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A general route for the synthesis of β,β-difluorocarboxylic acids

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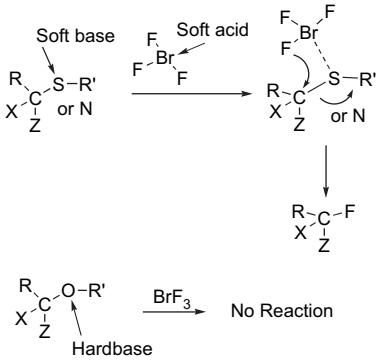
ABSTRACT

A new method for the preparation of β,β-difluoro- (and other *gem*-difluoro) acids has been developed. It is based on the fact that 3-oxocarboxylic esters are easy to make and convert to the corresponding dithiane derivatives. These dithianes reacted with BrF_3, a commercial, but rarely used reagent in organic chemistry, under very mild conditions to form the corresponding difluoroesters, which in turn could be quantitatively hydrolyzed to the free *gem*-difluoroacids.

1. Introduction

As with so many fluoro derivatives, various fluorocarboxylic acids are a subject of enormous biological interest.[1] Many schemes have been developed by us and others for the synthesis of α-fluoro-,[2] α,α-difluoro-,[3] ω-fluoro-[4] or α-trifluoromethylcarboxylic acids.[5] The family of β,β-difluorocarboxylic acids, however, is almost unknown.[6] Some specific acids of this type were tailor made and found to be, among other things, inhibitors of the biosynthesis of certain sex pheromones.[7] We report here a new general method for the preparation of β,β-difluorocarboxylic acids using BrF_3 and β-dithiane esters readily synthesized from β-ketoesters and dithiols. While some of these esters are commercially available, most of them can be readily synthesized from the corresponding acyl halides and esters via a Claisen type condensation.

Bromine trifluoride is a commercial reagent, but it can also be prepared directly from the elements. Until recently, organic chemists shied away from it, mainly because of its violent nature when handled improperly (using it with oxygenated or hydrocarbon solvents such as THF or hexane—see Section 3). In the past only a few examples of its use were reported,[8] but over the last decade, we have shown that bromine trifluoride can serve as a selective reagent for many reactions using halogenated solvents, such as chloroform or $CFCl_3$ and ordinary glass apparatuses. It can electrophilically brominate most aromatic rings, including very deactivated ones even in the absence of any Friedel–Crafts catalyst.[9] Regarding fluorination, it can transform carbonyls to the CF_2 group,[10] nitriles to the corresponding CF_3 moiety,[11] and alcohols or acids to acyl fluorides.[12] Bromine trifluoride can also help in synthesizing trifluoromethyl ethers,[13] trifluoro-[14] and difluoromethyl alkanes[15] starting from the corresponding alkyl halides, and more.[16] Most transformations were made possible due to the fact that the bromine in BrF_3 is a soft acid, which complexes most effectively with soft bases such as sulfur and nitrogen atoms. The complexation positions the 'naked' nucleophilic fluorides near the potential reaction center and eventually substitute the nitrogen or sulfur heteroatom (Scheme 1). This complexation also reduces the chances of possible radical brominations and fluorinations.[17]



Scheme 1. The complexation of BrF_3 with soft heteroatoms.

2. Results and discussion

When the 1,3-dithiane of ethyl 3-oxooctadecanoate (**1**) was reacted for 1–2 min at 0 °C with a threefold excess of BrF_3, the expected ethyl 3,3-difluorohexadecanoate (**2**) was formed in 75% yield. Similarly, the 1,3-dithiane of diethyl 3-oxoglutarate (**3**) was converted to diethyl β,β-difluoroglutarate **4**[18] in 60% yield (Table 1).

