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### STUDIES ON CARBOHYDRATES X. A NEW METHOD FOR THE PREPARATION OF ISOPROPYLIDENE SACCHARIDES

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Abstract: Cabohydrates reacting with acetone in the presence of molecular sieve and p-toluene sulfonic acid provided a simple, convenient, high yield and good selective process for preparation of isopropylidene carbohydrates.

The formation of acetal and ketal was widely applied to carbohydrate chemistry, which played important part in the selective protection for hydroxy group of carbohydrates. Isopropylidenation was more widely used in the carbohydrate chemistry, because it would not introduce chiral center. Therefore it was significant to seek a handy and effective method of isopropylidenation.

Classical isopropylidenation was achieved in the presence of sulfuric acid-copper sulfate or other acids as catalytic agent<sup>1)</sup>. This method was successful for some saccharides, but ineffective for some others. For example, isopropylidenation of  $\alpha$ -methyl-D-glucoside failed with sulfuric acid-copper sulfate as catalyst and only produced a small amount of  $\alpha$ -methyl-4, 6-isopropylidene-D-glucoside with ZnCl<sub>2</sub> as catalytic agent<sup>2)</sup>. Since the sixties, 2, 2-dimethoxy propane was developed as an isopropylidenation agent. However, besides the normal product, side reaction took place with this method<sup>3)</sup>. Although Catelani et al.<sup>4)</sup> recently found a method to remove 2-methoxy isopropyl group from protected carbohydrate which would not affect isopropylidene group, it need more reaction steps. In this paper, we reported a new method of isopropylidenation by the addition of molecular sieve. It was easy

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Reactant	Time(h)	Products	mp(°C)	Yield(%)	
L-rhamnose	1	2, 3-isopropylidene-L-rhamnose	8889	•94.5	<sup>▶</sup> 52. 5 <sup>5)</sup>
α-allyl-D- galactoside	1.5	α-allyl-3,4-isopropylidene-D -galactoside	syrup	81.3	68. 0 <sup>6)</sup>
-		α-allyl-4,6-isopropylidene-D -galactoside	syrup	16.0	
D-ribose	1	2,3-isopropylidene-D-ribofuranose	syrup	84.0	36. 07)
		1,2-isopropylidene-D-ribofuranose	85-87	8.0	
D-galactose	8	1,2:3,4-diisopropylidene-D -galactose	89-91	89.0	
1,6-anhydro- D-galactose	2	1,6-anhydro-3,4-isopropylidene- D-galactose	148-9	92. 0	
α-methyl-D- mannoside	48	α-methyl-2,3:4,6-diisopropylidene- D-mannoside	syrup	29.6	11. 38)
		α-methyl-2,3-isopropylidene-D- mannoside	syrup	37.0	6.6
D-mannose	36	diisopropylidene-D-mannose	122-3	86.1	
a-methyl-D glucoside	48	α-methyl-4,6-isopropylidene-D -glucoside	76-77	66.6	*little <sup>2)</sup>
glycerin	2	1,2-isopropylidene-glycerin	syrup	89.0	
		1,3-isopropylidene-glycerin	syrup	8.5	

Table 1: Preparation of Isopropylidene Carbohydrates Using a new Method

\* The yields obtained with the new method.

<sup>b</sup> The yields obtained with classic methods.

to operate and enabled the reaction to be completed in a mild condition. The substrate, molecular sieve (4Å) and catalytic quantity of p-toluene sulfonic acid were added to acetone and the mixture was refluxed for several hours. The overall yields were usually high, e. g., the isopropylidenation of L-rhamnose gave nearly quantitatively 2,3-isopropylidene-L-rhamnose (yield: 94.5%), while the yield of product was only 50-55% with hydrogen chloride as catalyst<sup>50</sup>. In the case of  $\alpha$ -allyl-D-galactoside, it gave 97% yield of products in which  $\alpha$ -allyl-3, 4-isopropylidene-D-galactoside and  $\alpha$ -allyl-4, 6-iso-

propylidene-D-galactoside were 81% and 16% respectively, while the yield of  $\alpha$ -allyl-3, 4-isopropylidene-D-galactoside was 68% with 2, 2dimethoxypropane as isopropylidening agent<sup>6</sup>). Similarly 92% yield of 3, 4isopropylidene-1, 6-anhydrous-D-galactoside was obtained from 1, 6-anhydrous-D-galactoside. Isopropylidenation of  $\alpha$ -methyl-D-glucoside gave 66. 6% yield of  $\alpha$ -methyl-4, 6-isopropylidene-D-glucoside, while there was some trouble with the classical method<sup>2</sup>). The results obtained using a variety of carbohydrate were shown in Table 1.

