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Product-selective electroreduction of 2,3,4,5,6-pentafluorobenzoic acid to 2,3,5,6-tetrafluorobenzyl alcohol and 2,3,5,6-tetrafluorobenzaldehyde in a flow cell system

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2,3,4,5,6-Pentafluorobenzoic acid was found to be reduced product-selectively to either 2,3,5,6-tetrafluorobenzyl alcohol or 2,3,5,6-tetrafluorobenzaldehyde at a lead cathode in dilute sulphuric acid containing small amounts of a quaternary ammonium salt. A preliminary optimization of electrolytic conditions for production of either 2,3,5,6-tetrafluorobenzyl alcohol or 2,3,5,6-tetrafluorobenzal dehyde was systematically performed using a laboratory-scale flow-cell system.

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1. Introduction

Organic fluoro compounds have become of great interest in recent years because of their unique biological activities. Synthetic methods for a variety of aliphatic fluoro compounds have been developed, whereas aromatic ones have been less extensively synthesized because of limited starting compounds. 2,3,4,5,6-Pentafluorobenzoic acid (**1**) should be regarded as one of the potential starting compounds which can be converted into practically useful intermediates by means of reduction of the carboxyl and/or fluoro groups. However, methods for the reduction of **1** have not been reported so far, except for the electroreduction [1–3].

In previous work [2, 3], the electroreductive conversion of **1** into 2,3,4,5,6-pentafluorobenzyl alcohol (**2**) and 2,3,5,6-tetrafluorobenzyl alcohol (**3**) was examined using a variety of cathodes, cathode potentials, supporting electrolytes, solvents and additives in batch and flow cells and, consequently, electrolytic conditions to result in high selectivities for either **2** or **3** were established.

Carboxylic acids may be reduced to give the corresponding aldehydes in reasonable yields only in special cases where their carboxyl groups are activated by electron-withdrawing groups [4] or they are reduced in a buffered medium emulsified with insoluble organic solvents such as benzene [5], since in general the reduction of aldehydes to the corresponding alcohols occurs at less negative potentials than that for carboxylic acids to the aldehydes. In this work, we attempted to reduce **1** selectively to 2,3,5,6-tetrafluorobenzaldehyde (**4**) by modifying the electrolytic conditions established for the selective reduction of **1** to **3**. The possibility of selective reduction of **1** to the aldehyde (**4**) was also considered, since **1** has electron-withdrawing fluoro groups. Consequently, it was found that **3** and **4** could be formed at a lead cathode in sulfuric acid solutions containing small amounts of a quaternary ammonium salt. A preliminary optimization of electrolytic conditions for the selective formation of either **4** or **3** was performed using a laboratory-scale flow-cell system.

2. Experimental details

2,3,4,5,6-Pentafluorobenzoic acid (**1**) was supplied commercially from the Tokyo Kasei Chemical Co. Standard samples of **2**–**4** and other products were donated by Nippon Carbide Industries Co. Tetraethylammonium tosylate was prepared from tri-ethylamine and ethyl tosylate by a standard method.

A micro flow-cell (Electrocell AB, Sweden) was used for electrolysis. A perfluoroalkylsulphonic acid-type cation-exchange membrane, a lead cathode (3.3 cm × 3.3 cm) and a ruthenium oxide-coated titanium anode (3.3 cm × 3.3 cm) were incorporated into the cell. The catholyte was an aqueous sulfuric acid solution containing **1** and tetraethylammonium tosylate, and the anolyte was also aqueous sulfuric acid. Both the catholyte (120 cm^3) and anolyte (120 cm^3) were circulated by pumps. A schematic illustration for the micro flow cell system is shown in Fig. 1. The electrolysis was carried out galvanostatically.

