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STANNOUS TRIFLATE MEDIATED ALDOL REACTION OF 3-ACYLTHIAZOLIDINE-2-THIONE: A CONVENIENT METHOD FOR THE STEREOSELECTIVE SYNTHESES OF β-HYDROXY ALDEHYDE AND β-HYDROXY CARBOXYLIC ACID DERIVATIVES

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Divalent tin enolates, formed from stannous triflate and 3-acylthiazolidine-2-thiones, react with aldehydes to afford the corresponding aldol products in high yields with high erythro-selectivities. The adducts are easily transformed into β-hydroxy aldehyde and β-hydroxy carboxylic acid derivatives.

Based on our studies on the stereoselective cross aldol reaction employing stannous trifluoromethanesulfonate (triflate),[1)] we have already established novel methods for directed cross aldol reaction between two ketones,[2)] enantioselective cross aldol reaction,[3)] and stereoselective synthesis of *cis*-α,β-epoxyketones.[4)] Our attention was further focused on the exploration of a convenient method for the preparation of various kinds of β-hydroxy aldehydes and β-hydroxy carboxylic acid derivatives (ester, amide etc.). In practice, the importance of β-hydroxy aldehyde as a synthetic building block for the construction of a variety of poly-oxygenated natural products is widely recognized.[5)] However, because of the difficulty in controlling the generation of aldehyde enolate, existing methods for the preparation of β-hydroxy aldehyde usually require tedious derivation from other carbonyl compounds. Therefore, a facile and stereoselective preparation of these β-hydroxy carbonyl compounds is strongly desired.

Our initial attempts to enolize various kinds of starting carbonyl compounds using stannous triflate have not yet met with success probably due to their low acidity of α-proton (ester,[6)] amide) or self-polymerization of the starting material (aldehyde). Thus, we decided to examine the equivalent of such carbonyl compounds.

Previously, we have reported that 3-acylthiazolidine-2-thione can be cleanly converted to the corresponding aldehyde by reduction with diisobutylaluminum hydride (DIBAL),[7)] and thereafter, the reaction of 3-acylthiazolidine-2-thione was widely screened and it was shown that it can be easily transformed into a variety of carboxylic acid derivatives under mild reaction conditions.[8)] Thus, 3-acylthiazolidine-2-thione was chosen as their equivalent molecule, and in this communication, we wish to describe our successful results on the stereoselective cross aldol reaction between 3-acylthiazolidine-2-thione and aldehydes, and the facile transformation of the adducts into various kinds of β-hydroxy carbonyl compounds, especially into β-hydroxy aldehyde.

3-Acylthiazolidine-2-thione is prepared from acyl chloride and thiazolidine-

2-thione or from carboxylic acid and thiazolidine-2-thione using DCC or pyridinium salt as a condensating reagent in high yield.[7,8]

Though the attempts to form the lithium enolate of the 3-acylthiazolidine-2-thione was not successful,[9] we have succeeded in forming the corresponding divalent tin enolate. Thus, according to the previously mentioned procedure,[1] 3-acylthiazolidine-2-thione was treated with stannous triflate in the presence of N-ethylpiperidine as a base in dichloromethane at -78°C, and then aldehyde was added to the reaction mixture. Usual work-up of the reaction mixture afforded the corresponding aldol product in high yield. And furthermore, in the case of 3-propanoylthiazolidine-2-thione or 3-(3-phenylpropanoyl)thiazolidine-2-thione, it was found that high erythro-selectivity is achieved. The results are summarized in the Table.

