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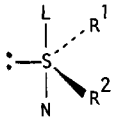
NUCLEOPHILIC SUBSTITUTION AT SULFINYL SULFUR. FACTORS AFFECTING THE INVERSION TO RETENTION RATIO IN ACID-CATALYZED ALCOHOLYSIS OF CHIRAL N,N-DIISOPROPYL p-TOLUENESULFINAMIDE

M.Mikołajczyk *, J.Drabowicz and B.Bujnicki

Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, Department of Organic Sulfur Compounds, 90-362 Łódź, Boczna 5, Poland

Summary: The reaction of chiral N,N-diisopropyl p-toluenesulfinamide with some alcohols catalyzed by trifluoroacetic acid has been found to occur with predominant retention of configuration. The stereochemistry of this reaction is strongly affected by silver perchlorate.

The vast majority of nucleophilic displacement reactions at chiral sulfinyl sulfur occur with inversion of configuration[1]. Such a stereochemical course may be explained in terms of the reaction proceeding synchronously by an S_N2-S mechanism involving a transition state, or stepwise by an addition-elimination (A-E) mechanism involving a trigonal-bipyramidal sulfurane intermediate, 1, that is formed by addition of the nucleophile (N) opposite to the leaving group (L) occupying the apical position and decomposed before any ligand reorganization have taken place[2]. The latter possibility is supported by the recent preparation of 10-S-4-sulfuranoxide, 2,[3] analogue of the postulated intermediate in the alkoxy-alkoxy exchange at sulfinyl center which has been shown by us[4] to occur with complete inversion of configuration.



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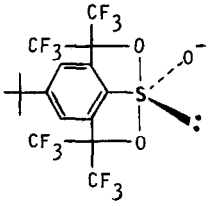

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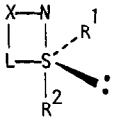

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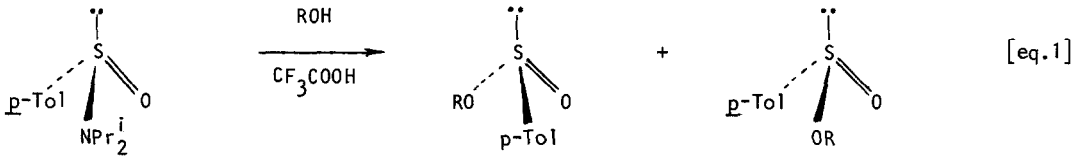
The addition-elimination mechanism also provides a satisfactory explanation for the less encountered nucleophilic substitution reactions at sulfur that occur with retention of configuration[1]. Analysis of all the examples reported so far in the literature indicates that retention at sulfur was due to the formation of a four-membered ring sulfurane intermediate, 3, with an apical-equatorial arrangement of entering and leaving groups. A single ligand reorganization of 3 should lead to a new sulfurane intermediate with the leaving group in apical position that decomposes to the product with retained configuration at sulfur. It is believed that more than one ligand reorganization of a sulfurane intermediate cause racemization (or epimerization). Most probably such a situation is observed in the conversion of chiral sulfoxides into aminosulfonium salts[5,6].

We report herein a unique observation that the steric course of acid-catalyzed alcoholysis of chiral N,N-diisopropyl p-toluenesulfinamide, 4, varies from inversion to predominant retention of configuration depending on the structure of the alcohol used and the presence of silver cation. In a previous study[7], we found that acid-catalyzed alcoholysis of chiral N,N-diethyl p-toluenesulfinamide, 5, proceeded with complete or predominant inversion of configuration. The lower stereoselectivity of the reaction of (+)-(S)-5 observed with secondary and tertiary alcohols was caused by racemization of (+)-5 under the reaction conditions and was not due to a competition with the retention mechanism. In contrast to 5, chiral sulfinamide (+)-4[8] bearing bulky substituents at nitrogen was found to be optically stable[10]. Therefore, it was treated with various alcohols in the presence of trifluoroacetic acid[11] in the hope to obtain the corresponding sulfinates, 6, with complete inversion at sulfur irrespective of the alcohol structure.



(+)-(S)-4 → (-)-(S)-6 + (+)-(R)-6 [eq.1]

However, it was found that reaction of (+)-(S)-4 with primary alcohols was not fully stereoselective and occured with predominant inversion of configuration. With secondary alcohols such as isopropanol and its hexadeutero- and hexafluoro-analogues, cyclopentanol and cyclohexanol (+)-(S)-4 gave the corresponding sulfinates 6 unexpectedly with predominant retention of configuration. The use of pentanol-3, which is sterically more hindered than isopropanol[12], gave, however, the corresponding sulfinate, 6j, with a slight predominance of inversion. The inversion to retention ratio in the experiments discussed above together with some other experimental details are summarized in Table 1. These findings show clearly that steric factors in the attacking alcohol and departing dialkylamino group exert an important influence on the stereochemistry of acid-catalyzed alcoholysis of sulfinamides although the relationship is rather complex.