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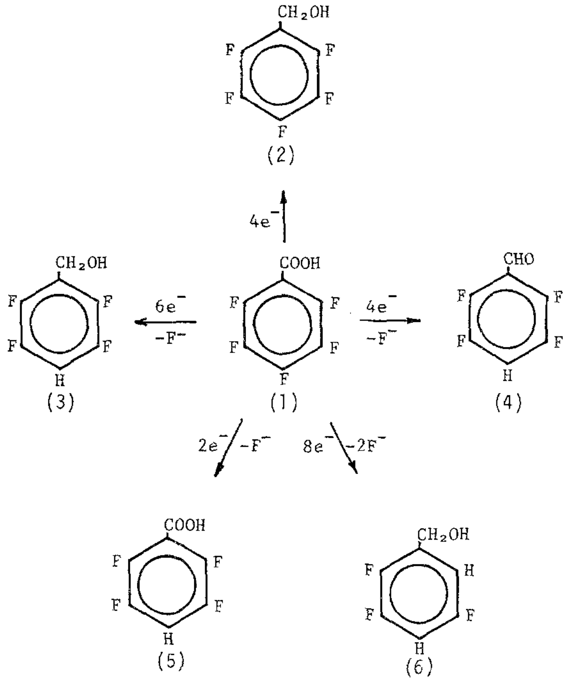


Scheme 1. Electroreduction of 2,3,4,5,6-pentafluorobenzoic acid (1).

The products and unreacted **1** were analysed using a procedure described previously [2].

3. Results and discussion

3.1. *Influence of concentration of the starting compound* (1)

As shown in Fig. 2, the yield of one (**4**) of the desired products decreased with increase in the concentration of **1**, whereas that of another (**3**) exhibited a maximum at 50 mM of **1**. Considerable amounts of 2,3,5,6-tetrafluorobenzoic acid (**5**) and 2,3,5-trifluorobenzyl alcohol (**6**) were formed as undesirable byproducts for concentrations higher than 50 mM. The products **3**–**5** were accompanied by very small amounts of their 2,3,4,5-tetrafluoro analogues which could not be quantitatively analysed. A trace of **2** was also detected. Products other than **2**–**6** were not quantitatively analysed. Material balances based on the unreacted starting compound **1** and the products **2**–**6** were in the range 90–97%. Current efficiency for the reduction of **1** to **3** + **4** also exhibited a maximum at 50 mM. A saturated concentration of **1** in the electrolytic solution used was about 90 mM.

3.2. *Influence of concentration of sulphuric acid supporting electrolyte*

Figure 3 shows the influence of sulphuric acid concentration at a constant concentration (50 mM) of **1**. The yields of **3** and **4** increased and decreased, respectively, with increase in the sulphuric acid concentration. The total yield and current efficiency for **3** + **4** had maxima at about 100 mM. Small amounts of **2** (< 1%) and **5** (< 2%) were also formed, but **6** was not detected.

3.3. *Influence of concentration of tetraethylammonium tosylate additive*

Figure 4 shows the influence of tetraethylammonium tosylate concentration at constant concentration of **1** (50 mM) and sulphuric acid (100 mM). The yield of **3** exhibited a broad maximum at about 20 mM tetraethylammonium tosylate concentration, while that of **4** did not. The total yield and current efficiency for **3** + **4** also exhibited maxima at about 20 mM. Formation of the byproducts of **2** and **5** was completely suppressed at concentrations higher than 20 mM.

