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A NEW SYNTHETIC APPROACH TO α-HYDROXYALDEHYDES USING METHYL METHYLTHIOMETHYL SULFOXIDE

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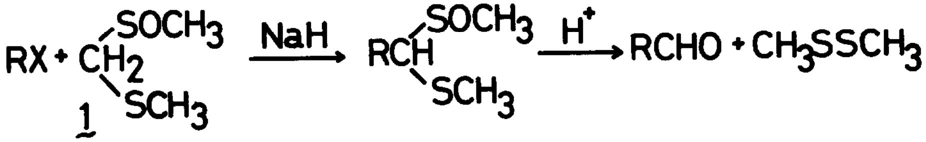
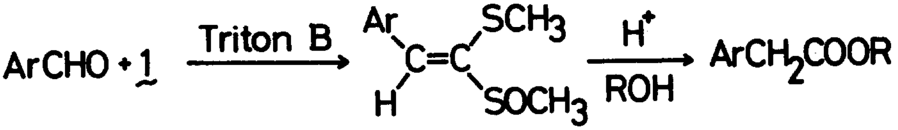
Methyl methylthiomethyl sulfoxide (1) appeared to be a versatile reagent for the syntheses of labile aldehydes[1)] and derivatives of phenylacetic acid[2)].

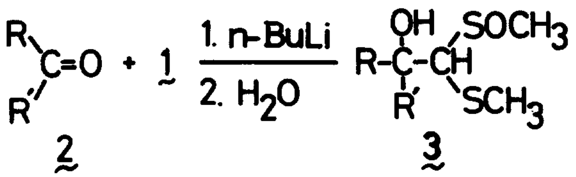


(eq. 1)



(eq. 2)

We have further investigated the synthetic utility of this new reagent[3)], and this communication will describe that the use of 1 provides a convenient way to synthesize derivatives of α-hydroxyaldehydes; the lithio-derivative of 1 reacts smoothly with a carbonyl compound to afford an α-hydroxyaldehyde dimethyl mercaptal S-oxide (3) as shown in eq. 3 and various types of α-hydroxyaldehyde derivatives are obtained, starting from 3.



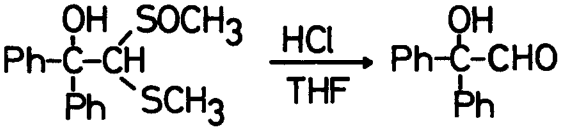
2 3

a. $R=R'=C_6H_5$
b. $R=C_6H_5, R'=H$
c. $R=CH_2\genfrac{<}{>}{0pt}{}{O}{O}C_6H_3$, $R'=H$
d. $R+R'=-(CH_2)_5-$

(eq. 3)

To a solution containing 550 mg of methyl methylthiomethyl sulfoxide (1) in 10 ml of tetrahydrofuran, 3 ml of n-butyl lithium solution (15% in n-hexane) was added and then, after the addition of 900 mg of benzophenone (2a), the mixture was stirred for 1 hr while being cooled with ice-salt. Methylene chloride (50 ml) and water (2 ml) were added successively and the resulting mixture was dried on anhydrous sodium sulfate. After evaporation under reduced pressure, the residue was crystallized from carbon tetrachloride-cyclohexane, giving 915 mg (67%) of diphenylglycelic aldehyde dimethyl mercaptal S-oxide (3a) which was shown by an NMR analysis to consist of two diastereomers of 3a (45 : 55)[4]. In a similar manner, such carbonyl compounds as 2b~2d respectively afforded the corresponding α-hydroxyaldehyde dimethyl mercaptal S-oxides in satisfactry yields.

These dimethyl mercaptal S-oxides were expected to be easily transformed into the corresponding α-hydroxyaldehydes on the analogy of eq. 1.[1] In fact, when diphenylglycelic aldehyde dimethyl mercaptal S-oxide (3a) was treated with conc. hydrochloric acid in tetrahydrofuran at room temperature for 1.5 hr, diphenylglycelic aldehyde (4), mp 53-54° (lit.[5] mp 52-53°), was obtained in a 59% yield. We assigned this structure by its IR (KBr: 3440 and 1720 cm^{-1}) and NMR (δ in CCl_4 : 4.05 broad s (1H), 7.30s (10H) and 9.89s (1H)) spectra. *Anal.* Calcd. for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 78.97; H, 5.98.

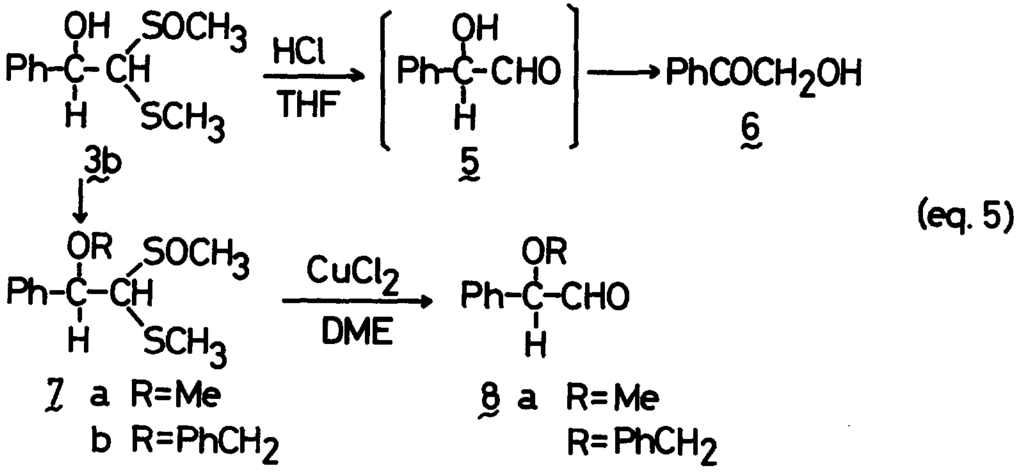


$$\mathrm{Ph{-}\overset{OH}{\underset{Ph}{C}}{-}CH(SOCH_3)(SCH_3)} \xrightarrow[\text{THF}]{\text{HCl}} \mathrm{Ph{-}\overset{OH}{\underset{Ph}{C}}{-}CHO} \qquad \text{(eq. 4)}$$

