

Electrochemical Hydrotrifluoromethylation of Dialkyl Fumarates

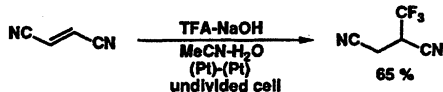
Yasufumi Dan-oh and Kenji Uneyama*

Department of Applied Chemistry, Faculty of Engineering, Okayama University, Okayama 700

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Dialkyl fumarates were electrochemically hydrotrifluoromethylated. The reaction was explained in terms of anodic bistrifluoromethylation and subsequent hydrolysis of one of the trifluoromethyl groups under the basic condition near cathode surface.

Recently, trifluoromethylated compounds have been accepting a great interest in medicinal, agricultural, and material sciences,¹⁾ and many reagents for trifluoromethylation have been utilized.²⁾ Especially, trifluoroacetic acid is one of the most available reagents for introducing trifluoromethyl group to target molecules. Among trifluoromethylations with trifluoroacetic acid (TFA), electrochemical generation of trifluoromethyl radical ($F_3C\cdot$) from TFA and its utilization are useful.³⁾ In particular, electrochemical introduction of $F_3C\cdot$ radical into olefins is convenient. Trifluoromethylation accompanied with dimerization of methyl acrylate and the related olefins,⁴⁾ bistrifluoromethylation of ethyl fumarate⁵⁾ and acrylamide,⁶⁾ and trifluoromethylation of enol acetate⁷⁾ and active methylene compounds⁸⁾ have been demonstrated. One of the interesting trifluoromethylation is hydrotrifluoromethylation of fumaronitrile (Scheme 1),⁹⁾ in which a hydrogen and a CF_3 group are incorporated in a carbon-carbon double bond. The reaction was explained in terms of paired reaction in which both anodic oxidation and cathodic reduction were employed; trifluoroacetic acid was electrochemically oxidized to trifluoromethyl radical, and fumaronitrile was electrochemically reduced to anion radical, and then, the two radical species coupled to 2-trifluoromethylsuccinonitrile. This one-step hydrotrifluoromethylation¹⁰⁾ of an olefin is synthetically useful, but it has never been explored in detail. In order to get any generality and reaction mechanism of this novel reaction, trifluoromethylation of fumaric esters was examined.

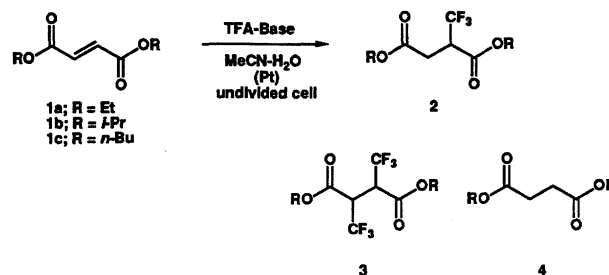


Scheme 1.

Results and Discussion

At first, the reaction of diethyl fumarate was examined under conditions which were as same as the case of fumaronitrile. However, the yields of the desired compound **2a** was low (13%), and the undesired compounds such as bistrifluoromethylated compound **3a** ($R=Et$) and diethyl succinate **4a** were mainly obtained (Scheme 2).¹¹⁾ So, effect of electrolyte was examined at first to optimize the yield of **2a**. The yield was dependent on the electrolyte under the conditions employed [**1a** (1 mmol), electrolyte (2.5 mmol), TFA (4 mmol), current density 50 mA cm^{-2} , at 50°C , electrolyte (Yield of **2a**): NaHCO_3 (10%), NaOH (14%), Na_2CO_3 (21%), KOH (26%), KHCO_3 (29%), K_2CO_3 (42%)]. The use of K_2CO_3 resulted in the preferable formation of the desired product **2a** so far as examined. Then, other factors were also examined and the results are shown in Figs. 1, 2, 3, and 4.

Molar amounts of K_2CO_3 affected also the yields of the products. When small amount of K_2CO_3 was used, major product was **3a**. But, when over 1.5 molar amounts of the base were used, major product was the desired **2a** although yields of products decreased gradually. Next, effect of temperature was examined. Low temperature favored the formation of **3a**. However, high temperature from 40 to 55°C induced preferential formation of **2a**, but the undesired product **4a**



Scheme 2.

