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TWO NEW METHODS FOR THE SYNTHESIS OF C-GLYCOSIDES

Gary E. Keck,*[,1] Eric J. Enholm, and David F. Kachensky

Department of Chemistry
University of Utah
Salt Lake City, Utah 84112

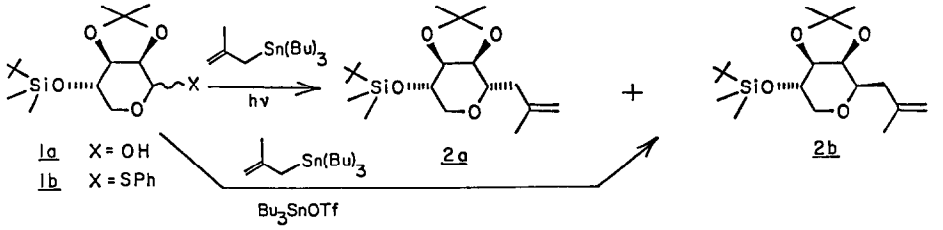
Summary: Thiophenyl glycosides are converted to C-glycosides by reaction with allyl or methallyltri-n-butylstannane using both "one-electron" and "two-electron" procedures, which give different stereoselectivities in some cases.

Recently considerable attention has been focussed on the development of methodology for the synthesis of C-glycosides, particularly C-allyl glycosides[2], due to the potential utility of such materials in the total synthesis of natural products such as the pseudomonic acids[3] and palytoxin.[4] For some time, we have also been engaged in the development of methods to accomplish this task. We record herein two new methods for the synthesis of such C-glycosides.

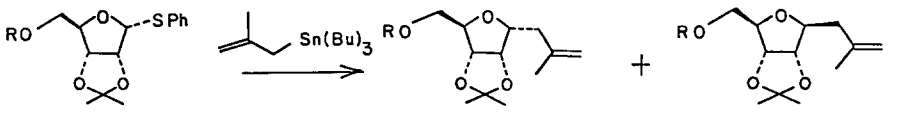
Key to the first version of the process is the somewhat unexpected finding that thiophenyl glycosides are excellent substrates for free radical allylation.[5,6] Conversion of the L-lyxose derivative 1a to thiophenyl glycoside 1b was accomplished in 87% yield by treatment with 2.0 eq each of diphenyldisulfide and tri-n-butylphosphine in methylene chloride at room temperature.[7] Reaction of this material (toluene, 0.3 M in 1b) with methallyltri-n-butylstannane (2.0 eq) using photochemical initiation[5] then gave 2 in 87% isolated yield after column chromatography, as a VPC separable mixture of α and β anomers (2a and 2b) in a ratio of 92:08. The stereochemical assignment was verified by conversion (OsO_4, $NaIO_4$) to the corresponding methyl ketones, which were independently synthesized by reaction of 1a with acetylmethylenetriphenylphosphorane in refluxing acetonitrile.[8] Using allyltri-n-butylstannane an 82% isolated yield of the corresponding allyl derivative was obtained, again with 90:10 selectivity for formation of the α anomer.

Conversion of thiophenyl glycoside 1b to the methallylated products 2 also proved possible utilizing a procedure designed to allow for chemospecific activation of the thiophenyl moiety as a leaving group. Thus, reaction of 1b (toluene solution, ca 1 M in substrate) with methallyltri-n-butylstannane (2.0 eq) in the presence of tri-n-butylstannanyltriflate[9] as catalyst (0.2 eq) at 90°C for 2 h gave 2 in 95% isolated yield. However, using this procedure the β anomer 2b is produced preferentially with extremely high (99:1)

stereoselectivity. Parallel results were obtained for allylation of 1b, which yielded the β anomer with 95:5 selectivity.



In the ribofuranose series, (vide infra) stereoselectivity was found to depend upon the nature of the C_5 substituent. The results are summarized in equation (2) and the Table below.[10]

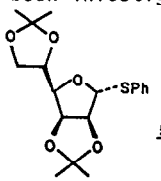


3 4a 4b

Substrate	Method	α/β Ratio (Yield)
3a R = CH_2OCH_2Ph	"One-electron"	-----
3a	"Two-electron	<1:99 (80%)
3b R = Si^tBuMe_2	"One-electron"	40:60 (79%)
3b	"Two-electron"	59:41 (91%)
3c R = $Si^tBu(Ph)_2$	"One-electron"	17:83 (86%)
	"Two-electron"	54:46 (96%)

Application of the free radical procedure with benzyloxymethyl protected substrate 3a was complicated by the production of substantial amounts (ca. 50%) of unidentified by-products, such that product ratios could not be accurately determined in this case. However, the "two-electron" procedure afforded exclusively (within our limits of detection) the β anomer 4b. Careful scrutiny of the reaction product by 300 MHz ^1H NMR, ^{13}C NMR, TLC, HPLC, packed column VPC, and capillary VPC all failed to reveal the presence of the α anomer in this case. Stereochemistry was assigned by oxidative cleavage of the double bond to afford a single ketone, which isomerized upon exposure to base (catalytic $NaOCH_3$ in methanol) to a ca. 5:95 mixture of the original ketone and a new ketone, thus establishing the stereochemistry of the original ketone, and thus its precursor, as β.[11] In contrast, use of either procedure with the the silyl protected derivatives 3b and 3c yields mixtures of products 4a and 4b in the indicated ratios, perhaps because these groups may more effectively screen approach from the β face of the molecule.[12]

These procedures have also been investigated with the mannose and glucose derived substrates 5 and 6 respectively.



