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C-GLYCOSIDATION OF PYRIDYL THIOGLYCOSIDES

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Summary: The pyridylthioglycosides 1 are efficiently transformed into the corresponding C-glycosides via reaction with silver(I) triflate and a variety of carbon nucleophiles.

The formation of C-C bonds at the anomeric center of carbohydrates has become an increasingly important area in synthetic organic chemistry. In particular, a wide variety of medicinally important C-nucleosides[1] have been discovered as well as several C-glycosyl flavonoids[2] and other naturally occurring C-glycosides.[3] Efficient and stereo-controlled methods for C-glycosidation remains an important synthetic objective, not only for the preparation of naturally occurring C-glycosides, but also for the homologation of carbohydrates to serve as chiral templates for more complex synthetic targets.[4]

As part of an ongoing program in these areas, we wish to report a mild method for the C-glycosidation of pyridyl thioglycosides[5] using Ag(I) activation. This method nicely complements the silyl-based systems of Kishi,[4a] and Kozikowski [4c] as well as the trichloroacetimidate method of Schmidt.[4d]

Reaction of β-2,3,4,6-tetra-O-benzyl-1-(2'-mercaptopyridyl)glucopyranose[6] 1 with silver(I) triflate and several trimethylsilyl enol ethers or electron-rich aromatics at room temperature affords the C-glycosides 2 and 3 (SCHEME I) respectively. Table I provides the yields and other physical data.[7]

It is known from the work of Schuerch[8] that exclusive β-attack in dichloromethane is observed on the 2,3,4,6-tetra-O-benzylglucopyranosyl triflate 8. Our results with 1,3,5-trimethoxy benzene are consistent with these findings. However, under exactly identical conditions, 1,3-dimethoxy benzene gave exclusive α-stereochemistry. On the other hand,if 1 is reacted with 1,3,5-trimethoxy benzene and silver(I)triflate in ether, the α-product becomes the predominant species ($\alpha:\beta = 5:1$). This can be readily explained by the solvent participation in the case of ether to give the stabilized[9] β-oxonium ion (9) which is preferentially attacked from the α-face. Kishi[4a] has observed virtually exclusive α-attack

SCHEME 1

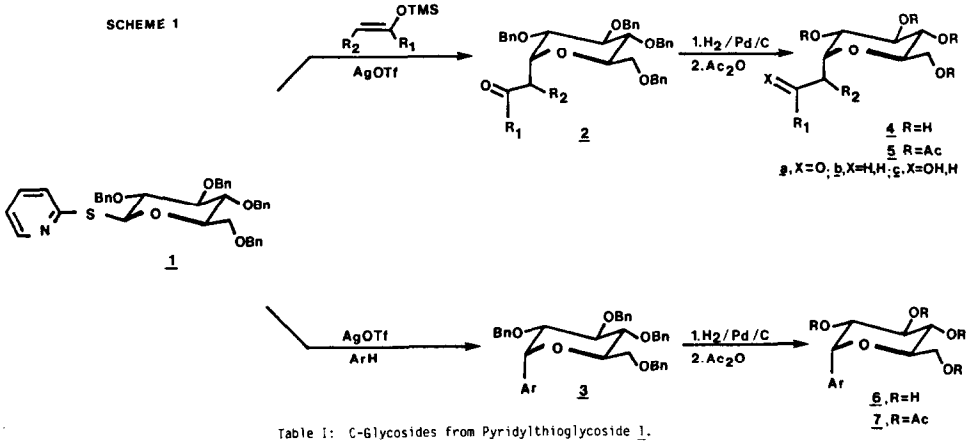
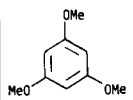
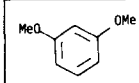
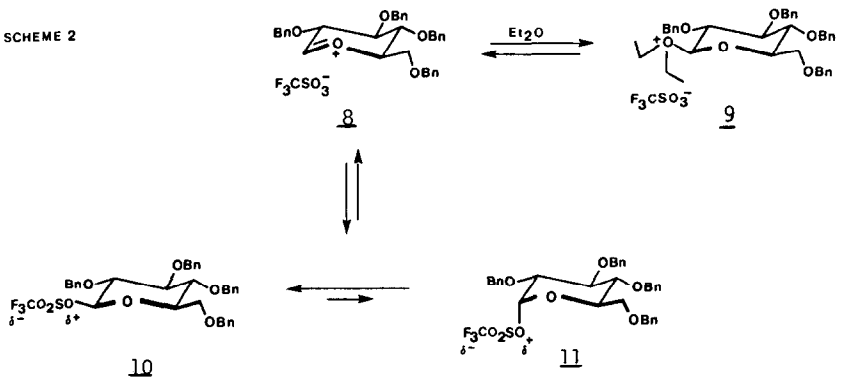


Table I: C-Glycosides from Pyridylthioglycoside 1.

