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Novel Method for Incorporating the CHF_2 Group into Organic Molecules Using BrF_3

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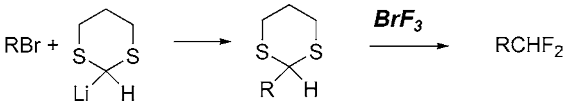
ABSTRACT



2-Alkyl-1,3-dithiane derivatives, easily made from alkyl bromides and the parent 1,3-dithiane, were reacted with BrF_3 to form the corresponding 1,1-difluoromethyl alkanes ($RCHF_2$) in 60–75% yield. The reaction proceeds well with primary alkyl halides. The limiting step for secondary alkyl halides is the relatively low yield of the dithiane preparation. The two sulfur atoms of the dithiane are essential for the reaction.

The difluoromethyl group, CHF_2, often contributes special biological properties to organic molecules. Apart from its high lipophilicity similar to the CF_3 group, CHF_2 is able to act as a hydrogen donor through hydrogen bonding[1] and is actively pursued for enhancing biological activities.[2] CHF_2 has been used in sugar chemistry,[3] incorporated into amino acids as enzyme inhibitors,[4] and plays an important role in the field of herbicides,[5] liquid crystals,[6] and most importantly in many modern anesthetics such as desflurane and isoflurane.[7]

Until today, the most common route for constructing the CHF_2 moiety was the reaction of aldehydes with SF_4 and DAST,[8] although SeF_4[9] was also used. Other methods employed the reaction of *gem*-bistriflate, also an aldehyde derivative, with Bu_4NF[10] and the addition of CBr_2F_2 to double bonds.[11] Some years ago, we developed efficient ways for replacing ketones and even carboxylic acid carbonyls with the CF_2 group via the reactions of IF and BrF with an array of hydrazone derivatives[12] or thioesters.[13] The only type of carbonyls that failed to react cleanly was aldehydes, where the formation of the CHF_2 group proceeded with very low yields, the balance consisting of various tars. Recently, we tried to prepare this moiety from tris(methylthio)alkyl derivatives, but once again the yields were poor.[14] After further studies, however, we report now a novel and simple method for the successful construction of this group, starting from alkyl halides, which are more readily available than aldehydes, especially in the field of the nonaromatic chemistry.

More than 15 years ago, Katzenellenbogen had shown that carbonyls, via their 1,3-dithiolanes, can react with the combination of R_2NBr and HF (the so-called [BrF] reagent) to form the corresponding CF_2 derivatives.[15] We decided to examine the reaction of the more versatile dithianes with BrF_3.

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[1] Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626.

[2] Pu, Y. M.; Torok, D. S.; Ziffer, H.; Pan, X. Q.; Meshnick, S. R. *J. Med. Chem.* **1995**, *38*, 4120.

[3] Houlton, S. J.; Motherwell, W. B.; Ross, B. C.; Tozer, M. J.; Williams, D. J.; Slawin, A. M. Z. *Tetrahedron* **1993**, *49*, 8087. Kaneko, S.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1993**, *58*, 2302.

[4] d'Orchymont, H. *Synthesis* **1993**, 961.

[5] Goure, W. F.; Leschinsky, K. L.; Wratten, S. J.; Chupp, J. P. *J. Agric. Food Chem.* **1991**, *39*, 981.

[6] Kitazume, T.; Ohnogi, T.; Ito, K. *J. Am. Chem. Soc.* **1990**, *112*, 6608.

[7] Rozov, L. A.; Huang, C.; Halpern, D. F.; Vernice, G. G. U.S. Patent 5,283,372, 1994. Halpern, D. F.; Robin, M. L. U.S. Patent 4,996,371, 1991.

[8] Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

[9] Olah, G. A.; Nojima, M.; Kerekes, I. *J. Am. Chem. Soc.* **1974**, *96*, 925.

[10] Martinez, G. A.; Barcina, O. J.; Rys, A. Z.; Subramanian, L. R. *Tetrahedron Lett.* **1992**, *33*, 7787.

[11] Gonzales, J.; Foti, C. J.; Elsheimer, S. *J. Org. Chem.* **1991**, *56*, 4322.

[12] Rozen, S.; Brand, M.; Zamir, D.; Hebel, D. *J. Am. Chem. Soc.* **1987**, *109*, 896.

[13] Rozen, S.; Mishani, E. *J. Chem. Soc., Chem. Commun.* **1993**, 1761.

[14] Hagooly, A.; Ben-David, I.; Rozen, S. *J. Org. Chem.* **2002**, *67*, 8430.

