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TRIFLUOROMETHYLATION OF ORGANIC DISULFIDES WITH SODIUM TRIFLUOROMETHANESULFINATE UNDER OXIDATIVE CONDITIONS: SYNTHESIS OF TRIFLUOROMETHYL THIOETHERS

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TRIFLUOROMETHYLATION OF ORGANIC DISULFIDES WITH SODIUM TRIFLUOROMETHANESULFINATE UNDER OXIDATIVE CONDITIONS: SYNTHESIS OF TRIFLUOROMETHYL THIOETHERS.

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Abstract Trifluoromethyl thioethers can be obtained from disulfides, sodium trifluoromethanesulfinate and an oxidizer like t-BuOOH, CAN or K₂S₂O₈. The reaction seems to be a radical one and one half of the disulfide molecule only is used for trifluoromethylation. Yields are related to the nucleophilicity of the sulfur atoms. The choice of the solvent can be crucial, especially with aromatic disulfides for which sulfur trifluoromethylation competes with nucleus one.

INTRODUCTION

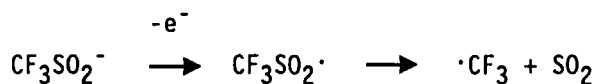
Because of the high lipophilicity of the trifluoromethylthio moiety (Hansch's parameter $\Pi_R = 1.44$ (1)), a lot of organic compounds bearing this substituent have been synthesised for agrochemical (2) or pharmaceutical (3-6) purposes.

Trifluoromethyl thioethers can be prepared with very toxic reagents (7-9) or very expensive ones (10-12). Cheaper and safer methods use CF₃Br (13-15) but must be performed under pressure and side-reductions can occur during the trifluoromethylation of disulfides with CF₃Br and SO₂⁻ precursors. Thus, a complementary technique was needed.

DISCUSSION

During our studies on a new chemical synthesis of "triflic" acid (16), we observed that the oxidation of sodium trifluoromethanesulfinate with t-BuOOH led to the extensive cleavage of the C-S bond with evolution of SO₂ or NaHSO₃.

formation. As the $\text{CF}_3\text{SO}_2^\cdot$ radical is known to be very unstable, a single electron oxidation has been postulated:



As it was known that trifluoromethyl radicals cleave organic disulfides (9,15), we put in reaction disulfides and $\text{CF}_3\text{SO}_2\text{Na}$, in the presence of $t\text{-BuOOH}$ (possibly activated by $\text{MoO}_2(\text{acac})_2$ (17)) and obtained trifluoromethyl thioethers under very mild conditions:

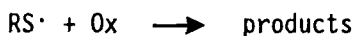
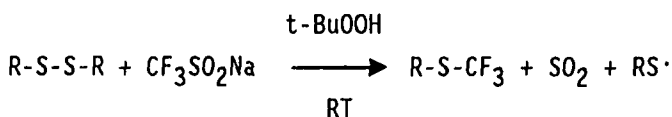


TABLE Trifluoromethyl thioethers from disulfides- conditions

RT				
$\text{R-S-S-R} + \text{CF}_3\text{SO}_2\text{Na} \longrightarrow \text{R-S-CF}_3$				
R	solv.	Ox	cata	yield (%)
$\text{CH}_2\text{CH}_2\text{E}$	$\text{MeCN}/\text{H}_2\text{O}$	$t\text{-BuOOH}$	-	73
d^\cdot	MeCN	d^\cdot	-	71
d^\cdot	$\text{MeCN}/\text{H}_2\text{O}$	d^\cdot	Mo^{VI}	100
d^\cdot	d^\cdot	$\text{K}_2\text{S}_2\text{O}_8 +$ Mohr's salt	-	64
d^\cdot	d^\cdot	CAN	-	34
CH_2E	d^\cdot	$t\text{-BuOOH}$	Mo^{VI}	62*
$n\text{-C}_8\text{H}_{17}$	d^\cdot	d^\cdot	-	0
d^\cdot	MeCN	d^\cdot	-	96
d^\cdot	AcOEt	d^\cdot	-	100
$c\text{-C}_6\text{H}_{11}$	d^\cdot	d^\cdot	-	8
d^\cdot	MeCN	d^\cdot	-	45
$t\text{-Bu}$	d^\cdot	d^\cdot	-	11

