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GENERATION OF THIOALDEHYDES VIA FLUORIDE INDUCED ELIMINATION OF α-SILYLDISULFIDES

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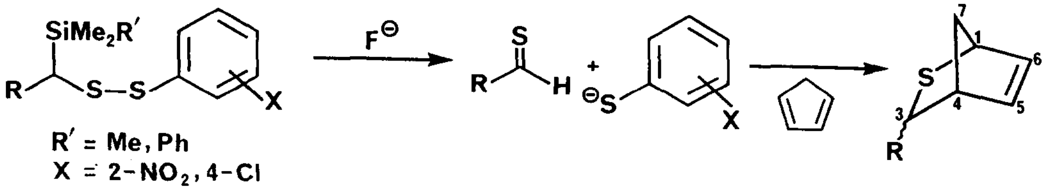
Summary: A mild, efficient and general method for the generation of reactive thioaldehydes from α-silyldisulfides is described.

The interest in thioaldehydes and their chemistry has grown significantly in recent years, due to the recognition that thioaldehydes are more stable than historically thought, and that they participate in efficient and useful chemical reactions.[2] A major limitation in the exploitation of thioaldehyde chemistry has been the difficulty in generating the reactive thioaldehydes under mild conditions. Several pyrolytic methods for thioaldehyde generation have been reported,[2c,d] but these conditions impose significant limitations upon the subsequent thioaldehyde chemistry. Thioaldehydes also may be generated by a photochemically induced Norrish II cleavage of phenacyl sulfides,[3] however, this process is inefficient for some reactants and reaction conditions.[3c] In this communication we report a mild, efficient and generally applicable method for the generation of thioaldehydes from α-silyldisulfides.

We have found that thioaldehyde formation occurs readily by fluoride induced β-elimination of stabilized aryl thiolate anions from α-silyldisulfides as outlined in Equation 1. The efficiency of the cleavage reaction and the stability of the α-silyldisulfides depend upon the stability of the arylthiolate leaving group. The 2-nitro- and 4-chloro- substituted phenyl disulfides are reasonably stable thioaldehyde precursors, and efficiently participate in the elimination reaction to generate thioaldehydes. The unsubstituted phenyldisulfides require elevated temperatures to react, while the 2,4,6-trichlorophenyldisulfides are quite unstable and difficult to isolate. The rate of the elimination reaction is also influenced by the

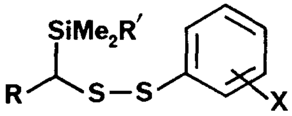
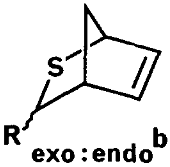
(1)



activity of the fluoride source. Cesium fluoride or potassium fluoride in the presence of 18-crown-6 generates thioaldehyde slowly at room temperature, while tetrabutylammonium fluoride in THF generates thioaldehyde rapidly, at temperatures from 0°C to -78°C.

A variety of thioaldehydes have been generated by this method and trapped by Diels-Alder cycloaddition to cyclopentadiene.[4] The results of these experiments are presented in Table 1. The isolated yields of cycloadducts were excellent, ranging from 58 to 94%. A mixture of exo and endo cycloadducts was obtained from each substituted thioaldehyde, with the endo isomer predominating in all reactions.[5] While this endo preference may be a kinetic phenomenon, inspection of Dreiding models suggests that the endo isomers suffer less steric congestion and may be the more stable isomers.

Table 1

 R	R'	X	Conditions[a]	 exo:endo[b]	Yield,%[c]
H	Me	4-Cl	A	—	67
Me	Ph	$2\text{-}NO_2$	A	2 :7	89
Et	Ph	$2\text{-}NO_2$	A	1:6	92
n-Pr	Ph	$2\text{-}NO_2$	A	2:9	94
n-Bu	Ph	$2\text{-}NO_2$	A	2:9	91
i-Pr	Ph	$2\text{-}NO_2$	B	1 :7	66
Ph	Me	4-Cl	A	1:7	90
$PhCH_2$	Ph	$2\ NO_2$	B	2:7	80
c-Hex	Ph	$2\text{-}NO_2$	B	1:5	58
 R(+)	Ph	$2\text{-}NO_2$	A	1:4	65

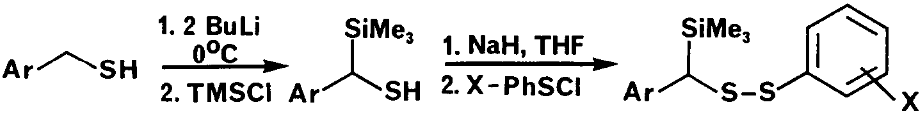
[a]Method A - CsF, THF, R.T.; B - Bu_4NF, 0°C. [b]NMR ratios. [c]Isolated yields.

