Tetrahedron Vol. 47, No. 4/5, pp. 555-562, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

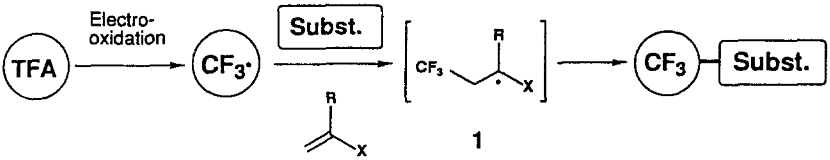
ELECTROCHEMICAL TRIFLUOROMETHYLATION OF OLEFINS; PRODUCT-SELECTIVITY AND MECHANISTIC ASPECTS

Kenji Uneyama
Department of Applied Chemistry, Faculty of Engineering,
Okayama University, Okayama 700, Japan

(*Received in USA* 26 *August* 1990)

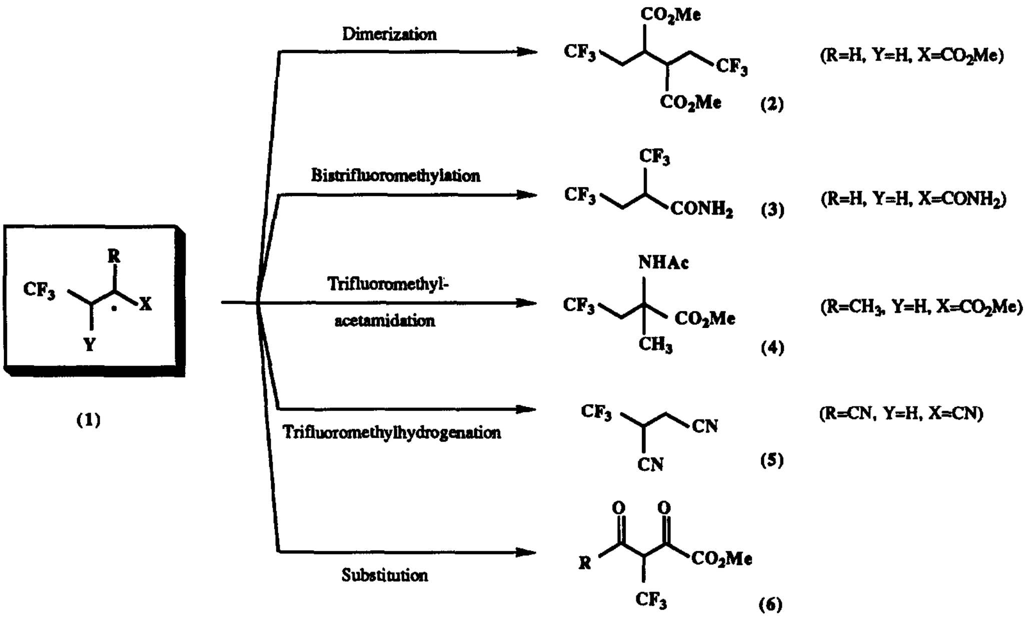
Summary; Trifluoroacetic acid (TFA) can be converted almost quantitatively to the trifluoromethyl radicals by electrochemical oxidation of TFA. The electrolysis is conducted in an MeCN-H_2O-(Pt) system using an undivided cell. The electrochemically generated CF_3•radicals can attack mostly electron-deficient olefins leading to the trifluoromethylated carbon radicals of which chemical and electrochemical fate can be controlled by current density, reaction temperature, and substituents of olefins.

Organofluorine compounds have attracted increasing attention for medicinal and agricultural usage and for material science.[1,2] Among them the trifluoromethylated compounds are promising so that a variety of trifluoromethylated compounds have been prepared. Trifluoromethyl metal complexes have been extensively employed for trifluoromethylation of carbonyl compounds[3-5] and aryl halides.[6-8] Perfluoroalkanoyl peroxide,[9-11] N-(trifluoromethyl)-N-nitrosotrifluoromethanesulfonamide,[12,13] and xenon difluoride-trifluoroacetic acid[14] can trifluoromethylate aromatic compounds. Recently, electrochemical trifluoromethylation has been recognized as a useful method for the preparation of aliphatic trifluoromethylated compounds. Electroreductive generation of CF_3^- anion[15] or CF_3• radicals[16] from CF_3Br has been actively investigated by Saveant et. al. Trifluoroacetic acid (TFA) is one of the most available and economically feasible starting material for trifluoromethylation and a promising source of CF_3• radicals.



