A Novel and Convenient Synthesis of Thiazol-2(3*H*)-imine-Linked Glycoconjugates

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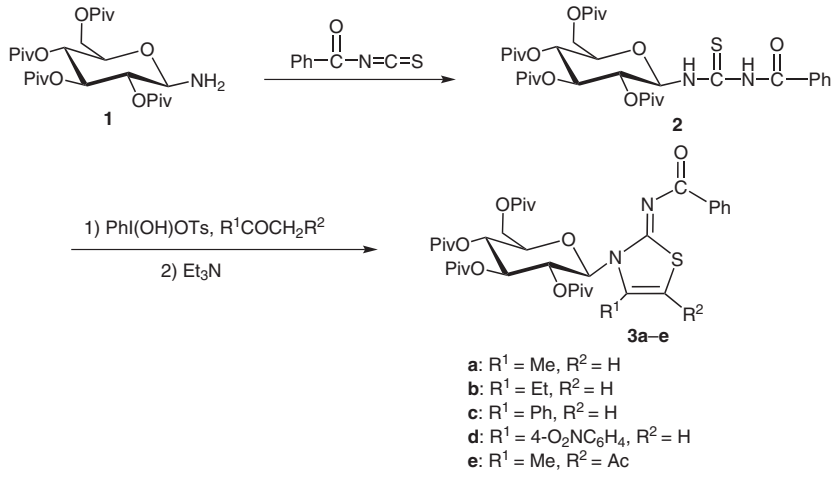
Abstract: A novel and convenient synthetic approach for the preparation of thiazol-2(3*H*)-imine-linked glycoconjugates, which involves the cyclization of 1-benzoyl-3-(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl)thiourea with a variety of carbonyl compounds bearing an α-H in the presence of [hydroxy(tosyloxy)iodo]benzene (HTIB) and triethylamine, has been developed. The methodology has advantages such as avoiding the use of lachrymatory and toxic bromine, simplicity of procedure, mild reaction conditions, and high yields.

Key words: thiazol-2(3*H*)-imine, glycoconjugate, [hydroxy(tosyloxy)iodo]benzene, synthesis

In recent years, thiazolidene and its derivatives have received considerable attention because of their bioactivity and many applications in organic and medicinal chemistry.[1–6] For example, Masuda's group has reported that a series of thiazolidenebenzenesulfonamide derivatives are a novel class of non-nucleoside HIV-1RT inhibitors.[2,3] Therefore, the preparation of these compounds has become increasingly important. Our considerable current research interests focus on the synthesis of glycoconjugates, which exert important effects on many complex biological events,[7–9] including cellular recognition in the processes of inflammation, immune response, tumor metastasis, and bacterial and viral infections. During our research, we developed a novel route, which utilizes the work of Singh et al.,[10] for the synthesis of thiazol-2(3*H*)-imine-linked glycoconjugates from the cyclization of 1-aroyl-3-glycosylthiourea with carbonyl compounds in the presence of [hydroxy(tosyloxy)iodo]benzene (HTIB)[11] and triethylamine. To the best of our knowledge, it is the first example of the preparation of thiazol-2(3*H*)-imine-linked glycoconjugates.

In this paper, we would like to report a novel and convenient procedure for the synthesis of thiazol-2(3*H*)-imine-linked glycoconjugates, which includes α-tosyloxylation of carbonyl compounds with [hydroxy(tosyloxy)iodo]benzene, followed by treatment with 1-benzoyl-3-glycosylthiourea at ambient temperature (Scheme 1).

As shown in Scheme 1, the reaction of 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosylamine (**1**)[12] with benzoyl isothiocyanate proceeded smoothly in acetone at room temperature to afford the desired product, 1-benzoyl-3-(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl)thiourea (**2**), in 92% yield.[13]



