Conversion of Esters to α,α-Difluoro Ethers using Bromine Trifluoride

Shlomo Rozen* and Eyal Mishani

School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel-Aviv University, Tel-Aviv 69978, Israel

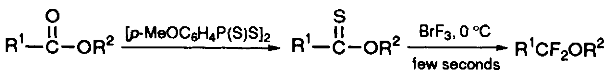
Bromine trifluoride reacts rapidly with *O*-substituted thioesters to form α,α-difluoro ethers, a family of almost unknown compounds.

Bromine trifluoride is a commercial reagent, but can also be easily prepared from the elements by placing Br_2 (20 ml, 0.37 mol) in a brass container equipped with two tubes, one of which dips into the bromine and the other is an outlet leading to a soda lime trap. With the reactor temperature maintained between 0 and 10 °C, fluorine gas (3 equiv., 1.11 mol) is slowly bubbled through the bromine for about 4 h. The yellow-brown liquid BrF_3 (obtained in >90% yield) can be stored indefinitely in a well closed Teflon container.† Despite its availability, however, most organic chemists have shied away from it, recalling the attitude towards elemental fluorine 15 years ago. The few reactions published involve oxidative fluorination of heteroatoms,[1] and substituting certain eliphatic halogens and tertiary hydrogens with fluorine.[2] We report here a new, general, efficient and fast reaction of BrF_3 leading to rare α,α-difluoro ethers, a moiety mentioned only twice before in the chemical literature.[3]

Most of the 'carbonyl to CF_2' transformations performed with halogen fluorides use hydrazone[4] and dithiolane[5] derivatives, since nitrogen and sulfur atoms serve as better centres for complexation to various reagents. The ester carbonyl cannot be easily transformed into such derivatives so we turned our attention to *O*-substituted thioesters which are readily prepared in 80–90% yield with Lawesson's reagent[6] and should be attacked by the nucleophilic fluorine atoms of the BrF_3.

A cold $CFCl_3$ (0 °C; 25 ml) solution of BrF_3 (10 mmol) was added to *O*-methyl adamantane-1-carbothioate **1** (10 mmol) also dissolved in the same cold solvent (15 ml) during *ca.* 10 min. The reaction is instantaneous, as can be judged from the immediate disappearance of the reagent. After the addition was complete the mixture was quickly neutralized with aqueous hydrogen sulfite and hydrogen carbonate. 1-Adamantyldifluoromethyl methyl ether **2**[3a] was distilled at 65 °C (1.5 mmHg) and obtained in 95% yield. The difluoro ethers are not very stable and we were unable to purify the products by chromatography, since they were slowly hydrolysed or eliminated HF with an autocatalytic effect encouraging further HF elimination. Eventually the difluoro ethers were purified by distillation, usually from traces of quinoline to absorb and stop the HF elimination.

We tested the generality of the reaction with straight-chain, alicyclic and aromatic esters. Thus, *O*-ethyl octathioate **3** formed in 70% yield the expected 1,1-difluorooctyl ethyl ether **4** b.p. 50 °C (25 mmHg), while the *O*-ethyl 4-methylcyclohexanecarbothioate **5** produced the ether **6** in 90% yield, b.p. 60 °C (22 mmHg). The fast reaction between the thiocarbonyl and BrF_3 is demonstrated in the case of *O*-methyl thiobenzoate **7** which produced α,α-difluorobenzyl methyl ether **8**[3a] in 70% yield with no appreciable bromination of the aromatic ring.[7] The reaction of **7** with BrF made either directly from the corresponding elements[8] or from BrF_3 and Br_2 resulted only in an intractable mixture which contained several bromo-



$$R^1-\overset{\overset{O}{\|}}{C}-OR^2 \xrightarrow{[p\text{-}MeOC_6H_4P(S)S]_2} R^1-\overset{\overset{S}{\|}}{C}-OR^2 \xrightarrow[\text{few seconds}]{BrF_3,\ 0\ ^\circ C} R^1CF_2OR^2$$

1	R^1 = 1-Adamantyl; R^2 = Me	**2**
3	R^1 = Heptyl; R^2 = Et	**4**
5	R^1 = 4-methylcyclohexyl; R^2 = Et	**6**
7	R^1 = Ph, R^2 = Me	**8**

---

† *Caution*: BrF_3 should be treated with care since it reacts violently with solvents such as water and acetone. Dry trichlorofluoromethane, chloroform, carbon tetrachloride or acetonitrile are suitable as reaction solvents.

aromatic derivatives, but none of the desired difluoro derivative **8**.

The compounds, which could be stored under nitrogen at 0 °C for more than a month, were 93–95% pure and their structures were in excellent agreement with all spectral data including high resolution MS.

This research was supported by Grant No. 89-00079 from the USA–Israel Binational Science Foundation (BSF), Jerusalem, Israel.

Received, 12th July 1993; Com. 3/04054B

References

1 R. S. Michalak, S. R. Wilson and J. C. Martin, *J. Am. Chem. Soc.*, 1984, **106**, 7529.

2 A. V. Kartashov, N. N. Chuvatkin and L. S. Boguslavskaya, *J. Org. Chem., USSR (Engl. Transl.)*, 1988, **24**, 2276; L. S. Boguslavskaya, A. V. Kartashov and N. N. Chuvatkin, *J. Org. Chem., USSR (Engl. Transl.)*, 1989, **25**, 1835.

3 (*a*) W. H. Bunnelle, B. R. McKinnis and B. A. Narayanan, *J. Org. Chem.*, 1990, **55**, 768; (*b*) L. S. Boguslavskaya, I. Y. Panteleeva and N. N. Chuvatkin, *J. Org. Chem., USSR (Engl. Transl.)*, 1982, **18**, 198.

4 S. Rozen and D. Zamir, *J. Org. Chem.*, 1991, **5**, 4695; G. K. S. Prakash, V. P. Reddy, X. Y. Li and G. A. Olah, *Synlett*, 1990, 594.

5 S. C. Sondej and J. A. Katzenellenbogen, *J. Org. Chem.*, 1986, **51**, 3508; R. A. Berglund and P. L. Fuchs, *Synth. Commun.*, 1989, **19**, 1965.

6 B. S. Pederson, S. Scheibye, K. Clausen and S. O. Lawesson, *Bull. Soc. Chim. Belg.*, 1978, **87**, 293; M. P. Cava and M. L. Levinson, *Tetrahedron*, 1985, **41**, 5061.

7 For ring bromination, see: S. Rozen and O. Lerman, *J. Org. Chem.*, 1993, **58**, 239.

8 S. Rozen and M. Brand, *J. Org. Chem.*, 1986, **51**, 222.