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Preparation of Trifluoromethylated Compounds by Anodic Oxidation of 3-Hydroxy-2-trifluoromethylpropionic Acid

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Electrochemical Oxidation of 3-hydroxy-2-trifluoromethylpropionic acid(1) produced 2,3-bis(trifluoromethyl)-1,4-butanediol in quantitative yield. Furthermore, 2-trifluoromethylated alcohols were obtained by the crossed Kolbe reaction of 1 with carboxylic acids or dicarboxylic acid mono esters.

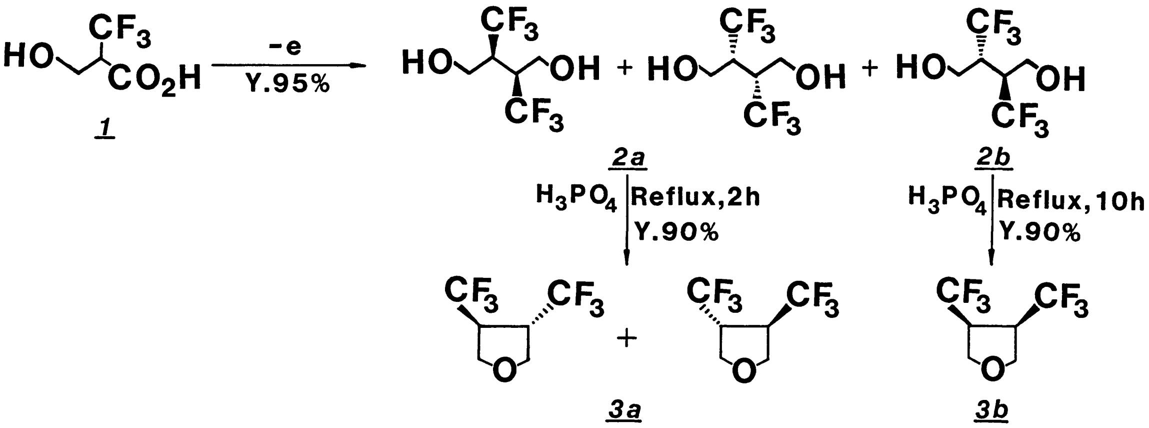
Recently, the synthesis of trifluoromethylated organic compounds has been studied actively owing to biological interests.1) Especially, the advance in the synthesis and utilization of trifluoromethylated synthons has been remarkable for these several years.2) There are few reports on the synthesis of 2-trifluoromethylated alcohols except for the synthesis of methyl β-hydroxy-α-trifluoromethylcarboxylates via Refomatsky reaction by using methyl 3,3,3-trifluoropropionate.3) On the electrolysis of trifluoromethylated compounds, anodic oxidation of trifluoroacetic acid4) or phenyl 2,2,2-trifluoroethyl sulfide,5) and the synthesis of 1-trifluoromethylated alcohols from 3-hydroxy-4,4,4-trifluorobutyric acid6) were reported.

We found that 2,3-bis(trifluoromethyl)-1,4-butanediols(2) could be obtained by the electrochemical oxidation of 3-hydroxy-2-trifluoromethylpropionic acid(1).7) It is interesting that the Kolbe reaction of 1 more smoothly proceeded than 3-hydroxypropionic acid. This fact suggests that α-trifluoromethyl group facilitates this electrochemical reaction.

Now we wish to report a new electrochemical synthetic route for trifluoromethylated synthons.

The mixture of acid(1)(1.58 g, 10 mmol), sodium methoxide(0.05 g, 1.0 mmol) and dry methanol(40 ml) was electrolyzed under a constant current(2.00 A) at 5 °C using a beaker-type undivided cell attached with platinum electrodes(40 mm × 40 mm). After passing charge of 10 F/mol, reaction mixture was poured into water , and extracted with ether. Solvent was removed in vacuo. Vacuum distillation of the oily matter gave diol(2) in a 95% yield. The diol(2) was obtained as a mixture of dl- and meso-form, which was separated into each component by column chromatography(silica gel, chloroform).8)

The dehydration of dl- and meso-diol(2a, 2b) with phosphoric acid to 3,4-bis(trifluoromethyl)tetrahydrofuran(3a, 3b) was carried out.9) The dehydration of 2a was completed within 2 h, but that of 2b was prolonged to 10 h. This result might be caused by the difference of the steric hindrance between two trifluoromethyl groups in each transition states.



