ORGANIC LETTERS

2004
Vol. 6, No. 6
973−975

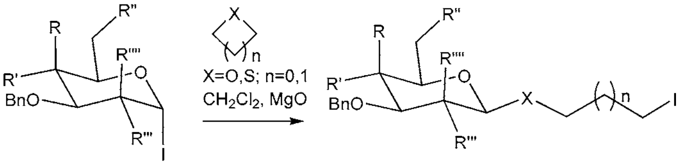
Unique Reactions of Glycosyl Iodides with Oxa- and Thiocycloalkane Acceptors

Darrin R. Dabideen and Jacquelyn Gervay-Hague*

Department of Chemistry, University of California Davis, Davis, California 95616
gervay@chem.ucdavis.edu

Received January 5, 2004

ABSTRACT

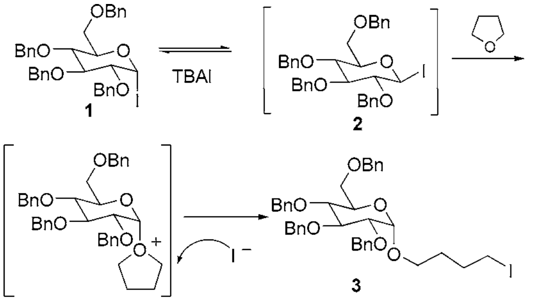


Glc: R, R'''' = H; R', R'', R''' = OBn
Gal: R', R''''=H; R, R'', R''' = OBn
Man: R, R'''=H; R', R''''=OBn; R''=OAc

Glucosyl-, galactosyl-, and mannosyl iodides efficiently react with strained oxacycloalkane acceptors to afford *O*-glycosides with high *β*-selectivity. The mechanism of ring opening was investigated by reacting mannosyl iodides with pure enantiomers of propylene oxide and styrene oxide. Competition experiments between three- and five-membered oxacycloalkanes were also investigated. Finally, *β*-thiomannosides were synthesized from thiocycloalkane acceptors.

In recent years, we have demonstrated the widespread utility of glycosyl iodides en route to synthetically challenging glycoconjugates.[1] Early in these investigations, difficulties were encountered when performing the reactions in THF. Under conditions that promote in situ anomerization, the THF adduct (**3**) was obtained rather than the desired α-glycoside (Scheme 1).[2] The α-glycoside likely results from attack of the acceptor on the more reactive *β*-iodide (**2**) to yield an oxonium intermediate that undergoes ring opening to yield **3**. This is essentially the reverse reaction to that invoked by Fraser-Reid to explain the remarkable reactivities of pent-4-enyl glycosides.[3] Although mechanistically interesting, we initially viewed THF addition as a limitation and avoided using it as a solvent in subsequent studies. We have now revisited this anomalous result and report our findings as they relate to the unique reactivity of glycosyl iodides with both oxa- and thiocyclic ethers.

Scheme 1



Major product of 3:1 α:β mixture

Glycosyl iodides are quantitatively prepared from the corresponding glycosyl acetate upon reaction with TMSI.[4] Trimethylsilyl acetate (TMSOAc) is liberated, and it too can act as an acceptor, giving rise to the *β*-glycosyl acetate.

---

[1] (a) Lam, S. N.; Gervay-Hague, J. *Org. Lett.* **2002**, *4*, 2039−2042. (b) Lam, S. N.; Gervay-Hague, J. *Carbohydr. Res.* **2002**, *337*, 1953−1965. (c) Bhat, A. S.; Gervay-Hague, J. *Org. Lett.* **2001**, *3*, 2081−2084. (d) Gervay, J. *Organic Synthesis*: *Theory and Applications*; JAI Press: Greenwich, 1998; pp 121−153. (e) Hadd, M. J.; Gervay, J. *Carbohydr. Res.* **1999**, *320*, 61−69. (f) Gervay, J.; Hadd, M. J. *J. Org. Chem.* **1997**, *62*, 6961−6967.