1

Renaud,[17,18] Brookes,[19,20] and Muller,[21-23] have demonstrated usefulness of electrochemical trifluoromethylation with TFA. However, they are still unclear that the factors which control the product selectivity and the scope and limitation of the reaction. This study focuses an efficient generation of CF_3.radicals by electrochemical oxidation of TFA and their utilization for trifluoromethylation of olefins.



1. Electrolysis conditions for the generation of CF_3•radicals from TFA.

Optimized electrolysis conditions are as follows; TFA was partially (10 %) neutralized with NaOH in $MeCN-H_2O$ (7:1) and electrooxidized using platinum electrodes in an undivided beaker type cell at constant currents (50 mA-100 mA/cm^2). The efficiency for the CF_3•radicals generation is shown in Fig. 1 and 2. Fig. 1 is a relation between terminal voltage and electricity and shows that a sharp increase of the voltage after 1 F/mol is observed, where most of TFA is completely consumed.[24] Fig. 2 reveals that the current efficiency of TFA consumption is strongly dependent on the electrolysis temperature.[25] At around 0 °C, more than 95 % current efficiency is performed, while at higher temperature oxygen evolution predominates. Generally, 1.1-1.5 F/mol of electricity to TFA is passed at room temperature. The high current density (50-100 mA/cm^2) is usable for the large scale preparative reactions.

Fig. 1

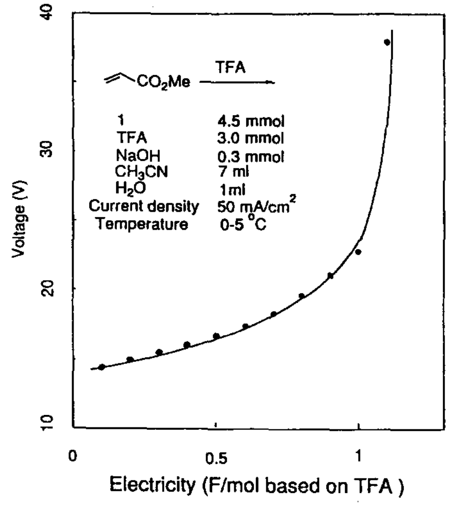
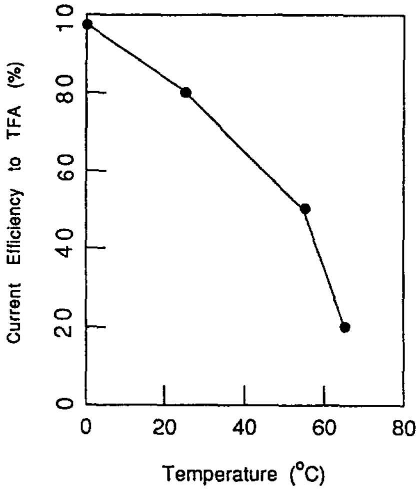
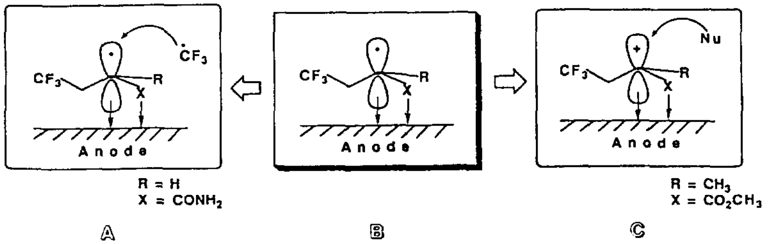


