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EFFECTIVE FRIEDEL-CRAFTS ACYLATIONS OF *O*- AND *C*-ARYLGLYCOSIDES WITH TRIFLIC ACID

Makoto Hashimoto* and Miho Takahashi

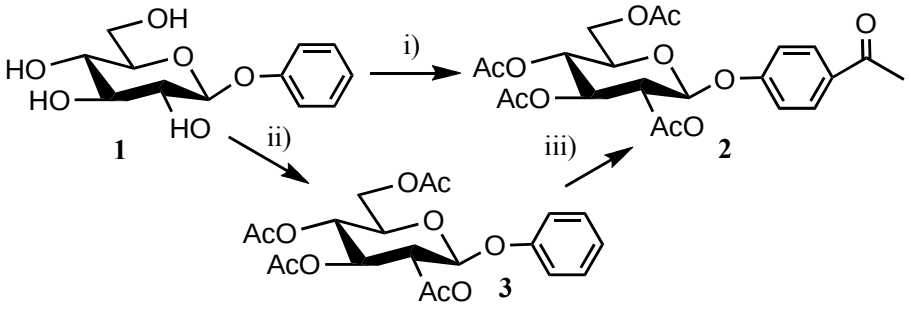
Department of Agricultural and Life Science, Obihiro University of Agriculture and Veterinary Medicine, Inada-cho, Obihiro 080-8555, Hokkaido, Japan. E-mail; hasimoto@obihiro.ac.jp

Abstract – Triflic acid is well known not only as a Friedel-Crafts promoter, but also as a deglycosidation reagent. In this study, we promote effective Friedel-Crafts acylations for *O*- or *C*-arylglucosides without deglycosidation and check their inhibitory activities for β-glucosidase.

Carbohydrates carrying aromatic aglycons are important compounds; examples of which promote many biological functions (antibiotics, etc).[1] The aromatic substitutions of these compounds have been performed by glycosidation of glycosyl donors and appropriate aromatic compounds. These methodologies required several steps for protection, glycosidation and deprotection to synthesize each glycoside. Although Friedel-Crafts reactions are one of the most popular means of derivatization for aromatic compounds, few applications of the reactions for the derivatization of aryl-*O*-glycosides have been reported. There are several reasons to explain the low solubility of unprotected aromatic glycosides in reaction media and competitive deglycosidation in the acidic conditions for *O*-glycosides. Trifluoromethanesulfonic acid (triflic acid) is widely used as a de-*O*-glycosidation reagent for glycoprotein and glycolipids.[2] Carbohydrate analysis of the reaction mixture indicated that triflic acid can dissolve carbohydrates easily without decomposition of each carbohydrate unit occurring. The results promoted the notion that selective Friedel-Crafts acylation of arylglucosides with triflic acid might be applied as a competitive reaction against de-*O*-glycosidation. Phenyl-β-D-glucoside (**1**) was suspended in excess acetyl chloride, and then triflic acid was added, dropwise, at 0 °C. The suspension became a solution and was stirred for 10 min., then poured into cold water. A colorless solid formed immediately and was filtered and no sugar moiety was included in the aqueous solution. The filtrate was subjected to NMR analysis in $CDCl_3$ and the analysis indicated both Friedel-Crafts reaction for the benzene ring and

This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

acetylation for hydroxyl groups (**2**) occurred, but deglycosidation of *O*-aryl group was not observed. These results indicated that triflic acid promoted the acylation of hydroxyl groups and the benzene ring (this occurred within 10 minutes), over de-*O*-glycosidation in the presence of excess acetyl chloride. The long incubation caused de-*O*-glycosidation and afforded a complex mixture within an hour. The effectiveness of the triflic acid equivalents was examined for Friedel-Crafts acylations. Compound **1** was treated with 1.6 equivalents of triflic acid afforded only *O*-acetylated compound **3** in 88% yield.