[2] Hadd, M. J. Ph.D. Thesis, University of Arizona, Tucson, AZ, 1998.

[3] Fraser-Reid, B.; Konradsson, P.; Mootoo, D. R.; Udodong, U. *J. Chem. Soc., Chem. Commun.* **1988**, 823−825.

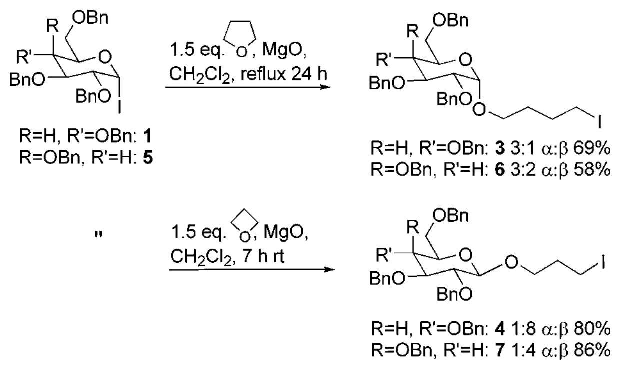
[4] Thiem, J.; Meyers, B. *Chem. Ber.* **1980**, *113*, 3075−85.

10.1021/ol049966w CCC: $27.50

Recombination can be minimized by removing TMSOAc in vacuo, but this maneuver is tedious because judicious exclusion of water is required. We now find that the addition of MgO effectively deactivates TMSOAc toward addition. In all of the reactions reported in this study, MgO (2 equiv) is added to the acetate prior to the introduction of TMSI. MgO does not interfere with glycosyl iodide formation or acceptor reactivity. Similar results were obtained in the absence of MgO with in vacuo removal of TMSOAc, supporting the hypothesis that MgO serves only as a Lewis base that sequesters TMSOAc.

Initial studies focused on reacting per-*O*-benzylated glucosyl iodide **1** with 1.5 equiv of THF and MgO in CH_2Cl_2 (Scheme 2). The reaction was sluggish at room temperature but proceeded to completion at reflux for 24 h. Upon workup and purification, a 69% yield of **3** was obtained in a 3:1 α:*β* anomeric ratio. Encouraged by these results we next reacted **1** with tetrahydropyran, but the reaction was far more sluggish, giving only low yields of the expected product. In contrast, reaction of **1** with trimethylene oxide occurred within 7 h at room temperature giving predominantly the *β*-glycoside **4** (1:8).

Scheme 2

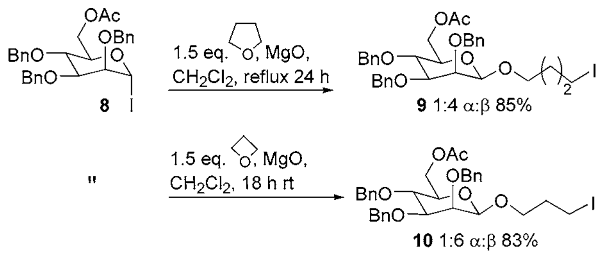


Previous mechanistic studies in our laboratory suggest that *β*-glycosides result from S_N2-like displacement of the α-iodide. We believe that cyclic ethers, rather than ring-opened iodo alcohols or iodo alcoholates, serve as the acceptors in these reactions as we saw no evidence of iodo alcohol byproducts in any of our investigations. Moreover, we were unable to effect ring opening under analogous reactions where only the glycosyl iodide was omitted. The relative reactivities of these cyclic ethers correlate well with calculated strain energies with increased ring strain translating to increased reactivity.[5] Analogous reactions with per-*O*-benzylated galactosyl iodide (**5**) were equally productive, as shown in Scheme 2.

