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NUCLEOPHILIC SUBSTITUTION ON SULFUR WITH RETENTION OF CONFIGURATION IN THE FORMATION OF o-METHOXYPHENYL PHENYL-N-POLYHALOACETYLSULFILIMINES

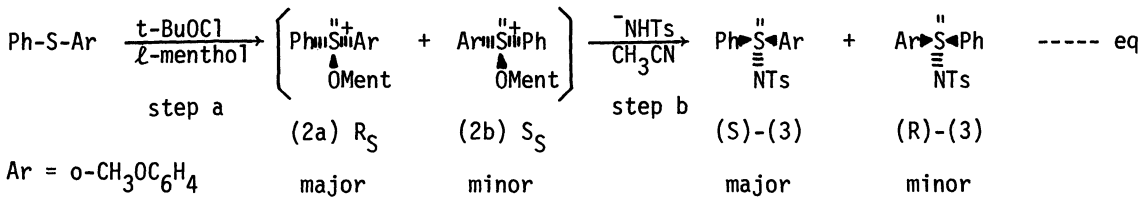
Shigeru OAE*, Katsuaki KIKUCHI, Masaru MORIYAMA, and Naomichi FURUKAWA

Department of Chemistry, The University of Tsukuba, Sakura-mura, Niihari-gun, Ibaraki 305

Optically active o-methoxyphenyl phenyl-N-polyhaloacetylsulfilimines obtained in good yields upon simple treatment of a mixture of o-methoxyphenyl phenyl sulfide and t-butyl hypochlorite in the presence of ℓ-menthol and polyhaloacetamide anion, are found to be rich in R-configuration. This means that the nucleophilic substitution of the incipiently formed (R_S)-ℓ-menthyloxysulfonium salt with the polyhaloacetamide anion proceeds with retention of configuration.

Recently we suggested that the reaction to form optically active o-methoxyphenyl (or o-methylphenyl) phenyl-N-p-tosylsulfilimine upon simple treatment of a mixture of the corresponding ℓ-menthyloxysulfonium salt with N-sodio p-toluenesulfonamide as shown in eq. proceeds through the following stereochemical course.[1] Namely, in the early stage of the reaction i.e., step a, to form a diastereomeric mixture of the two ℓ-menthyloxysulfonium salts (2a and 2b), the formation of one diastereomer, R_S conformer (2a) is more favored than that of the other salt, S_S conformer (2b) due to the steric reason, while in the subsequent step b, ℓ-menthyloxy group in the diastereomer (2a and 2b) is replaced by p-toluenesulfonamide anion with inversion of configuration at sulfur atom to afford optically active N-p-tosylsulfilimine (3) which is in excess of S-configuration. This method has now become a simple and hence the most general preparative method to synthesize optically active o-substituted phenyl aryl sulfilimines.

However, when we used such polyhaloacetamides as dichloro-, trichloro-, and trifluoroacetamide



anions instead of p-toluenesulfonamide or benzamide anion in the reaction with ℓ-menthyloxysulfonium salt (2a and 2b), we obtained unexpectedly the corresponding sulfilimines each having excess of R-configuration in good yields. The result clearly indicates that the replacement of the ℓ-menthyloxy group of the sulfonium salt (2a or 2b) by the polyhaloacetamide anion proceeds with retention of configuration around the sulfur atom. This communication deals with the unusual stereochemistry of the reaction together with the mechanistic implication.

A typical run is as follows: A mixture of 3 mmol of o-methoxyphenyl phenyl sulfide, 3.5 mmol of ℓ-menthol, and 3.5 mmol of dry pyridine was dissolved in 10 ml dry acetonitrile. Into the well-stirred solution kept at -40°C, at first 3.5 mmol of t-BuOCl in 2 ml dry acetonitrile and then sodium trichloroacetamide (prepared by treating trichloroacetamide with sodium hydride in dry acetonitrile) was added. After the whole mixture was stirred at the temperature for 2 hours, it was warmed up to room temperature. Then into the reaction mixture was added aq. dil. $Na_2S_2O_3$ and the aqueous solution was extracted with chloroform. The extract was evaporated under reduced pressure. The residue was chromatographed on silica gel by elution with benzene-AcOEt (2:1). Yield of N-trichloroacetylsulfilimine was 72%. $[\alpha]_D^{20}$=+26.4° (c=0.85, chloroform), 47.2% enantiomeric excess. Similarly, monochloro-, dichloro-, and trifluoroacetamides were treated as described above and the results thus obtained are summarized in Table. The configuration of these sulfilimines were determined by comparing their signs of optical rotations with those of authentic samples prepared by treating the optically active N-unsubstituted sulfilimine, of which the absolute configuration is known, with the respective acid anhydrides or chlorides. CD spectra of these sulfilimines also support their configurations. These results reveal that the amide derivative of higher acidic acid tends to afford the corresponding sulfilimine enriched with more R-configuration (i.e. higher retention). The formation of optically active ℓ-menthyloxysulfonium salt as an intermediate was confirmed by actual isolation of optically active o-methoxyphenyl phenyl ℓ-menthyloxysulfonium perchlorate by addition of silver perchlorate to the mixture of o-methoxy-

Table. Preparations of N-polyhaloacetylsulfilimines

$$\text{Ph-S-Ar} \xrightarrow[\text{ℓ-menthol, pyridine, in } CH_3CN]{\text{1)t-BuOCl, 2)NaNHR}} \text{Ph-}\overset{*}{\underset{\downarrow}{\text{S}}}\text{-Ar (NR)} \qquad \text{Ar} = o\text{-}CH_3OC_6H_4$$