In addition, this method usually proceeds with good selectivity. Isopropylidenation of  $\alpha$ -methyl-D-glucoside, D-mannose, D-galactose, L-rhamnose or 1,6-anhydro-D-galactose gave only one product respectively and in the case of  $\alpha$ -allyl-D-galactoside, a small amount of side product,  $\alpha$ -allyl-4, 6-isopropylidene-D-galactoside, was also formed.

#### EXPERIMENTAL

General — Melting points were talen on a X4 micro hot-stage m. p. apparatus, and are uncorrected.  ${}^{1}$ H — NMR spectra were taken in CDCl<sub>3</sub> solution with TMS as an internal standard in a VARIAN-FX90 or XL300 spectrometer. Optical rotations were measured in acetone with a polartronic-D-automatic polarimeter. Column chromatography was performed on silica-gel H (Qing Dao Chemical Co.).

General procedure for the isopropylidenation of saccharides—Substrate (2.0g) was dissolved in a mixture of acetone (50.0ml) and p-toluene sulfonic acid (2.0g) in the presence of molecular sieve (4 Å) (5.0g). The whole was stirred and refluxed for several hours with exclusion of moisture. When TLC showed the absence of substrate and the presence of product, the mixture was cooled. Molecular sieve was filtered off and washed thoroughly with small quantities of acetone  $(4 \times 5ml)$ . Pyridine (0.2ml) was added to neutralize the acid and the solvent was evaporated off. Fractionation of the residue on a column of silica gel H, products were obtained.

2,3-Isopropylidene-L-rhamnose. — Reaction time 1 h, yield 94.5%, m. p. 88-89°,  $[\alpha]_D^{25}$ +17.8°(c 1.1, water). <sup>1</sup>H NMR(CDCl<sub>3</sub>):  $\delta$  5.35(s, 1 H, H-1), 4.84-3.82(m, 4 H, H-2, H-5), 3.18(bs, 2 H, 2 OH), 1,50 and 1. 44(2s, 6 H, CCH<sub>3</sub>), 1.33(d, 3 H, sugar CH<sub>3</sub>).

Anal. Calc. for C<sub>9</sub>H<sub>16</sub>O<sub>5</sub>(204. 23): C, 52. 93; H, 7. 90. Found: C, 52. 87; H, 7. 98.

Allyl 3,4-isopropylidene- $\alpha$ -D-galactopyranoside and allyl 4, 6-isopropylidene- $\alpha$ -D-galactopyranoside. — Reaction time 1.5 h, 3,4-isopropylidene derivative was obtained in 81.3% yield as a syrup,  $[\alpha]_{5}^{5}+131^{\circ}(c 1.0, chlo$  $roform); <sup>1</sup>H NMR(CDCl<sub>3</sub>): <math>\delta$  6.18-5.72(m,1 H, -CH=), 5.40-5.12(m, 2 H, =CH<sub>2</sub>), 4. 93(d,  $J_{1,2}$ =4. 2 Hz, H-1), 4. 32-3. 80(m, 8 H, OCH<sub>2</sub>CH= and sugar CH, CH<sub>2</sub>), 3. 59(bs, 2 OH), 1. 50 and 1. 36(2s, 6H, CCH<sub>3</sub>).

Anal. Calc. for C<sub>12</sub>H<sub>20</sub>O<sub>6</sub>(260. 29): C, 55. 37; H, 7. 75. Found: C, 55. 56; H, 7. 46.

4,6-Isopropylidene derivative was obtained in 16.0% yield as a syrup;  $[\alpha]_D^{25}$ -125.5(c 1.1,chloroform). <sup>1</sup>H NMR(CDCl<sub>3</sub>):  $\delta$  6.40-5.60(m, 1 H, -CH=), 5.52-5.08(m, 2 H, =CH<sub>2</sub>), 5.00(s, 1 H, H-1), 4.40-3.40(m, 8 H, OCH<sub>2</sub>CH= and sugar CH, CH<sub>2</sub>), 1.48(s, 6 H, CCH<sub>3</sub>).

