

Simplified Chiral Aminolysis
of Prochiral σ -Symmetric Dicarboxylic Anhydrides
with Sodium Salt of 4(S)-IPTT¹⁾

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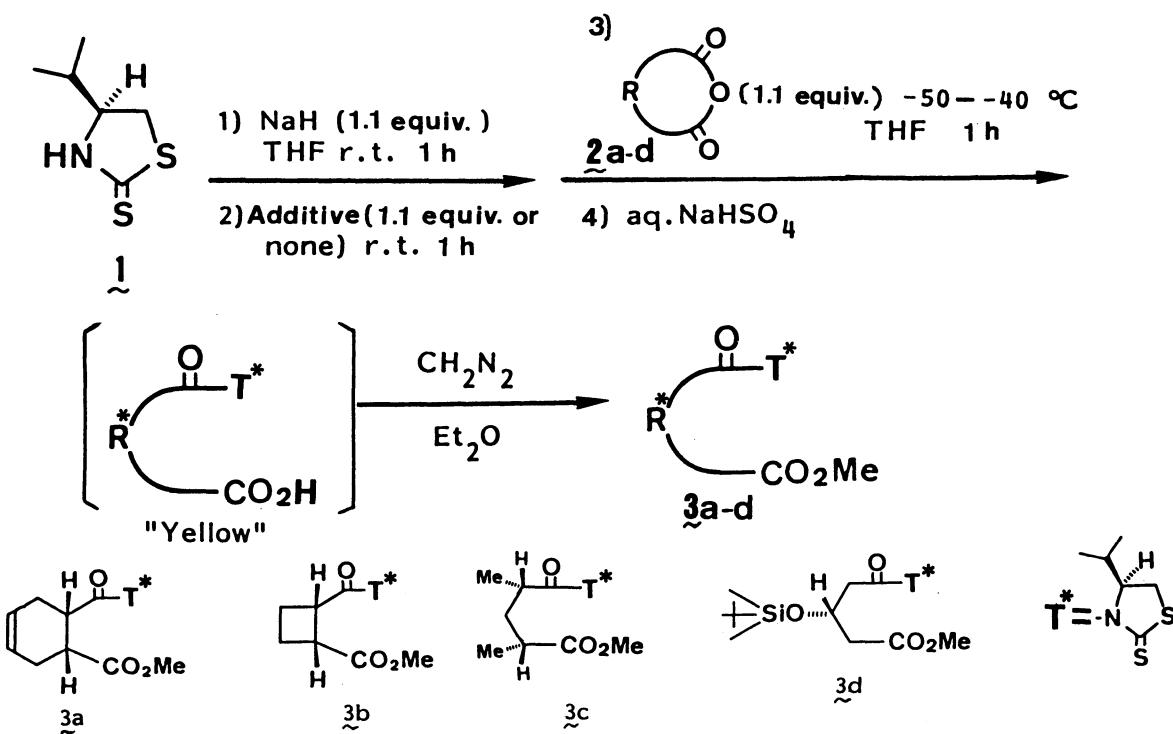
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Highly enantioselective chiral aminolysis of cis-4-cyclohexen-1,2-ylenebis(carboxylic acid) anhydride has been performed by employing sodium salt of 4(R)-isopropyl-1,3-thiazolidine-2-thione in THF-DMSO. Other chiral aminolyses of prochiral σ -symmetric dicarboxylic anhydrides such as cis-cyclobutan-1,2-ylenebis(carboxylic acid) anhydride, meso-2,4-dimethylglutaric anhydride, and 3-[(t-butyldimethylsilyl)oxy]glutaric anhydride were similarly investigated.

Chiral Differentiation between two identical carboxyl groups in prochiral σ -symmetric dicarboxylic acids utilizing enzymatic or nonenzymatic procedure should be a rational strategy for chiral syntheses of biologically active compounds because the resultant chiral product(s) can be available for its (or thier) further "enantioconvergent" transformations on the basis of the latent σ -symmetry.²⁾ Previously, we disclosed a novel nonenzymatic chiral induction into prochiral σ -symmetric dicarboxylic acids employing a functional heterocycle, 4(R or S)-methoxycarbonyl-1,3-thiazolidine-2-thione.²⁻⁵⁾ In the course of our series of studies on the chiral induction utilizing C4-chiral thiazolidines,³⁻⁷⁾ we anticipated that 4(S)-isopropyl-1,3-thiazolidine-2-thione [4(S)-IPTT] (1)⁷⁾ would be available for chiral aminolysis of prochiral dicarboxylic anhydrides 2 [e. g., cis-4-cyclohexen-1,2-ylenebis(carboxylic acid) anhydride (2a)] (See Scheme 1).¹⁾ From the viewpoint that anhydride 2a is regarded as a useful prochiral precursor for the chiral synthesis of carbapenems and (+)-carbacyclin,^{8,9)} we firstly attempted its chiral aminolysis with 4(S)-IPTT (1) as follows.

