Research Article

Synthesis of Novel S-Glucosides Containing 5-Methylisoxazole Substituted 1,2,4-Triazole

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Nine new S-β-D-glucosides containing 4-aryl-5-(5-methylisoxazol-3-yl)-1,2,4-triazol-3-thiols have been synthesized by the direct glycosylation of 4-aryl-5-(5-methylisoxazol-3-yl)-1,2,4-triazol-3-thiols with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide in ethanol in the presence of potassium hydroxide followed by deacetylation using dry ammonia in dry methanol. All the compounds synthesized have been characterized by their elemental analyses and spectral data.

1. Introduction

Much attention has been focused on 1,2,4-triazole derivatives for their broad-spectrum activities, such as antitumor [1], anticonvulsant [2], antifungal [3], herbicidal, and plant growth regulatory activities [4]. Up till now, many 1,2,4-triazole derivatives have been synthesized, and some of them have been patented for commercial uses. Similarly, 5-methylisoxazole derivatives have also shown biological effects such as antibacterial [5] and phytohormone effects [6].

Recently thioglycosides have received considerable attention, because they are widely employed as biological inhibitors, inducers, and ligands for affinity chromatography for carbohydrate processing-enzymes and proteins [7, 8]. In 1972, Witkoski et al. synthesized Ribavirin [9] and proved that it not only possesses inhibitory activity against a range of DNA and RNA viruses [10,11] but also displays antitumor activity [12] in mice. After the recognized biological properties of Ribavirin, the synthesis and biological evaluation of N-glucosides [13] and C-glucosides [14] containing 1,2,4-triazole have been greatly emphasized, but only a few S-glucosides [15] containing 1,2,4-triazole have been reported. To the best of our knowledge, S-glucosides containing 5-methylisoxazole substituted 1,2,4-triazole have not been reported to date. In view of these observations and our interests in the synthesis of biologically active heterocyclic compounds, herein we describe the synthesis of novel S-glucosides containing 5-methylisoxazole substituted 1,2,4-triazole from 4-aryl-5-(5-methylisoxazol-3-yl)-1,2,4-triazol-3-thiols and 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (Scheme 1).

2. Experimental

Melting points were determined on an X-4 microscopic melting point apparatus and were uncorrected. 1H NMR spectra were determined on a Varian Mercury-300 MHz spectrometer at room temperature using TMS as internal standard, coupling constants (J) were measured in Hz. Elemental analysis were performed by Elementar Vario EL apparatus. Commercially available reagents were used throughout without further purification unless otherwise stated.

General procedure for Preparation of 3-S-((2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)-4-aryl-5-(5-methylisoxazol-3-yl))1,2,4-triazoles (2a–2i).

To a solution of KOH (2 mmol) in ethanol (25 mL) was added 1a-1i (2 mmol). After the mixture was stirred for 30 min at room temperature, 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (2 mmol) was added to the solution. The reaction was stirred for an appropriate time and monitored by TLC until the final conversion. The mixture was filtered and washed with water. The crude product was purified by silica gel column chromatography using
petroleum ether/ethyl acetate as eluent to afford the pure product.

(2a) Yield 74%. Mp 172–173°C. [α]D 4° (c 1, CH2Cl2). 1H
NMR (300 MHz, CDCl3): δ 1.96 (s, 3H, CH3-C(O)),
1.97 (s, 3H, CH(C(O)), 1.98 (s, 3H, CH3-C(O)), 1.99
(s, 3H, CH3-C(O)), 2.42 (s, 3H, Het-CH3)), 3.82 (m,
1H), 4.07 (dd, J = 12.6, 2.1 Hz, 1H), 4.21 (dd, J =
12.6, 4.2 Hz, 1H), 5.04–5.11 (m, 2H), 5.25 (t, J =
9.3 Hz, 1H), 5.54 (d, J = 10.5 Hz, 1H), 6.55 (s, 1H,
C29H38N6O10S: C, 53.06; H, 4.79; N, 9.52. Found: C,
52.89; H, 4.67; N, 9.25.

