

A New Reaction Manifold for the Barton Radical Intermediates: Synthesis of *N*-Heterocyclic Furanosides and Pyranosides via the Formation of the C₁–C₂ Bond

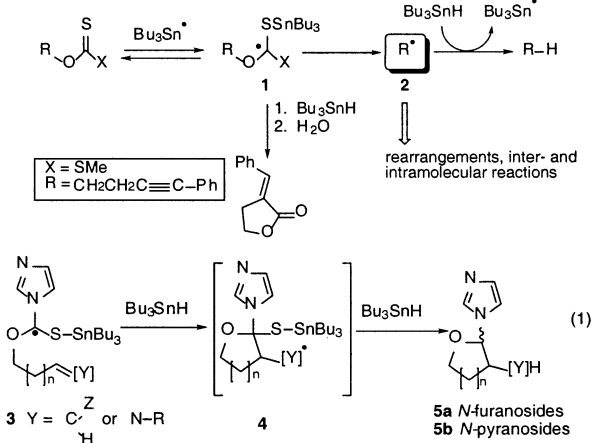
Jong Uk Rhee, Brian I. Bliss, and T. V. RajanBabu*

Department of Chemistry, 100 West 18th Avenue, The Ohio State University, Columbus, Ohio 43210

Received September 19, 2002; E-mail: rajanbabu.1@osu.edu

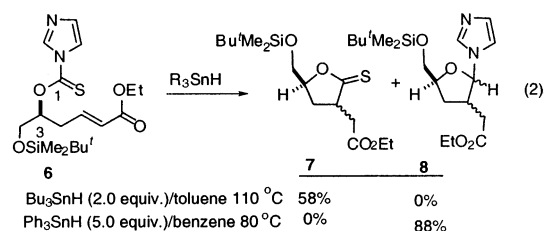
Deoxygenation of secondary alcohols through the use of the corresponding xanthate and thiourethane derivatives (The Barton–McCombie reaction) is one of the most useful radical reactions (Scheme 1).¹ In the presence of suitable radical acceptors, the

Scheme 1. Intermediates in the Barton Deoxygenation Reaction



intermediate radical **2** can be used for intra-² and intermolecular³ carbon–carbon bond-forming reactions.⁴ The slow step in the deoxygenation process is the collapse of the intermediate **1**. Under carefully controlled conditions, this intermediate is also able to take part in various radical reactions including *exo*-hex-5-enyl type cyclizations^{5,6} leading to lactones after hydrolytic workup. Except for one isolated example,⁷ in which the expected thiolactone was formed, the fate of the intermediate radicals generated from the thiocarbonyl imidazolides (eq 1, **1**, X = 1-imidazolyl → **3**) and related thiourethanes has not been examined. Under the optimum conditions, a radical such as **3** can be expected to undergo cyclization leading to a product in which the heterocyclic moiety is retained in the product **5** (eq 1). With an appropriately substituted carbohydrate precursor this could lead to *N*-heterocyclic glycosides⁸ of 2-amino- or C₂-branched sugars.⁹ Additionally, this would provide direct support for the involvement of the radical **1** in the major reaction pathway leading to deoxygenation.¹⁰ These expectations have been borne out, and in this communication we report our initial results which demonstrate the generality of this concept in the context of hex-5-enyl and hept-6-enyl radical cyclizations with a variety of radical acceptors (**3**) which include α,β -unsaturated esters, oxime ethers, and hydrazine derivatives.

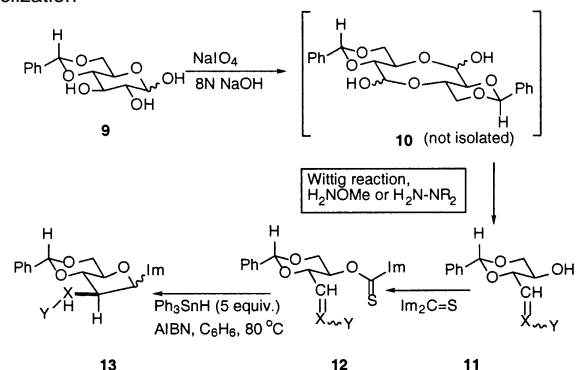
Initial feasibility studies were carried out on a simple carbohydrate-derived imidazole thioate **6** (eq 2). This readily available substrate¹¹ with a *tert*-butyldimethylsiloxy-methyl substituent at the C₃-position (radical numbering) was chosen not only to optimize the reaction conditions but also to examine any inherent stereochemical preferences in the cyclization in an unbiased system. Reaction of the



