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A Simple Regioselective Partial Hydrolysis of Di-*O*-isopropylidene Monosaccharides with Copper(II) Ion

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Synopsis. Copper(II) ion was found to be effective for regioselective removal of the 5,6-O-isopropylidene group of α-D-mannose and α-D-glucose derivatives in alcohols at ambient temperature.

In connection with a series of reactions promoted by copper(II) ion in organic solvent,[1)] a convenient method was developed for the preparation of 1-*O*-benzoyl-2,3-*O*-isopropylidene-α-D-mannofuranose (**3**), benzyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (**4**), 3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**6**), and 6-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**7**) from the corresponding diisopropylidene monosaccharides.

Monoisopropylidene-D-mannose and -D-glucose are useful starting materials for the preparation of numerous derivatives and chiral natural products.[2)] Monoisopropylidene derivatives of monosaccharides are usually prepared from the corresponding diisopropylidene derivatives by preferential partial hydrolysis of the more acid labile 5,6-*O*-isopropylidene group. Methods reported so far[3)] have employed acetic acid or mineral acids as promoters, thus making it necessary to control pH, temperature, and/or reaction time, and evaporate a large quantity of solvent occasionally giving rise to further hydrolysis. The present method is easy, giving quantitative yield under mild conditions and not requiring certain manipulation required in other procedures.

The 5,6-*O*-isopropylidene group was regioselectively hydrolyzed by stirring a mixture of 1-*O*-benzoyl-2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**1**), benzyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside (**2**), or 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**5**) and five molar equivalents[4)] of copper(II) chloride dihydrate in ethanol or 2-propanol[5)] at room temperature to give **3**, **4**, or **6** in 97, 99, or 99% yields, respectively, after neutralization by sodium hydrogencarbonate. The prolonged reaction time and scale-up of the preparation from 0.5 to 40 g can be achieved without reduction in the yield.

Interestingly, however, when the reaction mixture of **5** was neutralized by sodium carbonate, the product was solely 6-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**7**). On the other hand, when an ethanol solution of **6** was stirred in the presence of 1 M—Na_2CO_3 at room temperature for 10—30 min, quantitative transformation of **6** into **7** was observed by measurement of the specific rotation change before and after the reaction.[6)] Thus, it was confirmed that the benzoyl group is labilized and easily migrates to the C_6-position by subtle pH change.[7)]

The β-anomer of **2** was more acid-sensitive than **2**. When a mixture of the β-anomer of **2** and a molar equivalent[9)] of copper(II) chloride dihydrate in 2-propanol was stirred at room temperature for 44 h, silica gel chromatographic separation ($CHCl_3$–MeOH 9:1 v/v) of the product after work-up provided benzyl 2,3-*O*-isopropylidene-β-D-mannofuranoside (**8**) in 30% yield, benzyl β-D-mannofuranoside (**9**) in 12% yield, and benzyl 5,6-*O*-isopropylidene-β-D-mannofuranoside (**10**) in 20% yield, along with 34% recovery of the starting diisopropylidenemannoside. The formation of **10** was rationalized by the isopropylidenation of **9** with liberated acetone *in situ*.[10)]

The copper(II)-ion promoted partial hydrolysis was inhibited in the presence of pyridine; thus, a copper complex of sugar may be a possible intermediate in this reaction which could be supported by other circumstantial evidence.[4,5)]

Experimental

Merck silica gel 60 (Art. 7734, 0.063—0.20 mm) was used for the column chromatography and Wakogel B-5 FM (Wako Pure Chem. Co., Ltd.), for the analytical TLC. TLC plates were visualized by spraying *p*-methoxybenzaldehyde–concd sulfuric acid–methanol (5:10:85 v/v) followed by heating. The optical rotations were measured with Perkin-Elmer model 241 MC polarimeter. The IR spectra were recorded on a Shimadzu IR 27 instrument. Elemental analyses were carried out in this Institute. The mp is uncorrected.

*Preparation of 1-*O*-Benzoyl-2,3-*O*-isopropylidene-α-D-mannofuranose (**3**).* A mixture of 20 g (0.055 mol) of **1** and 48 g (0.28 mol) of copper(II) chloride dihydrate in 500 ml of ethanol was magnetically stirred at room temperature for 14 h (overnight). The reaction was terminated by addition of 48 g of sodium hydrogencarbonate crystals and the mixture was stirred (mostly for 0.5—1 h) until no more carbon dioxide was evolved. Then 100 ml of water was added, further amount of carbon dioxide being evolved, and the mixture was diluted with 400 ml of water to promote precipitation. The pale blue precipitate was filtered off through celite (No. 545). The filtrate was extracted with *ca.* 500 ml of chloroform and dried over $MgSO_4$ followed by filtration. After removal of the solvent, the residue was chromatographed on a silica gel column eluted with chloroform and then with chloroform–methanol (9:1 v/v) to give 17.2 g (97% yield based on **1**, colorless amorphous powder) of **3**; $[\alpha]_D^{20}$ 37.4° (*c* 0.968, $CHCl_3$) (lit,[11)] $[\alpha]_D^{20}$ 52.5° (*c* 1.7, ethanol); IR (KBr disc) $\nu_{C=O}$ 1724 cm^{-1}.

