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Electrochemical Oxy-trifluoromethylation of Butyl Acrylate

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Synopsis. Electrooxidation of trifluoroacetic acid in the presence of butyl acrylate in an MeCN–H_2O–*i*-PrOH–(Pt) system under oxygen-bubbling provided a mixture of butyl 4,4,4-trifluoro-2-oxobutanoate and butyl 4,4,4-trifluoro-2-hydroxybutanoate.

Organofluorine compounds have attracted increasing attention for medicinal, agricultural, and material science.[1,2] Among them, trifluoromethylated compounds are promising so that a variety of trifluoromethylated compounds have been prepared.[3] Recently, electrochemical trifluoromethylation of olefins[4] has been recognized as one of the useful methods for the preparation of aliphatic trifluoromethylated compounds since electrooxidation of trifluoroacetic acid (TFA) in an MeCN–H_2O–(Pt) system generates trifluoromethyl radicals almost quantitatively[5] and TFA is one of the economically feasible trifluoromethyl sources. Renaud,[6,7] Brookes,[8,9] Muller,[10—12] and our group[13—17] have demonstrated the usefulness of electrochemical trifluoromethylation. A highlight of the electrochemical trifluoromethylation of butyl acrylate (**1**) is how to control the reactivity and lifetime of the trifluoromethylated radical intermediate **2** in the reaction media or on the electrode surface. The initially formed trifluoromethylated radical intermediates **2** undergo dimerization, coupling with another trifluoromethyl radical, or further one-electron oxidation to the corresponding carbocation followed by solvolysis and/or deprotonation. Carbon radicals in general are very reactive toward molecular oxygen so that the radical intermediate **2** should be in principle trapped with oxygen and thus oxygenated at the α-carbon of **1**. This paper describes electrochemical preparation of butyl 4,4,4-trifluoro-2-oxobutanoate (**3**) and butyl 4,4,4-trifluoro-2-hydroxybutanoate (**4**), precursors of trifluoromethylated α-amino acid, and some chemical transformations of **3**.

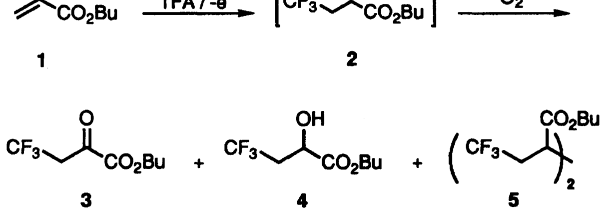
Results and Discussion

Electrochemical reaction of **1** was conducted in an MeCN–H_2O–*i*-PrOH–NaOH system (**1** : TFA=3 : 1) using platinum electrodes in an undivided beaker-type cell under oxygen bubbling. After passage of 4.0 F mol^{-1} of charge under a constant current density (5 mA cm^{-2}), **3** and **4** were produced as major products (G.C. Yield 40% in total), and di-butyl 2,3-bis(2,2,2-trifluoroethyl)succinate (**5**) was obtained as a minor product (G.C. Yield 10%). Under no oxygen bubbling in the same conditions, the succinate **5** was a major product (G.C. Yield 35%), and **3** and **4** became minor products (G.C. Yield 9% in total) (Scheme 1).[18]

Current density affected markedly the product selectivity. The oxygenated products **3** and **4** were produced as major products at the lower current density conditions. In contrast, the dimer **5** was a major product at the higher current density conditions where the radical intermediate **2** would be concentrated on the anode surface, so that dimerization would be promoted (Fig. 1).

Interestingly, the formation of **5** was suppressed by the use of sodium perchlorate instead of sodium hydroxide as an electrolyte although the current efficiency of the consumption of TFA was slightly lowered. Perchlorate ion adsorbs on the anode preferentially so as to decrease the concentration of trifluoroacetate ion.[19] In fact, about 20% of TFA remained unreacted whereas TFA was consumed completely in NaOH–MeCN–H_2O–*i*-PrOH system after 4.0 F mol^{-1} of charge was passed.[20]

Temperature was also one of the important factors for the yield of **3** and **4**. At around 0 °C, the total yield of **3** and **4** became optimum (G.C. Yield 43%; **3** : **4**=2 : 1) af-



Scheme 1.

