

Thermal effect in β -selective glycosylation reactions using glycosyl iodides

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Abstract—The unique reactivity of glycosyl iodides and the fact that they react under neutral conditions makes them the donors of choice in our glycosylation strategies. Glycosyl iodides are generated in situ from either the anomeric acetate or the anomeric silylated derivative yielding the α -iodide. In the reported glycosylation reactions, protected glucosyl, galactosyl, and mannosyl iodides were reacted with trimethylene oxide as the acceptor, yielding the β -anomer as the major product. In the absence of neighboring group participation, β -selectivity is thought to arise from nucleophilic displacement of the α -iodide in an S_N2 -like mechanism, while the α -product is the result of nucleophilic attack on the β -iodide. In this study, increased β -selectivity using an inverse thermal effect is demonstrated.

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Recent studies in our laboratory have shown the unique reactivity and selectivity of oxacyclic ethers as acceptors in glycosylation reactions with glycosyl iodides.¹ Highly strained cyclic ethers² such as trimethylene oxide proved especially useful due to symmetrical ring opening upon exposure to the iodide. β -Selectivity is believed to arise from an S_N2 -like displacement of the α -iodide (1) by acceptor (2) leading to the formation of the β -oxonium ion (3), which is susceptible to ring opening by the iodide to yield the β -glycoside (4) (Fig. 1).

While we were able to achieve as high as 8:1 β -selectivity, α -glycoside (7) formation could not be avoided. Our current hypothesis is that α -glycosidation occurs from a combination of ring opening of the α -oxonium ion (6) resulting from addition to oxonium intermediate (5)

and from nucleophilic displacement of the β -glycosyl iodide (8) generated from in situ anomerization (Fig. 2). We reasoned that lower reaction temperatures would suppress the formation of 5,³ and since at the onset of the reaction the concentration of iodide anion is low, the combination of these two factors would lead to increased β -selectivity. Thus we initiated the current study on the thermal effect of β -glycosidation using glycosyl iodides.

Glycosyl iodides⁴ are quantitatively generated from either the anomeric acetate or the anomeric silylated derivative by treatment with TMSI.⁵ The side product of the acetate reaction is TMSOAc, which is capable of reforming the glycosyl acetate. This problem may be overcome by azeotroping the iodide with toluene⁶ or by introducing MgO as an effective trap.¹ A typical experimental example is the galactosylation of

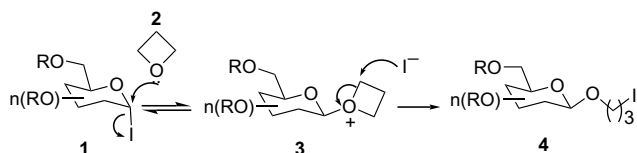


Figure 1. Mechanism of β -glycoside formation.

Keywords: Glycosyl iodide; β -Selective glycosidation.

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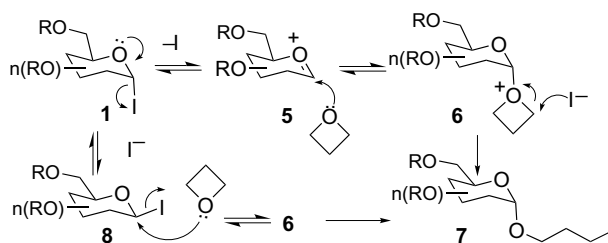
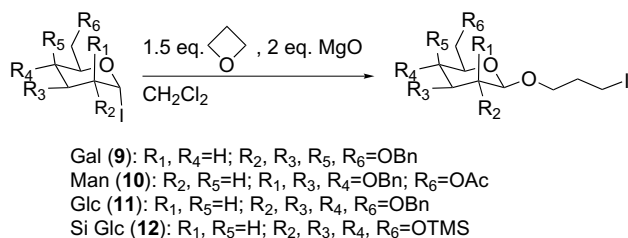


Figure 2. Mechanism of α -glycoside formation.



