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Synthetic application of 3,3-dichloro-1,1,1-trifluoroacetone (DCTFA) and 3,3,3-trichloro-1,1,1-trifluoroacetone (TCTFA) for trifluorolactic acid derivatives

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Abstract

Synthetic application of 3,3-dichloro-1,1,1-trifluoroacetone (DCTFA) and 3,3,3-trichloro-1,1,1-trifluoroacetone (TCTFA) for industrially important trifluorolactic acid derivatives is described. Trifluorolactic acid was obtained by hydrolysis of DCTFA under basic conditions. On the other hand, α-substituted trifluorolactic acid derivatives, such as α-methyltrifluorolactic acid and Mosher's acid, were obtained by addition reaction between TCTFA and carbon nucleophiles, followed by subsequent transformation of trichloromethyl group.

Keywords: Fluorinated synthons; 3,3-Dichloro-1,1,1-trifluoroacetone (DCTFA); 3,3,3-Trichloro-1,1,1-trifluoroacetone (TCTFA); Trifluorolactic acid; α-Methyltrifluorolactic acid; Mosher's acid

1. Introduction

3,3-Dichloro-1,1,1-trifluoroacetone (DCTFA) and 3,3,3-trichloro-1,1,1-trifluoroacetone (TCTFA) are regarded as fluorinated synthons consisting of three carbons and having a trifluoromethyl group. DCTFA is produced on an industrial scale through a modified Swarts reaction from pentachloroacetone [1]. However, industrial synthetic application of DCTFA has been quite limited. Only a hydrolysis of DCTFA has been reported to produce a trifluoropyruvaldehyde equivalent [2]. On the other hand, DCTFA is chlorinated to produce TCTFA. TCTFA also has been used only as a trifluoroacetylating agent of amino group [3].

Trifluorolactic acid derivatives are industrially important intermediates in pharmaceutical chemistry and opto-electronic material science. Many synthetic researchers have previously reported practical synthetic methods of these derivatives, however, they are not necessarily effective from an industrial point of view [4].

In this paper, we report industrial synthetic methods of trifluorolactic acid derivatives using DCTFA and TCTFA (Scheme 1).

2. Results and discussion

In non-fluorinated counterpart, transformation of 1,1-dichloroacetone to lactic acid has been well-known [5]. If a similar reaction would proceed in the fluorinated DCTFA, trifluorolactic acid could be directly produced in a single step. After optimization of reaction conditions, the expected trifluorolactic acid was obtained in a high yield (Scheme 2). Critical reaction conditions were use of DCTFA in a hydrate form and control of pH, in which more than 12 must be maintained always. In this reaction, an intramolecular redox reaction might occur, namely a reduction of carbonyl group equivalent and an oxidation of dichloromethyl group. From this consideration, a tentative 1,2-hydride transfer mechanism in in situ formed epoxide might be proposed as shown in Fig. 1.

DCTFA was easily chlorinated by chlorine gas in the presence of a catalytic amount of quinoline to produce TCTFA in a high yield. Next, industrial synthetic methods of α-substituted trifluorolactic acid derivatives using TCTFA are described. Addition reaction between TCTFA and carbon nucleophile has never been reported to the best of our knowledge. If an adduct product would be obtained, a subsequent transformation of trichloromethyl group could provide α-substituted trifluorolactic acid derivatives, such as

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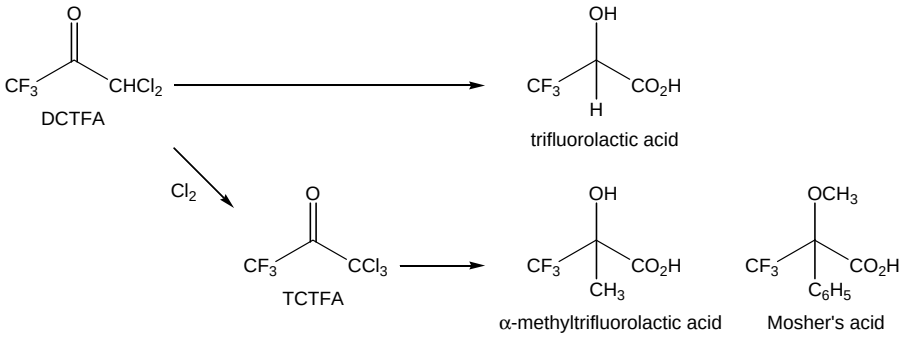
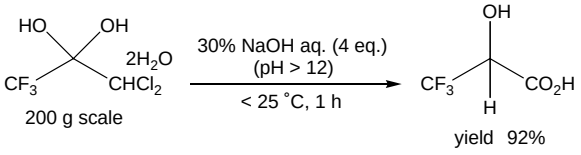


Scheme 1. Industrial synthetic methods of trifluorolactic acid derivatives using DCTFA and TCTFA.



