Optically Stable Thiosulphinate *S*-Esters: Asymmetric Synthesis and Nucleophilic Substitution at Sulphinyl Sulphur

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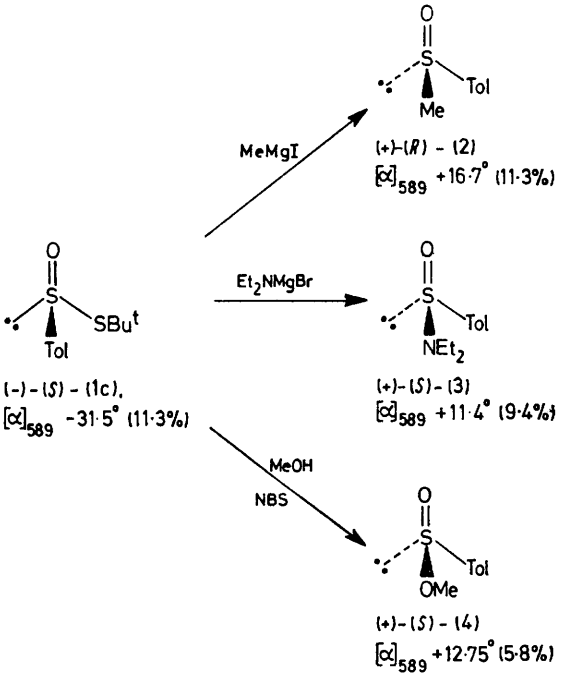
Summary Optically stable thiosulphinate *S*-esters containing the t-butylthio-group have been prepared by the asymmetric condensation of sulphinyl chlorides with achiral thiols in the presence of optically active tertiary amines; they have been converted into sulphoxides, sulphinamides, and sulphinates.

RECENTLY the chemistry and stereochemistry of thiosulphinates[1,2] have been investigated, in particular the mechanism of racemization of optically active thiosulphinates. The resolution of cystine (±)-*S*-monoxides by Savige *et al.*,[3] as well as the recent separation of diastereoisomers of steroidal thiosulphinates[4] demonstrated that the pyramidal configuration at the sulphinyl sulphur atom can be maintained. However, the optical stability of simple thiosulphinates (**1**) with sulphur as the sole chirality centre so far prepared[5] is low. They readily undergo thermal and acid- and nucleophile-catalysed racemization. In the latter case the loss of optical activity is due to scission of the sulphur–sulphur bond and the formation of achiral sulphenic acid as an intermediate.[5a,6] Fava and his coworkers have proposed that the unusually rapid thermal racemization of *S*-aryl arenethiosulphinates involves an internal displacement of sulphenyl sulphur rather than pyramidal inversion at sulphinyl sulphur.† Block[2] has attributed the very low optical stability of optically active esters (**1**) to their ready, concerted reaction with sulphenic acid.

Since nucleophilic substitution at the sulphenyl sulphur atom plays an important role in all these processes the presence of the bulky t-butyl group should substantially hinder substitution, increasing the chemical and optical



SCHEME. Optical purity is given in parentheses.

† This proposal has been critically discussed by P. Laur, in 'Sulfur in Organic and Inorganic Chemistry,' ed. A. Senning, Marcel Dekker, New York, 1971, vol. 3, p. 203.

TABLE

Asymmetric synthesis of the thiosulphinates (**1**)

(**1**)	R^1	R^2	Amine[a]	$[\alpha]_{589}$ (c, C_6H_6)	Optical purity (%)	Absolute configuration
a	Bu^t	Bu^t	(−)-A	− 3·7°(7·18)[b]	2·4	—
b	Ph	Bu^t	(−)-A	−21·8°(1·73)	9·0	(*S*)
b	Ph	Bu^t	(+)-B	− 7·15°(2·89)	3·0	(*S*)
c	*p*-MeC_6H_4	Bu^t	(−)-A	−31·5°(2·57)	11·3	(*S*)
c	*p*-MeC_6H_4	Bu^t	(+)-B	−10·7°(2·51)	3·8	(*S*)
d	Ph	Pr^i	(+)-B	−10·8°(2·90)	4·3	(*S*)
e	Ph	Et	(+)-B	− 2·6°(2·45)	1·0	(*S*)
f	*p*-MeC_6H_4	Pr^i	(−)-A	−26·0°(2·26)	8·9	(*S*)

