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A Novel Method for the Preparation of α,α′-Difluoroesters and Acids Using BrF_3

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Abstract: Alkyl-, haloalkyl-, and ketoalkyl-2-ethoxycarbonyl-1,3-dithianes were easily made from the appropriate primary or secondary alkyl bromides, 1,3-dithiane, and ethyl chloroformate. They were reacted with BrF_3 to form the corresponding α,α-difluoro esters in 65−75% yield. Reaction conditions are very mild (1−2 min, 0 °C). The two sulfur atoms of the dithiane are essential for the reaction.

Since the discovery of Fried in the mid-1950s that fluorocortisone is more active then cortisone itself,[1] thousands of works on selective introduction of the fluorine atom into organic molecules have established today's common knowledge that such compounds are potentially biologically important. The finding that α,α′-difluoroketones can serve as enzyme inhibitors[2] prompted a development of synthetic routes for constructing a difluoromethylene group adjacent to a carbonyl. A very significant subgroup of this family is the α,α′-difluoroesters. The most common methods for making such compounds are based on variations of the Reformatsky reaction using halodifluoroacetic acid[3] and of the reaction of sulfur tetrafluoride or DAST with α-keto esters.[4]

Bromine trifluoride, BrF_3, has been used in the synthesis of some modern anesthetics, such as sevoflurane,[5] but otherwise is rarely mentioned in the organic chemistry literature. A few years ago, we started to examine possibilities of turning this long-known, but rather underutilized, molecule into an acceptable and selective reagent for reactions involving organic compounds that are not heavily halogenated. We have used it in bromination of deactivated aromatic rings,[6] transformation of a carbonyl to the CF_2 group,[7] and transformation of nitriles to the corresponding CF_3 ones.[8] It was also instrumental in transforming RX to RCF_3,[9] as well as to $RCHF_2$ compounds,[10] for synthesis of trifluoromethyl ethers[11] and more.[12] Most of the above procedures were made possible because of the tendency of the electrophilic soft acidic bromine of BrF_3 to complex itself with soft basic heteroatoms, such as nitrogen and sulfur. This process brings the naked nucleophilic fluorides near the reaction center and reduces undesirable radical or other side reactions.

About two years ago, we tried for the first time to make α,α′-difluoroesters by reacting BrF_3 with methyl oxime ether of pyruvic esters in a somewhat parallel process of transforming ketones to the CF_2 group.[7] The reaction resulted, however, in a unique rearrangement,[13] but none of the desired α,α′-difluoroester was formed. After some additional experiments, we now report a new and easy synthesis for these esters from commercially available alkyl bromides, cyclic 1,3-dithiane (**1**), and bromine trifluoride.

Following a known procedure,[14] decylbromide (**2a**) was first reacted with the lithium salt of **1** and then with ethyl chloroformate to produce 2-decyl-2-ethoxycarbonyl-1,3-dithiane (**3a**). The main idea was for the two sulfur atoms to serve as an anchor for the BrF_3 as mentioned above. Indeed, when **3a** was reacted for 1−2 min at 0 °C with 3-fold excess of BrF_3, the expected ethyl 2,2-difluorododecanoate (**4a**)[15] was formed in 75% yield. Because the fluorine atoms in bromine trifluoride can act in certain cases as an electrophile[16] and substitute tertiary hydrogens similarly to F_2,[17] we performed this reaction also with alkyl halides possessing tertiary hydrogens and found that the dithiane moiety reacts much faster. Thus, bromomethylcyclohexane (**2b**) and 3-bromomethylheptane (**2c**) were converted to 2-methylcyclohexyl-2-ethoxycarbonyl-1,3-dithiane (**3b**) and 2-(2-ethyl)hexyl-2-ethoxycarbonyl-1,3-dithiane (**3c**), which, after treatment with BrF_3, produced the desired unknown ethyl 3-cyclohexyl-2,2-difluoropropanoate (**4b**) and ethyl 4-ethyl-2,2-difluorooctanoate (**4c**) in 75% yield each. Similar results were obtained with 3,7-dimethyloctylbromide (**2d**) and 2-(2-norbornyl)ethylbromide (**2e**), which were first converted to 2-(3,7-dimethyl)octanyl-2-ethoxycarbonyl-1,3-dithiane (**3d**) and 2-(2-norbornyl)ethyl-2-ethoxycarbonyl-1,3-dithiane (**3e**) and then successfully reacted with BrF_3 to produce ethyl 2,2-difluoro-5,9-dimethyldecanoate (**4d**) and ethyl 2,2-difluoro-4-(2-norbornyl)butanoate (**4e**) in 70 and 75% yields, respectively.

