Electrochemical Hydrotrifluoromethylation of Dialkyl Fumarates

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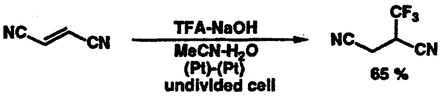
Dialkyl fumarates were electrochemically hydrotrifluoromethylated. The reaction was explained in terms of anodic bistrifluoromethylation and subsequent hydrolysis of one of the trifluoromethyl groups under the basic condition near cathode surface.

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 fumarate[5] and acrylamide,[6] and trifluoromethylation of enol acetate[7] and active methylene compounds[8] 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 hydrotrifluoromethylation[10] 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.

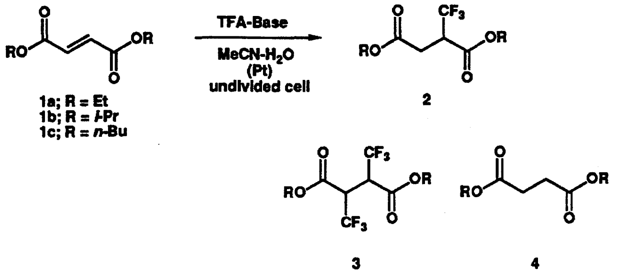


Scheme 1.

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.

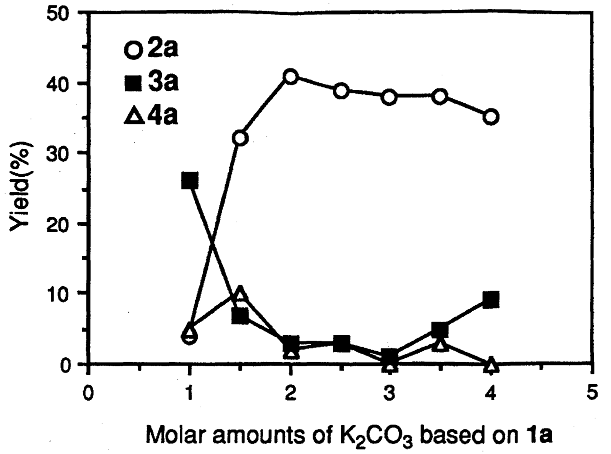


Fig. 1. Effects of molar amounts of K_2CO_3 based on **1a**.

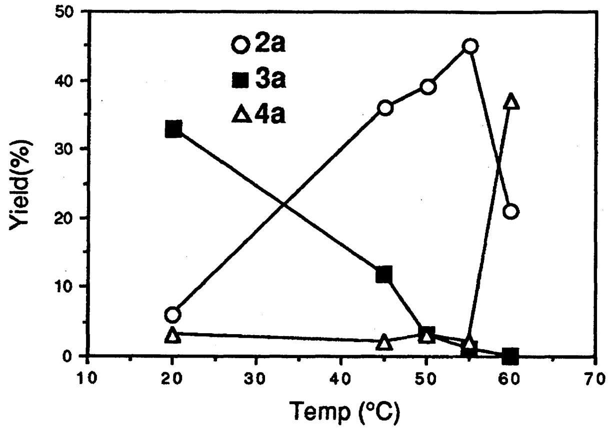


Fig. 2. Effects of temperature.

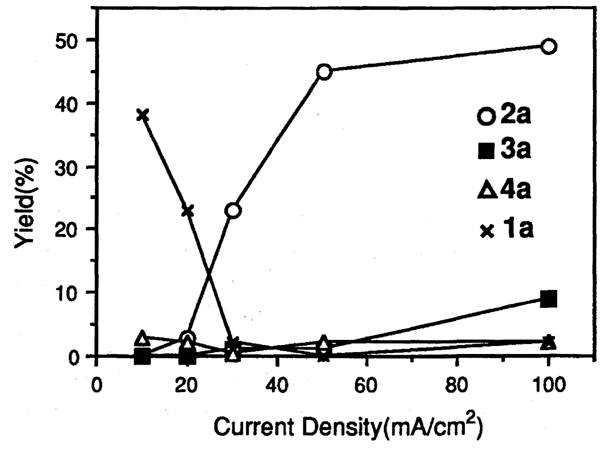


Fig. 3. Effects of current density.

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 K_2CO_3 (2.5 mmol) dissolved in MeCN (6 ml) and H_2O (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 cm^2 for an anode and 1.5×2 cm^2 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.

