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A NOVEL PREPARATION OF 3-METHYLTHIO-2-OXOPROPANAL ACETALS USING METHYLTHIOMETHYL p-TOLYL SULFONE[a]

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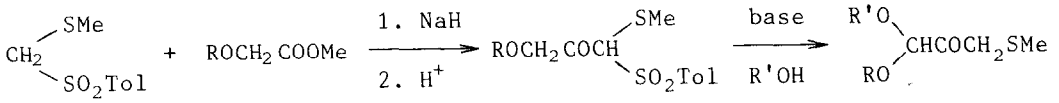
Abstract: *Treatment of an alkoxyacetyl derivative (3) of methylthiomethyl p-tolyl sulfone (1), easily obtainable from an alkoxyacetic ester and 1, with such a base as triethylamine or DABCO affords 3-methylthio-2-oxopropanal acetal (4).*

To date, we have reported that methylthiomethyl p-tolyl sulfone (1)[1] is an efficient reagent for synthesizing many kinds of organic compounds such as S-methyl α-ketocarbothioate,[2,3] carboxylic esters,[2] cycloalkanones,[2] α-methoxy-α-arylacetic esters,[2] aldehydes,[2,3] dialkyl ketones,[4,5] α,β-unsaturated ketones,[6] and α-hydroxy aldehydes.[7] During our investigation to develop further utilization of 1 in organic synthesis, we have found that an alkoxyacetyl derivative (3) of 1 exhibits an intriguing behavior on treatment with a base to give 3-methylthio-2-oxopropanal acetals (4), a new class of compounds containing three functionalities which are useful for organic synthesis.



1 2a: R = $PhCH_2$ b: R = Me 3a: R = $PhCH_2$ b: R = Me 4a: R = $PhCH_2$ R'= Me b: R = $PhCH_2$ R'= Et c: R = R'= $PhCH_2$ d: R = $PhCH_2$ R'=i-Pr

When (benzyloxy)acetyl derivative (3a) of 1 was treated with triethylamine (2 equiv) in methanol at room temperature for 1 d, a 3-methylthio-2-oxopropanal acetal (4a)[8] was produced as a major product together with a small amount of 1. Although DABCO and sodium acetate also works more effectively to slightly raise the yield of 4a, treatment with DBU quantitatively afforded 1 instead of 4a. In ethanol or benzyl alcohol, a smooth reaction took place and the corresponding acetal (4b or 4c) was given. The reaction in isopropyl alcohol proceeded slowly, but the expected acetal (4d) was obtained in good yield. In contrast, the reaction of 3a in t-butyl alcohol resulted in the

[a]Dedicated to the late Prof. Gen-ichi Tsuchihashi

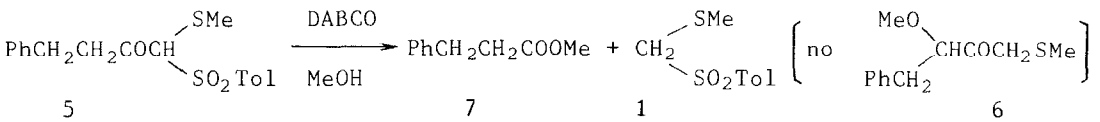
Table 1. Yields in the Reaction of 3 with a Base in an Alcohol (2)[a]

R of 3	R'OH (2)	Base	Reaction Time	4	1
$PhCH_2$	MeOH	Et_3N	24 h	55%	32%
		DABCO	24 h	65%	17%
		DBU	24 h	---	100%
		AcONa	24 h	61%	24%
	EtOH	Et_3N	37 h	56%	6%
	i-PrOH	Et_3N	48 h	67%	10%
	$PhCH_2OH$	DABCO	24 h	68%	
Me	$PhCH_2OH$	DABCO	24 h	69%	

[a]Stirring a solution containing 3 (ca. 1 mmol) and a base (2.0 equiv) in an alcohol (2.5 ml) at room temperature.

formation of a complex mixture. Similar treatment of a methoxyacetyl derivative (3b) in benzyl alcohol also gave **4a** as shown in Table 1.

It should be noted that, on treatment with DABCO in methanol, 3-phenylpropanoyl derivative (5) of **1** did not give the corresponding acetal (6), but methyl 3-phenylpropanoate (7) and **1** were quantitatively recovered. This fact suggests that the presence of the alkoxyl group in 3 is crucial in the conversion of 3 to 4.