This method can be used for the formation of relatively hindered difluoroesters as well. 2-Bromodecane (**2f**) and 2-bromopropane (**2g**) were transformed to their corresponding dithiane derivatives **3f** and **3g** and then reacted

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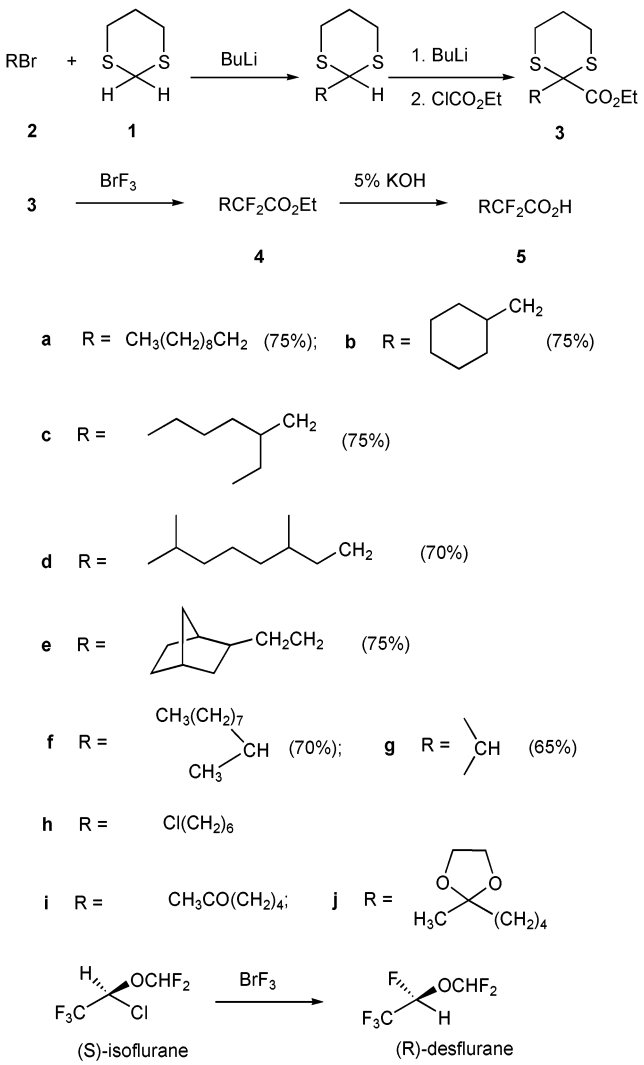

with BrF_3 to produce ethyl 2,2-difluoro-3-methylundecanoate (**4f**) and ethyl 2,2-difluoro-3-methylbutanoate (**4g**)[4] in 70 and 65% yields, respectively.

Compounds containing aromatic rings are not suitable for reactions with BrF_3 since the rings are easily brominated.[6] However, other functional groups such as halogens and ketones are not affected during the reaction of bromine trifluoride with the dithiane moiety. While one of the best-known reactions of BrF_3 is the S_N2 displacement of an activated chlorine with fluorine as shown in the conversion of (*S*)-isoflurane to the most useful anesthetics (*R*)-desflurane,[18] the majority of the halogen atoms are less susceptible to nucleophilic substitution. We found that they are tolerated when the far more reactive dithiane moiety is present. We prepared the dithiane **3h** from 1-bromo-6-chlorohexane (**2h**), reacted it with BrF_3, and obtained the ethyl 2,2-difluoro-8-chlorooctanoate (**4h**) in 55% yield.

Ketones constitute another very common group in organic chemistry, and their presence is also well tolerated by BrF_3, especially when the much faster reaction with the soft basic sulfur atoms of the dithiane is in progress. However, since ketones are usually affected by strong bases, they have to be protected first in order to prepare the desired dithiane derivative. The reaction of 6-chloro-2-hexanone (**2i**) can serve as a typical example. It was converted to its ketal (**2j**) and treated with the anion of the dithiane (**1**) followed by BuLi and ethyl chloroformate, forming ethyl 7-diethyleneketal-2-dithiane octanoate (**3j**). At this point, strong bases were no longer needed and the ketal was removed with HCl. The resulted ketodithiane **3i** was reacted with BrF_3 to produce ethyl 2,2-difluoro-7-ketooctanoate **4i**[19] in 65% yield.