Scheme 2. Industrial synthetic method of trifluorolactic acid using DCTFA.

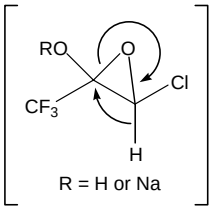


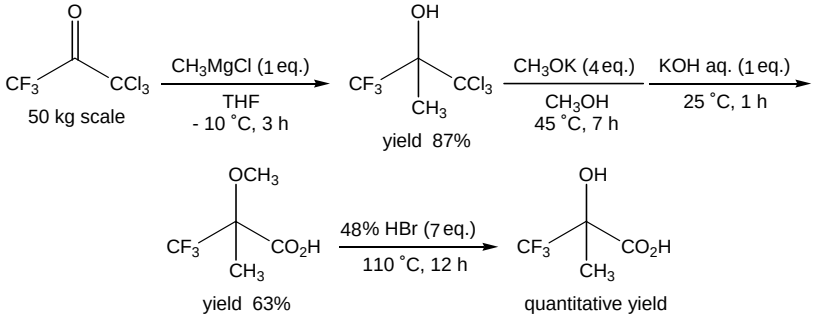
Fig. 1. 1,2-Hydride transfer mechanism.

α-methyltrifluorolactic acid and Mosher's acid. The former compound is a very important intermediate in the development of therapeutic agent for urinary incontinence [6].

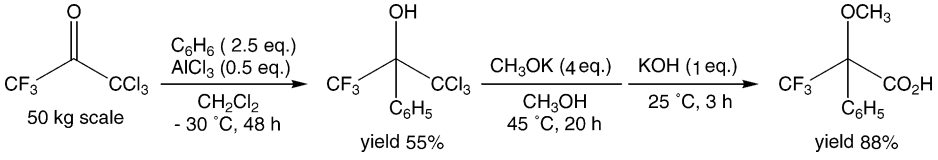
Grignard reaction between TCTFA and methylmagnesium chloride was examined (Scheme 3). The expected adduct product was obtained in a high yield in a usual manner. Methanolysis of the obtained adduct product under a basic condition, followed by hydrolysis of in situ formed methyl ester produced α-methyltrifluorolactic acid methyl ether in a good yield. Subsequent demethylation of methyl ether proceeded smoothly in a quantitative yield using an excess amount of hydrobromic acid.

Friedel–Crafts reaction between TCTFA and benzene was also examined. After screening of Lewis acid, only aluminium chloride was found to be effective. In this Friedel–Crafts reaction, reaction temperature was critical (Table 1). In more than −25 °C, trityl type by-product greatly increased, so in order to obtain a reasonable yield, −30 °C must be maintained for a relatively long reaction time. Under the optimized reaction temperature, an industrial synthetic method of Mosher's acid was examined (Scheme 4). The trityl type by-product could be easily removed by a fractional distillation. A similar methanolysis could be applied to the further transformation. The expected Mosher's acid was obtained in a high yield.

In both methanolyses, the ring opening reaction of in situ formed epoxide occurred regioselectively on the carbon attached to a trifluoromethyl group (Fig. 2).

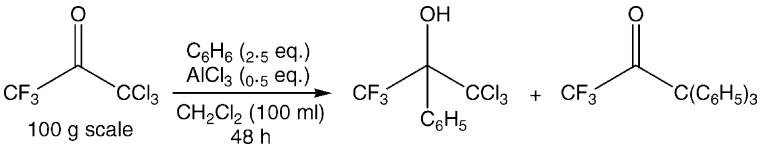


Scheme 3. Industrial synthetic method of α-methyltrifluorolactic acid using TCTFA.



Scheme 4. Industrial synthetic method of Mosher's acid using TCTFA.

Table 1
Friedel–Crafts reaction between TCTFA and benzene



run	temp.[a]	conv.[b]	yield[c]	expected pro. : by-pro.[d]
1	−20 °C	>90%	20%	1:1
2	−30 °C	80%	55%	3:1
3	−40 °C	75%	60%	6:1

[a] Temperature.
[b] Coversion.
[c] Isolated yield of expected product after fractional distillation.
[d] Expected product : by-product.

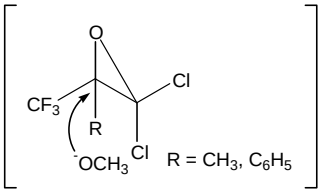


Fig. 2. Regioselective ring opening.

In summary, the industrial synthetic methods of trifluorolactic acid derivatives, such as trifluorolactic acid, α-methyltrifluorolactic acid and Mosher's acid using DCTFA and TCTFA have been developed. These are alternative synthetic methods that do not demand the use of troublesome alkali cyanide.

