β-Selective Glycosidation of a 5-Thioglucosamine Derivative

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(Received September 16, 2008; CL-080890; E-mail: hyuasa@bio.titech.ac.jp)

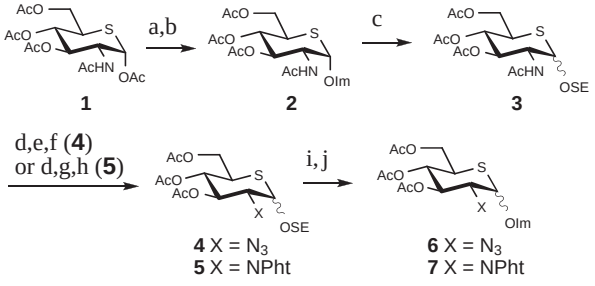
The first β-selective chemical 5-thioglycosylation of a secondary alcohol was attained with the 2-deoxy-2-phthalimido-5-thioglucose derivative. Requirements of the carbonyl functional groups at C2 to exert anchimeric assistance are discussed on the basis of the results with various functional groups.

5-Thiosugars, the ring sulfur analogs of monosaccharides, are glycosidase resistant in their glycosidic forms.[1] Therefore, oligosaccharide analogs that have 5-thiosugars at their nonreducing termini would have longer life time in organisms than their natural counterparts. Durability is sometimes essential for drug candidates and thus facile and stereoselective 5-thioglycosylation could be a pivot in the development of oligosaccharide-based drugs.

5-Thioglycosylations have been achieved both chemically and enzymatically.[1] While enzymatic procedures have afforded both anomers according to the specificities of the glycosyltransferases, chemical methods have been generally α-selective regardless of the sugar configurations with a few exceptions.[2]

We herein studied the glycosidation reactions of 5-thioglucosamine derivatives for the first time. We selected 1-*O*-trichloroacetimidate derivatives of three 5-thioglucosamine, i.e., acetamido (**2**), azido (**6**), and phthalimido (**7**) groups at C-2, as glycosyl donors and 3-O-protected 1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranose **8** as a reactive secondary alcohol.

Peracetyl 5-thioglucosamine **1**[3] was converted to the 1-*O*-trichloroacetimidate (Im) derivative **2**, which was subjected to the glycosylation of 2-(trimethylsilyl)ethyl (SE) alcohol to give the glycoside **3** with α-selectivity (α:β = 3:1) (Scheme 1). It should be noted that the glycosidations of the ring oxygen counterpart generally have given a significant amount of the oxazoline derivative aside from the desired glycoside.[4] The different reactivity toward oxazoline formation is discussed later.

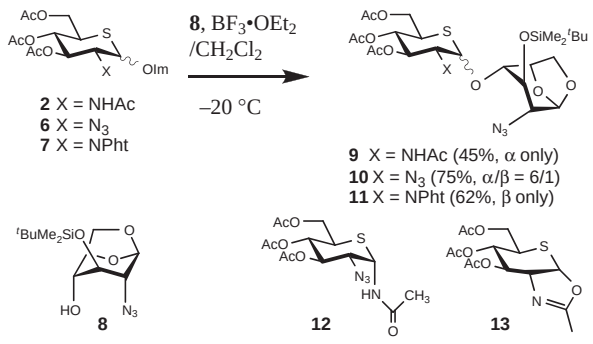


Scheme 1. a) H_2NNH_2·AcOH/DMF; b) CCl_3CN, DBU/CH_2Cl_2 (72%); c) 2-(trimethylsilyl)ethyl alcohol, BF_3·OEt_2, MS4A/CH_2Cl_2, −20 °C (78%, α:β = 3:1); d) 1 M NaOH, reflux; e) TfN_3, DMAP/MeOH; f) Ac_2O, DMAP/pyridine (52% for **4**); g) Phthalic anhydride/pyridine, 60 °C; h) Ac_2O/pyridine (62% for **5**); i) TFA/CH_2Cl_2; j) CCl_3CN, DBU/CH_2Cl_2 (quant for **6**; 97% for **7**).

The glycoside **3** was deacetylated with refluxing 1 M NaOH and treated with trifluoromethanesulfonyl azide (TfN_3) and acetic anhydride to give the azide derivative **4**. The 2-(trimethylsilyl)ethyl group of **4** was removed with trifluoroacetic acid to give the hemiacetal, which was converted into the 1-*O*-trichloroacetimidate derivative **6**. The 2-amino group after deacetylation of **3** in the same way as above was converted into the phthalimide (NPht) derivative **5**. The same conversions as those for **6** led to the 1-*O*-trichloroacetimidate derivative **7**.