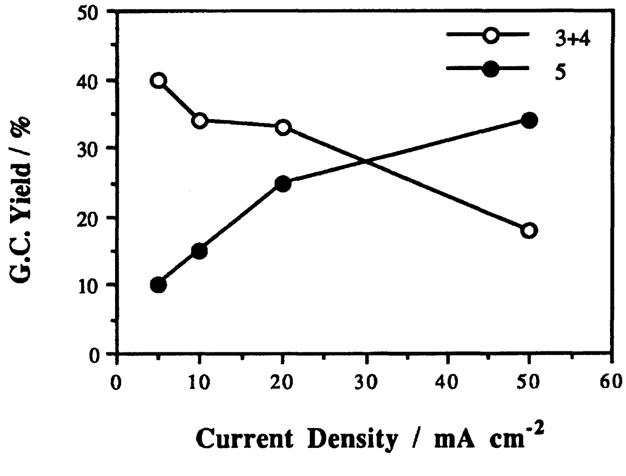
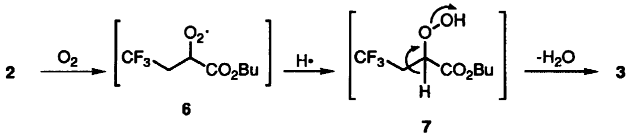


Fig. 1. Effect of current density for the yield of **3**, **4**, and **5** in the presence of NaOH as an electrolyte (MeCN–H_2O–*i*-PrOH, 0 °C, 4 F mol^{-1}).

ter 4.0 F mol^{-1} of charge to TFA was passed. Whereas, the yield of **3** and **4** and efficiency of TFA consumption decreased gradually as the temperature was raised up to 40 °C.[14)]

Electrooxidation of TFA has been conducted mostly in a mixture of acetonitrile and water.[5)] It is noteworthy that the isopropyl alcohol added to a mixture of MeCN and H_2O promoted the present oxy-trifluoromethylation although the reason is not clear at this stage.[21)]

Three reaction mechanisms are plausible. The first is the reaction of the radical intermediate **2** with molecular oxygen to form peroxide **7** which undergoes dehydration leading to the ketone **3** (Scheme 2). The second is dimerization of the peroxyl radical **6** followed by disproportionation to the ketone **3** and the alcohol **4**.[22)] The third is a sequence of oxidation of the radical intermediate **2** to the corresponding carbocation followed by hydrolysis with water to form the alcohol **4** as an initial product. Time-dependent product distributions of **3** and **4** revealed that both **3** and **4** were produced in a similar manner depending on electricity and that the yield of **3** was higher than that of **4** (Fig. 2). And the ketone **3** was neither reduced nor the alcohol **4** was oxidized under the same electrolysis conditions in an undivided cell. These facts along with the result of a promotion of the reaction with oxygen suggest that the third mechanism is not the case. The second mechanism would be plausible in the absence of isopropyl alcohol, whereas both the first and the second mechanisms would competitively occur in the presence of isopropyl alcohol. In fact, the almost same amount of both **3** and **4** were produced in the absence of isopropyl alcohol.



Scheme 2.

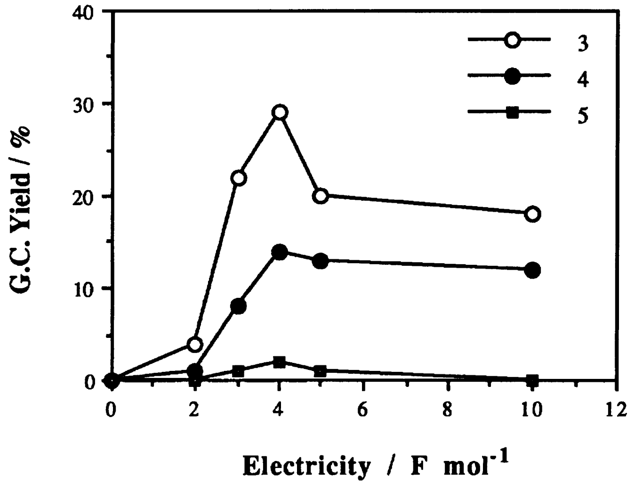


Fig. 2. Effect of electricity for the yield of **3**, **4**, and **5** (MeCN–H_2O–*i*-PrOH–$NaClO_4$, 0 °C, 5 mA cm^{-2}).

