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N-(1-Cyano-D-glycosyl)amides – Novel Anomeric α-Amino-acid Derivatives

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Abstract: In the presence of basic silver salts *C*-(1-bromo-1-deoxy-D-glycopyranosyl)formamides and various nitriles applied as solvents give *N*-(1-cyano-D-glycopyranosyl)amides in a highly stereoselective reaction.

Carbohydrate molecules attached to α-amino-acid residues are of crucial importance in nature as constituents of glycopeptides and glycoproteins participating in many biological events.[1] In order to understand and mimic the biological functions of these glycoconjugates containing *O*- and *N*-glycosidic bonds a great variety of unnatural *C*-glycosyl amino-acid derivatives have been synthesised.[1] A unique combination of a sugar and an α-amino-acid arises when the anomeric carbon is the asymmetric center of the amino-acid. Such anomeric α-amino-acids[2,3] as well as their precursors,[4] prepared by various methods, can be useful for the synthesis of new types of glycopeptidomimetics. Expectedly, anomeric α-amino-acid derivatives with a free amino group are prone, similarly to glycosylamines, to anomerization because of their *O,N*-acetal character.[1,2] This feature makes their ensuing reactions more or less inconvenient because of more complex spectroscopic analyses and/or separation procedures. On the contrary, *N*-acylated glycosylamine derivatives[3] are configurationally more stable. Therefore, synthetic methods for the formation of *N*-glycosyl-amides in general,[5a-c] and of anomeric α-amido-acid derivatives in particular,[3b,c,5d] starting from non-anomerisable precursors and excluding glycosylamine intermediates can be advantageous in view of stereoselectivity. Indeed, transformations yielding *N*-glycosyl-amides by omitting the glycosylamine stage generally give a single anomer.[3b,c,5]

Herein we wish to communicate a novel transformation based on a Ritter-type reaction of nitriles with glycosylium ions[6] which produces *N*-acylated anomeric α-amino-acid derivatives from readily available starting materials with high stereoselectivity under very simple conditions.[5d]

The reactions of *C*-(1-bromo-1-deoxy-D-glycopyranosyl)formamides[4d,7] (**1-3**) with silver carbonate, or -fluoride in various nitriles as solvents[8] gave the corresponding *N*-(1-cyano-D-glycopyranosyl)amides **4-12** as the sole products (Scheme, Table 1). The formation of these new compounds can be rationalised by assuming that the reaction is started by the silver ion cleaving the bromide from **1-3** to give 1-aminocarbonyl-glycosylium

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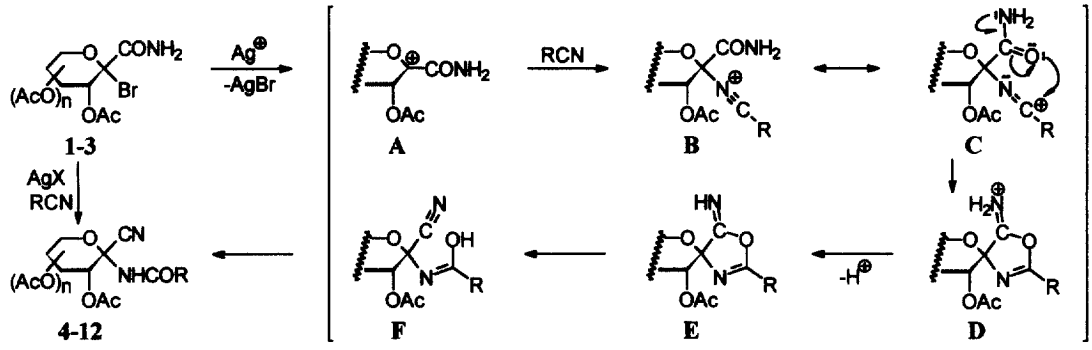
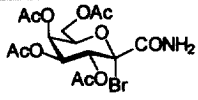
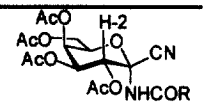
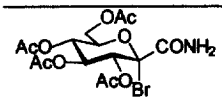
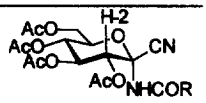
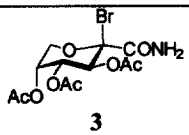
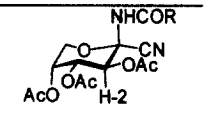
intermediate **A** (Scheme). This destabilised carbocation can capture a nitrile (RCN) to result in the formation of nitrilium ion **B**. Intramolecular nucleophilic attack by the amide oxygen as shown in resonance form **C** furnishes the spirocyclic intermediate **D**. Subsequent deprotonation, presumably by the basic components present in the reaction mixture, gives **E**. A tautomeric ring opening to **F** and a second tautomerization yield then the products **4-12**.



