Synthesis of Optically Active Chlorofluoroacetyl Chloride

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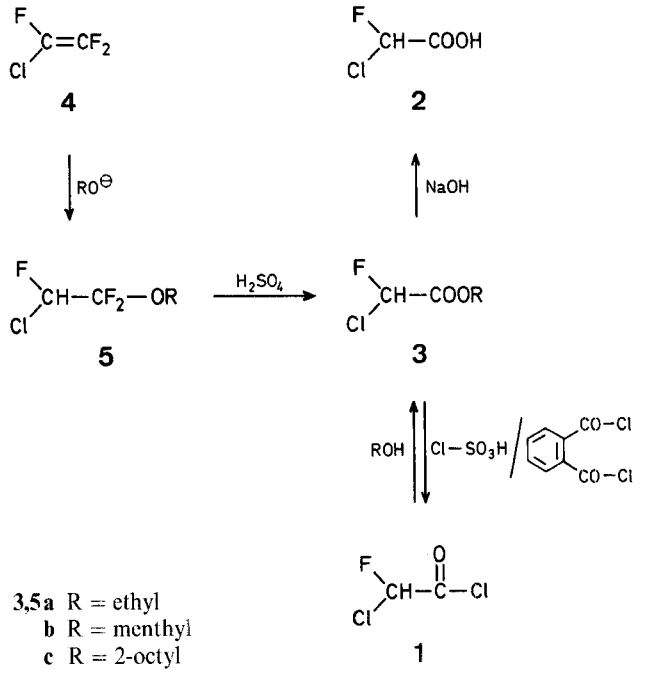
Optically active chlorofluoroacetyl chloride (**1**) was needed for physico-chemical studies[1]. We describe here a method avoiding resolution of the racemic acid **2** by dehydroabiethylamine[2]. Racemic chlorofluoroacetic acid (**2**) has been obtained from chlorotrifluoroethylene (**4**) by hydrolysis of the ethyl ester **3a**[3,4]. The free acid is difficult to prepare in good yield because of its volatility and extreme water solubility[5].



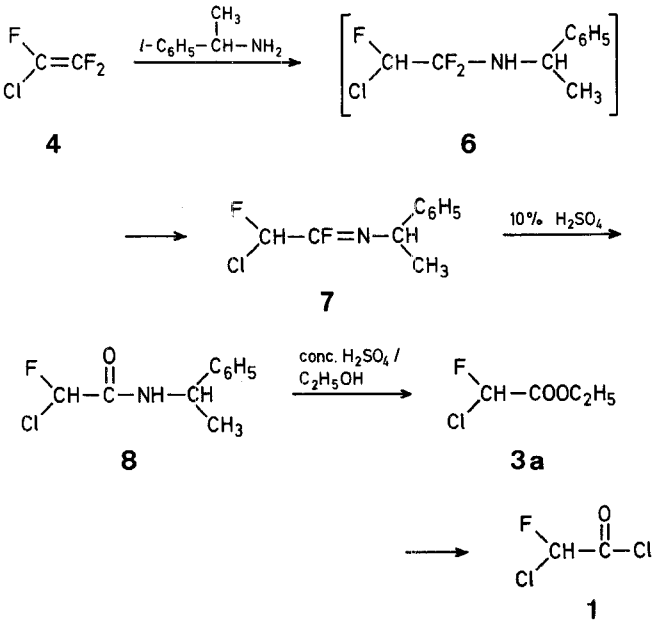
3,5a R = ethyl
b R = menthyl
c R = 2-octyl

Recently Middleton described a straightforward conversion of ethyl chlorofluoroacetate (**3a**) to chlorofluoroacetyl chloride (**1**) by a mixture of chlorosulfuric acid and phthaloyl chloride[5].

Addition of an optically active alkoxide to chlorotrifluoroethylene should give two diastereoisomeric esters, which after separation, should be converted to chiral chlorofluoroacetyl chloride (**1**). In fact, *l*-menthol adds to chlorotrifluoroethylene to give compound **5b** in 50% yield. However, all the attempts to obtain ester **3b** failed, probably because the ester hydrolyses quickly to the acid **2** which remains in the water phase.

Thus, another approach was studied. Acetylation[6] of *l*-menthol by chlorofluoroacetyl chloride (prepared according to Ref.[5]) gives two diastereoisomeric esters **3b** (yield 75%). Attempts to convert these esters to the acyl chloride **1** were unsuccessful. If *l*-octanol is used the same negative results are observed.

To solve the problem a third method was used. Primary and secondary amines are known to add to chlorotrifluoroethylene (**4**)[7,8]. We found that addition of *l*-α-methylbenzylamine to chlorotrifluoroethylene gives compound **7**; the intermediate **6** was not isolated: hydrofluoric acid is captured by the chiral amine (if a tertiary amine or potassium fluoride is used to avoid the consumption of the chiral amine, the yield is not improved). Hydrolysis of **7** by refluxing with 10% sulfuric acid gives a 1 : 1 mixture of the two diastereoisomeric *N*-α-methylbenzyl-α-chloro-α-fluoroacetamides (**8**) (overall yield 46%). The two diastereoisomers have been separated by chromatography on silica gel. The slower moving isomer has been converted to optically active ethyl ester **3a** by a mixture of ethanol and concentrated sulfuric acid[9]. Optically active chlorofluoroacetyl chloride (**1**) is then obtained according to Middleton's procedure[5].



