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PREPARATION OF BROMODIFLUOROMETHYL SULFIDE AND ITS CONVERSION TO TRIFLUOROMETHYL SULFIDE

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Bromodifluoromethyl sulfides are prepared by the reaction of mercaptides with CF_2BrX (x=Br,Cl). And treatment of bromodifluoromethyl sulfides with various inorganic fluorides produced trifluoromethyl sulfides.

There have been found many biologically active compounds possessing a trifluoromethylthio group. Trifluoromethylthioacetic acid[1] is an important intermediate in the preparation of a semisynthetic cephalosporin antibiotic. 3-(Trifluoromethylthio)propionyl compounds have been patented for their high activity as plant protectant against soil fungi.[2] Another example is ethyl p-trifluoromethylthiophenoxyisobutyrate,[3] which is useful in the treatment of hypocholesterolemia in mammals. And several synthetic methods [4] have been developed so far to produce this functional moiety. In this communication, we would like to report an efficient two-step sequence for the preparation of trifluoromethyl sulfides starting from mercaptans using only nonpoisonous, inexpensive reagents.

Dibromodifluoromethane has been known to be quite labile toward nucleophilic reagents.[5] It is a sharp contrast with trifluoromethyl iodide, which is quite stable toward these reagents. Thus we expected that polyfluorinated one-carbon unit would be easily attached to mercaptans using CF_2Br_2, and found the expectation to be the case. Experimentally, mercaptan 1 was treated with a base (preferably sodium hydride) in an aprotic solvent (THF, DME, DMF, etc.), and then with CF_2Br_2 or CF_2BrCl.[6] Usual work-up and purification(column chromatography or distillation) afforded the corresponding bromodifluoromethyl sulfide 2[7] in fair yields. The results are summarized in Table 1. Preferable reaction temperature is dependent upon the structure of the mercaptan; generally,

$$\underset{\underline{1}}{R\text{-}SH} \longrightarrow R\text{-}S^- \xrightarrow{CF_2BrX} \underset{\underline{2}}{R\text{-}SCF_2Br}$$

reactive alkyl mercaptans were treated at a low temperature (about -40--70°C), while aryl mercaptans were allowed to react at room temperature until no further change in the ^{19}F-NMR spectrum was observed.

Formation of bromodifluoromethyl sulfides can be explained by the chain mechanism involving the intermediate formation of difluorocarbene, as shown in the following scheme.

initiation;

$$RS^- + CF_2BrX \longrightarrow RS\text{-}Br + :CF_2 + X^- \quad (1)$$

propagation;

$$RS^- + :CF_2 \longrightarrow \underset{\underline{3}}{RS\text{-}CF_2^-} \quad (2)$$

$$\underset{\underline{3}}{RS\text{-}CF_2^-} + CF_2BrX \longrightarrow \underset{\underline{2}}{RS\text{-}CF_2Br} + :CF_2 + X^- \quad (3)$$

secondary reactions;

$$RS\text{-}Br + RS^- \longrightarrow \underset{\underline{5}}{RS\text{-}SR} + Br^- \quad (4)$$

$$\underset{\underline{3}}{RS\text{-}CF_2^-} + H\text{-}Y(\text{proton source}) \longrightarrow \underset{\underline{4}}{RS\text{-}CF_2H} \quad (5)$$

$$\underset{\underline{3}}{RS\text{-}CF_2^-} + RS\text{-}Br(\text{or } RS\text{-}SR) \longrightarrow \underset{\underline{6}}{RS\text{-}CF_2\text{-}SR} \quad (6)$$

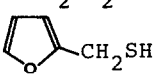
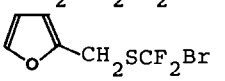
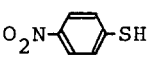
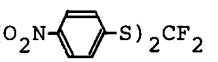
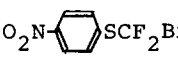
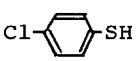
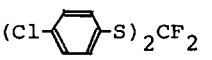
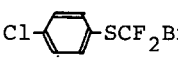
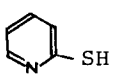
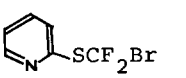
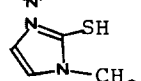
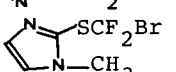
Following observations would support the above mechanism. Even when bromochlorodifluoromethane was used in place of dibromodifluoromethane, the same bromodifluoromethyl sulfides were obtained; almost no chlorodifluoromethyl sulfide was formed. This cannot be explained by the normal substitution reactions. Also, difluoromethyl sulfides 4 and disulfides 5 were always present in the crude reaction mixture as minor products. The former was produced when anion 3 was trapped by a proton source (present as an impurity) and the latter by the reaction between mercaptide and RSBr.