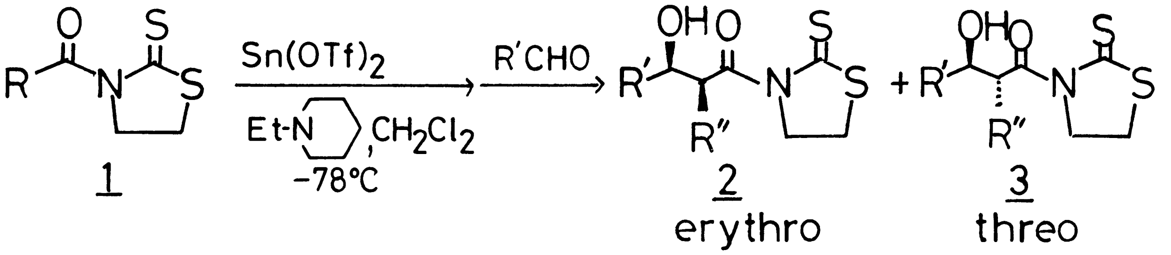


Table. The Aldol Reaction of 3-Acylthiazolidine-2-thione with Aldehyde[a]

R in 1	Aldehyde	Yield(%)[b]	Erythro:Threo
CH_3	PhCHO	90	–
	$PhCH_2CH_2CHO$	88	–
	$(CH_3)_2CHCHO$	94	–
CH_3CH_2	PhCHO	94	97 : 3[c]
	$PhCH_2CH_2CHO$	91	>97 : 3[d]
	$(CH_3)_2CHCHO$	95	>97 : 3[d]
$PhCH_2CH_2$	PhCHO	88	>97 : 3[d]
	$PhCH_2CH_2CHO$	95	>97 : 3[d]

a) Enolization was carried out in CH_2Cl_2 at -78°C for 15 min, then aldehyde added and reaction run for 20 min. Molar ratio of $Sn(OTf)_2$: N-ethylpiperidine : 3-acylthiazolidine-2-thione : aldehyde = 1.0 : 1.2 : 0.8-0.85 : 1.15-1.2.

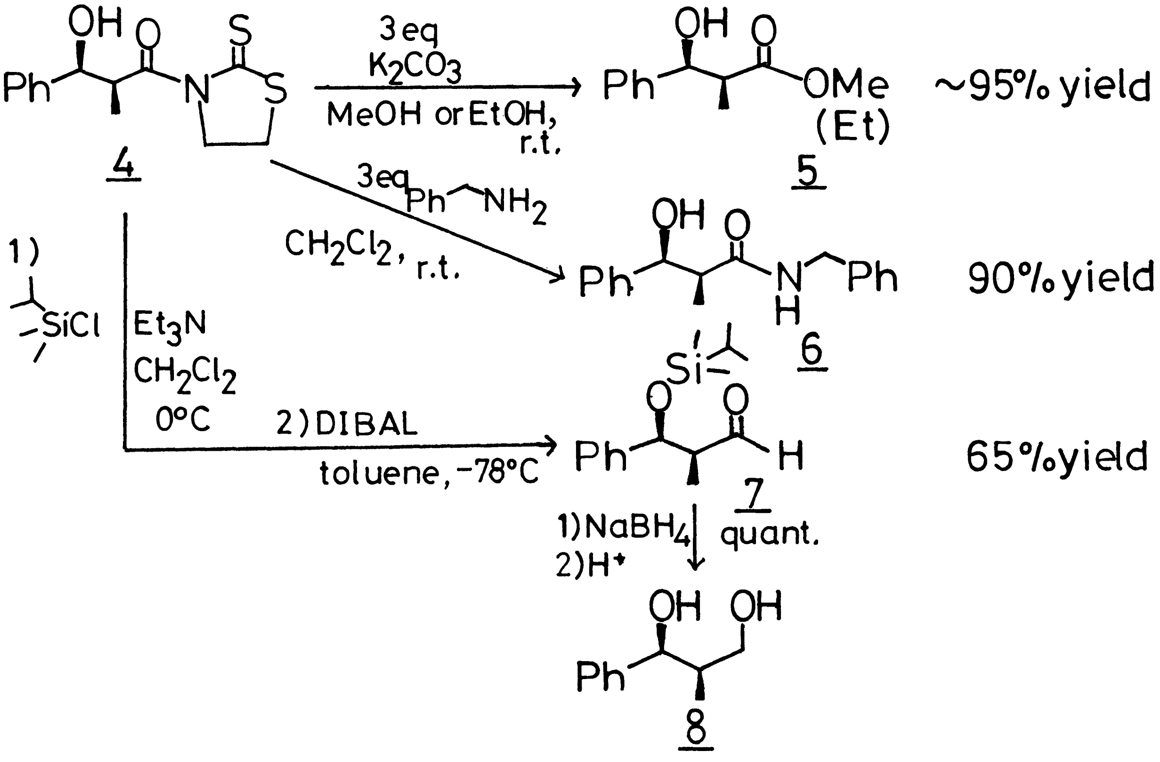
b) Isolated yield. All samples gave satisfactory ^1H NMR and IR spectra. The structures were further confirmed by converting to the corresponding methyl ester according to the procedure described afterwards.

