Reactions of Bromotrifluoromethane and Related Halides: Synthesis of Trifluoromethyl Sulphides from Disulphides

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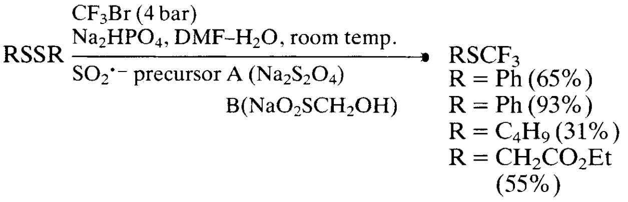
The reaction of trifluoromethyl bromide with disulphides in the presence of dithionite or hydroxymethanesulphinate salts in DMF–H_2O (DMF = dimethylformamide) medium leads to the formation of aliphatic and aromatic trifluoromethyl sulphides.

The trifluoromethylthio group is one of the most lipophilic substituents.[1] Its presence enhances the rate of absorption and transport of organic molecules *in vivo*.[2] This property explains the interest in trifluoromethyl sulphides in the pharmaceutical and agrochemical fields.[3] On the other hand, oxidation of the sulphur atom gives the corresponding trifluorosulphones, which are interesting intermediates for organic synthesis.[4]

We describe here a new synthesis of these fluorinated sulphides from easily available starting materials: bromotrifluoromethane and disulphides.† This reaction was performed under mild conditions with a reductant which can initiate the formation of the sulphur dioxide radical anion, such as sodium dithionite or sodium hydroxymethanesulphinate (Scheme 1).‡

Both aliphatic and aromatic disulphides were transformed to their corresponding fluorinated sulphides. This reaction involved stoichiometric amounts of reductants. Disodium hydrogenophosphate was added in the DMF–H_2O mixture in order to neutralize the sulphur dioxide formed in the reaction. The condensation was performed generally at room temperature within few hours. Alkyl and aryl trifluoromethyl sulphides were obtained in fair yields. Various functional groups, such as cyano, amino, carboxylic esters are compatible with this chemical transformation.[5]



$$\mathrm{RSSR}\ \xrightarrow[\substack{\mathrm{SO_2^{\cdot -}}\text{ precursor A }(\mathrm{Na_2S_2O_4})\\ \mathrm{B(NaO_2SCH_2OH)}}]{\substack{\mathrm{CF_3Br}\ (4\text{ bar})\\ \mathrm{Na_2HPO_4},\ \mathrm{DMF{-}H_2O},\text{ room temp.}}}\ \mathrm{RSCF_3}$$

$R = Ph\ (65\%)$
$R = Ph\ (93\%)$
$R = C_4H_9\ (31\%)$
$R = CH_2CO_2Et\ (55\%)$

Scheme 1

Recently, we have shown that trifluoromethyl bromide in the presence of a sulphur dioxide radical anion precursor produced the electrophilic trifluoromethyl radical which was captured by electron-rich aromatic compounds.[6,7] Owing to the susceptibility of the weak sulphur–sulphur bond in disulphides to free radical attack, the mechanism in eqns. (1) and (2) could be considered.

$$CF_3Br + SO_2^{\cdot -} \rightarrow CF_3^{\cdot} + Br^- + SO_2 \qquad (1)$$

$$RSSR + CF_3^{\cdot} \rightarrow RSCF_3 + RS^{\cdot} \qquad (2)$$

Attack on dialkyl disulphides by perfluoralkyl radicals, formed from perfluoroalkyl iodides under UV irradiation, has been reported.[8] This photochemical transformation was rather slow; UV irradiation of diethyl disulphide and the expensive trifluoromethyl iodide was performed during 48 days and gave ethyl trifluoromethyl sulphide in a 43% yield. However, the easy reduction of disulphides to thiolate ions is well-known and we had already observed that arenethiolates reacted with trifluoromethyl bromide by an $S_{RN}1$ process to give also aryl trifluoromethyl sulphides.[9] We have checked that disulphides are not reduced under our mild conditions of temperature. Consequently, a radical mechanism is more likely.§ This reaction involving disulphides can be employed with other perfluorinated perhalogenoalkyl halides.

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‡ A mixture of sulphur dioxide and a reductant, such as zinc, can also be used.

§ Formation of chlorodifluoromethyl phenyl sulphide from the similar condensation using bromochlorodifluoromethane and diphenyl disulphide is also in agreement with a radical pathway since benzenethiolate leads from the same halide to the bromo analogue by an ionic process.[12]

In the course of the experiments, some trifluoromethanesulphinate salt was formed following the normal reaction of trifluoromethyl bromide with sulphur dioxide radical anion precursors.[10] Depletion of its amount was due to the capture of the intermediate trifluoromethyl radical by the disulphide added in the medium. A striking difference with the trapping by electron-rich aromatic compounds appears.[6,7] In this latter case, 0.1 mol. equiv. of reductant was sufficient to promote the reaction. In order to explain such a catalytic effect, we have proposed that the SO_2 which is formed can be reduced back to its radical anion by an intermediate cyclohexadienyl radical. This step could induce a chain formation of the trifluoromethyl radical. In the present case, a stoichiometric amount of dithionite or hydroxymethanesulphinate salt was necessary to perform the reaction with disulphides because a similar oxidisable intermediate was not formed in the medium. Nevertheless, the reductants used are not expensive.

Reaction of the cheap trifluoromethyl bromide with disulphides allows the preparation of aliphatic and aromatic trifluoromethyl sulphides and avoids the use of toxic or expensive reagents, harsh conditions or sensitive salt derivatives involved in the previous methods.[11]

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