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Indirect Electrooxidation by Using Ruthenium Tetraoxide and Chloride Ion as Recycling Mediators. Optimization for the Oxidation of Diisopropylidene-D-glucose to the Ulose

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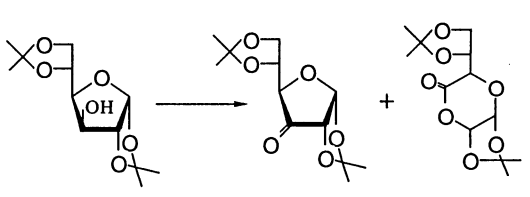
Synopsis. Various factors related to the yield and selectivity for the indirect electrooxidation of diisopropylideneglucose (**1**) to the ulose **2** with ruthenium tetraoxide (RuO_4) and chloride ion are investigated. The following is found to be optimum conditions: pH, ca. 10: solvent system, carbon tetrachloride and *t*-butyl alcohol (ca. 9:1); current density, 10—40 mA cm^{-2}; temperature, 20—40 °C; catalyst amount, 2 mol% of $RuO_2 \cdot 2H_2O$ (based on **1**). The optimized electrolysis affords the desired **2** in 90% yield along with a trace of the cleavaged product **3** (0.2%) by an overoxidation.

Ruthenium tetraoxide (RuO_4) has been utilized as a versatile reagent for oxidative transformations[1] since the first example was reported by Djerassi et al.[2] In the preceding paper, we have developed an in situ regeneration of RuO_4 from $RuO_2 \cdot 2H_2O$ or $RuCl_3$ by the electrolysis in a two-phase system consisting of an aqueous sodium chloride and an appropriate organic solvent.[3–5] This electrochemical procedure involves following three reaction steps: (1) oxidation of the substrate by RuO_4, (2) regeneration of RuO_4 from RuO_2 by the action of oxidizing chlorine species, and (3) anodic oxidation of chloride ion to the oxidizing chlorine species. Optimization of the reaction by controlling the electrolysis conditions, however, has not been examined in details. We chose 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (diisopropylideneglucose, **1**), prepared from D-glucose by isopropylidenation,[6] as a substrate for the following reasons: (a) synthetic utility of the product as a chiron pool[7] and (b) structural diversity of **1**, bearing acid-labile groups, to know the range of applicability of the method.



1 2 3

Scheme 1.

The preparation of 1,2:5,6-di-*O*-isopropylidene-α-D-ribo-hexofuranos-3-ulose (**2**) by oxidation of diisopropylideneglucose **1** has been carried out by using $CrO_3 \cdot 2Py$ (yield: 6%),[8a] PCC-Molecular Sieves (yield: 85%),[8b] DMSO-Ac_2O (yield: 62%),[9] DMSO-DCC (yield: 0—70%),[10] DMSO-P_2O_5 (yield: 45—65%),[11] DMSO-TFAA (yield: 85%),[12] RuO_4-$NaIO_4$ (yield: 75—95%),[13] photochemical oxidation of pyruvic ester,[14] and others.[15] Most of these oxidizing agents suffer from one of the following disadvantages: high cost of reagents, troublesome workup, and hazardous waste products from the oxidants. In addition, the overoxidation of **2** to the corresponding δ-lactone **3** is a problem to be circumvented.[13] In this study we have investigated the influential factors which are related with the formation of **2** from **1** in the RuO_4-mediated electrochemical process.

Experimental

Material. $RuO_2 \cdot 2H_2O$ purchased from Nippon Engelhard Company was used. The starting compound **1** prepared by the known methods[6] was purified by recrystallization from cyclohexane prior to the use. Chloroform ($CHCl_3$) was washed with water to remove ethanol before use. Aqueous buffer solutions were prepared by dissolving an appropriate phosphate or carbonate in aqueous saturated sodium chloride.

Electrolysis Apparatus. Electrolyses were usually carried out in a simple 30 ml beaker-type cell (2.5 cm diameter and 10 cm height) fitted with a condenser, a stirring bar, a thermometer, and two platinum foil electrodes (3 cm^2) being placed parallel to each other 10 mm apart. The vessel was immersed in a thermostated water bath and approximately maintained at prescribed temperature.

