Tetrahedron Letters,Vol.30,No.28,pp 3659-3662,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

AN EFFICIENT ROUTE TO CHIRAL t-BUTYL SULFOXIDES

F. REBIERE and H.B. KAGAN*

Laboratoire de Synthèse Asymétrique
Associé au CNRS
Institut de Chimie Moléculaire d'Orsay
Université Paris-Sud 91405 Orsay, France.

Summary: *The cyclic sulfite 2 of (S)-1,1-diphenyl-propane-1,2-diol 1 gave chiral sulfinates 3 or 4 with high regio- and stereoselectivities, by reaction with various organometallics. The chiral sulfinates were then transformed in almost quantitative yields into enantiomerically pure sulfoxides by addition of a second organometallic reagent.*

Chiral sulfoxides are important intermediates in the preparation of optically active compounds[1-4]. The asymmetric oxidation of sulfides gives a route to chiral sulfoxides [5-10]. Andersen's method with (S)-menthyl *p*-toluenesulfinate and Grignard reagents has been, and still is, widely used[1-5, 11]. The existing methods are not very convenient for production of several classes of sulfoxides such as dialkyl sulfoxides or alkyl aryl sulfoxides (alkyl ≠ methyl, aryl = p-tolyl). For example *t*-butyl *n*-alkyl sulfoxides give interesting stereoselective 1-4 additions but are difficult to prepare enantiomerically pure[12]. We wish to describe here our preliminary results on the easy preparation of optically active sulfoxides R^1-S(O)-R^2 in which R^1= *t*-butyl and R^2 stand for almost any type of alkyl or aryl group

The cyclic sulfite **2** is synthetized from (S)-**1** as a mixture of diastereomers (90 : 10) from which stereochemically pure **2** (mp = 108-110°C ; $[\alpha]_D$ = -247°, c=0.7 in chloroform) is easily isolated by crystallization in hexane (overall yield = 60 %). The starting diol (S)-**1** is available in one step from a cheap chiral material, (S)-ethyl lactate, and the Grignard reagent of bromobenzene[13, 14]. We prepared pure crystalline (S)-**1** (mp = 91-93°C ; $[\alpha]_D$ = -100°, c=1 in methanol) on a 1 mol scale in 75 % yield. The trans stereochemistry is tentatively assigned to sulfite **2**, based on subsequent chemical transformations. Reaction of organometallics R^1M on **2** should give in principle access to sulfinates **3** or **4** (or the mixture), because of the presence of two different leaving groups at sulfur. We can also expect full inversion at sulfur in the reaction, by analogy with sulfinate chemistry [4]. The stereoselectivity of reactions occuring during monosubstitution on sulfites is not discussed in literature[15], but it is reasonable to also assume inversion of stereochemistry. We found that the Grignard reagent derived from *t*-butyl bromide