Scheme

Table 1. Preparation[a] of per-*O*-acetylated *N*-(1-cyano-D-glycopyranosyl)amides

Starting compound	AgX	*R*-CN	Isolated yield (%)	$[\alpha]_D^{20}$ (CHCl₃)	Mp (°C)		Product
 **1**	Ag_2CO_3	CH_3	76	+48.7	155-156	**4**	
	AgF	CH_3	70[b]			**4**	
	Ag_2CO_3	CH_3CH_2	74	+55.4	186-187	**5**	
	Ag_2CO_3	CH_2=CH	57	+60.7	158-160	**6**	
	Ag_2CO_3	CH_2=CH-CH_2	62	+57.1	149-150	**7**	
	Ag_2CO_3	CH_3OCH_2	24	+28.9	149-151	**8**	
 **2**	AgF	CH_3	36[b]	+57.3[c]	179-181	**9**	
	Ag_2CO_3	CH_3CH_2	53	+24.6	187-189	**10**	
 **3**	Ag_2CO_3	CH_3	41	-29.5	170-172	**11**	
	Ag_2CO_3	CH_2=CH	43	-28.8	syrup	**12**	

[a] For the experimental procedure see ref. 8. [b] A small amount of the corresponding *C*-(2,3,4,6-tetra-*O*-acetyl-1-deoxy-1-fluoro-α-D-glycopyranosyl)formamide (~3 %) was also isolated. [c] In acetone.

It is remarkable that even in the presence of a participating acetoxy substituent at C-2 the incorporation of the nitrile occurs from the axial direction. Hitherto this orientation has been observed only with 2-O-benzylated sugars[6a,b] while with 2-O-benzoylated derivatives an equatorial attack led to the main product.[6c]

Structure elucidation of the new compounds was straightforward by using NMR methods. Instead of two NH resonances in the starting amides the products **4-12** exhibited a single exchangable proton (δ_{NHCOR} ($CDCl_3$) 6.80-

8.50 ppm) in the ^{1}H NMR spectra. The presence of the CN group was indicated by the characteristic resonances (δ_{CN} ($CDCl_3$) 114-116 ppm) in the ^{13}C NMR spectra. The conformations of the sugar rings ($^4C_1$ for **4-10** and $^1C_4$ for **11** and **12**) were evident from the vicinal proton-proton couplings. The CN ^{13}C-resonances appeared as double doublets in the proton coupled ^{13}C NMR spectra with small values (~3 Hz) for both $^3J_{H\text{-}2,CN}$ and $^3J_{NH,CN}$ couplings. It follows from this that H-2 and CN are in a *gauche* arrangement[4c] in **4-12** in the given ring conformations (Table 1) which proves the anomeric configuration of the new compounds.

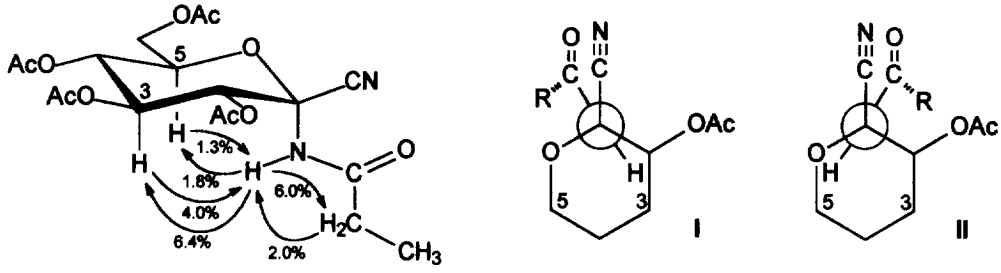


Figure 1. Selected NOE-s measured in **10** and dominant *syn* conformers (**I** and **II**)

The conformational preferences around the C-1–N bond as well as the amide configurations (*E* or *Z*) in *N*-glycosyl amides are of obvious interest[1] and have been studied in detail.[9] All compounds investigated here (**4-12**) display a single set of resonances in their NMR spectra, therefore, *E/Z* isomerism about the (O=)C–N amide bond can be excluded. NOE data shown in Figure 1 clearly establish *Z* configuration for the amide moiety in **10** on the one hand, and the preponderance of *syn* conformers (**I**: synperiplanar N–H and C-1–C-2 bonds; **II**: synperiplanar N–H and C-1–O-5 bonds) around the C-1–N bond on the other. This is also compatible with the small value of the coupling constant between the amide proton and the CN carbon in these compounds. Based on the magnitudes of the NOE-s between the NH proton and H-3 and H-5, respectively, conformation **I** seems to be more populated than **II**; this may be due to lifting of the steric hindrance present in **II** between the amide COR moiety and the *equatorial* 2-OAc substituent, however, a slight *exo*-anomeric stabilization[10] by the interaction of orbitals $n_N \rightarrow \sigma^*_{O\text{-}5\text{-}C\text{-}1}$ cannot be excluded.

In conclusion, we have found a highly stereoselective new reaction for the preparation of novel anomeric α-amino acid derivatives. Scope and limitations of the transformation as well as ensuing reactions of the new compounds are currently being investigated in our laboratory.

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8. *Experimental procedure:* A solution of a compound **1-3** (0.25 mmol) in a nitrile (RCN) (1 mL) was stirred with Ag_2CO_3 (0.25 mmol) in the dark at room temperature for 2-3 days. After dilution with acetone, filtration, and solvent removal the pure products **4-12** were isolated by silica gel column chromatography (eluent: $CHCl_3$–EtOAc 3 : 1). The compounds were crystallised from CH_2Cl_2–Et_2O (EtOAc for **4** and **10**).
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