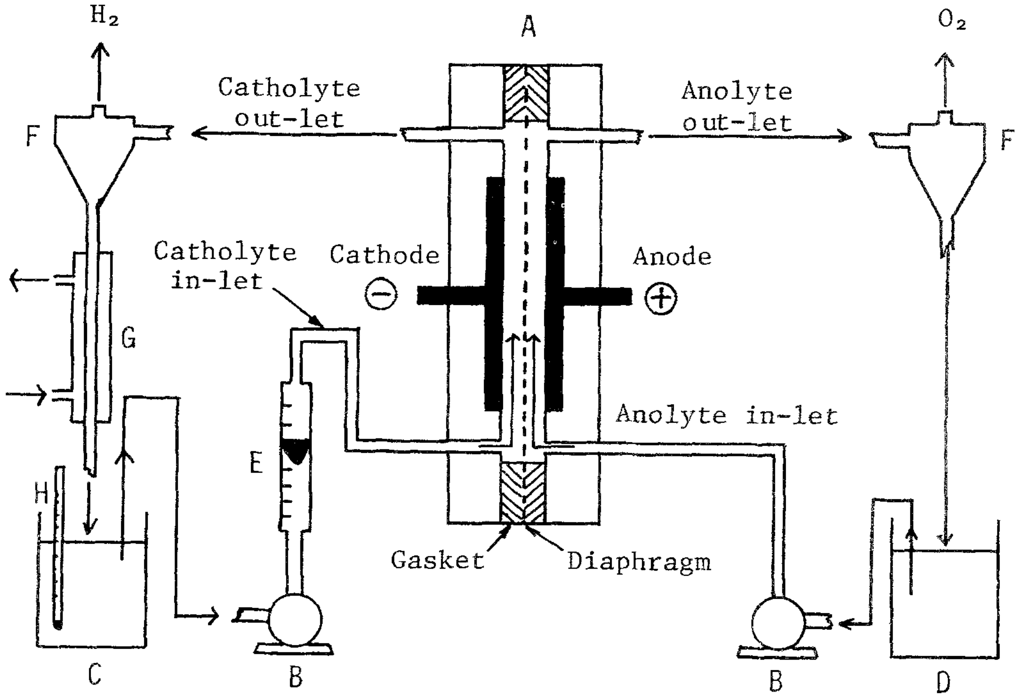


Fig. 1. Micro flow-cell system. A: Micro flow-cell (Electrosyn AB), B: Pump, C: Catholyte reservoir, D: Anolyte reservoir, E: Float-type flow meter, F: Hydrocyclone, G: Heat exchanger, H: Thermometer.

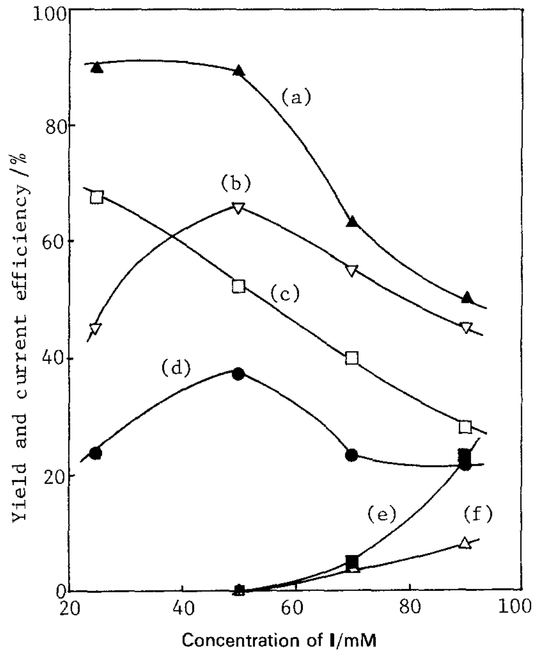


Fig. 2. Influence of concentration of 2,3,4,5,6-pentafluorobenzoic acid (**1**). Electrolytic conditions: 100 mM sulphuric acid, 20 mM tetraethylammonium tosylate. Current density: 40 mA cm^{-2}, charge passed: 2.5 F mol^{-1}, velocity: 2.3 m min^{-1}, and 25 °C. Curves (a) total yield of **3** + **4**, (b) total current efficiency for **3** + **4**, (c) yield of **4**, (d) yield of **3**, (e) yield of **5**, and (f) yield of **6**.

