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3-Acyl-4(S)-Isopropyl-1, 3-Thiazolidine-2-Thione 과 라세미아민의 입체선택적인 반응

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A Highly Stereoselective Reaction in Aminolysis of 3-Acyl-4(S)-isopropyl-1, 3-thiazolidine-thione with Racemic Amines

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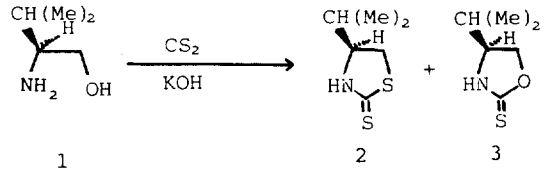
요 약. 키랄 보조제가 붙어있는 3-acyl-4(S)-isopropyl-1, 3-thiazoildine-2-thione[4(S)-AITT]을 라세미 아민과 가아민 분해반응을 시켰을때 광학활성을 갖는 아미드(S-excess)와 아민(R-excess)이 얻어지는 입체 선택적인 반응이 관찰되었다. 이와같은 입체 선택적인 반응은 macrocyclic diamide, macrocyclic sperimidine alkaloid, peptide 합성에 이용될 수 있다. 가아민 분해반응의 속도는 아민의 입체적인 영향을 많이 받았고 반응이 종료점은 노란색의 소실로 쉽게 관찰되었다. 4(S)-AITT 는 4(S)-isopropyl-1, 3-thiazolidine-2-thione 과 carboxylic acid 로부터 얻었다.

ABSTRACT. A chiral recognition was observed in aminolysis of 3-acyl-4(S)-isopropyl-1, 3-thiazolidine-2-thione by racemic amine to give an optically active amide (S-excess) and amine (R-excess). This procedure can be applied to synthesis of macrocyclic diamide macrocyclic spermidine alkaloid, and peptide. The rate of this aminolysis is remarkably affected by steric surrounding; completion of reaction can be easily judged by the disappearance of the original yellow color of 4(S)-AITT. These features of the aminolysis suggested a potential recognition racemic amines by a chiral 4(S)-AITT derivative. Thus 4(S)-AITT was synthesized from 4(S)-isopropyl-1, 3-thiazolidine-2-thione and carboxylic acids.

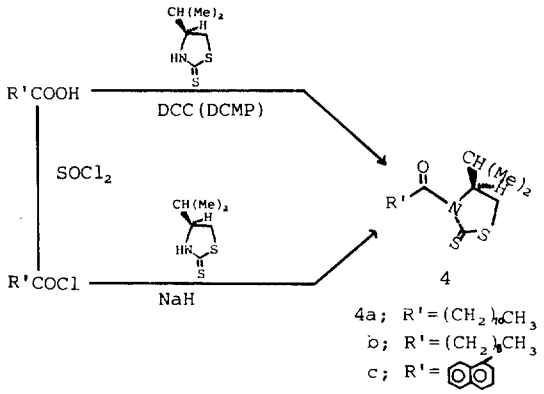
Introduction

In recent years, many useful new reactions using thiazolidine-2-thione have been exploited.[1,2]. We have also focused our interest on the exploitation of useful reactions utilizing the excellent leaving property of 2-thiocarbonyl-thiazolidino group. It reported previously a new method for amide preparation by the monitored aminolysis of 3-acyl-1, 3-thiazolidine-2-thiones (ATTs)[3] and its application to the synthesis of macrocyclic spermidine alkaloid[4]. Also, ATTs could be used as a chiral auxiliary of a highly enantioselective aldol-type reaction forming various β-hydroxy carbonyl compound[5]. During this research, We found some remarkable features in aminolysis of ATTs. (1) The end point of the reaction can be judged conveniently

by the disappearance the original yellow color. (2) ATTs can be used to detect weak intramolecular five or six membered hydrogen bonding between an amino group and an imino group[6]. (3) ATTs show a high chemoselectivity to amines. When an ATT was allowed to react with an amino alcohol, amino phenol or amino thiol, respectively, only the corresponding amide was obtained.[7] (4) ATTs are fairly stable in aqueous solvents. These chemical aspects of ATTs seemed to be very useful for a new chiral recognition in aminolysis. We report here in full details of the aminolysis of 4(S)-AITT with racemic amines.