A considerable change in the inversion to retention ratio was observed when reaction of (+)-(S)-4 with alcohols catalyzed by trifluoroacetic acid was carried out in the presence of silver perchlorate[13]. Generally, the added silver salt favours the formation of the inversion product (see eq.2). Thus, methanolysis and n-propanolysis occured with complete inversion of configuration. Particularly interesting is that predominant inversion was observed with isopropanol and cyclohexanol which reacted with predominant retention in the absence of silver ion.

(+)-(S)-4 ($[\alpha]_D$ +103.4°, 50.4% e.e) $\xrightarrow[CF_3COOH+AgClO_4]{ROH}$ (-)-(S)-6 + (+)-(R)-6 [eq.2]

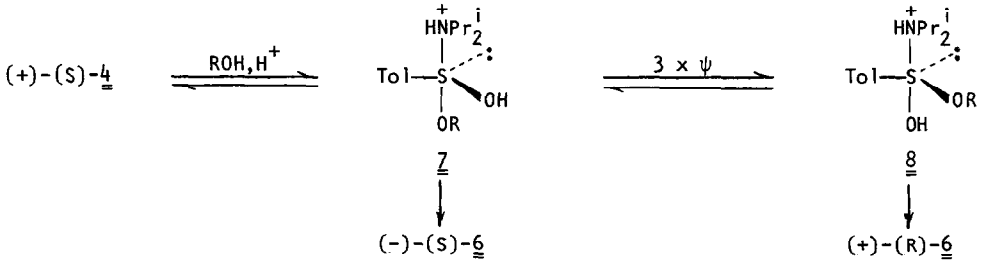
	Inv/Ret.Ratio
R=Me	100/0
R=Et	91/9
R=n-Pr	100/0
R=i-Pr	82/8
R=c-Hex	65.5/34.5

Table 1. Reaction of (+)-(S)-4 with Alcohols Catalyzed by Trifluoroacetic Acid.

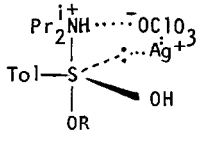
Tol-S(O)NPr^i_2,4 $[\alpha]_D$ (o.p.%)		Tol-S(O)OR,6 R	$[\alpha]_D$(o.p.%)	Stereoselectivity	% Inv. or Ret.
94.4°(45.3)	6a,	Me	-35.0°(17.0)	37.5%	68.75% Inv.
94.4°(45.3)	6b,	Et	-7.1°(3.4)	7.5%	53.75% Inv.
94.4°(45.3)	6c	Pr^n	-13.9°(7.25)	16.0%	58.00% Inv.
95.0°(45.35)	6d	Bu^i	-2.7°(1.4)	3.0%	51.50% Inv.
94.4°(45.3)	6e	Pr^i	+15.8°(7.9)	17.4%	58.70% Ret.
86.9°(42.3)	6f	Pr^i-D_6	+10.1°(4.6)	10.9%	55.45% Ret.
86.9°(42.3)	6g	Pr^i-F_6	+3.4°(1.7)	4.0%	52.00% Ret.
95.0°(45.35)	6h	Hex[c]	+41.0°(22.4)	49.0%	74.50% Ret.
95.0°(45.35)	6i	Pen[c]	+3.3°(1.8)	4.0%	52.00% Ret.
95.0°(45.35)	6j	Et_2CH	-4.4°(2.3)	5.0%	52.50% Inv.

It is worthy of note that in spite of a difference in stereochemistry of acidic alcoholysis of (+)-4 and (+)-5, both reactions are typical bimolecular nucleophilic substitutions at sulfur as evidenced by their activation parameters. The values of E_a and $\Delta S^{\neq}$ for the reaction of (+)-4 with isopropanol in the presence of trifluoroacetic acid[14] are 68.2 kJ/mol (16.3 kcal/mol) and -90.4 $KJ^{-1}mol^{-1}$ (-21.6 e.u.) - respectively. The corresponding values for (+)-5 are 58.6 kJ/mol (14.0 kcal/mol) and -119.3 $JK^{-1}mol^{-1}$ (-28.5 e.u.).

