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Constructing the CF_3 group; unique trifluorodecarboxylation induced by BrF_3

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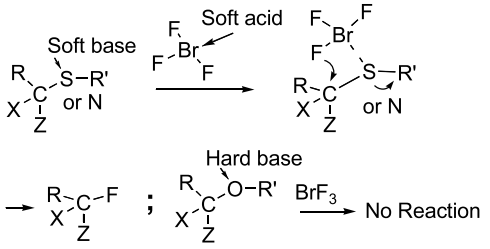
Abstract—A variety of 2-alkyl-1,3-dithiane-2-carboxylic acids was prepared from the appropriate alkyl halides, 1,3-dithiane and CO_2. These acids were reacted with BrF_3 to form the trifluoromethylalkyl derivatives via a combination of ionic and radical trifluorodecarboxylation in about 50–60% yield.

1. Introduction

The trifluoromethyl group has a great impact on a wide range of man-made chemicals such as dyes, polymers, agrochemicals, pharmaceuticals. Incorporating this group into a molecule can often modify the biological activity and physiological properties. These modifications are associated with increased stability and lipophilicity, while the steric distortion, compared to the parent compound, is relatively small. Quite a few methods for trifluoromethylation have been developed using trifluoromethyl trimethylsilane (Ruppert's reagent-CF_3SiMe_3),[1] fluoroform or trifluoromethyl halides,[2] (trifluoromethyl) dibenzothiophenium triflate salt,[3] and more.[4]

In recent years, we and others have devised several methods for incorporating fluorine atom(s) into organic molecules by employing bromine trifluoride. The synthesis of α-trifluoromethyl carboxylic acids,[5] transformation of carbonyls to the CF_2 group,[6] forming alkyltrifluoromethyl ethers,[7] synthesizing modern anaesthetics[8] and converting RX to $RCHF_2$ derivatives,[9] are only a few examples. These works have already established the conditions for selective reactions of BrF_3 with organic substrates. Such substrates should possess soft bases such as nitrogen or sulfur atoms, in order to complex the soft acidic bromine in BrF_3 and place the naked nucleophilic fluorides close to the electrophilic carbon positioned α to the heteroatom (Scheme 1).

The Hunsdiecker reaction is one of the oldest and most well known reactions in organic chemistry dealing with halodecarboxylation of carboxylic acids. Chlorine, bromine or iodine are brought in contact with the acids' salt (usually silver) forming the corresponding alkyl halides.[10] Fluorine, however, was conspicuously missing from this list of halogens. Fluorodecarboxylation reactions are very rare and the few described required xenon difluoride. These reactions proceeded through the RCOOXeF intermediate characterized by the very weak bonds around the Xe atom.[11] We now report a new method for transforming alkyl halides to the trifluoromethyl moiety via a crucial Hunsdiecker-like trifluorodecarboxylation, using BrF_3.



Scheme 1. General mechanism for selective reactions with BrF_3.

2. Results and discussion

Following a known procedure,[12] the lithium salt of dithiane (**1**) was reacted with decyl bromide (**2a**) followed by reaction with carbon dioxide to produce 2-decyl-1,3-dithiane-2-carboxylic acid (**3a**). Reacting **3a** with BrF_3 resulted in a fast trifluorodecarboxylation producing 1,1,1-trifluoroundecane (**4a**)[13] in 60% yield (Scheme 2). The reaction with the disubstituted 1,10-dibromodecane (**2b**)

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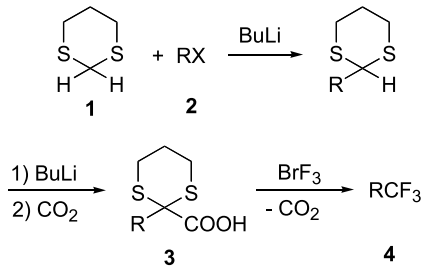


