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Ruthenium catalyzed synthesis of 2,3-unsaturated *C*-glycosides from glycals

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ABSTRACT

A highly efficient and convenient C-glycosylation method was developed using ruthenium(III) chloride for the synthesis of 2,3-unsaturated *C*-glycosides. Various nucleophiles such as allyl trimethylsilane, triethylsilane, trimethylsilyl cyanide, trimethylsilyl azide and heterocycles such as thiophene and furan reacted smoothly with glycals in the presence of catalytic amount of ruthenium trichloride under mild reaction conditions.

1. Introduction

The *C*-glycosides are subject of considerable interest due to the role played by them as versatile chiral synthons and key intermediates for the synthesis of several carbohydrate compounds of biological significance.[1] Significantly, the *C*-glycosides are utilized as valuable intermediates in the synthesis of several natural products such as palytoxin, spongistatin, halichondrin,[2] and various functionalized β-*C*-saccharides.[3] Furthermore, they are employed as powerful synthetic tools for the synthesis of modified carbohydrates and analogs of naturally occurring *C*-nucleosides antibiotics[4] and *C*-linked α(2,3)sialylgalactose lactone.[5] Besides, the *C*-glycosides are more stable to hydrolytic cleavage hence utilized as glycosidase inhibitors and served as potential therapeutic agents for understanding the mechanism of carbohydrate-processing enzymes and other critical cellular processes.[6] Particularly, 2,3-unsaturated *C*-glycosides are attractive due to the presence of 2,3-olefinic moiety in pyran rings, which could be further functionalized into other carbohydrates derivatives and useful chiral molecules by using various complexity generating reactions.[7]

As evident, several reagent systems have been evolved to effect the Ferrier glycosylation of glycals to obtain 2,3-unsaturated *C*-glycosides.[8] Another reported procedure for the synthesis of 2,3-unsaturated *C*-glycosides involves a two step process, Tebbe methylenation and thermal Claisen rearrangement[9a] On the other hand, the scope of Pd-mediated glycosylation[9b,c] has been demonstrated in the stereoselective and regioselective construction of glycosidic linkage via a Pd π-allyl intermediate. However, a combination of Pd-catalyst and phosphine ligand with a sub-stoichiometric amount of diethyl zinc as an additive at high temperature is required for the success of these reactions. In a recent report,[9d] Mukherjee and co-worker developed a highly efficient and reliable catalytic system for the C-glycosylation of glycals with unactivated alkynes using a combination of $Cu(OTf)_2$ and ascorbic acid. Similarly, the Ferrier-type C-alkynylations with silylacetylene[9e] and alkynyltrifluoroborates[9f] compounds have been reported using stoichiometric amount of $BF_3 \cdot OEt_2$. However, the indium-mediated C-alkynylation with iodoalkynes using Barbier reaction required refluxing conditions and excess loading of indium metal and iodoalkyne.[9g]

Over the decade, the palladium-catalyzed Heck reaction has been employed for the syntheses of aryl-*C*-glycosides[10] by cross coupling of glycals with aryl halides,[10b,c] aryl boronic acids,[10d,e] and benzoic acids.[10f] More recently, Liu and co-worker demonstrated the synthesis of aryl-*C*-glycosides by a Pd-catalyzed oxidative Heck cross-coupling of inactivated glycals and aryl hydrazines.[10g] However the Heck type C-glycosylation represent a significant approach of aryl-C-glycosylation, with restricted substrate scope, use for expensive and relatively toxic reagents, wherein less stable and

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moisture sensitive organometallic compounds, use of additives such as strong bases and phosphine ligands,[10b] harsh conditions and tedious work-up remains unsolved issues. Therefore, the development of an efficient and general protocol utilizing nontoxic and environmental friendly reagent system is desirable for the synthesis of *C*-glycosides and carbohydrate intermediates en route to several biologically important sugar molecules.

2. Results and discussion

Recently, we have demonstrated the expeditious synthesis of α-D-mannopyranosides and 2,3-unsaturated O-glycosides from glycal employing ruthenium catalysis.[11b,d] In continuation of our research interest towards developing efficient glycosylation methods,[11] we envisioned that the use of ruthenium(III) chloride as eco-friendly and economical catalyst would be advantage in the carbohydrate chemistry particularly in the *C*-glycosides syntheses. Herein, we report a novel, convenient and efficient method for the C-glycosylation using ruthenium(III) chloride as a versatile and efficient catalyst under mild reaction conditions.

To begin with, the C-glycosylation reactions were optimized using 3,4,6-tri-O-acetyl glucal (**1a**) as the glycal donor and allyl trimethylsilane (**2a**) as the model acceptor in different organic solvents, results are summarized in Table 1. In initial experiments, the C-glycosylation coupling reaction of compound **1a** with **2a** was carried out in the presence of 5 mol % of $RuCl_3$ in dichloromethane at room temperature. Whilst moderate conversion was observed in 8 h, the rate of conversion improved to 80% at 40 °C and the corresponding 4,6-di-O-acetyl-2,3-unsaturated *C*-allylglucoside (**3a**) was obtained in 65% yield with an α/β ratio of 90:10 (Table 1, entry 2). However, no improvement was realized when 1,2-dichloroethane was used as solvent (Table 1, entries 3,4).

