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Conversion of β-glycopyranoside to α-glycopyranoside by photo-activated radical reaction

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ABSTRACT

By using carbon tetrachloride as the chloride radical and boron trifluoride etherate as the Lewis acid, the halogen-light-activated anomeric inversion of glycoside was achieved. This reaction is a novel guide to invert the glycosidic bond from a β-anomer to an α-anomer.

Introduction

Radical intermediates play an important role in modern synthetic chemistry, and the reaction of the anomeric radical of carbohydrates has been extensively studied.[1,2] In general, radical Barton decarboxylation of 1-carboxylated glycosides is effective in constructing β-glycosidic bonds,[3–9] via a mechanism in which abstraction of the axial hydrogen is eight times faster than that of the corresponding equatorial hydrogen.[10] Giese and co-workers[11–14] significantly contributed to the development of an intermolecular radical C-glycosylation reaction with α-selectivity and reflecting a quasi-anomeric effect.[15,16] This stereoelectronic effect on the anomeric radical was shown to be due to the periplanar arrangement, with the nonbonding electrons on the ring oxygen and the anti-bonding orbital on the glycosidic 2-substituent.[17,18] In addition, radical hydrogen-atom transfer reactions for oligosaccharides have been developed to modify cyclodextrin[19] and to photodegrade the target D-galactofuranose residue[20] selectively.

Study with pyranosyl radical preparation is the conversion of the protected D-glycopyranosyl bromide using AIBN/Bu_3SnH,[21] which eliminates the protected alkoxyl group attached to the pyranose. To overcome this problem, we developed a method of radical generation from a protected carbohydrate that does not involve dismantling the hydroxyl group and that allows for anomeric inversion. In contrast to the pyranosyl carbons, the anomeric carbon is covalently bound to two alkoxyl oxygens, resulting in a more electron-withdrawing bonding structure such that the anomeric proton is slightly more acidic than the others. A suitable radical can be expected to absorb the anomeric proton, yielding a π-radical and enrichment of the α-anomer. The stereoselective β-glycosidation of a sugar residue can be controlled by the neighboring group participation of 2-*O*-acetyl or by the *O*-benzoyl protecting group,[22] whereas in the alternative α-glycoside route synthesis involves direct inversion of the β-anomer. Here, we report the photo-activated anomeric inversion of protected hexose using carbon tetrachloride or *N*-chlorosuccinimide (NCS) as the chlorine radical source.

Results and discussion

As shown in Table 1, the radical reaction can be activated with halogen light and $BF_3{\cdot}OEt_2$, using NCS as the chloride radical source. The anomeric conversion of β-D-galactopyranosyl acetate **1β** into α-major product resulted in a good yield within 1 h, with an α/β ratio of 5.7/1 (Table 1, entry 1). NMR analysis showed that the α/β ratio was almost identical when α-D-galactopyranosyl acetate **1α** and β-D-glucopyranosyl acetate **2β** were tested (Table 1, entries 2 and 3). The α/β conversion ratio of methyl glucopyranoside **3β** was 2.9/1, corresponding to a yield of 70%, after 1 h of activation, and remained nearly the same in the presence of excess NCS or with a longer reaction time. Anomeric conversions of other glucopyranosides (Table 1, entries 4, 6–8) with NCS were not observed; negative results were also obtained with the bromine radical reagent *N*-bromosuccinimide (NBS).

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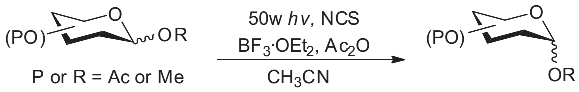
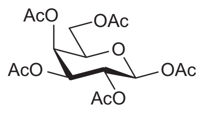
Table 1
Photo-activated glycosidic inversion of hexoses to the corresponding α-glycosides with *N*-chlorosuccinimide[26]

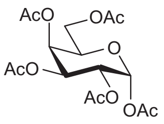


Entry	Hexose	Time (h)	Yield (%)	α/β[a]
1	**1β**	1	88	5.7/1
2	**1α**	1	99	6.3/1
3	**2β**	1	76	6.0/1
4	**2α**	1	NR[b]	–
5	**3β**	1	70	2.9/1
6	**3α**	1	NR[b]	–
7	**4β**	1	NR[b]	–
8	**4α**	1	NR[b]	–

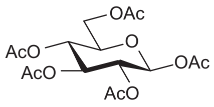
[a] NMR result, see Supporting information Figure S1.
[b] No reaction.



