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Convenient synthesis of 3,3,3-trifluoropropanoic acid by hydrolytic oxidation of 3,3,3-trifluoropropanal dimethyl acetal

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Abstract

A convenient and efficient method for preparing 3,3,3-trifluoropropanoic acid (**1**) is reported. The starting material is 1-chloro-3,3,3-trifluoropropene (**2**) that can be easily transformed into 3,3,3-trifluoropropanal dimethyl acetal (**4**) on treatment with methanol and KOH followed by acid-catalyzed addition of methanol. Direct transformation of **4** into **1** was efficiently achieved with 30% aqueous hydrogen peroxide (4.0 equiv.) in the presence of $FeCl_3$ (0.025 equiv.) and hydrochloric acid (0.5 equiv.).

Keywords: 3,3,3-Trifluoropropanoic acid; Acetal; Hydrogen peroxide; Hydrolytic oxidation

1. Introduction

Since 3,3,3-trifluoropropanoic acid (**1**) is an important intermediate for the synthesis of some medicines [1a,b], agricultural chemicals [2], and fluorinated polymers [3a–c], several methods have been reported for preparing it; (i) the trifluoromethylation of 3-bromo-1-propene with CF_3CdBr followed by oxidation with potassium permanganate and 18-crown-6 [4a]; (ii) the radical addition of CF_3I to the *t*-butyldimethylsilyl enol ether of *t*-butyl acetate and the subsequent acidic hydrolysis [4b]; (iii) the reaction of monoethyl malonate with SF_4 to give ethyl 3,3,3-trifluoropropanoate that is transformed by hydrolysis to give **1** [4c]; (iv) the Bayer–Villiger oxidation of cyclohexyl 2,2,2-trifluoroethyl ketone, which is derived by the $AlCl_3$-mediated addition of cyclohexylcarbonyl chloride to 1,1-difluoroethene, followed by hydrolysis [4d]; (v) four-step derivation of 1,3-dithiane into 2-(2,2,2-trifluoroethylidene)-1,3-dithiane that can be hydrolyzed with sulfuric acid and mercury oxide to produce **1** [4e]. Most of these methods involve many steps and utilize hazardous or expensive reagents. Hence, we started our investigation to develop an environmentally benign route leading to **1**, which can be performed in an industrial scale. Here, we report a convenient method for deriving **1** from 1-chloro-3,3,3-trifluoropropene (**2**) that is commercially available as a raw material of 1,1,1,3,3-pentafluoropropane (Scheme 1). The key process of the present route is the direct conversion of 3,3,3-trifluoropropanal dimethyl acetal (**4**) to **1**.

2. Results and discussion

The key material, 3,3,3-trifluoropropanal dimethyl acetal (**4**) was synthesized from 1-chloro-3,3,3-trifluoropropene (**2**) by the substitution of chlorine atom with methoxyl group and the subsequent addition of methanol. According to the literature [5a], the reaction of **2** with methanol (5.58 equiv.) in the presence of potassium hydroxide (1.06 equiv.) was performed except for the reaction temperature (70 °C. Lit. temperature: 100 °C). After insoluble solid was filtered off, the obtained filtrate was distilled. By the distillation, potassium hydroxide was completely removed. After the addition of methanesulfonic acid (0.20 equiv.), the distillate was heated at 70 °C for 4 h [5b]. By further distillation, we obtained the expected acetal (**4**) in 47% overall yield (from **2**).

With the key intermediate (**4**) in hand, we initiated the investigation to convert it to 3,3,3-trifluoropropanoic acid (**1**). It is generally known that the aldehydes having strong electron-withdrawing group(s) (for example, chloral) is so reactive to

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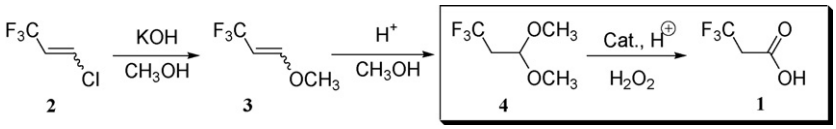
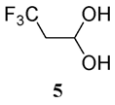


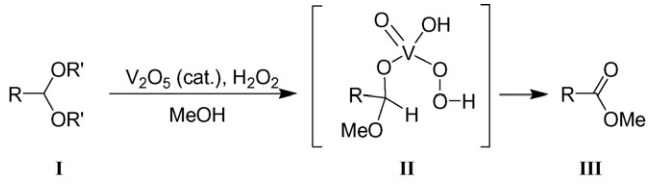
Scheme 1.

easily form the corresponding acetal or hydrate with an alcohol or water, respectively. Therefore, we employed the reaction path via 3,3,3-trifluoropropanal hydrate (**5**), which can be produced by hydrolysis of **4**. The concurrent oxidation of the thus-formed **5** would give the expected **1**.