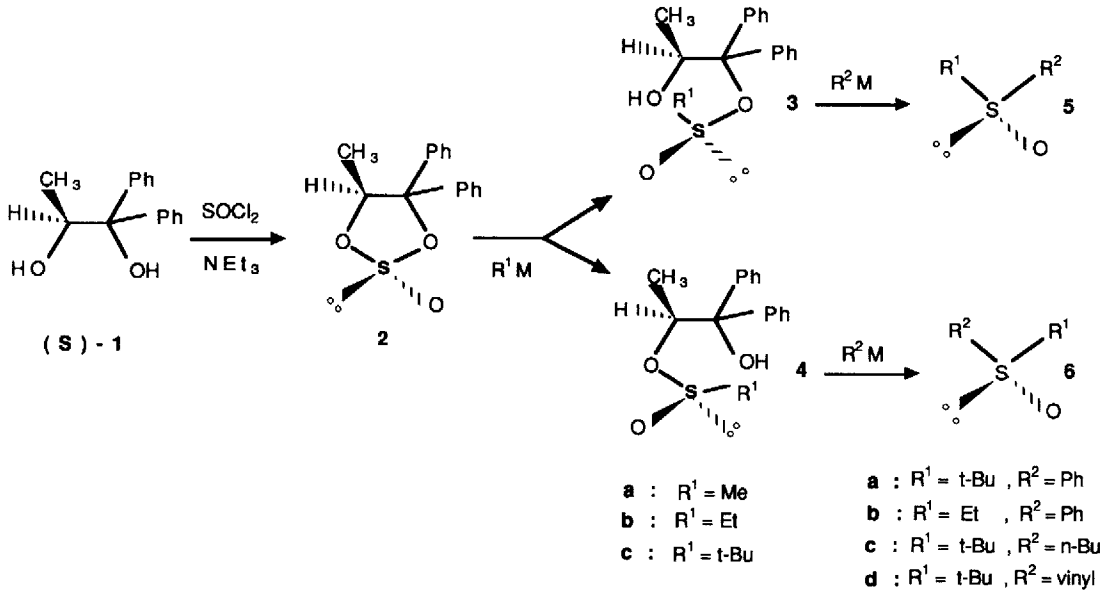

Figure 1

cleanly reacts in THF at room temperature on sulfite **2** with predominant formation of the sulfinate **4c** deriving from cleavage at the more hindered side. The minor isomer **3c** could be removed by crystallization. The yield of purified **4c** is close to 60 %. Similarly, the Grignard reagent of *t*-butyl chloride leads to **4c** in good yield (see Table1).

In all experiments, sulfinate **4c** was isolated as crystalline compound, apparently as a pure stereoisomer at the sulfinyl sulfur (only one diastereomer is detected by ^{1}H or ^{13}C nmr). This is confirmed by its further transformation into sulfoxides. For example the *t*-butylsulfinate **4c** has been quantitatively transformed into sulfoxide (S)-**6a** of 100 % ee (Table 2). Many chiral sulfoxides have been prepared from sulfinate **4c**; some results are listed in Table 2. Usually, yields and ee's are excellent. From the absolute configuration of the sulfoxides, and assuming an inversion of configuration at each step of Figure 1, one concludes that the cyclic sulfite **2** has the (R) configuration at sulfur, which gives a trans-relationship between the oxygen of the sulfinyl group and the methyl group.

In conclusion, the two step asymmetric synthesis of *t*-butyl sulfoxides that we discovered is an useful complement to existing methods[18]. We are actively investigating the scope and the development of the reaction to other classes of chiral sulfoxides [23].

Acknowledgment
One of us (F.R.) acknowledges the help of M.R.E.S. for a fellowship.

Table 1

Synthesis of chiral alkylsulfinates from sulfite (S)-**2** (see Figure 1)

	R^1M [a]	**3** / **4** ratio [b]	Isolated yield [c] of sulfinate(major isomer)[e]	
1	MeMgI	80:20	**3a**	56 %
2	MeLi	75:25	**3a**	55 %
3	EtMgBr	92:8	**3b**	57 %
4	*t*-BuMgBr	5:95	**4c**	60 %
5	*t*-BuMgCl	10:90	**4c**	70 %

a Reaction performed in THF, at -78°C (except entry 4 : 25°C). For a standard procedure see (d).
b Measured by nmr on the crude product.
c Purification by crystallization after flash-chromatography.
d A solution of sulfite **2** (1.5 g , 5.5 mmol) in 30 ml THF is cooled at -78°C in a Schlenk. 12 ml of a solution of 0.5 M *t* BuMgCl (6 mmol) in THF at -78°C is added in 0.5 h. After stirring 0.5 h at this temperature the reaction is quenched by addition of 30 ml water. The crude product (**4c** / **3c** = 90:10) is isolated by flash-chromatography on silica (solvent : ethyl acetate / cyclohexane = 1 : 5). Crystallization from hexane gives 1.3 g (70 % yield) of pure **4c** : mp=135-137°C, $[\alpha]_D$ = -120° (c 0.9, $CHCl_3$).
e Data for stereochemically pure sulfinates : **3a** : mp=92-94°C, $[\alpha]_D$ = +46° (c 0.5, chloroform) ; **3b** : mp=76-78°C, $[\alpha]_D$ = -31° (c 0.5, acetone); **4c** : see note d.

Table 2

Synthesis of chiral *t* -butyl sulfoxides from sulfinate **4c** (see Figure 1)

Sulfinate	R^2M [a]	Isolated Yield[b]		Config. and ee		Spec. rotation
4c	PhLi	**6a**	99 %	(S)	100 % [c]	-175° (c 1, CHCl3)
3b	PhLi	**5b**	27 %	(R)	85 % [c]	+151° (c 1, EtOH)
4c	*n* BuLi	**6c**	99 %	(R)	100 % [c]	+125° (c 1, acet.)
4c	VinylMgCl	**6d**	99 %	(R)	100 % [d]	+207° (c.0.3, acet.)

