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Novel C-3 Epimerization of Glycals by Metal Chlorides

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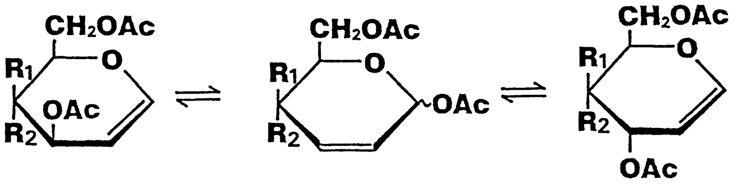
Treatment of tri-O-acetyl-D-glycals, e.g., tri-O-acetyl-D-glucal, tri-O-acetyl-D-allal and tri-O-acetyl-D-galactal, with metal chlorides in acetic anhydride afforded the C-3 epimer of the glycal triacetate with *pseudo*-glycal triacetate and unreacted glycal triacetate as an equilibrium mixture. The C-3 epimer of the glycal was readily separated from the reaction mixture using preparative HPLC.

Glycals are considered to be potential candidates for constructing many functional materials in both the pharmaceutical and industrial fields. Semi-synthetic aminocyclitols, for instance, may be constructed from a *pseudo*-disaccharide and a glycal in either of two ways, with the glycal being the synthon for either the "prime ring" or the "double-prime ring". [1,2] Recently, naturally rare sugars have been attracting much interest because of their unique biological properties. Naturally rare aldohexoses may be obtained by the epimerization of the hydroxyl group at the C-3 position of naturally abundant aldohexoses. Glycals will be one of the most promising intermediates for the preparation of naturally rare aldohexoses, because glycals can be readily converted to the corresponding glycopyranoses. Klaić et al. reported that heptamolybdate catalyzed the isomerization of tri-O-acetyl-D-glycal into *pseudo*-glycal triacetate in acetic anhydride.[3] But the formation of the C-3 epimer in the reaction mixtures was not recognized. The method for the C-3 epimerization, so far, has not been developed.



1 **2** **3**

1a, 2a, 3a	R_1 = H, R_2 = OAc
1b, 2b, 3b	R_1 = OAc, R_2 = H

This communication deals with the novel C-3 epimerization of glycals by the metal chlorides in acetic anhydride.

3,4,6-Tri-O-acetyl-D-glucal (1a) (185.0 mg, 0.68 mmol) was reacted in the presence of nickel chloride hexahydrate (161.6 mg, 0.68 mmol) in acetic anhydride (8 mL) as a solvent at 120 ℃ for 1 h with stirring. After the reaction, the solvent was evaporated in vacuum and the methanolic solution of the residue was passed through a cation-exchange resin column (Amberlyst 15, Na^+ type. Rohm and Haas Co., Philadelphia, USA) to remove nickel chloride. The combined eluent was evaporated to dryness, the residue was redissolved in ethyl acetate to remove the insoluble salt, filtered and then evaporated in vacuum to give the product as a syrup. From the measurements of ^{13}C NMR and ^1H NMR spectroscopy, it was indicated that the reaction product consisted exclusively of 3,4,6-tri-O-acetyl-D-allal (3a), the C-3 epimer of the glucal, 1,4,6-tri-O-acetyl-α,β-D-erythro-hex-2-enopyranose (*Pseudo*-D-glucal triacetate) (2a) and the recovered 3,4,6-tri-O-acetyl-D-glucal (1a). Deacetylated product was fractionated using a preparative HPLC column to confirm the structures of each component.4) Figure 1 shows the ^{13}C NMR spectrum for the reaction mixture of 1a and nickel chloride (Run 1) after ion exchange chromatography. Figure 2 shows the preparative HPLC profiles of the deacetylated reaction product. The preparative HPLC4) allowed the complete resolution of the mixture into three fractions, of which that eluted first was crystalline; the ^{13}C NMR and ^1H NMR spectra of its acetylated product indicated the crystalline compound

