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The Synthesis of α -Acetoxy Sulfides and Their Lewis Acid-Mediated Reactions

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Abstract: α -Acetoxy sulfides can be conveniently prepared by the reaction of dithioacetals with mercuric acetate at ambient temperature. They react with allyltrimethylsilane, enol silyl ethers, and cyanotrimethylsilane in the presence of SnCl4 to afford butenyl sulfides, γ -keto sulfides and α -cyano sulfides, respectively.

The reaction of nucleophilic reagents such as enol silyl ethers and allylic silanes with acetals has been developed by Mukaiyama and by Noyori.¹ It is a well established reaction. The related reaction of α -chloro ethers with enol silyl ethers has also been extensively studied.² The reactions of enol silyl ethers with dithioacetals has been reported by Mukaiyama³ and by Reetz,⁴ but the scope and limitations of this reaction has not been determined.

In the course of developing a direct synthetic route to the zaragozic acids, we discovered that the stable α -acetoxy sulfide 2 could be generated from dithioacetal 1 using mercuric acetate.⁵ The reaction of α -acetoxy sulfide 2 with 2-(trimethylsilyloxy)-1-butene (3) in the presence of SnCl4 provided ketone 4 in 65% yield. Interestingly, the reaction of 1 with 3 in the presence of SnCl4 or TrBF4 generated a complex mixture of products. Since the Lewis acid mediated reactions of α -acetoxy sulfides have not been studied and since the facile conversion of 2 into ketone 4 demonstrated that this reaction may have synthetic utility, we decided to study this reaction in more detail. We report herein a study of the reactions of α -acetoxy sulfides with nucleophilic reagents.



In order to determine the generality of this variant of the aldol reaction, we first studied the reaction of mercuric acetate with representative thioacetals and a thioketal. The formation of an α -acetoxy sulfide rather than the usual hydrolysis product from the reaction of mercuric acetate and a dithioacetal has been reported only once.⁶ The primary method for the preparation of α -acetoxy sulfides is the Pummerer reaction.⁷ Unfortunately, the Pummerer rearrangement lacks regioselectivety in unsymmetrical sulfoxides. For example, the Pummerer reaction on benzyl methyl sulfoxide affords roughly an equal mixture of isomeric products.⁸ The absence of a convenient method of preparation has undoubtedly limited the use of α -acetoxy sulfides in organic synthesis.

PhCH₂SOCH₃
$$\xrightarrow{Ac_2O}$$
 Ph-CHSMe + PhCH₂SCH₂OAc
39% 45 55

The reaction of isobutyraldehyde and benzaldehyde with ethanethiol and TiCl₄ afforded compounds 5 and 6 in 98% and 99% yields, respectively.⁹ The reaction of isobutyraldehyde with diphenyl disulfide and tributylphosphine afforded compound 7 in 86% yield.¹⁰

$$Me_{2}CHCHO \xrightarrow{EtSH}_{TiCl_{4}} Me_{2}CHCH(SEt)_{2} \xrightarrow{Hg(OAc)_{2}} Me_{2}CHCHSEt$$

$$FhCHO \xrightarrow{EtSH}_{TiCl_{4}} PhCH(SEt)_{2} \xrightarrow{Hg(OAc)_{2}} PhCHSEt$$

$$6 \qquad 9$$

$$Me_{2}CHCHO \xrightarrow{PhSH}_{Bu_{3}P} Me_{2}CHCH(SPh)_{2} \xrightarrow{Hg(OAc)_{2}} Me_{2}CHCHSPh$$

$$10$$

Compounds 5 and 7 upon treatment with mercuric acetate in acetic acid at ambient temperature afforded acetoxy sulfides 8 and 10 in 82% and 99% isolated yields, respectively. The reaction of dithioacetal 6 with mercuric acetate provided acetoxy sulfide 9. Chromatography of 9 on silica gel provided dithioacetal 6 in 90% yield.

$$\begin{array}{c} OAc \\ | \\ PhCHSEt \\ 9 \\ 6 \end{array} \qquad PhCH(SEt)_2$$

Fortunately, we found that compound 9 could be used without purification. The reaction of the dithioketal of cyclohexanone with mercuric acetate produced only cyclohexenyl ethyl sulfide in 67% yield.



The SnCl4 mediated reactions of acetoxy sulfides 8, 9 and 10 were next studied. To the best of our knowledge, only one report of the reaction of α -acetoxy sulfides with nucleophiles has been published.¹¹ Table 1 shows the results of several SnCl4-mediated reactions. Allyltrimethylsilane (11), 2-(trimethylsilyloxy)-1-pentene (12), 1-trimethylsilyloxycyclohexene (13) and cyanotrimethylsilane (14) were chosen as the nucleophiles. These nucleophiles reacted with the acetoxy sulfides to generate olefinic sulfides, γ -keto sulfides and α -cyano sulfides in good to excellent yields.

