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A VERSATILE REAGENT FOR SYNTHESIS OF α-HYDROXY ALDEHYDES AND KETONES — METHYLTHIOMETHYL p-TOLYL SULFONE

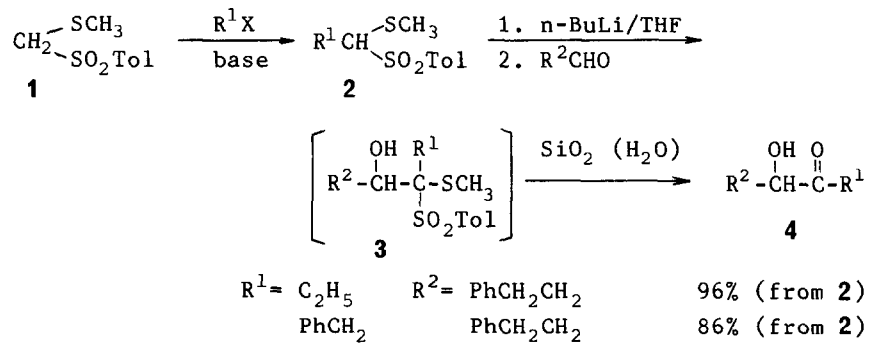
Katsuyuki Ogura*, Toshihiko Tsuruda, Kazumasa Takahashi, and Hirotada Iida
Department of Synthetic Chemistry, Faculty of Engineering,
Chiba University, Yayoicho 1-33, Chiba 260, Japan

*Abstract: Methylthiomethyl p-tolyl sulfone (**1**) can be utilized for synthesizing α-hydroxy ketones as well as α-hydroxy aldehydes, the hydroxyl group of which is protected with acetyl, tetrahydropyranyl, or methoxymethyl group.*

α-Hydroxy aldehydes and ketones have proved to be very important precursors for making biologically active compounds such as ionophores, pheromones, and carbohydrates, because many types of reactions have been developed for the addition of carbon and hydride nucleophiles to their carbonyl groups to give erytho or threo form of 1,2-diols with high stereoselectivity.[1] In this letter, we wish to describe a preliminary result of our finding that methylthiomethyl p-tolyl sulfone (**1**)[2] provides a simple and general way to produce α-hydroxy ketones (**4**) as well as OH-protected α-hydroxy aldehydes (**13**).

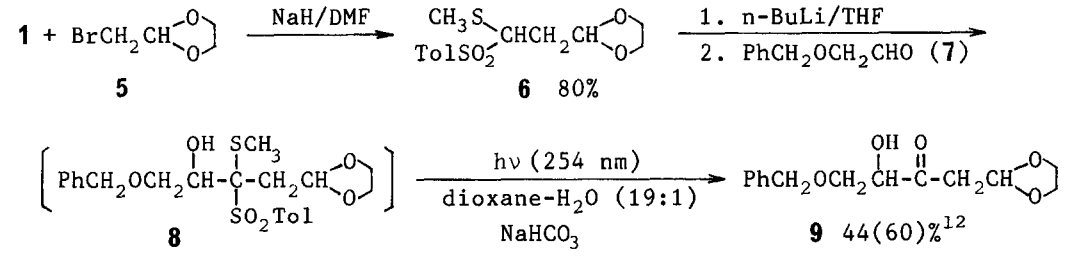
The present synthesis of α-hydroxy ketones (**4**) comprises two steps: (i) the addition of an alkyl derivative (**2**) of **1** to an aldehyde leading to an adduct (**3**) and (ii) the subsequent hydrolysis of **3** on silica gel. As shown in Scheme 1, isolation of the intermediary **3** is not necessary and the overall yield of **4** from **2** is excellent. This method seems to be superior to the method using 1,3-dithiane which utilizes expensive reagents[9] for the hydrolysis of the dithioacetal functionality. Smooth hydrolysis of **3** with silica gel is an unanticipated result, because dithioacetal S,S-dioxides have been known to undergo hydrolysis by the action of hydrochloric acid in methanol or cupric chloride on silica gel.[4,6,10,11] This may be attributable to the presence of the neighbouring hydroxyl group which assists heterolytic dissociation of the C-SO_2 bond of **3**.

