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Rearrangement of 1-*O*-(thio-*p*-nitrobenzoyl)thiocarbonyl galactoside: a novel access to α-thioglycoside derivatives

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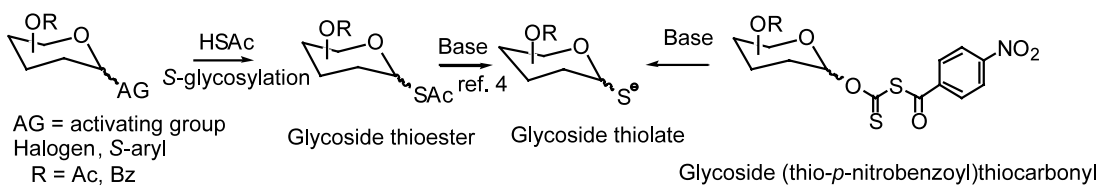
Abstract—The synthesis of galactosides thiolate and thioester is described by direct *S*-glycosylation process from 1-*O*-(thio-*p*-nitrobenzoyl)thiocarbonyl galactoside. Three novel anomeric groups are presented as potent glycoside activators: *O*-(thio-*p*-nitrobenzoyl)thiocarbonyl, *O*-(imidazolyl)thiocarbonyl and *S*-thio-*p*-nitrobenzoyl.

The diastereoselective synthesis of thioglycosides is an important goal not only because they are the most commonly used shelf-stable glycoside donors[1] but also they have shown significant potential as competitive inhibitors of oligosaccharide processing enzymes.[2] Thus, several reports have highlighted a renewed interest in the synthesis of 1-thioglycosides.[2,3] The straightforward stereospecific construction of 1-thioglycosides from configurationally pure glycosyl thiolates, which is essentially independent of neighbouring group effects, makes their access more attractive.[2–4] Glycosyl thiolates mostly result in basic *S*-deacetylation of thioacetate glycosyl donors obtained by usual *S*-glycosylation from activate glycosides (Scheme 1).[4]

This work reports the stereospecific original access to α-thiogalactoside derivatives by the rearrangement of the hitherto unknown 1-*O*-(thio-*p*-nitrobenzoyl)thiocarbonyl galactoside as an alternative avoiding the use of osidic activators generally required for the preparation of 1-thioglycoside donors (Scheme 1).

The synthesis of the 2,3,4,6-tetra-*O*-benzyl-1-*O*-(thio-*p*-nitrobenzoyl)thiocarbonyl α- and β-D-galactopyranosides **3** was achieved, in 80% overall yield, following two efficient steps from the galactopyranose tetrabenzyl **1**[5] (Scheme 2). Thus, carbon disulfide reacted with the galactopyranose **1** in the presence of sodium hydride to give the xanthate salt intermediate **2** which was quenched in situ by *p*-nitrobenzoyl chloride (1.1 equiv.) yielded the xanthate **3**. The stable anomers **3α** and **3β** were isolated by flash chromatography on silica gel in 7/3 ratio.[6]

The treatment of the (thio-*p*-nitrobenzoyl)thiocarbonyl galactopyranoside **3α** by 1 equiv. of imidazole in dry 1,2-dichloroethane solution, in the presence of DBU (1 equiv.), afforded, as single product of the reaction, the 1-*S*-(2′-chloro)ethyl α-D-thioglycoside **4α**[7] in 30% yield (Scheme 3). The reaction yield was significantly increased to 50% when supplementary amount of DBU (1 equiv.) and imidazole (1 equiv.) were added. The presence of DBU seems to be essential for the reaction



Scheme 1.