*Preparation of Benzyl 2,3-*O*-Isopropylidene-α-D-mannofuranoside (**4**).* A mixture of 40.54 g (0.116 mol) of **2** and 98.7 g (0.58 mol) of copper(II) chloride dehydrate in 400 ml of 2-propanol was stirred overnight (*ca.* 14 h). A similar work-up to that for **1** afforded 35.5 g (99% yield, syrup) of **4**; $[\alpha]_D^{30}$ 71.1° (*c* 0.771, $CHCl_3$) (lit,[12)] mp 60—61 °C, $[\alpha]_D^{30}$ 90° (*c* 1, $CHCl_3$)).

*Preparation of 3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**6**).* A mixture of 0.5 g (1.37 mmol) of **5** and 1.2 g (7 mmol) of copper(II) chloride dihydrate in 20 ml of ethanol was stirred overnight (*ca.* 15 h). The reaction mixture was neutralized with 1.2 g of sodium hydrogencarbonate followed by a similar work-up to that for **1** to give 0.441 g (99% yield) of **6** (syrup); $[\alpha]_D^{25}$ −26.5° (*c* 0.941, ethanol) (lit,[3d] −26° (ethanol); lit,[13] −26.5° (*c* 0.859, ethanol)).

Preparation of 6-O-Benzoyl-1,2-O-isopropylidene-α-D-glucofuranose (7). A mixture of 0.5 g (1.37 mmol) of **5** and 1.2 g (7 mmol) of copper(II) chloride dihydrate in 20 ml of ethanol was stirred at room temperature for 19 h followed by neutralization with 1.2 g of sodium carbonate. A similar work-up to that for **1** afforded 0.43 g (97% yield) of **7**; recryst. from ethanol (minor)–chloroform (major); mp 195—196 °C (lit,[7] 195—197 °C); $[\alpha]_D^{26.5}$ 4.71° (*c* 0.488, ethanol) (lit,[8] 7.4° (*c* 0.535, ethanol)).

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4) The molar ratio was not optimized. However, it was found by changing the ratio of copper(II) ion quantity to diisopropylidene monosaccharide that when one molar equivalent of copper(II) ion is used in ethanol at room temperature, **2** is obtained in 79% yield in 46 h along with 20% recovery of **1**. When two molar equivalents of copper(II) ion was employed under the same conditions, **2** was obtained in 85% yield with 14% recovery of **1** in 43 h.

5) Qualitatively, the relative reaction rate was greater in ethanol than in 2-propanol. Aprotic solvents such as benzene, dioxane, *N*,*N*-dimethylformamide, and dimethyl sulfoxide were found to be unsuitable for the hydrolysis due to insolubility of copper(II) ion or the formation of copper(II) ion–solvent complex.

6) When the reaction mixture was divided into two equal parts and neutralized by sodium hydrogencarbonate and sodium carbonate, respectively, both chloroform extracts showed $[\alpha]_D^{25}$ −23° (*c* 1.12, ethanol) (lit,[3d] −26° (*c* 0.94 ethanol)) and 1.3° (*c* 0.547, ethanol) (lit,[8] 7.4° (*c* 0.535, ethanol)), respectively.

7) The migration of the acetyl group in a glucose derivative from C_3 to C_6 induced by ammonium hydroxide (pH *ca.* 9) has been reported by K. Josephson, *Justus Liebigs Ann. Chem.*, **472**, 217 (1929).

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9) When molar ratio of copper(II) ion was increased up to five, yield of **8** decreased and that of **9** increased. When the *β*-anomer of **2** was hydrolyzed by 90% acetic acid at around 50 °C for 1 h, **9** was obtained quantitatively.

10) When **9** was acetonated in acetone in the presence of one molar equivalent of copper(II) chloride dihydrate at room temperature, **9** was lost in 2 h accompanied by the formation of **10** and the diisopropylidenemannoside in equal ratio on TLC, **10** being converted into the diisopropylidenemannoside in 18 h.

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