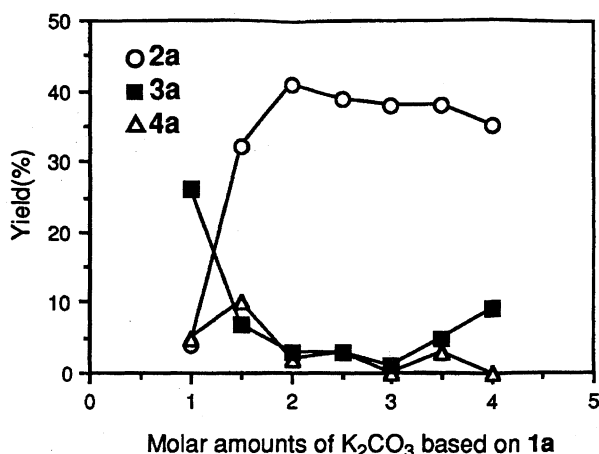
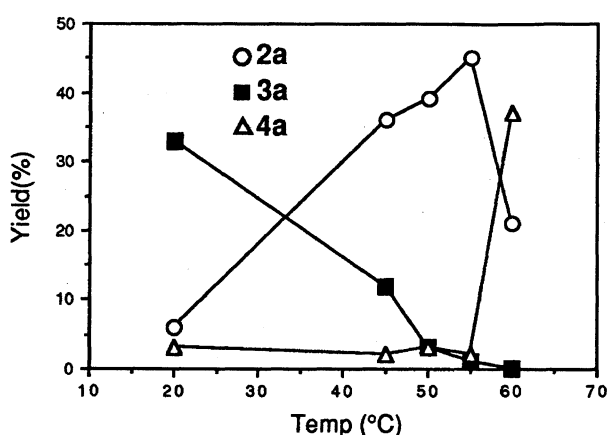
Fig. 1. Effects of molar amounts of K₂CO₃ based on 1a.

Fig. 2. Effects of temperature.

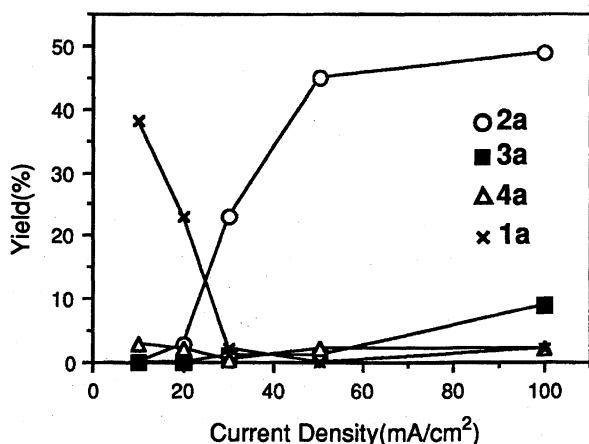


Fig. 3. Effects of current density.

also increased. Current density of over 50 mA cm⁻² was necessary for getting good yields (Fig. 3). Finally, effect of molar amounts of TFA was checked and the best results were obtained by the use of four molar amounts of TFA to the substrate 1a.

The conditions usable for the preferential formation of 2a is as follows; a mixture of 1a (1 mmol), TFA (4 mmol), and K₂CO₃ (2.5 mmol) dissolved in MeCN (6

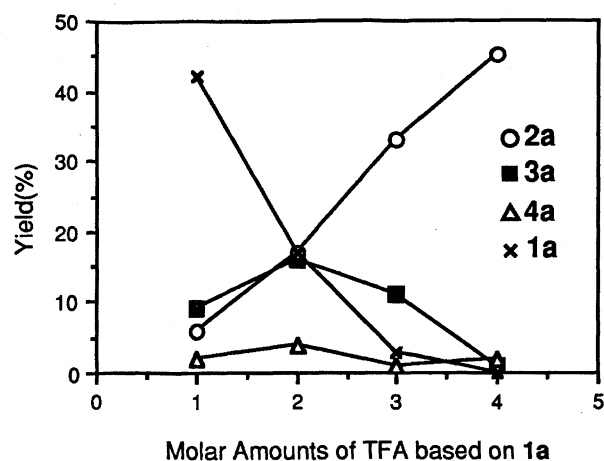


Fig. 4. Effects of molar amounts of TFA based on 1a.

