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A CONVENIENT METHOD FOR THE PREPARATION OF γ-KETOSULFIDES FROM THIOACETALS

Masahiro OHSHIMA, Masahiro MURAKAMI, and Teruaki MUKAIYAMA
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

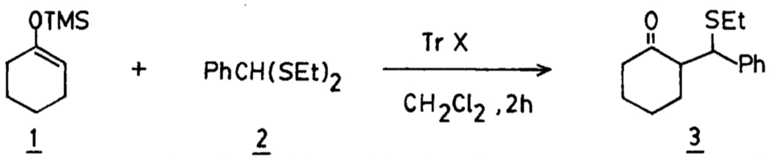
In the presence of trityl tetrafluoroborate, silyl enol ethers react with thioacetals to give the corresponding γ-ketosulfides in good yields with high stereoselectivity. In a similar manner, γ-ketosulfides are obtained in good yields by the one pot reaction directly from ketones and thioacetals via tin(II) enolates.

γ-Ketosulfides are useful intermediates in organic synthesis, and there have been many reports on the preparation of γ-ketosulfides from silyl enol ethers and α-chlorosulfides by the promotion of Lewis acids such as $TiCl_4$, $ZnBr_2$.1) However, some problems remain in the preparation of α-chlorosulfides, because the sulfides are generally unstable. On the other hand, thioacetals are stable and readily available from carbonyl compounds, and a few methods have been reported for the synthesis of γ-ketosulfides from thioacetals and silyl enol ethers.2) However, no method have been reported for the preparation of γ-ketosulfides directly from ketones and thioacetals.

In this communication, we wish to describe the preparation of γ-ketosulfides from thioacetals and silyl enol ethers, and the one pot synthesis of γ-ketosulfides directly from thioacetals and ketones via tin(II) enolates promoted by trityl tetrafluoroborate.

Recently, we have reported that trityl perchlorate effectively activates carbonyl compounds or acetals, and several new and useful synthetic reactions have been developed.3) In our continuous investigation, we found that trityl cation also activates thioacetals to generate thiocarbocations which in turn react with silyl enol ethers to afford the corresponding γ-ketosulfides.

First, we screened the reaction conditions by taking the reaction of 1-trimethylsilyloxy-1-cyclohexene (1) and α,α-bis(ethylthio)toluene (2) as a model (Scheme 1). As shown in Table 1, the reaction proceeds smoothly in CH_2Cl_2 at -45 °C in the presence of an equimolar amount of $TrBF_4$ to give the corresponding γ-ketosulfide (3) in excellent yield. In contrast to the reaction of acetals with silyl enol ethers, an equimolar amount of trityl salt was required in the present reaction. While, the reaction could be carried out in the presence of a catalytic amount of $TrClO_4$ in co-existance of an equimolar amount of TrCl, a thiolate ion scavenger.



TMS = $SiMe_3$
Tr = Ph_3C

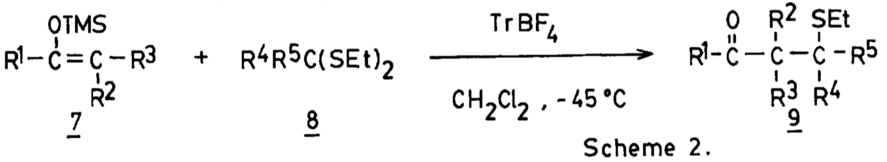
Scheme 1.

Table 1. The effect of the reaction conditions

Tr X	Molar ratio of Tr X per 2	Solvent	Temp/°C	Yield of 3/%
$TrClO_4$ 4	0.2	CH_2Cl_2	-78	27
4	1.0	CH_2Cl_2	-78	88
TrOTf 5	1.0	CH_2Cl_2	-78	80
$TrBF_4$ 6	1.0	CH_2Cl_2	-78	92
6	1.0	CH_2Cl_2	-45	95
6	1.0	THF	-78	70
6	1.0	CH_3CN	-45	90
4	0.1	CH_2Cl_2	-78	74[a]

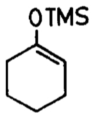
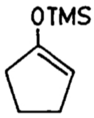
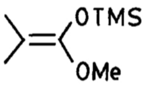
[a] An equimolar amount of TrCl was added.

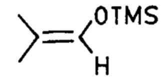
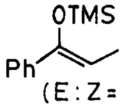
The reaction of various silyl enol ethers (7) with thioacetals (8) were studied, and the corresponding γ-ketosulfides (9) were obtained in good yields with high stereoselectivity as depicted in Table 2.



Scheme 2.

Table 2. The reaction of silyl enol ethers with thioacetals

Entry	Silyl enol ether	Thioacetal	Reaction time/h	Yield of 9/%	Diastereomer ratio
1	 1	$PhCH(SEt)_2$ 2	2	95	94 : 6[a]
2	1	$Me_2CHCH(SEt)_2$	13	82	75 : 25[b]
3	1	$Me_2C(SEt)_2$	19	80	
4	1	$CH(SEt)_3$	3	76	
5		2	2[c]	97	82 : 18[d]
6		2	4	79	

7		$\underline{2}$	4	86	
8	 (E:Z= 3:97)	$Me_2CHCH(SEt)_2$	5	82	95 : 5[b)]

a) The diastereomer ratio was determined by 90MHz ^1H-NMR in the presence of $Eu(fod)_3$. The value of chemical shift and coupling constant of benzylic proton was as follows. Major isomer : δ 4.4 (J=7.5 Hz). Minor isomer : δ 4.3 (J=9 Hz).

b) The diastereomer ratio was determined by GC.

c) The reaction was carried out at -78 °C.