In a typical experiment for thioaldehyde generation (Method **A**) 1.0 mmol of the α-silyldisulfide, 5.0 mmol cyclopentadiene and 2.0 mmol cesium fluoride were mixed in 25 mL tetrahydrofuran and stirred at room temperature until the disulfide had reacted completely (4-12 h). The solvent and excess cyclopentadiene were evaporated and the residue purified by flash chromatography on silica gel (hexane: ether: dichloromethane, 25:1:1).

An alternative method (**B**) involved the slow addition (30-60 min.) of a THF solution (.01 M) of Bu_4NF to a solution of disulfide and two equivalents of cyclopentadiene at 0°C, followed by similar work-up and purification.

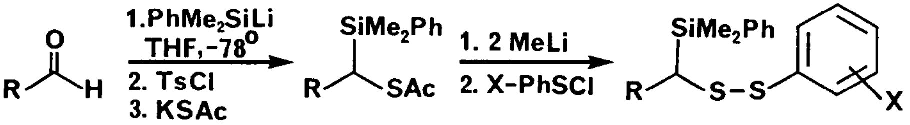
The α-silyldisulfides were prepared by two alternative routes. In several instances, generation of a mercaptan dianion[6] was possible, and these dianions were silylated to afford α-trimethylsilyl mercaptans. Sulfenylation of these mercaptans with 2-nitro- or 4-chlorophenylsulfenyl chloride provided the α-trimethylsilyldisulfides (Scheme **1**).

Scheme 1



For all other cases, the α-phenyldimethylsilyl disulfides were prepared from the corresponding aldehydes by the synthetic pathway outlined in Scheme 2. Addition of aldehyde to phenyldimethylsilyl anion[7], tosylation and displacement with thioacetate provided 50-75% yields of the α-silylthioacetates in a one-pot procedure. Sulfenylation of the mercaptide anion, generated by treatment of the thioacetate with methyl lithium, afforded pure α-silyldisulfides in 45-70% overall yield from the aldehydes.[8]

Scheme 2



This highly efficient method of thioaldehyde generation under ambient conditions will permit new investigations of thioaldehyde reactivity with a variety of organic substrates and reagents. These investigations are continuing in our laboratories.

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References and Notes.

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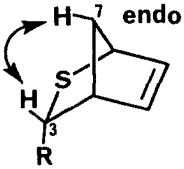
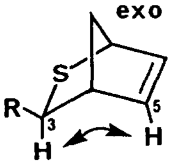
4. All adducts gave satisfactory IR, NMR and mass spectral data.
NMR data for the endo and exo cycloadducts (R = Et) are as follows: Endo - ^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$, ppm): 6.38 (dd, 1H, J = 2.6, 2.6 Hz), 5.75 (dd, 1H, J = 2.6, 2.6 Hz), 3.93 (bs, 1H), 3.64 (ddd, 1H, J = 5.3, 7.0 3.5 Hz), 3.36 (bs, 1H), 1.62 (AB quartet, 2H), 1.56 (m, 1H), 1.26 (m, 1H), 0.96 (t, 3H, J = 7.5 Hz); ^{13}C NMR (63 MHz, $\mathrm{CDCl_3}$, ppm): 137.6 (d, C-6), 128.9 (d, C-5), 54.3 (d, C-1), 51.7 (d, C-3), 51.3 (d, C-4), 48.6 (t, C-7), 27.9 (t, $\mathrm{-CH_2CH_3}$), 13.8 (q, $\mathrm{-CH_2CH_3}$). Exo - ^{1}H NMR: 6.27 (dd, 1H, J = 2.6, 2.6 Hz), 5.92 (dd, 1H, J = 2.6, 2.6 Hz), 3.98 (bs, 1H), 3.04 (bs, 1H), 2.71 (dd, 1H, J = 6.1, 8.8 Hz), 1.84 (m, 2H), 1.63 (AB quartet, 2H), 1.14 (t, 3H, J = 7.3 Hz); ^{13}C NMR: 136.9 (d, C-6), 133.0 (d, C-5), 54.4 (d, C-1), 50.8 (d, C-3), 49.6 (d, C-4), 47.4 (t, C-7), 30.5 (t, $\mathrm{-CH_2CH_3}$), 14.2 (q, $\mathrm{-CH_2CH_3}$).

5. Cycloadduct stereochemistry was determined by NOE experiments. Enhancement of the C-5 vinylic resonance was observed upon irradiation of the C-3 methine resonance in the predominant (endo) isomer. Similar irradiation of the C-3 methine in the minor (exo) isomer induced enhancement in the C-7 methylene proton resonance.





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8. All disulfides gave satisfactory IR, NMR and mass spectral data.

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