c) The ratio was determined by separating each isomer. The stereochemistry of each compound was assigned by converting to the methyl ester.

d) Only one stereoisomer was detected from ^{13}C NMR spectrum. The stereochemistry was determined by converting to the corresponding methyl ester and comparison of ^1H or ^{13}C NMR spectrum with that of authentic sample.[10]

Next, derivations of the aldol product to a variety of β-hydroxy carbonyl compounds were tried taking the adduct 4 as a model compound.

Conversion to the methyl or ethyl ester was easily achieved in high yield by treating 4 in methyl or ethyl alcohol solvent at room temperature in the pres-



ence of potassium carbonate as a base. And corresponding amide was also spontaneously formed only by mixing 4 with the corresponding amine in dichloromethane. Their stereochemical integrities were ascertained from their ^{1}H NMR spectra.

Preparation of β-hydroxy aldehyde was also carried out in a straightforward way by protection of the hydroxy function with isopropyldimethylsilyl group and subsequent reduction with DIBAL in good yield. In this case also, the stereochemical integrity was rigorously established by converting to the known 1,3-diol 8,$^{11)}$ and it was made clear that there is no detectable isomerization during these procedures.

A general procedure is described for the preparation of 3-isopropyldimethylsiloxy-2-methyl-3-phenylpropanal via the cross aldol reaction between 3-propanoylthiazolidine-2-thione and benzaldehyde: To the dichloromethane suspension (2.0 ml) of stannous triflate (480 mg, 1.15 mmol) and N-ethylpiperidine (155 mg, 1.37 mmol) was added dropwise the dichloromethane solution (1.2 ml) of 3-propanoylthiazolidine-2-thione (163 mg, 0.93 mmol) at -78°C. After further stirring at this temperature for 15 min, the dichloromethane solution (1.2 ml) of benzaldehyde (146 mg, 1.38 mmol) was added to the reaction mixture, and the reaction mixture was further stirred for 20 min. The reaction was quenched with pH 7 phosphate buffer solution and precipitated white mass was removed through Celite. The organic material was extracted with ether three times, the extracts were dried over Na_2SO_4, and evaporated in vacuo. The residual oil was purified by silica-gel column chromatography to afford the corresponding aldol product in 94% yield. The hydroxy function of the adduct was protected under the standard conditions$^{12)}$ (2 eq. isopropyldimethylsilyl chloride, 2 eq. Et_3N in CH_2Cl_2 at 0°C, overnight) in 87% yield.

To the toluene solution (1.0 ml) of this protected compound (82 mg, 0.22 mmol) was added the toluene solution (0.80 ml, 1.83 ml/mmol) of DIBAL at -78°C and the reaction mixture was further stirred for 10 min at this temperature. The reaction was quenched with pH 7 phosphate buffer solution (0.2 ml) and Na_2SO_4 was added as a drying agent. After the removal of the precipitates through Celite, the solvent was evaporated in vacuo and the residual oil was purified by silica-gel column chromatography to afford 3-isopropyldimethylsilyloxy-2-methyl-3-phenylpropanal in 75% yield.

Thus, an efficient and general method for the preparation of various kinds of β-hydroxy carbonyl compounds, especially β-hydroxy aldehyde, is established employing stannous triflate mediated cross aldol reaction of 3-acylthiazolidine-2-thione. Further studies directed towards the syntheses of polyoxygenated natural products and asymmetric version of this reaction are now in progress.

References

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