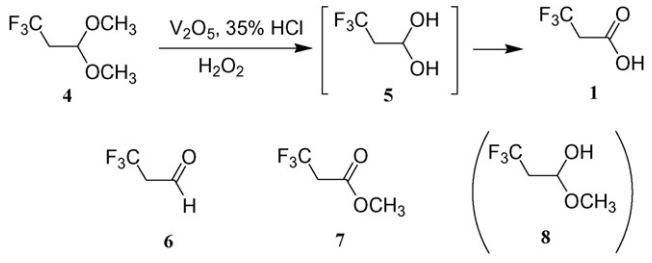


Direct conversion of a protected lactol to the corresponding lactone was known to take place with a combination of *m*-chloroperbenzoic acid and BF_3 etherate [6]. The Jones oxidation was also applied to this conversion [7]. Recently, Patel et al. reported a mild and efficient method using a catalytic amount of V_2O_5 and 30% aqueous hydrogen peroxide for the oxidative transformation of acetals into the corresponding esters [8]: when the reaction was performed in methanol at about 5 °C, a methyl ester (**III**) was formed as shown Scheme 2 [8a]. The reaction seems to proceed through a V_2O_5-hydrogen peroxide complex (**II**) to give **III** [8b]. In the absence of methanol, the corresponding carboxylic acid was produced.

First, we applied this reaction system to the conversion of **4** to **1**. But, the acetal (**4**) was too stable to react. Hence, we added conc. hydrochloric acid to the reaction system in order to promote the production of the hydrate (**5**). The oxidizing reagent, which was prepared by mixing 30% hydrogen peroxide, conc. hydrochloric acid, and V_2O_5 (0.05 mol-equiv.) at −15 °C, was added to **4** and then the reaction mixture was stirred. At an elevated temperature (60–80 °C), the reaction occurred smoothly (Scheme 3).



Scheme 2.



Scheme 3.

The results that were obtained by GC analysis were summarized in Table 1. The aldehyde (**6**) in Table 1 means that it was detected by GC, but it is thought to exist as the hydrate form (**5**) in the reaction mixture. It is likely that the formation of the methyl ester (**7**) was attributable to the oxidation of the intermediary hemiacetal (**8**). At the present time, we cannot eliminate the possibility that a part of the methyl ester (**7**) was formed by HCl-catalyzed esterification of **1** with methanol. This is because methanol is produced in the hydrolysis of **4**. The best result was attained under the conditions using 4 equiv. of hydrogen peroxide and 1 equiv. of HCl (Entry 4 in Table 1).

Next, we examined whether other cheap metal oxide and metal salts can be employed instead of V_2O_5. The metal oxides and metal salts examined here are listed in Table 2, which showed the results using them. In the reaction using no metal

Table 1
Oxidation of the acetal (**4**) with V_2O_2–H_2O_2 in the presence of HCl[a]

Entry	H_2O_2[b] (equiv.)	HCl[c] (equiv.)	Temperature (°C)	Conversion of **4** (%)[c]	Yield (%)[d]		
					1	**6**	**7**
1	2	1	60	95	37	42	2
2	4	1	60	99	64	23	7
3	4	1	80	100	87	4	6
4	4	2	80	100	87	1	12

[a] V_2O_5 (0.05 mol-equiv.) was used.
[b] 30% aq. H_2O_2 was used.
[c] 35% hydrochloric acid was used.
[d] Determined by GC analysis.

Table 2
Oxidation of **4** with H_2O_2 and HCl in the presence of various metal compounds[a]

Entry	Metal compound	Conversion of **4** (%)[b]	Yield (%)[b]		
			1	**6**	**7**
1	V_2O_5	100	87	4	6
2	–	93	12	22	31
3	Fe	100	85	1	9
4	$FeCl_3$	100	91	1	5
5	Fe_2O_3	100	70	0	4
6	$RuCl_3$	99	56	13	20
7	CuCl	100	87	2	9
8	Cu_2O	100	91	2	7
9	$AlCl_3$	100	53	16	14
10	$ZnCl_2$	99	49	18	15
11	$MoCl_5$	99	24	30	11
12	MnO_2	99	50	19	16
13	WCl_6	99	9	44	4
14	$NiCl_2$	99	47	19	20