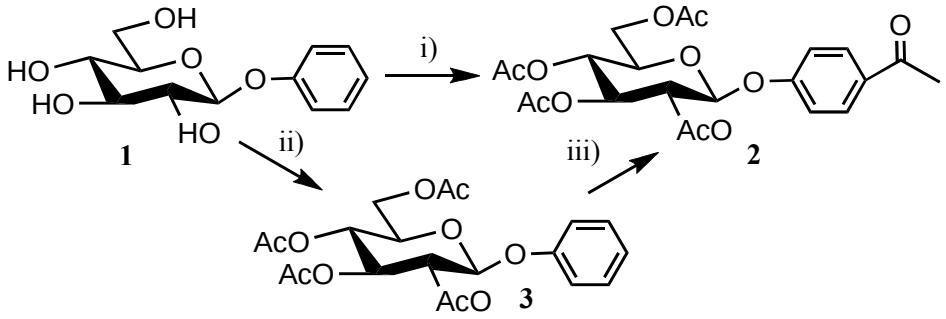
Scheme 1. Friedel-Crafts acylations and *O*-acetylation of phenyl-β-D-glucoside **1**. i) TfOH (16 equivalents), 90%/. ii) TfOH (1.6 equivalents), 98%. iii) TfOH (16 equivalents), 90%, common conditions: AcCl (solvent), 0 °C, 10 min.

Compound **3** was re-treated with 16 equivalents of triflic acid, which afforded Friedel-Crafts product (**2**) in 90% yield. The results indicated *O*-acylation was faster than Friedel-Crafts acylations. (Scheme 1) Table 1 shows summarized proportions of compounds **2** and **3** and phenol derivatives, which were derived from de-*O*-glycosidation of aglycon, in various amounts of triflic acid. This demonstrates that five equivalents of triflic acid facilitated equivalent amounts of compounds **2** and **3** being detected and compound **2** being reduced in a reaction mixture with over 12.5 equivalents of triflic acid.

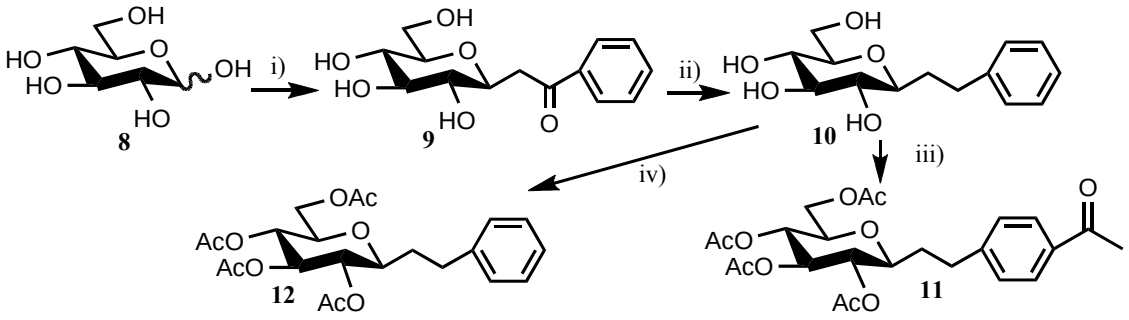
Table 1. Effect of TfOH quantities for Friedel-Crafts acylations, *O*-acetylation and de-*O*-glycosidation of phenyl-β-D-glucoside **1**.

TfOH (equivalent)	**2** (Friedel-Crafts and *O*-acylated)	**3** (*O*-acetylated)	phenol derivatives
1	1	98	1
2	2	95	3
5	35	35	30
8	45	20	35
12.5	80	5	15
16	90	5	5

The acylations with triflic acid were applied to other *O*-arylglucosides. 4-hydroxyphenyl β-glucoside **4** afforded per-*O*-acetylated compound **5** in 63% yield and no Fries rearrangement products were detected. 4-Methoxyphenyl β-glucoside **6** afforded 3-acetyl-4-methoxypheyl tetra-*O*-acetyl β-glucoside **7**[3] in 66% and no regioisomer of acetyl group on the aromatic ring was detected from NOE measurement. *O*-Arylglucosides which have electron-withdrawing groups (CHO, COOH and NO_2) on the benzene ring afforded a complex mixture, because acidic hydrolysis was preferred to a Friedel-Crafts reaction.



