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

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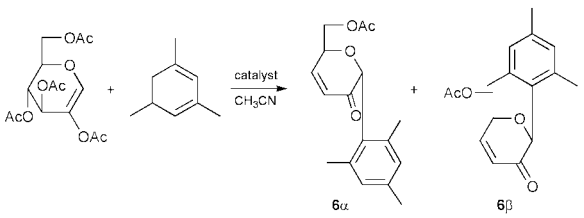
A variety of aromatic substrates were treated with 2-acetoxy-D-glucal in the presence of HF–pyridine to give 1-arylhex-3-enopyranosiduloses in high yield and in high α-selectivity.

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 Me_3SiOTf, $BF_3{\cdot}OEt_2$ 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, Me_3SiOTf 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 ^{1}H NMR spectral analysis.

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



6α 6β

	Conditions			Product	
Entry	Catalyst (mol%)	*T*/°C	*t*/h	Yield (%)[b]	α:β[c]
1	Me_3SiOTf (20)	0	1	90	88:12
2	$BF_3{\cdot}OEt_2$ (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] ^{1}H NMR 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 $NaHCO_3$ solution and extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed with brine (20 mL × 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) $[\alpha]_D^{23}$ −149.1° (*c*. 1.2, $CHCl_3$); **6**β (more polar) $[\alpha]_D^{22}$ −53.1° (*c*. 1.2, $CHCl_3$).

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.

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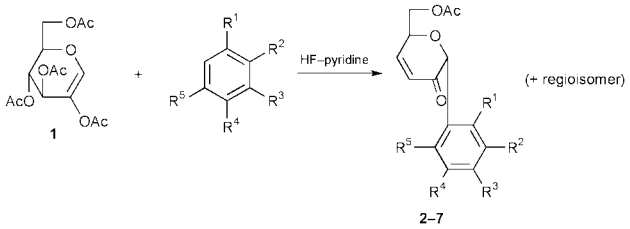
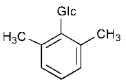
Table 2 HF–pyridine promoted reaction of 2,3,4,6-tetra-*O*-acetyl-D-glucal (**1**) with some aromatic compounds[a]



	Aromatic compound					HF–pyridine mL/g of substrate	Conditions		Product[b] Yield (%)[c] (regioisomer ratio)[d]	α:β[d]
	R^1	R^2	R^3	R^4	R^5		T/°C	t/h		
1	H	H	CH_3	H	H	2.2	18	15	**2** 88 ($o:p$ = 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 ($o:p$ = 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 ^{1}H NMR (400 MHz) analysis. [e] Isomers not separated. [f] minor isomer:  [g] minor isomer:  [h] Minor isomer was β.

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