Mercaptomethylation Reaction Using Cyclohexanone Dimethyl Dithioacetal *S*-Oxide

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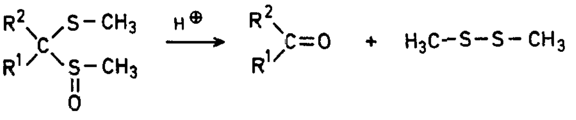
A dimethyl dithioacetal *S*-oxide (**1**), which can be derived either by selective oxidation of the corresponding dimethyl dithioacetal[1] or by alkylation of formaldehyde dimethyl dithioacetal *S*-oxide (**1**, $R^1=R^2=H$)[2], undergoes the acid hydrolysis to decompose into a carbonyl component (**2**) and dimethyl disulfide (**3**).



1 **2** **3**

Hence, this reaction has been used as one of the methods for deprotection of aldehyde (or ketone) dimethyl dithioacetal *S*-oxides[2]. Now, we wish to report the first application of this reaction to the mercaptomethylation of a carbonyl compound, an imine, and an alkyl halide as shown in Schemes **A** and **B**, which consists of four steps: (i) selective formation of the carbanion on the methyl group adjacent to the sulfinyl group in **1**, (ii) the reaction of the thus-formed carbanion with an appropriate functional group, (iii) the subsequent acid hydrolysis, and (iv) reduction of the disulfides obtained in this manner. Among a variety of dimethyl dithioacetal *S*-oxides, we employed cyclohexanone dimethyl dithioacetal *S*-oxide (**4**, m.p. 58.5–59.5°) as a starting compound because it can be easily obtained in a pure form[3] and the carbon between the sulfinyl and the thio groups in **4** is masked from the carbanion formation[4].

The carbanion **5**, which could be formed by the action of lithium diethylamide on **4** in tetrahydrofuran at −15°, was allowed to react at −78° to room temperature with benzophenone to afford a hydroxysulfoxide **6a** in 96% yield. Treatment of **6a** with a small amount of 9*N* sulfuric acid in diethyl ether gave a mixture consisting of two disulfides (**7a** and **8a**, mol ratio of 76:24), which was reduced with lithium aluminum hydride in tetrahydrofuran to form a monothioglycol **9a** (overall yield from **4**: 87%). In a similar way, piperonal was also transformed into the corresponding monothioglycol **9b** (overall yield of **4**→**9b**: 65%).

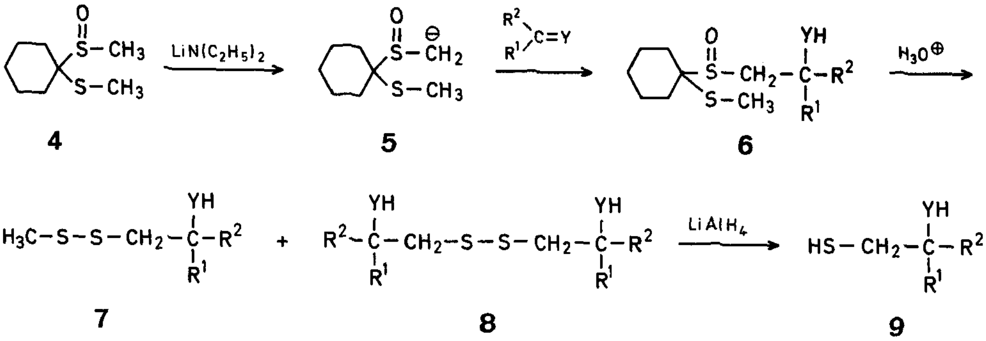
This method can be also applied to the mercaptomethylation of an imine. As a typical example, we now show the conversion of *N*-benzylideneaniline into 2-phenylamino-2-phenylethanethiol (**9c**). *N*-Benzylideneaniline reacted with the carbanion **5** to yield an adduct **6c**, which was converted into **9c** by treatment with 9*N* sulfuric acid in ether, followed by reduction with lithium aluminum hydride in tetrahydrofuran (overall yield: 73%).

