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Stereoselective synthesis of α-aminonitriles at non-anomeric positions of monosaccharides

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Abstract

α-Aminonitriles have been stereoselectively introduced at non-anomeric positions of monosaccharides, in which the carbon C-α is one of the atoms of the sugar ring. Target compounds were prepared from various ulose derivatives and amines using titanium(IV) isopropoxide as a mild and effective Lewis acid.

α-Aminonitriles are important starting materials for the synthesis of many aminoacids and heterocycles with biological activities.[1] Moreover, they are readily hydrolyzed to give α-aminocarboxamides or reduced to give 1,2-diamines, which are of interest as ligands for platinum(II) complexes with potential antitumor properties.[2,3] It is envisaged that α-aminonitriles might serve as precursor of new azaspironucleoside analogues of TSAO.[4,5] Also, aminonitriles have been used to synthesize various 4-amino-2,3-dihydroisothiazole-1,1-dioxides via carbanion mediated sulfonamide intramolecular cyclizations (CSIC).[6,7] In contrast, attempts to synthesise 4-amino-2,3-dihydroisothiazole-1,1-dioxides from uloses have not been successful due to difficulties encountered in the preparation of the required aminonitrile precursors.[7]

Optically active α-aminonitriles have been obtained by asymmetric Strecker syntheses.[1,8] Optical induction is effected by chiral and hindered amines such as L-1-phenylethylamine or tetra-*O*-pivaloyl-β-D-galactosamine. In such a reaction enantiomeric excess is solvent dependant.[9] Chiral aminonitriles have been obtained by resolution of racemates corresponding optically active organic acid.[1] More recently, α-aminonitriles have been obtained by the hydrogenation of α-azidonitriles derived from a S_N2 reaction of N_3^- with optically α-methanesulfonyloxynitrile derivatives.[10,11]

We now report the stereoselective synthesis of new α-aminonitriles at non-anomeric positions of monosaccharides, where the C-α is also one of the carbon atoms of the sugar ring.

Treatment of the ulose derivative **1** with KCN, NH_4Cl and either octylamine or benzylamine (Strecker synthesis) (Scheme 1) at room temperature gave the cyanohydrine **2** but no α-aminonitrile

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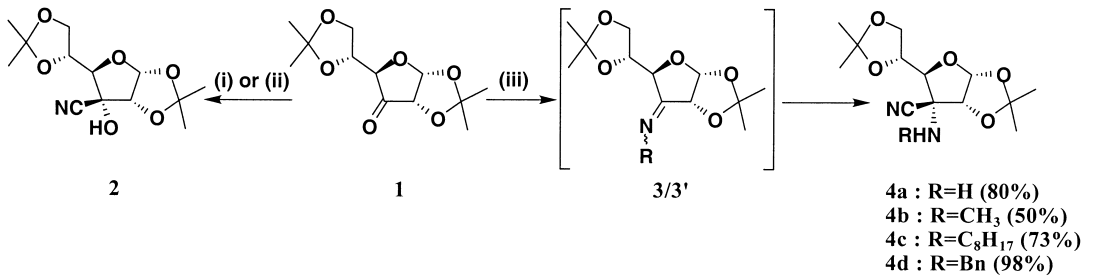
was detected. The same cyanohydrine was also observed, in a similar reaction in which crushed molecular sieve was added. The lack of reactivity could be explained by the following: (i) ketoses are generally more sterically hindered than aldehydes; and (ii) ketose carbonyl carbons are generally less electrophilic than those of aldehydes or α-ketoesters.



Scheme 1. (i) Octylamine or benzylamine, KCN, NH_4Cl, MeOH; (ii) benzylamine, molecular sieves (4 Å), *i*PrOH; (iii) RNH_2, $Ti(OiPr)_4$, MeOH then TMSiCN

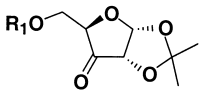
In order to increase the electrophilic character of the ulose carbonyl in **1**, the aminocyanation was performed in the presence of titanium(IV) isopropoxide as the Lewis acid catalyst. This reagent is known to be mild, effective and compatible with a variety of acid-sensitive functional groups such as lactams, *tert*-butyldimethylsilyl ethers or acetonides.[12]

The aminocyanation of the D-glucose derivative **1** was performed by a reaction with NH_3, methylamine, octylamine and benzylamine, respectively. The (*Z*/*E*) imine intermediates **3**/**3′** were not isolated and the cyanating agent TMSiCN was added after 12 h. Under these conditions, the α-aminonitrile derivatives **4a**–**d** were obtained in 50–98% yield.[13]

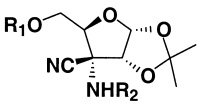
The configuration at the quaternary carbon was determined by both X-ray crystallography and ^1H NMR spectroscopy. In the latter, NOE effects were studied by selective irradiation of the amino proton and inspection of the behaviour of the H-4 signal. These indicated that the diastereoisomer with the (*R*)-configuration at the α-carbon (C-3) was exclusively formed by stereoselective attack of CN^- at the β-face of the sugar ring.

