**Regioselective Electrochemical Carboxylation of Polyfluoroarenes**

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**ABSTRACT**

Constant current electrolysis of polyfluoroarenes in DMF containing 0.1 mol dm⁻³ Bu₄NBF₄ in the presence of carbon dioxide by using a one-compartment cell equipped with a Pt cathode and a Mg anode at −40°C resulted in regiodefective cleavage of a C-F bond of the phenyl ring followed by reaction with carbon dioxide in highly regio- and chemoselective manners to give the corresponding mono-carboxylated products, polyfluorobenzoic acids, in moderate to good yields.

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1. Introduction

Since carbon dioxide (CO₂) is abundant, economical, and nontoxic and has a great potential as an environmentally benign C1 chemical source for organic synthesis, fixation of carbon dioxide in organic molecules has been an attractive project in organic synthesis. Electrochemical reduction in the presence of carbon dioxide has contributed greatly to this area because it enables efficient fixation of carbon dioxide in organic molecules even under atmospheric pressure of carbon dioxide when a reactive metal, such as magnesium or aluminum metal, is used as a sacrificial anode. There have been a number of reports on electrochemical fixation of carbon dioxide, and we have also reported synthesis of useful carboxylic acids by electrochemical carboxylation of various organic compounds. During the course of our continuous studies on the synthesis of useful carboxylic acids by electrochemical fixation of carbon dioxide, we recently found that electrochemical reduction of polyfluoroarenes in the presence of carbon dioxide resulted in a regio- and chemoselective cleavage of a C-F bond of the phenyl ring followed by reaction with carbon dioxide to give the corresponding mono-carboxylated products, polyfluorobenzoic acids, in moderate to good yields. Although synthesis of pentafluorobenzoic acid in 34% yield from reaction of hexafluorobenzene and magnesium anthracene (MgC₁₀H₈) in THF, with carbon dioxide has been reported, to the best of our knowledge, this is the first example of electrochemical carboxylation of polyfluoroarenes. We report herein the results for electrochemical carboxylation of polyfluoroarenes yielding the corresponding polyfluorobenzoic acids.

2. Experimental

Polyfluoroarenes 1a–d were commercially available and used without further purification. Pentafluorophenyl acetate (1e) was prepared in 83% yield from commercially available pentafluorophenol by reaction with acetyl chloride in the presence of triethylamine in CH₂Cl₂ according to a standard procedure. THP-protected polyfluorobenzoate 1f was prepared in 98% yield from commercially available pentafluorobenzyal alcohol by reaction with 3,4-dihydro-2H-pyran in the presence of p-toluenesulfonic acid monohydrate in CH₂Cl₂ according to a standard procedure.

Electrochemical reactions were carried out using a Constant Power Supply (model 5944), Metronix Corp. Tokyo. A solution of polyfluoroarenes 1 (1.0 mmol) in anhydrous DMF (10 cm³) containing Bu₄NBF₄ (0.1 mol dm⁻³) was electrolyzed at −40°C with 5 mA cm⁻² of constant current under atmospheric pressure of bubbling carbon dioxide. A test tube-like undivided cell (Φ 25 mm) equipped with a Pt plate cathode (2 × 2 cm²), a Mg rod anode (Φ 3 mm), and a Teflon® tube (Φ 1 mm) for supplying carbon dioxide was used for the electrolysis. After 3 mol l⁻¹ of electricity was passed, the electrolyzed solution was poured into 1 mol dm⁻³ hydrochloric acid (100 cm³) and then extracted with EtOAc (3 × 30 cm³). The combined EtOAc solution was washed with water and dried over MgSO₄. Evaporation of the solvent gave a solid, which was purified by recrystallization with hexane-acetone to give pure polyfluorobenzoic acids 2.
Figure 1. Electrochemical carboxylation of THP-protected polyfluoroarene 1f.

We next tried electrochemical carboxylation of THP-protected pentfluorobenzyl alcohol 1f, and the results are shown in Scheme 1. THP-protected polyfluoroarene 1f was readily prepared from pentafluorobenzyl alcohol in 98% yield by reaction with 3,4-dihydro-2H-pyran in the presence of a catalytic amount of p-toluenesulfonic acid. Electrochemical carboxylation of 1f at 5 mA cm\(^{-2}\) of current density with 2 F mol\(^{-1}\) of electricity also took place regio- and chemoselectively to give 2,3,5,6-tetrafluorophenyl acetate (1e) in 70% \(^{19}\)F NMR yield and 57% isolated yield after recrystallization. The tetrahydroprpyran-2-yl group of the product was hydrolyzed and removed by an acid treatment during work-up after the electrolysis.

