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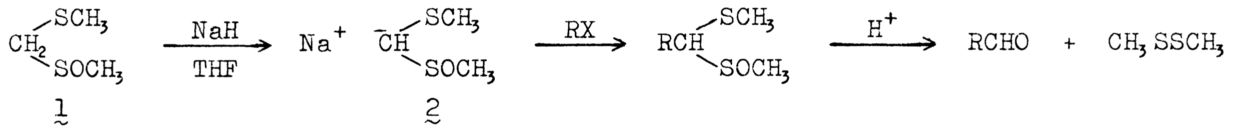
A NEW TRANSFORMATION OF AN ESTER INTO ITS HOMOLOG AND AN α-HYDROXYALDEHYDE USING METHYL METHYLTHIOMETHYL SULFOXIDE

Katsuyuki OGURA, Shigeko FURUKAWA, and Gen-ichi TSUCHIHASHI
Sagami Chemical Research Center
Nishi-Ohnuma, Sagamihara, Kanagawa 229

The carbanion (**2**) generated from methyl methylthiomethyl sulfoxide (**1**) reacts with an ester to afford an acylated product (**3**). This compound can be transformed into derivatives of the corresponding α-hydroxyaldehyde and also into the ester which has one more methylene group than the original ester (Scheme 2).

We recently established methods of synthesizing labile aldehydes (Scheme 1),[1] α-hydroxyaldehydes,[2] phenylacetic acid derivatives,[3] and amino acids[4] by the reaction of the carbanion (**2**) generated from methyl methylthiomethyl sulfoxide (**1**).

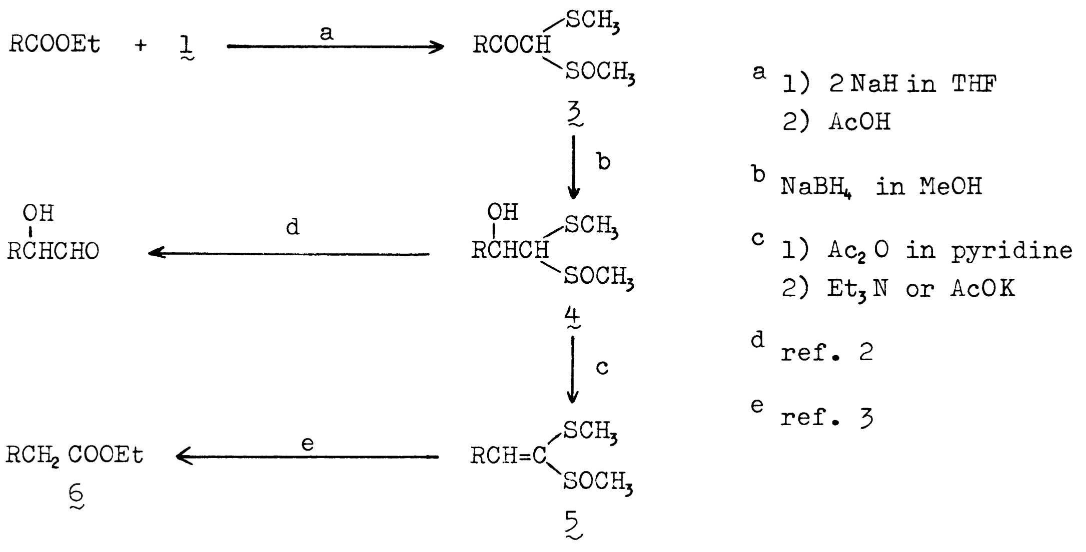
Scheme 1



We now report a new way of making derivatives of an α-hydroxyaldehyde and homologation of an ester by using **1**.

Methyl methylthiomethyl sulfoxide (**1**) reacts with an ester in the presence of sodium hydride (2 equiv) in tetrahydrofuran at room temperature to give an acyl derivative (**3**)[5,7] as shown in Scheme 2. The selective reduction of **3** can be achieved by the action of sodium borohydride in methanol, affording the corresponging α-hydroxyaldehyde dimethyl dithioacetal S-oxide (**4**). Starting from **4**, various derivatives of an α-hydroxyaldehyde are obtained by the known method.[2] The dehydration of **4** is effected by sequential treatment with acetic anhydride - pyridine and with triethylamine or potassium acetate to yield a ketene dimethyl dithioacetal S-oxide (5). The treatment of 5 with hydrogen chloride in ethanol affords the ester (6) which has one more methylene group than the starting ester.

Scheme 2



a 1) 2 NaH in THF
2) AcOH

b NaBH$_4$ in MeOH

c 1) Ac$_2$O in pyridine
2) Et$_3$N or AcOK

d ref. 2

e ref. 3

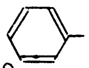
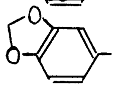
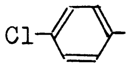
The following procedure is representative. Methyl methylthiomethyl sulfoxide (1, 2.400 g, 19.4 mmol) was treated with sodium hydride (2.10 equiv) in tetrahydrofuran (20 ml) at room temperature for 1.5 hr and, after the addition of ethyl benzoate (3.40 ml, 23.8 mmol), the resulting mixture was stirred at room temperature for 15 hr. Methylene chloride (40 ml), water (4 ml), and acetic acid (2.4 ml) were successively added and the solid deposited was filtered off. After dried over anhydrous sodium sulfate, the filtrate was evaporated under reduced pressure. The residue was crystallized from carbon tetrachloride-cyclohexane to give 3.521 g (15.4 mmol) of 3 (R = Ph).[8,9,10]

