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CYANO AND FLUORODESTANNYLATION: A NEW METHODOLOGY USING SOME POWERFUL SULFUR TRANSFER REAGENTS, THE ORGANOTIN SULFIDES[1]

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Abstract: *Fluoride and cyanide ions destannylate bis(aralkyl)tin sulfides [R_3Sn-S-SnR_3] and trialkyltin sulfides [R_3Sn-S-R' (R = alkyl)] giving, in the presence of a variety of alkyl and activated halides, the corresponding thioether derivatives in excellent yield. The conditions are mild, neutral and anhydrous; a strong solvent effect is noted. Special comments are made concerning work-up procedures.*

Fluorodesilylation techniques have been recognized to be very important as applied to the cleavage of silyl ethers[2], in aldol condensations[3] as well as a variety of elimination reactions[4]. We felt that a parallel procedure could be developed using fluoride or cyanide ions to destannylate various tin-protected functionalities such as alcohols, amines and thiols.

Fluoride ion and many tin compounds are found to associate strongly to form "polymers" [5a]. Indeed, while carrying out this work, the first examples of fluorodestannylation (elimination, alkylation) were published[6].

We wish to report that sulfur transfer reagent bis(tributyltin) sulfide 1[1,7] combines with a "naked" fluoride ion to release a powerful sulfur nucleophile; the counterion is a quaternary ammonium or a cesium cation complexed with a crown-ether. In the presence of alkyl halides, sulfides are formed in excellent yield[8]. Cyanide ion was also successful as a destannylating agent although it is less reactive than fluoride; it represents the first example of this type of reaction.

$$R_3Sn\text{-}S\text{-}SnR_3$$

1

The process was found to be general (Eq. 1, Table 1) with a variety of organotin sulfides (readily available)[9].

$$\mathbf{2\,R\text{-}X + R'_3Sn\text{-}S\text{-}SnR'_3 + 2\,Z^- \text{------>} R\text{-}S\text{-}R + 2\,R'_3Sn\text{-}Z + 2X^-} \qquad \text{(Eq. 1)}$$

$$R = \text{alkyl};\ R' = \text{Me, Ph, Bu, or } [Bu_2Sn\text{-}S]_3;\ X = \text{Cl, Br, I};\ Z = CN^-, F^-$$

Also, unsymmetrical sulfides have been prepared starting from trialkyltin mercaptides (R''_3SnSR') and an organic halide. The yields are good and the conditions anhydrous, mild and neutral (Eq. 2, Table 2).

$$\mathbf{R\text{-}X + R''_3Sn\text{-}SR' + Z^- \text{------>} R\text{-}S\text{-}R' + R''_3Sn\text{-}Z + X^-} \qquad \text{(Eq. 2)}$$

$$R = \text{alkyl};\ R' = R'' = \text{alkyl};\ X = \text{Cl, Br, I};\ Z = CN^-, F^-$$

Several common sources of fluoride ion (usually commercially available) were evaluated including tetrabutylammonium fluoride trihydrate ($TBAF.3H_2O$), the "anhydrous" version[10], cesium fluoride (complexed with 18-crown-6 or not)[11] and potassium fluoride (complexed with 18-crown-6 or not)[12]. Only reactions with TBAF and cesium fluoride were effective.

Fluoride ion was employed in a catalytic amount as with some desilylations for reactive halides (see entry 1 in Table 1)[4]. The choice of fluoride source varies with the organic halide used. For activated halides or where a 6-membered ring is formed (entries 9-19) either $TBAF.3H_2O$ or CsF can be used. Where the reactions are slow (as with 1-bromohexane) the use of $TBAF.3H_2O$ produces significant amounts of thiol. For these as well as the other substrates CsF with 18-crown-6 would appear to be the reagents of choice.

The effect of the tin substituent was found to be negligible compared to that of the source of the fluoride ion. Thus, various organotin sulfides, easily made or commercially available, were used in this study with little difference except for the toxicity[13] and purification[14,15].