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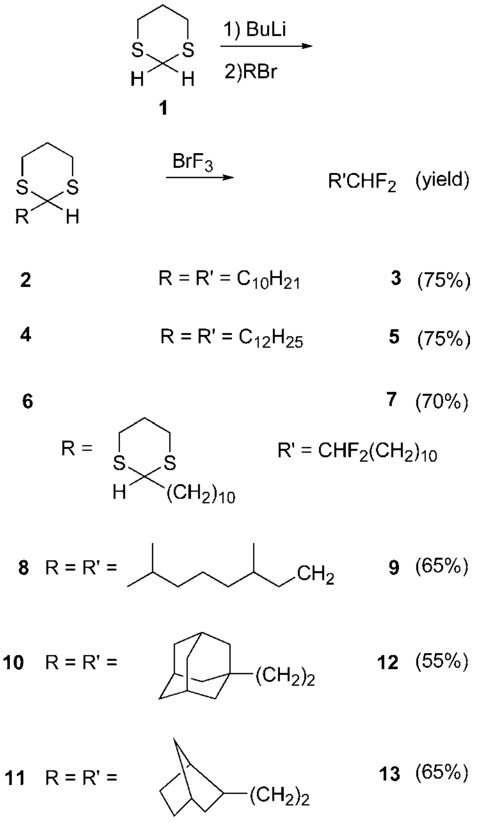
Recently, we started to experiment with bromine trifluoride, a reagent known for a long time and yet practically ignored by organic chemists. This "ban" was a result of bromine trifluoride's violent reactivity toward many organic solvents such as hexane, acetone, ethers, and the like. The fact that it could be safely employed in solvents such as $CHCl_3$, $CFCl_3$, and CCl_4 was overlooked. We have shown, however, that this reagent can be of help in many organic transformations such as difficult bromination of deactivated aromatic rings,[16] transformations of carbonyls to the CF_2 group[17] and of nitriles to the corresponding CF_3 compounds,[18] oxidation of alcohols to acyl fluorides,[19] synthesis of trifluoromethyl ethers,[20] construction of trifluoromethyl alkanes,[14] and more.[21] Most of the above transformations were made possible because of the tendency of the electrophilic bromine in BrF_3 to complex itself around basic heteroatoms, especially sulfur. Such complexation brings the naked and efficient nucleophilic fluorides near the potential reaction center and reduces the prospects of undiscriminating radical brominations and fluorinations.

Cyclic 1,3-dithiane (**1**) is available either commercially or through a simple synthesis. Its lithium salt is also readily accessible and reacts with alkyl halides to form the corresponding 2-alkyl-1,3-dithianes.[22]

When 2-decane-1,3-dithiane (**2**) was reacted for 1−2 min under mild conditions with BrF_3,[23] we were able to isolate the yet unknown 1,1-difluoroundecane (**3**) in 75% yield.[24] Similarly, dodecyl bromide, through its dithiane derivative **4**, was converted to 1,1-difluorotridecane (**5**).[10] Bis-dithiane derivatives also work as demonstrated by the bis-dithiane of 1,10-dibromodecane **6**, which was converted in good yield to the previously unknown 1,1,12,12-tetrafluorododecane (**7**).

The fluorine atoms in bromine trifluoride can in certain cases act as electrophiles[25] and substitute tertiary hydrogens similarly to F_2.[26] It was of interest to see if such processes take place during the reactions with dithianes when tertiary centers are present. We found that the reaction around the sulfur atoms is by far the dominant one. No tertiary fluorination was observed with the dithiane of 2,6-dimethyloctane (**8**), which behaved as expected to produce the 1,1-difluoro-4,8-dimethylnonane (**9**). The polycyclic core of compounds such as 1-ethyladamantane and 1-ethylnorbornane had been unintentionally fluorinated in the past with BrF_3. Their corresponding dithianes **10** and **11**, however, react satisfactorily to form the corresponding difluoromethyl derivatives **12** and **13** in 55 and 65% yields, respectively.



Placing the CHF_2 group on a secondary site is somewhat more problematic. The limiting factor of the whole reaction in these cases is the construction of the appropriate dithiane since the basic lithium derivative of **1** may induce an elimination of the secondary bromine. The best procedure found in the literature for making such dithianes consists of coupling the Grignard derivative of the secondary alkyl halide

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(15) Sondej, S. C.; Katzenellenbogen, J. A. *J. Org. Chem.* **1986**, *51*, 3508.

(16) Rozen, S.; Lerman, O. *J. Org. Chem.* **1993**, *58*, 239.

(17) Rozen, S.; Mishani, E.; Bar- Haim, A. *J. Org. Chem.* **1994**, *59*, 2918.

(18) Rozen, S.; Rechavi, D.; Hagooly, A. *J. Fluorine Chem.* **2001**, *111*, 161.

(19) Rozen, S.; Ben-David, I. *J. Fluorine Chem.* **1996**, *76*, 145.

(20) Ben-David, I.; Rechavi, D.; Mishani, E.; Rozen, S. *J. Fluorine Chem.* **1999**, *97*, 75.

(21) Rozen, S.; Ben-David, I. *J. Org. Chem.* **2001**, *66*, 496.

(22) For the general procedure for preparing the 2-alkyl-1,3-dithiane derivatives, see: Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.

