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Simplified Chiral Aminolysis of Prochiral σ-Symmetric Dicarboxylic Anhydrides with Sodium Salt of 4(S)-IPTT[1)]

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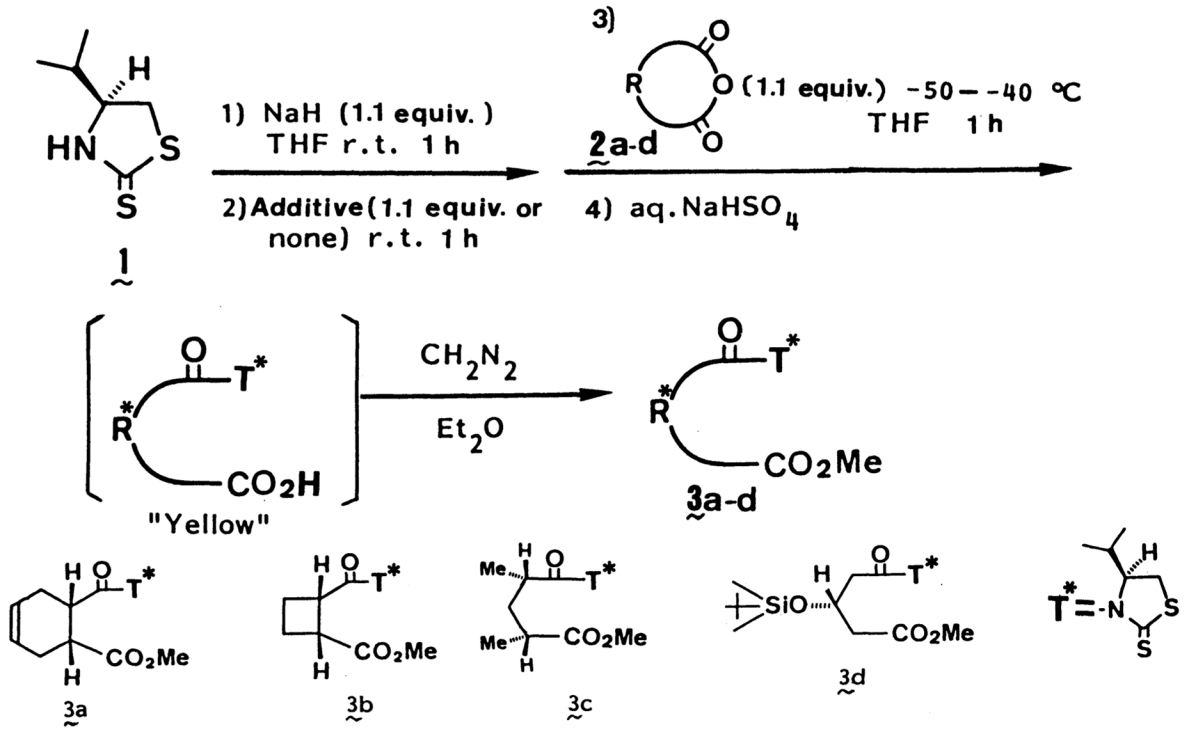
Highly enantioselective chiral aminolysis of cis-4-cyclohexen-1,2-ylenebis(carboxylic acid) anhydride has been performed by employing sodium salt of 4(R)-isopropyl-1,3-thiazolidine-2-thione in THF-DMSO. Other chiral aminolyses of prochiral σ-symmetric dicarboxylic anhydrides such as cis-cyclobutan-1,2-ylenebis(carboxylic 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 3a [1.30 g (80.2% yield); 94% diastereomer excess (de), $[\alpha]_D^{24}$ +217.9° (c 1.12, $CHCl_3$)] as a yellow oil after chromatographic purification (Run 5 in Table 1). This simple chiral induction[10] into 2a can be promised for the big-scale synthesis of the useful chiral synthon for carbapenems and (+)-carbacyclin.[8,9]



Scheme 1.

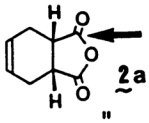
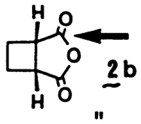
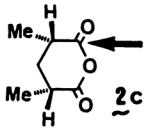
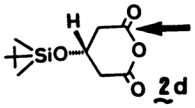
The absolute configuration of the product 3a was established by its chemical conversion to the antipodal compound 4 [62% overall yield from 3a; $[\alpha]_D^{25}$ +78.5° (c 0.7, acetone)] of the known lactone [$[\alpha]_D^{25}$ - 85.4° (c 2.63, acetone)][9] via reduction of 3a with $NaBH_4$ in aqueous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

Although similar aminolyses of 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 3a (Runs 1-4 in Table 1).

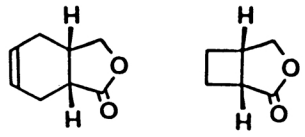
Based on the result of 2a, chiral aminolyses of anhydrides 2b - 2d with or without 1.2 mol equiv. of DMSO as an effective additive were similarly examined by employing sodium salt of 4(S)-IPTT(1). All results were listed in Table 1 (Runs 6 - 11). The product (Run 7) obtained from the chiral aminolysis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

9), the 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 6 [91% yield; $[\alpha]_D^{20}$ + 0.92° (c 3.5, $CHCl_3$); lit.[5] $[\alpha]_D^{25}$ + 2.45° (c 3.26, $CHCl_3$)]. The stereochemistry of the major aminolysis product (Run 10) of 2d[10] was clarified to be 3d [38.8% yield; mp 64 - 65 °C (ether - hexane); $[\alpha]_D^{20}$+219° (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 2a - d with sodium salt of 4(S)-IPTT (1)

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

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



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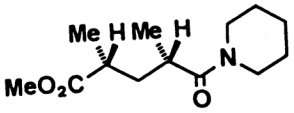

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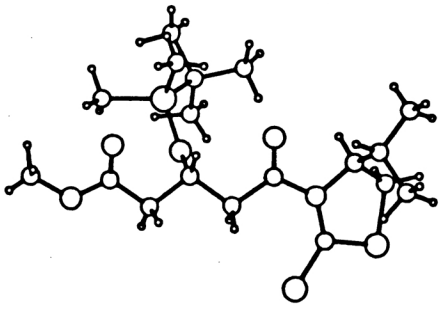
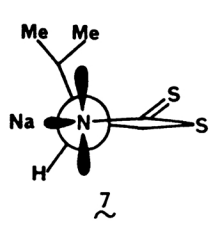


Fig. 1. Perspective view of the crystallographic structure of compound 3d.

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



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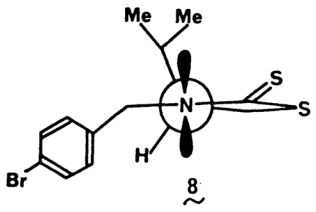

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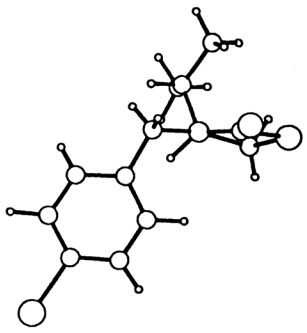

Fig. 2. X-Ray analysis of compound 8.

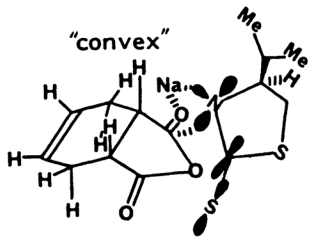

Fig. 3.

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