucopyranosyl bromide (3) gave substituted N-glucosidated-s-triazolo[3,4-6][1,3,4]-thiadiazoles (4) [Scheme-II].



The compounds show N-H stretching band between 3150-3100 cm^{-1} . The C = O stretching band of acetyl carbonyl occurs at 1770-1750 cm^{-1} . In the NMR of the compounds show the C-H as singlet at δ value of 5.65 to 5.80.

Group		Time in hr.	Yield (%)
R ₁	R ₂		
CH ₃	C ₆ H ₅	1hr-20min.	60
C ₂ H ₅	p-CH ₃ O-C ₆ H ₄	1hr-25 min.	62
C ₃ H ₇	p-CH ₃ O-C ₆ H ₄	1hr-22 min.	65
CH ₃	p-Cl-C ₆ H ₄	1hr-20min.	63
CH ₃	p-Br-C ₆ H ₄	1hr-27min.	67
C ₂ H ₅	p-Cl-C ₆ H ₄	1hr-28min.	66
CH ₃	p-2,4-dichlorophenyl	1hr-35min.	68
CH ₃	p-CH ₃ O-C ₆ H ₄	1hr-30min.	69

III. Experimental

Preparation of thiocarbazine (I). A mixture of 156.25 ml (80%) of hydrazine hydrate and 95 ml of water was stirred well for 10 minutes and 38 ml of CS₂ as added in small increments with constant stirring. After this the reaction mixture was allowed to reflux for 2-3 hours. The flask was cooled and the reaction mixture was filtered and recrystallised with hot water, when shining white crystals with m.pt 169 °C were obtained.

Preparation of 4-Amino-5-mercapto-3-alkyl-s-triazole (II)

Thiocarbazine and carboxylic acid (1:10 molar ratio) was refluxed for three to four hours. When the crystals started separating out. These were recrystallised with hot water.

Preparation of 3-Alkyl-6-phenyl-5,6-dihydro-s-triazolo[3,4-6][1,3,4]thiadiazoles (III)

The equimolar mixture of compound II benzaldehyde and TsOH were taken in a flask and to it 100 ml of dry benzene was added. The contents were refluxed for 10 hours using Dean-Stark apparatus, to remove the traces of water formed during the course of reaction. The reaction was monitored with thin layer chromatography of the eluates taken out of reaction mixture from time to time. After the completion of reaction, the reaction mixture was cooled and treated with water. Organic layer was separated dried and the solvent was evaporated. The residue was recrystallised using ethanol.

Preparation of 3-Alkyl-6(H)-6-phenyl-5-[N-2,3,4,6-tetra-o-acetyl- β -D-glucopyranosyl]-s-triazole[3,4-6][1,3,4]-thiadiazole (V)

A mixture of compound(III) (0.05 mol) sodium hydride (50% suspension in mineral oil) (0.05 mol) were stirred in 225 ml of acetonitrile at room temperature for one hour. Tetra-o-acetyl- α -D-glucopyranosyl bromide(IV) [Prepared through the methods reported in literature] was added to it in 1:1 mole ratio in small quantities and allowed to stir for another 25-30 minutes to complete the reaction. The mixture was filtered through celite and washed with CHCl₃. The product were recrystallised on silica gel (10-230 mesh) on column chromatography using graded solvents.

All the solvent were of LR and were obtained from Merck. The elemental analysis of the compounds was performed on CHN elementary (Analysen System Gm6H, Germany) The elemental analysis (C,H,N) of compounds was found within a limit of $\pm 0.5\%$ theoretical values of 0.5 mm thickness. The TLC plates were prepared from silica gel G Merck Iodine chamber was used for visualization of TLC spots. The FT-IR spectrum

was recorded in KBr pellets on a Perkin Elmer FT-IR spectrometer. The melting points were determined on Yorko melting point apparatus and thermometer was uncorrected. ¹H NMR spectra was recorded in CDCl₃ with TMS as internal standard on Bruker NMR spectrophotometer operating at 200 MHz chemical shifts are expressed in δ-values (in ppm) relative to TMS as internal standard.

(Va). 3-Methyl-6(H)-6-phenyl-5-[N-2,3,4,6-tetra-o-acetyl-β-D-glucopyranosyl]-s-triazolo[3,4,6][1,3,4]-thiadiazole.

Colourless crystals, m.pt 178 °C. IR(KBr)_{ν_{max}} 3100, 1770, 1585, 1350, 1245, 690 cm⁻¹. ¹H NMR (CDCl₃): 1.66 – 1.80(m, 2H, COCH₃), 2.10(s, 3H), 3.85 – 4.25(m, 5H, -OCH₂, 3',4',5' - H), 4.5-4.65(m, 1', 2'-H), 5.70(s, 1H, 6-H), 7.70-7.80(m, 5H, Ar-H).

Anal. CHN(%): Found C, 52.05; H, 5.07; N, 10.18. C₂₄H₂₈N₄O₉S. Calcd. C, 52.55; H, 5.10; N, 10.21.

(Vb). 3-Ethyl-6(H)-6-[(4'-methoxy)phenyl]-5[N-2,3,4,6-tetra-o-acetyl-β-D-glucopyranosyl]-s-triazolo[3,4,6][1,3,4]-thiadiazole.

Light grey coloured crystals, m.pt 162 °C. IR(KBr)_{ν_{max}} 3150, 1790, 1590, 1360, 1235, 695. ¹H-NMR(CDCl₃): δ 1.17(t, 3H), 3.72(s, 3H), 4.15(q, 2H), 3.96-4.55(m, 5H), 4.65- 4.73(m, 2H), 7.54-8.10(m, 4H).

