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Ritter-type reaction of *C*-(1-bromo-1-deoxy-D-glycopyranosyl)formamides and its application for the synthesis of oligopeptides incorporating anomeric α-amino acids

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ABSTRACT

O-Peracetylated or -perbenzoylated *C*-(1-bromo-1-deoxy-D-glycopyranosyl)formamides of D-*gluco*, D-*galacto*, and D-*arabino* configuration were reacted with Ag(I)-salts or HgO in nitrile solvents to give *N*-acyl-1-cyano-D-glycopyranosylamines with an axial C–N bond at the anomeric centre. In the presence of $HgBr_2$, $Hg(CN)_2$, or $InCl_3$ the anomer of the above glycosylamine with an equatorial C–N bond was also isolated or detected. In CH_3NO_2 solutions as few as 5–10 equiv of the nitrile were sufficient to get acceptable yields for the products. Under similar conditions N-substituted *C*-(2,3,4,6-tetra-*O*-acetyl-1-bromo-1-deoxy-β-D-galactopyranosyl)formamides gave anomeric spiro-oxazoline derivatives which, upon mild acidic hydrolysis, opened up to di- and tripeptides of anomeric α-amino acids.

1. Introduction

Ritter-type reactions involve combination of a carbocation (carbenium ion) with a nitrile (generally applied in high excess or as the solvent) to give a nitrilium ion which, after ensuing transformations by nucleophiles, may furnish carboxamides as well as heterocycles.[1,2] Glycosyl-nitrilium ions (**II** formed from glycosylium ions **I** and nitriles, Scheme 1) are known to play important roles in directing the stereoselectivity of glycosylation reactions towards the formation of equatorial glycosides.[3] On the other hand, attack of various external or internal nucleophiles onto glycosyl-nitrilium ions lead to several types of products rendering these transformations highly valuable in the carbohydrate field as well. Protecting groups in the sugar moieties can have a bearing on the configuration of glycosyl-nitrilium ions which tend to be axial (**II**) in the presence of non-participating protective groups demonstrated by NMR and computational methods[4] as well as by the structure of the end-products (vide infra). However, participating protection of the substituent in position 2 may force the formation of equatorial glycosyl-nitrilium ions (**III**). In these cases high equatorial selectivity can be observed in the products but, interestingly, exclusive axial selectivities were also reported in some transformations.

Thus, in the presence of non-participating 2-substituents, axial *N*-glycopyranosylamides were obtained from type **II** intermediates on the action of water,[5] and *N,N*-bis-acylamide products were formed with several aromatic carboxylic acids[6–8] and amino acids[9–11] as external nucleophiles. Carboxylic acids were also used as internal nucleophiles for the synthesis of several anomeric β-amino acid and peptide derivatives.[12–15] Further internal O-nucleophiles, such as a 2-*O*-Zn salt obtained from a 1,2-epoxide[16] and a 2-*O*-benzyl group[17] gave 1,2-annelated oxazolines, while the CH_2OH appendage of heptulopyranose[18] or fructopyranose[19] derivatives furnished spiro-oxazolines, each with an axial C–N bond at the anomeric carbon. 2-*N*-Substituents were also observed to attack the axial glycosyl-nitrilium ion and furnished 1,2-annelated imidazolines.[20,21]

With participating substituents next to the anomeric carbon, the outcome of the reactions is less predictable. With amino acids as well as aromatic carboxylic acids as external nucleophiles 2-deoxy-2-phthalimido[22] and 2-deoxy-2-tetrachlorophthalimido[11] D-glucopyranosyl derivatives gave equatorial *N,N*-bis-acylamide type products. Starting from *O*-perbenzoylated D-glucose, the equatorial amide was formed in low yield accompanied by several by-products in the presence of water as the nucleophile.[23] Under similar conditions *O*-peracetylated D-glucose, D-galactose, and D-mannose each gave mixtures of axial and equatorial amides with a large excess of the latter. To explain this for the D-mannose case, equilibration of the amides was invoked.[24] The internal

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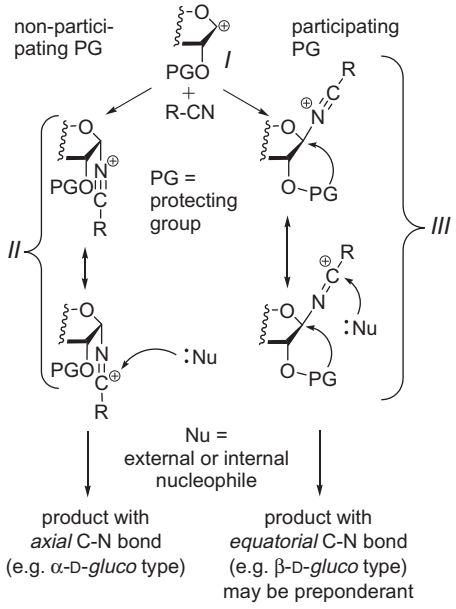


Scheme 1.

