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# Preparation of Trifluoromethylated Compounds via Anodic Oxidation of 4,4,4-Trifluoro-3,3-dimethoxybutyric Acid

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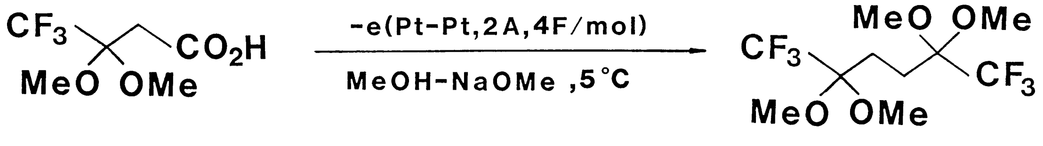
The Kolbe electrolysis of 4,4,4-trifluoro-3,3-dimethoxybutyric acid (TDBA) gave corresponding homo-coupling product, 1,1,1,6,6,6-hexafluoro-2,2,4,4-tetramethoxyhexane, which could be converted to the diene by treating with $TiCl_4$ followed by dehydrochlorination. Furthermore, the crossed Kolbe product from TDBA and 3-hydroxy-2-trifluoromethylpropionic acid was converted to tetrahydrofurans and an 1-olefine.

The application of many kinds of trifluoromethylated syntons has been actively studied owing to the development of organofluorine compounds in the field of biochemistry. Recently, trifluoromethylated organic compounds were focused further, because of some successful use for optelectronic materials.1)

On the electrolytic synthesis of organofluorine compounds, there are a few reports on the anodic oxidation of trifluoroacetic acid2) and 2,2,2-trifluoroethyl phenyl sulfide.3) However, the electrochemical behavior of fluorine-containing compounds has been hardly clarified. In our continuing work on the synthetic application of trifluoromethylated building blocks, we have already reported the synthesis of 2-trifluoromethylated alcohols by Kolbe electrolysis of 3-hydroxy-2-trifluoromethylpropionic acid (HTPA).4)

Now we wish to report the anodic oxidation of 4,4,4-trifluoro-3,3-dimethoxybutyric acid and the following derivatizations to diene 4.

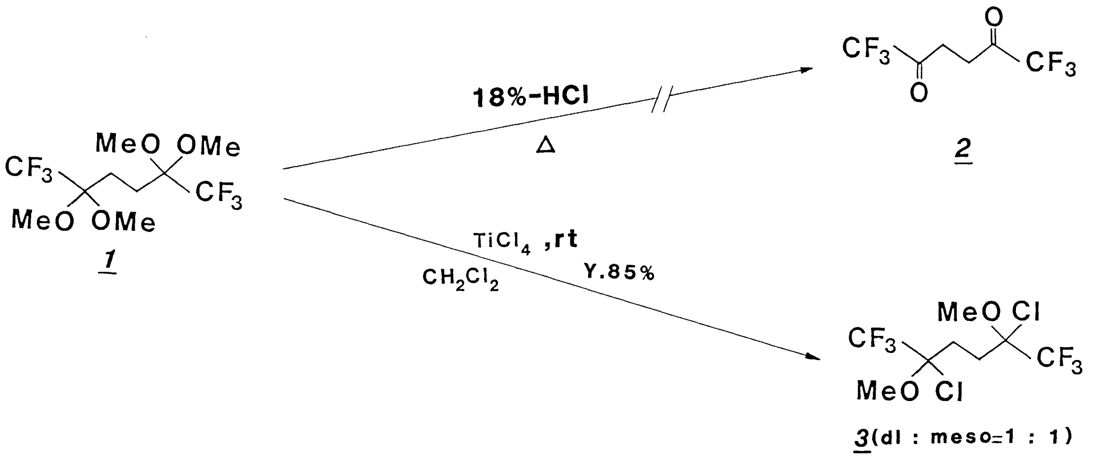
The mixture of TDBA (10.1 g, 50 mmol),5) sodium methoxide (0.27 g, 5 mmol) and dry methanol (50 ml) was electrolyzed under constant current (2.00 A) at 5 °C using a beaker-type undivided cell attached with platinum electrodes(40 mm × 40 mm). After passing charge of 4 F/mol, the reaction mixture was extracted with ether. Solvent was removed in vacuo. Vacuum distillation of the oily matter gave homo-coupling product, 1,1,1,6,6,6-hexafluoro-2,2,4,4-tetramethoxyhexane (1) (5.46 g) in 86% yield.6)



