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FISCHER GLYCOSIDATION USING ORGANOTITANIUM CATALYST ORGATIX

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Abstract – Fischer glycosidation was performed at room temperature and 60 °C using the organotitanium compound ORGATIX, especially TC-310, which worked as an acid catalyst in the presence of alcohol. ORGATIX could be readily quenched by water and removed by simple filtration using silica-gel column chromatography.

Organotitanium compounds have been used as organometallic catalysts.[1-3] However, there are concerns about their safety. ORGATIX is a registered trademark for organometallic compounds, such as organotitanium, organozirconium, and organoaluminum, manufactured and sold by Matsumoto Fine Chemical Co., Ltd (Chiba, Japan). They are used in inks, paints, primers, high refractive index films, electronic materials, ceramics, plastic films, metals, glass, etc.[4-6] ORGATIX has high catalytic activity and safety and little effect on the final product since the catalytic activity is lost through hydrolysis eventually. Since most of the ORGATIX is liquid, it is easy to use in experiments.

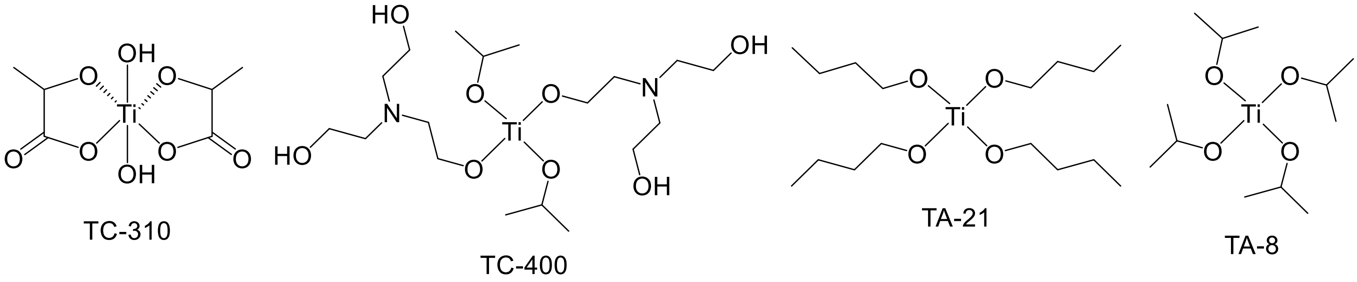


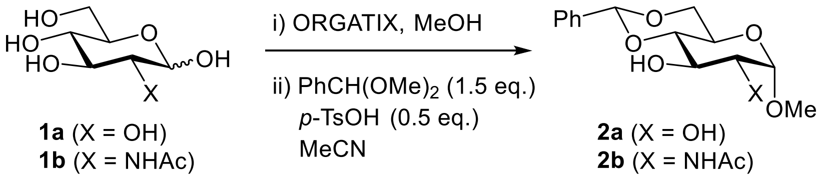
Figure 1. Four types of ORGATIX

Fischer glycosidation is a classical reaction method for glycoside synthesis from alcohols and sugars in a single step in the presence of an acid catalyst.[7] However, strong acid catalysts such as hydrochloric and sulfuric acids promote side reactions. Trimethylsilyl chloride (TMSCl) is used as an acid catalyst in a simple

Fischer glycosidation reaction.[8] Since TMSCl is also a dehydrating agent, the reaction proceeds even at room temperature and produces high yield of the corresponding α-glycoside without any heating related side reactions.

This study examined the Fischer glycosidation reaction using ORGATIX as an acid catalyst. Figure 1 shows the four types of ORGATIX used in this study: Dihydroxybis(hydrogen lactato)titanium(IV) (TC-310), Titanium bis(triethanolamine)diisopropoxide (TC-400), Tetrabutyl orthotitanate (TA-21), and Tetraisopropyl orthotitanate (TA-8). Glycosidation was performed by suspending the monosaccharides in 25 mL alcohol, adding 5 mL ORGATIX, and stirring at room temperature and 60 °C. Since the glycoside is highly polar and difficult to purify from the reaction mixture, the yield was determined by leading to the 4,6-*O*-benzylidene compound with subsequent crystallization (Table 1).[9] The addition of *p*-TsOH was needed since the acetalization did not proceed without it.

Table 1. Fischer glycosidation using ORGATIX in MeOH

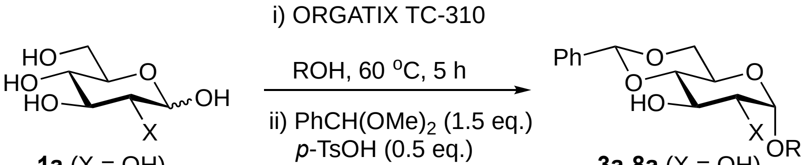


Entry	Compound	ORGATIX	Temp.	Time	Product	Yield (%) (α:β)[a]
1	**1a**	TC-310	rt	7 d	**2a**	30 (9:1)
2		TC-400				n.d.[b]
3		TA-21				n.d.
4		TA-8				n.d.
5	**1a**	TC-310	60 °C	5 h	**2a**	38 (1:0)
6		TC-400				n.d.
7		TA-21				n.d.
8		TA-8				n.d.
9	**1b**	TC-310	rt	7 d	**2b**	n.d.
10		TC-400				n.d.
11		TA-21				n.d.
12		TA-8				n.d.
13	**1b**	TC-310	60 °C	5 h	**2b**	29 (3:4)
14		TC-400				31 (1:1)
15		TA-21				n.d.
16		TA-8				n.d.

