

HF-pyridine promoted Friedel-Crafts type arylation of 2-acetoxy-D-glucal. Stereoselective synthesis of 1-arylhex-3-enopyranosiduloses

Masahiko Hayashi,* Shu-zo Nakayama and Hirotohi Kawabata

Department of Chemistry, Faculty of Science, Yamaguchi University, Yamaguchi 753-8512, Japan.
E-mail: hayashi@po.cc.yamaguchi-u.ac.jp

Received (in Cambridge, UK) 25th April 2000, Accepted 7th June 2000

A variety of aromatic substrates were treated with 2-acetoxy-D-glucal in the presence of HF-pyridine to give 1-arylhex-3-enopyranosiduloses in high yield and in high α -selectivity.

C-Glycosylarenes or C-aryl glycosides are C-glycosides found in natural products.¹ These compounds often exhibit interesting biological activity, such as antibacterial, anti-tumor, enzyme inhibitory effects, and inhibition of platelet aggregation.² Therefore, the study of the synthesis of C-glycosylarenes is of interest to synthetic organic chemists. The most straightforward synthesis of C-glycosylarenes should be the Friedel-Crafts type reaction between glycosyl donors and aromatic compounds.^{3,4}

We recently reported the reaction of acetylated and unprotected D-glucal with trimethylsilyl cyanide which led to the synthesis of 2,3-unsaturated glycosyl cyanides.⁵ During the course of this study, we became interested in the reaction of D-glucal with aromatic compounds, which should be an efficient synthetic route to C-aryl glycosides.⁶ Here we would like to report the Friedel-Crafts type reaction of acetylated D-glucal with aromatic compounds.

First, we examined the reaction of 3,4,6-tri-O-acetyl-D-glucal with mesitylene (1,3,5-trimethylbenzene) in the presence of a variety of Lewis acids such as Me₃SiOTf, BF₃·OEt₂ and Sc(OTf)₃. However, all reactions resulted in the formation of complex mixtures and the desired 1-aryl glycoside was not obtained. Then we employed the reaction of 2,3,4,6-tetra-O-acetyl-D-glucal (1) with mesitylene using the above Lewis acids. In these cases, 1-arylated hex-3-enopyranosidulose (6) was obtained in high yield.⁷ Some of the results are summarized in Table 1. Among the Lewis acids we examined, Me₃SiOTf

showed the best results (20 mol%, 0 °C, 1 h, 90% yield, α : β = 88:12). The configuration of the major anomeric center was determined as α by ¹H NMR spectral analysis.

Interestingly, rare-earth metal triflates other than Sc(OTf)₃, such as Sm(OTf)₃, Y(OTf)₃ and Yb(OTf)₃ were inactive in the above reaction. HF-pyridine was found to work as an effective promoter and to be superior to the conventional Lewis acids as for a variety of aromatic compounds (Table 2). HF-pyridine is used as a fluorinating agent,⁸ for example in the synthesis of glycosyl fluorides.⁹ However, in the present case, HF-pyridine worked as a promoter in the Friedel-Crafts coupling reaction. As shown in Table 2, a variety of α -1-arylated hex-3-enopyranosidulose products were obtained in high yields. As for the relative reactivity, among the aromatic compounds we examined, anisole reacted with 1 faster than the other aromatic compounds. For methylated benzene derivatives, the order of the reactivity is as follows; mesitylene > *m*-xylene > *o*- and *p*-xylene, toluene. Isomerization was not observed under the reaction conditions, indicating that the observed stereochemical outcome resulted from kinetic control.

The reactions proceed via a Ferrier type reaction.¹⁰ The reaction is initiated by the reaction of 2-acetoxy-D-glucal with HF-pyridine to generate an oxocarbenium ion which then reacts with aromatic substrates such as xylene and mesitylene to give 1-aryl-2,3-unsaturated glycosides, though these compounds were not isolated. Then deacetoxylation at the 4-position affords the 1-arylhex-3-enopyranosiduloses. In the case of the reaction of 3,4,6-tri-O-acetyl-2-bromo-D-glucal with mesitylene, a Ferrier type product, that is, the 2,3-unsaturated 1-arylated product was obtained in 86% yield (α : β = 77:23).

