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Synthesis of *N*-Glycosyl-2-oxindoles by Pd-Catalyzed N-Arylation of 1-Amidosugars

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ABSTRACT: An efficient intramolecular Pd-catalyzed N-arylation of *o*-iodo-amidosugars for the synthesis of N-glycosylated oxindoles has been reported. The coupling reaction takes place in toluene and involves $Pd(OAc)_2/RuPhos$ catalytic systems in the presence of K₂CO₃. This versatile approach was extended successfully to the synthesis of other N-glycosylated heterocycles.

The 2-oxindole scaffold has attracted considerable attention due to its widespread application in organic synthesis and in the design of pharmaceuticals.¹ This common motif was found in many biologically active compounds with applications in various therapeutic areas.² Of the many drugs developed so far containing a 2-oxindole core, four marketed molecules have emerged (Figure 1A). Sunitinib is used to treat renal cell carcinoma, gastrointestinal stromal, and pancreatic neuroendocrine tumors. Ropinirol is recommended in Parkinson's disease; nintedanib is a medication delivered against idiopathic pulmonary fibrosis, and ziprasidone is used to treat schizophrenia and bipolar disorder. Other 2-oxindole derivatives are also under clinical trials against various diseases.³

The incorporation of a sugar moiety in bioactive molecules may have several benefits such has enhancing their bioavailability,⁴ their solubility,⁵ or their biological activity by targeting, for example, selectively cancer tissues through the Warburg effect.⁶ Such a transformation was achieved in the 2oxindole series, by chemical synthesis,⁷ and recently by biotransformation using *Streptomyces* sp. SANK 60895,⁸ delivering N-glycosylated oxindoles that displayed interesting biological activities. Interestingly, these latter structures were also found in living systems (Figure 1B) as illustrated by compound **A**, extracted from the seeds of *Ziziphus jujuba* var. *spinosa*,⁹ and compound **B**, found in the stems of *Brucea mollis*.¹⁰



Figure 1. Example of biologically active oxindoles.

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Despite the high level of importance of *N*-glycosyl-2oxindoles, direct methods for their synthesis are scarce. To the best of our knowledge, only two methods based on a multistep sequence synthesis are reported. The best known one^{7d} relies on a four-step synthesis (Scheme 1, a) starting

Scheme 1. Strategies for the Synthesis of *N*-Glycosyl Oxindoles



from aniline and glucose, to produce *N*-glycosyl isatines. The extra C3 carbonyl group was used for further functionalization. This method, however, suffers from drawbacks such as low overall yields and difficulties of purification linked to the β/α anomeric composition of the starting materials (\leq 2:1). Another approach to *N*-glycosyl-2-oxindoles involves a six-steps procedur, including N-glycosylation of indoline, oxidation, protection, functionalization, and deprotection. Only one unsubstituted oxindole was reported to be produced via this procedure in 26% overall yield (Scheme 1, b).¹¹

As part of our continuing effort to functionalize sugars under transition metal catalysis,¹² we became interested in developing an efficient and convergent approach to the synthesis of substituted *N*-glycosyl oxindoles. We postulated that these glycosides may be obtained simply through an intramolecular N-arylation of 1-amidosugar using a catalytic amount of palladium (Scheme 1, c). Herein, we report our success in the development of such a protocol.

To determine optimal conditions for the selective intramolecular arylation of 1-amidosugars, (2-iodophenyl)acetamidoglucopyranose [3a (Table 1)] was initially selected Table 1. Optimization of the Coupling Reaction of Tetraacetylated β -Amidoglucose $3a^{a}$



•		•			
1	Pd(dba) ₂ (10 mol %)	DavePhos (10 mol %)	toluene/ MeCN (3:1)	24	trace
2	Pd(dba) ₂ (5 mol %)	SPhos (5 mol %)	toluene/ MeCN (3:1)	12	15
3	Pd(dba) ₂ (10 mol %)	SPhos (10 mol %)	toluene/ MeCN (3:1)	12	20
4	Pd(dba) ₂ (10 mol %)	SPhos (10 mol %)	toluene	3	55
5	Pd(dba) ₂ (10 mol %)	SPhos (20 mol %)	toluene	3	72
6	Pd(dba) ₂ (10 mol %)	RuPhos (20 mol %)	toluene	3	78
7	$\begin{array}{c} Pd(OAc)_2 \\ (10 \text{ mol } \%) \end{array}$	RuPhos (20 mol %)	toluene	3	82
8	Pd(OAc) ₂ (10 mol %)	RuPhos (40 mol %)	toluene	3	90

