Improved Syntheses of Ethyl 3,3,3-Trifluoropropionate and 3,3,3-Trifluoropropionic Acid

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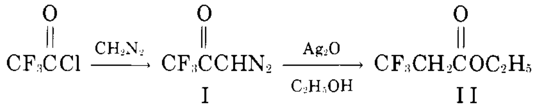
Ethyl 3,3,3-trifluoropropionate was synthesized by treatment of monoethylmalonate with sulfur tetrafluoride. 3,3,3-Trifluoropropionic acid was prepared by acid hydrolysis. The physical properties of these compounds are compared to the literature values.

Our continuing research on the synthesis and reactions of fluorinated nitroaliphatic compounds (*9, 10*), required ethyl 3,3,3-trifluoropropionate (II) in relatively large quantities. Brown and Musgrave (*2*) reported that treatment of cold trifluoroacetyl chloride with diazomethane gave trifluorodiazoacetone (I) which, when heated with silver oxide in absolute ethanol (Reaction 1) produced a 40% yield of II.



$$\underset{}{CF_3\overset{O}{\overset{\|}{C}}Cl} \xrightarrow{CH_2N_2} \underset{I}{CF_3\overset{O}{\overset{\|}{C}}CHN_2} \xrightarrow[C_2H_5OH]{Ag_2O} \underset{II}{CF_3CH_2\overset{O}{\overset{\|}{C}}OC_2H_5} \qquad (1)$$

Our attempts to repeat the Arndt-Eistert reaction were unsuccessful. Considerable polymerization occurred, probably arising from thermal decomposition of the trifluorodiazoacetone to trifluoromethyl ketene, $CF_3CH=C=O$, which is known to polymerize rapidly. However, a low yield of volatile products was obtained. Analysis by gas liquid partition chromatography (glpc) indicated only a small amount of volatile material subsequently identified by ir, nmr, and elemental analyses as 2-chloro-2-trifluoromethyloxetane. To confirm this oxide structure, the compound was treated with absolute ethanol for 16 hr at reflux. A fair yield of 4,4,4-trifluoro-3-chloro-3-ethoxybutanol, $CF_3CCl(OC_2H_5)CH_2CH_2OH$, was obtained and identified by ir, ^1H and ^{19}F nmr, and elemental analyses.

The authors now wish to report that II can be prepared consistently in good yield (50–60%) by treating monoethyl malonate (III) (*13*) with sulfur tetrafluoride (Reaction 2) at elevated temperatures.

$$\underset{III}{HOOCCH_2COOC_2H_5} \xrightarrow{SF_4} \underset{II}{CF_3CH_2COOC_2H_5} \qquad (2)$$

Hasek et al. (*5*) found that sulfur tetrafluoride replaced oxygen with fluorine in acids, aldehydes, ketones, and esters. They were able thereby to prepare a large number of novel fluorinated organic compounds. The original reaction conditions for sulfur tetrafluoride reported by these workers were severe: 120–300° C. However, product yields often improve if such refinements as lower temperatures, Lewis catalysts (*11*), excess sulfur tetrafluoride, longer reaction times (*4*), and solvents such as methylene chloride (*3*) are employed.

Recently, Blake and Schaar (*1*) found that reaction pressure can also have a profound effect on the extent of fluorination in the reaction of dichloromaleic anhydride. Pressures in excess of 3000 psi were required to obtain good yields of the desired 3,4-dichloro-2,2,5,5-tetrafluoro-2,5-dihydrofuran.

Because monoethyl adipate was converted to ethyl 6,6,6-trifluoroadipate in less than 30% yield using sulfur tetrafluoride at 130° C for 7 hr (*5*), it was reasonable to expect that sulfur tetrafluoride could be used to prepare II. Although electron-withdrawing substituents in the α or β position relative to the carbonyl group would be expected to retard the fluorination, we reasoned that a subtle balance of reaction conditions could be employed to obtain II. We, therefore, treated III with sulfur tetrafluoride and a trace of hydrogen fluoride catalyst at 50° C for 3 days and obtained the intermediate monoethyl malonyl fluoride (68% yield). This acid fluoride was subsequently converted to II in 51% yield using excess sulfur tetrafluoride with excess hydrogen fluoride at 80° C for 3 days. Eventually, II (55% yield) was obtained from III using excess sulfur tetrafluoride and a stoichiometric amount of hydrogen fluoride as catalyst at 80° C for 3 days.

As additional proof of structure, II was converted to 3,3,3-trifluoropropionic acid (IV) in 60% yield (Reaction 3) with 2.70*M* sulfuric acid at 105° C.

$$\underset{II}{CF_3CH_2COOC_2H_5} \xrightarrow[\substack{H_2SO_4 \\ 105^\circ}]{H_2O} \underset{IV}{CF_3CH_2COOH} \qquad (3)$$

Compound IV was also observed by hydrolysis of II with concentrated nitric acid at 100° C. Brown and Musgrave (*2*) report the preparation of IV in low yield by treatment of I with dioxane and silver oxide, followed by aqueous sodium thiosulfate. Henne and coworkers (*6–8*) have also reported the preparation of IV in 80% yield, using a chromic acid oxidation of 3,3,3-trifluoropropanol.