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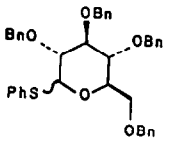

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As expected,[5] the mannose derivative affords the α methallylated derivatives (91% yield) selectively (99:1) using the free radical procedure. Parallel results were also obtained using the stannyltriflate catalyzed procedure which again gave 99:1 selectivity and 90% isolated yield for formation of the α methallyl derivative.[13] Substrate 6, which lacks the steric bias of previous examples, was found to give synthetically useless (ca 1:1) mixtures of anomers using either the "one-electron" or "two-electron" procedures.[14] In this case, where both anomers of the thiphenylglycoside substrate could be isolated by column chromatography, the same mixture of products was obtained using either anomer of starting material as substrate for the reaction.

Finally, it should be noted that the stannyl triflate catalyzed procedure is not limited in application to sugar derivatives; as expected, the process is much more facile in less highly oxygenated systems. For example, α-thiophenylpyran is quantitatively converted to the corresponding allyl derivative within 10 min at 23° using this procedure. This observation suggests that the concept of chemospecific activation of sulfur by stannyl triflates, in the presence of sensitive oxygen functionality, may prove of general utility in synthesis. We are presently exploring this hypothesis.[15]

References and Notes

1. Fellow of the Alfred P. Sloan Foundation, 1981 - 1985.

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6. a) Previous attempts[b] to use simple thioethers as substrates for this reaction were unsuccessful in cases where the corresponding phenylselenides or bromides gave high yields of allylated products. Thus, α alkoxy substitution is critical for the success of this reaction. b) Yates, J. B. Ph.D. Thesis, Univ. of Utah, 1983. c) Such thiophenyl glycosides are far superior to halides or thionocarbonates as substrates for the reactions described herein.

7. The precise origin of this procedure is unclear. Note K. C. Nicolau, S. P. Seitz, D. P. Papahatjis, J. Am. Chem. Soc. **105**, 2430 (1983) and references therein.

8. It is known that the major isomer produced in very similar cases is the α anomer, which isomerizes upon treatment with base to the β anomer.[3a] Oxidative cleavage of 2a affords a 9:1 mixture of ketones which upon base catalyzed (cat. NaOMe, MeOH) equilibration affords a 5:95 mixture of the same ketones, thus establishing the structure of the major C-glycoside as the α anomer.

9. This material was prepared by reaction of tri-n-butyltin chloride with triflic acid. Note M. Schmeisser, P. Sartari, B. Lippsmeir, Chem. Ber. **103**, 868 (1973).

10. a) Similar results were also obtained for allylation reactions using allyltri-n-butylstannane. b) Here "one-electron" refers to the photochemically initiated free radical procedure, while "two-electron" refers to the procedure using Bu_3SnOTf catalysis. c) The thiophenylglycosides 3a-3c were obtained as single anomers tentatively assigned the stereochemistry shown.

11. a) Stereochemical assignments in this series are based on the elegant work of Moffatt and coworkers,[11b] and thus ultimately correlate with x-ray crystallographic structure determination. Note also reference 11c. b) H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Mudder, A. T. Christensen, S. K. Byran, J. Am. Chem. Soc. **97**, 4602 (1975). c) M. C. Clingerman, J. A. Secrist, III, J. Org. Chem. **48**, 3141 (1983).

12. The following observations which may bear on mechanism for the "two electron" procedure have been made; a) No conversion to products is detected if the stannyl triflate is omitted from the reaction; b) Omission of the allyl stannane leads to decomposition of starting material and the formation of unidentified products; c) Exposure of ribose derivative 3c to a catalytic amount of Bu_3SnOTf in toluene at 23°C for 24 h results in the formation of a ca 50:50 mixture of 3c and the β anomer corresponding to 3c. Hence, equilibration of starting materials under the reaction conditions appears possible. Chromatographic isolation of the β anomer followed by reaction according to the same "two electron" protocol utilized for the α anomer provides the same product distribution as obtained using the α anomer as substrate.

13. Assignment of stereochemistry in this case is again based on the work of Moffatt. Note reference 11.

14. Product structures for this case were verified by independent synthesis as described by Kishi.[2b]

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