A Facile Synthesis of Acetyl Alkyl Disulfides

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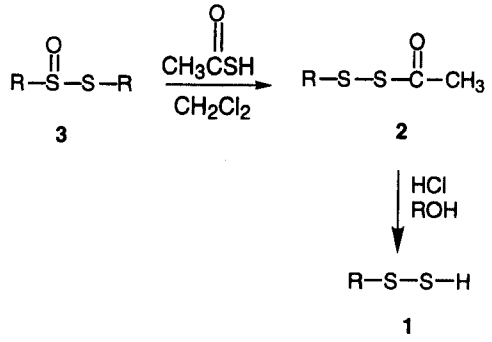
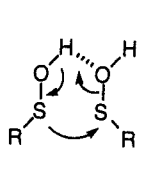
The preparation of acetyl alkyl disulfides **2**, which are key intermediates for the synthesis of alkyl hydrodisulfides **1**, from disulfides is described. Disulfides are oxidized to sulfinothioic acid *S*-esters (thiosulfinates) which thioalkylate thioacetic acid to form acetyl alkyl disulfides **2**.

Although hydrodisulfides (RSSH, **1**) have been postulated as intermediates in various enzymatic reactions[1-5] and are useful for the preparation of polysulfanes,[6,7] very little is known about the chemistry of this family of organosulfur compounds.[6-14] Many of the procedures for the preparation of hydrodisulfides **1** require multistep synthesis of the key acetyl alkyl disulfide **2**. In addition, many of the reactants and intermediates are hazardous, labile, or highly odorous compounds.[6,9,15-18] Acid catalyzed alcoholysis of **2** affords the hydrodisulfide **1**. Owing to our interest in using hydrodisulfides as reactants, we needed a facile synthesis of acetyl alkyl disulfides **2**.



We have prepared acetyl alkyl disulfides **2** from readily available bis(alkyl) disulfides. The 3-chloroperbenzoic acid (MCPBA)[19] oxidation of disulfides affords alkanesulfinothioic acid *S*-esters (thiosulfinates, **3**)[20,21] which were treated with thioacetic acid to yield the acetyl alkyl disulfides **2**.[8,9,22-26] Although the thioalkylation reaction is sensitive to steric factors (tertiary thiosulfinates **3** were only partially converted after 48 hours), thioacetic acid reacts with **3** to form **2** in high yields. Another advantage of the reaction is that the liberated alkanesulfenic acid can undergo cyclodehydration via the hydrogen-bonded dimer **4**[27] or the sulfurane-like structure **5**[28] to form the corresponding thiosulfinate **3** which reacts with thioacetic acid or can be isolated from experiments carried to partial conversion. Thus, all of **3** is utilized in the reaction.



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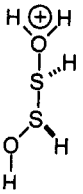

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Table 1. Acetyl Alkyl Disulfides **2** Prepared

Compound	R	Time (h)	Yield (%)[a]	HRGCMS (70 eV) *m/z* (%)
2a[17]	Et	0.25	52	136.0014 (M^+, 100), 93 (3.22), 66 (9.09)
2b[b]	Bu	0.25	81	164.0327 (M^+, 91.28), 79 (15.78), 58 (100)
2c[11,25]	$PhCH_2$	0.25	58	198.0168 (M^+, 10.14), 91 (100), 65 (14.75)
2d[b]	*i*-Pr	1.5	76	150.0173 (M^+, 100), 108 (34.86), 66 (19.03), 59 (29.87)
2e[9,26]	*t*-Bu	48	66[c]	164.0327 (M^+, 14.54), 107 (2.91), 57 (100)
2f[b]	*t*-C_5H_{11}	48	45[c]	178.0484 (M^+, 12.68), 71 (100), 55 (11.73)
2g[8]	1-Adamantyl[d]	48	41[c]	242.0799 (M^+, 3.44), 135 (100), 93 (13.48), 79 (14.16), 67 (5.90)

[a] Yield of isolated pure product.
[b] Satisfactory microanalyses obtained: C ± 0.30, H ± 0.20.
[c] Partial conversion of **3** to **2**.
[d] 1-Adamantyl = (tricyclo[3.3.1.1]decan-1-yl).