nucleophile CH_2OH group of a 3-*O*-benzoyl D-fructopyranose derivative gave only one spiro-oxazoline with an axial C–N bond.[19]

Unprotected sugars were reported to give 1,2-*cis* configured *N*-glycosylamides in liquid HF with both furanoid and pyranoid rings depending on the sugar configuration.[25] D-Glucose was converted to *N*-β-D-glucopyranosylamides with several nitriles in the presence of TMSOTf–$AgClO_4$ under mechanochemical conditions.[26]

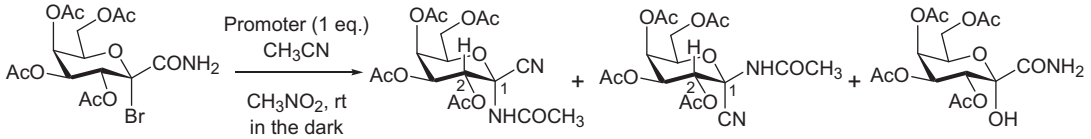
Some years ago we reported on the facile transformation of *C*-(1-bromo-1-deoxy-D-glycopyranosyl)formamides into *N*-acyl-1-cyano-D-glycopyranosylamines in the presence of Ag_2CO_3 in nitriles as solvents.[27] In this paper, a detailed investigation of this reaction and its extension to the synthesis of some oligopeptide derivatives with an anomeric α-amino acid moiety are presented.

2. Results and discussion

A Ritter-type reaction of *C*-(2,3,4,6-tetra-*O*-acetyl-1-bromo-1-deoxy-β-D-galactopyranosyl)formamide[28] (**1**, Table 1, entry 1) was first observed during an attempted exchange of the bromine to fluorine by AgF in dry CH_3CN. Under such conditions, widely applied for the synthesis of glycosyl fluoride derivatives (see Refs. 29–31 and references cited therein), an unexpected product, actually compound **2** was isolated in 70% yield instead of the expected *C*-(2,3,4,6-tetra-*O*-acetyl-1-deoxy-1-fluoro-α-D-galactopyranosyl)-formamide. In the presence of Ag_2CO_3 **1** was transformed to **2** in a very clean reaction (entry 2), while AgOTf gave the same result under significantly shorter reaction time (entry 6). The new product crystallized out during removal of the solvent after the usual work-up, did not exhibit characteristic fluoride couplings, had one exchangeable proton, and five methyl resonances in its ^1H NMR spectrum, and showed a CN signal in the ^{13}C NMR spectrum. Vicinal proton–proton couplings indicated that the sugar ring adopted a $^4C_1$ conformation. The CN resonance appeared as a pseudo triplet in the proton coupled carbon spectrum with ~3 Hz splittings due to couplings with H-2 and the NH protons. This allowed us to deduce the equatorial orientation for the CN group based on the $^3J_{H\text{-}2,CN}$ coupling in the $^4C_1$ conformation.[32–34]

Some other promoters[3] were also tried to perform this transformation. HgO (entry 7) gave similar results to those obtained with silver salts, but in the presence of $HgBr_2$, HgO–$HgBr_2$, $Hg(CN)_2$, and $InCl_3$ (entries 8, 12, 13, and 17, respectively) a second product identified as **3**, the anomer of **2**, was also detected and isolated from the mixtures. Appearance of **4**[35] in the reaction conducted

Table 1
Reaction of *C*-(2,3,4,6-tetra-*O*-acetyl-1-bromo-1-deoxy-β-D-galactopyranosyl)formamide (**1**) with CH_3CN under various conditions



1 **2** **3** **4**

Entry	Promoter	CH_3CN (equiv)	Reaction time	Product ratio (%) by ^1H NMR		
				2	**3**	**4**
1	AgF	As solvent	3 d	70[a,b]	—	—
2	Ag_2CO_3	As solvent	3 d	100	—	—
3		10	5 d	77	—	23
4		5	7 d	68	—	32
5		1.5	12 d	30		55[c]
6	AgOTf	As solvent	1 min	100	—	—
7	HgO	As solvent	8 h	100	—	—
8	$HgBr_2$	As solvent	1 d	72	28	—
9		10	1 d	41	33	26
10		5	1 d	30	25	36[c]
11		1.5	1 d	24	17	46[c]
12	HgO–$HgBr_2$	As solvent	16 h	91	9	—
13	$Hg(CN)_2$	As solvent	1 d	84	8	8
14		10	1 d	63	13	13[c]
15		5	1 d	53	16	21[c]
16		1.5	1 d	52	10	23[c]
17	$InCl_3$	As solvent	1 d	83	17	—
18		10	1 d	59	29	12
19		5	1 d	71	14	15
20		1.5	1 d	35	24	27[c]

[a] Isolated yield.
[b] *C*-(2,3,4,6-Tetra-*O*-acetyl-1-fluoro-α-D-galactopyranosyl)formamide was isolated in ~3% yield from the mother liquor.
[c] Together with an unidentified product in ~10–15% ratio.