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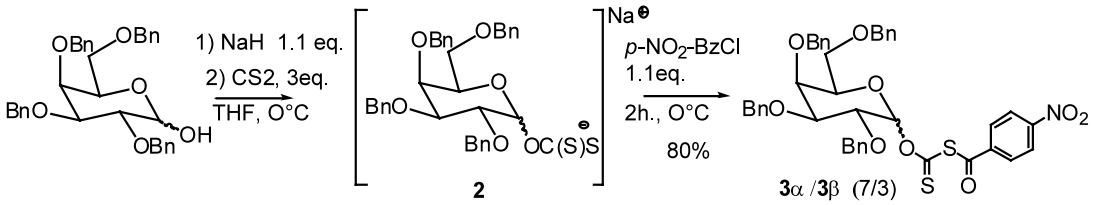
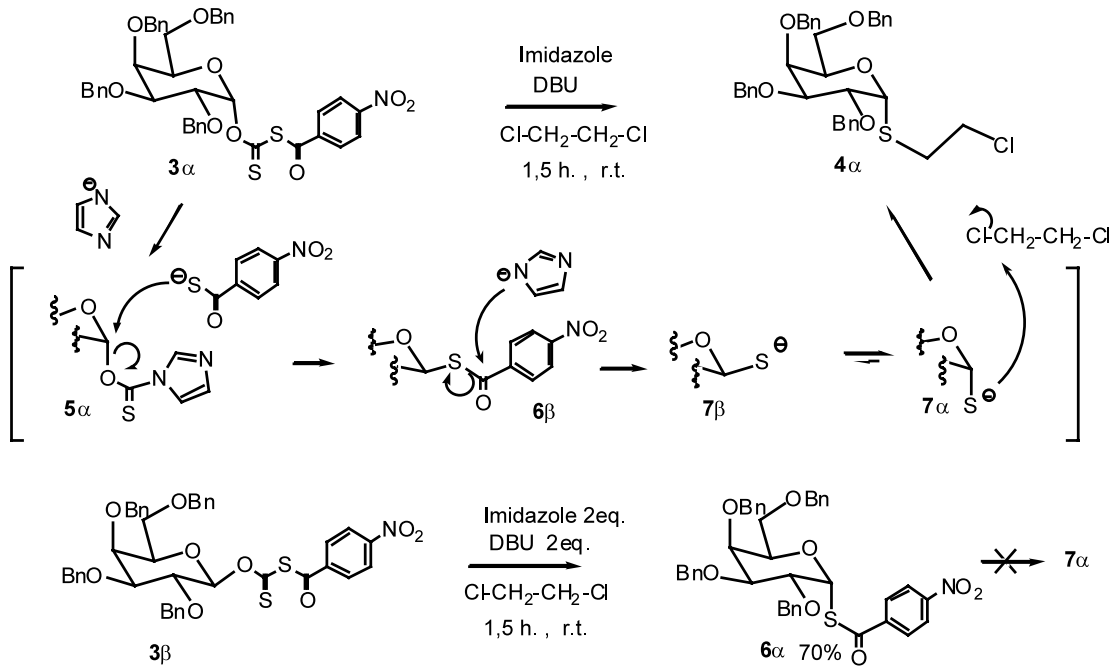


Scheme 2.

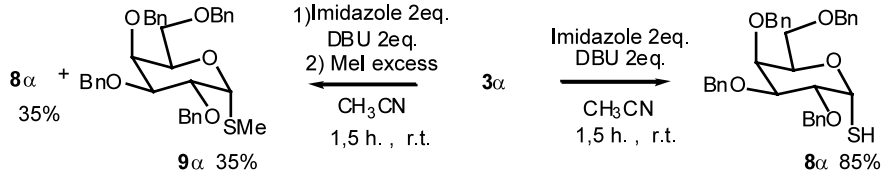


Scheme 3.

as the glycoside **3α** was recovered quantitatively on treating with just an excess of imidazole in 1,2-dichloroethane. It is interesting to note that compound **4α** can be regarded as a protected α-thiogalactoside tethered to a reactive spacer arm.[8]

Based on the literature data[4] the stereospecific formation of the thioglycoside **4α** from the glycoside precursor **3α** should take into account the nucleophilic substitution from a galactoside thiolate **7α**, generated in situ, with the 1,2-dichloroethane exhibiting an unusual electrophilic reactivity. Following this hypothesis, a possible reaction mechanism has been proposed. The activation of imidazole by DBU allowed its addition to the thiocarbonyl function of the *p*-nitrobenzoyl xanthate **3α** leading to the 1-*O*-(imidazolyl)thiocarbonyl α-D-galactoside **5α**. This intermediate represents an interesting new osidic activator displaced in situ by the released *p*-nitrobenzoylthiolate to afford the 1-*S*-thio-*p*-nitrobenzoyl β-galactoside **6β**. The latter thioester intermediate can be finally deacetylated into a reactive glycoside thiolate in the presence of a second equivalent of imidazole, prior to react with 1,2-dichloroethane. Therefore, the stereochemistry of the unique thioglycoside reaction product **4α**, suggests a the occurrence of a previous anomeric equilibrium, either from the thioester intermediate **6β** or from the thiolate **7β**, in favour of the corresponding α-anomers. In the same conditions as precedently used for the rearrangement of **3α** (imidazole 2 equiv., DBU 2 equiv., 1,2-$ClCH_2CH_2Cl$), the 1-*S*-thio-*p*-nitrobenzoyl α-galactopyranoside **6α**[9] was isolated in 70% yield from the 1-*O*-(thio-*p*-nitrobenzoyl)thiocarbonyl β-glycoside **3β**. This latter result seems to be in favour of a mutarotational equilibrium at the level of the thiolate intermediate **7β**, instead of an anomeric effect from **6β**. As it seems admitted that alkylation of glycosyl thiolates mainly occurs with retention of the anomeric configuration,[4] the formation of an oxonium intermediate from the imidazole carbamate **5α** can also be advocated directing the introduction of the *p*-nitrobenzoyl carboxythiolate to the α-face of the cyclic oxycarbonium. However, the resulting major formation of the intermediate **6α**, expected in this case, would not unambiguously explained the obtention of the chloroethyl thioglycoside **4α**, as **6α** remains stable under the above conditions.

