Graphical Abstract

Chemoselective hydration of glycosyl cyanides to *C*-glycosyl formamides using ruthenium complexes in aqueous media

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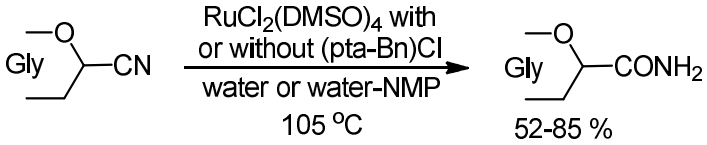

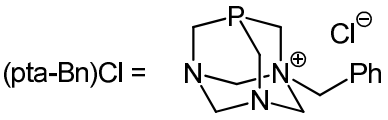

NMP = *N*-methylpyrrolidone

OAc, OBz, OBn protective groups, anomeric Br and N_3 substituents, and double bonds are compatible with the reaction conditions

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Chemoselective hydration of glycosyl cyanides to *C*-glycosyl formamides using ruthenium complexes in aqueous media

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ABSTRACT

$RuCl_2(DMSO)_4$ in the presence of *N*-benzylated 1,3,5-triaza-7-phosphaadamantane efficiently catalyzed the hydration of glycosyl cyanides to the corresponding formamide derivatives in pure water or water–*N*-methylpyrrolidone solvent mixtures at 105 ºC. *O*-Acetyl, *O*-benzoyl, and *O*-benzyl protecting groups, anomeric bromide and azide substituents as well as double bonds proved compatible with these reaction conditions.

C-Glycosyl formamide (anhydro-aldonamide) derivatives are an important class of molecules used in the synthesis of several *C*-glycosylated as well as glycosylidene-spiro-heterocyclic compounds with promising pharmaceutical applications.[1,2] The most straightforward and atom economical approach for the preparation of these compounds is the hydration of glycosyl cyanides (anhydro-aldononitriles). This transformation is conventionally performed using harsh acidic reaction conditions (e.g. HBr-AcOH[3] or $TiCl_4$[4]), involving the requirement of several additional precautionary measures. Therefore, it is quite pertinent to develop a mild, neutral and user friendly reaction to obtain these versatile intermediates.

A large number of reports appeared for the chemoselective hydration of the nitrile group using a variety of reaction conditions.[5] Among several approaches, metal catalyzed reactions attracted special attention due to the fact that metal ions are able to favour the transformation by activating the nitrile centre and water as nucleophile by forming a coordination transition state complex. In this direction, efforts have been made to develop transition metal catalyzed homogeneous[6] and heterogeneous[7] reaction conditions. Besides these, chitosan supported ruthenium catalyst,[8] potassium *tert.*-butoxide mediated hydration,[9] and microwave assisted hydration of nitriles[10] were also studied. Several reports appeared on the use of biocatalysis for this transformation.[11] Recently, hydration of aromatic and aliphatic nitriles under aqueous reaction conditions has been reported from one of our laboratories using a combination of $RuCl_2(DMSO)_4$ complex, a water soluble catalyst and *N*-benzylated 1,3,5-triaza-7-phosphaadamantane (pta-Bn)Cl, as ligand (catalyst: ligand ratio; 1:3).[12]

Taking cue from the earlier report, here we disclose the exploration of the potentiality of this catalyst system for the preparation of *C*-glycosyl formamide derivatives from glycosyl cyanides (Table 1). In a set of initial experiments, to a suspension of *O*-peracetylated β-D-galactopyranosyl cyanide (**1a**; 100 mg) in water (5 mL) was added a combination of $RuCl_2(DMSO)_4$ (10 mol%) and (pta-Bn)Cl, (30 mol%) and the reaction mixture was allowed to stir briskly in an oil bath at 105 °C. A clear solution was obtained after 10 min and clean formation of the *C*-galactosyl formamide derivative **2a** was observed in 85% yield in 2 h. After optimizing the reaction conditions, it was established that the use of a combination of 5 mol% catalyst and 15 mol% ligand in water (4 mL/100 mg of substrate) was sufficient to furnish compound **2a** in 85% yield. Applying the same conditions, other *O*-acetyl protected glycosyl cyanides (**1b,c**) were treated with the catalyst-ligand combination to furnish excellent yields of the corresponding products **2b,c** (Table 1).