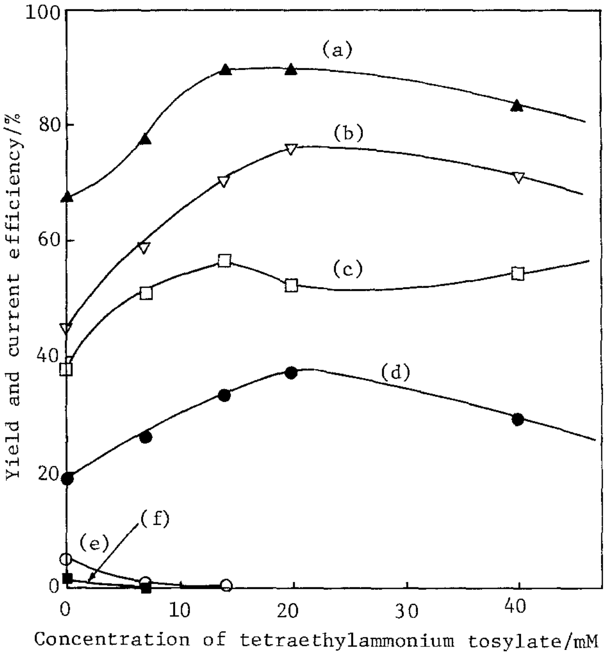


Fig. 4. Influence of concentration of tetraethylammonium tosylate. Electrolytic conditions: 50 mM 2,3,4,5,6-pentafluorobenzoic acid (**1**), 100 mM sulphuric acid. Current density: 40 mA cm^{-2}, charge passed: 2.5 F mol^{-1}, velocity: 2.3 m min^{-1} and 25 °C. Curves (a) total yield of **3** + **4**, (b) total current efficiency for **3** + **4**, (c) yield of **4**, (d) yield of **3**, (e) yield of **2**, and (f) yield of **5**.

3.4. *Influence of cathodic current density*

As shown in Fig. 5 obtained for constant concentrations of **1** (50 mM), sulphuric acid (100 mM) and tetraethylammonium tosylate (20 mM), the results were greatly affected by current density. The yield of **3** exhibited a maximum at 40 mA cm^{-2}, whereas that of **4** increased with increase in current density. The total yield and current efficiency for **3** + **4** also exhibited maxima near 40 mA cm^{-2}. It was noted that considerable amounts of **5** were formed at current densities lower than 40 mA cm^{-2}.

3.5. *Influence of amount of charge passed*

Figure 6 shows results obtained when the amount of charge passed was varied at constant concentrations

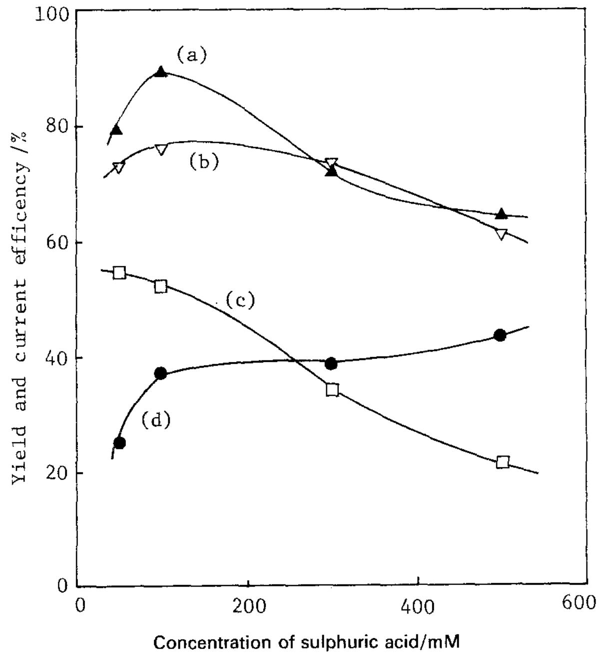


Fig. 3. Influence of concentration of sulphuric acid. Electrolytic conditions: 50 mM 2,3,4,5,6-pentafluorobenzoic acid (**1**), 20 mM tetraethylammonium tosylate. Current density: 40 mA cm^{-2}, charge passed: 2.5 F mol^{-1}, velocity: 2.3 m min^{-1} and 25 °C. Curves (a) total yield of **3** + **4**, (b) total current efficiency for **3** + **4**, (c) yield of **4**, and (d) yield of **3**.

