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A VERSATILE REAGENT FOR ALDEHYDE SYNTHESIS. METHYL METHYLTHIOMETHYL SULFOXIDE.

Katsuyuki Ogura and Gen-ichi Tsuchihashi
Sagami Chemical Research Center
Ohnuma, Sagamihara, Kanagawa 229 Japan

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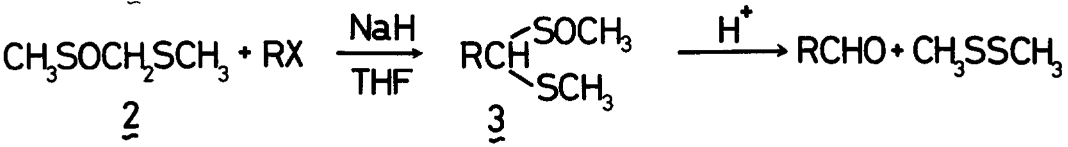
Synthesis of aldehyde from formaldehyde mercaptal was achieved by the early work of Fröling and Arens.1) This route was further developed by Corey and Seebach to the generally applicable aldehyde- and ketone-syntheses by using 1,3-dithiane as a starting substance.2)

$$RX + CH_2(SR')_2 \longrightarrow \underset{\mathbf{1}}{RCH(SR')_2} \longrightarrow RCHO$$

However, the transformation of the mercaptal 1 to the corresponding aldehyde requires rather complicated procedures.3)

We have found that carbanion can be easily generated from methyl methylthiomethyl sulfoxide (2) by the action of sodium hydride (1 equiv.), and this carbanion reacts with an alkyl halide to give an aldehyde dimethyl mercaptal S-oxide (3).



$$\underset{\mathbf{2}}{CH_3SOCH_2SCH_3} + RX \xrightarrow[THF]{NaH} \underset{\mathbf{3}}{RCH\genfrac{}{}{0pt}{}{SOCH_3}{SCH_3}} \xrightarrow{H^+} RCHO + CH_3SSCH_3$$

The dimethyl mercaptal S-oxide 3 thus obtained is easily hydrolyzed in the presence of a catalytic amount of sulfuric acid to give the corresponding aldehyde and dimethyl disulfide.4)

The aldehyde synthesis by this pathway is superior to that by the previously reported route in view of the following points. i) The carbanion is easily generated and stable. ii) The hydrolysis of 3 can be accomplished under a mild condition and the only by-product is dimethyl disulfide in this hydrolysis. iii) The dimethyl mercaptal S-oxide 3 can be used as an aldehyde-equivalent. For example, the treatment of 3 with ethyl orthoformate directly affords diethyl acetal of the corresponding aldehyde.

In this communication, we would like to report the general procedure of this new method and the application to the synthesis of labile aldehydes such as (p-methoxyphenyl)acetaldehyde and (3,4-dihydroxyphenyl)acetaldehyde. These kinds of aldehydes are considered as key-intermediates for the biosynthesis of isoquinoline alkaloids. Further, from the latter aldehyde, DL-dopa was obtained by applying the Strecker reaction, in a high yield.

First, the general procedure will be described. Methyl methylthiomethyl sulfoxide was treated with sodium hydride in tetrahydrofuran, and then, after the addition of alkyl or aralkyl halide, the reaction mixture was stirred at room temperature, or, if necessary, at an elevated temperature (30-40°). The solid deposited by the addition of dichloromethane was filtered off and the filtrate was evaporated. The dimethyl mercaptal S-oxide 3 was separated by column-chromatography on silica gel or florisil. The S-oxide 3 was treated with a catalytic amount of such acid as sulfuric or hydrochloric acid in tetrahydrofuran to yield an aldehyde. The aldehyde which is sensitive to an acid can be trapped once as the corresponding acetal by treatment of 3 with a trace of sulfuric acid in the presence of ethyl orthoformate in ethanol, and then the resulting acetal is easily converted to the aldehyde under milder acidic condition. The results were summarized in Table I.

Table I. Yields of 3 and Aldehyde

Halide	Yield (%) of 3[a]	Yield (%) of Aldehyde[b]
CH_3I	92	84[c]
n-C_4H_9I	72	91[c]
$C_6H_5CH_2Br$	92	88[d]
p-$BrC_6H_4CH_2Br$	37	85[d]

[a] Based on the reacted 2.

