Facile Elimination of Ethanethiol in the Reaction of α-Hydroxy-β-bis(ethylthio)acetals with Copper(I) Chloride in Dimethylformamide

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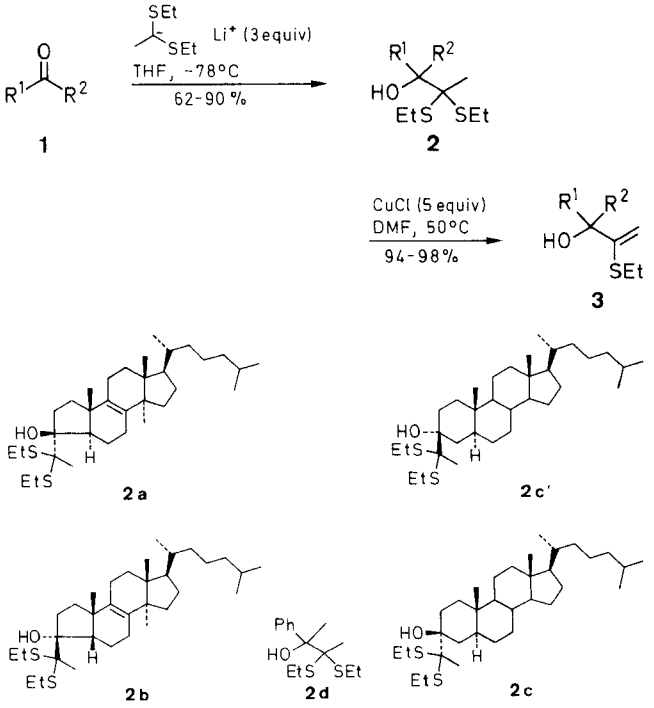
Bis(ethylthio)acetals possessing a hydroxy group in the α-position eliminate, upon reaction with copper(I) chloride in dimethylformamide, cleanly and quantitatively one molecule of ethanethiol with the formation of substituted ethyl vinyl sulfides.

Hydrolysis of *S,S*-acetals to the parent carbonyl compound is accomplished most often in reactions catalyzed by acids (a mineral or Lewis acid) or metal ions.[1] Soft or borderline acceptors such as Hg^{2+}, Ce^{4+}, Tl^{3+}, Ag^{+}, and Cu^{2+} are effective catalysts in such reactions.[2] Alkylative[3] or oxidative[4] cleavages are also efficient. Other recently reported procedures include electroreduction[5] and photolysis.[6] Hard–soft affinity inversion has been postulated in the dehalogenation of α-chloro(fluoro) ketones by using a soft sulfur nucleophile.[7] Also copper(II) chloride/copper oxide acts as dethioacetalization system for dithianes.[8]

In the course of our investigation on sulfur-mediated ring expansions in alicyclic systems,[9] it was found that α-hydroxy-β-bis(ethylthio)acetal **2a**, which was obtained in the reaction of 14α-methyl-A-nor-5α-cholest-8-en-3-one (**1a**) with the lithio 1,1-(diethylthio)ethane, reacted with copper(I) chloride in dimethylformamide with elimination of one molecule of ethanethiol to give the respective vinyl sulfide **3a**. A similar elimination of thiophenol from thioacetals and thioketals induced by the benzene complex of cuprous trifluoromethanesulfonate has been described.[10]

A series of ethylthioacetals **2a–2c'**, derivatives of steroidal ketones, was prepared by the reaction of the appropriate ketone **1a–c** with 1,1-(diethylthio)ethane and butyllithium (Table 1). The stereochemistry of adducts **2** was assigned on the basis of C(19)-methyl shift comparison[11] in ^{1}H-NMR spectra and on the assumption that bulky, sulfur-stabilized carbanion approaches the carbonyl group from the less hindered side of the molecule.



In all cases studied, the reaction of α-hydroxy-β-bis(ethylthio)acetals **2** with copper(I) chloride in dimethylformamide at 50 °C for 15 minutes resulted in the quantitative formation of vinyl sulfides of general formula **3**. Similar elimination of ethanethiol occured in the reaction of the hydroxythioacetal **2d**, obtained from acetophenone.

Table 1. α-Hydroxy-β-bis(ethylthio)acetals **2** and Bis(ethylthio)acetal **4** Prepared