Scheme 1 Synthesis of thiazol-2(3*H*)-imine-linked glycoconjugates

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Hypervalent iodine reagents have received much attention due to their low toxicity, ready availability, easy handling, and reactivities similar to those of heavy metal reagents[14–17] and they have been found to be an effective reagent for the one-step conversion of enolizable ketones into the corresponding α-tosyloxy ketones.[18] As part of our programme directed towards the use of hypervalent iodine reagents in organic synthesis, we have reported a one-pot procedure for the synthesis of imidazoles.[11] Hence, we utilized [hydroxy(tosyloxy)iodo]benzene instead of bromine for the synthesis of thiazol-2(3*H*)-imine derivatives following the reported procedure of Singh et al.[10] When 1-benzoyl-3-(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl)thiourea (**2**) was reacted with acetone in the presence of [hydroxy(tosyloxy)iodo]benzene and triethylamine, the reaction was found to be complete within a short period of time under extremely mild conditions to obtain the expected product, 1-benzoyl-4-methyl-3-(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl)thiazol-2(3*H*)-imine (**3a**); its structure was confirmed by ^{1}H and ^{13}C NMR, IR, MS, and elemental analysis.

To further demonstrate the scope of the reaction, the cyclizations of 1-benzoyl-3-(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl)thiourea (**2**) and a variety of carbonyl compounds bearing α-H in the presence of [hydroxy(tosyloxy)iodo]benzene and triethylamine were carried out at room temperature and the corresponding thiazol-2(3*H*)-imine-linked glycoconjugates **3b–e** were obtained in yields of 80% or higher. The results are listed in Table 1.

Table 1 Results of Cyclizations of 1-Benzoyl-3-(2,3,4,6-tetra-*O*-pivaloyl-D-glucopyranosyl)thiourea with HTIB/Carbonyl Compounds

Entry	R^1	R^2	Product	Time (h)	Yield (%)	Mp (°C)
1	Me	H	**3a**	1.0	90	181–183
2	Et	H	**3b**	1.5	87	162–163
3	Ph	H	**3c**	3.5	82	155–158
4	4-$O_2NC_6H_4$	H	**3d**	2.5	86	96–98
5	Me	Ac	**3e**	3.0	85	174–177

In conclusion, we have developed a novel and convenient method for the synthesis of thiazol-2(3*H*)-imine-linked glycoconjugates, which has advantages such as avoiding the use of lachrymatory and toxic bromine reagent, simplicity of procedure, and higher yields. Further work is currently on-going to extend our synthetic protocol and study the biological activity and applications of deprotected thiazol-2(3*H*)-imine-linked glycoconjugates.

Chemicals and solvents were either purchased or purified by standard techniques. Analytical TLC was performed on a Merck precoated TLC (silica gel 60 F254) plate. Melting points were recorded on an X4-Data microscopic melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet 380 FT-IR spectrophotometer using KBr discs. ESI-MS were acquired on a Bruker Esquire 3000 plus spectrometer. ^{1}H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on a Bruker Avance 400 spectrometer using TMS as internal standard. Elemental analyses were performed on Carlo-Erba 1106.

1-Benzoyl-3-(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl)thiourea (2)

A soln of benzoyl isothiocyanate (2 mmol) in acetone (10 mL) was added to 2,3,4,6-tetra-*O*-pivaloyl-D-glucopyranosylamine (**1**; 1.03 g, 2 mmol) and the mixture was refluxed; the reaction was monitored by TLC. After 1.5 h, the reaction was complete and the solvent was removed under reduced pressure and the residue was recrystallized (95% EtOH) to give **2** as a solid; yield: 92%; mp 209–211 °C.

IR (KBr): 3416, 3238, 2971, 2874, 1737, 1681, 1525, 1482, 1396, 1369, 1321, 1281, 1143, 1093, 985, 919, 798, 718, 614 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 11.09 (d, *J* = 4.4 Hz, 1 H), 9.03 (s, 1 H), 7.83 (t, *J* = 3.6 Hz, 2 H), 7.63 (t, *J* = 3.8 Hz, 1 H), 7.51 (t, *J* = 4.2 Hz, 2 H), 5.87 (t, *J* = 4.6 Hz, 1 H), 5.47 (t, *J* = 4.6 Hz, 1 H), 5.17–5.29 (m, 2 H), 4.22 (q, *J* = 0.8 Hz, 1 H), 4.13 (q, *J* = 2.6 Hz, 1 H), 3.90–3.94 (m, 1 H), 1.11–1.27 (m, 36 H).

^{13}C NMR ($CDCl_3$): δ = 182.73, 178.08, 177.19, 176.95, 176.40, 166.04, 133.77, 131.28, 129.14, 127.53, 82.91, 74.50, 72.29, 70.15, 67.61, 61.67, 38.70–38.86, 26.92–27.13.

