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Room Temperature Pd-Catalyzed Synthesis of 1-(Hetero)aryl Selenoglycosides

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Supporting Information Placeholder

ABSTRACT: A general protocol for functionalization of anomeric selenonate anion at room temperature has been reported. By using PdG₃ XantPhos catalyst, the cross-coupling between the *in situ* generated glycosyl selenolate and a broad range of (hetero)aryl and alkenyl iodides furnished a series of functionalized selenoglycosides in excellent yields with a perfect control of the anomeric configuration.

1-selenoglycosides constitute a privileged class of glycosides and are considered as a one of the promising family of glycomimetics with some significant enhanced *in vivo* stabilities. Although it has been less explored in carbohydrate chemistry, they received during the last years an increasing attention due to their versatile biologically significant applications^[1] including ligand based-therapeutics to carbohydrate-binding proteins,^[2] X-ray crystallographic studying of carbohydrate-protein complexes,^[3] and ⁷⁷Se-NMR spectroscopy handles for carbohydrate-protein interactions (compound **1**, Figure 1).^[4] Since the discovery of the first selenoglycoside (**2**) (Figure 1) in rat and human urine as a hepatic Se-metabolite,^[5] the design and synthesis of bioactive selenoglycosides have gained more attention within the chemistry community. Selected biologically active 1-selenoglycosides are represented in Figure 1, including Se-KRN7000 (**3**)^[6] as analogue of the potent immunostimulant α -GalCer (KRN7000), the anti-invasive and anti-metastatic organoselenium glycoconjugate (**4**)^[7] which targets multiple kinases in preclinical models, the di- β -D-galactopyranosyl-diselenide (**5**)^[8] with an antitumoral activity and ligand for lectin and the selenoglycoside AcSG (**6**)^[9] as activator of phosphatases 1 and 2-A, two proteins involved in cancers. From the organic synthesis point of view, selenoglycosides have been investigated as unique glycosyl donors in glycosylation reactions.^[10]

The usual approach employed for the synthesis of selenoglycosides relies on the use of selenium sources in the nucleophilic substitution of 1-halosugars^[11] (Figure 2A) or a nucleophilic opening of the Danishefsky 1, 2-anhydro sugars (Figure 2B).^[12] Azidophenylselenation of glycals,^[13] was also

as an efficient method to prepare selenoglycosides bearing an azido group at

Figure 1. Example of Biologically Active Selenoglycosides

the C2-position. However, selenium nucleophiles such as arylselenols are not commercially available and must be prepared usually from potassium selenocyanate (KSeCN) and arylodonium salts followed by the reduction of the Se-CN bond in the presence of reducing agent such as NaBH₄.^[11e] Another major drawback of this approach is the use of toxic, unstable and unpleasantly smelling arylselenols and diselenides.

Ando, Ishihira and co-workers^[14] developed an elegant method to prepare various alkyl Se-glycosides by an *in situ* generating of an anomeric selenolate anion from β -*p*-methylbenzoylselenoglycoside, which reacts with alkyl halides

(Cl, Br and I) to yield selenoglycosides with retention of the anomeric stereochemistry (Figure 2C). However, this method is limited to only alkyl halides. Only one example for the synthesis

Figure 2. Strategies for the synthesis of selenoglycosides.

of aryl-selenoglycoside was reported by this approach using the highly activated 4-nitro fluorobenzene substrate in a nucleophilic aromatic substitution reaction (SN_{Ar}).

Recently, Walczak and co-workers^[1a] described an original approach (Path D) to the preparation of selenoglycosides based on the coupling of glycosyl stannane with symmetrical diselenide in the presence of 1.5 equiv of CuCl. This method is clearly attractive. However, it necessitates high reaction temperature (110 °C) and requires the use of the toxic alkyltin species in a multi-steps approach to prepare the starting 1-stannylated sugars.

