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SYNTHESIS OF 3,3,3-TRIFLUOROPROPIONIC AND 4,4,4-TRIFLUORO-2-KETOBUTYRIC ACIDS

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SUMMARY

Trifluoroethyl cyclohexyl ketone (4) is prepared by acylation of difluoroethylene (2) with cyclohexanecarboxylic acid chloride (1), followed by Cl→F exchange with potassium fluoride in the presence of triethylbenzylammonium chloride. Bayer-Villiger oxidation of ketone (4) with trifluoroperacetic acid gives cyclohexyl trifluoropropionate (5). 3,3,3-trifluoropropionic acid (6) is obtained by treatment of (5) with trimethylsilyl iodide. Condensation of 2,2,2-trifluorodiazoethane (7) with ethyl glyoxylate (8) gives mainly ethyl 4,4,4-trifluoro-2-ketobutyric acid ester (9) which leads after hydrolysis to the corresponding acid (12).

INTRODUCTION

Introduction of a trifluoromethyl substituent α to an acid group is capable of altering the properties of the molecule. Until now attention has been focused on the α trifluoromethylacetic acid and not on the α trifluoromethylpyruvic acid which remains unknown. We report here a new preparation of 3,3,3-trifluoropropionic acid and the first synthesis of 4,4,4-trifluoro-2-ketobutyric acid.

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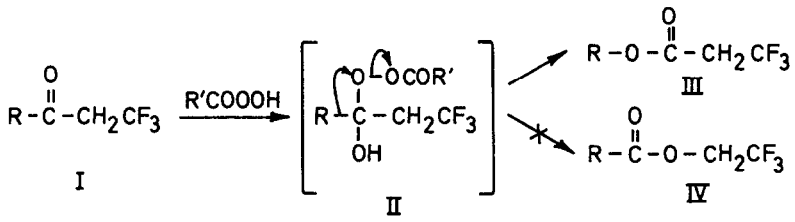
3,3,3-Trifluoropropionic acid

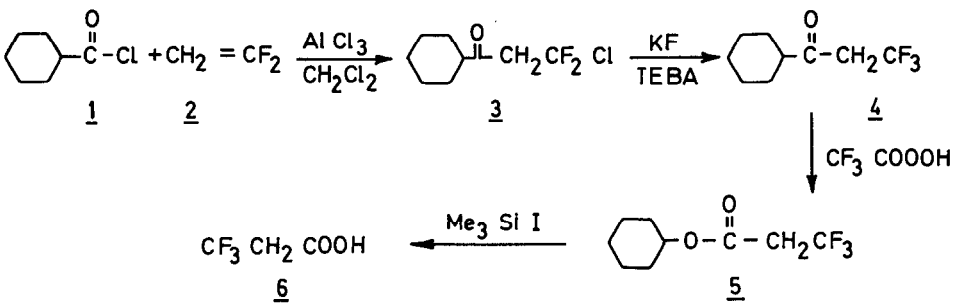
Several preparations of trifluoropropionic acid CF_3CH_2COOH and its esters have been proposed. They use various chemical transformations : trifluoropropyne hydrolysis [1], trifluoromethyldiazoketone transposition [2], oxidation of 1,1,1-trifluoro-3-chloropropane Grignard reagent [3], fluorination with sulfur tetrafluoride of ethylhemimalonate [4], electrochemical oxidation of this malonate in the presence of trifluoroacetic acid [5], hydrolysis of trifluoromethylmalonates produced from perfluoroisobutylene [6]. Generally, they require the use of expensive or dangerous products or reagents or unusual technics. They could not always be repeated with the same yields [4].

We propose here an alternative synthesis of 3,3,3-trifluoropropionic acid from α trifluoromethylketones I. We recently studied the synthesis of these ketones [7,8,9,10]. They can be transformed to trifluoropropionic esters III by a Bayer-Villiger oxidation.



