A New Enantioselective Asymmetric Synthesis of Alkyl t-Butylsulphinates

Józef Drabowicz, Sławomir Legędź, and Marian Mikołajczyk*

Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Department of Organic Sulphur Compounds, 90–362 Łódź, Boczna 5, Poland

The reaction of symmetrical sulphites with t-butylmagnesium chloride in the presence of chiral aminoalcohols has been found to proceed in an asymmetric way affording chiral t-butylsulphinates in 40—70% enantiomeric excess.

Chiral sulphoxides and sulphinates are the most important compounds among a vast number of various classes of chiral organosulphur compounds.[1] Chiral sulphoxides play an important role in asymmetric synthesis, especially in the asymmetric C–C bond formation.[1,2] Since chiral sulphinates are very convenient precursors of chiral sulphoxides[3] as well as model compounds in stereochemical studies,[4] their synthesis has also attracted much attention. Up to now, however, the synthetic approaches to chiral sulphinates with the sulphur atom as a sole centre of chirality have been far from satisfactory. Asymmetric oxidation of sulphenates,[5] kinetic resolution of racemic sulphinates in the transesterification

Table 1. Asymmetric synthesis of chiral alkyl t-butylsulphinates (1) $Bu^tS(O)OR$.

	Sulphite (2),R	Chiral amine (4)	Molar ratio (2):(3):(4)	Reaction time (h)	Sulphinate (1)	Yield (%)[a]	$[\alpha]_{589}$[b]	E.e. (%)[c]	Abs. conf.[c]
1	(2a), Me	(4a)	1:4:2	8	(1a)	62	+72.0	53.3[d]	*S*
2	(2a), Me	(4a)	1:8:4	13	(1a)	66	+70.0	51.8	*S*
3	(2b), Et	(4a)	1:5:2.5	9	(1b)	62	+100.0	69.0	*S*
4	(2b), Et	(4a)	1:8:4	14	(1b)	60	+96.2	66.4	*S*
5	(2c), Pr^n	(4a)	1:2:1	14	(1c)	50	+62.0[e]	46.2	*S*
6	(2c), Pr^n	(4a)	1:3:1	14	(1c)	79	+63.2	47.1	*S*
7	(2c), Pr^n	(4a)	1:4:2	14	(1c)	77	+81.7	60.8	*S*
8	(2c), Pr^n	(4a)	1:8:4	12	(1c)	79	+97.7	72.7	*S*
9	(2c), Pr^n	(4a)	1:16:8	12	(1c)	79	+99.7	74.2	*S*
10	(2c), Pr^n	(4c)	1:8:4	12	(1c)	63	−37.9	28.2	*R*
11	(2c), Pr^n	(4d)	1:8:4	12	(1c)	67	+15.9	11.8	*S*
12	(2c), Pr^n	(4e)	1:8:4	12	(1c)	69	+3.3	2.5	*S*
13	(2d), Pr^i	(4a)	1:8:4	14	(1d)	70	+54.3	43.0	*S*
14	(2d), Pr^i	(4b)	1:8:4	14	(1d)	69	−25.3	20.0	*R*
15	(2e), Bu^n	(4a)	1:8:4	18	(1e)	84	+83.3	62.4	*S*

[a] Yields of the products with purity higher than 98% (g.l.c. assay). [b] All optical rotations were measured in ethanol. [c] E.e. values and absolute configurations of (1) were determined chemically *via* their conversion into known t-butyl phenyl sulphoxide[12] assuming that the reaction with phenyl-lithium proceeds with full inversion of configuration at sulphur. [d] The e.e. value 52% was obtained from the ^1H n.m.r. measurement using tris[3-(trifluoromethylene)-(+)-camphorato]europium (TFMC). [e] In mixture with 35% of (2c).

reaction with chiral alcohols[4a] and upon treatment with chiral Grignard reagents[6], direct optical resolution *via* β-cyclodextrin inclusion complexes,[7] and asymmetric condensation of sulphinyl chlorides with achiral alcohols in the presence of chiral tertiary amines[8] give only moderate to high enantiomeric excesses in some cases. The first stereospecific synthesis of chiral sulphinates,[9] which consists of the acid-catalysed alcoholysis of chiral sulphinamides, also has serious limitations connected with the synthetic availability and optical stability of a chiral substrate.

We now present a simple asymmetric synthesis of chiral alkyl t-butylsulphinates (1) which is based on our earlier observation[10] that esters (1) are formed exclusively upon treatment of symmetrical sulphites (2) with t-butylmagnesium chloride (3) and on the fact that Grignard reagents interact with chiral amines giving chiral complexes.[11] The latter species were expected to react at the prochiral sulphur atom in (2) in an enantioselective way affording chiral sulphinates (1). This was found to be the case.

$$\underset{\text{(2)}}{ROS(O)OR} + \underset{\text{(3)}}{Bu^tMgCl} \xrightarrow{\text{(4)}} \underset{\text{(1)}}{Bu^{t*}S(O)OR}$$

For (1),(2):
a; R = Me
b; R = Et
c; R = Pr^n
d; R = Pr^i
e; R = Bu^n

For (4):
a; (−)-Quinine
b; (+)-Quinidine
c; (+)-Cinchonine
d; (−)-*N*-Methylephedrine
e; (−)-Brucine

The experimental procedure for synthesis of chiral sulphinates (1) is as follows. To a solution of t-butylmagnesium chloride (3) in diethyl ether 0.5 mol equiv. of optically active amine (4) is added. The resulting solution is heated for a short time. Then, sulphite (2) is added dropwise and the reaction mixture is refluxed for an appropriate time (see Table 1). After the typical work-up (quenching with saturated ammonium chloride solution, extraction with diethyl ether) optically active sulphinates (1) are isolated by distillation. The optical rotations, enantiomeric excess (e.e.) values, and absolute configurations of (1) obtained in this way are summarized in Table 1.