(2b) Yield 72%. Mp 152–154°C. [α]D 5° (c 1, CH2Cl2). 1H
NMR (300 MHz, CDCl3): δ 1.94 (s, 3H, CH3-C(O)),
1.96 (s, 3H, CH3-C(O)), 1.97 (s, 3H, CH3-C(O)), 2.00
(s, 3H, CH3-C(O)), 2.02 (s, 3H, CH3)), 2.41 (s, 3H,
Het-CH3)), 3.80–3.85 (m, 1H), 4.03–4.04 (m, 1H),
4.20–4.29 (m, 1H), 5.05–5.14 (m, 2H), 5.25–5.32 (m,
1H), 5.64–5.76 (m, 1H), 5.65 (s, 1H, HetH), 6.87 (d,
J = 7.5 Hz, 1H, ArH), 6.99–7.46 (m, 3H, ArH). Anal.
Calcd. for C27H39N6O10S: C, 53.81; H, 5.02; N, 9.30.
Found: C, 53.45; H, 4.95; N, 8.92.

(2c) Yield 66%. Mp 146–147°C. [α]D 3° (c 1, CH2Cl2). 1H
NMR (300 MHz, CDCl3): δ 1.94 (s, 3H, CH3-C(O)),
1.95 (s, 3H, CH3-C(O)), 1.96 (s, 3H, CH3-C(O)), 1.97
(s, 3H, CH3-C(O)), 2.31 (s, 3H, CH3)), 2.42 (s, 3H,
Het-CH3)), 3.75–3.80 (m, 1H), 4.02–4.06 (m, 1H),
4.21 (dd, J = 12.9, 4.5 Hz, 1H), 5.02–5.10 (m, 2H), 5.23 (t,
J = 9.3 Hz, 1H), 5.54 (d, J = 10.8 Hz, 1H), 6.54 (s, 1H,
HetH), 6.86 (d, J = 7.8 Hz, 1H, ArH), 6.94–7.47 (m,

(2d) Yield 78%. Mp 88–90°C. [α]D 9° (c 1, CH2Cl2). 1H
NMR (300 MHz, CDCl3): δ 1.99 (s, 3H, CH3-C(O)),
2.00 (s, 3H, CH3-C(O)), 2.01 (s, 3H, CH3-C(O)),
2.03 (s, 3H, CH3-C(O)), 2.41 (s, 3H, Het-CH3)), 3.65
(s, 3H, CH3-O), 3.75–3.82 (m, 1H), 4.02–4.10 (m, 1H),
4.20–4.30 (m, 1H), 5.03–5.14 (m, 2H), 5.22–5.30 (m,
1H), 5.53–5.58 (m, 1H), 5.65 (s, 1H, HetH), 6.87 (d,
J = 6.9 Hz, 1H, ArH), 6.96–7.49 (m, 3H, ArH). Anal.
Calcd. for C29H38N6O10S: C, 52.42; H, 4.89; N, 9.06.
Found: C, 52.60; H, 4.93; N, 9.31.

(2e) Yield 64%. Mp 86–88°C. [α]D 5° (c 1, CH2Cl2). 1H
NMR (300 MHz, CDCl3): δ 1.99 (s, 3H, CH3-C(O)),
2.00 (s, 3H, CH3-C(O)), 2.02 (s, 3H, CH3-C(O)), 2.04 (s,
3H, CH3-C(O)), 2.41 (s, 3H, Het-CH3)), 3.78–3.82 (m,
1H), 4.03–4.13 (m, 1H), 4.22–4.27 (m, 1H), 5.03–5.17
(d, J = 9.9 Hz, 1H), 5.27 (t, J = 9.3 Hz, 1H), 5.58 (d, J =
9.9 Hz, 1H), 6.63 (s, 1H, HetH), 6.87–7.47 (m, 4H, ArH).
Anal. Calcd. for C29H37BrN6O10S: C, 46.78; H, 4.08;
N, 8.39. Found: C, 46.48; H, 3.97; N, 8.51.

(2f) Yield 55%. Mp 98–100°C. [α]D 3° (c 1, CH2Cl2). 1H
NMR (300 MHz, CDCl3): δ 2.00 (s, 3H, CH3-C(O)),
2.02 (s, 3H, CH3-C(O)), 2.04 (s, 3H, CH3-C(O)), 2.05
(s, 3H, CH3-C(O)), 2.44 (s, 3H, Het-CH3)), 3.77–3.82
(1H), 4.08–4.13 (m, 1H), 4.24 (dd, J = 12.9, 4.8 Hz,
1H), 5.07–5.16 (m, 2H), 5.28 (t, J = 9.3 Hz, 1H), 5.54
(d, J = 10.5 Hz, 1H), 6.60 (s, 1H, HetH), 6.84–7.51
(m, 4H, ArH). Anal. Calcd. for C28H37BrN6O10S: C,
46.78; H, 4.08; N, 8.39. Found: C, 46.45; H, 3.83; N,
8.20.