Since BrF_3 is known to be able to substitute chlorine atoms with fluorine (e.g., the conversion of (*S*)-isoflurane to the (*R*)-desflurane)[19] it was of interest to see if such processes take place during

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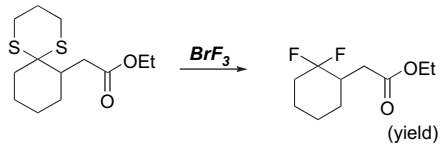
Table 1
Preparation of β,β-difluoroesters

	(Yield, %)
1 R=$C_{15}H_{31}$; R′=H; R″=Et	**2** (75)
3 R=CH_2COOEt; R′=H; R″=Et	**4** (60)
5 R=Cl$(CH_2)_4$; R′=H; R″=Et	**6** (65)
7 R=Me; R′=Et; R″=Et	**8** (75)
9 R=R′=$(CH_2)_4$; R″=Et	**10** (80)
11 R=  ; R′=H; R″=Et	**12** (70)
13 R=Me; R′=R″=$(CH_2)_2$	**14** (55)

the reactions with dithiane derivatives when chlorine atoms are present. Evidently, the complexation of the reagent with the sulfur atoms is by far the dominant reaction as demonstrated by 1,3-dithiane of ethyl 7-chloro-3-oxoheptanoate (**5**), which resulted in ethyl 7-chloro-3,3-difluoroheptanoate (**6**) in 65% yield.

The fluorine atoms in bromine trifluoride can in certain cases act as electrophiles[8b] and substitute tertiary hydrogens similar to F_2.[20] Such outcomes, however, seem to require long reaction times and do not compete with the rapid complexation of the soft bromine with the soft sulfur atoms. Indeed when we reacted the dithiane derivatives of ethyl 2-ethyl-3-oxobutyrate (**7**), ethyl 2-oxocyclohexanecarboxylate (**9**), and ethyl 3-cyclohexyl-3-oxopropionate (**11**) all possessing tertiary hydrogens, the only products formed in good yields were ethyl 2-ethyl-3,3-difluorobutyrate (**8**),[6a] ethyl 2,2-difluorocyclohexanecarboxylate (**10**),[6b] and ethyl 3-cyclohexyl-3,3-difluoropropionate (**12**) in reactions completed in less then a minute. The speed of the reaction and the mild conditions employed were responsible for the fact that even lactones such as the dithiane of α-(1-oxoethyl)-γ-butyrolactone (**13**) was found to be a suitable substrate for the formation the corresponding α-(1,1-difluoroethyl)-γ-butyrolactone **14** although the yield (55%) was somewhat lower than usual. It should be mentioned that occasionally small fractions of the products, in addition to the difluoro moiety, contained also a bromine atom. This, however, could easily and quantitatively be removed by tributyltin hydride, thus increasing the overall yield of the desired product.

The above method seems to be suitable for transforming any ketoester to its difluoro derivative. This could be demonstrated by reacting the dithiane of ethyl 2-(2-oxocyclohexyl)ethanoate (**15**) with BrF_3 forming ethyl 2-(2,2-difluorocyclohexyl)ethanoate (**16**) (γ,γ-difluoroesters) in 55% yield (Scheme 2).

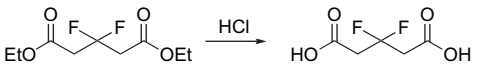


15 **16** (55%)

Scheme 2. Preparation of γ,γ-difluoroesters.

The difluoroesters could be hydrolyzed almost quantitatively to the free acids by refluxing them with concentrated HCl for 4 h. Thus, for example, diethyl 3,3-difluoroglutarate (**4**) was converted to the known 3,3-difluoroglutaric acid (**17**)[18] in higher than 95% yield (Scheme 3).

In conclusion, the above method has the advantage of being a general one for the synthesis of many types of *gem*-difluoroacids. The mild conditions, as expressed in the short reaction times and



4 **17**

Scheme 3. Hydrolysis of difluoroesters.

low temperatures, make this reaction suitable to many types of compounds.