These results prompted us to attempt the preparation of galactoside thiol derivatives from the thio-*p*-nitrobenzoyl thiocarbonyl α-glycoside **3α** in absence of 1,2-dichloroethane solvent (Scheme 4).



Scheme 4.

Thus, in acetonitrile, the treatment of galactoside **3α** with imidazole (2 equiv.) and DBU (2 equiv.), followed by hydrolysis, led exclusively to the α-galactoside thiol **8α** in 85% yield (**H_1**: 5.39 ppm, d, 1H, $J_{1-2}=5.49$ Hz). Same experimental conditions applied in the presence of an excess of methyl iodide afforded a 1/1 mixture of the corresponding thiomethyl α-D-galactoside **9α** (**H_1**: 5.40 ppm, d, 1H, $J_{1-2}=5.50$ Hz) and its thiol precursor **8α**, in 70% yield.

In conclusion to this work, we have designed a new access to glycosides thiolate and thioester. α-Galactoside thiol derivatives are stereospecifically produced, in one pot procedure, from protected 1-*O*-(thio-*p*-nitrobenzoyl)thiocarbonyl α-galactoside in the presence of imidazole and DBU. Therefore, the *p*-nitrobenzoyl α-thiogalactoside ester can be isolated from the β-anomer precursor. The effect of base and solvent in the stereochemistry of the rearrangement, as well as, the influence of xanthate type anomeric group, are under evaluation. The application to other glycosidic derivatives is also in due course to achieve the synthesis of oligothioglycosides in absence of any osidic catalysts.

