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A Novel Stereospecific Synthesis of Glycosyl Cyanides from 1,2-*O*-Sulfinyl Derivatives

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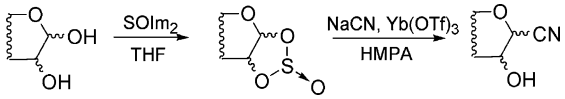
ABSTRACT



An efficient synthesis of 1,2-*trans*-glycosyl cyanides via 1,2-*O*-sulfinyl monosaccharides is described. Such S_N2-type displacements at the anomeric center are stereospecific and are best performed with sodium cyanide in the presence of ytterbium triflate. Significantly, the resulting 1,2-*trans*-glycosyl cyanides have a free hydroxyl group at C-2 ready for further modification.

The stereoselective synthesis of functionalized *C*-glycosides has become an important area of carbohydrate research, as many naturally occurring *C*-glycosides have shown useful antibacterial, antiviral, and antitumor properties.[1] One of the most important types of *C*-glycoside intermediates are glycosyl cyanides, as such compounds can be readily converted to the corresponding C-1 aminomethyl (as glycosidase inhibitor) and carboxylic acid derivatives.[2,3]

In this regard, they have served as important intermediates in the synthesis of a wide variety of sugar derivatives such as *C*-glycosyl α-glycines, cyclopeptides containing a sugar amino acid moiety, *C*-nucleoside derivatives, and *C*-glycoside heterocycles.[4−7]

Generally, the direct cyanation of per-*O*-benzyl-protected electrophilic substrates yields mainly or exclusively the 1,2-*cis* cyanoglycosides.[8]

The corresponding acylated donors, however, give the 1,2-*trans*-glycosyl cyanides.[9]

In previous work, we have shown that *O*-sulfinyl monosaccharide derivatives are useful substrates for stereoselective *N*-glycosylation reactions to form glycosyl azides and 1,2-cyclic carbamates[10,11] and for *O*-glycosylations aimed at obtaining aryl glycosides.[12] Given our past successes with these substrates, we became interested in studying their reactivity toward *C*-nucleophiles, and in this paper, we describe a new procedure for cyanoglycosylation that commences from 1,2-*O*-sulfinylglycose derivatives. We have

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Scheme 1

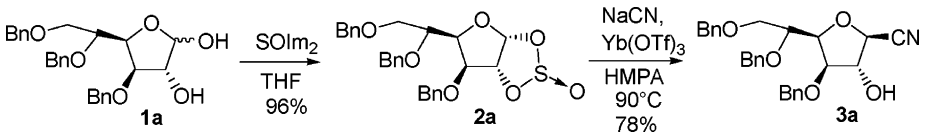


Table 1. OptimizAtion of Cyanation Reaction with Cyclic Sulfite **2a**

solvent[a]	YCN (equiv)	reaction time (h)	% yield
DMF	NaCN (4)	24	26
DMF	NaCN (6)	24	43
DMAC	NaCN (6)	15	46
HMPA/THF (2/8)	NaCN (6)	4	56
HMPA	NaCN (4)	4	55
HMPA	NaCN (6)	4	73
HMPA	TBACN (6)	4	66
HMPA	KCN (6)	4	42
HMPA	NaCN (6) + $Yb(OTf)_3$ (cat.)	2.5	78

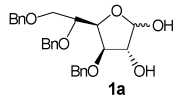
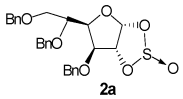
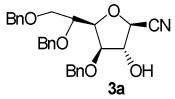
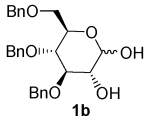
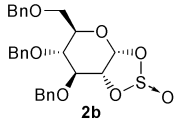
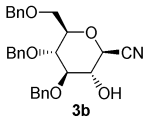
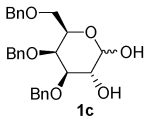
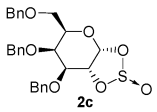
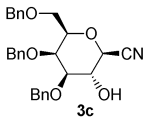
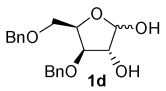
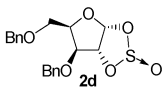
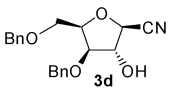
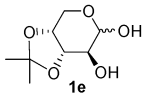
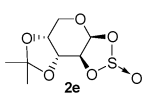
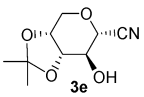
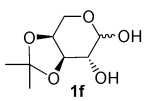
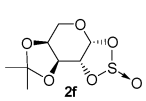
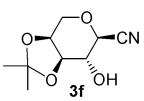
[a] Reaction were stirred at 90 °C under argon atmosphere.

found that this gives glycosyl cyanides with a free hydroxyl group at carbon 2.