$\text{E} = \text{CO}_2\text{Et}$

$\text{Mo}^{\text{VI}} = \text{MoO}_2(\text{acac})_2$

yield = $(\text{RSCF}_3/\text{RSSR}) \times 100$

* oxidizer introduced manually

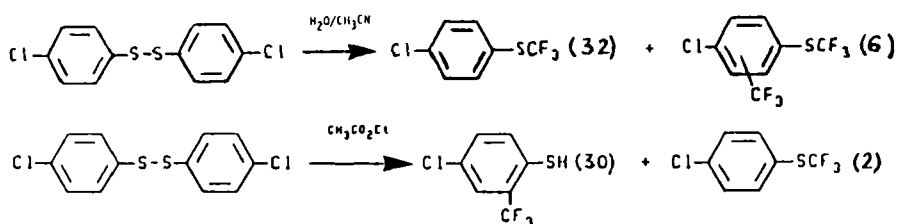
Yields are very sensitive to local overconcentrations and best results were obtained when *t*-BuOOH was introduced by the mean of a syringe pump. The most suitable solvents were acetonitrile, acetonitrile-water and ethyl acetate which dissolve $\text{CF}_3\text{SO}_2\text{Na}$. Conversions and yields indicated clearly that only one RS moiety of the disulfide led to RSCF_3 , the second part being oxidised without trifluoromethylation. For this reason, yields are given as $(\text{RSCF}_3/\text{RSSR}) \times 100$.

Aliphatic disulfides reactivities were in the order: primary > secondary > tertiary and rise with the nucleophilicity of the sulfur atoms as expected because of the electrophilicity of the trifluoromethyl radical.

As the redox potential of $\text{CF}_3\text{SO}_2\text{Na}$ has been checked at 1.2 V (v.s. SCE) in acetonitrile by electrochemical measurements, CAN and $\text{K}_2\text{S}_2\text{O}_8$ /Mohr's salt can be also suitable oxidizers, though less selective (TABLE).

Phenyl disulfide is not very reactive (total yield = 13%) and S-trifluoromethylation competed with C-trifluoromethylation (several isomers), depending on the solvent ($\text{SCF}_3/\text{CCF}_3 = 36/64$ (MeCN) or 60/40 (MeCN/ H_2O)).

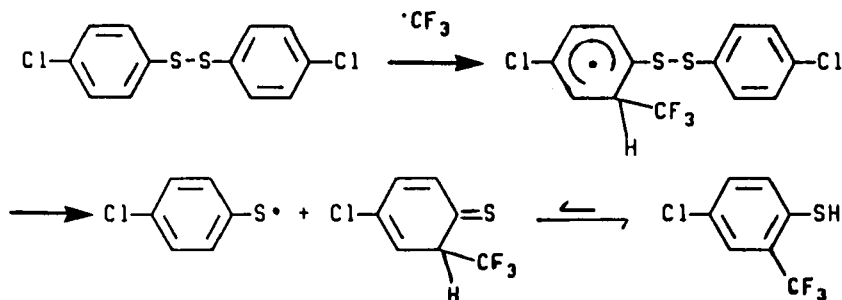
The choice of the solvent was still more crucial when using 4,4'-dichlorodiphenyl disulfide: in rather protic solvents like $\text{CH}_3\text{CN}-\text{H}_2\text{O}$, S-trifluoromethylation predominated but in strictly aprotic solvents like ethyl acetate, C-trifluoromethylation (1 isomer), together with S-S bond cleavage, was the major process.



Explanations could be searched in different behaviours of the solvent towards the nucleophilic sites of aromatic disulfides represented in the following mesomeric form:



Protic solvents would solvate the δ^- carbons (and favour S-trifluoromethylation) whereas aprotic solvents would not. The consecutive S-S bond breaking would be rationalized as follows:



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