As a typical procedure, the preparation of 8 follows: To a stirred solution of dithioacetal 5 (4.0 g, 22.5 mmol) in glacial acetic acid (50 mL) at 17 °C was added mercuric acetate (7.53 g, 23.6 mmol). After the mixture was stirred at room temperature for 1 hour, the acetic acid was removed under reduced pressure. To the residue

was added saturated aqueous sodium bicarbonate and ethyl acetate. The precipitate was filtered. The organic layer separated in the filtrate was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane:ethyl acetate, 50:1) to afford 2.88 g (82%) of 8 as a colorless oil.¹²

As a typical procedure, the preparation of 17 follows: To a stirred solution of 8 (146 mg, 0.83 mmol)

Dithioacetal	α-Acetoxy Sulfide yield (%)	Nucleophile	Product Yield (%)
Me ₂ CHCH(SEt) ₂	Me ₂ CHCHSEt	Me ₃ SiCH ₂ CH=CH ₂ 11	$Me_{2}CHCH(SEt)CH_{2}CH=CH_{2}$ 15 (76)
5	ÓAc 8 (82)	CH ₂ =C(OTMS)Pr 12	Me ₂ CHCH(SEt)CH ₂ COPr 16 (80) SEt
		OTMS	Me
		13	0 17 (92)
		TMSCN 14	Me ₂ CHCH(SEt)CN 18 (75)
PhCH(SEt) ₂	PhCHSEt	11	PhCH(SEt)CH ₂ CH=CH ₂ 19 $(71)^{2}$
0	OAc 9 ¹⁾	13	Ph
		14	20 (88) ²⁾ PhCH(SEt)CN 21 (69) ²⁾
Me ₂ CHCH(SPh) ₂ 7	Me ₂ CHCHSPh OAc 10 (99)	11	$Me_{2}CHCH(SPh)CH_{2}CH=CH_{2}$ 22 (65)
		13	Me Me O
		14	23 (96) Me ₂ CHCH(SPh)CN 24 (89)

Table 1. The Synthesis of α -Acetoxy Sulfides and Their SnCl4-Mediated Reactions.

1) This compound was used without purification.

2) Yield from dithioacetal 6.

and 13 (169 mg, 0.99 mmol) in anhydrous methylene chloride (5 mL) at -78° C was added 1M stannic chloride in methylene chloride (0.87 mL, 0.87 mmol). After 20 min, the reaction was quenched with saturated aqueous sodium bicarbonate. The aqueous layer was separated and extracted with methylene chloride. The combined organic extracts were washed with brine, were dried over magnesium sulfate, and were concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate, 35:1) to afford 162 mg (92%) of 17 as a colorless oil.¹³

The reaction of α -acetoxy sulfides with nucleophiles in the presence of SnCl4 provides a convenient method for carbon-carbon bond formation. The products resulting from the reactions of α -acetoxy sulfides with nucleophiles are bifunctional compounds which are of considerable use in synthetic organic chemistry. The facile generation of dithioacetals combined with their widespread use makes our methodology particularly relevant.

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- Fuchigami, T.; Yamamoto, K.; Yano, H. J. Org. Chem., 1992, 57, 2946. This group studied selected fluorinated examples using nucleophiles plus an electrogenerated acid. In this paper, the α-acetoxy sulfides were prepared directly from the corresponding sulfides by way of electrochemical oxidation with sodium acetate in acetic acid.
- 12. Acetoxy sulfide 8: IR (CHCl₃) 1737 cm⁻¹; ¹H NMR (CDCl₃) δ 1.01 (d, J = 6.8 Hz, 6 H), 1.26 (t, J = 7.4 Hz, 3 H), 1.98-2.14 (m, 1 H), 2.11 (s, 3 H), 2.54-2.76 (m, 2 H), 5.89 (d, J = 5.5 Hz, 1 H); mass spectrum M/Z (M⁺) calcd for C₈H₁₆O₂S 176.08710, found 176.08710.
- 13. Keto sulfide 17: IR (CHCl₃) 1709 cm⁻¹; ¹H NMR (CDCl₃) δ 0.96 and 1.01 (2d, J = 6.6 Hz, 6 H x 2/3), 0.95 and 1.00 (2d, J = 6.6 Hz, 6 H x 1/3), 1.23 (t, J = 7.4 Hz, 3 H x 2/3), 1.21 (t, J = 7.4 Hz, 3 H x 1/3), 1.51-2.56 (m, 12 H), 2.98 (t, J = 6.1 Hz, 1 H); mass spectrum M/Z (M⁺) calcd for C₁₂H₂₂OS 214.13914, found 214.13968.

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