Plausible reaction pathways are shown in Scheme 2. At the cathode, one-electron reduction of polyfluoroarene 1 would occur to generate the corresponding radical anion of 1. Elimination of a fluoride ion from thus-generated radical anion followed by further one-electron reduction would generate aryl anion species A–p.\(^{11}\) Fixation of carbon dioxide to A–p gives carboxylate ion B. On the other hand, at the anode, dissolution of a magnesium metal takes place to give magnesium ion. Carboxylate ion B would readily capture magnesium ion in the reaction medium to give salts C and/or D, which upon an acid treatment give polyfluorinated benzoic acid 2.

Although the reason for the highly regioselective carboxylation in the present electrochemical carboxylation is not clear at the

present stage, one plausible explanation is inductive effects of fluorine atoms attached to the phenyl ring. In polyfluoroarenes 1b-f, there are three kinds of C-F bonds of which a reductive cleavage can occur by electrochemical reduction to generate aryl anion species. Among them, the C-F bond at the para-position of the substituents of H, CH3, OAc and CH2OR, in other words the C-F bond located in middle of five C-F bonds, would receive the largest inductive effects from the neighboring fluorine atoms. Therefore, electrochemical reduction resulting in cleavage of a C-F bond would occur at the para-position in 1b-f to generate the corresponding aryl anion species regioselectively. Similar results in electrochemical reduction of pentfluorobenzene in DMF afforded 1,2,4,5-tetrafluorobenzene were also reported.12 On the other hand, thus-generated aryl anion A-p would also be stabilized more strongly than other possible aryl species A-o and A-m by inductive effects of two fluorine atoms at both sides of the ortho-positions and two fluorine atoms at both sides of the meta-position (Scheme 3). These stabilizations induced by inductive effects of neighboring fluorine atoms would also be the reason for regioselectivity.

4. Conclusion

We successfully carried out electrochemical fixation of carbon dioxide into polyfluoroarenes regio- and chemoselectively to yield polyfluoroarbenzoic acids in moderate to good yields. Further extension of the scope and the reaction mechanism, especially regarding regioselectivity and effects of the number and position of fluorine atoms on the phenyl ring, are under investigation.

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References


8. a) If (CDCl3): ¹H NMR (400 MHz): δ 1.53-1.81 (6H, m), 3.56-3.59 (1H, m), 3.85-3.90 (1H, m), 4.57 (1H, d, J = 11.2 Hz), 4.76 (1H, brs), 4.83 (1H, d, J = 11.2 Hz). ¹C NMR (100 MHz): δ 18.7, 25.2, 30.1, 55.8, 61.6, 98.4, 111.4-111.8 (1C, m), 135.9-147.1 (5C, m). ¹F NMR (373 MHz, CD2F2): δ -162.3 ppm as an internal reference. b) If -162.8 (2F, dt, J = 8.4 and 21.0 Hz), -154.8 (1F, t, J = 21.0 Hz). ¹9F NMR (373MHz): δ -143.5 (2F, dd, J = 8.4 and 21.0Hz). MS (EI): m/z 281 (M-H)+, 194 (119), 181 (100), 85 (41), 55 (33), 21 (42). HRMS: Found [M-H]+ 281.0597. Caled for C12H10F5O2 281.0601.


10. Spectral data of 2a, 2b, 2d and 2f are identical with the reported data: ¹H NMR (400 MHz): δ 1.53-1.81 (6H, m), 3.56-3.59 (1H, m), 3.85-3.90 (1H, m), 4.57 (1H, d, J = 11.2 Hz), 4.76 (1H, brs), 4.83 (1H, d, J = 11.2 Hz). ¹C NMR (100 MHz): δ 18.7, 25.2, 30.1, 55.8, 61.6, 98.4, 111.4-111.8 (1C, m), 135.9-147.1 (5C, m). ¹F NMR (373 MHz, CD2F2): δ -162.3 ppm as an internal reference. b) If -162.8 (2F, dt, J = 8.4 and 21.0 Hz), -154.8 (1F, t, J = 21.0 Hz). ¹9F NMR (373MHz): δ -143.5 (2F, dd, J = 8.4 and 21.0Hz). MS (EI): m/z 281 (M-H)+, 194 (119), 181 (100), 85 (41), 55 (33), 21 (42). HRMS: Found [M-H]+ 281.0597. Caled for C12H10F5O2 281.0601.