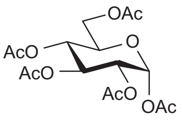
1β



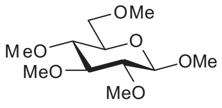
1α



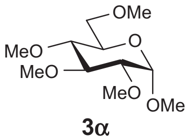
2β



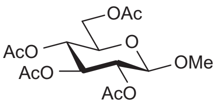
2α



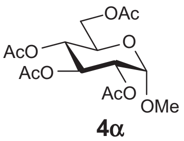
3β



3α

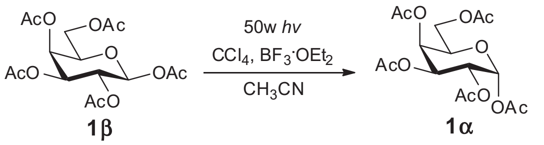


4β



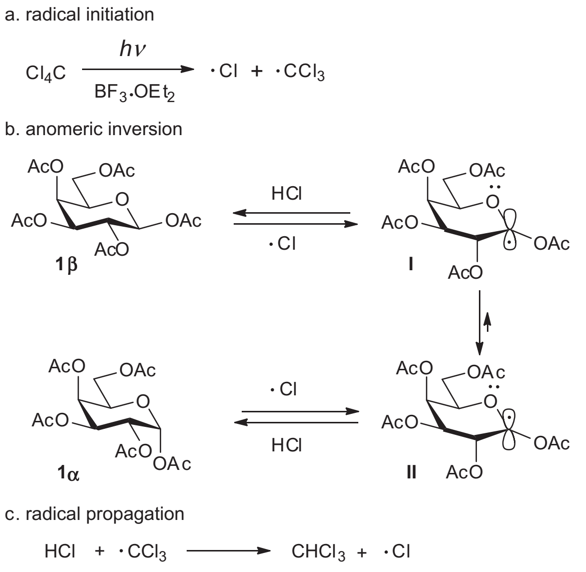
4α

Table 2
Photo-activated glycosidic inversion of β-galactose to the corresponding α-galactopyranose with CCl_4[27]



Entry	$BF_3·OEt_2$ (equiv)	CCl_4 (equiv)	Time (min)	Yield (%)	α/β[d]
1	1.1	1.2	1	86	5.9/1
2	1.1	1.2	2	91	6.1/1
3	1.1	1.2	20	66	6.2/1
4	0.55	1.2	20	59	3.9/1
5	0.55	0.5	20	51	2.1/1
6	0.55	0.1	20	77	1/2
7[a]	1.1	1.2	20	69	5.7/1
8[b]	1.1	1.2	30	NR[e]	–
9[c]	1.1	1.2	30	NR[e]	–

[a] Without CCl_4, with CBr_4.
[b] Without 50 W of light.
[c] With 1 equiv DMSO.
[d] NMR result, see Supporting information Figure S2.
[e] No reaction.



Scheme 1. Postulated photo-activated radical mechanism for anomeric inversion.

Table 1 also shows that β-D-galactopyranosyl acetate **1β** was a more active monosaccharide; it was therefore chosen for further study. The acidic conditions were similar and carbon tetrachloride was used as the chlorine radical source. To optimize the conversion conditions, CCl_4 (1.2 equiv) and $BF_3·OEt_2$ (1.1 equiv) were added to a solution of hexose **1β** in Pyrex glass (Table 2). The anomeric inversion started immediately under halogen light. The α/β ratio was 5.9/1 within 1 min, with an 86% yield. Similarly, within 2 min the α/β ratio and yield were 6.1/1 and 91%, respectively. The isolated yield was 66% after 20 min, during which pyranosyl acetate underwent anomeric hydrolysis. A longer reaction time provided a nearly identical α/β ratio of 6.2/1, and the nature of the quasi-anomeric effect seemed to influence the selectivity of the reaction. Decreasing the quantity of $BF_3·OEt_2$ from 1.1 to 0.55 equiv led to an α/β ratio of 3.9/1, while following a reduction of the amount of CCl_4 from 1.1 to 0.5 or 0.1 equiv the α/β ratio was 2.1/1 and 1/2, respectively. With CBr_4 (Table 2, entry 7) treatment, the conversion of β-anomer **1β** into a mixture of **1α** and **1β** provided the same results as obtained with CCl_4. The presence of