Such stereochemical and kinetic features of the reaction under discussion are best rationalized in terms of an addition-elimination mechanism involving a sulfurane intermediate that is able to undergo ligand reorganization[15]. Among the four possible apical attacks of an alcohol on the N-protonated sulfinamide (+)-(S)-4 that leading to sulfurane, 7,[16] seems to be the most probable. Its decomposition affords (-)-(S)-6 with inversion of configuration. After three consecutive ligand reorganizations in 7 by Berry pseudorotation (BPR) a new sulfurane intermediate, 8, may be formed which undergoes decomposition to (+)-(R)-6 e.g. the product with retention of configuration.



As a driving force for ligand reorganization in 7 an unfavourable equatorial position of the hydroxy group and the presence of two bulky substituents (for example, isopropylamino and cyclohexyloxy groups) in apical positions may be taken into account.



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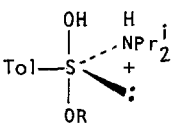

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The effect of the added silver salt on the steric course of the reaction may be explained if one assumes that sulfurane 7 forms a complex 9 in which silver cation is coordinated to sulfur. This should facilitate the direct S-N bond breaking as well as increase the energy of pseudorotation in 9 in comparison with 7. An alternative explanation for the mixed stereochemistry of acidic alcoholysis of (+)-(S)-4 consists in the parallel formation of two sulfurane intermediates 7 and 10 which are responsible for inversion and retention at sulfur. The relative stabilities and concentrations of these intermediates will determine the overall stereochemistry of the reaction.

Finally, it should be noted that we found the first example of retention at sulfur which is not due to the formation of a four-membered ring sulfurane intermediate.

References and Notes

(1) Mikołajczyk,M.; Drabowicz,J. Topics in Stereochemistry, 1982, 13, 333.

(2) For a detailed discussion on S_N2 and A-E mechanism in nucleophilic substitution at sulfur in favour of the latter see: Kice,J. Adv.Phys.Org.Chem. 1980, 17, 65.

(3) Perkins,C.W.; Martin,J.C. J.Am.Chem.Soc., 1983, 105, 1377.

(4) Mikołajczyk,M.; Drabowicz,J.; Slebocka-Tilk,H. J.Am.Chem.Soc. 1979, 101, 1302.

(5) Drabowicz,J.; Bujnicki,B.; Mikołajczyk,M. J.Org.Chem. 1981, 46, 2788.

(6) Schwöbel,A.; Kresze,G.; Perez,M.A. Tetrahedron Lett. 1982, 23, 1243.

(7) Mikołajczyk,M.; Drabowicz,J.; Bujnicki,B. J.Chem.Soc.Chem.Commun. 1976, 568.

(8) Sulfinamide (+)-(S)-4 was prepared according to Montanari et al.[9] from (-)-(S)-menthyl p-toluenesulfinate and N,N-diisopropylaminomagnesium bromide. However, in our hands this reaction afforded (+)-(S)-4 with ca.50% optical purity only.

(9) Colonna,S.; Giovini,R.; Montanari,F. J.Chem.Soc.Chem.Comm. 1968, 865.

(10) When methanolysis of (+)-(S)-4, $[\alpha]_D$+93.8° (45% op) was quenched at the half-conversion, we recovered starting sulfinamide with almost the same optical rotation, $[\alpha]_D$+91.3° (44%op). In the case of isopropanolysis of (+)-(S)-4, $[\alpha]_D$+93.8° (45% op), the recovered sulfinamide exhibited $[\alpha]_D$+81° (39% op)

(11) In a typical experiment 0.001 mol of (+)-(S)-4 was dissolved in the appropriate alcohol (5 mL) and 0.002 mol of trifluoroacetic acid was added at room temperature. The progress of reaction was followed polarimetrically. After completion of reaction, to the mixture water (25 mL) was added and sulfinate 6, formed was extracted with n-hexane (2 x 20 mL) and chloroform (1 x 10 mL) and purified by column chromatography.

(12) t-Butanol did not react with (+)-4 under these reaction conditions.

(13) Two moles of $AgClO_4$ in respect to (+)-4 were used;TFA is necessary.

(14) The reaction kinetics was measured polarimetrically using isopropanol in a 200 molar excess.

(15) For structure and ligand reorganization in sulfuranes see: Holmes, R. Accounts Chem.Res. 1979, 12, 257.

(16) It was assumed that the bond breaking and forming processes occur only in the apical position of the trigonal-bipyramidal sulfurane intermediate and that under acidic reaction conditions the negatively charged sulfinyl oxygen atom is protonated.

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