Organic LETTERS

Letter

pubs.acs.org/OrgLett

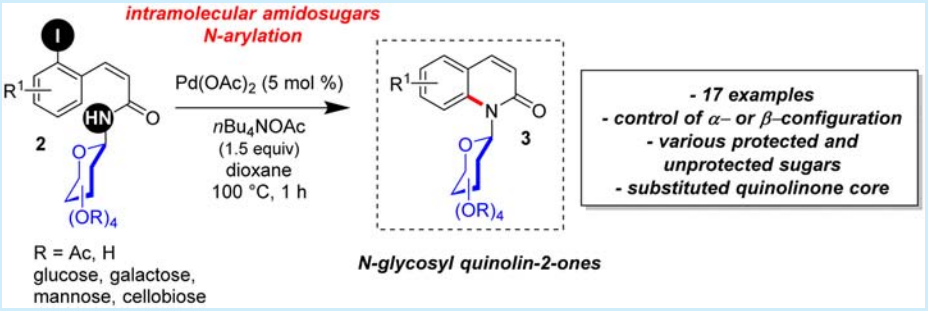
Intramolecular Pd-Catalyzed Arylation of 1-Amidosugars: A New Route to *N*-Glycosyl Quinolin-2-ones

Thi Thanh Huyen Luong,[†] Jean-Daniel Brion,[†] Ewen Lescop,[‡] Mouad Alami,*[,†] and Samir Messaoudi*[,†]

[†]BioCIS, Univ. Paris-Sud, CNRS, University Paris-Saclay, Châtenay-Malabry, France

[‡]Institut de Chimie des Substances Naturelles ICSN-CNRS, Gif-sur-Yvette, France

Supporting Information

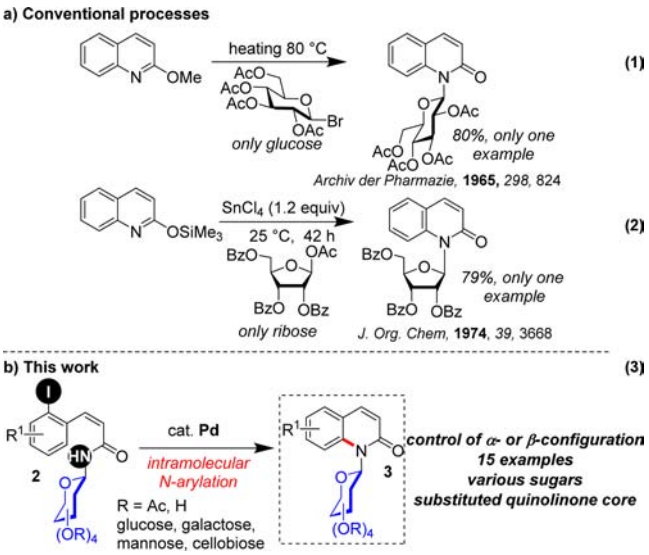


ABSTRACT: The synthesis of *N*-glycosylated quinolin-2-ones via an intramolecular *N*-arylation of glycosylamides is reported. The coupling involves the use of only $Pd(OAc)_2$ as the catalyst and nBu_4NOAc as the base in 1,4-dioxane. This versatile approach allows the synthesis of various *N*-glycosylated quinolin-2-ones with exclusive α or β selectivity.

The 1-aminosugar moiety is a privileged unit in pharmaceutical science[1] due to its unique properties. This group has been increasingly used to address many of the issues that are commonly encountered in the process of drug discovery and optimization such as ADMET parameters.[2] The attachment of glycosyl units to a biologically active quinolin-2-one core[3] can cause several changes in its features, including its chemical, physical, and biochemical properties such as oral absorption and bioavailability.[2] While *N*-glycosylated quinolin-2-one derivatives **3** are of wide interest, their synthesis has been problematic due to the difficulty in stereoselectively introducing a nitrogen scaffold at the anomeric position of the sugar moiety.[4] Only two reports have dealt with the synthesis of these target compounds, and both have involved the same basic strategy. Mustafa et al.[5] have described, as a single example, the use of 2-methoxyquinoline as aglycon and tetra-*O*-acetyl-α-D-glucopyranosyl bromide as the glycosyl donor (Scheme 1, eq 1). In a similar approach, Niedballa et al.[6] have disclosed a single example of the conversion of trimethylsilyloxy quinolin-2-one into the corresponding glycosyl quinolin-2-one, in the presence of a glycosyl donor and tin tetrachloride (Scheme 1, eq 2). However, both methods are limited in substrate scope with respect to the quinolinone partner and the sugar unit.

