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3-아세틸티아졸리딘-2-티온을 이용한 입체선택적인 알돌-축합반응

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Highly Diastereoselective Aldol-Type Reaction Using 3-Acetylthiazolidine-2-thione

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요 약. 아미노 알콜에서 합성한 티아졸리딘치온[4(S)-IPTT, 4(S)-ETT]은 주석을 매개체로한 알돌 축합반응의 키랄 보조제로 이용되었다. Stannous triflate와 3-아세틸티아졸리딘-2-티온을 반응시켜 얻은 2가주석 엔올레이트를 어키랄 알데히드와 반응시켜 β-하이드록시 카르보닐 화합물을 입체선태적으로 얻었다. 이러한 키랄 보조제는 가메탄올 분해반응으로 쉽게 에스터화 되기 때문에 절대구조 동정을 용이하게 하는 장점도 있었다.

ABSTRACT. Amino alcohol-derieved thiazolidinethiones [4-(S)-IPTT, 4(S)-ETT] serve as efficient chiral auxiliary in tin medicated aldol condensation. A highly enantioselective aldol-type reaction forming various β-hydroxy carbonyl compounds from 3-acetylthiazolidine-2-thione and achiral aldehyde is achieved via divalent tin enolate. The other advantages of these chiral auxiliaries were the ease of removal by methanolysis.

INTRODUCTION

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.[1,2] However, the efficiency of these reaction is greatly diminished by the necessity of tedidious procedures for the attachment and removal of the chiral sources.[3,4]

Ideally, such asymmetric reactions should employ chiral auxiliaries that are readily available and readily acetylated promote efficient enantioselective carbon-carbon bond formation and can be easily removed by solvolysis or aminolysis.[5,6] Our attention was further focused on the exploration of a convenient method for the preparation of variouskinds of β-hydroxy aldehydes and β-hydroxy carboxylic acid derivatives. A variety of published methods have illustrated the utility of chiral auxiliary and tin triflate for enantioselective aldol condensation. Especially C-4 chiral 4(S)-isopropyl-1,3 thiazolidine-2-thione[4(S)-IPTT], which was synthesized from L-valine, has been shown to the most effective for the regioselectivity and enantioselectivity of asymmetric synthesis.

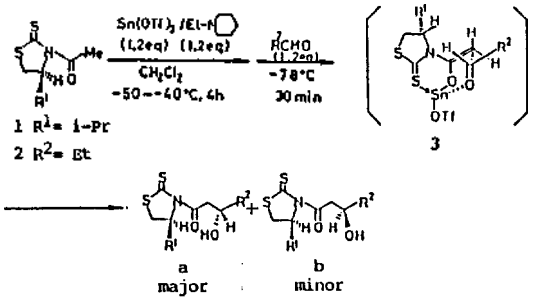
Now we wish to report that diavalent tin enolates formed from stannous trifluoromethanesulfonate (triflate) and 3-acetylthiazolidine-2-thiones,

react with achiral aldehydes to afford the corresponding aldol-type products in high yields with high stereoselectivities.

RESULT AND DISCUSSION

3-Acetylthiazolidine-2-thione(ATT) was easily preapared by dehydration between acetic acid and thiazolidine thione(TT) under presence of dicyclohexylcarbodiamide(DCC)[7] [sometimes together with catalytic amount of 4-dimethylaminopyridine (DMAP)[8]] or by treatment of acethylchloride with sodium salt of TT.

We have succeed that diavalent tin enolates formed from stannous trifluoromethanesulfonate (triflate) and 3-acethylthiazolidine-2-thiones, react with aldehydes to afford the corresponding aldol-selectivities, and the products are transformed into β-hydroxy aldehyde and β-hydroxy carboxylic acid derivatives (*Scheme* 1). Following to the previously reported procedure,[11] stannous triflate was treated with 3-acethylthiazolidine-2-thione in methylenechloride in presence of N-ethylpiperidine as a base at -40 -50 ℃ under Ar gas for 4 hr

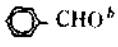


Scheme 1.