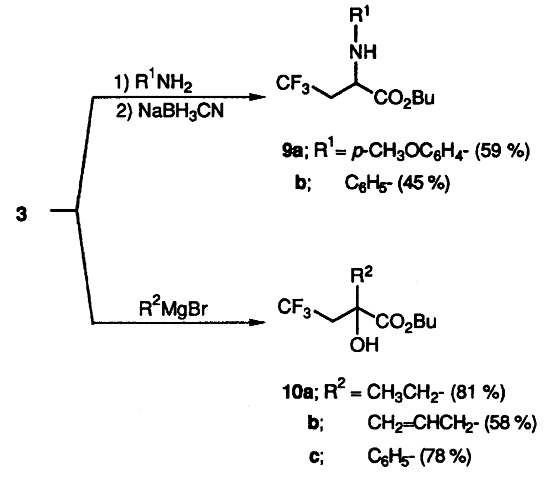
A few reports on the preparation of 4,4,4-trifluoro-2-oxocarboxylates appeared.[23,24)] Umemoto et al. previously reported a chemical oxy-perfluoroalkylation of electron-rich olefins by use of (perfluoroalkyl)phenyliodonium sulfonates under oxygen atmosphere.[25)] The Umemoto's reagent does not react with electron-poor olefins. The present electrochemical method is alternative.

Some preliminary results of the transformation of **3** are shown in the Scheme 3. Compound **3** was transformed to 2-amino-4,4,4-trifluorobutanoates **9** on reacting with some arylamines and then being reduced with $NaBH_3CN$. And, **3** was allowed to react with Grignard reagents to give 2-alkyl-4,4,4-trifluoro-2-hydroxybutanoates **10**.

Experimental

Infrared spectra were taken on a Hitachi 270-30 spectrometer. The ^{1}H- and ^{19}F NMR spectra were measured on a Varian VXR-500 and -200 instruments using TMS for ^{1}H NMR and C_6F_6 for ^{19}F NMR as internal standards. Mass spectra (MS) were obtained with a Hitachi M-80 spectrometer. Boiling points are indicated by a temperature of a glass tube oven (°C/mmHg, 1 mmHg≈133.322 Pa). G.C. yields were obtained with a column of Silicone OV-101 using diethyl fumarate as an internal standard.

General Procedure of Electrolysis. A mixture of butyl acrylate (1.30 ml, 9.0 mmol), trifluoroacetic acid (TFA) (0.23 ml, 3.0 mmol), $NaClO_4$ (367 mg, 3.0 mmol), MeCN (48 ml), H_2O (8 ml), and *i*-PrOH (8 ml) was electrolyzed at 0 °C in an undivided beaker-type cell (20 cm tall and 3.0 cm in diameter) fitted with platinum foils (anode; 6×4 cm^2, cathode; 1.5×2 cm^2) as the electrodes. Oxygen gas was passed through a glass capilary into the stirred and cooled solution for about 15 min before electrolysis, and the gas bubbling was maintained throughout the electrolysis. A constant current density (5.0 mA cm^{-2}) was supplied until the charge reached to 4.0 F mol^{-1} to TFA. After the electrolysis, the solvent was evaporated under a reduced pres-



Scheme 3.

sure and the organic residue was extracted with AcOEt. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified through a short silica-gel column (Hexane–AcOEt) and the combined mixture of **3** and **4** was oxidized with CrO_3–H_2SO_4 to give **3** (254 mg, 40%) as a colorless liquid.

Butyl 4,4,4-Trifluoro-2-oxobutanoate (3). A colorless liquid (G.C. Yield 29%); bp 75—85 °C (5 mmHg); IR (neat) 1758 (C=O), 1736 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta=4.30$ (2H, t, $J=6.6$ Hz, OCH_2), 3.73 (2H, q, $J_{H-F}=9.8$ Hz, $CF_3C\underline{H}_2$), 1.80—1.65 (2H, m, CH_2), 1.51—1.33 (2H, m, CH_2), 0.95 (3H, t, $J=7.2$ Hz, CH_3); ^{19}F NMR ($CDCl_3$) $\delta=99.1$ (t, $J_{H-F}=10.0$ Hz); MS m/z (rel intensity) 140 ($M^+-C_4H_8O$, 3), 111 (M^+-CO_2Bu, 20), 57 (Bu, 100), 41 (81); Anal. Calcd for $C_8H_{11}O_3F_3$: C, 45.29; H, 5.23%. Found: C, 45.40; H, 5.34%.

