THE ACID-CATALYZED EPIMERIZATION AT THE SULFUR ATOM OF OPTICALLY ACTIVE 1,2,3-BENZOXATHIAZINE 2-OXIDE AND STEREOSPECIFICITY IN ITS NUCLEOPHILIC SUBSTITUTION

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Abstract —— The acid-catalyzed epimerization of 2a was accomplished under extremely mild conditions by using hydrogen chloride, BF_3etherate, trifluoroacetic acid, acetic acid, and $AlCl_3$ to give 2b. The action of nucleophiles to 2 proceeded highly stereospecifically with inversion of configuration.

In recent years much attention has been devoted to the synthetic and stereochemical studies of organo-sulfur compounds having chirality at a sulfur atom.[1]

Along with expenditious progress of the chiral sulfur chemistry, considerable efforts have been made for the investigation on their optical properties from the points of the theoretical interest and their utility in organic synthesis.

The racemization at a chiral sulfur atom may be induced by various kinds of means; e.g. for sulfoxides thermally,[2a] photochemically,[2b] and by treatment with hydrogen chloride,[2c] sulfuric acid,[2d] polyphosphoric acid,[2e] perchloric acid,[2f] acetic anhydride,[2g] and methyllithium;[2h] for sulfinates by acetic acid;[3] for thiolsulfinates thermally[4a] and by the nucleophile- and acid-catalysis.[4b]

However few report has appeared on the racemization of chiral amidosulfites except on the epimerization of an oxathiazolidine derivative.[5]

We wish to describe herein the first example of the epimerization at the chiral sulfur atom of an optically active 1,2,3-oxathiazine 2-oxide with various acidic catalysts and the stereospecificity in its nucleophilic substitution.

The compound, 4-methyl-3-α-naphthylethyl-1,2,3-benzoxathiazine 2-oxide (2a,b) was prepared by reaction of 1 with thionyl chloride in a 2 : 1 ratio of 2a and 2b.[6] Treatment of 2a with hydrogen chloride in toluene at 0° induced the epimerization of the amidosulfite function to give a mixture of 2a and 2b, the ratios

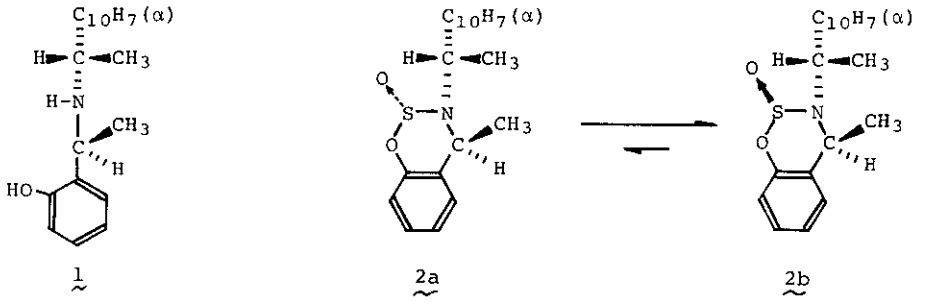
Table I Studies on Epimerization of 2a with Hydrogen Chloride[a]

Concentration of Hydrogen Chloride	Reaction Time (h)	Yield of 2a,b (%)	Ratio of 2a to 2b[b] 2a : 2b
0.016 N	2.0	84	33 : 67
0.032 N	0.5	88	87 : 13
0.032 N	1.0	86	39 : 61
0.032 N	2.0	81	4 : 96
0.032 N	3.0	73	3 : 97

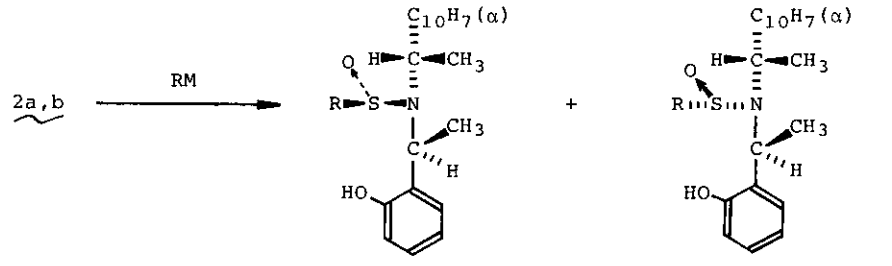
a. The reaction was carried out in toluene at 0°. b. Calculated by nmr analysis.

of which are calculated by nmr analysis and listed in Table I.