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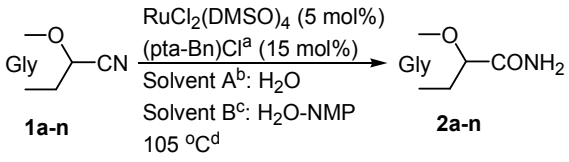
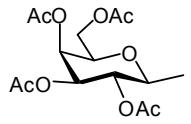
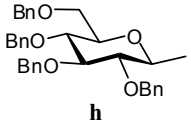
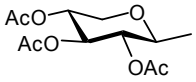
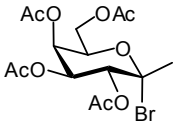
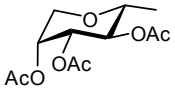
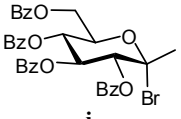
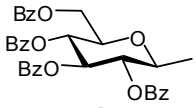
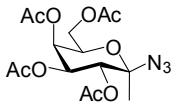
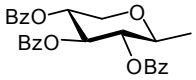
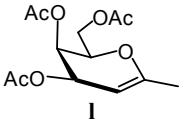
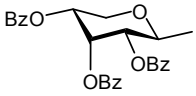
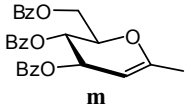
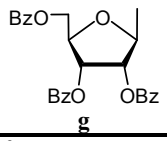
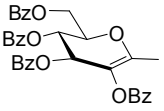
Table 1. Chemoselective hydration of glycosyl cyanides.



Gly	Solvent	Time (h)	**2** (yield[e] %)	Ref.	Gly	Solvent	Time (h)	**2** (yield[e] %)	Ref.
 **a**	A	2	85 (84)[f]	[4]	 **h**	A[g]	55	50	[16]
						B	30	74	
 **b**	A	3	82	[13]	 **i**	A[g]	4	--[h]	--
						B	3	--[h]	
 **c**	A	3	87	-	 **j**	A[g]	60	--	[3b]
						B	48	52[i]	
 **d**	A[g]	60	65	[3b]	 **k**	A[g]	72	--[h]	[17]
	B	20	82			B	8	72[j]	
 **e**	A[g]	50	68	[14]	 **l**	A	2	84	[2h]
	B	5	80						
 **f**	B	4	80	--	 **m**	A	6	80	--
 **g**	B	3	84	[15]	 **n**	A[g]	48	--[h]	--
						B	48	--[h]	

[a] (pta-Bn)Cl: *N*-benzylated 1,3,5-triaza-7-phosphaadamantane; [b] 4 mL/100 mg; [c] *N*-Methyl-2-pyrrolidone (2:1 v/v; 3 mL/100 mg); [d] oil bath temp.; [e] Isolated yield; [f] yield obtained in 2 g scale of the substrate; [g] sodium dodecyl sulphate (SDS, 5 mol%) was added; [h] starting material consumed to produce a complex reaction mixture; [i] starting material was not consumed fully and recovered (20%); [j] the reaction was carried out using $RuCl_2(DMSO)_4$ (15 mol%) in the absence of (pta-Bn)Cl.

When the *O*-perbenzoylated β-D-glucopyranosyl cyanide **1d** was treated with the catalyst combination in water at 105 °C the reaction mixture did not become homogeneous, the compound remained suspended even after 48 h, and TLC indicated no transformation. It was reasoned that the total failure of the reaction could be due to the significantly worse solubility of the *O*-benzoyl derivatives as compared to that of the *O*-acetylated ones. Therefore, sodium dodecyl sulphate (SDS) as a surfactant (5 mol%) was added to the reaction mixture that allowed the formation of the corresponding formamide derivative **2d** in 65% yield in 60 h. Addition of SDS was also beneficial in the cases of **1e** and the *O*-perbenzylated **1h**, which gave the corresponding formamide derivatives **2e** and **2h** in good yields (Table 1).