[a] The reaction was performed with 30% aq. H_2O_2 (4 equiv.), 35% hydrochloric acid (1 equiv.), and the metal compound (0.05 mol-equiv.) at 80 °C.
[b] Determined by GC analysis.

compound (Entry 2), some unknown compounds were formed except for **1**, **6**, and **7**. Thus, the metal compound was confirmed to play an important role in the present reaction. As shown in Table 2, Fe, $FeCl_3$, Fe_2O_3, CuCl, Cu_2O, and V_2O_5 accelerated the reaction to produce **1** in good to high yields. Probably, Fe, Fe_2O_3, and Cu_2O reacted with HCl to be converted to the corresponding metal chlorides. Among the metal compounds examined here, we selected $FeCl_3$ because it is economically advantageous and environmentally benign.

In the reactions listed in Tables 1 and 2, the required quantity of hydrogen peroxide was 4 equiv. Although we made our effort to reduce the amount of hydrogen peroxide, it was shown that the best result was obtained with 4 equiv. of hydrogen peroxide. The results are summarized in Table 3. As shown in Entries 1–3, the yield of 3,3,3-trifluoropropanoic acid (**1**) became lower as the amount of 30% aqueous hydrogen peroxide decreased. To our surprise, the yield of methyl 3,3,3-trifluoropropionate (**7**) increased with the decreasing amount of 30% aqueous hydrogen peroxide. This tendency was also observed when 0.025 equiv. of $FeCl_3$ and 15% aqueous hydrogen peroxide were employed (Entries 5–7).

The reaction mechanism is unclear at the present time, but the reaction most likely proceeds via an intermediary hydroperoxide (**9**), which is converted to **1** by the assistance of $FeCl_3$ and HCl. This is in analogy with the mechanism proposed for the reaction of 2-halocyclohexanone with hydrogen peroxide, which forms 2-halo-1-hydroxy-1-hydroperoxycyclohexane in the presence or the absence of mineral acid [9] (Scheme 4).

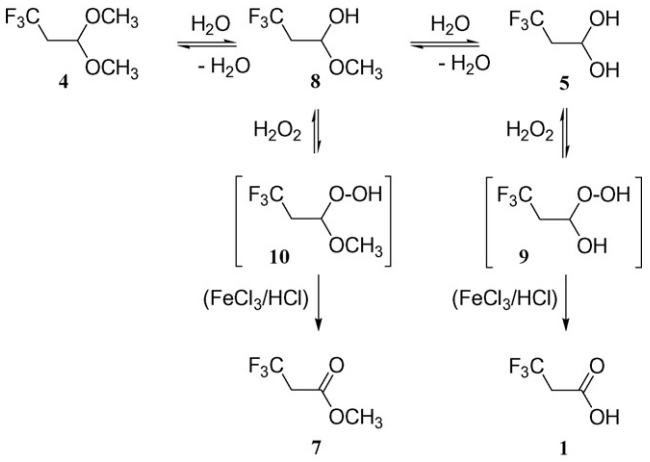
As mentioned previously, water reacts with **4** to produce the hydrate (**5**) via the hemiacetal (**8**). Since these reactions are reversible, a large amount of water pushes the equilibrium toward the hemiacetal site and then toward the hydrate site. If the concentration of water becomes lower, the concentration of the hydrate would be lower. As a result, the oxidation process from the hemiacetal (**8**) should become more favorable. Therefore, it is reasonably rationalized in terms of the amount of water in the system that the yield of **7** increases with the decreasing amount of aqueous hydrogen peroxide.

Finally, it should be noted that the best result was obtained in the reaction of **4** with 30% aqueous hydrogen hydroperoxide

Table 3
Oxidation of **1** with $FeCl_3$–HCl–H_2O_2

Entry	$FeCl_3$ (equiv.)	HCl[a] (equiv.)	H_2O_2[b] (equiv.)	Conversion of **4**[c] (%)	Yield[c] (%)		
					1	**6**	**7**
1	0.05	1.0	4.0	100	91	1	5
2	0.05	1.0	3.0	100	54	–	44
3	0.05	1.0	2.0	99	34	1	58
4	0.025	0.5	4.0	100	95	–	3
5	0.025	0.5	4.0[d]	100	92	–	5
6	0.025	0.5	3.0[d]	100	84	–	13
7	0.025	0.5	2.0[d]	99	65	2	19

[a] 35% hydrochloric acid was used.
[b] 30% aq. H_2O_2 was used unless otherwise noted.
[c] Determined by GC analysis.
[d] 15% aq. H_2O_2 was used.