A solution of 60% NaH (coated type with mineral oil, 220 mg, 5.5 mmol) in THF (6 ml) was added to a solution of 4(S)-IPTT (1) (805 mg, 5 mmol) in THF (5 ml) at 0 °C with stirring. The mixture was stirred at 0 °C for 10 min and then anhydrous DMSO (0.43 ml, 6 mmol) was added at room temperature. After being stirred at room temperature for 1 h, the reaction mixture was added to a solution of 2a (836.8 mg, 5.5 mmol) in THF (6 ml) at -50 °C. The mixture was stirred at

-50 - -40 °C for 1 h, acidified with saturated aqueous NaHSO_4 (20 ml), and extracted with CH_2Cl_2 . The usual work-up of the CH_2Cl_2 extract gave a crude carboxylic acid, which was treated with CH_2N_2 in ether affording methyl ester $\tilde{3}$ [1.30 g (80.2% yield); 94% diastereomer excess (de), $[\alpha]_D^{24} + 217.9^\circ$ (c 1.12, CHCl_3)] as a yellow oil after chromatographic purification (Run 5 in Table 1). This simple chiral induction¹⁰ into $\tilde{2}$ a can be promised for the big-scale synthesis of the useful chiral synthon for carbapenems and (+)-carbacyclin.^{8,9}



Scheme 1.

The absolute configuration of the product $\tilde{3a}$ was established by its chemical conversion to the antipodal compound $\tilde{4}$ [62% overall yield from $\tilde{3a}$; $[\alpha]_D^{25} + 78.5^\circ$ (c 0.7, acetone)] of the known lactone $[[\alpha]_D^{25} - 85.4^\circ$ (c 2.63, acetone)]⁹ via reduction of $\tilde{3a}$ with NaBH_4 in aqueous EtOH followed by lactonization with a catalytic amount of TSOH in toluene at 110 °C for 3 h.

Although similar aminolyses of $\tilde{2a}$ with sodium salt of $4(S)$ -IPTT were carried out in the absence or in the presence of some additives such as HMPA, 18-Crown-6, and TMEDA, their results might be unsatisfactory with respect to the chemical and/or optical yield(s) of $\tilde{3a}$ (Runs 1-4 in Table 1).

Based on the result of $\tilde{2a}$, chiral aminolyses of anhydrides $\tilde{2b} - \tilde{2d}$ with or without 1.2 mol equiv. of DMSO as an effective additive were similarly examined by employing sodium salt of $4(S)$ -IPTT($\tilde{1}$). All results were listed in Table 1 (Runs 6 - 11). The product (Run 7) obtained from the chiral aminolysis of cis-4-cyclobutan-1,2-ylenebis(carboxylic acid) anhydride ($\tilde{2b}$) proved to be the $\tilde{3b}$ -excess compound by its chemical conversion to the antipodal compound $\tilde{5}$ [42% overall yield from $\tilde{3b}$; $[\alpha]_D^{24} - 77.9^\circ$ (c 1.2, CHCl_3)] of the known lactone¹⁰ $[[\alpha]_D^{24} + 118.7^\circ$ (c 10, CHCl_3)] in the same manner as the case of $\tilde{3a}$. In anhydride $\tilde{2c}$ (Run

9), the $\tilde{3c}$ - excess product was obtained, which was confirmed by its aminolysis with piperidine (1.0 mol equiv.) in CH_2Cl_2 at 0°C giving the known amide $\tilde{6}$ [91% yield; $[\alpha]_D^{20} + 0.92^\circ$ (c 3.5, CHCl_3); lit.⁵⁾ $[\alpha]_D^{25} + 2.45^\circ$ (c 3.26, CHCl_3)]. The stereochemistry of the major aminolysis product (Run 10) of $\tilde{2d}^{10})$ was clarified to be $\tilde{3d}$ [38.8% yield; mp $64 - 65^\circ\text{C}$ (ether - hexane); $[\alpha]_D^{20} + 219^\circ$ (c 0.8, CHCl_3)] by its X-ray analysis (Fig. 1) after separation of the major diastereomer on a silica gel column [hexane-AcOEt (4 : 1)].