By using the analogous method as mentioned above, transformation of an alkyl halide into the alkanethiol, which has a longer carbon chain by one methylene unit than the original halide, is successfully achieved (Scheme **B**). For example, dodecanethiol was obtained in an overall yield of 64% on sequential treatment of undecyl iodide with **5** to give **10a**, acid hydrolysis to a mixture of **11a** and **12a**, and reduction with lithium aluminum hydride.

Transformation of Benzophenone into 9a; Typical Procedure:
To a solution containing diethylamine (1.4 ml) in tetrahydrofuran (30 ml), was added an *n*-hexane solution (8.1 ml) of *n*-butyllithium (1.4 mmol/ml) at −15°, followed by stirring for 20 min. After addition of **4** (2.189 g, 11.38 mmol), the solution was stirred at −15° for 20 min. Then benzophenone (2.283 g, 12.53 mmol) was added at −75°, and the resulting mixture was stirred at −75° for 2.5 h and at room temperature for 16 h. After addition of water (10 ml), the reaction mixture was extracted with dichloromethane (50 ml × 3). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. Recrystallization of the residue from *n*-hexane/benzene gave **6a** as colorless crystals; yield: 4.085 g, 10.9 mmol (96%); m.p. 110–112°. These crystals were used for the following reaction without further purification.

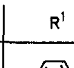
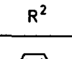
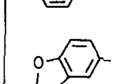
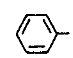
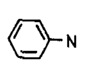
I.R. (KBr): ν_{max} = 3180, 1445, 1055, 1025, 1010, 700 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ = 1.72 (broad s, 10H), 1.96 (s, 3H), 3.72 (ABq, 2H, J = 13 Hz), 5.62 (s, 1H, OH), 7.15–7.75 ppm (m, 10H).

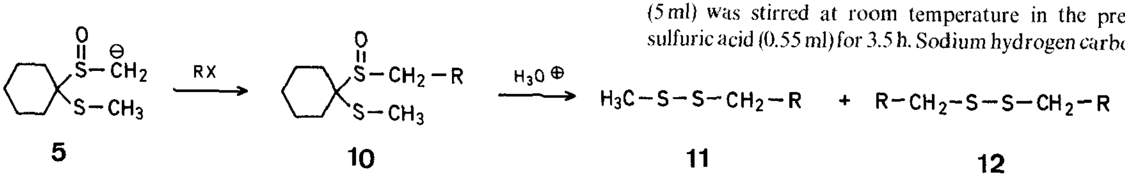


4 5 6

7 8 9

	R^1	R^2	Y	Yield (%) 4→6	Yield (%) 6→9
a			O	96	91
b		H	O	77	84
c		H		82	89

Scheme **A**



5 10 11 12

13a R = n-C$_{11}$H$_{23}$

Scheme **B**

Synthesis of Cyclohexanone Dimethyl Dithioacetal *S*-Oxide (4):
To a solution containing cyclohexanone dimethyl dithioacetal (101.6 g, 0.577 mol) in methanol (150 ml), after the addition of sodium tungstate (150 mg), was dropwise added a 30% aqueous solution (53 ml, 0.47 mol) of hydrogen peroxide during 30 min under cooling with ice-water, and then the resulting mixture was stirred at room temperature for 30 min. After evaporation of the methanol and the water under reduced pressure, the residue was dissolved in chloroform (200 ml) and dried over anhydrous sodium sulfate. Evaporation under reduced pressure and crystallization from *n*-hexane gave cyclohexanone dimethyl dithioacetal *S*-oxide (**4**) as colorless crystals; yield: 84.01 g, 0.437 mol (76%); m.p. 58.5–59.5°.

$C_8H_{16}OS_2$	calc.	C 49.95	H 8.22	S 33.34
(192.4)	found	50.08	8.22	33.26

I.R. (KBr): ν_{max} = 1045 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ = 1.5–2.1 (m, 10H), 2.08 (s, 3H), 2.60 ppm (s, 3H).