Substrate	Product	Yield (%)	mp (°C) (solvent)	$[\alpha]_D^{20}$ ($c = 1$, CH_2Cl_2)	Molecular Formula[a]	IR ($CHCl_3$) ν_{OH}	^{1}H-NMR ($CDCl_3$/TMS)[b] δ, J(Hz)
14α-Methyl-A-nor-5α-cholest-8-en-3-one **(1a)**	**2a**	78	54–56 (MeOH/acetone)	+64	$C_{33}H_{58}OS_2$ (534.9)	3520	0.73 (s, 3H, 18-CH_3), 1.11 (s, 3H, 19-CH_3), 1.24 (t, 6H, $J = 7.3$, $CH_2C\underline{H}_3$), 2.62 (br s, 1H, OH), 2.69, 2.71 (2q, 2H each, $J = 7.3$, $C\underline{H}_2CH_3$)
14α-Methyl-A-nor-5β-cholest-8-en-3-one **(1b)**	**2b**	65	71–73 (acetone)	−21	$C_{33}H_{58}OS_2$ (534.9)	3510, 3410	0.72 (s, 3H, 18-CH_3), 1.11 (s, 3H, 19-CH_3), 1.23 (t, 6H, $J = 7$, $CH_2C\underline{H}_3$), 2.69, 2.72 (2q, 2H each, $J = 7$, $C\underline{H}_2CH_3$)
5α-Cholestan-3-one **(1c)**	**2c**	53	oil	+16	$C_{33}H_{60}OS_2$ (536.9)	3505	0.65 (s, 3H, 18-CH_3), 0.88 (s, 3H, 19-CH_3), 1.24 (t, 6H, $J = 7$, $CH_2C\underline{H}_3$), 2.70 (q, 4H, $J = 7.3$, $C\underline{H}_2CH_3$)
5α-Cholestan-3-one **(1c)**	**2c′**	37	157–158 (MeOH/CH_2Cl_2)	+ 6.5	$C_{33}H_{60}OS_2$ (536.9)	3495	0.64 (s, 3H, 18-CH_3), 0.74 (s, 3H, 19-CH_3), 1.24 (t, 6H, $J = 7.3$, $CH_2C\underline{H}_3$), 2.31 (br s, 1H, OH), 2.69 (q, 4H, $J = 7.3$, CH_2CH_3)
Acetophenone **(1d)**	**2d**	62	oil	–	$C_{14}H_{22}OS_2$ (270.5)	3590, 3480	0.96, 0.99 (2t, 3H each, $J = 7.3$, $CH_2C\underline{H}_3$), 1.47, 1.79 (2s, 3H each, CCH_3), 2.20, 2.35 (2q, 2H each, $J = 7.3$, $C\underline{H}_2CH_3$), 3.31 (s, 1H, OH), 7.12–7.30 (m, $3H_{arom}$), 7.67–7.78 (m, $2H_{arom}$)[c]
3β-Acetoxy-5-pregnen-20-one **(1e)**	**4**	43	103–104 (MeOH)	−83.5	$C_{27}H_{44}O_2S_2$ (464.8)	–	0.89 (s, 3H, 18-CH_3), 1.02 (s, 3H, 19-CH_3), 1.21 (t, 6H, $J = 7.2$, $CH_2C\underline{H}_3$), 1.83 (s, 3H, 21-CH_3), 2.02 (m, 3H, CH_3CO), 2.59 (m, 4H, $C\underline{H}_2CH_3$), 4.56 (m, 1H, H-3α), 5.34 (m, 1H, H-6)

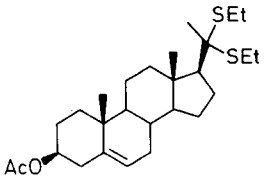
[a] Satisfactory microanalyses obtained: C ±0.24, H ±0.09. Mass spectral fragmentations are in accordance with the proposed structures.
[b] Only relevant signals are given.
[c] Measured in C_6D_6.

Table 2. Vinyl Sulfides **3** Prepared

Product	Yield (%)	mp (°C) (solvent)	$[\alpha]_D^{20}$ ($c = 1$, CH_2Cl_2)	Molecular Formula[a]	IR ($CHCl_3$) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[b] δ, J(Hz)
3a	98	95–96 (MeOH)	+115	$C_{31}H_{52}OS$ (472.8)	3590, 1595	0.73 (s, 3H, 18-CH_3), 1.12 (s, 3H, 19-CH_3), 1.30 (t, 3H, $J = 7.3$, $CH_2C\underline{H}_3$), 2.73 (q, 2H, $J = 7.3$, $C\underline{H}_2CH_3$), 4.81, 5.41 (2 br s, 1H each, $=CH_2$)
3b	97	oil	− 58.5	$C_{31}H_{52}OS$ (472.8)	3590, 3525, 1595	0.73 (s, 3H, 18-CH_3), 1.14 (s, 3H, 19-CH_3), 1.31 (t, 3H, $J = 7.3$, $CH_2C\underline{H}_3$), 2.10 (br s, 1H, OH), 2.74 (q, 2H, $J = 7.3$, $C\underline{H}_2CH_3$), 4.82, 5.48 (2 br s, 1H each, $=CH_2$)
3c	96	100–101 (Et_2O/MeOH)	+ 48.5	$C_{31}H_{54}OS$ (474.8)	3580, 3450, 1604	0.64 (s, 3H, 18-CH_3), 0.85 (s, 3H, 19-CH_3), 1.32 (t, 3H, $J = 7.6$, $CH_2C\underline{H}_3$), 2.25 (br s, 1H, OH), 2.74 (q, 2H, $J = 7.6$, $C\underline{H}_2CH_3$), 4.98, 5.45 (2 br s, 1H each, $=CH_2$)
3c′	97	111–113 (Et_2O/MeOH)	+ 22	$C_{31}H_{54}OS$ (474.8)	3585, 3490, 1600	0.65 (s, 3H, 18-CH_3), 0.80 (s, 3H, 19-CH_3), 1.31 (t, 3H, $J = 7.6$, $CH_2C\underline{H}_3$), 1.69 (br s, 1H, OH), 2.73 (q, 2H, $J = 7.6$, $C\underline{H}_2CH_3$), 4.77, 5.43 (2 br s, 1H each, $=CH_2$)
3d	94	oil	–	$C_{12}H_{16}OS$ (208.3)	3595, 3490, 1595	0.91 (t, 3H, $J = 7.3$, $CH_2C\underline{H}_3$), 1.70 (s, 3H, CCH_3), 2.27 (q, 2H, $J = 7.3$, $C\underline{H}_2CH_3$), 2.68 (br s, 1H, OH), 4.83, 5.48 (2 br s, 1H each, $=CH_2$), 7.10–7.29 (m, $3H_{arom}$), 7.51–7.68 (m, $2H_{arom}$)[c]