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6. **1-*O*-(Thio-*p*-nitrobenzoyl)thiocarbonyl-2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside 3**:
   α-Anomer: ^{1}H NMR† 400 MHz ($CDCl_3$): δ 3.52 (dd, 1H, $J_{6a-6b}=9.3$, $J_{6a-5}=5.5$, H_{6a}); 3.63 (m, 2H, H_{6b}, H_3); 3.97 (t, 1H, $J_{5-6b}=9.5$, $J_{5-6a}=6.7$, H_5); 4.03 (d, 1H, H_4); 4.39 (m, 2H, CH_2 OBn); 4.48 (dd, 1H, $J_{2-3}=10.1$, $J_{2-1}=5.4$, H_2); 4.57–4.97 (m, 6H, CH_2 OBn); 6.50 (d, 1H, $J_{1-2}=5.2$, H_1); 7.22–7.36 (m, 20H, CH OBn); 8.13 (d, 2H, $J=9.2$, CH *p*-NO_2-Ph); 8.27 (d, 2H, $J=9.2$, CH *p*-NO_2-Ph). ^{13}C NMR† 100 MHz ($CDCl_3$): δ 68.3 (C_6); 72.9, 73.3, 73.6, 75.1 (CH_2 OBn); 74 (C_5); 74.5 (C_4); 75.4 (C_2); 80.6 (C_3); 84.1 (C_1); 123.9 (CH *p*-NO_2-Ph); 127.5–128.7 (CH OBn and CH *p*-NO_2-Ph); 138.5, 137.7, 137.8 (C_q OBn); 141.7, 150.7 (C_q *p*-NO_2-Ph); 161.7 (C=O); 199.3 (C=S).
   β-Anomer: ^{1}H NMR† ($CDCl_3$): δ 3.59 (m, 2H, $J=6.7$, H_{6a}, H_{6b}); 3.71 (dd, 1H, $J_{3-4}=2.7$, $J_{3-2}=9.6$, H_3); 3.79 (t, 1H, $J=6.7$, H_5); 4.04 (d, 1H, $J_{4-3}=2.7$, H_4); 4.13 (dd, 1H, $J_{2-1}=8$, $J_{2-3}=9.6$, H_2); 4.44 (m, 2H, CH_2 OBn); 4.76 (m, 6H, CH_2 OBn); 5.83 (d, 1H, $J_{1-2}=8$, H_1); 7.33 (m, 20H, CH OBn); 8.09 (d, 2H, $J=9$, CH *p*-NO_2-Ph); 8.23 (d, 2H, $^3J=9.4$, CH *p*-NO_2-Ph). ^{13}C NMR† ($CDCl_3$): δ 68 (C_6); 73 (C_4); 73.1, 73.6, 74.9, 75.4 (CH_2 OBn); 74.5 (C_5); 77.8 (C_2); 82.7 (C_3); 95.4 (C_1); 123.6, 131.3 (CH *p*-NO_2-Ph); 128 (CH OBn); 134.7, 150.8 (C_q *p*-NO_2-Ph); 137.7, 138.1, 138.4 (C_q OBn); 163.2 (C=O); 201.1 (C=S).
7. **1-*S*-(2′-Chloro)ethyl-2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside 4α**: ICMS (NH_3) [M+18]=636; ^{1}H NMR† 400 MHz ($CDCl_3$): δ 2.87 (m, 2H, H_{8a}, H_{8b}); 3.5 (m, 2H, $J_{6a-5}=6$, $J_{6a-6b}=10$, H_{6a}, H_{6b}); 3.64 (m, 2H, H_{7a}, H_{7b}); 3.75 (dd, 1H, $J_{3-2}=10$, $J_{3-4}=3$, H_3); 3.9 (d, 1H, $J_{4-3}=2$, H_4); 4.24 (t, 1H, $J_{5-6a}=6$, H_5); 4.27 (dd, 1H, $J_{2-1}=5$, $J_{2-3}=10$, H_2); 4.97–4.94 (m, 8H, CH_2 OBn); 5.47 (d, 1H, $J_{1-2}=5.2$, H_1); 7.23–7.38 (m, 20H, CH OBn). ^{13}C NMR† 100 MHz ($CDCl_3$): δ 32.2 (C_8); 43.4 (C_7); 69.2 (C_6); 70.3 (C_5); 72.8, 73.5, 73.6, 74.9 (CH_2 OBn); 75.1 (C_4); 76.2 (C_2); 79.4 (C_3); 84.6 (C_1); 127.6–128.5 (CH OBn); 138.0, 138.2, 138.6, 138.7 (C_q OBn).
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9. **1-*S*-Thio-(*p*-nitrobenzoyl)-2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside 6α**: ^{1}H NMR† 400 MHz ($CDCl_3$): δ 3.52–3.63 (m, 1H, H_6); 3.98 (dd, 1H, $J_{3-4}=4$, $J_{3-2}=12$, H_3); 4.09–4.11 (m, 2H, H_5, H_4); 4.28 (dd, 1H, $J_{2-1}=4$, $J_{2-3}=12$, H_2); 4.39 (d, 1H, $J=12$, CH_2 OBn); 4. (d, 1H, $J=12$, CH_2 OBn); 4.61 (d, 1H, $J=12$, CH_2 OBn); 4.74 (s, 2H, CH_2 OBn); 4.78 (d, 1H, $J=12$, CH_2 OBn); 4.83 (d, 1H, $J=12$, CH_2 OBn); 4.98 (d, 1H, $J=12$, CH_2 OBn); 6.59 (d, 1H, $J_{1-2}=4$, H_1); 7.24–7.39 (m, 20H, CH OBn); 8.12 (d, 2H, $J=8$, CH *p*-NO_2-Ph); 8.27 (d, 2H, $J=8$, CH *p*-NO_2-Ph). ^{13}C NMR† 100 MHz ($CDCl_3$): δ 68.4 (C_6); 72.7 (C_4 or C_5); 73.0, 73.6, 73.8 (CH_2 OBn); 74.4 (C_4 or C_5); 75.1 (CH_2 OBn); 75.5 (C_2); 78.3 (C_3); 92.9 (C_1); 123.7 (CH *p*-NO_2-Ph); 127.7–128.6 (CH OBn); 131.1 (CH *p*-NO_2-Ph); 135.6 (C_q *p*-NO_2-Ph); 137.8, 138.0, 138.4, 138.5 (C_q OBn); 150.8 (C_q *p*-NO_2-Ph); 163.4 (C=O).

† δ (chemical shifts) in ppm and J (coupling constants) in Hz.