The intermediate II collapses, the migrating group being that which is able to best accomodate a positive charge [11]. The study of solvolytic reactions [12,13] and the results of theoretical calculations [14] show that th trifluoromethyl group does not stabilize a carbocation. Accordingly the migration aptitude should follow the order $R>CH_2CF_3$ and the oxidation should give the ester III rather than its isomer IV. This prediction has been verified experimentaly.

We describe here the synthesis of trifluoroethylketone 4, its oxidation to ester 5 and the transformation of 5 into trifluoropropionic acid 6.



1 2 3 4 5 6

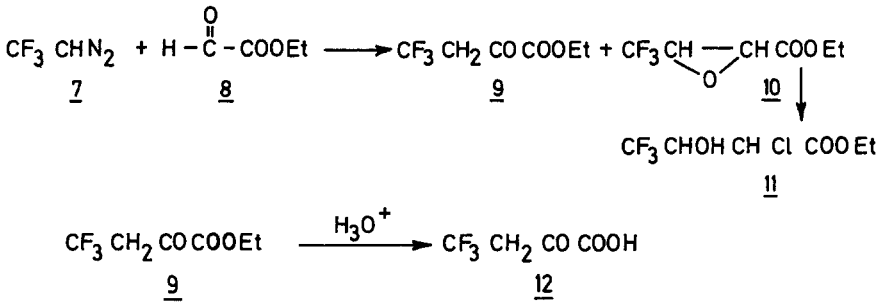
The cyclohexyl group was chosen for three reasons. The secondary group R must have a good migrating aptitude when the intermediate II collapses ; a secondary group should be prefered to a tertiary one in order to stabilize the acylium ion in the condensation of the acyl chloride with difluoroethylene. Compounds 3, 4, 5 should have low vapor pressure in order to purify them easily.

Ketone 3 is prepared by acylation of the difluoroethylene [15,16] with the acyl chloride 1. It is known that α chlorodifluoromethyl ketones are easily transformed into their trifluoromethyl analogues [17,10].. Potassium fluoride in dichloromethane, in the presence of triethylbenzylammonium chloride (TEBA) is used as fluorinating reagent for the transformation of 3 into 4. The Bayer-Villiger reaction is performed with peroxytrifluoroacetic acid [11] . It is indeed univocal and produced the ester 5 to the exclusion of ester of type IV ; however, the rate of the oxidation is rather slow. The hydrolysis of 5 to the acid 6 appears difficult. The saponification is forbidden because of the loss of fluorine atoms. The acidic conversion according to [4] is not complete ; we check that the ethyl ester obtained with a low yield according to [4] is not completely transformed in these conditions. Finally we use iodotrimethyl silane which cleaves the esters in smooth conditions [18,19] . After spinning band fractionation anhydrous 3,3,3-trifluoropropionic acid is obtained.

4,4,4-trifluoro-2-ketobutyric acid (12)

Among the various methods to place a trifluoromethyl substituent α to a carbonyl group [7,8,9,10] we chose the condensation of 2,2,2-trifluorodiazoethane with an aldehyde.

This type of reaction needs generally a Lewis acid catalysis [9]. However, the addition is spontaneous in the case of halogenated aldehydes [20,21]. The electron withdrawing property of the ester substituent of ethyl glyoxylate is also able to polarise the aldehyde group and facilitate the condensation. Indeed, we have observed that this reaction is spontaneous and leads to compounds (9) and (10) [22].



The quick hydrolysis of the reaction mixture with hydrochloric acid gives also the chlorohydrin 11 [22] formed by opening of the epoxide (10).

By this one step synthesis ethyl 4,4,4-trifluoro-2-ketobutyric acid ester 9 is obtained in a 41 % yield. Acid hydrolysis of this ester is slow and leads to 4,4,4-trifluoro-2-ketobutyric acid (12) (Bp 51°). It is necessary to be careful with these products ; some people in the laboratory have felt headaches during this synthesis.