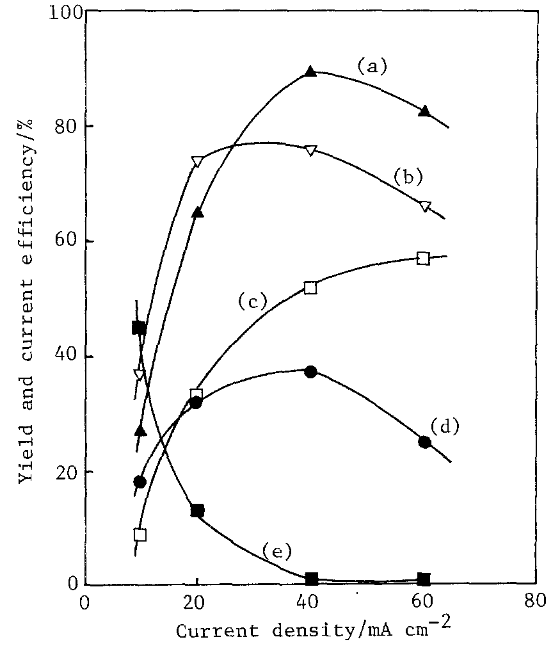


Fig. 5. Influence of cathodic current density. Electrolytic conditions: 50 mM 2,3,4,5,6-pentafluorobenzoic acid (**1**), 100 mM sulphuric acid, 20 mM tetra-ethylammonium tosylate. Charge passed: 2.5 F mol^{-1}, velocity: 2.3 m min^{-1} and 25 °C. Curves (a) total yield of **3** + **4**, (b) total current efficiency for **3** + **4**, (c) yield of **4**, (d) yield of **3**, and (e) yield of **5**.

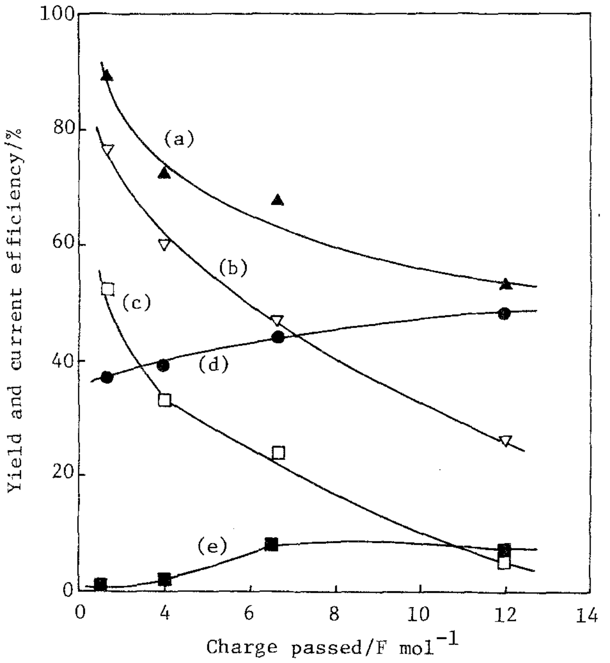


Fig. 6. Influence of charge passed. Electrolytic conditions: 50 mM 2,3,4,5,6-pentafluorobenzoic acid (**1**), 100 mM sulphuric acid, 20 mM tetra-ethylammonium tosylate. Current density: 40 mA cm^{-2}, velocity: 2.3 m min^{-1} and 25 °C. Curves (a) total yield of **3** + **4**, (b) total current efficiency for **3** + **4**, (c) yield of **4**, (d) yield of **3**, and (e) yield of **5**.