Scheme 1.

trimethylene oxide in which a mixture of 2,3,4,6-tetra-*O*-benzyl- α -D-galactopyranosyl acetate (1 equiv) and MgO (2 equiv) in CH₂Cl₂ (0.17 M) is stirred at 0 °C and TMSI (1.1 equiv) is then added. The reaction mixture is stirred for 2 h at 0 °C to give galactosyl iodide **9** (Scheme 1). Trimethylene oxide (1.5 equiv) is subsequently added at 0 °C and the mixture is then stirred at the selected temperature (Table 1). Upon the completion of the reaction, the mixture is diluted with EtOAc (20 mL) and washed with saturated aq Na₂S₂O₃ (3×10 mL), then with saturated aq NaCl (2×10 mL). The organic extract is then dried over Na₂SO₄, stripped of solvent in vacuo, and the concentrated residue is purified by FCC to afford the corresponding galactoside as a mixture of anomers in the yield specified in Table 1. The β : α ratio can be obtained from integration of the anomeric signals in the ¹H and ¹³C NMR spectra (δ_{H} 4.95 (β -anomer), 5.05 (α -anomer); δ_{C} 104.2 (β -anomer), 98.2 (α -anomer)).

All of the reactions reported in Table 1 were performed a minimum of three times, and the average of the selectivity was calculated and reported. Galactosyl, mannosyl, and glucosyl iodides were studied. Mannosyl iodide **10** was employed instead of the perbenzylated analogue to avoid glycal formation resulting from 1,2-elimination.⁶ In general terms, the reactivity of 2,3,4,6-tetra-*O*-benzyl- α -D-galactopyranosyl iodide > 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranosyl iodide > 6-*O*-acetyl-2,3,4-tri-*O*-benzyl- α -D-mannopyranosyl iodide.

As illustrated in Table 1, β -selectivity exponentially increased upon lowering the temperature. There was

little difference between performing the reactions at room temperature and 0 °C, but dramatic differences were observed at lower temperatures. At –60 °C, only 2% α -galactoside (entry 4), and less than 4% α -glucoside (entry 12) was formed. β -Selectivity was not as great for the mannosyl iodide as 10% of the α -mannoside was present in the product distribution and the reaction took more than 6 days for completion. Achieving β -selectivity in mannosidations is notoriously difficult as neither the anomeric effect nor the axial group at C2 favors this conversion.⁷ Finally, entries 13–16 support our hypothesis that the α -anomer arises at least in part from the formation of the oxacarbenium ion **5**. The electron donating capacity of silyl protecting groups is known to stabilize formation of the oxacarbenium ion,⁸ which we predicted would lead to diminished β -selectivity. Indeed, this was the case; the selectivity dropped from 29:1 β : α with per-*O*-benzylated glucosyl iodide (entry 12) to 10:1 β : α (entry 16) when using the per-*O*-silylated analogue.

In conclusion, the thermal effect is a useful strategy for the efficient formation of β -glycosides using glycosyl iodide donors. Increased β -selectivity is inversely proportional to the temperature and the highest reactivity and stereoselectivity were obtained when using per-*O*-benzylated galactopyranosyl iodide. Steric effects in mannose hinder nucleophilic attack of the acceptor via an S_N2-like mechanism and the electronic effects of silicon increase the propensity for oxonium ion formation; both of which lead to lower β -selectivity.

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References and notes

Table 1. Temperature dependence of β -selectivity

Entry	Donor	Temp	Time	% Yield	α : β Ratio
1	9	40	5 min	83	1:4
2		23	10 min	76	1:8
3		0	30 min	74	1:9
4		–60	12 h	73	1:50
5	10	40	2 h	87	1:4
6		23	6 h	83	1:4
7		0	2 days	74	1:5
8		–60	>6 days	50	1:10
9	11	40	2 h	82	1:2
10		23	3 h	80	1:4
11		0	5 h	76	1:5
12		–60	3 days	76	1:29
13	12	40	1 h	80	1:4
14		23	2 h	78	1:5
15		0	15 h	76	1:6
16		–60	4 days	69	1:10

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