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A CONVENIENT SYNTHESIS OF ETHYL 3,3,3-TRIFLUOROPROPANOATE AND ITS 2-BROMO DERIVATIVE

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SUMMARY

Ethyl 3,3,3-trifluoropropanoate and ethyl 2-bromo-3,3,3-trifluoropropanoate have been synthesized. A common intermediate ethyl 3-chloro (or 3-bromo)-3,3-difluoropropanoate is involved in the two syntheses. These esters are obtained by oxidation of the corresponding acetals resulting from the radical addition of CF_2BrCl or CF_2Br_2 to ethyl vinyl ether.

INTRODUCTION

Ethyl 3,3,3-trifluoropropanoate (I) and ethyl 2-bromo-3,3,3-trifluoropropanoate (II) are useful building blocks in synthesis for the introduction of trifluoromethyl groups into organic molecules [1,2,3].

Various syntheses of ethyl 3,3,3-trifluoropropanoate (I) were reported [4]. Generally, they required the use of expensive or dangerous reagents or products, or unusual techniques. Ethyl 2-bromo-3,3,3-trifluoropropanoate (II) was recently used without description of its preparation [3].

Here we wish to report a convenient synthesis of compounds (I) and (II) using cheap and easily available starting materials : CF_2BrCl (IIIa), or CF_2Br_2 (IIIb), and ethyl vinyl ether (IV). The use of these halides requires an halogen exchange in order to build up the trifluoromethyl group, but the yield by this way is much higher than those obtained with the very expensive trifluoromethyl iodide [5].

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SYNTHESES

The first step was a condensation of bromochlorodifluoromethane (IIIa) with ethyl vinyl ether (IV) under ultraviolet irradiation following Tarrant's procedure [6]. The resulting α-bromoether (Va) was treated with ethanol to give the chlorodifluoroacetal (VIa) with 77 % yield from (IV). Similarly, addition of dibromodifluoromethane (IIIb) to (IV) produced (Vb) which was transformed to the bromodifluoroacetal (VIb) as described in [6].

The oxidation of acetals (VI) to ethyl esters (VII) was performed using Caro's acid with 38 % (X=Cl) and 49 % (X=Br) yields from ethyl vinyl ether [7].

Bromine-fluorine exchange with tetrabutylammonium fluoride in tetrahydrofuran on the esters (VII) gave ethyl 3,3,3-trifluoropropanoate (I) in good yields (62 % and 80 % respectively).

$$CF_2BrX + CH_2{=}CH\text{-}OC_2H_5 \xrightarrow{h\nu} CF_2X\text{-}CH_2\text{-}CHBrOC_2H_5$$

(III) (IV) (V)

a X=Cl
b X=Br

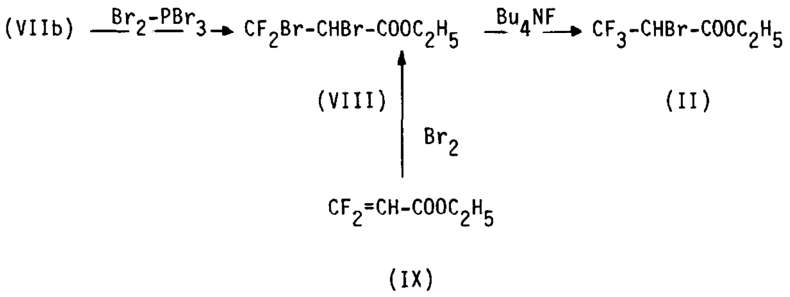
$$\xrightarrow{EtOH} CF_2X\text{-}CH_2\text{-}CH(OC_2H_5)_2 \xrightarrow{\text{Caro's acid}} CF_2X\text{-}CH_2\text{-}COOC_2H_5$$

(VI) (VII)

$$\xrightarrow{Bu_4NF} CF_3\text{-}CH_2\text{-}COOC_2H_5$$

(I)

For the synthesis of ethyl 2-bromo-3,3,3-trifluoropropanoate (II), the bromodifluoroester (VIIb) was treated first with a bromine-phosphorus tribromide mixture [8] and second with tetrabutylammonium fluoride ; (II) was obtained with 48 % yield from (VIIb). The intermediate ethyl 2,3-dibromo-3,3-difluoropropanoate (VIII) could also be obtained by bromine addition on ethyl 3,3-difluoroacrylate (IX) (which we have described in ref. [7]) with 90 % yield.