	X	2	3	4 (%)*
a	Br	R = $CH_3(CH_2)_9$		(60 %)#
b	Br	R = $Br(CH_2)_{10}$	R = HOOC $(CH_2)_{10}$	R = $CF_3(CH_2)_{10}$ (40 %)
c	Cl	R = $(CH_2)_3$		(60 %)
d	Br	R = $(CH_2)_2$		(60 %)
e	Br	R = C_6H_{13}, CH_3		(35 %)#
f	Cl	R = $Cl(CH_2)_{10}$		(55 %)#
g	Cl	R = $HO(CH_2)_8$		
h	Cl	R = $THPO(CH_2)_8$	R = $THPO(CH_2)_8$	
i			AcCl/AcOH → R = $AcO(CH_2)_8$	R = $AcO(CH_2)_8$ (50 %)

Scheme 2. Formation of trifluoromethyl derivatives. (*) Yield of the trifluorodecarboxylation step; (#) these compounds could not be fully analyzed by conventional MS (no molecular ion could be detected). However, we have successfully used the Amirav's supersonic GC–MS developed in our department. The main feature of this method is to provide electron ionization while the sample is vibrationally cooled in a supersonic molecular beam. This considerably enhances the relative abundance of molecular ions.[20]

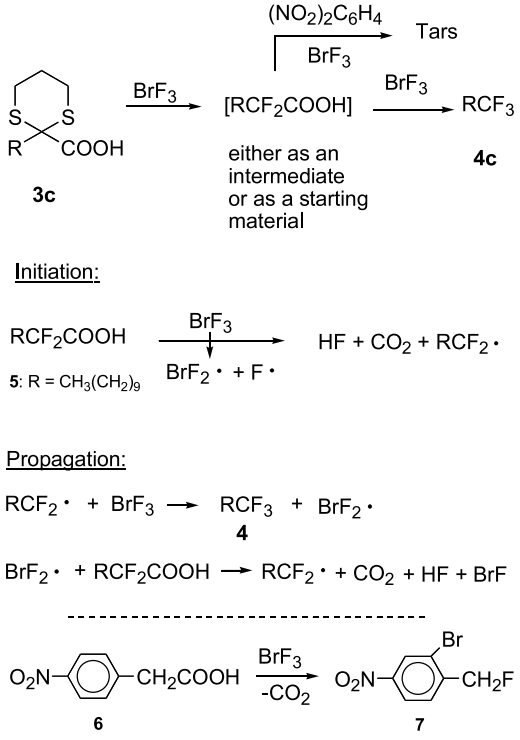
also proceeded as expected and 1,1,1,12,12,12-hexafluorododecane (**4b**)[14] was obtained in 40% yield.

While the fluorine atoms in BrF_3 can act in some cases as electrophiles,[15] substituting tertiary hydrogens in a similar way to F_2,[16] the reaction with the dithiane moiety seems to be much faster. Thus, 2-(3-cyclohexylpropyl)-1,3-dithiane-2-carboxylic acid (**3c**) and 2-(2-norbonylethyl)-1,3-dithiane-2-carboxylic acid (**3d**), made correspondingly from 1-chloro-3-cyclohexylpropane (**2c**) and 1-bromo-2-(2-norbornyl)ethane (**2d**), were reacted with BrF_3 forming the by now expected 4-cyclohexyl-1,1,1-trifluorobutane (**4c**)[17] and 2-(3,3,3-trifluoropropyl)norbornane (**4d**)[13] in 50 and 55% yields, respectively.

In many cases the chemistry of a functional group attached to a primary carbon differs from the chemistry of the same group bonded to a secondary site. The present chemistry, however, is applicable for both primary and secondary carbons. Thus, 2-bromooctane (**2e**) was eventually converted to 1,1,1-trifluoro-2-methyloctane (**4e**) although in a somewhat lower yield of 35%.

Bromine trifluoride is known to substitute chlorine atoms for fluorine ones as demonstrated in the syntheses of modern anaesthetics such as sevoflurane.[18] Here again, the reaction with the dithiane moiety is much faster, and hence chlorine atoms can be tolerated in this reaction. 1,10-Dichlorodecane (**2f**) was easily converted to 2-(10-chlorodecyl)-1,3-dithiane-2-carboxylic acid (**3f**) and when reacted with BrF_3, the previously unknown 11-chloro-1,1,1-trifluoroundecane (**4f**) was obtained in 55% yield. Despite the fact that alcohols are easily oxidized by BrF_3 to acyl fluorides,[19] the presence of an hydroxyl group in a molecule is not a reason for excluding it from the list of materials which can participate in this reaction. Protecting the hydroxyl group of 1-chloro-8-hydroxyoctane (**2g**) as a tetrahydropyranyl (THP) (**2h**) enabled the clean formation of **3h** under the strong basic conditions characteristic to BuLi. The protecting THP was then replaced by acetyl to form 2-(8-acetoxyoctyl)-1,3-dithiane-2-carboxylic acid (**3i**) suitable for the fast reaction with BrF_3 forming eventually 9,9,9-trifluorononyl acetate (**4i**) in 50% yield.