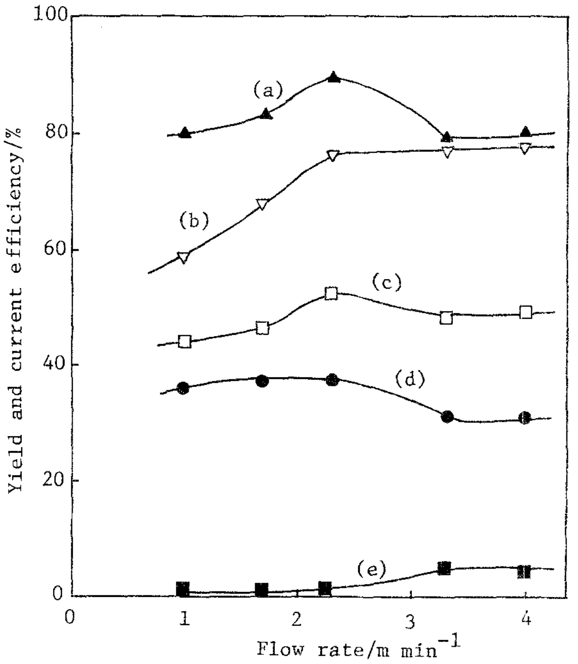


Fig. 7. Influence of flow rate. Electrolytic conditions: 50 mM 2,3,4,5,6-pentafluorobenzoic acid (**1**), 100 mM sulphuric acid, 20 mM tetra-ethylammonium tosylate. Current density: 40 mA cm^{-2}, charge passed: 2.5 F mol^{-1} and 25 °C. Curves (a) total yield of **3** + **4**, (b) total current efficiency for **3** + **4**, (c) yield of **4**, (d) yield of **3**, and (e) yield of **5**.

of **1** (50 mM), sulphuric acid (100 mM) and tetraethylammonium tosylate (20 mM) at a constant current density of 40 mA cm^{-2}. The yield of **3** increased slightly with increase in the amount of charge passed, while that of **4** decreased severely. Consequently, the total yield and current efficiency for **3** + **4** also decreased. Formation of byproduct **5** was promoted for a charge greater than 2.5 F mol^{-1}. A trace amount ($< 0.1\%$) of **2** was also formed.

3.6. *Influence of flow rate of catholyte*

Figure 7 shows the influence of catholyte flow rate at constant concentrations of **1** (50 mM), sulphuric acid (100 mM) and tetraethylammonium tosylate (20 mM) at constant current density (40 mA cm^{-2}) and amount of charge passed (2.5 F mol^{-1}). Although the influence of flow rate on the yields of **3** and **4**, and on the total yield and current efficiency for **3** + **4** was not significant, maxima appeared near 2.3 m min^{-1} flow velocity. Moreover, considerable amounts ($< 5\%$) of **5** were formed at velocities higher than 2.3 m min^{-1}.

3.7. *Influence of temperature*

The yield of **3** exhibited a maximum at 25 °C, whereas that of **4** decreased with increase in temperature, as shown in Fig. 8, which was obtained at a variety of temperatures for constant concentrations of **1** (50 mM), sulphuric acid (100 mM) and tetraethylammonium tosylate (20 mM) at constant current density (40 mA cm^{-2}) and flow velocity (2.3 m min^{-1}). The total yield and current efficiency for **3** + **4** had maxima at about 25 °C. Formation of considerable amounts of byproduct **5** took place at temperatures higher than 25 °C.

3.8. *Results under optimized conditions*

Through Figs 2–8 the highest yield (48%) and product-selectivity (80%) for the desired product **3** were obtained under the conditions of Run 1 in Table 1. On the other hand, the highest yield (67%) and selectivity (75%) for product **4** were obtained in Run 3 which also gave the highest total yield (90%) for **3** + **4**. Run