Scheme 1



Scheme 2

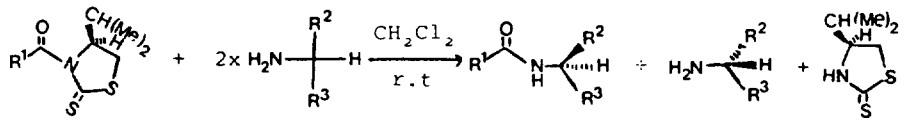
Result and Discussion

4(S)-isopropyl-1, 3-thiazolidine-2-thione[4(S)-IPTT] **2** was synthesized from L-valine[8](Scheme 1). 4(S)-AITT **4** was easily prepared by dehydration between carboxylic acid and 4(S)-IPTT under presence of dicyclohexylcarbodiamide(DCC)[9] (sometimes together with catalytic amount of 4-dimethylaminopyridine(DMAP)[10]) or by treatment of carboxylic acid chloride with sodium salt of 4(S)-IPTT(Scheme 2).

Now, 4(S)-AITT was found to be subject to aminolysis under very mild condition offering amide **6** in high yield. This reaction can be monitored by disappearance yellow color of the starting material **4** (*Scheme* 3).

Aminolysis is done by the following procedure. A solution of amine **5**(2mol equiv.) in CH_2Cl_2 was added to a yellow solution of 4(S)-AITT (**4**(1mol equiv.) in the same solvent with stiring in N_2. After being stirred at room temperature until original yellow color of the soution disappeared, the reaction was quenched with 10% HCl and then exracted with CH_2Cl_2. A usual work up of CH_2Cl_2 extract afforded an optically active amide **6** (S-excess). The aqueous layer on usual treatment gave the optically active amine **9** (R-excess).

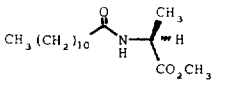
Each example is summarized in *Table* 1. Calculation of ee% and determination of (S)-configuration for each amide **6** were done on



Scheme 3

Table 1. Preparation of optically active amide **6** by aminolysis of 4(S)-AITT with racemic amines

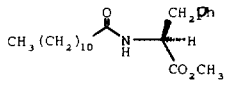
4(S)-AITT **4**	R^2 amine **5**	R^3	reaction time	amide **6** cy (%)	amide **6** ee (%)
4a	CH_3	CO_2CH_3	3h	96	(S)54
4a	CH_2ph	CO_2CH_3	20h	82	(S)17
4a	$CH(CH_3)_2$	CO_2CH_3	8h	92	(S)38
4a	$CH_2CH(CH_3)_2$	CO_2CH_3	12h	83	(S)32
4c	CH_3	CO_2CH_3	72h	26	(S)13



7

$[\alpha]_D$ = +13.4

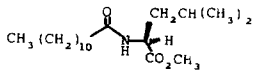
(c=1.20,$CHCl_3$)



8

$[\alpha]_D$ = +42.5

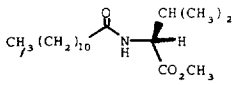
(c=1.20,$CHCl_3$)



10

$[\alpha]_D$ = +32.5

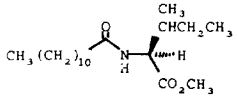
(c=1.46,$CHCl_3$)



9

$[\alpha]_D$ = +65.2

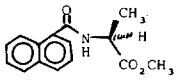
(c=2.50,$CHCl_3$)



11

$[\alpha]_D$ = +18.6

(c=1.21,$CHCl_3$)



12

$[\alpha]_D$ = +34.5

(c=1.34,$CHCl_3$)

the basis of the specific rotations of the authentic amides (**7**~**12**), which were derived from optically inactive ATTs and the corresponding optiaclly pure amines.