Nucleophile	Yield[a]	$[\alpha]_D^{25}$	Reaction Solvent and Temperature °C	TLC Solvent (silica gel) R_f	Stereochemistry $J_{H_1H_2}$ (360 MHz)
	57%	β, +5.40° ($CHCl_3$) α, +40.0° ($CHCl_3$)	CH_2Cl_2, 25° Et_2O, 0°	0.40 50% Et_2O/Hexanes 0.27 50% Et_2O/Hexanes	7β: δ 5.02(1H, d, J=10.5Hz)[c] α:β (5:1) 7α: δ 6.03(1H, d, J=7.6Hz)[c]
	50%	+22.7° ($CHCl_3$)	CH_2Cl_2, 25°	0.51 50% Et_2O/Hexanes	7:α δ 5.51(1H, d, J=4.14Hz)[c]
	81%	+48.2° (CH_2Cl_2)	CH_2Cl_2, 25°	0.55 50% Et_2O/Hexanes	5b (R_1=Ph, R_2=H) 5bα: δ 5.10(1H, dd, J=5.5Hz)[c]
	62%	β, +28.7° (CH_2Cl_2) α, +42.5° (CH_2Cl_2)	Et_2O[d], 25°	α = 0.37 β = 0.50 50% CCl_4/Et_2O	α:β (3:2) 5a(R_1=O, R_2=-CH_2-CH_2-) δ 4.43(1H, dd, $J_{1,2}$=5.13Hz)[c] 5a(R_1=O, R_2=-CH_2CH_2-) β, δ 4.61(1H, dd, $J_{1,2}$=7.6Hz)
	36%[b]	+29.7 (CH_2Cl_2)[b]	CH_2Cl_2, 25°	0.31 33% EtOAc/Hexanes[b]	5c (R_1,R_2=H) α, δ4.23(1H,ddd $J_{1,2}$=5.6Hz)[b]

a. Yields refer to isolated and purified materials.
b. Obtained on the corresponding tetra-O-benzyl-1-[(2'-hydroxy)ethyl] glucopyranose derivative.
c. Determined on the corresponding per-O-acetylated derivatives 5 and 7.
d. The same result was obtained in CH_2Cl_2.

SCHEME 2



on a related 2,3,4,6-tetra-O-benzylglucopyranosyl substrate in acetonitrile and rationalized the stereochemical outcome in terms of an anomeric effect in the corresponding oxonium ion. However, it is unlikely that a solvent separated oxonium ion pair would be the reactive species in the strongly participating solvent acetonitrile[9]; it would seem more plausible that a stabilized[9] β-nitrilium ion favors the α-attack which is consistent with Schuerchs' results as well as our results in ether. In our case, the stereochemical discrepancy between trimethoxybenzene and the four other nucleophiles examined in dichloromethane may be explained by considering the relative nucleophilicity of these compounds and the possible reactive species present.

It is unlikely that the initially formed Ag^+ complex of β-1 is the reactive intermediate since the highly nucleophilic 1,3,5-trimethoxybenzene would be expected to intercept such a species as readily as the other nucleophiles from the α-face. It is more plausible that in either solvent, reaction of 1 and silver(I)triflate will rapidly produce oxonium ion 8 which can equilibrate with the α- and β-triflates 10 and 11 (Scheme 2). The more electron-rich and reactive nucleophiles (trimethoxybenzene and the TMS enol-ether of γ-butyrolactone) display poorer selectivity. With the less reactive nucleophiles, it is reasonable to assume that the β-triflate 10 and the β-oxonium ion 9 are the predominant reactive species in dichloromethane and ether, respectively; α-attack being the predominant reaction course. Unfortunately, an attempt to assess the role of solvent participation in more polar solvents such as THF or acetonitrile failed to produce the expected products; hydrolysis to the free hemiacetal being the only identifiable products.

A typical experimental procedure is represented as follows: To a stirred, room temperature solution of 1 (78 mg,0.123 mmol, 1.0 equiv) and the TMS enol-ether of acetophenone (118 mg, 0.615 mmol, 5.0 equiv) in dry CH_2Cl_2 (2.5 mL) was added silver(I)triflate (63 mg, 0.246 mmol, 2.0 equiv) in one portion. After stirring the mixture for 30 min, CH_2Cl_2 (5 mL) was added and extractive washing with 0.1 N NaOH followed by drying the organic layer over anhydrous sodium sulfate, filtration, removal of the solvent and chromatographic isolation afforded 64.3 mg (81%) of ketone 2 (R_1= Ph, R_2= H) (chromatographed on silica gel, eluted with 33% ether in hexane) mp 74.5-75°C.

The methodology described herein offers a mild and stereocontrolled means to form carbon-carbon bonds at the anomeric carbon. The range of C-nucleophiles disclosed in this preliminary account provide useful C-homologated substrates that may be manipulated for a variety of synthetic objectives. In particular, the carbonyl addition products afford potential precursors for the synthesis of C-nucleoside antibiotics; investigations along these lines are presently under study in these laboratories.

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References and Footnotes

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6. Compound 1 was conveniently prepared by a different procedure than that described in reference 5. Reaction of 2,3,4,6-tetra-O-benzyl glucopyranose (1.0 equiv) with 2,2'-dipyridyl disulfide (1.3 equiv) and tri-n-butyl phosphine (1.3 equiv) in CH_2Cl_2 at 25°C for 3 hr followed by extractive work-up and chromatography (silica gel, 33% Et_2O in hexanes) affords 1 (69%) as a waxy solid $[\alpha]_D^{25}$ +33.6° ($CHCl_3$) as the β-anomer: ^1H NMR (100 MHz, $CDCl_3$) δ TMS: 3.40-3.86(6H, m); 4.24-5.07(8H, m); 5.43(1h, d, J=9.6 Hz); 6.50-7.60(23H, m); 8.42(1H, m).mp 74-76 C.

7. Satisfactory ^1H NMR, IR, mass spectrum, consistent with the assigned structures was obtained for all new compounds.

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