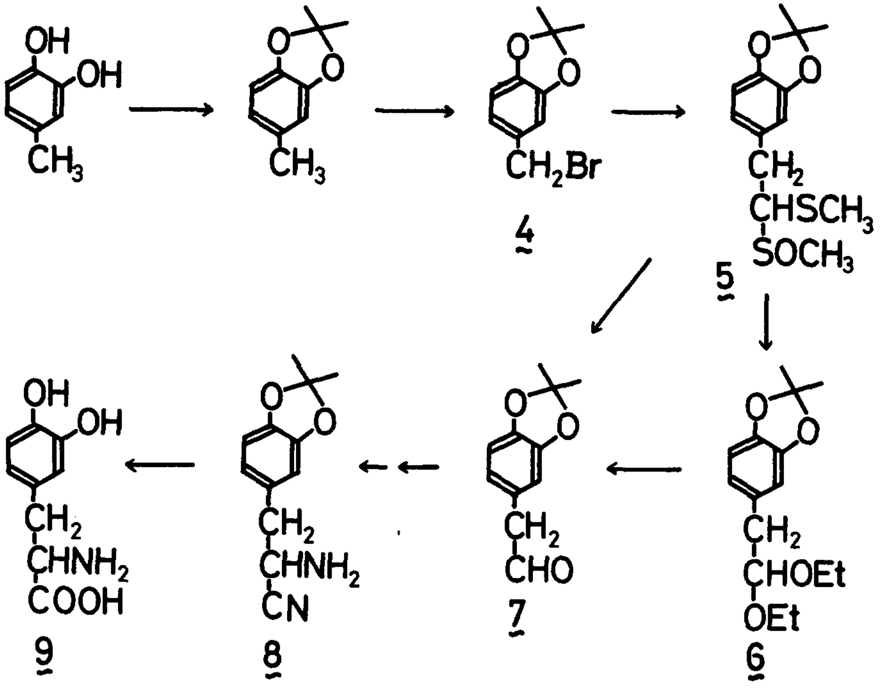
[b] Based on 3.

[c] Trapped as 2,4-dinitrophenylhydrazone.

[d] Trapped as the corresponding diethyl acetal.

Similarly, the reaction of p-methoxybenzyl bromide with 2 gave (p-methoxyphenyl)acetaldehyde dimethyl mercaptal S-oxide in a 79% yield. This dimethyl mercaptal S-oxide was converted to the diethyl acetal with ethyl orthoformate in ethanol, and upon the hydrolysis of the diethyl acetal, (p-methoxyphenyl)-acetaldehyde was obtained in a yield of 82% (based on the dimethyl mercaptal S-oxide).

(3,4-Isopropylidenedioxyphenyl)acetaldehyde was synthesized by the following sequence.



3,4-Isopropylidenedioxytoluene, which was synthesized by the condensation of 4-methylcatechol with acetone in a 70% yield, was brominated by N-bromosuccinimide in refluxing carbon tetrachloride (initiated by benzoyl peroxide) to afford 3,4-isopropylidenedioxybenzyl bromide (4) in a 73% yield. To a solution containing 2 (2.13 g) and sodium hydride (413 mg) in tetrahydrofuran (7.5 ml), 4 (3.23 g) was added, followed by stirring at room temperature for 12 hr and finally at 30° for 2 hr to yield 2.42 g of (3,4-isopropylidenedioxyphenyl)-acetaldehyde dimethyl mercaptal S-oxide (5, 62% based on 4). Although

(3,4-isopropylidenedioxyphenyl)acetaldehyde (**7**) was directly obtained by the acid-treatment of **5**, the optimum yield (65%) of **7** from **5** was achieved by the route passing through the acetal **6**. The aldehyde **7** showed an IR absorption at 1728 cm^{-1} and NMR signals at δ 1.65s (6H), 3.45d (2H, J = 3.7 Hz), 6.55m (3H), and 9.59t (1H, J = 3.7 Hz). Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 69.01; H, 6.27.

The aldehyde **7** was further led to DL-dopa (**9**). The addition of hydrogen cyanide to **7** under a mild alkaline condition in water-methanol was followed by saturation with ammonia to yield the aminonitrile **8**. The hydrolysis of **8** was effected with 6N hydrochloric acid by refluxing for 2 hr, giving DL-dopa directly. The yield was 86% from **7** to **9**.

We have also found that the carbanion derived from **3** reacts with ketones and aldehydes to afford dimethyl mercaptal S-oxide of α-hydroxyaldehydes in excellent yields. Studies on synthesis of α-hydroxyaldehyde by this method are now in progress.

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