3. Experimental

3.1. General

^{1}H NMR (400 MHz) or ^{13}C NMR (100 MHz) spectra were measured with a JEOL α-400 FT-NMR spectrometer in $CDCl_3$ or CD_3OD solutions with $(CH_3)_4Si$ as internal standard. ^{19}F NMR (376 MHz) spectra were measured with a JEOL α-400 FT-NMR spectrometer in $CDCl_3$ or CD_3OD solutions with C_6F_6 as internal standard. High-resolution mass spectra were obtained with a Hitachi M-2500.

3.2. Industrial synthetic method of trifluorolactic acid using DCTFA

DCTFA trihydrate 235 g (1 mol, 1 eq.) was added to 30 wt.% NaOH aqueous solution 533 g (4 mol, 4 eq.) at less than 25 °C. After stirring for 1 h at the same temperature, 37 wt.% hydrochloric acid 197 g (2 mol, 2 eq.) and water 180 g were added to the reaction mixture. Extraction with ethyl acetate 500 ml (twice), washing with saturated brine 500 ml and concentration under a reduced pressure gave a crude product. Heptane 270 ml was added to the crude product. After stirring for 12 h at room temperature, the precipitated crystal was filtered to give the expected trifluorolactic acid [4b] 133 g (92% yield).

^{1}H NMR (CD_3OD), δ 4.53 (q, 7.6 Hz, 1H); Hydroxy group and carboxyl group could not be assigned.

^{13}C NMR (CD_3OD), δ 70.9 (q, 31.7 Hz), 124.4 (q, 281.4 Hz), 169.5.

^{19}F NMR (CD_3OD), δ +87.75 (d, 7.6 Hz, 3F).

3.3. Synthesis of TCTFA by chlorination of DCTFA

Chlorine gas 0.716 kg (10.1 mol, 1.01 eq.) bubbled into anhydrous DCTFA 1.809 kg (10.0 mol, 1 eq.) containing quinoline 0.018 kg (1 wt.% of DCTFA) at 70 °C. Sequential direct fractional distillation gave the purified TCTFA [3] 2.046 kg in 95% yield. Boiling point; 79 °C/atmospheric pressure.

^{13}C NMR ($CDCl_3$), δ 89.6, 115.2 (q, 291.6 Hz), 172.7 (q, 37.2 Hz).

^{19}F NMR ($CDCl_3$), δ +95.16 (s, 3F).

3.4. Industrial synthetic method of α-methyltrifluorolactic acid using TCTFA

Two moles per kilogram methylmagnesium chloride in tetrahydrofuran solution 116.1 kg (232.1 mol, 1.0 eq.) was added to anhydrous TCTFA 50.0 kg (232.1 mol, 1 eq.) at less than −10 °C under nitrogen atmosphere. After stirring for 3 h at the same temperature, 10 wt.% hydrochloric acid 93.1 kg (255.3 mol, 1.1 eq.) was added to the reaction mixture. After stirring for 1 h at room temperature, the organic layer was recovered. Sequential direct fractional distillation gave the tetrahydrofuran solution of adduct product. Quantitative analysis (internal reference method, C_6F_6, ^{19}F NMR) indicated that the expected adduct product [7] 46.7 kg was contained in the tetrahydrofuran solution (87% yield).

^{1}H NMR ($CDCl_3$), δ 1.83 (q, 1.5 Hz, 3H); hydroxy group could not be assigned.

^{13}C NMR ($CDCl_3$), δ 19.7 (q, 1.7 Hz), 82.3 (q, 27.6 Hz), 101.3, 123.9 (q, 287.7 Hz).

^{19}F NMR ($CDCl_3$), δ + 89.43 (s, 3F). HRMS (EI), calculated for $C_4H_4Cl_2F_3O$ (M − Cl) 194.9591, found 194.9586.

The total amount of adduct product 46.7 kg (201.9 mol, 1 eq.) was added to 32% CH_3OK in methanol solution 177.0 kg (807.6 mol, 4.0 eq.) at 45 °C. After stirring for 7 h at the same temperature, 30 wt.% KOH aqueous solution 37.8 kg (201.9 mol, 1.0 eq.) was added to the reaction mixture at less than 30 °C. After stirring for 1 h at 25 °C, the precipitated inorganic salt was filtered off. The filtrate was concentrated under a reduced pressure, and then water 55 l and toluene 55 l were added to the residue. After stirring for 1 h, the aqueous layer was recovered. 37 wt.% hydrochloric acid 37.8 kg (383.6 mol, 1.9 eq.) was added to the aqueous layer. Extraction with ethyl acetate 50 l (twice), washing with 10% brine 50 l and concentration under a reduced pressure gave a crude product. Quantitative analysis by a similar method indicated that the expected α-methyltrifluorolactic acid methyl ether [8] 21.9 kg was contained in the crude product (63% yield).