To fully harness the potential of this class of carbohydrates there is a strong impetus to develop mild and general reactions for the synthesis of complex selenoglycosides. As part of our interest to explore the reactivity of sugars under transition-metal catalysis,^[15] combined with the lack of general method to Se-glycosides, we became interested in developing an efficient and simple Pd-catalyzed cross-coupling protocol for the preparation of (hetero)aryl-selenoglycosides which may occur under mild reaction conditions. Catalytic methods generally avoid the use of harsh reaction conditions and maintain the compatibility with most organic functions. However, the use of selenium nucleophilic partners in Pd(0)-cross couplings is highly challenging as they are well known to be poison of the catalyst through the formation of off-cycle complexes.^[16] Herein we report a direct and programmable synthesis of selenoglycosides *via* Pd-G3-XantPhos catalyzed coupling of an *in situ* generated anomeric selenolate-anion with various (hetero)aryl and alkenyl iodides at room temperature.

In the first part of this study, the coupling of tetra-*O*-acetylated β -*p*-methylbenzoylselenoglycoside **1a** (1 equiv) with *p*-iodoanisole **2a** (2 equiv) was used as a model study, and various reaction conditions were examined. Representative results are summarized in Table 1 and the full optimization is reported in SI. The coupling of **1a** with **2a** was first investigated under our previously reported protocol for the coupling of thiosugars^[17] using PdG3-XantPhos precatalyst (10 mol%).

Cs_2CO_3 (3 equiv) and piperazine (1.2 equiv) were added and the

Table 1 Optimization of the Coupling Reaction of **1a** with **2a**^a

entry	base	solvent	Time (h)	3a (%) ^b
1	Cs_2CO_3	THF	12	95
2	Cs_2CO_3	THF	12	81 ^c
3	CsF	THF	2	83
4	NaOAc	THF	2	65
5	Cs_2CO_3	dioxane	2	95
6	Cs_2CO_3	DCE	2	83
7	Cs_2CO_3	DMF	2	89
8	Cs_2CO_3	THF	1	80
9	Cs_2CO_3	THF	2	95

^a A sealable tube was charged with β -*p*-methylbenzoylselenoglycoside **1a** (1 equiv, 0.1 mmol), iodoanisole **2a** (2 equiv), [PdG3-XantPhos precatalyst (10 mol %), piperazine (1.2 equiv), base (3 equiv) in dry and degassed solvent (0.1 M). ^b Yield of isolated product. ^c 5 mol% of PdG3-XantPhos were used.

reaction was performed in THF at room temperature (Table 1, entry 1). By the action of piperazine and Cs_2CO_3 , the β -selenolate anomer anion was readily generated *in situ* (according to the Ando and Ishihira methods,^[14]) and fully converted under our conditions to the β -selenoglycoside **3a** in 95% yield as a single β -anomer ($J_{1,2} = 9$ Hz). Decreasing the catalyst loading from 10 mol% to 5 mol% led to **3a** in a slightly lower yield (81% yield, entry 2). With these encouraging results, we continued the optimization of the reaction conditions with respect to other parameters (base, solvent, reaction time, amount of the reagents). We confirmed that Cs_2CO_3 is the base of choice since the use of CsF or NaOAc produced the desired selenoglycoside **3a** in 83% and 65% yields, respectively. Moreover, performing the cross-coupling in other polar solvents such as dioxane, DCE or DMF produced the desired product **3a** in yields ranging from 83% to 95% (entries 5-7). Finally, performing the reaction for 1 h furnished **3a** in only 80% yield (entry 8), while 95 % yield was obtained when the reaction time adjusted to 2 h (entry 9). A control experiment showed that the PdG3-XantPhos precatalyst was essential for this coupling since no reaction occurred when $Pd(OAc)_2$ (10 mol%) and XantPhos (10 mol%) were used (see SI).

With these results in hand, we investigated the scope for this coupling by varying the nature of the aryl iodide partner **2** and the *p*-methylbenzoylselenyl glycosides **1a-g** (Scheme 1). Pleasantly, this coupling proceeded cleanly in excellent yields. Various electron- rich and electron-deficient aryl iodides having *para*- and *meta*-substitution effectively underwent reaction with β -*p*-methylbenzoylselenoglycoside **1a** in yields up to 99% (products **3a-q**). Interestingly, this coupling tolerates various reactive functional groups such as isopropyl (**3f**), nitrile (**3h**), halogens (**3j**), nitro (**3k**), aldehyde (**3l**), ketone (**3o**) and ester (**3m, n** and **3p, q**). Moreover, the coupling is not limited to aryl halides, but works also with halogenated alkenes such as *E*- β -styryl iodide (compound **3g**). In addition, the reaction of **1a** with heteroaryl halides such as 4-iodopyridine and 5-iodoindole have been performed successfully, furnishing **3r-s** in 87% and 85% yield, respectively. *Ortho*-substituted aryl iodides such as

ortho-methoxyl iodobenzene, *ortho*-cyano iodobenzene and *ortho*-CF₃ iodobenzene were not effective coupling partners