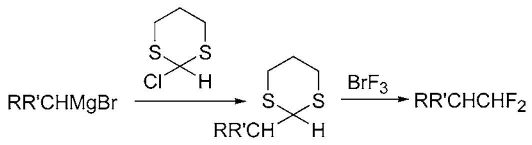
(23) **Preparation and Handling of BrF_3.** Although commercially available, we prepare our own BrF_3 by simply passing 0.58 mol of pure fluorine through 0.2 mol of bromine placed in a copper reactor and cooled to 0−10 °C. At this temperature, the higher oxidation state, BrF_5, will not form in any appreciable amount (Stein, L. *J. Am. Chem. Soc.* **1959**, *81*, 1269); however, we always use a small excess of bromine, thereby keeping the reagent from disproportionation to BrF_5. 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. Work using BrF_3 should be conducted in a well ventilated area, and caution and common sense should be exercised.* **General Procedure for Reaction of 2-Alkyl-1,3-dithianes with BrF_3.** The 2-alkyl-1,3-dithianes (1 mmol) were dissolved in 10−15 mL of dry $CFCl_3$. About three mmols of BrF_3 were dissolved in the same solvent, cooled to 0 °C and added dropwise to the solutions of dithianes. The reaction mixture was then washed with saturated aqueous $Na_2S_2O_3$ until colorless. The aqueous layer was extracted with CH_2Cl_2 and the organic layer dried over $MgSO_4$. Evaporation of the solvent followed by purification by flash chromatography gave the target difluoro products.

(24) The spectral properties of the known and referenced products are in full agreement with the properties described in the literature. Those properties, as well as the microanalysis of all new difluoromethyl products (oils) presented in this work, are in excellent agreement with their structures. The main characteristic features of **3**, **7**, **9**, **12**, and **13** are as follows: ^1H NMR δ 5.78−5.81 ppm (1 H, tt, $J_1 = 57$ Hz, $J_2 = 5$ Hz), ^{19}F NMR: −116 ppm (dt, $J_1 = 57$ Hz, $J_2 = 17$ Hz); ^{13}C NMR δ 117−118 (t, $J = 239$ Hz), 32−34 ppm (t, $J = 20$ Hz). **17**: ^1H NMR 5.6 ppm (1 H, td, $J_1 = 57$ Hz, $J_2 = 4$ Hz); ^{19}F NMR δ −125 (1 F, ddd, $J_1 = 275$ Hz, $J_2 = 57$ Hz, $J_3 = 17$ Hz), −122.6 ppm (1 F, ddd, $J_1 = 275$ Hz, $J_2 = 57$ Hz, $J_3 = 13$ Hz); ^{13}C NMR δ 119.4 (t, $J = 242$ Hz), 37.2 (t, $J = 19$ Hz), 29.7 (t, $J = 4$ Hz), 12.1 ppm (t, $J = 5$ Hz).

(25) Boguslavskaya, L. S.; Kartashov, A. V.; Chuvatkin, N. N. *Zh. Org Khim.* (English translation) **1989**, *25*, 1835.

(26) Rozen, S.; Gal, C. *J. Org. Chem.* **1987**, *52*, 2769. Rozen, S.; Gal, C. *J. Org. Chem.* **1987**, *52*, 4928.

with 2-chloro-1,3-dithiane. The yields of such reactions rarely exeed 50%,[27] but once the product is obtained, the reaction with BrF_3 proceeds as expected. We have prepared 2-cyclohexane-1,3-dithiane (**14**) and eventually obtained the target molecule of difluoromethylcyclohexane (**15**)[10] in 70% yield. Similarly, the dithiane derived from 2-bromooctane (**16**) was reacted to produce 1,1-difluoro-2-methyloctane (**17**) in 60% yield.

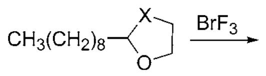


14 **15** 70%

R + R' = $-(CH_2)_5-$

16 **17** 60%

R = $CH_3(CH_2)_5$; R' = Me



18 X = O $\Rightarrow$ tars

19 X = S $\Rightarrow$ $CH_3(CH_2)_8CHO$

As with all successful BrF_3 reactions, the presence of the heteroatom anchor is essential. Since the bromine atom in BrF_3 is a soft acid, it complexes itself best with soft bases such as sulfur atoms. Indeed, when we reacted the acetal of decanal **18** with BrF_3, no substantial complexation took place between the soft bromine and the hard oxygen atoms resulting in radical reactions leading to bromine and fluorine containing tars. Repeating the reaction with the corresponding oxothioacetal **19** resulted mainly in the formation of decanal since the BrF_3 could in this case attach itself to the sulfur atom enabling nucleophilic replacement of the sulfur atom with oxygen.

It should be noted that the main limitation of using bromine trifluoride for the construction of the difluoromethyl group is the presence of an aromatic ring that usually is susceptible to attacks from the electrophilic bromine of the reagent.

In conclusion, we hope that this work is an additional step along the road toward establishing BrF_3 as a “legitimate” reagent for organic chemistry. About 20 years ago, F_2 was also considered a reagent to avoid in organic chemistry, but today numerous laboratories use it routinely. The present use of BrF_3, converting alkyl halides into difluoromethyl derivatives, may be one more step toward this goal.

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Supporting Information Available: Complete ^{1}H NMR, ^{13}C NMR, IR and microanalysis data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[27] Kruse, C. G.; Wijsman, A.; van der Gen, A. *J. Org. Chem.* **1979**, *44*, 1847.