To the best of our knowledge, there are only three references relating to the nucleophilic substitution of cyclic sulfites with cyanide anion. The cyclic sulfites derived from glycerol react with NaCN to give the corresponding cyanide derivative, only in the presence of tetrabutylammonium chloride.[13] Likewise, cyanation of the cyclic sulfite of 1-phenyl-1,2-ethanediol with tetraethylammonium cyanide gives the desired 3-hydroxy-3-phenylpropanenitrile in 65% yield.[14] By way of contrast, the reaction of aliphatic cyclic sulfites with NaCN is reported to give the corresponding diols. Also aromatic cyclic sulfites and cyclic sulfite of 1,2-cyclohexanediol fail to react with NaCN under reflux in DMF.[15]

Our cyanation process was first studied with 3,4,6-tri-*O*-benzyl-1,2-*O*-sulfinyl-D-glucofuranose **2a** which was prepared from 3,4,6-tri-*O*-benzylated glucofuranose **1a**,[16] which was derived from diisopropylidene D-glucofuranose (Scheme 1).

Table 2. Cyanosugars Syntheses from 1,2 Cyclic Sulfite Derivatives

Starting Material	Cyclic Sulfite	% Yield	Product	% Yield	δ^a Anomeric Proton	J1,2 (Hz)	δ^b Anomeric Carbon	δ^b Cyano Carbon
 1a	 2a	96	 3a	78	4.48	0	72.8	117.8
 1b	 2b	90	 3b	70	4.02	9.9	69.2	116.7
 1c	 2c	83	 3c	76	4.02	9.9	69.5	116.8
 1d	 2d	97	 3d	70	4.59	0	72.5	117.9
 1e	 2e	82	 3e	79	4.01	9.0	68.2	116.8
 1f	 2f	88	 3f	63	4.11[c]	9.1[c]	68.0[c]	117.0[c]

[a] ^1H NMR chemical shift (ppm) of cyanosugars in $CDCl_3$. [b] ^{13}C NMR chemical shift (ppm) of cyanosugars in $CDCl_3$. [c] ^1H and ^{13}C NMR chemical shift (ppm) of cyanosugars in CD_3OD.

Sulfinylation of the 1,2-diol sugar **1a** was accomplished with *N*,*N*′-thionyldiimidazole.[10] Several sets of cyanation reaction conditions were investigated en route to **1a** (Table 1). Solvents such as DMF or DMAC, classically used in reactions with *O*- or *N*-nucleophiles,[10−12] were found to be less effective for promoting nucleophilic displacement.

The reaction time was typically between 15 and 24 h. The use of HMPA accelerated the nucleophilic opening of the cyclic sulfite, resulting in a shorter reaction time and complete consumption of the starting material in 4 h.

Displacement reactions with TBACN or KCN gave cyanosugars in lower yields compared with NaCN.

Lanthanide(III) triflates have been shown to be useful Lewis acid promoters for the stereoselective *O*-glycosylation of cyclic sulfites.[17] They have also enjoyed extensive application as catalysts in a variety of Lewis acid activated carbon−carbon bond-forming reactions.[18] In each case, the cheap lanthanide triflate, $Yb(OTf)_3$, was chosen.

We observed in this case both an enhanced yield (78%) and a reduced reaction time (2.5 h). This optimized cyanation reaction was applied to five others sugars (Table 2). Starting materials were the sugar 1,2-diols **1b**−**f**. 3,4,6-Tri-*O*-benzyl-D-gluco- and D-galactopyranose **1b** and **1c** were obtained from the corresponding commercial 3,4,6-tri-*O*-acetylglycals following the reaction sequence: deacetylation, benzylation, and dihydroxylation with catalytic osmium tetraoxide in acetone/water.[11b] For the pentose series, 3,5-di-*O*-benzyl-D-xylofuranose **1d** was prepared from diisopropylidene-D-xylofuranose.[16] The 3,4-*O*-isopropylidene-D- and L-arabinopyranoses **1e** and **1f** were selectively synthesized by treatment of D- and L-arabinose, respectively, with 2,2-dimethoxypropane in dry DMF in the presence of a trace of *p*-TsOH.[19]

The 1,2-*O*-sulfinyl sugars **2b**−**f** were prepared from the corresponding 1,2-diols **1b**−**f** as previously described for **1a** (Table 2).

Compared with past literature, the known cyclic sulfites **2d** and **2f**[2] were isolated with the system thionyl chloride−imidazole in high yields. The sulfite derivatives **2a**−**f** were characterized by NMR spectroscopy which showed a mixture of *endo*/*exo* diastereoisomers. Compounds **2b**−**f** were treated with NaCN in the presence of a catalytic $Yb(OTf)_3$ to give the 1,2-*trans* cyanosugars **3b**−**f** in 63−79% yield. The cyanosugars **3a**−**f** were characterized by NMR spectroscopy, which showed the anomeric proton between δ 4.02−4.59 ppm and coupling constants $J_{1,2}$ between 9 and 9.9 Hz for pyranose sugars and $J_{1,2} = 0$ Hz for furanose derivatives, both of which indicated the 1,2-*trans* configuration.

In summary, we have reported a new method for the synthesis of 1,2-*trans*-glycosyl cyanides using 1,2-*O*-sulfinyl sugars as readily available and useful starting materials.

The reactions were shown to be stereospecific, giving only one anomer. Studies with other *C*-nucleophiles are currently under investigation.

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Supporting Information Available: General experimental protocols and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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