ethyl (*E*)-hex-2-enoate derivative **6** with 2 equiv of Bu_3SnH in refluxing toluene gave the expected thiolactone **7** (cis/trans = 2.1/1.0) in 58% yield. After an extensive investigation¹² in which we systematically varied the concentrations of the reactants, rates of additions, and reaction temperatures, it was found that when a dilute solution of the substrate in benzene was added to an excess (5 equiv) of a good hydrogen donor (Ph_3SnH) maintained at 80 °C (*reverse addition*), a surprisingly high yield (88%) of an imidazole glycoside (**8**) was produced. The product, not unexpectedly, was a mixture (51:15:29:5) of all possible isomers of the furanosides. Even though the major isomer could be separated, no attempts were made to identify the individual isomers. Instead, we decided to explore ways of improving the stereochemical outcome and expanding the scope of the reaction through the use of alternate radical acceptors and heterocyclic thiocarbonyl derivatives.

Conformational control by a preexisting ring can often be used to improve the stereoselectivity of radical annulation processes.¹³ To explore this possibility in the present context, we prepared¹² a series of thiocarbonyl imidazolides (**12a–12d**) starting from readily available 4,6-*O*-phenylmethylglucopyranose (**9**) and subjected them to the cyclization conditions (Scheme 2). The substrates with

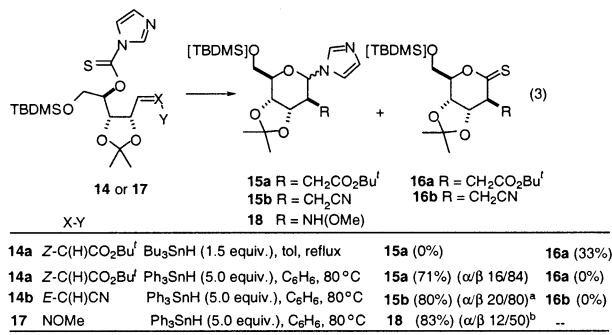
Scheme 2. Synthesis of Imidazole Furanosides via Radical Cyclization



entry	X-Y	isolated yield (13)	α/β
1.	12a (<i>E</i>)-CHCO ₂ Et	54	0.8/1.0
2.	12b (<i>Z</i>)-CHCN	81	1.0/0.8
3.	12c (<i>Z+E</i>)-NOMe	63	1.0/0.8
4.	12d CH=N-NMe ₂	54	1.0/0.3

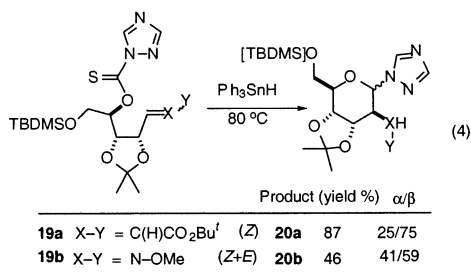
electron-deficient acceptor olefins gave moderate-to-good yields of the furanoside product (**13**) as a mixture of the two anomers (entries 1, 2). Substrates with oxime ether¹⁴ and hydrazone¹⁵ acceptors, which would serve as 2-amino-2-deoxy-furanoside precursors, likewise gave good yields of the imidazole glycosides (entries 3, 4). These glycosides can be separated by column chromatography. Even though there is little stereochemical control in the formation of the two anomers, there is exquisite control at the C₂-position. In each case only the β -epimer is formed.

Formation of cyclohexane derivatives via 6-*exo*-heptenyl radical cyclization is approximately 20–30 times slower than hex-5-enyl radical cyclization,¹⁶ and synthetic applications involving these reactions are few compared to those involving the latter. Therefore, we were surprised to find that the imidazolidine **14a** prepared from a ribose-derived precursor gave 71% isolated yield of a C₂-branched glycoside **15a** (eq 3) rather than deoxygenation/reduction products. In general, (*Z*)-isomers of the acrylate or the acrylonitrile were found to give exclusively the *altro*-isomers as a mixture of anomers, the β -isomer being the major one.¹⁷ The corresponding *E*-olefins (e.g., **14b**) gave, in addition, minor amounts of the *allo*-isomers of the products.¹² As we had recognized¹² in our initial scouting studies, at higher temperature with lower amounts of the hydride source, the expected thionolactone (**16**) was the sole cyclization product. The oxime ether (**17**) was also found to undergo the cyclization giving the 2-deoxy-2-amino-mannopyranoside derivatives **18** in remarkably high yield.



^a 13% *allo*-isomers; the *Z*-nitrile gave exclusively *altro*-isomers (α/β 1:4); ^b 38% *allo*-isomers

Experiments with thiocarbonyl triazole derivatives suggest for the first time that the new glycoside synthesis may not be limited to imidazolides. Thus, the hept-6-enyl radical precursors **19a** and **19b** gave the triazole glycosides **20a** and **20b** in acceptable yields (eq 4).