A suspension containing **6a** (304 mg, 0.812 mmol) in diethyl ether (5 ml) was stirred at room temperature in the presence of 9*N* sulfuric acid (0.55 ml) for 3.5 h. Sodium hydrogen carbonate (excess) was added, followed by additional stirring. After the addition of dichloromethane (10 ml), the insoluble matter was filtered off and the filtrate was dried over anhydrous sodium sulfate. Evaporation under reduced pressure afforded a yellow oil (252 mg) which was shown by N.M.R. analysis to consist of **7a** and **8a**.

The similar oil obtained in another run was separated by column chromatography on silica gel [eluted with *n*-hexane/benzene (1:1), benzene, dichloromethane, and ethyl acetate] to afford **7a** (71%) and **8a** (22%).

7a: colorless oil

$C_{15}H_{16}OS_2$	calc.	C 65.17	H 5.83	S 23.20
(276.4)	found	65.29	5.67	23.31

I.R. (film): ν_{max} = 3450, 1490, 1445, 700 cm^{-1}

^{1}H-N.M.R. (CDCl$_3$): δ=2.33 (s, 3H), 3.33 (s, 1H, OH), 3.78 (s, 2H), 7.10–7.55 ppm (m, 10H).

8a: pale yellow crystals; m.p. 107.5–108°.

$C_{28}H_{26}O_2S_2$	calc.	C 73.32	H 5.71	S 13.98
(458.6)	found	73.08	5.70	13.77

I.R. (KBr): ν_{max}=3500, 1490, 1445, 1055, 980, 775, 755, 700, 695 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ=3.26 (s, 2H, 2 OH), 3.62 (s, 4H), 7.12–7.42 ppm (m, 20H).

When **6a** (1.705 g, 4.55 mmol) was stirred in the presence of 9*N* sulfuric acid (2 ml) in diethyl ether (20 ml), a thiosulfinate **14** was formed in 44% yield, together with **7a** (45%) and **8a** (13%).
The thiosulfinate **14** was also reduced with lithium aluminum hydride to give **9a**.

14; colorless crystals; m.p. 145–148°.

$C_{28}H_{26}O_3S_2$	calc.	C 70.85	H 5.52	S 13.51
(474.6)	found	70.87	5.54	13.72

I.R. (KBr): ν_{max}=3375, 1490, 1450, 1055, 755, 695 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ=3.39 (broad s, 1H, OH), 3.88 (s, 2H), 3.92 (ABq, 2H, J=14 Hz), 4.86 (broad s, 1H, OH), 7.08–7.54 ppm (m, 20H).

This oil (**7a**+**8a**) was dissolved in tetrahydrofuran (5 ml) and lithium aluminum hydride (52 mg, 1.37 mmol) was added, followed by stirring at room temperature for 1.5 h. After the addition of water (20 ml) and saturated aqueous solution (1.5 ml) of ammonium chloride, the mixture was extracted with diethyl ether (30 ml × 4). The extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was column-chromatographed on silica gel [eluted with *n*-hexane/benzene (1:1)] to give **9a** as colorless crystals; yield of **6a**→**9a**: 170 mg, 0.738 mmol (91%); m.p. 49–52°.

$C_{14}H_{14}OS$	calc.	C 73.00	H 6.13	S 13.92
(230.3)	found	73.00	6.20	13.89

I.R. (KBr): ν_{max}=3420, 2550, 1490, 1445, 755, 700 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ=1.21 (t, 1H, J=8.8 Hz), 3.34 (d, 2H, J=8.8 Hz), 3.52 (s, 1H, OH), 7.14–7.47 ppm (m, 10H).

In a similar manner, piperonal and *N*-benzylideneaniline were converted to **9b** and **9c**, respectively.

9b: m.p. 54–55°.

$C_9H_{10}O_3S$	calc.	C 54.53	H 5.08	S 16.18
(198.2)	found	54.69	4.93	16.12

I.R. (KBr): ν_{max}=3130, 1500, 1240, 1040 cm^{-1} [5].