3. Experimental section

3.1. General

^{1}H NMR spectra were recorded using a 200 MHz spectrometer with $CDCl_3$ as a solvent and Me_4Si as an internal standard. The ^{19}F NMR spectra were measured at 188.1 MHz using $CFCl_3$ as an internal standard. The proton broadband decoupled ^{13}C NMR spectra were recorded at 100.5 MHz. Here too, $CDCl_3$ served as a solvent and Me_4Si as an internal standard. IR spectra were recorded neat or in CH_2Cl_2 solution on a FTIR spectrophotometer. MS spectra were measured under ESI–QqTOF or CI conditions.

3.2. Preparing and handling of BrF_3

Although commercially available, we usually prepare our own BrF_3 simply by passing 0.6 mol fluorine through 0.2 mol of bromine placed in a copper reactor and held at temperatures between 0 and +10 °C. Under these conditions, the higher oxidation state of bromine, BrF_5, will not be formed in any appreciable amount. The reagent can be stored in Teflon® containers indefinitely. *BrF_3 is a strong oxidizer and tends to react very exothermically with water and oxygenated organic solvents such as acetone or THF. Alkanes, like petrol ether, cannot serve as solvents either since they also react quickly with BrF_3. Solvents such as $CHCl_3$, CH_2Cl_2, $CFCl_3$ or, if solubility is not an issue, any perfluoroalkane or perfluoroether can be used. Any work using BrF_3 should be conducted in a well ventilated area and caution and common sense should be exercised.*

3.3. General procedure for preparing difluoroesters

A dithiane (1–10 mmol) was dissolved in 10–20 mL of $CFCl_3$ and cooled to 0 °C. About 3 mol equiv of BrF_3 was dissolved in the same solvent, cooled to 0 °C, and added dropwise to the reaction mixture for 1–2 min. After the addition was completed, the reaction mixture was washed with $Na_2S_2O_3$ solution till colorless. The aqueous layer was extracted with CH_2Cl_2 and the organic layer dried over $MgSO_4$. Evaporation of the solvent followed by flash chromatography (using 5% ethyl acetate in petroleum ether as eluent) gave the desired difluoro ester derivative. In the case of the reaction of **11** and **13** a minor fraction, which contained bromine was also found. This atom was substituted with hydrogen with the help of tributyltin hydride, increasing the overall yield of the products **12** and **14** to 70 and 55%, respectively (see below).

*3.3.1. Ethyl 3,3-difluorooctadecanoate (**2**)*

Compound **2** was prepared from **1** (417 mg, 1 mmol) as described above in 75% yield. δ_H 4.19 (2H, q, J=7 Hz), 2.89 (2H, t, J=14 Hz), 2.06–1.54 (2H, m), 1.53–1.43 (2H, m), 1.25 (27H, br s), 0.88 (3H, t, J=7 Hz); δ_C 167.1, 122.3 (t, J=242 Hz), 61.1, 41.7 (t, J=28.5 Hz), 36.1 (t, J=24 Hz), 31.9, 29.7, 29.6, 29.3 (t, J=11 Hz), 22.7, 22.2, 14.1; δ_F −94.3 (quin, J=14 Hz); IR 1740 cm^{-1}; HRMS (ESI–QqTOF) (m/z) calcd for $C_{20}H_{38}F_2O_2$=371.2732 $(M+Na)^+$, found 371.2759. Anal. Calcd for $C_{20}H_{38}F_2O_2$: C, 68.93; H, 10.95; F, 10.90. Found: C, 68.88; H, 10.95; F, 10.54.