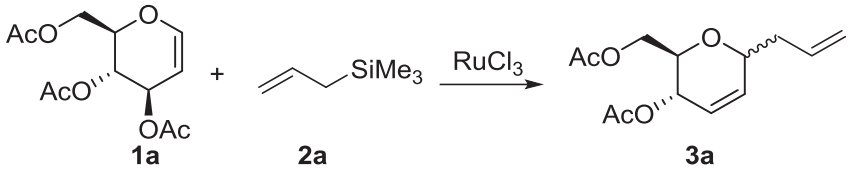
Remarkably, when acetonitrile was employed as the solvent, the reaction proceeded smoothly at room temperature and furnished **3a** in excellent yield (96%) and high selectivity (α:β, 96:4) within 30 min (Table 1, entry 5). On the other hand, solvents such as toluene, THF, diethyl ether could not afford any desired *C*-glycoside. Notably, when the catalytic quantity was further decreased to 2 mol %, reaction was slow and sluggish (Table 1, entries 6,7). Nevertheless, acetonitrile as the solvent in the presence of 5 mol % $RuCl_3$ was found to be optimal requirement for the C-glycosylation of glycals.

The structure and stereochemistry of compound **3a** was established through spectroscopic analysis and correlated with that of literature data.[12a] The ^{1}H NMR spectrum of **3a** revealed the absence of characteristic resonance due to anomeric proton of glucal **1a** at δ 6.47 (d, $J_{1\text{-}2}$=6.2 Hz, 1H), whilst anomeric proton of *C*-glycoside **3a** was observed at δ 4.29 (ddd, *J*=7.7, 5.7, 1.9 Hz, 1H). Furthermore, the ^{13}C spectrum of *C*-glycoside **3a** unambiguously proved the presence of olefinic carbons at δ 133.8, 132.6, 123.5 and 117.4 ppm, whilst all other resonances were in complete agreement with the assigned structure. In addition, compound **3a** gave satisfactory MS/HRMS analysis [HRMS (ESI) *m*/*z* $[M+Na]^+$ calcd for $C_{13}H_{18}O_5Na^+$: 277.10464; found: 277.10428].

Next, we investigated the generality of the current protocol for various silylated *C*-nucleophiles under optimized condition. Accordingly, the C-glycosylation reactions of glycal **1a** with trimethylsilyl cyanide (**2b**) and triethylsilane (**2c**) furnished glycosyl cyanide **3b** and 2,3-unsaturated glycoside **3c**, respectively in excellent yields (Table 2, entry 1,2). Interestingly, the reaction of trimethylsilyl azide (**2d**) as the acceptor with glycal **1a** afforded a mixture of the *C*-3 azido glycal (**3d**) with epimeric ratio of 72:28 and the *C*-1 glycosyl azide (**3d′**) with an α/β ratio of 89:11 (Table 2, entry 3). The anomeric and epimeric ratios were measured by ^{1}H NMR spectroscopy by relative integration of anomeric or separable protons. These results were consistent and with conformity with that of observed by other research groups.[12a,b] The silyl enol ether **2e** worked equally well to obtain the corresponding *C*-glycosides **3e** in 95% yield as stereoisomeric mixture due to prochirality at α-carbon (entry 4). Similarly, the C-glycosylation of β-keto ester **2f** proceeded efficiently to afford the corresponding 2,3-unsaturated *C*-glycoside **3f** in high yield as a stereoisomeric mixture. It is pertinent to mention that the *C*-glycosides such as allyl glycosides, glycosyl azide and glycosyl cyanides offers further synthetic usefulness in the construction of carbon chains into sugar core and the preparation of glycopeptides and glycoconjugates bearing chiral sugar-scaffolds.[13]

Encouraged by these results, we next focused on coupling of heterocycles using present protocol to obtain sugar-heterocycles hybrid *C*-glycosides, since these compounds have significant synthetic utility for the preparation of biologically active molecules with potent antiviral and anticancer activities.[14] Accordingly, the Ferrier C-glycosylation of **1a** with thiophene (**2g**) in the presence of 5 mol % $RuCl_3$ in acetonitrile at ambient temperature resulted the

Table 1
$RuCl_3$ catalyzed C-glycosylation of glycal **1a** with allyl trimethylsilane (**2a**) under various conditions[a]



Entry	Solvent	Time (h)	Temp (°C)	Conv. (%)[b]	Yield (%)[c]	α:β ratio[d]
1	CH_2Cl_2	8	rt	60	—	—
2	CH_2Cl_2	16	40	80	65	90:10
3	$C_2H_4Cl_2$	8	rt	40	—	—
4	$C_2H_4Cl_2$	16	40	80	60	90:10
5	**CH_3CN**	**0.5**	**rt**	**100**	**96**	**96:4**
6[e]	CH_3CN	48	rt	10	—	—
7[e]	CH_3CN	16	40	60	52	96:4

Entry 5 represents the best reaction conditions, shown in bold.
[a] Reaction conditions: Glycal **1a** (1 equiv), allyltrimethylsilane (1.2 equiv) and 5 mol% $RuCl_3$.
[b] Progress of reaction was monitored by TLC analysis at given time, rt=room temperature, n. r.=no reaction.
[c] Isolated yields.
[d] The α/β ratios were based on the relative integration of anomeric or separable protons (^{1}H NMR spectrum).
[e] The reactions were performed with 2 mol % of $RuCl_3$.