As part of our continuing effort in the functionalization of heterocycles via metal-catalyzed reactions,[7] combined with our interest in functionalizing sugars under transition-metal catalysis,[8] we report herein that *N*-glycosyl quinolin-2-ones **3** can be synthesized efficiently and stereoselectively via the intramolecular *N*-arylation of 1-amidosugars using a catalytic amount of $Pd(OAc)_2$ (Scheme 1, eq 3).

Scheme 1. Synthesis of *N*-Glycosyl Quinolin-2-ones

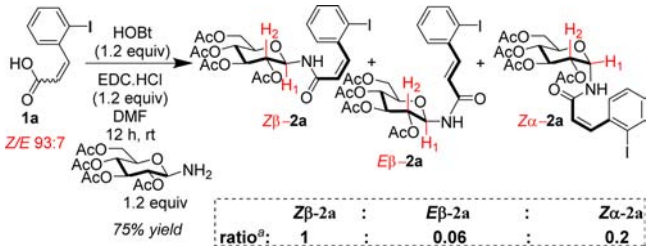


To establish appropriate conditions for the selective intramolecular arylation of 1-amidosugars of type **2** (Scheme 1), (2-iodophenyl)acrylamidoglycopyranose **2a** was initially selected as the model substrate (Scheme 2). This compound **2a** was prepared by coupling the acrylic acid **1a** as a mixture of isomers (Z/E = 93:7) with the tetraacetylated 1-amino-β-

Received: March 15, 2016
Published: April 13, 2016

DOI: 10.1021/acs.orglett.6b00752
Org. Lett. 2016, 18, 2126–2129

Scheme 2. Synthesis of the Model Substrate 2-Iodophenyl)acrylamidoglycopyranose 2a

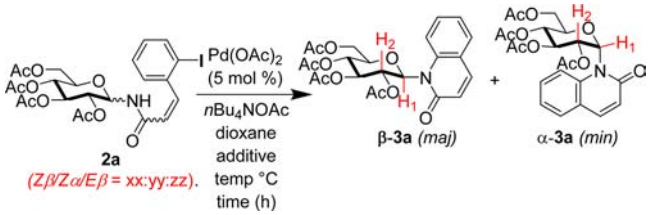


[a]Isomer ratios were measured by integration of well-resolved signals in the 300 MHz 1H NMR ($CDCl_3$).

glycopyranose employing Xu's conditions[9] (Scheme 2). In contrast to Xu's results, the expected coupling product (*Zβ*)-**2a** was isolated together with two other byproducts in 75% yield (Scheme 2). After a tedious separation, 1D- and 2D-NMR analysis revealed that these byproducts corresponded to the (*Eβ*)-**2a** and (*Zα*)-**2a**-isomers. The final ratio between the three isomers *Zβ*/*Zα*/*Eβ* was 1:0.2:0.06 (see Supporting Information) (Scheme 2).