A typical experimental procedure is as follows: In a 50 mL polyethylene vessel, 2,3,4,6-tetra-O-acetyl-D-glucal (1.0 g, 3.04 mmol) and mesitylene (0.84 mL) were placed. To this mixture was added 70% HF-pyridine (1.5 mL) at 0 °C and the whole mixture was stirred for 1 h at 0 °C. After the confirmation of the completion of the reaction by TLC, the mixture was poured into saturated NaHCO₃ solution and extracted with ethyl acetate (20 mL \times 3). The combined organic layer was washed with brine (20 mL \times 3), and then evaporated. Chromatography of the residue on a silica gel column afforded 6 (777 mg, 90%). Separation of the anomers was effected by column chromatography on silica gel (1:2 ethyl acetate-hexane as an eluent): 6 α (less polar) [α]_D²³ -149.1° (c. 1.2, CHCl₃); 6 β (more polar) [α]_D²² -53.1° (c. 1.2, CHCl₃).

In conclusion, we have developed a HF-pyridine promoted Friedel-Crafts type arylation of 2-acetoxy-D-glucal with a variety of aromatic compounds which facilitated the synthesis of 1-aryl-2-hex-3-enopyranosiduloses.

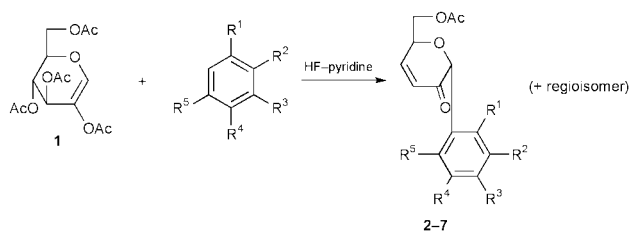
We would like to acknowledge Dr Hidemitsu Uno of the Center for Advanced Chemical Analysis and Instrumentation of Ehime University for his help in the structure determination of compound 6. Support from Monbusho (Grant-in-Aid for Scientific Research on Priority Areas, No. 706: Dynamic Control of Stereochemistry), the Shorai Foundation for Science

Table 1 Reaction of 2,3,4,6-tetra-O-acetyl-D-glucal with mesitylene^a

Entry	Conditions			Product	
	Catalyst (mol%)	T/°C	t/h	Yield (%) ^b	α : β ^c
1	Me ₃ SiOTf (20)	0	1	90	88:12
2	BF ₃ ·OEt ₂ (20)	15	20	58	80:20
3	Sc(OTf) ₃ (10)	20	24	65	79:21
4	HF-pyridine	0	1	90	90:10

^a All reactions were carried out in acetonitrile except for entry 4.

^b Isolated yield after silica-gel column chromatography. ^c ¹H NMR analysis.

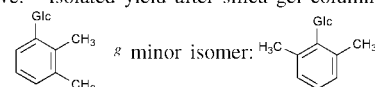
Table 2 HF–pyridine promoted reaction of 2,3,4,6-tetra-*O*-acetyl- β -glucal (**1**) with some aromatic compounds^a

	Aromatic compound					HF–pyridine mL/g of substrate	Conditions		Product ^b	
	R ¹	R ²	R ³	R ⁴	R ⁵		T/°C	t/h	Yield (%) ^c (regioisomer ratio) ^d	α : β ^d
1	H	H	CH ₃	H	H	2.2	18	15	2 88 (<i>o</i> : <i>p</i> = 25:75) ^e	α
2	H	CH ₃	CH ₃	H	H	2.5	20	23	3 76 (86:14) ^f	α
3	CH ₃	H	CH ₃	H	H	2.6	20	2	4 100 (91:9) ^g	α
4	CH ₃	H	H	CH ₃	H	2.3	16	7	5 76	α
5	CH ₃	H	CH ₃	H	CH ₃	1.4	0	1	6 90	90:10
6	OCH ₃	H	H	H	H	2.4	0	0.5	7 84 (<i>o</i> : <i>p</i> = 57:43)	α

^a All reactions were carried out in a polyethylene vessel. ^b The structures of major isomers are given above. ^c Isolated yield after silica gel column

chromatography. ^d Determined by ¹H NMR (400 MHz) analysis. ^e Isomers not separated. ^f minor isomer:

^h Minor isomer was β .



and Technology and the Nagase Science and Technology Foundation is gratefully acknowledged.

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