$$\begin{tikzcd}
(VIIb) \arrow[r, "Br_2-PBr_3"] & CF_2Br\text{-}CHBr\text{-}COOC_2H_5 \arrow[r, "Bu_4NF"] & CF_3\text{-}CHBr\text{-}COOC_2H_5 \\
& (VIII) & (II) \\
& CF_2=CH\text{-}COOC_2H_5 \arrow[uu, "Br_2"'] & \\
& (IX) &
\end{tikzcd}$$

EXPERIMENTAL

^{1}H NMR (60 MHz) and ^{19}F NMR (56.4 MHz) were recorded on a Varian EM360L spectrometer equipped with a proton/fluorine probe.

IR spectra were obtained on a Perkin-Elmer 167 spectrometer.

Elemental analyses were performed by the Service de Microanalyses, Université P. et M. Curie, Paris.

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Ethyl vinyl ether and tetrabutylammonium fluoride were purchased from Aldrich.

Ether was diethylether.

Synthesis of acetals (VI)

(i) 3-Chloro-3,3-difluoropropanal diethylacetal (VIa) was prepared by Tarrant's procedure [6]. In a horizontal flask fitted with an internal mercury lamp (low pressure, TNN 15/32 original Hanau), condensed bromochlorodifluoromethane (165.5 g, 0.1 mol) was added to ethyl vinyl ether (29.5 g, 0.41 mol) at 0° C under a nitrogen atmosphere. Then, the mixture was irradiated at 0° C with magnetic stirring for 10 h. The unstable resultant solution of 3-bromo-1-chloro-3-ethoxy-1,1-difluoropropane (Va) must be stored at 0° C under an inert atmosphere and processed as soon as possible.

Absolute ethanol (100 ml) was added dropwise to the stirred previously prepared solution of (Va) at 0° C under a nitrogen atmosphere. After 1 h, at 0° C, the mixture was diluted with cold water (600 ml), the organic products were decanted off and added to ether (200 ml). This solution was washed with brine (3x75 ml) and dried over sodium sulfate.

The solvent was distilled off and the residue was distilled at reduced pressure using a large flask due to foam, to give 3-chloro-3,3-difluoropropanal diethylacetal (VIa) (nc) as a colourless liquid (64.3 g, 0.318 mol, 77 %) ; b.p. 58° C at 20 mmHg ; Calc. for $C_7H_{13}ClF_2O_2$ (202.62) : C, 41.5 ; H, 6.47 % ; found : C, 41.57 ; H, 6.61 % ; I.R. ($CHCl_3$) : ν=2940, 2900, 1450, 1385, 1360 and 1325 cm^{-1}. ^1H N.M.R. ($CDCl_3$, TMS) : δ =1.27 (t, 6H, $^3J_{HH}$=7 Hz) ; 2.72 (td, 2H, $^3J_{HH}$=5 Hz, $^3J_{FH}$=13 Hz) ; 3.7 (2q, 4H, $^3J_{HH}$=7 Hz) ; 4.97 ppm (t, 1H, $^3J_{HH}$=5 Hz). ^{19}F N.M.R. ($CDCl_3$, $CFCl_3$) : δ =-48 ppm (t, $^3J_{FH}$=13 Hz).

(ii) 3-Bromo-3,3-difluoropropanal diethylacetal (VIb).For this, the same procedure as in (i) was followed. Ethyl vinyl ether (72 g, 1 mol) gave (VIb) [6] (160 g, 0.65 mol, 65 %) ; b.p. 64-67° C at 14 mmHg ; only the NMR spectra not described in [6] are given : ^1H N.M.R. ($CDCl_3$, TMS) : δ=1,2 (t, 6H, $^3J_{HH}$=7 Hz) ; 2.75 (td, 2H, $^3J_{HH}$= 5 and $^3J_{FH}$=14 Hz) ; 3.6 (AB type spectrum, 8 lines, 4H) ; 4.9 ppm (t, 1H, $^3J_{HH}$=5 Hz) ; ^{19}F N.M.R. ($CDCl_3$, $CFCl_3$) : δ =-42 ppm (t, $^3J_{FH}$=14 Hz).