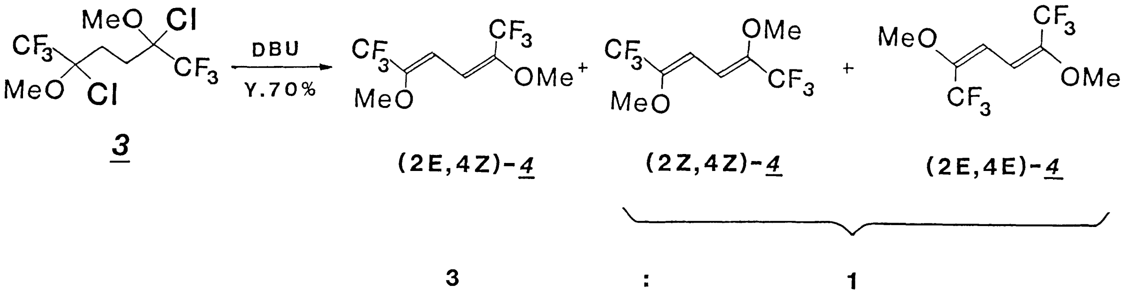
TDBA

1 Y. 86%

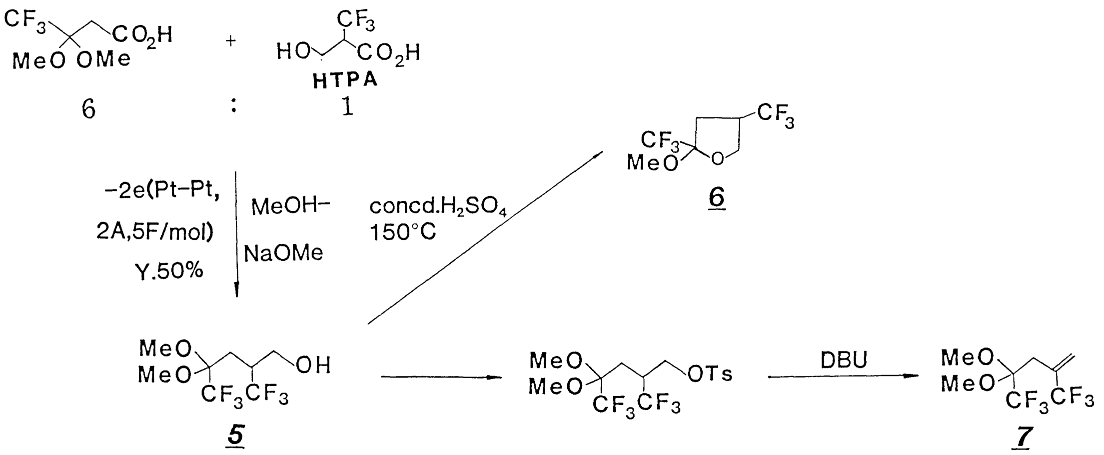
The tetramethoxyhexane(1) was so stable ketal that even by heating of 1 in 18%-hydrochloric acid 1 did not decompose to diketone(2). The tetramethoxyhexane 1 reacted with titanium tetrachloride in dichloromethane at room temperature to form 2,4-dichloro-1,1,1,6,6,6-hexafluoro-2,4-dimethoxyhexane(3) in high yield.[7] On the displacement of alkoxy group of ketals or acetals, there are several reports on the alkyl-substitution by Grignard reagent incorporated with titanium tetrachloride,[8] but no reports on chloro-substitution by titanium tetrachloride as the above synthesis.