The following is a typical procedure for the preparation of thioethers such as di-*n*-hexyl sulfide. In a 50 ml flask 1-bromohexane (409 mg; 2.48 mmol) bis(trimethyltin)sulfide (445 mg; 1.24 mmol) and a catalytic amount of 18-crown-6 (132 mg; 0.50 mmol). Ten mL of acetonitrile (dried over CaH_2 and P_2O_5) is added. Cesium fluoride (800 mg; 5.27 mmol, dried at 110°C for 2 days at 5mm Hg) is added in one portion. The mixture is stirred vigorously under nitrogen and heated at 75°C for 75 min. After cooling, the solvent is removed and 50 ml of ethyl acetate is added. After stirring for 5 min, the mixture is filtered over celite and then silica gel using ethyl acetate as eluent. Ethyl acetate is the preferred solvent to use to insure maximum removal of "polymeric" fluoride[5] especially when using silica gel purification. Di-*n*-hexyl sulfide is obtained as a colorless liquid (250 mg, quant.; ^{1}Hnmr($CDCl_3$) 200 MHz: 2.50 (t,4H); 1.58 (m,4H); 1.30 (m,12H); 0.89 (t,6H); TMS as internal standard; MS (EI): 202(M^+, 40), 117(100), 84(86), 69(45), 61(77), 56(63), 55(65), 43(72), 42(67), 41(69), 28(66).

A strong solvent effect suggests an ionic mechanism. Polar aprotic solvents such as acetonitrile (CH_3CN) or dimethylformamide (DMF) are the best to effect an efficient reaction, but acetonitrile is preferred in that purification is easier. In solvents like methylene chloride or chloroform, the reaction is very slow and mostly incomplete even using higher temperatures.

Volatile R'S units such as CH_3SH, can be handled easily if they are converted to the triorganotin mercaptide (R_3SnSR'; R' = R = alkyl); such tin derivatives have high boiling points[16], thus, the unpleasant odor of the thiol is greatly attenuated. Many synthetic pathways are available to make these tin mercaptides[17]; thus, using the fluorodestannylation reaction for sulfur-deprotection combined with an

Table 1 : Formation of Symmetrical Sulfides Using Organotin Sulfides and Alkyl Halides

Entry	Halide	Organotin	Solvent[i]	T°C	Time(hr)	F^-or CN^-(mol)	Sulfide	Yield%[a]
1	CH_3COCH_2Cl	$(Bu_3Sn)_2S^f$	A	20	0.8	$TBAF.3H_2O(1.0)$	$(CH_3COCH_2)_2S$	83^e
2	$PhCOCH_2Br$	$(Bu_3Sn)_2S^f$	B	20	1.0	CsF(xs)	$(PhCOCH_2)_2S$	98
3	$PhCOCH_2Br$	$(Bu_3Sn)_2S^f$	B	20	0.3	$TBAF.3H_2O(2.2)$	$(PhCOCH_2)_2S$	99
4	$PhCH_2Br$	$(Bu_3Sn)_2S^f$	B	20	0.8	$TBAF.3H_2O(4.6)$	$(PhCH_2)_2S$	85^e
5	$PhCH_2Br$	$(Bu_3Sn)_2S^g$	A	20	0.3	$TBAF.3H_2O(4.0)$	$(PhCH_2)_2S$	99^b
6	$PhCH_2Br$	$(Bu_3Sn)_2S^h$	A	20	1.0	$TBAF.3H_2O(2.1)$	$(PhCH_2)_2S$	86^e
7	$CH_3COCH(CH_3)Br$	$(Bu_3Sn)_2S^h$	B	20	24	$TBAF.3H_2O(1.0)$	$(CH_3COCH(CH_3))_2S$	75^e
8	$CH_3COCH(CH_3)Br$	$(Bu_3Sn)_2S^h$	B	20	7	$TBAF.3H_2O(2.0)$	$(CH_3COCH(CH_3))_2S$	57^c
9	$Br(CH_2)_5Br$	$(Bu_3Sn)_2S^g$	A	20	0.5	$TBAF.3H_2O(2.0)^j$	thiane	99^c
10	$Br(CH_2)_5Br$	$(Bu_3Sn)_2S^g$	A	42	0.5	$TBAF.3H_2O(2.0)$	thiane	99^c
11	$Br(CH_2)_5Br$	$(Bu_3Sn)_2S^g$	A	20	0.8	$TBAF.3H_2O(2.0)$	thiane	99^c
12	$Br(CH_2)_5Br$	$(Bu_3Sn)_2S^g$	B	60	0.5	$TBAF.3H_2O(2.0)$	thiane	96^c
13	$Br(CH_2)_5Br$	$(Bu_3Sn)_2S^g$	A	40	0.5	TBAF(anh.,2.0)	thiane	26^c
14	$Br(CH_2)_5Br$	$(Me_3Sn)_2S^g$	A	40	5	$TBAF.3H_2O(2.0)$	thiane	91^c
15	$Br(CH_2)_5Br$	$(Me_3Sn)_2S^g$	A	50	0.5	$TBAF.3H_2O(2.4)$	thiane	90^c
16	$Br(CH_2)_5Br$	$(Bu_2SnS)_3$	A	50	0.8	$TBAF.3H_2O(2.4)^j$	thiane	99^c
17	$Br(CH_2)_5Br$	$(Ph_3Sn)_2S^g$	B	60	2	$TBAF.3H_2O(2.0)$	thiane	99^c
18	$Br(CH_2)_5Br$	$(Ph_3Sn)_2S^g$	B	60	0.5	$TBAF.3H_2O(2.0)$	thiane	88^c
19	$Br(CH_2)_5Br$	$(Ph_3Sn)_2S^g$	B	60	1.0	$TBAF.3H_2O(2.0)$	thiane	94^c
20	$EtCH(CH_3)CH_2Br$	$(Me_3Sn)_2S^h$	A	80	2.5	CsF.18C6(xs)	$(EtCH(CH_3)CH_2)_2S$	63^e
21	$CH_3(CH_2)_5Br$	$(Bu_3Sn)_2S^h$	A	20	2.5	TBAF(anh.,3.0)	$(CH_3(CH_2)_5)_2S$	13
22	$CH_3(CH_2)_5Br$	$(Me_3Sn)_2S^h$	A	75	1.0	CsF.18C6(xs)	$(CH_3(CH_2)_5)_2S$	99
23	$PhCH_2Br$	$(Bu_3Sn)_2S^h$	A	20	1.1	TBACN(2.1)	$(PhCH_2)_2S$	41