Synthesis of esters (VII)

(i) Ethyl 3-chloro-3,3-difluoropropanoate (VIIa). In this procedure, Caro's acid, prepared from ammonium persulfate (114 g, 0.5 mol) and 85 % sulfuric acid (144 g) [9] , was added to a vigorously stirred solution of 3-chloro-3,3-difluoropropanal diethylacetal (VIa) (20.25 g, 0.1 mol) in absolute ethanol (200 ml) at 5-10° C. The mixture was well stirred at room temperature for a day, then diluted with a large quantity of cold water (600 ml) and extracted with ether (3x250 ml). The organic phase was washed with brine (2x200 ml) and dried over sodium sulfate. The solvent was distilled off at atmospheric pressure and the residue was distilled under reduced pressure to give ethyl 3-chloro-3,3-difluoropropanoate (VIIa) (nc) as a colourless liquid (8.46 g, 0.049 mol, 49 %) ; b.p. 47-48° C at 13 mmHg ; Calc. for $C_5H_7ClF_2O_2$ (172.55) : C, 34.8 ; H, 4.08 % ; Found : C, 34.79 ; H, 4.05 %. I.R. ($CHCl_3$) : ν=1750, 1470, 1450, 1400, 1380, 1345, 1180, 1100 cm^{-1} ; ^1H N.M.R. ($CDCl_3$, TMS) : δ=1.3 (t, 3H, $^3J_{HH}$=7 Hz) ; 3.4 (t, 2H, $^3J_{FH}$=13 Hz) ; 4.3 ppm (q, 2H, $^3J_{HH}$=7 Hz) ; ^{19}F N.M.R. ($CDCl_3$, $CFCl_3$) : δ =-49 ppm (t, $^3J_{FH}$=13 Hz).

(ii) Ethyl 3-bromo-3,3-difluoropropanoate (VIIb) was prepared as in (i) and reported in [7] with 75 % yield (16.3 g, 0.075 mol) from acetal (VIb) (24.7 g, 0.1 mol) ; b.p. 60-61° C at 20 mmHg ; Calc. for $C_5H_7BrF_2O_2$ (217.01) : C, 27.67 ; H, 3.25 % ; Found : C, 27.55 ; H, 3.42 % ; I.R. ($CHCl_3$) : ν=1750, 1570, 1380, 1180, 1100, 1030 cm^{-1} ; ^1H N.M.R. ($CDCl_3$, TMS) : δ=1.3 (t, 3H, $^3J_{HH}$=7 Hz) ; 3.5 (t, 2H, $^3J_{FH}$=13 Hz) ; 4.3 ppm (q, 2H, $^3J_{HH}$=7 Hz) ; ^{19}F N.M.R. ($CDCl_3$, $CFCl_3$) : δ=-43 ppm (t, $^3J_{FH}$=13 Hz).

Ethyl 3,3,3-trifluoropropanoate (I).

(i) From ethyl 3-bromo-3,3-difluoropropanoate (VIIb). A 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (40 ml, 0.04 mol) was added dropwise to ethyl 3-bromo-3,3-difluoropropanoate (VIIb) (8.7 g, 0.04 mol) at 0° C. At the end of the addition, water was added (50 ml), the two layers were separated, the aqueous phase was extracted with ether (2x50 ml). The organic phase was washed with brine (30 ml) and dried with sodium sulfate. The solvents were distilled off using a spinning band column. The residue was distilled at atmospheric pressure to give ethyl 3,3,3-trifluoropropanoate (I) (5 g, 0.032 mol, 80 %) ; b.p. 106-108° C (Ref [10] : 57-58° C at 100 mmHg).

(ii) From ethyl 3-chloro-3,3-difluoropropanoate (VIIa). The same experimental procedure as (i) was followed ; ethyl 3-chloro-3,3-difluoropropanoate (VIIa) (5.17 g, 0.03 mol) gave ethyl 3,3,3-trifluoropropanoate (I) (2.9 g, 0.0186 mol, 62 %).