We are currently investigating new methods for the synthesis of novel carbohydrate-derived thiourethanes and mixed thiocarbonates with the hope of expanding the scope of the newly discovered cyclization reactions for the synthesis of nucleosides, *N*-glycosyl amino acids, and unusual *O*- and *C*- disaccharides.

Acknowledgment. We acknowledge the financial support by NSF (CHE 0079948) and an Alumni Association Fellowship from Myong Ji University (Korea) to J.U.R.

Supporting Information Available: Details of the synthesis and characterization of radical precursors and products of reactions (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (a) Barton, D. H. R.; Ferreira, J. A.; Jaszberenyi, J. C. Free Radical Deoxygenation of Thiocarbonyl Derivatives of Alcohols. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; pp 15–172. (b) Zard, S. Z. Xanthates and Related Derivatives as Radical Precursors. In *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 90–108. (c) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413.
- (a) Hart, D. J.; Tsai, Y.-M. *J. Org. Chem.* **1982**, *47*, 4403. (b) Clive, D. L. J.; Beaulieu, P. L.; Set, L. *J. Org. Chem.* **1984**, *49*, 1313. (c) Hanessian, S.; Dhanoa, D. S.; Beaulieu, P. L. *Can. J. Chem.* **1987**, *65*, 1859. (d) RajanBabu, T. V. *J. Am. Chem. Soc.* **1987**, *109*, 609.
- (a) Giese, B.; González-Gómez, J. A.; Witzel, T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 69. (b) Araki, Y.; Endo, T.; Tanji, M.; Nagasawa, J.; Ishido, Y. *Tetrahedron Lett.* **1988**, *29*, 351. (c) Keck, G. E.; Enholm, E. J. *Tetrahedron* **1985**, *41*, 4079.
- For a recent monograph containing highly readable reviews, see: Renaud, P.; Sibi, M. P.; Eds. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, 2001.
- (a) Bachi, M. D.; Bosch, E. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1517. (b) Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 6127. (c) Yamamoto, M.; Uruma, T.; Iwasa, S.; Kohmoto, S.; Yamada, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1265.
- For elegant applications of related cyclization of thioamides for the synthesis of pyrrolidines and indoles, see: (a) Bachi, M. D.; Melman, A. *J. Org. Chem.* **1997**, *62*, 1896. (b) Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 3791 and references therein.
- Angoh, A. G.; Clive, D. L. *J. Chem. Soc., Chem. Commun.* **1985**, 980.
- For reviews of *N*-heterocyclic glycosides, see: (a) Garner, P. *Synthetic Approaches to Complex Nucleoside Antibiotics*. In *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1, Part A, pp 397–434. (b) Knapp, S. *Chem. Rev.* **1995**, *95*, 1859. (c) Vorbriegen, H. *Handbook of Nucleoside Synthesis*; Wiley: New York, 2001.
- For the importance of C₂-branched sugars see: (a) Linker, T.; Sommermann, T.; Kahlenberg, F. *J. Am. Chem. Soc.* **1997**, *119*, 9377. (b) Beyer, J.; Madsen, R. *J. Am. Chem. Soc.* **1998**, *120*, 12137.
- Radical **1** has previously been identified by EPR methods. For a discussion of the mechanism of Barton deoxygenation see: (a) Barton, D. H. R.; Crich, D.; Löbberding, A.; Zard, S. Z. *Tetrahedron* **1986**, *42*, 2329. (b) Forrest, D.; Ingold, K. U.; Barton, D. H. R. *J. Phys. Chem.* **1977**, *81*, 915. (c) Barker, P. J.; Beckwith, A. L. *J. Chem. Soc., Chem. Commun.* **1984**, 683.
- Synthesized from (*S*)-3-hydroxy- γ -butyrolactone in five steps¹² (Huang, G.; Hollingsworth, R. I. *Tetrahedron* **1998**, *54*, 1355).
- See Supporting Information for details.
- (a) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139. (b) Several natural product syntheses based on radical cyclization methodology also exploit such stereochemical control. See ref 4.
- (a) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821. (b) Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631. (c) Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633. (d) Grissom, J. W.; Klingberg, D.; Huang, D.; Slattery, B. J. *J. Org. Chem.* **1997**, *62*, 603.
- Sturino, C. F.; Fallis, A. G. *J. Org. Chem.* **1994**, *59*, 6514.
- Beckwith, A. L. *J. Tetrahedron* **1981**, *37*, 3073.
- For another example of such difference between the geometrical isomers of the acceptor, see: Enholm, E. J.; Trivellas, A. *J. Am. Chem. Soc.* **1989**, *111*, 6463.

JA028617Z