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THE FIRST STEREOSELECTIVE SYNTHESIS OF OPTICALLY ACTIVE THIOSULFINATES

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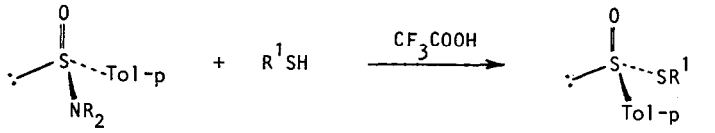
Summary: Treatment of optically active p-toluenesulfinamides (1) with thiols(2) in the presence of trifluoroacetic acid was found to give optically active p-toluenethiosulfinates (3) with predominant inversion of configuration. Stereospecificity of this reaction varies from 30 to 80%. Some mechanistic aspects of the reaction are also discussed.

Chiral thiosulfinates containing a labile S(O)S-grouping are very promising starting materials for synthesis of other chiral sulfinyl compounds as well as interesting model compounds in the study of the mechanism and stereochemistry of nucleophilic substitution reaction at sulfur[1]. Till now, however, utilization of chiral thiosulfinates in stereochemical studies is strongly limited at least for two reasons. The first is that all the reported syntheses of chiral thiosulfinates (including asymmetric oxidation of disulfides[2], asymmetric condensation of racemic sulfinyl chlorides in the presence of chiral tertiary amines[3], asymmetric decomposition of di-t-butyl sulfoxide in the presence of chiral tertiary amines[4] and partial optical resolution via β-cyclodextrin inclusion complexes[5]) afford these esters usually of low optical purity (up to 25%). The second limiting factor is a moderate or low optical stability of simple dialkyl or diaryl thiosulfinates[6] with the exception of those containing t-butyl group at one or both sulfur atoms[3,5].

Greatly encouraged by our results on the synthesis of chiral sulfinates[7], we focused our attention on the acid-catalyzed reaction of sulfinamides with thiols. To our surprise, this simple reaction has not been reported in the literature. Moreover, its stereochemical course was interesting for us in view of the fact that the acid-catalyzed alcoholysis of chiral sulfinamides was found to proceed either with predominant inversion or retention of configuration at sulfur depending in the first place on the structure of both reaction components[7c].

Herein we wish to report the first stereoselective synthesis of chiral thiosulfinates (3) consisting in the reaction of chiral p-toluenesulfinamides (1) with thiols (2) used in excess in the presence of two molar equivalents of trifluoroacetic acid as a catalyst. The reaction was found to occur very fast at room temperature affording chiral thioesters 3 generally in high chemical yields and with optical purities much higher than those reported in the literature (see Table I) .



(+)-(S)-1 2 (-)-(S)-3

a, R = Et a, $R^1 = Pr^n$
b, R = Pr^i b, $R^1 = Pr^i$
c, $R_2 = (CH_2)_4$ c, $R^1 = Bu^t$

Table I. Synthesis of Optically Active Thiosulfinates 3, p-Tol S(O)OR^1 [a]

Sulfinamide 1				Thiosulfinate 3				Stereospecificity of 1→3 conversion
R_2	$[\alpha]_D$ [b]	(e.e.) [c]	Abs.conf.	R^1	yield(%) [d]	$[\alpha]_D$ [f]	(e.e.) [h] Abs.conf.	
1a, Et_2	+90°	(74)	S	3a, Pr^n	>90 [e]	-180.0° [g]	(60) S	>80
1a, Et_2	+100°	(82)	S	3b, Pr^i	65	-102.0°	(35) S	43
1a, Et_2	+110°	(89)	S	3c, Bu^t	86	- 74.0°	(26) S	30
1b, Pr^i_2	+ 87°	(42)	S	3a, Pr^n	>90 [e]	-110.0° [g]	(37) S	>80
1b, Pr^i_2	+ 71°	(34)	S	3b, Pr^i	20	- 46.6°	(16) S	47
1b, Pr^i_2	+ 87°	(42)	S	3c, Bu^t	67	- 41.5°	(15) S	36
1c, $(CH_2)_4$	+205°	(77)	S	3b, Pr^i	>90 [e]	-150.0° [g]	(51) S	66
1c, $(CH_2)_4$	+205°	(77)	S	3c, Bu^t	100	- 88.2°	(32) S	41

[a] Reactions were carried out using 0.3 mmol, 0.6 mmol and 20 mmol of sulfinamide 1, trifluoroacetic acid and thiol (2), respectively; [b] Optical rotations of 1 were measured in acetone; [c] The e.e. values of 1 were calculated based on the following data: $[\alpha]_D$+121.6° for 1a and $[\alpha]_D$+206.8° for 1b from S.Colonna, R.Giovini and F.Montanari, JCS Chem.Commun. 1968, 865; $[\alpha]_D$+266° for 1c from ref. 7b.; [d] Thiosulfinates 3 isolated by preparative silica gel TLC showed spectral properties in agreement with their structures; [e] Yield refers for the crude product; [f] Optical rotations of 3 were measured in benzene; [g] Optical rotation was calculated for 3a and 3b based on the rotation of the reaction solution after completion of the reaction; [h] The e.e.values of 3 were calculated based on the following data: $[\alpha]_D$-292.0° for 3b and $[\alpha]_D$-278.8° for 3c from ref. 7a; $[\alpha]_D$-300.0° for 3a from J.Drabowicz and M.Mikołajczyk, unpublished results

