

A CONVENIENT METHOD FOR GENERATION OF TIN(II)
THIOESTER ENOLATE AND ITS REACTION WITH ALDEHYDE

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Tin(II) enolates of thioesters are conveniently generated by the addition of stannous thiolates to ketenes. The tin(II) enolates thus formed react with aldehydes to afford the corresponding β -hydroxythioesters in a syn-selective manner. And this method is applied to an enantioselective formation of β -hydroxythioesters by the use of a chiral diamine as ligand.

Various cross aldol type reactions via tin(II) enolates formed from stannous trifluoromethanesulfonate (stannous triflate) and ketone,¹⁾ or 3-acylthiazolidine-2-thiones²⁾ have been reported from our laboratory. However, tin(II) thioester enolate could not be generated smoothly according to the above mentioned method because of the relatively low acidity of α -proton of the starting thioester.

On the other hand, we have already shown that ketenes and thioborinates smoothly afford vinyloxyboranes which in turn react with carbonyl compounds to give the corresponding β -hydroxythioesters in excellent yields under mild conditions.^{3,4)} According to this preparative method, the thioesters are produced in the form of borinates and it is necessary to work up further with oxidant such as aqueous hydrogen peroxide to cleave boron-oxygen bond for the isolation of the desired thioesters.

Now, we wish to report on a convenient method for the preparation of β -hydroxythioesters via tin(II) thioester enolates generated from stannous thiolates and ketenes. In the first place, ketene was allowed to react with aldehyde in the presence of stannous thiolate, generated from 1,1'-dimethylstannocene and thiol,⁵⁾ and the corresponding β -hydroxythioester was obtained in a high yield. In this reaction, it is assumed that tin(II) thioester enolate is initially generated as a key intermediate by the addition of stannous thiolate to ketene, and this enolate in turn reacts with aldehyde to form the corresponding β -hydroxythioester. After the conditions were optimized, it was found that various β -hydroxythioesters are prepared in good yields (see Table 1).

The following is a typical procedure for the preparation of *t*-butyl 3-hydroxy-2-methyl-5-phenylpentanethioate. To a THF solution (2 ml) of 1,1'-dimethylstannocene (0.54 mmol) was added 2-methyl-2-propanethiol (1.1 mmol) using a microsyringe at room temperature under an argon atmosphere. After the mixture was stirred for 20 min, 3-phenylpropanal (0.41 mmol) in THF (1 ml) and

methylketene (1.5 ml, 0.76 mmol) in THF⁷⁾ were successively added at $-78\text{ }^{\circ}\text{C}$. After the mixture was stirred at this temperature for 1 h, 10% aqueous citric acid was added to the reaction mixture which was subsequently extracted with chloroform. The organic layer was washed with a saturated solution of NaCl, dried with Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by preparative TLC (silica gel) to afford *t*-butyl 3-hydroxy-2-methyl-5-phenylpentanethioate (89%, syn:anti = 97:3).

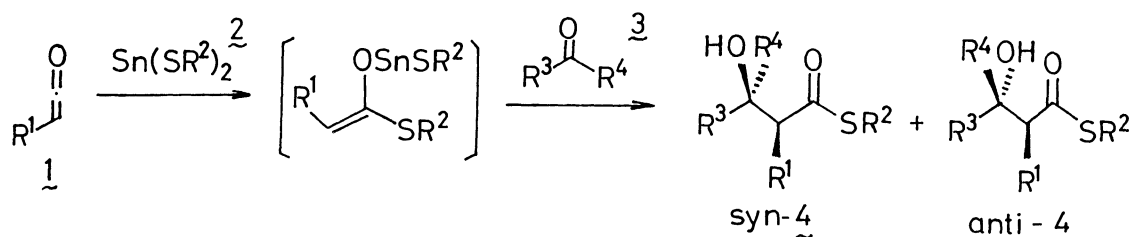
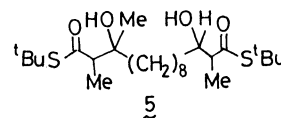


Table 1.

	R ¹	R ²	R ³	R ⁴	Conditions		yield/%	syn:anti
					Temp/ $^{\circ}\text{C}$	Time/h		
1	Me	<i>t</i> -Bu	$\text{Ph}(\text{CH}_2)_2$	H	-78	1	89	97: 3 ^{b, f)}
2	Me	<i>t</i> -Bu	<i>i</i> -Pr	H	-23	3.5	78	93: 7 ^{c, f)}
3	Me	<i>t</i> -Bu	<i>t</i> -Bu	H	-78	1	72	90:10 ^{c, g)}
4	Me	<i>t</i> -Bu	Ph	H	-78	2 ^{a)}	98	90:10 ^{d, f)}
5	Et	<i>t</i> -Bu	Ph	H	-78	1	90	>95: 5 ^{e, f)}
6	H	<i>t</i> -Bu	Ph	H	-78	1	75	—
7	Me	2-pyridyl	Ph	H	-100	2	89	93: 7 ^{d, f)}
8	Me	<i>t</i> -Bu	$-(\text{CH}_2)_5-$		-78	2	78	—
9	Me	<i>t</i> -Bu	Ph	Me	-78	2	77	70:30 ^{c, h)}
10	Me	<i>t</i> -Bu	$\text{Ph}(\text{CH}_2)_2$	Me	-78	12	69	58:42 ^{d, i)}
11	Me	<i>t</i> -Bu	EtO_2C	Me	-78	1	96	19:81 ^{c, j)}
12	Me	<i>t</i> -Bu	$\text{CH}_3\text{CO}(\text{CH}_2)_8$	H	-100	1	67	— ⁱ⁾
13	Me	<i>t</i> -Bu	$\text{CH}_3\text{CO}(\text{CH}_2)_8$	H	-45	1	81 ^{k)}	— ⁱ⁾