Similarly, uloses of the D-xylose derivatives **5**, **7**, **9**, and the D-fructose derivative **11** stereoselectivally led to the α-aminonitriles **6a**–**d**, **8**, **10** and **12a**,**c** in, respectively, 60–98% yield.[14]

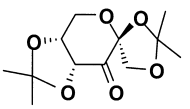
It would appear that the titanium(IV) isopropoxide acts as both a dehydrating agent and Lewis acid to give the imine intermediate. Moreover, this catalyst would seem to be inducing stereoselectivity by chelating with the N-atom of the imine group and the O-atom at C-2; such a complex would hinder the α-face of the sugar ring and give preference for the addition of CN^- at the β-face.



5 : R_1=Tr
7 : R_1= Bn
9 : R_1= Bz



6a : R_1=Tr ; R_2=H (98%)
6b : R_1=Tr ; R_2=CH_3 (60%)
6c : R_1=Tr ; R_2= C_8H_{17} (83%)
6d : R_1=Tr ; R_2=Bn (86%)
8 : R_1=Bn ; R_2=H (70%)
10 : R_1=Bz ; R_2=H (82%)



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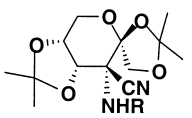
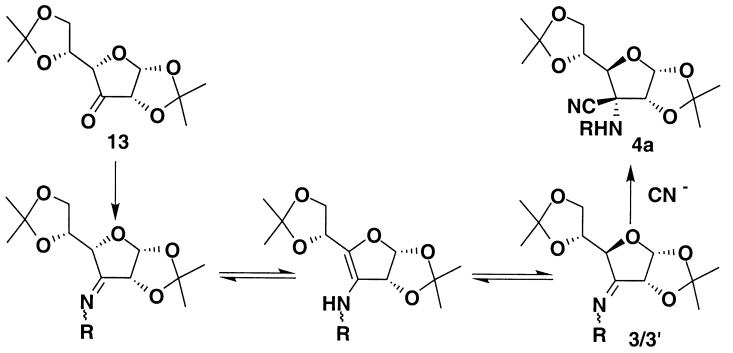


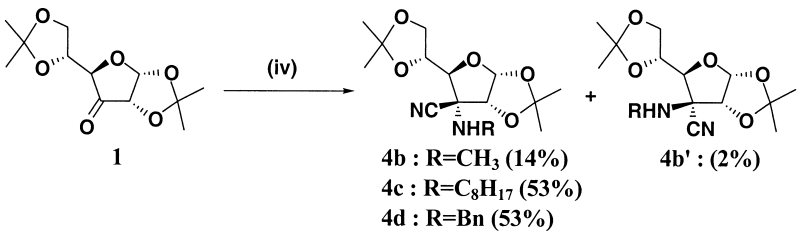
12a : R=H (98%)
12c : R= C_8H_{17} (80%)

The treatment of the D-galactofuranose derivative **13** using the same conditions resulted in inversion at C-4 (Scheme 2) to give the D-glucose α-aminonitrile **4a** in poor yield (12%).



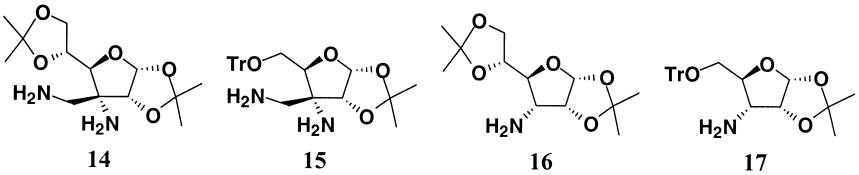
Scheme 2.