Having accomplished the aforementioned *β*-selective glycosidations, we naturally turned our attention to mannosyl iodides. Achieving *β*-selectivity with mannose-derived donors is notoriously difficult as both the anomeric effect and anchiomeric assistance favor α-glycoside formation.[6] One way around this problem is to utilize tethering strategies to deliver the acceptor from the *β*-face.[7] Other approaches involve functionalizing mannose in a fashion that conformationally biases *β*-attack.[8]

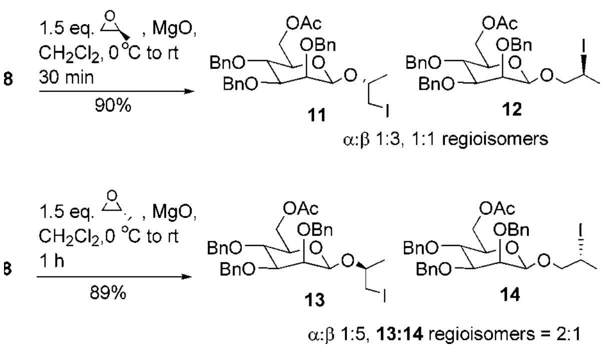
Initially, we reacted per-*O*-benzyl-α-mannosyl iodide with THF, but elimination of HI was the major reaction manifold. This difficulty was easily overcome by replacing the C-6 *O*-benzyl with an electron-withdrawing group (*O*-acetyl) (Scheme 3).[9] Mannosyl iodide (**8**) gave predominantly *β* products with both THF (**9**) and trimethylene oxide acceptors (**10**), and as seen with **1** and **5**, the more highly strained oxacyclobutane afforded greater reactivity and stereoselectivity.

Scheme 3



To probe the mechanism of ring opening, **8** was independently reacted with pure enantiomers of propylene oxide. Unsymmetrical cyclic ether systems introduce the possibility of both regio- and stereoisomers in the resulting products. If ring opening proceeds through an S_N2 mechanism, as suggested in Scheme 1, then each enantiomer of propylene oxide could afford four possible products, i.e., one set of regioisomers for each anomer. This was indeed the case as determined from analysis of the ^1H and ^{13}C NMR of the products resulting from the reaction shown in Scheme 4. Reaction of **8** with (*R*)-propylene oxide was complete within 30 min, and a 1:1 ratio of regioisomers was obtained. Reaction with

Scheme 4



---

[5] Vila, A.; Mosquera, R. A. *Tetrahedron* **2001**, *57*, 9415−9422.

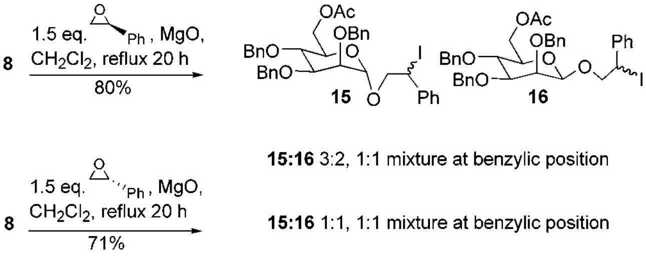
[6] Gridley, J. J.; Osborn H. M. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1471−1491.

[7] (a) Barresi, F.; Hindsgaul, O. *Front. Nat. Prod. Res.* **1996**, *1*, 251−276. (b) Stork, G.; LeClair, J. J. *J. Am. Chem. Soc.* **1996**, *118*, 247−248.

the (*S*)-enantiomer required 1 h for completion, and the regioisomeric distribution favored attack at the least-substituted epoxide carbon (2:1). These epoxides are even more reactive than trimethylene oxide, albeit somewhat less β-selective.

We reasoned that regiochemical scrambling could be overcome by incorporating a stabilizing functionality proximal to the incipient positive charge. Again, this proved to be true. However ring opening proceeded in a stepwise rather than concerted process. For example, when **8** was treated with (*R*)- and (*S*)-styrene oxide, the reaction was far more sluggish (reflux, 20 h) and the only products resulted from an S_N1 mechanism at the benzylic position (Scheme 5).