a) isolated yields except if noted NMR or GC yield; identified by NMR, IR, MS and compared to authentic material; b)^{1}H NMR yield; c) GC yield without internal standard; d) cyclic trimer; e) not optimized; f)1.1 mol; g) 2.0 mol; h) 1.05 mol; i) A = acetonitrile; B = DMF/EtOAc (5:1); j) 2.0 mol of tetrapropylammonium iodide added.

Table 2 : Formation of Unsymmetrical Sulfides from Organotin Sulfides and Alkyl Halides

Entry	Halide	Organotin[e]	Solvent[d]	T°C	Time(hr)	F^- or CN^-(mol)	Sulfide	Yield%[a]
1	$CH_3(CH_2)_5Br$	$PhCH_2SSnBu_3$	A	24	2	CsF.18C6(xs)	$PhCH_2S(CH_2)_5CH_3$	82^b
2	$CH_3(CH_2)_5Br$	$PhCH_2SSnBu_3$	A	24	2	CsF.18C6(xs)	$PhCH_2S(CH_2)_5CH_3$	76
3	$CH_3(CH_2)_5Br$	$PhCH_2SSnBu_3$	A	24	12	CsF(xs)	$PhCH_2S(CH_2)_5CH_3$	55
4	$CH_3(CH_2)_5Br$	$PhCH_2SSnBu_3$	A	20	2.3	TBACN(2.2)	$PhCH_2S(CH_2)_5CH_3$	84^c

a) isolated yields except if noted as NMR or GC yield. Identified by NMR, IR, MS and compared to authentic material; b) ^{1}HNMR yield; c)GC yield without internal standard; d) A = acetonitrile; e) 1.05 mol.

appropriate electrophile (halides used here or those reported elsewhere)[1] give access to symmetrical (Table 1) or unsymmetrical sulfides (Table 2). In sum, this method provides a new and simple procedure for cleaving the sulfur-tin bond and in this case a means of preparing sulfides in high yield under mild, neutral and anhydrous conditions.

Acknowledgements

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8. When hexamethyldisilthiane is used with fluoride ion and an alkyl halide, both *di* and monosulfide are formed in about equal amounts.

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