Anal. Calc. for C<sub>12</sub>H<sub>20</sub>O<sub>6</sub>(260. 29): C, 55. 37; H, 7. 75. Found: C, 55. 47; H, 7. 83.

2, 3-Isopropylidene-D-ribofuranose. — Reaction time 1 h, yield, 80. 0%, syrup;  $[\alpha]_{D}^{25}$ -27.5(c 1.0, chloroform), <sup>1</sup>H NMR(CDCl<sub>3</sub>):  $\delta$  5.43(s, 1 H, H-1), 4.85(d, 1 H, J<sub>3,2</sub>=6.0Hz, H-3), 4.75(bs, 2 H, OH), 4.59(d, 1 H, J<sub>2,3</sub>=6.0Hz, H-2), 4.42(t, 1 H, H-4), 3.75(d, 2 H, J<sub>5,4</sub>=3.6 Hz, H-5), 1.41(s, 6 H, CMe<sub>2</sub>).

Anal. Calc. for C<sub>8</sub>H<sub>14</sub>O<sub>5</sub>(190. 20): C, 50. 52; H, 7. 42. Found: C, 50. 40; H, 7. 25.

1,2-Isopropylidene-D-ribofuranose. - It was separated on the above same column of silica gel, yield 8.0%, m. p. 85-87°; <sup>1</sup>H NMR(CDCl<sub>3</sub>): $\delta$  5.94(d, 1 H, J<sub>1,2</sub>=3.8 Hz, H-1), 5.3-3.0(m, 7 H, 2 OH, H-2 to H-5), 1.4(m, 6 H, CMe<sub>2</sub>).

Anal. Calc. for C<sub>8</sub>H<sub>14</sub>O<sub>5</sub>(190. 20): C, 50. 52; H, 7. 42. Found: C, 50. 36; H, 7. 51.

1, 2: 3, 4-Diisopropylidene-D-galactose. — Reaction time 8 h, yield 89%, m. p. 89-91°;  $[\alpha]_{b}^{25}$ -60. 9°(c 1. 1, chloroform). <sup>1</sup>H NMR(CDCl<sub>3</sub>): 8 5. 92(d, 1 H, J<sub>1,2</sub>=4 Hz, H-1), 4. 58(dd, 1 H, J<sub>2,1</sub>=4 Hz, J<sub>2,3</sub>=1. 2 Hz, H-2), 4. 40(q, 1 H, J<sub>5,4</sub>=J<sub>5,6b</sub>=7 Hz, H-5), 4. 15(dd, 1 H, J<sub>3,2</sub>=1. 2 Hz, J<sub>3,4</sub>=4. 5 Hz, H-3), 4. 11(dd, 1 H, J<sub>64,5</sub>=7 Hz, J<sub>64,6b</sub>=8. 4 Hz, H-6a), 3. 90(dd, 1 H, J<sub>4,3</sub>=4. 5 Hz, J<sub>4,5</sub>=7 Hz, H-4), 3. 88(dd, 1 H, J<sub>6b,5</sub>=7 Hz, J<sub>6b,6a</sub>=8. 4 Hz, H-6b), 2. 61(bs, 1 H, OH), 1. 58, 1. 49, 1. 41 and 1. 39(4s, 12 H, CCH<sub>3</sub>).

Anal. Calc. for C<sub>12</sub>H<sub>20</sub>O<sub>6</sub>(260. 29): C, 55. 37; H, 7. 74. Found: C, 55. 48; H, 7. 59.

1,6-Anhydro-3,4-isopropylidene-D-galactopyranose. — Reaction time 2 h, yield 92%, m. p. 148-9°,  $[\alpha]_D^{25}$  — 60. 7 (c 0. 9, CH<sub>2</sub> Cl<sub>2</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  5. 36(s, 1H, H-1), 4. 50-3. 52(m, 6 H, sugar CH, CH<sub>2</sub>), 2. 34 (bs, 1 H, OH), 1. 56 and 1. 38(2s, 6 H, CCH<sub>3</sub>).

Anal. Calc. for C<sub>9</sub>H<sub>14</sub>O<sub>5</sub>(202. 21): C, 53. 46; H, 6. 98. Found: C, 53. 55; H, 7. 24.