[a] The ratio was determined by ^{1}H NMR. [b] Prodcut was not detected on TLC.

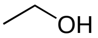
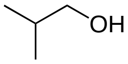
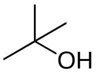
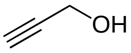
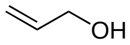
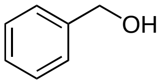
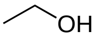
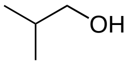
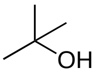
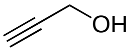
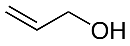
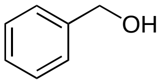
First, the glycosidation reaction with four different ORGATIX was examined using D-glucose **1a** and methanol as solvent. After 7 days at room temperature, the progress of glycosidation reaction with TC-310 was analyzed using thin layer chromatography for 30% product yield.[10] However, the reaction did not proceed with the other three types of ORGATIX (Table 1, entry 1–4). The reaction progressed with TC-310 after 5 hours of reaction at 60 °C, resulting in 38% product yield,[11] but not with TC-400, TA-21 and TA-8 (Table 1, entry 5–8). In the case of *N*-Ac-D-glucosamine **1b**, TC-310, and TC-400 at 60 °C were sufficient to produce significant product yield (Table 1, entry 9–16). The nuclear magnetic resonance (NMR) spectra agreed with previous reports.[7,8]

Table 2. Fischer glycosidation using ORGATIX TC-310 in different alcohols



1a (X = OH)
1b (X = NHAc)

3a-8a (X = OH)
3b-8b (X = NHAc)

Entry	Compound	R-OH	Product	Yield (%) (a:b)[a)]
1	**1a**		**3a**	31 (1:0)
2			**4a**	18 [b)]
3			**5a**	19 [b)]
4			**6a**	61 (1:0)
5			**7a**	27 (1:0)
6			**8a**	trace
7	**1b**		**3b**	22 (1:0)
8			**4b**	16 [b)]
9			**5b**	14 [b)]
10			**6b**	20 (1:0)
11			**7b**	n.d. [c)]
12			**8b**	trace

[a)] The ratio was determined by ^1H NMR. [b)] The ratio was not able to be determined by ^1H NMR. [c)] Prodcut was not detected on TLC.

Fischer glycosidation using ORGATIX TC-310 was investigated by combining different monosaccharides and alcohols. For example, propargyl glycoside, readily cleaved on treatment with $Co_2(CO)_8$ and trifluoroacetic acid (TFA), was prepared by this Fischer glycosidation method with propargyl alcohol. At 60 °C, the glycosidation reaction proceeded more rapidly and only 5 mL of ORGATIX TC-310 was sufficient for the reaction than at room temperature (Table 2). The NMR spectra agreed with previous reports;[7,8] however, the ratio of α and β isomers could not be determined by ^{1}H NMR in the four compounds (Table 2, entries 2, 3, 8, and 9).

As described, ORGATIX TC-310 works as an acid catalyst in the presence of alcohol. The yields were not satisfactory even though excess ORGATIX TC-310 was present. ORGATIX could be readily quenched by water and removed by simple filtration using silica-gel column chromatography.

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10. Fischer glycosidation procedure at room temperature used 5.0 mL ORGATIX TC-310: ORGATIX TC-310 (1.0 mL) was added to a suspension of glucose **1a** (1.80 g, 10 mmol) in MeOH (25.0 mL). The mixture was stirred at room temperature for 7 days and then concentrated under reduced pressure. Toluene was added to the residue, and the solution was evaporated. Further, benzaldehyde dimethyl acetal (2.25 mL, 15 mmol) and *p*-toluenesulfonic acid (0.95 g, 5 mmol) were added to the residue solution in MeCN (25 mL). The mixture was stirred at room temperature for 1 day. Adding a saturated aqueous $NaHCO_3$ (50 mL) to the reaction mixture formed a solid precipitate, which was washed successively with water and Et_2O–hexane (1:1). The resultant was removed by simple filtration using silica-gel column chromatography to obtain pure product **2a** yield of 0.92 g (30%).
11. The typical procedure for Fischer glycosidation at 60 °C used 5.0 mL of ORGATIX TC-310: ORGATIX TC-310 (5.0 mL) was added to a suspension of D-glucose **1a** (1.80 g, 10 mmol) in MeOH (25.0 mL). The mixture was stirred at 60 °C for 5 h and then concentrated under reduced pressure. After toluene addition, the rest of the procedure is the same as for Fischer glycosidation at room temperature. Finally, the resultant was removed by simple filtration using silica-gel column chromatography to obtain a pure product **2a** yield of 1.17 g (38%).