Molar ratio of 1 : 2 : 3 = 1.4 : 1 : 0.75.

a) The reaction was carried out in toluene. b) The ratio was determined by HPLC (reversed phase). c) Each isomer was isolated by PTLC. d) The ratio was determined by ^1H NMR spectroscopy. e) Only one isomer was detected from ^1H NMR spectroscopy. f) The stereochemistry was determined by ^1H NMR spectroscopy.⁴⁾ g) The stereochemistry was determined by ^{13}C NMR spectroscopy. δ α -Me(ppm): anti:19.2; syn:13.5. h) After conversion to the corresponding methyl ester, the stereochemistry was determined by ^1H NMR spectroscopy.⁶⁾ i) The stereochemistry was not determined. j) The stereochemistry was determined by comparison of ^1H NMR spectra with those of products in entry 9. k) Thioester 5 was isolated in 14% yield.



The results, listed in Table 1, reveal that i) the reactions with aldehydes take place syn-selectively (entries 1-5, 7); ii) the tin(II) enolate reacts even with bulky aldehyde such as pivalaldehyde to give the product in a high yield (entry 3), while vinyloxyborane does in a very low yield ($\approx 20\%$); iii) the tin(II) enolate also reacts with ketones, while vinyloxyborane does not add to ketones except acetone (entries 8, 9, 10); iv) the reactions proceed chemoselectively: in the case of ketoaldehyde the tin(II) enolate preferentially adds to aldehydic carbonyl group (entries 12, 13): in the case of ketoester, the enolate attacks only ketonic carbonyl group (entry 11); v) the tin(II) 2-pyridylthioester enolate can be easily generated and it reacts with aldehyde to give the desired product in a high yield, while the corresponding lithium enolate cannot be cleanly generated from lithium diisopropylamide and 2-pyridyl propanethioate.

Further, we have recently reported a highly enantioselective aldol type reaction via tin(II) enolate using chiral diamine derived from (S)-proline.⁸⁾ Based on this result, we next tried to apply the reaction of tin(II) thioester enolate with aldehyde to an enantioselective reaction.

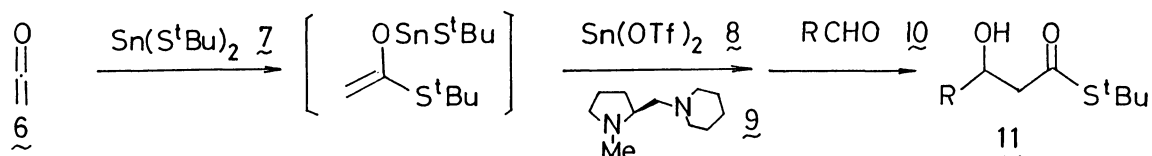


Table 2.

	R	Yield of <u>11</u> /%	Optical purity/ee%	Recovery of <u>10</u> /%
1	Ph(CH ₂) ₂	55	58 ^{b)}	10
2	Ph	70	76 ^{c, d)}	14
3	α -naphthyl	68	80 ^{c)}	16
4	<i>t</i> -Bu	64	76 ^{c)}	—

Molar ratio of 6 : 7 : 8 : 9 : 10 = 1.2 : 1 : 2 : 3 : 0.75.

a) The optical purity was determined by ¹H NMR spectra of the corresponding MTPA ester using Eu(hfc)₃. b) The optical purity was determined by ¹⁹F NMR of the corresponding MTPA ester. c) In this case, the absolute configuration of the adduct was determined to be S by the optical rotation of the corresponding carboxylic acid. In other cases, the absolute configuration was not established.

In the first place, aldehyde was allowed to react with the tin(II) enolate which was coordinated by chiral diamine. However, according to this procedure, the aldol type reaction did not occur at all. It is assumed that the Lewis acidity of tin(II) atom of the enolate is decreased by the coordination of the diamine. So we further added stannous triflate as an acidic component to the solution of enolate. That is, to a CH₂Cl₂ solution of stannous 2-methyl-2-propanethiolate was added freshly prepared ketene in CH₂Cl₂.⁹⁾ After the mixture

was stirred for 20 min at $-78\text{ }^{\circ}\text{C}$, stannous triflate, (2S)-1-methyl-2-[(piperidin-1-yl)-methyl]-pyrrolidine were subsequently added, and then aldehyde was added at $-100\text{ }^{\circ}\text{C}$. The mixture was further stirred for 20 min. After the usual work up, the product was isolated by preparative TLC in a moderate yield. Good enantioselectivities can be realized in the cases of aromatic and bulky aldehyde, as shown in Table 2.

It is noted that tin(II) enolates, generated from stannous thiolates and ketenes, smoothly react with ketones or aldehydes to give the corresponding β -hydroxythioesters in good yields. In the cases of aldehydes, the reaction proceeds in a syn-selective manner, and, by the use of chiral diamine, the enantioselective reaction can be achieved via the coordinated complexes.

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- 9) Ketene was prepared by thermal decomposition of diketene at $550\text{ }^{\circ}\text{C}$, distilled, and collected in CH_2Cl_2 . And the concentration of ketene in CH_2Cl_2 was determined by HPLC analysis of N-acetylaniline, obtained from ketene and aniline ($-45\text{ }^{\circ}\text{C}$, 10 min, THF).

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