Three 5-thioglucosaminyl donors **2**, **6**, and **7** were reacted with 1,6-anhydrosugar **8**. This glycosyl acceptor is one of the most reactive secondary alcohols, which we have used as a first choice in testing 5-thioglycosylations.[1a] The acetamide **2** gave α-disaccharide **9α** and the oxazoline derivative **13** (39%), but no β-disaccharide (Scheme 2). The formation of **13** was unavoidable under the other conditions: trimethylsilyl triflate (TMSOTf) as a Lewis acid or acetonitrile as a solvent. The significant glycoside formation is notable, since the glycosylation of secondary alcohols with the ring oxygen counterpart is almost hopeless.[4] The glycosidation with the azide derivative **6** also afforded α-selectivity to mainly give disaccharide **10α** with a small amount of β-disaccharide **10β**. The use of TMSOTf in CH_3CN predominantly gave the glycosylacetamide **12** (25%). A striking result was obtained, when the phthalimide derivative **7** was used as a donor and only the β-disaccharide **11β** was produced.[5] This is the first chemical 5-thioglycosylation of a secondary alcohol where a predominant β-selectivity was obtained.

The difference in the stereoselectivity of the glycosidation reactions of acetamide (**2**) and phthalimide (**7**) derivatives is remarkable and deserves further discussion. First of all, we focus on the retarded oxazoline formation from acetamide derivative **2** in comparison with the ring oxygen counterpart, since this is presumably related to anchimeric assistance. The coupling constants of the oxazoline **13** ($J_{1,2}$ 1.2, $J_{2,3}$ 5.3, $J_{3,4}$ 5.3, $J_{4,5}$ 9.9 Hz) are consistent with an envelop conformation (E_5), which is slightly different from the skew boat conformation ($^0S_2$) report-



Scheme 2.

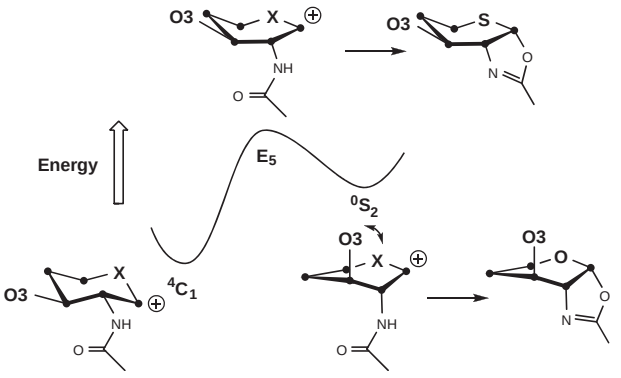
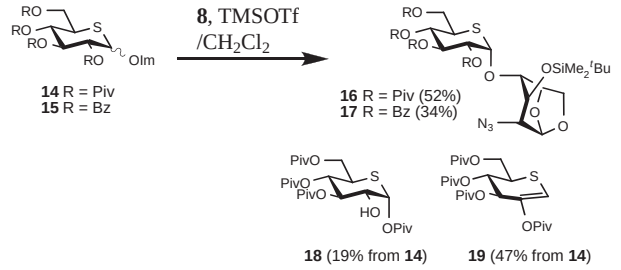


Figure 1. A proposed mechanism for the different oxazonline formation reactivities of *N*-acetylglycosamines.

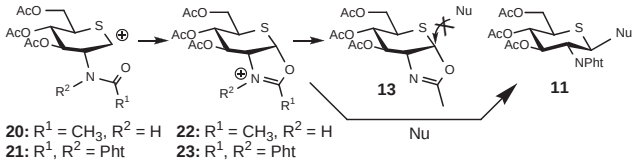
ed for the ring oxygen counterpart.[6] E_5 conformation is a transition structure between $^4C_1$ and $^0S_2$ (Figure 1) and has about 25 kJ/mol higher heat of formation than $^0S_2$ in regard to cyclohexane.[7] As the ring sulfur atom is larger and more protruded out of the ring plane than the ring oxygen atom,[1c] there may be repulsion between the ring sulfur atom and O3 in $^0S_2$ conformation. Therefore, it is most probable that a higher energy is necessary for the oxazoline formation reaction of 5-thioglucosamine derivative than that of the ring oxygen counterpart owing to the conformational restriction from the ring sulfur atom. The same explanation is applicable to the absence of anchimeric assistance in the glycosidation of **2**.