The results in Table 1 indicate that our new asymmetric reaction is efficient and gives sulphinates (1) in high chemical yield and with enantiomeric excess often in the range of 40—70%. The highest e.e.'s (~70%) were observed for the reactions with quinine (4a) as a chiral auxiliary agent. It should be stressed that the highest e.e. value (74%) observed for (1c) is much better than those obtained by any other known method of asymmetric synthesis of chiral sulphinates. An inspection of the results in Table 1 shows that there is a strong dependence between the e.e. values of (1) and the ratio of reagents. For example, the reaction of sulphite (2c) with (3) in the presence of quinine (4a) used in a molar ratio 1:2:1 affords sulphinate (1c) with 46.2% e.e. whereas the change of the reagents ratio to 1:16:8 leads to (1c) with 74.2% e.e. (entries 5 and 9).

It is also interesting to point out that either enantiomer of sulphinate (1) can be obtained by the choice of the amine (4) used as complexing reagent. For instance, (+)-(*S*)-isopropyl t-butylsulphinate (+)-(*S*)-(1d) is formed in the reaction of sulphite (2d) with (3) in the presence of quinine (4a) while the use of quinidine (4b) leads to (−)-(*R*)-(1d) (entries 13 and 14). Similarly, the reaction of sulphite, (2c) with (3) in the presence of cinchonine (4c) and (−)-*N*-methylephedrine (4d), having also opposite configurations at the carbon atoms connected with the hydroxy group, gives n-propyl t-butylsulphinate (1c) with (−)-(*R*)- and (+)-(*S*)-chirality, respectively (entries 10 and 11). These observations indicate that there is a clear relationship between the chirality at sulphur in sulphinates (1) formed and at the carbon atom bearing the hydroxy function in the aminoalcohols (4a—d) used as asymmetric reagents.

Moreover, it appears that the extent of asymmetric induction in the reaction investigated increased when the structure of (**4**) becomes more rigid.

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References

1 M. Mikołajczyk and J. Drabowicz, *Top. Stereochem.*, 1982, **13**, 333.

2 G. Solladie, *Synthesis*, 1981, 185; S. Colonna, R. Anunziata, and M. Cinquini, *Phosphorus Sulfur*, 1981, **10**, 197; G. H. Posner, J. P. Mallamo, K. Miura, and M. Hulce in 'Asymmetric Reactions and Processes in Chemistry,' American Chemical Society, Washington, DC, 1982; *ACS Symp. Ser.*, 185, p. 139.

3 K. K. Andersen, *Tetrahedron Lett.*, 1962, 93; K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, *J. Am. Chem. Soc.*, 1965, **87**, 1958; D. N. Harpp, S. Vines, J. P. Montillier, and T. H. Chan, *J. Org. Chem.*, 1976, **41**, 3987; J. Drabowicz, B. Bujnicki, and M. Mikołajczyk, *ibid.*, 1982, **47**, 3325; D. D. Ridley and M. A. Smal, *J. Chem. Soc., Chem. Commun.*, 1981, 505; K. K. Andersen, B. Bujnicki, J. Drabowicz, M. Mikołajczyk, and J. B. O'Brien, *J. Org. Chem.*, 1984, **49**, 4070.

4 (a) H. Phillips, *J. Chem. Soc.*, 1925, 127, 2552; (b) M. Mikołajczyk, J. Drabowicz, and H. Slebocka-Tilk, *J. Am. Chem. Soc.*, 1979, **101**, 1302; (c) C. W. Perkins and J. C. Martin, *J. Am. Chem. Soc.*, 1983, **105**, 1377.

5 L. Sagramora, P. Koch, A. Garbesi, and A. Fava, *J. Chem. Soc., Chem. Commun.*, 1967, 985.

6 W. H. Pirkle and M. S. Hoekstra, *J. Am. Chem. Soc.*, 1976, **98**, 1832.

7 M. Mikołajczyk and J. Drabowicz, *J. Am. Chem. Soc.*, 1978, **100**, 2510.

8 M. Mikołajczyk and J. Drabowicz, *J. Chem. Soc., Chem. Commun.*, 1974, 547.

9 M. Mikołajczyk, J. Drabowicz, and B. Bujnicki, *J. Chem. Soc., Chem. Commun.*, 1976, 568; M. Mikołajczyk, B. Bujnicki, and J. Drabowicz, *Bull. Acad. Pol. Sci., Ser. Sci. Chem.*, 1977, **25**, 267; K. Hiroi, R. Kitayama, and S. Sato, *Synthesis*, 1983, 1040; B. Bujnicki, unpublished results.

10 M. Mikołajczyk and J. Drabowicz, *Synthesis*, 1974, 124.

11 J. Toney and G. D. Stucky, *J. Chem. Soc., Chem. Commun.*, 1967, 1169; A. L. Spek, P. Voorbergen, G. Schat, C. Blomberg, and F. Bickelhaupt, *J. Organomet. Chem.*, 1974, **77**, 147.

12 U. Folli, F. Montanari, and G. Torre, *J. Chem. Soc. C*, 1968, 1317.