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Efficient Synthesis of α-Aldopyranosyl Cyanides via Radical Cyanation Reactions

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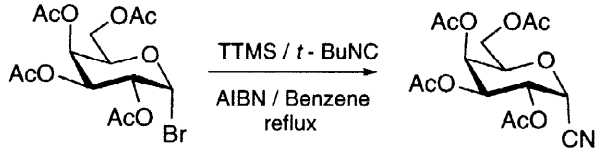
Abstract: α-Aldopyranosylcyanides were efficiently prepared by a radical cyanation reaction between glycosyl bromides or glycosyl dithiocarbonates with *tert*-butylisocyanide, tris(trimethylsilyl)silane and 2, 2'-azoisobutyronitriles.

The C-C bond formation at the anomeric position of a carbohydrate has become an important area in carbohydrate research especially after many naturally occurring C-glycosides have shown antibacterial, antiviral, and antitumor properties.[1-2] The C-glycoside analogs of biologically active carbohydrates[3] have been recognized as potentially stable pharmacophores which could be used to prepare novel enzyme inhibitors[4] with structures that may be difficult or impossible to construct utilizing conventional carbohydrate chemistry. In the synthesis of C-glycosides, glycosyl cyanides are useful and versatile intermediates[5] because the cyano group can be easily transformed into a variety of other functionalities.[6] Early methods for the preparation of glycosyl cyanides involved the reaction of peracylated glycosyl halides with mercury(II)[7] or silver[8] cyanides. The yields and levels of stereochemical control of these reactions vary and by-products such as isocyanides, unsaturated sugars, and 1, 2-*O*-(cyanoalkylidene)glycosyl derivatives could be formed in large percentage. Recently, the use of trimethylsilyl cyanide (TMSCN) as a CN donor along with a Lewis acid has been the most popular method for the cyanation reaction.[6h, 9-11] Other approaches for the preparation of glycosyl cyanides involved the cyanation of fluoroglycosides with Me_2AlCN[12] and the reduction of C-glycopyranosyl nitromethanes[13] with PCl_3 and pyridine. In essence, all the existing methods for the formation of 1-C-cyanoglycosides[14] are based on or related to ionic mechanisms with the electrophilic species derived from the sugar component. Generally, the direct cyanation of per-*O*-benzyl-protected electrophilic substrates yields mainly or exclusively 1,2-*cis* C-cyanoglycosides whereas per-*O*-acylated donors give the corresponding glycosyl cyanides with a high degree of 1,2-*trans* stereoselectivity. We describe here a new method for the stereoselective formation of α-cyanoglycosides through glycosyl radical cyanation. This work represents a new successful application of the Stork method[15] for the cyano group transfer via regiospecific radical trapping of *tert*-butylisocyanide (t-BuNC) promoted by tris(trimethylsilylsilane [TTMS or $(Me_3Si)_3SiH$].[16] Although Somsak, *et al.*[16] studied the radical reduction of 1-bromo-1-cyano glycosides for the preparation of glycosyl cyanide, the direct cyanation at anomeric position via glycosyl radical reaction has not been previously reported.

Scheme 1



Our approach for the preparation of α-per-*O*-acetyl-cyanoglycosides involves the generation of the glycosyl radicals from corresponding glycosyl bromides and subsequent radical trapping with a CN donor, *tert*-butylisocyanide. As depicted in Scheme 1, starting compound 2, 3, 4, 6-tetra-*O*-acetyl-α-D-galactosyl bromide **1a** was reacted with *tert*-butylisocyanide (*t*-BuNC) in the presence of a radical initiating/promoting system of