(2g) Yield 62%. Mp 90–92°C. [α]D 6° (c 1, CH2Cl2). 1H
NMR (300 MHz, CDCl3): δ 1.95 (s, 3H, CH3-C(O)),
1.97 (s, 3H, CH3-C(O)), 1.98 (s, 3H, CH3-C(O)), 2.00
(s, 3H, CH3-C(O)), 2.42 (s, 3H, Het-CH3)), 3.75–3.80 (m,
1H), 3.99–4.09 (m, 1H), 4.17–4.22 (m, 1H), 4.99–5.12
(2H), 5.24 (t, J = 9.0 Hz, 1H), 5.49–5.55 (m, 1H),
6.64 (s, 1H, HetH), 6.86–7.54 (m, 4H, ArH). Anal.
Calcd. for C28H37ClN6O10S: C, 50.12; H, 4.37; N,
8.99. Found: C, 49.75; H, 4.10; N, 8.65.

(2h) Yield 59%. Mp 157–158°C. [α]D 1° (c 1, CH2Cl2). 1H
NMR (300 MHz, CDCl3): δ 1.98 (s, 3H, CH3-C(O)),
2.00 (s, 3H, CH3-C(O)), 2.01 (s, 3H, CH3-C(O)), 2.03
(s, 3H, CH3-C(O)), 2.43 (s, 3H, Het-CH3)), 3.75–3.80

Scheme 1: 4-Aryl-5-(5-methylisoxazol-3-yl)-1,2,4-triazol-3-thiols (1a–11) were synthesized according to the literature [16, 17].
(m, 1H), 4.09 (dd, J = 12.3, 1.8 Hz, 1H), 4.22 (dd, J = 12.3, 4.5 Hz, 1H), 5.04–5.14 (m, 2H), 5.26 (t, J = 9.0 Hz, 1H), 5.52 (d, J = 9.9 Hz, 1H), 6.61 (s, 1H, HetH), 6.86 (d, J = 8.1 Hz, 1H, ArH). Anal. Calcd. for C_{18}H_{19}BrN_{2}O_{5}: C, 43.30; H, 3.84; N, 11.22. Found: C, 43.48; H, 4.15; N, 11.03.

(3f) Yield 91%. Mp 140–142 °C. [α]_{D}^{29} − 29° (c 1, CH_{3}OH).

1H NMR (300 MHz, D_{2}O): δ 2.35 (s, 3H, Het-CH_{3}), 3.29–3.39 (m, 3H), 3.41–3.47 (m, 1H), 3.57–3.63 (m, 1H), 3.76 (d, J = 12.3 Hz, 1H), 4.83–4.86 (m, 1H), 6.42 (s, 1H, HetH), 7.03–7.38 (m, 4H, ArH). Anal. Calcd. for C_{18}H_{19}BrN_{2}O_{5}: C, 43.30; H, 3.84; N, 11.22. Found: C, 43.48; H, 4.08; N, 3.52.

(3g) Yields 83%. Mp 144–146 °C. [α]_{D}^{29} − 73° (c 1, CH_{3}OH).

1H NMR (300 MHz, D_{2}O): δ 2.33 (s, 3H, Het-CH_{3}), 3.21–3.37 (m, 3H), 3.39–3.48 (m, 1H), 3.52–3.61 (m, 1H), 3.67–3.75 (m, 1H), 6.63 (s, 1H, HetH), 6.95–7.63 (m, 4H, ArH). Anal. Calcd. for C_{18}H_{19}ClN_{2}O_{5}: C, 47.53; H, 4.21; N, 12.32. Found: C, 47.81; H, 4.36; N, 12.08.

(3h) Yields 90%. Mp 130–132 °C. [α]_{D}^{29} − 44° (c 1, CH_{3}OH).