EXPERIMENTAL

^{1}H and ^{19}F nmr spectra are recorded in deuterochloroform on Jeol C 60 HL instrument. The chemical shift values δ and $\emptyset$ are expressed in ppm relative to tetramethylsilane (for ^{1}H nmr spectra) or chlorotrifluoromethane (for ^{19}F nmr spectra). IR spectra are recorded with a Perkin Elmer 167 spectrometer. Mass spectra are obtained with an AEI MS 30 instrument at 70 ev. The 2,2,2-trifluorodiazoethane in ether is prepared according to [23] and the ethyl glyoxylate according to [24]. Another distillation on P_2O_5 under argon is necessary to obtain anhydrous glyoxylate.

Caution ! 2,2,2-trifluorodiazoethane requires stringent safety precautions [21]

2-chloro-2,2-difluoroethyl cyclohexyl ketone 3 (nc)

14.6 g of cyclohexanecarbonyl chloride is added to a mixture of 13.3 g of aluminium chloride and 100 ml of dichloromethane at 0°C. Gaseous 1,1-difluoroethylene is then introduced into the flask at such a rate that the absorbtion is complete. After 4 hours, no more gas is absorbed. 100 ml of 10 % hydrochloric acid is added under vigorous stirring. A solid is formed which dissolves after half an hour. The mixture is extracted with dichloromethane. The organic layer is washed twice with 10 % hydrochloric acid, aqueous sodium carbonate and sodium chloride and dried over magnesium sulfate. After evaporation of the solvent 10.6 g of 3 is distilled (bp : 58°/0.5 mmHg) yield 50 %: ØF 47 ppm (t, J_{HF} 12.3 Hz) δ_H 3.83 ppm (2H, J_{HF} 12.3 Hz): ir 1717 cm^{-1}: ms m/e=210,212 (M), 111.
calc % : C 51.31 H 6.22 Cl 16.83 found % : C 51.15 H 6.12 Cl 16.64

2,2,2-trifluoroethylcyclohexyl ketone 4

10.5 g of 3 in 20 ml of dichloromethane are added to a mixture of 10 g of potassium fluoride, 0.5 g of triethylbenzylammonium chloride and 20 ml of dichloromethane. The mixture is stirred for 12 hours. After filtration and evaporation of the solvent 7.3 g of 4 [8] (yield 75 %) is distilled (bp : 96°/22 mmHg). ØF 60 ppm (t, J_{HF} 10.1 Hz) δ_H 3.2 ppm (2H, q, J_{HF} 10.1 Hz) ir 1720 cm^{-1}: ms 194 (M), 152, 111.

Cyclohexyl trifluoropropionate 5 (nc)

A solution of peroxytrifluoroacetic acid is prepared by dropwise addition of 9.7 ml of trifluoroacetic anhydride to a suspension of 1.65 ml of 85 % hydrogen peroxide in 10 ml of cold dichloromethane. This solution is added over a 20 minutes period to a stirred suspension of 4.5 g of 4, 16.6 g of dry, finely ground disodium hydrogen phosphate and 19 ml of dichloromethane. After the end of the addition, the solution is heated under reflux for 3 hours and the insoluble salts are filtered. The salts are washed with water, 10 % sodium carbonate and dried over magnesium sulfate. The oxidation is not complete and it is necessary to do it once more. 3.65 g of 5 (yield 66 %) is obtained by distillation (bp 84°/21 mmHg): ØF 62 ppm (t, J_{HF} 10.2 Hz) δ_H 4.67 ppm (1H, m) 3.02 ppm (2H, q, J_{HF} 10.2 Hz) ir 1755 cm^{-1}: ms m/e 210 (M) 194, 156, 111.