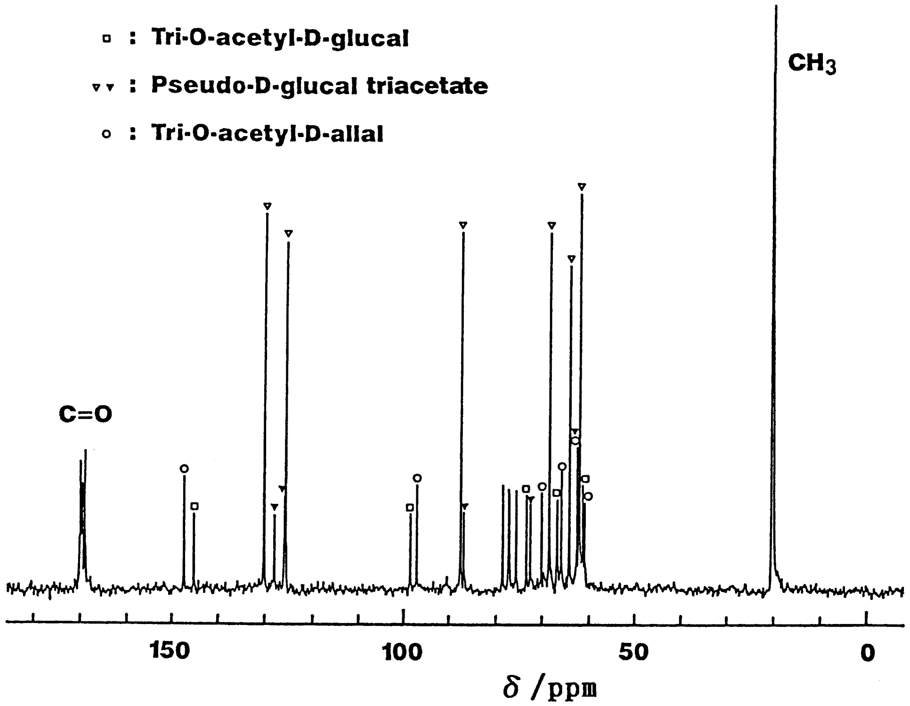


Fig. 1. ^{13}C NMR spectrum for the reaction mixture of tri-O-acetyl-D-glucal (1a) and $NiCl_2 \cdot 6H_2O$ (Run 1) after ion exchange chromatography.

to be α, β-D-erythro-hex-2-enopyranose. D-allal and D-glucal were then eluted.[5] ^{13}C NMR[6] and ^{1}H NMR spectra of each acetylated fraction were completely assigned and agreed with the data given in the literature.[1] Compositions of the equilibrium mixtures as determined by ^{1}H NMR[7] and HPLC[4] calibrated with the authentic standards were 14.6%, 65.5%,and 19.9% for 3a, 2a,and 1a, respectively. From these results, it was confirmed that the novel C-3 epimerization of tri-O-acetyl-D-glucal (1a) occurred by the reaction of nickel chloride in acetic anhydride. Figure 3 shows the correlation between the yield of the C-3 epimer, 3a, and the molar ratio of nickel chloride and 1a as determined by the HPLC and ^{1}H NMR. It was found that the yield of 3a increased when increasing amounts of nickel chloride was used. But the yield of the C-3 epimer, 3a, reached its maximum value of 19.9% when the molar ratio of $NiCl_2 \cdot 6H_2O$/glucal was greater than 1.0.

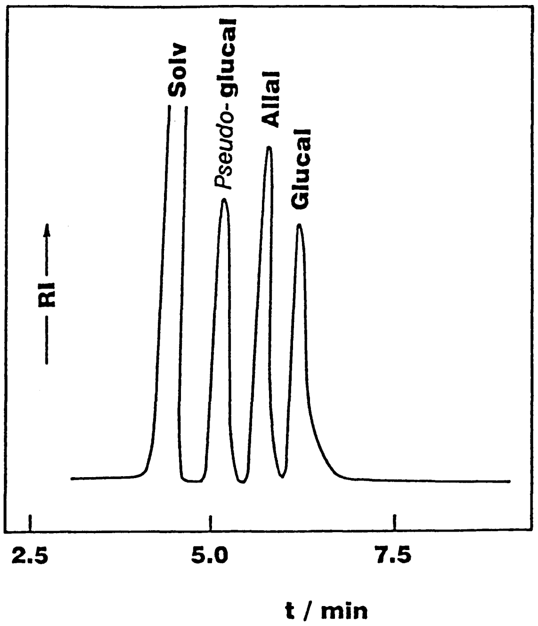


Fig. 2. HPLC chromatogram of D-glucal, α, β-D-erythro-hex-2-enopyranose (*pseudo*-D-glucal) and D-allal.[4]