Next, we continued our study by exploring the feasibility of the intramolecular key step C(sp^2)−N bond formation of the 1-amidosugar *Zβ*-**2a** contaminated with a small amount of its *Eβ*- and *Zα*-isomers (*Zβ*/*Zα*/*Eβ* = 1:0.2:0.06). To our surprise, heating the mixture in the presence of $Pd(OAc)_2$ (5 mol %), tetrabutylammonium acetate (3 equiv) as the base, and tetrabutylammonium bromide (3 equiv) in dioxane at 130 °C for 4 h led to *N*-*β*-glycosyl quinolin-2-one *β*-**3a** ($J_{1,2}$ = 9.9 Hz) in 63% yield (entry 1, Table 1) together with its anomer *α*-**3a** derived from this cyclization of (*Zα*)-**2a**. Further optimization revealed that stirring the reaction for only 30 min under otherwise the same conditions led to a mixture of the desired products *β*-**3a** and *α*-**3a** in an 85:15 ratio and the same yield for the isolated *β*-**3a** (62%, entry 2). The screening reaction was optimized with respect to the amount of the base. The use of 1.5 equiv of *n*-Bu_4NOAc was found to be sufficient, giving rise to *β*-**3a** in a good 62% yield (compare entries 2 and 4, 5). Pleasingly, the yield of *β*-**3a** improved to 69% by omitting TBAB as an additive (entry 6). In the next set of experiments, pure (2-iodophenyl)-*Z*-acrylamide-*β*-glycopyranose (*Zβ*)-**2a** was used as starting material. Under the optimal conditions, *N*-glycosyl quinolin-2-one *β*-**3a** was formed in 76% yield as a single *β*-isomer without any anomerization (entry 7). This result suggested that *α*-**3a** was formed from (*Zα*)-**2a**. To clarify this hypothesis, the coupling of pure (*Zα*)-**2a** was further investigated under the optimized conditions. Accordingly, only *α*-**3a** was isolated as a single anomer, and the coupling constant between H_1 and H_2 ($J_{1,2}$ = 6.3 Hz) reflected the *α*-glycosides structure (entry 8; see Supporting Information). Moreover, to verify the hypothesis that the (*Eβ*)-**2a** isomer does not react or isomerize into the more reactive (*Zβ*)-**2a**, we carried out the reaction with the pure (*Eβ*)-**2a** isomer. Under the optimized conditions, no reaction occurred and the formation of compound **3a** was never detected (entry 9). Of note, performing the reaction using the (2-bromophenyl)acrylamidoglycopyranose instead of the iodinated derivative **2a** furnished the desired product **3a** in 46% yield; however, the same reaction with the (2-chlorophenyl)acrylamidoglycopyranose failed.

Table 1. Survey of Reaction Conditions for the Intramolecular *N*-Arylation of Tetraacetyl *β*-Amidoglucose 2a[a]



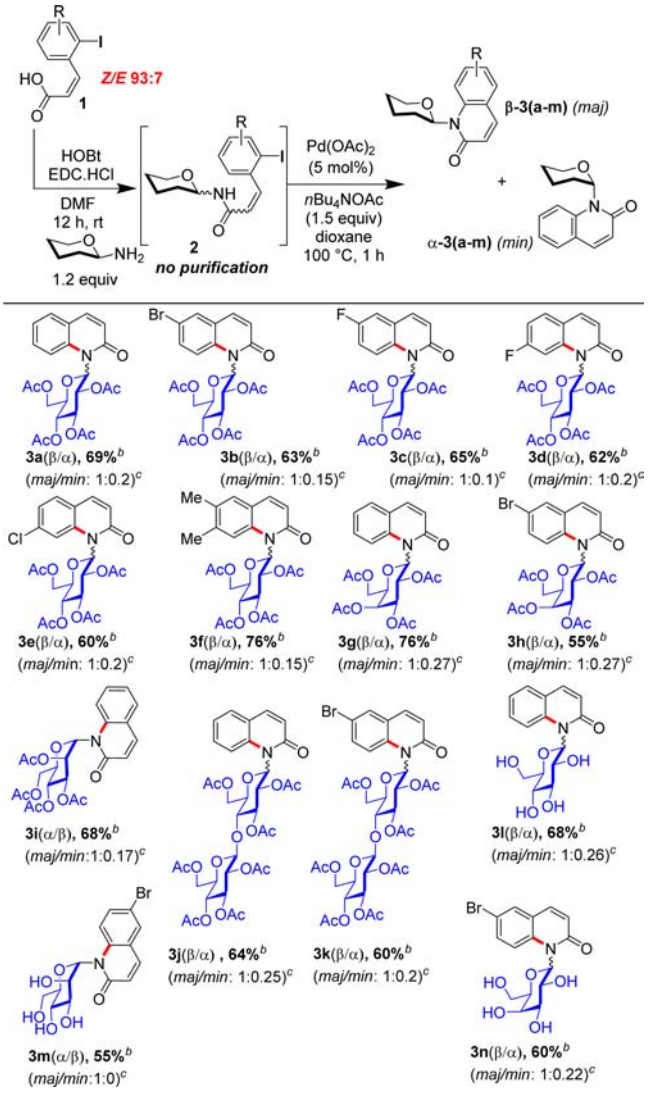
entry	ratio of **2a** *Zβ*/*Zα*/*Eβ*	temp (°C)	*t* (h)	additive[b]	ratio *β*-**3a**/*α*-**3a**[c]	yield of *β*-**3a**(%)[d]
1	1:0.2:0.06	130	4	TBAB	85:15	63
2	1:0.2:0.06	130	0.5	TBAB	85:15	62
3	1:0.2:0.06	130	0.25	TBAB	–	–[e]
4	1:0.2:0.06	130	0.5	TBAB	85:15	63[f]
5	1:0.2:0.06	130	0.5	TBAB	85:15	62[g]
6	**1:0.2:0.06**	**100**	**1**	–	**85:15**	**69**
7	1:0:0	100	1	–	100:0	76
8	0:1:0	100	1	–	0:100	72[h]
9	0:0:1	100	1	–	–	00