The electrolysis aimed at crossed Kolbe reaction of the equimolar mixture of 1 and 3-chloropropionic acid(4) mainly gave homo-coupling product 2 and the desired product, 4-chloro-2-trifluoromethylbutanol(5a) was obtained only as a minor. When 6 times mol of 4 to 1 was used, the formation of 2 was suppressed below 5% and 5a was obtained selectively. It might result from the difference of acidity between 1 and 4 that the Kolbe reaction of 1 was proceeded in preference to the crossed Kolbe reaction between 1 and 4.

The mixture of 1(1.58 g, 10 mmol), 4(6.27 g, 60 mmol), sodium methoxide(3.78 g, 7 mmol) and dry methanol(40 ml) was electrolyzed under similar conditions described above. After passing charge of 6 F/mol, the reaction mixture was work-up as usual. Vacuum distillation of the oily matter gave 5a in a 70% yield.$^{10)}$ The crossed Kolbe reaction of 1 with butyric acid and 3-hydroxypropionic acid under similar conditions to the case of 4 also proceeded to form the corresponding trifluoromethylated alcohols(5b, 5c).$^{11)}$ The results are given in Table 1.

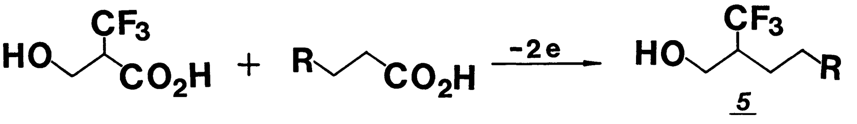
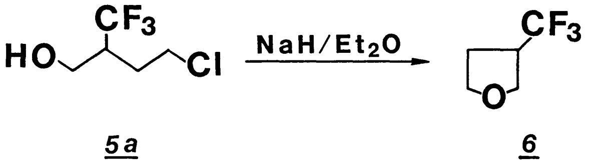


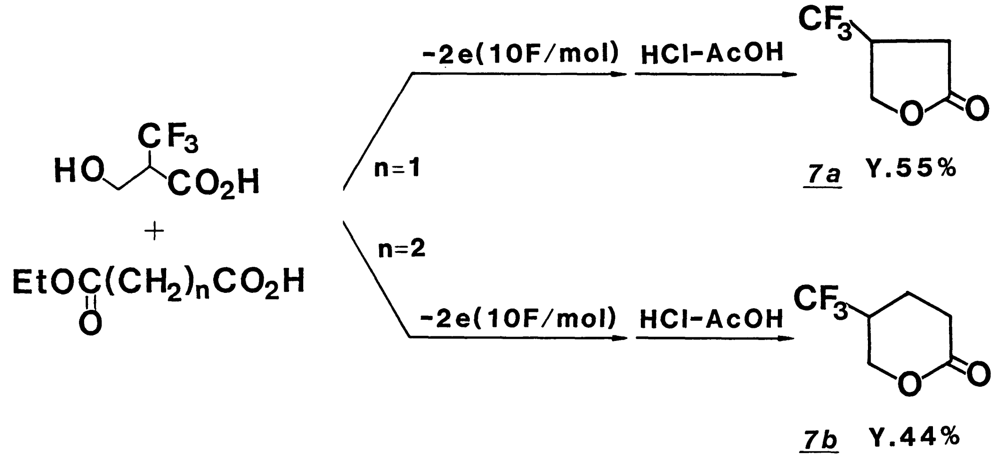
Table 1. The Synthesis of 2-Trifluoromethylated alcohls

5	R	Passing Charge F mol^{-1}	Bp θ_b/°C(mmHg)	Yield %
5a	Cl	6	36-40(20)	70
5b	Me	4	63-66(34)	50
5c	OH	13	80-85(2)	14

By treating of 5a with sodium hydride in ether, the cyclization product, 3-trifluoromethyltetrahydrofuran(6) was obtained in good yield.$^{12)}$



Furthermore, the crossed Kolbe reaction of 1 with ethyl hydrogen malonate and ethyl hydrogen succinate followed by treatment with concentrated HCl-acetic acid produced 3-trifluoromethyl-4-butanolide(7a)[13] and 4-trifluoromethyl-5-pentanolide (7b)[14] respectively. This Procedure for 7a is more convenient and successful than the process reported hitherto.[15]



Consequently, we believe that these electrochemical oxidations of 3-hydroxy-2-trifluoromethylpropionic acid and the following reaction provide the excellent route to trifluoromethylated synthons.