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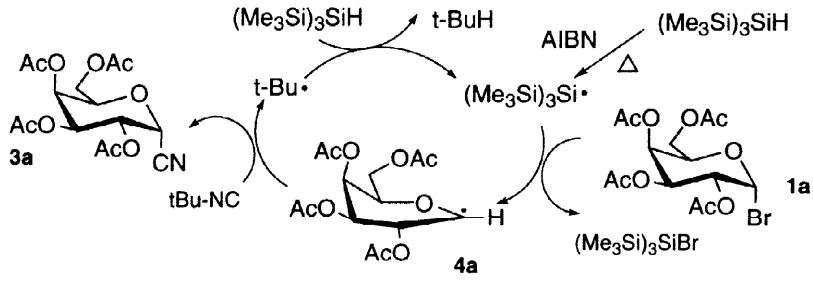
TTMS[17] and 2, 2'-azoisobutyronitriles (AIBN) to afford 2, 3, 4, 6-tetra-*O*-acetyl-α-D-galactosyl cyanide **3a** exclusively in 73% yield.

The suggested mechanism of the reaction is illustrated in Scheme 2. The silyl radical $[(Me_3Si)_3Si^{\bullet}]$[17c] was first generated through the initiation by AIBN leading to the formation of the glycosyl radical **4a** by capturing a bromine atom from the substrate. The glycosyl radical **4a** was then trapped by isocyanide followed by fragmentation yielding a *tert*-butyl radical and the desired glycosylcyanide **3a**. The *tert*-butyl radical then extracted a hydrogen atom from TTMS and regenerated the tris(trimethylsilyl)silyl radical which reacted with another molecule of glycosyl bromide **1a**.

Scheme 2 Mechanism of Galactopyranosyl Radical Cyanation



The same reaction conditions were also applied to other pyranosyl donors including **1b**, **1c**, **1d**, **2a**, and **2e**, which all underwent the cyanation to form corresponding α-glycosyl cyanides exclusively in yields from 22 to 73% (see Table 1).[18]

Table 1. Free radical cyanation of α-pyranosyl bromides

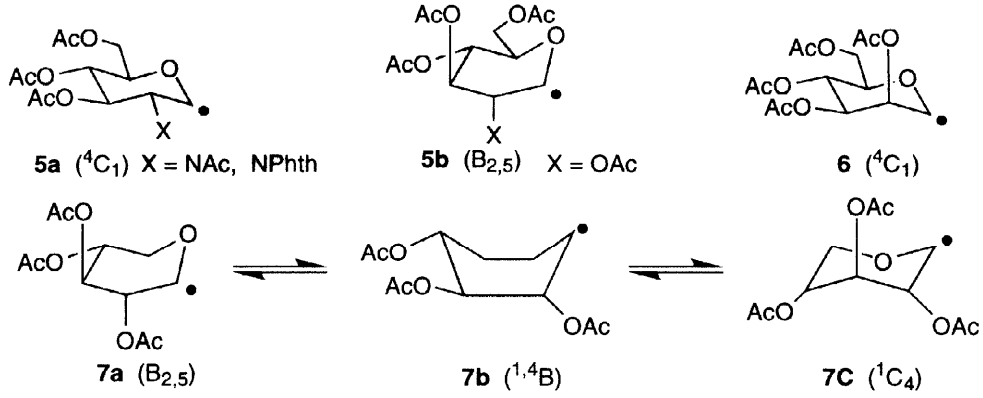
peracetyl sugar	reactant	product[18]	δ 1H	δ CN	Yield[a]
α-D-Gal bromide	**1a**	**3a**	5.17	113.92	73
α-D-Glc bromide	**1b**	**3b**	5.12	113.61	71
α-D-Man bromide	**1c**	**3c**	4.89	113.43	40
α-L-Fuc bromide	**1d**	**3d**	5.10	114.40	25
β-D-Gal dithiocarbonate	**2a**	**3a**	5.17	113.92	66
β-D-Xyl dithiocarbonate	**2e**	**3e**	5.02	113.75	22

[a]Yields are referred to isolated products by flash column chromatography.