Mps were obtained in open capillaries on a Thomas-Hoover melting point apparatus and are uncorrected. ^1H and ^{13}C NMR (300 and 500 MHz) spectra were recorded in $CDCl_3$. Analytical TLC was performed on Analtech Uniplate 10 × 20 cm^2 (250 μm thick) silica gel GF prescored glass plates. The plates were analyzed under UV light, and/or developed in a diiodine chamber. Flash column chromatography was performed on 230–400 mesh silica gel.

Reagents and solvents were purified by standard procedures. N_2 was dried by passing it through a column of Drierite and 4 Å molecular sieves. 3-Chloroperbenzoic acid was purified as previously described.[19] Disulfides are commercially available or were prepared by literature procedures. Sulfinothioic acid *S*-esters (thiosulfinates, **3**) were prepared by the MCPBA oxidation of the corresponding disulfides.[20,21]

Acetyl Alkyl Disulfides 2; General Procedure, Preparation of Acetyl *tert*-Butyl Disulfide (2e):[9,26]

Et_3N (190 mg, 0.26 mL, 1.88 mmol) in CH_2Cl_2 (10 mL) was added to a solution of thiosulfinate (**3e**, 388 mg, 2 mmol), thioacetic acid (304 mg, 0.28 mL, 4 mmol, 2 equiv) in CH_2Cl_2 (10 mL). The reaction was stirred at r.t. for 2 days, the mixture was washed with sat. aq NaCl (3 × 20 mL), dried (Na_2SO_4), and purified by silica gel chromatography (15:1, hexanes/EtOAc) to give **2e** (157 mg, 66%) and (3:1, hexanes/EtOAc) to give the thiosulfinate **3e** (247 mg, 36.3% conversion).

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Table 2. Spectroscopic Data of Acetyl Alkyl Disulfides **2**

Compound	IR ($CHCl_3$) ν (cm^{-1})	^1H NMR ($CDCl_3$) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ
2a	2974, 1726 (C=O), 1449, 1114, 910, 732	1.13 (t, 3H, J = 7.33), 2.31 (s, 3H, MeCO), 2.59 (q, 2H, J = 7.33)	13.87, 28.52, 32.43, 194.53
2b	2958, 1729 (C=O), 1459, 1351, 1112, 941, 733	0.90 (t, 3H, J = 7.35), 1.40 (m, 2H), 1.60 (m, 2H), 2.43 (s, 3H, MeCO), 2.70 (t, 2H, J = 7.30)	13.61, 21.58, 28.40, 31.20, 38.72, 194.20
2c	3031, 1726 (C=O), 1493, 1454, 1352, 1114, 908, 730	2.34 (s, 3H, MeCO), 3.93 (s, 2H, CH_2Ph), 7.31 (m, 5H, Ph)	28.44, 42.72, 127.59, 128.40, 129.25, 135.89, 194.80
2d	2979, 1736 (C=O), 1373, 1245, 1047, 913, 734	1.15, 1.16 (d, 3H, J = 1.34), 1.17, 1.18 (d, 3H, J = 1.34), 2.34 (s, 3H, MeCO), 2.91–2.96 (m, 1H, CH)	22.09, 28.55, 41.22, 194.86
2e	2963, 1735 (C=O), 1456, 1364, 1111, 939, 863, 741	2.26 (s, 9H), 2.41 (s, 3H, MeCO)	29.81, 41.89, 48.68, 195.13
2f	2965, 1734 (C=O), 1689, 1458, 1351, 1110, 939, 863	0.92–0.97 (t, 3H, J = 7.42), 1.23 (s, 6H), 1.54–1.58 (q, 2H, J = 7.42), 2.44 (s, 3H, MeCO)	9.16, 26.98, 28.78, 34.10, 52.60, 195.42
2g	2906, 2849, 2361, 1732 (C=O), 1697, 1450, 1347, 1109, 1040, 939	1.63 (m, 6H), 1.79–1.80 (m, 6H), 2.03 (br, 3H), 2.43 (s, 3H, MeCO)	28.70, 29.79, 35.85, 42.16, 50.32, 195.74

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