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HIGHLY ENANTIOSELECTIVE ALDOL-TYPE REACTION OF 3-ACETYLTHIAZOLIDINE-2-THIONE WITH ACHIRAL ALDEHYDES

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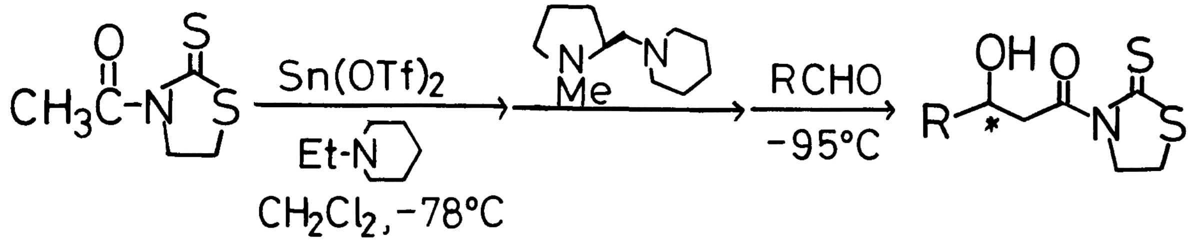
A highly enantioselective aldol-type reaction forming various β-hydroxy carbonyl compounds from 3-acetylthiazolidine-2-thione and achiral aldehydes is achieved via divalent tin enolate employing chiral diamine derived from (S)-proline as a ligand.

Recent development in the field of stereoselective aldol reaction has resulted in the exploitation of asymmetric version of this reaction, and several successful results have been reported by using chiral carbonyl compounds as one of the component compounds or by using chiral boron triflate as a generator of boron enolate.$^{1)}$ However, the efficiency of these reactions is greatly diminished by the necessity of tedious procedures for the attachment and removal of the chiral sources. So, development of a highly enantioselective aldol reaction between two achiral carbonyl compounds utilizing chiral chelating agents is strongly desired. But, the influence of such chiral addends in the aldol reaction had not met with much success$^{2-4)}$ until we reported the first example of forming highly optically active aldols from aromatic ketones and various aldehydes via divalent tin enolates employing chiral diamines derived from (S)-proline as ligands.$^{1)}$

Recently, we have reported that divalent tin enolates formed from stannous trifluoromethanesulfonate (triflate) and 3-acylthiazolidine-2-thione, react with aldehydes to afford the corresponding aldol-type products in high yields with high erythro-selectivities, and the adducts are easily transformed into β-hydroxy aldehyde and β-hydroxy carboxylic acid derivatives.$^{5)}$

Now, we wish to report a highly enantioselective aldol-type reaction of 3-acetylthiazolidine-2-thione and various achiral aldehydes via divalent tin enolate using chiral diamine derived from (S)-proline as a ligand.

According to the previously reported procedure, stannous triflate was treated with 3-acetylthiazolidine-2-thione in CH_2Cl_2 in the presence of N-ethylpiperidine as a base at -78°C for 15 min, and then (S)-1-methyl-2-[(piperidin-1-yl)-methyl]pyrrolidine,$^{6)}$ a chiral diamine, was added and the reaction mixture was cooled to -95°C. Then, aldehyde was added and the reaction mixture was stirred at this temperature for 1 h. Usual work-up of the reaction mixture afforded the corresponding aldol-type product in good yield and the optical purity of the product was determined by measuring the ^{1}H NMR spectra of the corresponding methyl ester using chiral shift reagent. And it was made clear that, in some cases, the optical purities more than 90% enantiomeric excess were achieved.



Sn(OTf)$_2$:N-ethylpiperidine:chiral diamine:3-acetylthiazolidine-2-thione:aldehyde =1.0:1.2:1.2:0.85:1.15.

Table. Enantioselective Aldol-Type Reaction of 3-Acetylthiazolidine-2-thione.

RCHO	Yield(%)[a]	$[\alpha]_D^{21}$ (c, C_6H_6)	Optical Purity (%)[b]
PhCHO	79	-48.4°(1.1)	65 [c]
$(CH_3)_2CHCHO$	63	-68.8°(0.8)	> 90
$PhCH_2CH_2CHO$	76	-40.2°(1.4)	> 90
cyclo-$C_6H_{11}CHO$	81	-61.5°(1.6)	88
C_2H_5CHO	70	-64.8°(1.0)	90
n-$C_5H_{11}CHO$	65	-51.6°(0.9)	90

a) Isolated yield. Satisfactory NMR and IR spectra were obtained for each compound.

b) Determined by the measurement of the ^{1}H NMR spectrum of the corresponding methyl ester using Eu(hfc)$_3$ as a chiral shift reagent. The -OCH$_3$ signal was completely separated.

c) In this case, the absolute configuration of the adduct was determined to be S by the optical rotation of the β-hydroxy carboxylic acid. In other cases, the absolute configurations were not rigorously established; however, judging from the similarity in the chemical shifts of -OCH$_3$ signals using the chiral shift reagent, other aldol products are thought to have the same absolute configuration.

As we have already reported the derivations of the adduct,[5)] this stannous triflate mediated enantioselective aldol-type reaction of 3-acetylthiazolidine-2-thione would become a general method for the preparation of highly optically active β-hydroxy aldehyde and β-hydroxy carboxylic acid derivatives. Further studies directed towards the asymmetric syntheses of polyoxygenated natural products are now in progress.

References

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6) Prepared from Boc-(S)-proline in good yield via coupling with piperidine using dicyclohexylcarbodiimide and subsequent reduction with LiAlH$_4$.

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