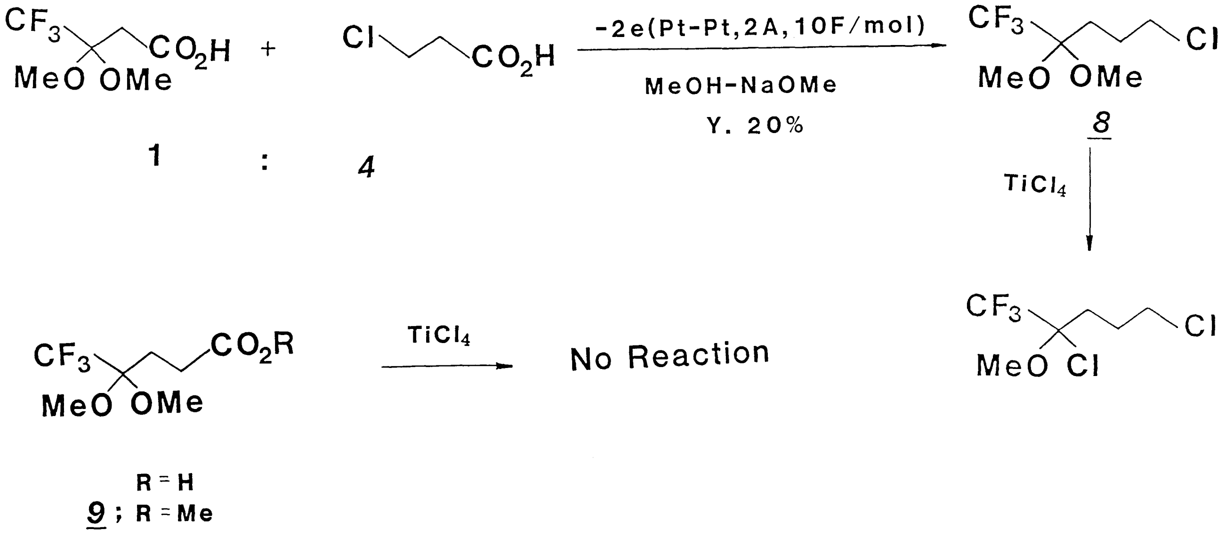
The dehydrochlorination of 3 by 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) gave (2E,4Z)-1,1,1,6,6,6-hexafluoro-2,5-dimethoxy-2,4-hexadiene(4) as a major product.[9]



There are no reports on the crossed Kolbe reaction between two kinds of fluorine-containing carboxylic acids. Then, the electrolysis of the equimolar mixture of TDBA and HTPA was tried, but the desired cross-coupling product, 5,5,5-trifluoro-4,4-dimethoxy-2-trifluoromethylpentanol(5) was obtained in poor yield (Y.17%)[10] and the homo-coupling product of HTPA, 2,3-bis(trifluoromethyl)-1,4-butanediol was produced in major( Y.65% ). This might be caused by the fact that the oxidation potential of HTPA is lower by 0.66 V than that of TDBA. So, when TDBA was used six times mol of HTPA in this electrolysis, cross-coupled alcohol 5 was obtained in 50% yield based on HTPA. In this electrolysis, homo-coupling product from HTPA was not found but that from TDBA. The alcohol 5 was cyclized to 2-methoxy-2,4-bis(trifluoromethyl)tetrahydrofuran(6)[11] in 42% yield by heating with concentrated sulfuric acid at 150 °C. 5,5,5-Trifluoro-4,4-dimethoxy-2-trifluoromethylpent-1-ene(7)[12] was derived from the tosylate of 5 by treating with DBU in 42% yield.



Similarly, the crossed Kolbe reaction of TDBA with fluorine-free carboxylic acids, 3-chloropropionic acid proceeded to form 5,5,5-trifluoro-4,4-dimethoxypentyl chloride(8)13) in 20% yield based on TDBA. In this electrolysis, the feed ratio of TDBA / 3-chloropropionic acid was 1/4, in spite of the oxidation potentials of the two substrates are close each other, the formation of homocoupling product 1 was predominant over that from pentyl chloride 8. One of the methoxy groups of 7 was replaced by chlorine atom by treating with titanium tetrachloride in dichloromethane in the same manner as the substitution of 1. It is remarkable that the methoxy group replacement by chlorine was occurred in cases of ketal 1 and 8, but not occurred in cases of TDBA, methyl ester of TDBA(9) and pentanol 5, despite of having the same ketal structure as 1 and 8. One of the reasons why TDBA, 9 and 5 do not react with titanium tetrachloride seemed to be favorable chelation of titanium on their carbonyl or hydroxy group which is not present in 1 and 8.



Although there are still many unknown factors on the electrolysis of organofluorine compounds, we believe that our synthetic procedures using anodic oxidation of fluorine-containing carboxylic acid and the following derivatization provide the excellent routes to a variety of trifluoromethylated compounds.

## References

1) K. Yoshino, M. Ozaki, H. Taniguchi, M. Ito, N. Yamazaki, and T. Kitazume, Jpn. J. Appl. Phys., 25, L77 (1987).

2) K. Uneyama, O. Morimoto, H. Nanbu, and T. Ito, 5th National Meeting of the Chemical Society of Japan, Tokyo, April 1988, Abstr. No. 1 XI B18.