Fig. 2



2. Control of radical reactivities at the electrode surface.

The reactivity of the trifluoromethylated radical intermediates 1 formed from the CF_3.radicals attack to olefins is quite different from that of the homogeneous radical reactions. This is one of the characteristic feature of the electrochemical reactions. The concentration of the radicals on the electrode surface can be controlled by the current density. The higher current density can concentrate the radicals locally on the electrode surface and thus promote the radical coupling reaction. Meanwhile, the radical 1 would be electrochemically oxidized to the carbenium ion ℂ on keeping the low current density which can be trapped with nucleophiles such as water and acetonitrile. So, trifluoromethyl-acetamidation of methyl methacrylate arises from the sequential radical and ionic reactions and is one of the unique electrochemical reactions otherwise difficult to realize. The affinity of the substituent to the electrode markedly affects the stability and the life-time of the radicals on the electrode. Nitrogen atom of the amide group of acrylamide adsorbs on the platinum electrode so strongly that the intermediate radicals 𝔸 (R=H, X=$CONH_2$) diffuse slowly to the bulk solution and are consequently trapped with another CF_3•radicals on the electrode surface, promoting bistrifluoromethylation when the current density is kept high.



3. Electrochemical trifluoromethylation of olefins.

The trifluoromethyl radicals are electrophilic and must be reactive toward the electron rich olefins. However, the electron rich olefins are much more electrooxidizable than TFA so that they are oxidized faster than TFA and not feasible substrates for the purpose. The electron deficient olefins such as methyl acrylate (MA), methyl methacrylate (MMA), acrylamide (AA), acrylonitrile (AN), and fumaronitrile (FN) are useful.

One of the typical mole scale electrolysis conditions is as follows; A mixture of TFA (1 mol), methyl acrylate (1.3 mol), and sodium hydroxide (0.1 mol) dissolved in acetonitrile (560 ml) and water (80 ml) was electrolyzed under 83 mA/cm^2 at 0-5 ^{o}C using platinum electrodes (15 cm^2) in an undivided cell. After distillation compound 2 was obtained in a 50% yield as crystals.[24,26] It is interesting that the electrochemical radical reaction of MA is not a polymerization but dimerization. Change of substituent on C=C double bond from methoxycarbonyl to carbamoyl group dramatically affects the products. Acrylamide (AA) provides bistrifluoromethylated compound 3 in a 35 % yield.[27] The yield of 3 increases by raising the current density(Fig. 3). The higher current density concentrates the CF_3•radicals on the electrode surface, and thus promotes the radical coupling of CF_3•radicals with the strongly adsorbed nitrogen containing radical intermediates A.[28]

Fig. 3

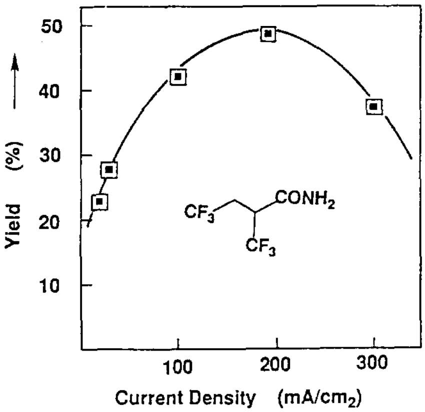
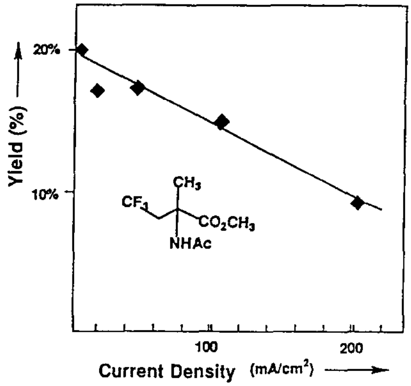
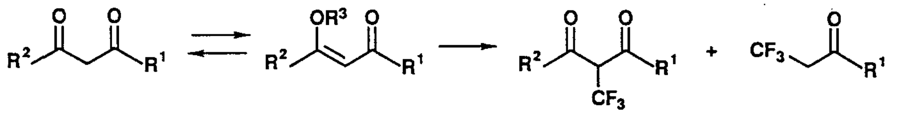


Fig. 4

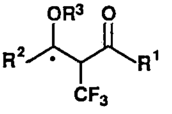


In contrast, trifluoromethylacetamidation of MMA preferentially occurs at the lower current density, providing 4.[29](Fig. 4) Trifluoromethyl-dimerization of MMA was found unfavorable (3 % yield).[30] Likewise, trifluoromethylhydroxylation takes place in aqueous acetone.[31] Methyl group of MMA enhances further one electron oxidation of 1 (R=Me), leading to the corresponding carbenium ion which can be trapped with acetonitrile or water. In contrast, methyl 2-phenylacrylate does not provide the desired acetamide because the substrate is oxidized more easily than TFA.