^{1}H-N.M.R. spectra (60 MHz, TMS) and ^{19}F-N.M.R. spectra (56.4 MHz, $CFCl_3$) were recorded on a Varian EM360L spectrometer. I.R. spectra were obtained with a Perkin-Elmer 167 instrument. Melting points were taken on a Mettler FP61 apparatus. Rotatory powers were taken on a Perkin-Elmer 241 polarimeter.

N-α-Methylbenzyl-α-chloro-α-fluoroacetimidyl Fluoride (7):
(l)-α-Methylbenzylamine (5.15 ml, 0.04 mol), chlorotrifluoroethylene (**4**; 3.5 g, 0.03 mol) and dry diethyl ether (40 ml) in a 125 ml steel autoclave, are heated at 60°C for 1 h, and then shaken at 20°C for 12 h. The solid is filtered off and washed with diethyl ether (2 × 50 ml). After removal of the solvent from the filtrate under vacuum (20 torr) *N*-α-methylbenzyl-α-chloro-α-fluoroacetimidyl fluoride (**7**) is obtained: yield: 6.3 g (96%); oil.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.4 (d, 3H, $^3J_{HH}$ = 6 Hz); 5 (q, 1H, $^3J_{HH}$ = 6 Hz); 6.3 (dd, 1H, $^2J_{HF}$ = 49 Hz, $^3J_{HF}$ = 10 Hz); 7.2 ppm (m, 6H).

^{19}F-N.M.R. ($CDCl_3$): δ = − 53 (m, 6 lines); − 143 ppm (m, 8 lines).

N-α-Methylbenzyl-α-chloro-α-fluoroacetamide (8):
The acetimidyl fluoride **7** (6.3 g) and 10% sulfuric acid (20 ml) are refluxed for 2 h, then cooled. Products are extracted with diethyl ether (3 × 50 ml). The ether extract is washed with brine (100 ml) and dried with sodium sulfate. After evaporation of the solvent under vacuum (20 torr), a mixture of the two diastereoisomeric *N*-α-methylbenzyl-α-chloro-α-fluoroacetamides A and B (**8**) is obtained; yield: 3 g (46% based on **4**).

$C_{10}H_{11}ClFNO$	calc.	C 55.69	H 5.14	Cl 16.44	N 6.49
(215.7)	found	55.66	5.07	16.21	6.39

^{19}F-N.M.R. ($CDCl_3$): δ = − 144 ppm (d, $^2J_{HF}$ = 51 Hz), the chemical shift of isomer A is at 0.15 ppm higher field.

The two diastereoisomers (7 g) are separated by chromatography on silica gel (230–400 mesh ASTM, column: diameter 5 cm, height 20 cm) under pressure (0.2 bar) with ethyl acetate/ 40–60°C pet-

roleum ether (12/88) as eluent. Between 0.1 g and 1 g of pure A first eluted and between 0.6 g and 1.2 g of pure B are obtained. The other fractions are a mixture of A and B which are again separated.

– *Diastereoisomer A;* m.p. 73 °C:

I.R. ($CHCl_3$): ν = 3425, 2955, 1700 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.57 (d, 3H, $^3J_{HH}$ = 7 Hz); 5.15 (m, 5 lines); 6.3 (d, 1H, $^2J_{FH}$ = 51 Hz); 7.45 ppm (m, 5H).

^{19}F-N.M.R. ($CDCl_3$): δ = – 144 ppm (d, $^2J_{FH}$ = 51 Hz).

– Diastereoisomer B; m.p. 50 °C:

I.R. ($CHCl_3$): ν = 3425, 2950, 1700 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.57 (d, 3H, $^3J_{HH}$ = 7 Hz); 5.15 (m, 5 lines); 6.35 (d, 1H, $^2J_{FH}$ = 51 Hz); 7.45 ppm (m, 5H).

^{19}F-N.M.R. ($CDCl_3$): δ = – 144 ppm (d, $^2J_{FH}$ = 51 Hz).

Ethyl Chlorofluoroacetate (3a):

A mixture of the diastereoisomer B of *N*-α-methylbenzyl-α-chloro-α-fluoroacetamide (**8**; 7.5 g, 0.035 mol) in absolute ethanol (9 ml) and concentrated sulfuric acid (1.5 ml) is refluxed for at least 30 h. The end of the reaction is controlled by ^{19}F-N.M.R. (no signal of the acetamide). The mixture is cooled and bulb to bulb distilled (under 20 torr, the receiver cooled at – 78 °C). The condensate is distilled to give ethyl chlorofluoroacetate; yield: 3.5 g (71%); b.p. 126–129 °C/atmospheric pressure; $[\alpha]_{365}^{25}$: – 79.7° (*c* 1.55, $CDCl_3$) (Ref.[4], b.p. 129–130 °C/atmospheric pressure).

Chlorofluoroacetyl Chloride (1):

Chlorofluoroacetyl chloride is prepared from (–)-ethyl chlorofluoroacetate (1 g) according to Middelton's procedure[5]; yield: 0.5 g (53%); b.p. 65–70 °C/atmospheric pressure; $[\alpha]_{365}^{20}$: – 81.5° (*c* 1.70, $CDCl_3$) (Ref.[5], b.p. 69–70 °C/atmospheric pressure).

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