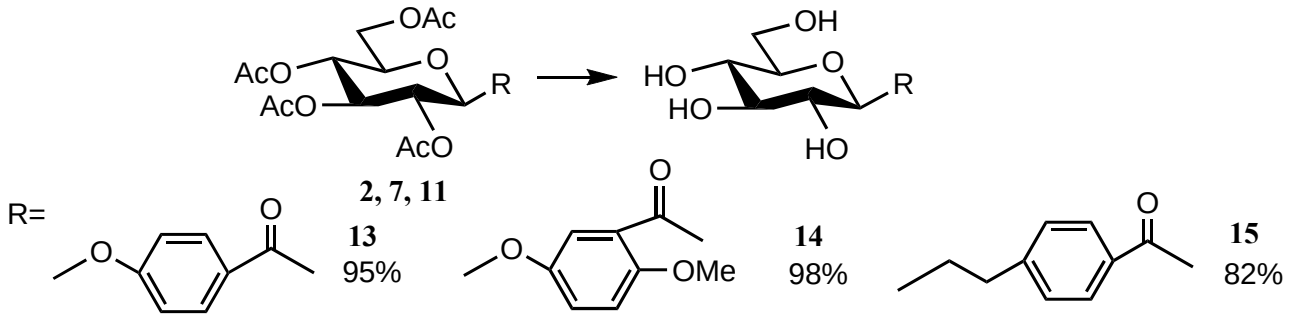
Scheme 2. Friedel-Crafts acylations and *O*-acetylation of phenyl-β-D-glucoside derivatives **4** and **6**. TfOH (30 equivalents), AcCl (solvent), 0 °C, 10 min, 63 and 66% for **5** and **7**, respectively.



Scheme 3. Synthesis of phenylethyl *C*-glucoside and its Friedel-Crafts acylations. i) 1-phenyl 1,3-butanedione, $NaHCO_3$, 80 °C, 3 h, 24%. ii) H_2, Pd/C, CF_3COOH, rt, 10 h, 70%. iii) TfOH (30 equivalents), AcCl (solvent), 0 °C, 20 min, 90%. iv) TfOH (10 equivalents), AcCl (solvent), 0 °C, 20 min, 13 and 87% for **11** and **12**, respectively.

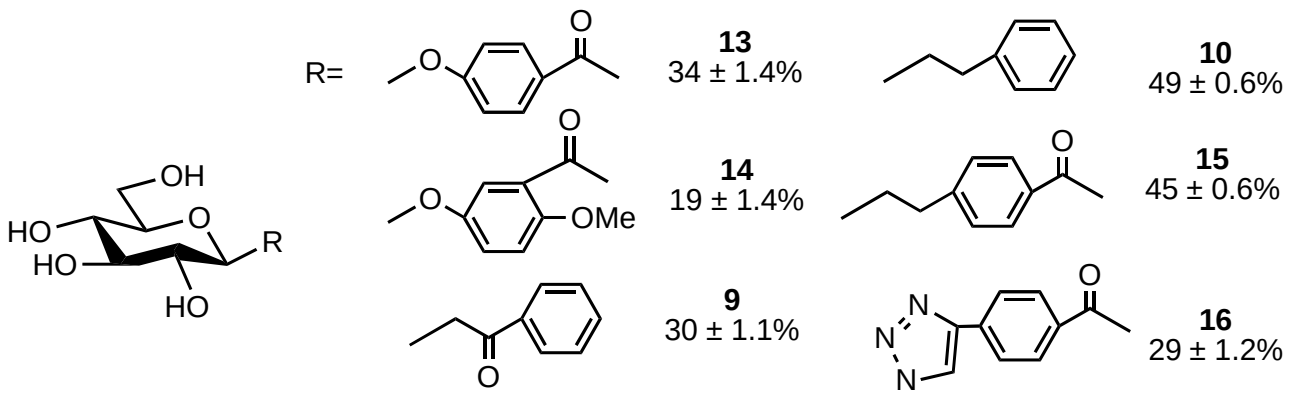
Post-functionalizations for aryl glucoside were applied to *C*-glycoside, which is one of the major foci for the glycobiology. Glucose **8** was treated with 1-phenyl 1,3-butanedione in the presence of $NaHCO_3$ in accordance with the literature,[4] then **9** was subjected to reduction of aryl carbonyl group with hydrogenation to afford phenylethyl *C*-glycoside **10**. Acylations of hydroxyl and aromatics were achieved with slightly large amounts of triflic acid (30 equivalents) and a long incubation time (20 min) with good yield (**11**[5], 90%), because there was less activation of aromatic moiety than that of aryl-*O*-glycosides.

Less triflic acid (10 eq) was required to afford a mixture of per-*O*-acetyl glucoside with (**11**) and without (**12**) acylated on the aromatic ring in proportions of 13 and 87, respectively. (Scheme 3)



Scheme 4. De-*O*-acetylation of alkaline labile compounds. Bu_2SnO, methanol, reflux, 12 h.

