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PII: S0008-6215(18)30078-8

DOI: 10.1016/j.carres.2018.03.002

Reference: CAR 7533

To appear in: *Carbohydrate Research*

Received Date: 6 February 2018

Revised Date: 4 March 2018

Accepted Date: 4 March 2018

Please cite this article as: Z. Begum, G. Shankar, K. Sirisha, B.V.S. Reddy, Pd(II)/PhI(OAc)$_2$ promoted direct cross coupling of glucals with aromatic acids, *Carbohydrate Research* (2018), doi: 10.1016/j.carres.2018.03.002.

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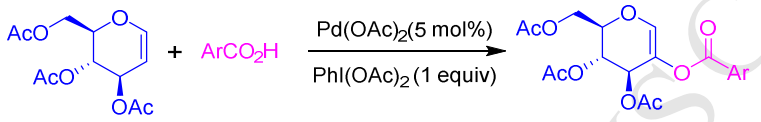

Graphical Abstract

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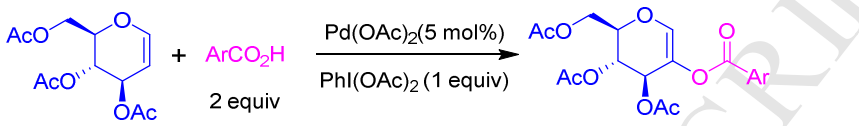

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Pd(II)/PhI(OAc)$_2$ promoted direct cross coupling of glucals with aromatic acids

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords: C2-Aroyloxyglycals; C-H activation; D-Glucal; Hypervalent iodonium reagent; Transition metal catalysis

ABSTRACT

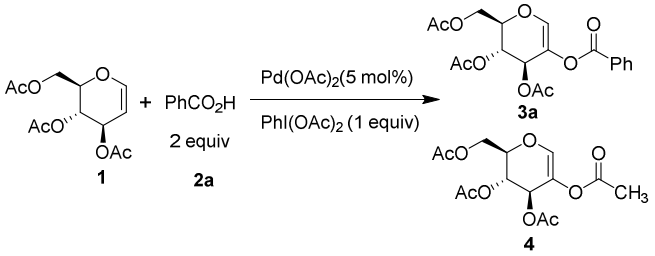
A highly efficient oxidative C2-aroyloxylation of *D*-glucal with aromatic carboxylic acids has been achieved for the first time using 5 mol% Pd(OAc)$_2$ and 1 equiv of PhI(OAc)$_2$ to produce C2-aroyloxyglycals in good yields. The use of excess of PhI(OAc)$_2$ (2 equiv) provides C2-acyloxyglycal exclusively.

Introduction

Transition metal catalyzed modification of glycals is a powerful tool to produce substituted glycals and glycosides.[1] In particular, the cross-coupling of glycals with activated alkenes through a transition metal catalysis is a versatile strategy to generate C-2 functionalized glycals.[2] These C-2 substituted glycals are common intermediates for natural products and other biological active molecules.[3,4] On the other hand, 2-hydroxy-/2-acyloxyglycals are common building blocks for the synthesis of *O*-glycosides, *C*-glycosides, *S*-glycosides and *N*-glycosides.[5] Generally, these 2-acetoxy glycals are prepared from glycosyl bromides,[6] or from thioglycosides.[7] Subsequently, alternative routes for 2-hydroxyglycals have been developed.[8] Recently, C2-acyloxyglycals are preapred from glucose pentaacetate in two steps using I_2/PMHS and excess of DBU.[9] In addition, the substrtae directed aroyloxylation of aromatic system has been also reported using a transition metal catalysis.[10] However, there are no reports on the C2-aroyloxylation of glycals.

Results and Discussion

Following our interest on transition metal catalyzed C-H bond functionalization,[11] we herein report a novel strategy for the synthesis of C2 functionalized glycals using a catalytic amount of Pd(OAc)$_2$ and a stoichiometric amount of PhI(OAc)$_2$ through an oxidative cross-coupling of glycals with carboxylic acids (Scheme 1).