A further way to improve the solubility of the substrates by adding a co-solvent to the reaction mixture was also tried. Thus, compounds **1d-h** were treated with the catalyst combination in a mixed solvent [water-NMP (*N*-Methyl-2-pyrrolidone) = 2:1 v/v] at 105 °C for appropriate time mentioned in Table 1. The reaction mixtures became clear after 5 min and smooth formation of the corresponding formamide derivatives **2d-h** were achieved in very good yield in significantly shorter time (Table 1).

Next, more complex substrates with bromo (**1i,j**) and azido (**1k**) substituents as well as double bonds (**1l-n**) were studied under the above conditions. Using water as the solvent and SDS (5 mol%) as the additive, compounds **1i-k** produced complex reaction mixtures wherein the expected products could not be detected by TLC. In the water-NMP mixed solvent the *O*-acetylated **1i** gave also a complex mixture, however, the analogous *O*-benzoylated **1j** produced the corresponding formamide **2j** in 52% yield together with some unreacted starting material in 48 h. Since these substrates contain bromo and azido groups in the molecules, which might have cross reactivity with the (pta-Bn)Cl ligand, the reactions were carried out in the absence of (pta-Bn)Cl. However, the bromo-cyanide **1i** produced a complex mixture on treatment with $RuCl_2(DMSO)_4$ (15 mol%) both in water and the mixed solvent. Most gratifyingly the azido-cyanide **1k** furnished the corresponding formamide derivative **2k** in 72% yield in 8 h on treatment with $RuCl_2(DMSO)_4$ (15 mol%)

in the mixed solvent, while in water only the formation of a complex reaction mixture could be observed. It is presumed that the azido and cyano group being adjacent to each other could form a coordination complex with the Ru atom, which could support the hydration of the nitrile. The unsaturated compounds **1l** and **1m** furnished the respective formamides **2l** (84%) and **2m** (80%) in water even without the requirement of the surfactant additive (SDS). The enolester type **1n** did not furnish any expected product under the reaction conditions.

In order to check the role of the ligand in the reaction, compound **1a** was treated with $RuCl_2(DMSO)_4$ (with varied quantities from 5 to 15 mol%) in water as well as mixed solvent in the absence of the ligand, (pta-Bn)Cl. Under these conditions only decomposition of **1a** could be observed in prolonged reaction time in 2 days, while the formation of the expected product **2a** could not even be detcted by TLC.

It is worth mentioning that no trace of the formation of the carboxylic acid (over hydrolyzed by-product) was observed under the reaction conditions. The *C*-glycosyl formamide derivatives were identified by their NMR and mass spectral analysis.[18] The reaction was successfully applied in a scale up preparation of the *C*-glycosyl formamide **2a** (84 % yield in a 2 g batch). In case of compounds **1a-c,l,m** the catalyst combination present in the aqueous phase after work-up of the reaction mixture was recycled up to three times without any significant loss of the catalytic potential.

Typical procedure using water as solvent: To a solution of compound **1a** (100 mg, 0.28 mmol) in water (4 mL) were added $RuCl_2(DMSO)_4$ (7 mg, 0.014 mmol) and (pta-Bn)Cl (12 mg, 0.042 mmol) and the reaction mixture was stirred at 105 °C for 2 h. The mixture was cooled to room temperature and extracted with EtOAc (20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was crystallized from EtOH to give pure **2a** (90 mg, 85%). The aqueous layer was reused for another batch of reaction by adding **1a** (100 mg, 0.28 mmol) and stirring at 105 °C for 2 h to give **2a** (90 mg, 85%). Similar recycling of the catalyst system was applied for the preparation of **2b,c,l,m** to furnish the products as mentioned in Table 1.