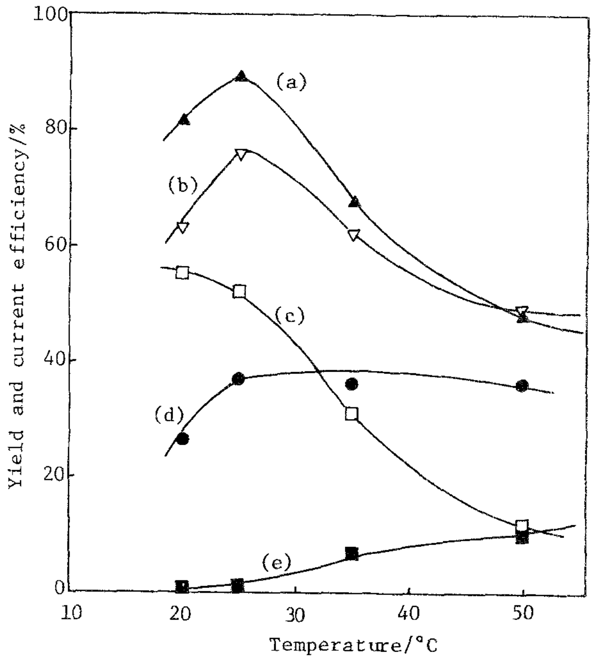


Fig. 8. Influence of temperature. Electrolytic conditions: 50 mM 2,3,4,5,6-pentafluorobenzoic acid (**1**), 100 mM sulphuric acid, 20 mM tetra-ethylammonium tosylate. Current density: 40 mA cm^{-2}, charge passed: 2.5 F mol^{-1} and velocity: 2.3 m min^{-1}. Curves (a) total yield of **3** + **4**, (b) total current efficiency for **3** + **4**, (c) yield of **4**, (d) yield of **3**, and (e) yield of **5**.

Table 1. Electrolytic results under optimized electrolytic conditions

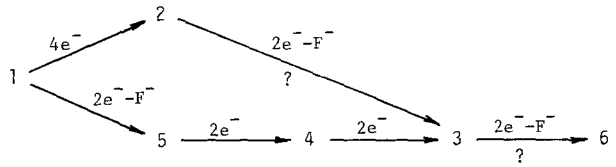
Run		*1*	*2*	*3*
Optimized conditions	Concentration of **1** (mM)	50	50	25
	Concentration of sulphuric acid (mM)	100	100	100
	Concentration of tetraethylammonium tosylate (mM)	20	20	20
	Cathodic current density (mA cm^{-2})	40	40	40
	Charge passed (F mol^{-1})	12	2.5	2.5
	Flow rate of catholyte (m min^{-1})	2.3	4.0	2.3
	Temperature (°C)	25	25	25
Electrolytic results	Yield of **3** (%)	48	31	23
	Yield of **4** (%)	5	40	67
	Selectivity for **3** (%)	80	41	25
	Selectivity for **4** (%)	8	53	75
	Total yield of **3** + **4** (%)	53	71	90
	Total current efficiency for **3** + **4** (%)	26	78	45
	Byproducts	**2** (0.1%) **5** (7%)	**5** (4%)	**2** (0.1%) **5** (trace) **6** (trace)

2 afforded the highest total current efficiency (78%) for **3** + **4**, though the selectivity for either **3** (41%) or **4** (53%) was very low.

2,3,4,5,6-Pentafluorobenzyl alcohol (**2**) is also a useful polyfluorinated aromatic chemical, and it has been reported that **2** can be selectively synthesized by the cathodic reduction of **1** at mercury [1] or amalgamated metal [2] cathodes in strongly acidic catholytes. Combining this fact with the results obtained in the present work, it is concluded that each of the three polyfluorinated aromatic chemicals (**2**, **3** and **4**) and their mixtures can be synthesized from the common starting compound **1** with high product-selectivities and current efficiencies, respectively.

3.9. *Reaction pathways*

Reduction of **1** involves the transformation of the carbonyl group to formyl and hydroxymethyl groups and the elimination of fluorine on the aromatic ring. Therefore, the reaction pathway and mechanism are complex. The most likely and simplest reaction pathway is shown in Scheme 2, in which the reduction of **2** to **3** and of **3** to **6** is unlikely. In fact, it was confirmed that the former reduction does not take place under the conditions used.



Scheme 2. Electroreduction pathway of 2,3,4,5,6-pentafluorobenzoic acid (**1**).

Formation of not only the desired products (**3** and **4**) but also byproducts (**2**, **5** and **6**) was greatly affected by the electrolytic conditions, as shown in Figs. 2–8. Therefore, the reaction pathway is probably more complex than that represented in Scheme 2. A further mechanistic study is in progress.

4. Conclusions

Optimized conditions for the selective electroreduction of 2,3,4,5,6-pentafluorobenzoic acid (**1**) to 2,3,5,6-tetrafluorobenzyl alcohol (**3**) and 2,3,5,6-tetrafluorobenzaldehyde (**4**) were established in a flow cell system. Maximum selectivities for **3** and **4** were 80 and 75%, respectively.

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