References

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7) 3-Hydroxy-2-trifluoromethylpropionic acid(1) was prepared by 10 h refluxing of aqueous solution of 2-trifluoromethylacrylic acid in a quantitative yield.
8) 2a ; Bp 84-87 °C/2 mmHg. ^{19}F-NMR(CCl_4) : δ -10.57 ppm from external CF_3COOH, (d, J = 8.8 Hz). ^{1}H-NMR(CCl_4) : 2.50-3.23(2H, br), 3.98(4H, d, J = 5.0 Hz), 4.69(2H, s). MS : m/e 226(M^+).
2b ; Bp 84-87 °C/2 mmHg. ^{19}F-NMR(CCl_4) : -12.47(d, J = 8.8 Hz). ^{1}H-NMR(CCl_4) : 2.55-3.32(2H, br), 3.93(4H, d, J = 6.0 Hz), 4.75(2H, s). MS : m/e 226(M^+).

The discrimination between dl- and meso-diol was carried out by GC and ^{19}F-NMR analysis of the diesters(2a', 2b') derived from (+)-2-perfluoropropoxy-propionyl chloride and diol(2a, 2b). On the chromatogram of 2a', the separation pattern of mixture of diastereomers was observed. On the ^{19}F-NMR spectrum of trifluoromethyl group at diol part of 2a', the two doublet signals (δ -10.14, -10.49) from diastereomers were observed. From these results, it was determined that 2a was dl- and 2b was meso-form.

9) 3a ; Bp 70-72 °C/150 mmHg. ^{19}F-NMR(CCl$_4$) : δ -7.43(d, J = 7.7 Hz). ^{1}H-NMR (CCl$_4$) : 3.12(2H, qm, J = 7.7 Hz), 4.02(4H, d, J = 5.5 Hz). MS : m/e 206(M$^+$).
3b ; Bp 70-72 °C/150 mmHg. ^{19}F-NMR(CCl$_4$) : δ -12.60(d, J = 8.0 Hz). ^{1}H-NMR (CCl$_4$) : 2.83-3.47(2H, m), 4.11(4H, d, J = 7.5 Hz). MS : m/e 206(M$^+$).

10) 5a ; ^{19}F-NMR(CCl$_4$) : δ -7.77 (d, J = 8.1 Hz). ^{1}H-NMR(CCl$_4$) : 2.17 (2H, dt, J = 1.6, 7.0 Hz), 2.20-2.83 (1H, m), 3.37 (1H, br), 3.66 (2H, t, J = 7.0 Hz), 3.80 (2H, d, J = 4.8 Hz). MS : m/e 176, 178(M$^+$).

11) 5b ; ^{19}F-NMR(CCl$_4$) : δ -8.17 (d, J = 9.0 Hz). ^{1}H-NMR(CCl$_4$) : 0.73-1.14 (3H, m), 1.22-1.77 (4H, m), 1.97-2.48 (1H, m), 2.70-3.05 (1H, m), 3.37 (2H, J = 5.8 Hz). MS : m/e 155(M$^+$).
5c ; ^{19}F-NMR(CCl$_4$) : δ -11.80 (d, J = 8.8 Hz). ^{1}H-NMR(CCl$_4$) : 1.99 (2H, dt, J = 1.4, 1.6 Hz), 2.61-3.29 (3H, m), 3.69 (2H, t, J = 6.4 Hz), 3.81 (2H, d, J = 7.2 Hz). MS : m/e 159(M$^+$).

12) 6 ; Bp 103-105 °C. ^{19}F-NMR(CCl$_4$) : δ -6.52 (d, J = 8.3 Hz). ^{1}H-NMR(CCl$_4$) : 2.17 (2H, dt, J = 7.5, 8.3 Hz), 2.62-3.32 (1H, m), 3.77 (2H, t, J = 6.6 Hz), 3.83 (2H, d, J = 8.3 Hz). MS : m/e 140(M$^+$).

13) 7a ; Bp 96-102 °C/25 mmHg. ^{19}F-NMR(CCl$_4$) : δ -4.33 (dm J = 7.7 Hz). ^{1}H-NMR (CCl$_4$) : 2.63 (1H, d, J = 4.1 Hz), 2.75 (1H, d, J = 6.2 Hz), 3.15-3.67 (1H, m), 4.37 (1H, s), 4.47 (1H, d, J = 6.0 Hz). MS : m/e 154(M$^+$).

14) 7b ; Bp 76-78 °C/4 mmHg. ^{19}F-NMR(CCl$_4$) : δ -6.00 (d, J = 8.5 Hz). ^{1}H-NMR (CCl$_4$) : 1.91-2.32 (2H, m), 2.35-2.83 (3H, m), 4.44 (2H, d, J = 6.0 Hz). MS : m/e 168(M$^+$).

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