Interestingly, when p-nitrophenyl mercaptan was treated with CF_2Br_2 and CF_2BrCl, different products were isolated. Thus, reaction with CF_2Br_2 produced the expected sulfide 2, while reaction with CF_2BrCl gave bis(arylthio)difluoromethane 6 as the major product. Judging from the fact that 6 is not formed from 2 under the same reaction conditions, we feel that intermediate anion 3 reacted selectively with RSBr or RSSR, as CF_2BrCl is less reactive than CF_2Br_2.

Next, bromine-fluorine exchange of bromodifluoromethyl sulfides 2 to trifluoromethyl sulfides 7 was examined using various kinds of inorganic fluorides. The results are summarized in Table 2. Not only metal fluoride but also silver fluoroborate and hydrogen fluoride were effective for the exchange. Noteworthy is the reactivity of alkyl bromodifluoromethylacetate. When 2-ethylhexyl bromo-

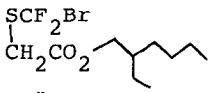
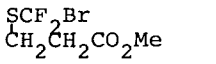
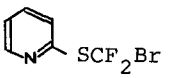
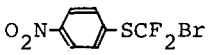
$$\underset{\underline{2}}{RS\text{-}CF_2Br} \xrightarrow{\text{fluoride}} \underset{\underline{7}}{RS\text{-}CF_3}$$

Table 1. Reaction between mercaptan and CF_2BrX(X=Br or Cl).

mercaptan	base	X in CF_2BrX	solvent	reaction tem.	product	yield (%)
$C_{12}H_{25}SH$	BuLi	Cl	DME	-70°C	$C_{12}H_{25}SCF_2Br$	67
$C_7H_{15}SH$	BuLi	Cl	DME	-70°C	$C_7H_{15}SCF_2Br$	63
"	BuLi	Br	DME	-70°C	"	14
"	NaH	Cl	DME	-50°C	"	48
$HSCH_2CO_2Et$	NaH	Br	DMF	-60°C	CH_2CO_2Et | SCF_2Br	34
"	NaH	Cl	DME	-70°C	"	35
$HSCH_2CH_2CO_2Me$	NaH	Cl	DMF	-70°C	$CH_2CH_2CO_2Me$ | SCF_2Br	14
$HSCH_2CH_2CN$	NaH	Cl	DMF	-70°C	$BrCF_2SCH_2CH_2CN$	53
	NaH	Cl	DMF	-60°C		42
PhSH	NaH	Br	DMF	-60°C	$PhSCF_2Br$	58
"	K_2CO_3	Br	DMF	rt	"	11
	NaH	Cl	DMF	rt		44
"	NaH	Br	DMF	rt		30
	NaH	Cl	DMF	-40°C		47
"	NaH	Br	DMF	-40°C		53
	NaH	Cl	DMF	rt		67
	NaH	Cl	DMF	rt		18

difluoromethylthioacetate was stirred with benzyltrimethylammonium fluoride in acetonitrile at room temperature for one hour, the starting suflide disappeared completely, and subsequent work-up afforded 2-ethylhexyl trifluoromethylthioacetate in 57% yield. On the other hand, all other sulfides 1 were stable under the same reaction conditions. This unique reactivity would be due to the intramolecular participation of carbalkoxy group in the ionization process of C-Br bond.

Table 2. Conversion of $RSCF_2Br$ to $RSCF_3$

substrate	fluoride	solvent	reaction temp.	yield(%)
$C_7H_{15}SCF_2Br$	CsF	sulfolane	150°C	44
$NC\text{-}CH_2CH_2SCF_2Br$	$AgBF_4$	ether	rt	22
	$PhCH_2\overset{+}{N}Me_3\ F^-$	acetonitrile	rt	57
"	HF	pyridine	rt	45
	HF	pyridine	rt	29
$PhSCF_2Br$	HgF_2	chloroform	reflux	17
"	$AgBF_4$	dichloromethane	rt	41
	HgF_2	chloroform	reflux	24
	$AgBF_4$	ether	rt	38

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2) US patent 3,522,293.

3) US patent 3,632,629.

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5) P. Bey, J. P. Vevert, V. V. Dorsselaer, and M. Kolb, J. Org. Chem.,44, 2732(1979); D. J. Burton and R. M. Flynn, Synth., 1979, 615.

6) Recently, I. Rico and C. Wakselman(Tetrahedron Lett., 1981, 323) reported the preparation of bromodifluoromethylthiobenzene as a 7:3 mixture with difluoromethylthiobenzene under phase transfer conditions. We independently found this reaction. In our case, all reactions were carried out in an aprotic solvent using mostly sodium hydride as the base.

7) All new compounds were characterized by spectroscopic properties and (partly) by elemental analysis.

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