a Reaction performed in THF at 25°C. Standard procedure see (e), except for **3b** (-78°C, one-pot reaction from **2** with sequential addition of EtMgBr and then PhLi)
b Isolation by flash-chromatography.
c Measured from the known specific rotations.
d Measured by nmr with a chiral shift reagent ($Eu(hfc)_3$) or a solvating reagent[22].
e To a solution of 1.3 g (4 mmol) **4c** in 20 ml THF in a Schlenk was dropwise added at room temperature 9 ml of a 1 M hexane solution of PhLi (9 mmol). After 0.5 h at rt 30 ml water was added. Usual workup gave the crude product which was purified by flash-chromatography on silica (solvent; AcOEt/cyclohex. = 2:1). Sulfoxide (S)- **6a** is obtained in quantitative yield (0.72 g) : mp=86-88 °C, $[\alpha]_D$ = -175° (c 1, chloroform), 100 % ee (lit. : $[\alpha]_D$ =174° in chloroform[15]).

REFERENCES and NOTES

(1) Solladié, G. , Synthesis , 1981, 185.

(2) Barbachyn, M. R. and Johnson, C. R. , Asymmetric Synthesis, Morrison, J.D., Ed., Vol. 4, p.227, Academic Press (New York, 1984).

(3) Posner, G., Acc. Chem. Res. , **1987**, 20, 72.

(4) Mikolajczjyk, M. and Drabowicz, J., Topics in Stereochem., **1982**, 13, 333.

(5) Biochemical reaction have been reviewed [6]. Several enantioselective chemical systems have been described, such as chiral titanium complexes/ hydroperoxides[7-9] or chiral oxaziridines [10].

(6) Holland, H. L., Chem. Rev., **1988**, 88, 473.

(7) Pitchen, P.; Deshmukh, M.; and Kagan, H. B., J. Am. Chem. Soc., **1984**, 106, 5974.

(8) Zhao, S.; Samuel, O.; Kagan, H. B., Tetrahedron, **1987**, 43, 5135.

(9) Di Furia, F.; Modena, G.; Seraglia, R., Synthesis , **1984**, 325.

(10) Davis, F.A.; McCauley, J.P.; Chattopadhyay, S.; Hrakal, M.L.; Towson, J.C.; Watson, W.H.;Tavanaiepour, I., J. Am. Chem. Soc., **1987**, 109, 3370.

(11) Andersen, K. K., J. Org.Chem., **1964**, 29, 1953.

(12) Casey, M.; Manage, A.C.; Nezhat, L., Tetrahedron Lett., **1988**, 29, 5821.

(13) Tiffeneau, M., C.R. Acad.Sci. (Paris), **1908**, 29, 5821.

(14) Thaker, K.A.; Vassi, T.G., J. Sci. Industr. Res., **1961**, 20 B, 66.

(15) An asymmetric synthesis of alkyl *t*- butyl sulfinates from symmetrical sulfites and *t*-butylmagnesium chloride has been described (ee < 70 %) : Drabowicz, J.; Legedz, S. and Mikolajczyk, M., J. C. S. Chem. Commun., **1985**, 1670.

(16) We attempted to prepare (R)-1 by asymmetric OsO_4 dihydroxylation of 1,1-diphenyl-propene according to the recent Sharpless procedure [17]. By using quinidine *p*-chloro-benzoate as a chiral catalyst, (R)-(+)-1 was isolated with 10 % ee (reaction temperature : 25°C).

(17) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. , J. Am. Chem. Soc.,**1988**, 110, 1968.

(18) A cyclic 1,2,3-oxathiazolidine 2-oxide derived from (-)-ephedrine has been used to prepare methyl aryl sulfoxides [19]. A chiral benzoxathiazine 2-oxide has been transformed into phenyl alkyl sulfoxides [20]. Epimeric cholesteryl methanesulfinates have been separated by fractional crystallizations and are starting materials for preparation of various methyl sulfoxides [21].

(19) Wudl, F. ; Lee, T. B. K. , J. Am.Chem.Soc. , **1973**, 95, 6349.

(20) Hiroi, K. ; Sato, S.; Kitayama, R., Chem. Letters , **1980**, 1595.

(21) Andersen, K. K.; Bujnicki, B.; Drabowicz, J.; Mikolajczyk, M.; O'Brien, J. B., J.Org.Chem.,,**1984**, 42, 4070.

(22) Deshmukh, M.; Dunach, E.; Jugé, S.; Kagan, H. B., Tetrahedron Lett., **1984**, 25, 3467; Erratum : *ibidem* ,**1985**, 26, 402.

(23) The structure of the Grignard reagent controls the regioselectivity of the ring opening of 1 (See table 1). We are investigating the possibility of interconversions between sulfinates **3** and **4** during or after the reaction.

(Received in France 19 April 1989)