3a 4

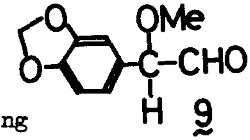
It should be noted that the α-hydroxyaldehyde (4), which is known to undergo the thermal degradation and the acid-catalyzed isomerization,[6] was directly isolated by our method.

When the same procedure was applied to phenylglycelic aldehyde dimethyl mercaptal S-oxide (3b), the expected phenylglycelic aldehyde (5) could not be isolated, but ω-hydroxyacetophenone (6) was obtained. The formation of the latter compound may be rationalized by considering the isomerization of phenylglycelic aldehyde (5). Therefore, in order to obtain the derivatives of 5, it is necessary to protect either the hydroxy group of 3b or the newly-formed



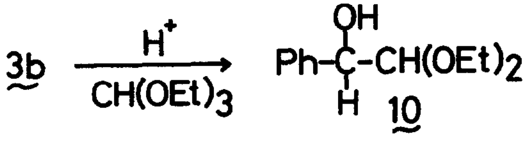
(eq. 5)

formyl group of 5. First, the protection of the hydroxyl group of 3b was achieved by the treatment with sodium hydride, followed by the addition of methyl iodide or benzyl bromide, in dimethyl sulfoxide at room temperature. Thus, the corresponding methyl ether (7a) or benzyl ether (7b) was obtained in 71% or 89% yield, respectively. The transformation of these ethers into the aldehydes (8a and 8b) was accomplished by stirring 7a and 7b with cupric chloride dihydrate in 1,2-dimethoxyethane at room temperature for several hours. The yields of 8a and 8b were 64% and 55%, respectively.[7] Analogously, methoxy(3,4-methylenedioxyphenyl)acetaldehyde (9) was obtained by the similar methylation (76%) of 3c and the subsequent treatment with cupric chloride in refluxing 1,2-dimethoxyethane for 3 min (55%).



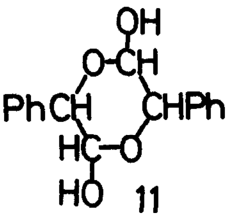
9

Second, the newly-formed formyl group of 5 was found to be protected by the acid-catalyzed reaction of 3b in the presence of ethyl orthoformate. To a solution containing 159 mg of 3b in 5 ml of ethanol, 0.3 ml of ethyl orthoformate and 5 drops of conc. sulfuric acid were added and then the mixture was stirred for 4 days at room temperature. Phenylglycelic aldehyde diethyl acetal (10) was obtained in an 87% yield.

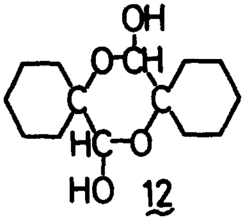


$$3b \xrightarrow[CH(OEt)_3]{H^+} Ph\text{-}\overset{OH}{\underset{H}{C}}\text{-}CH(OEt)_2 \quad \mathbf{10} \qquad \text{(eq. 6)}$$

Direct treatment of 3 with cupric chloride gave quite interesting results; when the solution of 3b and one mole-equivalent of cupric chloride in 1,2-dimethoxyethane was refluxed for 2 min, a dimer (11)[8] of phenylglycelic aldehyde was given in a 76% yield. In a similar manner, 3d was converted into a dimer (12) of 1-formylcyclohexanol in an 81% yield.



11



12

In conclusion, the whole reaction sequence shown here provides a simpler and more efficient way to approach dimers or O-protected derivatives of α-hydroxyaldehydes and α-hydroxyaldehyde acetals. The application of these procedures to the synthesis of sugars is being studied.

REFERENCES

1) K. Ogura and G. Tsuchihashi, Tetrahedron Lett., 3151 (1971).
2) K. Ogura and G. Tsuchihashi, Tetrahedron Lett., 1383 (1972).
3) The method of making this reagent will be disclosed in Bull. Chem. Soc. Japan, No. 7 (1972).
4) Each of these diastereomers could be isolated by the separation with column chromatography on silica gel and the subsequent recrystallization. The structures were assigned by IR, NMR and elemental analyses.
5) T. A. Favorskaya and L. A. Remizova, Zhur. obshchei Khim., **23**, 667 (1953); C. A., **48**, 7588d (1953).
6) S. M. McElvain, S. B. Mirviss, C. L. Stevens, J. Amer. Chem. Soc., **73**, 3807 (1951).
7) The treatment of formaldehyde diphenyl mercaptal S-oxide with cupric chloride gave diphenyl disulfide in a high yield. The detailed result of the reaction of aldehyde dimethyl mercaptal S-oxides with cupric chloride will be reported elsewhere.
8) D. W. Griffiths, C. D. Gutsche, J. Org. Chem., **36**, 2184 (1971).