With the exception of ammonia, aminocyanations were also achieved using an alternative procedure. The solvent and cyanating agent were added to a stirred mixture of titanium(IV) isopropoxide and amine after complete disappearance of the ketone band in the IR spectrum was observed. This method gave the α-aminonitriles **4c** and **4d** in 53% yield (Scheme 3). A low yield was obtained when **1** was reacted with methylamine to give the α-aminonitriles **4b** and **4′b** (16%). However, the epimeric mixture showed a large excess of the CN β-face form (**4b**:**4′b**, 7:1).



Scheme 3. (iv) $Ti(OiPr)_4$, RNH_2 then TMSiCN

Reduction of the cyano group of the α-aminonitriles **4a** and **6a** with $LiAlH_4$ gave the corresponding 1,2-diamine derivatives **14** (52%) and **15** (66%). The byproducts **16** (12%) and **17** (26%) were also isolated, resulting from base-catalyzed elimination of HCN and subsequent reduction of the corresponding imine.



Work is now underway to explore reaction conditions which might best preserve the nitrile group during the total deacetalation of the α-aminonitrile derivatives.

In conclusion, we have reported a simple and short stereoselective synthesis of α-aminonitriles and 1,2-diamines from monosaccharides, based on the use of titanium(IV) isopropoxide as a mild Lewis acid catalyst. These compounds represent a new class of disubstituted sugar derivatives which are good precursors of various glyco-α-aminoacids, glycopeptides and spiroheterocycles. Such modification leaves the anomeric position free for further derivatization. Such studies are being continued in our laboratory.

Acknowledgements

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13. *Procedure for the preparation of 3-amino-3-* C*-cyano-3-deoxy-1,2:5,6-di-O-isopropylidene-α-*D*-allofuranose* ***4a***: A mixture of **1** (1 g), MeOH–NH_3 (7N, 5.4 mL), Ti(O*i*Pr)$_4$ (1.2 equiv.) and dry MeOH (2.4 mL) was stirred at room temperature. After 5 h, TMSiCN (1 equiv., 0.5 mL) was added and the solution was stirred for 5 h. Water (0.5 mL) and EtOAc were added and the solution was evaporated under reduced pressure. Silica gel column chromatography (eluent hexane:ethyl acetate, 4:1) gave **4a** (0.88 g, 80%) as a solid; m.p. 79–82°C; $[\alpha]_D$ +5 (*c* 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 5.84 (d, 1H, H-1, $J_{1,2}$ = 3.5 Hz), 4.68 (d, 1H, H-2), 4.29 (m, 1H, H-5, $J_{5,6b}$ = 4.5 Hz), 4.10 (dd, 1H, H-6a, $J_{5,6a}$ = 6.0 Hz), 3.92 (dd, 1H, H-6b, $J_{6a,6b}$ = 9.0 Hz), 3.59 (d, 1H, H-4, $J_{4,5}$ = 9.0 Hz), 2.02 (s, 2H, NH_2), 1.49 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.29 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ 118.6 (CN), 113.7 (CH_3CCH_3), 110.1 (CH_3CCH_3), 103.9 (C-1), 83.3 (C-2), 81.6 (C-4), 75.0 (C-5), 67.6 (C-6), 62.7 (C-3), 27.1 (CH_3), 26.8 (CH_3), 26.7 (CH_3), 25.2 (CH_3).
14. *Selected spectroscopic values*: compound **6a**: ^{13}C NMR ($CDCl_3$) δ 143.3 (3C, C *ipso*), 128.6, 128.1, 127.4 (15C, Ph), 118.5 (CN), 113.4 (CH_3CCH_3), 103.9 (C-1), 87.9 (Ph_3C), 83.3 (C-2), 79.9 (C-4), 63.3 (C-5), 62.3 (C-3), 26.5, 26.4 (2C, CH_3); compound **8**: ^{13}C NMR ($CDCl_3$) δ 137.2, 128.5, 127.9 (6C, Ph), 118.5 (CN), 113.5 (CH_3CCH_3), 104.1 (C-1), 83.0 (C-2), 79.7 (C-4), 74.0 ($PhCH_2O$), 69.1 (C-5), 62.4 (C-3), 26.5, 26.3 (2C, CH_3); compound **10**: ^{13}C NMR ($CDCl_3$) δ 166.0 (C=O), 133.3, 129.8, 129.3, 128.4 (6C, Ph), 118.0 (CN), 113.5 (CH_3CCH_3), 104.0 (C-1), 82.9 (C-2), 79.4 (C-4), 62.8 (C-5), 61.1 (C-3), 26.4, 26.2 (2C, CH_3).