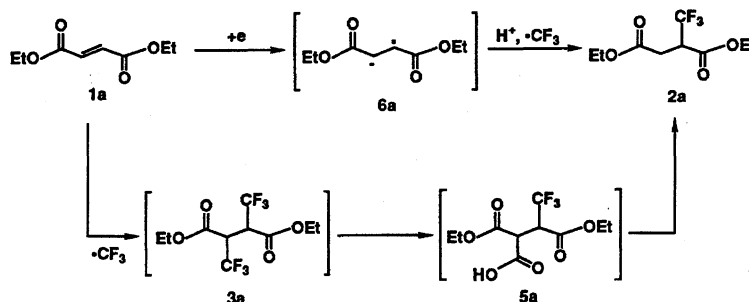
ml) and H₂O (1 ml) was electrolyzed at 55 °C in an undivided beaker-type cell (10 cm tall and 1.8 cm in diameter) fitted with platinum foils (1.5×1 cm² for an anode and 1.5×2 cm² for a cathode) as electrodes. A constant current (50 mA cm⁻²) was supplied until the charge reached to 1.5 F (F=96480 C) of TFA.

The reactions of the related fumarates were also examined under the optimized conditions (Table 1).

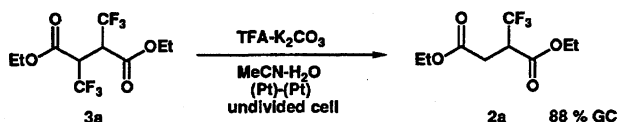
Two mechanisms can be proposed to explain the results. One is the paired reaction pathway as proposed for fumaronitrile:⁹⁾ olefin 1 would be electrochemically reduced to anion radical 6, and then, the anion radical coupled with trifluoromethyl radical which was produced by electrochemical oxidation of TFA (Scheme 3). Another mechanism of bistrifluoromethylation followed by hydrolysis and decarboxylation must be considered. Therefore, the bistrifluoromethylated compound 3a was subjected to the electrolysis under the same conditions for 1a. Trifluoromethylated product 2a was obtained in 88% yield. This result suggests 3a must be one of the intermediates to 2a (Scheme 4). Taking into account of the fact that the higher current density favored bistrifluoromethylation of ethyl fumarate⁵⁾ and acrylamide,⁶⁾ the result of Fig. 3, the higher current density favored the formation of 2a, is consistent with the mechanism of the intermediacy of 3a to 2a. It is well known that CF₃ group is a synthon of carboxyl group.¹²⁾ Higher temperature (Fig. 2) and the use of an excess amount of K₂CO₃ (Fig. 1) would promote the hydrolysis of CF₃ group to carboxyl group and also decarboxylation of 5 and would lead to the preferential formation of 2a. At 60 °C, CF₃ group of 2a also would be hydrolyzed to give ethyl fumarate as a final product as shown in Fig. 2.

Table 1. Yields of Related Fumarates 2

	R	Yield of 2 (%)
2a	Et	45
2b	<i>i</i> -Pr	19
2c	<i>n</i> -Bu	52



Scheme 3.



Scheme 4.

Question is why the desired product **2a** was not obtained but **3a** was mainly produced in a divided cell.⁵⁾ The bistrifluoromethylated compound **3a** formed on the anodic surface, migrates to the cathode surface where **3a** is easily hydrolyzed to **5a** in a strongly basic medium. Fumaronitrile could neither be bistrifluoromethylated electrochemically even in a divided cell nor chemically by the action of XeF₂-TFA system, while ethyl fumarate could.⁹⁾ This result may arise from the more highly electron-deficient nature of carbon-carbon double bond of fumaronitrile as compared with that of fumarates.