MS (ESI): *m*/*z* = 679.1 $[M + H]^+$.

Anal. Calcd for $C_{34}H_{50}N_2O_{10}S$: C, 60.16; H, 7.42; N, 4.13. Found: C, 60.57; H, 7.48; N, 4.05.

1-Benzoyl-4-methyl-3-(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl)thiazol-2(3*H*)-imine (3a); Typical Procedure

Into a 50-mL 3-neck flask, thiourea **2** (0.678 g, 1 mmol), Et_3N (1 mmol), and acetone (5 mL) were added, then a soln of HTIB (1 mmol) in acetone (5 mL) was added dropwise. When the reaction was complete, the mixture was filtered and concentrated in vacuo to give the crude product, which was recrystallized (EtOH) to give pure **3a** as a solid. yield: 90%; mp 181–183 °C.

In the synthesis of **3b–e**, $CHCl_3$ was used instead of acetone as the solvent and the molar ratio of **2**–HTIB–Et_3N was 1:1:1.

IR (KBr): 3459, 2974, 2874, 2361, 1743, 1605, 1571, 1474, 1397, 1339, 1279, 1242, 1135, 1039, 918, 759, 716 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.29 (d, *J* = 3.4 Hz, 2 H), 7.50 (q, *J* = 4.4 Hz, 3 H), 6.97 (d, *J* = 4.8 Hz, 1 H), 6.26 (s, 1 H), 5.57–5.66 (m, 2 H), 5.36 (t, *J* = 4.8 Hz, 1 H), 4.29 (q, *J* = 7.6 Hz, 1 H), 4.17 (d, *J* = 6.4 Hz, 1 H), 4.07 (d, *J* = 5.0 Hz 1 H), 2.65 (s, 3 H), 0.88–1.23 (m, 36 H).

^{13}C NMR ($CDCl_3$): δ = 177.68, 177.18, 177.00, 176.15, 173.86, 170.93, 136.34, 134.35, 131.71, 129.20, 128.12, 106.07, 83.20, 75.44, 72.39, 69.42, 66.76, 60.87, 38.67–38.81, 26.68–27.09, 15.31.

Anal. Calcd for $C_{37}H_{52}N_2O_{10}S$: C, 61.99; H, 7.31; N, 3.91. Found: C, 62.03; H, 7.27; N, 4.04.

1-Benzoyl-4-ethyl-3-(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl)thiazol-2(3*H*)-imine (3b)

Solid; yield: 87%; mp 162–163 °C.

IR (KBr): 2975, 2937, 2874, 1744, 1603, 1571, 1472, 1398, 1367, 1343, 1315, 1275, 1230, 1135, 1036, 905, 760, 722 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.29 (q, *J* = 4.8 Hz, 2 H), 7.47–7.52 (m, 3 H), 7.00 (d, *J* = 4.6 Hz, 1 H), 5.59–5.62 (m, 2 H), 5.36 (s, 1 H), 4.06–4.28 (m, 3 H), 2.53 (s, 2 H), 2.19 (s, 2 H), 2.04 (s, 1 H), 1.36 (t, *J* = 7.2 Hz, 1 H), 0.85–1.27 (m, 36 H).

^{13}C NMR ($CDCl_3$): δ = 177.62, 177.07, 176.96, 176.13, 173.59, 168.85, 140.62, 136.45, 131.55, 129.15, 128.03, 103.96, 82.86,

75.31, 72.43, 69.34, 66.69, 60.87, 38.62–38.78, 26.58–27.05, 21.35, 11.58.

Anal. Calcd for $C_{38}H_{54}N_2O_{10}S$: C, 62.44; H, 7.45; N, 3.83. Found: C, 62.48; H, 7.41; N, 3.81.

1-Benzoyl-4-phenyl-3-(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl)thiazol-2(3*H*)-imine (3c)
Solid; yield: 82%; mp 155–158 °C.