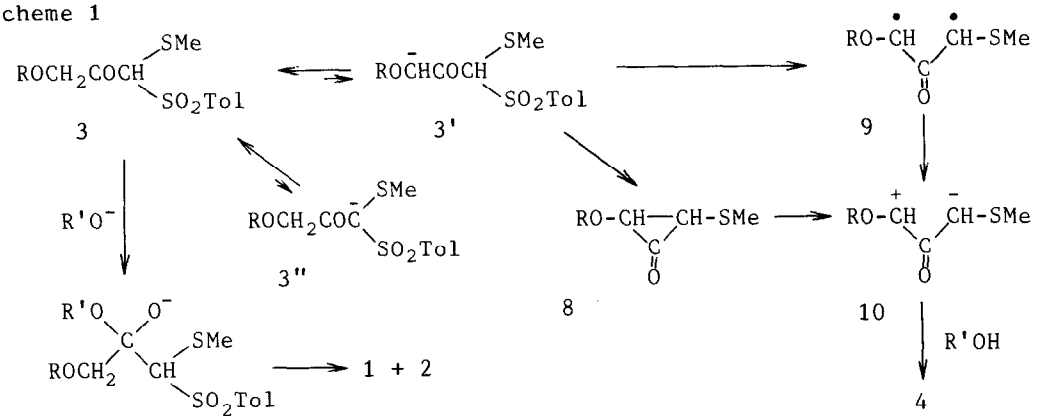


5 7 1 6

The present conversion may reasonably be accounted for by the routes depicted in Scheme 1. The first one is the route via a cyclopropanone derivative (8), which resembles the mechanism suggested for the Favorskii reaction of halo ketones.[9] In the presence of a relatively weak base such as triethylamine, DABCO, or sodium acetate, 3 is in equilibrium with two carbanions (3' and 3"). The carbanion 3', a minor component in this equilibrium, causes intramolecular displacement reaction to afford 8, where p-tolylsulfonyl group serves as a leaving group. Then, heterolytic bond cleavage of 8 produces a zwitterion (10), in which the carbenium cation is stabilized by the benzyloxyl group and the carbanion undergoes stabilization by carbonyl and methylthio groups. Another way leading to 10 must be taken into consideration: Electron transfer from the anionic site of 3' into its p-tolylsulfonyl site followed by elimination of p-toluenesulfinate anion affords a biradical (9), probably due to the stabilization of the formed radicals by the captodative effects[10] which are brought about by an electron-withdrawing carbonyl group (captive group) as well as electron-donating methylthio and benzyloxyl groups

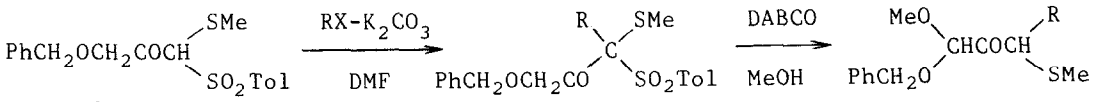
(dative groups). Further transfer of an electron converts the biradical 9 to a more stable zwitterion 10. The last step to produce 4 is the reaction of 10 with an alcohol (R'OH). At the present time, we cannot eliminate the possibility that 4 is directly formed by the reaction of 8 with an alcohol.

Scheme 1



Under the present conditions using a base in an alcohol, the corresponding alkoxide is also produced besides the carbanions 3' and 3". If the alkoxide anion attacks on the carbonyl carbon of 3, 1 is recovered. When a strong base is employed, a large amount of the alkoxide anion may be produced, resulting in quantitative production of 1. This appears to be the case when DBU is used as a base.

Reaction of 3a with methyl iodide, ethyl iodide, or allyl bromide in the presence of potassium carbonate in DMF at room temperature gave a C-alkylation product (11) in 68%, 38%, or 95% yield, respectively. On treatment with DABCO in methanol, this product (11) was also transformed into the corresponding acetal (12) in 89%, 70%, or 83% yield, respectively, which was shown by an NMR analysis to consist of two diastereomers in the ratio of ca. 1:1.



11a: R = Me
b: R = Et
c: R = CH_2=$CHCH_2$

12a: R = Me
b: R = Et
c: R = CH_2=$CHCH_2$

In conclusion, treatment of an alkoxyacetyl derivative (3) of 1 with a relatively weak base causes intramolecular transposition of the oxidation state of the dithioacetal S,S-dioxide functionality to provide useful 3-methylthio-2-oxopropanal acetals (4). Furthermore, the methyl and allyl derivatives (12) of 4 were also produced from the C-alkylated products (11) of 3a. Since an alkoxyacetyl derivative (3) of 1 can be prepared by the reaction of the corresponding ester (2) with 1 in the presence of easily handled NaH, the present reaction provides a novel and convenient method for the synthesis

of 4 and 9. Now we are continuing our studies on a detailed mechanism of the present transformation including an attempt to trap the zwitterion 10 with an olefin.

A typical procedure is illustrated for preparing 12c. To a solution of 1 (24.1 mmol) in THF (70 ml), were successively added NaH (60% content in an oil; 3.11 equiv) and methyl (benzyloxy)acetate (1.59 mol-equiv) under ice-cooling. After being slowly warmed up to room temperature, the reaction mixture was stirred for 15 h. The usual workup and recrystallization from hexane-benzene afforded 3a (6.25 g: 87% yield). To a solution of 3a (6.71 mmol) in DMF (20 ml), were added allyl bromide (23.0 mmol) and potassium carbonate (4.56 mmol) and then the resulting mixture was stirred at room temperature for 4 h. Addition of 0.5 mol/l hydrochloric acid and extraction with diisopropyl ether followed by chromatography on silica gel (eluent: ethyl acetate-benzene (1:30)) gave 11c (6.40 mmol: 95% yield). A solution of 11c (1.06 mmol) and DABCO (1.23 mmol) in methanol (2.5 ml) was stirred at an ambient temperature for 24 h. After addition of dichloromethane (50 ml), the resulting solution was washed with water (50 ml) and 0.5 mol/l hydrochloric acid (30 ml), the washings were extracted with dichloromethane (50 ml X 3). The combined organic layers were dried over magnesium sulfate and evaporated. The residue was separated by column-chromatography on silica gel (eluent: benzene) to give 12c as a yellow oil (0.88 mmol: 83%).

References and Notes

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8. A yellow oil; IR (neat) 1728 cm^{-1}; ^1H NMR (CCl_4) δ 2.00 (3H, s), 3.24 (2H, s), 3.31 (3H, s), 4.50 (2H, s), 4.79 (1H, s), 7.18 (5H, s); MS (70 eV) m/e (relative intensity) 151 (40; M^+-$COCH_2SMe$), 91 (100; $PhCH_2$), 65 (26; C_5H_5), 61 (45; CH_2SMe). Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.98; H, 6.71. Found: C, 59.79; H, 6.67.
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