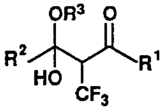
The active methylene compounds such as methyl acetoacetate and its enol acetate can be trifluoromethylated in the similar conditions (6, 40-60 % yield).[32]



7 8a R^3=H 8b R^3=Ac 6 9

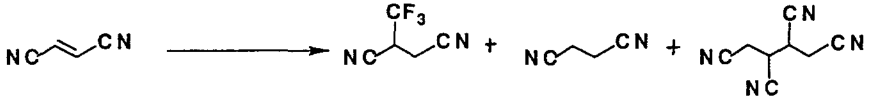


10



11

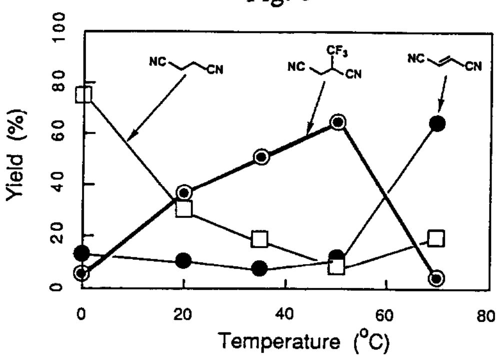
Fumaronitrile (FN), one of the highly electron-deficient olefins, provides 2-trifluoromethylsuccinonitrile 5 in a 65 % yield.[25] The compound 5 is a trifluoromethyl-hydrogenated product which has never been obtained as a major product both in the chemical and electrochemical trifluoromethylation reactions.[33] The question is whether the trifluoromethylated radical intermediate corresponding to 1 can be formed and abstract predominantly hydrogen from solvents such as water and acetonitrile. In order to clarify the mechanism, several experiments are studied.



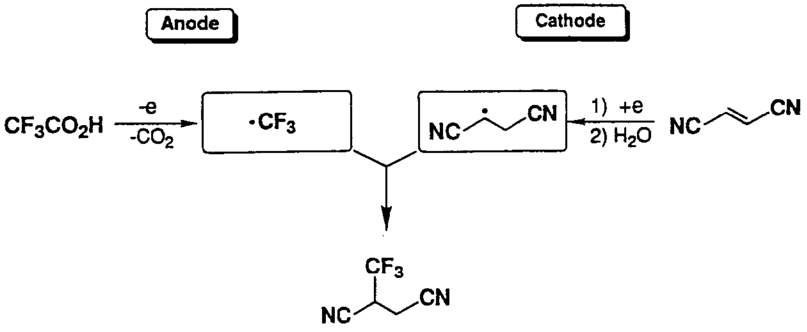
5 65% 13 7% 14 8%

In a divided cell electrolysis, FN was recovered from the anode compartment and converted to succinonitrile in the cathode compartment. In the same conditions, MA was converted to the trifluoromethylated dimer 2 in an anode compartment. This result reveals that the CF_3.radicals are generated in the divided cell but do not attack FN. Then, xenon difluoride-TFA system[14] which is known to generate CF_3•radicals in CH_2Cl_2 was applied to fumaronitrile to see whether the chemically generated CF_3.radicals react with FN. Here again, FN was recovered intact. In contrast to this, MA was converted to 2. This result is quite similar to that obtained in the electrolysis reaction, revealing that CF_3.radicals do not attack the electron deficient carbon-carbon double bond of FN. Judging from the above mentioned results and taking into account of the electro-reduction of FN to succinonitrile and efficient formation of 5 in an undivided cell system, the formation of 5 may arise from the radical coupling of CF_3.radicals and succinonitrile radicals which must be generated by the one-electron reduction of FN followed by protonation. Succinonitrile radicals dimerize partially leading to 1,2,3,4-tetracyanobutane (14, 8 % yield).