Ethyl 2,3-dibromo-3,3-difluoropropanoate (VIII).

(i) From ethyl 3-bromo-3,3-difluoropropanoate (VIIb). Phosphorus tribromide (6 g, 0.022 mol) was added dropwise to ethyl 3-bromo-3,3-difluoropropanoate (VIIb) (4.35 g, 0.02 mol) at 0° C. After removal of the cooling bath, bromine (2 ml, 0.04 mol) was added dropwise until the reaction mixture became deep red coloured and then the remaining bromine was added all at once. The mixture was heated at 90° C for 1.5 h, then bromine (0.5 ml, 0.01 mol) was added and the heating at 90° C was continued for 4-5 days. After cooling, absolute ethanol (15 mol) was added and the mixture was refluxed for 1 h, then water (50 ml) was added. The two layers were separated, ether (50 ml) was added to the lower one. The organic phase was washed with cooled saturated aqueous sodium hydrogen carbonate (10 ml), brine (2x50 ml) and dried with sodium sulfate. The solvent was evaporated (20 mmHg) and the residue distilled under reduced pressure to give ethyl 2,3-dibromo-3,3-difluoropropanoate (VIII) (4.15 g, 0.014 mol, 70 %) ; b.p. 80-82° C at 20 mmHg ; I.R. ($CHCl_3$) : ν=1755, 1375, 1335, 1270, 1150, 1110 cm^{-1} ; ^1H N.M.R. ($CDCl_3$, TMS) : δ=1.33 (t, 3H, $^3J_{HH}$=7 Hz) ; 4.35 (q, 2H, $^3J_{HH}$=7 Hz) ; 4.9 ppm (dd, 1H, $^3J_{FH}$=6 and 14 Hz). ^{19}F N.M.R. ($CDCl_3$, $CFCl_3$, ABX type spectrum) : δ=-47.8 ($^2J_{FF}$=162 Hz, $^3J_{FH}$=6 Hz) ; -53.3 ppm ($^2J_{FF}$=162 Hz, $^3J_{FH}$=14 Hz).

(ii) From ethyl 3,3-difluoroacrylate (IX). Bromine (2 ml, 0.04 mol) was added dropwise to a solution of ethyl 3,3-difluoroacrylate (IX) (5.45 g, 0.04 mol ; prepared as we described in ref [7]) in carbon tetrachloride (20 ml) under irradiation (high pressure mercury lamp, 125 W) at room temperature. At the end of the addition, the solvent was evaporated (20 mmHg) and the residue distilled to give ethyl 2,3-dibromo-3,3-difluoropropanoate (VIII) (10.7 g, 0.036 mol, 90 %).

Ethyl 2-bromo-3,3,3-trifluoropropanoate (II). A 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (28 ml, 0.028 mol) was added to a solution of ethyl 2,3-dibromo-3,3-difluoropropanoate (VIII) (8.3 g, 0.028 mol) in tetrahydrofuran (24 ml) at 0° C. At the end of the addition, water (30 ml) was added. The two layers were separated. The aqueous phase was extracted with ether (2x50 ml). The organic phase was washed with brine (50 ml) and dried over sodium sulfate. The solvents were evaporated (20 mmHg) and the residue was distilled to give ethyl 2-bromo-3,3,3-trifluoropropanoate (II) (4.47 g, 0.019 mol, 68 %) ; b.p. 48-49°C at 20 mmHg ; Calc. for $C_5H_6BrF_3O_2$ (235.0) : C, 25.56 ; H, 2.57 % ; Found : C, 25.46 ; H, 2.77 % ; I.R. ($CHCl_3$) : ν=1755, 1470, 1375, 1350, 1280, 1145, 1120 cm^{-1} ; ^1H N.M.R. ($CDCl_3$, TMS) : δ =1.33 (t, 3H, $^3J_{HH}$=7 Hz) ; 4.35 (q, 2H, $^3J_{HH}$=7 Hz) ; 4.65 ppm (q, 1H, $^3J_{FH}$=7 Hz). ^{19}F N.M.R. ($CDCl_3$, $CFCl_3$) : δ=-70 ppm (d, $^3J_{FH}$=7 Hz).

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