IR (KBr): 2985, 2909, 1694, 1636, 1596, 1577, 1512, 1485, 1471, 1449, 1393, 1358, 1321, 1293, 1225, 1161, 1127, 1095, 1070, 1009, 988, 905, 878, 719, 688 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 9.99 (d, *J* = 4.0 Hz, 1 H), 8.13 (t, *J* = 4.4 Hz, 2 H), 7.85 (t, *J* = 4.2 Hz, 2 H), 7.43–7.60 (m, 6 H), 5.50 (t, *J* = 9.6 Hz, 1 H), 5.29 (d, *J* = 4.4 Hz, 1 H), 5.19 (t, *J* = 9.6 Hz, 1 H), 4.96 (s, 1 H), 4.17 (d, *J* = 0.8 Hz, 2 H), 4.13 (d, *J* = 2.6 Hz, 1 H), 1.08–1.17 (m, 36 H).

^{13}C NMR ($CDCl_3$): δ = 189.84, 178.03, 177.03, 176.86, 176.29, 168.78, 158.54, 140.14, 133.15, 132.29, 131.30, 128.89, 128.35, 128.05, 126.96, 81.00, 79.08, 73.95, 72.06, 69.98, 67.75, 62.03, 38.63–38.74, 26.85–27.05.

Anal. Calcd for $C_{42}H_{54}N_2O_{10}S$: C, 64.76; H, 6.99; N, 3.60. Found: C, 64.71; H, 7.05; N, 3.67.

1-Benzoyl-4-(4-nitrophenyl)-3-(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl)thiazol-2(3*H*)-imine (3d)
Solid; yield: 86%; mp 96–98 °C.

IR (KBr): 3323, 2973, 2874, 1744, 1625, 1601, 1525, 1477, 1398, 1343, 1283, 1228, 1145, 1036, 986, 868, 721 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.93 (q, *J* = 17.0 Hz, 2 H), 7.51 (t, *J* = 7.2 Hz, 4 H), 7.34 (d, *J* = 3.8 Hz, 1 H), 7.19 (q, *J* = 10.6 Hz, 2 H), 6.51 (d, *J* = 4.4 Hz, 1 H), 5.52 (t, *J* = 9.4 Hz, 1 H), 5.10–5.20 (m, 3 H), 4.21 (d, *J* = 5.6 Hz, 1 H), 4.13 (q, *J* = 9.0 Hz, 1 H), 3.94 (t, *J* = 5.0 Hz, 1 H), 0.78–1.36 (m, 36 H).

^{13}C NMR ($CDCl_3$): δ = 188.01, 178.39, 177.93, 176.85, 176.39, 168.68, 154.38, 140.41, 137.47, 132.56, 130.57, 129.81, 129.13, 128.09, 125.35, 122.76, 83.92, 74.10, 71.80, 70.51, 67.61, 61.72, 38.67–38.91, 26.89–27.06.

Anal. Calcd for $C_{42}H_{53}N_3O_{12}S$: C, 61.22; H, 6.48; N, 5.10. Found: C, 61.16; H, 6.53; N, 5.12.

4-Acetyl-1-benzoyl-5-methyl-3-(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl)thiazol-2(3*H*)-imine (3e)
Solid; yield: 85%; mp 174–177 °C.

IR (KBr): 3466, 2975, 2937, 2875, 1745, 1680, 1652, 1608, 1571, 1472, 1395, 1366, 1334, 1282, 1228, 1169, 1128, 1074, 923, 892, 719, 666, 584 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.28 (d, *J* = 3.6 Hz, 2 H), 7.50–7.58 (m, 3 H), 7.07 (t, *J* = 4.6 Hz, 1 H), 5.64 (t, *J* = 4.4 Hz, 2 H), 5.38 (d, *J* = 4.8 Hz, 1 H), 4.18–4.28 (m, 2 H), 4.06 (d, *J* = 5.2 Hz, 1 H), 3.02 (s, 3 H), 2.49 (s, 3 H), 0.87–1.23 (m, 36 H).

^{13}C NMR ($CDCl_3$): δ = 190.41, 177.67, 177.03, 176.98, 176.03, 174.51, 167.82, 143.38, 135.57, 132.30, 129.34, 128.27, 118.38, 83.29, 75.61, 72.26, 69.22, 66.46, 60.64, 38.63–38.82, 30.51, 26.65–27.05, 14.10.

Anal. Calcd for $C_{39}H_{54}N_2O_{11}S$: C, 61.72; H, 7.17; N, 3.69. Found: C, 61.76; H, 7.10; N, 3.77.

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