1H NMR (300 MHz, D_{2}O): δ 2.35 (s, 3H, Het-CH_{3}), 3.30–3.34 (m, 3H), 3.41–3.47 (m, 1H), 3.55–3.61 (m, 1H), 3.74 (d, J = 11.1 Hz, 1H), 4.83 (d, J = 10.2 Hz, 1H), 6.42 (s, 1H, HetH), 7.02–7.44 (m, 4H, ArH). Anal. Calcd. for C_{18}H_{19}ClN_{2}O_{5}: C, 47.53; H, 4.21; N, 12.32. Found: C, 47.65; H, 4.34; N, 12.10.

(3i) Yields 92%. Mp 138–140 °C. [α]_{D}^{29} − 40° (c 1, CH_{3}OH).

1H NMR (300 MHz, D_{2}O): δ 2.35 (s, 3H, Het-CH_{3}), 3.28–3.36 (m, 3H), 3.41–3.43 (m, 1H), 3.56–3.62 (m, 1H), 3.75 (d, J = 12.3 Hz, 1H), 6.42 (s, 1H, HetH), 7.02–7.44 (m, 4H, ArH). Anal. Calcd. for C_{18}H_{19}N_{2}O_{5}: C, 47.53; H, 4.21; N, 12.32. Found: C, 47.73; H, 4.29; N, 12.02.

3. Results and Discussion

5-Methylisoxazole-3-carboxylic acid, which is required as a starting material, was prepared according to the literature [16]. As shown in Scheme 1, 4-aryl-5-(5-methylisoxazol-3-yl)-1,2,4-triazoles (3a–3i) were prepared via the reaction of 5-methylisoxazole-3-carboxylic acid with arylisothiocyanates and then cyclization in the presence of 2 mol/L aqueous potassium carbonate solution.

S-β-D-acyetylglucosides (2a–2i) were obtained with the improved Koenigs-Knorr method. We use potassium hydroxide as the base to avoid the use of more expensive or toxic reagents as promoters, such as phase transfer catalyst (BuNBr) [18] or heavy metal salts (Hg[CN]_{2}) [13]. The coupling reaction of 4-aryl-5-(5-methylisoxazol-3-yl)-1,2,4-triazol-3-thiols with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide was conducted in ethanol in the presence of potassium hydroxide, and nine new S-β-D-acyetylglucosides were afforded. The results showed that the reaction is a typical SN_{2} reaction and a convenient method to stereoselectively synthesis of only the single β-anomer.

The classical method of deacetylation of the sugar moiety employing a catalytic amount of sodium methoxide in methanol is described by Zemplén and Kuntz [19]. However,
the Zemplén deacetylation is not suitable for the deprotection of carbohydrates containing 5-methylisoxazole-substituted 1,2,4-triazole due to the instability of the isoxazole ring under strong basic condition. Finally, the removal of the protecting groups was easily achieved by treatment with dry ammonia gas in dry methanol. The final desired S-glucosides containing 5-methylisoxazole-substituted 1,2,4-triazole (3a-3i) were successfully obtained in good yields.

The structures of 2a-2i and 3a-3i were confirmed by elemental analyses and spectral data. The $^1$H NMR spectral data of compounds 2a-2i showed the presence of four acetyl groups through the four singlets in the region of 1.94–2.05 ppm. In addition, seven hydrogen atoms of the sugar moiety were also observed in these spectra. They exhibited multiplets at 3.75–5.58 ppm. Only $\beta$-anomer was obtained as judged by a doublet at $\delta$ 5.52–5.58 ($J_{H1,H2} = 9.9–10.8$ Hz) of the anomeric proton (H-1) in the sugar moiety. Compounds 2a-2i showed two singlets at $\delta$ 2.41–2.44 and 6.54–6.64, which were assigned to the protons of methyl and isoxazole ring, respectively.

The $^1$H NMR spectra of 3a-3i provided support to successful deacetylation reaction by the disappearance of the four sharp singlets in the region of 1.94–2.05 ppm as observed in the spectra of 2a-2i. The aryl groups of compounds 2a-2i and 3a-3i were found in the region of 6.84–7.71 ppm. The other $^1$H NMR spectral data was found approximately the same as observed in the case of the corresponding acetylated glucosides. The elemental analysis of these compounds was good agreement with calculated values.

Compounds 3a-3i were screened for their antibacterial activity against Escherichia coli and Staphylococcus aureus. The results showed that most of the compounds were inactive against these microorganisms. Further investigation on biological activities is in progress.

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References


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