Scheme 4.

(4 equiv.) in the presence of $FeCl_3$ (0.025 equiv) and conc. hydrochloric acid (0.5 equiv.), as shown in Entry 4 of Table 3. The yields of **1** was 95%.

3. Conclusion

We found the favorable reaction conditions for preparing 3,3,3-trifluoropropanoic acid (**1**) by the hydrolytic oxidation of 3,3,3-trifluoropropanal dimethyl acetal (**4**), which was easily derived from 1-chloro-3,3,3-trifluoropropene. Thus, the hydrolytic oxidation of **4** with a high efficiency was attained with 30% aqueous hydrogen peroxide (4.0 equiv.) by the assistance of $FeCl_3$ (0.025 equiv.) and hydrochloric acid (0.5 equiv.).

4. Experimental

^{1}H NMR and ^{19}F NMR spectra were recorded at 400 MHz on a JEOL α-400 and JEOL AL-400. ^{1}H NMR data are given in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal standard. ^{19}F NMR data are given in ppm upfield from CCl_3F (an internal standard). The abbreviations used are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (*J* values) are given in hertz (Hz). MS analyses were performed using a Shimadzu GCMS-QP2010 (EI at 70 eV). Gas chromatography (GC) analyses were performed on a Shimadzu GC17A equipped with J & W DB-5 capillary column (30 m) and a FID detector.

4.1. Preparation of 3,3,3-trifluoropropanal dimethyl acetal (4)

Methanol (307 g, 9.6 mol), water (22.5 g), KOH (102 g, 1.8 mol), and 1-chloro-3,3,3-trifluoropropene (**2**, 225 g, 1.7 mol) were placed in a 1000 ml pressure-proof stainless steel (SUS316) reactor equipped with a thermometer, a pressure gauge, and a stirrer. The reactor was heated at 70 °C (internal temperature) in an oil bath for 6 h under being stirred. It was found by GC analysis that the reaction mixture involves 3,3,3-trifluoro-1-methoxypropene (**3**), 1-chloro-3,3,3-trifluoropropene (**2**), and 3,3,3-trifluoropropanal dimethyl acetal (**4**) in

74%, 21%, and 5% yields, respectively. After insoluble solid was filtered off, the filtrate was distilled to give a colorless liquid (381.5 g). By this distillation, potassium hydroxide was completely removed. After the addition of methanesulfonic acid (33.0 g, 0.34 mol), the distillate was heated at 70 °C for 4 h. It was shown by GC analysis that the reaction mixture contains 3,3,3-trifluoropropanal dimethyl acetal (**4**) and 3,3,3-trifluoro-1-methoxypropene (**3**) in 96% and 1% yields, respectively. After the reaction mixture was washed with water (300 g), the organic layer was separated and dried over MS 4 Å (20 g). The obtained reaction mixture was purified by distillation (89–90 °C) to give 3,3,3-trifluoropropanal dimethyl acetal (**7**; 128 g; 47% yield) as a colorless liquid; ^{1}H NMR ($CDCl_3$): δ 2.51 (2H, dq, J = 10.6 and 5.6 Hz), 3.33 (6H, s), 4.70 (1H, d, J = 5.6 Hz); ^{19}F NMR ($CDCl_3$): δ −63.34 (3F, d, J = 10.6 Hz); EI-MS *m/z* (rel. int.): 158 $[M]^+$ (0.05), 127 $[M–CH_3O]^+$ (47), 83 $[CF_3CH_2]^+$ (3), 75 $[M–CF_3CH_2]^+$ (51), 69 $[CF_3]^+$ (5), 64 $[CF_2CH_2]^+$ (5), 63 $[CF_2CH]^+$ (100), 59 $[C_2H_3O_2]^+$ (3), 47 $[CH_3O_2]^+$ (15), 45 $[CFCH_2]^+$ (5), 43 $[C_2H_3O]^+$ (4), 31 $[CH_3O]^+$ (17), 29 $[CHO]^+$ (26), 28 $[CO]^+$ (3). Anal. Calcd. for $C_5H_9F_3O_2$: C, 37.98; H, 5.74. Found: C, 38.12; H, 5.78.