We next turned our attention to β-selective glycosidation with phthalimide derivative **9**, which is ordinary for the ring oxygen counterparts and either electronic participation as with acetamido groups or the steric hindrance at the α-face have been suspected for the origin of the stereoselectivity. If the steric hindrance alone is responsible, then β-selectivity should be obtained for 5-thiosugar donors with bulky 2-*O*-acyl groups. Indeed, Ohara and co-workers succeeded in the β-selective 5-thioglucosylation of primary alcohols with 2-*O*-pivaloyl- and 2-*O*-benzoyl-5-thioglucose derivatives.[2] However, when we conducted the glycosidation for the secondary alcohol **8** with the same glycosyl donors, **14** and **15**, we obtained only α-glycosides, **16** and **17** (Scheme 3). Therefore it is unlikely that the bulkiness of the phthalimido group alone is responsible for the β-selectivity.

Overall, the ability to form the oxazolinium ions **22** and **23** is a key to the different stereoselectivities in the glycosidation reaction of 5-thioglucosamine donors (Scheme 4). The fast conversion of the acetamido-derived oxazolinium ion **22** to the less reactive oxazoline derivative **13** is likely to repress the reaction of **22** with the nucleophile. On the other hand, the reaction from the phthalimido-derived oxazolinium ion **23** to glycoside **11** is straightforward without oxazoline formation. We thus suggest that fast formation of the oxazolinium ion **23** from the phthalimide glycosyl cation **21** led to the absolute β-selectivity. The exclusive α-glycoside formation from acetamide glycosyl cation **20** is most likely due to kinetic anomeric effect as often discussed for α-selective 5-thioglucosylations.[1] Relatively slow formation of the oxazolinium ion **22** might have helped the extraordinary glycosylation of a secondary alcohol in contrast to the ring oxygen counterparts. The origin of difference in the abil-



Scheme 3.



Scheme 4.

ity to form oxazolinium ions from glycosyl cations **20** and **21** is unclear and we need to collect further information to elucidate the mechanism.

This work was supported by a Grant-in-Aid for Scientific Research (No. 19655056) from Japanese Ministry of Education, Culture, Sports, Science and Technology.

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5 The synthesis of **11β**: To a stirred mixture of **7** (34 mg, 57 µmol), **8** (25 mg, 83 µmol), and MS4A (70 mg) in CH_2Cl_2 (1.5 mL) was added a solution of $BF_3{\cdot}OEt_2$ (2 µL, 16 µmol) in CH_2Cl_2 (0.3 mL) at -20 °C under argon. After 1 h, excess CH_2Cl_2 was added to the mixture and it was neutralized with triethylamine and filtered through celite. The filtrate was evaporated and chromatographed on a silica gel column (hexane:ethyl acetate = 4:3) to give **11β** (26 mg, 62%) as a syrup: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84–7.69 (m, 4H, Ph), 5.70 (d, 1H, $J_{1',2'} = 9.9$ Hz, H-1′), 5.65, 5.37 (each t, 2H, $J_{2',3'} = J_{3',4'} = J_{4',5'} = 9.9$ Hz, H-3′, 4′), 5.07 (s, 1H, H-1), 4.79 (t, 1H, $J_{2',3'} = 9.9$ Hz, H-2′), 4.53 (bd, 1H, $J_{5,6b} = 5.6$ Hz, H-5), 4.37 (dd, 1H, $J_{5',6a'} = 5.6$, $J_{6'a,6'b} = 11.9$ Hz, H-6′a), 4.17 (dd, 1H, $J_{5',6'b} = 3.3$, $J_{6'a,6'b} = 11.9$ Hz, H-6′b), 4.08 (d, 1H, $J_{6a,6b} = 7.3$ Hz, H-6a), 3.71, 3.56 (each s, 2H, H-3, 4), 3.68 (t, 1H, $J_{5,6b} = J_{6a,6b} = 7.3$ Hz, H-6b), 3.30 (ddd, 1H, $J_{4',5'} = 9.9$, $J_{5',6a'} = 5.6$, $J_{5',6'b} = 3.3$ Hz, H-5′), 2.89 (s, 1H, H-2), 2.11, 2.03, 1.83 (each s, 9H, Ac × 3), 0.87 (s, 9H, ^{t}Bu), 0.11, 0.07 (each s, 6H, Me × 2).

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Published on the web (Advance View) December 5, 2008; doi:10.1246/cl.2008.1288