3) T. Fuchigami, Y. Nakagawa, and T.Nonaka, Tetrahedron Lett., 27, 3869(1986).

4) T. Kubota, R. Aoyagi, H. Sando, M.Kawasumi, and T. Tanaka, Chem. Lett., 1987, 1435.

5) TDBA was prepared by the method reported by A. Watanabe and H. Kono (The 13th Symposium on Fluorine Chemistry, 1988, 4D119) as following procedure. Into the mixture of dimethyl carbonate(50 mmol), sodium methoxide(100 mmol) and tetrahydofuran(50 ml), 2-bromo-3,3,3-trifluoropropene(50 mmol) was dropped at 0 °C. After 2 h stirring, the reaction mixture was poured into 100 ml of water, and extracted with ether. Vacuum distillation gave TDBA in 80% yield.

6) 1 ; Bp 54-55 °C/2 mmHg. $^{19}$F-NMR(MeOH) : $\delta$ -1.01 ppm from external trifluoroacetic acid, (s). $^{1}$H-NMR($CCl_4$) : 1.93(4H, s), 3.33(12H, s). MS : m/e 314($M^+$).

7) 2 ; Bp 69-71 °C/11 mmHg. The product was obtained as the diastereomeric mixture( dl-form : meso-form = 1 : 1). $^{19}$F-NMR($Et_2O$) : -0.68(s), -0.80(s). $^{1}$H-NMR($CCl_4$) : 2.35(4H, s), 3.59(6H, s). MS : m/e 287, 289($M^+$-Cl).

8) H. Ishikawa, T. Mukaiyama, and S. Ikeda, Bull. Chem. Soc. Jpn., 54, 776 (1981).

9) (2Z, 4E)-4 ; $^{19}$F-NMR($CDCl_3$) : -10.00(3F, s), -12.60(3F, s). $^{1}$H-NMR($CDCl_3$) : 3.73(6H, m), 5.75(1H, d, J = 11.0 Hz), 6.38(1H, d, J = 11.0 Hz). MS : m/e 250 ($M^+$).

Although both (2E, 4E)-4 and (2Z, 4Z)-4 were isolated by silica gel column chromatography, these two isomers are not identified hitherto.

{One of the isomer-4 ; $^{19}$F-NMR($CDCl_3$) : -9.93(s). $^{1}$H-NMR($CDCl_3$) : 3.73(6H, m), 6.30(2H, s). MS : m/e 250 ($M^+$).

The other isomer-4 ; $^{19}$F-NMR($CDCl_3$) : -13.17(s). $^{1}$H-NMR($CDCl_3$) : 3.73(6H, m), 5.86(2H, s). MS : m/e 250($M^+$).}

10) 5 ; Bp 80-82 °C/10 mmHg. $^{19}$F-NMR($CDCl_3$) : -1.40(3F,s), -7.53(3F, d, J = 8.1 Hz). $^{1}$H-NMR($CDCl_3$) : 2.15(2H, d, J = 7.6 Hz), 2.37-2.65(1H, m), 3.35(6H, s), 3.61(1H, s), 3.81(2H, d, J = 3.6 Hz). MS : m/e 271($M^+$+1).

11) The tetrahydrofuran 6 was obtained as the 1:2 mixture of cis- and trans-isomer. Bp 131-132 °C. $^{19}$F-NMR($CDCl_3$) : [cis-6 ; -5.43(d, J = 7.2 Hz), 2.07(s)], [trans-6 ; -6.43(d, J = 7.2 Hz), 3.73(s)]. $^{1}$H-NMR($CDCl_3$) : 2.27-2.52(2H, m), 2.76-3.19(1H, m), 3.41(3H, s), 4.06-4.28(2H, m). MS : m/e 238($M^+$).

12) 7 ; Bp 143-144 °C. $^{19}$F-NMR($CDCl_3$) : -1.73(s), -8.27(s). $^{1}$H-NMR($CDCl_3$) : 2.39 (2H, s), 3.05(6H, s), 5.41(1H, m), 5.50(1H, m). MS : m/e 252($M^+$).

13) 8 ; $^{19}$F-NMR($CDCl_3$) : -1.95(s). $^{1}$H-NMR($CDCl_3$) : 1.93-2.14(4H, m), 3.39(6H, s), 3.46-3.60(2H, m). MS : m/e 189, 191($M^+$-OMe).

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