[a]**2a** (1 equiv), $Pd(OAc)_2$ (5 mol %), base (3 equiv), additive (3 equiv), anhydrous dioxane (0.1 M). [b]TBAB = *n*Bu_4NBr (tetrabutylamonium bromide). [c]Ratio was determined by ^1H NMR in the crude reaction mixture based on the chemical shift (ppm) of the proton signal H2 for *β*-**3a** (*δ* = 5.90) and H3 for *α*-**3a** (*δ* = 6.15). [d]Yield of isolated *β*-**3a**. [e]Only 25% of conversion of **2a**. [f]2 equiv of base were used. [g]1.5 equiv of base were used. [h]Yield of isolated *α*-**3a**.

With this encouraging result in hand, we next turned our attention to examining the scope and limitations of the coupling reaction of various *β*- or *α*-substituted (2-iodophenyl)-*Z*-acrylamidosugars. As shown in Scheme 3, the amidosugars **2** were prepared from the coupling of substituted 3-(2-iodophenyl)acrylic acids **1** as a mixture of *Z*/*E*-isomers (*Z*/*E* = 93:7) with 1-aminosugar derivatives. In all cases studied, the desired coupling amidosugars *Zβ*-**2** were obtained as the major product contaminated by their isomers *Eβ* and *Zα* (see Supporting Information for the ratios), and this mixture was used crude for the next step. Gratifyingly, various substituted (2-iodophenyl)-*Z*-acrylamido-*β*-glycopyranoses reacted efficiently to give the *N*-glycosylated quinolin-2-ones **3a**−**n** as a mixture of *β* and *α* anomers in ratios ranging from 1:0.1 to 1:0.27 and yields up to 76%. Interestingly, this cross-coupling tolerated the presence of C−halogen bonds (e.g., −Br, −Cl, −F) which offers a platform for further metal-catalyzed cross-coupling reactions (compounds **3b**−**e**, **3h**, **3k**, and **3m,n**). In addition, the protocol was compatible with different amidosugars such as galactoside and mannoside giving the corresponding products **3g**−**i** in 76%, 55%, and 68% yields, respectively. This coupling is not limited to monoamidosaccharides, but also works with peracetylated *β*-D-disaccharides derived from D-cellobiose octaacetate. The *N*-glycosylated quinolin-2-ones **3j,k** were obtained in 64% and 60% yields, respectively. Interestingly, this study was extended successfully to unprotected amidosugars. As shown in Scheme 3, derivatives **2l**−**n** reacted efficiently under our optimized conditions leading to the product **3l**−**n** bearing unprotected sugar moieties. Of note in all cases, the *β* and *α* anomers were separated by SiO_2 flash chromatography or preparative HPLC and the NMR of pure single anomers has been reported (see Supporting Information).