The results indicate that the isomer 2b might be thermodynamically more stable than the other one 2a as shown in the figure. This can be reasonably confirmed by their nmr analyses based on the anisotropy effect of the sulfinyl function[5] as follows; the methine proton ($CH_3\underline{C}H\text{-}C_6H_4$) syn to the sulfinyl group in 2a is deshielded to appear at the lower chemical shift (δ4.60) as a quartet than that of 2b (δ3.90), and the methyl protons ($\underline{C}H_3CH\text{-}C_6H_4$) anti to this group in 2a are shielded to shift in the higher field (δ1.55) as a doublet than those of 2b (δ1.67).



1 2a 2b



(S^R)-3-I a) R=C6H5 b) =CH3 c) =Bu^n

(S^S)-3-II a) R=C6H5 b) =CH3 c) =Bu^n

Table II Studies on Epimerization of 2a with Other Acidic Catalysts [a]

Catalyst	(equiv)	Reaction Time (h)	Yield of 2a,b (%)	Ratio of 2a to 2b [b] 2a : 2b
$BF_3 \cdot OEt_2$	0.04	3.0	71	46 : 54
$BF_3 \cdot OEt_2$	0.07	1.0	91	- : 100
CF_3CO_2H	0.07	3.0	70	33 : 67
CF_3CO_2H	0.12	1.5	66	- : 100
CH_3CO_2H	0.20	4.0	62	25 : 75
CH_3CO_2H	0.60	14.0	57	- : 100
$AlCl_3$	0.07	14.0	66	50 : 50
$AlCl_3$	0.20	1.0	55	- : 100

a. Toluene (2 ml) was used for 0.45 mM of 2a. Reacted at 0°. b. Calculated by nmr analysis.

Results of the epimerization of 2a with other catalysts are listed in Table II. Inspection of the Table indicates that the amidosulfite group in 2a could be easily epimerized with all of the acidic catalysts employed here under extremely mild conditions to give the other isomer 2b almost quantitatively.

It is well known that normally a nucleophilic substitution reaction on chiral acyclic organo-sulfur compounds proceeds indeed highly stereospecifically with inversion of configuration at the sulfur atoms.[7] However only a few examples have been reported in cyclic amidosulfite systems,[5] and no report has appeared on the stereospecificity in the nucleophilic substitutions of 1,2,3-oxathiazine 2-oxides.

The compound 2a was reacted with phenylmagnesium bromide at -78° for 2 h to give 3a-I (mp 154-155°) and 3a-II (mp 132-134°) (92 : 8) in 84% yield. Analogously the action of the reagent to the other isomer 2b was carried out under the same condition to produce reversely 3a-I and 3a-II (8 : 92) in 98% yield.

The sulfinamides (-)-3a-I and (+)-3a-II were reacted with n-butyllithium at -78° for 2 h to give (R)-(+)- and (S)-(-)-n-butyl phenyl sulfoxide (4)[8] with 98% and 99% optical purity, respectively. This means that these nucleophilic substitutions proceeded with exceedingly high stereospecificity and the absolute configurations of these compounds are assigned to be (S^R)-(-)-3a-I and (S^S)-(+)-3a-II, provided the nucleophilic substitution reaction occurred with inversion of configuration at the sulfur atom.

The stereochemical outcomes of the alternative nucleophilic substitutions of 2a,b using other nucleophiles are summarized in Table III.

From these results, it should be concluded that this kind of the nucleophilic substitution of the 1,2,3-benzoxathiazine 2-oxide system proceeds in an extremely high degree of stereospecificity with inversion of configuration.

These efficient stereochemical aspects suggest that this system should be

Table III Stereospecificity in the Nucleophilic Substitution of 2a,b [a]

Nucleophile RM	2	Reaction Time (h)	3	R	Product (3) Yield of 3 (%)	3-I	: 3-II (%)
C_6H_5MgBr	2a	2.5	a	C_6H_5	84	92	8
C_6H_5MgBr	2b	2.5	a	C_6H_5	98	8	92
CH_3MgBr	2a	3.0	b	CH_3	75 [b]	90	10
CH_3MgBr	2b	3.0	b	CH_3	90 [b]	10	90
CH_3Li	2a	2.0	b	CH_3	43	93	7
CH_3Li	2b	2.0	b	CH_3	35	7	93
Bu^nLi	2a	2.0	c	Bu^n	44	83	17
Bu^nLi	2b	2.0	c	Bu^n	37	17	83

a. Each reaction was carried out at -78° in THF. b. Corrected based on recovered 2a,b.

available for the asymmetric syntheses of various kinds of organo-sulfur compounds as a potential chiral director and the results will be reported in due course.

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8. The absolute configuration and the optical rotation of the optically pure sulfoxide (4) are determined to be (S)-(-)- 4 and $[\alpha]_D$ -158° (MeOH) by chemical correlation with methyl phenyl sulfoxide of known configuration.[2h]

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