[a] Satisfactory microanalyses obtained: C ±0.29, H ±0.11. Mass spectral fragmentations are in accordance with the proposed structures.
[b] Only relevant signals are given.
[c] Measured in C_6D_6.

The bis(ethylthio)acetal **4** lacking the properly positioned hydroxy group did not react in the above conditions and was isolated unchanged. A series of sulfur spiro compounds **5**, derivatives of 5α-cholestan-3-one (**1c**), were also investigated. However, no selective cleavage of C–S bond was observed. Instead, in reactions of thiazolidine **5b**[12] and oxathiolane **5c**,[13] the parent ketones were isolated. These were formed evidently at the workup stage. In the cases of dithiolane **5a**[14] and oxathiolane **5d**[13] the substrates were isolated unchanged.



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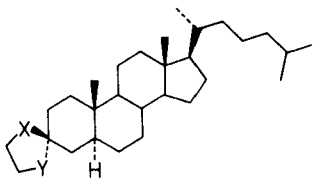

5a X = Y = S
b X = NH, Y = S
c X = O, Y = S
d X = S, Y = O

These results suggest that tertiary hydroxy group in α-position to the thioacetal moiety is required for a selective elimination of one molecule of ethanethiol under the reaction conditions. Thus, the reaction of 2α-hydroxy-5α-cholestan-3-one bis(ethylthio)acetal gave a complicated mixture, which was not further investigated.

Melting points were measured with Kofler apparatus and are uncorrected. $[\alpha]_D$ were measured with a Polamat-A Carl-Zeiss Jena polarimeter. IR-spectra were recorded on a Perkin-Elmer 580 IR spectrophotometer and ^{1}H-NMR on a JEOL FX 90 Q spectrometer. Ketones **1a** and **1b** were prepared according to literature,[16] ketones **1c,d** and **e** are commercially available.

α-Hydroxy-β-bis(ethylthio)acetals 2a–d; General Procedure:
1,1-Diethylthioethane[15] (10 mmol) is dissolved in anhydrous THF (15 mL) and the solution is cooled to −78 °C. A 1.25 M solution of BuLi in hexanes (8.0 mL, 10 mmol) is then added and the temperature is raised to 0 °C. After stirring for 2 h the mixture is again cooled to −78 °C. To this a solution of the ketone **1a–d** (3.4 mmol) in dry THF (4 mL) is added rapidly with stirring over 3 min period. After additional 2 h of stirring at −78 °C the reaction is quenched with water (10 drops). The mixture is allowed to warm to r.t. and Et_2O (80 mL) is added. The organic phase is washed with water (100 mL), dried (Na_2SO_4), and concentrated *in vacuo* to an oil. This is purified and separated by chromatography on silica gel (80 g) with benzene/hexane (3:1) as eluent. Pure adducts **2** are crystallized (Table 1).

3β-Acetoxy-20-bis(ethylthio)-5-pregnene (4):
To a solution of 3β-acetoxy-5-pregnen-20-one (**1e**; 405 mg, 1.13 mmol) in benzene (15 mL), ethanethiol (2 mL) and $Et_2O \cdot BF_3$ (0.3 mL) are added. The mixture is refluxed 22 h under Ar, cooled, then washed with NaOH (5%, 5 mL), H_2O (2 × 10 mL), and dried (Na_2SO_4). Evaporation under reduced pressure gives the crude product, which is chromatographed on silica gel (15 g) with benzene as eluent (Table 1).

Elimination of Ethanethiol from α-Hydroxy-β-bis(ethylthio)acetals 2 to Vinyl Sulfides 3; General Procedure:
Compound **2** (0.4 mmol) is dissolved in anhydrous DMF (20 mL) and the mixture is stirred at 50 °C under N_2. Anhydrous CuCl powder (2.0 mmol) is added in one portion and stirring is continued for 15 min. The mixture is cooled to r.t., diluted with benzene/petroleum ether (bp 45 °C) (1:1, 50 mL), washed with 10% NH_4Cl/aq NH_3 (2 × 50 mL), and H_2O (3 × 50 mL). The organic layer is dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield a residue as a white solid, which is purified on a column of silica gel (10 g). Elution with benzene affords the vinyl sulfide **3** in almost quantitative yield (Table 2).

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