Anal. CHN(%) for C₂₆H₃₂N₄O₁₀S, Found: C, 52.60; H, 5.05; N, 9.38. Calcd. C, 52.72; H, 5.40; N, 9.45.

(Vc). 3-n-propyl-6(H)-6-[(4'-methoxy)phenyl]-5[N-2,3,4,6-tetra-o-acetyl-β-D-glucopyranosyl]-s-triazolo[3,4,6][1,3,4]-thiadiazole.

Brown coloured crystals m.pt = 151 °C. IR(KBr): _{ν_{max}} 3130, 1765, 1560, 1330, 1230, 670. ¹H-NMR(CDCl₃): δ 1.20(t, 3H), 1.90-2.00(m, 12H), 2.40-2.66(m, 4H), 3.7(s, 3H), 3.75-4.33(m, 5H), 4.55-4.67(m, 6H), 5.70(s, 1H), 7.65-8.05(m, 4H).

Anal. Calcd. For C₂₇H₃₄N₄O₁₀S. Found: C, 53.40; H, 5.25; N, 9.02. Calcd. C, 53.46; H, 5.61; N, 9.24.

(Vd). 3-Methyl-6(H)-6-[4'Chlorophenyl]-5-[N-2,3,4,6-tetra-o-acetyl-β-D-glucopyranosyl]-s-triazolo[3,4,6][1,3,4]-thiadiazole.

Colourless crystals m.pt 163 °C. IR(KBr): _{ν_{max}} 3243, 1760, 1550, 1320, 1210, 675. ¹H-NMR(CDCl₃): δ 1.16(s, 3H), 1.85-2.10(m, 12H), 2.30-2.50(m, 4H), 3.70-4.30(m, 5H), 5.60(s, 1H), 7.40-7.56(m, 4H).

Anal. Calcd. For C₂₄H₂₇O₉N₄SCl. Found: C, 49.60; H, 4.52; N, 9.54. Calcd. C, 49.52; H, 4.64; N, 9.62.

(Ve) 3-Methyl-6(H)-6-[4-Bromophenyl]-5[N-2,3,4,6-tetra-o-acetyl-β-D-glucopyranosyl]-s-triazolo[3,4,6][1,3,4]-thiadiazole.

Colourless crystals m.pt 161 °C. IR(KBr)_{ν_{max}} 3234, 2993, 1750, 1565, 1325, 1220, 680 cm⁻¹. ¹H-NMR(CDCl₃): δ 1.28(s, 3H), 1.80-2.00(m, 12H), 2.25-2.40(m, 4H), 3.70-4.20(m, 5H), 6.5-7.5(s, 1H), 7.20-7.36(m, 4H).

Anal. Calcd. For C₂₄H₂₇O₉N₄SBr. Found: C, 46.10; H, 4.18; N, 8.76. Calcd. C, 45.96; H, 4.30; N, 8.92.

(Vf). 3-Ethyl-6(H)-6-[4-Chlorophenyl]-5[N-2,3,4,6-tetra-o-acetyl-β-D-glucopyranosyl]-s-triazolo[3,4,6][1,3,4]-thiadiazole.

Colourless crystals m.pt 158 °C. IR(KBr)_{ν_{max}}: 3345, 3040, 1693, 1080, 670 cm⁻¹. ¹H NMR(CDCl₃): δ 1.16(t, 3H), 1.80-2.00(m, 12H), 3.98(q, 2H), 4.15-4.40(m, 5H), 4.60-4.75(m, 2H), 7.50-7.80(m, 4H).

Anal. Calcd. For C₂₅H₂₉N₄O₉SCl. Found: C, 50.38; H, 5.30; N, 9.26. Calcd. C, 50.32; H, 5.36; N, 0.38.

(Vg). 3-Methyl-6(H)-6-[2',4'-dichlorophenyl]-5-[N-2,3,4,6-tetra-o-acetyl-β-D-glucopyranosyl]-s-triazolo[3,4,6][1,3,4]-thiadiazole.

Colourless crystals m.pt 182 °C.

IR(KBr)_{ν_{max}}: 3291, 1754, 1595, 1346, 1050, 680 cm⁻¹. ¹H NMR(CDCl₃): δ 1.74 – 2.12(m, 12H), 2.30(s, 3H), 3.85 – 4.25(m, 5H), 4.54-4.71(m, 2H), 5.83(s, 1H), 7.35 – 7.93(m, 3H).

Anal. Calcd. For C₂₄H₂₆N₄O₉SCl₂. Found: C, 46.82; H, 4.28; N, 9.17. Calcd.: C 46.70; H, 4.21; N, 9.07.

(Vh). 3-Methyl-6(H)-6-[4'Methoxyphenyl]-5-[N-2,3,4,6-Tetra-o-acetyl-β-D-glucopyranosyl]-s-triazolo[3,4,6][1,3,4]-thiadiazole.

Colourless crystal m.pt 164 °C. IR(KBr)_{ν_{max}} 3291, 1758, 1575, 1360, 1220, 685 cm⁻¹. ¹H NMR(CDCl₃): δ 1.70-1.98(m, 12), 2.15(s, 3H), 2.35(s, 3H), 3.72 – 3.98(m, 5H), 4.6 – 4.7(m, 2H), 5.88(s, 1H), 7.80 - 7.95(m, 4H).

Anal. Calcd. For C₂₅H₃₀N₄O₁₀S. Found: C, 51.18; H, 5.22; N, 9.62. Calcd.: C, 51.92; H, 5.18; N, 9.68.

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