The difluoroester derivatives could eventually be hydrolyzed to the corresponding acids by refluxing with 5% KOH in $EtOH/H_2O$ for 1 h in nearly quantitative yields, as demonstrated for **4a** and **4e**, which were converted to **5a**[15] and **5e**.

In conclusion, we hope that this work, which opens a new route for synthesis of difluoroacids using BrF_3, will give one more reason not to shy away from this reagent when organic synthesis is involved.

Experimental Section

^1H NMR spectra were recorded using a 200-MHz spectrometer with $CDCl_3$ as a solvent and Me_4Si as an internal standard. Only the relevant and characteristic peaks are reported. The ^{19}F NMR spectra were measured at 188.1 MHz and are reported upfield from $CFCl_3$, serving as an internal standard. The proton broadband decoupled ^{13}C NMR spectra were recorded at 50.2 MHz. Here too, $CDCl_3$ served as a solvent and Me_4Si as an internal standard. IR spectra were recorded in $CHCl_3$ solution on a FTIR spectrophotometer. HRMS spectra were measured under CI conditions.

Preparing and Handling BrF_3. Although commercially available, we usually prepare our own BrF_3 by simply passing 0.58 mol of pure fluorine through 0.2 mol of bromine placed in a copper reactor and cooled to 0−10 °C. Under these conditions, the higher oxidation state, BrF_5, will not form in any appreciable amount.[20] The product 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 such as petrol ether cannot serve as solvents either since they also react fast with BrF_3. Any work using BrF_3 should be conducted in a well-ventilated area, and caution and common sense should be exercised. It is recommended that face shield and comfortable yet heavy-duty gloves should be worn when working with this reagent.*

General Procedure for Reaction of 2-alkyl-2-ethoxycarbonyl-1,3-dithiane with BrF_3. The 2-alkyl-2-ethoxycarbonyl-1,3-dithiane (usually 1 mmol) was dissolved in 10−15 mL of dry $CFCl_3$. About 3 mmol of BrF_3 was dissolved in 10 mL of the same solvent, and the resulting solution was cooled to 0 °C and added dropwise during 1−2 min to the dithiane derivative solution. While most reactions were performed under the above scale, this is by no means a necessary restriction. In some cases, we have scaled up the reaction by at least an order of magnitude without any appreciable reduction of the yield. This is reflected, for example, in the description of compound **4a**. Upon completion, the reaction was quenched with saturated aqueous Na_2SO_3 and the reaction mixture was washed until colorless. The aqueous layer was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$. Evaporation of the solvent followed by purification by flash chromatography gave the target difluoroesters.

Ethyl 2,2-difluorododecanoate (4a)[15] was prepared from **3a** (10 mmol) as described above, resulting in 75% yield of an oil. IR cm^{-1}: 1761. ^1H NMR: 4.32 (2 H, q, J = 7 Hz), 1.36 (3 H, t, J = 7 Hz), 0.89 ppm (3 H, t, J = 7 Hz). ^{19}F NMR: −106.4 ppm (t, J = 17 Hz). ^{13}C NMR: 164.4 (t, J = 33 Hz), 116.4 (t, J = 250

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Hz), 62.6, 33.4 (t, J = 23 Hz), 31.8, 29.5, 29.3, 29.2, 29.1, 29.0, 22.6, 21.3, 14.0, 13.9 ppm. HRMS (CI) (m/z): $(MH)^+$ calcd for $C_{14}H_{27}F_2O_2$, 265.1979; found, 265.1980. Anal. Calcd for $C_{14}H_{26}F_2O_2$: C, 63.61; H, 9.91; F, 14.37. Found: C, 63.44; H, 10.26; F, 13.95.

Ethyl 3-cyclohexyl-2,2-difluoropropanoate (4b) was prepared from **3b** as described above, resulting in 75% yield of an oil. IR cm^{-1}:1761. ^1H NMR: 4.32 (2 H, q, J = 7 Hz), 1.95 (2 H, td, J_1 = 17 Hz, J_2 = 6 Hz), 1.35 ppm (3 H, t, J = 7 Hz). ^{19}F NMR: −103.8 ppm (t, J = 17 Hz). ^{13}C NMR: 164.5 (t, J = 33 Hz), 116.4 (t, J = 250 Hz), 62.6, 41.4 (t, J = 22 Hz), 33.4, 31.8, 25.9, 13.8 ppm. HRMS (CI) (m/z): $(MH)^+$ calcd for $C_{11}H_{19}F_2O_2$, 221.1353; found, 221.1352. Anal. Calcd for $C_{11}H_{18}F_2O_2$: C, 59.98; H, 8.24; F, 17.25. Found: C, 59.67; H, 8.02; F, 18.00.