DOI: 10.1021/acs.orglett.6b00752
Org. Lett. 2016, 18, 2126−2129

Scheme 3. Scope of Substituted Amidosugars 2 for the Intramolecular Pd-Catalyzed *N*-Arylation[a]

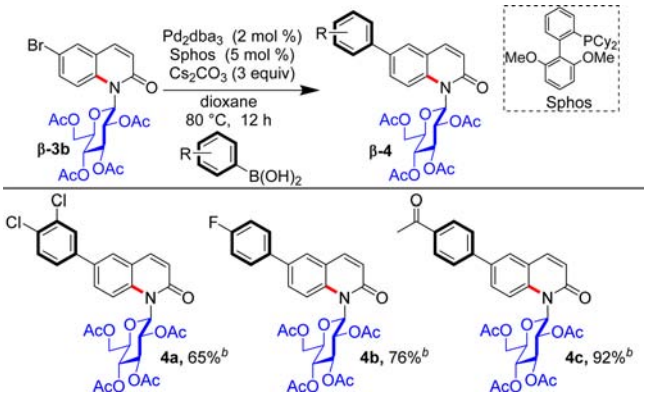


[a]Conditions: reactions of **2** (1 equiv) were performed in a Schlenk tube by using $Pd(OAc)_2$ (5 mol %), nBu_4NOAc (1.5 equiv) in dioxane (0.1 M) at 100 °C. [b]Yield of isolated mixture of both anomers β-**3** and α-**3**. [c]Ratio was determined by ^1H NMR of the mixture of **3**-β/α after flash chromatography purification.

In a further set of experiments, we tested whether multiple modifications could be made to the C−Br bond of derivative β-**3b** (Scheme 4). Thus, 6-arylated β-N_1-glycosyl quinolin-2-ones **4a−c**, which are difficult to obtain by other methods, could easily be prepared as single β-anomers in excellent yields via a Pd-catalyzed Suzuki coupling reaction[10] of β-**3b** with various arylboronic acids.

In summary, we have succeeded in the intramolecular *N*-arylation of various β- or α-substituted (2-iodophenyl)-*Z*-acrylamidosugars to furnish *N*-glycosyl quinolin-2-ones. To the best of our knowledge, this is the first time that the $C(sp^2)$−N bond of *N*-glycosyl quinolin-2-ones has been formed in this way, via the direct use of glycosylamides as nucleophile partners with $Pd(OAc)_2$ as the catalyst. We expect this simple and general methodology to be of broad utility for the synthesis and development of new medicinal agents.

Scheme 4. Pd-Catalyzed Suzuki Arylation of β-3b[a]



[a]Conditions: reactions of β-**3b** (1 equiv) with arylboronic acids (1.25 equiv) were performed in a Schlenk tube at 80 °C in dioxane by using Pd_2dba_3 (2 mol %), Sphos (5 mol %), Cs_2CO_3 (3 equiv). [b]Yield of isolated product.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00752.

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

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: samir.messaoudi@u-psud.fr.
*E-mail: mouad.alami@u-psud.fr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The CNRS is gratefully acknowledged for financial support of this research. We also thank ARC (association pour la recherche sur le cancer), for their financial support of this research and for a Ph.D. grant to T.T.H.L. Our laboratory BioCIS-UMR 8076 is a member of the Laboratory of Excellence LERMIT supported by a grant from ANR (Agence Nationale de la Recherche, ANR-10-LABX-33).

■ REFERENCES

(1) (a) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683. (b) Abdel-Rahman, A. A.-H.; El Ashry, E. S. H.; Schmidt, R. R. *Carbohydr. Res.* **1999**, *315*, 106. (c) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745. (d) Knölker, H. J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303. (e) Messaoudi, S.; Anizon, F.; Léonce, S.; Pierré, A.; Pfeiffer, B.; Prudhomme, M. *Eur. J. Med. Chem.* **2005**, *40*, 961. (f) Messaoudi, S.; Anizon, F.; Léonce, S.; Pierré, A.; Prudhomme, M. *Tetrahedron* **2005**, *61*, 7304. (g) Henon, H.; Messaoudi, S.; Hugon, B.; Anizon, F.; Pfeiffer, B.; Prudhomme, M. *Tetrahedron* **2005**, *61*, 5599.