^{1}H-N.M.R. (CDCl$_3$): δ=1.39 (t, 1H, J=8.7 Hz), 2.60–2.84 (m, 2H), 2.80 (s, 1H, OH), 4.56 (d of d, 2H, J=6.6 and 6.0 Hz), 5.89 (s, 2H), 6.74 (broad s, 2H), 6.78 ppm (d, 1H, J=1.6 Hz).

9c: colorless oil.

I.R. (film): ν_{max}=3370, 2550, 1600, 1505, 755, 695 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ=1.25 (broad s, 1H), 2.92 (broad s, 2H), 4.48 (broad s, 1H), 4.47 (t, 1H, J=6.0 Hz), 6.46–6.68 (m, 3H), 6.9–7.2 (m, 2H), 7.2–7.4 ppm (m, 5H).

Mass spectrum: m/e=230.0944 ($M^{\oplus}$+1, calc. 230.0958), 229.0904 ($M^{\oplus}$, calc. 229.0924).

Derivation of Undecyl Iodide into Dodecanethiol:
To a solution of lithium diethylamide, prepared by the action of *n*-butyllithium [2.6 ml of *n*-hexane solution (1.4 mmol/ml)] on diethylamine (0.29 ml) in tetrahydrofuran (10 ml), was added **4** (533 mg, 2.77 mmol) at −15°, followed by stirring at −15° for 2 h. After the addition of undecyl iodide (947 mg, 3.36 mmol), the resulting solution was stirred at −70° for 2 h and at room temperature for 14 h. Then water (10 ml) was added and the organic component was extracted with dichloromethane (30 ml × 4). The extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was column-chromatographed on Florisil (eluted with *n*-hexane) to give **10a** as a colorless oil; yield (from **4**): 670 mg, 1.93 mmol (70%).

This oil (**10a**; 532 mg, 1.53 mmol) was dissolved in diethyl ether (10 ml) and 9*N* sulfuric acid (1 ml) was added. Then the resulting mixture was stirred for 62 h at room temperature. After the sequential work-up consisting of neutralization with sodium hydrogen carbonate, filtration of the insoluble matter, and drying over anhydrous sodium sulfate, the solution was evaporated under reduced pressure to afford yellow crystals (389 mg), which were shown by N.M.R. analysis to consist of **11a** and **12a** (ca. 3:1). These crystals were dissolved in tetrahydrofuran (6 ml) and lithium aluminum hydride (60 mg, 1.58 mmol) was added, followed by stirring at room temperature for 3 h. After the addition of water (20 ml) and saturated aqueous solution (1.5 ml) of ammonium chloride, the reaction mixture was extracted with diethyl ether (30 ml × 4), and the organic layer was dried over anhydrous sodium sulfate. Evaporation under reduced pressure gave a yellow oil (321 mg), which was column-chromatographed on silica gel [eluted with *n*-hexane/benzene (1:1)] to afford a colorless oil; yield: 284 mg, 1.40 mmol. This oil was identified as dodecanethiol by the comparison of its N.M.R. and I.R. spectra with those of an authentic specimen. The yield of dodecanethiol from **10a** was 91%.

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[2] K. Ogura, G. Tsuchihashi, *Tetrahedron Lett.* **1971**, 3151.
H. Nieuwenhuyse, R. Louw, *Tetrahedron Lett.* **1971**, 4141.
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See also: G. Schill, P. R. Jones, *Synthesis* **1974**, 117.

[3] Ketone dimethyl dithioacetal *S*-oxides (**1**, $R^1=R^2$=alkyl or aryl) are relatively unstable under an acidic condition or at an elevated temperature. Hence, **1**, which is crystalline and can be readily purified by recrystallization, is one of the best choice for the starting material.

[4] Formation of the dianion of **1** ($R^1=R^2=H$) and its reaction are now being studied. These results will be reported in the near future.

[5] The infrared absorption of the SH group in **9b** is too weak to be observed.