Scheme 1 Scope of Coupling of β -*p*-methylbenzoylselenoglycoside **1a** with Halo(hetero)arenes and Alkenyl Halides **2**

Reaction conditions: A sealable tube was charged with β -*p*-methylbenzoylselenoglycoside **1a** (1 equiv, 0.1 mmol), **2** (2 equiv), PdG3-XantPhos precatalyst (10 mol %), piperazine (1.2 equiv), Cs₂CO₃ (3 equiv) in dry and degassed THF (0.1 M) under Ar for 2 h. ^a Yield of isolated product.

probably due to the hindrance effect, implying that the oxidative addition of aryl iodides to palladacycle is not facile. Finally, this method tolerates other *selenosugars* such selenogalactose, selenofucose and selenocellobiose or OBz-

protected selenoglucose which were successfully coupled with **2a** or **2d** to give β -Se-glycosides **3t-v** in good yields. Besides *p*-

Figure 3. Strategy for the trapping of the *p*-methylbenzoyl group of **1a** by using a double action (electrophilic-nucleophilic) of the partner

methylbenzoylselenyl β -glycosides α -glycoside is also an effective substrate for this methodology giving the desired Se-glycosides **3x** in excellent yield and with exclusive α -selectivity. Of note attempts to react the unprotected selenoglycoside failed: **3y** was never detected and only the degradation of starting materials was observed.

In a next part of this study, we focused our attention on demonstrating whether our cross-coupling could be employed with functionalized aryl iodides bearing a secondary amino group (Figure 3). We may assume that these bis-electrophilic - nucleophilic partners could be involved in two concomitant reactions: at first by a nucleophilic action, the secondary amine such as piperazine, traps the *p*-methylbenzoyl group of the selenoglycoside **1a** and generates the anomeric selenolate anion. Then, this later will react with the electrophilic part (C-I bond) *via* the Pd-catalyzed Se-C(sp²) bond forming reaction. By this way, all the atoms of the reactants will be incorporated into the final desired products, resulting in high atom economy and environmental process which avoid the generation of wastes.

Scheme 2 Scope of Coupling of **1a** with Functionalized Aryl iodides Bearing a Secondary Amino Group **5a-c**

Reaction conditions: A sealable tube was charged with β -*p*-methylbenzoylselenoglycoside **1a** (1 equiv, 0.1 mmol), **5a-c** (1.2 equiv), PdG3-XantPhos precatalyst (10 mol %), Cs₂CO₃ (3 equiv) in

dry and degassed THF (0.1 M) under Ar for 12 h. ^a Yield of isolated product **6a-c**.

As shown in Scheme 2, the proof-of-concept of this green process was demonstrated by coupling of bis-electrophilic-nucleophilic partners **5a-c** with *p*-methylbenzoylselenoglycoside **1a** in the presence of PdG3-XantPhos (10 mol%), Cs₂CO₃ (3 equiv) in THF at room temperature. Under these conditions, the synthesis of phenylpiperazine functionalized selenoglycosides **6a** and **6c** were achieved with 90% and 82% yields, respectively. This finding is of high interest since piperazine is known as one of the most promising ring displaying various biological activities for the treatment of Parkinson's disease, Alzheimer's disease and depression.^[18] In addition, this methodology led to the synthesis of the *N*-benzyl selenoglycoside **6b** in good 95% yield (Scheme 2).

In summary, we have shown that anomeric selenolate anions are competent nucleophilic partners in the Pd-catalyzed cross-coupling reactions. To our best of our knowledge the C(sp²)-Se bond of (hetero)aryl selenoglycosides was formed, for the first time, directly by a Pd-catalyzed cross-coupling of selenosugar with aryl halides at room temperature. Because of the mildness of the reaction conditions, this protocol tolerates a wide range of functional groups and proceeds in good to excellent yields. In addition, a variety of selenosugars could be used. This method opens new opportunities for using glycosyl selenolate in synthetic methodology and medicinal chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, spectroscopic data and NMR spectra of new compounds.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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