We believe that the first step of the reaction is ionic in nature. First, the sulfur atoms serve as a coordinating site for the BrF_3 and when the complexation is completed these atoms are substituted by the nucleophilic fluorides which by now are in suitable close proximity.[9,21] As a result of this substitution, however, BrF_3 can no longer complex itself around any particular site of the reactant. Consequently, radical reactions, which are always option for this reagent, become dominant and a process with a chain radical decarboxylation (Scheme 3) takes place. Indeed, when the



Scheme 3. Radical chain trifluorodecarboxylation.

reaction of **3c** with bromine trifluoride was carried under either oxygen-rich atmosphere or in the presence of dinitrobenzene, the radical chain process was interrupted and the yields of **4c** dropped to 15 and 0%, respectively. Additional support for this mechanism was found in reactions with α,α-difluoro acids. Thus, for example, α,α-difluorododecanoic acid (**5**) was reacted with BrF_3 resulting in a fast fluorodecarboxylation forming 1,1,1-trifluoroundecane (**4a**) in 60% yield. For comparison, no such reaction takes place with the corresponding dodecanoic acid itself. The fluorodecarboxylation can be explained by pointing out that the difluoromethylene radical is more stable than the methylene counterpart and better sustains a chain reaction with BrF_3 to form the CF_3 group. This hypothesis was also confirmed by reacting BrF_3 with 4-nitrophenylacetic acid (**6**). Since the benzylic radical is relatively stable, fluorodecarboxylation occurs producing 2-bromo-4-nitrobenzylfluoride (**7**) in 50% yield. The ring bromination is unavoidable as BrF_3 is a very powerful brominating agent.[22]

In conclusion, this paper widens the scope of reactions with bromine trifluoride, especially when the construction of the important trifluoromethyl group is concerned. We hope that this work will be an additional step in demonstrating that BrF_3, like F_2 some years ago, can and should be used, as a powerful fluorinating agent in organic chemistry.

3. Experimental

^1H and ^{13}C NMR were obtained at 200 and 50.2 MHz, respectively, with $CDCl_3$ as solvent and Me_4Si as an internal standard. The ^{19}F NMR spectra were measured at 188.1 MHz and are reported upfield from $CFCl_3$, serving as an internal standard. IR spectra were recorded in $CHCl_3$ solution on a FTIR spectrophotometer. HRMS spectra were measured under CI conditions. In extreme cases where the CI method could not detect the molecular ion, we have successfully used the Amirav's supersonic GC–MS developed in our department. The main feature of this method is to provide electron ionization while the sample is vibrationally cooled in a supersonic molecular beam. This considerably enhances the relative abundance of molecular ions.[20]

3.1. Preparing and handling BrF_3

Although commercially available, we usually prepare our own BrF_3 by simply passing 0.6 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. The product can be stored in Teflon containers indefinitely. *Caution*: BrF_3 is a strong oxidizer and tends to react exothermically with water and oxygenated organic solvents such as acetone or THF. Any work using BrF_3 should be conducted in a well-ventilated area, and caution and common sense should be exercised.

3.2. General procedure for preparing 2-alkyl-1,3-dithiane-2-carboxylic acid derivatives.[12]

To a cold (−45 °C) THF solution of 10 mmol of 2-alkyl-1,3-dithiane was added 10.5 mmol of *n*-butyllithium (1.6 M in *n*-hexane) under nitrogen. The mixture was stirred for 1.5 h and poured on to freshly chopped dry ice. After stirring for another hour at room temperature, 10% NaOH was added. The organic layer was extracted twice with the NaOH solution and the combined alkaline layers were acidified with concentrated HCl. The aqueous layer was extracted three times with ether and the organic layer was dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash chromatography (using petroleum ether/ethyl acetate as eluent) or recrystallization. The main characteristic features are as follows: ^1H NMR: 3.3 (2H, td, $J_1=13$ Hz, $J_2=2.5$ Hz), 2.7 ppm (2H, dt, $J_1=13$ Hz, $J_2=3.5$ Hz); ^{13}C NMR: 177.0, 52.9 ppm; IR: 1697 cm^{-1}.