Fig. 5



The intensive temperature-dependence on the product selectivity observed in the present trifluoromethyl-hydrogenation suggests that the intermediate fumaronitrile anion radicals preferentially diffuse to the bulk solution at the higher temperature, and in contrast, adsorb tightly on the electrode surface and thus hydrogenated to succinonitrile as a final product at the lower temperature electrolysis (Fig. 5).



The area of the electrodes and the distance between the anode and the cathode also slightly affected the yield of 5. A shorter electrode distance and a larger cathode area compared to that of the anode favored the formation of 5.

4. Conclusion

Trifluoromethyl radicals can be generated almost quantitatively in the electrooxidation of TFA at 0 °C in an MeCN-H_2O-Pt system. Olefins bearing electron-withdrawing groups are suitable for the electrochemical trifluoromethylation because electron rich olefins are oxidized more easily than TFA. Yield and product-selectivity are intensively affected by the substituents on C=C bond, current density and reaction temperature, which would control the concentration and the chemical fate of the intermediate radicals 1 on the electrode surface.

5.Experimental

Electrolysis of MA. Methyl acrylate (120 mL, 1.3 mol), TFA (80 mL, 1.0 mol), and NaOH (4 g, 0.1 mol) were dissolved into a mixture of acetonitrile (560 mL) and water (80 mL) in a cylindrical electrolysis cell (20 cm^2 tall and 8 cm diameter), equipped with two platinum foils (6 cm x 4 cm). The mixture was electrolyzed under a constant current of 2.0 A (83 mA/cm^2) at 0-10 °C for 16 h (1.2 F/mol based on TFA). Acetonitrile and the unreacted methyl acrylate were almost evaporated under reduced pressure, and 100 mL of water was added to the residue. The aqueous layer was extracted three times with AcOEt. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was distilled (78-102 °C / 7 mmHg) to give a mixture of 2, diastereomers (81 g, 50 %) as colorless crystals which were separated by repeated recrystallization from hexane.

Electrolysis of FN. A mixture of FN (156 mg, 2.0 mmol), trifluoroacetic acid (0.62 mL, 8.0 mmol), NaOH (32mg, 0.8 mmol), MeCN (6 mL), and H_2O (1 mL) was electrolyzed at 50 °C in an undivided beaker-type cell (10 cm tall and 1.8 cm in diameter) fitted with platinum foils (1.5 x 1 cm^2 for an anode and 1.5 x 2 cm^2 for a cathode) as the electrodes. A constant current (50 mA/cm^2) was supplied until the charge reached 1.5 F/mol of TFA. The solvent was evaporated under reduced pressure, and the organic residue was extracted with AcOEt, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silicagel (hexane-AcOEt), to give 5 (193 mg, 65 %) as a slightly green liquid, 13 (11 mg, 7 %), and 14 (12 mg, 8 %, a mixture of dl and meso) as colorless crystals.

References and Notes

1) Filler, R.; Kobayashi, Y., *Biomedicinal Aspects of Fluorine Chemistry*; Kodansha: Tokyo, 1982.
2) Hudlicky, M., *Chemistry of Organic Fluorine Compounds*; Ellis Horwood: New York, 1976.
3) Kitazume, Y.; Ishikawa, N., *Chem. Lett.*, 1981, 1679.
4) Kitazume, Y.; Ishikawa, N. *J. Am. Chem. Soc.*, 1985, *107*, 5186.
5) Francese, C.; Tordeux, M.; Wakselman, C., *Tetrahedron Lett.*, 1988, *29*, 1029.
6) Kobayashi, Y.; Kumadaki, I., *Ibid.*, 1969, 4095.
7) Leroy, J.; Rubinstein, M.; Walling, C., *J. Fluorine Chem.*, 1985, *27*, 291.
8) Kitazume, T.; Ishikawa, N., *Chem. Lett.*, 1982, 137.
9) Zhao, C.; El-Taliawi, G. M.; Walling, C., *J. Org. Chem.*, 1983, *48*, 4908.
10) Sawada, H.; Kobayashi, M., *Yuki Gosei Kagaku Kyokaishi*, 1986, *44*, 600.
11) Yoshida, M.; Yoshida, T.; Kobayashi, M.; Kamigata, N., *J. Chem. Soc. Perkin Trans.*, *1* 1989, 909.