Methyl 2,3:4,6-diisopropylidene-α-D-mannoside. — Reaction time 48 h, yield 29.6%, syrup; [α]<sup>25</sup>+3°(c 2.4, MeOH). <sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 4.91

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(s, 1 H, H-1), 4. 16-3. 50(m, 6 H, sugar CH, CH<sub>2</sub>), 3. 37(s, 3 H, OCH<sub>3</sub>), 1. 56, 1. 53, 1. 43 and 1. 35(4s, 12 H, CCH<sub>3</sub>).

Anal. Calc. for C<sub>13</sub>H<sub>22</sub>O<sub>6</sub>(274. 32): C, 56. 92; H, 8. 08. Found: C, 57. 13; H, 8. 24.

Methy 2,3-isopropylidene- $\alpha$ -D-mannoside. — It was obtained also from the above reaction, yield 37.0%, syrup,  $[\alpha]_D^{25}$ +44.9 (c 1.0, chloroform). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$ 4.80(s, 1 H, H-1), 4.20-3.50(m, 8 H, CH, CH<sub>2</sub>, OH), 3.40(s, 3H, OCH<sub>3</sub>), 1.40(m, 6 H, CCH<sub>3</sub>).

Anal. Calc. for C<sub>10</sub>H<sub>18</sub>O<sub>6</sub>(234. 25): C, 51. 27; H, 7. 74. Found: C, 51. 36; H, 7. 53.

Diisopropylidene-D – mannose. – Reaction Time 36 h, yield 86. 1%, m. p. 122-3°;  $[\alpha]_{5}^{6}+26.8^{\circ}(c 1.0, chloroform)$ . <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  5. 40 (s, 1 H, H-1), 4. 80 (dd, 1 H, J<sub>3,2</sub>=5.4 Hz, J<sub>3,4</sub>=3.6 Hz, H-3), 4. 60 (d, 1 H, J<sub>2,3</sub>=5.4 Hz, H-2), 4. 38 (t, 1 H, J<sub>5,6</sub>=5.4 Hz, H-5), 4. 22 (d, 1 H, J<sub>4,3</sub>=3.6 Hz, J<sub>4,5</sub>=1.0 Hz, H-4), 4. 06 (d, 2 H, J<sub>6,5</sub>=5.4 Hz, CH<sub>2</sub>), 3. 26 (bs, 1 H, OH), 1. 46, 1. 38 and 1. 32(3s, 12H, CCH<sub>3</sub>).

Anal. Calc. for C<sub>12</sub>H<sub>20</sub>O<sub>6</sub>(260. 29): c, 55. 37; H, 7. 74. Found: C, 55. 12; H, 7. 88.

Methyl 4, 6-isopropylidene- $\alpha$ -D-glucopyranoside. — Reaction time 48 h, yield 66. 6%, m. p. 76-7°,  $[\alpha]_{0}^{25}$  + 105° (c 1. 1, water); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  4. 77 (d, 1 H, J<sub>1.2</sub> = 4 Hz, H-1), 3. 92-3. 51 (m, 6 H, CH, CH<sub>2</sub>), 3. 44 (s, 3 H, OCH<sub>3</sub>), 3. 10 (bs, 2 H, OH), 1. 53 and 1. 46 (2s, 6 H, CCH<sub>3</sub>).

Anal. Calc. for C<sub>10</sub>H<sub>18</sub>O<sub>6</sub>(234. 25); C, 51. 27; H, 7. 74. Found: C, 51. 43; H, 7. 91.

1,2-Isopropylidene-glycerin. — Reaction time 2 h, yield 89%, syrup; <sup>1</sup>H NMR(CDCl<sub>3</sub>):  $\delta$  4. 23 (m, 1 H, CH), 4. 04 and 3. 77(2dd, 2 H, J=6. 3, 8. 1, CH<sub>2</sub>OC), 3. 69 and 3. 60 (2dd, 2 H, J=4. 2, 11. 4, 5. 4 Hz, CH<sub>2</sub>OH), 3. 16 (bs, 1 H, OH), 1. 45 and 1. 35 (2s, 6 H, CCH<sub>3</sub>).

Anal. Calc. for C<sub>6</sub>H<sub>12</sub>O<sub>3</sub>(132.16): C,54.53; H, 9.15. Found: C, 54.28; H, 9.41.

1,3-Isopropylidene-glycerin was also separated on the same column of silica gel in 8.5% yield, syrup.

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