*3.3.2. Diethyl β,β-difluoroglutarate (**4**)*[18]

Compound **4** was prepared from **3** (400 mg, 1.44 mmol) as described above in 60% yield. δ_H 4.19 (4H, q, J=7 Hz), 3.25 (4H, t, J=15 Hz), 1.28 (6H, t, J=7 Hz); δ_C 167.3 (t, J=9 Hz), 119.8 (t, J=242 Hz), 61.4, 40.8 (t, J=27.5 Hz), 14.2; δ_F −89.5 (quin, J=14.7 Hz); IR 1745 cm^{-1}; HRMS (ESI–QqTOF) (m/z) calcd for $C_9H_{14}F_2O_4$=247.0752 $(M+Na)^+$, found 247.0668.

*3.3.3. Ethyl 7-chloro-3,3-difluoroheptanoate (**6**)*

Compound **6** was prepared from **5** (297 mg, 1 mmol) as described above in 65% yield. δ_H 4.19 (2H, q, J=7 Hz), 3.56 (2H, t, J=6.3 Hz), 2.91 (2H, t, J=14.5 Hz), 2.19–1.58 (6H, m), 1.29 (3H, t, J=7 Hz); δ_C 167.7 (t, J=8 Hz), 122.8 (t, J=242 Hz), 62.0, 45.2, 42.7 (t, J=28.5 Hz), 35.9 (t, J=24.5 Hz), 32.7, 20.4 (t, J=4.5 Hz), 14.2; δ_F −94.5 (quin, J=15.5 Hz); IR 1743 cm^{-1}; HRMS (ESI–QqTOF) (m/z) calcd for $C_9H_{15}ClF_2O_2$=251.0635 $(M+Na)^+$, found 251.0620. Anal. Calcd for $C_9H_{15}ClF_2O_2$: C, 47.27; H, 6.61; F, 16.62. Found: C, 47.60; H, 6.51; F, 16.40.

*3.3.4. Ethyl 2-ethyl-3,3-difluorobutyrate (**8**)*[6a]

Compound **8** was prepared from **7** (497 mg, 2 mmol) as described above in 75% yield. δ_H 4.21 (2H, q, J=7 Hz), 2.90–2.71 (1H, m), 1.83–1.57 (5H, m), 1.29 (3H, t, J=7 Hz), 0.95 (3H, t, J=7 Hz); δ_C 171.3, 123.6 (t, J=243 Hz), 61.8, 56.0 (t, J=26 Hz), 21.8 (t, J=27 Hz), 21.2 (dd, J=5.4, 2.7 Hz), 14.9, 12.6; δ_F −89.3 (1F, dqd, J=262, 20, 10 Hz), −91.4 (1F, dqd, J=262, 20, 14 Hz); IR 1739 cm^{-1}; HRMS (ESI–QqTOF) (m/z) calcd for $C_8H_{14}F_2O_2$=203.0842 $(M+Na)^+$, found 203.0854.

*3.3.5. Ethyl 2,2-difluorocyclohexanecarboxylate (**10**)*[6b]

Compound **10** was prepared from **9** (521 mg, 2 mmol) as described above in 80% yield. δ_H 4.19 (2H, q, J=7 Hz), 2.95–2.73 (1H, m), 2.33–1.61 (8H, m), 1.28 (3H, t, J=7 Hz); δ_C 170.2 (d, J=6 Hz), 122.1 (t, J=246 Hz), 61.3, 49.2 (t, J=23 Hz), 33.6 (t, J=23 Hz), 26.9, 22.7, 14.5; δ_F −94.5 (1F, dd, J=240, 17 Hz), −105.0 (1F, d, J=239 Hz); IR 1737 cm^{-1}; HRMS (ESI–QqTOF) (m/z) calcd for $C_9H_{14}F_2O_2$=215.0854 $(M+Na)^+$, found 218.0850.