12) Umemoto, T.; Miyano, O., *Tetrahedron Lett.*, 1982, *23*, 3929.
13) Umemoto, T.; Ando, A., *Bull. Chem. Soc. Jpn.*, 1986, *59*, 447.
14) Tanabe, Y.; Matsuo, N.; Ohno, N., *J. Org. Chem.*, 1988, *53*, 4582.
15) Andrieux, C. P.; Gelis, L.; Medebielle, M.; Pinson, J.; Saveant, J-M., *J. Am. Chem. Soc.*, 1990, *112*, 3509.
16) Andrieux, C. P.; Gelis, L.; Saveant, J-M., *Tetrahedron Lett.*, 1989, *30*, 4961.
17) Renaud, R. N.; Sullivan, D. E., *Can. J. Chem.*, 1972, *50*, 3084.
18) Renaud, R. N.; Champagne, P. J., *Ibid.*, 1979, *57*, 2617.
19) Brookes, C. J.; Coe, P. L.; Owen, D. M.; Pedler, A. E.; Tatlow, J. C., *J. Chem. Soc. Chem. Commun.*,1974, 323.
20) Brookes, C. J.; Coe, P. L.; Pedler, A. E.; Tatlow, J. C., *J. Chem. Soc. Perkin Trans.*, *1*, 1978, 202.
21) Muller, N., *J. Org. Chem.*, 1983, *48*, 1370.
22) Muller, N., *Ibid.*, 1986, *51*, 263.
23) Muller, N., *J. Fluorine Chem.*, 1987, *36*, 163.
24) Uneyama, K.; Makio, S.; Nanbu, H., *J. Org. Chem.*, 1989, *54*, 872.
25) Uneyama, K.; Watanabe, S., *J. Org. Chem.*, 1990, *55*, 3909.
The remaining TFA was analyzed by ^{19}F-NMR in D_2O.
26) Diastereomeric mixture, dl : meso = 1 : 1 (VPC and ^{19}F-NMR)
27) Uneyama, K.; Morimoto, O.; Nanbu, H., *Tetrahedron Lett.*, 1989, *30*, 109.
28) Bistrifluoromethylation takes place in the high current density (150 mA/cm^2) electrolysis of ethyl fumarate (47 % yield) and N-ethyl maleimide (42% yield). Renaud. R. N.; Champagne, P. J.; Savard, M., *Can. J. Chem.*, 1979, *57*, 2617.
29) Uneyama, K.; Nanbu, H., *J. Org. Chem.*, 1988, *53*, 4598.
30) Renaud has reported the formation of dimethyl 2,3-bis(2,2,2-trifluoroethyl)-2,3-bismethylsuccinate (9.8% yield) as the only isolable product in the electrolysis of MMA in methanol or acetic acid. Ranaud, R. N.; Champagne, P. J., *Can. J. Chem.*, 1975, *53*, 529.
31) Uneyama, K.; Kitagawa, K.; Watanabe, S., Unpublished results.
32) Uneyama, K.; Ueda, K., *Chem. Lett.*, 1988, 853.
33) The electrochemical trifluoromethylation of methyl acrylate, acrylonitrile, methyl 3-butenoate, and methallyl cyanide provided the trifluoromethyl-hydrogenated products such as methyl 4,4,4-trifluorobutanoate (5%) and 4,4,4-trifluorobutyronitrile (5%),[19] a mixture of 3-methyl-5,5,5-trifluoropentenonitriles,[23] and methyl 5,5,5-trifluoropentanoate[34].
34) Brookes, C. J.; Coe, P. L.; Pedler, A. E.; Tatlow, J. C., *J. Chem. Soc., Perkin I*, 1978, 202.

35) The author is grateful to the Ministry of Education, Culture and Science of Japan for financial support Grant-in-Aid for Scientific Research (No.01550675 and 02555179).