The synthesized products should be de-*O*-acetylated to measure the inhibition for β-glycosidase activities and subjected to de-*O*-acetylation methods for alkaline labile compounds, because these compounds have α-hydrogene of acetophenone moiety. Bu_2SnO in methanol with refluxing[6] was very effective for these compounds.[7] (Scheme 4) Preliminary experiments for inhibition of β-glucosidase from sweet almond were performed as indicated below. In 96 well plate, the assay mixture, which consisted of *p*-nitrophneyl β-$_D$-glucoside (1 mM) and synthesized aryl glucoside (20 mM) in 100 mM acetate buffer (pH 5.0), was pre-incubated at 37 °C for 5 min. The enzymatic reactions were initiated by addition of β-glucosidase (1.25 units) and terminated by the addition of 0.2 M Na_2CO_3 after 15 min. Inhibitions were calculated by measurement of free *p*-nitrophenol at 400 nm with a titer plate reader. The results indicated *C*-glycosides (**9, 10, 15**) have more inhibition potential than *O*-glycosides **13**, **14**, and triazole derivative **16**; the last of which was synthesized with click chemistry of azide glycosides and acetylene derivatives.



Scheme 5. Inhibition rates of synthetic aryl *O*- or *C*-β-glycosides (20 mM) for the β-glucosidase from sweet almond in the presence of *p*-nitorophenyl-β-glucoside (1 mM).

The Friedel-Crafts reactions for aromatic glycosides in this paper were simplified for the preparation of many aromatic glycosides and were able to examine their biological activities more easily.

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3. Compound **7**; FAB-MS m/z: 497 (MH^+), ^{1}H-NMR ($CDCl_3$) 7.41 (1H, d, J = 2.9 Hz), 7.13 (1H, dd, J = 9.2, 2.9 Hz), 6.90 (1H, d, J = 9.2 Hz), 5.30 – 5.23 (1H, m), 5.15 (1H, t, J = 9.2 Hz), 5.03 (1H, d, J = 7.4 Hz), 4.26 (1H, dd, J = 12.0, 5.1 Hz), 4.18 (1H, dd, J = 12.0, 2.3 Hz), 3.90 (3H, s), 3.87 - 3.84 (1H, m), 2.41 (3H, s), 2.08 (3H, s), 2.05 (3H, s), 2.03 (3H, s), 2.00(3H, s).
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5. Compound **11**; FAB-MS m/z: 479 (MH^+), ^{1}H-NMR ($CDCl_3$) 7.89 (2H, d, J = 8.0 Hz), 7.27 (2H, d, J = 8.0 Hz), 5.14 (1H, t, J = 9.2 Hz), 5.06 (1H, t, J = 9.7 Hz), 4.93 (1H, t, J = 9.7 Hz), 4.26 (1H, dd, J = 12.0, 6.0 Hz), 4.15 (1H, dd, J = 12.0, 3.2 Hz), 4.08 (1H, m) 3.63 - 3.59 (1H, m), 2.77 – 2.71 (2H, m), 2.43 (3H, s), 2.05 (3H, s), 2.03 (3H, s), 2.02 (3H, s), 2.00(3H, s), 1.83-1.79 (2H, m).
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7. Compound **14**; FAB-MS m/z: 329 (MH^+), ^{1}H-NMR (CD_3OD) 7.42 (1H, d, J = 3.4 Hz), 7.30 (1H, dd, J = 9.2, 3.4 Hz), 7.07 (1H, d, J = 9.2 Hz), 4.80 (1H, d, J = 8.0 Hz), 3.89 (3H, s), 3.87 (1H, m), 3.70 (1H, dd, J = 11.7, 4.9 Hz), 3.68 (1H, dd, J = 11.7, 2.3 Hz), 3.45 - 3.39 (2H, m), 2.57(3H, s). Compound **15**; FAB-MS m/z: 311 (MH^+), ^{1}H-NMR (CD_3OD) 7.91 (2H, d, J = 8.0 Hz), 7.36 (2H, d, J = 8.0 Hz), 4.32-4.24 (2H, m), 4.05-3.92 (3H, m), 3.89 (1H, dd, J = 12.0, 2.3 Hz), 3.66 (1H, dd, J = 12.0, 6.0 Hz), 2.84 – 2.78 (2H, m), 2.57(3H, s), 1.83-1.79 (2H, m).