***n*-Butyl 4,4,4-Trifluoro-2-hydroxybutanoate (4).** A colorless liquid (G.C. Yield 14%); bp 80—90 °C (5 mmHg); IR (neat) 3512 (OH), 1744 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta=4.50$—4.40 (1H, m, $CH_2C\underline{H}(OH)CO_2Bu$), 4.24 (2H, t, $J=6.7$ Hz, OCH_2), 3.05 (1H, d, $J=5.1$ Hz, $CH(O\underline{H})$-CO_2Bu), 2.82—2.33 (2H, m, $CF_3C\underline{H}_2CH$), 1.75—1.54 (2H, m, CH_2), 1.48—1.26 (2H, m, CH_2), 0.95 (3H, t, $J=7.2$ Hz, CH_3); ^{19}F NMR ($CDCl_3$) $\delta=98.3$ (t, $J_{H-F}=10.0$ Hz); MS m/z (rel intensity) 113 (M^+-CO_2Bu, 23), 93 (13), 57 (Bu, 100), 41 (52); Anal. Calcd for $C_8H_{13}O_3F_3$: C, 44.86; H, 6.12%. Found: C, 44.88; H, 6.23%.

Dibutyl 2,3-Bis(2,2,2-trifluoroethyl)succinate (5). A colorless liquid of a mixture of *dl*- and *meso*-isomers (G.C. Yield 2%); bp 90—100 °C (4 mmHg); IR (neat) 1744 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta=4.24$—4.08 (4H, m, OCH_2), 3.09—2.99 (2H, m, $CH_2C\underline{H}(CO_2Bu)$), 2.87—2.68 (2H, m, $CF_3C\underline{H}_2CH$), 2.46—2.35 (1H, dq, $J_1=4.0$ Hz, $J_2=10.5$ Hz, $CF_3C\underline{H}_2CH$), 2.22—2.13 (1H, dq, $J_1=2.5$ Hz, $J_2=10.5$ Hz, $CF_3C\underline{H}_2CH$), 1.67—1.58 (4H, m, CH_2), 1.43—1.34 (4H, m, CH_2), 0.95 (6H, t, $J=7.5$ Hz, CH_3); ^{19}F NMR ($CDCl_3$) $\delta=96.3$ (t, $J_{H-F}=10.4$ Hz), 96.2 (t, $J_{H-F}=10.3$ Hz); MS m/z (rel intensity) 395 (M+1, 0.1), 294 ((M+1)−CO_2Bu, 1.5), 73 (OBu, 13), 57 (Bu, 100), 41 (25); Anal. Calcd for $C_{16}H_{24}O_4F_6$: C, 48.73; H, 6.13%. Found: C, 48.95; H, 6.17%.

Butyl 4,4,4-Trifluoro-2-(4-methoxyphenylamino)-butanoate (9a). Into a stirred solution of **3** (106 mg, 0.5 mmol) in toluene (3 ml), a solution of *p*-anisidine (61.6 mg, 0.5 mmol) in toluene (2 ml) was added at 0 °C. The mixture was stirred at 65 °C for 12 h. The AcOEt extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Into the residue dissolved in ethanol (3 ml), $NaBH_3CN$ (25.2 mg, 0.4 mmol) was added. The solution was stirred at room temperature for 12 h and then taken up in brine. The AcOEt extracts were dried over Na_2SO_4 and freed of solvent in vacuo. The crude product was chromatographed on silica gel (Hexane–AcOEt) to give **9a** (94 mg, 59%): A yellow liquid; bp 100—110 °C (3 mmHg); IR (neat) 3384 (NH), 1738 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta=6.79$—6.74 (2H, m, ArH), 6.64—6.59 (2H, m, ArH), 4.26 (1H, t, $J=6.3$ Hz, $CH_2C\underline{H}(NH)$), 4.11 (2H, t, $J=6.6$ Hz, OCH_2), 3.72 (3H, s, OCH_3), 2.74—2.48 (2H, m, $CF_3C\underline{H}_2CH$), 1.62—1.50 (2H, m, CH_2), 1.39—1.20 (2H, m, CH_2), 0.88 (3H, t, $J=7.2$ Hz, CH_3); ^{19}F NMR ($CDCl_3$) $\delta=98.3$ (t, $J_{H-F}=10.5$ Hz); Anal. Calcd for $C_{15}H_{20}NO_3F_3$: C, 56.42; H, 6.31; N, 4.39%. Found: C, 56.15; H, 6.32; N, 4.21%.