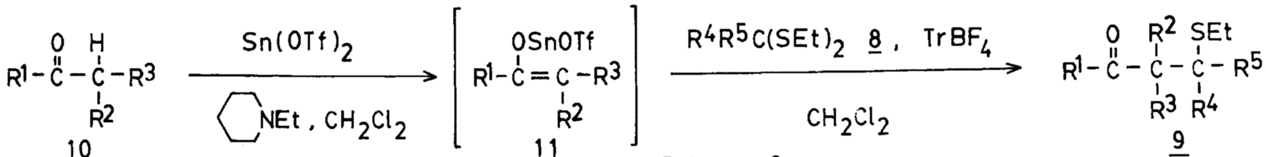
d) The diastereomer ratio was determined by 90MHz ^1H-NMR.

Typical procedure is described for the reaction of 1-trimethylsilyloxy-1-cyclohexene ($\underline{1}$) and α,α-bis(ethylthio)toluene ($\underline{2}$): Under an argon atmosphere, to a stirred suspension of $TrBF_4$ (0.31 mmol)[4)] in CH_2Cl_2 (1 ml) was added a mixture of $\underline{1}$ (0.31 mmol) and $\underline{2}$ (0.30 mmol) in CH_2Cl_2 (3 ml) at -45 °C (dry ice - CH_3CN). Stirring was continued for 2 h, and then the reaction was quenched with a mixture of pyridine and methanol. After the evaporation of the solvent, the residue was purified by preparative TLC to afford the corresponding γ-ketosulfide ($\underline{3}$) (0.29 mmol, 95%).

From the synthetic point of view, it is more desirable to prepare γ-ketosulfides directly from ketones and thioacetals without isolation of the intermediate enolates. Based on this consideration, we investigated the reaction of thioacetals ($\underline{8}$) with tin(II) enolates ($\underline{11}$), easily formed from ketones ($\underline{10}$) and stannous triflate in the presence of N-ethylpiperidine,[6)] and it was found that the reaction was also promoted by $TrBF_4$ to afford the corresponding γ-ketosulfides ($\underline{9}$) as shown in Scheme 3.

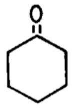
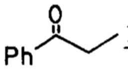
It should be pointed out that the relative configuration of the γ-ketosulfide obtained by this reaction from cyclohexanone and $\underline{2}$ (entries 1,2) was reversed compared with the sulfide obtained from 1-trimethylsilyloxy-1-cyclohexene and $\underline{2}$.

Thus, according to the present methods mentioned above, the γ-ketosulfides are prepared from thioacetals and silyl enol ethers with high stereoselectivity, or directly from thioacetals and ketones via tin(II) enolates in good yields under mild conditions.



Scheme 3.

Table 3. The reaction of ketones with thioacetals via tin(II) enolates

Entry	Ketone	Thioacetal	Conditions Temp/°C	 Time/h	Yield of 9/%	Diastereomer ratio
1	 12	$PhCH(SEt)_2$ 2	-45	2	78	77 : 23[a]
2	12	2	-78	18	87	87 : 13[a]
3	 13	$Me_2CHCH(SEt)_2$	-78	14	64	56 : 44[b]
4	13	$CH(SEt)_3$	-45	14	80	

a) The diastereomer ratio was determined by 90MHz ^1H-NMR in the presence of $Eu(fod)_3$. The value of chemical shift and coupling constant of benzylic proton was as follows. Major isomer : δ 4.3 (J=9 Hz). Minor isomer : δ 4.4 (J=7.5 Hz).

b) The diastereomer ratio was determined by GC.

References

1) For a few recent examples of synthesis of γ-ketosulfides from silyl enol ethers and α-chlorosulfides, see; L. Duhamel and J. Chauvin, Chem. Lett., 1985, 693; T. V. Lee and N. Visani, Tetrahedron Lett., 25, 5559 (1984); I. Fleming and J. Iqbal, ibid., 24, 2913 (1983); D. J. Ager, ibid., 24, 419 (1983); A. Hosomi, Y. Sakata, and H. Sakurai, Chem. Lett., 1983, 405.

2) M. T. Reetz and A. Giannis, Synth. Commun., 11, 315 (1981); B. M. Trost and E. Murayama, J. Am. Chem. Soc., 103, 6529 (1981).

3) T. Mukaiyama, S. Kobayashi, and M. Murakami, Chem. Lett., 1984, 1759; 1985, 447; S. Kobayashi, M. Murakami, and T. Mukaiyama, ibid., 1985, 953; T. Mukaiyama, H. Nagaoka, M. Murakami, and M. Ohshima, ibid., 1985, 977; J. Kato, N. Iwasawa, and T. Mukaiyama, ibid., 1985, 743; T. Mukaiyama, J. Kato, N. Miyoshi, and N. Iwasawa, ibid., 1985, 1255; T. Mukaiyama and H. Iwakiri, ibid., 1985, 1363.

4) $TrBF_4$ was purified by the following procedure; Under an argon atmosphere, crude $TrBF_4$ (2.5 g, 7.6 mmol)[5] was dissolved in dry CH_3NO_2 (10 ml), and then dry ether (50 ml) was added at once. The yellow precipitates were collected by filtration, and washed with dry ether (10 ml) three times, and then dried in vacuo.

5) H. J. Dauben, Jr., L. R. Honnen, and K. M. Harmon, J. Org. Chem., 25, 1442 (1960).

6) T. Mukaiyama, N. Iwasawa, R. W. Stevens, and T. Haga, Tetrahedron, 40,1381 (1984).

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