The results so far obtained indicate that optically active thiosulfinates 3 are formed in the reaction shown above with inversion of configuration at the sulfinyl centre. However, the stereospecificity of the 1→3 conversion is influenced primarily by the structure of the thiols (2) used and to some extent by the substituents at nitrogen in the starting sulfinamides 1. For instance, whereas the stereospecificity of the reaction of n-propanethiol (2a) with sulfinamides 1a and 1b was higher than 80%, with *iso*-propanethiol (2b) it varied from 43 to 66% and was dependent on the structure of 1. In the case of t-butanethiol (2c) the stereospecificity of the reaction was still lower (30 to 40%).

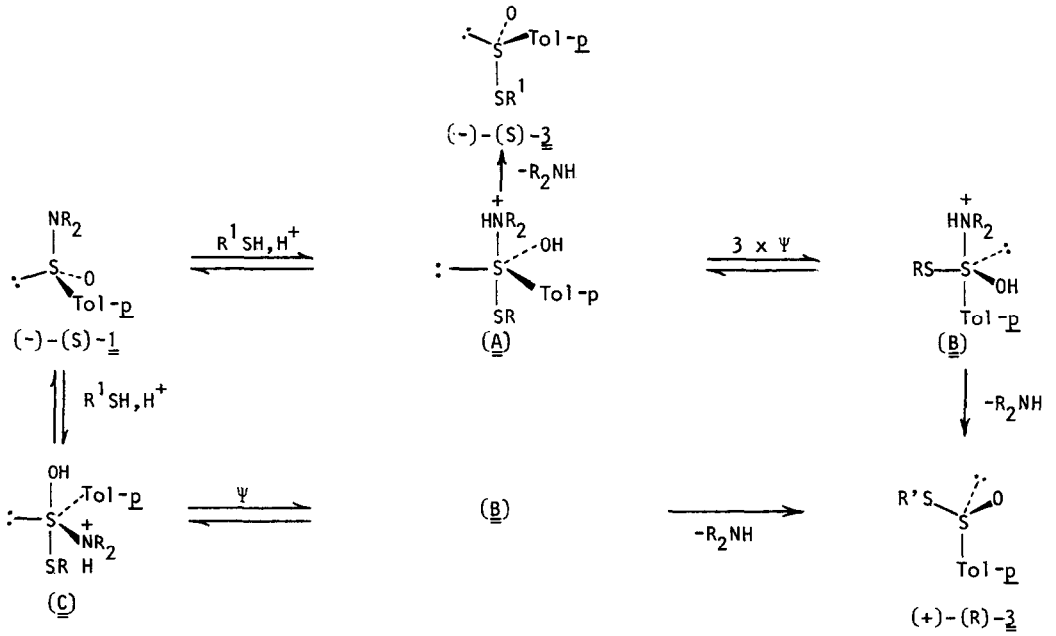
With regard to the mechanism of the reaction under discussion, it is noteworthy that optically active thiosulfinates 3 do not racemize in the reaction medium and that the racemization of optically active sulfinamides 1a and 1b is rather slow during the reaction in a thiol solution containing trifluoroacetic acid. Some experimental data pertinent to the matter in hand are collected in Table II.

Table II. Racemization of Sulfinamides 1 in a Solution of t-Butanethiol (2c) in the Presence of Trifluoroacetic Acid[a]

		Sulfinamide 1		Thiosulfinate 3	
	R_2	Starting $[\alpha]_D$ (e.e.)	Recovered $[\alpha]_D$ (e.e.)		$[\alpha]_D$ (e.e.)
1a,	Et_2	+100.0° (82)	+79.0 (65)	3c,	-90.0° (32)
1b,	Pr^i_2	+ 87.0° (42)	+82.0 (39)	3c,	-42.0° (15)

[a] The reactions were quenched at ca. 50% conversion and sulfinamides 1 as well as thiosulfinates 3 formed were isolated.

Therefore, much lower optical purity values of the thiosulfinates 3 obtained in comparison with those of the starting sulfinamides 1 are most probably due to a competition between the inversion and retention mechanism. Such a situation, which is similar to that observed by us for the acid-catalyzed alcoholysis of 1b[7c], may be best explained by assuming that addition-elimination mechanism[8] operates in this case.



Thus, the first sulfurane intermediate A with the alkylmercapto and protonated dialkylamino groups in apical positions gives on decomposition a thiosulfinate 3 with inversion of configuration. This is the main reaction course. However, after three consecutive pseudorotations by Berry mechanism a new sulfurane intermediate B is formed which is responsible for the formation of 3 with retention of configuration. The extent of the latter process determines the stereospecificity of the reaction.

Our results may also be rationalized in terms of the parallel formation of two sulfurane intermediates A and C, which are responsible for inversion and retention at sulfur, respectively.

In conclusion, the acid-catalyzed reaction of thiols with chiral sulfinamides provides a viable route to optically active thiosulfinates. Further studies on kinetic and stereochemical aspects of this reaction are in progress.

References and Notes

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9. 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 is protonated.

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