Butyl 4,4,4-Trifluoro-2-(phenylamino)butanoate (9b). A colorless liquid; bp 90—100 °C (3 mmHg); IR (neat) 3400 (NH), 1742 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta=$ 7.26—7.16 (2H, m, ArH), 6.84—6.76 (1H, m, ArH), 6.69—6.64 (2H, m, ArH), 4.39 (1H, t, $J=6.3$ Hz, $CH_2C\underline{H}(NH)$), 4.16 (2H, t, $J=6.7$ Hz, OCH_2), 2.80—2.53 (2H, m, $CF_3C\underline{H}_2CH$), 1.68—1.54 (2H, m, CH_2), 1.43—1.23 (2H, m, CH_2), 0.91 (3H, t, $J=7.4$ Hz, CH_3); ^{19}F NMR ($CDCl_3$) $\delta=98.4$ (t, $J_{H-F}=10.3$ Hz); Anal. Calcd for $C_{14}H_{18}NO_2F_3$: C, 58.12; H, 6.27; N, 4.84%. Found: C, 58.07; H, 6.41; N, 5.13%.

Butyl 2-Ethyl-4,4,4-trifluoro-2-hydroxybutanoate (10a). Into a stirred solution of **3** (106 mg, 0.5 mmol) in dist. ether (1.5 ml), a solution of ethyl Grignard reagent (1.0 ml, 1.0 mmol) was added under N_2 at 0 °C and the mixture was stirred at room temperature for 5 h and then poured into a saturated aqueous solution of NH_4Cl. The ether extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was chromatographed on silica gel (Hexane–AcOEt) to give **10a** (97 mg, 81%): A colorless liquid; bp 30—40 °C (3 mmHg); IR (neat) 3544 (OH), 1738 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta=4.23$ (2H, t, $J=6.4$ Hz, OCH_2), 3.52—3.43 (1H, br, OH), 2.74—2.44 (2H, m, $CF_3C\underline{H}_2C(OH)$), 1.90—1.53 (4H, m, CH_2), 1.49—1.39 (2H, m, CH_2), 0.95 (3H, t, $J=7.4$ Hz, CH_3), 0.88 (3H, t, $J=7.4$ Hz, CH_3); ^{19}F NMR ($CDCl_3$) $\delta=100.3$ (t, $J_{H-F}=10.3$ Hz); Anal. Calcd for $C_{10}H_{17}O_3F_3$: C, 49.58; H, 7.07%. Found: C, 49.80; H, 7.15%.

Butyl 2-(2,2,2-trifluoroethyl)-2-hydroxy-4-pentenoate (10b). A colorless liquid; bp 40—50 °C (3 mmHg); IR (neat) 3540 (OH), 3088 (=CH), 1740 (C=O), 1644 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta=5.87$—5.66 (1H, m, $CH_2=C\underline{H}CH_2$), 5.25—5.06 (2H, m, $CH_2=CHCH_2$), 4.22 (2H, t, $J=6.7$ Hz, OCH_2), 3.62—3.32 (1H, br, OH), 2.75—2.50 (2H, m, $CF_3C\underline{H}_2C(OH)$), 2.46 (2H, d, $J=7.1$ Hz, $CH_2=CHC\underline{H}_2C(OH)$), 1.76—1.52 (2H, m, CH_2), 1.50—1.33 (2H, m, CH_2), 0.96 (3H, t, $J=7.5$ Hz, CH_3); ^{19}F NMR ($CDCl_3$) $\delta=100.4$ (t, $J_{H-F}=10.1$ Hz); Anal. Calcd for $C_{11}H_{17}O_3F_3$: C, 51.97; H, 6.74%. Found: C, 52.22; H, 6.84%.

Butyl 4,4,4-Trifluoroethyl-2-hydroxy-2-phenylbutanoate (10c). A colorless liquid; bp 80—90 °C (3 mmHg); IR (neat) 3532 (OH), 1736 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta=7.62$—7.54 (2H, m, ArH), 7.43—7.26 (3H, m, ArH), 4.32—4.13 (2H, m, OCH_2), 3.36—3.13 (1H, dq, $J_1=10.2$ Hz, $J_2=15.3$ Hz, $CF_3C\underline{H}_2C(OH)$), 2.89—2.67 (1H, dq, $J_1=10.0$ Hz, $J_2=15.2$ Hz, $CF_3C\underline{H}_2C(OH)$), 1.71—1.57 (2H, m, CH_2), 1.43—1.21 (2H, m, CH_2), 0.90 (3H, t, $J=7.2$ Hz, CH_3); ^{19}F NMR ($CDCl_3$) $\delta=101.0$ (t, $J_{H-F}=10.0$ Hz); Anal. Calcd for $C_{14}H_{17}O_3F_3$: C, 57.93; H, 5.90%. Found: C, 57.97; H, 5.96%.

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