*3.3.6. Ethyl 3-cyclohexyl-3,3-difluoropropionate (**12**)*

Compound **12** was prepared from **11** (577 mg, 2 mmol) as described above. The mixture of the desired and the brominated products (370 mg) was dissolved in 20 mL anhydrous THF into which 100 mg of 1,1′-azobis(cyclohexane-carbonitrile) (ABCN 0.4 mmol) and 2.4 mL of tributyltin hydride (8.9 mmol) were added. The solution was refluxed for 2 h. After evaporation of the solvent, the product was purified by flash chromatography (using 5% ethyl acetate in petroleum ether) and **12** was obtained in 70% yield. δ_H 4.20 (2H, q, J=7.1 Hz), 2.89 (2H, t, J=15.8 Hz), 2.06–1.90 (1H, m), 1.90–1.65 (4H, m), 1.32–1.10 (9H, m); δ_C 167.9, 123.9 (t, J=245 Hz), 61.8, 44.2 (t, J=23 Hz), 40.8 (t, J=28.3 Hz), 26.6, 26.3, 26.2, 14.8; δ_F −102.4 (q, J=15 Hz); IR 1745 cm^{-1}; HRMS (ESI–QqTOF) (m/z) calcd for $C_{11}H_{18}F_2O_2$=243.1158 $(M+Na)^+$, found 243.1167. Anal. Calcd for $C_{11}H_{18}F_2O_2$: C, 59.98; H, 8.24. Found: C, 60.05; H, 8.35.

*3.3.7. α-(1,1-Difluoroethyl)-γ-butyrolactone (**14**)*

Compound **14** was prepared from **13** (2.18 g, 10 mmol) as described above. Eventually 2.5 g of a mixture of the desired product along with its minor brominated companion was dissolved in 100 mL anhydrous THF. ABCN (530 mg, 2.17 mmol) and 5.67 mL (21.7 mmol) of tributyltin hydride were added and the solution was refluxed for 1 h. After evaporation of the solvent, and flash chromatography using 5% ethyl acetate in petroleum ether, **14** was obtained in 55% yield. δ_H 4.41 (1H, dt, J=8.8, 5.0 Hz), 4.28 (1H, q, J=8.2 Hz), 3.09–2.96 (1H, m), 2.60–2.41 (2H, m), 1.87 (3H, dd, J=19.8, 18.7 Hz); δ_C 173.6 (d, J=11 Hz), 122.6 (t, J=241 Hz), 67.4, 47.6 (t, J=30 Hz), 23.8, 22.7 (t, J=26.0 Hz); δ_F −86.3 (1F, dqd, J=248, 19.6, 4.1 Hz), −97.6 (1F, dqd, J=248, 24.5, 18.4 Hz); IR 1790 cm^{-1}; HRMS (CI, MeOH) (m/z) calcd for $C_6H_8F_2O_2$=151.0571 $(M+H)^+$, found 151.0572. Anal. Calcd for $C_6H_8F_2O_2$: C, 48.00; H, 5.37. Found: C, 47.68; H, 5.12.

*3.3.8. Ethyl 2-(2,2-difluorocyclohexyl)ethanoate (**16**)*

Compound **16** was prepared from **15** (823 mg, 3 mmol) as described above in 55% yield. δ_H 4.15 (2H, q, J=7 Hz), 2.77 (1H, dd, J=16, 4 Hz), 2.22–2.08 (2H, m), 1.86–1.83 (1H, m), 1.78–1.61 (5H, m), 1.33–1.29 (2H, m), 1.26 (3H, J=7 Hz); δ_C 173.2, 124.4 (t, J=244 Hz), 61.3, 41.3 (t, J=21 Hz), 34.8 (dd, J=25, 22 Hz), 14.9; δ_F −95.1 (1F, dm, J=236 Hz), −112.5 (1F, dm, J=237 Hz); IR 1742 cm^{-1}; HRMS (ESI–QqTOF) (m/z) calcd for $C_{10}H_{16}F_2O_2$= 229.0994 $(M+Na)^+$, found 229.1010. Anal. Calcd for $C_{10}H_{16}F_2O_2$: C, 58.24; H, 7.82; F, 18.42. Found: C, 58.49; H, 7.63; F, 18.48.

Acknowledgements

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