Our attempts to produce IV by basic hydrolysis were not successful. When II was treated with a cold 0.4*M* potassium hydroxide at pH 7–10 followed by acidification with hydrochloric acid, none of IV was observed, but a 27% yield of malonic acid was obtained.

In addition, the physical constants previously reported for II and IV do not agree with the values we obtained (Tables I and II). We can only assume that the literature constants for II and IV are in error because of undetected impurities in the compounds.

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Table I. Physical Properties of Ethyl 3,3,3-Trifluoropropionate (II)

Preparation	Yield, %	Bp, °C (mm Hg)	n'_{D}, °C
Arndt-Eister (2)	40	50 (12)	1.3912 (23)
Sulfur tetrafluoride	55	57-8 (100)	1.3390 (25)

Table II. Physical Properties of 3,3,3-Trifluoropropionic Acid (IV)

Preparation	Yield, %	Mp, °C	Bp, °C (mm Hg)	n'_{D}, °C
Arndt-Eistert (2)	...	...	144	...
Oxidation (6)	80	9.7	144.8 (746)	1.3316 (27)
Oxidation (7)	...	~0	27-30 (14-15)	...
Hydrolysis (acid)	60	3-6	64 (16)	1.3368 (24)

EXPERIMENTAL

Melting points and boiling points are uncorrected. Elemental analyses were performed by the Stanford University Microanalytical Laboratory. The nmr data were obtained by Dr. L. J. Durham, Stanford University; ^{19}F spectra were compared to $CFCl_3$ and ^1H spectra to tetramethylsilane. The ir spectra were recorded with a Perkin-Elmer infracord spectrophotometer.

CAUTION: Sulfur tetrafluoride is a reactive gas that is highly toxic; $LD_{50} \sim 20$ ppm. Toxicity is equivalent to that of phosgene. Also, sulfur tetrafluoride liberates hydrofluoric acid on contact with water; care must be taken to avoid hydrogen fluoride burns when this material is used. Since many fluorinated compounds are toxic in varying degrees, care should be taken to avoid contact with II and IV.

Ethyl 3,3,3-Trifluoropropionate (II). Monoethyl malonate (13.1 grams, 0.1 mole), methylene chloride (25 ml), and aqueous (49%) hydrogen fluoride (1 ml) were placed in a 300-cc stainless steel hydrogenation vessel. The vessel was cooled to −78° C, evacuated to 1 mm, and flushed 3 times with nitrogen. Sulfur tetrafluoride (66 grams, 0.61 mole) was distilled into the cold evacuated vessel, which was then sealed and gently rocked at 80° C for 3 days at autogenous pressure (360 psi). After reaction, the vessel was placed in a bath at −78° C until no pressure registered on the gage. The gaseous reaction components (excess sulfur tetrafluoride and thionyl fluoride) were then vented through a 10% potassium hydroxide solution as the reaction vessel warmed to room temperature. The vessel was opened, and the brown fuming liquid was poured into sodium fluoride (5 grams) in cold pentane (25 ml). The vessel was then rinsed three times with 30-ml portions of pentane. The washings and the reaction product were combined, and magnesium sulfate (5 grams) was added to dry the solution and remove residual hydrogen fluoride. The solvents were distilled at atmospheric pressure through a 15-cm glass helix-packed column and the colorless product (II) was isolated by vacuum distillation: bp, 57–58° (100 mm); 8.62 grams (55%); glpc showed a single peak (SE-30, 5' × ¼", He 60 ml/min, 35° C, R_f 6.7 min); ir (neat) 1735 (*s*, C=O ester) and 1400-1000 cm^{-1} (*b, s*, C—F); nmr ($CDCl_3$) δ 1.28 (*t*, 3; J = 7 Hz, CH_2CH_3), 3.15 (*q*, 2, J = 11 Hz, CF_3CH_2) and 4.24 ppm (*q*, 2, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_5H_7F_3O_2$: C, 28.45; H, 4.48; F, 36.5. Found: C, 28.74; H, 4.62; F, 36.2.

3,3,3-Trifluoropropionic Acid (IV). Ethyl 3,3,3-trifluoropropionate (6.0 grams, 0.038 mole) was suspended in 2.70*M* sulfuric acid (57 ml) and heated with stirring at 105° C for 14 hr. On cooling, a small amount of unreacted ester oiled from the solution. The ester was decanted. The acid solution was saturated with sodium chloride and extracted with ether (30 ml). The ethereal extract was dried over magnesium sulfate, filtered, concentrated, and distilled giving 2.90 grams (60%) of IV: bp 64° (16 mm); ir (neat) 3000 (*s*, O—H) 1750 (C=O acid) and 1400–1100 cm^{-1} (*s, b*, C—F); nmr ($CDCl_3$) δ 13.0 (*s*, 1, COOH), 3.20 (*q*, 2, J = 8 Hz, CH_2CF_3), and ϕ 64.5 ppm (*t*, J = 8 Hz, CF_3CH_2).

Anal. Calcd for $C_3H_3F_2O_2$: C, 28.4; H, 2.36. Found: C, 27.89; H, 2.54.

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