4.2. General procedure for the hydrolytic oxidation of 3,3,3-trifluoropropanal dimethyl acetal (4)

The oxidizing reagent, which was prepared by mixing 35% hydrochrolic acid, metal compound, and 30% hydrogen peroxide at −15 to −10 °C, were added to 3,3,3-trifluoropropanal dimethyl acetal (**4**) at 60 °C or 80 °C and the reaction mixture was stirred at the same temperature for 1 h. An aliquot of the reaction mixture was taken out and analyzed by GC. The isolation of **1** and its characterization are given in the following section. The authentic sample of **6** was purchased from SynQuest Labs., Inc. (Florida, U.S.A.) The structure of **7** was confirmed by the independent syntheses that were described below.

4.3. Characterization of 3,3,3-trifluoropropanoic acid (1) [4c–f]

The oxidizing reagent, which was prepared by mixing 35% hydrochrolic acid (3.30 g, 32 mmol), $FeCl_3$ (0.26 g, 1.6 mmol), and 30% aqueous hydrogen peroxide (28.7 g, 250 mmol) at −15 to −10 °C, was added to 3,3,3-trifluoropropanal dimethyl acetal (**4**; 10.0 g, 63 mmol) at 80 °C and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was shown by GC analysis to contain 3,3,3-trifluoropropanoic acid (**1**) and methyl 3,3,3-trifluoropropionate (**7**) in 95% and 3% yields, respectively. The reaction mixture was extracted with CH_2Cl_2 (25 ml × 4 ml), and the organic extracts were combined and dried over anhydrous $MgSO_4$. Filtration followed by distillation (92–100 °C/13 kPa (1.0 kPa = 7.5 Torr)) gave 3,3,3-trifluoropropanoic acid (**1**; 5.0 g, 62% yield) as a colorless liquid: ^{1}H NMR ($CDCl_3$): δ 3.43 (2H, q, J = 10.8 Hz), 11.07 (1H, bs); ^{19}F NMR ($CDCl_3$): δ −63.47 (3F, t, J = 10.8Hz); EI-MS *m/z* (rel. int.): 128 $[M]^+$ (11), 111 $[M–OH]^+$ (38), 91 $[CF_2CHCO]^+$ (15), 89 $[M–HF_2]^+$ (20), 83 $[CF_3CH_2]^+$ (20), 69 $[CF_3]^+$ (25), 64 $[CF_2CH_2]^+$ (75), 63 $[CF_2CH]^+$ (10), 51 $[CHF_2]^+$ (3), 47 $[COF]^+$ (3), 45 $[CFCH_2]^+$ (100), 42 $[CH_2CO]^+$ (19), 29 $[CHO]^+$ (11), 28 $[CO]^+$ (3). Anal. Calcd. for $C_3H_3F_3O_2$: C, 28.14; H, 2.36. Found: C, 28.13; H, 1.91.

4.4. Independent synthesis of methyl 3,3,3-trifluoropropionate (7)

Thionyl chloride (8.4 g, 0.071 mol) and a few drops of DMF were placed in a 50 ml round-bottomed flask fitted with a stirrer, a thermometer, a reflux condenser, and a dropping funnel. After 3,3,3-trifluoropropanoic acid (**7**; 10.0 g, 0.078 mol) was dropwise added at 40 °C, the mixture was stirred at 60–70 °C for 3 h. Then, methanol (2.3 g, 0.072 mol) was added at room temperature and the mixture was stirred at 50 °C for 1 h. The reaction mixture was purified by distillation (96–97 °C) to give methyl 3,3,3-trifluoropropionate (**7**; 7.5 g, 74% yield) as a colorless liquid; ^{1}H NMR ($CDCl_3$): δ 3.19 (2H, q, J = 10.6 Hz), 3.77 (3H, s); ^{19}F NMR ($CDCl_3$): δ −64.16 (3F, t, J = 10.6 Hz); EI-MS *m/z* (rel. int.): 142 $[M]^+$ (9), 122 $[M–HF]^+$ (16), 111 $[M–CH_3O]^+$ (100), 91 $[CF_2CHCO]^+$ (25), 83 $[CF_3CH_2]^+$ (26), 69 $[CF_3]^+$ (13), 64 $[CF_2CH_2]^+$ (15), 63 $[CF_2CH]^+$ (5), 59 $[C_2H_3O_2]^+$ (47), 42 $[CH_2CO]^+$ (4), 31 $[CH_3O]^+$ (116), 29 $[CHO]^+$ (12). Anal. Calcd. for $C_4H_5F_3O_2$: C, 33.81; H, 3.55. Found: C, 33.80; H, 3.14.

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