Ethyl 4-ethyl-2,2-difluorooctanoate (4c) was prepared from **3c** as described above, resulting in 75% yield of an oil. IR cm^{-1}: 1761. ^1H NMR: 4.31 (2 H, q, J = 7 Hz), 2.00 (2 H, td, J_1 = 18 Hz, J_2 = 6 Hz), 0.92−0.81 ppm (6 H, m). ^{19}F NMR: −104.2 ppm (td, J_1 = 18, J_2 = 4 Hz). ^{13}C NMR: 164.5 (t, J = 33 Hz), 116.7 (t, J = 250 Hz), 62.6, 37.8 (t, J = 22 Hz), 33.1, 32.9, 28.3, 26.1, 22.7, 13.9, 13.8, 10.1 ppm. HRMS (CI) (m/z): $(MH)^+$ calcd for $C_{12}H_{23}F_2O_2$, 237.1666; found, 237.1663. Anal. Calcd for $C_{12}H_{22}F_2O_2$: C, 60.99; H, 9.38; F, 16.08. Found: C, 61.29; H, 9.30; F, 16.59.

Ethyl 2,2-difluoro-5,9-dimethyldecanoate (4d) was prepared from **3d** as described above, resulting in 70% yield of an oil. IR cm^{-1}: 1763. ^1H NMR: 4.33 (2 H, q, J = 7 Hz), 2.21−1.90 (2 H, m), 1.12−0.85 ppm (9 H, m). ^{19}F NMR: −106.5 ppm (t, J = 16 Hz). ^{13}C NMR: 164.4 (t, J = 33 Hz), 116.5 (t, J = 250 Hz), 62.6, 39.1, 36.6, 32.2, 32.1 (t, J = 23 Hz), 28.0, 27.8, 24.5, 22.5, 19.2, 13.9 ppm. HRMS (CI) (m/z): $(MH)^+$ calcd for $C_{14}H_{27}F_2O_2$, 265.1979; found, 265.1979. Anal. Calcd for $C_{14}H_{26}F_2O_2$: C, 63.61; H, 9.91; F, 14.37. Found: C, 62.95; H, 9.73; F, 14.80.

Ethyl 2,2-difluoro-4-norbornanebutanoate (4e) was prepared from **3e** as described above, resulting in 75% yield of an oil. IR cm^{-1}: 1762. ^1H NMR: 4.32 (2 H, q, J = 7 Hz), 1.35 ppm (3 H, t, J = 7 Hz). ^{19}F NMR: −106.3 ppm (t, J = 17 Hz). ^{13}C NMR: 164.3 (t, J = 33 Hz), 116.3 (t, J = 250 Hz), 62.6, 41.6, 40.8, 37.8, 36.4, 35.1, 32.9 (t, J = 24 Hz), 29.9, 28.5, 28.0, 13.9 ppm. HRMS (CI) (m/z): $(MH)^+$ calcd for $C_{13}H_{21}F_2O_2$, 247.1509; found, 247.1512. Anal. Calcd for $C_{13}H_{20}F_2O_2$: C, 63.40; H, 8.18; F, 15.43. Found: C, 63.69; H, 8.30; F, 15.48.

Ethyl 2,2-difluoro-3-methylundecanoate (4f) was prepared from **3f** as described above, resulting in 70% yield of an oil. IR cm^{-1}: 1759. ^1H NMR: 4.32 (2 H, q, J = 7 Hz), 1.35 (3 H, t, J = 7 Hz), 1.02 (3 H, t, J = 7 Hz), 0.88 ppm (3 H, t, J = 7 Hz). ^{19}F NMR: −113.3 ppm (dd, J_1 = 40, J_2 = 15 Hz). ^{13}C NMR: 164.4 (t, J = 33 Hz), 117.8 (t, J = 250 Hz), 62.5, 37.7 (t, J = 22 Hz), 31.7, 29.5, 29.4, 29.3, 28.7, 22.5, 13.9, 13.2, 11.8 ppm. HRMS (CI) (m/z): $(MH)^+$ calcd for $C_{14}H_{27}F_2O_2$, 265.1979; found, 265.1983.

