Tetrahedron Letters No. 15, pp 1383 - 1386, 1972. Pergamon Press. Printed in Great Britain.

A NEW SYNTHESIS OF PHENYLACETIC ACID DERIVATIVES USING METHYL METHYLTHIOMETHYL SULFOXIDE

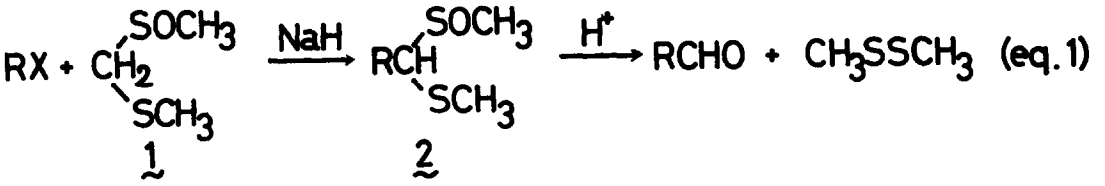
Katsuyuki Ogura and Gen-ichi Tsuchihashi

Sagami Chemical Research Center

Ohnuma, Sagamihara, Kanagawa 229 Japan

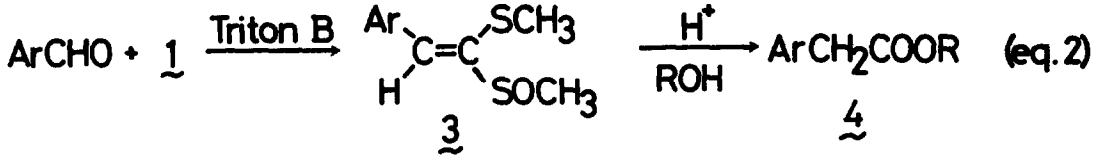
(Received in Japan 8 February 1972; received in UK for publication 2 March 1972)

Recently, we have reported a new method for synthesizing labile aldehydes by using methyl methylthiomethyl sulfoxide (1) according to the following scheme.[1)]



(eq. 1)

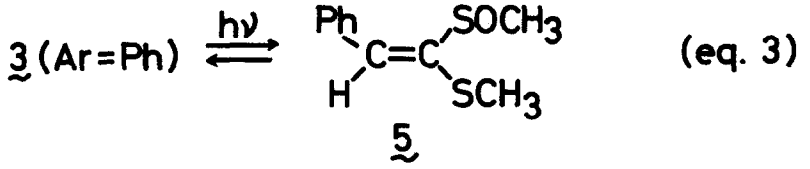
We have further examined the synthetic applicability of this versatile reagent,[2)] and the present communication describes that the sulfoxide 1 undergoes the Knoevenagel-type condensation with benzaldehyde and substituted benzaldehydes to afford 1-methylsulfinyl-1-methylthio-2-arylethylenes (3), of which the decomposition with an acid in ethanol gives ethyl arylacetates (4, R=Et) in high yields.



(eq. 2)

To a solution containing 2.57 g of methyl methylthiomethyl sulfoxide (1) and 3 ml of benzaldehyde in 5 ml of tetrahydrofuran, 2 ml of Triton-B solution (40%) in methanol was added, and then the resultant mixture was refluxed for 4 hr. Separation by column-chromatography on silica gel gave 3.99 g of a colorless oil, $bp_{0.08\ mmHg}$ 149-150°, which was characterized as 1-methylsulfinyl-1-

methylthio-2-phenylethylene (3, Ar=Ph) on the basis of the following evidence. Molecular formula, $C_{10}H_{12}OS_2$, for this oil was confirmed by its mass spectrum (parent peak, m/e 212 and base peak, 149) and elemental analysis.[6] The NMR and IR spectra indicated that it consists of only one stereoisomer and that it has a phenyl group (NMR in CCl_4: δ 7.32m (3H) and 7.85m (2H); IR: 756 and 692 cm^{-1}), an olefinic proton (δ 7.51s (1H)), a methylsulfinyl group (δ 2.62s (3H); 1062 cm^{-1}), and a methylthio group (δ 2.26s (3H)). Reduction of this oil with lithium aluminum hydride afforded phenylacetaldehyde dimethyl mercaptal. The stereoisomer (5) was obtained by irradiation of 3 (Ar=Ph) in methanol with a low-pressure mercury arc lamp (Vycor filter).



