## Enantioselectivity in the Ritter-type Substitution Reaction via Episulfonium Ion: Retention of Configuration

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Abstract: Ritter-type substitution reaction of optically active  $\beta$ -hydroxyalkyl phenyl sulfides was found to proceed with retention of configuration through the participation of phenylthio group to afford optically active amides.

Episulfonium ion is widely accepted as reaction intermediate in the electrophilic addition reaction of arylthio group to alkenes<sup>1</sup> and also in the substitution reaction on the carbon atom  $\beta$  to the arylthio group.<sup>2,3</sup> Diastercoselectivity in these reactions has been well established; *i.e.* trans addition to alkenes as well as threo — threo and erythro — erythro selectivities. However, enantioselectivity in these reactions has not yet been studied.<sup>3</sup> Possibility of racemization through the equilibrium shown in Scheme 1 has not yet been ruled out.<sup>4</sup> We prepared optically active alcohols bearing phenylthio group on  $\beta$ -carbon atom and studied the stereochemistry of the substitution of hydroxy group by nitrile to afford  $\beta$ -amidoalkyl phenyl sulfides. As a result, we found that optical purities of the amides are similar to those of starting alcohols, indicating that "asymmetric episulfonium ion"(episulfonium ion with asymmetric carbon atom in the ring) racemizes so slowly as to be useful in the preparation of optically active compounds. We also describe herein that partial racemization tobserved in certain substrates can be suppressed by the control of the reaction temperature.



Optically active oxiranes were converted to  $\beta$ -hydroxyalkyl phenyl sulfides in excellent yields by the reaction with sodium benzenethiolate. In the cases of alkyl-substituted oxiranes (1a and 1b), the phenylthio group was introduced to a less substituted carbon atom to afford 2a or 2b selectively. While, aryl-substituted oxiranes (1c and 1d) afforded mixtures of almost equal amounts of regioisomers (2c+3c and 2d+3d) which were separated by column chromatography (Scheme 2). Optical purity of each alcohol was determined from integrals of NMR spectrum of its MTPA<sup>5</sup> ester and confirmed to be same to that of starting oxirane.

By the reaction of 2a with 2 equivalents of trifluoromethanesulfonic acid and water<sup>6</sup> in acetonitrile as solvent (r.t., 3 h), substitution of the hydroxy group by a nitrogen atom of the nitrile proceeded to afford  $\beta$ -acetamidododecyl phenyl sulfides(5a+6a, 90%, 9:1)<sup>1a,1e,7</sup>(Scheme 2). Optical purities of 5a and 6a were determined to be 85% and 86%, respectively, either by integrals of NMR spectrum of the MTPA amide<sup>8</sup> or by

liquid chromatography using chiral column.<sup>9</sup> As the optical purity of the starting alcohol 2a is 86%, it may be concluded that episulfonium ion 4a does not racemize (on C<sub>2</sub>) to afford the Markovnikov-type 5a with overall retention (double inversion) and anti Markovnikov-type 6a with inversion(2a - 4a) (vide infra) (entry 1 in Table).



In the case of tertiary alcohol **2b**, substitution reaction proceeded regioselectively to afford **5b** (-40° C, 19 h, 92%) accompanied by a slight amount of elimination products.<sup>10</sup> As shown in Table(entry 2), optical purity of the amide **5b** was slightly lower than that of starting alcohol. This suggests that episulfonium ion **4b** racemizes (on  $C_2$ ) slowly during the substitution reaction. This may be ascribed to the stability of the tertiary carbenium ion or to the instability of **4b** by steric hindrance of two alkyl groups on  $C_2$ .

In the cases of phenyl-substituted alcohols, Markovnikov-type amide 5c was produced selectively starting from either alcohol 2c or 3c. These reactions were accompanied by partial racemization (26-27%) when carried out at ambient temperature. Fortunately, the racemization was less favored reaction path and could be suppressed by the control of the reaction temperature. The reactions at -40° C required much more amount of acid and longer reaction time, but the optical purities of the amide (5c) were similar to those of starting alcohols(2 c or 3 c)(entries 3-6 in Table). Configurations of 5c were confirmed to be same starting from either alcohol by the NMR spectra of the (S)-MTPA-amides. These facts indicate that both reactions proceed through the same intermediate 4 c. To confirm the absolute configuration, 5c (obtained from 2c) was desulfurized by the reaction with nickel boride<sup>11</sup> to give N-acetylmethylbenzylamine. Α comparison of the optical rotation of this compound with that of the authentic sample prepared from commercially available (S)-methylbenzylamine indicated that 5 c has R configuration.<sup>12</sup> As we used (R)-1c as starting material, we can conclude that 2c has R configuration and the substitution of 2c to give 5c proceeds with retention of configuration.

When pentafluorophenyl-substituted 2d or 3d was used as starting alcohol, 5d was obtained regioselectively and the configurations of 5d obtained from either alcohol were confirmed to be same. Again the reactions proceeded through the same intermediate 4d starting from either alcohol. In this case loss of optical purity was not observed even in the reaction at ambient temperature(entries 7 and 8 in Table).

entry	alcohol (% e.e.)		acid (eq.)	temp. (°C)	time (h)	amide	yield (%)	optical purity (% e.e.)
1	2a	(86)	2	r.t.	3	5a 6a	81 9	85 86
2	2b	(86)	5	-40	19	5b	92	82
3	2c	(100)	1	r.t.	2	5c	96	74
4	2c	(100)	5	-40	15	5c	74	100
5	3c	(100)	1	r.t.	2	5c	68	73
6	3c	(100)	10	-40	72	5c	71	99
7	2d	(97)	5	r.t.	6	5d	95	97
8	3d	(97)	5	r.t.	23	5d	92	97

Table. Optical Purities and Chemical Yields of Amides

It is reasonable that (open chain) carbenium ion could not intervene due to the destabilization by electron withdrawing fluorine substituent and episulfonium ion **4d** did not racemize even at ambient temperature.

As a conclusion, we disclosed for the first time that the racemization of asymmetric carbon in episulfonium ion is slow as compared to the intermolecular substitution reaction and "asymmetric episulfonium ion" is useful in the synthesis of asymmetric amides. Our methodology depends on the availability of optically active oxiranes or optically active  $\beta$ -hydroxyalkyl phenyl sulfides and recent development in these fields<sup>13</sup> encourage us this would be applicable to the synthesis of a wide range of asymmetric amides.

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- 8. The amide was hydrolyzed by heating with aq. HCl in methanol to afford the amine which was acylated by (R)-MTPA-Cl in the presence of N,N-dimethyl-4-aminopyridine (DMAP) in dichloromethane.
- 9. CHIRALCEL OD, Daicel, Hexane:2-propanol(10:1) as eluant.
- 10. When the reaction was carried out at ambient temperature, almost equal amounts of substitution (5b) and elimination products were obtained.
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