



Azidochlorination reaction of tri-*O*-acetyl-D-galactal

Kotaro Kanzaki¹ and Osamu Kanie, Ph.D.²

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Introduction

2-Azido-sugar, 2-azido-galactopyranose in particular, has been frequently used in the synthesis of complex oligosaccharides containing aminosugars. Among various forms of glycosides, *N*-acetyl galactosamine (GalNAc) often present in a form of α -glycoside. Having an azido group at the 2-position is advantageous for the synthesis of α -glycoside owing to the anomeric effect.

Lemieux and Ratcliffe introduced a famous and still frequently used azidonitration in 1979 (1). The desired compounds with *galacto*-configuration can be obtained in 75% yield after careful column chromatography. The anomeric nitrate can then be converted into various leaving groups.

In 1990, a direct preparation method for 1-chloro-2-azido-sugar from tri-*O*-acetyl glycal was patented (2). Later in 2011, the method was simplified (3), which was practical and provided slightly better yields compared to azidonitration in our hands.

Protocol

In this chapter, a protocol to prepare 2-azido-3,4,6-tri-*O*-acetyl-2-deoxy-D-galactopyranosyl chloride (compound 2) from 3,4,6-tri-*O*-acetyl-D-galactal (compound 1), as reported by Sewald *et al.*, is described (Figure 1).

Materials

1. 3,4,6-Tri-*O*-acetyl-D-galactal (compound 1, prepared inhouse)
2. CH₃CN (Guaranteed Reagent stored over MS 3A)
3. FeCl₃·6H₂O (Guaranteed Reagent)
4. NaN₃ (Guaranteed Reagent)
5. 30% H₂O₂ (Extra Pure Reagent)
6. TLC silica gel 60 F₂₅₄ 25 glass plates for reaction monitoring with 5% H₂SO₄-EtOH.
7. Ethyl acetate for extraction
8. Saturated NaHCO₃ for washing the organic phase
9. Brine for washing the organic phase

Author Affiliations: 1 Graduate School of Engineering, Tokai University. 2 Graduate School of Engineering, Tokai University; Email: kanie@tokai-u.jp.

 Corresponding author.

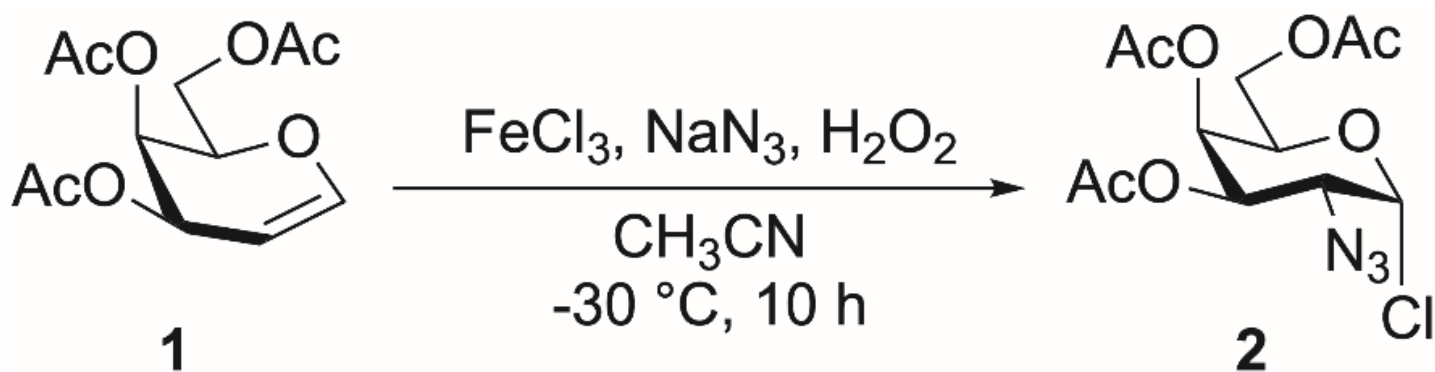


Figure 1: Azidochlorination of acetyl galactal.

10. Na_2SO_4 for drying the organic phase
11. Silica gel (Chromatorex PSQ 100B) for purification
12. CDCl_3 containing 1% $(\text{CH}_3)_4\text{Si}$ (internal standard) for NMR measurement

Instruments

1. Round bottom flask (reaction vessel)
2. Magnetic stirring bar
3. Rotary evaporator for removing organic solvents
4. Circulating cooling bath
5. Separating funnel
6. Erlenmeyer flask
7. Chromatography tube for silica gel chromatography (for purification).
8. Fraction collector (for chromatography)
9. Diaphragm pump (for filtration under reduced pressure)
10. Vacuum pump (for drying up)
11. AVANCE 500 spectrometer (Bruker Biospin Inc.) for obtaining ^1H NMR (500 MHz).