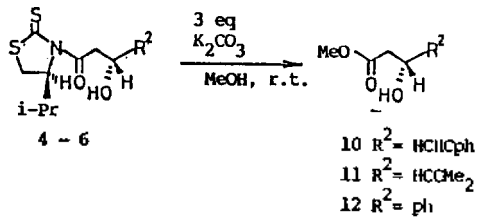
and the reaction mixture was cooled to -78 ℃. Then aldehyde was added and the reaction mixture was stirred at this temperature for 30 min. The reaction mixture was quenched by adding excess pH 7 phosphate buffer, and resulting mixture was stirred vigorously at room temperature for 5 min. More methylene chloride was added, and the suspension was filtered through Celite. Usual work-up of the reaction mixture afforded the corresponding aldol type product in good yield.

All chiral recognition data listed in Table 1 can be rationalised by an assumed transition state (*Scheme* 1). The resulting "ate" complex should eventually react to provide aldol products resulting

Table 1. Diastereoselective aldol reaction of 3-acetylthiazolidine-2-thione with aldehydes

No	R^1	R^2CHO	Diastereoisomer ratio[a] a : b	Isolated yield[c]
(4)	*i*-Pr	Ph-CH=CH-CHO	97.1 : 2.9 4a 4b	81%
(5)	*i*-Pr	Me-CH=C(Me)-CHO	97.3 : 2.7 5a 5b	70%
(6)	*i*-Pr	 [b]	96.5 : 3.5 6a 6b	72%
(7)	Et	Ph-CH=CH-CHO	92.7 : 7.3 7a 7b	77%
(8)	Et	Me-CH=C(Me)-CHO	88.6 : 11.4 8a 8b	74%
(9)	Et	$(CH_3)_2CHCHO$	91.6 : 8.4 9a 9b	59%

[a] Checked by HPLC: UV(305 nm). [b] In this case, the absolute configuration of the product was determined to be S by optical rotation of the β-hydroxy carboxylic acid. In other cases, the absolute configurations were not rigorously estabilished; however, judging from the similarity in the chemicl shifts of $-OCH_3$ signals using $Eu(hfc)_3$ as a chiral shift reagent, other aldol products are thoguht to have the same absolute configuration. [c] Diastereomeric mixture.



Scheme 2.

from opposite facial selectivity of the enolate.

Methanolysis of the yellow aldol products provide the corresponding known colorless optically active methyl ester for comparison of optical purity (*Scheme* 2). Conversion to the methyl ester was easily achieved in high yield by treating(4) in methyl alcohol at room temperature in the presence of potassium carbonate as a base.[12]

The ratio of each diastereoisomer was readily checked by HPLC equipped with a UV detectol.[13,14] Preparative TLC of each diastereoisomer gave optically pure compounds. Absolute configuration[15] was confirmed by comparision of the physical data of β-hydroxycarboxilic acids (or their methylesters) derived from the cores-sponding aldol products with those of the authentic samples (*Table* 1). Futher studies directed towards the syntheses of β-Lactams and asymmetric version of their reaction are now in progress.

EXPERIMENTAL

Melting points were determined with a capillary method. Infrared spectra were run using KBr plates on a Hitachi 270-50 spectrophotometer. Optical rotations were measured on a DDr-69 Jena polarimeter. Mass spectra were recorded on a JMS-DX300 mass spectrometer. Proton NMR specta were recorded on Bruker Aw-80 or Bruker Am 200 NMR spectrometer in $CDCl_3$ solutions with Me_4Si as internal standard. Analytical HPLC was carried out on a Water's Associates, equipped with UV detector, using (4.6×250 mm FINEDAC SIL column (flow rate: 2.5 m*l*/min). Extracts were dried over Na_2SO_4. Silicagel 60 (70~230 mesh) was used for column chromatography. TLC was performed silicagel 0.25 mm, 60 F 254(Merk).

Preparation of 3-Acetyl-4(S)-isopropyl-1,3-thiazolidine-2-thione(1). To suspension of 60% NaH (0.279g, 6.83 mmol) in 3 m*l* of THF under nitrogen was added 4(S)-isopropyl-1,3-thiazolidine-2-thione[4(S)-IPTT](1.0g, 6.21 mmol) in THF (3m*l*) followed by addition of acetyl chloride (0.51g, 6.21 mmol) in THF (3 m*l*) followedby addition of acetyl chloride (0.51g, 6.52 mmol). The reaction mixture was stirred at room temperature for 30 min. 30% aqueous $NaHSO_4$ was added at 0 °C, and the reaction mixture was extracted with methylene chloride, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The oily residue was chromatographed on silicagel using methylenechloride-hexane(1:1) to provide 1.18g (94%) of (1) as light yellow oil: $[\alpha]_D$ + 324 ° (c = 1.31, $CHCl_3$); V_{max} 2950, 1710, and 1440 cm^{-1}; ^1H NMR (80 MHz) δ 0.91(3H, *d*, J = 7.2 Hz), 1.08(3H, *d*, J = 6.75 Hz), 2.31(1H, *m*), 2.78(3H, *S*), 3.52(2H, *m*), 5.08 (1H, *m*); M^+ (*m/e*) 203.