Table 1. Chiral aminolysis of prochiral dicarboxylic anhydrides $\tilde{2a} - \tilde{d}$ with sodium salt of $4(\text{S})\text{-IPPT}$ (1)

Run	Anhydride	Additive	Yield/% of $\tilde{3a} - \tilde{d}$	Diastereomer excess/% ^{a)}
1		None	96 ($\tilde{3a}$ excess)	86
2	"	HMPA	48 ($\tilde{3a}$ excess)	96
3	"	18-Crown-6	6 ($\tilde{3a}$ excess)	76
4	"	TMEDA	68 ($\tilde{3a}$ excess)	82
5	"	DMSO	80 ($\tilde{3a}$ excess)	94
6		None	81 ($\tilde{3b}$ excess)	62
7	"	DMSO	85 ($\tilde{3b}$ excess)	68
8		None	87 ($\tilde{3c}$ excess)	28 ^{b)}
9	"	DMSO	86 ($\tilde{3c}$ excess)	46 ^{b)}
10		None	62 ($\tilde{3d}$ excess)	40
11	"	DMSO	46 ($\tilde{3d}$ excess)	16

a) Checked by HPLC unless otherwise stated. b) Checked by $^1\text{H-NMR}$.

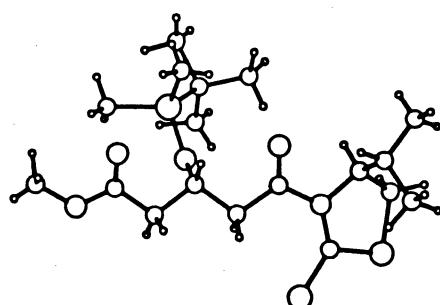
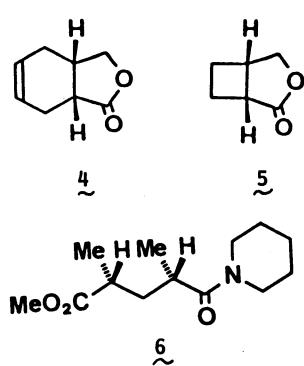


Fig. 1. Perspective view of the crystallographic structure of compound $\tilde{3d}$.

We assigned a structure $\tilde{7}$ to the sodium salt of 4(S)-IPTT based on its ^{13}C -NMR spectrum (δ 180 ppm : $\text{C}=\text{S}$)¹²⁾ in d8-THF and X-ray analysis of 3-(*p*-bromobenzyl)-4(S)-isopropyl-1,3-thiazolidine-2-thione($\tilde{8}$) [mp 108 °C (CHCl_3 -hexane)] (Fig. 2). Thus, stereochemical outcome of the chiral aminolysis of anhydrides $\tilde{2a}$ can be rationalized by assuming a transition state (Fig. 3) where the sodium salt $\tilde{7}$ attacks the S-site carbonyl carbon from the least hindered convex side. Another transition state where compound $\tilde{7}$ may approach the R-site carbonyl carbon on the convex face should be eliminated due to the severe steric hindrance between two axial-like protons of $\tilde{2a}$ and C4- and C5-protons of $\tilde{7}$. In other three cases of $\tilde{2b}$ - $\tilde{2d}$, the similar consideration would also be available for their stereochemical results.

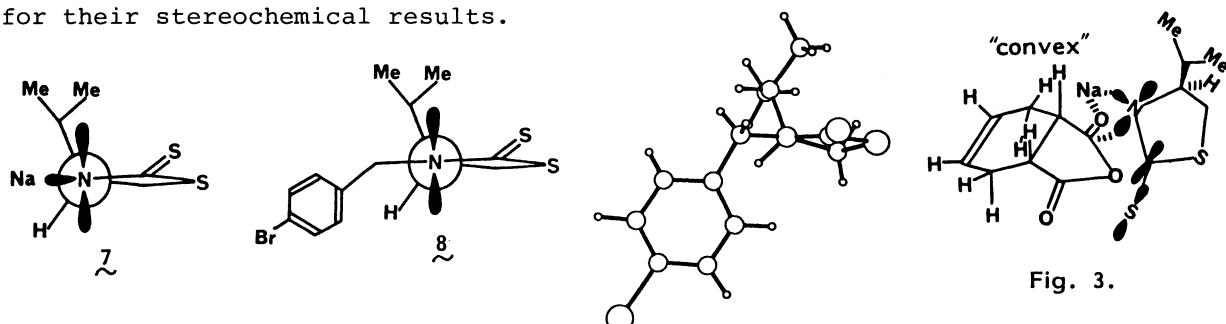


Fig. 2. X-Ray analysis of compound $\tilde{8}$.

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(Received December 2, 1987)