Thus a significant chiral recognition was realized in aminolysis of 4(S)-AITT with racemic amine; optically active amide was obtained in considerable enantiomeric excess. It is remarkably interesting that only the (S)-configuration excess amide **6** were afforded in all the cases where we tried. Thus, it is suggested that this new method can be useful for determination of the absolute configuration of amino compounds.[11]

EXPERMENTAL

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 spectra were recorded on a Bruker AW-80MHz spectrometer in $CDCl_3$ solutions with Me_4Si as internal standard. Extracts were dried over Na_2SO_4. Silca gel 60 (70-230mesh) was used for column chromatography. TLC was performed silica gel 0.250mm, 60F254 (Merk).

Preparation of 4(S)-isopropyl-1, 3-thiazolidene-2-thione **2**. To a solution of valinol **1** (3.5g, 33.98mmol) in EtOH (20m*l*) was added a carbon disulfide (5.2g, 68.4mmol) at 0°C. After the addition of KOH(4.0g, 71.3mmol) in water (1.5m*l*), the mixture was refluxed overnight. Evaporation of solvent under reduced pressure gave an oily residue. Methylene chloride (50m*l*) was added and the organic solution was washed with aqueous 20% HCl, dried over Na_2SO_4, filtered, and concentrated to provide crude **2** as an orange-yellow oil. Column chromatography on silicagel eluting with ethylacetate-hexane (1 : 2) provided 3.17g (58%) of

pure **2** and 1.3g (23%) of pure **3**. 4(S)-isopropyl-1, 3-thiazolidine-2-thiazolidine-2-thion **2**. Yellow needles, mp 64-66°C; $[\alpha]_D$−47°(c=2.0, $CHCl_3$); ν_{max}. 3250, 1490, and 1290cm^{-1}; δ 0.91(6H, d, J=6.4Hz), 1.9(1H, m), 3.4(2H, m), 4.1(1H, m), 8.6(1H, bs); M^+161.

4(S)-isopropyl-1, 3-oxazolidinė-2-thione **3**. Yellow plate, mp 42-44°C; $[\alpha]_D$−16°(c=2.4, $CHCl_3$); ν_{max}. 3200, 1510, and 1270cm^{-1}; δ 0.87 (3H, d, J=4.4Hz), 0.95(3H, d, J=4.8Hz), 1.82 (1H, m), 3.8(1H, m), 4.5(2H, m), 8.9(1H, bs); M^+ 145.

Typical preparation of 4(S)-IPTT amides **3**. To suspension of 60% NaH(0.279g, 6.83mmol) in 3m*l* of THF under nitrogen was added 4(S)-IPTT (1.0g, 6.21mmol) in THF(3m*l*) followed by addition of lauroyl chloride (1.43g, 6.52mmol). The reaction mixture was stirred at room temperature for 30min. 30% aqueous $NaHSO_4$ was added at 0°C, and reaction mixture was extracted with methylene chloride, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The oily residue was chromatographed on silica gel using methylene chloride-hexane(1 : 1) to provide 1.96g (92%) of **4b** as a light yellow oil, which solified upon standing. Recrystallization from $CHCl_3$−Et_2O gave yellow needles.

Physical data of 4(S)-IPTTamides. N-Decanoyl-4(S)-isopropyl-1, 3-thiazolidine-2-thione **4a**. Yellow needles, mp 31∼33°C; $[\alpha]_D$+302.5°(c=1.34, $CHCl_3$); ν_{max}. 2950, 1710, and 1440cm^{-1}; δ0.82 (3H, d, J=3.6Hz), 0.91(3H, d, J=3Hz), 0.94(3H, m), 1.0−1.9(14H, m); 2.51(1H, m), 5.3(1H, m); M^+315