"A sealable tube was charged with 1-amidoglucose 3a (1 equiv, 0.2 mmol), a Pd precatalyst ($n \mod \%$), a ligand ($x \mod \%$), and K₂CO₃ (2 equiv) in solvent (1.0 mL, 0.015 M). ^bYield of the isolated product.

as a model substrate. This compound was prepared by reacting 2-iodophenylacetic acid (1a) with tetraacetylated 1-amino- β glucopyranose (2a) in the presence of hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl). Under these coupling conditions, compound **3a** was obtained in 67% yield as a β/α mixture in a 20:1 ratio [determined by ¹H NMR, comparing integrations of the two anomeric protons (see the Supporting Information)]. With a subsequent amount of 3a in hand, we turned our attention to examine the intramolecular N-arylation of this substrate. The first tentative compound was produced by using our previously reported Pd-catalyzed conditions¹³ for the synthesis of N-glycosyl quinolin-2-ones $[Pd(OAc)_2 (5 mol \%))$, n-Bu₄NOAc (1.5 equiv), dioxane, 100 °C, 1 h]. However, under these conditions, even traces of 4a were not identified by LC-MS analysis.

Therefore, we turned our attention toward a systematic screening of literature reaction conditions¹⁴ that have proven their efficiency in accomplishing the intramolecular N-arylation of secondary amines or amides (Table 1 and the Supporting Information). Among this series, only conditions using Pd(dba)₂/DavePhos^{14e} (entry 1) provided traces (by LC-MS) of the desired cyclized product, thus establishing the starting point of our optimization process. We next evaluated monophosphine SPhos (entry 2) and the bidentate phosphine ligand [XantPhos (see the Supporting Information)] usually involved in such a pallado-catalyzed coupling reaction to find

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Scheme 2. Scope of the Intramolecular N-Arylation of 1-Amidosugars 3^e



^{*a*}Yield of the isolated product. ^{*b*}The reaction was conducted on a 1 mmol scale. ^{*c*}The β : α ratio was determined by ¹H NMR after purification on flash chromatography. ^{*d*}4k and its precursor 3k were obtained as a racemic mixture with regard to the stereogenic center. ^{*c*}Reaction conditions: 1-amidosugar 3 (0.036–0.1 mmol), Pd(OAc)₂ (10 mol %), RuPhos (40 mol %), K₂CO₃ (2 equiv) in toluene (0.015–0.021 M), 130 °C, 3 h.

that only SPhos (entry 2) could, in toluene and acetonitrile solvents, to afford desired glycoside oxindole 4a in 15% yield as a β/α mixture (20:1 ratio). Doubling the catalyst ratio to 10 mol % (entry 3) allowed a small improvement in the yield (20%), and gratefully, after the polar aprotic acetonitrile solvent had been removed, the yield of the reaction increased to 55% in only 3 h (entry 4). An increase in the Pd:L ratio from 1:1 to 1:2 leads to an improved yield (entry 4, 55% yield, vs entry 5, 72% yield). Shifting from SPhos to a more hindered ligand RuPhos allowed a slight improvement in the yield (entry 6, 78% yield). In addition, performing the reaction with a $Pd(OAc)_2$ precatalyst instead of $Pd(dba)_2$ led to 4a in 82% yield (entry 7). We next succeeded in reaching an excellent yield (90%) by combining 10 mol % Pd(OAc)₂ and 40 mol % RuPhos (entry 8). It can be noted that 4a was isolated in all cases as a mixture of β and α anomers in a 20:1 ratio, indicating that no anomerization occurred during the process. This was confirmed by conducting the intramolecular coupling reaction from a pure β anomer **3a** that led to β -glycosylated oxindole **4a** without traces of the α anomer.

With optimal conditions in hand, the scalability and robustness of this methodology were demonstrated on a 1 mmol scale. As shown in Scheme 2, 4a was obtained in 83% yield when the N-arylation reaction of 3a was conducted on a 1 mmol scale. The scope and limitations of the reaction were then examined with a diversity of substituted 1-amidosugars 3 (Scheme 2). These later compounds were prepared from a readily available carboxylic acids 1 and the appropriate 1-amino- β -sugars. In all cases, the expected β -amidosugars 3 were obtained as the major glycosides contaminated in some cases, by a small amount of the α isomer (see the Supporting Information for the β : α ratios), and this mixture was used for the next step.