[a] A = *NN*-dimethylamphetamine; (−)-A had $[\alpha]_{589}$ −9·3° (*c* 3·21, MeOH, 95% optically pure); B = *NN*-dimethyl-α-fenchylamine; (+)-B, had $[\alpha]_{589}$ +4·85° (*c* 2·04, Me_2CO, 95% optically pure) [b] This rotation was measured in ethanol.

stability of the thiosulphinates. This was found to be the case.

We have now obtained optically active thiosulphinate *S*-esters by the asymmetric condensation of sulphinyl chlorides with achiral thiols in the presence of optically active tertiary amines at *ca.* −70 °C in ether solution.‡ The rotations,

$$R^1\text{–}\underset{\underset{O}{\|}}{S}\text{–Cl} + R^2SH \xrightarrow[-Me_2N\overset{*}{R}\cdot HCl]{Me_2N\overset{*}{R}} R^1\text{–}\underset{\underset{O}{\|}}{\overset{*}{S}}\text{–}SR^2 \quad (\mathbf{1})$$

* Optically active centre.

optical purities, and absolute configurations of the esters (**1a**—**f**) synthesized are given in the Table.

As expected, the thiosulphinates (**1a**—**c**) containing the Bu^tS group are quite optically stable, their optical rotation remaining unchanged after several weeks at room temperature. Furthermore, no racemization of (**1a**—**c**) was observed in pyridine solution at room temperature, in benzene solution containing CF_3CO_2H at room temperature, or under reflux in benzene solution for 10 h. However, the other thiosulphinates (**1d**—**f**) which do not contain the Bu^tS group have low optical stability, the thiosulphinate (**1d**) being completely racemized after 30 h at room temperature.

Assignment of the chirality at sulphur and the optical purity of the thiosulphinates (**1**) was based on the results of their stereospecific conversion into known sulphoxides with Grignard reagents, a reaction which has been shown to proceed with inversion of configuration at sulphinyl sulphur.[4,5] The only exception was the ester (**1a**) which did not react with Grignard reagents (MeMgI or *p*-MeC_6H_4-MgBr) even on prolonged heating in tetrahydrofuran solution. Its optical purity was estimated,§ however, by an n.m.r. technique using the chiral tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium.[7]

We have also accomplished new stereospecific nucleophilic substitutions at sulphinyl sulphur in thiosulphinate *S*-esters using (−)-(*S*)-(**1c**) as substrate. Thus, the reaction with Et_2NMgBr and with MeOH in the presence of *N*-bromosuccinimide (NBS) gave (+)-(*S*)-*NN*-diethyl toluene-*p*-sulphinamide (**3**)[8] and (+)-(*R*)-methyl toluene-*p*-sulphinate (**4**),[9] respectively. Both reactions, like that with MeMgI affording (+)-(*R*)-methyl-*p*-tolyl sulphoxide (**2**), most likely proceed with inversion at the sulphinyl centre. The optical rotations, purities and absolute configurations of compounds (**2**)—(**4**) are in the Scheme.

(*Received*, 14*th January* 1976; *Com.* 028.)

‡ Optically active tertiary amines have recently been used in the synthesis of optically active sulphinates[9] and trivalent phosphorus acids esters.[10]

§ The enantiomeric content and optical purity was estimated using a sample of (**1a**), with $[\alpha]_{589}$ + 21·1°, which has been obtained from optical resolution *via* β-cyclodextrin inclusion compounds (J. Drabowicz, doctoral thesis, Łódź, 1974).

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