Methods

1. Dissolve compound **1** (109.7 mg, 0.403 mmol) in CH_3CN (2 mL).
2. Add $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (174 mg, 0.644 mmol), NaN_3 (57.6 mg, 0.886 mmol), and 30% H_2O_2 (90.4 μL , 0.886 mmol) to a solution written above at -30°C .
3. Stir the resulting mixture at the temperature for 10 h. (**Note 1**)
4. Confirm the reaction completion by TLC (toluene-ethyl acetate = 4:1).
5. Dilute the reaction mixture with 50 mL of ethyl acetate, and washed with water, saturated sodium bicarbonate, and brine.
6. Dry organic solution over Na_2SO_4 , and evaporate the solvents *in vacuo* to give crude compound **2** (132.2 mg, Figure 2).
7. Perform column chromatography of the mixture to yield pure compound **2** (74%).

Note

- 1 The homogeneous reaction prevents stirring problems in heterogeneous reaction.

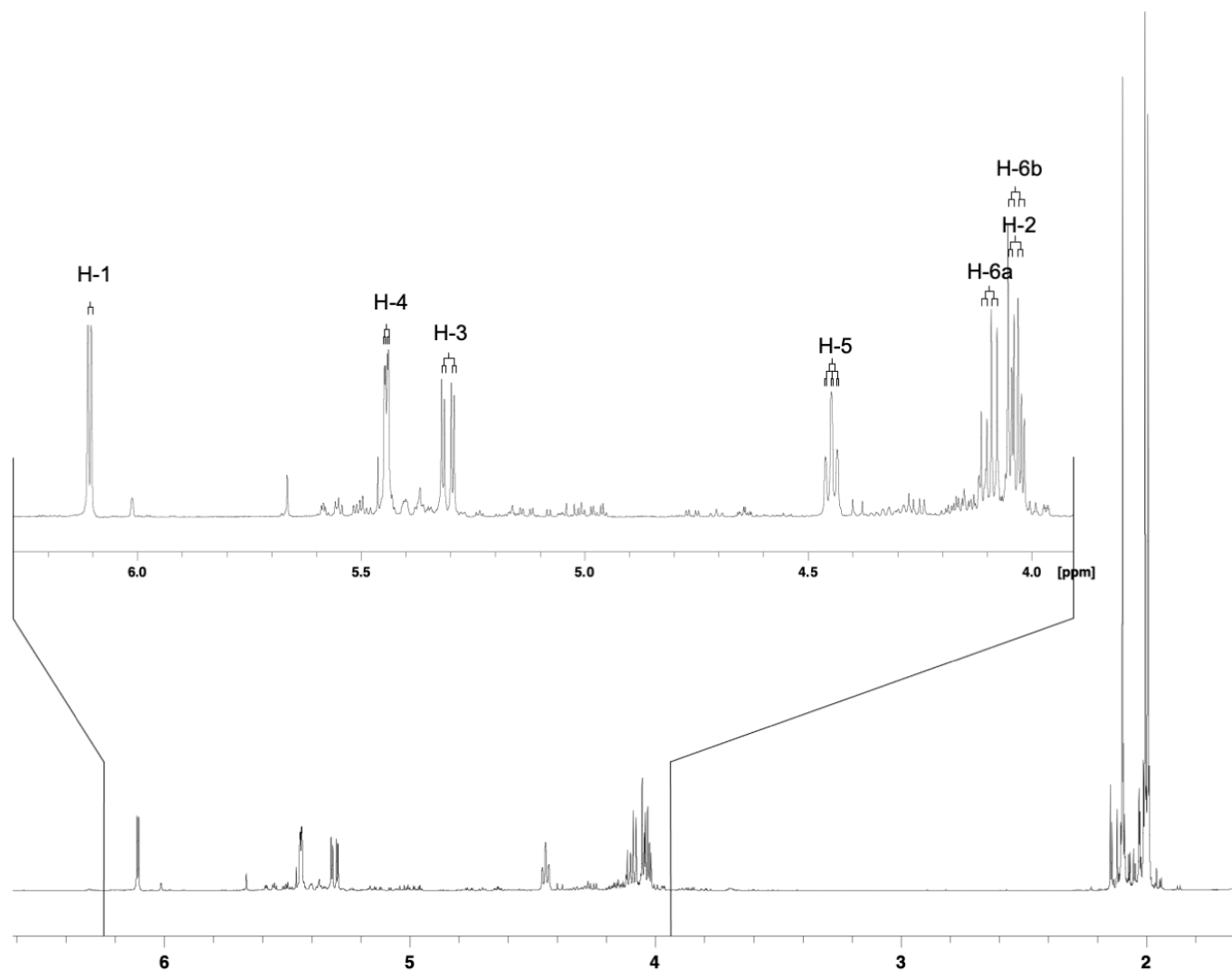


Figure 2: ¹H NMR spectrum of a crude compound 2.

References

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