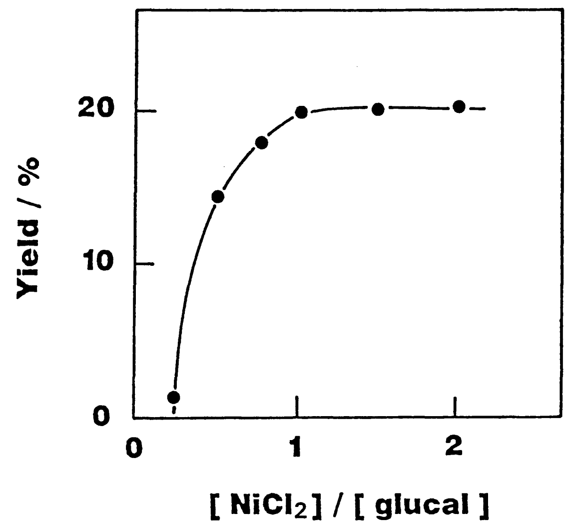


Fig. 3. Yield of tri-O-acetyl-D-allal (3a) by the C-3 epimerization of 1a *vs.* molar ratio of nickel chloride and 1a.

On the other hand, treatment of tri-O-acetyl-D-allal (3a) with nickel chloride hexahydrate in acetic anhydride also afforded the same equilibrium mixture as that obtained from tri-O-acetyl-D-glucal (1a) (Table 1, Run 2). It seems that the C-3 epimerization occurs through the initial isomerization of 1a to 2a followed by the production of the C-3 epimer, 3a, as shown in the reaction scheme. Similar results were obtained using some other metal halides as shown in Table 1. The ratios of 3a, 2a,and 1a in the reaction mixtures were essentially identical.

Table 1. C-3 epimerization reaction of tri-O-acetyl-D-glycal by metal chloride in acetic anhydride at 120 ℃ for 1 h[a)]

Run	Substrate	Metal chloride	Reaction composition / %[b)]		
			1a	2a	3a
1	1a	$NiCl_2 \cdot 6H_2O$	14.6	65.5	19.9
2	3a	$NiCl_2 \cdot 6H_2O$	14.1	67.8	18.1
3	1a	$CuCl_2 \cdot 2H_2O$	14.5	67.3	18.2
4	1a	$CoCl_2 \cdot 6H_2O$	15.2	65.5	19.3
5	1a	$MnCl_2 \cdot 4H_2O$	14.5	66.1	19.4

a) Molar ratio of [metal chloride]/[glycal] = 1/1.

b) Reaction composition was determined both by ^{1}H NMR and HPLC.

It was also found that this C-3 epimerization occurred in tri-O-acetyl-D-galactal (1b) to yield an equilibrium mixture containing tri-O-acetyl-D-gulal (3b) (26.8%) and *pseudo*-D-galactal triacetate (2b) (65.9%) and recovered tri-O-acetyl-D-galactal (1b) (7.3%). The yield of the C-3 epimer, 3b, obtained from 1b was higher than that obtained from 1a. This is probably due to the relative thermodynamic stability of these compounds.

This novel C-3 epimerization method will have potential applicability for the preparation of both naturally rare aldohexoses and glycals.

References

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4) HPLC column : TOSOH Co. Ltd., TSKgel Amide-80 ; Eluent : acetonitrile/water=75/25 ; Detection : refractive index (RI) detector (JASCO 830-RI).

5) The isolated yield of D-allal from 1a was 15.8%.

6) ^{13}C NMR ($CDCl_3$) : 1a δ 169.5, 169.1 (C=O), 145.3 (C-1), 98.7 (C-2), 73.6 (C-5), 67.1 (C-3), 66.9 (C-4), 61.0 (C-6), 20.7 (CH_3) ; 2a δ 170.0, 169.6, 169.1, 168.9 (C=O), 130.2 (β-C-3), 128.0 (α-C-3), 126.0 (α-C-2), 125.6 (β-C-2), 87.7 (β-C-1), 87.0 (α-C-1), 72.8 (α-C-4), 68.7 (β-C-4), 64.4 (β-C-5), 62.8 (α-C-5, α-C-6), 62.2 (β-C-6), 20.7, 20.5 (CH_3) ; 3a δ 170.0, 169.1 (C=O), 147.5 (C-1), 97.2 (C-2), 70.3 (C-5), 66.1 (C-4), 62.8 (C-3), 61.5 (C-6), 20.6 (CH_3).

7) Molar ratio of 1a and 3a was determined from the peak area of the methyne proton at C-1 of each epimer by ^{1}H NMR spectroscopy (270 MHz, $CDCl_3$).

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