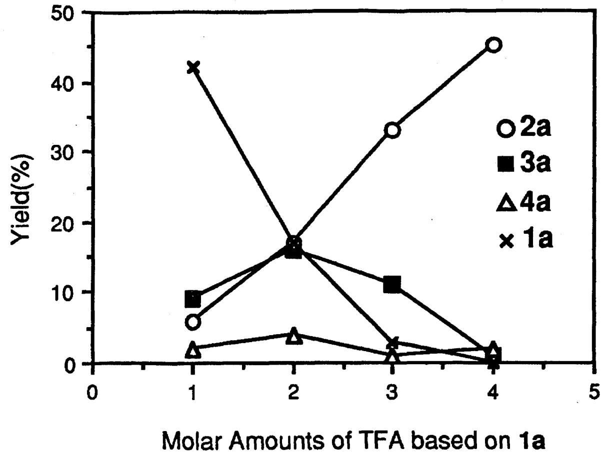


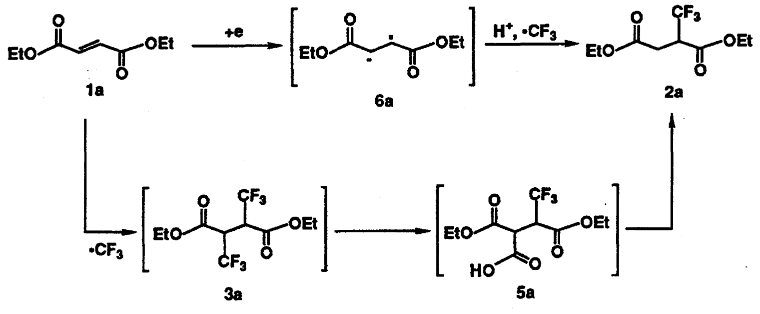
Fig. 4. Effects of molar amounts of TFA based on **1a**.

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

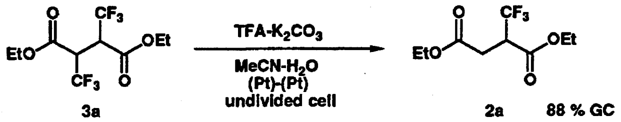
Two mechanisms can be proposed to explain the results. One is the paired reaction pathway as proposed for fumaronitrile:[9] olefin **1** would be electrochemically reduced to anion radical **6**, and then, the anion radical coupled with trifluoromethyl radical which was produced by electrochemical oxidation 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 fumarate[5] 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 CF_3 group is a synthon of carboxyl group.[12] Higher temperature (Fig. 2) and the use of an excess amount of K_2CO_3 (Fig. 1) would promote the hydrolysis of CF_3 group to carboxyl group and also decarboxylation of **5** and would lead to the preferential formation of **2a**. At 60 °C, CF_3 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*-Pr	19
2c	*n*-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 neighther be bistrifluoromethylated electrochemically even in a divided cell nor chemically by the action of XeF_2–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 ^{1}H and ^{19}F NMR spectra were measured on a Varian VXR-200 instrument using TMS for ^{1}H and C_6F_6 for ^{19}F NMR as internal standards and $CDCl_3$ 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 $MgSO_4$ and concentrated. The residue was chromatographed (SiO_2, EtOAc–Hexane) to give a colorless liquid. IR (neat) 2992, 2944, 2912, 1738, 1376, 1314, 1270, 1226, 1170, 1114, 1028 cm^{-1}; ^{1}H NMR δ=1.22—1.33 (6H, m, CH_3), 2.71 (1H, dd, J_1=17.2 Hz, J_2=4.0 Hz, CH_2), 3.04 (1H, dd, J_1=17.2 Hz, J_2=10.6 Hz, CH_2), 3.63 (1H, dqd, J_1=10.6 Hz, J_2=8.8 Hz, J_3=4.0 Hz, $CHCF_3$), 4.17 (2H, q, J=7.2 Hz, OCH_2), 4.27 (2H, qd, J_1=7.2 Hz, J_2=1.5 Hz, OCH_2); ^{19}F NMR δ=93.6 (3F, d, J=8.8 Hz, CF_3). Found: C, 44.41; H, 5.20%. Calcd for $C_9H_{13}O_4F_3$: 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}; ^{1}H NMR δ=1.21—1.30 (12H, m, CH_3), 2.67 (1H, dd, J_1=17.1 Hz, J_2=4.1 Hz, CH_2), 2.99 (1H, dd, J_1=17.1 Hz, J_2=10.7 Hz, CH_2), 3.48—3.69 (1H, dqd, J_1=10.7 Hz, J_2=9.0 Hz, J_3=4.1 Hz, $CHCF_3$), 4.91—5.18 (2H, m, OCH); ^{19}F NMR δ=93.49 (3F, d, J=8.97 Hz, CF_3). Found: C, 48.67; H, 6.22%. Calcd for $C_{11}H_{17}O_4F_3$: C, 48.89; H, 6.34%.

Dibutyl 2-Trifluoromethylsuccinate (2c). IR (neat) 2968, 2880, 1746, 1468, 1396, 1310, 1170, 1116, 1060, 1022 cm^{-1}; ^{1}H NMR δ=0.90—0.97 (6H, m, CH_3), 1.29—1.50 (4H, m, CH_2), 1.55—1.72 (4H, m, CH_2), 2.73 (1H, dd, J_1=17.2 Hz, J_2=4.0 Hz, CH_2), 3.05 (1H, dd, J_1=17.2 Hz, J_2=10.7 Hz, CH_2), 3.55—3.75 (1H, dqd, J_1=10.7 Hz, J_2=8.5 Hz, J_3=4.0 Hz, $CHCF_3$), 4.13 (2H, q, J=6.6 Hz, OCH_2), 4.08—4.35 (2H, m, OCH_2); ^{19}F NMR δ=93.8 (3F, d, J=8.5 Hz, CF_3). Found: C, 52.28; H, 6.93%. Calcd for $C_{13}H_{21}O_4F_3$: C, 52.34; H, 7.10%.

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