General Procedure for the Electrooxidation of 1. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**1**, 400 mg, 1.45 mmol) was dissolved in CCl_4 (5 ml) in an electrolysis vessel and then $RuO_2 \cdot 2H_2O$ (10 mg, 0.06 mmol) and saturated NaCl buffered at pH 9 with 0.03 M $NaHCO_3$ (10 ml) were added to this solution. To the upper aqueous layer of two phase mixture were immersed two platinum electrodes and then the entire mixture was electrolyzed under a constant current of 20 mA cm^{-2} at room temperature with a vigorous stirring. The electrolysis was continued until the organic phase has changed slightly to a yellow solution from greenish black. It required the passage of about 5 F mol^{-1} of electricity based on **1**. The mixture was treated with 2-propanol (0.5 ml) to deactivate the excess ruthenium tetraoxide. The CCl_4 layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined extracts were washed with water, dried over Na_2SO_4, and concentrated in vacuo to give 360 mg of the crude oily products. The product yields were determined with quantitative analysis with gas chromatography. The yields of the ulose **2** and the lactone **3** were 82% and 1.2%, respectively and a small amount of the starting glucofuranose **1** was recovered (7.2%).

Similar electrolysis of 1.20 g (4.62 mmol) of **1** using 0.02 g (0.12 mmol) of $RuO_2 \cdot 2H_2O$ in the mixed solvent of CCl_4 (7 ml), *t*-butyl alcohol (1 ml), and saturated NaCl buffered at pH 10 with 0.03M $NaHCO_3$ and 0.01M Na_2CO_3 (12 ml) as above required 5.1 F mol^{-1} of electricity and then the desired ketone **2**, the lactone **3**, and **1** were obtained in 90%, 0.2%, and 7% yields, respectively.

Analysis. The starting diisopropylideneglucose **1** and the products were analyzed with gas chromatography (1 m, 10% ucone oil 50HB5100/chromosorb W-HP 80/100 mesh). The quantitative analysis was performed in an internal standard method by gas chromatography (an internal standard: sulfolane).

Results and Discussion

The electrolyses of **1** were carried out in a two-phase system consisted of an organic solvent and an aqueous saturated sodium chloride solution. In order to find a suitable electrolysis solvent system, we first plotted the yields of the diisopropylidene ulose **2** by changing the kind of organic solvents under different pH ranges of an aqueous phase (Fig. 1). Carbon tetrachloride (CCl_4), 4-methyl-2-pentanone, and *t*-butyl alcohol were found to be useful for the present purpose. Of interest to note is that the product yield of the ulose **2** in a halogenated solvent such as carbon tetrachloride (CCl_4) and chloroform ($CHCl_3$) increases at basic pH range. On the other hand, acetone and 4-methyl-2-pentanone were preferable ones in the acidic conditions. The overoxidation of the ulose **2** to the δ-lactone **3** is a major problem to be solved in the present RuO_4-mediated electrooxidation. The formation of **3** can be suppressed to less than 5% by employing CCl_4 or $CHCl_3$.

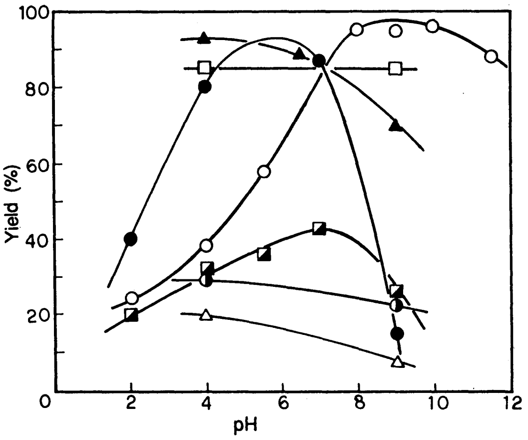


Fig. 1. Effect of pH of the aqueous phase for the formation of **2** in a two phase system consisting of a different sort of organic solvents and saturated NaCl (8 ml/12 ml). Data points of this figure were obtained by electrolysis of **1** (170 mg) in the presence of $RuO_2 \cdot 2H_2O$ (10 mg) at a current of 10 mA cm^{-2} by passing 5 F mol^{-1} of electricty. ○: CCl_4; ◑: diisopropyl ether; ●: acetone; □: *t*-butyl alcohol; ◪: $CHCl_3$; △: CH_3CN; ▲: 4-methyl-2-pentanone.