(2) Moradi, S. V.; Hussein, W. M.; Varamini, P.; Simerska, P.; Toth, I. *Chem. Sci.* **2016**, *7*, 2492.

(3) (a) Audisio, D.; Messaoudi, S.; Cegielkowski, L.; Peyrat, J.-F.; Brion, J.-D.; Methy-Gonnot, D.; Radanyi, C.; Renoir, J.-M.; Alami, M. *ChemMedChem* **2011**, *6*, 804. (b) Hewawasam, P.; Chen, N.; Ding, M.; Natale, J. T.; Boissard, C. G.; Yeola, S.; Gribkoff, V. K.; Starrett, J.; Dworetzky, S. I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1615. (c) Raitio, K.

DOI: 10.1021/acs.orglett.6b00752
Org. Lett. 2016, 18, 2126−2129

H.; Savinainen, J. R.; Vepsäläinen, J.; Laitinen, J. T.; Poso, A.; Järvinen, T.; Nevalainen, T. *J. Med. Chem.* **2006**, *49*, 2022.
(4) Fosso, M. Y.; Nziko, V. P. N.; Chang, C. W. T. *J. Carbohydr. Chem.* **2012**, *31*, 603.
(5) Mustafa, A.; Mansour, A. K. *Arch. Pharm.* **1965**, *298*, 824.
(6) Niedballa, U.; Vorbrueggen, H. *J. Org. Chem.* **1974**, *39*, 3668.
(7) (a) Sahnoun, S.; Messaoudi, S.; Brion, J.-D.; Alami, M. *ChemCatChem* **2011**, *3*, 893. (b) Carrër, A.; Brion, J.-D.; Messaoudi, S.; Alami, M. *Adv. Synth. Catal.* **2013**, *355*, 2044. (c) Carrër, A.; Brion, J.-D.; Messaoudi, S.; Alami, M. *Org. Lett.* **2013**, *15*, 5606.
(8) (a) Bruneau, A.; Brion, J.-D.; Alami, M.; Messaoudi, S. *Chem. Commun.* **2013**, *49*, 8359. (b) Brachet, E.; Brion, J.-D.; Messaoudi, S.; Alami, M. *Adv. Synth. Catal.* **2013**, *355*, 477. (c) Brachet, E.; Brion, J.-D.; Alami, M.; Messaoudi, S. *Adv. Synth. Catal.* **2013**, *355*, 2627. (d) Brachet, E.; Brion, J.-D.; Alami, M.; Messaoudi, S. *Chem. - Eur. J.* **2013**, *19*, 15276. (e) Al-Shuaeeb, R. A. A.; Galvani, G.; Bernadat, G.; Brion, J.-D.; Alami, M.; Messaoudi, S. *Org. Biomol. Chem.* **2015**, *13*, 10904. (f) Bruneau, A.; Roche, M.; Hamze, A.; Brion, J.-D.; Alami, M.; Messaoudi, S. *Chem. - Eur. J.* **2015**, *21*, 8375.
(9) Liu, K.; Yao, S.; Lou, Y.; Xu, Y. *Carbohydr. Res.* **2013**, *381*, 83.
(10) Klein, T.; Abgottspon, D.; Wittwer, M.; Rabbani, S.; Herold, J.; Jiang, X. H.; Kleeb, S.; Luthi, C.; Scharenberg, M.; Bezencon, J.; Gubler, E.; Pang, L. J.; Smiesko, M.; Cutting, B.; Schwardt, O.; Ernst, B. *J. Med. Chem.* **2010**, *53*, 8627.

DOI: 10.1021/acs.orglett.6b00752
Org. Lett. 2016, 18, 2126−2129