The stereoselectivity and the yield variations of the reactions may be explained as the result of the preferred conformation and the stability of the intermediate glycosyl radical caused by stereoelectronic effects according to ESR studies developed by Giese, Sustmann et al.[19] The galactosyl radical **4a** likely exists in a ^4H half-chair coformation (Scheme 2). The glucosyl radical adopt the slightly distroted $B_{2,5}$ boat conformation **5b** (Scheme 3) when the substituent X on 2-C is OR (R = Ac, Me) and the $^4C_1$ chair conformation **5a** with substituent X = D, -OTs.[20] The mannosyl radical **6** retains the parent chair conformation ($^4C_1$) and the xylosylradical is observed as an equilibrium between conformations **7a** ($B_{2,5}$), **7b** ($^{1,4}B$) and **7C** ($^1C_4$). An optimal planar arrangement of the singly occupied *p*-orbital at C-1 (SOMO) with the *p*-type lone pairs at the ring oxygen and the σ*-LUMO of the adjacent 2-C-OR bond provides the maximum electron delocalization. With the conformations **4a, 5b** and **6,** the radical intermediates are more energetically favored and the reactions

proceed to afford the corresponding products (with better yields) through a *trans* attack with respect to the lone electron pair of the anomeric oxygen.

Scheme 3 Glycosyl Conformers



Pyranosides with 2-deoxy-2-nitrogen substituting group such as 3, 4, 6-tri-*O*-acetyl-2-phthaloyl-2-deoxy-α-D-glucopyranosyl bromide, *O*-ethyl-*S*-(3, 4, 6-tri-*O*-acetyl-2-deoxy -2-acetamido-β-D-glucopyranosyl) dithiocarbonate, and *O*-ethyl-*S*-(3, 4, 6-tri-*O*-acetyl-2-deoxy -2-azido-β-*D*-galalactopyranosyl) dithiocarbonate were also inveatigated for the radical cyanation reaction. However, none of them afforded the desired product. The lack of activity of these pyranosides, compared with their peraceylated counterparts, may be attributed to the difference in stereoelectronic effects between 2-N substituents (such as 2-NPhth, 2-NHAc and 2-N_3) and 2-OAc group. Presumably, only the chair conformation **5a** (Scheme 3), which is energetically less favored, is adopted because the stereoelectronic effect does not suffice to compensate for the increase of the steric strain in the chair-boat interchange. The slow cyanation reaction would compete with the CN transfer to tris(trimethyl)silyl radicals, since significant amounts of the by-product $(Me_3Si)_3SiCN$ was observed in such examples.

In summary, a novel and highly stereoselective radical cyanation method for introducing cyano group into anomeric position of carbohydrates has been developed, with which the α-aldopyranosyl cyanide anomers were produced exclusively in reasonable yields. This approach provides a facile alternative route to the synthesis of glycosyl cyanides which are important building blocks for constructing complex C-glycosides.