To a solution containing 3 (R = Ph, 363 mg, 1.59 mmol) in methanol (25 ml), was added sodium borohydride (61 mg, 1.6 mmol) under cooling with ice-water, and the mixture was stirred at room temperature for 3 hr. After the addition of acetone (2 ml) and the removal of the solvent, the residue was dissolved in methylene chloride and the resulting solid was filtered off. The filtrate was evaporated under reduced pressure to give 365 mg (98%) of mandelaldehyde dimethyl dithioacetal S-oxide (4, R = Ph).[2]

Pyridine (6 ml) and acetic anhydride (6 ml) were added to crude 4 (R = Ph), obtained from 3 (R = Ph, 877 mg, 3.81 mmol), and the mixture was stirred at room temperature for 17.5 hr. After the removal of pyridine, acetic anhydride, and acetic acid under reduced pressure, the residue was chromatographed (on silica gel, eluted with methylene chloride) to afford 927 mg (89% from 3, R = Ph) of the corresponding acetate. The acetate (830 mg, 3.05 mmol) was dissolved in methanol (50 ml) and, after the addition of triethylamine (0.90 ml), the solution was refluxed for 19 hr. The solvent was removed under reduced pressure and the residue was separated by column chromatography (on silica gel, eluted with methylene chloride) to yield 573 mg (85%) of phenylketene dimethyl dithioacetal S-oxide (5, R = Ph). By the procedure previously reported,[3] 5 (R = Ph) can be converted into the ethyl ester (6, R = Ph) in 78% yield.

In a similar way, esters of homopiperonylic acid, (p-chlorophenyl)acetic acid, and 4-phenylbutyric acid were obtained from esters of piperonylic acid, p-chlorobenzoic acid, and hydrocinnamic acid, respectively. The yields are shown in the Table.

Table. Yields (%) of Products

R	1 → 3	3 → 4	3 → 5	5 → 6
	83 (84)[a]	98	76	78[b]
	77 (81)[a]	96	76	91[b]
	66	77	61	92[b]
$PhCH_2CH_2$-	50 (69)[a]	99	80	76

[a] the yield based on the unrecovered 1.

[b] ref. 3

It should be noted that the transformation of 5 into 6 (step e in Scheme 2) proceeds successfully not only in the case that R is aryl,[3] but also in the case that R is alkyl. Thus, this whole sequence provides a simple and efficient way of homologation of esters.

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REMARKS AND REFERENCES

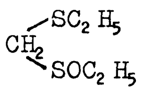
1) K. Ogura and G. Tsuchihashi, Tetrahedron Lett., **1971**, 3151.

2) K. Ogura and G. Tsuchihashi, Tetrahedron Lett., **1972**, 2681.

3) K. Ogura and G. Tsuchihashi, Tetrahedron Lett., **1972**, 1383.

4) K. Ogura and G. Tsuchihashi, J. Amer. Chem. Soc., **96**, 1960 (1974).

5) During the course of our investigation, Schlessinger and his co-workers reported the reaction of the lithio derivative of ethyl ethylthiomethyl sulfoxide (**7**) with an ester to form the corresponding acylated product (the ethyl analog of **3**).[6] In this case, two equivalents of the lithio derivative is required per one equivalent of the ester and one equivalent of the starting sulfoxide should remain unchanged.



$CH_2(SC_2H_5)(SOC_2H_5)$

7

6) J. L. Herrmann, J. E. Richman, P. J. Wepplo, and R. H. Schlessinger, Tetrahedron Lett., **1973**, 4707.

7) The acyl derivative (**3**) can be converted into the ester of the corresponding α-ketocarboxylic acid. Thus, the reaction of **3** with one mol-equivalent of $CuCl_2$ ($SnCl_4$) in 1,2-dimethoxyethane or R'OH (R' = Me or Et) afforded $RCOCOSCH_3$ or RCOCOOR', respectively, in moderate yields.

8) The mother liquor was evaporated under reduced pressure, and the residue was chromatographed (on silica gel, eluted with methylene chloride) to give additional 149 mg of **3** (R = Ph). The yield of **3** (R = Ph) amounted to 83%.

9) The obtained crystals were shown by an NMR analysis to consist of two diastereomers (5 : 4), of which the ratio was not reproducible since the interconversion between these isomers took place thermally. The NMR signals of the major isomer appeared at δ 2.20 (s, 3H), 2.87 (s, 3H), 5.27 (s, 1H), 7.68 (m, 3H), and 8.00 (m, 2H), while those of the minor isomer appeared at δ 2.27 (s, 3H), 2.67 (s, 3H), 5.17 (s, 1H), 7.68 (m, 3H), and 8.00 (m, 2H). The mixture was purified by recrystallization from carbon tetrachloride to give colorless crystals (the ratio of the diastereomers = 8 : 3); mp 99.5 - 101°C, IR (KBr): 1665 cm^{-1} (C=O) and 1047 cm^{-1} (S=O). *Anal*. Calcd for $C_{10}H_{12}O_2S_2$: C, 52.60; H, 5.30; S, 28.09. Found: C, 52.54; H, 5.33; S, 28.05.

10) Satisfactory elemental analyses and acceptable spectral data were obtained for all new compounds reported herein.

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