3-Acetyl-4(S)-ethyl-1,3-thiazolidine-2-thione (2). Was prepared in 96% yield from-4(S)-ethyl 1,3-thiazolidine-2-thione[4(S)-ETT] and acetylcholine in same manner: in yellow oil; $[\alpha]_D$ + 263.2 ° (c = 1.41, $CHCl_3$); H NMR (80 MHz) δ 1.03(3H, *t*, J = 7 Hz), 1.84~2.0(2H, *m*), 2.30(1H, *m*), 2.68(3H, *S*), 3.52(2H, *m*), 5.08(1H, *m*); M^+ (*m/e*) 187.

General Procedure for the Aldol Condensation. Preparation of (4). To a suspension of tin triplate (500 mg, 1,2 mmol) of methylene chloride at -40 °-50 °C under nitrogen was added N-ethylpiperidine (138 mg, 1.2 mmol). After the mixture was stirred for 10 min. at -40~-50 °C, the suspension turned light yellow. A solution of (1) (189 mg, 1,00 mmol) in methylene chloride was added, the mixture was stirred for 4 hr while the temperature was maintained between -40 and -50 °C. The mixture was

cooled to −78 °C and a solution of cinnamic aldehyde (158.4 mg, 1.2 mmol) in 1 m*l* of methylenechloride was added to the reaction mixture, and the reaction mixture was further stirred for 30 min. The reaction was quenched by adding excess pH 7 phosphate buffer, and the resulting mixture was stirred vigorously at room temperature for 3 min. More methylenechloride (50 m*l*) was added, and the suspension was filtered through Celite. The methylenechloride layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

The only residue was purified by column chromatography (silicagel, hexane:methylenechloride = 1:1) to provide the aldol product (4) (271 mg, 81% yield): $[\alpha]_D$ + 348.1 ° (*c* = 1.41, $CHCl_3$); V_{max} 3450, 1685, cm^{-1}; ^1H NMR (200 MHz) δ 0.92(3H, *d*, *J* = 7.1 Hz), 1.08(3H, *d*, *J* = 6.75 Hz), 2.31(1H, *m*), 3.02(2H, *m*), 3.40(1H, *s*, OH), 3.58(2H, *m*), 4.72(1H, *m*, **4b** CHOH), 4.89(1H, *m*, **4a** CHOH), 5.20(1H, *m*), 5.98-6.52(2H, *m*), 7.43(5H, *m*, aromatic); M^+ (*m/e*) 335.

Aldol Product (5) was formed from (1) and 3,3-dimethylacrolein as a light yellow oil in 70% yield: [ ]$_D$ + 237.8 ° (*c* = 1.10, $CHCl_3$); V_{max} 3480, 1690 cm^{-1}, ^1H NMR (200 MHz) δ0.91(3H, *d*, *J* = 7.2 Hz), 1.08(3H, *d*, *J* = 7.5 Hz), 1.71(3H, *d*, *J* = 1.5 Hz), 1.73(3H, *d*, *J* = 1.5 Hz), 2.31(1H, *m*), 3.02 (2H, *m*), 3.42(1H, *s*, OH), 3.58(2H, *m*), 4.91(1H, *m*, **5a** CHOH), 5.21(1H, *m*), 5.34(1H, *m*); M^+(*m/e*) 287.

Aldol Product (6) was formed from (1) and benzaldehyde as a light yellow oil in 72% yield: $[\alpha]_D$ + 68.5 C (*c* = 1.20, $CHCl_3$), V_{max} 3460, 1690 cm^{-1}; ^1H NMR (200 MHz) δ 0.91(3H, *d*, J = 7.2 Hz), 1.08(3H, *d*, *J* = 7.80 Hz), 2.32(1H, *m*), 3.02(2H, *m*), 3.43(1H, *s*, OH), 3.58(1H, *m*), 4.76(1H, *m*, **6b** CHOH), 4.89(1H, *m*, **6a** CHOH), 5.21(1H, *m*), 7.52(5H, *m*, aromatic) M^+(*m/e*) 309.