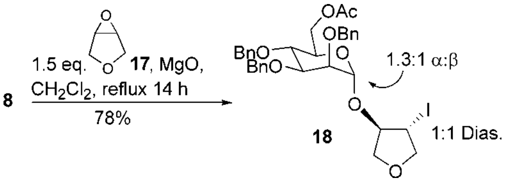
Scheme 5



Slightly different anomeric ratios were obtained for each acceptor. Product distributions were determined from evaluation of the reaction mixture ^{13}C NMR, which showed four anomeric signals (δ_c 98.2, 98.5, 101.7, 102.1) corresponding to the four diastereomers resulting from attack of the iodide at the benzylic position (δ_c 29.7, 29.9, 30.0, 30.9).

In an effort to access more highly functionalized systems we also reacted **8** with **17**. As anticipated, epoxide opening predominated, but the reactivity of **17** more closely paralleled styrene epoxide, requiring 14 h at reflux and yielding a 1.3:1 α: β anomeric mixture (Scheme 6).

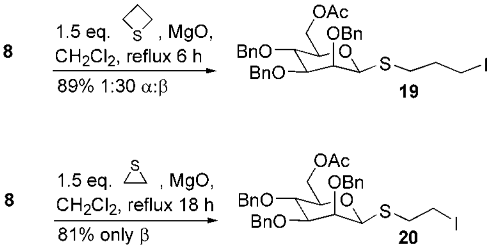
Scheme 6



Several important features are evident from the combined experiments using strained ether acceptors with glycosyl iodide donors. First, reactions proceed without donor activation. Glycosyl iodides are unique in this respect, as analogous reactions with glycosyl bromides were not productive. Highly β-selective glycosidations occur with glucosyl, galactosyl, and mannosyl iodides when combined with reactive acceptors such as propylene oxide and trimethylene oxide. Less reactive acceptors including THF and deactivated epoxides tend to favor α-attack. Finally, in the absence of carbocation stabilization, ring opening of the ether acceptor proceeds by S_N2 attack.

Having demonstrated the unique acceptor reactivity of cyclic oxygenated ethers, we were naturally curious about analogous thioether acceptors. Reaction of **8** with tetrahydrothiophene gave no reaction, which is perhaps not surprising considering it has little strain energy (3.1 kcal/mol).[10] In contrast, reaction of trimethylene sulfide with **8** provided predominantly the β-anomer after 6 h at reflux, and ethylene sulfide afforded only the β-anomer after 18 h at reflux (Scheme 7).[11]

Scheme 7



The relative reactivities of these thioethers directly correlate with reported strain energies of 22.2 and 19.1 kcal/mol for thietan and thiirane, respectively.[10] Further studies probing the mechanism and extended applications of these remarkably β-selective reactions are currently underway in our laboratory.[12]

Acknowledgment. We thank the NSF (CHE-0196482) for generous financial support.

Supporting Information Available: General experimental procedure and NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049966W

---

(8) (a) Hodosi, G.; Kovác, P. *J. Am. Chem. Soc.* **1997**, *118*, 22335-2336. (b) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198−99.

(9) Lam, S. N.; Gervay-Hague, J. *Org. Lett.* **2003**, *22*, 4219−22.

(10) Gronert, S.; Lee, J. M. *J. Org. Chem.* **1995**, *60*, 6731−36.

(11) Anomeric stereochemistry was assigned on the basis of $^1J_{C,H}$ coupling constant data as per: Bock, K.; Lundt, I.; Pedersen, C. *Tetrahedron Lett.* **1973**, *14*, 1037−1040.

(12) For examples of conformationally biased β-selective thioglycosidations, see: Crich, D.; Li, H. *J. Org. Chem.* **2000**, *65*, 801−805 and references therein.