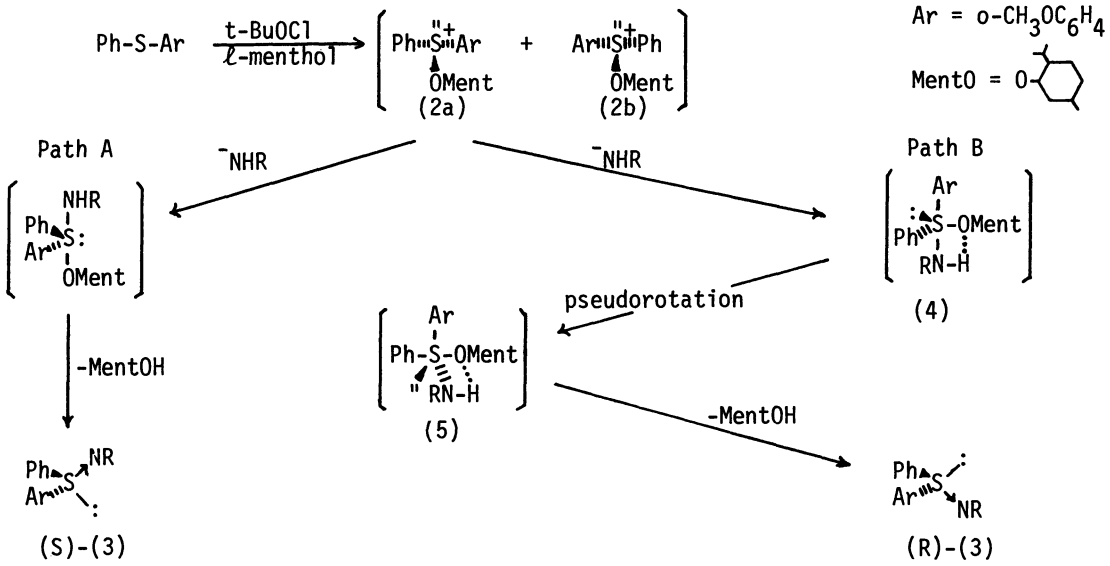
R	Yield(%)	$[\alpha]_D^{20}$ [a]	e.e.(%) [b]	configuration
$COCH_2Cl$	47	-45.5°	35.5	S
$COCHCl_2$	34	+11.7°	12.5	R
$COCCl_3$	72	+26.4°	47.2	R
$COCF_3$	53	+35.4°	47.2	R

a) Chloroform as solvent.

b) Determined by NMR using Eu(hfc) as shift reagent.

phenyl phenyl sulfide, ℓ-menthol, and t-BuOCl. When this optically active ℓ-menthyloxysulfonium perchlorate was treated with polyhaloacetamide anions, the corresponding sulfilimines are resulted in good to moderate yields, respectively. For example, treatment of optically active o-methoxyphenyl phenyl ℓ-menthyloxysulfonium perchlorate, R_S : S_S = 83 : 17, with trichloroacetamide anion in CH_3CN gave the corresponding optically active sulfilimine, 39% yield, $[\alpha]_D^{20}$=+15° (c=1.1, chloroform), 26% enantiomeric excess. The partial racemization in this treatment is due mainly to the alkoxy exchange reaction which takes place between the optically active ℓ-menthyloxysulfonium salt with ℓ-menthylate formed upon treatment with sodio polyhaloacetamide. Furthermore the CD spectra of the initial sulfonium salt and N-dichloro-, N-trichloro-, and N-trifluoroacetylsulfilimines thus obtained show the same configuration around the sulfur atom. These stereochemical results show that nucleophilic substitution of o-methoxyphenyl phenyl ℓ-menthyloxysulfonium salt with polyhaloacetamides proceeds with retention of configuration.

Retention of configuration has been reported in several nucleophilic substitutions on both phosphorus[2,3] and silicon atoms[2,4,5] but only a few cases on sulfur atom. The first reported example is the oxygen exchange reaction of optically active methyl p-tolyl sulfoxide with DMSO which proceeds with retention of configuration.[6] Subsequently Cram et al. and Christensen reported another examples of retention in the formation of an optically active methyl p-tolyl sulfilimine in the reaction of optically active methyl p-tolyl sulfoxide with TsNSNTs or TsNSO in nonpolar solvents.[7] Maricich et al. also described the formation of an optically active sulfilimine with retention of configuration on sulfur atom in the reaction of the corresponding optically active sulfoxides with sulfinyl azide.[8] Most of these reactions which take place with retention of configuration around a sulfur atom have been considered to proceed via 4-membered cyclic intermediates or through 4-membered cyclic transition states. One conceivable factor to



determine the steric course of the reaction, i.e. via retention or inversion around a sulfur atom is the stereoelectronic effect of acyl group of the amide nucleophile. In the reaction of polyhaloacetamide which proceeds with retention of configuration, a strong hydrogen bonding interaction between acidic amide hydrogen and oxygen atom of ℓ-menthyloxy group would lead to facile formation of a 4-membered cyclic intermediate or a transition state as shown in (4) or (5). Then after either pseudo- or turnstile rotation, ℓ-menthyloxy group is expected to shift to the apical position as shown by (5) prior to be released. Therefore, the overall stereochemical course is retention of configuration. Whereas arenesulfonamide anion may be a bit too bulky to be placed at perpendicular to the leaving group, while the sulfonamide hydrogen may not be acidic enough to form a strong hydrogen bonding to ℓ-menthyloxy oxygen atom as compared to those of polyhaloacetamides. Thus, arenesulfonamide anion would approach from strain-free apical position to result in the formation of the N-p-tosylsulfilimine with inversion of configuration around the sulfur atom (Path A). A question may arise how strong a dipolar interaction is necessary to form a 4-membered cyclic intermediate for the substitution on the sulfur atom with retention of configuration. Further study on nucleophilic substitution with retention of configuration will tell us the answer.

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