Scheme 1. C2-aroyloxylation of 3,4,6-triacetyl-*D*-glucal

Initially, we attempted the cross-coupling of 3,4,6-triacetyl-D-glucal (**1**) with benzoic acid (**2a**) in the presence of 5 mol% of Pd(OAc)$_2$ under diverse reaction conditions. The reaction was carried out with 1 equiv of benzoic acid and 1 equiv of PhI(OAc)$_2$ at 80 ^{o}C. The desired product was obtained in 70% yield as a mixture of **3a** and **4** in a 1:1 ratio (Table 1, entry a). To improve the ratio, the reaction was performed again with 2 equiv of benzoic acid and 1 equiv of PhI(OAc)$_2$ at the same temperature. To our delight, the ratio of **3a** and **4** was increased to 3:1 (Table 1, entry b). To know the effect of temperature, the above reaction was carried out at 100 ^{o}C. A slight increase in yield was observed (Table 1, entry c). The best conversion and selectivity were achieved when the reaction was conducted using 2 equiv of benzoic acid and 1.0 equiv of PhI(OAc)$_2$ at 120 ^{o}C (Table 1, entry d). A trace

amount of desired product was formed in the absence of $PhI(OAc)_2$ (Table 1, entry e). On the other hand, in the absence of $PhCO_2H$, the product **4** was formed exclusively (Table 1, entry f). To know the effect of the solvent, the reaction was performed in different solvents such as DMF, 1,4-dioxane and toluene. These solvents failed to give the required product (Table 1, entries, g-i). Furthermore, no desired product was obtained in the absence of $Pd(OAc)_2$ (Table 1, entry j).

Table1. Optimization of reaction conditions

Entry	$PhCO_2H$ (equiv)	$PhI(OAc)_2$ (equiv)	$Pd(OAc)_2$ (mol%)	Solvent	Temp (^oC)	Ratio (3/4)	Yield (%)[a]
a	1.0	1.0	5.0	CH_3CN	80	(50/50)	(80)
b	2.0	1.0	5.0	CH_3CN	80	(75/25)	(80)
c	2.0	1.0	5.0	CH_3CN	100	(75/25)	(85)
d	2.0	1.0	5.0	CH_3CN	120	(98/2)	(90)
e	2.0	-	5.0	CH_3CN	120	(99/0)	(10)
f	-	2.0	5.0	CH_3CN	120	(0/99)	(90)
g	2.0	0.75	5.0	DMF	120	-	-
h	2.0	0.75	5.0	Dioxane	120	-	-
i	2.0	0.75	5.0	Toluene	120	-	-
j	2.0	0.75	-	CH_3CN	120	-	-

[a]Yield refers to pure products after chromatography.

Inspired by these initial results, we extended this method to different substrates bearing various substituents such as halide, methyl, methoxy, trifluoromethyl and nitro groups on the aromatic ring of the carboxylic acid (Table 2). This method is compatible and quite successful with a wide range of aromatic carboxylic acids. No dehalogenation was observed in case of chloro-, bromo-, and fluoro- substituted aromatic acids (Table 2, entries b,c,j,m,n & o). The substituent present on the aromatic rind had shown some effect on the conversion. Indeed, electron rich aromatic carboxylic acids are found to be superior than electron deficient counter parts. A sterically hindered 2-naphthoic acid also gave the product in good yield (Table 2, entry l). The structure of **3k** was confirmed by the incisive NMR studies and *J*-coupling analysis (Figure 1). From the one dimensional ^1H NMR data, the observed strong scalar coupling constants, $^3J_{4\text{-H}/3\text{-H}/5\text{-H}} = 4.7$, clearly indicate that the 4-H protons are in axial position in the six-membered ring. 3-H and their corresponding scalar coupling values $^3J_{3\text{-H}/4\text{-H}} = 4.3$Hz, respectively have suggested that 3H protons are in equatorial position in the six membered ring. The characteristic NOE correlations {5H-4H}, {4H-3H}, {4H-6H(a)}, and {10H-11H}, along with scalar coupling constant analysis have confirmed that the six-membered ring is in half-chair conformation. The energy-minimized structure of **3k** adequately supports our NMR analysis (Figure 1).