Scheme 1



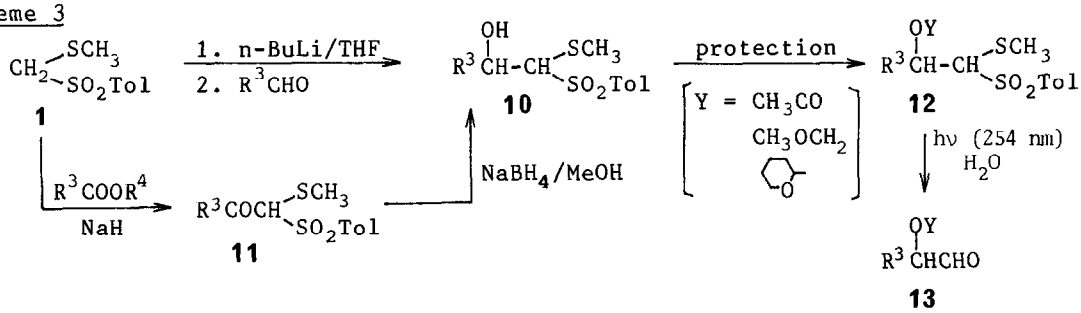
When a silica gel-sensitive functional group is involved in R^1 or R^2, transformation of **3** into **4** can be accomplished by photo-induced hydrolysis.[6] Thus a synthetic precursor (**9**) of 2-deoxyribose was conveniently produced by the use of **1** (Scheme 2).

Scheme 2



Further we extended the above reaction to a convenient method for synthesizing an α-hydroxy aldehyde (**13**) with an appropriate protective group. As shown in Scheme 3, the lithio derivative of **1** reacted with an aldehyde to afford an adduct (**10**), which was also obtained by the reduction of an acyl derivative (**11**) of **1**.[5] Since most of α-hydroxy aldehydes are so unstable as to easily dimerize, the hydroxyl group of **10** must be protected with an easily removable group prior to hydrolysis. As a result of surveying various conditions, acetyl, tetrahydropyranyl, and methoxymethyl groups were favorably employed without affecting the dithioacetal S,S-dioxide functionality. These facts make it possible to prepare **13**, which were given by irradiation of the OH-protected derivative (**12**) of **10** with a 254 nm light under neutral or basic conditions. These results are summarized in Table 1, which also shows the synthesis of a novel derivative of glycelaldehyde having two different protective groups, benzyl and methoxymethyl (Run 7). It should be noted that the present method is in sharp contrast with the conventional one using a dithioacetal S-oxide[13,14] which does not provide **13** protected with methoxymethyl or tetrahydropyranyl group, but **13** with acetyl or alkyl group.[15]

Scheme 3



Typical procedures are as follows. Synthesis of 1,5-diphenyl-3-hydroxy-2-pentanone (**4**; R^1=$PhCH_2$, R^2=$PhCH_2CH_2$): To a solution of **2** (R^1=$PhCH_2$) (1.18 mmol) in THF (10 ml), was dropwise added a hexane solution of n-BuLi (1.55 mmol) over 1 min at -78 °C. After being stirred at -50 °C for 30 min,

Table 1. Synthesis of OH-Protected α-Hydroxy Aldehydes (**13**)

Run	R^3	**1** → **10**		**10** → **12**			**12** → **13**	
		Condi.[a]	Yield	Y	Condi.[b]	Yield	Condi.[c]	Yield[d]
1	$PhCH_2CH_2$	A	83%	CH_3CO	A	85%	A	53%
2							B	58(78)%
3					B	95%	B	46%
4				CH_3OCH_2	C	100%	A	66%
5	Ph	B	98%	CH_3OCH_2	C	100%	A	26%
6	$PhCH_2OCH_2$	C	86%	CH_3CO	A	86%	A	39%
7				CH_3OCH_2	C	97%	A	45(63)%