^{1}H NMR ($CDCl_3$), δ 1.67 (q, 1.2 Hz, 3H), 3.52 (q, 0.8 Hz, 3H), 7.75 (br, 1H).

^{13}C NMR ($CDCl_3$), δ 16.6 (q, 1.6 Hz), 53.8, 80.3 (q, 28.7 Hz), 123.3 (q, 286.0 Hz), 172.7.

^{19}F NMR ($CDCl_3$), δ + 85.28 (s, 3F). HRMS (EI), calculated for $C_4H_5F_3O_2$ (M − CH_2O) 142.0242, found 142.0233.

Forty-eight percent HBr 150.2 kg (891.1 mol, 7.0 eq.) was added to the total amount of α-methyltrifluorolactic acid methyl ether 21.9 kg (127.3 mol, 1 eq.). The reaction mixture was stirred at 110 °C for 12 h. After cooling, 48 wt.% NaOH aqueous solution 53.0 kg (636.5 mol, 5.0 eq.) was added to the reaction mixture. Extraction with ethyl acetate 35 l (twice), washing with 10% brine 35 l and concentration under a reduced pressure gave a crude product. Heptane 60 l was added to the crude product. After stirring for 12 h at room temperature, the precipitated crystal was filtered to give the expected α-methyltrifluorolactic acid [6c] 20.1 kg (quantitative yield).

^{1}H NMR (CD_3OD), δ 1.53 (q, 0.8 Hz, 3H); hydroxy group and carboxyl group could not be assigned.

^{13}C NMR (CD_3OD), δ 20.3 (q, 1.7 Hz), 75.9 (q, 29.2 Hz), 125.6 (q, 284.1 Hz), 172.2.

^{19}F NMR (CD_3OD), δ +84.12 (s, 3F).

3.5. Industrial synthetic method of Mosher's acid using TCTFA

A mixture of TCTFA 50.0 kg (232.1 mol, 1 eq.) and benzene 45.3 kg (580.3 mol, 2.5 eq.) was added to a solution containing aluminium chloride 15.5 kg (116.1 mol, 0.5 eq.) and dichloromethane 65 kg at less than −30 °C. After stirring for 48 h at the same temperature, the reaction mixture was added to water 75 l. Extraction with dichloromethane 75 l, washing with 10% brine 75 l and concentration under a reduced pressure gave a crude product. Fractional distillation gave the purified adduct product [7] 39.5 kg (55% yield).

^{1}H NMR ($CDCl_3$), δ 3.90 (br, 1H), 7.38–7.49 (Ar–H, 3H), 7.88–7.94 (Ar–H, 2H).

^{13}C NMR ($CDCl_3$), δ 84.2 (q, 28.2 Hz), 100.9, 123.6 (q, 288.5 Hz), 127.7, 128.3, 129.9, 131.3.

^{19}F NMR ($CDCl_3$), δ +93.81 (s, 3F). HRMS (EI), calculated for $C_9H_6Cl_3F_3O$ (M) 291.9436, found 291.9149.

The total amount of adduct product 39.5 kg (127.7 mol, 1 eq.) was added to 32% CH_3OK in methanol solution 111.9 kg (510.8 mol, 4.0 eq.) at 45 °C. After stirring for 20 h at the same temperature, 25 wt.% KOH methanol solution 28.7 kg (127.7 mol, 1.0 eq.) was added to the reaction mixture at less than 30 °C. After stirring for 3 h at 25 °C, the precipitated inorganic salt was filtered off. The filtrate was concentrated under a reduced pressure, and then water 50 l and 37% hydrochloric acid 25.2 kg (255.4 mol, 2.0 eq.) were added to the residue. Extraction with ethyl acetate 70 l (twice), washing with 10% brine 50 l and concentration under a reduced pressure gave a crude product. Quantitative analysis by a similar method indicated that the expected Mosher's acid [9] 26.3 kg was contained in the crude product (88% yield). The crude product was contaminated by benzoic acid (ca. 10%). Further purification was carried out through a distillation of the corresponding acid chloride (ca. 80% total purification recovery yield).

^{1}H NMR ($CDCl_3$), δ 3.56 (q, 1.2 Hz, 3H), 7.40–7.47 (Ar–H, 3H), 7.55–7.62 (Ar–H, 2H), 9.10 (br, 1H).

^{13}C NMR ($CDCl_3$), δ 55.5, 84.4 (q, 28.2 Hz), 123.0 (q, 287.4 Hz), 127.3, 128.6, 129.9, 131.0, 171.3.

^{19}F NMR ($CDCl_3$), δ +90.55 (s, 3F).

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