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[Chemical reaction diagram]

OAc, OBz, OBn protective groups, anomeric Br and N3 substituents, and double bonds are all compatible with the reaction conditions.
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**ABSTRACT**

[\( \text{RuCl}_2(\text{DMSO})_4 \)] 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 water or water–\( N \)-methylpyrrolidone solvent mixtures at 105 °C. \( O \)-Acetyl, \( O \)-benzoyl, and \( O \)-benzyl protecting groups, anomeric bromide and azide substituents as well as double bonds were shown to be compatible with these reaction conditions.

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C-Glycosyl formamide (anhydro-aldonamide) derivatives are an important class of molecules used in the synthesis of several C-glycosylated and glycosylidene-spiro-heterocyclic compounds which possess promising pharmaceutical applications.\textsuperscript{12} 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\textsuperscript{5} or TiCl\textsubscript{4},\textsuperscript{1b,c}) 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 have appeared regarding chemoselective hydration of the nitrile group using a variety of reaction conditions.\textsuperscript{5} Among several approaches, metal catalyzed reactions have attracted special attention due to the fact that metal ions are able to activate the nitrile group and water as the nucleophile by forming a coordination transition state complex. Efforts have been made to develop transition metal catalyzed homogeneous\textsuperscript{6} and heterogeneous\textsuperscript{7} reaction conditions. Besides these, chitosan supported ruthenium catalyst,\textsuperscript{8} potassium tert-butoxide mediated hydration,\textsuperscript{9} and microwave assisted hydration of nitriles\textsuperscript{10} were also studied. Several reports have also appeared on the use of biocatalysis for this transformation.\textsuperscript{11} Recently, the hydration of aromatic and aliphatic nitriles under aqueous reaction conditions has been reported from one of our laboratories using a combination of a water soluble catalyst, [RuCl\textsubscript{2}(DMSO)\textsubscript{4}], and N-benzylated 1,3,5-triazá-7-phosphaadamantane (pta-Bn)Cl, as a ligand (catalyst:ligand ratio; 1:3).\textsuperscript{12}

Expanding on this earlier report, herein, we disclose the application of this catalyst system for the preparation of C-glycosyl formamide derivatives from glycosyl cyanides (Table 1). Initially a combination of [RuCl\textsubscript{2}(DMSO)\textsubscript{4}] (10 mol%) and (pta-Bn)Cl (30 mol%) were added to a suspension of O-peracetylated β-D-galactopyranosyl cyanide (1a; 100 mg) in water (5 mL) and the reaction mixture stirred vigorously at 105 °C. A clear solution was observed after 10 min, and the C-galactosyl formamide derivative 2a was formed cleanly in 85% yield after 2 h. After optimizing the reaction conditions, it was established that a combination of 5 mol% catalyst and 15 mol% ligand in water (4 mL/100 mg of substrate) was sufficient to obtain compound 2a in 85% yield. Application of the optimized conditions to other O-acetyl protected glycosyl cyanides (1b,c) furnished the corresponding products 2b,c with excellent yields (Table 1).\textsuperscript{13}

![Table 1](image)

**Table 1.** Chemoselective hydration of glycosyl cyanides.
When 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 and the compound remained suspended even after 48 h, with TLC indicating no transformation. It was reasoned that the failure of the reaction could be due to the significantly lower solubility of the O-benzoyl derivatives in comparison to that of the O-acetylated compounds. Therefore, sodium dodecyl sulphate (SDS, 5 mol%) was added to the reaction mixture as a surfactant resulting in the formation of the corresponding formamide derivative 2d in 65% yield after 60 h. Addition of SDS was also beneficial in the cases of 1e and the O-perbenzoylated 1h, which gave the corresponding formamide derivatives 2e and 2h in good yields (Table 1).

An additional method to improve the solubility of the substrates by adding a co-solvent 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. In these cases the reaction mixtures became clear after 5 min and smooth formation of the corresponding formamide derivatives 2d-h was achieved in very good yields and significantly shorter times (Table 1).

Next, more complex substrates with bromo (1i-l) and azido (1k) substituents as well as double bonds (1l-n) were studied under the optimized conditions. Using water as the solvent and SDS (5 mol%) as the additive, the reactions of compounds 1i-k produced complex mixtures from which the expected products could not be detected by TLC. In the mixed water-NMP solvent, O-acetylated 1i also gave a complex mixture, however, the analogous O-perbenzoylated 1j produced the corresponding formamide 2j in 52% yield together with unreacted starting material. Since these substrates contained bromo and azido groups, which might have cross reactivity with the (pta-Bn)Cl ligand, the reactions were then carried out in the absence of (pta-Bn)Cl. However, bromo-cyanide 1i produced a complex mixture upon treatment with [RuCl₃(DMSO)₅] (15 mol%) both in water and the mixed solvent. Although the reaction in water resulted in formation of a complex mixture, gratifyingly azido-cyanide 1k furnished the corresponding formamide derivative 2k in 72% yield after 8 h upon treatment with [RuCl₃(DMSO)₅] (15 mol%) in the mixed solvent. It is presumed that the adjacent azido and cyano groups could form a coordination complex with the Ru atom, which could support the hydration of this nitrile. Unsaturated compounds 1l and 1m furnished the respective formamides 2l (84%) and 2m (80%) in water without the requirement of the surfactant additive (SDS). The enol-ester type 1n did not furnish any of the expected product under the examined reaction conditions.

In order to check the role of the ligand in the reaction, compound 1a was treated with [RuCl₃(DMSO)₅] (varied quantities from 5 to 15 mol%) in water as well as mixed solvent in the absence of the (pta-Bn)Cl ligand. Under these conditions only decomposition of 1a was observed even after a prolonged reaction time of 2 days, while formation of the expected product 2a could not be detected by TLC.

It is worth mentioning that no trace of the corresponding carboxylic acid resulting from over-hydrolysed product was observed under the reaction conditions. The C-glycosyl formamide derivatives were identified by NMR and mass spectral analysis. The reaction was successfully applied in a scaled up preparation of C-glycosyl formamide 2a (84% yield in 2 g batch). In the cases of compounds 1a-c,m the catalyst combination present in the aqueous phase after reaction work-up 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 [RuCl₃(DMSO)₅] (7 mg, 0.014 mmol) and (pta-Bn)Cl (12 mg, 0.042 mmol) and the reaction mixture was stirred at 105 °C (bath temperature) for 2 h. The mixture was cooled to room temperature and extracted with EtOAc (20 mL). The organic layer was dried (Na₂SO₄) 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 [RuCl₃(DMSO)₅] (4 mg, 0.008 mmol)
and (p-tol-Bn)Cl (7 mg, 0.024 mmol) and the reaction mixture was stirred at 105 °C (bath temperature) for 2 h. The mixture was cooled to room temperature, diluted with H₂O (30 mL) and extracted with EtOAc (20 mL). The organic layer was dried (Na₂SO₄) 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 practical alternatives to the existing protocols for this transformation due to their environmental compatibility, mild conditions, operational simplicity, high yields with excellent chemoselectivity, and applicability in the presence of the acid and base sensitive functional groups used in carbohydrate derivatization.

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References and notes