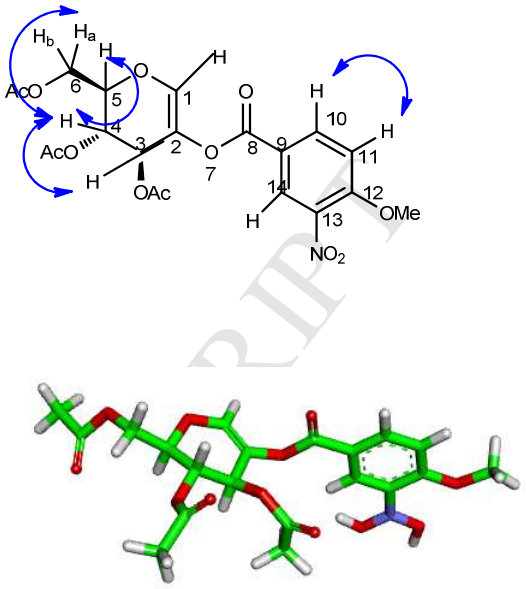
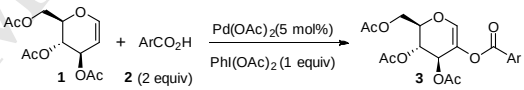
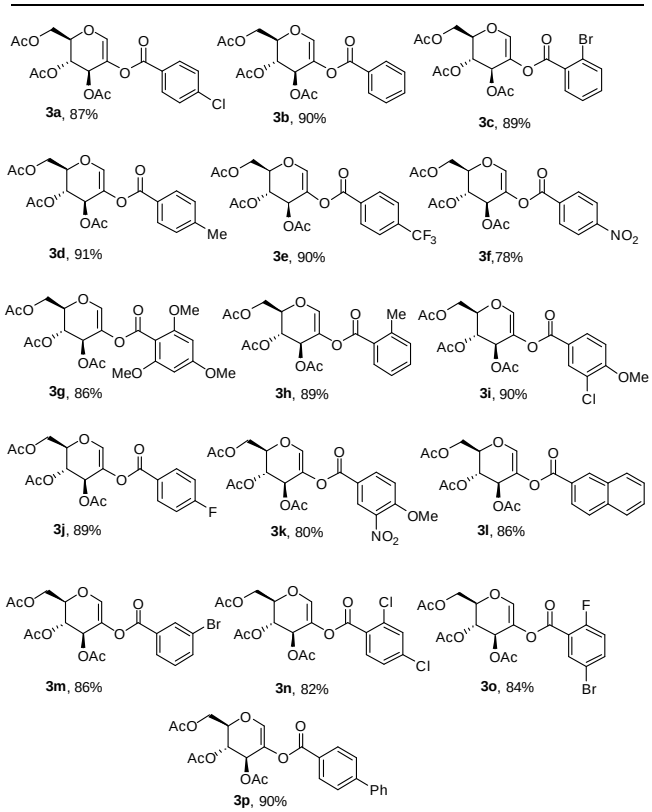


Figure 1. Characteristic NOEs and energy-minimized structure of **3k**

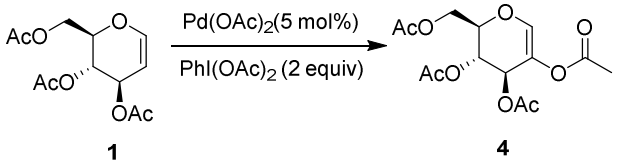
Table 2. Synthesis of C2-aroyloxy-glycals





[a]All products were characterzed by NMR, IR and mass spectroscopy.
[b]Yield refers to pure products after chromatography.

The use of 2 equiv of $PhI(OAc)_2$, the product **4** was formed exclusively in 90% yield. In this case, $PhI(OAc)_2$ acts as an oxidant as well as the source of acetoxy group (Scheme 2).



1 **4**

Scheme 2. C2-acyloxylation of 3,4,6-triacetyl-*D*-glucal

The structure of **4** was confirmed by comparing its spectral data with the data reported in the literature.[3i]

Conclusion

In summary, a novel strategy has been developed for the synthesis C2 functionalized glycals through an oxidative cross coupling of glucal with aromatic carboxylic acids. These C2-acyloxyglycals are useful building blocks for the synthesis of biologically active natural products. This method is simple, exquisitely selective and works with a diverse range of aromatic acids, which makes it an attractive strategy.

Supporting Information

Characterization data and copies of ^{1}H & ^{13}C NMR spectra of products **3a-p** and **4** are provided in the supporting information.

Acknowledgements

ZB thanks CSIR, New Delhi for the award of a fellowship

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Highlights

- First report on aroyloxylation of glycals at C2 position.
- C2-acyloxyglycals are useful chiral building blocks.
- It is compatible with various functional groups.
- This method works with a diverse range of acids.