We were pleased to note that the coupling conditions were efficient starting from either iodo- or bromo- and chloro-aryl substrates, delivering product 4a in the same yield (90%). Interestingly, in contrast to the iodide substrate 3a (20:1 β : α)

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used, bromide 3a' (20:1 $\beta:\alpha$) or chloride 3a'' (9:1 $\beta:\alpha$) analogues delivered a pure β -N-glycosyl oxindole 4a, although they were used as a mixture of β and α anomers. This result indicates clearly that anomerization occurs during the process when bromide or chloride substrates (3a' or 3a'', respectively)were used. Substrates with electron-donating (3b,c,e,f) and electron-withdrawing (3d,g-i) substituents on various positions of the aromatic ring were also successfully converted into the corresponding N-glycosyl oxindoles in good to excellent vields (<90%). Additionally, the chemoselectivity of this coupling was examined with dihalogenated substrate 3h bearing two different C-X bonds (C-I and C-Cl) at the orth-ortho' positions of the benzene ring. Interestingly, under our optimized conditions, only the C-I reacted delivering the corresponding glycoside 4h in 84% yield and anomeric stereoselectivity $\beta:\alpha$ of 20:1. The presence of an aryl fused ring was also tolerated well as shown with compound 4i. Moreover, the N-glycosyl congested tetracycle 4k was obtained in 84%. In addition, the spiro-oxindole N-glycosylated compound 41 with a cyclopropyl ring at the C3 position was prepared in good 58% yield as a pure β anomer.

The successful synthesis of \hat{N} -glucosides $4\mathbf{a}-\mathbf{l}$ from 1amido-glucose $3\mathbf{a}-\mathbf{l}$ encouraged us to investigate other sugar partners on this coupling. Pleasantly, the coupling reaction was successfully extended to substrates with various peracetylated mono-, di-, and triglycosides $(3\mathbf{m}-\mathbf{p})$. The corresponding oxindoles bearing a mannose $(4\mathbf{m})$, a galactose $(4\mathbf{n})$, a cellobiose $(4\mathbf{o})$, or a maltotriose $(4\mathbf{p})$ were all prepared with excellent yields ($\leq 90\%$) and high stereoselectivity.

Encouraged by these results, we investigated the feasibility of this approach with the aim of synthesizing N-glycosylated sixmembered heterocycles (Scheme 3). In this context, we were





^aYield of the isolated product. ^bThe β : α ratio was determined by ¹H NMR after purification via flash chromatography. ^cReaction conditions: 1-amidosugar **5a**-**c** (0.08–0.11 mmol), Pd(OAc)₂ (10 mol %), RuPhos (40 mol %), K₂CO₃ (2 equiv) in toluene (0.016–0.018 M), 130 °C, 3 h.

pleased to see that substrates 5a and 5b bearing an ether linkage or their thioether congener 5c all reacted successfully under our reaction conditions to furnish N-glycosylated dihydroquinolinone 6a, benzoxazinone 6b, and benzothiazinone 6c in 70%, 68%, and 24% yields, respectively. These results represent the first examples of diversification of this family of N-heterocycle glycosides through this methodology.

With substantial amounts of 4a in hand (Scheme 4), we focused our attention on demonstrating whether our method could be employed for molecular diversity. At first, the unprotected glycoside-indolin-2-one 7a was synthesized by deacetylation of 4a under Zamplen conditions. This N-

Scheme 4. Further Functionalization of 4a and Application to the Synthesis of a Glycosylated Sugen Derivative 9a



"Yield of the isolated product. ^bThe β : α ratio was determined by ¹H NMR after purification via flash chromatography.

glucosyloxindole 7a was thus obtained in a six-step procedure, starting from 1a, in 22% overall yield.

Finally, this methodology was applied to the synthesis of bioactive drug analogues. As shown in Scheme 4, β -N-glucosyl SUGEN derivative 8a, which is an N-glycosylated analogue of semaxanib (SU5416, a tyrosine-kinase inhibitor drug used as a cancer therapeutic), was obtained in 72% yield by post-functionalization of the N-glycosyl oxindole 4a, via condensation with 3,5-dimethyl-1H-pyrrole-2-carbaldehyde. As it was previously described,¹⁵ only the Z isomer of the alkene was observed presumably because of the hydrogen bond formed between the nitrogen of the pyrrole and the carbonyl of the oxindole. The deprotected analogue 9a was further prepared by removal of the acetate groups in the presence of a catalytic amount of potassium carbonate in methanol in 84% yield.

In summary, we succeeded in synthesizing N-glycosylated oxindoles by intramolecular Pd-catalyzed N-arylation of 1amidosugars. This is the first methodology reporting an efficient way to prepare a large variety of substituted N-glycosyl oxindoles. This coupling reaction tolerates various functional groups and sugar moieties. Moreover, this approach was extended to the synthesis of N-glycosylated dihydroquinolinone, benzoxazinone, and benzothiazinone. Finally, because of this methodology, we described for the first time the synthesis of an N-glycosylated SUGEN derivatives and expect to apply this general methodology to other therapeutic compounds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01262.

Experimental procedures, spectroscopic data, and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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