Typical procedure using water-NMP as solvent: To a solution of compound **1d** (100 mg, 0.16 mmol) in water-NMP (3 mL; 2:1 v/v) were added $RuCl_2(DMSO)_4$ (4 mg, 0.008 mmol) and (pta-Bn)Cl (7 mg, 0.024 mmol) and the reaction mixture was stirred at 105 °C for 20 h. The mixture was cooled to room temperature, diluted with H_2O (30 mL) and extracted with EtOAc (20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was crystallized from EtOH to give pure **2d** (85 mg, 82%). Similar reaction conditions were applied for the preparation of **2e-h,j,k**.

In summary, efficient chemoselective reaction conditions have been developed for the hydration of glycosyl cyanides to *C*-glycosyl formamide derivatives using a water soluble ruthenium complex in aqueous media. These conditions can be considered as superior practical alternatives to the existing protocols for this transformation because of their environmental compatibility, mild circumstances, operational simplicity, high yields with excellent chemoselectivity, and applicability in the presence of acid and base sensitive functional groups used in carbohydrate derivatization.

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References and notes

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18. Analytical data for the compounds which have not been reported earlier:
Compound 2c: R_f = 0.2 (hexane-EtOAc; 2:3); $[\alpha]_D^{25}$ – 53.1 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.46 (br s, 1 H, N*H*), 6.12 (br s, 1 H, N*H*), 5.40 (t, *J* = 8.0 Hz each, 1 H, H-3), 5.32 (br s, 1 H, H-5), 5.13 (dd, *J* = 11.0, 3.5 Hz, 1 H, H-4), 4.09 (dd, *J* = 12.5, 4.0 Hz, 1 H, H-6_a), 3.84 (d, *J* = 8.0 Hz, 1 H, H-2), 3.77 (dd, *J* = 12.5, 2.5 Hz, 1 h, H-6_b), 2.16, 2.08, 2.02 (3 s, 9 H, 3 COC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1 (*C*ONH$_2$), 169.9 (3 C, 3 *C*OCH$_3$), 76.7 (C-2), 70.7 (C-4), 67.9 (C-5), 67.3 (C-6), 66.8 (C-3), 20.8, 20.7, 20.5 (3 CO*C*H$_3$); ESI-MS: 326.0 $[M+Na]^+$.
Compound 2f: R_f = 0.2 (hexane-EtOAc; 3:2); $[\alpha]_D^{25}$ – 41.4 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.10-7.29 (m, 15 H, Ar-H), 6.47

(br s, 1 H, N*H*), 6.15-6.13 (m, 1 H, H-4), 5.82 (br s, 1 H, N*H*), 5.62 (dd, *J* = 7.8, 2.4 Hz, 1 H, H-3), 5.50-5.45 (m, 1 H, H-5), 4.53 (d, *J* = 7.8 Hz, 1 H, H-2), 4.27 (dd, *J* = 9.3, 4.5 Hz, 1 H, H-6_a), 4.04 (t, *J* = 9.3 Hz each, 1 H, H-6_b); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2 (*C*ONH_2), 165.2, 165.1 (2 C) (3 Ph*C*O), 133.5-128.2 (Ar-C), 73.9 (C-2), 68.7 (C-3), 68.4 (C-4), 67.1 (C-5), 63.8 (C-6); ESI-MS: 512.1 $[M+Na]^+$.

Compound 2m: R_f = 0.18 (hexane-EtOAc; 7:3); $[\alpha]_D^{25}$ − 21.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05-7.38 (m, 15 H, Ar-H), 6.51 (br s, 1 H, N*H*), 6.30 (d, *J* = 2.7 Hz, 1 H, H-3), 6.12 (br s, 1 H, N*H*), 5.91 (ddd, *J* = 4.8, 3.8, 0.9 Hz, 1 H, H-4), 5.81 (dd, *J* = 6.7, 5.3 Hz, 1 H, H-5), 4.85-4.81 (m, 1 H, H-6), 4.78-4.67 (m, 2 H, H-7_{ab}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 165.4, 165.0 (3 Ph*C*O), 162.7 (*C*ONH_2), 146.5 (C-2), 133.6-128.3 (Ar-C), 103.6 (C-3), 75.3 (C-4), 67.3 (C-5), 67.2 (C-6), 61.5 (C-7); ESI-MS: 524.1 $[M+Na]^+$.