So far as the effect of current density and temperature is concerned, satisfactory conversion yields were obtained under the conditions of 10—40 mA cm^{-2} at 20—40 °C.

In order to visualize the correlation of the amount of ruthenium reagent for the ulose electrosynthesis, the conversion yields together with the current efficiencies with changing the amount of $RuO_2 \cdot 2H_2O$ are plotted in the Fig. 2. The results show the minimum amount of ruthenium reagent required for the oxidation of **1**. The both conversion yields and current efficiencies reach a plateau under the conditions of more than 1.5 mol% of $RuO_2 \cdot 2H_2O$ (based on the substrate **1**) at a current density of 20 mA cm^{-2}.

In order to clarify the correlation of the amount of ruthenium dioxide toward the current efficiency, the molar ratio of ruthenium dioxide vs. current density was plotted in terms of the conversion yield as well as the current efficiency of the ulose **2** as compiled in Fig. 3. Apparently, both the yields and the current efficiencies increase with increasing the value of RuO_2 amount divided by current density. The maximum points were obtained when the value reached about 0.2×10^{-2} [mol (A $cm^{-2})^{-1}$].

The conversion yields and the current efficiencies in the ulose electrosynthesis are referred to the substrate concentration in the media. The curves in Fig. 4 indicate that the current efficiencies and conversion yields of the ulose **2** decrease in proportion to the increase of the substrate concentration. Carbon tetrachloride can not be used for the large scale operation due to the limited solubility of the substrate **1** (maximum solubility in carbon tetrachloride: 4

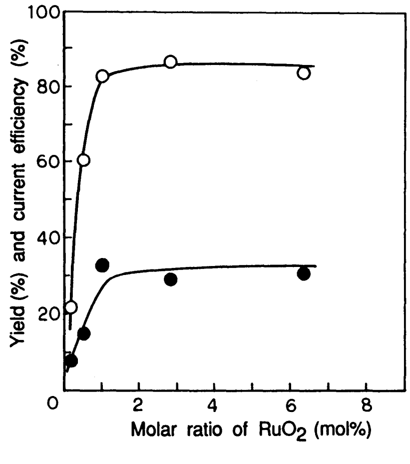


Fig. 2. Effect of molar ratio of $RuO_2 \cdot 2H_2O$ (to **1**) for the formation of **2**. Data points were obtained by electrolysis in CCl_4/saturated NaCl (8 ml/12 ml) by passing 5 F mol^{-1} of electricity. Symbols follows: product yield (○), current efficiency (●).

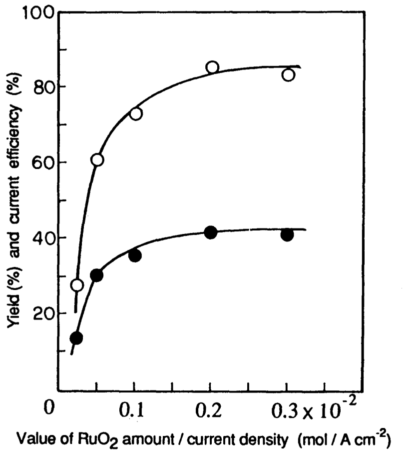


Fig. 3. Effect of value of RuO_2 amount divided by current density for the formation of **2**. Data points were obtained by the electrolysis in CCl_4/saturated NaCl (8 ml/12 ml) at a current of 20 mA cm^{-2} by passing 5 F mol^{-1} of electricity at pH 8—9. Symbols follows: product yield (○), current efficiency (●).

wt%). The co-solvent system may be a choice for the present electrooxidation in order to attain higher concentration of the substrate.