[a][A]: by the addition of the lithio derivative of **1** to 3-phenylpropanal (see Text); [B]: acylation of **1** with PhCOOPh and NaH followed by reduction with $NaBH_4$ (ref. 5); [C]: acylation of **1** with $PhCH_2OCH_2COOCH_3$ (1.5 equiv)-NaH (2.9 equiv) in THF followed by reduction with $NaBH_4$.
[b][A]: with Ac_2O and pyridine at room temperature; [B]: with 2,3-dihydropyran and PTS (cat.) in CH_2Cl_2 at room temperature; [C]: with $CH_2(OMe)_2$ and P_2O_5 in $CHCl_3$ at room temperature (see Text).
[c][A]: irradiated with a 30 W low-pressure Hg lamp (Vycor filter) in diethyl ether in the copresence of $NaHCO_3$ (3 equiv) (see Text); [B]: the same conditions except further addition of a catalytic amount of 15-Crown-5.
[d]the value in parenthesis is the yield based on the unrecovered **12**.

3-phenylpropanal (1.54 mmol) was added at -78 °C and the resulting solution was further stirred at the same temperature for 1 h. The usual workup (addition of water, extraction with Et_2O, and evaporation) gave a pale yellow oil, which was shown by its ^1H NMR spectrum to mainly consist of **3** (R^1=$PhCH_2$, R^2=$PhCH_2CH_2$). To a solution of this oil in benzene (5 ml), was added silica gel[16] (2.5 g) and the resulting mixture was allowed to stand at room temperature for 12 h and then at 45 °C for 27 h. After silica gel was filtered off, the filtrate was evaporated and subjected to column chromatography on silica gel using benzene-AcOEt as an eluent to afford **4** (R^1=$PhCH_2$, R^2=$PhCH_2CH_2$) in 86% yield.

Synthesis of 2-methoxymethoxy-4-phenylbutanal (**13**; R^3=$PhCH_2CH_2$, Y=CH_3OCH_2): After addition of n-BuLi (39 mmol; hexane solution) to a solution of **1** (32.8 mmol) in THF (100 ml) followed by being stirred at -78 °C for 10 min and then at room temperature for 1 h, 3-phenylpropanal (30.9 mmol) was added at -78 °C over 20 min and the resulting mixture was stirred at -78 °C for 1 h. Addition of a saturated aqueous solution of $NaHCO_3$ and water (100 ml), extraction with diethyl ether, and evaporation gave pale yellow crystals, which were subjected to column chromatography on silica gel to afford **10** (R^3=$PhCH_2CH_2$) in 88% yield. To a solution of **10** (R^3=$PhCH_2CH_2$) (1.2 mmol) in $CHCl_3$ (10 ml), were added methylal (5 ml) and P_2O_5 (150 mg) and the resulting mixture was stirred at room temperature for 1 h. After a saturated aqueous solution (10 ml) of $NaHCO_3$ was added, the usual workup (extraction with diethyl ether and evaporation) and column chromatography on Florisil afforded **12** (R^3=$PhCH_2CH_2$, Y=CH_3OCH_2) in a quantitative

yield. To a solution of **12** (R^3=$PhCH_2CH_2$, Y=CH_3OCH_2) (0.475 mmol) in diethyl ether (76 ml), was added an aqueous solution (4 ml) of $NaHCO_3$ (3 equiv) and the resulting mixture was internally irradiated with a 30 W low-pressure Hg lamp (a Vycor filter) under cooling with tap water. After irradiation for 1 h, water was added and the organic layer was separated. Evaporation and column chromatography on Florisil gave **13** (R^3=$PhCH_2CH_2$, Y=CH_3OCH_2) in 66% yield.

In conclusion, methylthiomethyl p-tolyl sulfone (**1**) has proved to be a versatile reagent for the preparation of α-hydroxy ketones as well as α-hydroxy aldehydes having easily-removable protective groups. Further application of the present method to biologically active polyhydroxy compounds is the subject of an on-going study.

References and Footnotes

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2. This reagent (**1**) can be conveniently prepared by the reaction of acetoxymethyl methyl sulfide with sodium p-toluenesulfinate,[3]. Now **1** is commercially availabe from Nissan Chemical Industries Co. Hitherto we have reported that **1** is a useful reagent for making various organic compounds such as S-methyl α-ketocarbothioate, carboxylic esters, cycloalkanones, α-methoxy-α-arylacetic esters, aldehydes, and α,β-unsaturated ketones.[4-8]
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