calc % :	C 51.42	H 6.23	F 27.12
found % :	51.65	6.29	26.90

3,3,3-trifluoropropionic acid 6

4 g of the ester 5, 6 ml of iodotrimethylsilane in 20 ml of chloroform are heated to 65°C during 9 hours. After cooling 10 ml of water is added. The mixture is stirred for 2 hours. 150 ml of ether is added. The aqueous layer is decanted. The organic layer is washed 3 times with 10 ml of cold N sodium hydroxide. The aqueous layers are combined, acidified immediately with 10 ml of concentrated sulfuric acid at 0°C and extracted 4 times with ether. This organic layer is dried over magnesium sulfate. After solvent removal 1.8 g (yield 73 %) of the acid 6 is distilled (bp 61°/16 mmHg): ϕ_F 61ppm(t, J=9.75 Hz) δ_H 3.15 ppm (2H, q, J_{HF} 9.75 Hz) 10.3 ppm (1H, s). 4 g of this acid is fractionated with a spinning band column (Perkin Elmer M 131 T) to give 1.7 g of the anhydrous acid 6 (bp 56-57°/25 mmHg): δ_H 3.17 ppm (2H, q, J_{HF} 9.75 Hz) 11.3 ppm (1H, s): ms m/e 128 (M) 111.

Ethyl 4,4,4-trifluoro-2-ketobutyrate 9 (nc)

15 g (0.15 Mole) of ethyl glyoxylate in 50 ml of ether is added to a solution of about 0.05 ml of trifluorodiazoethane in 225 ml of ether. After 2 days the solution is hydrolysed with 50 ml of 10 % hydrochloric acid for 4 hours washed with aqueous sodium bicarbonate and saturated sodium chloride and dried over magnesium sulfate. After solvent removal and short path distillation the products are fractionated on a spinning band column (Perkin Elmer M 131 T) to give :

1) Ethyl trans-trifluoromethylglycidate 10

0.5 g (yield 5 %) (bp 46°/10 mmHg) (145-146°C [22]). ϕ_F 73 ppm (3F, d, J=4.2 Hz) δ_H 4.23 ppm (2H, q, J=7 Hz) 3.73 ppm (1H, q, J=4.2 Hz) 3.63 ppm (1H, s) 1.3 ppm (3H, t, J=7 Hz) ir 1740-1760 cm^{-1}. ms m/e 185 (M+1).

2) Ethyl 4,4,4-trifluoro-2-ketobutyrate 9 (nc)

3.8 g (yield 41 %) (bp 59°/10 mmHg). ϕ_F 62 ppm (3F, t, J=10 Hz) δ_H 4.37 ppm (2H, q, J=7 Hz) 3.7 ppm (2H, q, J=10 Hz) 1.37 ppm (3H, t, J=7 Hz) ir 1720-1755 (shoulder) cm^{-1}.

calc. %	:	C	39.14	H 3.83
found %	:		39.06	3.78

CAUTION ! This compound could be very toxic.

3) Ethyl erythro-2-chloro-3-hydroxy-4,4,4-trifluorobutyrate 11

1.1 g (yield 11 %) bp 72°/10 mmHg [22] . $\emptyset_F$ 68 ppm (3F, d, J=6.1 Hz) δ_H 4.7-3.7 ppm (5H, m, 1H exchanged with D_2O) 1.3 ppm (3H, t, J=7 Hz).

4,4,4-trifluoro-2-ketobutyric acid 12 (nc)

1.95 g of the pyruvate 9, 12 ml of 5 % sulfuric acid are vigorously stirred for 12 days at room temperature. The product is extracted 6 times with ether. The ethers are treated very quickly with a cold solution of sodium bicarbonate until PH 7. This solution is then acidified at 0°C with 20 % sulfuric acid and extracted with ether. After drying and evaporation of the solvent 0.4 g of the acid 12 (yield 25 %) is recrystallized from benzene. mp 51°C. $\emptyset_F$ (H_2O) (external reference) 60 ppm t, J=10.3 ppm δ_H (hot benzene) 2.73 ppm (q, J=10.3 Hz): ms m/e 157 (M+1) 156 (M), 111. (100 % ; accurate top mass : 111.006 ; calc. : 111.0058).

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