N-Lauroyl-4(S)-isopropyl-1, 3-thiazolidine-2-thione **4b**. Yellow needles, mp 43∼45°C; $[\alpha]_D$+294. 1°(c=1.20, $CHCl_3$); ν_{max}. 2960, 1710, and 1480cm^{-1}; δ0.81(3H, d, J=3.4Hz), 0.90(3H, d, J=3Hz), 0.95(3H, m), 1.0∼1.8 (18H, m), 2.1(1H, m), 3.4(4H, m), 5.3(1H, m); M^+343

3-(1-Naphthoyl)-4(S)-isopropyl-1, 3-thiazolidine-2-thione **4c**. Yellow needles, mp 179∼181°C; $[\alpha]_D$+223°(c=1.20, $CHCl_3$); ν_{max}. 3070, 1690, and 1600cm^{-1}; δ1.2(6H, m), 2.6 (1H, m), 3.5(2H, m), 5.1(1H, m), 7.4∼8.1 (7H, m); M^+315.

A typical of the aminolysis of 4(S)-AITT 4 with amines[12]. A solution of (±)valine methyl ester (334mg, 2mmol) in methylene chloride (2m*l*) was added to a yellow solution of **4a** (343mg, 1mmol) in the same solvent (5m*l*) with stirring in nitrogen. Afetr being stirred at room temperature until original yellow color of the medium vanished, The reaction was quenched with 10% HCl and then extracted with methylene chloride. The reaction mixture was concentrated under reduced pressure to give an oily residues, which was dissolved in a minimum amount of $CHCl_3$. The solution was passed through a short silica gel column impregenated with 10% $AgNO_3$, and elution with $CHCl_3$ afforded N-lauroyl-valine methylester (294mg, 92% yield).

Physical data for each amide. N-lauroyl-alanine methyl ester **7**. Colorless needles, mp46∼48°C; $[\alpha]_D$+13.8° (c=1.20, $CHCl_3$); ν_{max}. 3350, 1750, and 1670 cm^{-1}; δ0.82 (3H, *d*, J=2.8Hz), 0.97 (3H, m), 1.05∼2.15 (16H, m), 3.6(1H, m), 3.65(3H, *s*), 4.5(2H, m), 6.05(1H, *bs*); M^+285

N-Lauroyl-Phenylalanine methyester **8**. Colorless needles, mp 59∼61°C; $[\alpha]_D$+42.5°(c=1.20, $CHCl_3$); ν_{max}. 3340, 3070, 1750, and 1660cm^{-1}; δ0.8∼2.2 (23H, m), 3.86(3H, *s*), 3.9(1H, m), 4.8(2H, m), 5.96(1H, *bs*), 6.95∼7.17 (5H, m); M^+361

N-Lauroyl Valine methylester **9**. Colorless needles, mp50∼52°C; $[\alpha]_D$+65.2° (c=2.50, $CHCl_3$); ν_{max}. 3350, 1750, and 1670cm^{-1}; δ0.83 (6H, m), 1.0∼1.8 (22H, m), 3.65 (3H, *s*), 3.8

(1H, m), 4.8(2H, m), 6.2 (1H, *bs*); M^+313

N-Lauryl leucine methyleseter **10**. Colorless needles, mp 54~56°C; $[\alpha]_D$+32.5° (C=1.46, $CHCl_3$); ν_{max}. 3300, 1760, and 1640 cm^{-1}; δ0.8 ~1.1 (12H, m), 3.86(3H, *s*), 3.9(1H, m), 4.72 (2H, *m*), 6.17(1H, *bs*); M^+327

N-Naphtonyl alanine methyl ester **12**. Colorless needles, m.p 164°C; $[\alpha]_D$+34.5° (c= 1.34, $CHCl_3$); ν_{max}. 3350, 3070, and cm^{-1}; δ0.91 (3H, *m*), 3.92 (3H, *m*), 5.93 (1H, *bs*), 7.4~8.2 (7H, *m*); M^+257

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