Taking the data in Fig. 1 into the account, we chose *t*-butyl alcohol as an additional solvent to carbon tetrachloride, since *t*-butyl alcohol can maintain almost same current efficiency as carbon tetrachloride. The experimental results are summarized in Fig. 5. The yields of the ulose **2** obtained in various co-solvent ratios and different pH ranges are shown as a form of contour line like as on a map. The horizontal zones are made by binding the points of the same yields. The contour lines summarize the correlation between pH values and co-solvent systems in terms of the conversion yields of the ulose **2**. Of interest to note is that two maximum zones are observed in the region of 90 vol% of carbon tetrachloride (to *t*-butyl alcohol) at about pH 10 and 10 vol% of CCl_4 (to *t*-butyl alcohol) at about pH 4. From a practical point of view, however, it is desirable to choose the electrolysis conditions of slightly basic media to prevent hydrolysis of the acetonide protecting groups.

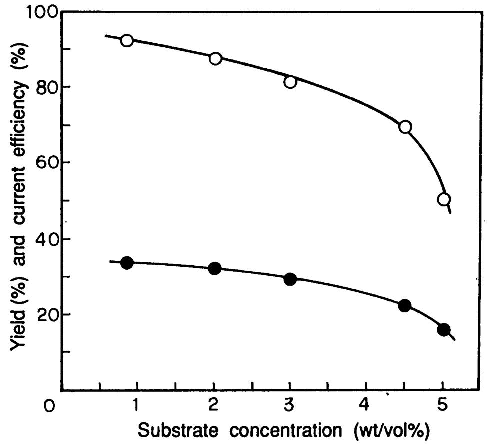


Fig. 4. Effect of substrate concentration for the formation of **2**. Data points were obtained by electrolysis in CCl_4-saturated NaCl (7 ml/14 ml) at a current density of 10 $mA\,cm^{-2}$ by passing 5.5 $F\,mol^{-1}$ of electricity at pH 8—9. Symbols follows: product yield (○), current efficiency (●).

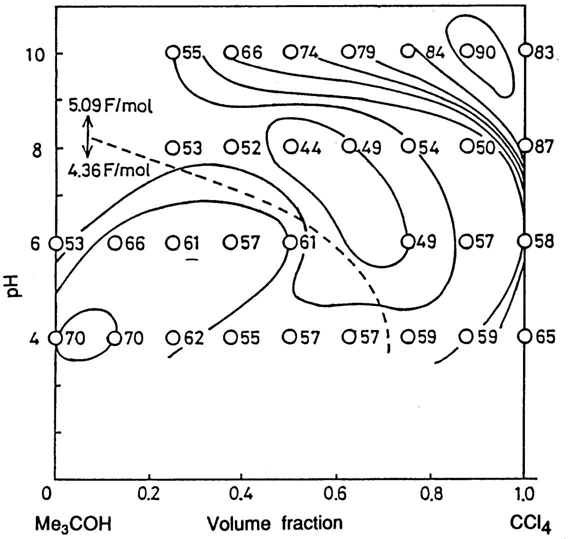


Fig. 5. Correlation between pH and CCl_4/*t*-butyl alcohol ratio for the formation of **2**. The suffix number of data points denotes the yield of **2**. These data were obtained by electrolysis at a current density of 20 $mA\,cm^{-2}$ by passing 4.36 $F\,mol^{-1}$ of electricity. The substrate concentration was 6 (wt/vol).

In conclusion, ruthenium tetraoxide has proven to be an efficient mediator as an oxidizing reagent in the present electrolysis system. The constant current electrolysis at 20 $mA\,cm^{-2}$ of **1** (1.20 g) with 20 mg of $RuO_2 \cdot 2H_2O$ at about pH 10 in CCl_4-Me_3COH (ca. 9 : 1)-saturated NaCl-(Pt) system gives **2** (ratio of **2** to **3**=ca. 450 : 1) in about 90% yields.

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