Ethyl 2,2-difluoro-3-methylbutanoate (4 g)[4] was prepared from **3g** as described above, resulting in 65% yield of an oil. IR cm^{-1}: 1760. ^1H NMR: 4.32 (2 H, q, J = 7 Hz), 2.36 (1 H, m), 1.35 (3 H, t, J = 7 Hz), 1.03 ppm (6 H, d, J = 7 Hz). ^{19}F NMR: −115.0 ppm (d, J = 15 Hz). ^{13}C NMR: 164.4 (t, J = 33 Hz), 117.7 (t, J = 250 Hz), 62.9, 33.0 (t, J = 23 Hz), 14.7, 14.0 ppm.

Ethyl 2,2-difluoro-8-chlorooctanoate (4h) was prepared from **3h** as described above, resulting in 55% yield of an oil. IR cm^{-1}: 1761. ^1H NMR: 4.31 (2 H, q, J = 7 Hz), 3.52 (2 H, t, J = 7 Hz), 2.05 (2 H, m), 1.77 (2 H, m), 1.44 (6 H, m), 1.34 ppm (3 H, t, J = 7 Hz). ^{19}F NMR: −106.4 ppm (t, J = 17 Hz). ^{13}C NMR: 164.3 (t, J = 34 Hz), 116.2 (t, J = 250 Hz), 62.7, 44.8, 34.2 (t, J = 24 Hz), 32.2, 28.2, 26.4, 21.2, 13.9 ppm. HRMS (CI) (m/z): $(MH)^+$ calcd for $C_{10}H_{17}ClF_2O_2$, 243.0963; found, 243.0963. Anal. Calcd for $C_{10}H_{17}ClF_2O_2$: C, 49.49; H, 7.06. Found: C, 50.04; H, 7.18.

Ethyl 2,2-difluoro-7-ketooctanoate (4i)[19] was prepared from **3i** as described above, resulting in 65% yield of an oil. HRMS (CI) (m/z): $(MH)^+$ calcd for $C_{10}H_{17}F_2O_3$, 223.1146; found, 223.1142. All other spectral data are in full agreement with the literature.

2,2-Difluorododecanoic acid (5a)[15] was obtained in almost quantitative yield by heating 150 mg of **4a** in refluxing 5% aqueous KOH (20 mL) and 2 mL of EtOH. After acidification, the aqueous layer was extracted with ether, dried over $MgSO_4$, and evaporated. The acid was purified by flash chromatography (Merck silica gel 60H) using petrol ether−ethyl acetate as eluent to yield an oil. IR cm^{-1}: 1757. ^1H NMR: 8.99 (1 H, br), 2.00 (2 H, m), 1.51 (2 H, m), 0.88 ppm (3 H, t, J = 7 Hz). ^{19}F NMR: −107.0 ppm (t, J = 17 Hz). ^{13}C NMR: 169.0 (t, J = 34 Hz), 116.0 (t, J = 250 Hz), 34.1 (t, J = 23 Hz), 32.0, 29.6, 29.4, 29.3, 29.2, 29.1, 29.0, 23.0, 21.0, 14.0 ppm. HRMS (CI) (m/z): $(MH)^+$ calcd for $C_{12}H_{23}F_2O_2$, 237.1661; found, 237.1666. Anal. Calcd for $C_{12}H_{22}F_2O_2$: C, 60.99; H, 9.38. Found: C, 61.39; H, 9.54.

2,2-Difluoro-4-norbornanebutanoic acid (5e) was prepared from **4e** as described above in the almost quantitative yield of an oil. IR cm^{-1}: 1758. ^1H NMR: 5.10 (1 H, br), 2.20−1.91 ppm (4 H, m). ^{19}F NMR: −107.0 ppm (t, J = 17 Hz). ^{13}C NMR: 167.0 (t, J = 33 Hz), 116.0 (t, J = 250 Hz), 41.6, 40.9, 37.8, 36.4, 35.1, 32.8 (t, J = 22 Hz), 29.9, 28.6, 28.0 ppm. HRMS (CI) (m/z): $(MH)^+$ calcd for $C_{11}H_{17}F_2O_2$, 219.1196; found, 219.1192.

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