3.3. General procedure for reaction of 2-alkyl-1,3-dithiane-2-carboxylic acid derivatives with BrF_3

The 2-alkyl-1,3-dithiane-2-carboxylic acid (usually 2 mmol) was dissolved in 10–15 mL of $CFCl_3$. About 6 mmol of BrF_3 was dissolved in 10 mL the same solvent, and the resulting solution was cooled to 0 °C and added dropwise during 1–2 min to the dithiane derivative solution. The reaction mixture was quenched with aqueous $Na_2S_2O_3$ till colorless. The aqueous layer was extracted twice with CH_2Cl_2 and the organic layer was dried over $MgSO_4$. Evaporation of the solvent followed by purification by flash chromatography (using petroleum ether as eluent) gave the target trifluoromethyl derivatives.

3.3.1. 1,1,1-Trifluoroundecane.[13] (4a) Compound was prepared from **3a** as described above, resulting in 60% yield of an oil. ^1H NMR: 2.06–2.00 (2H, m), 1.59–1.51 (2H, m), 1.27 (14H, br s), 0.89 ppm (3H, t, $J=6.8$ Hz). ^{13}C NMR: 127.2 (q, $J=276$ Hz), 33.6 (q, $J=28$ Hz), 31.8, 29.4, 29.3, 29.2, 29.1, 28.6, 22.6, 21.8, 14.0 ppm. ^{19}F NMR: −67.0 ppm (t, $J=11$ Hz). MS (supersonic molecular beam): m/z 210 $(M)^+$.

3.3.2. 1,1,1,12,12,12-Hexafluorododecane.[14] (4b) Compound was prepared from **3b** as described above, resulting in 40% yield of an oil. ^1H NMR: 2.2–2.0 (4H, m), 1.62–1.51 (4H, m), 1.4–1.3 ppm (12H, br s). ^{13}C NMR: 127.3 (q, $J=276$ Hz), 33.7 (q, $J=28$ Hz), 29.2, 29.1, 28.7, 21.8 ppm. ^{19}F NMR: −66.9 ppm (t, $J=11$ Hz).

3.3.3. 4-Cyclohexyl-1,1,1-trifluorobutane.[17] (4c) Compound was prepared from **3c** as described above, resulting in 55% yield of an oil. ^1H NMR: 2.06–2.00 (2H, m), 1.71–1.68 (6H, m), 1.55 (2H, m), 1.27–1.25 ppm (7H, m). ^{13}C NMR: 127.3 (q, $J=276$ Hz), 37.8, 36.4, 34.0 (q, $J=28$ Hz), 31.1, 26.6, 26.3 ppm. ^{19}F NMR: −66.9 ppm (t, $J=11$ Hz).

3.3.4. 2-(3,3,3-Trifluoropropyl)norbornane.[13] (4d) Compound was prepared from **3d** as described above, resulting in 55% yield of an oil. ^1H NMR: 2.22 (1H, br s), 2.06–2.00 (2H, m), 1.96 (1H, br s), 1.53–1.26 (7H, m) 1.15–1.00 ppm (4H, m). ^{13}C NMR: 127.3 (q, $J=276$ Hz), 41.7, 40.8, 37.8, 36.4, 35.1, 32.2 (q, $J=28$ Hz), 29.9, 29.6, 28.5 ppm. ^{19}F NMR: −66.8 ppm (t, $J=11$ Hz).