Aldol Product (7) was formed from (2) and cinnamic aldehyde as a light yellow oil in 77% yield: $[\alpha]_D$ + 52.8 ° (*c* = 0.91, $CHCl_3$); V_{max} 3450, 1690 cm^{-1}; ^1H NMR (200 MHz) δ 1.03(3H, *t*, *J* = 6.8 Hz), 1.84-2.0(2H, *m*), 3.05(2H, *m*), 3.43(1H, *s*, OH), 3.58(2H, *m*), 4.90(1H, *m*, **7a** CHOH), 5.98-6.72(2H, *m*), 7.41(5H, *s*, aromatic); M^+(*m/e*) 302.

Aldol Product (8) was formed from (2) and 3,3-dimethylacrolein as a light yellow oil in 74% yield; $[\alpha]_D$ + 358.1 ° (*c* = 1.41, $CHCl_3$), V_{max} 3450, 1685 cm^{-1}; ^1H NMR (200 MHz) δ1.03(3H, *t*, *J* = 7 Hz), 1.71(3H, *d*, *J* = 1.5 Hz), 1.73(3H, *d*, *J* = 1.5 Hz), 1.84 2.0(2H, *m*), 2.98(2H, *m*), 3.30(1H, s, OH), 3.58(2H, *d*, *J* = 7.3 Hz), 4.89(1H, *m*, **8a** CHOH), 5.14(1H, *m*), 5.24(1H, *m*); M^+ (*m/e*) 273.

Aldol Product (9) was formed from 2 and isobutylaldehyde as a light yellow oil in 69% yield: $[\alpha]_D$ + 60.6 ° (*c* = 1.12, $CHCl_3$); V_{max} 3445, 1690 cm^{-1}; ^1H NMR (200 MHz) δ 0.96(3H, *d*, *J* = 6.5 Hz), 0.98 (3H, *d*, *J* = 6.4 Hz), 1.03(3H, *d*, *J* = 6.8 Hz), 1.84 2.0(2H, m), 3.02(2H, m), 3.41(1H, s, OH), 3.43 (1H, *m*), 3.58(2H, *m*), 4.90(1H, *m*, **9a** CHOH), 5.23 (1H, *m*); M^+ (*m/e*) 261.

General Procedure for the Methanolysis of Aldol products

Preparation of (10). To a solution of 405 mg (1.21 mmol) of (4) in 10 m*l* of methanol at 0 °C was added 500 mg (300 mol %) potassium carbonate. The cooling bath was removed and the reaction mixture was stirred for 5 min. TLC analysis indicated the complete absence of (4).

The reaction mixture was diluted ether hexane (1:1), and the suspension was filtered through a plug of Celite. The filtrate was concentrate under vaccumn and the residue was purified by column chromatography, to provide the desired methyl ester (10) in 96% yield (238 mg) as a colorless plate; mp 37-38 °C, V_{max} 3460, 1715 cm^{-1}; ^1H NMR (200 MHz) δ3.38(1H, *m*), 3.58(2H, *m*), 3.67 (3H, *s*, OCH_3), 4.75(1H, *m*), 5.98~6.42(2H, *m*), 7.41(5H, *m*, aromatic); M^+ (*m/e*) 206.

Methyl Ester (11) was prepared by the methanolysis of (5) in 95% yield as a colorless oil;

$[\alpha]_D$+ 1.25°(c=0.91, $CHCl_3$) V_{max} 3480, 1720 cm^{-1}, ^1H NMR (200 MHz) 1.71(2, *d*, J=1.5 Hz), 1.73 (2H, *d*, J=1.7 Hz), 3.40(1H, *m*), 3.58(2H, *m*), 3.71 (3H, *s*, OCH_3), 4.91(1H, *m*), 5.24(1H, *m*), M^+ (*m/e*) 158.

Methyl Ester (12) was prepared by the methanolysis of (**6**) in 92% yield as a colorless plate; mp 46.5 48°C; $[\alpha]_D$ + 8.2° (c = 0.85, $CHCl_3$) $[[\alpha]_D^{18.5}$ + 6.4° (EtOH)][16].

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