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18. In a typical experiment, to a refluxing mixture of pyranosyl bromide **1a** (200 mg, 0.49 mmol) or S-xanthate **2a** (220 mg, 0.49 mmol) and tertbutyl isocyanide (0.30 mL, 8 × 0.49 mmol) in argon flushed benzene (6 mL), an argon flushed solution of TTMS (0.30 mL, 2 × 0.49 mmol) and AIBN (12 mg, 0.15 × 0.49 mmol) in benzene (8 mL) was added dropwise over a period of 5h. The reaction mixture was stirred for 4h and then concentrated. The residue was purified by flash column chromatography on silica gel (170-400 mesh) with hexane / ethyl acetate (5/1; v/v) as eluent to give product **3a** (127 mg, 73% from **1a**); (115 mg, 66% from **2a**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.50 (1H, dd, *J* = 1.2, 2.8 Hz), 5.28 (1H, dd, *J* = 2.8, 10.8 Hz), 5.21 (1H, dd, *J* = 5.6, 10.8 Hz), 5.15 (1H, d, *J* = 5.6 Hz), 4.28 (1H, t d, *J* = 1.0, 6.8 Hz), 4.10 (2H, m), 2.12 (2 CH_3, s), 2.04 (CH_3, s), 1.99 (CH_3, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 169.8; 169.8, 169.5, 113.9, 72.5, 68.4, 66.9, 65.8, 65.1, 61.1, 20.5, 20.5. IR (neat): 2255.9 CN; MS (C.I.), m / e: 358 $[M+1]^+$, 331 $[M-CN]^+$, 298 $[M-COOMe]^+$, HRMS: m/e 298.0935, 100%. Data for other products: **2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl cyanide (3b)**: Yield 71 %, ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.45 (1H, t, *J* = 9.9 Hz), 5.13 (1H, d, *J* = 6.3 Hz), 5.08 (1H, t, *J* = 10.2 Hz), 5.03 (1H, dd, *J* = 6.3, 9.9 Hz), 4.31 (1H, dd, *J* = 4.2, 12.6 Hz), 4.16 (1H, dd, *J* = 2.1, 12.6 Hz), 4.00 (1H, ddd, 2.1, 4.2, 9.9 Hz), 2.13 (CH3, s), 2.10 (CH3, s), 2.06 (CH3, s),2.04 (CH3, s); ^{13}C NMR (75 MHz, CDCl3): δ 169.6, 169.4, 113.7, 73.6, 70.6, 67.8, 67.2, 65.1, 61.1, 20.5; MS (C.I.), m / e: 358 $[M+1]^+$, 331 [M–CN]+, 298 [M–COOMe]+, mass exact 298.0923, 100%. **2,3,4,6-Tetra-O-acetyl-α–D-mannopyranosyl cyanide (3c)**: Yield 40 %, ^{1}H NMR (300. MHz, $CDCl_3$): δ 5.42 (1H, dd, *J* = 2.4, 3.3 Hz), 5.35 (1H, dd, *J* = 3.3, 9.9 Hz), 5.29 (1H, t, *J* = 9.6 Hz), 4.89 (1H, d, *J* = 2.4 Hz), 4.32 (1H, dd, *J* = 5.7, 12.6 Hz), 4.14 (1H, dd, *J* = 2.1, 12.6 Hz), 2.12 (2 CH3, s), 2.04 (CH3, s), 1.99 (CH3, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 169.6; 169.5, 113.4, 74.2, 68.8, 68.6, 65.6, 64.9, 61.6, 20.6, 20. 5.; MS (C.I.), m / e: 358 [M+1]+, 331 $[M-CN]^+$, 298 [M–COOMe]+, 100% , mass exact 357.1062.
2,3,4 -Tri-acetyl-α-L-fucopyranosyl cyanide (3d): Yield 25 %, ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.35 (1H, dd, *J* = 1.0, 3.3 Hz), 5.29 (1H, dd, *J* = 2.9, 10.5 Hz), 5.21 (1H, dd, *J* = 5.7, 10.5 Hz), 5.10 (1H, d, *J* = 5.7 Hz), 4.20 (1H, dq, *J* = 6.3 Hz), 2.14 (CH3, s), 2.11 (CH3, s), 2.01 (CH3, s), 1.2 (CH3, d, *J* = 6.3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 170.1, 169.5, 114.4, 70.8, 69.8, 68.8, 65.6, 65.0, 20.5, 16.3; MS (FAB.), m / e: 330 [M+1]+, 322 $[M+Na]^+$.
2,3,4 -Tri-O-acetyl-α-D-xylopyranosyl cyanide (3e): Yield 22 %, ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.40 (1H, dd, *J* = 9.9, 9.3 Hz), 5.01 (1H, d, *J* = 5.7 Hz), 4.95 (1H, dd, *J* = 5.7, 9.3 Hz), 4.94 (1H, td, *J* = 5.4, 9.9Hz), 4.10 (1H, dd, *J* = 5.4, 12 Hz), 3.73 (1H, dd, *J* = 9.6, 12 Hz); 2.12 (CH3, s), 2.05 (CH3, s), 2.05 (CH3, s), ^{13}C NMR (75 MHz, $CDCl_3$): δ 113.8, 69.6, 67.9, 65.5, 64.2, 29.1, 20. 6.
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