Experimental

Infrared spectra were taken on a Hitachi 270-30 spectrometer. The ¹H and ¹⁹F NMR spectra were measured on a Varian VXR-200 instrument using TMS for ¹H and C₆F₆ for ¹⁹F NMR as internal standards and CDCl₃ as the solvent. Elemental analysis was performed on a Perkin-Elmer 2400 CHNS/O.

Diethyl 2-Trifluoromethylsuccinate (2a). The electrolyzed solution was concentrated under reduced pressure and the residue was extracted with ethyl acetate. The extracts was washed with brine, dried over MgSO₄ and concentrated. The residue was chromatographed (SiO₂, EtOAc-Hexane) to give a colorless liquid. IR (neat) 2992, 2944, 2912, 1738, 1376, 1314, 1270, 1226, 1170, 1114, 1028 cm⁻¹; ¹H NMR δ=1.22–1.33 (6H, m, CH₃), 2.71 (1H, dd, *J*₁=17.2 Hz, *J*₂=4.0 Hz, CH₂), 3.04 (1H, dd, *J*₁=17.2 Hz, *J*₂=10.6 Hz, CH₂), 3.63 (1H, dqd, *J*₁=10.6 Hz, *J*₂=8.8 Hz, *J*₃=4.0 Hz, CHCF₃), 4.17 (2H, q, *J*=7.2 Hz, OCH₂), 4.27 (2H, qd, *J*₁=7.2 Hz, *J*₂=1.5 Hz, OCH₂); ¹⁹F NMR δ=93.6 (3F, d, *J*=8.8 Hz, CF₃). Found: C, 44.41; H, 5.20%. Calcd for C₉H₁₃O₄F₃: C, 44.63; H, 5.41%.

Diisopropyl 2-Trifluoromethylsuccinate (2b). IR (neat) 2988, 2944, 2884, 1738, 1470, 1418, 1378, 1310, 1170, 1106, 1006, 964, 914 cm⁻¹; ¹H NMR δ=1.21–1.30 (12H, m, CH₃), 2.67 (1H, dd, *J*₁=17.1 Hz, *J*₂=4.1 Hz, CH₂), 2.99 (1H, dd, *J*₁=17.1 Hz, *J*₂=10.7 Hz, CH₂), 3.48–3.69 (1H, dqd, *J*₁=10.7 Hz, *J*₂=9.0 Hz, *J*₃=4.1 Hz, CHCF₃), 4.91–5.18 (2H, m, OCH); ¹⁹F NMR δ=93.49 (3F, d, *J*=8.97 Hz,

CF₃). Found: C, 48.67; H, 6.22%. Calcd for C₁₁H₁₇O₄F₃: C, 48.89; H, 6.34%.

Dibutyl 2-Trifluoromethylsuccinate (2c). IR (neat) 2968, 2880, 1746, 1468, 1396, 1310, 1170, 1116, 1060, 1022 cm⁻¹; ¹H NMR δ=0.90–0.97 (6H, m, CH₃), 1.29–1.50 (4H, m, CH₂), 1.55–1.72 (4H, m, CH₂), 2.73 (1H, dd, *J*₁=17.2 Hz, *J*₂=4.0 Hz, CH₂), 3.05 (1H, dd, *J*₁=17.2 Hz, *J*₂=10.7 Hz, CH₂), 3.55–3.75 (1H, dqd, *J*₁=10.7 Hz, *J*₂=8.5 Hz, *J*₃=4.0 Hz, CHCF₃), 4.13 (2H, q, *J*=6.6 Hz, OCH₂), 4.08–4.35 (2H, m, OCH₂); ¹⁹F NMR δ=93.8 (3F, d, *J*=8.5 Hz, CF₃). Found: C, 52.28; H, 6.93%. Calcd for C₁₃H₂₁O₄F₃: C, 52.34; H, 7.10%.

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(1987).

11) Material balance in this electrolysis was rather poor so far as the volatile products were analyzed. Some carboxylic acids produced by hydrolysis of **1**, **2**, **3**, and **4** would dissolve in aqueous layer and nonvolatile products such as

oligomers remained as a residue in a distillation pot.

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