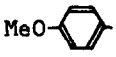
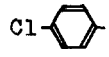
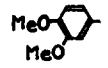
The stereochemical structures of 3 (Ar=Ph) and 5 were assigned by the comparison of the pseudo-contact effects of the shift reagent, tris(dipivaloylmethanato)-europium ($Eu(dpm)_3$), which formed complexes at oxygen atom of a sulfoxide,[7] on the chemical shifts of their olefinic protons. The singlet at δ 7.51 of 3 (Ar=Ph) was shifted downfield to δ 16.49 by adding 0.51 equiv. of $Eu(dpm)_3$, while the olefinic proton (δ 7.02 in CCl_4) of 5 appeared at δ 9.71 in CCl_4-$Eu(dpm)_3$ (0.51 equiv.). These facts indicated that the olefinic proton and the sulfoxide group of 3 (Ar=Ph) are much closer in a space than those of 5. Thus, the stereochemical structure of 3 (Ar=Ph) was established as shown in eq. 2.

The acid-catalyzed degradation of this condensation product took place easily. A solution containing 300 mg of 3 (Ar=Ph) in 10 ml of ethanol was bubbled with hydrogen chloride gas under ice-cooling and then was allowed to stand at room temperature. After evaporation under reduced pressure, the residue was column-chromatographed on silica gel to give 179 mg (78%) of ethyl phenylacetate. When a solution of 3 (Ar=Ph) in 1,2-dimethoxyethane was treated with conc. hydrochloric acid at room temperature, phenylacetic acid was obtained in

a 63% yield.

In a similar manner, various kinds of substituted benzaldehydes condensed with methyl methylthiomethyl sulfoxide (1) to give 1-methylsulfinyl-1-methylthio-2-arylethylene (3), and the hydrolysis of 3 afforded the corresponding phenylacetic acid derivatives (4). The results are summarized in Table 1.

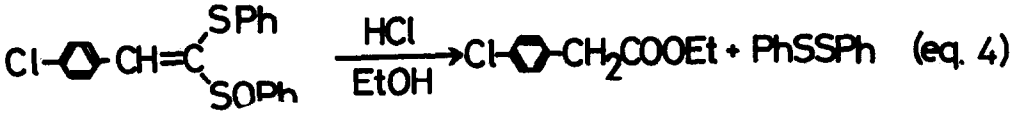
Table 1. Yields (%) of 3 and 4

Ar	3[a]	4 (R=Et)
	91	78
	99	94
	73[b]	92
	87[b]	40
	81	91

[a] based on the reacted 1. [b] at 80° in dioxane.

This route to phenylacetic acid derivatives is particularly suited for the preparation of such acids as homopiperonylic acid and homoveratric acid which are key-intermediates for the synthesis of isoquinoline alkaloids.[8] The usual way of making these acids involves the following scheme; starting from piperonal and veratraldehyde and passing through the corresponding benzyl alcohols and benzyl cyanides, the latter compounds are hydrolyzed to afford the aimed acids.[9] The present reaction provides a simpler and more efficient way to approach these acids and their derivatives.

The easy conversion of 3 to 4 raises an interesting question as to the mechanism of the reaction. The acid-catalyzed ethanolysis of 1-phenylsulfinyl-1-phenylthio-2-(p-chlorophenyl)ethylene (6), which was obtained from the condensation of phenyl phenylthiomethyl sulfoxide with p-chlorobenzaldehyde in the presence of Triton B, afforded ethyl p-chlorophenylacetate and diphenyl disulfide



6

in yields of 90% and 89%, respectively. The formation of the latter compound in this reaction suggests a mechanism analogous to that of the acid-catalyzed hydrolysis of mercaptal S-oxides 2 to the corresponding carbonyl compounds.[1,10] Presumably, the present reaction involves an intermediacy of arylketene which, in turn, changes to phenylacetic acid derivatives. Studies on the detailed mechanism of this intringuing transformation is being undertaken.

REFERENCES

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

(2) Although 1 can be obtained by the substitution reaction of chloromethyl methyl sulfoxide with methyl mercaptide anion,[3,4] the oxidation of formaldehyde dimethyl mercaptal appeared to be more convenient way of making 1.[5]

(3) G. Tsuchihashi and K. Ogura, Bull. Chem. Soc. Japan, 44, 1726 (1971).

(4) K. Ogura and G. Tsuchihashi, Chem. Commun., 1689 (1970).

(5) K. Ogura and G. Tsuchihashi, submitted to Bull. Chem. Soc. Japan.

(6) Satisfactory elemental analyses have been obtained for all new compounds reported herein.

(7) R. R. Fraser and Y. Y. Wigfield, Chem. Commun., 1471 (1970).

(8) For example, E. Späth and N. Lang, Monatsh. Chem., 42, 273 (1921).

(9) E. R. Shepard, H. D. Porter, J. F. Noth, and C. K. Simmans, J. Org. Chem., 17, 568 (1952).

(10) H. Nieuwembuyse and R. Louw, Tetrahedron Lett., 4141 (1971).