3.3.5. 1,1,1-Trifluoro-2-methyloctane (4e). Compound

was prepared from **3e** as described above, resulting in 35% yield of an oil. ^{1}H NMR: 2.0–2.2 (1H, m), 1.8–1.6 (2H, m), 1.3 ppm (8H, br s), 1.05 (3H, d, $J=7$ Hz), 0.89 ppm (3H, t, $J=7$ Hz). ^{13}C NMR: 128.3 (q, $J=279$ Hz), 37.6 (q, $J=26$ Hz), 31.6, 29.4, 28.7, 26.5, 22.3, 13.8 ppm. ^{19}F NMR: -73.8 ppm (d, $J=9$ Hz). MS: *m/z* 182 $(M)^+$, 162 $(M-HF)^+$, 142 $(M-2\,HF)^+$, 113 $(M-CF_3)^+$.

3.3.6. 11-Chloro-1,1,1-trifluoroundecane (4f). Compound was prepared from **3f** as described above, resulting in 55% yield of an oil. ^{1}H NMR: 3.53 (2H, t, $J=6.7$ Hz), 2.06–2.00 (2H, m), 1.77 (4H, quin, $J=6.7$ Hz), 1.30 ppm (12H, br s). ^{13}C NMR: 127.3 (q, $J=276$ Hz), 45.1, 33.7 (q, $J=28$ Hz), 32.6, 29.3, 29.2, 29.1, 28.8, 28.7, 26.7, 22.7 ppm. ^{19}F NMR: -66.9 ppm (t, $J=11$ Hz). MS (supersonic molecular beam): *m/z* 244 $(M)^+$. Anal. Calcd for $C_{11}H_{20}ClF_3$: C, 53.99; H, 8.24; Cl, 14.49. Found: C, 54.59; H, 8.45; Cl, 14.30.

3.3.7. 9,9,9-Trifluorononyl acetate (4i). Compound was prepared from **3i** as described above, resulting in 50% yield of an oil. ^{1}H NMR: 4.04 (2 H, t, $J=6.7$ Hz), 2.03 (3 H, s), 2.07–2.00 (2 H, m), 1.60–1.46 (4H, m), 1.32 ppm (8H, br s). ^{13}C NMR: 171.1, 127.2 (q, $J=276$ Hz), 64.4, 33.6 (q, $J=28$ Hz), 28.9, 28.8, 28.5, 28.4, 25.7, 21.7, 20.8 ppm. ^{19}F NMR: -67.0 ppm (t, $J=11$ Hz). IR: 1720 cm^{-1}. HRMS (CI) (*m/z*): $(MH)^+$ calcd for $C_{11}H_{19}F_3O_2$, 241.1425; found, 241.1454. Anal. Calcd for $C_{11}H_{19}F_3O_2$: C, 54.99; H, 7.97. Found: C, 54.98; H, 8.08.

3.3.8. 2-Bromo-4-nitrobenzylfluoride (7). About 18 mmol of BrF_3 was dissolved in 25 mL of $CFCl_3$, and the resulting solution was cooled to 0 °C and added dropwise during 1–2 min to a solution of 4-nitrophenylacetic acid (**6**) (10 mmol) in 40 mL of $CFCl_3$. The reaction mixture was quenched with aqueous $Na_2S_2O_3$ till colorless. The aqueous layer was extracted twice with CH_2Cl_2 and the organic layer was dried over $MgSO_4$. Evaporation of the solvent followed by purification by flash chromatography (using petroleum ether/ethyl acetate as eluent) gave **7** in 50% yield. ^{1}H NMR: 8.42 (1 H, d, $J=2$ Hz), 8.24 (1 H, dd, $J=8.5$, 2 Hz), 7.67 (1 H, d, $J=8.5$ Hz) 5.53 (2H, d, $J=47$ Hz). ^{13}C NMR: 148.0, 143.1 (d, $J=18$ Hz), 127.6 (d, $J=11$ Hz), 127.5, 122.5, 120.3 (d, $J=6$ Hz) 82.7 (d, $J=174$ Hz) ppm. ^{19}F NMR: -222.4 ppm (t, $J=46$ Hz). HRMS (CI) (*m/z*): $(MH)^+$ calcd for $C_7H_5BrFNO_2$, 233.9559; found, 233.9566. Anal. Calcd for $C_7H_5BrFNO_2$: C, 35.93; H, 2.15; F, 8.12; Br, 34.14; N, 5.99. Found: C, 35.55; H, 2.05; F, 7.67; Br, 34.21; N, 5.68.

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